

6-HYDROXY-4-OXO-1,4-DIHYDROPYRIMIDINE-5-CARBOXAMIDES AS APJ  
AGONISTS

CROSS-REFERENCE TO RELATED APPLICATIONS

5           This application claims priority of U.S. Provisional Application Serial No.  
62/312,780, filed March 24, 2016, which is incorporated herein in its entirety.

FIELD OF THE INVENTION

10           The present invention provides novel 1,4-dihydropyrimidine-5-carboxamides, 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

15           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  
20           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  
25           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  
30           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)).

5 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)).

10 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  
15 (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.

20 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  
25 (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)).

30 The mechanisms underlying inotropic action of apelin are not well understood, but appear to be distinct from clinically used  $\beta_1$ -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)).

5           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, 10   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 15 (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 20   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.

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#### SUMMARY OF THE INVENTION

The present invention provides 1,4-dihydropyrimidine-5-carboxamides, and their analogues thereof, which are useful as APJ agonists, including stereoisomers, tautomers, pharmaceutically acceptable salts, or solvates thereof.

30           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.

5 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  
10 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.

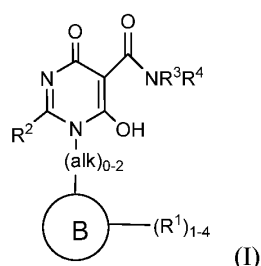
15 The compounds of the invention can be used alone, in combination with other compounds of the present invention, or in combination with one or more other agent(s).

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

## 20 DETAILED DESCRIPTION OF THE INVENTION

### I. COMPOUNDS OF THE INVENTION

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



25 or a stereoisomer, an enantiomer, a diastereoisomer, a tautomer, a pharmaceutically acceptable salt, a prodrug, or a solvate thereof, wherein:



- alk is C<sub>1-6</sub> alkylene substituted with 0-5 R<sup>e</sup>;
- ring B is independently selected from C<sub>3-6</sub> cycloalkyl, C<sub>3-6</sub> cycloalkenyl, aryl, bicyclic carbocyclyl, and 6-membered heteroaryl;
- R<sup>1</sup>, at each occurrence, is independently selected from H, halogen, NO<sub>2</sub>, -(CH<sub>2</sub>)<sub>n</sub>OR<sup>b</sup>,
- 5 (CH<sub>2</sub>)<sub>n</sub>S(O)<sub>p</sub>R<sup>c</sup>, -(CH<sub>2</sub>)<sub>n</sub>C(=O)R<sup>b</sup>, -(CH<sub>2</sub>)<sub>n</sub>NR<sup>a</sup>R<sup>a</sup>, -(CH<sub>2</sub>)<sub>n</sub>CN, -  
 (CH<sub>2</sub>)<sub>n</sub>C(=O)NR<sup>a</sup>R<sup>a</sup>, -(CH<sub>2</sub>)<sub>n</sub>NR<sup>a</sup>C(=O)R<sup>b</sup>, -(CH<sub>2</sub>)<sub>n</sub>NR<sup>a</sup>C(=O)NR<sup>a</sup>R<sup>a</sup>, -  
 (CH<sub>2</sub>)<sub>n</sub>NR<sup>a</sup>C(=O)OR<sup>b</sup>, -(CH<sub>2</sub>)<sub>n</sub>OC(=O)NR<sup>a</sup>R<sup>a</sup>, -(CH<sub>2</sub>)<sub>n</sub>C(=O)OR<sup>b</sup>, -  
 (CH<sub>2</sub>)<sub>n</sub>S(O)<sub>p</sub>NR<sup>a</sup>R<sup>a</sup>, -(CH<sub>2</sub>)<sub>n</sub>NR<sup>a</sup>S(O)<sub>p</sub>NR<sup>a</sup>R<sup>a</sup>, -(CH<sub>2</sub>)<sub>n</sub>NR<sup>a</sup>S(O)<sub>p</sub>R<sup>c</sup>, C<sub>1-4</sub> alkyl  
 substituted with 0-3 R<sup>e</sup>, -(CH<sub>2</sub>)<sub>n</sub>-C<sub>3-6</sub> carbocyclyl substituted with 0-3 R<sup>e</sup>, and -
- 10 (CH<sub>2</sub>)<sub>n</sub>-heterocyclyl substituted with 0-3 R<sup>e</sup>;
- R<sup>2</sup> is independently selected from C<sub>1-5</sub> alkyl substituted with 0-3 R<sup>e</sup>; C<sub>2-5</sub> alkenyl  
 substituted with 0-3 R<sup>e</sup>, aryl substituted with 0-3 R<sup>e</sup>, heteroaryl substituted with 0-  
 3 R<sup>e</sup>, and C<sub>3-6</sub> cycloalkyl substituted with 0-3 R<sup>e</sup>; provided when R<sup>2</sup> is C<sub>1-5</sub> alkyl,  
 the carbon atoms and the groups attached thereto except the carbon atom attached
- 15 to the pyrimidine ring may be replaced by O, N, and S;
- R<sup>3</sup> is independently selected from H and C<sub>1-5</sub> alkyl;
- R<sup>4</sup> is independently selected from -(CR<sup>7</sup>R<sup>7</sup>)<sub>n</sub>-R<sup>6</sup>, -(CR<sup>7</sup>R<sup>7</sup>)<sub>n</sub>OR<sup>6</sup>, -(CR<sup>7</sup>R<sup>7</sup>)<sub>n</sub>S(O)<sub>p</sub>R<sup>6</sup>, -  
 (CR<sup>7</sup>R<sup>7</sup>)<sub>n</sub>C(=O)R<sup>6</sup>, -(CR<sup>7</sup>R<sup>7</sup>)<sub>n</sub>NR<sup>a</sup>R<sup>6</sup>, -(CR<sup>7</sup>R<sup>7</sup>)<sub>n</sub>C(=O)NR<sup>a</sup>R<sup>6</sup>, -  
 (CR<sup>7</sup>R<sup>7</sup>)<sub>n</sub>NR<sup>a</sup>C(=O)R<sup>6</sup>, -(CR<sup>7</sup>R<sup>7</sup>)<sub>n</sub>S(O)<sub>p</sub>NR<sup>a</sup>R<sup>6</sup>, and -(CR<sup>7</sup>R<sup>7</sup>)<sub>n</sub>NR<sup>a</sup>S(O)<sub>p</sub>R<sup>6</sup>;
- 20 alternatively, R<sup>3</sup> and R<sup>4</sup> together with the nitrogen atom to which they are both attached  
 form a heterocyclic ring or a spiro heterocyclic ring comprising carbon atoms and  
 additional 1 to 4 heteroatoms selected from NR<sup>5a</sup>, O, and S and substituted with 0-  
 5 R<sup>5</sup>;
- R<sup>5</sup>, at each occurrence, is independently at each occurrence, selected from OH, halogen, -
- 25 (CR<sup>7</sup>R<sup>7</sup>)<sub>n</sub>-R<sup>6</sup>, -OR<sup>6</sup>, -S(O)<sub>p</sub>R<sup>6</sup>, -C(=O)R<sup>6</sup>, -NR<sup>a</sup>R<sup>6</sup>, -C(=O)NR<sup>a</sup>R<sup>6</sup>, -NR<sup>a</sup>C(=O)R<sup>6</sup>, -  
 NR<sup>a</sup>C(=O)OR<sup>6</sup>, -OC(=O)NR<sup>a</sup>R<sup>6</sup>, -C(=O)OR<sup>6</sup>, -S(O)<sub>p</sub>NR<sup>a</sup>R<sup>6</sup>, -NR<sup>a</sup>S(O)<sub>p</sub>NR<sup>a</sup>R<sup>6</sup>,  
 and -NR<sup>a</sup>S(O)<sub>p</sub>R<sup>6</sup>;
- R<sup>5a</sup>, at each occurrence, is independently selected from -C(=O)OR<sup>6</sup>, C(=O)NR<sup>a</sup>R<sup>6</sup>, -  
 (CR<sup>7</sup>R<sup>7</sup>)<sub>n</sub>-R<sup>6</sup>, -C(=O)-R<sup>6</sup>, and -S(O)<sub>p</sub>R<sup>6</sup>;
- 30 R<sup>6</sup>, at each occurrence, is independently selected from -(CR<sup>7</sup>R<sup>7</sup>)<sub>n</sub>-C<sub>3-10</sub> carbocyclyl and -  
 (CR<sup>7</sup>R<sup>7</sup>)<sub>n</sub>-heteroaryl, each substituted with 0-3 R<sup>8</sup>;

- $R^7$ , at each occurrence, is independently selected from H,  $C_{1-4}$  alkyl, and  $(CH_2)_n-C_{3-12}$  carbocyclyl substituted with 0-3  $R^e$ ;
- $R^8$ , at each occurrence, is independently selected from H, halogen,  $-(CH_2)_nOR^b$ ,  $(CH_2)_nS(O)_pR^c$ ,  $-(CH_2)_nC(=O)R^b$ ,  $-(CH_2)_nNR^aR^a$ ,  $-(CH_2)_nCN$ , -
- 5  $(CH_2)_nC(=O)NR^aR^a$ ,  $-(CH_2)_nNR^aC(=O)R^b$ ,  $-(CH_2)_nNR^aC(=O)NR^aR^a$ , -  
 $(CH_2)_nNR^aC(=O)OR^b$ ,  $-(CH_2)_nOC(=O)NR^aR^a$ ,  $-(CH_2)_nC(=O)OR^b$ , -  
 $(CH_2)_nS(O)_pNR^aR^a$ ,  $-(CH_2)_nNR^aS(O)_pNR^aR^a$ ,  $-(CH_2)_nNR^aS(O)_pR^c$ ,  $C_{1-5}$  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  $R^e$ ;
- 10  $R^a$ , at each occurrence, 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  $R^e$ ;
- 15  $R^b$ , at each occurrence, 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  $R^e$ ;
- $R^c$ , at each occurrence, 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;
- 20  $R^e$ , at each occurrence, 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  $-(CH_2)_nNR^fR^f$ ;
- 25  $R^f$ , at each occurrence, is independently selected from H, F, Cl, Br, CN, OH,  $C_{1-5}$ alkyl (optionally substituted with halogen 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  
30 heterocyclic ring optionally substituted with  $C_{1-4}$ alkyl;
- $n$ , at each occurrence, is independently selected from zero, 1, 2, 3, and 4; and
- $p$ , at each occurrence, is independently selected from zero, 1, and 2.

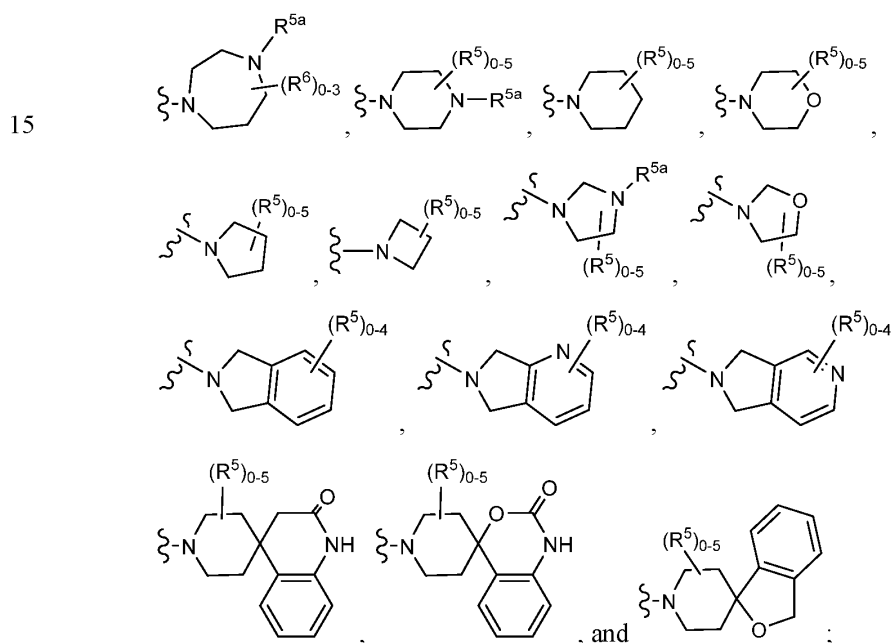
In a second aspect, the present disclosure provides a compound of Formula (I), or a stereoisomer, an enantiomer, a diastereoisomer, a tautomer, a pharmaceutically acceptable salt, a prodrug, or a solvate thereof, within the scope of the first aspect,

5 wherein:

R<sup>1</sup>, at each occurrence, is independently selected from H, F, Cl, Br, NO<sub>2</sub>, -(CH<sub>2</sub>)<sub>n</sub>OR<sup>b</sup>, -(CH<sub>2</sub>)<sub>n</sub>C(=O)R<sup>b</sup>, -(CH<sub>2</sub>)<sub>n</sub>NR<sup>a</sup>R<sup>a</sup>, -(CH<sub>2</sub>)<sub>n</sub>CN, -(CH<sub>2</sub>)<sub>n</sub>C(=O)NR<sup>a</sup>R<sup>a</sup>, -(CH<sub>2</sub>)<sub>n</sub>NR<sup>a</sup>C(=O)R<sup>b</sup>, C<sub>1-4</sub> alkyl substituted with 0-3 R<sup>e</sup> and C<sub>3-6</sub> cycloalkyl substituted with 0-3 R<sup>e</sup>.

10 R<sup>2</sup> is independently selected from C<sub>1-5</sub> alkyl substituted with 0-3 R<sup>e</sup>; C<sub>2-5</sub> alkenyl, aryl substituted with 0-3 R<sup>e</sup>, heteroaryl substituted with 0-3 R<sup>e</sup>, C<sub>3-6</sub> cycloalkyl, –(CH<sub>2</sub>)<sub>1-4</sub>OC<sub>1-5</sub>alkyl, –(CH<sub>2</sub>)<sub>1-4</sub>NHC<sub>1-5</sub>alkyl, and –(CH<sub>2</sub>)<sub>1-3</sub>OC<sub>3-6</sub>cycloalkyl;

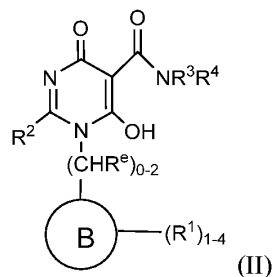
R<sup>3</sup> and R<sup>4</sup> together with the nitrogen atom to which they are both attached form a heterocyclic ring or a spiro heterocyclic ring selected from



20 R<sup>5</sup>, at each occurrence, is independently selected from OH, -(CH<sub>2</sub>)<sub>n</sub>-R<sup>6</sup>, -(CR<sup>7</sup>R<sup>7</sup>)<sub>n</sub>-R<sup>6</sup>,  
OR<sup>6</sup>, -S(O)<sub>p</sub>R<sup>6</sup>, -C(=O)R<sup>6</sup>, -NR<sup>a</sup>R<sup>6</sup>, -C(=O)NR<sup>a</sup>R<sup>6</sup>, -NR<sup>a</sup>C(=O)R<sup>6</sup>, -  
NR<sup>a</sup>C(=O)OR<sup>6</sup>, -OC(=O)NR<sup>a</sup>R<sup>6</sup>, -C(=O)OR<sup>6</sup>, -S(O)<sub>p</sub>NR<sup>a</sup>R<sup>6</sup>, -NR<sup>a</sup>S(O)<sub>p</sub>NR<sup>a</sup>R<sup>6</sup>,  
and -NR<sup>a</sup>S(O)<sub>p</sub>R<sup>6</sup>;

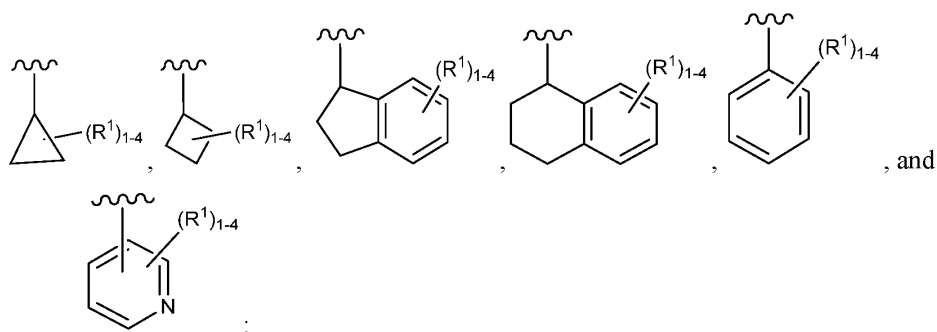
- $R^{5a}$ , at each occurrence, is independently selected from  $-C(=O)OR^6$ ,  $C(=O)NR^aR^6$ ,  $-(CR^7R^7)_n-R^6$ ,  $-C(=O)-R^6$ , and  $-S(O)_pR^6$ ;
- $R^6$ , at each occurrence, is independently selected from  $-(CR^7R^7)_n$ -aryl,  $-(CR^7R^7)_n$ -C<sub>3-6</sub> cycloalkyl, and  $-(CR^7R^7)_n$ -heteroaryl, each substituted with 0-3  $R^8$ ;
- 5  $R^7$ , at each occurrence, is independently selected from H, C<sub>1-4</sub> alkyl, and  $(CH_2)_n$ -C<sub>3-12</sub> carbocyclyl substituted with 0-3  $R^e$ ;
- $R^8$ , at each occurrence, 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<sub>1-4</sub> alkyl substituted with 0-3  $R^e$ ,  $(CH_2)_n$ -C<sub>3-6</sub> carbocyclyl substituted with 0-3  $R^e$ , and  $-(CH_2)_n$ -heterocyclyl substituted with 0-3  $R^e$ ;
- 10  $R^a$ , at each occurrence, is independently selected from H, C<sub>1-6</sub> alkyl substituted with 0-5  $R^e$ ,  $-(CH_2)_n$ -C<sub>3-10</sub>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  $R^e$ ;
- 15  $R^b$ , at each occurrence, is independently selected from H, C<sub>1-6</sub> alkyl substituted with 0-5  $R^e$ , C<sub>2-6</sub> alkenyl substituted with 0-5  $R^e$ , C<sub>2-6</sub> alkynyl substituted with 0-5  $R^e$ ,  $-(CH_2)_n$ -C<sub>3-10</sub>carbocyclyl substituted with 0-5  $R^e$ , and  $-(CH_2)_n$ -heterocyclyl substituted with 0-5  $R^e$ ;
- $R^e$ , at each occurrence, is independently selected from C<sub>1-6</sub> alkyl substituted with 0-5  $R_f$ , C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl,  $-(CH_2)_n$ -C<sub>3-6</sub> cycloalkyl,  $-(CH_2)_n$ -C<sub>4-6</sub> heterocyclyl,  $-(CH_2)_n$ -aryl,  $-(CH_2)_n$ -heteroaryl, F, Cl, Br, CN, NO<sub>2</sub>, =O, CO<sub>2</sub>H,  $-(CH_2)_nOR_f$ ,  $S(O)_pR^f$ ,  $C(=O)NR^fR^f$ ,  $NR^fC(=O)R^f$ ,  $S(O)_pNR^fR^f$ ,  $NR^fS(O)_pR^f$ ,  $NR^fC(=O)OR^f$ ,  $OC(=O)NR^fR^f$  and  $-(CH_2)_nNR^fR^f$ ;
- 20  $R^f$ , at each occurrence, is independently selected from H, F, Cl, Br, CN, OH, C<sub>1-5</sub>alkyl (optionally substituted with halogen and OH), C<sub>3-6</sub> cycloalkyl, and phenyl;
- 25  $n$ , at each occurrence, is independently selected from zero, 1, 2, 3, and 4; and
- $p$ , at each occurrence, is independently selected from zero, 1, and 2.

In a third aspect, the present disclosure provides a compound of Formula (II):



or a stereoisomer, an enantiomer, a diastereoisomer, a tautomer, a pharmaceutically acceptable salt, a prodrug, or a solvate thereof, within the scope of the first or second aspect, wherein:

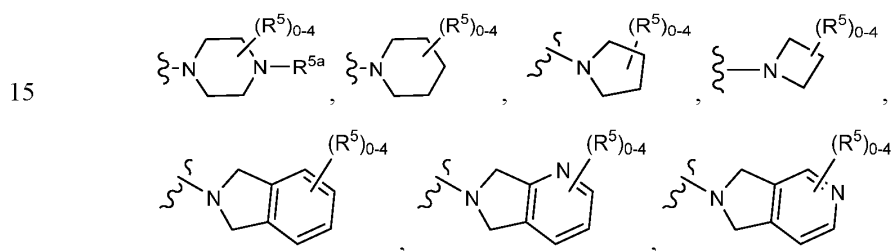
- 5 ring B is independently selected from



$R^1$ , at each occurrence, is independently selected from H, F, Cl, OH, CN,  $OC_{1-4}$  alkyl, and  $C_{3-6}$  cycloalkyl;

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

$R^3$  and  $R^4$  together with the nitrogen atom to which they are both attached form a heterocyclic ring selected from



$R^5$ , at each occurrence, is independently selected from OH,  $-(CH_2)_n-R^6$ ,  $-(CR^7R^7)_n-R^6$ ,  $-OR^6$ ,  $-S(O)_pR^6$ ,  $-C(=O)R^6$ ,  $-NR^aR^6$ ,  $-C(=O)NR^aR^6$ ,  $-NR^aC(=O)R^6$ , -

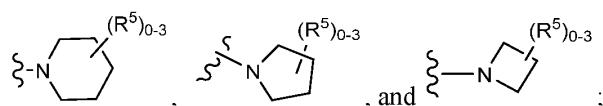
- $\text{NR}^a\text{C}(=\text{O})\text{OR}^6$ ,  $-\text{OC}(=\text{O})\text{NR}^a\text{R}^6$ ,  $-\text{C}(=\text{O})\text{OR}^6$ ,  $-\text{S}(\text{O})_p\text{NR}^a\text{R}^6$ ,  $-\text{NR}^a\text{S}(\text{O})_p\text{NR}^a\text{R}^6$ ,  
 and  $-\text{NR}^a\text{S}(\text{O})_p\text{R}^6$ ;  
 $\text{R}^{5a}$ , at each occurrence, is independently selected from  $-\text{C}(=\text{O})\text{OR}^6$ ,  $\text{C}(=\text{O})\text{NR}^a\text{R}^6$ ,  $-(\text{CR}^7\text{R}^7)_n\text{R}^6$ ,  $-\text{C}(=\text{O})\text{R}^6$ , and  $-\text{S}(\text{O})_p\text{R}^6$ ;  
 5  $\text{R}^6$ , at each occurrence, is independently selected from  $-(\text{CR}^7\text{R}^7)_n\text{-aryl}$ ,  $-(\text{CR}^7\text{R}^7)_n\text{-C}_{3-6}$  cycloalkyl, and  $-(\text{CR}^7\text{R}^7)_n\text{-heteroaryl}$ , each substituted with 0-3  $\text{R}^8$ ;  
 $\text{R}^7$ , at each occurrence, is independently selected from H,  $\text{C}_{1-4}$  alkyl, and  $(\text{CH}_2)_n\text{-C}_{3-12}$  carbocyclyl substituted with 0-3  $\text{R}^e$ ;  
 $\text{R}^8$ , at each occurrence, is independently selected from H, F, Cl, Br,  $-\text{OR}^b$ ,  $-(\text{CH}_2)_n\text{C}(=\text{O})\text{R}^b$ ,  $-(\text{CH}_2)_n\text{C}(=\text{O})\text{OR}^b$ ,  $-(\text{CH}_2)_n\text{NR}^a\text{R}^a$ , CN,  $-(\text{CH}_2)_n\text{C}(=\text{O})\text{NR}^a\text{R}^a$ ,  $\text{C}_{1-4}$  alkyl substituted with 0-3  $\text{R}^e$ ,  $(\text{CH}_2)_n\text{-C}_{3-6}$  carbocyclyl substituted with 0-3  $\text{R}^e$ , and  $-(\text{CH}_2)_n\text{-heterocyclyl}$  substituted with 0-3  $\text{R}^e$ ;  
 10  $\text{R}^a$ , at each occurrence, is independently selected from H,  $\text{C}_{1-6}$  alkyl substituted with 0-5  $\text{R}^e$ ,  $-(\text{CH}_2)_n\text{-C}_{3-10}\text{carbocyclyl}$  substituted with 0-5  $\text{R}^e$ , and  $-(\text{CH}_2)_n\text{-heterocyclyl}$  substituted with 0-5  $\text{R}^e$ ; or  $\text{R}^a$  and  $\text{R}^a$  together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5  $\text{R}^e$ ;  
 15  $\text{R}^b$ , at each occurrence, is independently selected from H,  $\text{C}_{1-6}$  alkyl substituted with 0-5  $\text{R}^e$ ,  $\text{C}_{2-6}$  alkenyl substituted with 0-5  $\text{R}^e$ ,  $\text{C}_{2-6}$  alkynyl substituted with 0-5  $\text{R}^e$ ,  $-(\text{CH}_2)_n\text{-C}_{3-10}\text{carbocyclyl}$  substituted with 0-5  $\text{R}^e$ , and  $-(\text{CH}_2)_n\text{-heterocyclyl}$  substituted with 0-5  $\text{R}^e$ ;  
 20  $\text{R}^e$ , at each occurrence, is independently selected from  $\text{C}_{1-6}$  alkyl (optionally substituted with F and Cl), OH,  $\text{OCH}_3$ ,  $\text{OCF}_3$ ,  $-(\text{CH}_2)_n\text{-C}_{3-6}$  cycloalkyl,  $-(\text{CH}_2)_n\text{-C}_{4-6}$  heterocyclyl,  $-(\text{CH}_2)_n\text{-aryl}$ ,  $-(\text{CH}_2)_n\text{-heteroaryl}$ , F, Cl, Br, CN,  $\text{NO}_2$ ,  $=\text{O}$ ,  $\text{CO}_2\text{H}$ , and  
 25 n, at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

In a fourth aspect, the present disclosure provides a compound of Formula (II), or a stereoisomer, an enantiomer, a diastereoisomer, a tautomer, a pharmaceutically acceptable salt, a prodrug, or a solvate thereof, within the scope of any of the first, second  
 30 and third aspects, wherein:  
 $\text{R}^1$ , at each occurrence, is independently selected from H, F, Cl, OH, and  $\text{OC}_{1-4}$  alkyl;

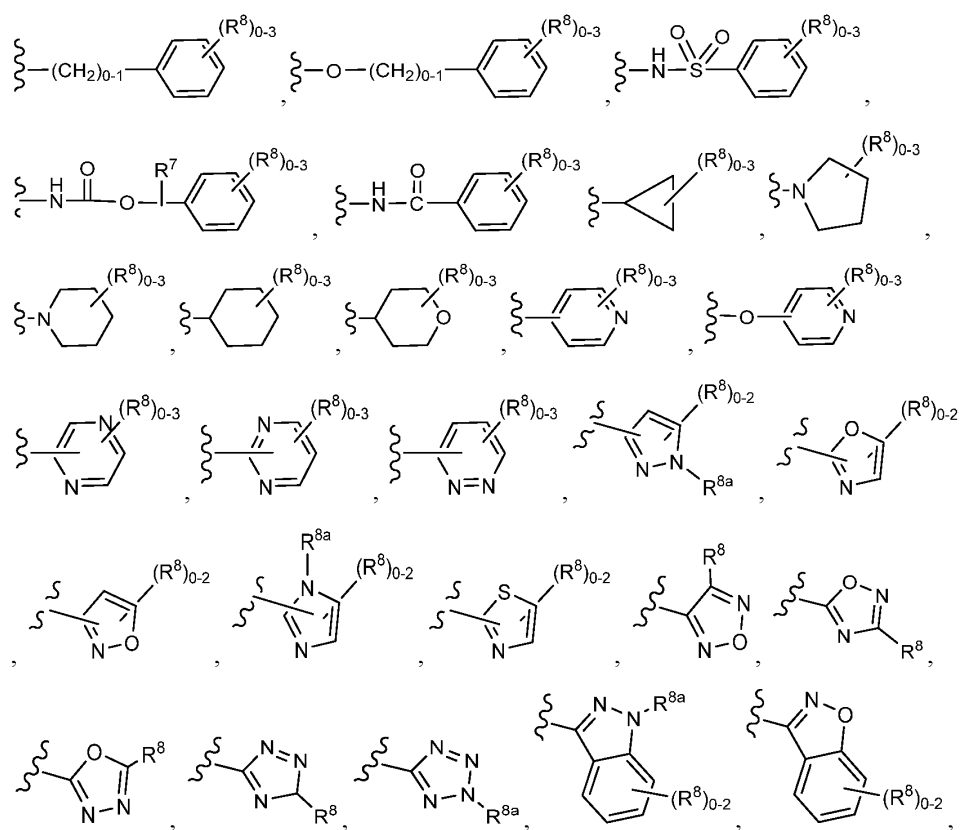
R<sup>2</sup> is independently selected from C<sub>1-5</sub> alkyl substituted with 0-3 R<sup>e</sup>; C<sub>2-5</sub> alkenyl, phenyl substituted with 0-3 R<sup>e</sup>, 6-membered heteroaryl substituted with 0-3 R<sup>e</sup>, C<sub>3-6</sub> cycloalkyl; and CH<sub>2</sub>O(CH<sub>2</sub>)<sub>1-3</sub>CH<sub>3</sub>;

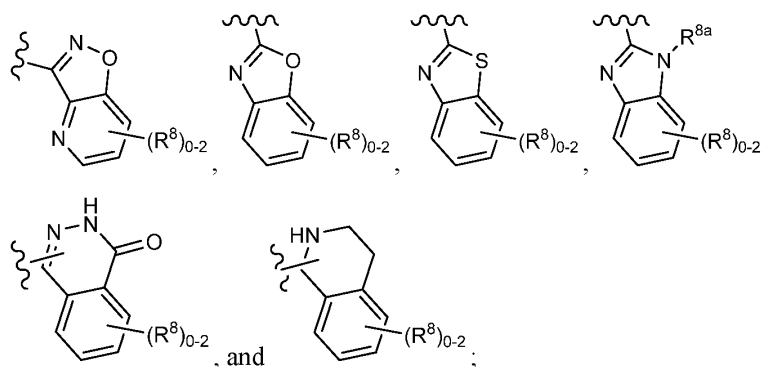
R<sup>3</sup> and R<sup>4</sup> together with the nitrogen atom to which they are both attached form a

5 heterocyclic ring selected from



$R^5$  is independently at each occurrence, selected from OH,





$R^8$ , at each occurrence, is independently selected from H, F, Cl, Br,  $-\text{OCH}_3$ ,  $-\text{OCF}_3$ ,  $=\text{O}$ , CN,  $\text{CH}_3$ ,  $\text{CF}_3$ ,  $-(\text{CH}_2)_n$ -aryl,  $-(\text{CH}_2)_n$ - $\text{C}_{3-6}$  cycloalkyl substituted with 0-3  $R^e$ , and  $-(\text{CH}_2)_n$ -heterocyclyl substituted with 0-3  $R^e$ ;

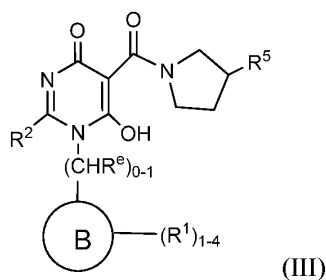
$R^{8a}$ , at each occurrence, is independently selected from H,  $\text{CH}_3$ , aryl substituted with 0-3  $R^e$ , and heterocyclyl substituted with 0-3  $R^e$ ;

$R^a$ , at each occurrence, is independently selected from H,  $\text{C}_{1-6}$  alkyl substituted with 0-5  $R^e$ ,  $-(\text{CH}_2)_n$ - $\text{C}_{3-10}$  carbocyclyl substituted with 0-5  $R^e$ , and  $-(\text{CH}_2)_n$ -heterocyclyl substituted with 0-5  $R^e$ ;

$R^e$ , at each occurrence, is independently selected from  $\text{C}_{1-6}$  alkyl (optionally substituted with F and Cl), OH,  $\text{OCH}_3$ ,  $\text{OCF}_3$ ,  $-(\text{CH}_2)_n$ - $\text{C}_{3-6}$  cycloalkyl,  $-(\text{CH}_2)_n$ - $\text{C}_{4-6}$  heterocyclyl,  $-(\text{CH}_2)_n$ -aryl,  $-(\text{CH}_2)_n$ -heteroaryl, F, Cl, Br, CN,  $\text{NO}_2$ ,  $=\text{O}$ ,  $\text{CO}_2\text{H}$ ; and

$n$ , at each occurrence, is independently selected from zero, 1, 2, and 3.

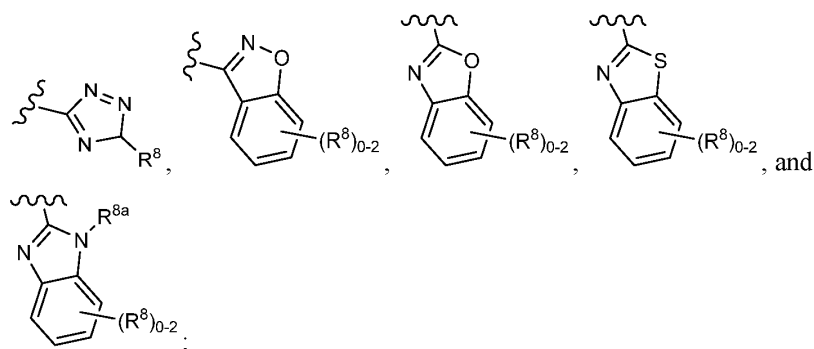
In a fifth aspect, the present disclosure provides a compound of Formula (III):



or a stereoisomer, an enantiomer, a diastereoisomer, a tautomer, a pharmaceutically acceptable salt, a prodrug, or a solvate thereof, within the scope of the first or second aspect, wherein:







$R^8$ , at each occurrence, is independently selected from H, F, Cl, Br,  $-\text{OCH}_3$ ,  $-\text{OCF}_3$ ,  $=\text{O}$ , CN,  $\text{CH}_3$ ,  $\text{CF}_3$ ,  $-\text{C}(=\text{O})\text{NH}_2$ ,  $-(\text{CH}_2)_n$ -aryl substituted with 0-3  $R^e$ ,  $-(\text{CH}_2)_n$ -C<sub>3-6</sub> cycloalkyl substituted with 0-3  $R^e$ , and  $-(\text{CH}_2)_n$ -heterocyclyl substituted with 0-3  $R^e$ ;

$R^{8a}$ , at each occurrence, is independently selected from H,  $\text{CH}_3$ , aryl substituted with 0-3  $R^e$ , and heterocyclyl substituted with 0-3  $R^e$ ;

$R^a$ , at each occurrence, is independently selected from H, C<sub>1-6</sub> alkyl substituted with 0-5  $R^e$ ,  $-(\text{CH}_2)_n$ -C<sub>3-10</sub>carbocyclyl substituted with 0-5  $R^e$ , and  $-(\text{CH}_2)_n$ -heterocyclyl substituted with 0-5  $R^e$ ;

$R^e$ , at each occurrence, is independently selected from C<sub>1-6</sub> alkyl (optionally substituted with F and Cl), OH,  $\text{OCH}_3$ ,  $\text{OCF}_3$ ,  $-(\text{CH}_2)_n$ -C<sub>3-6</sub> cycloalkyl,  $-(\text{CH}_2)_n$ -C<sub>4-6</sub> heterocyclyl,  $-(\text{CH}_2)_n$ -aryl,  $-(\text{CH}_2)_n$ -heteroaryl, F, Cl, Br, CN,  $\text{NO}_2$ ,  $=\text{O}$ ,  $\text{CO}_2\text{H}$ ; and

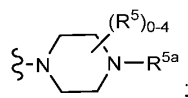
$n$ , at each occurrence, is independently selected from zero, 1, 2, and 3.

In a sixth aspect, the present disclosure provides a compound of Formula (III), or a stereoisomer, an enantiomer, a diastereoisomer, a tautomer, a pharmaceutically acceptable salt, a prodrug, or a solvate thereof, within the scope of any of the first, second and third aspects, wherein:

$R^1$ , at each occurrence, is independently selected from F, Cl, OH,  $-\text{OCH}_3$ , and  $-\text{OCD}_3$ ;

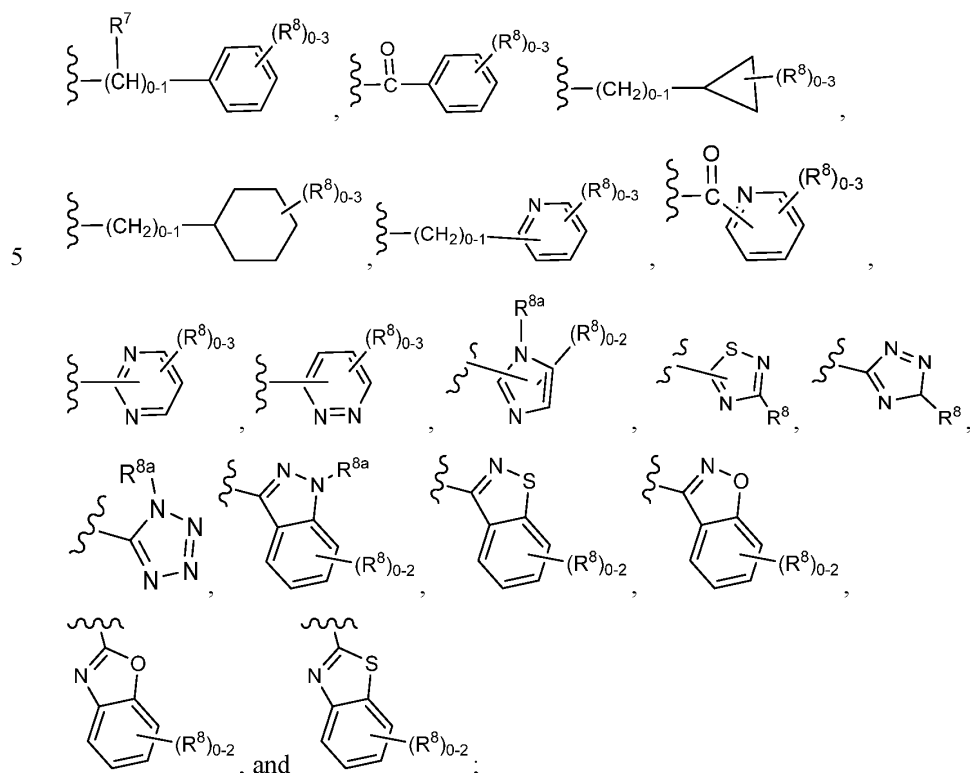
$R^2$  is independently selected from C<sub>1-5</sub> alkyl substituted with 0-3  $R^e$ ; C<sub>2-5</sub> alkenyl, phenyl substituted with 0-3  $R^e$ , 6-membered heteroaryl substituted with 0-3  $R^e$ , and C<sub>3-6</sub> cycloalkyl; and  $\text{CH}_2\text{O}(\text{CH}_2)_{1-3}\text{CH}_3$ ;

$R^3$  and  $R^4$  together with the nitrogen atom to which they are both attached form



R<sup>5</sup>, at each occurrence, is independently at each occurrence, selected from OH, F, and Cl;

$R^{5a}$  is independently at each occurrence, selected from



R<sup>8</sup>, at each occurrence, is independently selected from H, F, Cl, Br, -OCH<sub>3</sub>, -O(CH<sub>2</sub>)<sub>1-3</sub>OCH<sub>3</sub>, -OCF<sub>3</sub>, =O, CN, CH<sub>3</sub>, CF<sub>3</sub> -(CH<sub>2</sub>)<sub>n</sub>-aryl, -(CH<sub>2</sub>)<sub>n</sub>-C<sub>3-6</sub> cycloalkyl substituted with 0-3 R<sup>e</sup>, and -(CH<sub>2</sub>)<sub>n</sub>-heterocyclyl substituted with 0-3 R<sup>e</sup>;

R<sup>8a</sup>, at each occurrence, is independently selected from H, CH<sub>3</sub>, aryl substituted with 0-3 R<sup>e</sup>, and heterocyclyl substituted with 0-3 R<sup>e</sup>;

R<sup>a</sup>, at each occurrence, is independently selected from H, C<sub>1-6</sub> alkyl substituted with 0-5 R<sup>e</sup>, -(CH<sub>2</sub>)<sub>n</sub>-C<sub>3-10</sub>carbocyclyl substituted with 0-5 R<sup>e</sup>, and -(CH<sub>2</sub>)<sub>n</sub>-heterocyclyl substituted with 0-5 R<sup>e</sup>;

R<sup>b</sup>, at each occurrence, is independently selected from H, C<sub>1-6</sub> alkyl substituted with 0-5 R<sup>e</sup>, C<sub>2-6</sub> alkenyl substituted with 0-5 R<sup>e</sup>, C<sub>2-6</sub> alkynyl substituted with 0-5 R<sup>e</sup>, -

$(\text{CH}_2)_n\text{-C}_{3-10}\text{carbocyclyl}$  substituted with 0-5  $\text{R}^e$ , and  $-(\text{CH}_2)_n\text{-heterocyclyl}$  substituted with 0-5  $\text{R}^e$ ;

$\text{R}^e$ , at each occurrence, is independently selected from  $\text{C}_{1-6}$  alkyl (optionally substituted with F and Cl), OH,  $\text{OCH}_3$ ,  $\text{OCF}_3$ ,  $-(\text{CH}_2)_n\text{-C}_{3-6}$  cycloalkyl,  $-(\text{CH}_2)_n\text{-C}_{4-6}$  heterocyclyl,  $-(\text{CH}_2)_n\text{-aryl}$ ,  $-(\text{CH}_2)_n\text{-heteroaryl}$ , F, Cl, Br, CN,  $\text{NO}_2$ ,  $=\text{O}$ ,  $\text{CO}_2\text{H}$ ; and

$n$ , at each occurrence, is independently selected from zero, 1, 2, and 3.

In a seventh aspect, the present disclosures provides a compound of Formula (I), or a stereoisomer, an enantiomer, a diastereoisomer, a tautomer, a pharmaceutically acceptable salt, a prodrug, or a solvate thereof, within the scope of any of the first, second and third aspects, wherein:

$\text{R}^1$ , at each occurrence, is independently selected from  $-\text{CH}_2\text{OH}$ ,  $-\text{OCH}_3$ ,  $-\text{OCF}_3$ ,  $-\text{OCD}_3$ ,  $-\text{OCH}_2\text{Ph}$ ,  $-\text{C}(=\text{O})\text{NR}^a\text{R}^a$ ,  $-\text{NR}^a\text{R}^a$ ,  $\text{CH}_3$ ,  $\text{CH}_2\text{CH}_3$ ,  $\text{CH}(\text{CH}_3)_2$ , and cyclopropyl;

$\text{R}^2$  is independently selected from  $\text{C}_{1-4}$  alkyl substituted with 0-3  $\text{R}^e$ ;  $\text{C}_{2-4}$  alkenyl, phenyl substituted with 0-3  $\text{R}^e$ , 6-membered heteroaryl substituted with 0-3  $\text{R}^e$ ,  $\text{C}_{3-6}$  cycloalkyl, and  $\text{CH}_2\text{O}(\text{CH}_2)_{1-3}\text{CH}_3$ ;

$\text{R}^3$  is independently selected from H and  $\text{C}_{1-4}$  alkyl;

$\text{R}^4$  is independently selected from  $-(\text{CHR}^7)_{1-4}\text{-R}^6$ ,  $-(\text{CH}_2)_{1-3}\text{OR}^6$ ,  $-(\text{CH}_2)_{1-3}\text{NHR}^6$ , and  $-(\text{CH}_2)_{0-3}\text{NHC}(=\text{O})\text{R}^6$ ;

$\text{R}^6$ , at each occurrence, is independently selected from  $-(\text{CR}^7\text{R}^7)_n\text{-aryl}$ ,  $-(\text{CR}^7\text{R}^7)_n\text{-C}_{3-6}$  cycloalkyl, and  $-(\text{CR}^7\text{R}^7)_n\text{-heteroaryl}$ , each substituted with 0-3  $\text{R}^8$ ;

$\text{R}^7$ , at each occurrence, is independently selected from H,  $\text{C}_{1-4}$  alkyl, and aryl;

$\text{R}^8$ , at each occurrence, is independently selected from H, F, Cl,  $-\text{OR}^b$ ,  $-\text{NR}^a\text{R}^a$ ,  $\text{C}_{1-4}$  alkyl substituted with 0-3  $\text{R}^e$ , phenyl substituted with 0-3  $\text{R}^e$ , and heterocyclyl substituted with 0-3  $\text{R}^e$ ;

$\text{R}^a$ , at each occurrence, is independently selected from H,  $\text{C}_{1-6}$  alkyl substituted with 0-5  $\text{R}^e$ ,  $-(\text{CH}_2)_n\text{-phenyl}$  substituted with 0-5  $\text{R}^e$ , and  $-(\text{CH}_2)_n\text{-heteroaryl}$  substituted with 0-5  $\text{R}^e$ ;

$\text{R}^b$ , at each occurrence, is independently selected from H,  $\text{C}_{1-6}$  alkyl substituted with 0-5  $\text{R}^e$ ,  $-(\text{CH}_2)_n\text{-C}_{3-10}\text{carbocyclyl}$  substituted with 0-5  $\text{R}^e$ , and  $-(\text{CH}_2)_n\text{-heterocyclyl}$  substituted with 0-5  $\text{R}^e$ ;

$R^e$ , at each occurrence, 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,  $NO_2$ ,  $=O$ ,  $CO_2H$ ; and  
 5 n is independently selected from zero, 1, 2, 3, and 4.

In an eighth aspect, the present disclosure provides a compound, or a stereoisomer, an enantiomer, a diastereoisomer, a tautomer, a pharmaceutically acceptable salt, a prodrug, or a solvate thereof, within the scope of the first, second, and  
 10 third aspects, wherein:

$R^1$ , at each occurrence, is independently selected from  $-CH_2OH$ ,  $-OCH_3$ ,  $-OCF_3$ ,  $OCH_2Ph$ ,  $-C(=O)NR^aR^a$ ,  $-NR^aR^a$ ,  $CH_3$ ,  $CH_2CH_3$ ,  $CH(CH_3)_2$ , and cyclopropyl;

$R^2$  is independently selected from  $C_{1-5}$  alkyl substituted with 0-3  $R^e$ ;  $C_{2-5}$  alkenyl, phenyl substituted with 0-3  $R^e$ , 6-membered heteroaryl substituted with 0-3  $R^e$ ,  $C_{3-6}$  cycloalkyl and  $CH_2O(CH_2)_{1-3}CH_3$ ;  
 15

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

$R^6$ , at each occurrence, is independently selected from H, halogen,  $-(CH_2)_nOR^b$ ,  $-(CH_2)_nNR^aR^a$ ,  $-(CH_2)_nC(=O)NR^aR^a$ ,  $-(CH_2)_nNR^aC(=O)R^b$ ,  $-(CH_2)_nNR^aC(=O)OR^b$ ,  $-(CH_2)_nOC(=O)NR^aR^a$ ,  $-(CH_2)_nC(=O)OR^b$ ,  $-(CH_2)_nS(O)_pNR^aR^a$ ,  $-(CH_2)_nNR^aS(O)_pNR^aR^a$ ,  $C_{1-5}$  alkyl substituted with 0-3  $R^e$ , phenyl substituted with 0-3  $R^e$ , and heterocyclyl substituted with 0-3  $R^e$ ;  
 20

$R^a$ , at each occurrence, is independently selected from H,  $C_{1-6}$  alkyl substituted with 0-5  $R^e$ ,  $-(CH_2)_n$ -phenyl substituted with 0-5  $R^e$ , and  $-(CH_2)_n$ -heteroaryl substituted with 0-5  $R^e$ ;  
 25

$R^b$ , at each occurrence, 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  $R^e$ ;

$R^e$ , at each occurrence, 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,  $-(CH_2)_n-C_{4-6}$   
 30

heterocyclyl,  $-(CH_2)_n$ -aryl,  $-(CH_2)_n$ -heteroaryl, F, Cl, Br, CN,  $NO_2$ , =O,  $CO_2H$ ;  
and

n, at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

5 In a ninth aspect, the present disclosure provides a compound selected from the exemplified examples or stereoisomers, enantiomers, diastereoisomers, tautomers, pharmaceutically acceptable salts, prodrugs, or solvates thereof.

10 In another aspect, the present disclosure provides a compound selected from any subset list of compounds within the scope of the eighth aspect.

In another aspect, the present disclosure provides compounds of Formula (I), or stereoisomers, enantiomers, diastereoisomers, tautomers, pharmaceutically acceptable salts, prodrugs, or solvates thereof, wherein:

15 alk is  $C_{1-6}$  alkylene substituted with 0-5  $R^e$ ;

ring B is independently selected from  $C_{3-6}$  cycloalkyl,  $C_{3-6}$  cycloalkenyl, aryl, bicyclic carbocyclyl, and 6-membered heteroaryl;

$R^1$ , at each occurrence, is independently selected from H, halogen,  $NO_2$ ,  $-(CH_2)_nOR^b$ ,  $(CH_2)_nS(O)_pR^c$ ,  $-(CH_2)_nC(=O)R^b$ ,  $-(CH_2)_nNR^aR^a$ ,  $-(CH_2)_nCN$ , -

20  $(CH_2)_nC(=O)NR^aR^a$ ,  $-(CH_2)_nNR^aC(=O)R^b$ ,  $-(CH_2)_nNR^aC(=O)NR^aR^a$ , -

$(CH_2)_nNR^aC(=O)OR^b$ ,  $-(CH_2)_nOC(=O)NR^aR^a$ ,  $-(CH_2)_nC(=O)OR^b$ , -

$(CH_2)_nS(O)_pNR^aR^a$ ,  $-(CH_2)_nNR^aS(O)_pNR^aR^a$ ,  $-(CH_2)_nNR^aS(O)_pR^c$ ,  $C_{1-4}$  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  $R^e$ ;

25  $R^2$  is independently selected from  $C_{1-10}$  alkyl substituted with 0-3  $R^e$ ;  $C_{2-5}$  alkenyl substituted with 0-3  $R^e$ ; aryl substituted with 0-3  $R^e$ ; heteroaryl substituted with 0-3  $R^e$ ; and  $C_{3-6}$  cycloalkyl substituted with 0-3  $R^e$ ; provided when  $R^2$  is  $C_{1-10}$  alkyl, the carbon atoms and the groups attached thereto except the carbon atom attached to the pyrimidine ring may be replaced by O, N, and S;

30  $R^3$  is independently selected from H and  $C_{1-5}$  alkyl:

- $R^4$  is independently selected from  $-(CR^7R^7)_nR^6$ ,  $-(CR^7R^7)_nOR^6$ ,  $-(CR^7R^7)_nS(O)_pR^6$ ,  $-(CR^7R^7)_nC(=O)R^6$ ,  $-(CR^7R^7)_nNR^aR^6$ ,  $-(CR^7R^7)_nNR^aC(=O)R^6$ ,  $-(CR^7R^7)_nS(O)_pNR^aR^6$ , and  $-(CR^7R^7)_nNR^aS(O)_pR^6$ ;  
 alternatively,  $R^3$  and  $R^4$  together with the nitrogen atom to which they are both attached  
 5 form a heterocyclic ring or a spiro heterocyclic ring comprising carbon atoms and additional 1 to 4 heteroatoms selected from  $NR^{5a}$ , O, and S and substituted with 0-5  $R^5$ ;  
 $R^5$ , at each occurrence, is independently selected from OH, halogen,  $-(CR^7R^7)_nR^6$ ,  $-OR^6$ ,  $-S(O)_pR^6$ ,  $-C(=O)R^6$ ,  $-NR^aR^6$ ,  $-C(=O)NR^aR^6$ ,  $-NR^aC(=O)R^6$ ,  $-NR^aC(=O)OR^6$ ,  $-OC(=O)NR^aR^6$ ,  $-C(=O)OR^6$ ,  $-S(O)_pNR^aR^6$ ,  $-NR^aS(O)_pNR^aR^6$ , and  $-NR^aS(O)_pR^6$ ;  
 10  $R^{5a}$ , at each occurrence is independently selected from  $-C(=O)OR^6$ ,  $C(=O)NR^aR^6$ ,  $-(CR^7R^7)_nR^6$ ,  $-C(=O)-R^6$ , and  $-S(O)_pR^6$ ;  
 $R^6$ , at each occurrence, is independently selected from  $-(CR^7R^7)_n-C_{3-10}$  carbocyclyl and  $-(CR^7R^7)_n$ -heteroaryl, each substituted with 0-3  $R^8$ ;  
 15  $R^7$ , at each occurrence, is independently selected from H,  $C_{1-4}$  alkyl, and  $(CH_2)_n-C_{3-12}$  carbocyclyl substituted with 0-3  $R^e$ ;  
 $R^8$ , at each occurrence, is independently selected from H, halogen,  $-(CH_2)_nOR^b$ ,  $=O$ ,  $(CH_2)_nS(O)_pR^c$ ,  $-(CH_2)_nC(=O)R^b$ ,  $-(CH_2)_nNR^aR^a$ ,  $-(CH_2)_nCN$ ,  $-(CH_2)_nC(=O)NR^aR^a$ ,  $-(CH_2)_nNR^aC(=O)R^b$ ,  $-(CH_2)_nNR^aC(=O)NR^aR^a$ ,  $-(CH_2)_nNR^aC(=O)OR^b$ ,  $-(CH_2)_nOC(=O)NR^aR^a$ ,  $-(CH_2)_nC(=O)OR^b$ ,  $-(CH_2)_nS(O)_pNR^aR^a$ ,  $-(CH_2)_nNR^aS(O)_pNR^aR^a$ ,  $-(CH_2)_nNR^aS(O)_pR^c$ ,  $C_{1-5}$  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  $R^e$ ;  
 20  $R^a$ , at each occurrence, 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  $R^e$ ;  
 $R^b$ , at each occurrence, is independently selected from H,  $C_{1-6}$  alkyl substituted with 0-5  
 30  $R^e$ ,  $C_{2-6}$  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  $R^e$ ;

$R^e$ , at each occurrence, 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;

5  $R^e$ , at each occurrence, is independently selected from F, Cl, Br, CN,  $NO_2$ , =O,  $CO_2H$ ,  $C_{1-6}$  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,  $-(CH_2)_nOR^f$ ,  $S(O)_pR^f$ ,  $C(=O)NR^fR^f$ ,  $NR^fC(=O)R^f$ ,  $S(O)_pNR^fR^f$ ,  $NR^fS(O)_pR^f$ ,  $NR^fC(=O)OR^f$ ,  $OC(=O)NR^fR^f$  and  $-(CH_2)_nNR^fR^f$ ;

10  $R^f$ , at each occurrence, is independently selected from H, F, Cl, Br, CN, OH,  $C_{1-5}$  alkyl (optionally substituted with halogen 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;

$n$ , at each occurrence, is independently selected from zero, 1, 2, 3, and 4; and

$p$ , at each occurrence, is independently selected from zero, 1, and 2.

15

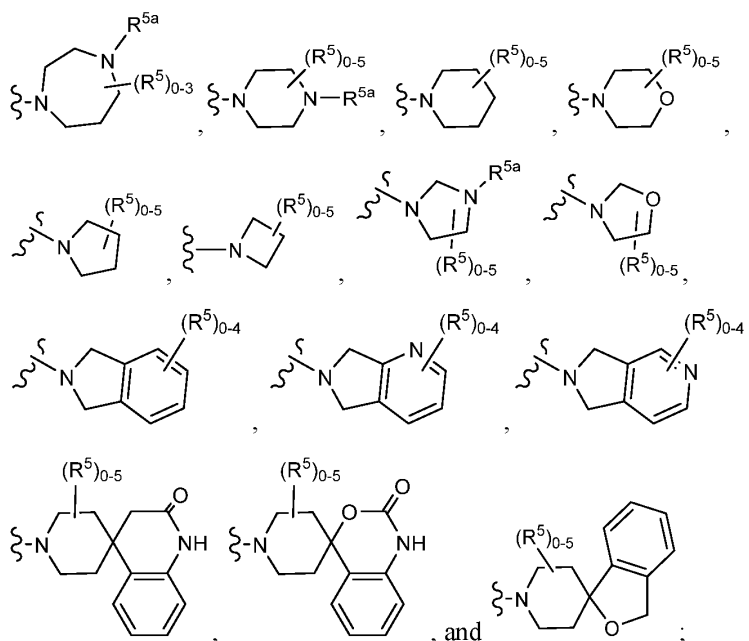
In another aspect, the present disclosure provides compounds of Formula (I), or stereoisomers, enantiomers, diastereoisomers, tautomers, pharmaceutically acceptable salts, prodrugs, or solvates thereof, wherein:

20  $R^1$ , at each occurrence, is independently selected from H, F, Cl, Br,  $NO_2$ ,  $-(CH_2)_nOR^b$ ,  $-(CH_2)_nC(=O)R^b$ ,  $-(CH_2)_nNR^aR^a$ ,  $-(CH_2)_nCN$ ,  $-(CH_2)_nC(=O)NR^aR^a$ ,  $-(CH_2)_nNR^aC(=O)R^b$ ,  $C_{1-4}$  alkyl substituted with 0-3  $R^e$  and  $C_{3-6}$  cycloalkyl substituted with 0-3  $R^e$ ;

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

$R^3$  and  $R^4$  together with the nitrogen atom to which they are both attached form a heterocyclic ring or a spiro heterocyclic ring selected from

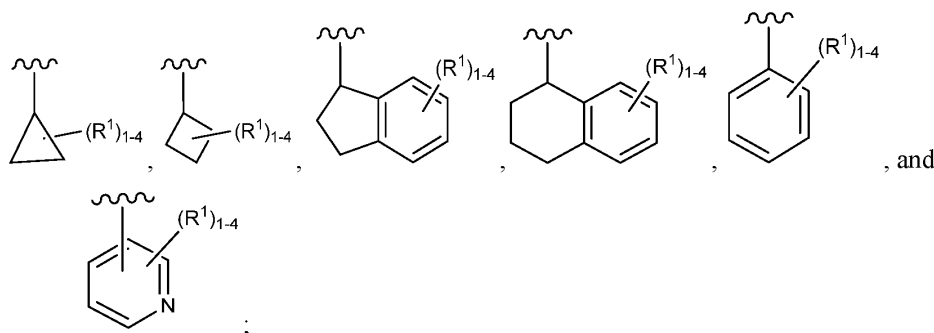




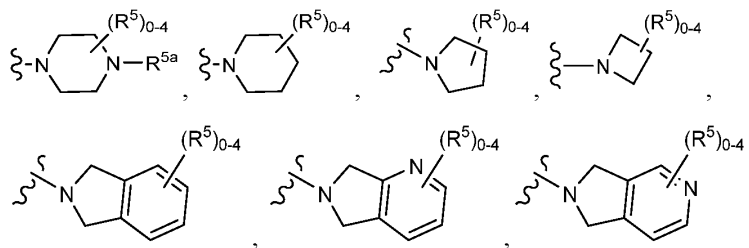
- 5  $R^5$ , at each occurrence, is independently selected from OH,  $-(CH_2)_n-R^6$ ,  $-(CR^7R^7)_n-R^6$ ,  $OR^6$ ,  $-S(O)_pR^6$ ,  $-C(=O)R^6$ ,  $-NR^aR^6$ ,  $-C(=O)NR^aR^6$ ,  $-NR^aC(=O)R^6$ ,  $-NR^aC(=O)OR^6$ ,  $-OC(=O)NR^aR^6$ ,  $-C(=O)OR^6$ ,  $-S(O)_pNR^aR^6$ ,  $-NR^aS(O)_pNR^aR^6$ , and  $-NR^aS(O)_pR^6$ ;
- $R^{5a}$ , at each occurrence, is independently selected from  $-C(=O)OR^6$ ,  $C(=O)NR^aR^6$ ,  $-(CR^7R^7)_n-R^6$ ,  $-C(=O)-R^6$ , and  $-S(O)_pR^6$ ;
- 10  $R^6$ , at each occurrence, is independently selected from  $-(CR^7R^7)_n$ -aryl,  $-(CR^7R^7)_n$ -C<sub>3-6</sub> cycloalkyl, and  $-(CR^7R^7)_n$ -heteroaryl, each substituted with 0-3  $R^8$ ;
- $R^7$ , at each occurrence, is independently selected from H, C<sub>1-4</sub> alkyl, and  $(CH_2)_n$ -C<sub>3-12</sub> carbocyclyl substituted with 0-3  $R^e$ ;
- 15  $R^8$ , at each occurrence, 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<sub>1-4</sub> alkyl substituted with 0-3  $R^e$ ,  $(CH_2)_n$ -C<sub>3-6</sub> carbocyclyl substituted with 0-3  $R^e$ , and  $-(CH_2)_n$ -heterocyclyl substituted with 0-3  $R^e$ ;
- $R^a$ , at each occurrence, is independently selected from H, C<sub>1-6</sub> alkyl substituted with 0-5  $R^e$ ,  $-(CH_2)_n$ -C<sub>3-10</sub>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  $R^e$ ;
- 20

- $R^b$ , at each occurrence, 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  $R^e$ ;
- 5  $R^e$ , at each occurrence, is independently selected from F, Cl, Br, CN,  $NO_2$ ,  $=O$ ,  $CO_2H$ ,  $C_{1-6}$  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,  $-(CH_2)_nOR^f$ ,  $S(O)_pR^f$ ,  $C(=O)NR^fR^f$ ,  $NR^fC(=O)R^f$ ,  $S(O)_pNR^fR^f$ ,  $NR^fS(O)_pR^f$ ,  $NR^fC(=O)OR^f$ ,  $OC(=O)NR^fR^f$  and  $-(CH_2)_nNR^fR^f$ ;
- 10  $R^f$ , at each occurrence, is independently selected from H, F, Cl, Br, CN, OH,  $C_{1-5}$  alkyl (optionally substituted with halogen and OH),  $C_{3-6}$  cycloalkyl, and phenyl;
- $n$ , at each occurrence, is independently selected from zero, 1, 2, 3, and 4; and
- $p$ , at each occurrence, is independently selected from zero, 1, and 2.

- 15 In another aspect, the present disclosure provides compounds of Formula (II), or stereoisomers, enantiomers, diastereoisomers, tautomers, pharmaceutically acceptable salts, prodrugs, or solvates thereof, wherein:
- ring B is independently selected from



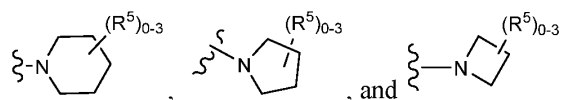
- $R^1$ , at each occurrence, is independently selected from H, F, Cl, OH, CN,  $C_{1-4}$  alkyl,  $OC_{1-4}$  alkyl, and  $C_{3-6}$  cycloalkyl;
- $R^2$  is independently selected from  $C_{1-5}$  alkyl substituted with 0-3  $R^e$ ,  $C_{2-5}$  alkenyl, aryl substituted with 0-3  $R^e$ , heteroaryl substituted with 0-3  $R^e$ ,  $C_{3-6}$  cycloalkyl,  $-(CH_2)_{1-4}OC_{1-5}$  alkyl, and  $-(CH_2)_{1-3}OC_{3-6}$  cycloalkyl;
- 25  $R^3$  and  $R^4$  together with the nitrogen atom to which they are both attached form a heterocyclic ring selected from



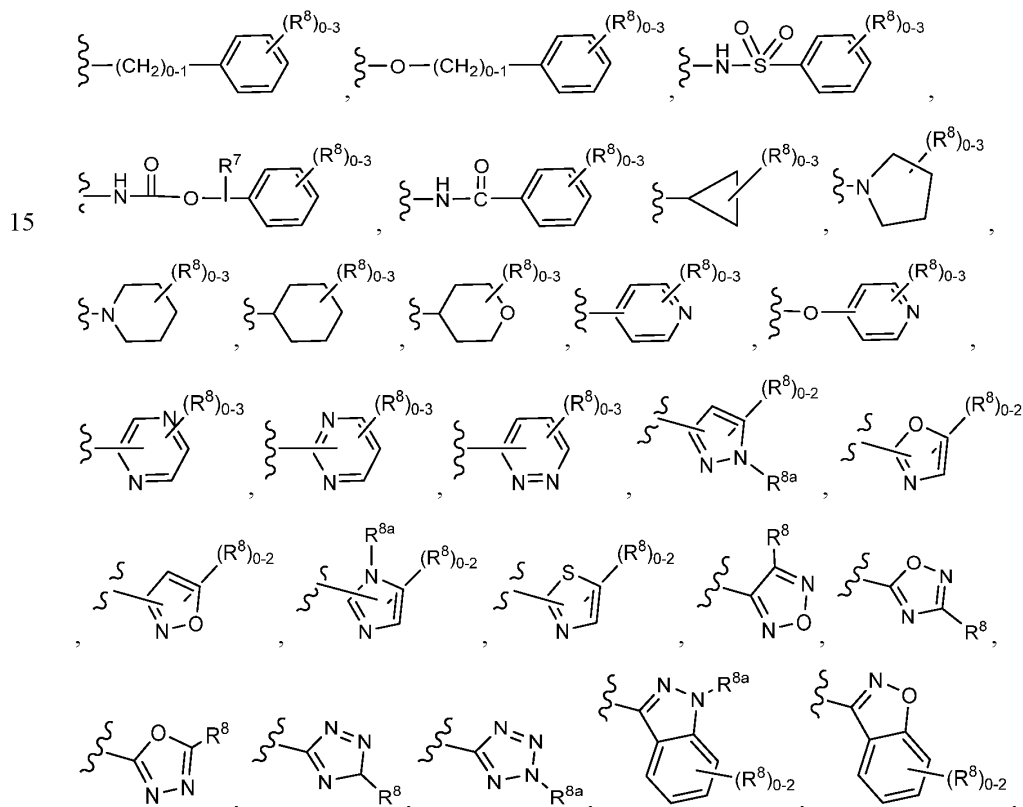
- $R^5$ , at each occurrence, is independently selected from OH,  $-(CH_2)_n-R^6$ ,  $-(CR^7R^7)_n-R^6$ , -OR<sup>6</sup>,  $-S(O)_pR^6$ ,  $-C(=O)R^6$ ,  $-NR^aR^6$ ,  $-C(=O)NR^aR^6$ ,  $-NR^aC(=O)R^6$ , -NR<sup>a</sup>C(=O)OR<sup>6</sup>,  $-OC(=O)NR^aR^6$ ,  $-C(=O)OR^6$ ,  $-S(O)_pNR^aR^6$ ,  $-NR^aS(O)_pNR^aR^6$ , and  $-NR^aS(O)_pR^6$ ;
- $R^{5a}$ , at each occurrence, is independently selected from  $-C(=O)OR^6$ ,  $C(=O)NR^aR^6$ ,  $-(CR^7R^7)_n-R^6$ ,  $-C(=O)-R^6$ , and  $-S(O)_pR^6$ ;
- $R^6$ , at each occurrence, is independently selected from  $-(CR^7R^7)_n$ -aryl,  $-(CR^7R^7)_n$ -C<sub>3-6</sub> cycloalkyl, and  $-(CR^7R^7)_n$ -heteroaryl, each substituted with 0-3 R<sup>e</sup>;
- $R^7$ , at each occurrence, is independently selected from H, C<sub>1-4</sub> alkyl, and  $(CH_2)_n$ -C<sub>3-12</sub> carbocyclyl substituted with 0-3 R<sup>e</sup>;
- $R^8$ , at each occurrence, is independently selected from H, F, Cl, Br, -OR<sup>b</sup>, - $(CH_2)_nC(=O)R^b$ ,  $-(CH_2)_nC(=O)OR^b$ ,  $-(CH_2)_nNR^aR^a$ , CN,  $-(CH_2)_nC(=O)NR^aR^a$ , C<sub>1-4</sub> alkyl substituted with 0-3 R<sup>e</sup>,  $(CH_2)_n$ -C<sub>3-6</sub> carbocyclyl substituted with 0-3 R<sup>e</sup>, and  $-(CH_2)_n$ -heterocyclyl substituted with 0-3 R<sup>e</sup>;
- $R^a$ , at each occurrence, is independently selected from H, C<sub>1-6</sub> alkyl substituted with 0-5 R<sup>e</sup>,  $-(CH_2)_n$ -C<sub>3-10</sub>carbocyclyl substituted with 0-5 R<sup>e</sup>, and  $-(CH_2)_n$ -heterocyclyl substituted with 0-5 R<sup>e</sup>; or R<sup>a</sup> and R<sup>a</sup> together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5 R<sup>e</sup>;
- $R^b$ , at each occurrence, is independently selected from H, C<sub>1-6</sub> alkyl substituted with 0-5 R<sup>e</sup>, C<sub>2-6</sub> alkenyl substituted with 0-5 R<sup>e</sup>, C<sub>2-6</sub> alkynyl substituted with 0-5 R<sup>e</sup>, - $(CH_2)_n$ -C<sub>3-10</sub>carbocyclyl substituted with 0-5 R<sup>e</sup>, and  $-(CH_2)_n$ -heterocyclyl substituted with 0-5 R<sup>e</sup>;
- $R^e$ , at each occurrence, is independently selected from F, Cl, Br, CN, NO<sub>2</sub>, =O, CO<sub>2</sub>H, C<sub>1-6</sub> alkyl (optionally substituted with F and Cl), OH, OCH<sub>3</sub>, OCF<sub>3</sub>,  $-(CH_2)_n$ -C<sub>3-6</sub> cycloalkyl,  $-(CH_2)_n$ -C<sub>4-6</sub> heterocyclyl,  $-(CH_2)_n$ -aryl,  $-(CH_2)_n$ -heteroaryl, and  $-(CH_2)_nOC_{1-4}$ alkyl; and
- n, at each occurrence, is independently selected from zero, 1, 2, 3, and 4.

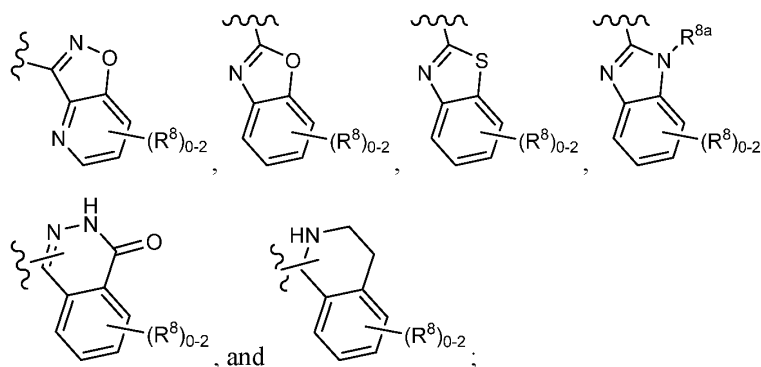
In another aspect, the present disclosure provides compounds of Formula (II), or stereoisomers, enantiomers, diastereoisomers, tautomers, pharmaceutically acceptable salts, prodrugs, or solvates thereof, wherein:

- 5 R<sup>1</sup>, at each occurrence, is independently selected from H, F, Cl, OH, CN, C<sub>1-4</sub> alkyl, and OC<sub>1-4</sub> alkyl;  
R<sup>2</sup> is independently selected from C<sub>1-5</sub> alkyl substituted with 0-3 R<sup>e</sup>; C<sub>2-5</sub> alkenyl, phenyl substituted with 0-3 R<sup>e</sup>, 5- to 6-membered heteroaryl substituted with 0-3 R<sup>e</sup>, C<sub>3-6</sub> cycloalkyl, and CH<sub>2</sub>O(CH<sub>2</sub>)<sub>1-3</sub>CH<sub>3</sub>;  
10 R<sup>3</sup> and R<sup>4</sup> together with the nitrogen atom to which they are both attached form a heterocyclic ring selected from



$R^5$  is independently at each occurrence, selected from OH,





$R^8$ , at each occurrence, is independently selected from H, F, Cl, Br,  $-OCH_3$ ,  $-OCF_3$ ,  $=O$ , CN,  $CH_3$ ,  $CF_3$ ,  $-(CH_2)_n$ -aryl,  $-(CH_2)_n$ - $C_{3-6}$  cycloalkyl substituted with 0-3  $R^e$ , and  $-(CH_2)_n$ -heterocyclyl substituted with 0-3  $R^e$ ;

$R^{8a}$ , at each occurrence, is independently selected from H,  $CH_3$ , aryl substituted with 0-3  $R^e$ , and heterocyclyl substituted with 0-3  $R^e$ ;

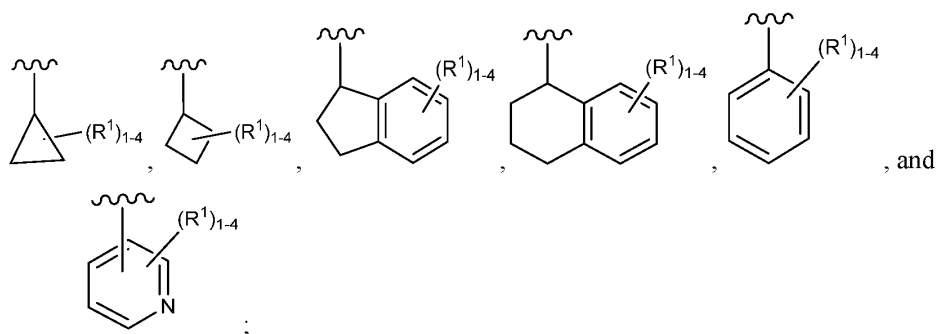
$R^a$ , at each occurrence, is independently selected from H,  $C_{1-6}$  alkyl substituted with 0-5  $R^e$ ,  $-(CH_2)_n$ - $C_{3-10}$  carbocyclyl substituted with 0-5  $R^e$ , and  $-(CH_2)_n$ -heterocyclyl substituted with 0-5  $R^e$ ;

$R^e$ , at each occurrence, is independently selected from F, Cl, Br, CN,  $NO_2$ ,  $=O$ ,  $CO_2H$ ,  $C_{1-6}$  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, and  $-(CH_2)_n$ - $OC_{1-4}$ alkyl; and

$n$ , at each occurrence, is independently selected from zero, 1, 2, and 3.

In another aspect, the present disclosure provides compounds of Formula (III), or stereoisomers, enantiomers, diastereoisomers, tautomers, pharmaceutically acceptable salts, prodrugs, or solvates thereof, wherein:

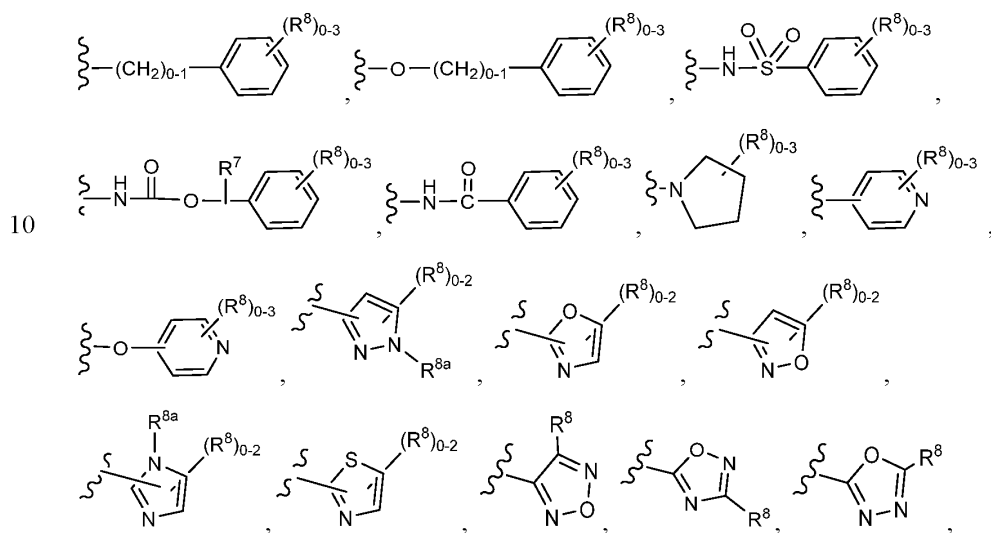
ring B is independently selected from

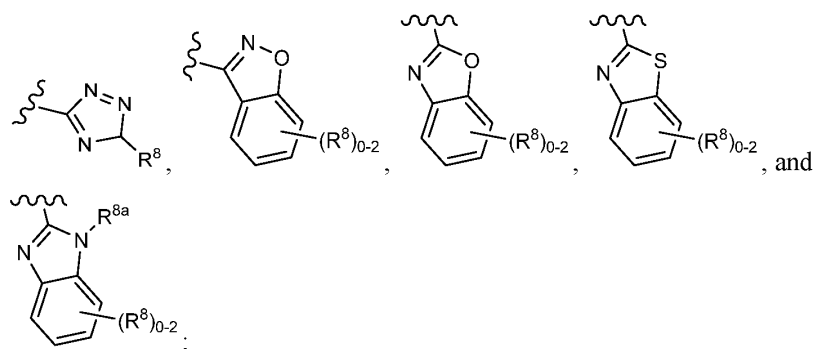


R<sup>1</sup>, at each occurrence, is independently selected from H, F, Cl, OH, CN, C<sub>1-4</sub> alkyl, and OC<sub>1-4</sub> alkyl;

- 5 R<sup>2</sup> is independently selected from C<sub>1-5</sub> alkyl substituted with 0-3 R<sup>e</sup>; C<sub>2-5</sub> alkenyl, phenyl substituted with 0-3 R<sup>e</sup>, 5- to 6-membered heteroaryl substituted with 0-3 R<sup>e</sup>, C<sub>3-6</sub> cycloalkyl, and CH<sub>2</sub>O(CH<sub>2</sub>)<sub>1-3</sub>CH<sub>3</sub>;

$R^5$  is independently at each occurrence, selected from OH,





R<sup>8</sup>, at each occurrence, is independently selected from H, F, Cl, Br, -OCH<sub>3</sub>, -OCF<sub>3</sub>, =O, CN, CH<sub>3</sub>, CF<sub>3</sub>, -C(=O)NH<sub>2</sub>, -(CH<sub>2</sub>)<sub>n</sub>-aryl substituted with 0-3 R<sup>e</sup>, -(CH<sub>2</sub>)<sub>n</sub>-C<sub>3-6</sub> cycloalkyl substituted with 0-3 R<sup>e</sup>, and -(CH<sub>2</sub>)<sub>n</sub>-heterocyclyl substituted with 0-3 R<sup>e</sup>;

R<sup>8a</sup>, at each occurrence, is independently selected from H, CH<sub>3</sub>, aryl substituted with 0-3 R<sup>e</sup>, and heterocyclyl substituted with 0-3 R<sup>e</sup>;

R<sup>a</sup>, at each occurrence, is independently selected from H, C<sub>1-6</sub> alkyl substituted with 0-5 R<sup>e</sup>, -(CH<sub>2</sub>)<sub>n</sub>-C<sub>3-10</sub>carbocyclyl substituted with 0-5 R<sup>e</sup>, and -(CH<sub>2</sub>)<sub>n</sub>-heterocyclyl substituted with 0-5 R<sup>e</sup>;

R<sup>e</sup>, at each occurrence, is independently selected from F, Cl, Br, CN, NO<sub>2</sub>, =O, CO<sub>2</sub>H, C<sub>1-6</sub> alkyl (optionally substituted with F and Cl), OH, OCH<sub>3</sub>, OCF<sub>3</sub>, -(CH<sub>2</sub>)<sub>n</sub>-C<sub>3-6</sub> cycloalkyl, -(CH<sub>2</sub>)<sub>n</sub>-C<sub>4-6</sub> heterocyclyl, -(CH<sub>2</sub>)<sub>n</sub>-aryl, -(CH<sub>2</sub>)<sub>n</sub>-heteroaryl, and -(CH<sub>2</sub>)<sub>n</sub>OC<sub>1-4</sub>alkyl; and

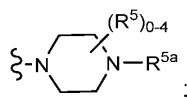
n, at each occurrence, is independently selected from zero, 1, 2, and 3.

In another aspect, the present disclosure provides compounds of Formula (II), or stereoisomers, enantiomers, diastereoisomers, tautomers, pharmaceutically acceptable salts, prodrugs, or solvates thereof, wherein:

R<sup>1</sup>, at each occurrence, is independently selected from F, Cl, OH, CH<sub>2</sub>CH<sub>3</sub>, -OCH<sub>3</sub>, and OCD<sub>3</sub>;

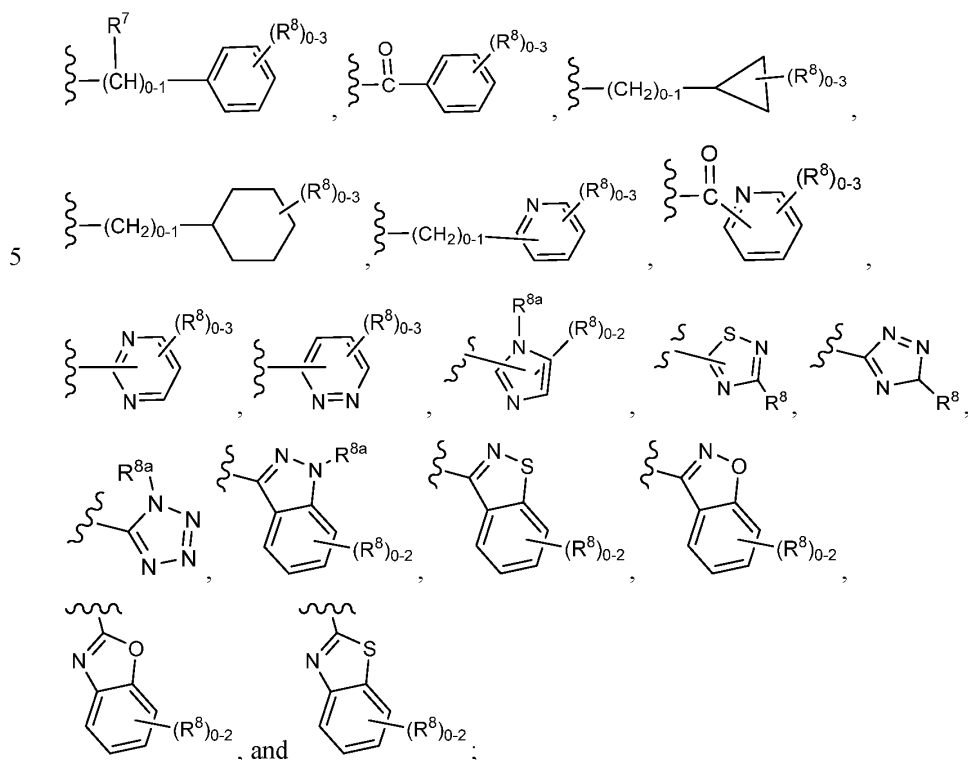
R<sup>2</sup> is independently selected from C<sub>1-5</sub> alkyl substituted with 0-3 R<sup>e</sup>; C<sub>2-5</sub> alkenyl, phenyl substituted with 0-3 R<sup>e</sup>, 5- to 6-membered heteroaryl substituted with 0-3 R<sup>e</sup>, C<sub>3-6</sub> cycloalkyl, and CH<sub>2</sub>O(CH<sub>2</sub>)<sub>1-3</sub>CH<sub>3</sub>;

R<sup>3</sup> and R<sup>4</sup> together with the nitrogen atom to which they are both attached form



$R^5$ , at each occurrence, is independently selected from OH, F, and Cl;

$R^{5a}$ , at each occurrence, is independently selected from



$R^8$ , at each occurrence, is independently selected from H, F, Cl, Br,  $-OCH_3$ ,  $-O(CH_2)_{1-3}OCH_3$ ,  $-OCF_3$ ,  $=O$ , CN,  $CH_3$ ,  $CF_3$ ,  $-(CH_2)_n$ -aryl,  $-(CH_2)_n$ -C<sub>3-6</sub> cycloalkyl

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

$R^{8a}$ , at each occurrence, is independently selected from H,  $CH_3$ , aryl substituted with 0-3  $R^e$ , and heterocyclyl substituted with 0-3  $R^e$ ;

$R^a$ , at each occurrence, is independently selected from H, C<sub>1-6</sub> alkyl substituted with 0-5  $R^e$ ,  $-(CH_2)_n$ -C<sub>3-10</sub>carbocyclyl substituted with 0-5  $R^e$ , and  $-(CH_2)_n$ -heterocyclyl substituted with 0-5  $R^e$ ;

$R^b$ , at each occurrence, is independently selected from H, C<sub>1-6</sub> alkyl substituted with 0-5  $R^e$ , C<sub>2-6</sub> alkenyl substituted with 0-5  $R^e$ , C<sub>2-6</sub> alkynyl substituted with 0-5  $R^e$ , -



$(\text{CH}_2)_n\text{-C}_{3-10}\text{carbocyclyl}$  substituted with 0-5  $\text{R}^e$ , and  $-(\text{CH}_2)_n\text{-heterocyclyl}$  substituted with 0-5  $\text{R}^e$ ;

$\text{R}^e$ , at each occurrence, is independently selected from F, Cl, Br, CN,  $\text{NO}_2$ ,  $=\text{O}$ ,  $\text{CO}_2\text{H}$ ,  $\text{C}_{1-6}$  alkyl (optionally substituted with F and Cl), OH,  $\text{OCH}_3$ ,  $\text{OCF}_3$ ,  $-(\text{CH}_2)_n\text{-C}_{3-6}$  cycloalkyl,  $-(\text{CH}_2)_n\text{-C}_{4-6}$  heterocyclyl,  $-(\text{CH}_2)_n\text{-aryl}$ , and  $-(\text{CH}_2)_n\text{-heteroaryl}$ ; and  $n$ , at each occurrence, is independently selected from zero, 1, 2, and 3.

In another aspect, the present disclosure provides compounds of Formula (I), or stereoisomers, enantiomers, diastereoisomers, tautomers, pharmaceutically acceptable salts, prodrugs, or solvates thereof, wherein:

$\text{R}^1$ , at each occurrence, is independently selected from  $-\text{CH}_2\text{OH}$ ,  $-\text{OCH}_3$ ,  $-\text{OCH}_2\text{Ph}$ ,  $-\text{C}(=\text{O})\text{NR}^a\text{R}^a$ ,  $-\text{NR}^a\text{R}^a$ ,  $\text{CH}_3$ ,  $\text{CH}_2\text{CH}_3$ ,  $\text{CH}(\text{CH}_3)_2$ , and cyclopropyl;

$\text{R}^2$  is independently selected from  $\text{C}_{1-4}$  alkyl substituted with 0-3  $\text{R}^e$ ;  $\text{C}_{2-4}$  alkenyl, phenyl substituted with 0-3  $\text{R}^e$ , 5- to 6-membered heteroaryl substituted with 0-3  $\text{R}^e$ ,  $\text{C}_{3-6}$  cycloalkyl, and  $\text{CH}_2\text{O}(\text{CH}_2)_{1-3}\text{CH}_3$ ;

$\text{R}^3$  is independently selected from H and  $\text{C}_{1-4}$  alkyl;

$\text{R}^4$  is independently selected from  $-(\text{CHR}^7)_{1-4}\text{-R}^6$ ,  $-(\text{CH}_2)_{1-3}\text{OR}^6$ ,  $-(\text{CH}_2)_{1-3}\text{NHR}^6$ , and  $-(\text{CH}_2)_{0-3}\text{NHC}(=\text{O})\text{R}^6$ ;

$\text{R}^6$ , at each occurrence, is independently selected from  $-(\text{CR}^7\text{R}^7)_n\text{-aryl}$ ,  $-(\text{CR}^7\text{R}^7)_n\text{-C}_{3-6}$  cycloalkyl, and  $-(\text{CR}^7\text{R}^7)_n\text{-heteroaryl}$ , each substituted with 0-3  $\text{R}^8$ ;

$\text{R}^7$ , at each occurrence, is independently selected from H,  $\text{C}_{1-4}$  alkyl, and aryl;

$\text{R}^8$ , at each occurrence, is independently selected from H, F, Cl,  $-\text{OR}^b$ ,  $-\text{NR}^a\text{R}^a$ ,  $\text{C}_{1-4}$  alkyl substituted with 0-3  $\text{R}^e$ , phenyl substituted with 0-3  $\text{R}^e$ , and heterocyclyl substituted with 0-3  $\text{R}^e$ ;

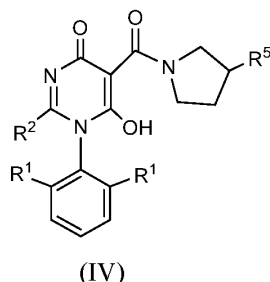
$\text{R}^a$ , at each occurrence, is independently selected from H,  $\text{C}_{1-6}$  alkyl substituted with 0-5  $\text{R}^e$ ,  $-(\text{CH}_2)_n\text{-phenyl}$  substituted with 0-5  $\text{R}^e$ , and  $-(\text{CH}_2)_n\text{-heteroaryl}$  substituted with 0-5  $\text{R}^e$ ;

$\text{R}^b$ , at each occurrence, is independently selected from H,  $\text{C}_{1-6}$  alkyl substituted with 0-5  $\text{R}^e$ ,  $-(\text{CH}_2)_n\text{-C}_{3-10}\text{carbocyclyl}$  substituted with 0-5  $\text{R}^e$ , and  $-(\text{CH}_2)_n\text{-heterocyclyl}$  substituted with 0-5  $\text{R}^e$ ;

$R^e$ , at each occurrence, is independently selected from F, Cl, Br, CN,  $NO_2$ ,  $=O$ ,  $CO_2H$ ,  $C_{1-6}$  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; and n is independently selected from zero, 1, 2, 3, and 4.

5

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

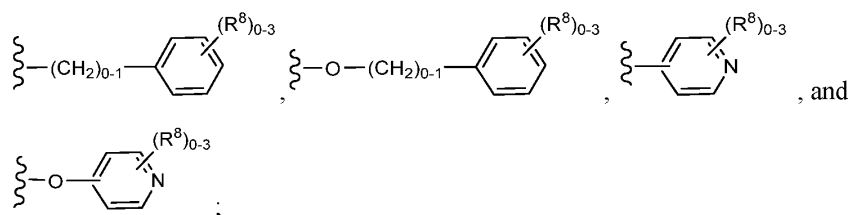


or stereoisomers, enantiomers, diastereoisomers, tautomers, pharmaceutically acceptable salts, prodrugs, or solvates thereof, wherein:

$R^1$ , at each occurrence, is independently selected from F, Cl, OH,  $C_{1-2}$  alkyl, and  $OC_{1-2}$  alkyl;

$R^2$  is independently selected from  $-CH_2CH_2CH_2CH_3$ ,  $-CH_2CH_2CH(CH_3)_2$ ,  $CH_2CH_2CH_2CF_3$ ,  $-CH_2$ -cyclopropyl,  $-CH_2CH_2$ -cyclopropyl, cyclobutyl, cyclopentyl,  $CH_2O(CH_2)_{1-3}CH_3$ ,  $CH_2OCH(CH_3)_2$ , phenyl substituted with 0-2  $R^e$ , and 5- to 6-membered heteroaryl substituted with 0-2  $R^e$ ;

$R^5$ , at each occurrence, is independently selected from



$R^8$ , at each occurrence, is independently selected from F, Cl, Br,  $-OCH_3$ ,  $-OCF_3$ ,  $=O$ , CN,  $CH_3$ ,  $CF_3$ ,  $-C(=O)NH_2$ ,  $-(CH_2)_n$ -aryl substituted with 0-3  $R^e$ ,  $-(CH_2)_n-C_{3-6}$  cycloalkyl substituted with 0-3  $R^e$ , and  $-(CH_2)_n$ -heterocyclyl substituted with 0-3  $R^e$ ;

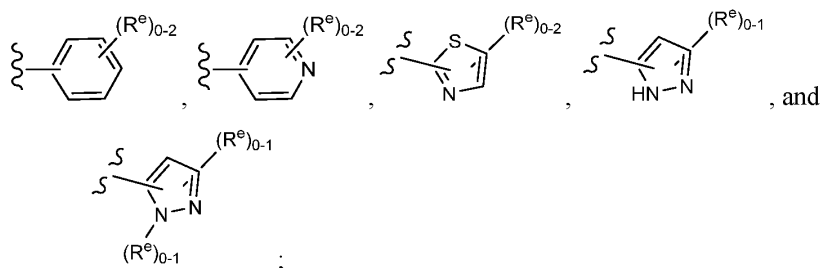
$R^e$ , at each occurrence, is independently selected from F, Cl, Br, CN,  $\text{NO}_2$ ,  $=\text{O}$ ,  $\text{CO}_2\text{H}$ ,  $\text{C}_{1-6}$  alkyl (optionally substituted with F and Cl), OH,  $\text{OCH}_3$ ,  $\text{OCF}_3$ ,  $-(\text{CH}_2)_n\text{-C}_{3-6}$  cycloalkyl,  $-(\text{CH}_2)_n\text{-C}_{4-6}$  heterocyclyl,  $-(\text{CH}_2)_n\text{-aryl}$ , and  $-(\text{CH}_2)_n\text{-heteroaryl}$ ; and  $n$  is independently selected from zero, 1, 2, 3, and 4.

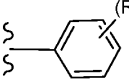
5

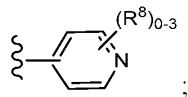
In another aspect, the present disclosure provides compounds of Formula (IV), or stereoisomers, enantiomers, diastereoisomers, tautomers, pharmaceutically acceptable salts, prodrugs, or solvates thereof, wherein:

$R^1$  is both  $\text{CH}_2\text{CH}_3$  or both  $\text{OCH}_3$ ;

10  $R^2$  is independently selected from



$R^5$  is independently at each occurrence, selected from  and

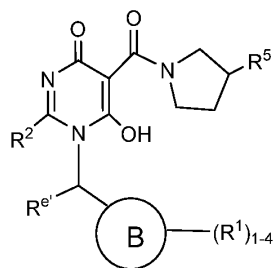


15  $R^8$ , at each occurrence, is independently selected from F, Cl, Br,  $-\text{OCH}_3$ ,  $-\text{OCF}_3$ , CN,  $\text{CH}_3$ , and  $\text{CF}_3$ ; and

$R^e$ , at each occurrence, is independently selected from F, Cl, Br,  $\text{C}_{1-3}$  alkyl, and cyclopropyl.

20

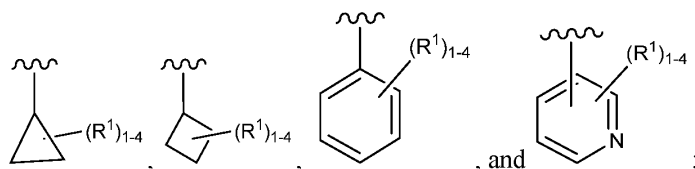
In another aspect, the present disclosure provides compounds of Formula (V):



(V)

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

5 ring B is independently selected from



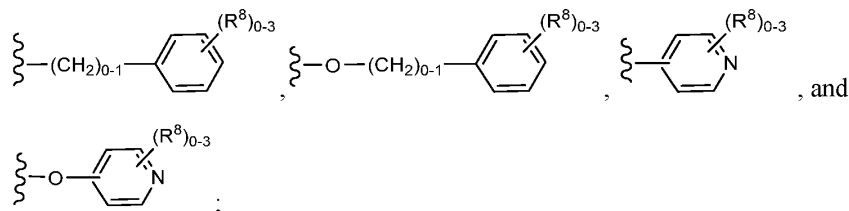
$R^1$ , at each occurrence, is independently selected from H, F, Cl, OH, CN, and  $OC_{1-4}$  alkyl;

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

$CH_2CH_2CH_2CF_3$ ,  $-CH_2$ -cyclopropyl,  $-CH_2CH_2$ -cyclopropyl, cyclobutyl,

10 cyclopentyl,  $CH_2O(CH_2)_{1-3}CH_3$ , and  $CH_2OCH(CH_3)_2$ , phenyl substituted with 0-2  $R^e$ , and 5- to 6-membered heteroaryl substituted with 0-2  $R^e$ ;

$R^5$ , at each occurrence, is independently selected from



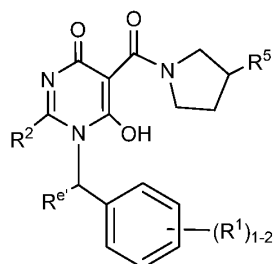
15  $R^8$ , at each occurrence, is independently selected from F, Cl, Br,  $-OCH_3$ ,  $-OCF_3$ ,  $=O$ , CN,  $CH_3$ ,  $CF_3$ ,  $-C(=O)NH_2$ ,  $-(CH_2)_n$ -aryl substituted with 0-3  $R^e$ ,  $-(CH_2)_n$ -C<sub>3-6</sub> cycloalkyl substituted with 0-3  $R^e$ , and  $-(CH_2)_n$ -heterocyclyl substituted with 0-3  $R^e$ ;

$R^e$ , at each occurrence, is independently selected from F, Cl, Br, CN,  $NO_2$ ,  $=O$ ,  $CO_2H$ , C<sub>1-6</sub> alkyl (optionally substituted with F and Cl), OH,  $OCH_3$ ,  $OCF_3$ ,  $-(CH_2)_n$ -C<sub>3-6</sub> cycloalkyl,  $-(CH_2)_n$ -C<sub>4-6</sub> heterocyclyl,  $-(CH_2)_n$ -aryl, and  $-(CH_2)_n$ -heteroaryl;

20

$R^{e'}$  is independently selected from  $C_{1-2}$  alkyl,  $-CH_2OC_{1-2}$  alkyl, and cyclopropyl; and  $n$  is independently selected from zero, 1, 2, 3, and 4.

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

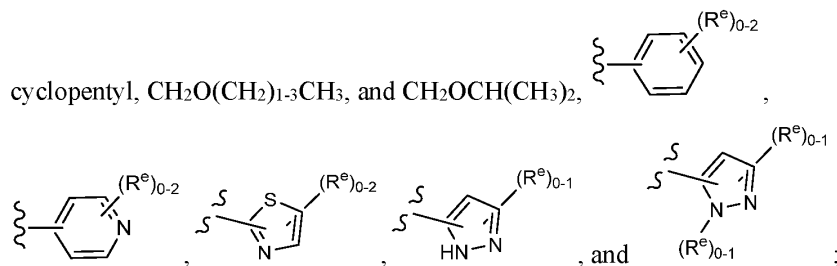


(VI)

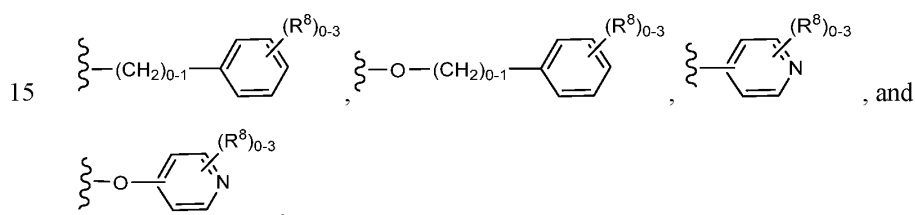
or stereoisomers, enantiomers, diastereoisomers, tautomers, pharmaceutically acceptable salts, prodrugs, or solvates thereof, wherein:

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

10  $R^2$  is independently selected from  $-CH_2CH_2CH_2CH_3$ ,  $-CH_2CH_2CH(CH_3)_2$ ,  $CH_2CH_2CH_2CF_3$ ,  $-CH_2$ -cyclopropyl,  $-CH_2CH_2$ -cyclopropyl, cyclobutyl,



$R^5$ , at each occurrence, is independently selected from



$R^8$ , at each occurrence, is independently selected from F, Cl, Br,  $-OCH_3$ ,  $-OCF_3$ ,  $=O$ , CN,

$CH_3$ ,  $CF_3$ ,  $-C(=O)NH_2$ ,  $-(CH_2)_n$ -aryl substituted with 0-3  $R^e$ ,  $-(CH_2)_n$ - $C_{3-6}$

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

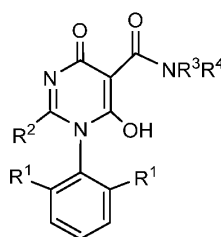
20  $R^e$ ;

R<sup>c</sup>, at each occurrence, is independently selected from F, Cl, Br, CN, NO<sub>2</sub>, =O, CO<sub>2</sub>H, C<sub>1-6</sub> alkyl (optionally substituted with F and Cl), OH, OCH<sub>3</sub>, OCF<sub>3</sub>, -(CH<sub>2</sub>)<sub>n</sub>-C<sub>3-6</sub> cycloalkyl, -(CH<sub>2</sub>)<sub>n</sub>-C<sub>4-6</sub> heterocyclyl, -(CH<sub>2</sub>)<sub>n</sub>-aryl, and -(CH<sub>2</sub>)<sub>n</sub>-heteroaryl;

Re' is independently selected from C<sub>1-2</sub> alkyl, -CH<sub>2</sub>OC<sub>1-2</sub> alkyl, and cyclopropyl; and

5      $n$  is independently selected from zero, 1, 2, 3, and 4.

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



(VII)

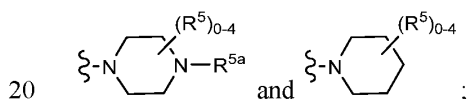
10 or stereoisomers, enantiomers, diastereoisomers, tautomers, pharmaceutically acceptable salts, prodrugs, or solvates thereof, wherein:

R<sup>1</sup>, at each occurrence, is independently selected from F, Cl, OH, C<sub>1-2</sub> alkyl, and OC<sub>1-2</sub> alkyl;

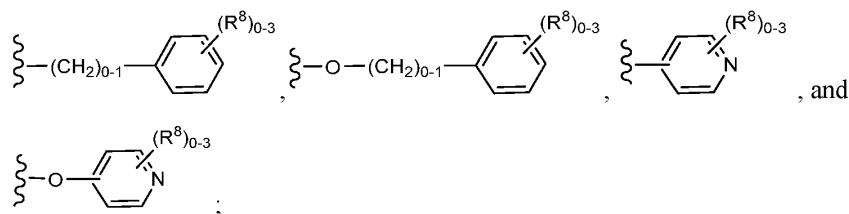
R<sup>2</sup> is independently selected from -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>,

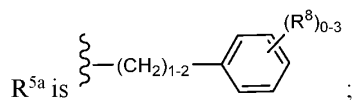
15 CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CF<sub>3</sub>, -CH<sub>2</sub>-cyclopropyl, -CH<sub>2</sub>CH<sub>2</sub>-cyclopropyl, cyclobutyl, cyclopentyl, CH<sub>2</sub>O(CH<sub>2</sub>)<sub>1-3</sub>CH<sub>3</sub>, CH<sub>2</sub>OCH(CH<sub>3</sub>)<sub>2</sub>, phenyl substituted with 0-2 R<sup>e</sup>, and 5- to 6-membered heteroaryl substituted with 0-2 R<sup>e</sup>;

R<sup>3</sup> and R<sup>4</sup> together with the nitrogen atom to which they are both attached form a heterocyclic ring selected from



$R^5$  is independently at each occurrence, selected from

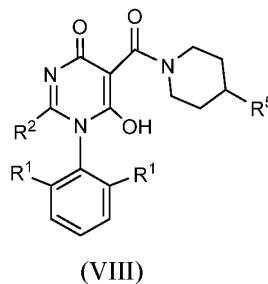




$R^8$ , at each occurrence, is independently selected from F, Cl, Br,  $-\text{OCH}_3$ ,  $-\text{OCF}_3$ ,  $=\text{O}$ , CN,  $\text{CH}_3$ ,  $\text{CF}_3$ ,  $-\text{C}(=\text{O})\text{NH}_2$ ,  $-(\text{CH}_2)_n$ -aryl substituted with 0-3  $R^e$ ,  $-(\text{CH}_2)_n$ -C<sub>3-6</sub> cycloalkyl substituted with 0-3  $R^e$ , and  $-(\text{CH}_2)_n$ -heterocyclyl substituted with 0-3  $R^e$ ;

$R^e$ , at each occurrence, is independently selected from F, Cl, Br, CN,  $\text{NO}_2$ ,  $=\text{O}$ ,  $\text{CO}_2\text{H}$ , C<sub>1-6</sub> alkyl (optionally substituted with F and Cl), OH,  $\text{OCH}_3$ ,  $\text{OCF}_3$ ,  $-(\text{CH}_2)_n$ -C<sub>3-6</sub> cycloalkyl,  $-(\text{CH}_2)_n$ -C<sub>4-6</sub> heterocyclyl,  $-(\text{CH}_2)_n$ -aryl, and  $-(\text{CH}_2)_n$ -heteroaryl; and  $n$  is independently selected from zero, 1, 2, 3, and 4.

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

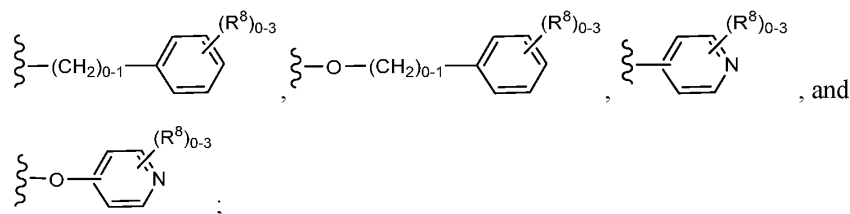


or stereoisomers, enantiomers, diastereoisomers, tautomers, pharmaceutically acceptable salts, prodrugs, or solvates thereof, wherein:

$R^1$  is both C<sub>1-2</sub> alkyl or both  $-\text{OC}_{1-2}$  alkyl;

$R^2$  is independently selected from  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ ,  $-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$ ,  $\text{CH}_2\text{CH}_2\text{CH}_2\text{CF}_3$ ,  $-\text{CH}_2$ -cyclopropyl,  $-\text{CH}_2\text{CH}_2$ -cyclopropyl, cyclobutyl, cyclopentyl,  $\text{CH}_2\text{O}(\text{CH}_2)_{1-3}\text{CH}_3$ ,  $\text{CH}_2\text{OCH}(\text{CH}_3)_2$ , phenyl substituted with 0-2  $R^e$ , and 5- to 6-membered heteroaryl substituted with 0-2  $R^e$ ;

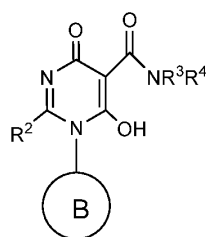
$R^5$ , at each occurrence, is independently selected from



$R^8$ , at each occurrence, is independently selected from F, Cl, Br,  $-OCH_3$ ,  $-OCF_3$ ,  $=O$ , CN,  $CH_3$ ,  $CF_3$ ,  $-C(=O)NH_2$ ,  $-(CH_2)_n$ -aryl substituted with 0-3  $R^e$ ,  $-(CH_2)_n$ -C<sub>3-6</sub> cycloalkyl substituted with 0-3  $R^e$ , and  $-(CH_2)_n$ -heterocyclyl substituted with 0-3  $R^e$ ;

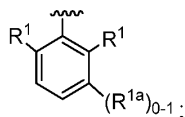
- 5  $R^e$ , at each occurrence, is independently selected from F, Cl, Br, CN,  $NO_2$ ,  $=O$ ,  $CO_2H$ , C<sub>1-6</sub> alkyl (optionally substituted with F and Cl), OH,  $OCH_3$ ,  $OCF_3$ ,  $-(CH_2)_n$ -C<sub>3-6</sub> cycloalkyl,  $-(CH_2)_n$ -C<sub>4-6</sub> heterocyclyl,  $-(CH_2)_n$ -aryl, and  $-(CH_2)_n$ -heteroaryl; and n is independently selected from zero, 1, 2, 3, and 4.

- 10 In another aspect, the present disclosure provides compounds of Formula (IX):



(IX)

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

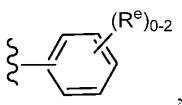


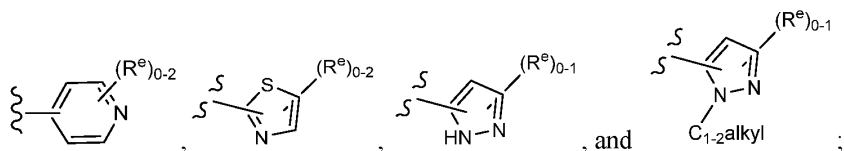
- 15 ring B is

$R^1$  is independently selected from H, F, Cl, OH, C<sub>1-3</sub> alkyl, and OC<sub>1-3</sub> alkyl;

$R^{1a}$  is independently selected from F and Cl;

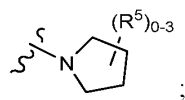
$R^2$  is independently selected from  $-CH_2CH_2CH_2CH_3$ ,  $-CH_2CH_2CH(CH_3)_2$ ,  $CH_2CH_2CH_2CF_3$ ,  $-CH_2$ -cyclopropyl,  $-CH_2CH_2$ -cyclopropyl, cyclobutyl,

- 20 cyclopentyl,  $CH_2O(CH_2)_{1-3}CH_3$ , and  $CH_2OCH(CH_3)_2$ , ,

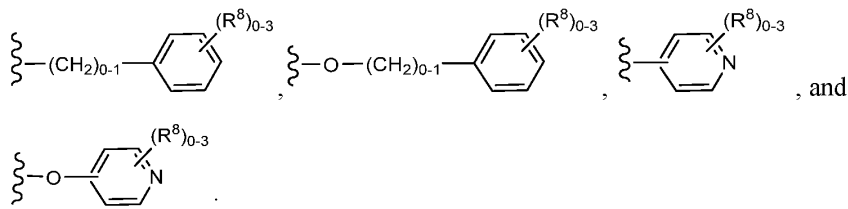


$R^3$  and  $R^4$  together with the nitrogen atom to which they are both attached form





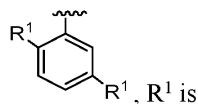
$R^5$ , at each occurrence, is independently selected from

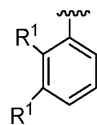


- 5  $R^8$ , at each occurrence, is independently selected from F, Cl, Br,  $-OCH_3$ ,  $-OCF_3$ , CN,  $CH_3$ , and  $CF_3$ ; and

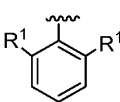
$R^e$ , at each occurrence, is independently selected from F, Cl, Br, and  $C_{1-3}$  alkyl.

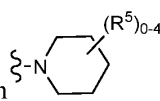
- 10 In another embodiment of Formula (IX), ring B is independently selected from H, F, Cl, OH,  $C_{1-3}$  alkyl, and  $OC_{1-3}$  alkyl, and other variables are as defined in Formula (IX).

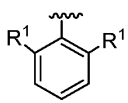


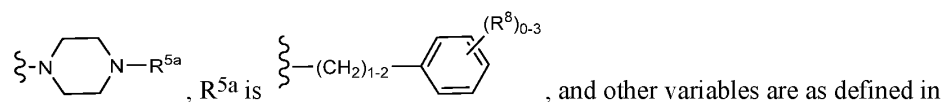
In another embodiment of Formula (IX), ring B is ,  $R^1$  is independently selected from H, F, Cl, OH,  $C_{1-3}$  alkyl, and  $OC_{1-3}$  alkyl, and other variables are as defined in Formula (IX).

15

In another embodiment of Formula (IX), ring B is ,  $R^1$  is both  $CH_2CH_3$  or both  $OCH_3$ ,  $R^3$  and  $R^4$  together with the nitrogen atom to which they are both

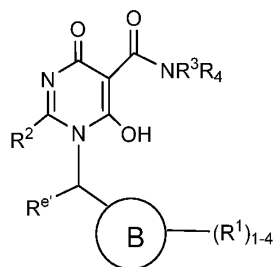
- 20 attached form , and other variables are as defined in Formula (IX).

In another embodiment of Formula (IX), ring B is , R¹ is both CH₂CH₃ or both OCH₃, R³ and R⁴ together with the nitrogen atom to which they are both attached form



5 Formula (IX).

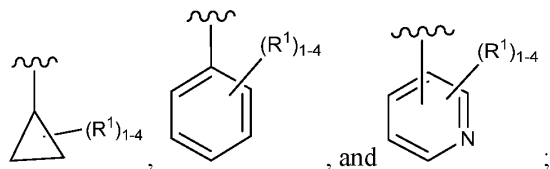
In another aspect, the present disclosure provides compounds of Formula (X):



(X)

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

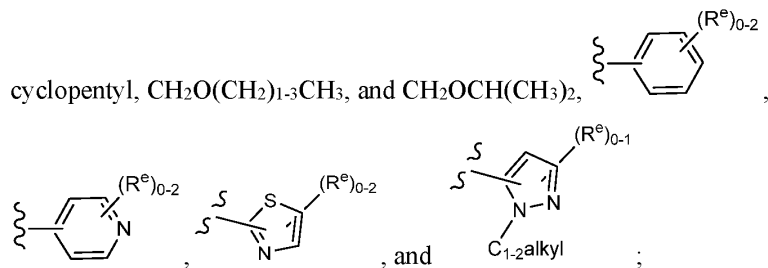
ring B is independently selected from



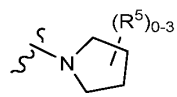
R¹, at each occurrence, is independently selected from H, F, Cl, OH, CN, and OC₁-₄ alkyl;

15 R² is independently selected from -CH₂CH₂CH₂CH₃, -CH₂CH₂CH(CH₃)₂,

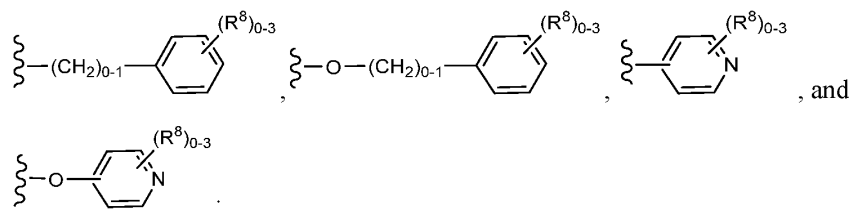
CH₂CH₂CH₂CF₃, -CH₂-cyclopropyl, -CH₂CH₂-cyclopropyl, cyclobutyl,



$\text{R}^3$  and  $\text{R}^4$  together with the nitrogen atom to which they are both attached form



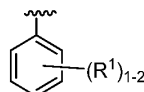
5  $\text{R}^5$ , at each occurrence, is independently selected from

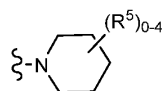


$\text{R}^8$ , at each occurrence, is independently selected from F, Cl, Br,  $-\text{OCH}_3$ ,  $-\text{OCF}_3$ ,  $=\text{O}$ , CN,  $\text{CH}_3$ ,  $\text{CF}_3$ ,  $-\text{C}(=\text{O})\text{NH}_2$ ,  $-(\text{CH}_2)_n$ -aryl substituted with 0-3  $\text{R}^e$ ,  $-(\text{CH}_2)_n$ -C<sub>3-6</sub> cycloalkyl substituted with 0-3  $\text{R}^e$ , and  $-(\text{CH}_2)_n$ -heterocyclyl substituted with 0-3  $\text{R}^e$ ;

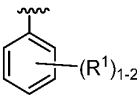
$\text{R}^e$ , at each occurrence, is independently selected from F, Cl, Br, CN,  $\text{NO}_2$ ,  $=\text{O}$ ,  $\text{CO}_2\text{H}$ , C<sub>1-6</sub> alkyl (optionally substituted with F and Cl), OH,  $\text{OCH}_3$ ,  $\text{OCF}_3$ ,  $-(\text{CH}_2)_n$ -C<sub>3-6</sub> cycloalkyl,  $-(\text{CH}_2)_n$ -C<sub>4-6</sub> heterocyclyl,  $-(\text{CH}_2)_n$ -aryl, and  $-(\text{CH}_2)_n$ -heteroaryl;

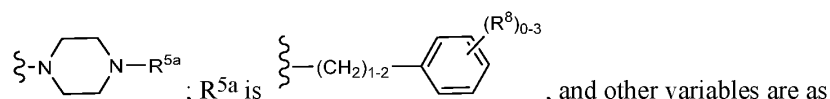
15  $\text{R}^e$  is independently selected from C<sub>1-2</sub> alkyl,  $-\text{CH}_2\text{OC}_{1-2}$  alkyl, and cyclopropyl; and  $n$  is independently selected from zero, 1, 2, 3, and 4.

In another embodiment of Formula (X), ring B is ,  $\text{R}^1$  is independently selected from H, F, Cl, and CN,  $\text{R}^3$  and  $\text{R}^4$  together with the nitrogen atom to which they are both attached form



and other variables are as defined in Formula (X).

In another embodiment of Formula (X), ring B is , R<sup>1</sup> is independently selected from H, F, Cl, and CN, R<sup>3</sup> and R<sup>4</sup> together with the nitrogen atom to which they are both attached form



5 defined in Formula (X).

In another aspect, the present invention provides a compound selected from  
2-Butyl-5-(3-(5-chloropyridin-2-yl)pyrrolidine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-6-hydroxypyrimidin-4(1H)-one (1),

10 (R)-2-Butyl-1-(2,6-dicyclopropylphenyl)-6-hydroxy-5-(3-phenylpyrrolidine-1-carbonyl)pyrimidin-4(1H)-one (2),

1-(2,6-Dimethoxyphenyl)-2-(ethoxymethyl)-6-hydroxy-5-(3-(pyridin-2-yl)pyrrolidine-1-carbonyl)pyrimidin-4(1H)-one (3),

15 (S)-2-(2-Cyclopropylethyl)-1-(2,6-dimethoxyphenyl)-6-hydroxy-5-(3-phenylpyrrolidine-1-carbonyl)pyrimidin-4(1H)-one (4),

(R)-1-(2,6-Bis(methoxy-d<sub>3</sub>)phenyl)-2-butyl-6-hydroxy-5-(3-phenylpyrrolidine-1-carbonyl)pyrimidin-4(1H)-one (5),

2-Butyl-6-hydroxy-3-((S)-1-phenylpropyl)-5-((R)-3-phenylpyrrolidine-1-carbonyl)pyrimidin-4(3H)-one (6),

20 1-(2,6-dimethoxyphenyl)-6-hydroxy-5-(3-(2-methoxyphenyl)pyrrolidine-1-carbonyl)-2-(5-methylpyridin-3-yl)pyrimidin-4(1H)-one (7),

(R)-2-(but-3-en-1-yl)-6-hydroxy-3-(2-methoxy-6-methylphenyl)-5-(3-phenylpyrrolidine-1-carbonyl)pyrimidin-4(3H)-one, diastereomer 1 and diastereomer (8),

25 1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(isopropoxymethyl)-5-(3-(p-tolyl)azetidine-1-carbonyl)pyrimidin-4(1H)-one (9),

2-(cyclopropoxymethyl)-1-(2,6-dimethoxyphenyl)-5-(3-(2-fluorophenyl)pyrrolidine-1-carbonyl)-6-hydroxypyrimidin-4(1H)-one (10),

(R)-2-(cyclopropoxymethyl)-3-(2,6-dimethoxyphenyl)-6-hydroxy-5-(3-phenylpyrrolidine-1-carbonyl)pyrimidin-4(3H)-one (11),

- (R)-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(isopropoxymethyl)-5-(3-phenylpyrrolidine-1-carbonyl)pyrimidin-4(1H)-one (12),  
2-(cyclopropoxymethyl)-1-(2,6-dimethoxyphenyl)-5-(3-(2-fluorophenyl)pyrrolidine-1-carbonyl)-6-hydroxypyrimidin-4(1H)-one (13),  
5 (R)-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-isopentyl-5-(3-phenylpyrrolidine-1-carbonyl)pyrimidin-4(1H)-one (14),  
2-(cyclopropoxymethyl)-1-(2,6-dimethoxyphenyl)-5-(3-(3-fluorophenyl)pyrrolidine-1-carbonyl)-6-hydroxypyrimidin-4(1H)-one (15),  
(S)-2-(but-3-en-1-yl)-3-(2,6-dimethoxyphenyl)-6-hydroxy-5-(3-phenylpyrrolidine-1-carbonyl)pyrimidin-4(3H)-one (16),  
10 (R)-3-(2,6-diethylphenyl)-6-hydroxy-2-(isopropoxymethyl)-5-(3-phenylpyrrolidine-1-carbonyl)pyrimidin-4(3H)-one (17),  
1-(2,6-diethylphenyl)-6-hydroxy-2-(isopropoxymethyl)-5-(3-(pyridin-2-yl)pyrrolidine-1-carbonyl)pyrimidin-4(1H)-one (18),  
15 2-(cyclopropoxymethyl)-1-(2,6-dimethoxyphenyl)-6-hydroxy-5-(3-(o-tolyl)pyrrolidine-1-carbonyl)pyrimidin-4(1H)-one (19),  
(R)-2-(cyclobutoxymethyl)-3-(2,6-dimethoxyphenyl)-6-hydroxy-5-(3-phenylpyrrolidine-1-carbonyl)pyrimidin-4(3H)-one (20),  
5-(3-(4-chlorophenyl)pyrrolidine-1-carbonyl)-2-(cyclopropoxymethyl)-1-(2,6-dimethoxyphenyl)-6-hydroxypyrimidin-4(1H)-one (21),  
20 5-(3-(2-chlorophenyl)pyrrolidine-1-carbonyl)-2-(cyclopropoxymethyl)-1-(2,6-dimethoxyphenyl)-6-hydroxypyrimidin-4(1H)-one (22),  
(R)-1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-6-hydroxy-5-(3-phenylpyrrolidine-1-carbonyl)pyrimidin-4(1H)-one (23),  
25 (S)-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-isopentyl-5-(3-phenylpyrrolidine-1-carbonyl)pyrimidin-4(1H)-one (24),  
1-(2,6-diethylphenyl)-5-(3-(2-fluorophenyl)pyrrolidine-1-carbonyl)-6-hydroxy-2-(isopropoxymethyl)pyrimidin-4(1H)-one (25),  
5-(3-(3-chlorophenyl)pyrrolidine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-6-hydroxypyrimidin-4(1H)-one (26),  
30 (R)-2-(but-3-en-1-yl)-3-(2,6-dimethoxyphenyl)-6-hydroxy-5-(3-phenylpyrrolidine-1-carbonyl)pyrimidin-4(3H)-one (27),

- 5-(3-(3-chlorophenyl)pyrrolidine-1-carbonyl)-2-(cyclopropylmethyl)-1-(2,6-dimethoxyphenyl)-6-hydroxypyrimidin-4(1H)-one (28),  
(S)-1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-6-hydroxy-5-(3-phenylpyrrolidine-1-carbonyl)pyrimidin-4(1H)-one (29),  
5 (R)-2-cyclopentyl-3-(2,6-dimethoxyphenyl)-6-hydroxy-5-(3-phenylpyrrolidine-1-carbonyl)pyrimidin-4(3H)-one (30),  
(S)-2-(cyclopropylmethyl)-3-(2,6-dimethoxyphenyl)-6-hydroxy-5-(3-phenylpyrrolidine-1-carbonyl)pyrimidin-4(3H)-one (31),  
(R)-2-(cyclopropylmethyl)-3-(2,6-dimethoxyphenyl)-6-hydroxy-5-(3-phenylpyrrolidine-1-carbonyl)pyrimidin-4(3H)-one (32),  
10 (S)-1-(2,6-dimethoxyphenyl)-6-hydroxy-5-(3-phenylpyrrolidine-1-carbonyl)-2-(4,4,4-trifluorobutyl)pyrimidin-4(1H)-one (33),  
(S)-2-cyclopentyl-3-(2,6-dimethoxyphenyl)-6-hydroxy-5-(3-phenylpyrrolidine-1-carbonyl)pyrimidin-4(3H)-one (34),  
15 (R)-2-(but-3-en-1-yl)-6-hydroxy-3-(2-methoxy-6-methylphenyl)-5-(3-phenylpyrrolidine-1-carbonyl)pyrimidin-4(3H)-one (35),  
(S)-1-(2,6-dimethoxyphenyl)-6-hydroxy-5-(3-phenylpyrrolidine-1-carbonyl)-2-(4,4,4-trifluorobutyl)pyrimidin-4(1H)-one (36),  
(R)-1-(2,6-dimethoxyphenyl)-6-hydroxy-5-(3-phenylpyrrolidine-1-carbonyl)-2-(4,4,4-trifluorobutyl)pyrimidin-4(1H)-one (40),  
20 2-butyl-5-(3-(5-chloropyridin-2-yl)pyrrolidine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-6-hydroxypyrimidin-4(1H)-one (41),  
2-[(*tert*-butoxy)methyl]-5-[3-(2-chlorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one (42),  
25 2-butyl-5-[3-(2-chlorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one (43),  
2-[(*tert*-butoxy)methyl]-1-(2,6-dimethoxyphenyl)-5-[3-(4-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one (44),  
2-butyl-5-[3-(4-chlorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one (45),  
30 2-butyl-5-[3-(4-chlorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one (46),

- 2-butyl-1-(2,6-dimethoxyphenyl)-6-hydroxy-5-[3-(pyridin-4-yl)pyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one (47),  
2-butyl-1-(2,6-dimethoxyphenyl)-6-hydroxy-5-[3-(pyridin-4-yl)pyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one (48),  
5 1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-5-[3-(2-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one (49),  
2-[(*tert*-butoxy)methyl]-1-(2,6-dimethoxyphenyl)-5-[3-(2-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one (50),  
2-[(*tert*-butoxy)methyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one (51),  
10 2-butyl-1-(2,6-dimethoxyphenyl)-5-[3-(2-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one (52),  
2-butyl-1-(2,6-dimethoxyphenyl)-5-[3-(2-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one (53),  
15 1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-6-hydroxy-5-[3-(pyridin-2-yl)pyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one (54),  
1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-6-hydroxy-5-[3-(pyridin-2-yl)pyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one (55),  
2-butyl-1-(2,6-dimethoxyphenyl)-5-(5-fluoro-2,3-dihydro-1H-isindole-2-carbonyl)-6-hydroxy-1,4-dihydropyrimidin-4-one (56),  
20 1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-5-[3-(4-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one (57),  
benzyl N-[(3S)-1-[2-butyl-1-(2,6-dimethoxyphenyl)-6-hydroxy-4-oxo-1,4-dihydropyrimidine-5-carbonyl]pyrrolidin-3-yl]carbamate (58),  
25 5-[(3R)-3-(benzyloxy)pyrrolidine-1-carbonyl]-2-butyl-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one (59),  
2-butyl-1-(2,6-dimethoxyphenyl)-6-hydroxy-5-{1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carbonyl}-1,4-dihydropyrimidin-4-one (60),  
2-butyl-1-(2,6-dimethoxyphenyl)-6-hydroxy-5-{5H,6H,7H-pyrrolo[3,4-b]pyridine-6-carbonyl}-1,4-dihydropyrimidin-4-one (61),  
30 benzyl N-[(3R)-1-[2-butyl-1-(2,6-dimethoxyphenyl)-6-hydroxy-4-oxo-1,4-dihydropyrimidine-5-carbonyl]pyrrolidin-3-yl]carbamate (62),

- 5-[(3S)-3-(benzyloxy)pyrrolidine-1-carbonyl]-2-butyl-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one (63),
- 2-butyl-1-(2,6-dimethoxyphenyl)-6-hydroxy-5-[(3S)-3-[(pyridin-2-yl)methoxy]pyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one (64),
- 5 2-[2-butyl-1-(2,6-dimethoxyphenyl)-6-hydroxy-4-oxo-1,4-dihydropyrimidine-5-carbonyl]-2,3-dihydro-1H-isoindole-5-carbonitrile (65),
- 2-butyl-5-(2,3-dihydro-1H-isoindole-2-carbonyl)-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one (66),
- 2-butyl-1-(2,6-dimethoxyphenyl)-5-{3-[(4-fluorophenyl)methyl]pyrrolidine-1-carbonyl}-6-hydroxy-1,4-dihydropyrimidin-4-one (67),
- 10 2-butyl-1-(2,6-dimethoxyphenyl)-6-hydroxy-5-[3-(pyridin-2-yl)pyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one (68),
- 2-butyl-1-(2,6-dimethoxyphenyl)-5-{4-[(3-fluorophenyl)methyl]piperazine-1-carbonyl}-6-hydroxy-1,4-dihydropyrimidin-4-one (69),
- 15 2-butyl-1-(2,6-dimethoxyphenyl)-6-hydroxy-5-[3-(pyridin-2-yl)pyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one (70),
- 2-butyl-1-(2,6-dimethoxyphenyl)-6-hydroxy-5-[4-(pyridin-4-yl)piperidine-1-carbonyl]-1,4-dihydropyrimidin-4-one (71),
- 2-butyl-1-(2,6-dimethoxyphenyl)-6-hydroxy-5-(4-phenylpiperidine-1-carbonyl)-1,4-dihydropyrimidin-4-one (72),
- 20 5-(3-benzylpyrrolidine-1-carbonyl)-2-butyl-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one (73),
- 2-butyl-1-(2,6-dimethoxyphenyl)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one (74),
- 25 2-butyl-1-(2,6-dimethoxyphenyl)-6-hydroxy-5-[3-(pyridin-3-yl)pyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one (75),
- 2-butyl-1-(2,6-dimethoxyphenyl)-6-hydroxy-5-[3-(pyridin-3-yl)pyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one (76),
- 2-butyl-1-(2,6-dimethoxyphenyl)-5-[3-(4-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one (77),
- 30 2-butyl-1-(2,6-dimethoxyphenyl)-5-[3-(3-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one (78),



- 2-butyl-1-(2,6-dimethoxyphenyl)-5-[3-(4-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one (79),
- 2-butyl-1-(2,6-dimethoxyphenyl)-5-[3-(3-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one (80),
- 5 1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-5-[3-(4-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one (81),
- 1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-6-hydroxy-5-[3-(pyridin-3-yl)pyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one (82),
- 1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-5-[3-(3-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one (83),
- 10 1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-5-[3-(3-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one (84),
- 1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-6-hydroxy-5-[3-(pyridin-3-yl)pyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one (85),
- 15 2-butyl-3-(2,6-diethylphenyl)-6-hydroxy-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one (86),
- 2-butyl-3-(2,6-dimethoxyphenyl)-5-[3-(4-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-3,4-dihydropyrimidin-4-one (87),
- 2-butyl-5-[3-(3-chlorophenyl)azetidine-1-carbonyl]-3-(2,6-dimethoxyphenyl)-6-hydroxy-3,4-dihydropyrimidin-4-one (88),
- 20 2-butyl-3-(2,6-diethylphenyl)-5-[3-(4-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-3,4-dihydropyrimidin-4-one (89),
- 2-butyl-3-(2,6-diethylphenyl)-6-hydroxy-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one (90),
- 25 2-butyl-3-(2,6-dimethoxyphenyl)-6-hydroxy-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one (91),
- 5-[3-(2-chlorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-[(propan-2-yloxy)methyl]-1,4-dihydropyrimidin-4-one (92),
- 1-(2,6-dimethoxyphenyl)-5-[3-(2-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-2-[(propan-2-yloxy)methyl]-1,4-dihydropyrimidin-4-one (93),
- 30 1-(2,6-dimethoxyphenyl)-5-[3-(4-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-2-[(propan-2-yloxy)methyl]-1,4-dihydropyrimidin-4-one (94),

- 1-(2,6-dimethoxyphenyl)-5-[3-(3-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-2-[(propan-2-yloxy)methyl]-1,4-dihydropyrimidin-4-one (95),  
2-(2-cyclopropylethyl)-1-(2,6-dimethoxyphenyl)-6-hydroxy-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one (96),  
5 1-(2,6-dimethoxyphenyl)-5-[3-(3-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-2-[(propan-2-yloxy)methyl]-1,4-dihydropyrimidin-4-one (97),  
1-(2,6-dimethoxyphenyl)-6-hydroxy-5-[3-(2-methylphenyl)pyrrolidine-1-carbonyl]-2-[(propan-2-yloxy)methyl]-1,4-dihydropyrimidin-4-one (98),  
1-(2,6-dimethoxyphenyl)-6-hydroxy-2-[(propan-2-yloxy)methyl]-5-{3-[2-(trifluoromethyl)phenyl]pyrrolidine-1-carbonyl}-1,4-dihydropyrimidin-4-one (99),  
10 2-(cyclopropoxymethyl)-1-(2,6-dimethoxyphenyl)-5-[3-(4-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one (100),  
1-(2,6-dimethoxyphenyl)-6-hydroxy-2-[(propan-2-yloxy)methyl]-5-{3-[2-(trifluoromethyl)phenyl]pyrrolidine-1-carbonyl}-1,4-dihydropyrimidin-4-one (101),  
15 1-(2,6-dimethoxyphenyl)-5-[3-(4-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-2-[(propan-2-yloxy)methyl]-1,4-dihydropyrimidin-4-one (102),  
2-(cyclopropoxymethyl)-1-(2,6-dimethoxyphenyl)-5-[3-(4-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one (103),  
1-[2,6-bis(<sup>2</sup>H<sub>3</sub>)methoxyphenyl]-2-butyl-6-hydroxy-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one (104),  
20 1-(2,6-dimethoxyphenyl)-6-hydroxy-5-[3-(2-methylphenyl)pyrrolidine-1-carbonyl]-2-[(propan-2-yloxy)methyl]-1,4-dihydropyrimidin-4-one (105),  
1-[2,6-bis(<sup>2</sup>H<sub>3</sub>)methoxyphenyl]-2-(ethoxymethyl)-6-hydroxy-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one (106),  
25 4-{1-[1-(2,6-dimethoxyphenyl)-6-hydroxy-4-oxo-2-[(propan-2-yloxy)methyl]-1,4-dihydropyrimidin-5-carbonyl]pyrrolidin-3-yl} benzonitrile (107),  
4-{1-[1-(2,6-dimethoxyphenyl)-6-hydroxy-4-oxo-2-[(propan-2-yloxy)methyl]-1,4-dihydropyrimidin-5-carbonyl]pyrrolidin-3-yl} benzonitrile (108),  
1-[2,6-bis(<sup>2</sup>H<sub>3</sub>)methoxyphenyl]-2-(ethoxymethyl)-6-hydroxy-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one (109),  
30 1-(2,6-dimethoxyphenyl)-6-hydroxy-5-(3-phenylazetidine-1-carbonyl)-2-[(propan-2-yloxy)methyl]-1,4-dihydropyrimidin-4-one (110),

- 1-(2,6-dimethoxyphenyl)-6-hydroxy-5-[3-(4-methylphenyl)azetidine-1-carbonyl]-  
2-[(propan-2-yloxy)methyl]-1,4-dihydropyrimidin-4-one (111),  
2-butyl-3-(4,6-dimethoxypyrimidin-5-yl)-6-hydroxy-5-[(3S)-3-phenylpyrrolidine-  
1-carbonyl]-3,4-dihydropyrimidin-4-one (112),  
5 2-butyl-3-(4,6-dimethoxypyrimidin-5-yl)-6-hydroxy-5-[(3R)-3-phenylpyrrolidine-  
1-carbonyl]-3,4-dihydropyrimidin-4-one (113),  
2-butyl-5-[3-(2-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-3-[(1S)-1-  
phenylpropyl]-3,4-dihydropyrimidin-4-one (114),  
2-butyl-5-[3-(3-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-3-[(1S)-1-  
10 phenylpropyl]-3,4-dihydropyrimidin-4-one (115),  
2-butyl-6-hydroxy-3-[(1R)-2-methoxy-1-phenylethyl]-5-[(3R)-3-  
phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one (116),  
2-butyl-6-hydroxy-3-[(1R)-1-phenylethyl]-5-[(3R)-3-phenylpyrrolidine-1-  
carbonyl]-3,4-dihydropyrimidin-4-one (117),  
15 2-butyl-5-[3-(2-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-3-[(1S)-1-  
phenylpropyl]-3,4-dihydropyrimidin-4-one (118),  
2-butyl-5-[3-(3-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-3-[(1S)-1-  
phenylpropyl]-3,4-dihydropyrimidin-4-one (119),  
2-butyl-6-hydroxy-3-[(1S)-1-(3-methoxyphenyl)ethyl]-5-[(3S)-3-  
20 phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one (120),  
2-butyl-6-hydroxy-3-[(1S)-1-phenylpropyl]-5-[(3S)-3-phenylpyrrolidine-1-  
carbonyl]-3,4-dihydropyrimidin-4-one (121),  
2-butyl-6-hydroxy-3-[(1R)-1-(2-methoxyphenyl)ethyl]-5-[(3R)-3-  
phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one (122),  
25 2-butyl-6-hydroxy-3-(1-phenylethyl)-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-  
3,4-dihydropyrimidin-4-one (123),  
2-butyl-6-hydroxy-3-[(1R)-1-phenylpropyl]-5-[(3R)-3-phenylpyrrolidine-1-  
carbonyl]-3,4-dihydropyrimidin-4-one (124),  
2-butyl-6-hydroxy-3-[(1S)-1-phenylethyl]-5-[(3S)-3-phenylpyrrolidine-1-  
30 carbonyl]-3,4-dihydropyrimidin-4-one (125),  
2-butyl-3-[(1S)-1-cyclopropylethyl]-6-hydroxy-5-[(3R)-3-phenylpyrrolidine-1-  
carbonyl]-3,4-dihydropyrimidin-4-one (126),

- 2-butyl-6-hydroxy-3-[(1R)-2-methoxy-1-phenylethyl]-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one (127),
- 2-butyl-6-hydroxy-3-[(1R)-1-phenylpropyl]-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one (128),
- 5 2-butyl-6-hydroxy-3-(2-methyl-1-phenylpropyl)-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one (129),
- 2-butyl-6-hydroxy-3-(2-methyl-1-phenylpropyl)-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one (130),
- 2-butyl-3-[(1S)-1-cyclopropylethyl]-6-hydroxy-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one (131),
- 10 2-butyl-6-hydroxy-3-[(1R)-1-phenylethyl]-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one (132),
- 2-butyl-3-[1-(2-chlorophenyl)ethyl]-6-hydroxy-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one (133),
- 15 2-butyl-3-[1-(2-chlorophenyl)ethyl]-6-hydroxy-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one (134),
- 2-butyl-6-hydroxy-3-[(1R)-1-(2-methoxyphenyl)ethyl]-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one (135),
- 2-butyl-6-hydroxy-3-(1-phenylethyl)-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one (136),
- 20 2-butyl-6-hydroxy-3-[(1S)-1-phenylbutyl]-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one (137),
- 3-[(1S)-1-{2-butyl-4-hydroxy-6-oxo-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-1,6-dihydropyrimidin-1-yl}ethyl]benzonitrile (138),
- 25 2-butyl-6-hydroxy-3-[(1S)-1-(3-methoxyphenyl)ethyl]-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one (139),
- 2-butyl-6-hydroxy-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-3-[1-(pyridin-3-yl)ethyl]-3,4-dihydropyrimidin-4-one (140),
- 2-butyl-6-hydroxy-3-[(1S)-1-phenylethyl]-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one (141),
- 30 2-butyl-3-[(1R)-1-cyclopropylethyl]-6-hydroxy-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one (142),

- 2-butyl-3-[(1S)-1-(4-fluorophenyl)ethyl]-6-hydroxy-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one (143),
- 2-butyl-6-hydroxy-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-3-[(1S)-1,2,3,4-tetrahydronaphthalen-1-yl]-3,4-dihydropyrimidin-4-one (144),
- 5 2-butyl-3-[(1R)-2,3-dihydro-1H-inden-1-yl]-6-hydroxy-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one (145),
- 2-butyl-6-hydroxy-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-3-[1-(pyridin-3-yl)ethyl]-3,4-dihydropyrimidin-4-one (146),
- 2-butyl-6-hydroxy-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-3-[(1S)-1,2,3,4-tetrahydronaphthalen-1-yl]-3,4-dihydropyrimidin-4-one (147),
- 10 2-butyl-6-hydroxy-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-3-[1-(pyridin-4-yl)ethyl]-3,4-dihydropyrimidin-4-one (148),
- 3-[(1S)-1-{2-butyl-4-hydroxy-6-oxo-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-1,6-dihydropyrimidin-1-yl}ethyl]benzonitrile (149),
- 15 2-butyl-6-hydroxy-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-3-(propan-2-yl)-3,4-dihydropyrimidin-4-one (150),
- 2-butyl-6-hydroxy-3-[(1S)-1-(2-methoxyphenyl)ethyl]-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one (151),
- 2-butyl-6-hydroxy-3-[(1S)-2-methoxy-1-phenylethyl]-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one (152),
- 20 2-butyl-6-hydroxy-3-[(1S)-1-phenylbutyl]-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one (153),
- 2-butyl-6-hydroxy-3-[(1S)-2-methoxy-1-phenylethyl]-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one (154),
- 25 2-butyl-3-[(1R)-1-cyclopropylethyl]-6-hydroxy-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one (155),
- 2-butyl-6-hydroxy-3-[(1S)-1-(2-methoxyphenyl)ethyl]-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one (156),
- 2-butyl-3-[(1S)-1-(4-fluorophenyl)ethyl]-6-hydroxy-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one (157),
- 30 2-butyl-3-[(1R)-2,3-dihydro-1H-inden-1-yl]-6-hydroxy-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one (158),

- 2-butyl-6-hydroxy-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-3-(propan-2-yl)-3,4-dihydropyrimidin-4-one (159),
- 1-(2,6-dimethoxyphenyl)-6-hydroxy-5-[3-(2-methoxyphenyl)pyrrolidine-1-carbonyl]-2-[(propan-2-yloxy)methyl]-1,4-dihydropyrimidin-4-one (160),
- 5 1-(2,6-dimethoxyphenyl)-6-hydroxy-5-[3-(2-methoxyphenyl)pyrrolidine-1-carbonyl]-2-[(propan-2-yloxy)methyl]-1,4-dihydropyrimidin-4-one (161),
- 5-[3-(2,4-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-[(propan-2-yloxy)methyl]-1,4-dihydropyrimidin-4-one (162),
- 5-[3-(2,4-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-[(propan-2-yloxy)methyl]-1,4-dihydropyrimidin-4-one (163),
- 10 5-[3-(2,6-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-[(propan-2-yloxy)methyl]-1,4-dihydropyrimidin-4-one (164),
- 2-{1-[1-(2,6-dimethoxyphenyl)-6-hydroxy-4-oxo-2-[(propan-2-yloxy)methyl]-1,4-dihydropyrimidine-5-carbonyl]pyrrolidin-3-yl} benzonitrile (165),
- 15 5-[3-(2,6-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-[(propan-2-yloxy)methyl]-1,4-dihydropyrimidin-4-one (166),
- 2-{1-[1-(2,6-dimethoxyphenyl)-6-hydroxy-4-oxo-2-[(propan-2-yloxy)methyl]-1,4-dihydropyrimidine-5-carbonyl]pyrrolidin-3-yl} benzonitrile (167),
- 2-(2-cyclopropylethyl)-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one (168),
- 20 2-(2-cyclopropylethyl)-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one (169),
- 5-[3-(5-chloropyridin-2-yl)pyrrolidine-1-carbonyl]-2-(2-cyclopropylethyl)-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one (170),
- 25 5-[3-(5-chloropyridin-2-yl)pyrrolidine-1-carbonyl]-2-(2-cyclopropylethyl)-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one (171),
- 5-[3-(5-chloropyridin-2-yl)-2,5-dihydro-1H-pyrrole-1-carbonyl]-2-(2-cyclopropylethyl)-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one (172),
- 30 2-(2-cyclopropylethyl)-5-{4-[(2,3-difluorophenyl)methyl]piperazine-1-carbonyl}-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one (173),

- 5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-1-(2,6-diethylphenyl)-6-hydroxy-2-(1-methyl-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one (174),
- 2-(2-cyclopropylethyl)-1-(2,6-dimethoxyphenyl)-5-[3-(5-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one (175),
- 5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-2-(2-cyclopropylethyl)-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one (176),
- 2-(2-cyclopropylethyl)-1-(2,6-dimethoxyphenyl)-5-[3-(5-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one (177),
- 2-(2-cyclopropylethyl)-1-(2,6-dimethoxyphenyl)-5-[3-(3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one (178),
- 2-(2-cyclopropylethyl)-1-(2,6-dimethoxyphenyl)-5-[3-(3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one (179),
- 5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-2-(2-cyclopropylethyl)-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one (180),
- 1-[(1S)-1-(3,5-difluorophenyl)propyl]-2-(1-ethyl-1H-pyrazol-3-yl)-5-[3-(3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one (181),
- 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(1-methyl-1H-pyrazol-4-yl)-1,4-dihydropyrimidin-4-one (182),
- 5-[3-(5-chloropyridin-2-yl)pyrrolidine-1-carbonyl]-1-[(1S)-1-(3,5-difluorophenyl)propyl]-6-hydroxy-2-(1-methyl-1H-pyrazol-4-yl)-1,4-dihydropyrimidin-4-one (183),
- 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(1-methyl-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one (184),
- 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(5-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(1-methyl-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one (185),
- 1-[(1S)-1-(3,5-difluorophenyl)propyl]-2-(1-ethyl-1H-pyrazol-3-yl)-5-[3-(3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one (186),

- 5-[3-(5-chloropyridin-2-yl)pyrrolidine-1-carbonyl]-1-[(1S)-1-(3,5-difluorophenyl)propyl]-6-hydroxy-2-(1-methyl-1H-pyrazol-4-yl)-1,4-dihydropyrimidin-4-one (187),
- 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(1-methyl-1H-pyrazol-4-yl)-1,4-dihydropyrimidin-4-one (188),
- 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(1-methyl-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one (189),
- 5-[3-(5-chloropyridin-2-yl)pyrrolidine-1-carbonyl]-1-[(1S)-1-(3,5-difluorophenyl)propyl]-6-hydroxy-2-(1-methyl-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one (190),
- 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(5-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(1-methyl-1H-pyrazol-4-yl)-1,4-dihydropyrimidin-4-one (191),
- 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-2-(1-ethyl-1H-pyrazol-3-yl)-6-hydroxy-1,4-dihydropyrimidin-4-one (192),
- 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(2-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(1-methyl-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one (193),
- 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(4-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(1-methyl-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one (194),
- 1-[(1S)-1-(3,5-difluorophenyl)propyl]-6-hydroxy-5-[3-(2-methoxyphenyl)pyrrolidine-1-carbonyl]-2-(1-methyl-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one (195),
- 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(2-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(1-methyl-1H-pyrazol-4-yl)-1,4-dihydropyrimidin-4-one (196),
- 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(4-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(1-methyl-1H-pyrazol-4-yl)-1,4-dihydropyrimidin-4-one (197),
- 1-[(1S)-1-(3,5-difluorophenyl)propyl]-6-hydroxy-5-[3-(2-methoxyphenyl)pyrrolidine-1-carbonyl]-2-(1-methyl-1H-pyrazol-4-yl)-1,4-dihydropyrimidin-4-one (198),
- 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(5-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(1-methyl-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one (199),
- 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(4-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(1-methyl-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one (200),



- 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(1-methyl-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one (201),  
1-[(1S)-1-(3,5-difluorophenyl)propyl]-2-(1-ethyl-1H-pyrazol-3-yl)-5-[3-(4-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one (202),  
5 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(4-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(1-methyl-1H-pyrazol-4-yl)-1,4-dihydropyrimidin-4-one (203),  
1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(4-methyl-1,3-thiazol-2-yl)-1,4-dihydropyrimidin-4-one (204),  
1-[(S)-1-(3,5-difluorophenyl)propyl]-5-(3-(4-fluoropyridin-2-yl)pyrrolidine-1-carbonyl)-6-hydroxy-2-(4-methylthiazol-2-yl)pyrimidin-4(1H)-one (205),  
10 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(5-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(4-methyl-1,3-thiazol-2-yl)-1,4-dihydropyrimidin-4-one (206),  
1-[(1S)-1-(3,5-difluorophenyl)propyl]-6-hydroxy-5-[3-(2-methoxyphenyl)pyrrolidine-1-carbonyl]-2-(4-methyl-1,3-thiazol-2-yl)-1,4-dihydropyrimidin-4-one (207),  
15 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(2-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(4-methyl-1,3-thiazol-2-yl)-1,4-dihydropyrimidin-4-one (208),  
5-[3-(5-chloropyridin-2-yl)pyrrolidine-1-carbonyl]-1-[(1S)-1-(3,5-difluorophenyl)propyl]-6-hydroxy-2-(4-methyl-1,3-thiazol-2-yl)-1,4-dihydropyrimidin-4-one (209),  
20 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(4-methyl-1,3-thiazol-2-yl)-1,4-dihydropyrimidin-4-one (210),  
1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(4-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(4-methyl-1,3-thiazol-2-yl)-1,4-dihydropyrimidin-4-one (211),  
25 1-[(1S)-1-(3,5-difluorophenyl)propyl]-2-(1-ethyl-1H-pyrazol-3-yl)-5-[3-(3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one (212),  
5-[3-(5-chloropyridin-2-yl)pyrrolidine-1-carbonyl]-1-[(1S)-1-(3,5-difluorophenyl)propyl]-2-(1-ethyl-1H-pyrazol-3-yl)-6-hydroxy-1,4-dihydropyrimidin-4-one (213),  
30 5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-1-[(1S)-1-(3,5-difluorophenyl)propyl]-2-(1-ethyl-1H-pyrazol-3-yl)-6-hydroxy-1,4-dihydropyrimidin-4-one (214),

- 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-2-(1-ethyl-1H-pyrazol-3-yl)-6-hydroxy-1,4-dihydropyrimidin-4-one (215),
- 1-[(1S)-1-(3,5-difluorophenyl)propyl]-2-(1-ethyl-1H-pyrazol-3-yl)-5-[3-(5-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one (216),
- 5 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(1-methyl-1H-pyrazol-4-yl)-1,4-dihydropyrimidin-4-one (217),
- 5-[3-(5-chloropyridin-2-yl)pyrrolidine-1-carbonyl]-1-[(1S)-1-(3,5-difluorophenyl)propyl]-6-hydroxy-2-(1-methyl-1H-pyrazol-4-yl)-1,4-dihydropyrimidin-4-one (218),
- 10 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(1-methyl-1H-pyrazol-4-yl)-1,4-dihydropyrimidin-4-one (219),
- 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(5-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(1-methyl-1H-pyrazol-4-yl)-1,4-dihydropyrimidin-4-one (220),
- 1-(2,6-diethylphenyl)-6-hydroxy-2-[(propan-2-yloxy)methyl]-5-[3-(pyridin-4-yl)pyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one (221),
- 15 5-[4-(6-chloropyridin-3-yl)piperidine-1-carbonyl]-3-(2,6-diethylphenyl)-6-hydroxy-2-[(propan-2-yloxy)methyl]-3,4-dihydropyrimidin-4-one (222),
- 5-[3-(4-chlorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-2-(4-fluorophenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one (223),
- 20 1-(2,6-dimethoxyphenyl)-2-(4-fluorophenyl)-6-hydroxy-5-[3-(pyridin-4-yl)pyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one (224),
- 1-(2,6-dimethoxyphenyl)-2-(4-fluorophenyl)-5-[3-(2-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one (225),
- 2-(cyclopropylmethyl)-1-(2,6-dimethoxyphenyl)-5-[3-(2-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one (226),
- 25 5-[4-(6-chloropyridin-3-yl)piperidine-1-carbonyl]-2-(cyclopropylmethyl)-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one (227),
- 5-[3-(4-chlorophenyl)pyrrolidine-1-carbonyl]-2-(cyclopropylmethyl)-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one (228),
- 30 5-[3-(2-chlorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-2-(4-fluorophenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one (229),

- 2-(cyclopropylmethyl)-1-(2,6-dimethoxyphenyl)-6-hydroxy-5-[3-(pyridin-4-yl)pyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one (230),
- 1-(2,6-dimethoxyphenyl)-2-[(4-fluorophenyl)methyl]-5-[3-(2-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one (231),
- 5 1-(2,6-dimethoxyphenyl)-5-[3-(4-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(5-methylpyridin-3-yl)-1,4-dihydropyrimidin-4-one (232),
- 1-(2,6-dimethoxyphenyl)-5-[3-(2-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(5-methylpyridin-3-yl)-1,4-dihydropyrimidin-4-one (233),
- 10 1-(2,6-dimethoxyphenyl)-6-hydroxy-5-[3-(2-methoxyphenyl)pyrrolidine-1-carbonyl]-2-(5-methylpyridin-3-yl)-1,4-dihydropyrimidin-4-one (234),
- 5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(6-methylpyridin-2-yl)-1,4-dihydropyrimidin-4-one (235),
- 1-(2,6-dimethoxyphenyl)-5-[3-(2-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(6-methylpyridin-2-yl)-1,4-dihydropyrimidin-4-one (236),
- 15 2-{1-[2-(3-chlorophenyl)-1-(2,6-dimethoxyphenyl)-6-hydroxy-4-oxo-1,4-dihydropyrimidine-5-carbonyl]pyrrolidin-3-yl} benzonitrile (237),
- 2-(3-chlorophenyl)-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one (238),
- 1-(2,6-dimethoxyphenyl)-5-[3-(2-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(4-methylpyridin-2-yl)-1,4-dihydropyrimidin-4-one (239),
- 20 2-{1-[1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(4-methylpyridin-2-yl)-4-oxo-1,4-dihydropyrimidine-5-carbonyl]pyrrolidin-3-yl} benzonitrile (240),
- 5-[3-(2,6-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(3-methylphenyl)-1,4-dihydropyrimidin-4-one (241),
- 25 2-{1-[1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(3-methylphenyl)-4-oxo-1,4-dihydropyrimidine-5-carbonyl]pyrrolidin-3-yl} benzonitrile (242),
- 2-{1-[2-(5-chloropyridin-3-yl)-1-(2,6-dimethoxyphenyl)-6-hydroxy-4-oxo-1,4-dihydropyrimidine-5-carbonyl]pyrrolidin-3-yl} benzonitrile (243),
- 5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(3-methylphenyl)-1,4-dihydropyrimidin-4-one (244),
- 30 1-(2,6-dimethoxyphenyl)-5-[3-(3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(3-methoxyphenyl)-1,4-dihydropyrimidin-4-one (245),

- 5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(3-methoxyphenyl)-1,4-dihydropyrimidin-4-one (246),
- 2-(5-chloropyridin-3-yl)-5-[3-(2,6-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one (247),
- 5 5-[3-(2,4-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(1-methyl-1H-pyrazol-4-yl)-1,4-dihydropyrimidin-4-one (248),
- 5-[3-(2,6-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(1-methyl-1H-pyrazol-4-yl)-1,4-dihydropyrimidin-4-one (249),
- 5-[3-(2,4-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(1-methyl-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one (25 ),
- 10 5-[3-(2,6-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(1-methyl-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one (251),
- 5-[3-(2,6-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(6-methylpyridin-3-yl)-1,4-dihydropyrimidin-4-one (252),
- 15 5-[3-(2,4-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(6-methylpyridin-3-yl)-1,4-dihydropyrimidin-4-one (253),
- 5-[3-(2,4-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(2-methylpyridin-4-yl)-1,4-dihydropyrimidin-4-one (254),
- 1-(2,6-dimethoxyphenyl)-2-(4-fluoro-3-methylphenyl)-5-[3-(3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one (255),
- 20 5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-2-(4-fluoro-3-methylphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one (256),
- 5-[3-(2,6-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(2-methylpyridin-4-yl)-1,4-dihydropyrimidin-4-one (257),
- 25 1-(2,6-diethylphenyl)-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(1-methyl-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one (258),
- 5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(1-methyl-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one (259),
- 30 2-(5-chloropyridin-3-yl)-5-[3-(2,4-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one (260),

- 5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(3-methoxyphenyl)-1,4-dihydropyrimidin-4-one (261),  
5-[3-(2,4-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(4-methylpyridin-2-yl)-1,4-dihydropyrimidin-4-one (262),  
5 5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(3-methylphenyl)-1,4-dihydropyrimidin-4-one (263),  
5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-2-(3-chlorophenyl)-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one (264),  
5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-2-(4-fluorophenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one (265),  
10 5-[3-(2,4-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(2-methyl-1,3-thiazol-4-yl)-1,4-dihydropyrimidin-4-one (266),  
1-(2,6-diethylphenyl)-5-[3-(2,6-difluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(1-methyl-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one (267),  
15 1-(2,6-diethylphenyl)-5-[3-(2-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(1-methyl-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one (268),  
5-[3-(2,4-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-2-(1-ethyl-1H-pyrazol-3-yl)-6-hydroxy-1,4-dihydropyrimidin-4-one (269),  
5-[3-(2,6-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(2-methyl-1,3-thiazol-4-yl)-1,4-dihydropyrimidin-4-one (270),  
20 5-[3-(2,6-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(4-methyl-1,3-thiazol-2-yl)-1,4-dihydropyrimidin-4-one (271),  
1-(2,6-diethylphenyl)-5-[3-(4-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(1-methyl-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one (272),  
25 5-[3-(2,6-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(4-methoxypyridin-2-yl)-1,4-dihydropyrimidin-4-one (273),  
5-[3-(2,6-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(5-methylpyridin-2-yl)-1,4-dihydropyrimidin-4-one (274),  
1-(2,6-diethylphenyl)-5-[3-(3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(1-methyl-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one (275),  
30 5-[3-(2,6-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-2-(1-ethyl-1H-pyrazol-3-yl)-6-hydroxy-1,4-dihydropyrimidin-4-one (276),

- 5-[4-(2,3-difluorophenoxy)piperidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(2-methyl-1,3-thiazol-4-yl)-1,4-dihydropyrimidin-4-one (277),
- 5-[3-(2,4-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(4-methoxypyridin-2-yl)-1,4-dihydropyrimidin-4-one (278),
- 5 2-(6-chloropyridin-3-yl)-5-[3-(2,4-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one (279),
- 2-(5-chloropyridin-2-yl)-5-[3-(2,6-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one (280),
- 2-(6-chloropyridin-3-yl)-5-[3-(2,6-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one (281),
- 10 5-[3-(2,4-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(5-methylpyridin-2-yl)-1,4-dihydropyrimidin-4-one (282),
- 1-(2,6-diethylphenyl)-6-hydroxy-2-(1-methyl-1H-pyrazol-3-yl)-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one (283),
- 15 1-(2,6-dimethoxyphenyl)-2-(1-ethyl-1H-pyrazol-3-yl)-6-hydroxy-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one (284),
- 1-(2,6-diethylphenyl)-6-hydroxy-2-(1-methyl-1H-pyrazol-3-yl)-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one (285),
- 1-(2,6-dimethoxyphenyl)-2-(1-ethyl-1H-pyrazol-3-yl)-6-hydroxy-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one (286),
- 20 2-(5-chloropyridin-2-yl)-5-[3-(2,4-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one (287),
- 2-(1-ethyl-1H-pyrazol-3-yl)-6-hydroxy-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-1-[3-(propan-2-yl)phenyl]-1,4-dihydropyrimidin-4-one (288),
- 25 1-(2,6-diethylphenyl)-6-hydroxy-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-2-[1-(propan-2-yl)-1H-pyrazol-3-yl]-1,4-dihydropyrimidin-4-one (289),
- 5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-1-(2,6-diethylphenyl)-6-hydroxy-2-[1-(propan-2-yl)-1H-pyrazol-3-yl]-1,4-dihydropyrimidin-4-one (290),
- 30 2-(1-ethyl-1H-pyrazol-3-yl)-6-hydroxy-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-1-[3-(propan-2-yl)phenyl]-1,4-dihydropyrimidin-4-one (291),

- 1-(2,6-diethylphenyl)-5-[3-(3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-2-[1-(propan-2-yl)-1H-pyrazol-3-yl]-1,4-dihydropyrimidin-4-one (292),  
5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-2-(1-ethyl-1H-pyrazol-3-yl)-6-hydroxy-1-[3-(propan-2-yl)phenyl]-1,4-dihydropyrimidin-4-one (293),  
5 2-(1-ethyl-1H-pyrazol-3-yl)-5-[3-(2-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-1-[3-(propan-2-yl)phenyl]-1,4-dihydropyrimidin-4-one (294),  
1-(2,6-diethylphenyl)-5-[3-(2-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-2-[1-(propan-2-yl)-1H-pyrazol-3-yl]-1,4-dihydropyrimidin-4-one (295),  
5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-1-(2,6-diethylphenyl)-6-hydroxy-2-(2-methyl-1,3-thiazol-4-yl)-1,4-dihydropyrimidin-4-one (296),  
10 1-(2,6-diethylphenyl)-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-2-[2-(propan-2-yl)-1,3-thiazol-4-yl]-1,4-dihydropyrimidin-4-one (297),  
1-(2,6-diethylphenyl)-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(2-methyl-1,3-thiazol-4-yl)-1,4-dihydropyrimidin-4-one (298),  
15 1-(2,6-diethylphenyl)-6-hydroxy-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-2-[2-(propan-2-yl)-1,3-thiazol-4-yl]-1,4-dihydropyrimidin-4-one (299),  
1-(2,6-diethylphenyl)-5-[3-(5-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-2-[2-(propan-2-yl)-1,3-thiazol-4-yl]-1,4-dihydropyrimidin-4-one (300),  
20 1-(2,6-diethylphenyl)-6-hydroxy-2-(2-methyl-1,3-thiazol-4-yl)-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one (301),  
1-(2,6-diethylphenyl)-5-[3-(3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(2-methyl-1,3-thiazol-4-yl)-1,4-dihydropyrimidin-4-one (302),  
1-(2,6-diethylphenyl)-6-hydroxy-2-(2-methyl-1,3-thiazol-4-yl)-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one (303),  
25 5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-1-(2,6-diethylphenyl)-6-hydroxy-2-(1-methyl-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one (304),  
1-(2,6-diethylphenyl)-5-[3-(2-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(1-methyl-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one (305),  
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- 5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-1-(2,6-diethylphenyl)-6-hydroxy-2-(4-methyl-1,3-thiazol-2-yl)-1,4-dihydropyrimidin-4-one (306),
- 1-(2,6-diethylphenyl)-5-[3-(3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(4-methyl-1,3-thiazol-2-yl)-1,4-dihydropyrimidin-4-one (307),
- 1-(2,6-diethylphenyl)-2-(1-ethyl-1H-pyrazol-3-yl)-5-[3-(3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one (308),
- 1-(2,6-diethylphenyl)-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-2-(1-ethyl-1H-pyrazol-3-yl)-6-hydroxy-1,4-dihydropyrimidin-4-one (309),
- 10 1-(2,6-diethylphenyl)-2-(1-ethyl-1H-pyrazol-4-yl)-5-[3-(2-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one (310),
- 5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-1-(2,6-diethylphenyl)-2-(1-ethyl-1H-pyrazol-3-yl)-6-hydroxy-1,4-dihydropyrimidin-4-one (311),
- 5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-1-(2,6-diethylphenyl)-6-hydroxy-2-(4-methyl-1,3-thiazol-2-yl)-1,4-dihydropyrimidin-4-one (312),
- 5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-1-(2,6-diethylphenyl)-2-(1-ethyl-1H-pyrazol-4-yl)-6-hydroxy-1,4-dihydropyrimidin-4-one (313),
- 2-(4-fluoro-3-methylphenyl)-6-hydroxy-1-[(1S)-1-phenylpropyl]-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one (314),
- 20 1-(2,6-diethylphenyl)-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-2-(1-ethyl-1H-pyrazol-4-yl)-6-hydroxy-1,4-dihydropyrimidin-4-one (315),
- 2-(1-cyclopropyl-1H-pyrazol-3-yl)-1-(2,6-diethylphenyl)-6-hydroxy-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one (316),
- 25 1-(2,6-diethylphenyl)-6-hydroxy-2-[1-(2-methylpropyl)-1H-pyrazol-3-yl]-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one (317),
- 1-(2,6-diethylphenyl)-5-[3-(5-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-2-[1-(2-methylpropyl)-1H-pyrazol-3-yl]-1,4-dihydropyrimidin-4-one (318),
- 2-(1-cyclopropyl-1H-pyrazol-3-yl)-1-(2,6-diethylphenyl)-5-[3-(3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one (319),
- 30 1-(2,6-diethylphenyl)-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-2-[1-(2-methylpropyl)-1H-pyrazol-3-yl]-1,4-dihydropyrimidin-4-one (320),



- 5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(4-methyl-1,3-thiazol-2-yl)-1-[(1S)-1-phenylpropyl]-1,4-dihydropyrimidin-4-one (321),
- 5-[3-(5-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(4-methyl-1,3-thiazol-2-yl)-1-[(1S)-1-phenylpropyl]-1,4-dihydropyrimidin-4-one (322),
- 5 5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(4-methyl-1,3-thiazol-2-yl)-1-[(1S)-1-phenylpropyl]-1,4-dihydropyrimidin-4-one (323),
- 5-[3-(2-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(4-methyl-1,3-thiazol-2-yl)-1-[(1S)-1-phenylpropyl]-1,4-dihydropyrimidin-4-one (324),
- 2-(1-cyclopropyl-1H-pyrazol-3-yl)-1-(2,6-diethylphenyl)-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one (325),
- 10 5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-1-[(1S)-1-(3,5-difluorophenyl)-2-methylpropyl]-2-(1-ethyl-1H-pyrazol-3-yl)-6-hydroxy-1,4-dihydropyrimidin-4-one (326),
- 15 1-[(1S)-1-(3,5-difluorophenyl)-2-methylpropyl]-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-2-(1-ethyl-1H-pyrazol-3-yl)-6-hydroxy-1,4-dihydropyrimidin-4-one (327),
- 2-(1-cyclopropyl-1H-pyrazol-3-yl)-1-(2,6-diethylphenyl)-5-[3-(5-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one (328),
- 20 6-hydroxy-3-[(1R)-2-methoxy-1-phenylethyl]-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-2-propyl-3,4-dihydropyrimidin-4-one (329),
- 6-hydroxy-3-[(1R)-2-methoxy-1-phenylethyl]-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-2-propyl-3,4-dihydropyrimidin-4-one (330),
- 3-[(1S)-1-{2-butyl-4-hydroxy-6-oxo-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-1,6-dihydropyrimidin-1-yl}propyl]benzonitrile (331),
- 25 3-[(1S)-1-{2-butyl-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-4-hydroxy-6-oxo-1,6-dihydropyrimidin-1-yl}propyl]benzonitrile (332),
- 3-[(1S)-1-{2-butyl-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-4-hydroxy-6-oxo-1,6-dihydropyrimidin-1-yl}propyl]benzonitrile (333),
- 30 3-[(1S)-1-{4-hydroxy-6-oxo-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-2-[(propan-2-yloxy)methyl]-1,6-dihydropyrimidin-1-yl}propyl]benzonitrile (334),

- 3-[(1S)-1-{2-butyl-5-[3-(5-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-4-hydroxy-6-oxo-1,6-dihydropyrimidin-1-yl}propyl]benzonitrile (335),
- 3-[(1S)-1-{2-butyl-5-[3-(5-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-4-hydroxy-6-oxo-1,6-dihydropyrimidin-1-yl}propyl]benzonitrile (336),
- 5 3-[(S)-{2-butyl-5-[3-(5-chloropyridin-2-yl)pyrrolidine-1-carbonyl]-4-hydroxy-6-oxo-1,6-dihydropyrimidin-1-yl}(cyclopropyl)methyl]benzonitrile (337),
- 3-[(S)-{2-butyl-5-[3-(5-chloropyridin-2-yl)pyrrolidine-1-carbonyl]-4-hydroxy-6-oxo-1,6-dihydropyrimidin-1-yl}(cyclopropyl)methyl]benzonitrile (338),
- 3-[(1S)-1-{2-butyl-5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-4-hydroxy-6-oxo-1,6-dihydropyrimidin-1-yl}propyl]benzonitrile (339),
- 10 2-butyl-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-3-[(1S)-1-(3-methoxyphenyl)propyl]-3,4-dihydropyrimidin-4-one (340),
- 2-butyl-5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-3-[(1S)-1-(3,5-difluorophenyl)propyl]-6-hydroxy-3,4-dihydropyrimidin-4-one (341),
- 15 2-butyl-5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-3-[(1S)-1-(3,5-difluorophenyl)propyl]-6-hydroxy-3,4-dihydropyrimidin-4-one (342),
- 2-butyl-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-3-[(1S)-1-phenylpropyl]-3,4-dihydropyrimidin-4-one (343),
- 2-butyl-5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-3-[(1S)-1-phenylpropyl]-3,4-dihydropyrimidin-4-one (344),
- 20 2-butyl-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-3-[(1S)-1-phenylpropyl]-3,4-dihydropyrimidin-4-one (345),
- 2-butyl-5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-3-[(1S)-1-phenylpropyl]-3,4-dihydropyrimidin-4-one (346),
- 25 2-butyl-3-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-3,4-dihydropyrimidin-4-one (347),
- 2-butyl-3-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-3,4-dihydropyrimidin-4-one (348),
- 2-butyl-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-3-[(1R)-2-methoxy-1-phenylethyl]-3,4-dihydropyrimidin-4-one (349),
- 30 2-butyl-5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-3-[(1R)-2-methoxy-1-phenylethyl]-3,4-dihydropyrimidin-4-one (350),

- 3-[(S)-{2-butyl-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-4-hydroxy-6-oxo-1,6-dihydropyrimidin-1-yl}(cyclopropyl)methyl]benzonitrile (351),
- 2-butyl-5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-3-[(1R)-2-methoxy-1-phenylethyl]-3,4-dihydropyrimidin-4-one (352),
- 5 5-[3-(2,6-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-6-hydroxy-1,4-dihydropyrimidin-4-one (353),
- 5-[3-(2,6-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-6-hydroxy-1,4-dihydropyrimidin-4-one (354),
- 2-butyl-5-(4-(2,3-dichlorobenzyl)piperazine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-6-hydroxypyrimidin-4(1H)-one (355),
- 10 2-butyl-5-(3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-6-hydroxypyrimidin-4(1H)-one (356),
- 2-butyl-5-(3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-6-hydroxypyrimidin-4(1H)-one (357),
- 15 2-butyl-5-(3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-6-hydroxypyrimidin-4(1H)-one (358),
- 2-butyl-5-(3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-6-hydroxypyrimidin-4(1H)-one (359),
- 5-(3-(2,4-difluorophenyl)pyrrolidine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-6-hydroxypyrimidin-4(1H)-one (360),
- 20 5-(3-(2,4-difluorophenyl)pyrrolidine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-6-hydroxypyrimidin-4(1H)-one (361),
- 2-(1-(1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-6-hydroxy-4-oxo-1,4-dihydropyrimidine-5-carbonyl)pyrrolidin-3-yl)benzonitrile (362),
- 25 2-(1-(1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-6-hydroxy-4-oxo-1,4-dihydropyrimidine-5-carbonyl)pyrrolidin-3-yl)benzonitrile (363),
- 2-(1-(2-butyl-1-(2,6-dimethoxyphenyl)-6-hydroxy-4-oxo-1,4-dihydropyrimidine-5-carbonyl)pyrrolidin-3-yl)benzonitrile (364),
- 2-(1-(2-butyl-1-(2,6-dimethoxyphenyl)-6-hydroxy-4-oxo-1,4-dihydropyrimidine-5-carbonyl)pyrrolidin-3-yl)benzonitrile (365),
- 30 2-butyl-1-(2,6-dimethoxyphenyl)-5-(3-(3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl)-6-hydroxypyrimidin-4(1H)-one (366),

- 2-butyl-1-(2,6-dimethoxyphenyl)-5-(3-(3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl)-6-hydroxypyrimidin-4(1H)-one (367),
- 2-(1-(2-(tert-butoxy methyl)-1-(2,6-dimethoxyphenyl)-6-hydroxy-4-oxo-1,4-dihydropyrimidine-5-carbonyl)pyrrolidin-3-yl)benzonitrile (368),
- 5 2-(1-(2-(tert-butoxy methyl)-1-(2,6-dimethoxyphenyl)-6-hydroxy-4-oxo-1,4-dihydropyrimidine-5-carbonyl)pyrrolidin-3-yl)benzonitrile (369),
- 2-butyl-1-(2,6-dimethoxyphenyl)-5-(3-(5-fluoropyridin-2-yl)pyrrolidine-1-carbonyl)-6-hydroxypyrimidin-4(1H)-one (370),
- 2-butyl-1-(2,6-dimethoxyphenyl)-5-(3-(5-fluoropyridin-2-yl)pyrrolidine-1-carbonyl)-6-hydroxypyrimidin-4(1H)-one (371),
- 10 5-(3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-6-hydroxypyrimidin-4(1H)-one (372),
- 2-butyl-5-(4-(4-chlorophenoxy)piperidine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-6-hydroxypyrimidin-4(1H)-one (373),
- 15 1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-5-(4-(4-fluorobenzyl)piperidine-1-carbonyl)-6-hydroxypyrimidin-4(1H)-one (374),
- 5-(4-(4-chlorobenzyl)piperidine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-6-hydroxypyrimidin-4(1H)-one (375),
- (S)-5-(3-(benzyloxy)pyrrolidine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-6-hydroxypyrimidin-4(1H)-one (376),
- 20 5-(4-(4-chlorophenoxy)piperidine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-6-hydroxypyrimidin-4(1H)-one (377),
- 5-(4-(2-chloro-5-fluorophenoxy)piperidine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-6-hydroxypyrimidin-4(1H)-one (378),
- 25 1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-5-(4-(2-fluorophenyl)piperidine-1-carbonyl)-6-hydroxypyrimidin-4(1H)-one (379),
- 2-butyl-1-(2,6-dimethoxyphenyl)-6-hydroxy-5-(4-(4-(trifluoromethyl)benzyl)piperidine-1-carbonyl)pyrimidin-4(1H)-one (380),
- 2-butyl-5-(4-(4-(tert-butyl)phenoxy)piperidine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-6-hydroxypyrimidin-4(1H)-one (381),
- 30 2-butyl-5-(4-(2-chlorophenoxy)piperidine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-6-hydroxypyrimidin-4(1H)-one (382),

- 2-butyl-5-(4-(2-chloro-3-fluorophenoxy)piperidine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-6-hydroxypyrimidin-4(1H)-one (383),  
2-butyl-5-(4-(2-chloro-3-fluorophenoxy)piperidine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-6-hydroxypyrimidin-4(1H)-one (384),  
5 2-butyl-5-(4-(2-chloro-5-fluorophenoxy)piperidine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-6-hydroxypyrimidin-4(1H)-one (385),  
2-butyl-5-(4-(2-chloro-3,5-difluorophenoxy)piperidine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-6-hydroxypyrimidin-4(1H)-one (386),  
2-butyl-5-(4-(2,3-difluorophenoxy)piperidine-1-carbonyl)-1-(2,6-  
10 dimethoxyphenyl)-6-hydroxypyrimidin-4(1H)-one (387),  
2-butyl-5-(4-(2,3-difluorobenzyl)piperazine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-6-hydroxypyrimidin-4(1H)-one (388).

The invention may be embodied in other specific forms without departing from  
15 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  
20 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.

25 In another embodiment, the compounds of the present invention have  $EC_{50}$  values  $\leq 10 \mu M$ , using the APJ hcAMP assay disclosed herein, preferably,  $EC_{50}$  values  $\leq 5 \mu M$ , more preferably,  $EC_{50}$  values  $\leq 1 \mu M$ , even more preferably,  $EC_{50}$  values  $\leq 0.5 \mu M$ , even more preferably,  $EC_{50}$  values  $\leq 0.1 \mu M$ , even more preferably,  $EC_{50}$  values  $\leq 0.01 \mu M$ .

In another aspect, the present invention provides compounds selected from any  
30 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<sub>50</sub> potency range is B.

In another aspect, the present invention provides compounds selected from the subset in which the APJ hcAMP EC<sub>50</sub> potency range is C.

5

## 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.

10 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.

15 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.

20 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.

25 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,  $\beta$ -adrenergic receptor blocker, angiotensin II receptor blocker, diuretic, aldosterone antagonist and digitalis compound.

30 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  $\beta$ -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.

5 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  
10 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  
15 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  
20 receptor antagonists, angiotensin receptor blockers, calcium channel blockers,  $\beta$ -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  
25 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.

30 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,  $\beta$ -blockers, diuretics, mineralocorticoid receptor antagonists, renin inhibitors, calcium channel blockers, angiotensin II receptor antagonists, nitrates, digitalis compounds, inotropic agents.

5 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.

10 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

15 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.

20 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

25 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

30 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<sub>1</sub> to C<sub>12</sub> alkyl" or "C<sub>1-12</sub> alkyl" (or alkylene), is intended to include C<sub>1</sub>, C<sub>2</sub>, C<sub>3</sub>, C<sub>4</sub>, C<sub>5</sub>, C<sub>6</sub>, C<sub>7</sub>, C<sub>8</sub>, C<sub>9</sub>, C<sub>10</sub>, C<sub>11</sub> and C<sub>12</sub> alkyl groups; "C<sub>4</sub> to C<sub>18</sub> alkyl" or "C<sub>4-18</sub> alkyl" (or alkylene), is intended to include C<sub>4</sub>, C<sub>5</sub>, C<sub>6</sub>, C<sub>7</sub>, C<sub>8</sub>, C<sub>9</sub>, C<sub>10</sub>, C<sub>11</sub>, C<sub>12</sub>, C<sub>13</sub>, C<sub>14</sub>, C<sub>15</sub>, C<sub>16</sub>, C<sub>17</sub>, and C<sub>18</sub> alkyl groups. Additionally, for example, "C<sub>1</sub> to C<sub>6</sub> alkyl" or "C<sub>1-6</sub> 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<sub>0</sub> alkyl" or "C<sub>0</sub> 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<sub>2</sub> to C<sub>6</sub> alkenyl" or "C<sub>2-6</sub> alkenyl" (or alkenylene), is intended to include C<sub>2</sub>, C<sub>3</sub>, C<sub>4</sub>, C<sub>5</sub>, and C<sub>6</sub> 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<sub>2</sub> to C<sub>6</sub> alkynyl" or "C<sub>2-6</sub> alkynyl" (or alkynylene), is intended to include C<sub>2</sub>, C<sub>3</sub>, C<sub>4</sub>, C<sub>5</sub>, and C<sub>6</sub> 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<sub>1</sub> to C<sub>6</sub> alkoxy" or "C<sub>1-6</sub> alkoxy" (or alkyloxy), is intended to include C<sub>1</sub>, C<sub>2</sub>, C<sub>3</sub>, C<sub>4</sub>, C<sub>5</sub>, and C<sub>6</sub> 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<sub>1-6</sub> haloalkoxy", is intended to include C<sub>1</sub>, C<sub>2</sub>, C<sub>3</sub>, C<sub>4</sub>, C<sub>5</sub>, and C<sub>6</sub> haloalkoxy groups. Examples of haloalkoxy include, but are not limited to, trifluoromethoxy, 2,2,2-trifluoroethoxy, and pentafluoroethoxy. 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<sub>3</sub> to C<sub>6</sub> cycloalkyl" or "C<sub>3-6</sub> cycloalkyl" is intended to include C<sub>3</sub>, C<sub>4</sub>, C<sub>5</sub>, and C<sub>6</sub> 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<sub>4-6</sub> cycloalkenyl is intended to include

C<sub>4</sub>, C<sub>5</sub>, and C<sub>6</sub> 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<sub>6-10</sub> 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)<sub>p</sub>, 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, azetidiny, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazoliny, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazoliny, carbazolyl, 4aH-carbazolyl, carboliny, chromanyl, chromenyl, cinnoliny, decahydroquinoliny, 2H,6H-1,5,2-dithiaziny, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazany, imidazolidiny, imidazoliny, imidazolyl, 1H-indazolyl, imidazolopyridiny, indoleny, indoliny, indoliziny, indoly, 3H-indoly, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindoliny, isoindoly, isoquinoliny, isothiazolyl, isothiazolopyridiny, isoxazolyl, isoxazolopyridiny, methylenedioxyphenyl, morpholiny, naphthyridiny, octahydroisoquinoliny, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidiny, oxazolyl, oxazolopyridiny, oxazolidiny, oxazolidiny, perimidiny, oxindoly, pyrimidiny, phenanthridiny, phenanthroliny,

phenaziny, phenothiaziny, phenoxathiiny, phenoxaziny, phthalaziny, piperaziny, piperidiny, piperidony, 4-piperidony, piperony, pteridiny, puriny, pyran, pyraziny, pyrazolidiny, pyrazoliny, pyrazolopyridiny, pyrazoly, pyridaziny, pyridooxazoly, pyridoimidazoly, pyridothiazoly, pyridiny, pyrimidiny, pyrrolidiny, pyrroliny, 5 2-pyrrolidony, 2*H*-pyrroly, pyrroly, quinazoliny, quinoliny, 4*H*-quinoliziny, quinoxaliny, quinuclidiny, tetrazoly, tetrahydrofurany, tetrahydroisoquinoliny, tetrahydroquinoliny, 6*H*-1,2,5-thiadiaziny, 1,2,3-thiadiazoly, 1,2,4-thiadiazoly, 1,2,5-thiadiazoly, 1,3,4-thiadiazoly, thianthreny, thiazoly, thieny, thiazolopyridiny, thienothiazoly, thienooxazoly, thienimidazoly, thiopheny, triaziny, 1,2,3-triazoly, 10 1,2,4-triazoly, 1,2,5-triazoly, 1,3,4-triazoly, and xantheny. 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, pyridiny, furany, thieny, pyrroly, pyrazoly, pyraziny, piperaziny, piperidiny, imidazoly, imidazolidiny, indoly, tetrazoly, isoxazoly, morpholiny, oxazoly, 15 oxadiazoly, oxazolidiny, tetrahydrofurany, thiadiaziny, thiadiazoly, thiazoly, triaziny, triazoly, benzimidazoly, 1*H*-indazoly, benzofurany, benzothiofurany, benzotetrazoly, benzotriazoly, benzisoxazoly, benzoxazoly, oxindoly, benzoxazolidiny, benzthiazoly, benzisothiazoly, isatinoy, isoquinoliny, octahydroisoquinoliny, tetrahydroisoquinoliny, tetrahydroquinoliny, isoxazolopyridiny, quinazoliny, 20 quinoliny, isothiazolopyridiny, thiazolopyridiny, oxazolopyridiny, imidazolopyridiny, and pyrazolopyridiny.

Examples of 5- to 6-membered heterocycles include, but are not limited to, pyridiny, furany, thieny, pyrroly, pyrazoly, pyraziny, piperaziny, piperidiny, imidazoly, imidazolidiny, indoly, tetrazoly, isoxazoly, morpholiny, oxazoly, 25 oxadiazoly, oxazolidiny, tetrahydrofurany, thiadiaziny, thiadiazoly, thiazoly, triaziny, and triazoly. 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 30 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).

5           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  
10       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,  
15       1,2,3,4-tetrahydro-quinoxalyl, 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,  
20       isoquinolyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrrolyl, 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  
25       substituent, if defined). The nitrogen and sulfur heteroatoms may optionally be oxidized (*i.e.*, N→O and S(O)<sub>p</sub>, 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,  
30       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  
5 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<sup>+</sup>), potassium (K<sup>+</sup>), ammonium (R<sub>n</sub>NH<sub>m</sub><sup>+</sup> where n=0-4 and m=0-4) and the like.

10 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, R<sub>4</sub>-M and R<sub>7</sub>-M, a nucleophile, a hydrazine  
15 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,  
20 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  
25 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,  
30 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).

5 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.

10 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.

15 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.

20 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  
25 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  
30 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

- 5 hydrolyzable esters of compounds of formula I include C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkylbenzyl, 4-methoxybenzyl, indanyl, phthalyl, methoxymethyl, C<sub>1-6</sub> alkanoyloxy-C<sub>1-6</sub>alkyl (*e.g.*, acetoxymethyl, pivaloyloxymethyl or propionyloxymethyl), C<sub>1-6</sub>alkoxycarbonyloxy-C<sub>1-6</sub>alkyl (*e.g.*, methoxycarbonyl-oxyethyl or ethoxycarbonyloxymethyl, glycyloxymethyl, phenylglycyloxymethyl, 10 (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 15 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 20 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. Deuterium has one proton and one neutron in its nucleus and that has twice the mass of ordinary hydrogen. Deuterium can be represented by symbols such as "<sup>2</sup>H" or "D". The term "deuterated" herein, by itself or used to modify 25 a compound or group, refers to replacement of one or more hydrogen atom(s), which is attached to carbon(s), with a deuterium atom. Isotopes of carbon include <sup>13</sup>C and <sup>14</sup>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 30 non-labeled reagent otherwise employed. Such compounds have a variety of potential uses, *e.g.*, as standards and reagents in determining the ability of a potential

pharmaceutical compound to bind to target proteins or receptors, or for imaging compounds of this invention bound to biological receptors *in vivo* or *in vitro*.

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, "1H" for proton, "δ" for delta, "s" for singlet, "d" for doublet, "t" for triplet, "q" for quartet, "m" for multiplet, "br" for broad, "Hz" for hertz, and "α", "β", "R", "S", "E", "Z" and "ee" are stereochemical designations familiar to one skilled in the art.

|              |              |
|--------------|--------------|
| AcOH or HOAc | acetic acid  |
| ACN          | acetonitrile |

|                                 |                                                                           |
|---------------------------------|---------------------------------------------------------------------------|
| Alk                             | Alkyl                                                                     |
| AlMe <sub>3</sub>               | Trimethylaluminum                                                         |
| BBr <sub>3</sub>                | boron tribromide                                                          |
| Bn                              | benzyl                                                                    |
| Boc                             | <i>tert</i> -butoxycarbonyl                                               |
| BOP reagent                     | benzotriazol-1-yloxytris(dimethylamino)phosphonium<br>hexafluorophosphate |
| Bu                              | butyl                                                                     |
| <i>i</i> -Bu                    | isobutyl                                                                  |
| <i>t</i> -Bu                    | <i>tert</i> -butyl                                                        |
| <i>t</i> -BuOH                  | <i>tert</i> -butanol                                                      |
| Cbz                             | carbobenzyloxy                                                            |
| CDCl <sub>3</sub>               | deutero-chloroform                                                        |
| CD <sub>3</sub> OD              | deutero-methanol                                                          |
| CH <sub>2</sub> Cl <sub>2</sub> | dichloromethane                                                           |
| CH <sub>3</sub> CN              | acetonitrile                                                              |
| CHCl <sub>3</sub>               | chloroform                                                                |
| DCM                             | dichloromethane                                                           |
| DIEA, DIPEA or<br>Hunig's base  | diisopropylethylamine                                                     |
| DMF                             | dimethyl formamide                                                        |
| DMSO                            | dimethyl sulfoxide                                                        |
| Et                              | ethyl                                                                     |
| Et <sub>3</sub> N or TEA        | triethylamine                                                             |
| Et <sub>2</sub> O               | diethyl ether                                                             |
| EtOAc                           | ethyl acetate                                                             |
| EtOH                            | ethanol                                                                   |
| HCl                             | hydrochloric acid                                                         |
| HPLC                            | high-performance liquid chromatography                                    |
| K <sub>2</sub> CO <sub>3</sub>  | potassium carbonate                                                       |
| K <sub>2</sub> HPO <sub>4</sub> | potassium hydrogenphosphate                                               |
| LCMS                            | liquid chromatography mass spectrometry                                   |

|                                    |                                           |
|------------------------------------|-------------------------------------------|
| LiHMDS                             | lithium bis(trimethylsilyl)amide          |
| LG                                 | leaving group                             |
| Me                                 | methyl                                    |
| MeOH                               | methanol                                  |
| MgSO <sub>4</sub>                  | magnesium sulfate                         |
| MsOH or MSA                        | methylsulfonic acid                       |
| NaCl                               | sodium chloride                           |
| Na <sub>2</sub> CO <sub>3</sub>    | sodium carbonate                          |
| NaHCO <sub>3</sub>                 | sodium bicarbonate                        |
| NaOH                               | sodium hydroxide                          |
| Na <sub>2</sub> SO <sub>4</sub>    | sodium sulfate                            |
| NH <sub>3</sub>                    | ammonia                                   |
| NH <sub>4</sub> Cl                 | ammonium chloride                         |
| NH <sub>4</sub> OAc                | ammonium acetate                          |
| Pd(OAc) <sub>2</sub>               | palladium(II) acetate                     |
| Pd(PPh <sub>3</sub> ) <sub>4</sub> | tetrakis(triphenylphosphine)palladium(0)  |
| PG                                 | protecting group                          |
| Ph                                 | phenyl                                    |
| Pr                                 | propyl                                    |
| <i>i</i> -Pr                       | isopropyl                                 |
| <i>i</i> -PrOH or IPA              | isopropanol                               |
| Rt                                 | retention time                            |
| SiO <sub>2</sub>                   | silica oxide                              |
| SFC                                | supercritical fluid chromatography        |
| TEA                                | triethylamine                             |
| TFA                                | trifluoroacetic acid                      |
| TFAA                               | Trifluoroacetic anhydride                 |
| THF                                | tetrahydrofuran                           |
| TiCl <sub>4</sub>                  | titanium tetrachloride                    |
| T <sub>3</sub> P                   | 1-propanephosphonic acid cyclic anhydride |

The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or by variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. The reactions are performed in a solvent or solvent mixture appropriate to the reagents and materials employed and suitable for the transformations being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention.

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.

## SYNTHESIS

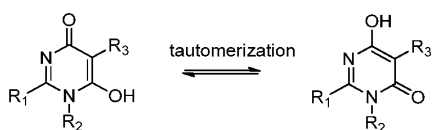
The compounds of Formula (I) may be prepared by the exemplary processes described in the following schemes and working examples, as well as relevant published literature procedures that are used by one skilled in the art. Exemplary reagents and procedures for these reactions appear hereinafter and in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

5 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<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> are as defined above, this disclosure is intended to cover all possible tautomers even when a structure depicts only one of them.



10 Description of Analytical LCMS methods:

Method A: Column: Waters Acquity UPLC BEH C18, 2.1 x 50 mm, 1.7  $\mu$ m particles; Mobile Phase A: 5:95 ACN:water with 10 mM NH<sub>4</sub>OAc; Mobile Phase B: 95:5 ACN:water with 10 mM NH<sub>4</sub>OAc; Temperature: 50 °C; Gradient: 0-100% B over 3 minutes, then a 0.75 minute hold at 100% B; Flow: 1.11 mL/min; Detection: UV at 220 nm.

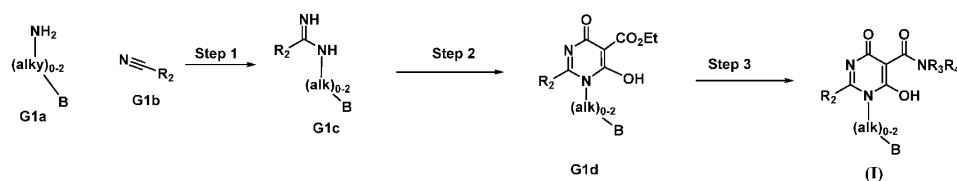
Method B: Column: Waters Acquity UPLC BEH C18, 2.1 x 50 mm, 1.7  $\mu$ m particles; Mobile Phase A: 5:95 ACN:water with 0.1% TFA; Mobile Phase B: 95:5 ACN:water with 0.1% TFA; Temperature: 50 °C; Gradient: 0-100% B over 3 minutes, then a 0.75 minute hold at 100% B; Flow: 1.11 mL/min; Detection: UV at 220 nm.

20 Method C: Column: PHENOMENEX<sup>®</sup> Luna 3  $\mu$ m C18 (2.0 x 30 mm); Mobile Phase A: 10:90 MeOH:water with 0.1% TFA; Mobile Phase B: 90:10 MeOH:water with 0.1% TFA; Gradient: 0-100% B over 2 minutes, then a 1 minute hold at 100% B; Flow: 1 mL/min; Detection: UV at 220 nm.

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

Generic Schemes

Scheme 1



Step 1 describes the preparation of compounds of Formula G1c from a compound of Formula G1a, by acylating with a nitriles of Formula G1b in the presence of a Lewis acid (like  $\text{AlMe}_3$  or  $\text{TMSOTf}$ ). Preferred solvents are aprotic solvents (such as toluene and the like).

Step 2 describes the preparation of pyrimidine compounds of Formula G1d from compounds of formula G1c by condensation with triethyl methanetricarboxylate with or without base. Preferred solvents are aprotic solvents (like toluene and xylenes). Preferred bases are tertiary amines (such as TEA, DIEA and the like) and alkaline metal alkoxides (such as sodium ethoxide and the like). The condensation may also be accomplished with  $\text{TMSCl}$  in preferred solvents such as 1,2-dichloroethane.

Step 3 describes the preparation of compounds of Formula (I) by conversion of the ester of compounds of Formula G1d to an amide ( $\text{NR}_3\text{R}_4$ ). The conversion of compounds of Formula G1d to compounds of Formula (I) can be accomplished from the amine ( $\text{NR}_3\text{R}_4$ ) in the presence of a Lewis acid (for example,  $\text{AlMe}_3$  or  $\text{Zr}(\text{OtBu})_4$ ) with or without the addition of a coupling agent (for example,  $\text{HOAt}$ ) in solvents such as toluene.

#### 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<sub>50</sub> 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  $\beta$ -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  
5 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  
10 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 its 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  
15 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  
20 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  
25 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  
30 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.

## A. ASSAY METHODS

## 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  $\mu$ M 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<sub>50</sub> 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<sub>50</sub> 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<sub>50</sub> 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; buccally; 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.

5 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  
10 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  
15 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  
20 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,  
25 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  
30 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,  $\beta$ -blockers, diuretics, mineralocorticoid receptor antagonists, renin inhibitors,



calcium channel blockers, angiotensin II receptor antagonists, nitrates, digitalis compounds, inotropic agents and  $\beta$ -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, ciprofibrate, gemfibrozil, vitamin B<sub>6</sub>, vitamin B<sub>12</sub>, anti-oxidant vitamins, anti-diabetes agents, platelet aggregation inhibitors, fibrinogen receptor antagonists, aspirin and fibric acid derivatives.

10           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

15   chlorpropamide, tolbutamide, acetohexamide, tolazamide, glyburide, glipizide, 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 PPAR $\alpha$ , PPAR $\beta$  and PPAR $\gamma$ ; dehydroepiandrosterone (also referred to as DHEA or its conjugated sulphate ester,

20   DHEA-SO<sub>4</sub>); anti-glucocorticoids; TNF $\alpha$  inhibitors; dipeptidyl peptidase IV (DPP4) inhibitor (such as sitagliptin, saxagliptin), GLP-1 agonists or analogs (such as exenatide),  $\alpha$ -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

25   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,  $\beta_3$ -adrenergic receptor agonist agents; sibutramine,

30   gastrointestinal lipase inhibitors (such as orlistat), and leptins. Other agents used in treating obesity or obesity-related disorders include neuropeptide Y, enterostatin, cholecystokinin, bombesin, amylin, histamine H<sub>3</sub> receptors, dopamine D<sub>2</sub> 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  
5 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  
10 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  
15 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  
20 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  
25 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  
30 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.

- 5 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,  
10 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  
15 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  
20 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  
25 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  
30 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.

- 5 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  
10 (*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  
15 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  
20 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  
25 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).

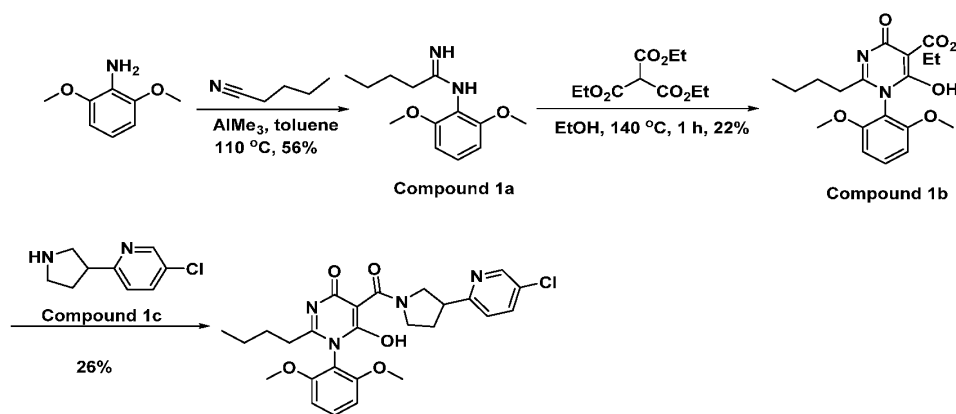
- Other features of the invention will become apparent in the course of the  
30 following descriptions of exemplary embodiments that are given for illustration of the invention and are not intended to be limiting thereof.

## VI. EXAMPLES

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

## Example 1

- 10 2-Butyl-5-(3-(5-chloropyridin-2-yl)pyrrolidine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-6-hydroxypyrimidin-4(1H)-one



## Example 1

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

- 15 To a solution of pentanenitrile (310 mg, 3.7 mmol) and 2-methoxy-6-methylaniline (518 mg, 3.40 mmol) in toluene (13 mL) at RT was added a solution of trimethylaluminum in toluene (1.7 mL, 3.4 mmol) at 0 °C. The reaction mixture was heated at 110 °C for 1 h. The cooled reaction mixture was quenched with saturated solution of Rochelle's salt (5 mL) and stirred at RT for 30 min. The reaction mixture was
- 20 extracted with EtOAc (3x20 mL). The combined organic layer was washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 20-100% EtOAc/hexanes with 0.5% Et<sub>3</sub>N to give Compound 1a (450 mg, 56%) as a brown oil. LCMS (Method D) retention

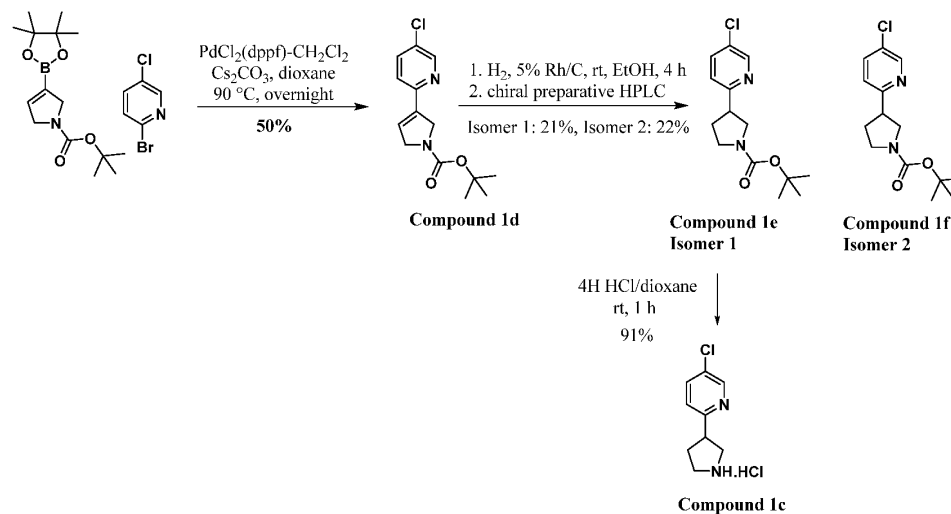
time = 0.65 min,  $m/z$  = 237.1 (M+H).  $^1\text{H}$  NMR (500MHz, chloroform- $d$ )  $\delta$  6.88 (t,  $J$ =8.4 Hz, 1H), 6.51 (d,  $J$ =8.3 Hz, 2H), 4.68 - 3.89 (m, 2H), 3.71 (s, 6H), 2.33 (br. s., 2H), 1.84 - 1.52 (m, 2H), 1.49 - 1.24 (m, 2H), 0.89 (br. s., 3H).

5 Compound 1b. Ethyl 2-butyl-1-(2, 6-dimethoxyphenyl)-6-hydroxy-4-oxo-1,4-dihydropyrimidine-5-carboxylate

A mixture of 1a (500 mg, 2.1 mmol) and triethyl methanetricarboxylate (590 mg, 2.5 mmol) in toluene (12 mL) was heated at 140 °C for 1 h in a microwave reactor. The reaction mixture was concentrated under reduced pressure and the residue was purified by  
 10 silica gel chromatography eluting with 0-100% EtOAc/DCM to give Compound 1b (170 mg, 22%) as a brown solid. LCMS (Method D) retention time = 0.87 min,  $m/z$  = 377.3 (M+H).  $^1\text{H}$  NMR (400MHz, chloroform- $d$ )  $\delta$  7.39 (t,  $J$ =8.5 Hz, 1H), 6.65 (d,  $J$ =8.6 Hz, 2H), 4.40 (q,  $J$ =7.2 Hz, 2H), 3.78 (s, 6H), 2.49 - 2.18 (m, 2H), 1.70 - 1.53 (m, 2H), 1.39 (t,  $J$ =7.2 Hz, 3H), 1.29 - 1.12 (m, 2H), 0.79 (t,  $J$ =7.3 Hz, 3H).

15

Compound 1c. 5-Chloro-2-(pyrrolidin-3-yl)pyridine



Compound 1d. *tert*-Butyl 3-(5-chloropyridin-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate

20 A mixture of *tert*-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate (commercially available, 106 mg, 0.360 mmol), 2-bromo-5-chloropyridine (76 mg, 0.40 mmol), cesium carbonate (350 mg, 1.10 mmol) and

PdCl<sub>2</sub>(dppf)-CH<sub>2</sub>Cl<sub>2</sub> (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 1d (50 mg, 0.18 mmol, 50 % yield) as a yellow solid. <sup>1</sup>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).

Compounds 1e and 1f. *tert*-Butyl 3-(5-chloropyridin-2-yl)pyrrolidine-1-carboxylate  
A mixture of 1d (530 mg, 1.90 mmol) and 5% Rh/C (390 mg, 0.190 mmol) in EtOH (8 mL) was stirred under hydrogen atmosphere (balloon) 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<sub>2</sub>; flow condition: 85 mL/min, 150 bar, 40 °C; wavelength: 220 nm) to give Compound 1e (designated as Isomer 1, 110 mg, 21% yield). Peak 1 retention time = 11.87 and Compound 1f (designated as Isomer 2, 118 mg, 22% yield). Peak 2 retention time = 13.24 (Chiralpak IC, 4.6 x 250 mm, 5 micron; mobile phase: 10% IPA/0.1%DEA/90% CO<sub>2</sub>; 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). <sup>1</sup>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).

Compound 1c. *tert*-Butyl 3-(5-chloropyridin-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate (HCl salt)

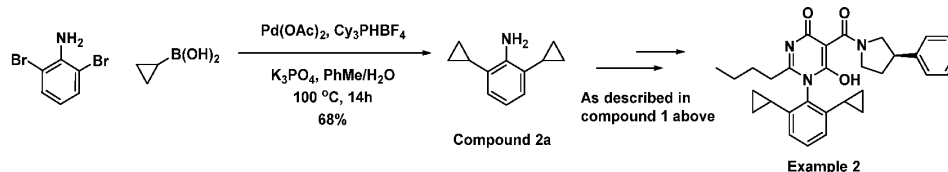
Compound 1e (110 mg, 0.38 mmol) and 4N HCl/dioxane (1.0 mL, 4.0 mmol) was stirred at rt for 5 h. The mixture was diluted with diethyl ether, and the solid was collected by filtration to give Compound 1c (89 mg, 0.35 mmol, 91 % yield) as a white solid. LCMS (Method B) Rt = 0.47 min, *m/z* = 183.1 (M+H). <sup>1</sup>H NMR (500MHz, DMSO-d<sub>6</sub>) 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 1. 2-Butyl-5-(3-(5-chloropyridin-2-yl)pyrrolidine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-6-hydroxypyrimidin-4(1H)-one

A mixture of Compound 1b (15 mg, 0.040 mmol), Compound 1c (10 mg, 0.040 mmol) and DIEA (0.021 mL, 0.12 mmol) were dissolved in EtOH (0.5 mL) was heated at 160 °C for 1.5 h. Example 1 was isolated by prep HPLC (5.3 mg, 10 µmol, 26 % yield). <sup>1</sup>H NMR (500MHz, DMSO-d<sub>6</sub>) δ 8.55 (br. s., 1H), 7.92 - 7.77 (m, 1H), 7.52 - 7.27 (m, 2H), 6.83 (br. s., 2H), 3.99 - 3.45 (m, 5H), 2.51 (br. s., 6H), 2.22 (br. s., 4H), 1.42 (br. s., 2H), 1.22 - 1.10 (m, 2H), 0.70 (d, J=6.3 Hz, 3H). LCMS retention time = 0.78 min, (M+H)<sup>+</sup> = 513.3. (BEH C18, 1.5x50 mm, flow rate 2 mL/min, 1 min gradient with 2-98% ACN/water/ 0.2% TFA). Human APJ cAMP EC<sub>50</sub> potency range A.

### Example 2

(R)-2-Butyl-1-(2,6-dicyclopropylphenyl)-6-hydroxy-5-(3-phenylpyrrolidine-1-carbonyl)pyrimidin-4(1H)-one



### Example 2a. 2,6-Dicyclopropylaniline

A mixture of 2,6-dibromoaniline (0.50 g, 2.0 mmol), cyclopropylboronic acid (0.70 g, 8.0 mmol), potassium phosphate (1.7 g, 8.0 mmol) and tricyclohexylphosphine (0.11 g, 0.40 mmol) in toluene (5 mL) and water (2 mL) was degassed with nitrogen then palladium acetate (0.12 g, 0.52 mmol) was added. The mixture was heated at 100 °C for 14 h. The reaction mixture was allowed to cool and ethyl acetate was added and the resulting mixture was washed with water, brine, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified on silica gel chromatography eluting with 0-50% EtOAc/hexane to give Compound 2a (240 mg, 68%) as a yellow oil. LCMS (Method D) retention time = 0.80 min, *m/z* = 174.2 (M+H). <sup>1</sup>H NMR (400MHz, DMSO-d<sub>6</sub>) δ 6.84 (d, J=7.7 Hz, 2H), 6.71 - 6.62 (m, 1H), 1.82 (tt, J=8.3, 5.4 Hz, 2H), 0.99 - 0.91 (m, 4H), 0.64 - 0.53 (m, 4H).



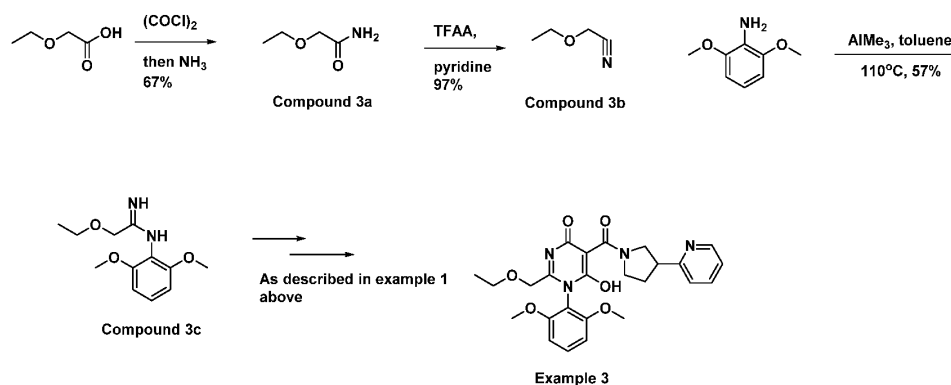
Example 2. (R)-2-Butyl-1-(2,6-dicyclopropylphenyl)-6-hydroxy-5-(3-phenylpyrrolidine-1-carbonyl)pyrimidin-4(1H)-one

Example 2 was prepared from Compound 2a following a similar procedure as described for Compound 1 (39% yield) as a clear oil. LCMS (Method A) retention time = 1.05 min,  $m/z$  = 498.2 (M+H).  $^1\text{H}$  NMR (400MHz, chloroform- $d$ )  $\delta$  7.37 - 7.11 (m, 6H), 6.80 (d,  $J$ =7.3 Hz, 2H), 3.95 - 3.22 (m, 4H), 2.39 - 2.24 (m, 3H), 2.08 - 1.92 (m, 1H), 1.72 (br. s., 3H), 1.43 (br. s., 2H), 1.31 - 1.17 (m, 3H), 0.91 - 0.57 (m, 11H). Human APJ cAMP Potency range A.

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### Example 3

1-(2,6-Dimethoxyphenyl)-2-(ethoxymethyl)-6-hydroxy-5-(3-(pyridin-2-yl)pyrrolidine-1-carbonyl)pyrimidin-4(1H)-one



15

#### Compound 3a. 2-Ethoxyacetamide

To a stirred solution of 2-ethoxyacetic acid (1.5 g, 14 mmol) in DCM (20 mL) at 0 °C was added oxalyl chloride (8.65 mL, 17.3 mmol), followed by DMF (2 drops). Cooling was removed and the reaction mixture was stirred at RT for 3h. The reaction mixture was concentrated under reduced pressure and dissolved in DCM (20 mL). Ammonia (20.6 mL, 144 mmol) (7 M in MeOH) was added carefully and the reaction mixture stirred for 16h. The reaction mixture was concentrated under reduced pressure, dissolved in DCM, filtered and washed with DCM. The filtrate was concentrated under reduced pressure to give Compound 3a (1.0 g, 67%) as a white solid.  $^1\text{H}$  NMR (500MHz,

20

CDCl<sub>3</sub>)  $\delta$  6.51 (br s, 1H), 5.46 (br s, 1H), 3.94 (s, 2H), 3.59 (q, J = 6.8 Hz, 2H), 1.25 (t, J = 7.2 Hz, 3H).

Compound 3b. 2-Ethoxyacetonitrile

- 5 To a stirred solution of Compound 3a (1.0 g, 9.7 mmol) in THF (10 mL) at 0 °C was added pyridine (1.57 mL, 19.4 mmol) followed by TFAA (6.85 mL, 48.5 mmol). The reaction mixture was stirred at RT for 1h. Aqueous NaHCO<sub>3</sub> solution was added carefully to the reaction mixture until pH = 8 was attained. The reaction mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2X). The combined organic layers were washed with 1N HCl, dried over
- 10 MgSO<sub>4</sub>, filtered and concentrated in vacuo to give Compound 3b (0.80 g, 97%) as a yellow liquid. <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta$  4.24 (s, 2H), 3.66 (q, J = 6.9 Hz, 2H), 1.27 (t, J = 6.9 Hz, 3H).

Compound 3c. N-(2,6-Dimethoxyphenyl)-2-ethoxyacetimidamide

- 15 Trimethylaluminum (2 M in toluene, 4.70 ml, 9.40 mmol) was added dropwise to a solution of 2,6-dimethoxyaniline (1.2 g, 7.8 mmol) and Compound 3b (0.80 g, 9.4 mmol) in toluene (10 ml) while cooling in an ice bath. After addition was complete, the reaction mixture was heated to 110 °C and was stirred at this temperature for 14h. The reaction mixture was allowed to cool and was partitioned between a saturated solution of
- 20 Rochelle's salt and EtOAc. The organic phase was separated, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was added to a silica gel (120 g) column and was eluted with 0-20% of 20% MeOH/DCM in 0.5% TEA/DCM to give Compound 3c (1.1 g, 57%) as a brown liquid. MS  $m/z$  = 239.0 (M+H). <sup>1</sup>H NMR (500MHz, CDCl<sub>3</sub>)  $\delta$  7.01(t, J = 8.3 Hz, 1H), 6.62 (d, J = 7.7 Hz, 2H), 5.32 (s, 2H), 4.88
- 25 (br s, 2H), 4.31 (s, 2H), 3.82 (s, 6H), 3.62-3.73 (m, 2H), 1.19-1.33 (m, 3H).

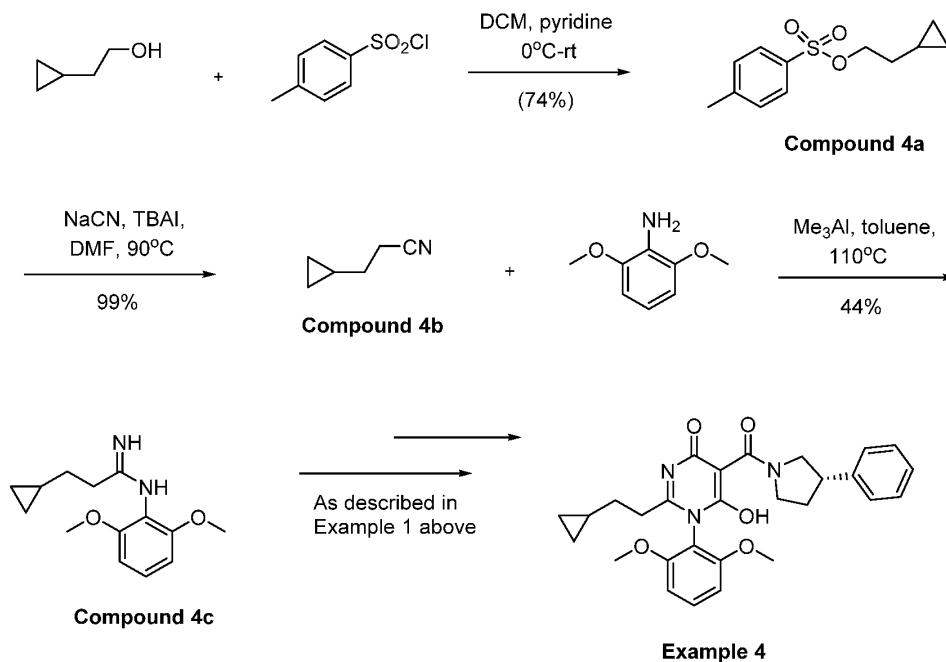
Example 3.

- Example 3 was prepared from Compound 3c following a similar procedure as described for example 1 (1.2 mg, 1%) as a colorless film. LCMS (Method A) retention
- 30 time = 1.15 min,  $m/z$  = 505.9 (M+H). <sup>1</sup>H NMR (500MHz, DMSO-d<sub>6</sub>)  $\delta$  7.87 (d, J = 7.9 Hz, 1H), 7.78 (d, J = 8.5 Hz, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.43 (t, J = 7.9 Hz, 1H), 7.42

(t,  $J = 7.0$  Hz, 1H), 6.81 (d,  $J = 8.5$  Hz, 2H), 4.80 (s, 2H), 3.95 (s, 2H), 3.76 (s, 6H), 3.33 (q,  $J = 6.7$  Hz, 2H), 1.01 (t,  $J = 6.7$  Hz, 3H). Human APJ cAMP Potency range A.

#### Example 4

- 5 (S)-2-(2-Cyclopropylethyl)-1-(2,6-dimethoxyphenyl)-6-hydroxy-5-(3-phenylpyrrolidine-1-carbonyl)pyrimidin-4(1H)-one



Compound 4a. 2-Cyclopropylethyl 4-methylbenzenesulfonate

- 10 To 2-cyclopropylethanol at 0 °C (0.98 g, 11 mmol) and pyridine (2.4 mL, 30 mmol) in DCM (15 mL) was added 4-methylbenzene-1-sulfonyl chloride (22 g, 11 mmol). The cold bath was removed and the mixture allowed to warm to room temperature for 14 h. The reaction mixture was diluted with water and Et<sub>2</sub>O and the phases were separated. The organic phase was washed sequentially with water, 10% aqueous HCl and brine, dried (MgSO<sub>4</sub>) filtered and concentrated under reduced pressure to give Compound 4a (2.0 g, 74%) as a clear colorless oil. Compound 4a was used in the next step without further purification. MS  $m/z = 241.4$  (M+H). <sup>1</sup>H NMR (400MHz, chloroform-d)  $\delta$  7.77 (d,  $J=8.1$  Hz, 2H), 7.32 (d,  $J=8.4$  Hz, 2H), 4.06 (t,  $J=6.7$  Hz, 2H),
- 15

2.42 (s, 3H), 1.56 - 1.45 (m, 2H), 0.70 - 0.57 (m, 1H), 0.44 - 0.32 (m, 2H), 0.04 - -0.10 (m, 2H).

Compound 4b. 3-Cyclopropylpropanenitrile

5 To a solution of Compound 4a (1.0 g, 4.2 mmol) in DMF (5 mL) was added NaCN (0.60 g, 13 mmol) and TBAI (0.06 g, 0.2 mmol) and the reaction mixture was stirred at 90°C for 14h. The reaction mixture was allowed to cool to room temperature, diluted with Et<sub>2</sub>O and brine and the phases were separated. The organic phase was washed with 10% aqueous LiCl, dried over MgSO<sub>4</sub>, filtered and concentrated under  
10 reduced pressure to give Compound 4b (0.39 g, 99%) as a clear colorless oil, which was used in the next step without further purification. <sup>1</sup>H NMR (chloroform-d) δ 2.27 (t, J=7.2 Hz, 2H), 1.34-1.46 (m, 2H), 0.62-0.74 (m, 1H), 0.34-0.45 (m, 2H), -0.05-0.04 (m, 2H).

Compound 4c. 3-Cyclopropyl-N-(2,6-dimethoxyphenyl)propanimidamide

15 To a mixture of Compound 4b (0.37 g, 3.9 mmol) and 2,6-dimethoxyaniline (0.5 g, 3 mmol) in toluene (5 mL), at 0°C, was added a 2M solution of trimethylaluminum in hexane (2 ml, 4 mmol) dropwise. The reaction mixture was allowed to warm to room temperature and heated at 110°C overnight. The reaction mixture was allowed to cool to RT and quenched with saturated aqueous Rochelle's salt and EtOAc. The phases were  
20 separated, the aqueous phase was extracted with EtOAc. The organic phases were combined and washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 0 to 30% MeOH/0.5% TEA in DCM to give Compound 4c (0.35 g, 44 % yield) as an orange oil. MS *m/z* = 249.4 (M+H). <sup>1</sup>H NMR (methanol-d<sub>4</sub>) δ 7.01 (t, J=8.3 Hz, 1H), 6.64  
25 (d, J=8.3 Hz, 2H), 2.29-2.48 (m, 2H), 1.50-1.67 (m, 2H), 0.78-0.93 (m, 1H), 0.44 (s, 2H), 0.02-0.16 (m, 2H).

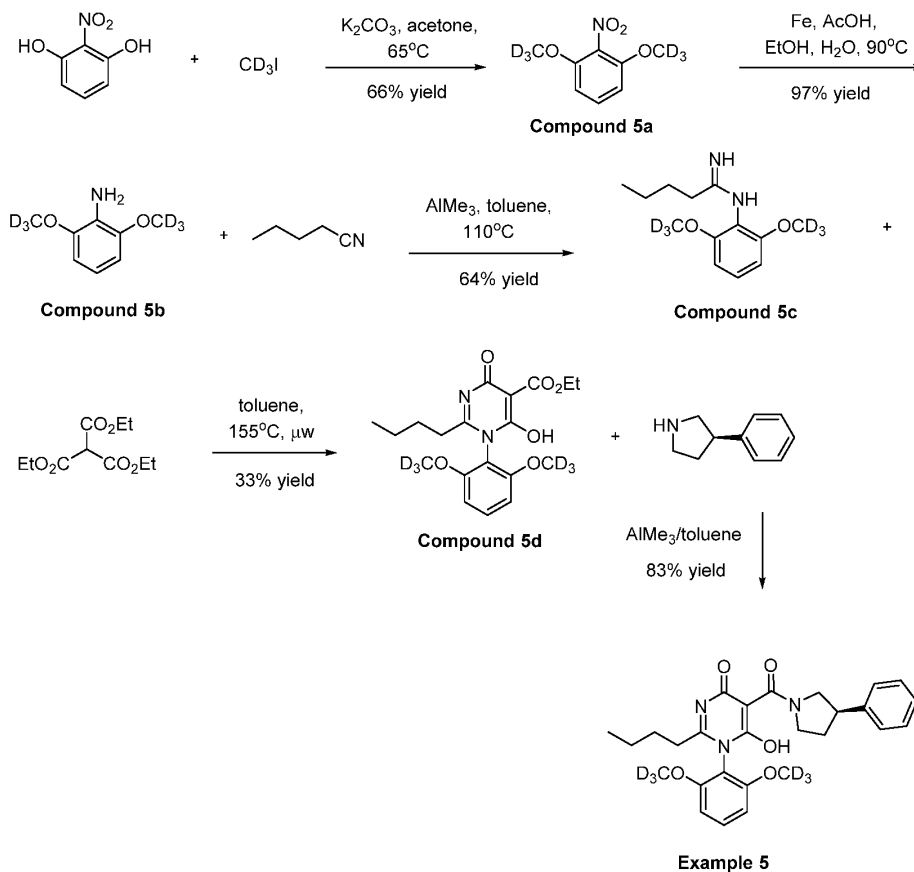
Example 4.

30 Example 4 was prepared from Compound 4c following a similar procedure as described for example 1 (15 mg, 59%) as a colorless film. LCMS (Method A) retention time = 1.42 min, *m/z* = 490.3 (M+H). <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 7.22-7.29 (m, 1H), 7.06-7.21 (m, 4H), 6.70-6.83 (m, 2H), 3.18-3.88 (m, 14H), 2.27-2.36 (m, 3H), 2.12-

2.23 (m, 1H), 1.83-1.99 (m, 1H), 0.85 (dd, J=5.85, 15.44 Hz, 6H). Human APJ cAMP Potency range A.

### Example 5

5 (R)-1-(2,6-Bis(methoxy-d<sub>3</sub>)phenyl)-2-butyl-6-hydroxy-5-(3-phenylpyrrolidine-1-carbonyl)pyrimidin-4(1H)-one



Compound 5a. 1,3-Di[<sup>2</sup>H<sub>3</sub>]methoxy-2-nitrobenzene

10 To a solution of 2-nitrobenzene-1,3-diol (1.75, 11.0 mmol) in acetone (175 mL) was added methyl-d<sub>3</sub> iodide (4.9 g, 34 mmol) and K<sub>2</sub>CO<sub>3</sub> (3.1 g, 23 mmol). The reaction mixture was stirred at 65 °C for 14h. After cooling to RT, the mixture was concentrated under reduced pressure. The residue was diluted with water and extracted with EtOAc (3x). The combined extracts were washed with brine, dried over MgSO<sub>4</sub>, filtered and

concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 0 to 80% EtOAc/hexanes to give Compound 5a (1.4 g, 66%) as a light yellow foam. MS  $m/z$  = 190.4 (M+H).  $^1\text{H}$  NMR (chloroform- $d$ )  $\delta$  7.25 (t,  $J=8.5$  Hz, 1H), 6.55 (d,  $J=8.4$  Hz, 2H).

5

Compound 5b. 2,6-Di[ $^2\text{H}_3$ ]methoxyaniline

To a solution of Compound 5a (1.4 g, 7.5 mmol) in a mixture of AcOH (40 mL), EtOH (40 mL) and  $\text{H}_2\text{O}$  (20 mL) was added iron (2.5 g, 45 mmol) portionwise and the reaction mixture was stirred at 90 °C for 14 h. The reaction mixture was allowed to cool to RT, poured onto ice, basified carefully with the addition of solid  $\text{Na}_2\text{CO}_3$  and extracted with EtOAc (3X). The combined organic extracts were washed with brine, dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure to give Compound 5b (1.2 g, 97%) as a dark solid. Compound 5a was used without further purification. MS  $m/z$  = 160.4 (M+H).

15

Compound 5c. N-(2,6-Di[ $^2\text{H}_3$ ]methoxyphenyl)pentanimidamide

To a mixture of Compound 4b (1.2 g, 7.2 mmol) and pentanenitrile (0.72 g, 8.6 mmol) in toluene (11 mL) at 0 °C was added 2M trimethylaluminum in hexane (4.3 mL, 8.6 mmol) dropwise. The reaction mixture was allowed to warm to room temperature and was heated at 100 °C for 14 h. The reaction mixture was allowed to cool to RT and quenched with saturated aqueous Rochelle's salt and EtOAc. The phases were separated and the aqueous phase was extracted with EtOAc. The organic phases were combined and washed with brine, dried ( $\text{MgSO}_4$ ), filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 0 to 30% MeOH/0.5% TEA in DCM to give Compound 5c (1.1 g, 64%) as an orange oil. MS  $m/z$  = 243.4 (M+H).  $^1\text{H}$  NMR (methanol- $d_4$ )  $\delta$  7.01 (t,  $J=8.3$  Hz, 1H), 6.64 (d,  $J=8.4$  Hz, 2H), 2.22-2.34 (m, 2H), 1.60-1.72 (m, 2H), 1.40-1.53 (m, 2H), 0.96 (t,  $J=6.7$  Hz, 3H).

25

Compound 5d. Ethyl 2-butyl-1-(2,6-di[ $^2\text{H}_3$ ]methoxyphenyl)-6-hydroxy-4-oxo-1,4-dihydropyrimidine-5-carboxylate

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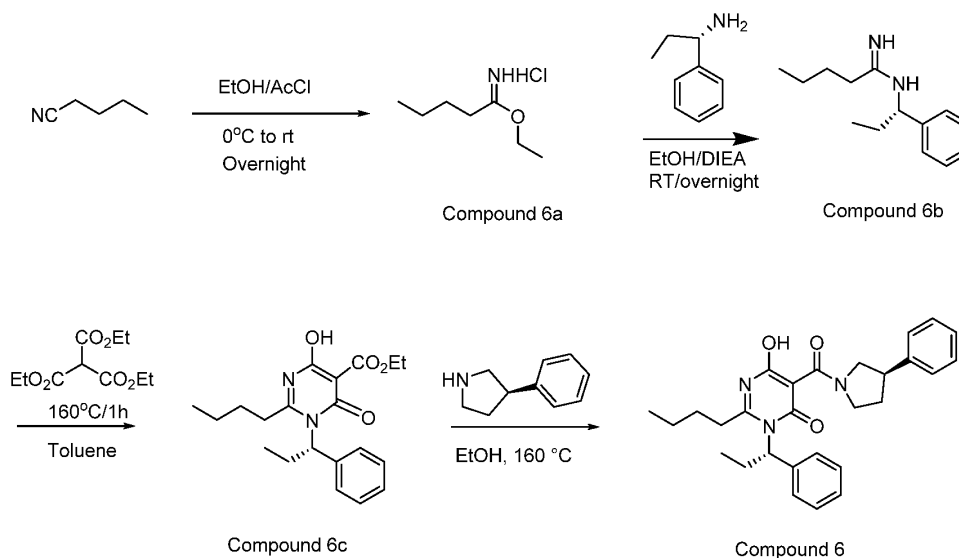
A solution of Compound 5c (0.35 g, 1.4 mmol) and triethyl methanetricarboxylate (0.50 g, 2.2 mmol) in toluene (10 mL) was heated at 155 °C in a microwave reactor for 15

min. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 0 to 100% EtOAc/hexanes to give Compound 5d (0.18 g, 33%) as a pale yellow solid. MS  $m/z$  = 383.4 (M+H).  $^1\text{H}$  NMR (methanol- $d_4$ )  $\delta$  7.88 (t,  $J$ =8.5 Hz, 1H), 7.22 (d,  $J$ =8.3 Hz, 2H), 4.73 (q,  $J$ =7.1 Hz, 2H), 2.75 (t,  $J$ =7.7 Hz, 2H), 1.88-1.97 (m, 2H), 1.72 (t,  $J$ =7.2 Hz, 3H), 1.56-1.65 (m, 2H), 1.16 (t,  $J$ =7.4 Hz, 3H)

Example 5. (R)-1-(2,6-Bis(methoxy- $d_3$ )phenyl)-2-butyl-6-hydroxy-5-(3-phenylpyrrolidine-1-carbonyl)pyrimidin-4(1H)-one

Compound 5 was prepared by the general procedures described in Example 1 (21 mg, 83%). LCMS (Method A)  $R_t$  = 1.44 min,  $m/z$  = 484.0 (M+H).  $^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  7.22-7.29 (m, 1H), 7.06-7.21 (m, 4H), 6.70-6.83 (m, 2H), 3.18-3.88 (m, 14H), 2.27-2.36 (m, 3H), 2.12-2.23 (m, 1H), 1.83-1.99 (m, 1H), 0.85 (dd,  $J$ =5.85, 15.44 Hz, 6H) Human APJ cAMP Potency range A.

Example 6. 2-butyl-6-hydroxy-3-((S)-1-phenylpropyl)-5-((R)-3-phenylpyrrolidine-1-carbonyl)pyrimidin-4(3H)-one



Compound 6a. Ethyl pentanimidate hydrochloride

Pentanenitrile (9 mL, 90 mmol) in EtOH (59.9 mL, 1030 mmol) was cooled to 0°C by ice bath. AcCl (48.64 mL, 685.0 mmol) was added dropwise over 3 hours. After complete addition, the reaction mixture was stirred at room temperature for 14h. The resulting solution was concentrated under reduced pressure and the residue washed with Et<sub>2</sub>O (2 x) to remove residual HCl. The solid was suspended in 200 ml of Et<sub>2</sub>O and stored at 4°C for 14h. Compound 6a (14 g, 85 mmol, 99 % yield) was obtained by filtration as a white solid. <sup>1</sup>H NMR (400MHz, CHLOROFORM-d) δ 4.64 (d, *J*=6.6 Hz, 2H), 2.74 (t, *J*=7.5 Hz, 2H), 1.87 - 1.64 (m, 2H), 1.49 (t, *J*=6.2 Hz, 3H), 1.45 - 1.38 (m, 2H), 0.95 (t, *J*=7.3 Hz, 3H).

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Compound 6b. (S)-N-(1-phenylpropyl)pentanimidamide

To a solution of Compound 6a (1.35 g, 8.15 mmol) in Ethanol (15 mL) was added (S)-1-phenylpropan-1-amine (0.918 g, 6.79 mmol) at 0°C. The reaction mixture was stirred from 0°C to room temperature for 14h, followed by addition of ammonia in MeOH (14.55 mL, 102.0 mmol) and was stirred at room temperature for 2 hours. The reaction mixture was concentrated and the residual was dissolved in MeOH and purified by prep HPLC. The fractions containing Compound 6b were collected and concentrated under reduced pressure. The residue was dissolved in DCM and washed with 1N NaOH. The combined organic layer was washed with brine and concentrated to Compound 6b (710mg, 3.25 mmol, 47.9 % yield) as colorless oil. MS *m/z* = 219 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400MHz, CHLOROFORM-d) δ 7.29 - 7.05 (m, 5H), 4.41 (br. s., 1H), 2.23 - 2.05 (m, 2H), 1.91 - 1.62 (m, 2H), 1.55 - 1.38 (m, 2H), 1.27 (sxt, *J*=7.4 Hz, 2H), 0.83 (td, *J*=7.4, 2.0 Hz, 6H).

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Compound 6c. (S)-ethyl 2-butyl-4-hydroxy-6-oxo-1-(1-phenylpropyl)-1,6-dihydropyrimidine-5-carboxylate

A mixture of Compound 6b (710 mg, 3.25 mmol), triethyl methanetricarboxylate (1.241 mL, 5.85 mmol) and Toluene (15 mL) was heated at 160°C for 1 hour in microwave reactor. The mixture was cooled to room temperature and loaded onto a 40 g ISCO column eluted with 0-70% EtOAc/DCM for 30min. The desired fraction was collected and concentrated to give Compound 6c (580 mg, 1.27 mmol, 39.0 % yield). MS *m/z* = 359.3 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400MHz, METHANOL-d<sub>4</sub> at 333K) δ 7.43 - 7.35 (m, 2H), 7.33 - 7.26 (m, 3H), 6.26 (br. s., 1H), 4.43 - 4.30 (m, 2H), 2.75 - 2.51 (m, 3H), 2.47 - 2.24

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(m, 1H), 1.67 - 1.51 (m, 1H), 1.40 - 1.28 (m, 4H), 1.26 - 1.13 (m, 2H), 1.04 (t,  $J=7.4$  Hz, 3H), 0.79 (t,  $J=7.4$  Hz, 3H).  $^{13}\text{C}$  NMR (101MHz, METHANOL- $d_4$  at 333K)  $\delta$  171.0, 169.5, 162.5, 140.7, 130.1, 128.7, 127.7, 93.0, 62.9, 60.3, 36.1, 30.4, 30.3, 25.7, 23.3, 14.6, 13.9, 11.5.

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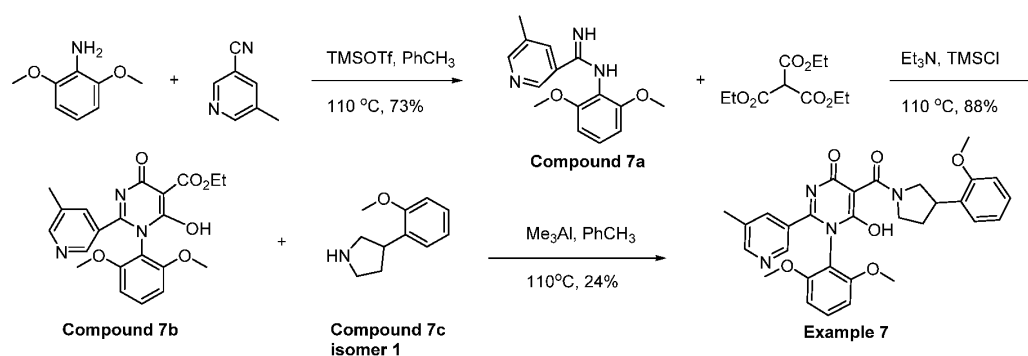
Compound 6. 2-Butyl-6-hydroxy-3-((S)-1-phenylpropyl)-5-((R)-3-phenylpyrrolidine-1-carbonyl)pyrimidin-4(3H)-one

To a solution of Compound 6c (50 mg, 0.139 mmol) and (R)-3-phenylpyrrolidine, HCl (33.3 mg, 0.181 mmol) in Ethanol (1 mL) was added DIEA (0.073 mL, 0.418 mmol). The mixture was stirred in microwave reactor at 160°C for 1 hour. The crude sample was diluted with MeOH and purified with prep HPLC (4 injections) : Phenomenex AXIA Luna 75 x 30mm 5u: A: 10% ACN - 90% H<sub>2</sub>O -10mM TFA B: 90% ACN - 10% H<sub>2</sub>O - 10mM TFA wavelength 254 nm; flow rate 40 mL/min; gradient time 10 min; 0 to 100% B. Compound 6 (31 mg, 0.067 mmol, 48.4 % yield) was obtained. LCMS (Method A) Rt = 1.75 min, MS  $m/z$  = 460.1  $[\text{M}+\text{H}]^+$ .  $^1\text{H}$  NMR (400MHz, CHLOROFORM- $d$  at 333K)  $\delta$  7.40 - 7.08 (m, 10H), 6.11 (br. s., 1H), 3.88 - 3.09 (m, 5H), 2.81 - 2.22 (m, 5H), 2.00 (quin,  $J=10.1$  Hz, 1H), 1.69 (br. s., 1H), 1.58 - 1.38 (m, 1H), 1.27 (d,  $J=6.4$  Hz, 2H), 1.04 (t,  $J=7.4$  Hz, 3H), 0.84 (t,  $J=6.7$  Hz, 3H).

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#### Example 7

1-(2,6-dimethoxyphenyl)-6-hydroxy-5-(3-(2-methoxyphenyl)pyrrolidine-1-carbonyl)-2-(5-methylpyridin-3-yl)pyrimidin-4(1H)-one



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## Compound 7a. N-(2,6-dimethoxyphenyl)-5-methylnicotinimidamide

To a solution of 2,6-dimethoxyaniline (0.51 g, 3.3 mmol) and 5-methylnicotinonitrile (0.39 g, 3.3 mmol) in toluene (10 ml) at 0 °C was added dropwise TMS-OTf (1.2 ml, 6.5 mmol). The resulting mixture was stirred at 0 °C for 10 min and heated to 110 °C for 2 days. The reaction mixture was cooled to 0 °C, quenched with 1N HCl (10 mL) solution and diluted with EtOAc. The organic layer was washed with 1N HCl solution and dried over sodium sulfate, decanted and concentrated to give a brown oil. The residue was added to a silica gel (40 g) column and was eluted with 0-100% 1% Et<sub>3</sub>N/EtOAc in DCM. Collected fractions to give Compound 7a (0.65 g, 73 % yield) as an off white solid.

MS m/z = 272.2 (M+H). <sup>1</sup>H NMR (500MHz, CHLOROFORM-d) δ 8.90 (s, 1H), 8.56 (s, 1H), 8.24 (s, 1H), 7.07 (t, J = 8.3 Hz, 1H), 6.68 (d, J = 8.3 Hz, 2H), 4.76 (br s, 2H), 3.84 (s, 6H), 2.43 (s, 3H).

## Compound 7b. ethyl 1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(5-methylpyridin-3-yl)-4-oxo-1,4-dihydropyrimidine-5-carboxylate

To a mixture of Compound 7a (75 mg, 0.28 mmol) and triethyl methanetricarboxylate (96 mg, 0.42 mmol) in Et<sub>3</sub>N (1.5 mL, 11 mmol) was added TMSCl (0.53 mL, 4.2 mmol) at 0 °C. The mixture was stirred for 10 min and heated to 110 °C for 20 hrs. The reaction mixture was concentrated in vacuo and diluted with EtOAc. The organic layer was washed with 0.1M HCl. The organic layer was dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo. The residue was added to a silica gel (12 g) column and was eluted with 0-100% EtOAc in hexanes, then 0-100% 1% TEA/EtOAc in DCM. Collected fractions to give Compound 7b (100 mg, 88 % yield) as a yellow solid. MS m/z = 412.2 (M+H). <sup>1</sup>H NMR (500MHz, CHLOROFORM-d) δ 8.37 (s, 1H), 8.34 (s, 1H), 7.57 (s, 1H), 7.24 (t, J = 8.5 Hz, 1H), 6.47 (d, J = 8.5 Hz, 2H), 4.76 (br s, 2H), 3.84 (s, 6H), 2.43 (s, 3H).

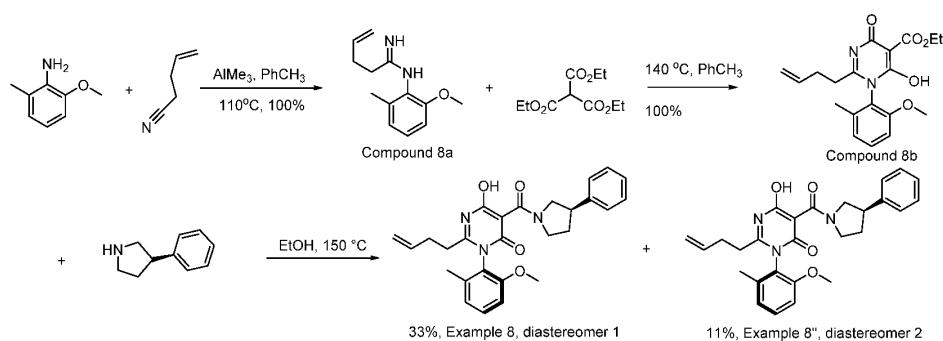
## Example 7. 1-(2,6-dimethoxyphenyl)-6-hydroxy-5-(3-(2-methoxyphenyl)pyrrolidine-1-carbonyl)-2-(5-methylpyridin-3-yl)pyrimidin-4(1H)-one

To a stirred mixture of Compound 7b (12 mg, 0.029 mmol) and Compound 7c, isomer 1 (6.7 mg, 0.038 mmol) in toluene (1 ml) was added trimethylaluminum (0.029 ml, 0.058 mmol) dropwise. The reaction mixture was heated at 110 °C for 3 hrs. The reaction mixture was concentrated in vacuo and diluted with EtOAc/THF. The organic layer was washed with sat NH<sub>4</sub>Cl. The organic layer was dried over MgSO<sub>4</sub>, filtered and

concentrated in vacuo. The residue was purified via preparative LC/MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5- $\mu$ m 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: 5-45% B over 19 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min. Fractions containing the desired product were combined and dried via centrifugal evaporation to give Example 7 (3.7 mg, 24%). LCMS (Method A)  $R_t$  = 1.37 min,  $m/z$  = 543.1 (M+H).  $^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  8.27-8.29 (m, 1H), 8.13-8.16 (m, 1H), 7.41-7.43 (m, 1H), 7.28 (t,  $J$  = 7.2 Hz, 1H), 7.19-7.26 (m, 2H), 6.96-7.01 (m, 1H), 6.89-6.92 (m, 1H), 6.53-6.61 (m, 2H), 3.76-3.85 (m, 6H), 3.65-3.70 (m, 3H), 3.37-3.63 (m, 5H), 2.17 (s, 3H), 2.11-2.15 (m, 1H), 1.92-2.02 (m, 1H). Human APJ cAMP Potency range A.

#### Example 8

(R)-2-(but-3-en-1-yl)-6-hydroxy-3-(2-methoxy-6-methylphenyl)-5-(3-phenylpyrrolidine-1-carbonyl)pyrimidin-4(3H)-one, diastereomer 1 and diastereomer 2



Compound 8a. N-(2-methoxy-6-methylphenyl)pent-4-enimidamide trimethylaluminum (6.6 ml, 13 mmol) was added dropwise to a solution of 2-methoxy-6-methylaniline (1.5 g, 11 mmol) and pent-4-enitrile (1.1 g, 13 mmol) in Toluene (10 ml) while cooling in an ice bath. After addition was complete, the reaction mixture was heated to 110 °C for 16 hrs. The reaction mixture was allowed to cool to RT and partitioned between saturated solution of Rochelle's salt and EtOAc. The organic phase was dried, filtered and concentrated. The residue was added to a silica gel (120 g) column and was eluted with 0-20% 0.5% Et<sub>3</sub>N/DCM in 20% MeOH/DCM. Collected fractions to give Compound 8a (2.4 g, 100 % yield) as an off white solid. MS  $m/z$  = 219.1 (M+H).  $^1\text{H}$  NMR (500MHz, CHLOROFORM- $d$ )  $\delta$  6.93 (t,  $J$  = 7.7 Hz, 1H), 6.83 (d,  $J$  = 7.4 Hz, 1H), 6.78 (d,  $J$  = 8.0

Hz, 1H), 5.94-6.06 (m, 1H), 5.16 (d, J = 17.1 Hz, 1H), 5.07 (d, J = 9.9 Hz, 1H), 4.27 (br s, 2H), 3.79 (s, 3H), 2.53-2.59 (m, 2H), 2.45-2.53 (m, 2H), 2.14 (s, 3H).

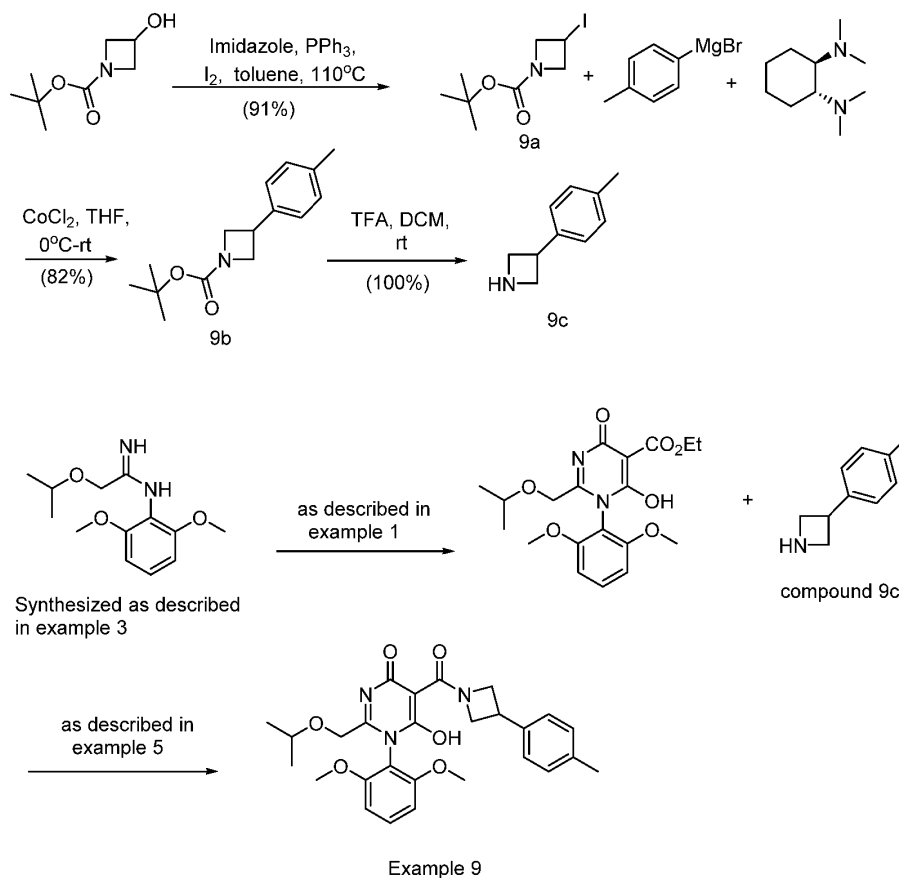
Compound 8b. ethyl 2-(but-3-en-1-yl)-6-hydroxy-1-(2-methoxy-6-methylphenyl)-4-oxo-1,4-dihydropyrimidine-5-carboxylate

- 5 A mixture of Compound 8a (15 mg, 0.069 mmol), acetic acid (7.9  $\mu$ l, 0.14 mmol) and triethyl methanetricarboxylate (32 mg, 0.14 mmol) in toluene (1ml) was heated at 140 °C for 105 min in a microwave reactor. The reaction mixture was concentrated in vacuo. The residue was added to a silica gel (12 g) column and was eluted with 20-100% EtOAc in hexanes. Collected fractions to give Compound 8b (24 mg, 100 % yield) as a clear liquid. MS  $m/z$  = 359.1 (M+H). <sup>1</sup>H NMR (500MHz, CHLOROFORM-*d*)  $\delta$  7.33 (t, J = 8.3 Hz, 1H), 6.94 (d, J = 7.4 Hz, 1H), 6.86 (d, J = 8.3 Hz, 1H), 5.67-5.75 (m, 1H), 4.93-4.98 (m, 2H), 4.42 (q, J = 7.2 Hz, 2H), 3.77 (s, 3H), 2.29-2.48 (m, 4H), 2.09 (s, 3H), 1.39 (t, J = 7.2 Hz, 3H).
- 10

- Example 8 and Example 8'' were prepared from compound 8b following a similar procedure as described for compound 1. The residue was purified via preparative LC/MS with the following conditions: Column: XBridge C18, 19 x 200 mm, 5- $\mu$ m particles; Mobile Phase A: 5:95 acetonitrile: water with 10- $\mu$ M ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10- $\mu$ M ammonium acetate; Gradient: 15-55% B over 20 minutes, then a 5-minute hold at 100% B; Flow: 20 mL/min. The first eluting fraction was collect and the stereochemistry was assigned as Example 8 (11 mg, 33%). LCMS (Method A)  $R_t$  = 1.36 min,  $m/z$  = 460.4 (M+H). <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  7.21-7.41 (m, 6H), 6.95-7.08 (m, 2H), 5.67-5.76 (m, 1H), 4.87-4.98 (m, 2H), 3.64-3.81 (m, 5H), 3.27-3.47 (3H), 2.18-2.34 (m, 5H), 1.90-2.06 (m, 4H). Human APJ cAMP Potency range A.
- 20

- 25 The second eluting fraction was collect and the stereochemistry was assigned as Example 8'' (3.4 mg, 11%). LCMS (Method A)  $R_t$  = 1.37 min,  $m/z$  = 460.4 (M+H). <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  7.20-7.41 (m, 6H), 6.95-7.07 (m, 2H), 5.65-5.77 (m, 1H), 4.88-4.97 (m, 2H), 3.63-3.79 (m, 5H), 3.28-3.52 (3H), 2.19-2.34 (m, 5H), 1.89-2.06 (m, 4H). Human APJ cAMP Potency range A.

- 30 Example 9. 1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(isopropoxymethyl)-5-(3-(p-tolyl)azetidine-1-carbonyl)pyrimidin-4(1H)-one.



#### Compound 9a. tert-butyl 3-iodoazetidine-1-carboxylate

To a solution of tert-butyl 3-hydroxyazetidine-1-carboxylate (400 mg, 2.31 mmol) in  
 5 toluene (23 ml), imidazole (472 mg, 6.93 mmol), triphenylphosphine (1.21 g, 4.62 mmol)  
 and iodine (879 mg, 3.46 mmol) were added successively and the reaction mixture was  
 heated at 110 °C for 4 h. The cooled reaction mixture was quenched with saturated  
 aqueous NaHCO<sub>3</sub> and extracted with Et<sub>2</sub>O (2 X). The Et<sub>2</sub>O layers were combined and the  
 composite was treated with iodine until a persistent brown color occurred and the mixture  
 10 was stirred at RT overnight. The Et<sub>2</sub>O solution was treated with saturated aqueous  
 Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> until colorless, the phases were split and the organic phase was dried over  
 MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by  
 silica gel chromatography eluting with 0 to 20% EtOAc in hexane to give Compound 9a  
 (594 mg, 91 % yield) as a clear colorless oil. MS m/z = 284.0, (M+H) <sup>1</sup>H NMR

(CHLOROFORM-d)  $\delta$ : 4.57 (t, J=8.4 Hz, 2H), 4.36-4.44 (m, 1H), 4.18-4.26 (m, 2H), 1.37 (s, 9H).

Compound 9b. tert-butyl 3-(p-tolyl)azetidine-1-carboxylate

- 5 To a 0°C solution of compound a (100 mg, 0.35 mmol), (1R, 2R)-N1, N1, N2, N2-tetramethylcyclohexane-1, 2, diamine (3.61 mg, 0.0210 mmol) and 0.05M cobalt(II) chloride in THF (0.35 ml, 0.018 mmol) was added 0.5M p-tolylmagnesium bromide (0.848 ml, 0.424 mmol) dropwise. The reaction mixture was allowed to cool to RT and was stirred for 14 h. The reaction mixture was quenched with saturated aqueous NH<sub>4</sub>Cl
- 10 and extracted with Et<sub>2</sub>O (2 X). The Et<sub>2</sub>O layers were combined and the composite was dried over over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 0 to 20% EtOAc in hexane to give Compound 9b (72 mg, 82 % yield) as a clear colorless oil. MS m/z = 249.2 (M+H), <sup>1</sup>H NMR (CHLOROFORM-d)  $\delta$ : 7.01-7.22 (m, 4H), 4.16-4.32 (m, 2H), 3.81-3.95 (m, 2H),
- 15 3.54-3.71 (m, 1H), 2.25 (s, 3H), 1.38 (s, 9H).

Compound 9c. 3-(p-tolyl)azetidine

- To a solution of compound b (71.5 mg, 0.289 mmol) in DCM (2 ml) was added TFA (165 mg, 1.45 mmol) and the reaction mixture was stirred at RT for 1 h. The reaction mixture
- 20 was concentrated under reduced pressure to give compound 9c that was used without further purification (76 mg, 100 % yield) as a yellow oil. MS m/z = 148.1 (M+H), (M+H) <sup>1</sup>H NMR (CHLOROFORM-d)  $\delta$ : 7.06-7.22 (m, 4H), 4.23-4.33 (m, 2H), 4.07-4.22 (m, 3H), 2.21-2.33 (s, 3H)

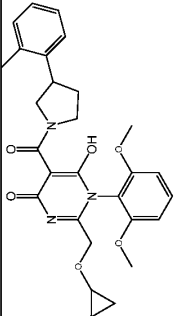
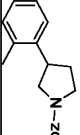
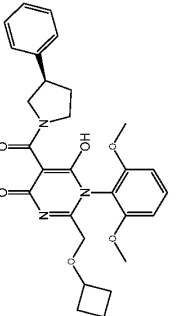
| Ex # | Structure | Name                                                                                                                     | Chiral amine intermediate with retention time                                                                                                                                         | <sup>1</sup> H NMR                                                                                                                                                                                                                                                 | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|--------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 10   |           | 2-(cyclopropoxymethyl)-1-(2,6-dimethoxyphenyl)-5-(3-(2-fluorophenyl)pyrrolidine-1-carbonyl)-6-hydroxypyrimidin-4(1H)-one | <br>10.65, 99.5%<br>Chiralpak IF, 4.6 x 250 mm, 5 micron;<br>mobile phase: 15% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 2.0 mL/min, 150 bar, 40°C, wavelength: 220 nm (Isomer 1) | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.22-7.30 (m, 2H), 7.14 (m, 1H), 6.99-7.05 (m, 2H), 6.59-6.64 (m, 2H), 3.52-3.76 (m, 1H), 3.47 (s, 2H), 3.11 (br s, 1H), 2.08 (br s, 1H), 1.80-1.87 (m, 1H), 0.12-0.15 (m, 2H), 0.02 (d, J = 14.1 Hz, 2H)      | 1.17<br>A<br>510.3        | A                                        |
| 11   |           | (R)-2-(cyclopropoxymethyl)-3-(2,6-dimethoxyphenyl)-6-hydroxy-5-(3-phenylpyrrolidine-1-carbonyl)pyrimidin-4(3H)-one       |                                                                                                                                                                                       | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.21-7.26 (m, 1H), 6.98-7.13 (m, 5H), 6.57-6.62 (m, 2H), 3.73-3.80 (m, 2H), 3.50-3.54 (m, 6H), 3.41 (s, 2H), 3.05-3.30 (m, 4H), 2.06 (br s, 1H), 1.69-1.72 (m, 1H), 0.11 (br s, 2H), 0.01 (d, J = 11.3 Hz, 2H) | 1.23<br>A<br>492.1        | A                                        |

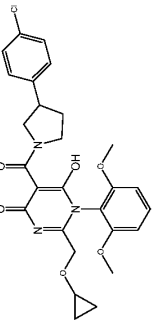
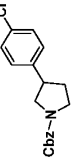
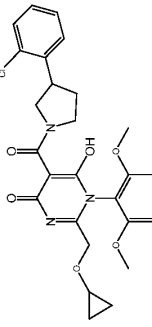
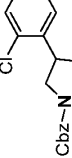
| Ex # | Structure | Name                                                                                                                     | Chiral amine intermediate with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                           | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|--------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 12   |           | (R)-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(isopropoxymethyl)-5-(3-phenylpyrrolidine-1-carbonyl)pyrimidin-4(1H)-one         |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.36-7.42 (m, 1H), 7.28-7.32 (m, 4H), 7.20-7.25 (m, 1H), 6.74-6.80 (m, 2H), 3.80-3.89 (m, 2H), 3.68-3.75 (m, 6H), 3.62 (s, 2H), 3.23-3.51 (m, 4H), 2.24 (br s, 1H), 1.89-1.95 (m, 1H), 0.86-0.90 (m, 6H) | 1.29 A 494.2              | A                                        |
| 13   |           | 2-(cyclopropoxymethyl)-1-(2,6-dimethoxyphenyl)-5-(3-(2-fluorophenyl)pyrrolidine-1-carbonyl)-6-hydroxypyrimidin-4(1H)-one |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.21-7.30 (m, 2H), 7.13 (m, 1H), 6.99-7.03 (m, 2H), 6.60-6.65 (m, 2H), 3.73-3.77 (m, 2H), 3.07-3.58 (m, 12H), 2.09 (br s, 1H), 1.81-1.89 (m, 1H), 0.13-0.16 (m, 2H), 0.02 (d, J = 13.0 Hz, 2H)           | 1.14 A 509.9              | A                                        |

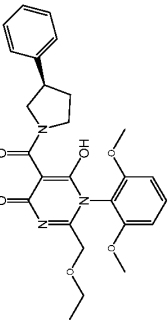
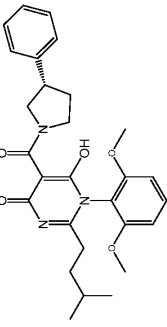


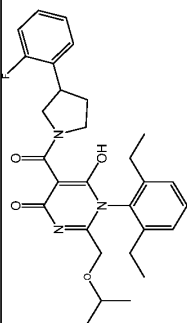
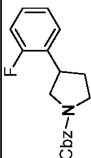
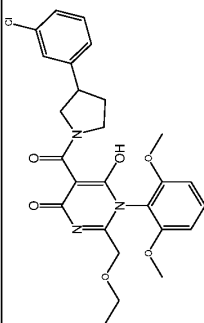
| Ex # | Structure | Name                                                                                                                                            | Chiral amine intermediate with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                           | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 14   |           | (R)-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-isopentyl-5-(3-phenylpyrrolidine-1-carbonyl)pyrimidin-4(1H)-one                                         |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.44-7.49 (m, 1H), 7.27-7.36 (m, 4H), 7.21-7.26 (m, 1H), 6.79-6.86 (m, 2H), 3.71-3.81 (m, 6H), 3.64 (br s, 2H), 3.26-3.51 (m, 3H), 2.23 (br s, 3H), 1.91-1.98 (m, 1H), 1.34 (br s, 3H), 0.66 (br s, 6H)                                  | 1.52 A 492.2              | A                                        |
| 15   |           | 2-(cyclopropoxymethyl)-1-(2,6-dimethoxyphenyl)-5-(3-(3-fluorophenyl)pyrrolidine-1-carbonyl)-6-hydroxy-2-isopentyl-5-carbonylpyrimidin-4(1H)-one |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.15-7.27 (m, 2H), 6.94-7.00 (m, 2H), 6.87 (t, J = 7.9 Hz, 1H), 6.59-6.64 (m, 2H), 3.73-3.75 (m, 2H), 3.53-3.57 (m, 6H), 3.45 (s, 2H), 3.07-3.33 (m, 4H), 2.08 (br s, 1H), 1.72-1.80 (m, 1H), 0.12 (br s, 2H), 0.02 (d, J = 12.5 Hz, 2H) | 1.27 A 510.2              | A                                        |
| 16   |           | (S)-2-(but-3-en-1-yl)-3-(2,6-dimethoxyphenyl)-6-hydroxy-5-(3-phenylpyrrolidine-1-carbonyl)pyrimidin-4(3H)-one                                   |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.44-7.49 (m, 1H), 7.27-7.35 (m, 4H), 7.21-7.26 (m, 1H), 6.81-6.88 (m, 2H), 5.71 (br s, 1H), 4.88-4.96 (m, 2H), 3.73-3.77 (m, 6H), 3.64 (br s, 2H), 3.36-3.48 (m, 2H), 3.30 (t, J = 10.7 Hz, 1H), 2.20-2.36 (m, 3H), 1.90-1.97 (m, 1H)   | 1.35 A 476.1              | A                                        |

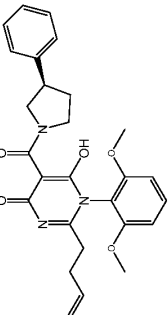
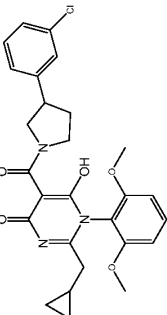
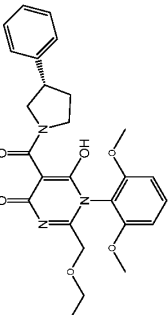
| Ex # | Structure | Name                                                                                                               | Chiral amine intermediate with retention time                                                                                                                                                      | <sup>1</sup> H NMR                                                                                                                                                                                                                                                  | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|--------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 17   |           | (R)-3-(2,6-diethylphenyl)-6-hydroxy-2-(isopropoxymethyl)-5-(3-phenylpyrrolidine-1-carbonyl)pyrimidin-4(3H)-one     |                                                                                                                                                                                                    | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.20-7.41 (m, 8H), 3.86-3.91 (m, 1H), 3.72-3.75 (m, 2H), 3.51-3.62 (m, 2H), 3.33-3.40 (m, 1H), 3.14-3.23 (m, 2H), 2.32-2.44 (m, 2H), 2.17-2.29 (m, 3H), 1.93 (br s, 1H), 0.98-1.14 (m, 6H), 0.81-0.85 (m, 6H)   | 1.65 A 490.2              | A                                        |
| 18   |           | 1-(2,6-diethylphenyl)-6-hydroxy-2-(isopropoxymethyl)-5-(3-(pyridin-2-yl)pyrrolidine-1-carbonyl)pyrimidin-4(1H)-one | <br>Cbz-N 7.62, 93.4%<br>Chiralpak AD-3, 4.6 x 150 mm, 3 micron;<br>mobile phase: 25% MeOH:DEA /75% CO <sub>2</sub> ;<br>Flow Conditions: 1.0 mL/min, 150 bar, 45°C, wavelength: 220 nm (Isomer 2) | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 8.46-8.50 (m, 1H), 7.69-7.74 (m, 1H), 7.18-7.42 (m, 5H), 3.67-3.72 (m, 3H), 3.38-3.55 (m, 3H), 3.12-3.21 (m, 2H), 2.27-2.41 (m, 3H), 2.11-2.27 (m, 3H), 2.02-2.08 (m, 1H), 0.92-1.16 (m, 6H), 0.80-0.83 (m, 6H) | 1.35 A 491.1              | A                                        |

| Ex # | Structure                                                                           | Name                                                                                                                  | Chiral amine intermediate with retention time                                                                                                                                                                                                                                  | <sup>1</sup> H NMR                                                                                                                                                                                                                                                     | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 19   |  | 2-(cyclopropoxymethyl)-1-(2,6-dimethoxyphenyl)-6-hydroxy-5-(3-(4-methoxyphenyl)pyrrolidin-1-yl)pyrimidin-4(1H)-one    | <br>12.72, >99%<br>Lux Cellulose-4 21 x 250 mm, 5 micron; mobile phase: 15% IPA:heptane (1:1)/85% CO <sub>2</sub> ; flow condition: 2.0 mL/min, 150 bar, 40°C, wavelength: 220 nm (Isomer 1) | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.23-7.28 (m, 1H), 7.13 (br s, 1H), 6.94-7.05 (m, 3H), 6.60-6.65 (m, 2H), 3.47-3.77 (m, 13H), 3.08-3.20 (m, 1H), 2.13-2.19 (m, 3H), 2.03 (br s, 1H), 1.77 (br s, 1H), 0.12-0.16 (m, 2H), 0.02 (d, J = 16.3 Hz, 2H) | 1.19<br>A<br>506.1        | A                                        |
| 20   |  | (R)-2-(cyclobutoxymethyl)-1-(2,6-dimethoxyphenyl)-6-hydroxy-5-(3-(4-methoxyphenyl)pyrrolidin-1-yl)pyrimidin-4(1H)-one |                                                                                                                                                                                                                                                                                | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.27-7.38 (m, 5H), 7.20-7.25 (m, 1H), 6.71-6.77 (m, 2H), 3.69-3.73 (m, 6H), 3.62-3.67 (m, 2H), 3.22-3.58 (m, 6H), 2.24 (br s, 1H), 1.92 (br s, 1H), 1.46-1.56 (m, 4H), 1.30-1.37 (m, 2H)                           | 1.36<br>A<br>506.0        | A                                        |

| Ex # | Structure                                                                           | Name                                                                                                              | Chiral amine intermediate with retention time                                                                                                                                                                                                                     | <sup>1</sup> H NMR                                                                                                                                                                                                                  | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 21   |  | 5-(3-(4-chlorophenyl)pyrrolidin-1-yl)-2-(cyclopropoxymethyl)-1-(2,6-dimethoxyphenyl)-6-hydroxypyrimidin-4(1H)-one | <br>6.69, 99.8%<br>Chiralcel OJ-H 4.6 x 250 mm; mobile phase: 15% IPA/85% CO <sub>2</sub> ; Flow Conditions: 3.0 mL/min, 140 bar, 40°C; wavelength: 220 nm (Isomer 1)           | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.15-7.28 (m, 6H), 6.60-6.65 (m, 2H), 3.70-3.75 (m, 2H), 3.55-3.59 (m, 6H), 3.06-3.41 (m, 6H), 2.11 (br s, 1H), 1.73-1.80 (m, 1H), 0.13-0.16 (m, 2H), 0.02 (d, J = 14.7 Hz, 2H) | 1.38<br>A<br>526.2        | A                                        |
| 22   |  | 5-(3-(2-chlorophenyl)pyrrolidin-1-yl)-2-(cyclopropoxymethyl)-1-(2,6-dimethoxyphenyl)-6-hydroxypyrimidin-4(1H)-one | <br>8.29, 98.2%<br>Chiralpak ID, 4.6 x 250 mm, 5 micron; mobile phase: 10% MeOH/90% CO <sub>2</sub> ; Flow Conditions: 2.0 mL/min, 150 bar, 40°C; wavelength: 220 nm (Isomer 2) |                                                                                                                                                                                                                                     | 1.23<br>A<br>526.1        | A                                        |

| Ex # | Structure                                                                           | Name                                                                                                           | Chiral amine intermediate with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                     | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|-----------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 23   |  | (R)-1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-6-hydroxy-5-(3-phenylpyrrolidin-1-yl)-carbonylpyrimidin-4(1H)-one |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.29-7.35 (m, 4H), 7.23-7.25 (m, 2H), 6.80-6.86 (m, 2H), 3.94-4.00 (m, 2H), 3.68-3.78 (m, 7H), 3.65 (s, 2H), 3.44-3.49 (m, 1H), 3.25-3.32 (m, 1H), 3.17 (t, J = 9.2 Hz, 2H), 2.21 (br s, 1H), 1.90-2.00 (m, 1H), 0.97-1.03 (m, 3H) | 1.20 A 480.1              | A                                        |
| 24   |  | (S)-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-isopentyl-5-(3-phenylpyrrolidin-1-yl)-carbonylpyrimidin-4(1H)-one      |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.42-7.48 (m, 1H), 7.27-7.35 (m, 4H), 7.21-7.26 (m, 1H), 6.81-6.88 (m, 2H), 3.73-3.77 (m, 6H), 3.64 (br s, 2H), 3.26-3.49 (m, 3H), 2.22 (br s, 3H), 1.90-1.99 (m, 1H), 1.35 (br s, 3H), 0.66 (br s, 6H)                            | 1.52 A 492.2              | A                                        |

| Ex # | Structure                                                                            | Name                                                                                                                | Chiral amine intermediate with retention time                                                                                                                                                                                                                           | <sup>1</sup> H NMR                                                                                                                                                                                                                        | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 25   |   | 1-(2,6-diethylphenyl)-5-(3-(2-fluorophenyl)pyrrolidin-1-carbonyl)-6-hydroxy-2-(isopropoxymethyl)pyrimidin-4(1H)-one | <br>10.65, 99.5%<br>Chiralpak IF, 4.6 x 250 mm, 5 micron;<br>mobile phase: 15% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 2.0 mL/min, 150 bar, 40°C, wavelength: 220 nm (Isomer 2) |                                                                                                                                                                                                                                           | 1.51<br>A<br>508.4        | A                                        |
| 26   |  | 5-(3-(3-chlorophenyl)pyrrolidin-1-carbonyl)-1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-6-hydroxypyrimidin-4(1H)-one   | Racemic pyrrolidine amine                                                                                                                                                                                                                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.24-7.45 (m, 5H), 6.78-6.83 (m, 2H), 3.88-3.96 (m, 2H), 3.73-3.77 (m, 6H), 3.65 (s, 2H), 3.37-3.54 (m, 3H), 3.25-3.31 (m, 1H), 2.27 (br s, 1H), 1.93-1.99 (m, 1H), 0.96-1.01 (m, 3H) | 1.39<br>A<br>513.9        | A                                        |

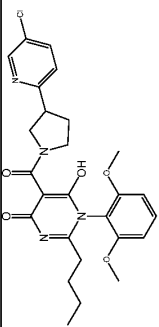
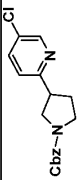
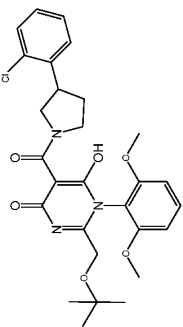
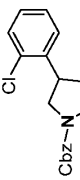
| Ex # | Structure                                                                             | Name                                                                                                                    | Chiral amine intermediate with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                        | LC/MS Rt (min) Method | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|---------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 27   |    | (R)-2-(but-3-en-1-yl)-3-(2,6-dimethoxyphenyl)-6-hydroxy-5-(3-phenylpyrrolidine-1-carbonyl)pyrimidin-4(3H)-one           |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.43-7.49 (m, 1H), 7.27-7.35 (m, 4H), 7.20-7.26 (m, 1H), 6.82-6.89 (m, 2H), 5.71 (br s, 1H), 4.88-4.97 (m, 2H), 3.70-3.79 (m, 6H), 3.64 (br s, 2H), 3.37-3.47 (m, 2H), 3.30 (t, J = 9.8 Hz, 1H), 2.21-2.35 (m, 3H), 1.91-1.98 (m, 1H) | 1.35 A 476.1          | A                                        |
| 28   |    | 5-(3-(3-chlorophenyl)pyrrolidine-1-carbonyl)-2-(cyclopropylmethyl)-1-(2,6-dimethoxyphenyl)-6-hydroxypyrimidin-4(1H)-one | Racemic pyrrolidine amine                     | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.41-7.47 (m, 1H), 7.25-7.39 (m, 4H), 6.78-6.84 (m, 2H), 3.73-3.76 (m, 6H), 3.58-3.69 (m, 4H), 3.39-3.49 (m, 1H), 2.26 (br s, 1H), 2.16 (br s, 2H), 1.89-1.99 (m, 1H), 0.80 (br s, 1H), 0.40 (br s, 2H), 0.00 (br s, 2H)              | 1.53 A 509.9          | A                                        |
| 29   |  | (S)-1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-6-hydroxy-5-(3-phenylpyrrolidine-1-carbonyl)pyrimidin-4(1H)-one            |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.42-7.46 (m, 1H), 7.20-7.37 (m, 5H), 6.77-6.86 (m, 2H), 3.92-3.97 (m, 2H), 3.67-3.79 (m, 6H), 3.35-3.66 (m, 5H), 3.24-3.34 (m, 2H), 2.27 (br s, 1H), 1.90-2.00 (m, 1H), 0.96-1.01 (m, 3H)                                            | 1.19 A 480.0          | A                                        |

| Ex # | Structure | Name                                                                                                              | Chiral amine intermediate with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                               | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|-------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 30   |           | (R)-2-(cyclopentyl-3-(2,6-dimethoxyphenyl)-6-hydroxy-5-(3-phenylpyrrolidine-1-carbonyl)pyrimidin-4(3H)-one        |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.38-7.47 (m, 1H), 7.27-7.36 (m, 4H), 7.21-7.27 (m, 1H), 6.77-6.86 (m, 2H), 3.70-3.79 (m, 6H), 3.59-3.67 (m, 4H), 3.28-3.53 (m, 2H), 2.26 (br s, 1H), 1.90-1.99 (m, 1H), 1.73-1.84 (m, 2H), 1.52-1.69 (m, 4H), 1.41 (br s, 2H)                               | 1.52 A 490.1              | A                                        |
| 31   |           | (S)-2-(cyclopropylmethyl)-3-(2,6-dimethoxyphenyl)-6-hydroxy-5-(3-phenylpyrrolidine-1-carbonyl)pyrimidin-4(3H)-one |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.42-7.50 (m, 1H), 7.26-7.36 (m, 4H), 7.21-7.26 (m, 1H), 6.79-6.89 (m, 2H), 3.72-3.77 (m, 6H), 3.64 (br s, 2H), 3.36-3.46 (m, 2H), 3.27-3.35 (m, 1H), 2.28 (br s, 1H), 2.17 (br s, 2H), 1.91-2.00 (m, 1H), 0.82 (br s, 1H), 0.41 (br s, 2H), 0.01 (br s, 2H) | 1.34 A 476.1              | A                                        |



| Ex # | Structure | Name                                                                                                               | Chiral amine intermediate with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                               | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|--------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 32   |           | (R)-2-(cyclopropylmethyl)-3-(2,6-dimethoxyphenyl)-6-hydroxy-5-(3-phenylpyrrolidine-1-carbonyl)pyrimidin-4(3H)-one  |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.42-7.49 (m, 1H), 7.26-7.35 (m, 4H), 7.20-7.26 (m, 1H), 6.80-6.87 (m, 2H), 3.72-3.76 (m, 6H), 3.64 (br s, 2H), 3.35-3.53 (m, 2H), 3.28-3.34 (m, 1H), 2.26 (br s, 1H), 2.17 (br s, 2H), 1.91-1.98 (m, 1H), 0.82 (br s, 1H), 0.40 (br s, 2H), 0.01 (br s, 2H) | 1.33 A 476.4              | A                                        |
| 33   |           | (S)-1-(2,6-dimethoxyphenyl)-6-hydroxy-5-(3-phenylpyrrolidine-1-carbonyl)-2-(4,4-trifluorobutyl)pyrimidin-4(1H)-one |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.40-7.49 (m, 1H), 7.20-7.36 (m, 5H), 6.78-6.87 (m, 2H), 3.69-3.80 (m, 6H), 3.63 (br s, 4H), 3.35-3.54 (m, 1H), 2.16-2.34 (m, 5H), 1.90-1.98 (m, 1H), 1.75 (br s, 2H)                                                                                        | 1.53 A 532.1              | A                                        |
| 34   |           | (S)-2-cyclopentyl-3-(2,6-dimethoxyphenyl)-6-hydroxy-5-(3-phenylpyrrolidine-1-carbonyl)pyrimidin-4(3H)-one          |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.39-7.48 (m, 1H), 7.27-7.36 (m, 4H), 7.20-7.27 (m, 1H), 6.77-6.85 (m, 2H), 3.69-3.79 (m, 6H), 3.60-3.69 (m, 4H), 3.27-3.52 (m, 2H), 2.26 (br s, 1H), 1.90-1.98 (m, 1H), 1.72-1.84 (m, 2H), 1.51-1.70 (m, 4H), 1.40 (br s, 2H)                               | 1.52 A 490.0              | A                                        |

| Ex # | Structure | Name                                                                                                               | Chiral amine intermediate with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                              | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|--------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 35   |           | (R)-2-(but-3-en-1-yl)-6-hydroxy-3-(2-methoxy-6-methylphenyl)-5-(3-phenylpyrrolidin-1-yl)-4(3H)-pyrimidin-4(3H)-one |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.21-7.41 (m, 6H), 6.97-7.09 (m, 2H), 5.72 (br s, 1H), 4.90-4.96 (m, 2H), 3.75-3.77 (m, 3H), 3.73 (br s, 2H), 3.65-3.69 (m, 2H), 3.28-3.37 (m, 1H), 2.22-2.33 (m, 5H), 2.00-2.03 (m, 2H), 1.90-1.98 (m, 2H) | 1.37 A 460.4              | A                                        |
| 36   |           | (S)-1-(2,6-dimethoxyphenyl)-6-hydroxy-5-(3-phenylpyrrolidin-1-yl)-2-(4,4-trifluorobutyl)pyrimidin-4(1H)-one        |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.54 (t, J = 8.24 Hz, 1H), 6.91 (d, J = 8.54 Hz, 2H), 3.81 (s, 6H), 2.32-2.36 (m, 2H), 2.31 (s, 3H), 2.13 (s, 3H), 1.48-1.57 (m, 2H), 1.16-1.25 (m, 2H), 0.76 (t, J = 7.02 Hz, 3H)                          | 2.00 A 443.0              | B                                        |
| 40   |           | (R)-1-(2,6-dimethoxyphenyl)-6-hydroxy-5-(3-phenylpyrrolidin-1-yl)-2-(4,4-trifluorobutyl)pyrimidin-4(1H)-one        |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.42-7.50 (m, 1H), 7.20-7.37 (m, 5H), 6.79-6.89 (m, 2H), 3.69-3.80 (m, 6H), 3.64 (br s, 4H), 3.27-3.50 (m, 1H), 2.17-2.36 (m, 5H), 1.89-1.99 (m, 1H), 1.77 (br s, 2H)                                       | 1.48 A 531.9              | A                                        |

| Ex # | Structure                                                                            | Name                                                                                                                              | Chiral amine intermediate with retention time                                                                                                                                                                                                                          | <sup>1</sup> H NMR                                                                                                                                                                                                                                            | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|--------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 41   |   | 2-butyl-5-(3-(5-chloropyrrolidin-2-yl)pyrrolidine-1-carbonyl)-6-(1-(2,6-dimethoxyphenyl)-6-hydroxypyrimidin-4(1H)-one             | <br>13.24, 91%<br>Chiralpak IC, 4.6 x 250 mm, 5 micron; mobile phase: 10% IPA/0.1%DEA/90% CO <sub>2</sub> ; flow condition: 2.0 mL/min, 150 bar, 40°C, wavelength: 220 nm (Isomer 2) | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 8.55 (br. s., 1H), 7.92 - 7.77 (m, 1H), 7.52 - 7.27 (m, 2H), 6.83 (br. s., 2H), 3.99 - 3.45 (m, 5H), 2.51 (br. s., 6H), 2.22 (br. s., 4H), 1.42 (br. s., 2H), 1.22 - 1.10 (m, 2H), 0.70 (d, J=6.3 Hz, 3H) | 0.78 A<br>513.3           | A                                        |
| 42   |  | 2-[(tert-butoxy)methyl]-5-[3-(2-chlorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>8.29, 98.2%<br>Chiralpak ID, 4.6 x 250 mm, 5 micron; mobile phase: 10% MeOH/90% CO <sub>2</sub> ; Flow Conditions: 2.0 mL/min, 150 bar, 40°C, wavelength: 220 nm (Isomer 2)      | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.55 - 7.37 (m, 3H), 7.28 (dd, J=14.7, 6.5 Hz, 2H), 6.84 - 6.73 (m, 2H), 3.87 (br. s., 2H), 3.73 (br. s., 2H), 3.62 - 3.23 (m, 2H), 2.51 (br. s., 7H), 2.34 - 1.84 (m, 2H), 0.83 (d, J=11.3 Hz, 9H)       | 0.88 A<br>542.3           | A                                        |

| Ex # | Structure | Name                                                                                                                              | Chiral amine intermediate with retention time                                                                                                                                    | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                 | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|-----------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 43   |           | 2-butyl-5-[3-(2-chlorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one                 | <br>8.29, 98.2%<br>Chiralpak ID, 4.6 x 250 mm, 5 micron;<br>mobile phase: 10% MeOH/90% CO <sub>2</sub> ;<br>Flow Conditions: 2.0 mL/min, 150 bar, 40°C;<br>Wavelength (Isomer 2) | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) d 7.43 (br. s., 3H), 7.30 (br. s., 2H), 6.83 (br. s., 2H), 3.71 (d, J=15.6 Hz, 3H), 3.41 (br. s., 2H), 2.51 (br. s., 6H), 2.22 (d, J=6.0 Hz, 3H), 2.03 (br. s., 1H), 1.39 (br. s., 2H), 1.19 - 1.03 (m, 2H), 0.78 - 0.56 (m, 3H) | 0.87 A<br>512.2           | A                                        |
| 44   |           | 2-[(tert-butoxy)methyl]-1-(2,6-dimethoxyphenyl)-5-[3-(4-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>9.93, 99%<br>Wheeler-O 1 (R,R), 4.6 x 250 mm, 5 micron;<br>mobile phase: 15% IPA/85% CO <sub>2</sub> ;<br>Flow Conditions: 2.0 mL/min, 150 bar, 40°C;<br>wavelength: 220 nm  | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) d 7.33 (d, J=16.2 Hz, 3H), 7.24 - 7.08 (m, 3H), 6.84 - 6.69 (m, 2H), 3.95 - 3.19 (m, 9H), 2.55 (s, 3H), 2.29 - 2.18 (m, 1H), 1.99 - 1.84 (m, 1H), 0.82 (d, J=13.0 Hz, 9H)                                                        | 0.85 A<br>526.4           | A                                        |

| Ex # | Structure | Name                                                                                                              | Chiral amine intermediate with retention time                                                                                                                         | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                           | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|-------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 45   |           | 2-butyl-5-[3-(4-chlorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>6.69, 99.8%<br>Chiralcel OJ-H 4.6 x 250 mm; mobile phase: 15% IPA/85% CO <sub>2</sub> ; Flow Conditions: 3.0 mL/min, 140 bar, 40°C, wavelength: 220 nm (Isomer 1) | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) d 7.49 - 7.28 (m, 5H), 6.87 - 6.76 (m, 2H), 3.81 - 3.16 (m, 6H), 2.52 (br. s., 6H), 2.18 (br. s., 3H), 1.42 (d, J=6.4 Hz, 2H), 1.13 (d, J=7.0 Hz, 2H), 0.79 - 0.63 (m, 3H)                                                                 | 0.90<br>A<br>512.2        | A                                        |
| 46   |           | 2-butyl-5-[3-(4-chlorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>7.71, 99.8%<br>Chiralcel OJ-H 4.6 x 250 mm; mobile phase: 15% IPA/85% CO <sub>2</sub> ; Flow Conditions: 3.0 mL/min, 140 bar, 40°C, wavelength: 220 nm (Isomer 2) | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) d 7.36 (br. s., 4H), 6.89 - 6.71 (m, 2H), 3.75 (br. s., 2H), 3.59 - 3.58 (m, 1H), 3.58 - 3.19 (m, 4H), 2.52 (br. s., 6H), 2.32 - 2.21 (m, 1H), 2.15 (d, J=6.1 Hz, 2H), 1.41 (d, J=6.4 Hz, 2H), 1.12 (d, J=7.3 Hz, 2H), 0.76 - 0.61 (m, 3H) | 0.90<br>A<br>512.3        | A                                        |

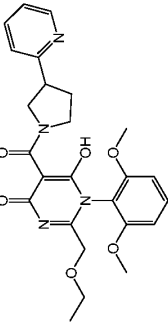
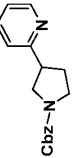
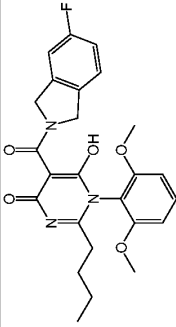
| Ex # | Structure | Name                                                                                                            | Chiral amine intermediate with retention time                                                                                                                                                         | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                               | LC/MS Rt (min) Method | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|-----------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 47   |           | 2-butyl-1-(2,6-dimethoxyphenyl)-6-hydroxy-5-[3-(pyridin-4-yl)pyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one | <br>Cbz-N<br>6.86, 99%<br>Chiralpak AS-H, 4.6 x 250 mm, 5 micron;<br>mobile phase: 10% MeOH/0.1%DEA/90% CO <sub>2</sub> ; Flow Conditions: 2.0 mL/min, 150 bar, 40°C, wavelength: 220 nm (Isomer 1)   | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 8.74 (d, J=8.5 Hz, 2H), 7.88 - 7.73 (m, 2H), 7.47 (d, J=8.2 Hz, 1H), 6.91 - 6.76 (m, 2H), 3.81 - 3.41 (m, 3H), 2.52 (br. s., 6H), 2.46 - 2.46 (m, 1H), 2.39 - 2.39 (m, 1H), 2.46 - 2.33 (m, 1H), 2.25 (d, J=7.3 Hz, 2H), 2.10 - 1.92 (m, 1H), 1.50 - 1.31 (m, 2H), 1.15 (br. s., 2H), 0.71 (q, J=7.7 Hz, 3H) | 0.57<br>A<br>479.3    | A                                        |
| 48   |           | 2-butyl-1-(2,6-dimethoxyphenyl)-6-hydroxy-5-[3-(pyridin-4-yl)pyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one | <br>Cbz-N<br>8.10, 98.6%<br>Chiralpak AS-H, 4.6 x 250 mm, 5 micron;<br>mobile phase: 10% MeOH/0.1%DEA/90% CO <sub>2</sub> ; Flow Conditions: 2.0 mL/min, 150 bar, 40°C, wavelength: 220 nm (Isomer 2) | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 8.74 (d, J=8.5 Hz, 2H), 7.88 - 7.73 (m, 2H), 7.47 (d, J=8.2 Hz, 1H), 6.91 - 6.76 (m, 2H), 3.81 - 3.41 (m, 3H), 2.52 (br. s., 6H), 2.46 - 2.46 (m, 1H), 2.39 - 2.39 (m, 1H), 2.46 - 2.33 (m, 1H), 2.25 (d, J=7.3 Hz, 2H), 2.10 - 1.92 (m, 1H), 1.50 - 1.31 (m, 2H), 1.15 (br. s., 2H), 0.71 (q, J=7.7 Hz, 3H) | 0.57<br>A<br>479.1    | A                                        |

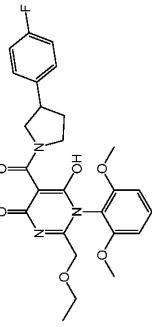
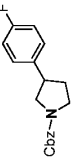
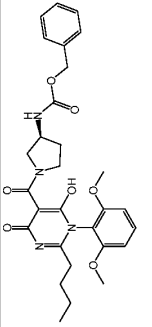
| Ex # | Structure | Name                                                                                                                             | Chiral amine intermediate with retention time                                                                                                                                         | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                               | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|----------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 49   |           | 1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-5-[3-(2-fluorophenyl)pyrrolidin-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one        | <br>10.65, 99.5%<br>Chiralpak IF, 4.6 x 250 mm, 5 micron;<br>mobile phase: 15% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 2.0 mL/min, 150 bar, 40°C, wavelength: 220 nm (Isomer 2) | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.51 - 7.27 (m, 3H), 7.22 - 7.16 (m, 2H), 6.83 (d, J=7.9 Hz, 2H), 3.97 (d, J=6.7 Hz, 2H), 3.77 (br. s., 3H), 3.63 - 3.55 (m, 1H), 3.70 - 3.54 (m, 2H), 3.45 - 3.11 (m, 2H), 2.52 (br. s., 6H), 2.31 - 2.22 (m, 1H), 2.11 - 1.95 (m, 1H), 1.06 - 0.87 (m, 3H) | 0.79 A<br>498.3           | A                                        |
| 50   |           | 2-[(tert-butoxy)methyl]-1-(2,6-dimethoxyphenyl)-5-[3-(2-fluorophenyl)pyrrolidin-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>10.65, 99.5%<br>Chiralpak IF, 4.6 x 250 mm, 5 micron;<br>mobile phase: 15% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 2.0 mL/min, 150 bar, 40°C, wavelength: 220 nm (Isomer 1) | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.39 (s, 3H), 7.16 (d, J=14.0 Hz, 2H), 6.88 - 6.65 (m, 2H), 3.99 - 3.21 (m, 11H), 2.56 (s, 2H), 2.27 (br. s., 1H), 2.08 - 1.94 (m, 1H), 0.85 (d, J=10.7 Hz, 9H)                                                                                              | 0.85 A<br>526.3           | A                                        |

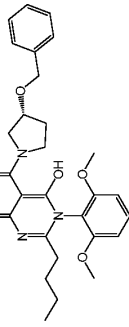
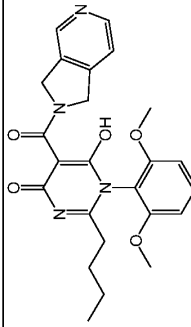
| Ex # | Structure | Name                                                                                                                                  | Chiral amine intermediate with retention time                                                                                                                                              | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                           | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|---------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 51   |           | 2-[( <i>tert</i> -butoxy)methyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one |                                                                                                                                                                                            | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) d 7.51 - 7.19 (m, 6H), 6.80 (d, J=8.9 Hz, 2H), 4.05 - 3.14 (m, 1H), 2.56 (s, 2H), 2.33 - 2.22 (m, 1H), 2.01 - 1.86 (m, 1H), 0.83 (s, 9H)                                                                                                   | 0.84 A 508.4              | A                                        |
| 52   |           | 2-butyl-1-(2,6-dimethoxyphenyl)-5-[3-(2-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one                     | <br>12.48, 99.5%<br>Chiralpak IF, 4.6 x 250 mm, 5 micron;<br>mobile phase: 15% IPA/85%CO <sub>2</sub> ;<br>Flow Conditions: 2.0 mL/min, 150 bar, 40°C,<br>wavelength: 220 nm<br>(Isomer 2) | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) d 7.48 - 7.36 (m, 2H), 7.30 (d, J=6.1 Hz, 1H), 7.23 - 7.09 (m, 2H), 6.90 - 6.72 (m, 2H), 3.87 - 3.29 (m, 5H), 2.52 (br. s, 6H), 2.29 - 2.11 (m, 3H), 2.05 - 1.94 (m, 1H), 1.50 - 1.35 (m, 2H), 1.20 - 1.07 (m, 2H), 0.71 (d, J=7.6 Hz, 3H) | 0.83 A 496.2              | A                                        |



| Ex # | Structure | Name                                                                                                                     | Chiral amine intermediate with retention time                                                                                                                                                | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                            | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|--------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 53   |           | 2-butyl-1-(2,6-dimethoxyphenyl)-5-[3-(2-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one        | <br>10.65, 99.5%<br>Chiralpak IF, 4.6 x 250 mm, 5 micron;<br>mobile phase: 15% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 2.0 mL/min, 150 bar, 40°C, wavelength: 220 nm (Isomer 1)        | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.48 - 7.36 (m, 2H), 7.30 (d, J=6.1 Hz, 1H), 7.23 - 7.09 (m, 2H), 6.90 - 6.72 (m, 2H), 3.87 - 3.29 (m, 5H), 2.52 (br. s., 6H), 2.29 - 2.11 (m, 3H), 2.05 - 1.94 (m, 1H), 1.50 - 1.35 (m, 2H), 1.20 - 1.07 (m, 2H), 0.71 (d, J=7.6 Hz, 3H) | 0.83 A<br>496.3           | A                                        |
| 54   |           | 1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-6-hydroxy-5-[3-(pyridin-2-yl)pyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one | <br>7.62, 93.4%<br>Chiralpak AD-3, 4.6 x 150 mm, 3 micron;<br>mobile phase: 25% MeOH:DEA /75% CO <sub>2</sub> ;<br>Flow Conditions: 1.0 mL/min, 150 bar, 45°C, wavelength: 220 nm (Isomer 2) | <sup>1</sup> H NMR (400MHz, chloroform-d) δ 8.53 (d, J=4.2 Hz, 1H), 7.64 - 7.56 (m, 1H), 7.38 (t, J=8.5 Hz, 1H), 7.20 - 7.09 (m, 2H), 6.65 (d, J=8.4 Hz, 2H), 4.07 (s, 2H), 3.76 (s, 9H), 3.46 (d, J=7.0 Hz, 4H), 2.34 - 2.14 (m, 2H), 1.11 (t, J=6.9 Hz, 3H)                                 | 0.53 A<br>481.3           | A                                        |

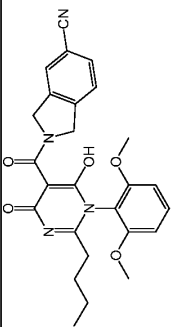
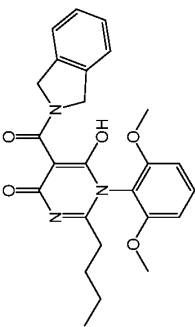
| Ex # | Structure                                                                            | Name                                                                                                                 | Chiral amine intermediate with retention time                                                                                                                                                                                                                                        | <sup>1</sup> H NMR                                                                                                                                                                                                                                            | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|--------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 55   |   | 1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-6-hydroxy-5-[3-(pyridin-2-yl)pyrrolidin-2-yl]-1,4-dihydropyrimidin-4-one    | <br>Cbz-N<br>6.77, 99%<br>Chiralpak AD-3, 4.6 x 150 mm, 3 micron;<br>mobile phase: 25% MeOH:DEA /75% CO <sub>2</sub> ;<br>Flow Conditions: 1.0 mL/min, 150 bar, 45°C, wavelength: 220 nm Isomer 1) | <sup>1</sup> H NMR (400MHz, chloroform-d) δ 8.53 (d, J=4.2 Hz, 1H), 7.64 - 7.56 (m, 1H), 7.38 (t, J=8.5 Hz, 1H), 7.20 - 7.09 (m, 2H), 6.65 (d, J=8.4 Hz, 2H), 4.07 (s, 2H), 3.76 (s, 9H), 3.46 (d, J=7.0 Hz, 4H), 2.34 - 2.14 (m, 2H), 1.11 (t, J=6.9 Hz, 3H) | 0.52<br>A<br>481.2        | A                                        |
| 56   |  | 2-butyl-1-(2,6-dimethoxyphenyl)-5-(5-fluoro-2,3-dihydro-1H-isindole-2-carbonyl)-6-hydroxy-1,4-dihydropyrimidin-4-one |                                                                                                                                                                                                                                                                                      | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.47 - 7.32 (m, 2H), 7.26 - 7.07 (m, 2H), 6.83 (d, J=8.5 Hz, 2H), 4.73 (s, 4H), 2.56 (s, 6H), 2.28 - 2.13 (m, 2H), 1.49 - 1.36 (m, 2H), 1.21 - 1.12 (m, 2H), 0.73 (t, J=7.3 Hz, 3H)                       | 0.80<br>A<br>468.3        | A                                        |

| Ex # | Structure                                                                           | Name                                                                                                                          | Chiral amine intermediate with retention time                                                                                                                                                                                                                          | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                               | LC/MS Rt (min) Method | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 57   |  | 1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-5-[3-(4-fluorophenyl)pyrrolidin-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one     | <br>10.7, 90%<br>Whekk-O 1 (R,R), 4.6 x 250 mm, 5 micron;<br>mobile phase: 15% IPA/85%CO <sub>2</sub> ;<br>Flow Conditions: 2.0 mL/min, 150 bar, 40°C, wavelength: 220 nm (Isomer 2) | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) d 7.35 (d, J=19.5 Hz, 3H), 7.19 - 7.08 (m, 2H), 6.85 - 6.72 (m, 2H), 3.97 - 3.51 (m, 7H), 3.31 - 3.22 (m, 2H), 2.56 (s, 6H), 2.31 - 2.15 (m, 1H), 1.99 - 1.85 (m, 1H), 0.97 (d, J=6.4 Hz, 3H)                                                                                  | 0.79 A<br>498.3       | A                                        |
| 58   |  | benzyl N-[1-(3S)-1-[2-butyl-1-(2,6-dimethoxyphenyl)-6-hydroxy-4-oxo-1,4-dihydropyrimidin-5-carbonyl]pyrrolidin-3-yl]carbamate |                                                                                                                                                                                                                                                                        | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) d 7.67 - 7.28 (m, 7H), 6.83 (d, J=8.2 Hz, 2H), 5.02 (d, J=11.6 Hz, 2H), 4.10 - 3.92 (m, 1H), 3.75 (br. s., 3H), 3.18 (s, 1H), 2.56 (s, 6H), 2.20 (t, J=7.5 Hz, 2H), 2.10 - 1.96 (m, 1H), 1.85 - 1.70 (m, 1H), 1.49 - 1.36 (m, 2H), 1.25 - 1.09 (m, 2H), 0.72 (t, J=7.3 Hz, 3H) | 0.80 A<br>551.3       | B                                        |

| Ex # | Structure                                                                           | Name                                                                                                                 | Chiral amine intermediate with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                          | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 59   |  | 5-[(3R)-3-(benzyloxy)pyrrolidine-1-carbonyl]-2-buty-1-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one   |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.46 (s, 1H), 7.37 - 7.23 (m, 5H), 6.84 (d, J=8.2 Hz, 2H), 4.56 - 4.41 (m, 2H), 4.25 - 4.11 (m, 1H), 3.77 (br. s., 3H), 3.18 (s, 1H), 2.52 (br. s., 6H), 2.22 (t, J=7.5 Hz, 2H), 2.05 - 1.90 (m, 2H), 1.45 (br. s., 2H), 1.16 (d, J=7.3 Hz, 2H), 0.72 (t, J=7.3 Hz, 3H) | 0.83 A 508.3              | A                                        |
| 60   |  | 2-buty-1-1-(2,6-dimethoxyphenyl)-6-hydroxy-5-{1H,2H,3H-pyrrolo[3,4-c]pyridine-2-carbonyl}-1,4-dihydropyrimidin-4-one |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 8.77 - 8.67 (m, 1H), 8.65 - 8.57 (m, 1H), 7.75 - 7.62 (m, 1H), 7.48 (t, J=8.4 Hz, 1H), 6.87 (d, J=8.5 Hz, 2H), 4.88 - 4.72 (m, 4H), 2.56 (s, 6H), 2.30 (br. s., 2H), 1.47 (br. s., 2H), 1.18 (d, J=7.3 Hz, 2H), 0.73 (t, J=7.3 Hz, 3H)                                  | 0.57 A 451.3              | B                                        |

| Ex # | Structure | Name                                                                                                                         | Chiral amine intermediate with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                               | LC/MS Rt (min) Method | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 61   |           | 2-butyl-1-(2,6-dimethoxyphenyl)-6-hydroxy-5H-pyrrolo[3,4-b]pyridine-6-carbonyl-1,4-dihydropyrimidin-4-one                    |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 8.55 - 8.34 (m, 1H), 7.79 (dd, J=18.8, 7.5 Hz, 1H), 7.53 - 7.39 (m, 1H), 7.31 (d, J=3.7 Hz, 1H), 6.83 (d, J=8.5 Hz, 2H), 4.77 - 4.51 (m, 4H), 2.56 (s, 6H), 2.24 - 2.13 (m, 2H), 1.52 - 1.38 (m, 2H), 1.25 - 1.09 (m, 2H), 0.73 (t, J=7.3 Hz, 3H)                            | 0.61 A 451.2          | B                                        |
| 62   |           | benzyl N-[(3R)-1-(2-butyl-1-(2,6-dimethoxyphenyl)-6-hydroxy-4-oxo-1,4-dihydropyrimidine-5-carbonyl)pyrrolidin-3-yl]carbamate |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.67 - 7.28 (m, 7H), 6.83 (d, J=8.2 Hz, 2H), 5.02 (d, J=11.6 Hz, 2H), 4.10 - 3.92 (m, 1H), 3.75 (br. s., 3H), 3.18 (s, 1H), 2.56 (s, 6H), 2.20 (t, J=7.5 Hz, 2H), 2.10 - 1.96 (m, 1H), 1.85 - 1.70 (m, 1H), 1.49 - 1.36 (m, 2H), 1.25 - 1.09 (m, 2H), 0.72 (t, J=7.3 Hz, 3H) | 0.80 A 551.3          | B                                        |

| Ex # | Structure | Name                                                                                                                           | Chiral amine intermediate with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                              | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|--------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 63   |           | 5-[(3S)-3-(benzyloxy)pyrrolidine-1-carbonyl]-2-buty-1-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one             |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.46 (s, 1H), 7.37 - 7.23 (m, 5H), 6.84 (d, J=8.2 Hz, 2H), 4.56 - 4.41 (m, 2H), 4.25 - 4.11 (m, 1H), 3.77 (br. s., 3H), 3.18 (s, 1H), 2.52 (br. s., 6H), 2.22 (t, J=7.5 Hz, 2H), 2.05 - 1.90 (m, 2H), 1.45 (br. s., 2H), 1.16 (d, J=7.3 Hz, 2H), 0.72 (t, J=7.3 Hz, 3H)     | 0.83 A 508.3              | A                                        |
| 64   |           | 2-buty-1-1-(2,6-dimethoxyphenyl)-6-hydroxy-5-[(3S)-3-[(pyridin-2-yl)methoxy]pyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 8.65 - 8.47 (m, 1H), 7.98 - 7.86 (m, 1H), 7.63 - 7.36 (m, 4H), 6.85 (d, J=8.2 Hz, 2H), 4.65 (br. s., 2H), 4.27 (br. s., 1H), 3.57 - 3.30 (m, 1H), 2.56 (s, 6H), 2.25 (t, J=7.5 Hz, 2H), 2.11 - 1.91 (m, 4H), 1.45 (br. s., 2H), 1.22 - 1.11 (m, 2H), 0.72 (t, J=7.3 Hz, 3H) | 0.59 A 509.3              | A                                        |

| Ex # | Structure                                                                           | Name                                                                                                                        | Chiral amine intermediate with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                     | LC/MS Rt (min) Method | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 65   |  | 2-[2-butyl-1-(2,6-dimethoxyphenyl)-6-hydroxy-4-oxo-1,4-dihydropyrimidin-5-carbonyl]-2,3-dihydro-1H-isoindole-5-carbonitrile |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.93 - 7.83 (m, 1H), 7.77 (br. s., 1H), 7.64 - 7.54 (m, 1H), 7.52 - 7.40 (m, 1H), 6.86 (d, J=8.5 Hz, 2H), 4.83 - 4.65 (m, 4H), 2.56 (s, 6H), 2.34 - 2.23 (m, 2H), 1.54 - 1.38 (m, 2H), 1.24 - 1.10 (m, 2H), 0.73 (t, J=7.2 Hz, 3H) | 0.75 A 475.3          | A                                        |
| 66   |  | 2-butyl-5-(2,3-dihydro-1H-isoindole-2-carbonyl)-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one                |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.45 (s, 1H), 7.40 - 7.23 (m, 4H), 6.84 (d, J=8.5 Hz, 2H), 4.68 (d, J=10.4 Hz, 4H), 2.56 (s, 6H), 2.27 - 2.18 (m, 2H), 1.55 - 1.41 (m, 2H), 1.24 - 1.11 (m, 2H), 0.73 (t, J=7.2 Hz, 3H)                                            | 0.78 A 450.3          | A                                        |

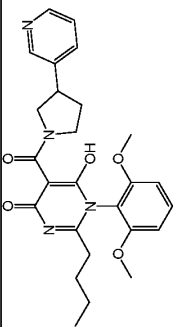
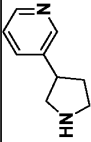
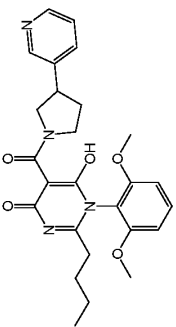
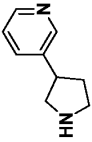
| Ex # | Structure | Name                                                                                                                       | Chiral amine intermediate with retention time                                                                                                                                                | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                     | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|----------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 67   |           | 2-butyl-1-(2,6-dimethoxyphenyl)-5-({3-[(4-fluorophenyl)methyl]pyrrolidine-1-carbonyl}-6-hydroxy-1,4-dihydropyrimidin-4-one | Racemic pyrrolidine amine                                                                                                                                                                    | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.45 (t, J=8.2 Hz, 1H), 7.32 (br. s., 1H), 7.07 (br. s., 3H), 6.83 (d, J=8.2 Hz, 2H), 3.79 - 3.74 (m, 2H), 3.01 (s, 2H), 2.69 (br. s., 2H), 2.52 (br. s., 6H), 2.47 - 2.36 (m, 1H), 2.19 (br. s., 2H), 1.96 - 1.81 (m, 1H), 1.60 - 1.52 (m, 1H), 1.43 (br. s., 2H), 1.15 (d, J=6.7 Hz, 2H), 0.72 (t, J=7.3 Hz, 3H) | 0.87 A<br>510.3           | A                                        |
| 68   |           | 2-butyl-1-(2,6-dimethoxyphenyl)-5-({3-[(pyridin-2-yl)pyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one                    | <br>7.62, 93.4%<br>Chiralpak AD-3, 4.6 x 150 mm, 3 micron;<br>mobile phase: 25% MeOH:DEA /75% CO <sub>2</sub> ;<br>Flow Conditions: 1.0 mL/min, 150 bar, 45°C, wavelength: 220 nm (Isomer 2) | <sup>1</sup> H NMR (400MHz, chloroform-d) δ 8.84 (d, J=4.4 Hz, 1H), 8.39 - 8.04 (m, 1H), 7.79 - 7.61 (m, 2H), 7.42 (t, J=8.5 Hz, 1H), 6.68 (d, J=8.4 Hz, 2H), 4.12 - 3.61 (m, 1H), 2.58 - 2.48 (m, 1H), 2.37 (br. s., 2H), 2.23 - 2.08 (m, 1H), 1.57 (quin, J=7.6 Hz, 2H), 1.30 - 1.13 (m, 2H), 0.76 (t, J=7.4 Hz, 3H)                                                 | 0.58 A<br>479.2           | A                                        |

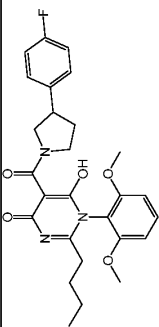
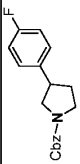
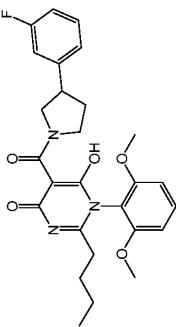
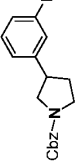


| Ex # | Structure | Name                                                                                                                     | Chiral amine intermediate with retention time                                                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                      | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|--------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 69   |           | 2-butyl-1-(2,6-dimethoxyphenyl)-5-{4-[(3-fluorophenyl)methyl]piperazine-1-carbonyl}-6-hydroxy-1,4-dihydropyrimidin-4-one |                                                                                                                                                                                                     | <sup>1</sup> H NMR (400MHz, chloroform-d) δ 7.53 - 7.33 (m, 2H), 7.22 - 7.07 (m, 3H), 6.70 (d, J=8.6 Hz, 2H), 4.15 (br. s., 2H), 3.93 - 3.02 (m, 14H), 2.40 (br. s., 2H), 1.61 - 1.41 (m, 2H), 1.30 - 1.12 (m, 2H), 0.75 (t, J=7.2 Hz, 3H)                                                                              | 0.65 A 525.3              | A                                        |
| 70   |           | 2-butyl-1-(2,6-dimethoxyphenyl)-5-{4-[(3-pyridyl)pyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one                      | <br>Cbz-N<br>6.77, 99%<br>Chiralpak AD-3, 4.6 x 150 mm, 3 micron;<br>mobile phase: 25% MeOH:DEA /75% CO <sub>2</sub> ;<br>Flow Conditions: 1.0 mL/min, 150 bar, 45°C, wavelength: 220 nm (Isomer 1) | <sup>1</sup> H NMR (400MHz, chloroform-d) δ 8.84 (d, J=4.4 Hz, 1H), 8.39 - 8.04 (m, 1H), 7.79 - 7.61 (m, 2H), 7.42 (t, J=8.5 Hz, 1H), 6.68 (d, J=8.4 Hz, 2H), 4.12 - 3.61 (m, 11H), 2.58 - 2.48 (m, 1H), 2.37 (br. s., 2H), 2.23 - 2.08 (m, 1H), 1.57 (quin, J=7.6 Hz, 2H), 1.30 - 1.13 (m, 2H), 0.76 (t, J=7.4 Hz, 3H) | 0.58 A 479.3              | A                                        |

| Ex # | Structure | Name                                                                                                           | Chiral amine intermediate with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|----------------------------------------------------------------------------------------------------------------|-----------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 71   |           | 2-butyl-1-(2,6-dimethoxyphenyl)-6-hydroxy-5-[4-(pyridin-4-yl)piperidine-1-carbonyl]-1,4-dihydropyrimidin-4-one |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 8.77 - 8.67 (m, 2H), 7.73 (d, J=5.8 Hz, 2H), 7.47 (s, 1H), 6.85 (d, J=8.5 Hz, 2H), 3.76 (br. s., 4H), 3.07 (t, J=12.1 Hz, 1H), 2.52 (br. s., 6H), 2.25 (t, J=7.5 Hz, 2H), 1.88 (br. s., 2H), 1.68 - 1.38 (m, 4H), 1.22 - 1.05 (m, 2H), 0.72 (t, J=7.3 Hz, 3H) | 0.59 A 479.3              | A                                        |
| 72   |           | 2-butyl-1-(2,6-dimethoxyphenyl)-6-hydroxy-5-(4-phenylpiperidine-1-carbonyl)-1,4-dihydropyrimidin-4-one         |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.42 (t, J=8.4 Hz, 1H), 7.33 - 7.26 (m, 2H), 7.23 - 7.16 (m, 3H), 6.82 (d, J=8.5 Hz, 2H), 3.74 (br. s., 5H), 2.52 (br. s., 6H), 2.15 (t, J=7.5 Hz, 2H), 1.92 (s, 2H), 1.77 (br. s., 2H), 1.48 - 1.38 (m, 2H), 1.20 - 1.08 (m, 2H), 0.72 (t, J=7.3 Hz, 3H)     | 0.86 A 492.3              | B                                        |

| Ex # | Structure | Name                                                                                                             | Chiral amine intermediate with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                | LC/MS Rt (min) Method | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 73   |           | 5-(3-benzylpyrrolidin-1-carbonyl)-2-butyl-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one           | Racemic pyrrolidine amine                     | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.42 (t, J=8.4 Hz, 1H), 7.34 - 7.13 (m, 5H), 6.81 (d, J=8.5 Hz, 2H), 3.74 (br. s., 2H), 3.00 (d, J=8.9 Hz, 1H), 2.66 (br. s., 1H), 2.52 (br. s., 6H), 2.38 (br. s., 1H), 2.13 (br. s., 2H), 1.92 (s, 3H), 1.59 - 1.50 (m, 1H), 1.42 (br. s., 2H), 1.18 - 1.08 (m, 2H), 0.71 (t, J=7.3 Hz, 3H) | 0.87 A 492.3          | A                                        |
| 74   |           | 2-butyl-1-(2,6-dimethoxyphenyl)-5-[4-(4-fluorophenyl)piperidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.48 - 7.37 (m, 1H), 7.29 - 7.17 (m, 2H), 7.10 (t, J=8.9 Hz, 2H), 6.82 (d, J=8.5 Hz, 2H), 3.74 (br. s., 5H), 2.52 (br. s., 6H), 2.18 (t, J=7.6 Hz, 2H), 1.82 - 1.65 (m, 2H), 1.43 (dt, J=15.0, 7.6 Hz, 4H), 1.18 - 1.10 (m, 2H), 0.71 (t, J=7.3 Hz, 3H)                                       | 0.87 A 510.3          | B                                        |

| Ex # | Structure                                                                            | Name                                                                                                             | Chiral amine intermediate with retention time                                                                                                                                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                  | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|--------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 75   |   | 2-butyl-1-(2,6-dimethoxyphenyl)-6-(hydroxy-5-[3-(pyridin-3-yl)pyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one | <br>12.0, 87.4%<br>Chiralpak AD-3, 4.6 x 150 mm, 3 micron;<br>mobile phase: 20% MeOH:0.1%DEA / 80% CO <sub>2</sub> ;<br>Flow Conditions: 1.0 mL/min, 150 bar, 45°C, wavelength: 260 nm (Isomer 2) | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 8.75 - 8.55 (m, 2H), 8.22 - 8.08 (m, 1H), 7.75 - 7.63 (m, 1H), 7.47 (q, J=8.9 Hz, 1H), 6.91 - 6.76 (m, 2H), 3.82 - 3.35 (m, 6H), 2.52 (br. s., 6H), 2.42 - 2.30 (m, 1H), 2.25 (d, J=7.3 Hz, 2H), 1.44 (d, J=6.4 Hz, 2H), 1.15 (br. s., 2H), 0.77 - 0.65 (m, 3H) | 0.58 A<br>479.2           | A                                        |
| 76   |  | 2-butyl-1-(2,6-dimethoxyphenyl)-6-(hydroxy-5-[3-(pyridin-3-yl)pyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one | <br>10.3, 92%<br>Chiralpak AD-3, 4.6 x 150 mm, 3 micron;<br>mobile phase: 20% MeOH:0.1%DEA / 80% CO <sub>2</sub> ;<br>Flow Conditions: 1.0 mL/min, 150 bar, 45°C, wavelength: 260 nm (Isomer 1)   | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 8.75 - 8.55 (m, 2H), 8.22 - 8.08 (m, 1H), 7.75 - 7.63 (m, 1H), 7.47 (q, J=8.9 Hz, 1H), 6.91 - 6.76 (m, 2H), 3.82 - 3.35 (m, 6H), 2.52 (br. s., 6H), 2.42 - 2.30 (m, 1H), 2.25 (d, J=7.3 Hz, 2H), 1.44 (d, J=6.4 Hz, 2H), 1.15 (br. s., 2H), 0.77 - 0.65 (m, 3H) | 0.58 A<br>479.2           | A                                        |

| Ex # | Structure                                                                            | Name                                                                                                       | Chiral amine intermediate with retention time                                                                                                                                                                                                                            | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                       | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|--------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 77   |   | 2-butyl-1-(2,6-dimethoxyphenyl)-5-[3-(4-fluorophenyl)pyrrolidin-1-yl]-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>9.93, 99%<br>Whelk-O 1 (R,R), 4.6 x 250 mm, 5 micron;<br>mobile phase: 15% IPA/85%CO <sub>2</sub> ;<br>Flow Conditions: 2.0 mL/min, 150 bar, 40°C, wavelength: 220 nm (Isomer 1)   | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.91 (s, 1H), 7.43 - 7.23 (m, 3H), 7.08 (t, J=8.1 Hz, 2H), 6.82 - 6.69 (m, 2H), 3.66 (s, 2H), 3.58 (br. s., 2H), 2.46 (br. s., 6H), 2.22 - 2.06 (m, 3H), 1.87 (s, 2H), 1.36 (d, J=6.7 Hz, 2H), 1.08 (br. s., 2H), 0.70 - 0.59 (m, 3H).                               | 0.87<br>A<br>496.1        | A                                        |
| 78   |  | 2-butyl-1-(2,6-dimethoxyphenyl)-5-[3-(4-fluorophenyl)pyrrolidin-1-yl]-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>9.81, 99.5%<br>Whelk-O 1 (R,R), 4.6 x 250 mm, 5 micron;<br>mobile phase: 15% IPA/85%CO <sub>2</sub> ;<br>Flow Conditions: 2.0 mL/min, 150 bar, 40°C, wavelength: 220 nm (Isomer 1) | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.97 (s, 1H), 7.49 - 7.32 (m, 2H), 7.15 (dd, J=18.5, 8.7 Hz, 2H), 7.06 (t, J=8.1 Hz, 1H), 6.87 - 6.74 (m, 2H), 3.74 - 3.19 (m, 6H), 2.52 (br. s., 6H), 2.34 - 2.22 (m, 1H), 2.16 (d, J=6.7 Hz, 2H), 1.42 (d, J=5.8 Hz, 2H), 1.20 - 1.10 (m, 2H), 0.77 - 0.65 (m, 3H) | 0.84<br>A<br>496.1        | A                                        |

| Ex # | Structure | Name                                                                                                              | Chiral amine intermediate with retention time                                                                                                                                                        | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                   | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|-------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 79   |           | 2-butyl-1-(2,6-dimethoxyphenyl)-5-[3-(4-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>9.93, 99%<br>Whekk-O 1 (R,R), 4.6 x<br>250 mm, 5 micron;<br>mobile phase: 15%<br>IPA/85%CO <sub>2</sub> ;<br>Flow Conditions: 2.0<br>mL/min, 150 bar, 40°C,<br>wavelength: 220 nm<br>(Isomer 1)  | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.50 - 7.30 (m, 3H), 7.14 (t, J=7.9 Hz, 2H), 6.88 - 6.75 (m, 2H), 3.79 - 3.61 (m, 6H), 2.52 (br. s., 6H), 2.30 - 2.09 (m, 3H), 1.48 - 1.37 (m, 2H), 1.22 - 1.10 (m, 2H), 0.81 - 0.65 (m, 3H)                                                     | 0.83<br>A<br>496.1        | A                                        |
| 80   |           | 2-butyl-1-(2,6-difluorophenyl)-5-[3-(4-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one  | <br>10.72, 92%<br>Whekk-O 1 (R,R), 4.6 x<br>250 mm, 5 micron;<br>mobile phase: 15%<br>IPA/85%CO <sub>2</sub> ;<br>Flow Conditions: 2.0<br>mL/min, 150 bar, 40°C,<br>wavelength: 220 nm<br>(Isomer 2) | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.97 (s, 1H), 7.53 - 7.31 (m, 2H), 7.23 - 7.11 (m, 2H), 7.09 - 7.02 (m, 1H), 6.89 - 6.76 (m, 2H), 3.74 - 3.24 (m, 6H), 2.52 (br. s., 6H), 2.32 - 2.22 (m, 1H), 2.16 (d, J=6.4 Hz, 2H), 1.43 (br. s., 2H), 1.15 (br. s., 2H), 0.78 - 0.65 (m, 3H) | 0.87<br>A<br>496.2        | A                                        |

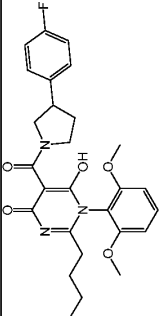
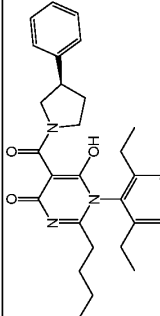
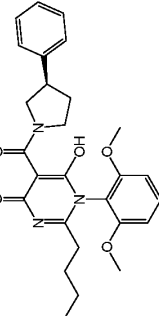
| Ex # | Structure | Name                                                                                                                      | Chiral amine intermediate with retention time                                                                                                                                                     | <sup>1</sup> H NMR                                                                                                                                                                                                                                                              | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|---------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 81   |           | 1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-5-[3-(4-fluorophenyl)pyrrolidin-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>9.93, 99%<br>Wheik-O 1 (R,R), 4.6 x 250 mm, 5 micron;<br>mobile phase: 15% IPA/85%CO <sub>2</sub> ;<br>Flow Conditions: 2.0 mL/min, 150 bar, 40°C, wavelength: 220 nm (Isomer 1)              | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.41 - 7.29 (m, 3H), 7.13 (d, J=4.6 Hz, 2H), 6.81 - 6.70 (m, 2H), 3.88 - 3.81 (m, 2H), 3.74 (br. s., 4H), 3.65 - 3.59 (m, 1H), 3.29 - 3.19 (m, 2H), 2.52 (br. s., 6H), 1.92 (s, 3H), 0.96 (dt, J=13.4, 6.9 Hz, 3H)          | 0.81 A<br>498.2           | A                                        |
| 82   |           | 1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-5-[3-(pyridin-3-yl)pyrrolidin-1-carbonyl]-1,4-dihydropyrimidin-4-one             | <br>12.0, 87.4%<br>Chiralpak AD-3, 4.6 x 150 mm, 3 micron;<br>mobile phase: 20% MeOH:0.1%DEA / 80% CO <sub>2</sub> ;<br>Flow Conditions: 1.0 mL/min, 150 bar, 45°C, wavelength: 260 nm (Isomer 2) | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 8.72 - 8.46 (m, 2H), 7.58 - 7.37 (m, 2H), 6.90 - 6.76 (m, 2H), 3.97 (d, J=8.9 Hz, 2H), 3.80 - 3.62 (m, 5H), 3.31 (dd, J=12.7, 6.6 Hz, 2H), 2.52 (br. s., 6H), 2.40 - 2.29 (m, 1H), 2.07 - 1.95 (m, 1H), 1.05 - 0.94 (m, 3H) | 0.52 A<br>481.2           | A                                        |

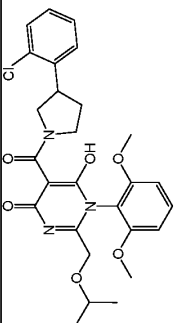
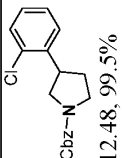
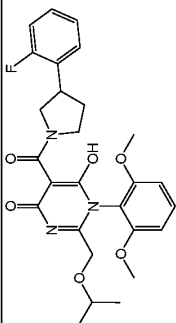
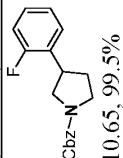
| Ex # | Structure | Name                                                                                                                       | Chiral amine intermediate with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                             | LC/MS Rt (min) Method | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|----------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 83   |           | 1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-5-[3-(3-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.45 (br. s., 1H), 7.39 - 7.33 (m, 1H), 7.20 - 7.02 (m, 4H), 6.87 - 6.77 (m, 2H), 3.97 (d, J=6.1 Hz, 2H), 3.80 - 3.63 (m, 5H), 3.31 (br. s., 2H), 2.52 (br. s., 6H), 2.29 (br. s., 1H), 1.97 (br. s., 1H), 1.04 - 0.88 (m, 3H)                             | 0.79 A<br>498.2       | A                                        |
| 84   |           | 1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-5-[3-(3-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.53 - 7.41 (m, 1H), 7.40 - 7.32 (m, 1H), 7.15 (br. s., 4H), 6.90 - 6.68 (m, 2H), 3.97 (d, J=5.8 Hz, 2H), 3.85 - 3.60 (m, 4H), 3.34 - 3.25 (m, 2H), 3.21 - 3.17 (m, 1H), 2.52 (br. s., 6H), 2.28 (br. s., 1H), 2.04 - 1.90 (m, 1H), 0.99 (d, J=6.4 Hz, 3H) | 0.79 A<br>498.3       | A                                        |



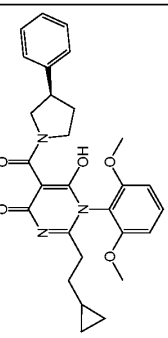
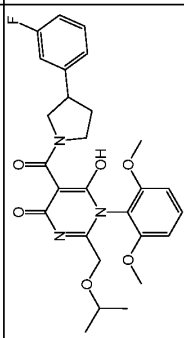
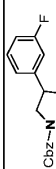
| Ex # | Structure | Name                                                                                                                     | Chiral amine intermediate with retention time                                                                                                                                                   | <sup>1</sup> H NMR                                                                                                                                                                                                                                                              | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|--------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 85   |           | 1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-6-hydroxy-5-[3-(pyridin-3-yl)pyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one | <br>10.3, 92%<br>Chiralpak AD-3, 4.6 x 150 mm, 3 micron;<br>mobile phase: 20% MeOH:0.1%DEA / 80% CO <sub>2</sub> ;<br>Flow Conditions: 1.0 mL/min, 150 bar, 45°C, wavelength: 260 nm (Isomer 1) | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 8.72 - 8.46 (m, 2H), 7.58 - 7.37 (m, 2H), 6.90 - 6.76 (m, 2H), 3.97 (d, J=8.9 Hz, 2H), 3.80 - 3.62 (m, 5H), 3.31 (dd, J=12.7, 6.6 Hz, 2H), 2.52 (br. s., 6H), 2.40 - 2.29 (m, 1H), 2.07 - 1.95 (m, 1H), 1.05 - 0.94 (m, 3H) | 0.52 A<br>481.2           | A                                        |
| 86   |           | 2-butyl-1-3-(2,6-diethylphenyl)-6-hydroxy-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one             |                                                                                                                                                                                                 | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.48 - 7.40 (m, 1H), 7.37 - 6.98 (m, 7H), 2.56 (s, 6H), 2.39 - 2.09 (m, 6H), 2.02 - 1.85 (m, 1H), 1.58 - 1.43 (m, 2H), 1.21 - 1.04 (m, 6H), 0.99 (br. s., 2H), 0.78 - 0.59 (m, 3H)                                          | 1.05 A<br>474.2           | A                                        |

| Ex # | Structure | Name                                                                                                              | Chiral amine intermediate with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                    | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|-------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 87   |           | 2-butyl-3-(2,6-dimethoxyphenyl)-5-[3-(4-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-3,4-dihydropyrimidin-4-one | Racemic pyrrolidine amine                     | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.50 - 7.42 (m, 1H), 7.40 - 7.30 (m, 2H), 7.14 (br. s., 2H), 6.84 (d, J=7.9 Hz, 2H), 4.00 - 3.50 (m, 2H), 3.46 - 3.35 (m, 1H), 2.59 - 2.54 (m, 6H), 2.24 (d, J=6.7 Hz, 3H), 1.99 - 1.82 (m, 1H), 1.52 - 1.39 (m, 2H), 1.22 - 1.09 (m, 2H), 0.71 (d, J=7.6 Hz, 3H) | 0.91 A 496.0              | A                                        |
| 88   |           | 2-butyl-5-[3-(3-chlorophenyl)azetidine-1-carbonyl]-3-(2,6-dimethoxyphenyl)-6-hydroxy-3,4-dihydropyrimidin-4-one   |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.48 - 7.35 (m, 3H), 7.34 - 7.27 (m, 2H), 6.83 (d, J=8.5 Hz, 2H), 4.39 (t, J=9.3 Hz, 2H), 3.85 (d, J=6.4 Hz, 1H), 3.74 (s, 6H), 2.54 (s, 2H), 2.22 (t, J=7.6 Hz, 2H), 1.43 (t, J=7.5 Hz, 2H), 1.19 - 1.09 (m, 2H), 0.70 (t, J=7.3 Hz, 3H)                         | 0.87 A 498.0              | A                                        |

| Ex # | Structure                                                                            | Name                                                                                                            | Chiral amine intermediate with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                                      | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|--------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|-----------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 89   |   | 2-butyl-3-(2,6-diethylphenyl)-5-[3-(4-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-3,4-dihydropyrimidin-4-one | Racemic pyrrolidine amine                     | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.48 - 7.26 (m, 5H), 7.18 - 7.07 (m, 2H), 3.61 - 3.23 (m, 8H), 2.37 - 2.17 (m, 2H), 2.17 - 2.09 (m, 2H), 2.01 - 1.83 (m, 1H), 1.56 - 1.45 (m, 2H), 1.22 - 1.04 (m, 6H), 1.01 - 0.93 (m, 2H), 0.73 (d, J=7.9 Hz, 3H) | 1.06 A 492.1              | A                                        |
| 90   |   | 2-butyl-3-(2,6-diethylphenyl)-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-6-hydroxy-3,4-dihydropyrimidin-4-one      |                                               | <sup>1</sup> H NMR (400MHz, chloroform-d) δ 7.31 (br. s., 8H), 2.45 - 1.99 (m, 13H), 1.72 - 1.58 (m, 2H), 1.16 (br. s., 8H), 0.80 (t, J=7.3 Hz, 3H)                                                                                                                     | 1.05 A 474.3              | A                                        |
| 91   |  | 2-butyl-3-(2,6-dimethoxyphenyl)-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-6-hydroxy-3,4-dihydropyrimidin-4-one    |                                               | <sup>1</sup> H NMR (400MHz, DMSO-d <sub>6</sub> ) δ 7.32 (br. s., 6H), 6.92 - 6.77 (m, 2H), 5.77 (s, 1H), 3.96 - 3.21 (m, 10H), 2.31 - 2.16 (m, 3H), 2.01 - 1.86 (m, 1H), 1.53 - 1.37 (m, 2H), 1.21 - 1.11 (m, 2H), 0.71 (d, J=8.1 Hz, 3H)                              | 0.88 A 478.1              | A                                        |

| Ex # | Structure                                                                            | Name                                                                                                                                                           | Chiral amine intermediate with retention time                                                                                                                                                                                                                                    | <sup>1</sup> H NMR                                                                                                                                                                                                                                   | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|--------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 92   |   | 5-[3-(2-chlorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-yl-(propan-2-yl)oxy)methyl-1,4-dihydropyrimidin-4-one                         | <br>Cbz-N<br>12.48, 99.5%<br>Chiralpak IF, 4.6 x 250 mm, 5 micron;<br>mobile phase: 15% IPA/85% CO <sub>2</sub> ;<br>Flow Conditions: 2.0 mL/min, 150 bar, 40°C, wavelength: 220 nm (Isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.35-7.52 (m, 3H), 7.22-7.35 (m, 2H), 6.72-6.84 (m, 2H), 3.86-3.93 (m, 2H), 3.19-3.86 (m, 12H), 2.17-2.32 (m, 1H), 1.93-2.08 (m, 1H), 0.80-0.93 (m, 6H)                                         | 1.26<br>A<br>528.0        | A                                        |
| 93   |  | 1-(2,6-dimethoxyphenyl)-5-[3-(2-fluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-yl-(propan-2-yl)oxy)methyl-1,4-dihydropyrimidin-4-one | <br>Cbz-N<br>10.65, 99.5%<br>Chiralpak IF, 4.6 x 250 mm, 5 micron;<br>mobile phase: 15% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 2.0 mL/min, 150 bar, 40°C, wavelength: 220 nm (Isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.33-7.46 (m, 2H), 7.23-7.33 (m, 1H), 7.10-7.22 (m, 2H), 6.71-6.85 (m, 2H), 3.89 (d, J=10.01 Hz, 2H), 3.19-3.77 (m, 12H), 2.18-2.29 (m, 1H), 1.93-2.05 (m, 1H), 0.87 (dd, J=5.72, 10.60 Hz, 6H) | 1.18<br>A<br>512.1        | A                                        |

| Ex # | Structure | Name                                                                                                                                  | Chiral amine intermediate with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                | LC/MS Rt (min) Method | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|---------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 94   |           | 1-(2,6-dimethoxyphenyl)-5-[3-(4-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-2-[(propan-2-yl)oxy)methyl]-1,4-dihydropyrimidin-4-one |                                               | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.33 (d, J=6.31 Hz, 3H), 7.04-7.18 (m, 3H), 6.63-6.77 (m, 1H), 3.72 (d, J=8.58 Hz, 2H), 2.91-3.64 (m, 12H), 2.14-2.33 (m, 1H), 1.77-1.91 (m, 1H), 0.82 (dd, J=5.60, 13.59 Hz, 6H)                                                                                            | 1.21 A<br>512.3       | A                                        |
| 95   |           | 1-(2,6-dimethoxyphenyl)-5-[3-(4-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-2-[(propan-2-yl)oxy)methyl]-1,4-dihydropyrimidin-4-one |                                               | <sup>1</sup> H NMR (500 MHz, methanol-d <sub>4</sub> ) δ 7.42-7.54 (m, 1H), 7.28-7.36 (m, 1H), 7.10-7.17 (m, 1H), 7.03-7.10 (m, 1H), 6.91-6.98 (m, 1H), 6.73-6.85 (m, 2H), 4.08 (br. s., 2H), 3.76-3.85 (m, 6H), 3.65-3.72 (m, 2H), 3.54-3.63 (m, 1H), 3.42-3.53 (m, 3H), 2.26-2.40 (m, 1H), 2.01-2.14 (m, 1H), 1.01 (br. s., 6H) | 1.34 A<br>512.3       | A                                        |

| Ex # | Structure                                                                            | Name                                                                                                                                   | Chiral amine intermediate with retention time                                                                                                                                                                                                                            | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                     | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|--------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 96   |   | 2-(2-cyclopropylethyl)-1-(2,6-dimethoxyphenyl)-6-hydroxy-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one            |                                                                                                                                                                                                                                                                          | <sup>1</sup> H NMR (400 MHz, methanol-d <sub>4</sub> ) δ 7.44-7.53 (m, 1H), 7.27-7.33 (m, 4H), 7.16-7.26 (m, 1H), 6.76-6.89 (m, 2H), 3.74-3.85 (m, 6H), 3.66 (br. s., 2H), 3.54-3.63 (m, 1H), 3.44-3.51 (m, 2H), 2.40-2.54 (m, 2H), 2.25-2.39 (m, 1H), 2.01-2.15 (m, 1H), 1.33-1.50 (m, 2H), 0.53-0.68 (m, 1H), 0.25-0.42 (m, 2H), -0.22--0.09 (m, 2H) | 1.46 A 490.1              | A                                        |
| 97   |  | 1-(2,6-dimethoxyphenyl)-5-[(3-(3-fluorophenyl)pyrrolidine-1-carbonyl)-6-hydroxy-2-[(propan-2-yl)oxy)methyl]-1,4-dihydropyrimidin-4-one | <br>9.81, 99.5%<br>Whekk-O 1 (R,R), 4.6 x 250 mm, 5 micron;<br>mobile phase: 15% IPA/85%CO <sub>2</sub> ;<br>Flow Conditions: 2.0 mL/min, 150 bar, 40°C, wavelength: 220 nm (Isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) Shift 7.39-7.48 (m, 1H), 7.31-7.38 (m, 1H), 7.09-7.20 (m, 2H), 7.05 (t, J=8.29 Hz, 1H), 6.73-6.85 (m, 2H), 2.83-3.98 (m, 12H), 2.27 (br. s., 1H), 1.86-2.02 (m, 1H), 0.76-0.93 (m, 6H)                                                                                                              | 1.23 A 512.3              | A                                        |

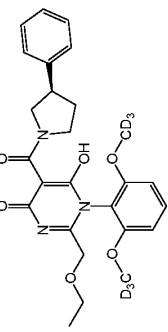
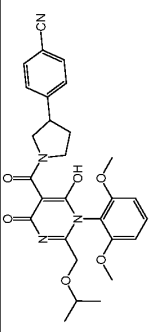
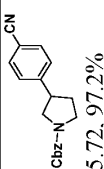
| Ex # | Structure | Name                                                                                                                                            | Chiral amine intermediate with retention time                                                                                                                                                                | <sup>1</sup> H NMR                                                                                                                                                                                                         | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 98   |           | 1-(2,6-dimethoxyphenyl)-6-hydroxy-5-[3-(2-methylphenyl)pyrrolidine-1-carbonyl]-2-[(propan-2-yloxy)methyl]-1,4-dihydropyrimidin-4-one            | <br>Cbz-N<br>14.99, >99%<br>Lux Cellulose-4 21 x 250 mm, 5 micron; mobile phase: 15% IPA:heptane (1:1)/85% CO <sub>2</sub> ; flow condition: 2.0 mL/min, 150 bar, 40°C, wavelength: 220 nm (Isomer 2)        | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.22-7.29 (m, 1H), 7.06-7.21 (m, 4H), 6.70-6.83 (m, 2H), 3.18-3.88 (m, 14H), 2.27-2.36 (m, 3H), 2.12-2.23 (m, 1H), 1.83-1.99 (m, 1H), 0.85 (dd, J=5.85, 15.44 Hz, 6H) | 1.22<br>A<br>508.1        | A                                        |
| 99   |           | 1-(2,6-dimethoxyphenyl)-6-hydroxy-2-[(propan-2-yloxy)methyl]-5-[3-(2-(trifluoromethyl)phenyl)pyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one | <br>F <sub>3</sub> C-<br>Cbz-N<br>5.27, >99%<br>Chiralpak IF, 4.6 x 250 mm, 5 micron; mobile phase: 10% MeOH/90% CO <sub>2</sub> ; Flow Conditions: 2.0 mL/min, 150 bar, 40°C, Wavelength: 220 nm (Isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.22-7.29 (m, 1H), 7.06-7.21 (m, 4H), 6.70-6.83 (m, 2H), 3.18-3.88 (m, 14H), 2.27-2.36 (m, 3H), 2.12-2.23 (m, 1H), 1.83-1.99 (m, 1H), 0.85 (dd, J=5.85, 15.44 Hz, 6H) | 1.41<br>A<br>562.4        | A                                        |

| Ex # | Structure | Name                                                                                                                                            | Chiral amine intermediate with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                  | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 100  |           | 2-(cyclopropoxymethyl)-1-(2,6-dimethoxyphenyl)-5-[3-(4-fluorophenyl)pyrrolidin-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one                 |                                               | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.22-7.27 (m, 1H), 7.12-7.22 (m, 4H), 6.89-7.03 (m, 1H), 6.53-6.67 (m, 1H), 3.74 (d, J=13.43 Hz, 2H), 3.58 (br. s., 3H), 3.53 (s, 3H), 3.46 (br. s., 1H), 3.24-3.39 (m, 2H), 3.18-3.25 (m, 1H), 3.03-3.15 (m, 2H), 2.00-2.12 (m, 1H), 1.71-1.80 (m, 1H), 0.07-0.21 (m, 2H), -0.07-0.06 (m, 2H) | 1.26 A 510.2              | A                                        |
| 101  |           | 1-(2,6-dimethoxyphenyl)-6-hydroxy-2-[(propan-2-yl)oxy)methyl]-5-[3-(2-(trifluoromethyl)phenyl)pyrrolidin-1-carbonyl]-1,4-dihydropyrimidin-4-one |                                               | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.59-7.77 (m, 3H), 7.32-7.52 (m, 2H), 6.69-6.88 (m, 2H), 3.18-3.95 (m, 14H), 2.17-2.30 (m, 1H), 1.98-2.13 (m, 1H), 0.75-0.91 (m, 6H)                                                                                                                                                           | 1.46 A 562.0              | A                                        |



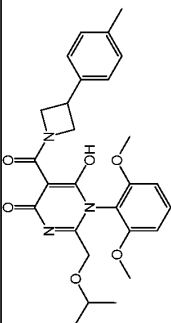
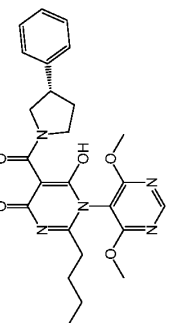
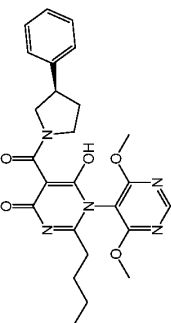
| Ex # | Structure | Name                                                                                                                                 | Chiral amine intermediate with retention time                                                                                                                                        | <sup>1</sup> H NMR                                                                                                                                                                        | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|--------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 102  |           | 1-(2,6-dimethoxyphenyl)-5-[3-(4-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-2-[(propan-2-yl)oxy]methyl-1,4-dihydropyrimidin-4-one | <br>10.7, 90%<br>Whelk-O 1 (R,R), 4.6 x 250 mm, 5 micron;<br>mobile phase: 15% IPA/85%CO <sub>2</sub> ;<br>Flow Conditions: 2.0 mL/min, 150 bar, 40°C, wavelength: 220 nm (Isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.30-7.38 (m, 2H), 7.08-7.25 (m, 3H), 6.75-6.87 (m, 2H), 3.21-4.00 (m, 14H), 2.19-2.34 (m, 1H), 1.88-2.01 (m, 1H), 0.84-0.97 (m, 6H) | 1.34<br>A<br>512.3        | A                                        |
| 103  |           | 2-(cyclopropyl)methyl-1-(2,6-dimethoxyphenyl)-5-[3-(4-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one      | <br>10.7, 90%<br>Whelk-O 1 (R,R), 4.6 x 250 mm, 5 micron;<br>mobile phase: 15% IPA/85%CO <sub>2</sub> ;<br>Flow Conditions: 2.0 mL/min, 150 bar, 40°C, wavelength: 220 nm (Isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.30-7.38 (m, 2H), 7.08-7.25 (m, 3H), 6.75-6.87 (m, 2H), 3.21-4.00 (m, 14H), 2.19-2.34 (m, 1H), 1.88-2.01 (m, 1H), 0.84-0.97 (m, 6H) | 1.26<br>A<br>510.2        | A                                        |

- 158 -

| Ex # | Structure                                                                           | Name                                                                                                                                   | Chiral amine intermediate with retention time                                                                                                                                                                                                            | <sup>1</sup> H NMR                                                                                                                                                                                          | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 106  |  | 1-[2,6-bis(2,6-dimethoxyphenyl)-6-hydroxy-5-oxo-1,4-dihydropyrimidin-4-one-3-phenyl]pyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one |                                                                                                                                                                                                                                                          | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.37-7.45 (m, 1H), 7.21-7.36 (m, 5H), 6.70-6.85 (m, 2H), 3.82-3.95 (m, 2H), 3.14-3.75 (m, 7H), 2.17-2.37 (m, 1H), 1.86-2.01 (m, 1H), 0.89-1.06 (m, 3H) | 1.37 A 486.0              | A                                        |
| 107  |  | 4-{1-[1-(2,6-dimethoxyphenyl)-6-hydroxy-4-oxo-2-[(propan-2-yl)oxy]methyl]-1,4-dihydropyrimidin-5-carbonyl]pyrrolidin-3-yl}benzonitrile | <br>5.72, 97.2%<br>Chiralpak AS-H 4.6 x 250 mm; mobile phase: 20% MeOH/80% CO <sub>2</sub> ; Flow Conditions: 2.0 mL/min, 150 bar, 40°C, wavelength: 220 nm (Isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.37-7.45 (m, 1H), 7.21-7.36 (m, 5H), 6.70-6.85 (m, 2H), 3.82-3.95 (m, 2H), 3.14-3.75 (m, 7H), 2.17-2.37 (m, 1H), 1.86-2.01 (m, 1H), 0.89-1.06 (m, 3H) | 1.23 A 519.2              | A                                        |

12495 WO PCT

| Ex # | Structure | Name                                                                                                                                   | Chiral amine intermediate with retention time                                                                                                                           | <sup>1</sup> H NMR                                                                                                                                                                                                                                       | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|----------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 108  |           | 4-{1-[1-(2,6-dimethoxyphenyl)-6-hydroxy-4-oxo-2-[(propan-2-ylloxy)methyl]-1,4-dihydropyrimidin-5-carbonyl]pyrrolidin-3-yl}benzonitrile | <br>4.55, ≥99.0%<br>Chiralpak AS-H 4.6 x 250 mm; mobile phase: 20% MeOH/80% CO <sub>2</sub> ; Flow Conditions: 2.0 mL/min, 150 bar, 40°C, wavelength: 220 nm (Isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) Shift 7.72-7.84 (m, 2H), 7.48-7.60 (m, 2H), 7.30-7.44 (m, 1H), 6.68-6.81 (m, 2H), 3.84 (d, J=14.95 Hz, 2H), 3.19-3.77 (m, 12H), 2.23-2.32 (m, 1H), 1.88-1.99 (m, 1H), 0.86 (dd, J=5.30, 13.90 Hz, 6H) | 1.22 A<br>519.2           | A                                        |
| 109  |           | 1-[2,6-bis(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-6-hydroxy-5-[(3S)-3-phenylpyrrolidin-1-carbonyl]-1,4-dihydropyrimidin-4-one           |                                                                                                                                                                         | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) d 7.35-7.44 (m, 1H), 7.20-7.34 (m, 5H), 6.70-6.83 (m, 2H), 3.87 (d, J=14.34 Hz, 2H), 3.33-3.75 (m, 5H), 3.17-3.33 (m, 2H), 2.19-2.32 (m, 1H), 1.87-1.98 (m, 1H), 0.89-1.04 (m, 3H)                    | 1.35 A<br>486.1           | A                                        |
| 110  |           | 1-(2,6-dimethoxyphenyl)-6-hydroxy-5-(3-phenylazetidine-1-carbonyl)-2-[(propan-2-ylloxy)methyl]-1,4-dihydropyrimidin-4-one              |                                                                                                                                                                         | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) d 7.31-7.39 (m, 5H), 7.21-7.27 (m, 1H), 6.75 (d, J=8.41 Hz, 2H), 3.72-4.38 (m, 7H), 3.71 (br. s., 6H), 3.19-3.29 (m, 1H), 0.85 (d, J=6.06 Hz, 6H)                                                     | 1.15 A<br>480.1           | B                                        |

| Ex # | Structure                                                                            | Name                                                                                                                                | Chiral amine intermediate with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                           | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|--------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 111  |   | 1-(2,6-dimethoxyphenyl)-6-hydroxy-5-[3-(4-methylphenyl)azetidine-1-carbonyl]-2-[(propan-2-ylloxy)methyl]-1,4-dihydropyrimidin-4-one |                                               | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.35 (t, J=8.20 Hz, 1H), 7.20-7.27 (m, 2H), 7.10-7.17 (m, 2H), 6.74 (d, J=8.16 Hz, 1H), 4.28 (br. s., 2H), 3.19-4.04 (m, 13H), 2.26 (br. s., 3H), 1.91 (s, 2H), 0.84 (d, J=5.81 Hz, 6H) | 1.30 A 494.4              | B                                        |
| 112  |   | 2-butyl-3-(4,6-dimethoxypyrimidin-5-yl)-6-hydroxy-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one                |                                               | <sup>1</sup> H NMR (400MHz, methanol-d <sub>4</sub> ) δ 8.56 (s, 1H), 7.32 (m, 5H), 4.01 (s, 6H), 3.89 (m, 2H), 3.49 (m, 3H), 2.42 (m, 3H), 2.18 - 2.04 (m, 1H), 1.70 - 1.53 (m, 2H), 1.36 - 1.20 (m, 2H), 0.84 (m, 3H)                      | 1.95 C 480.1              | A                                        |
| 113  |  | 2-butyl-3-(4,6-dimethoxypyrimidin-5-yl)-6-hydroxy-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one                |                                               | <sup>1</sup> H NMR (400MHz, methanol-d <sub>4</sub> ) δ 8.56 (s, 1H), 7.30 (m, 5H), 4.00 (s, 6H), 3.88 (m, 2H), 3.48 (m, 3H), 2.41 (m, 3H), 2.17 - 1.98 (m, 1H), 1.69 - 1.49 (m, 2H), 1.28 (m, 2H), 0.83 (m, 3H)                             | 1.95 C 480.1              | A                                        |

| Ex # | Structure | Name                                                                                                              | Chiral amine intermediate with retention time                                                                                                                                         | <sup>1</sup> H NMR                                                                                                                                                                                   | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|-------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 114  |           | 2-butyl-5-[3-(2-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-3-[(1S)-1-phenylpropyl]-3,4-dihydropyrimidin-4-one | <br>10.65, 99.5%<br>Chiralpak IF, 4.6 x 250 mm, 5 micron;<br>mobile phase: 15% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 2.0 mL/min, 150 bar, 40°C, wavelength: 220 nm (Isomer 1) | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.42 - 7.02 (m, 9H), 3.74 - 2.88 (m, 5H), 2.37 (d, J=9.2 Hz, 2H), 2.18 (br. s., 2H), 1.92 (br. s., 2H), 1.76 - 1.09 (m, 4H), 0.97 - 0.48 (m, 6H) | 1.67<br>A<br>478.0        | A                                        |
| 115  |           | 2-butyl-5-[3-(3-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-3-[(1S)-1-phenylpropyl]-3,4-dihydropyrimidin-4-one | <br>12.48, 99.5%<br>Chiralpak IF, 4.6 x 250 mm, 5 micron;<br>mobile phase: 15% IPA/85% CO <sub>2</sub> ;<br>Flow Conditions: 2.0 mL/min, 150 bar, 40°C, wavelength: 220 nm (Isomer 2) | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.44 - 6.89 (m, 9H), 3.97 - 3.09 (m, 5H), 2.42 (br. s., 2H), 2.24 (br. s., 2H), 1.90 (s, 2H), 1.73 - 1.09 (m, 4H), 1.00 - 0.68 (m, 6H).          | 1.79<br>A<br>478.0        | A                                        |

| Ex # | Structure | Name                                                                                                                       | Chiral amine intermediate with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                    | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|----------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 116  |           | 2-butoxy-1-phenylethyl-3-[(1R)-2-methoxy-1-phenylethyl]-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.46 - 6.85 (m, 10H), 5.47 (br. s., 1H), 4.34 - 3.41 (m, 7H), 3.26 (s, 3H), 2.93 - 2.59 (m, 2H), 2.28 - 1.78 (m, 2H), 1.54 (br. s., 2H), 1.40 - 1.12 (m, 2H), 0.97 - 0.51 (m, 3H) | 1.65 A 475.9              | A                                        |
| 117  |           | 2-butoxy-1-phenylethyl-3-[(1R)-1-phenylethyl]-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one           |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.41 - 6.99 (m, 10H), 3.94 - 3.30 (m, 5H), 2.17 (br. s., 1H), 1.87 (s, 1H), 1.74 (br. s., 3H), 1.44 (br. s., 1H), 1.21 - 0.92 (m, 3H), 0.67 (br. s., 3H)                          | 1.63 A 446.0              | A                                        |
| 118  |           | 2-butoxy-1-phenylethyl-3-[(2R)-2-fluorophenyl]pyrrolidine-1-carbonyl-3-[(1S)-1-phenylethyl]-3,4-dihydropyrimidin-4-one     |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.53 - 7.05 (m, 9H), 4.10 - 3.23 (m, 5H), 2.46 - 2.32 (m, 1H), 2.24 (br. s., 2H), 2.03 - 1.90 (m, 1H), 1.73 - 1.11 (m, 4H), 0.96 - 0.70 (m, 6H)                                   | 1.66 A 478.1              | A                                        |

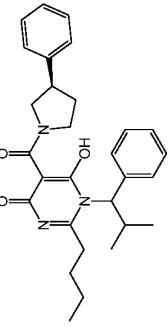
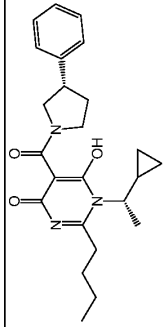
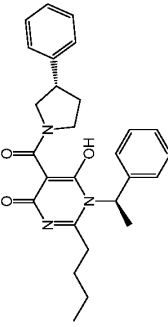
| Ex # | Structure | Name                                                                                                                   | Chiral amine intermediate with retention time                                                                                                                                         | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                          | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 119  |           | 2-butyl-5-[3-(3-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-3-[(1S)-1-phenylpropyl]-3,4-dihydropyrimidin-4-one      | <br>10.72, 92%<br>Whekk-O 1 (R,R), 4.6 x 250 mm, 5 micron;<br>mobile phase: 15% IPA/85%CO <sub>2</sub> ;<br>Flow Conditions: 2.0 mL/min, 150 bar, 40°C, wavelength: 220 nm (Isomer 2) | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.06 (d, J=9.0 Hz, 9H), 4.00 - 3.08 (m, 5H), 2.24 (br. s., 2H), 1.90 (br. s, 2H), 1.69 - 1.14 (m, 4H), 1.07 - 0.55 (m, 6H)                                                                                                                              | 1.71 A<br>478.4           | A                                        |
| 120  |           | 2-butyl-6-hydroxy-3-[(1S)-1-(3-methoxyphenyl)ethyl]-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one |                                                                                                                                                                                       | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.36 - 7.13 (m, 5H), 6.92 - 6.78 (m, 1H), 6.76 - 6.67 (m, 2H), 6.65 - 6.53 (m, 1H), 4.15 - 3.75 (m, 1H), 3.65 (br. s., 3H), 3.46 - 3.07 (m, 4H), 2.29 - 2.16 (m, 1H), 1.99 - 1.86 (m, 1H), 1.77 (br. s., 3H), 1.57 - 0.93 (m, 4H), 0.81 - 0.45 (m, 3H). | 1.56 A<br>476.4           | A                                        |



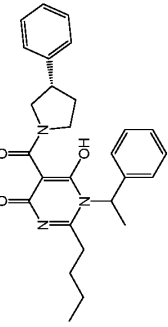
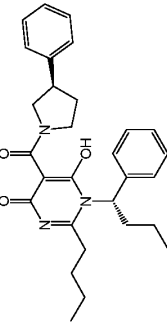
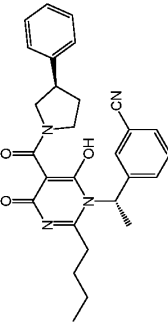
| Ex # | Structure | Name                                                                                                                 | Chiral amine intermediate with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                          | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|----------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 121  |           | 2-butyl-1-phenylpyrrolidine-1-carbonyl-3-[(1S)-1-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one            |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.42 - 7.09 (m, 10H), 4.23 - 3.17 (m, 5H), 2.41 (br. s., 1H), 2.23 (br. s., 1H), 1.90 (s, 2H), 1.66 - 1.00 (m, 4H), 0.94 - 0.51 (m, 6H)                                                 | 1.82 A 460.0              | A                                        |
| 122  |           | 2-butyl-1-phenylpyrrolidine-1-carbonyl-3-[(1R)-1-(2-methoxyphenyl)pyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.54 - 7.45 (m, 1H), 7.37 - 7.15 (m, 6H), 7.05 - 6.73 (m, 2H), 4.03 - 3.13 (m, 5H), 2.93 - 2.57 (m, 2H), 2.20 (br. s., 1H), 2.03 - 1.68 (m, 4H), 1.62 - 1.01 (m, 4H), 0.78 (br. s., 3H) | 1.83 A 476.1              | A                                        |
| 123  |           | 2-butyl-1-phenylpyrrolidine-1-carbonyl-3-[(1R)-1-(2-methoxyphenyl)pyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.42 - 7.07 (m, 10H), 4.02 - 3.05 (m, 5H), 2.22 (br. s., 1H), 1.91 (s, 1H), 1.86 - 1.72 (m, 3H), 1.52 (br. s., 1H), 1.40 - 0.95 (m, 3H), 0.89 - 0.59 (m, 3H)                            | 1.71 A 446.0              | A                                        |

| Ex # | Structure | Name                                                                                                            | Chiral amine intermediate with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                         | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|-----------------------------------------------------------------------------------------------------------------|-----------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 124  |           | 2-butyl-6-hydroxy-3-[(1R)-1-phenylpropyl]-5-[(3R)-3-phenylpyrrolidin-1-carbonyl]-3,4-dihydropyrimidin-4-one     |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.51 - 6.99 (m, 10H), 4.01 - 3.13 (m, 5H), 2.43 (br. s., 1H), 2.30 - 2.06 (m, 2H), 1.90 (s, 1H), 1.71 - 0.97 (m, 4H), 0.94 - 0.47 (m, 6H)                              | 1.73 A 460.2              | A                                        |
| 125  |           | 2-butyl-6-hydroxy-3-[(1S)-1-phenylethyl]-5-[(3S)-3-phenylpyrrolidin-1-carbonyl]-3,4-dihydropyrimidin-4-one      |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.38 - 7.19 (m, 10H), 4.03 - 3.13 (m, 5H), 2.64 (br. s., 2H), 2.23 (br. s., 1H), 2.03 - 1.89 (m, 1H), 1.83 (br. s., 3H), 1.61 - 1.08 (m, 4H), 0.75 (br. s., 3H)        | 1.68 A 446.1              | A                                        |
| 126  |           | 2-butyl-3-[(1S)-1-cyclopropylethyl]-6-hydroxy-5-[(3R)-3-phenylpyrrolidin-1-carbonyl]-3,4-dihydropyrimidin-4-one |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.47 - 6.83 (m, 5H), 4.05 - 3.44 (m, 5H), 2.58 (br. s., 1H), 2.20 (br. s., 1H), 1.99 - 1.81 (m, 2H), 1.63 - 1.24 (m, 6H), 0.86 (d, J=7.6 Hz, 3H), 0.64 - -0.26 (m, 4H) | 1.74 A 410.1              | A                                        |

| Ex # | Structure | Name                                                                                                                  | Chiral amine intermediate with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                      | LC/MS Rt (min) Method | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|-----------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 127  |           | 2-butyl-6-hydroxy-3-[(1R)-2-methoxy-1-phenylethyl]-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.52 - 6.91 (m, 10H), 4.55 - 3.76 (m, 4H), 3.61 - 3.07 (m, 6H), 2.94 - 2.57 (m, 2H), 2.21 (br. s., 1H), 1.90 (s, 1H), 1.69 - 1.12 (m, 4H), 0.96 - 0.61 (m, 3H).                                                                                     | 1.64 A 476.2          | B                                        |
| 128  |           | 2-butyl-6-hydroxy-3-[(1R)-1-phenylpropyl]-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one          |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.45 - 7.10 (m, 10H), 3.89 (s, 5H), 2.43 (br. s., 1H), 2.24 (br. s., 2H), 1.90 (s, 1H), 1.74 - 0.97 (m, 4H), 0.93 - 0.52 (m, 6H).                                                                                                                   | 1.74 A 459.9          | B                                        |
| 129  |           | 2-butyl-6-hydroxy-3-(2-methyl-1-phenylpropyl)-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one      |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.58 (br. s., 1H), 7.43 - 7.17 (m, 9H), 6.39 and 4.79 (br. s., 1H), 3.95 - 3.12 (m, 5H), 2.90 (br. s., 2H), 2.42 - 2.32 (m, 1H), 2.24 (br. s., 1H), 1.90 (s, 1H), 1.78 - 1.62 (m, 1H), 1.41 (br. s., 1H), 1.26 - 1.06 (m, 2H), 0.99 - 0.38 (m, 9H). | 1.73 A 474.0          | B                                        |

| Ex # | Structure                                                                            | Name                                                                                                              | Chiral amine intermediate with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                        | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|--------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 130  |   | 2-butyl-6-hydroxy-3-[(2-methyl-1-phenylpropyl)-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.54 (br. s., 1H), 7.38 - 7.04 (m, 9H), 6.35 and 4.78 (br. s., 1H), 3.67 - 3.05 (m, 5H), 3.01 - 2.79 (m, 2H), 2.36 (br. s., 1H), 2.21 (br. s., 1H), 1.86 (br. s., 1H), 1.68 (br. s., 1H), 1.38 (br. s., 1H), 1.25 - 0.98 (m, 2H), 0.97 - 0.26 (m, 9H) | 1.72 A 474.0              | B                                        |
| 131  |   | 2-butyl-3-[(1S)-1-cyclopropylethyl]-6-hydroxy-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one  |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.61 - 6.79 (m, 5H), 3.94 - 3.27 (m, 5H), 2.59 (br. s., 2H), 2.21 (br. s., 21H), 2.00 - 1.83 (m, 2H), 1.62 - 1.19 (m, 7H), 0.86 (d, J=7.6 Hz, 3H), 0.61 - -0.01 (m, 4H)                                                                               | 1.62 A 410.1              | B                                        |
| 132  |  | 2-butyl-6-hydroxy-3-[(1R)-1-phenylethyl]-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one       |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.43 - 6.94 (m, 10H), 4.11 - 3.04 (m, 5H), 2.22 (br. s., 1H), 1.90 (s, 1H), 1.85 - 1.70 (m, 3H), 1.67 - 0.97 (m, 4H), 0.73 (br. s., 3H)                                                                                                               | 1.74 A 446.1              | B                                        |

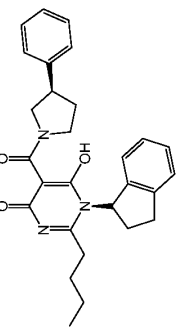
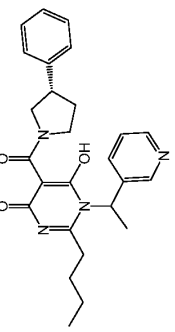
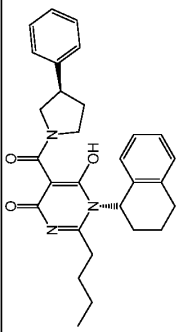
| Ex # | Structure | Name                                                                                                                                                            | Chiral amine intermediate with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                          | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 133  |           | 2-butyl-1-(2-chlorophenyl)ethyl-1-(2-chlorophenyl)ethyl-6-hydroxy-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one                            |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.80 - 7.60 (m, 1H), 7.49 - 7.08 (m, 9H), 3.93 - 2.94 (m, 5H), 2.21 (br. s., 1H), 1.97 - 1.87 (m, 1H), 1.80 (br. s., 3H), 1.58 - 1.05 (m, 4H), 0.89 - 0.61 (m, 3H)                                                                      | 1.80 A 480.3              | B                                        |
| 134  |           | 2-butyl-1-(2-chlorophenyl)ethyl-1-(2-chlorophenyl)ethyl-6-hydroxy-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one                            |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.68 (br. s., 1H), 7.45 - 6.96 (m, 9H), 4.23 - 3.09 (m, 5H), 2.76 - 2.53 (m, 2H), 2.17 (br. s., 1H), 1.95 - 1.64 (m, 4H), 1.54 - 1.04 (m, 4H), 0.81 - 0.57 (m, 3H)                                                                      | 1.85 A 480.1              | B                                        |
| 135  |           | 2-butyl-1-(2-methoxyphenyl)ethyl-1-(2-methoxyphenyl)ethyl-6-hydroxy-5-[(1R)-1-(2-methoxyphenyl)ethyl]-3-phenylpyrrolidine-1-carbonyl-3,4-dihydropyrimidin-4-one |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.49 (dd, J=18.0, 7.9 Hz, 1H), 7.40 - 7.07 (m, 6H), 7.01 - 6.59 (m, 2H), 3.99 - 2.96 (m, 8H), 2.90 - 2.59 (m, 2H), 2.26 - 2.09 (m, 1H), 1.90 (br. s., 1H), 1.79 (br. s., 3H), 1.51 (br. s., 1H), 1.36 - 0.97 (m, 3H), 0.80 (br. s., 3H) | 1.83 A 476.1              | B                                        |

| Ex # | Structure                                                                            | Name                                                                                                                    | Chiral amine intermediate with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                             | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|--------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 136  |   | 2-butyl-6-hydroxy-3-[(1S)-1-phenylethyl]-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one             |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.44 - 7.06 (m, 10H), 3.97 - 3.04 (m, 5H), 2.22 (br. s., 1H), 1.91 (s, 1H), 1.84 - 1.73 (m, 3H), 1.63 - 1.02 (m, 4H), 0.96 - 0.51 (m, 3H)                                                                  | 1.71 A 446.3              | B                                        |
| 137  |   | 2-butyl-6-hydroxy-3-[(1S)-1-phenylethyl]-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one             |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.43 - 7.21 (m, 10H), 3.68 - 2.85 (m, 5H), 2.42 - 2.17 (m, 3H), 1.90 (br. s., 1H), 1.46 - 1.05 (m, 4H), 1.02 - 0.47 (m, 8H)                                                                                | 1.78 A 474.4              | B                                        |
| 138  |  | 3-[(1S)-1-(2-butyl-4-hydroxy-6-oxo-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-1,6-dihydropyrimidin-1-yl)ethyl]benzonitrile |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.63 (br. s., 2H), 7.50 (d, J=14.0 Hz, 2H), 7.36 - 7.17 (m, 4H), 7.10 (br. s., 1H), 3.98 - 3.27 (m, 5H), 2.95 - 2.69 (m, 2H), 2.18 (br. s., 2H), 1.82 (br. s., 3H), 1.66 - 1.23 (m, 4H), 0.83 (br. s., 3H) | 1.43 A 471.1              | B                                        |

| Ex # | Structure | Name                                                                                                                     | Chiral amine intermediate with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                       | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|--------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 139  |           | 2-butyl-1-6-hydroxy-3-[(1S)-1-(3-methoxyphenyl)ethyl]-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one |                                               | (NMR peaks are too weak to summarize)                                                                                                                                                                                    | 1.56 A 476.3              | B                                        |
| 140  |           | 2-butyl-1-6-hydroxy-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-3-[(1-pyridin-3-yl)ethyl]-3,4-dihydropyrimidin-4-one         |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 8.39 (d, J=11.6 Hz, 2H), 7.55 (br. s., 1H), 7.42 - 6.93 (m, 6H), 3.96 - 2.95 (m, 5H), 2.26 - 2.00 (m, 2H), 1.80 (br. s., 3H), 1.60 - 1.09 (m, 4H), 0.78 (br. s., 3H) | 1.17 A 447.2              | B                                        |
| 141  |           | 2-butyl-1-6-hydroxy-3-[(1S)-1-phenylethyl]-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one            |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.43 - 7.11 (m, 10H), 4.00 - 2.98 (m, 5H), 2.63 (br. s., 2H), 2.23 (br. s., 1H), 2.01 - 1.77 (m, 4H), 1.61 - 1.11 (m, 4H), 0.76 (br. s., 3H)                         | 1.69 A 446.1              | B                                        |

| Ex # | Structure | Name                                                                                                                            | Chiral amine intermediate with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                          | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|---------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 142  |           | 2-butyl-3-[(1R)-1-cyclopropylethyl]-6-hydroxy-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one                |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.54 - 7.02 (m, 5H), 4.00 - 3.12 (m, 5H), 2.91 - 2.57 (m, 2H), 2.24 (br. s., 1H), 2.03 - 1.87 (m, 2H), 1.66 - 1.30 (m, 7H), 0.89 (d, J=9.2 Hz, 3H), 0.61 - 0.02 (m, 4H)                                                                 | 1.60 A 410.1              | B                                        |
| 143  |           | 2-butyl-3-[(1S)-1-(4-fluorophenyl)ethyl]-6-hydroxy-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one           |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.36 - 7.07 (m, 9H), 3.68 (d, J=9.7 Hz, 2H), 3.46 - 3.10 (m, 3H), 2.95 - 2.59 (m, 2H), 2.20 (br. s., 1H), 1.97 - 1.65 (m, 4H), 1.64 - 0.97 (m, 4H), 0.76 (br. s., 3H)                                                                   | 1.54 A 464.2              | B                                        |
| 144  |           | 2-butyl-6-hydroxy-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-3-[(1S)-1,2,3,4-tetrahydronaphthalen-1-yl]-3,4-dihydropyrimidin-4-one |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.34 - 6.81 (m, 8H), 6.74 - 6.48 (m, 1H), 5.26 (br. s., 1H), 3.87 - 2.86 (m, 5H), 2.86 - 2.58 (m, 4H), 2.40 - 2.08 (m, 2H), 2.08 - 1.82 (m, 4H), 1.74 (br. s., 1H), 1.58 (d, J=6.5 Hz, 1H), 1.33 (d, J=6.6 Hz, 2H), 1.03 - 0.42 (m, 3H) | 1.66 A 472.2              | B                                        |



| Ex # | Structure                                                                            | Name                                                                                                                            | Chiral amine intermediate with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                                    | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 145  |   | 2-butyl-3-[(1R)-2,3-dihydro-1H-inden-1-yl]-6-hydroxy-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one         |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.44 - 7.01 (m, 8H), 6.97 - 6.67 (m, 1H), 5.77 (d, J=8.3 Hz, 1H), 3.94 - 3.03 (m, 5H), 3.00 - 2.69 (m, 4H), 2.43 (br. s, 1H), 2.29 - 1.99 (m, 2H), 1.96 - 1.55 (m, 3H), 1.52 - 1.03 (m, 2H), 1.00 - 0.40 (m, 3H). | 1.60 A 458.2              | B                                        |
| 146  |   | 2-butyl-6-hydroxy-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-3-[1-(pyridin-3-yl)ethyl]-3,4-dihydropyrimidin-4-one                  |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 8.37 (d, J=12.6 Hz, 2H), 7.53 (d, J=17.6 Hz, 1H), 7.39 - 7.06 (m, 6H), 4.08 - 3.01 (m, 5H), 2.18 (br. s., 1H), 1.93 - 1.65 (m, 4H), 1.58 - 1.03 (m, 4H), 0.76 (br. s., 3H).                                       | 1.18 A 447.4              | B                                        |
| 147  |  | 2-butyl-6-hydroxy-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-3-[(1S)-1,2,3,4-tetrahydronaphthalen-1-yl]-3,4-dihydropyrimidin-4-one |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.36 - 6.99 (m, 7H), 6.98 - 6.55 (m, 2H), 5.34 (d, J=9.4 Hz, 1H), 4.20 - 3.02 (m, 5 H), 3.00 - 2.62 (m, 4H), 2.40 - 1.84 (m, 6H), 1.81 - 1.56 (m, 2H), 1.52 - 1.06 (m, 2H), 0.96 - 0.45 (m, 3H).                  | 1.69 A 472.3              | B                                        |

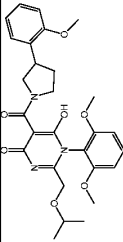
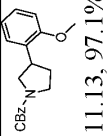
| Ex # | Structure | Name                                                                                                                    | Chiral amine intermediate with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                                 | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|-------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 148  |           | 2-butyl-6-hydroxy-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-3-[1-(pyridin-4-ylethyl)-3,4-dihydropyrimidin-4-one]          |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 8.52 - 8.24 (m, 2H), 7.30 - 7.06 (m, 7H), 5.80 - 5.36 (m, 1H), 3.72 - 2.96 (m, 5H), 2.92 - 2.55 (m, 2H), 2.16 (br. s., 1H), 1.85 (s, 1H), 1.76 (br. s., 3H), 1.63 - 1.00 (m, 4H), 0.78 (br. s., 3H)            | 1.15 A 447.0              | B                                        |
| 149  |           | 3-[(1S)-1-{2-butyl-4-hydroxy-6-oxo-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-1,6-dihydropyrimidin-1-yl}ethyl]benzonitrile |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.70 (br. s., 2H), 7.53 (br. s., 2H), 7.39 - 7.07 (m, 5H), 5.52 (br. s., 1H), 4.03 - 3.08 (m, 5H), 2.97 - 2.62 (m, 2H), 2.29 - 1.95 (m, 2H), 1.83 (br. s., 3H), 1.70 - 1.19 (m, 4H), 0.84 (br. s., 3H)         | 1.42 A 471.3              | B                                        |
| 150  |           | 2-butyl-6-hydroxy-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-3-(propan-2-yl)-3,4-dihydropyrimidin-4-one                    |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.36 - 7.19 (m, 5H), 4.47 (br. s., 1H), 4.06 - 3.01 (m, 5H), 2.88 - 2.65 (m, 2H), 2.24 (br. s., 1H), 1.98 - 1.87 (m, 1H), 1.61 (br. s., 2H), 1.50 (d, J=9.5 Hz, 6H), 1.38 (br. s., 2H), 0.91 (d, J=8.2 Hz, 3H) | 1.44 A 384.2              | B                                        |

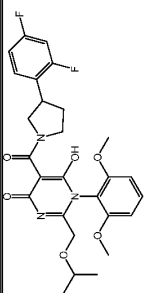
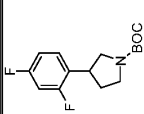
| Ex # | Structure | Name                                                                                                                         | Chiral amine intermediate with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                    | LC/MS Rt (min) Method | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 151  |           | 2-butyl-1-(2-methoxyphenyl)ethyl-1-(2-methoxyphenyl)ethyl-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.49 (d, J=8.5 Hz, 1H), 7.39 - 7.12 (m, 6H), 7.02 - 6.83 (m, 2H), 5.31 - 5.02 (m, 1H), 3.79 (s, 3H), 3.71 - 2.98 (m, 5H), 2.81 - 2.56 (m, 2H), 2.26 - 2.06 (m, 2H), 1.96 - 1.68 (m, 3H), 1.61 - 1.01 (m, 4H), 0.90 - 0.64 (m, 3H) | 1.73 A 476.3          | B                                        |
| 152  |           | 2-butyl-1-(2-methoxyphenyl)ethyl-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one                          |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.42 - 7.15 (m, 10H), 5.43 (br. s., 1H), 4.38 - 3.10 (m, 10H), 2.94 - 2.58 (m, 2H), 2.21 (br. s., 1H), 1.90 (s, 1H), 1.70 - 1.08 (m, 4H), 0.99 - 0.61 (m, 3H)                                                                     | 1.64 A 476.2          | B                                        |
| 153  |           | 2-butyl-1-(2-methoxyphenyl)ethyl-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one                          |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.40 - 7.20 (m, 10H), 4.07 - 3.08 (m, 5H), 3.00 - 2.57 (m, 2H), 2.44 - 2.17 (m, 3H), 1.90 (br. s., 1H), 1.65 - 1.10 (m, 4H), 0.98 - 0.43 (m, 6H)                                                                                  | 1.82 A 474.2          | B                                        |

| Ex # | Structure | Name                                                                                                                   | Chiral amine intermediate with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                             | LC/MS Rt (min) Method | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 154  |           | 2-butyl-6-hydroxy-3-[(1S)-2-methoxy-1-phenylethyl]-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one  |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.42 - 7.10 (m, 10H), 5.46 (br. s., 1H), 4.42 - 3.08 (m, 10H), 2.98 - 2.58 (m, 2H), 2.25 - 2.09 (m, 1H), 1.90 (s, 1H), 1.71 - 0.99 (m, 4H), 0.93 - 0.59 (m, 3H).                                                                           | 1.65 A 476.2          | B                                        |
| 155  |           | 2-butyl-3-[(1R)-1-cyclopropylethyl]-6-hydroxy-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one       |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.37 - 7.13 (m, 5H), 3.94 - 3.06 (m, 5H), 2.56 (br. s., 2H), 2.20 (br. s., 1H), 1.90 (d, J=9.8 Hz, 1H), 1.64 - 1.21 (m, 7H), 0.85 (d, J=9.5 Hz, 3H), 0.59 - 0.03 (m, 4H).                                                                  | 1.60 A 410.1          | C                                        |
| 156  |           | 2-butyl-6-hydroxy-3-[(1S)-1-(2-methoxyphenyl)ethyl]-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.44 (dd, J=17.5, 7.8 Hz, 1H), 7.32 - 7.05 (m, 6H), 6.99 - 6.65 (m, 2H), 5.14 (t, J=7.3 Hz, 1H), 3.90 - 2.94 (m, 8H), 2.88 - 2.55 (m, 2H), 2.25 - 1.97 (m, 1H), 1.86 (s, 1H), 1.75 (br. s., 3H), 1.53 - 1.07 (m, 4H), 0.86 - 0.60 (m, 3H). | 1.74 A 476.3          | C                                        |

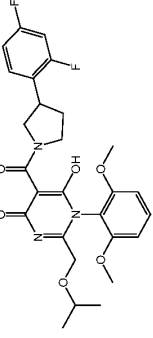
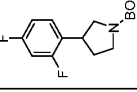
| Ex # | Structure | Name                                                                                                                    | Chiral amine intermediate with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                             | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|------|-----------|-------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 157  |           | 2-butyl-1-((1R)-2,3-dihydro-1H-inden-1-yl)-6-hydroxy-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.37 - 6.95 (m, 9H), 3.88 - 2.94 (m, 5H), 2.66 (d, J=18.2 Hz, 2H), 2.21 (br. s., 1H), 1.95 - 1.62 (m, 4H), 1.63 - 0.95 (m, 4H), 0.75 (br. s., 3H).                                                                                                         | 1.62 A 464.3              | C                                        |
| 158  |           | 2-butyl-1-((1R)-2,3-dihydro-1H-inden-1-yl)-6-hydroxy-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.50 - 6.71 (m, 9H), 5.78 and 5.23 (d, J=7.9 Hz, 1H), 4.08 (q, J=7.1 Hz, 1H), 3.90 - 2.98 (m, 4H), 2.95 - 2.74 (m, 4H), 2.30 - 2.04 (m, 1H), 1.97 - 1.62 (m, 3H), 1.59 - 0.99 (m, 4H), 0.97 - 0.22 (m, 3H).                                                | 1.60 A 458.1              | C                                        |
| 159  |           | 2-butyl-1-((1R)-2,3-dihydro-1H-inden-1-yl)-6-hydroxy-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-3,4-dihydropyrimidin-4-one |                                               | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.32 (br. s., 5H), 4.48 (br. s., 1H), 3.85 (d, J=7.6 Hz, 1H), 3.72 - 3.53 (m, 2H), 3.44 (d, J=15.9 Hz, 2H), 2.84 - 2.58 (m, 2H), 2.24 (br. s., 1H), 2.01 - 1.84 (m, 1H), 1.61 (br. s., 2H), 1.54 - 1.43 (m, 6H), 1.43 - 1.23 (m, 2H), 1.00 - 0.75 (m, 3H). | 1.61 A 406.3 (M+N a)      | C                                        |

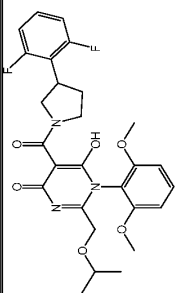
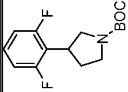
| Ex# | Structure | Name                                                                                                                         | Chiral amine intermediate<br>with retention time                                                                                                                                      | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                            | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-----------|------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 160 |           | 1-(2,6-dimethoxyphenyl)-5-[3-(2-methoxyphenyl)pyrrolidine-1-carbonyl]-2-[(propan-2-yl)oxy)methyl]-1,4-dihydropyrimidin-4-one | <br>Chiralpak IC, 4.6 x 250 mm, 5 micron;<br>mobile phase: 15% IPA:Heptane (1:1) /85% CO <sub>2</sub> ;<br>Flow Conditions: 2 mL/min, 150 bar, 40°C,<br>wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.46 - 7.35 (m, 1H), 7.28 - 7.17 (m, 2H), 7.03 - 6.95 (m, 1H), 6.94 - 6.86 (m, 1H), 6.83 - 6.72 (m, 2H), 3.93 - 3.84 (m, J=13.0 Hz, 3H), 3.83 - 3.76 (m, J=14.1 Hz, 4H), 3.76 - 3.68 (m, J=18.8 Hz, 6H), 3.66 - 3.58 (m, 4H), 2.21 - 2.08 (m, 1H), 2.03 - 1.93 (m, 1H), 0.87 (br dd, J=12.3, 6.1 Hz, 6H) | 1.28<br>A<br>524.3                    | A                                                    |

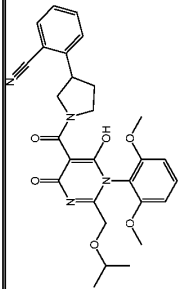
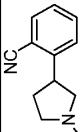
| Ex# | Structure                                                                           | Name                                                                                                                         | Chiral amine intermediate with retention time                                                                                                                                                                                                                                            | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                 | LC/MS Rt (min) Method | hAPI cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 161 |  | 1-(2,6-dimethoxyphenyl)-5-[3-(2-methoxyphenyl)pyrrolidine-1-carbonyl]-2-[(propan-2-yl)oxy)methyl]-1,4-dihydropyrimidin-4-one | <br>11.13, 97.1%<br>Chiralpak IC, 4.6 x 250 mm, 5 micron;<br>mobile phase: 15% IPA:Heptane (1:1) /85% CO <sub>2</sub> ;<br>Flow Conditions: 2 mL/min, 150 bar, 40°C,<br>wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.41 (q, J=8.8 Hz, 1H), 7.22 (br d, J=7.4 Hz, 2H), 7.05 - 6.94 (m, 1H), 6.94 - 6.85 (m, 1H), 6.84 - 6.72 (m, 2H), 3.93 - 3.84 (m, J=12.1 Hz, 4H), 3.83 - 3.67 (m, 9H), 3.62 (br s, 2H), 3.34 - 3.12 (m, 2H), 2.23 - 2.09 (m, 1H), 1.98 (br d, J=9.5 Hz, 1H), 0.87 (br dd, J=11.9, 6.0 Hz, 6H) | 1.28 A<br>524.4       | A                                        |

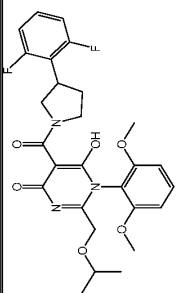
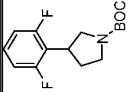
| Ex# | Structure                                                                           | Name                                                                                                                                      | Chiral amine intermediate with retention time                                                                                                                                                                                                                                                      | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                      | LC/MS Rt (min) Method | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 162 |  | 5-[3-(2,4-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-[(propan-2-yl)oxy)methyl]-1,4-dihydropyrimidin-4-one |  <p>2,53, 92.7%<br/>Chiralpak IC, 4.6 x 250 mm,<br/>5 micron;<br/>mobile phase: 10% IPA/90%<br/>CO<sub>2</sub>;<br/>Flow Conditions: 3 mL/min,<br/>140 bar, 45°C,<br/>wavelength: 200-400 nm<br/>(isomer 1)</p> | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.51 - 7.35 (m, 2H), 7.26 - 7.15 (m, 1H), 7.09 - 6.97 (m, 1H), 6.86 - 6.71 (m, 2H), 3.88 (br d, J=11.3 Hz, 3H), 3.79 - 3.68 (m, 6H), 3.64 (s, 4H), 3.51 - 3.19 (m, 1H), 2.31 - 2.16 (m, 1H), 2.05 - 1.93 (m, 1H), 0.88 (br dd, J=11.0, 6.1 Hz, 6H) | 1.35<br>A<br>530.3    | A                                        |

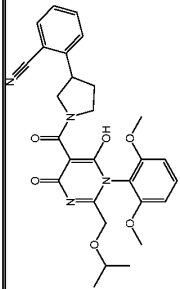
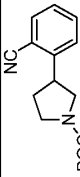


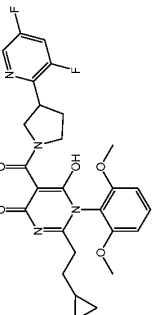
| Ex# | Structure                                                                           | Name                                                                                                                                      | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                                                         | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 163 |  | 5-[3-(2,4-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-[(propan-2-yl)oxy)methyl]-1,4-dihydropyrimidin-4-one | <br>2.78, 95.7%<br>Chiralpak IC, 4.6 x 250 mm,<br>5 micron;<br>mobile phase: 10% IPA/90%<br>CO <sub>2</sub> ;<br>Flow Conditions: 3 mL/min,<br>140 bar, 45°C,<br>wavelength: 200-400 nm<br>(isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.42 (br d, J=7.9 Hz, 2H), 7.19 (br s, 1H), 7.03 (br s, 1H), 6.88 - 6.72 (m, 2H), 3.90 (br d, J=9.2 Hz, 3H), 3.72 (br d, J=17.1 Hz, 6H), 3.63 (s, 4H), 3.36 - 3.21 (m, 1H), 2.23 (br d, J=5.2 Hz, 1H), 2.05 - 1.93 (m, 1H), 0.87 (br dd, J=10.1, 6.1 Hz, 6H) | 1.34<br>A<br>530.2                    | A                                                    |

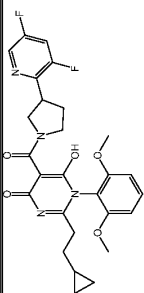
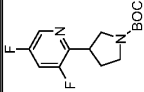
| Ex# | Structure                                                                           | Name                                                                                                                                      | Chiral amine intermediate with retention time                                                                                                                                                                                                          | <sup>1</sup> H NMR                                                                                                                                                                                                                                                         | LC/MS Rt (min) Method | hAPI cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 164 |  | 5-[3-(2,6-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-[(propan-2-yl)oxy)methyl]-1,4-dihydropyrimidin-4-one | <br>5.4, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.50 - 7.40 (m, 1H), 7.39 - 7.29 (m, 1H), 7.13 - 7.02 (m, 2H), 6.81 (br t, J=9.9 Hz, 2H), 4.01 - 3.85 (m, 4H), 3.65 - 3.50 (m, 9H), 3.46 - 3.22 (m, 1H), 2.20 (br d, J=10.1 Hz, 2H), 0.88 (br dd, J=17.2, 5.6 Hz, 6H) | 1.15 A<br>530.4       | A                                        |

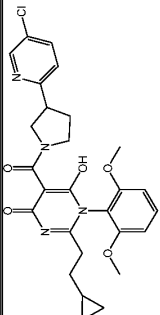
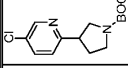
| Ex# | Structure                                                                           | Name                                                                                                                                    | Chiral amine intermediate with retention time                                                                                                                                                                                                                                     | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                    | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 165 |  | 2-{1-[1-(2,6-dimethoxyphenyl)-6-hydroxy-4-oxo-2-[(propan-2-yl)oxy)methyl]-1,4-dihydropyrimidin-5-carbonyl]pyrrolidin-3-yl} benzonitrile | <br>5.68, >99%<br>Chiralpak IC, 4.6 x 250 mm, 5 micron;<br>mobile phase: 15% IPA/0.1% DEA /85% CO <sub>2</sub> ;<br>Flow Conditions: 2 mL/min, 150 bar, 45°C,<br>wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.81 (br d, J=6.4 Hz, 1H), 7.68 (br s, 1H), 7.58 (br s, 1H), 7.45 (br t, J=7.5 Hz, 2H), 6.80 (br s, 2H), 3.90 (br s, 4H), 3.72 (br d, J=16.8 Hz, 9H), 3.54 - 3.19 (m, 1H), 2.32 (br s, 1H), 2.06 (br d, J=8.9 Hz, 1H), 0.88 (br d, J=8.5 Hz, 6H) | 1.08<br>A<br>518.9        | A                                        |

| Ex# | Structure                                                                           | Name                                                                                                                                      | Chiral amine intermediate with retention time                                                                                                                                                                                                          | <sup>1</sup> H NMR                                                                                                                                                                                                                                | LC/MS Rt (min) Method | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 166 |  | 5-[3-(2,6-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-[(propan-2-yl)oxy)methyl]-1,4-dihydropyrimidin-4-one | <br>5.9, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.48 - 7.30 (m, 2H), 7.17 - 7.03 (m, 2H), 6.79 (br dd, J=13.6, 8.1 Hz, 2H), 3.98 - 3.82 (m, 4H), 3.80 - 3.58 (m, 9H), 3.41 (br s, 1H), 2.31 - 2.10 (m, 2H), 0.87 (br dd, J=18.4, 5.8 Hz, 6H) | 1.14<br>A<br>529.9    | A                                        |

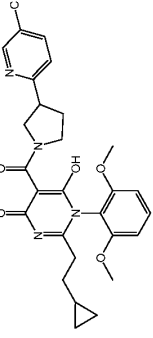
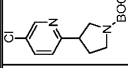
| Ex# | Structure                                                                           | Name                                                                                                           | Chiral amine intermediate with retention time                                                                                                                                                                                                                                     | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                             | LC/MS Rt (min) Method | hAPI cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 167 |  | 2-{1-[1-(2,6-dimethoxyphenyl)-6-hydroxy-4-oxo-2-[(propan-2-ylloxy)methyl]-1,4-dihydropyrimidin-3-yl]benzotrile | <br>4.87, >99%<br>Chiralpak IC, 4.6 x 250 mm, 5 micron;<br>mobile phase: 15% IPA/0.1% DEA /85% CO <sub>2</sub> ;<br>Flow Conditions: 2 mL/min, 150 bar, 45°C,<br>wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.86 - 7.76 (m, 1H), 7.67 (br s, 1H), 7.57 (br d, J=7.3 Hz, 1H), 7.50 - 7.30 (m, 2H), 6.79 (br s, 2H), 3.90 (br d, J=11.3 Hz, 4H), 3.76 - 3.39 (m, 9H), 3.33 - 3.20 (m, 1H), 2.32 (br s, 1H), 2.06 (br d, J=5.2 Hz, 1H), 0.87 (br dd, J=14.5, 5.3 Hz, 6H) | 1.07<br>A<br>518.9    | A                                        |

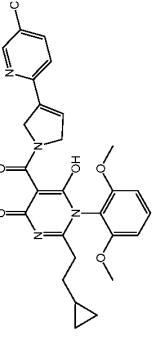
| Ex# | Structure                                                                           | Name                                                                                                                                    | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                             | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 168 |  | 2-(2-cyclopropylethyl)-5-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carboxylate (2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>5.6, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.67 (br s, 1H), 8.14 - 8.01 (m, 1H), 7.67 (br d, J=6.5 Hz, 1H), 7.05 (br t, J=8.5 Hz, 2H), 4.09 - 3.76 (m, 10H), 3.71 - 3.56 (m, 1H), 2.51 (br d, J=6.7 Hz, 3H), 2.38 - 2.23 (m, 1H), 1.53 (br s, 2H), 0.79 (br s, 1H), 0.49 (br s, 2H), 0.00 (br s, 2H) | 1.36<br>A<br>526.9                    | A                                                    |

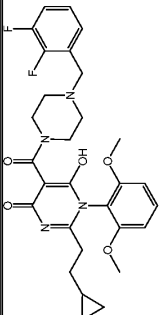
| Ex# | Structure                                                                           | Name                                                                             | Chiral amine intermediate with retention time                                                                                                                                                                                                          | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                             | LC/MS Rt (min) Method | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 169 |  | 2-(2-cyclopropylethyl)-5-[3,5-difluoropyridin-2-yl]pyrrolidine-1-carboxylate (1) | <br>6.3, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.66 (br s, 1H), 8.10 (br t, J=8.7 Hz, 1H), 7.65 (br s, 1H), 7.13 - 6.95 (m, 2H), 4.16 - 3.82 (m, 10H), 3.80 - 3.65 (m, 1H), 2.59 - 2.38 (m, 3H), 2.37 - 2.24 (m, 1H), 1.53 (br s, 2H), 0.78 (br s, 1H), 0.48 (br s, 2H), 0.00 (br s, 2H) | 1.24 A 527.4          | A                                        |

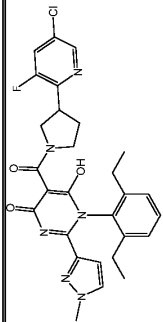
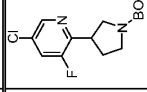
| Ex# | Structure                                                                           | Name                                                                                                                                   | Chiral amine intermediate with retention time                                                                                                                                                                                                          | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                   | LC/MS Rt (min) Method M <sup>+</sup> H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|------------------------------------------|
| 170 |  | 5-[3-(5-chloropyridin-2-yl)pyrrolidine-1-carbonyl]-2-(2-cyclopropylethyl)-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>7.9, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.75 (br s, 1H), 8.06 (dd, J=8.1, 2.0 Hz, 1H), 7.78 - 7.52 (m, 2H), 7.04 (br s, 2H), 3.94 (br d, J=17.1 Hz, 10H), 3.65 (br s, 1H), 2.61 - 2.38 (m, 3H), 2.34 - 2.17 (m, 1H), 1.54 (br s, 2H), 0.79 (br s, 1H), 0.48 (br s, 2H), 0.00 (br s, 2H) | 1.41 A 525.0                           | A                                        |

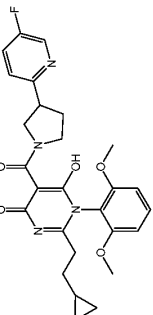
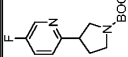


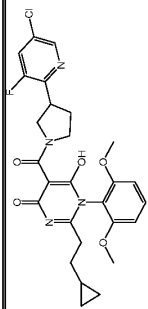
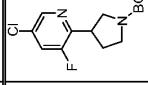
| Ex# | Structure                                                                           | Name                                                                                                                            | Chiral amine intermediate with retention time                                                                                                                                                                                                          | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                     | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 171 |  | 5-[3-(5-chloropyridin-2-yl)pyrrolidin-2-yl]-2-(2-cyclopropylethyl)-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>6.8, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.76 (br s, 1H), 8.08 (br d, J=7.9 Hz, 1H), 7.64 (dt, J=16.0, 8.1 Hz, 2H), 7.19 - 6.95 (m, 2H), 4.13 - 3.74 (m, 10H), 3.71 - 3.55 (m, 1H), 2.51 (br d, J=6.2 Hz, 3H), 2.34 - 2.19 (m, 1H), 1.53 (br d, J=6.6 Hz, 2H), 0.79 (br d, J=3.5 Hz, 1H), 0.49 (br s, 2H), 0.00 (br s, 2H) | 1.42 A 525.2              | A                                        |

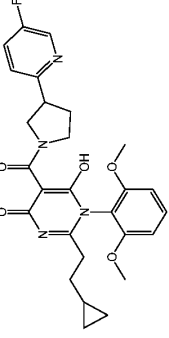
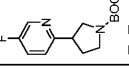
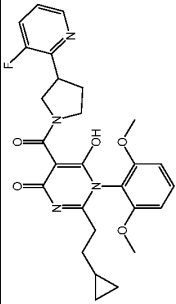
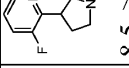
| Ex# | Structure                                                                           | Name                                                                                                                       | Chiral amine intermediate<br>with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                           | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 172 |  | 5-[3-(5-chloropyridin-2-yl)-2,5-dihydro-1H-pyrrole-1-carbonyl]-2-(2-cyclopropylethyl)-6-hydroxy-1,4-dihydropyrimidin-4-one | achiral                                          | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.85 - 8.69 (m, 1H), 8.12 (br d, J=8.3 Hz, 1H), 8.03 - 7.86 (m, 1H), 7.64 (br t, J=7.8 Hz, 1H), 7.02 (br d, J=8.4 Hz, 2H), 6.99 - 6.85 (m, 1H), 4.80 - 4.43 (m, 4H), 3.95 (br d, J=5.7 Hz, 6H), 2.52 (br d, J=6.8 Hz, 2H), 1.55 (br d, J=7.2 Hz, 2H), 0.79 (br s, 1H), 0.48 (br s, 2H), 0.00 (br s, 2H) | 1.42<br>A<br>523.4                    | A                                                    |

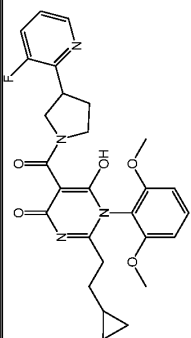
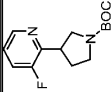
| Ex# | Structure                                                                           | Name                                                                          | Chiral amine intermediate<br>with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                        | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|--------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 173 |  | 2-(2-cyclopropylethyl)-5-((2,3-difluorophenyl)methyl)piperazine-1-carboxylate | achiral                                          | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.64 (br t, J=8.3 Hz, 1H), 7.55 (br d, J=9.4 Hz, 1H), 7.49 - 7.35 (m, 2H), 7.03 (br d, J=8.3 Hz, 2H), 3.94 (br s, 6H), 3.85 - 3.74 (m, 2H), 2.58 (br s, 8H), 2.44 (br s, 2H), 1.53 (br d, J=6.9 Hz, 2H), 0.79 (br s, 1H), 0.49 (br d, J=6.4 Hz, 2H), 0.00 (br s, 2H) | 1.43<br>A<br>555.2                    | A                                                    |

| Ex# | Structure                                                                           | Name                                                                                                                                                                    | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                               | LC/MS<br>Rt<br>(min)<br>Metho<br>d<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|------------------------------------------------------|
| 174 |  | 5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidin-1-yl]pyrrolidine-1-carboxylic acid (2,6-diethylphenyl)-6-hydroxy-2-(1-methyl-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one | <br>6.8, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 27°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.47 (br d, J=18.3 Hz, 1H), 8.06 (br t, J=10.3 Hz, 1H), 7.55 (br d, J=5.8 Hz, 1H), 7.45 - 7.32 (m, 1H), 7.27 - 7.15 (m, 2H), 5.56 (br d, J=5.8 Hz, 1H), 4.12 - 3.73 (m, 4H), 3.70 (br d, J=6.3 Hz, 3H), 3.60 (br t, J=9.6 Hz, 1H), 2.37 - 2.06 (m, 6H), 1.11 - 0.89 (m, 6H) | 1.29<br>A<br>551.3                        | A                                                    |

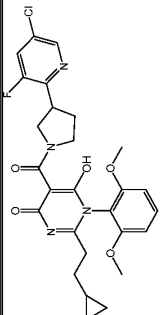
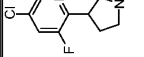
| Ex# | Structure                                                                           | Name                                                                                                                                        | Chiral amine intermediate with retention time                                                                                                                                                                                                          | <sup>1</sup> H NMR                                                                                                                                                                                                                                                      | LC/MS Rt (min) Method | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 175 |  | 2-(2-cyclopropylethyl)-1-(2,6-dimethoxyphenyl)-5-[3-(5-fluoropyridin-2-yl)pyrrolidin-2-yl]pyrrolidine-1-carboxyl-1,4-dihydropyrimidin-4-one | <br>8.4, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 10% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 340 mL/min, 45°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) Shift 8.71 (br s, 1H), 8.00 - 7.81 (m, 1H), 7.66 (br s, 2H), 7.14 - 6.93 (m, 2H), 4.16 - 3.71 (m, 11H), 2.61 - 2.37 (m, 3H), 2.35 - 2.15 (m, 1H), 1.54 (br s, 2H), 0.79 (br s, 1H), 0.49 (br s, 2H), 0.00 (br s, 2H) | 1.24 A<br>508.9       | A                                        |

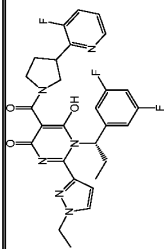
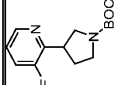
| Ex# | Structure                                                                           | Name                                                                                                                                     | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                         | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 176 |  | 5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidin-1-yl]-2-(2-cyclopropylethyl)-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>6.8, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 27°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.67 (br s, 1H), 8.25 (br d, J=9.8 Hz, 1H), 7.64 (br s, 1H), 7.03 (br s, 2H), 4.12 - 3.80 (m, 10H), 3.79 - 3.56 (m, 1H), 2.59 - 2.38 (m, 3H), 2.37 - 2.23 (m, 1H), 1.53 (br s, 2H), 0.78 (br s, 1H), 0.48 (br s, 2H), 0.00 (br s, 2H) | 1.50<br>A<br>543.0                    | A                                                    |

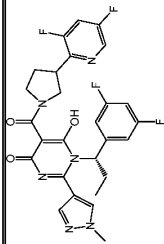
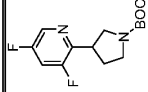
| Ex# | Structure                                                                            | Name                                                                                                                            | Chiral amine intermediate with retention time                                                                                                                                                                                                           | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                   | LC/MS Rt (min) Method M+H | hAPI cAMP EC <sub>50</sub> Potency range |
|-----|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 177 |   | 2-(2-cyclopropylethyl)-1-(2,6-dimethoxyphenyl)-5-[3-(5-fluoropyridin-2-yl)pyrrolidin-2-yl]-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>7.7, >95.5%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 10% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 340 mL/min, 45°C, wavelength: 220 nm (isomer 1)  | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.70 (br s, 1H), 8.00 - 7.80 (m, 1H), 7.65 (br d, J=7.3 Hz, 2H), 7.04 (br s, 2H), 4.07 - 3.74 (m, 10H), 3.67 (br d, J=6.4 Hz, 1H), 2.60 - 2.37 (m, 3H), 2.33 - 2.17 (m, 1H), 1.54 (br s, 2H), 0.79 (br s, 1H), 0.49 (br s, 2H), 0.00 (br s, 2H) | 1.26 A<br>509.0           | A                                        |
| 178 |  | 2-(2-cyclopropylethyl)-1-(2,6-dimethoxyphenyl)-5-[3-(5-fluoropyridin-2-yl)pyrrolidin-2-yl]-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>8.5, >99.8%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 10% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 340 mL/min, 45°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.59 (br s, 1H), 7.89 (br t, J=9.2 Hz, 1H), 7.66 (br s, 1H), 7.61 - 7.52 (m, 1H), 7.04 (br s, 2H), 4.13 - 3.58 (m, 11H), 2.53 (br d, J=7.1 Hz, 3H), 2.34 (br s, 1H), 1.53 (br s, 2H), 0.78 (br s, 1H), 0.48 (br s, 2H), 0.00 (br s, 2H)         | 1.12 A<br>509.3           | A                                        |

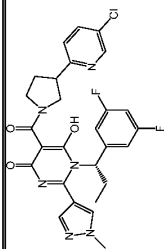
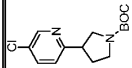
| Ex# | Structure                                                                           | Name                                                                                                                                   | Chiral amine intermediate with retention time                                                                                                                                                                                                         | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                | LC/MS Rt (min) Method | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 179 |  | 2-(2-cyclopropylethyl)-1-(2,6-dimethoxyphenyl)-5-[3-(3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>9.5, >99.8%<br>Welko, 5 x 50 cm, 10 micron;<br>mobile phase: 10% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 340 mL/min, 45°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.58 (br s, 1H), 7.88 (br t, J=8.7 Hz, 1H), 7.66 (br s, 1H), 7.61 - 7.51 (m, 1H), 7.04 (br s, 2H), 4.13 - 3.82 (m, 10H), 3.77 (br d, J=8.9 Hz, 1H), 2.61 - 2.40 (m, 3H), 2.34 (br s, 1H), 1.54 (br s, 2H), 0.79 (br s, 1H), 0.48 (br s, 2H), 0.00 (br s, 2H) | 1.13 A<br>509.2       | A                                        |

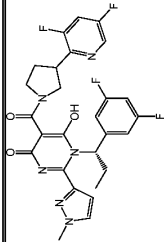


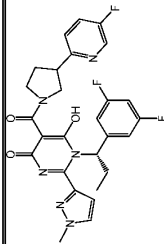
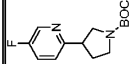
| Ex# | Structure                                                                           | Name                                                                                                                                            | Chiral amine intermediate with retention time                                                                                                                                                                                                          | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 180 |  | 5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-2-(2-cyclopropylethyl)-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>7.6, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 27°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) Shift 8.70 (br d, J=7.1 Hz, 1H), 8.27 (br d, J=8.2 Hz, 1H), 7.78 - 7.50 (m, 1H), 7.03 (br t, J=9.1 Hz, 2H), 4.20 - 3.65 (m, 11H), 2.44 (br s, 3H), 2.38 - 2.22 (m, 1H), 1.52 (br d, J=7.1 Hz, 2H), 0.79 (br s, 1H), 0.48 (br d, J=7.4 Hz, 2H), 0.00 (br s, 2H) | 1.31 A 543.3              | A                                        |

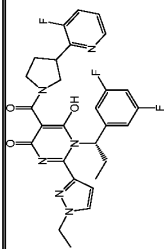
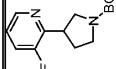
| Ex# | Structure                                                                           | Name                                                                                                                                                  | Chiral amine intermediate with retention time                                                                                                                                                                                                         | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                   | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 181 |  | 1-[(1S)-1-(3,5-difluorophenyl)propyl]-2-(1-ethyl-1H-pyrazol-3-yl)-5-fluoropyridin-2-yl)pyrrolidine-1-carboxylate-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>9.5, >99.8%<br>Welko, 5 x 50 cm, 10 micron;<br>mobile phase: 10% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 340 mL/min, 45°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.37 (br s, 1H), 8.05 - 7.82 (m, 1H), 7.76 - 7.58 (m, 1H), 7.37 (br s, 1H), 7.19 - 6.88 (m, 2H), 6.71 (br s, 1H), 6.19 - 5.86 (m, 1H), 4.17 (br d, J=7.0 Hz, 4H), 3.93 - 3.60 (m, 1H), 3.59 - 3.25 (m, 3H), 2.35 - 2.01 (m, 4H), 1.35 (br d, J=6.7 Hz, 3H), 0.94 - 0.64 (m, 3H) | 1.28<br>A<br>553.4        | A                                        |

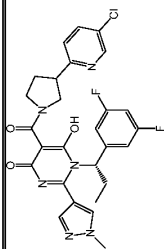
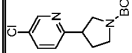
| Ex# | Structure                                                                           | Name                                                                                                                                                    | Chiral amine intermediate with retention time                                                                                                                                                                                                         | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                           | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 182 |  | 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidin-1-yl]-6-hydroxy-2-(1-methyl-1H-pyrazol-4-yl)-1,4-dihydropyrimidin-4-one | <br>6.3, >99.7%<br>Welko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) Shift 8.44 (br s, 1H), 8.06 - 7.92 (m, 1H), 7.87 (br t, J=8.7 Hz, 1H), 7.53 (br s, 1H), 7.03 (br s, 1H), 6.90 (br d, J=17.7 Hz, 2H), 3.85 (br s, 4H), 3.68 - 3.53 (m, 1H), 3.46 (br s, 3H), 3.32 - 3.13 (m, 1H), 2.36 - 1.99 (m, 4H), 0.87 - 0.64 (m, 3H) | 1.17 A 557.0              | A                                        |

| Ex# | Structure                                                                           | Name                                                                                                                                                              | Chiral amine intermediate with retention time                                                                                                                                                                                                          | <sup>1</sup> H NMR                                                                                                                                                                                                                                                             | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 183 |  | 5-[3-(5-chloropyridin-2-yl)pyrrolidin-1-yl]-1-carboxylate-1-[(1S)-1-(3,5-difluorophenyl)propyl]-6-hydroxy-2-(1-methyl-1H-pyrazol-4-yl)-1,4-dihydropyrimidin-4-one | <br>7.9, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) Shift 8.70 - 8.44 (m, 1H), 7.99 (br s, 1H), 7.91 - 7.76 (m, 1H), 7.57 (br s, 1H), 7.48 - 7.28 (m, 1H), 7.05 - 6.83 (m, 3H), 3.86 (br s, 4H), 3.71 - 3.23 (m, 5H), 2.39 - 2.13 (m, 3H), 2.10 - 1.96 (m, 1H), 0.75 (br s, 3H) | 1.22 A 555.5              | A                                        |

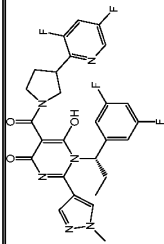
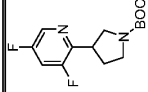
| Ex# | Structure                                                                           | Name                                                                                                                                                           | Chiral amine intermediate with retention time                                                                                                                                                                                                          | <sup>1</sup> H NMR                                                                                                                                                                                                                             | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 184 |  | 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(1-methyl-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one | <br>6.3, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) Shift 8.40 (br s, 1H), 7.79 (br d, J=7.7 Hz, 2H), 7.16 - 6.79 (m, 2H), 6.66 (br s, 1H), 6.25 - 5.81 (m, 1H), 3.86 (br s, 4H), 3.71 - 3.29 (m, 5H), 2.31 - 1.96 (m, 4H), 0.90 - 0.60 (m, 3H) | 1.54<br>A<br>557.2        | A                                        |

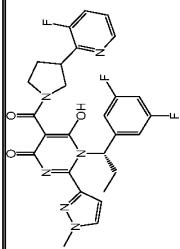
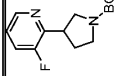
| Ex# | Structure                                                                           | Name                                                                                            | Chiral amine intermediate with retention time                                                                                                                                                                                                          | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                    | LC/MS Rt (min) Method M <sup>+</sup> H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|------------------------------------------|
| 185 |  | 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(5-fluoropyridin-2-yl)pyrrolidin-2-yl]-1-carboxylate | <br>8.4, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 10% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 340 mL/min, 45°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) Shift 8.59 - 8.35 (m, 1H), 7.81 (br s, 1H), 7.71 - 7.52 (m, 1H), 7.47 - 7.28 (m, 1H), 7.11 - 6.84 (m, 2H), 6.72 (br s, 1H), 6.07 (br d, J=6.1 Hz, 1H), 3.86 (br d, J=3.0 Hz, 4H), 3.69 - 3.13 (m, 5H), 2.47 - 2.36 (m, 1H), 2.25 (br d, J=6.8 Hz, 2H), 2.02 (br d, J=11.4 Hz, 1H), 0.76 (br s, 3H) | 1.22 A 539.0                           | A                                        |

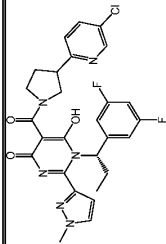
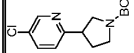
| Ex# | Structure                                                                           | Name                                                                                                                                                      | Chiral amine intermediate with retention time                                                                                                                                                                                                         | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                    | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 186 |  | 1-[(1S)-1-(3,5-difluorophenyl)propyl]-2-(1-ethyl-1H-pyrazol-3-yl)-5-[3-(3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>8.5, >99.8%<br>Wheko, 5 x 50 cm, 10 micron;<br>mobile phase: 10% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 340 mL/min, 45°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) Shift 8.38 (br d, J=6.7 Hz, 1H), 7.89 (br s, 1H), 7.67 (br d, J=8.1 Hz, 1H), 7.37 (br s, 1H), 7.16 - 6.86 (m, 2H), 6.70 (br s, 1H), 6.20 - 5.92 (m, 1H), 4.17 (br s, 4H), 3.91 - 3.43 (m, 4H), 2.34 - 2.02 (m, 4H), 1.34 (br d, J=6.6 Hz, 3H), 0.90 - 0.67 (m, 3H) | 1.44<br>A<br>553.0        | A                                        |

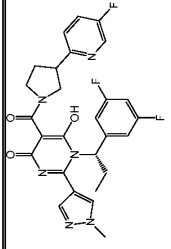
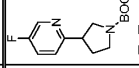
| Ex# | Structure                                                                           | Name                                                                                                                                                           | Chiral amine intermediate with retention time                                                                                                                                                                                                          | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                               | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 187 |  | 5-[3-(5-chloropyridin-2-yl)pyrrolidin-1-yl]-1-carbonyl-1-[(1S)-1-(3,5-difluorophenyl)propyl]-6-hydroxy-2-(1-methyl-1H-pyrazol-4-yl)-1,4-dihydropyrimidin-4-one | <br>6.8, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) Shift 8.53 (br d, J=9.3 Hz, 1H), 8.06 (br s, 1H), 7.85 (br d, J=8.1 Hz, 1H), 7.65 (br s, 1H), 7.49 - 7.31 (m, 1H), 7.07 (br s, 1H), 6.95 (br s, 2H), 3.86 (br s, 4H), 3.77 - 3.62 (m, 3H), 3.60 - 3.31 (m, 2H), 2.46 - 2.16 (m, 3H), 2.12 - 1.96 (m, 1H), 0.84 - 0.63 (m, 3H) | 1.36<br>A<br>554.9        | A                                        |

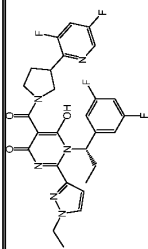
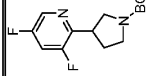


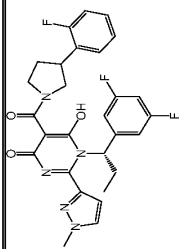
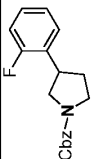
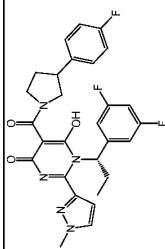
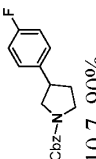
| Ex# | Structure                                                                           | Name                                                                                                                                                    | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                      | <sup>1</sup> H NMR                                                                                                                                                                                                                                              | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 188 |  | 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidin-1-yl]-6-hydroxy-2-(1-methyl-1H-pyrazol-4-yl)-1,4-dihydropyrimidin-4-one | <br>5.6, >99.7%<br>Welko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.58 - 8.32 (m, 1H), 8.09 - 7.95 (m, 1H), 7.87 (br s, 1H), 7.57 (br s, 1H), 7.20 - 6.77 (m, 3H), 4.00 - 3.80 (m, 4H), 3.50 (br s, 5H), 2.45 - 2.26 (m, 2H), 2.24 - 2.01 (m, 2H), 0.75 (br d, J=7.6 Hz, 3H) | 1.69<br>A<br>557.3                    | A                                                    |

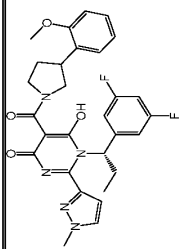
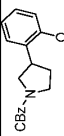
| Ex# | Structure                                                                           | Name                                                                                                                                                           | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                      | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                     | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 189 |  | 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(3-fluoropyridin-2-yl)pyrrolidin-2-yl]-1-carboxyl-6-hydroxy-2-(1-methyl-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one | <br>9.5, >99.8%<br>Welko, 5 x 50 cm, 10 micron;<br>mobile phase: 10% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 340 mL/min, 45°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.37 (br s, 1H), 7.83 (br s, 1H), 7.73 - 7.59 (m, 1H), 7.37 (br d, J=4.0 Hz, 1H), 7.15 - 6.87 (m, 2H), 6.70 (br s, 1H), 6.23 - 5.95 (m, 1H), 3.88 (br d, J=7.7 Hz, 4H), 3.66 (br s, 5H), 2.33 - 2.01 (m, 4H), 0.88 - 0.69 (m, 3H) | 1.37<br>A<br>539.0                    | A                                                    |

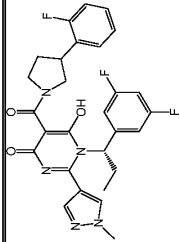
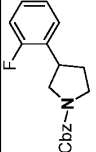
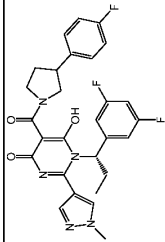
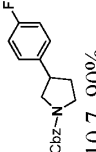
| Ex# | Structure                                                                           | Name                                                                                                                                                       | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                             | LC/MS<br>Rt<br>(min)<br>Metho<br>d<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|------------------------------------------------------|
| 190 |  | 5-[3-(5-chloropyridin-2-yl)pyrrolidine-1-carbonyl]-1-[(1S)-1-(3,5-difluorophenyl)propyl]-6-hydroxy-2-(1-methyl-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one | <br>7.9, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) Shift 8.66 - 8.44 (m, 1H), 7.98 - 7.74 (m, 2H), 7.56 - 7.25 (m, 1H), 7.16 - 6.85 (m, 2H), 6.69 (br s, 1H), 6.04 (br d, J=6.1 Hz, 1H), 3.88 (br s, 4H), 3.63 (br s, 5H), 2.34 - 2.12 (m, 3H), 2.10 - 1.95 (m, 1H), 0.78 (br d, J=6.1 Hz, 3H) | 1.45<br>A<br>554.9                        | A                                                    |

| Ex# | Structure                                                                           | Name                                                                                            | Chiral amine intermediate with retention time                                                                                                                                                                                                          | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                           | LC/MS Rt (min) Method | hAPI cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 191 |  | 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(5-fluoropyridin-2-yl)pyrrolidin-2-yl]-1-carboxylate | <br>7.7, >95.5%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 10% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 340 mL/min, 45°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.59 - 8.40 (m, 1H), 8.08 - 7.83 (m, 1H), 7.65 (br t, J=7.7 Hz, 1H), 7.57 - 7.30 (m, 2H), 7.21 - 7.00 (m, 1H), 6.98 - 6.79 (m, 2H), 3.84 (br d, J=6.1 Hz, 4H), 3.56 (br d, J=1.2 Hz, 5H), 2.35 - 2.13 (m, 3H), 2.12 - 1.93 (m, 1H), 0.83 - 0.60 (m, 3H) | 1.13 A 539.4          | A                                        |

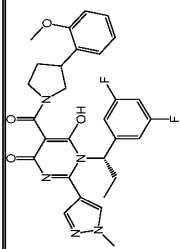
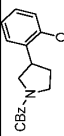
| Ex# | Structure                                                                           | Name                                                                                                                                                   | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                                                                                         | LC/MS<br>Rt<br>(min)<br>Method<br>M <sup>+</sup> H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|------------------------------------------------------|
| 192 |  | 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidin-1-yl]-2-(1-ethyl-1H-pyrazol-3-yl)-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>5.6, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.55 - 8.34 (m, 1H), 8.01 - 7.74 (m, 2H), 7.17 - 6.83 (m, 2H), 6.69 (br s, 1H), 6.23 - 5.83 (m, 1H), 4.16 (br s, 4H), 3.59 (br s, 3H), 3.47 - 3.20 (m, 1H), 2.33 - 2.01 (m, 4H), 1.33 (br s, 3H), 0.90 - 0.65 (m, 3H) | 1.51<br>A<br>571.0                                 | A                                                    |

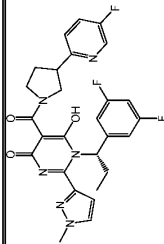
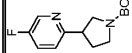
| Ex# | Structure                                                                            | Name                                                                                                                                                 | Chiral amine intermediate with retention time                                                                                                                                                                                                                                      | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                    | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|--------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 193 |   | 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(2-fluorophenyl)pyrrolidine-1-carboxyl]-6-hydroxy-2-(1-methyl-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one | <br>Cbz-N<br>10.65, 99.5%<br>Chiralpak IF, 4.6 x 250 mm, 5 micron;<br>mobile phase: 15% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 2.0 mL/min, 150 bar, 40°C, wavelength: 220 nm (Isomer 2)  | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) Shift 7.95 - 7.76 (m, 1H), 7.52 - 7.35 (m, 1H), 7.34 - 7.24 (m, 1H), 7.22 - 7.11 (m, 2H), 7.10 - 6.81 (m, 2H), 6.77 - 6.57 (m, 1H), 6.23 - 5.85 (m, 1H), 3.88 (br d, J=9.7 Hz, 4H), 3.53 (br s, 5H), 2.37 - 2.12 (m, 3H), 2.04 - 1.84 (m, 1H), 0.91 - 0.60 (m, 3H) | 1.37<br>A<br>537.9        | A                                        |
| 194 |  | 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(4-fluorophenyl)pyrrolidine-1-carboxyl]-6-hydroxy-2-(1-methyl-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one | <br>Cbz-N<br>10.7, 90%<br>Wheilk-O 1 (R,R), 4.6 x 250 mm, 5 micron;<br>mobile phase: 15% IPA/85% CO <sub>2</sub> ;<br>Flow Conditions: 2.0 mL/min, 150 bar, 40°C, wavelength: 220 nm (Isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) Shift 7.85 (br s, 1H), 7.33 (br s, 1H), 7.19 (br s, 1H), 7.14 - 7.04 (m, 2H), 7.02 - 6.88 (m, 2H), 6.74 (br s, 1H), 6.13 (br s, 1H), 3.88 (br s, 4H), 3.68 (br s, 5H), 2.27 (br dd, J=12.7, 6.6 Hz, 3H), 1.99 - 1.72 (m, 1H), 0.78 (br s, 3H)                      | 1.38<br>A<br>537.8        | A                                        |

| Ex# | Structure                                                                           | Name                                                                                                                                                  | Chiral amine intermediate with retention time                                                                                                                                                                                                                                            | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                    | LC/MS Rt (min) Method M+H | hAPI cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 195 |  | 1-[(1S)-1-(3,5-difluorophenyl)propyl]-6-hydroxy-5-[3-(2-methoxyphenyl)pyrrolidine-1-carbonyl]-2-(1-methyl-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one | <br>11.13, 97.1%<br>Chiralpak IC, 4.6 x 250 mm, 5 micron;<br>mobile phase: 15% IPA:Heptane (1:1) /85% CO <sub>2</sub> ;<br>Flow Conditions: 2 mL/min, 150 bar, 40°C,<br>wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.82 (br d, J=10.5 Hz, 1H), 7.21 (br t, J=6.9 Hz, 2H), 7.08 - 6.82 (m, 4H), 6.66 (br s, 1H), 6.18 - 5.94 (m, 1H), 3.86 (br d, J=10.1 Hz, 4H), 3.82 - 3.71 (m, 3H), 3.67 (br d, J=9.0 Hz, 4H), 3.46 - 3.26 (m, 1H), 2.32 - 2.03 (m, 3H), 2.00 - 1.88 (m, 1H), 0.86 - 0.59 (m, 3H) | 1.39<br>A<br>550.1        | A                                        |

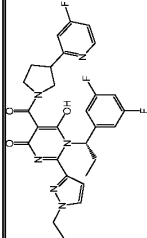
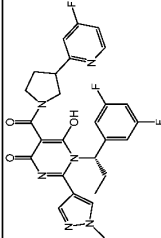
| Ex# | Structure                                                                            | Name                                                                                                                                                 | Chiral amine intermediate with retention time                                                                                                                                                                                                                                     | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                 | LC/MS Rt (min) Method | hAPI cAMP EC <sub>50</sub> Potency range |
|-----|--------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 196 |   | 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(2-fluorophenyl)pyrrolidine-1-carboxyl]-6-hydroxy-2-(1-methyl-1H-pyrazol-4-yl)-1,4-dihydropyrimidin-4-one | <br>Cbz-N<br>10.65, 99.5%<br>Chiralpak IF, 4.6 x 250 mm, 5 micron;<br>mobile phase: 15% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 2.0 mL/min, 150 bar, 40°C, wavelength: 220 nm (Isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.05 (br s, 1H), 7.63 (br s, 1H), 7.44 - 7.25 (m, 2H), 7.24 - 7.07 (m, 3H), 6.96 (br s, 2H), 3.87 (br d, J=6.2 Hz, 4H), 3.53 (br s, 5H), 2.44 - 2.14 (m, 3H), 2.06 - 1.89 (m, 1H), 0.86 - 0.62 (m, 3H)                                        | 1.27 A<br>538.0       | A                                        |
| 197 |  | 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(4-fluorophenyl)pyrrolidine-1-carboxyl]-6-hydroxy-2-(1-methyl-1H-pyrazol-4-yl)-1,4-dihydropyrimidin-4-one | <br>Cbz-N<br>10.7, 90%<br>Whelk-O 1 (R,R), 4.6 x 250 mm, 5 micron;<br>mobile phase: 15% IPA/85% CO <sub>2</sub> ;<br>Flow Conditions: 2.0 mL/min, 150 bar, 40°C, wavelength: 220 nm (Isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.07 (br s, 1H), 7.66 (br s, 1H), 7.39 - 7.26 (m, 1H), 7.24 - 7.17 (m, 1H), 7.10 (dt, J=16.7, 8.4 Hz, 3H), 7.00 - 6.87 (m, 2H), 4.06 - 3.71 (m, 4H), 3.66 - 3.24 (m, 5H), 2.48 - 2.13 (m, 3H), 1.98 - 1.71 (m, 1H), 0.75 (br d, J=6.9 Hz, 3H) | 1.34 A<br>538.4       | A                                        |

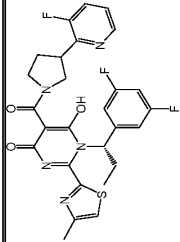
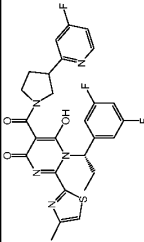


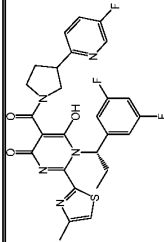
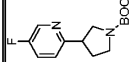
| Ex# | Structure                                                                           | Name                                                                                                                                                                 | Chiral amine intermediate with retention time                                                                                                                                                                                                                                            | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                  | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 198 |  | 1-[(1S)-1-(3,5-difluorophenyl)propyl]-6-hydroxy-5-[3-(2-methoxyphenyl)pyrrolidin-1-yl]pyrrolidine-1-carboxyl-2-(1-methyl-1H-pyrazol-4-yl)-1,4-dihydropyrimidin-4-one | <br>11.13, 97.1%<br>Chiralpak IC, 4.6 x 250 mm, 5 micron;<br>mobile phase: 15% IPA:Heptane (1:1) /85% CO <sub>2</sub> ;<br>Flow Conditions: 2 mL/min, 150 bar, 40°C,<br>wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.18 - 7.99 (m, 1H), 7.65 (br s, 1H), 7.34 - 7.19 (m, 2H), 7.17 - 7.03 (m, 1H), 7.02 - 6.93 (m, 3H), 6.92 - 6.82 (m, 1H), 3.88 (br d, J=8.5 Hz, 4H), 3.82 - 3.72 (m, 3H), 3.59 (br s, 4H), 3.45 - 3.19 (m, 1H), 2.46 - 2.24 (m, 2H), 2.20 - 2.07 (m, 1H), 1.97 (br s, 1H), 0.82 - 0.62 (m, 3H) | 1.42<br>A<br>550.2        | A                                        |

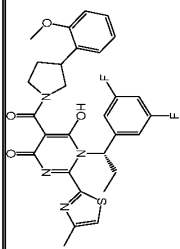
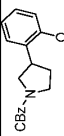
| Ex# | Structure                                                                           | Name                                                                                                                                                          | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                     | LC/MS<br>Rt<br>(min)<br>Method<br>M <sup>+</sup> H | hAPI<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|------------------------------------------------------|
| 199 |  | 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(5-fluoropyridin-2-yl)pyrrolidin-2-yl]-6-hydroxy-2-(1-hydroxy-1-methyl-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one | <br>7.7, >95.5%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 10% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 340 mL/min, 45°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.48 (br d, J=7.0 Hz, 1H), 7.81 (br d, J=8.2 Hz, 1H), 7.65 (td, J=8.7, 2.7 Hz, 1H), 7.50 - 7.32 (m, 1H), 7.17 - 6.84 (m, 2H), 6.62 (br s, 1H), 6.12 - 5.82 (m, 1H), 3.87 (br d, J=7.3 Hz, 4H), 3.67 - 3.22 (m, 5H), 2.36 - 2.13 (m, 3H), 2.09 - 1.94 (m, 1H), 0.88 - 0.58 (m, 3H) | 1.19<br>A<br>539.4                                 | A                                                    |

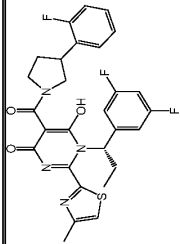
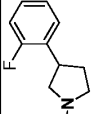
| Ex# | Structure | Name                                                                                                                                                                   | Chiral amine intermediate with retention time                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                 | LC/MS Rt (min) Method | hAPI cAMP EC <sub>50</sub> Potency range |
|-----|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 200 |           | 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(4-fluorophenyl)pyrrolidin-2-yl]pyrrolidine-1-carboxyl-2-(1-hydroxy-2-(1-methyl-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one | <br>Chiralpak IC, 4.6 x 250 mm, 5 micron; mobile phase: 10% IPA; DEA /90% CO <sub>2</sub> ; Flow Conditions: 2 mL/min, 150 bar, 40°C, wavelength: 254 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.66 - 8.46 (m, 1H), 7.89 (br s, 1H), 7.18 (br s, 1H), 7.05 - 6.85 (m, 3H), 6.78 (br s, 1H), 6.34 - 6.08 (m, 1H), 3.90 (br s, 4H), 3.77 - 3.23 (m, 5H), 2.47 - 2.18 (m, 3H), 2.17 - 1.98 (m, 1H), 0.89 - 0.72 (m, 3H)         | 1.19 A 539.4          | A                                        |
| 201 |           | 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(3-fluorophenyl)pyrrolidin-2-yl]pyrrolidine-1-carboxyl-2-(1-hydroxy-2-(1-methyl-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one | <br>8.5, >99.8%<br>Wheko, 5 x 50 cm, 10 micron; mobile phase: 10% IPA/90% CO <sub>2</sub> ; Flow Conditions: 340 mL/min, 45°C, wavelength: 220 nm (isomer 1)        | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.48 - 8.29 (m, 1H), 7.81 (br s, 1H), 7.73 - 7.57 (m, 1H), 7.46 - 7.29 (m, 1H), 7.10 - 6.82 (m, 2H), 6.64 (br s, 1H), 6.12 - 5.87 (m, 1H), 3.80 - 3.50 (m, 4H), 3.47 - 3.22 (m, 1H), 2.34 - 2.03 (m, 4H), 0.88 - 0.66 (m, 3H) | 1.19 A 539.4          | A                                        |

| Ex# | Structure                                                                            | Name                                                                                                                                                          | Chiral amine intermediate with retention time                                                                                                                   | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                   | LC/MS Rt (min) Method M+H | hAPI cAMP EC <sub>50</sub> Potency range |
|-----|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 202 |   | 1-[(1S)-1-(3,5-difluorophenyl)propyl]-2-(1-ethyl-1H-pyrazol-3-yl)-5-pyrazol-3-yl]-5-fluoropyridin-2-yl]pyrrolidine-1-carboxylate                              | Chiralpak IC, 4.6 x 250 mm, 5 micron; mobile phase: 10% IPA; DEA /90% CO <sub>2</sub> ; Flow Conditions: 2 mL/min, 150 bar, 40°C; wavelength: 254 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.68 - 8.42 (m, 1H), 7.94 (br s, 1H), 7.45 - 7.15 (m, 2H), 7.13 - 6.84 (m, 2H), 6.77 (br s, 1H), 6.28 - 6.06 (m, 1H), 4.19 (br d, J=6.2 Hz, 4H), 3.64 (br s, 3H), 3.45 - 3.18 (m, 1H), 2.40 - 2.16 (m, 3H), 2.15 - 1.97 (m, 1H), 1.55 - 1.24 (m, 3H), 0.79 (br t, J=7.3 Hz, 3H) | 1.40 A 553.2              | A                                        |
| 203 |  | 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(4-fluoropyridin-2-yl)pyrrolidine-1-carboxyl]-2-(1-hydroxy-2-(1-methyl-1H-pyrazol-4-yl)-1,4-dihydropyrimidin-4-one | Chiralpak IC, 4.6 x 250 mm, 5 micron; mobile phase: 10% IPA; DEA /90% CO <sub>2</sub> ; Flow Conditions: 2 mL/min, 150 bar, 40°C; wavelength: 254 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) Shift 8.65 - 8.43 (m, 1H), 8.06 - 7.86 (m, 1H), 7.47 (br s, 1H), 7.31 (br dd, J=19.9, 10.6 Hz, 1H), 7.24 - 7.12 (m, 1H), 6.98 - 6.77 (m, 2H), 6.55 - 6.34 (m, 1H), 3.80 (br s, 4H), 3.63 - 3.21 (m, 5H), 2.23 (br d, J=7.1 Hz, 3H), 2.11 - 1.97 (m, 1H), 0.75 (br s, 3H)          | 1.24 A 539.2              | A                                        |

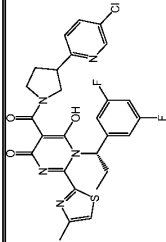
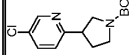
| Ex# | Structure                                                                            | Name                                                                                                       | Chiral amine intermediate with retention time                                                                                                                                         | <sup>1</sup> H NMR                                                                                                                                                                                                                                           | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|--------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 204 |   | 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(3-fluoropyridin-2-yl)pyrrolidin-1-yl]pyrrolidine-2-carboxylate | 9.5, >99.8%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 10% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 340 mL/min, 45°C, wavelength: 220 nm (isomer 2)                       | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.36 (br s, 1H), 7.67 (br s, 2H), 7.37 (br s, 1H), 7.19 - 6.83 (m, 3H), 4.05 - 3.55 (m, 4H), 3.51 - 3.13 (m, 2H), 2.45 - 2.30 (m, 5H), 2.27 - 2.02 (m, 2H), 0.80 (br d, J=6.7 Hz, 3H)                   | 1.44<br>A<br>556.4        | A                                        |
| 205 |  | 1-[(S)-1-(3,5-difluorophenyl)propyl]-5-[3-(4-fluoropyridin-2-yl)pyrrolidin-1-yl]pyrrolidine-2-carboxylate  | 10.34, 97.5%<br>Chiralpak IC, 4.6 x 250 mm, 5 micron;<br>mobile phase: 10% IPA: DEA /90% CO <sub>2</sub> ;<br>Flow Conditions: 2 mL/min, 150 bar, 40°C, wavelength: 254 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.68 - 8.43 (m, 1H), 7.73 (br s, 1H), 7.23 - 7.13 (m, 2H), 7.12 - 6.97 (m, 3H), 3.99 - 3.43 (m, 5H), 3.17 (s, 1H), 2.43 (br s, 5H), 2.32 - 2.17 (m, 1H), 2.16 - 1.98 (m, 1H), 0.83 (br t, J=7.2 Hz, 3H) | 1.44<br>A<br>556.4        | A                                        |

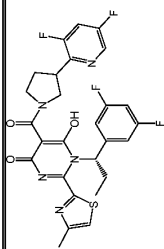
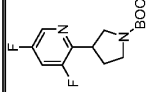
| Ex# | Structure                                                                           | Name                                                                                                                                                 | Chiral amine intermediate with retention time                                                                                                                                                                                                          | <sup>1</sup> H NMR                                                                                                                                                                                                                                                  | LC/MS Rt (min) Method M <sup>+</sup> H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|------------------------------------------|
| 206 |  | 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(5-fluoropyridin-2-yl)pyrrolidin-2-yl]-6-hydroxy-2-(4-methyl-1,3-thiazol-2-yl)-1,4-dihydropyrimidin-4-one | <br>8.4, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 10% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 340 mL/min, 45°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.60 - 8.38 (m, 1H), 7.83 - 7.57 (m, 2H), 7.51 - 7.27 (m, 1H), 7.20 - 6.89 (m, 3H), 3.61 (br s, 6H), 3.47 - 3.17 (m, 1H), 2.42 (br s, 5H), 2.31 - 2.12 (m, 1H), 2.11 - 1.95 (m, 1H), 0.81 (br t, J=7.2 Hz, 3H) | 1.49<br>A<br>555.8                     | A                                        |

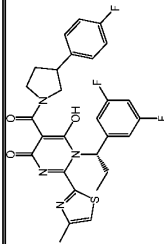
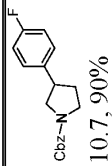
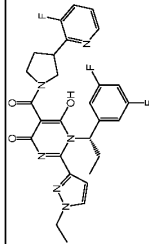
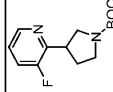
| Ex# | Structure                                                                           | Name                                                                                                                                                   | Chiral amine intermediate with retention time                                                                                                                                                                                                                                            | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                 | LC/MS Rt (min) Method | hAPI cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 207 |  | 1-[(1S)-1-(3,5-difluorophenyl)propyl]-6-hydroxy-5-[3-(2-methoxyphenyl)pyrrolidine-1-carbonyl]-2-(4-methyl-1,3-thiazol-2-yl)-1,4-dihydropyrimidin-4-one | <br>11.13, 97.1%<br>Chiralpak IC, 4.6 x 250 mm, 5 micron;<br>mobile phase: 15% IPA:Heptane (1:1) /85% CO <sub>2</sub> ;<br>Flow Conditions: 2 mL/min, 150 bar, 40°C,<br>wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.55 (br d, J=11.6 Hz, 1H), 7.30 - 7.17 (m, 2H), 7.08 - 6.93 (m, 3H), 6.92 - 6.85 (m, 1H), 6.78 (br s, 1H), 3.85 - 3.70 (m, 3H), 3.62 (br s, 5H), 3.42 - 3.19 (m, 1H), 2.38 (br d, J=10.7 Hz, 5H), 2.26 (br dd, J=12.8, 7.0 Hz, 1H), 2.17 - 2.03 (m, 1H), 0.90 - 0.68 (m, 3H) | 1.37 A<br>567.2       | A                                        |

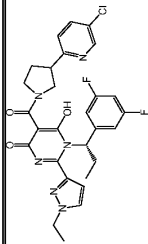
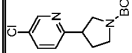
| Ex# | Structure                                                                           | Name                                                                                                                                                  | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                                                        | <sup>1</sup> H NMR                                                                                                                                                                                                                                                             | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 208 |  | 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(2-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(4-methyl-1,3-thiazol-2-yl)-1,4-dihydropyrimidin-4-one | <br>10.65, 99.5%<br>Chiralpak IF, 4.6 x 250 mm,<br>5 micron;<br>mobile phase: 15% IPA/90%<br>CO <sub>2</sub> ;<br>Flow Conditions: 2.0<br>mL/min, 150 bar, 40°C,<br>wavelength: 220 nm (Isomer<br>2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.69 (br d, J=8.9 Hz, 1H), 7.46 - 7.24 (m, 2H), 7.22 - 7.12 (m, 2H), 7.11 - 6.85 (m, 3H), 3.65 (br d, J=10.0 Hz, 5H), 3.46 - 3.22 (m, 1H), 2.46 - 2.31 (m, 5H), 2.22 (br s, 1H), 2.07 - 1.87 (m, 1H), 0.95 - 0.62 (m, 3H) | 1.66<br>A<br>555.2                    | A                                                    |

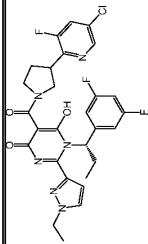
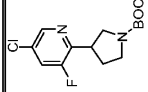


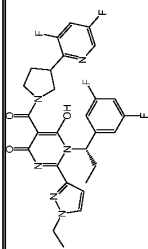
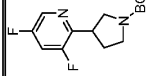
| Ex# | Structure                                                                           | Name                                                                                                                                                               | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                          | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPI<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 209 |  | 5-[3-(5-chloropyridin-2-yl)pyrrolidin-1-yl]-1-carboxylate-1-[(1S)-1-(3,5-difluorophenyl)propyl]-6-hydroxy-2-(4-methyl-1,3-thiazol-2-yl)-1,4-dihydropyrimidin-4-one | <br>7.9, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.65 - 8.42 (m, 1H), 7.84 (br s, 1H), 7.63 (br s, 1H), 7.49 - 7.15 (m, 1H), 7.13 - 6.70 (m, 3H), 3.88 - 3.54 (m, 5H), 3.37 - 3.12 (m, 1H), 2.39 (br s, 5H), 2.27 - 2.11 (m, 1H), 2.04 (br d, J=16.2 Hz, 1H), 0.80 (br d, J=5.8 Hz, 3H) | 1.60<br>A<br>572.0                    | A                                                    |

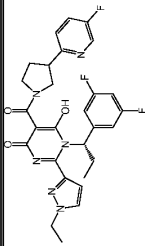
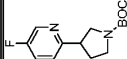
| Ex# | Structure                                                                           | Name                                                                                                                                                     | Chiral amine intermediate with retention time                                                                                                                                                                                                          | <sup>1</sup> H NMR                                                                                                                                                                                                                               | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 210 |  | 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidin-1-yl]-6-hydroxy-2-(4-methyl-1,3-thiazol-2-yl)-1,4-dihydropyrimidin-4-one | <br>6.3, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.54 - 8.34 (m, 1H), 7.91 - 7.80 (m, 1H), 7.76 - 7.54 (m, 1H), 7.21 - 6.76 (m, 3H), 3.96 - 3.57 (m, 5H), 3.52 - 3.20 (m, 1H), 2.43 - 2.29 (m, 5H), 2.25 - 2.01 (m, 2H), 0.90 - 0.64 (m, 3H) | 1.58 A 574.4              | A                                        |

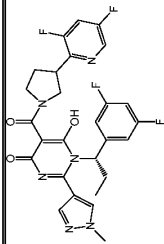
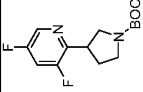
| Ex# | Structure                                                                            | Name                                                                                                                                                      | Chiral amine intermediate with retention time                                                                                                                                                                                                                              | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                   | LC/MS Rt (min) Method M+H | hAPI cAMP EC <sub>50</sub> Potency range |
|-----|--------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 211 |   | 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(4-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(4-methyl-1,3-thiazol-2-yl)-1,4-dihydropyrimidin-4-one     | <br>Cbz-N<br>10.7, 90%<br>Wheik-O 1 (R,R), 4.6 x 250 mm, 5 micron; mobile phase: 15% IPA/85%CO <sub>2</sub> ; Flow Conditions: 2.0 mL/min, 150 bar, 40°C, wavelength: 220 nm (Isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.55 (br s, 1H), 7.34 (br d, J=5.8 Hz, 1H), 7.21 (br s, 1H), 7.17 - 7.05 (m, 2H), 7.05 - 6.86 (m, 2H), 6.80 (br s, 1H), 3.71 - 3.23 (m, 5H), 3.22 - 3.04 (m, 1H), 2.38 (br s, 3H), 2.35 - 2.09 (m, 3H), 1.94 - 1.76 (m, 1H), 0.92 - 0.72 (m, 3H)                                | 1.65<br>A<br>555.4        | A                                        |
| 212 |  | 1-[(1S)-1-(3,5-difluorophenyl)propyl]-2-(1-ethyl-1H-pyrazol-3-yl)-5-[3-(3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>9.5, >99.8%<br>Wheik-O, 5 x 50 cm, 10 micron; mobile phase: 10% IPA/90% CO <sub>2</sub> ; Flow Conditions: 340 mL/min, 45°C, wavelength: 220 nm (isomer 2)                         | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.37 (br s, 1H), 8.09 - 7.84 (m, 1H), 7.77 - 7.57 (m, 1H), 7.37 (br s, 1H), 7.19 - 6.88 (m, 2H), 6.71 (br s, 1H), 6.20 - 5.97 (m, 1H), 4.17 (br d, J=7.0 Hz, 4H), 3.94 - 3.61 (m, 2H), 3.59 - 3.30 (m, 2H), 2.36 - 2.00 (m, 4H), 1.35 (br d, J=6.7 Hz, 3H), 0.92 - 0.66 (m, 3H) | 1.28<br>A<br>553.4        | A                                        |

| Ex# | Structure                                                                           | Name                                                                                                                                                               | Chiral amine intermediate with retention time                                                                                                                                                                                                          | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                               | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 213 |  | 5-[3-(5-chloropyridin-2-yl)pyrrolidin-1-yl]-1-carboxylate-1-(1-(1S)-1-(3,5-difluorophenyl)propyl)-2-(1-ethyl-1H-pyrazol-3-yl)-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>7.9, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.64 - 8.44 (m, 1H), 7.98 - 7.69 (m, 2H), 7.52 - 7.23 (m, 1H), 7.19 - 6.85 (m, 2H), 6.75 (br s, 1H), 6.10 (br s, 1H), 4.17 (br d, J=5.1 Hz, 4H), 3.68 (br s, 3H), 3.47 - 3.17 (m, 1H), 2.36 - 2.12 (m, 3H), 2.10 - 1.95 (m, 1H), 1.34 (br s, 3H), 0.78 (br d, J=5.0 Hz, 3H) | 1.47 A<br>569.0           | A                                        |

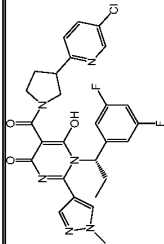
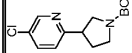
| Ex# | Structure                                                                           | Name                                                                                                                                                                    | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                        | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 214 |  | 5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidin-1-yl]-1-carboxylate [(1S)-1-(3,5-difluorophenyl)propyl]-2-(1-ethyl-1H-pyrazol-3-yl)-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>7.6, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 27°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.62 - 8.36 (m, 1H), 8.01 (br t, J=11.1 Hz, 1H), 7.83 (br s, 1H), 7.16 - 6.81 (m, 2H), 6.75 - 6.47 (m, 1H), 6.16 - 5.67 (m, 1H), 4.14 (br s, 4H), 3.94 - 3.54 (m, 2H), 3.53 - 3.25 (m, 2H), 2.10 (s, 4H), 1.33 (br d, J=5.5 Hz, 3H), 0.78 (br s, 3H) | 1.49<br>A<br>587.3                    | A                                                    |

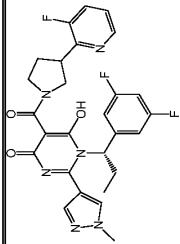
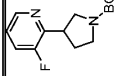
| Ex# | Structure                                                                           | Name                                                                                                                                                          | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                          | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 215 |  | 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-2-(1-ethyl-1H-pyrazol-3-yl)-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>6.3, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.46 (br s, 1H), 7.93 (br d, J=19.8 Hz, 2H), 7.09 - 6.93 (m, 2H), 6.76 (br s, 1H), 6.27 - 6.02 (m, 1H), 4.20 (br d, J=6.7 Hz, 4H), 3.97 - 3.60 (m, 2H), 3.59 - 3.22 (m, 2H), 2.40 - 2.02 (m, 4H), 1.37 (br d, J=5.5 Hz, 3H), 0.80 (br d, J=6.1 Hz, 3H) | 1.43<br>A<br>571.0                    | A                                                    |

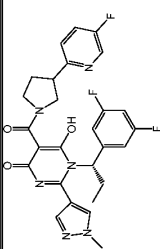
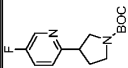
| Ex# | Structure                                                                           | Name                                                                                                                                                      | Chiral amine intermediate with retention time                                                                                                                                                                                                          | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                       | LC/MS Rt (min) Method | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 216 |  | 1-[(1S)-1-(3,5-difluorophenyl)propyl]-2-(1-ethyl-1H-pyrazol-3-yl)-5-[3-(5-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>7.7, >95.5%<br>Whecko, 5 x 50 cm, 10 micron;<br>mobile phase: 10% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 340 mL/min, 45°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.48 (br s, 1H), 7.86 (br s, 1H), 7.65 (br s, 1H), 7.50 - 7.31 (m, 1H), 7.00 (br s, 2H), 6.63 (br s, 1H), 6.12 - 5.84 (m, 1H), 4.16 (br d, J=5.5 Hz, 4H), 3.86 - 3.28 (m, 4H), 2.22 (br s, 3H), 2.11 - 1.94 (m, 1H), 1.34 (br d, J=6.1 Hz, 3H), 1.01 - 0.69 (m, 3H) | 1.44 A<br>552.9       | A                                        |

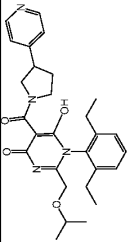
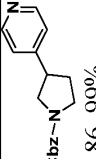
| Ex# | Structure                                                                           | Name                                                                                                                                                    | Chiral amine intermediate with retention time                                                                                                                                                                                                         | <sup>1</sup> H NMR                                                                                                                                                                                                                      | LC/MS Rt (min) Method | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 217 |  | 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidin-1-yl]-6-hydroxy-2-(1-methyl-1H-pyrazol-4-yl)-1,4-dihydropyrimidin-4-one | <br>6.3, >99.7%<br>Welko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.44 (br s, 1H), 8.08 - 7.82 (m, 2H), 7.53 (br s, 1H), 7.19 - 6.98 (m, 1H), 6.90 (br d, J=17.7 Hz, 2H), 3.85 (br s, 4H), 3.46 (br s, 5H), 2.41 - 2.01 (m, 4H), 0.87 - 0.67 (m, 3H) | 1.17 A<br>557.0       | A                                        |

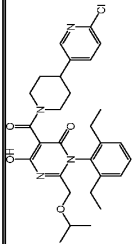
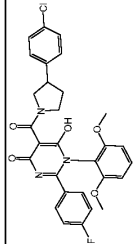
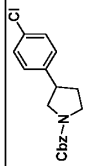


| Ex# | Structure                                                                           | Name                                                                                                                                                       | Chiral amine intermediate with retention time                                                                                                                                                                                                          | <sup>1</sup> H NMR                                                                                                                                                                                                                                                         | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 218 |  | 5-[3-(5-chloropyridin-2-yl)pyrrolidine-1-carbonyl]-1-[(1S)-1-(3,5-difluorophenyl)propyl]-6-hydroxy-2-(1-methyl-1H-pyrazol-4-yl)-1,4-dihydropyrimidin-4-one | <br>7.9, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.71 - 8.41 (m, 1H), 7.99 (br s, 1H), 7.91 - 7.76 (m, 1H), 7.57 (br s, 1H), 7.47 - 7.26 (m, 1H), 7.04 - 6.81 (m, 3H), 3.86 (br s, 4H), 3.72 - 3.25 (m, 5H), 2.40 - 2.14 (m, 3H), 2.11 - 1.96 (m, 1H), 0.75 (br s, 3H) | 1.22 A 555.5              | A                                        |

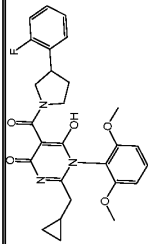
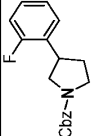
| Ex# | Structure                                                                           | Name                                                                                                       | Chiral amine intermediate with retention time                                                                                                                                                                                                          | <sup>1</sup> H NMR                                                                                                                                                                                                                                                       | LC/MS Rt (min) Method | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 219 |  | 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(3-fluoropyridin-2-yl)pyrrolidin-2-yl]pyrrolidine-1-carboxylate | <br>9.5, >99.8%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 10% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 340 mL/min, 45°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.37 (br s, 1H), 7.98 (br s, 1H), 7.66 (br d, J=7.6 Hz, 1H), 7.56 (br s, 1H), 7.36 (br s, 1H), 7.20 - 6.72 (m, 2H), 5.73 - 5.19 (m, 1H), 3.85 (br s, 4H), 3.49 (br s, 5H), 2.36 - 2.00 (m, 4H), 0.89 - 0.65 (m, 3H) | 1.09 A<br>539.0       | A                                        |

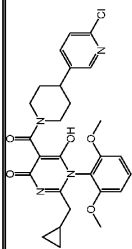
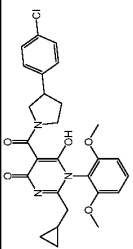
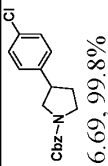
| Ex# | Structure                                                                           | Name                                                                                            | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                             | LC/MS<br>Rt<br>(min)<br>Method<br>M <sup>+</sup> H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|------------------------------------------------------|
| 220 |  | 1-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(5-fluoropyridin-2-yl)pyrrolidin-2-yl]-1-carboxylate | <br>8.4, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 10% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 340 mL/min, 45°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.55 - 8.37 (m, 1H), 7.99 (br d, J=14.0 Hz, 1H), 7.76 - 7.49 (m, 2H), 7.50 - 7.27 (m, 1H), 7.05 - 6.78 (m, 2H), 5.70 - 5.21 (m, 1H), 3.85 (br s, 4H), 3.64 (br s, 4H), 3.46 - 3.27 (m, 1H), 2.35 - 2.12 (m, 3H), 2.09 - 1.96 (m, 1H), 0.82 - 0.59 (m, 3H) | 1.10<br>A<br>539.1                                 | A                                                    |

| Ex# | Structure                                                                           | Name                                                                                                                       | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                                                    | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                 | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 221 |  | 1-(2,6-diethylphenyl)-6-hydroxy-2-[(propan-2-yl)oxy)methyl]-5-[3-(pyridin-4-yl)pyrrolidin-1-yl]-1,4-dihydropyrimidin-4-one | <br>6.86, 99%<br>Chiralpak AS-H, 4.6 x 250 mm, 5 micron;<br>mobile phase: 10% MeOH/0.1%DEA/90% CO <sub>2</sub> ;<br>Flow Conditions: 2.0 mL/min, 150 bar, 40°C,<br>wavelength: 220 nm (Isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.69 (br d, J=16.1 Hz, 2H), 7.77 (br d, J=4.9 Hz, 1H), 7.67 (br d, J=5.0 Hz, 1H), 7.52 - 7.38 (m, 1H), 7.34 - 7.20 (m, 2H), 4.09 - 3.88 (m, 1H), 3.87 - 3.71 (m, 6H), 3.66 - 3.35 (m, 1H), 3.33 - 3.12 (m, 1H), 2.45 - 2.28 (m, 4H), 2.25 - 2.10 (m, 1H), 2.09 - 1.88 (m, 1H), 1.08 (br d, J=7.3 Hz, 5H), 0.91 - 0.76 (m, 6H) | 1.15<br>A<br>491.0                    | B                                                    |

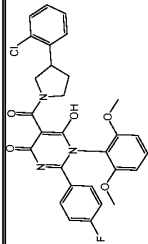
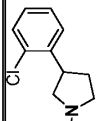
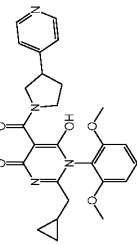
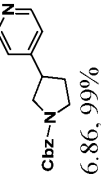
| Ex# | Structure                                                                            | Name                                                                                                                                   | Chiral amine intermediate with retention time                                                                                                                                                                                             | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                  | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|--------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 222 |   | 5-[4-(6-chloropyridin-3-yl)pyridine-1-carbonyl]-3-(2,6-diethylphenyl)-6-hydroxy-2-[(propan-2-yl)oxy)methyl]-3,4-dihydropyrimidin-4-one | achiral                                                                                                                                                                                                                                   | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.42 - 8.19 (m, 1H), 7.87 - 7.58 (m, 1H), 7.53 - 7.36 (m, 1H), 7.29 (br s, 1H), 7.22 - 7.01 (m, 2H), 4.70 - 4.44 (m, 1H), 4.05 - 3.78 (m, 2H), 3.52 (br s, 4H), 2.42 - 2.14 (m, 1H), 1.98 - 1.44 (m, 8H), 1.25 - 0.95 (m, 6H), 0.78 (br s, 6H) | 1.49 A 539.2              | C                                        |
| 223 |  | 5-[3-(4-chlorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-2-(4-fluorophenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one           | <br>Chiralcel OJ-H 4.6 x 250 mm; mobile phase: 15% IPA/85% CO <sub>2</sub> ; Flow Conditions: 3.0 mL/min, 140 bar, 40°C, wavelength: 220 nm (Isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.35 (br s, 4H), 7.31 - 7.15 (m, 3H), 7.03 (q, J=8.7 Hz, 2H), 6.71 - 6.48 (m, 2H), 4.01 - 3.47 (m, 10H), 3.39 (br s, 1H), 2.39 - 2.13 (m, 2H)                                                                                                  | 1.44 A 550.1              | B                                        |

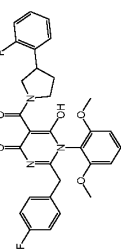
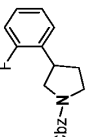
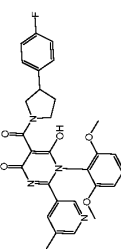
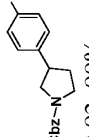
| Ex# | Structure | Name                                                                                                                                                                                                                                               | Chiral amine intermediate with retention time                                                                                                                                                 | <sup>1</sup> H NMR                                                                                                                                                                                                                                       | LC/MS Rt (min) Method | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 224 |           | 1-(2,6-dimethoxyphenyl)-2-(4-(fluorophenyl)-6-hydroxy-5-[3-(pyridin-4-yl)pyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one                                                                                                                        | <br>6.86, 99%<br>Chiralpak AS-H, 4.6 x 250 mm, 5 micron;<br>mobile phase: 10% MeOH/0.1%DEA/90% CO <sub>2</sub> ;<br>Flow Conditions: 2.0 mL/min, 150 bar, 40°C, wavelength: 220 nm (Isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.48 (br s, 2H), 7.46 - 7.31 (m, 2H), 7.24 (br dd, J=18.4, 8.6 Hz, 3H), 7.14 - 6.96 (m, 2H), 6.57 (br s, 2H), 3.98 - 3.49 (m, 10H), 3.43 (br s, 1H), 2.30 (br d, J=5.5 Hz, 1H), 2.05 - 1.91 (m, 1H) | 1.03 A<br>517.3       | B                                        |
| 225 |           | 1-(2,6-dimethoxyphenyl)-2-(4-(fluorophenyl)-5-[3-(2-(4-(fluorophenyl)pyrrolidine-1-carbonyl)-6-hydroxy-1,4-dihydropyrimidin-4-one)fluorophenyl]-2-(4-fluorophenyl)-6-hydroxy-5-(3-(pyridin-4-yl)pyrrolidine-1-carbonyl)-1,4-dihydropyrimidin-4-one | <br>10.65, 99.5%<br>Chiralpak IF, 4.6 x 250 mm, 5 micron;<br>mobile phase: 15% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 2.0 mL/min, 150 bar, 40°C, wavelength: 220 nm (Isomer 1)         | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.53 - 7.36 (m, 1H), 7.34 - 7.12 (m, 6H), 7.11 - 6.93 (m, 2H), 6.55 (br d, J=8.6 Hz, 2H), 4.02 - 3.45 (m, 10H), 3.44 - 3.27 (m, 1H), 2.25 (br s, 1H), 2.08 - 1.94 (m, 1H)                           | 1.25 A<br>534.2       | A                                        |

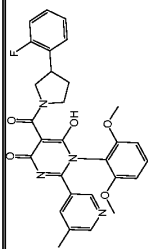
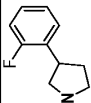
| Ex# | Structure                                                                           | Name                                                                                                                     | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                                                        | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                 | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPI<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 226 |  | 2-(cyclopropylmethyl)-1-(2,6-dimethoxyphenyl)-5-[3-(2-fluorophenyl)pyrrolidin-1-yl]-6-carboxy-1,4-dihydropyrimidin-4-one | <br>10.65, 99.5%<br>Chiralpak IF, 4.6 x 250 mm,<br>5 micron;<br>mobile phase: 15% IPA/90%<br>CO <sub>2</sub> ;<br>Flow Conditions: 2.0<br>mL/min, 150 bar, 40°C,<br>wavelength: 220 nm (Isomer<br>1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.41 (br s, 2H), 7.32 (br d, J=6.1 Hz, 1H), 7.26 - 7.11 (m, 2H), 6.92 - 6.73 (m, 2H), 3.75 (br d, J=18.8 Hz, 6H), 3.62 (br d, J=7.0 Hz, 2H), 3.52 - 3.41 (m, 1H), 3.35 (br t, J=8.9 Hz, 2H), 2.27 (br s, 1H), 2.20 - 2.10 (m, 2H), 2.07 - 1.97 (m, 1H), 0.81 (br s, 1H), 0.40 (br d, J=7.8 Hz, 2H), 0.01 (br d, J=7.2 Hz, 2H) | 1.36<br>A<br>494.3                    | A                                                    |

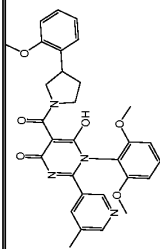
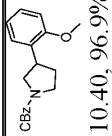
| Ex# | Structure                                                                            | Name                                                                                                                                | Chiral amine intermediate with retention time                                                                                                                                                                                              | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                       | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|--------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 227 |   | 5-[4-(6-chloropyridin-3-yl)piperidin-1-carbonyl]-2-(cyclopropylmethyl)-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one | achiral                                                                                                                                                                                                                                    | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.27 (br s, 1H), 7.71 (br d, J=7.9 Hz, 1H), 7.55 - 7.38 (m, 2H), 6.83 (br d, J=8.5 Hz, 2H), 3.90 (br s, 6H), 3.73 (br s, 4H), 3.01 - 2.81 (m, 1H), 2.18 (br d, J=6.7 Hz, 2H), 1.96 - 1.72 (m, 2H), 1.55 (br s, 2H), 0.78 (br d, J=5.5 Hz, 1H), 0.40 (br d, J=7.3 Hz, 2H), 0.00 (br d, J=3.7 Hz, 2H) | 1.28 A<br>525.3           | B                                        |
| 228 |  | 5-[3-(4-chlorophenyl)piperidin-1-carbonyl]-2-(cyclopropylmethyl)-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one       | <br>Chiralcel OJ-H 4.6 x 250 mm; mobile phase: 15% IPA/85% CO <sub>2</sub> ; Flow Conditions: 3.0 mL/min, 140 bar, 40°C, wavelength: 220 nm (Isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.55 - 7.43 (m, 1H), 7.43 - 7.31 (m, 4H), 6.96 - 6.78 (m, 2H), 3.86 - 3.63 (m, 10H), 3.51 - 3.22 (m, 1H), 2.28 (br s, 1H), 2.19 - 2.06 (m, 3H), 0.84 (br d, J=5.5 Hz, 1H), 0.51 - 0.33 (m, 2H), 0.01 (br d, J=9.4 Hz, 2H)                                                                           | 1.47 A<br>510.2           | A                                        |

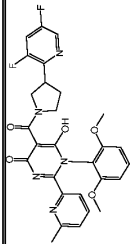
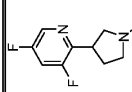


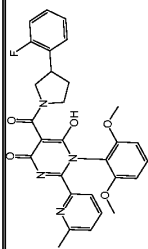
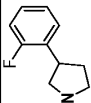
| Ex# | Structure                                                                            | Name                                                                                                                          | Chiral amine intermediate with retention time                                                                                                                                                                                                                                    | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                | LC/MS Rt (min) Method | hAPI cAMP EC <sub>50</sub> Potency range |
|-----|--------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 229 |   | 5-[3-(2-chlorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-2-(4-fluorophenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one  | <br>8.29, 98.2%<br>Chiralpak ID, 4.6 x 250 mm, 5 micron;<br>mobile phase: 10% MeOH/90% CO <sub>2</sub> ;<br>Flow Conditions: 2.0 mL/min, 150 bar, 40°C, Wavelength (Isomer 2)                 | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.45 (br t, J=7.7 Hz, 2H), 7.38 - 7.23 (m, 2H), 7.22 - 7.08 (m, 3H), 6.97 (q, J=9.1 Hz, 2H), 6.59 - 6.42 (m, 2H), 3.94 - 3.47 (m, 1H), 2.30 - 2.14 (m, 1H), 2.04 - 1.92 (m, 1H)                                                                              | 1.43<br>A<br>549.9    | A                                        |
| 230 |  | 2-(cyclopropylmethyl)-1-(2,6-dimethoxyphenyl)-6-hydroxy-5-[3-(pyridin-4-yl)pyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one | <br>6.86, 99%<br>Chiralpak AS-H, 4.6 x 250 mm, 5 micron;<br>mobile phase: 10% MeOH/0.1%DEA/90% CO <sub>2</sub> ;<br>Flow Conditions: 2.0 mL/min, 150 bar, 40°C, wavelength: 220 nm (Isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.48 (br s, 2H), 7.55 - 7.40 (m, 1H), 7.33 (br d, J=9.8 Hz, 2H), 6.91 - 6.74 (m, 2H), 3.96 - 3.53 (m, 8H), 3.50 - 3.26 (m, 3H), 2.29 (br s, 1H), 2.15 (br t, J=7.3 Hz, 2H), 2.04 - 1.86 (m, 1H), 0.79 (br s, 1H), 0.38 (br d, J=8.2 Hz, 2H), 0.00 (br s, 2H) | 1.02<br>B<br>477.0    | B                                        |

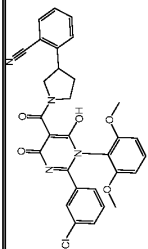
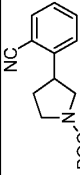
| Ex# | Structure                                                                            | Name                                                                                                                                 | Chiral amine intermediate with retention time                                                                                                                                                                                                                                | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                   | LC/MS Rt (min) Method | hAPI cAMP EC <sub>50</sub> Potency range |
|-----|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 231 |   | 1-(2,6-dimethoxyphenyl)-2-[(4-fluorophenyl)methyl]-5-[3-(2-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>10.65, 99.5%<br>Chiralpak IF, 4.6 x 250 mm, 5 micron;<br>mobile phase: 15% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 2.0 mL/min, 150 bar, 40°C,<br>wavelength: 220 nm (Isomer 1)  | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.47 - 7.34 (m, 2H), 7.28 (br d, J=5.7 Hz, 1H), 7.15 (br d, J=6.2 Hz, 2H), 7.07 - 6.91 (m, 2H), 6.80 (br d, J=5.0 Hz, 2H), 6.73 - 6.57 (m, 2H), 3.70 - 3.47 (m, 8H), 3.43 (br s, 4H), 3.36 - 3.26 (m, 1H), 2.22 (br s, 1H), 2.05 - 1.92 (m, 1H) | 1.36<br>A<br>548.4    | B                                        |
| 232 |  | 1-(2,6-dimethoxyphenyl)-2-[(4-fluorophenyl)methyl]-5-[3-(2-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>9.93, 99%<br>Wheilk-O 1 (R,R), 4.6 x 250 mm, 5 micron;<br>mobile phase: 15% IPA/85% CO <sub>2</sub> ;<br>Flow Conditions: 2.0 mL/min, 150 bar, 40°C,<br>wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.28 (br d, J=9.2 Hz, 1H), 8.14 (br d, J=18.0 Hz, 1H), 7.53 - 7.30 (m, 3H), 7.28 - 7.04 (m, 3H), 6.73 - 6.49 (m, 2H), 3.95 - 3.49 (m, 10H), 3.47 - 3.22 (m, 1H), 2.34 - 2.21 (m, 1H), 2.16 (br d, J=8.9 Hz, 4H)                                 | 1.11<br>A<br>531.1    | A                                        |

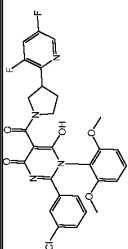
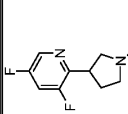
| Ex# | Structure                                                                           | Name                                                                                                                             | Chiral amine intermediate with retention time                                                                                                                                                                                                                               | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                          | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 233 |  | 1-(2,6-dimethoxyphenyl)-5-[3-(2-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-2-methylpyridine-3-yl)-1,4-dihydropyrimidin-4-one | <br>10.65, 99.5%<br>Chiralpak IF, 4.6 x 250 mm, 5 micron;<br>mobile phase: 15% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 2.0 mL/min, 150 bar, 40°C,<br>wavelength: 220 nm (Isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.27 (br d, J=8.5 Hz, 1H), 8.13 (br d, J=15.6 Hz, 1H), 7.41 (br d, J=11.9 Hz, 2H), 7.34 - 7.25 (m, 1H), 7.24 - 7.06 (m, 3H), 6.77 - 6.43 (m, 2H), 3.96 - 3.49 (m, 10H), 3.47 - 3.24 (m, 1H), 2.24 (br s, 1H), 2.20 - 2.10 (m, 3H), 2.08 - 1.95 (m, 1H) | 1.05<br>A<br>531.3        | A                                        |

| Ex# | Structure                                                                           | Name                                                                                                                      | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                                                                        | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                      | LC/MS<br>Rt<br>(min)<br>Metho<br>d<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|------------------------------------------------------|
| 234 |  | 1-(2,6-dimethoxyphenyl)-5-[3-(2-methoxyphenyl)pyrrolidine-1-carbonyl]-2-(5-methylpyridin-3-yl)-1,4-dihydropyrimidin-4-one | <br>10.40, 96.9%<br>Chiralpak IC, 4.6 x 250 mm,<br>5 micron;<br>mobile phase: 15%<br>IPA:Heptane (1:1) /85%<br>CO <sub>2</sub> ;<br>Flow Conditions: 2 mL/min,<br>150 bar, 40°C,<br>wavelength: 220 nm (isomer<br>1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.28 (br d, J=8.5 Hz, 1H), 8.15 (br d, J=15.9 Hz, 1H), 7.42 (br d, J=11.3 Hz, 1H), 7.34 - 7.11 (m, 3H), 7.08 - 6.95 (m, 1H), 6.95 - 6.82 (m, 1H), 6.56 (br d, J=8.5 Hz, 2H), 3.81 (br d, J=11.3 Hz, 3H), 3.72 - 3.48 (m, 10H), 3.46 - 3.17 (m, 1H), 2.23 - 2.07 (m, 4H), 1.99 (br d, J=9.2 Hz, 1H) | 1.07<br>A<br>543.4                        | A                                                    |

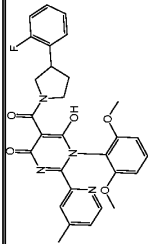
| Ex# | Structure                                                                           | Name                                                                                                                                         | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                      | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                         | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 235 |  | 5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(6-methylpyridin-2-yl)-1,4-dihydropyrimidin-4-one | <br>5.6, >99.7%<br>Welko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.49 (br d, J=6.2 Hz, 1H), 8.03 - 7.85 (m, 1H), 7.59 (q, J=8.0 Hz, 1H), 7.31 - 7.19 (m, 1H), 7.19 - 6.96 (m, 2H), 6.48 (br d, J=8.5 Hz, 2H), 3.94 - 3.72 (m, 2H), 3.72 - 3.38 (m, 9H), 2.36 - 2.20 (m, 1H), 2.17 (br d, J=9.7 Hz, 4H) | 1.19<br>A<br>550.2                    | A                                                    |

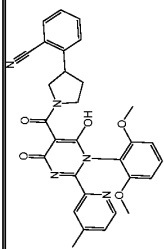
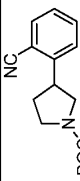
| Ex# | Structure                                                                           | Name                                                                                                                                   | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                                                        | <sup>1</sup> H NMR                                                                                                                                                                                                                                                        | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 236 |  | 1-(2,6-dimethoxyphenyl)-5-[3-(2-fluorophenyl)pyrrolidin-1-yl]-6-hydroxy-1-carboxyl-2-(6-methylpyridin-2-yl)-1,4-dihydropyrimidin-4-one | <br>10.65, 99.5%<br>Chiralpak IF, 4.6 x 250 mm,<br>5 micron;<br>mobile phase: 15% IPA/90%<br>CO <sub>2</sub> ;<br>Flow Conditions: 2.0<br>mL/min, 150 bar, 40°C,<br>wavelength: 220 nm (Isomer<br>1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.60 (q, J=8.2 Hz, 1H), 7.48 - 7.38 (m, 1H), 7.35 - 7.22 (m, 2H), 7.21 - 7.03 (m, 4H), 6.60 - 6.45 (m, 2H), 4.01 - 3.72 (m, 1H), 3.68 - 3.46 (m, 10H), 2.34 - 2.21 (m, 1H), 2.21 - 2.15 (m, 3H), 2.09 - 1.96 (m, 1H) | 1.26<br>A<br>531.2                    | A                                                    |

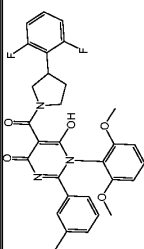
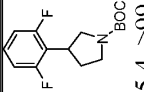
| Ex# | Structure                                                                           | Name                                                                                                                           | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                                                              | <sup>1</sup> H NMR                                                                                                                                                                                                                                                         | LC/MS<br>Rt<br>(min)<br>Metho<br>d<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|------------------------------------------------------|
| 237 |  | 2-{1-[2-(3-chlorophenyl)-1-(2,6-dimethoxyphenyl)-6-hydroxy-4-oxo-1,4-dihydropyrimidin-5-carbonyl]pyrrolidin-3-yl} benzonitrile | <br>4.87, >99%<br>Chiralpak IC, 4.6 x 250 mm,<br>5 micron;<br>mobile phase: 15%<br>IPA/0.1% DEA /85% CO <sub>2</sub> ;<br>Flow Conditions: 2 mL/min,<br>150 bar, 45°C,<br>wavelength: 220 nm (isomer<br>1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.82 (br d, J=6.7 Hz, 1H), 7.73 - 7.56 (m, 2H), 7.45 (br s, 1H), 7.32 (br d, J=9.4 Hz, 1H), 7.27 - 7.06 (m, 4H), 6.72 - 6.40 (m, 2H), 3.97 - 3.60 (m, 10H), 3.57 (br s, 1H), 2.42 - 2.25 (m, 1H), 2.13 - 1.95 (m, 1H) | 1.35<br>A<br>557.2                        | A                                                    |

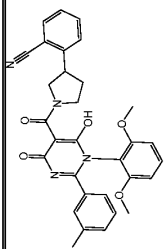
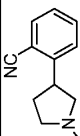
| Ex# | Structure                                                                           | Name                                                                                                                             | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                                      | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 238 |  | 2-(3-chlorophenyl)-5-[3-(3,5-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>5.6, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.49 (br d, J=7.3 Hz, 1H), 7.92 (br s, 1H), 7.36 - 6.97 (m, 5H), 6.64 - 6.41 (m, 2H), 3.98 - 3.53 (m, 10H), 3.51 - 3.12 (m, 1H), 2.30 - 2.06 (m, 1H), 1.90 (s, 1H) | 1.31<br>A<br>569.1                    | A                                                    |

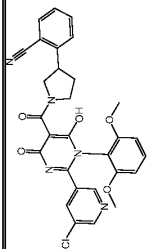
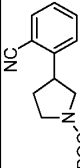


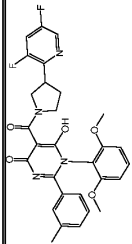
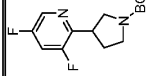
| Ex# | Structure                                                                           | Name                                                                                   | Chiral amine intermediate with retention time                                                                                                                                                                                                                               | <sup>1</sup> H NMR                                                                                                                                                                                                                             | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 239 |  | 1-(2,6-dimethoxyphenyl)-5-[3-(2-fluorophenyl)-1-pyrrolidinyl]pyrrolidine-1-carboxylate | <br>10.65, 99.5%<br>Chiralpak IF, 4.6 x 250 mm, 5 micron;<br>mobile phase: 15% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 2.0 mL/min, 150 bar, 40°C,<br>wavelength: 220 nm (Isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.07 (br dd, J=13.7, 4.3 Hz, 1H), 7.49 - 7.37 (m, 1H), 7.34 - 7.25 (m, 2H), 7.23 - 7.00 (m, 4H), 6.49 (br d, J=8.6 Hz, 2H), 3.95 - 3.25 (m, 1H), 2.32 - 2.17 (m, 4H), 2.11 - 1.95 (m, 1H) | 1.29 A 531.2              | A                                        |

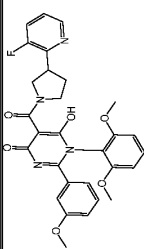
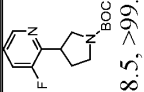
| Ex# | Structure                                                                           | Name                                                                                                                               | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                                                  | <sup>1</sup> H NMR                                                                                                                                                                                                             | LC/MS<br>Rt<br>(min)<br>Metho<br>d<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|------------------------------------------------------|
| 240 |  | 2-{[1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(4-methylpyridin-2-yl)-4-oxo-1,4-dihydropyrimidin-5-carbonyl]pyrrolidin-3-yl} benzonitrile | <br>4.87, >99%<br>Chiralpak IC, 4.6 x 250 mm, 5 micron;<br>mobile phase: 15% IPA/0.1% DEA /85% CO <sub>2</sub> ;<br>Flow Conditions: 2 mL/min, 150 bar, 45°C,<br>wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.49 (br d, J=7.3 Hz, 1H), 7.92 (br s, 1H), 7.35 - 7.01 (m, 5H), 6.64 - 6.40 (m, 2H), 3.96 - 3.32 (m, 10H), 3.30 - 3.12 (m, 1H), 2.30 - 2.06 (m, 1H), 2.00 - 1.68 (m, 1H) | 1.31<br>A<br>569.1                        | A                                                    |

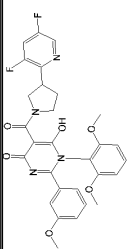
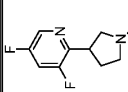
| Ex# | Structure                                                                           | Name                                                                                                                             | Chiral amine intermediate with retention time                                                                                                                                                                                                         | <sup>1</sup> H NMR                                                                                                                                                                    | LC/MS Rt (min) Method | hAPI cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 241 |  | 5-[3-(2,6-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(3-methylphenyl)-1,4-dihydropyrimidin-4-one | <br>5.4, >99.7%<br>Welko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.45 - 7.33 (m, 1H), 7.22 (q, J=8.4 Hz, 1H), 7.15 - 6.94 (m, 6H), 6.69 - 6.49 (m, 2H), 3.91 - 3.51 (m, 11H), 2.32 - 2.08 (m, 5H) | 1.45 A 548.2          | A                                        |

| Ex# | Structure                                                                           | Name                                                                                                                            | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                                                                      | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                               | LC/MS<br>Rt<br>(min)<br>Metho<br>d | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|------------------------------------------------------|
| 242 |  | 2-{1-[1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(3-methoxyphenyl)-4-oxo-1,4-dihydropyrimidin-5-carbonyl]pyrrolidin-3-yl} benzonitrile | <br>BOC-<br>4.87, >99%<br>Chiralpak IC, 4.6 x 250 mm,<br>5 micron;<br>mobile phase: 15%<br>IPA/0.1% DEA /85% CO <sub>2</sub> ;<br>Flow Conditions: 2 mL/min,<br>150 bar, 45°C,<br>wavelength: 220 nm (isomer<br>1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.83 (br d, J=7.3 Hz, 1H), 7.75 - 7.55 (m, 2H), 7.51 - 7.40 (m, 1H), 7.20 (q, J=9.0 Hz, 1H), 7.16 - 6.93 (m, 4H), 6.56 (br d, J=4.9 Hz, 2H), 3.95 - 3.43 (m, 10H), 3.42 - 3.12 (m, 1H), 2.35 (br d, J=4.3 Hz, 1H), 2.24 - 2.11 (m, 3H), 2.11 - 1.99 (m, 1H) | 1.40<br>A<br>537.1                 | A                                                    |

| Ex# | Structure                                                                           | Name                                                                                                                                 | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                                                              | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                       | LC/MS<br>Rt<br>(min)<br>Metho<br>d<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|------------------------------------------------------|
| 243 |  | 2-({1-[2-(5-chloropyridin-3-yl)-1-(2,6-dimethoxyphenyl)-6-hydroxy-4-oxo-1,4-dihydropyrimidin-5-carbonyl]pyrrolidin-3-yl}benzonitrile | <br>4.87, >99%<br>Chiralpak IC, 4.6 x 250 mm,<br>5 micron;<br>mobile phase: 15%<br>IPA/0.1% DEA /85% CO <sub>2</sub> ;<br>Flow Conditions: 2 mL/min,<br>150 bar, 45°C,<br>wavelength: 220 nm (isomer<br>1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.52 (br d, J=14.6 Hz, 1H), 8.37 - 8.21 (m, 1H), 7.82 (br t, J=6.7 Hz, 1H), 7.74 - 7.58 (m, 3H), 7.51 - 7.37 (m, 1H), 7.33 - 7.10 (m, 1H), 6.75 - 6.44 (m, 2H), 3.99 - 3.75 (m, 1H), 3.75 - 3.39 (m, 10H), 2.43 - 2.21 (m, 1H), 2.17 - 1.96 (m, 1H) | 1.21<br>A<br>558.3                        | A                                                    |

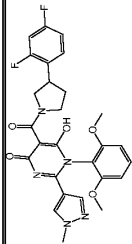
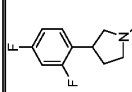
| Ex# | Structure                                                                           | Name                                                                                                                                                   | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                                       | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 244 |  | 5-[3-(3,5-difluoropyridin-2-yl)pyrrolidin-1-yl]pyrrolidine-1-carboxylate (2,6-dimethoxyphenyl)-6-hydroxy-2-(3-methylphenyl)-1,4-dihydropyrimidin-4-one | <br>5.6, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.48 (br s, 1H), 8.00 - 7.85 (m, 1H), 7.26 - 6.85 (m, 5H), 6.64 - 6.39 (m, 2H), 4.08 - 3.80 (m, 1H), 3.79 - 3.32 (m, 10H), 2.29 - 2.06 (m, 4H), 1.95 - 1.68 (m, 1H) | 1.34<br>A<br>549.4                    | A                                                    |

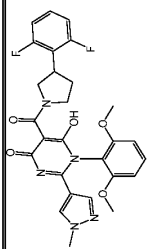
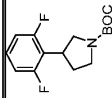
| Ex# | Structure                                                                           | Name                                                                                         | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                                                                  | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 245 |  | 1-(2,6-dimethoxyphenyl)-5-[3-(3-fluoropyridin-2-yl)pyrrolidin-1-yl]pyrrolidine-1-carboxylate | <br>8.5, >99.8%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 10% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 340 mL/min, 45°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.41 (br s, 1H), 7.80 - 7.63 (m, 1H), 7.38 (br d, J=3.7 Hz, 1H), 7.20 - 6.98 (m, 2H), 6.91 - 6.64 (m, 3H), 6.63 - 6.40 (m, 2H), 3.94 - 3.39 (m, 14H), 2.50 - 2.31 (m, 1H), 2.29 - 2.06 (m, 1H) | 1.16<br>A<br>547.3                    | A                                                    |

| Ex# | Structure                                                                           | Name                                                                                                                                    | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                                                                 | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 246 |  | 5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(3-methoxyphenyl)-1,4-dihydropyrimidin-4-one | <br>5.6, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.43 (br s, 1H), 7.82 (br t, J=9.0 Hz, 1H), 7.28 - 7.04 (m, 2H), 6.83 (br s, 2H), 6.72 (br d, J=11.6 Hz, 1H), 6.56 (br s, 2H), 4.09 - 3.38 (m, 14H), 2.36 - 2.18 (m, 1H), 2.19 - 2.04 (m, 1H) | 1.29<br>A<br>565.2                    | A                                                    |



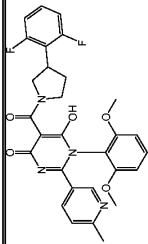
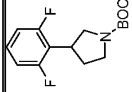
| Ex# | Structure | Name                                                                                                                                       | Chiral amine intermediate with retention time                                                                                                                                 | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                 | LC/MS Rt (min) Method | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-----------|--------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 247 |           | 2-(5-chloropyridin-3-yl)-5-[3-(2,6-difluorophenyl)pyrrolidin-1-yl]-1-carbonyl-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one | <p>5.4, &gt;99.7%<br/> Whelko, 5 x 50 cm, 10 micron;<br/> mobile phase: 20% IPA/80% CO<sub>2</sub>;<br/> Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 1)</p> | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.52 (br d, <i>J</i> =14.0 Hz, 1H), 8.39 - 8.21 (m, 1H), 7.79 - 7.60 (m, 1H), 7.35 (br d, <i>J</i> =6.4 Hz, 1H), 7.25 (q, <i>J</i> =8.9 Hz, 1H), 7.09 (br d, <i>J</i> =7.3 Hz, 2H), 6.77 - 6.51 (m, 2H), 3.98 - 3.22 (m, 1H), 2.21 (br s, 2H) | 1.29 A<br>569.3       | A                                        |

| Ex# | Structure                                                                           | Name                                                                                                                                       | Chiral amine intermediate with retention time                                                                                                                                                                                                                                      | <sup>1</sup> H NMR                                                                                                                                                                                                             | LC/MS Rt (min) Method M <sup>+</sup> H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|------------------------------------------|
| 248 |  | 5-[3-(2,4-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(1-methyl-1H-pyrazol-4-yl)-1,4-dihydropyrimidin-4-one |  <p>2,53, 92.7%<br/>Chiralpak IC, 4.6 x 250 mm, 5 micron;<br/>mobile phase: 10% IPA/90% CO<sub>2</sub>;<br/>Flow Conditions: 3 mL/min, 140 bar, 45°C,<br/>wavelength: 200-400 nm (isomer 1)</p> | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.58 - 7.36 (m, 3H), 7.29 - 7.16 (m, 1H), 7.04 (br d, J=6.0 Hz, 1H), 6.92 - 6.72 (m, 3H), 3.95 - 3.78 (m, 1H), 3.76 - 3.48 (m, 13H), 2.24 (br s, 1H), 2.10 - 1.94 (m, 1H) | 1.11<br>A<br>538.2                     | A                                        |

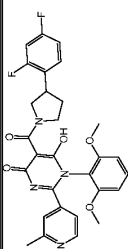
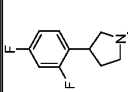
| Ex# | Structure                                                                           | Name                                                                                                                                       | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                             | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 249 |  | 5-[3-(2,6-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(1-methyl-1H-pyrazol-4-yl)-1,4-dihydropyrimidin-4-one | <br>5.4, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.60 - 7.42 (m, 2H), 7.36 (br d, J=5.0 Hz, 1H), 7.09 (br d, J=9.9 Hz, 2H), 6.94 - 6.70 (m, 3H), 3.94 - 3.39 (m, 14H), 2.36 - 2.09 (m, 2H) | 1.19<br>A<br>538.2                    | A                                                    |

| Ex# | Structure | Name                                                                                                                                       | Chiral amine intermediate<br>with retention time                                                                                                                                                      | <sup>1</sup> H NMR                                                                                                                                                                                                                                      | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPI<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-----------|--------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 250 |           | 5-[3-(2,4-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(1-methyl-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one | <br>2.53, 92.7%<br>Chiralpak IC, 4.6 x 250 mm,<br>5 micron;<br>mobile phase: 10% IPA/90%<br>CO <sub>2</sub> ;<br>Flow Conditions: 3 mL/min,<br>140 bar, 45°C,<br>wavelength: 200-400 nm<br>(isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.56 (br s, 1H), 7.50 - 7.31 (m, 2H), 7.31 - 7.17 (m, 1H), 7.04 (s, 1H), 6.80 - 6.64 (m, 2H), 5.87 (br s, 1H), 3.80 - 3.51 (m, 13H), 3.49 - 3.22 (m, 1H), 2.33 - 2.21 (m, 1H), 2.10 - 1.94 (m, 1H) | 1.06<br>A<br>538.1                    | A                                                    |

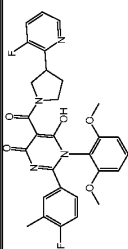
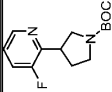
| Ex# | Structure | Name                                                                                                                                       | Chiral amine intermediate<br>with retention time                                                                                                                               | <sup>1</sup> H NMR                                                                                                                                                             | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPI<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-----------|--------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 251 |           | 5-[3-(2,6-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(1-methyl-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one | <br>5.4, >99.7%<br>Wheko, 5 x 50 cm, 10<br>micron;<br>mobile phase: 20% IPA/80%<br>CO <sub>2</sub> ;<br>Flow Conditions: 350<br>mL/min, 30°C, wavelength:<br>220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.56 - 7.21 (m, 3H), 7.19 - 6.95 (m, 2H), 6.77 - 6.48 (m, 2H), 5.82 (br s, 1H), 3.87 - 3.25 (m, 14H), 2.29 - 2.05 (m, 2H) | 1.26<br>A<br>537.9                    | A                                                    |

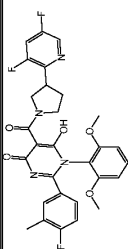
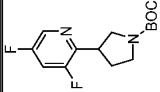
| Ex# | Structure                                                                           | Name                                                                                                                                   | Chiral amine intermediate with retention time                                                                                                                                                                                                          | <sup>1</sup> H NMR                                                                                                                                                                                                                                   | LC/MS Rt (min) Method | hAPI cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 252 |  | 5-[3-(2,6-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(6-methylpyridin-3-yl)-1,4-dihydropyrimidin-4-one | <br>5.4, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.33 - 8.12 (m, 1H), 7.59 - 7.30 (m, 2H), 7.22 (q, J=8.8 Hz, 1H), 7.16 - 6.98 (m, 3H), 6.68 - 6.45 (m, 2H), 3.91 - 3.49 (m, 10H), 3.47 - 3.26 (m, 1H), 2.42 - 2.29 (m, 3H), 2.26 - 2.11 (m, 2H) | 1.20 A<br>549.3       | A                                        |

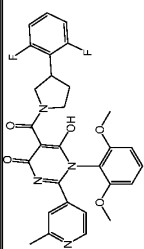
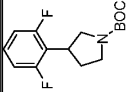
| Ex# | Structure | Name                                                                                                                                   | Chiral amine intermediate<br>with retention time                                                                                                                                                      | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                     | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPI<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-----------|----------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 253 |           | 5-[3-(2,4-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(6-methylpyridin-3-yl)-1,4-dihydropyrimidin-4-one | <br>2.53, 92.7%<br>Chiralpak IC, 4.6 x 250 mm,<br>5 micron;<br>mobile phase: 10% IPA/90%<br>CO <sub>2</sub> ;<br>Flow Conditions: 3 mL/min,<br>140 bar, 45°C,<br>wavelength: 200-400 nm<br>(isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.24 (br d, J=13.7 Hz, 1H), 7.46 (br dd, J=13.7, 7.4 Hz, 2H), 7.29 - 7.15 (m, 2H), 7.14 - 6.93 (m, 2H), 6.72 - 6.49 (m, 2H), 3.94 - 3.49 (m, 10H), 3.46 - 3.26 (m, 1H), 2.41 - 2.32 (m, 3H), 2.23 (br s, 1H), 2.06 - 1.92 (m, 1H) | 1.17<br>A<br>548.9                    | A                                                    |

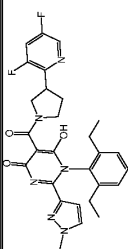
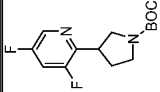
| Ex# | Structure                                                                           | Name                                                                                                                                 | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                                                         | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                   | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 254 |  | 5-[3-(2,4-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-methylpyridine-4-yl)-1,4-dihydropyrimidin-4-one | <br>2,53, 92.7%<br>Chiralpak IC, 4.6 x 250 mm,<br>5 micron;<br>mobile phase: 10% IPA/90%<br>CO <sub>2</sub> ;<br>Flow Conditions: 3 mL/min,<br>140 bar, 45°C,<br>wavelength: 200-400 nm<br>(isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.38 - 8.16 (m, 1H), 7.56 - 7.34 (m, 1H), 7.33 - 7.16 (m, 2H), 7.14 - 6.99 (m, 2H), 6.93 (br d, J=10.4 Hz, 1H), 6.69 - 6.52 (m, 2H), 3.93 - 3.52 (m, 10H), 3.34 (br d, J=5.9 Hz, 1H), 2.40 - 2.31 (m, 3H), 2.27 (br s, 1H), 2.08 - 1.94 (m, 1H) | 1.08<br>A<br>549.2                    | A                                                    |

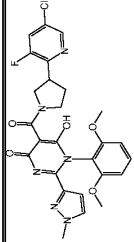
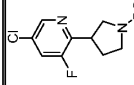


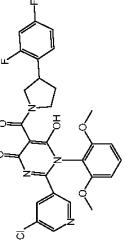
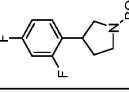
| Ex# | Structure                                                                           | Name                                                                                                                                              | Chiral amine intermediate with retention time                                                                                                                                                                                                         | <sup>1</sup> H NMR                                                                                                                                                                                                                          | LC/MS Rt (min) Method | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 255 |  | 1-(2,6-dimethoxyphenyl)-2-(4-fluorophenyl)-3-methylphenyl-5-[3-(3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>8.5, >99.8%<br>Wheko, 5 x 50 cm, 10 micron;<br>mobile phase: 10% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 340 mL/min, 45°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.40 (br s, 1H), 7.71 (br t, J=9.1 Hz, 1H), 7.49 - 7.35 (m, 1H), 7.32 - 7.15 (m, 2H), 7.13 - 6.92 (m, 2H), 6.61 (br s, 2H), 3.96 - 3.40 (m, 11H), 2.28 (br s, 1H), 2.21 - 2.04 (m, 4H) | 1.20 A<br>549.2       | A                                        |

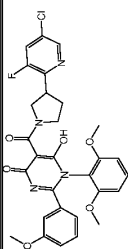
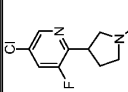
| Ex# | Structure                                                                           | Name                                                                                                                                                   | Chiral amine intermediate with retention time                                                                                                                                                                                                         | <sup>1</sup> H NMR                                                                                                                                                                                                                                    | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 256 |  | 5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-2-(4-fluoromethyl)-3-methylphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>5.6, >99.7%<br>Welko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.47 (br s, 1H), 7.91 (br t, J=9.3 Hz, 1H), 7.37 - 7.16 (m, 2H), 7.13 - 6.94 (m, 2H), 6.61 (br d, J=4.8 Hz, 2H), 4.04 - 3.55 (m, 10H), 3.55 - 3.40 (m, 1H), 2.35 - 2.23 (m, 1H), 2.11 (br s, 4H) | 1.38 A 567.3              | A                                        |

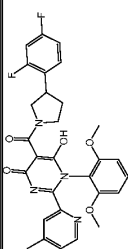
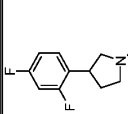
| Ex# | Structure                                                                           | Name                                                                                                                                | Chiral amine intermediate with retention time                                                                                                                                                                                                          | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                  | LC/MS Rt (min) Method | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 257 |  | 5-[3-(2,6-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-methylpyridin-4-yl)-1,4-dihydropyrimidin-4-one | <br>5.4, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.25 (br dd, J=16.6, 4.2 Hz, 1H), 7.46 - 7.30 (m, 1H), 7.26 - 7.16 (m, 1H), 7.14 - 6.97 (m, 3H), 6.96 - 6.82 (m, 1H), 6.64 - 6.42 (m, 2H), 4.15 - 3.47 (m, 10H), 3.46 - 3.25 (m, 1H), 2.41 - 2.27 (m, 4H), 2.26 - 2.13 (m, 1H) | 1.05 A<br>549.1       | A                                        |

| Ex# | Structure                                                                           | Name                                                                                                                                 | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                          | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPI<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 258 |  | 1-(2,6-diethylphenyl)-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidin-1-yl]-6-hydroxy-2-methyl-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one | <br>5.6, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.45 (br d, J=18.3 Hz, 1H), 8.01 - 7.83 (m, 1H), 7.53 (br d, J=6.2 Hz, 1H), 7.38 (q, J=7.9 Hz, 1H), 7.24 - 7.12 (m, 2H), 5.56 (br d, J=4.5 Hz, 1H), 3.97 - 3.61 (m, 7H), 3.57 - 3.25 (m, 1H), 2.33 - 2.07 (m, 6H), 1.09 - 0.88 (m, 6H) | 1.19<br>A<br>535.3                    | A                                                    |

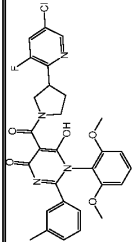
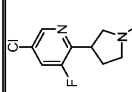
| Ex# | Structure                                                                           | Name                                                                                                                                                  | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                     | LC/MS<br>Rt<br>(min)<br>Metho<br>d<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|------------------------------------------------------|
| 259 |  | 5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(1-methyl-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one | <br>6.8, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 27°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.47 (br d, J=10.4 Hz, 1H), 8.17 - 7.93 (m, 1H), 7.63 - 7.47 (m, 1H), 7.35 (br d, J=6.9 Hz, 1H), 6.81 - 6.56 (m, 2H), 6.03 - 5.76 (m, 1H), 3.62 (d, J=5456.4 Hz, 13H), 3.39 - 3.14 (m, 1H), 2.27 (br d, J=7.2 Hz, 1H), 2.11 (br d, J=12.9 Hz, 1H) | 1.03<br>A<br>555.1                        | A                                                    |

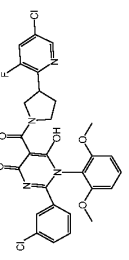
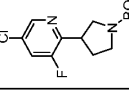
| Ex# | Structure                                                                           | Name                                                                                                                                   | Chiral amine intermediate with retention time                                                                                                                                                                                                                                                      | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                              | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 260 |  | 2-(5-chloropyridin-3-yl)-5-[3-(2,4-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one |  <p>2,53, 92.7%<br/>Chiralpak IC, 4.6 x 250 mm,<br/>5 micron;<br/>mobile phase: 10% IPA/90%<br/>CO<sub>2</sub>;<br/>Flow Conditions: 3 mL/min,<br/>140 bar, 45°C,<br/>wavelength: 200-400 nm<br/>(isomer 1)</p> | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.55 (br d, J=9.5 Hz, 1H), 8.31 (br d, J=16.1 Hz, 1H), 7.70 (br d, J=13.3 Hz, 1H), 7.54 - 7.39 (m, 1H), 7.33 - 7.15 (m, 2H), 7.09 - 6.97 (m, 1H), 6.74 - 6.54 (m, 2H), 4.06 - 3.44 (m, 10H), 3.43 - 3.23 (m, 1H), 2.37 - 2.15 (m, 1H), 2.10 - 1.89 (m, 1H) | 1.26<br>A<br>569.4        | A                                        |

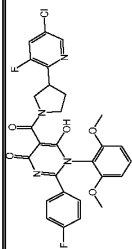
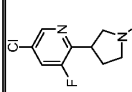
| Ex# | Structure                                                                           | Name                                                                                                                                         | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                      | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                      | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 261 |  | 5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(3-methoxyphenyl)-1,4-dihydropyrimidin-4-one | <br>6.8, >99.7%<br>Wheko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 27°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.47 (br s, 1H), 8.02 (br d, J=9.8 Hz, 1H), 7.34 - 7.07 (m, 2H), 6.84 (br s, 2H), 6.74 (br d, J=12.3 Hz, 1H), 6.58 (br d, J=4.5 Hz, 2H), 4.03 - 3.41 (m, 13H), 3.38 - 3.22 (m, 1H), 2.27 (br d, J=7.3 Hz, 1H), 2.18 - 2.02 (m, 1H) | 1.26<br>A<br>581.1                    | A                                                    |

| Ex# | Structure                                                                           | Name                                                                                                                                   | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                                                         | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                      | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 262 |  | 5-[3-(2,4-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(4-methylpyridin-2-yl)-1,4-dihydropyrimidin-4-one | <br>2.53, 92.7%<br>Chiralpak IC, 4.6 x 250 mm,<br>5 micron;<br>mobile phase: 10% IPA/90%<br>CO <sub>2</sub> ;<br>Flow Conditions: 3 mL/min,<br>140 bar, 45°C,<br>wavelength: 200-400 nm<br>(isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.09 (br dd, <i>J</i> =11.7, 4.2 Hz, 1H), 7.55 - 7.39 (m, 1H), 7.30 (br d, <i>J</i> =5.2 Hz, 1H), 7.26 - 7.09 (m, 3H), 7.04 (br t, <i>J</i> =8.3 Hz, 1H), 6.64 - 6.45 (m, 2H), 4.15 - 3.43 (m, 10H), 3.41 - 3.26 (m, 1H), 2.36 - 2.16 (m, 4H), 2.11 - 1.94 (m, 1H) | 1.22<br>A<br>549.2                    | A                                                    |

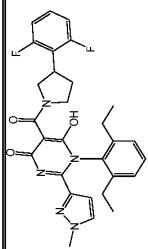
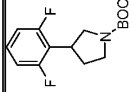


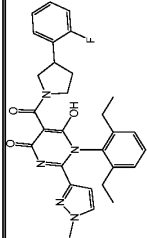
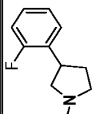
| Ex# | Structure                                                                           | Name                                                                                                                                 | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                                   | <sup>1</sup> H NMR                                                                                                                                                                                                                                                             | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 263 |  | 5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidin-1-yl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(3-methylphenyl)-1,4-dihydropyrimidin-4-one | <br>6.8, >99.7%<br>Whelko, 5 x 50 cm, 10<br>micron;<br>mobile phase: 20% IPA/80%<br>CO <sub>2</sub> ;<br>Flow Conditions: 350<br>mL/min, 27°C, wavelength:<br>220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.49 (br s, 1H), 8.06 (br d, J=9.3 Hz, 1H), 7.32 - 7.14 (m, 1H), 7.12 - 7.03 (m, 3H), 7.03 - 6.90 (m, 1H), 6.55 (br d, J=4.4 Hz, 2H), 3.97 - 3.54 (m, 10H), 3.53 - 3.22 (m, 1H), 2.36 - 2.21 (m, 1H), 2.21 - 2.03 (m, 4H) | 1.68<br>B<br>565.2                    | A                                                    |

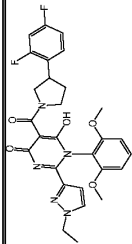
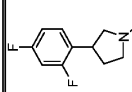
| Ex# | Structure                                                                           | Name                                                                                                                                        | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                                           | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 264 |  | 5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-2-(3-chlorophenyl)-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>6.8, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 27°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.47 (br s, 1H), 8.03 (br d, J=9.5 Hz, 1H), 7.37 (br s, 1H), 7.31 - 7.11 (m, 4H), 6.60 (br d, J=4.2 Hz, 2H), 4.03 - 3.35 (m, 11H), 2.27 (br s, 1H), 2.19 - 2.05 (m, 1H) | 1.40<br>A<br>585.1                    | A                                                    |

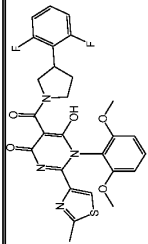
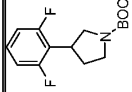
| Ex# | Structure                                                                           | Name                                                                                                                                 | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                                                    | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 265 |  | 5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidin-1-yl]-1-(2,6-dimethoxyphenyl)-2-(4-fluorophenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>6.8, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 27°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.48 (br s, 1H), 8.04 (br d, J=9.0 Hz, 1H), 7.37 - 7.15 (m, 3H), 7.12 - 6.95 (m, 2H), 6.68 - 6.47 (m, 2H), 4.01 - 3.27 (m, 11H), 2.25 (br d, J=12.1 Hz, 1H), 2.18 - 2.01 (m, 1H) | 1.30<br>A<br>568.9                    | A                                                    |

| Ex# | Structure | Name                                                                                                                                     | Chiral amine intermediate<br>with retention time                                                                                                                                                      | <sup>1</sup> H NMR                                                                                                                                                                                                                                | LC/MS<br>Rt<br>(min)<br>Method<br>M <sup>+</sup> H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-----------|------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|------------------------------------------------------|
| 266 |           | 5-[3-(2,4-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-methyl-1,3-thiazol-4-yl)-1,4-dihydropyrimidin-4-one | <br>2.53, 92.7%<br>Chiralpak IC, 4.6 x 250 mm,<br>5 micron;<br>mobile phase: 10% IPA/90%<br>CO <sub>2</sub> ;<br>Flow Conditions: 3 mL/min,<br>140 bar, 45°C,<br>wavelength: 200-400 nm<br>(isomer 1) | <sup>1</sup> H NMR (600 MHz, DMSO-d <sub>6</sub> ) δ 7.59 - 7.38 (m, 2H), 7.33 - 7.16 (m, 2H), 7.11 - 6.99 (m, 1H), 6.72 - 6.55 (m, 2H), 3.88 - 3.69 (m, 1H), 3.67 - 3.48 (m, 10H), 2.45 - 2.36 (m, 3H), 2.30 - 2.20 (m, 1H), 2.03 - 1.94 (m, 1H) | 1.19<br>A<br>555.2                                 | A                                                    |

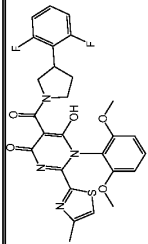
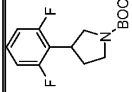
| Ex# | Structure                                                                           | Name                                                                                     | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                       | LC/MS<br>Rt<br>(min)<br>Metho<br>d<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|------------------------------------------------------|
| 267 |  | 1-(2,6-diethylphenyl)-5-[3-(2,6-difluorophenyl)pyrrolidin-1-yl]pyrrolidine-1-carboxylate | <br>5.4, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.52 (br d, J=14.6 Hz, 1H), 7.35 (br dd, J=14.2, 7.3 Hz, 2H), 7.17 (br dd, J=18.5, 7.6 Hz, 2H), 7.14 - 7.02 (m, 2H), 5.58 (br d, J=11.6 Hz, 1H), 3.93 - 3.63 (m, 7H), 3.62 - 3.31 (m, 1H), 2.35 - 2.13 (m, 6H), 1.13 - 0.80 (m, 6H) | 1.27<br>A<br>534.0                        | A                                                    |

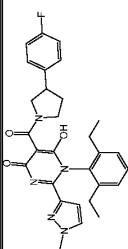
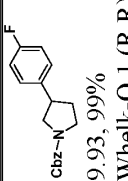
| Ex# | Structure                                                                           | Name                                                                                                                                 | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                                                                 | <sup>1</sup> H NMR                                                                                                                                                                                                                                 | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPI<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 268 |  | 1-(2,6-diethylphenyl)-5-[3-(2-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(1-methyl-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one | <br>Cbz-N<br>10.65, 99.5%<br>Chiralpak IF, 4.6 x 250 mm,<br>5 micron;<br>mobile phase: 15% IPA/90%<br>CO <sub>2</sub> ;<br>Flow Conditions: 2.0<br>mL/min, 150 bar, 40°C,<br>wavelength: 220 nm (Isomer<br>1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.53 (br d, J=7.9 Hz, 1H), 7.43 - 7.25 (m, 2H), 7.23 - 7.09 (m, 5H), 5.56 (br s, 1H), 3.95 - 3.55 (m, 7H), 3.52 - 3.30 (m, 1H), 2.33 - 2.14 (m, 5H), 2.10 - 1.92 (m, 1H), 1.11 - 0.77 (m, 6H) | 1.29<br>A<br>516.0                    | A                                                    |

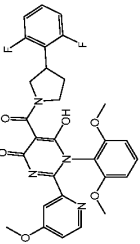
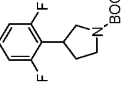
| Ex# | Structure                                                                           | Name                                                                                                                                      | Chiral amine intermediate with retention time                                                                                                                                                                                                                                   | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                          | LC/MS Rt (min) Method | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 269 |  | 5-[3-(2,4-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-2-(1-ethyl-1H-pyrazol-3-yl)-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>2.53, 92.7%<br>Chiralpak IC, 4.6 x 250 mm, 5 micron;<br>mobile phase: 10% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 3 mL/min, 140 bar, 45°C,<br>wavelength: 200-400 nm<br>(isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.61 (br s, 1H), 7.49 - 7.39 (m, 1H), 7.39 - 7.30 (m, 1H), 7.27 - 7.15 (m, 1H), 7.04 (br s, 1H), 6.82 - 6.59 (m, 2H), 6.07 (br s, 1H), 4.13 - 3.78 (m, 4H), 3.76 - 3.42 (m, 8H), 3.40 - 3.25 (m, 1H), 2.32 - 2.18 (m, 1H), 2.09 - 1.93 (m, 1H), 1.14 (q, J=6.6 Hz, 3H) | 1.21 A 552.2          | A                                        |

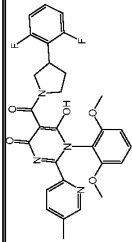
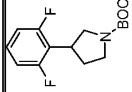
| Ex# | Structure                                                                           | Name                                                                                                                                     | Chiral amine intermediate with retention time                                                                                                                                                                                                          | <sup>1</sup> H NMR                                                                                                                                                                                                                                | LC/MS Rt (min) Method M <sup>+</sup> H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|------------------------------------------|
| 270 |  | 5-[3-(2,6-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-methyl-1,3-thiazol-4-yl)-1,4-dihydropyrimidin-4-one | <br>5.4, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.54 - 7.42 (m, 1H), 7.40 - 7.31 (m, 1H), 7.29 - 7.18 (m, 1H), 7.15 - 7.01 (m, 2H), 6.68 - 6.53 (m, 2H), 4.08 - 3.77 (m, 1H), 3.73 - 3.42 (m, 10H), 2.45 - 2.35 (m, 3H), 2.28 - 2.10 (m, 2H) | 1.09 A 555.0                           | A                                        |

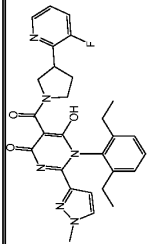
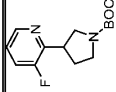


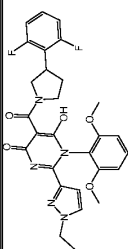
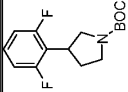
| Ex# | Structure                                                                           | Name                                                                                                                                        | Chiral amine intermediate with retention time                                                                                                                                                                                                          | <sup>1</sup> H NMR                                                                                                                                                                                                                 | LC/MS Rt (min) Method M <sup>+</sup> H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|------------------------------------------|
| 271 |  | 5-[3-(2,6-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(4-methyl-1,3-thiazol-2-yl)-1,4-dihydropyrimidin-4-one | <br>5.4, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.46 (br d, J=8.9 Hz, 1H), 7.43 - 7.30 (m, 2H), 7.18 - 6.99 (m, 2H), 6.83 - 6.64 (m, 2H), 4.09 - 3.85 (m, 1H), 3.73 - 3.44 (m, 10H), 2.29 - 2.17 (m, 2H), 2.14 - 2.06 (m, 3H) | 1.17<br>A<br>555.0                     | A                                        |

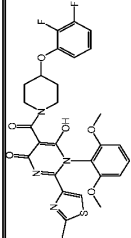
| Ex# | Structure                                                                           | Name                                                                                                                                 | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                                           | <sup>1</sup> H NMR                                                                                                                                                                                                          | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 272 |  | 1-(2,6-diethylphenyl)-5-[3-(4-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(1-methyl-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one | <br>9.93, 99%<br>Whelk-O 1 (R,R), 4.6 x 250 mm, 5 micron;<br>mobile phase: 15% IPA/85%CO <sub>2</sub> ;<br>Flow Conditions: 2.0 mL/min, 150 bar, 40°C,<br>wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.75 - 7.65 (m, 1H), 7.53 - 7.44 (m, 2H), 7.40 - 7.25 (m, 2H), 7.21 - 7.04 (m, 3H), 5.75 - 5.55 (m, 1H), 4.02 - 3.41 (m, 8H), 2.34 - 2.15 (m, 6H), 1.09 - 0.86 (m, 6H) | 1.36<br>A<br>516.3                    | A                                                    |

| Ex# | Structure                                                                           | Name                                                                                                                                    | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                                  | <sup>1</sup> H NMR                                                                                                                                                                                                                                     | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 273 |  | 5-[3-(2,6-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(4-methoxypyridin-2-yl)-1,4-dihydropyrimidin-4-one | <br>5.4, >99.7%<br>Welko, 5 x 50 cm, 10<br>micron;<br>mobile phase: 20% IPA/80%<br>CO <sub>2</sub> ;<br>Flow Conditions: 350<br>mL/min, 30°C, wavelength:<br>220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.04 (br d, J=16.0 Hz, 1H), 7.43 - 7.31 (m, 1H), 7.23 - 7.04 (m, 3H), 6.93 (br d, J=19.6 Hz, 1H), 6.80 (br d, J=7.2 Hz, 1H), 6.49 (br d, J=7.1 Hz, 2H), 3.98 - 3.46 (m, 14H), 2.34 - 2.10 (m, 2H) | 1.12<br>A<br>565.3                    | A                                                    |

| Ex# | Structure                                                                           | Name                                                                                                                                   | Chiral amine intermediate with retention time                                                                                                                                                                                                                     | <sup>1</sup> H NMR                                                                                                                                                                                                                                             | LC/MS Rt (min) Method M+H | hAPI cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 274 |  | 5-[3-(2,6-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(5-methylpyridin-2-yl)-1,4-dihydropyrimidin-4-one |  <p>5.4, &gt;99.7%<br/> Whelko, 5 x 50 cm, 10 micron;<br/> mobile phase: 20% IPA/80% CO<sub>2</sub>;<br/> Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 1)</p> | <sup>1</sup> H NMR (600 MHz, DMSO-d <sub>6</sub> ) δ 8.23 - 8.03 (m, 1H), 7.65 - 7.50 (m, 1H), 7.46 - 7.31 (m, 2H), 7.27 - 7.15 (m, 1H), 7.09 (q, J=8.1 Hz, 2H), 6.68 - 6.47 (m, 2H), 3.82 - 3.51 (m, 10H), 3.34 (dq, J=14.8, 5.4 Hz, 1H), 2.33 - 2.14 (m, 5H) | 1.12<br>A<br>548.9        | A                                        |

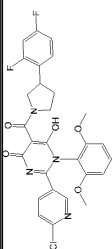
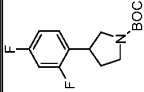
| Ex# | Structure                                                                           | Name                                                                                                                                                         | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                                                                                       | LC/MS<br>Rt<br>(min)<br>Metho<br>d<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|------------------------------------------------------|
| 275 |  | 1-(2,6-diethylphenyl)-5-[3-(3-fluoropyridin-2-yl)pyrrolidin-1-yl]pyrrolidine-1-carboxylate-6-hydroxy-2-(1-methyl-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one | <br>8.5, >99.8%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 10% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 340 mL/min, 45°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (600 MHz, DMSO-d <sub>6</sub> ) δ 8.50 - 8.28 (m, 1H), 7.79 - 7.60 (m, 1H), 7.47 (br d, J=12.7 Hz, 1H), 7.41 - 7.25 (m, 2H), 7.19 - 7.03 (m, 2H), 5.65 (br s, 1H), 4.10 - 3.57 (m, 7H), 3.40 - 3.26 (m, 1H), 2.33 - 2.10 (m, 6H), 1.10 - 0.89 (m, 6H) | 1.09<br>A<br>517.0                        | A                                                    |

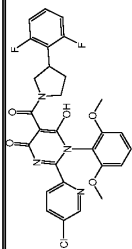
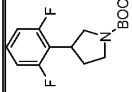
| Ex# | Structure                                                                           | Name                                                                                                                                      | Chiral amine intermediate with retention time                                                                                                                                                                                                          | <sup>1</sup> H NMR                                                                                                                                                                                                                                                             | LC/MS Rt (min) Method | hAPI cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 276 |  | 5-[3-(2,6-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-2-(1-ethyl-1H-pyrazol-3-yl)-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>5.4, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.57 (br d, J=10.6 Hz, 1H), 7.44 - 7.26 (m, 2H), 7.09 (br d, J=10.2 Hz, 2H), 6.67 (br d, J=8.7 Hz, 2H), 6.06 (br d, J=10.6 Hz, 1H), 3.94 (br s, 2H), 3.78 - 3.36 (m, 11H), 2.31 - 2.12 (m, 2H), 1.12 (br d, J=3.8 Hz, 3H) | 1.23 A 552.0          | A                                        |

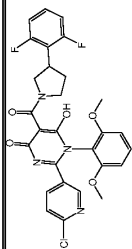
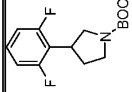
| Ex# | Structure                                                                           | Name                                                                                                                              | Chiral amine intermediate<br>with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                           | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 277 |  | 5-[4-(2,3-difluorophenoxy)piperidin-1-yl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-methyl-1,3-thiazol-4-yl)-1,4-dihydropyrimidin-4-one | achiral                                          | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.57 (br s, 1H), 7.30 (br d, J=16.7 Hz, 1H), 7.22 - 7.05 (m, 3H), 6.98 (br s, 1H), 6.66 (br s, 1H), 3.98 - 3.22 (m, 11H), 2.46 - 2.36 (m, 3H), 2.11 - 1.86 (m, 2H), 1.82 - 1.47 (m, 2H) | 1.23<br>A<br>585.0                    | A                                                    |

| Ex# | Structure | Name                                                                                                                                    | Chiral amine intermediate with retention time                                                                                                                                                         | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                               | LC/MS Rt (min) Method | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-----------|-----------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 278 |           | 5-[3-(2,4-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(4-methoxypyridin-2-yl)-1,4-dihydropyrimidin-4-one | <br>2.53, 92.7%<br>Chiralpak IC, 4.6 x 250 mm,<br>5 micron;<br>mobile phase: 10% IPA/90%<br>CO <sub>2</sub> ;<br>Flow Conditions: 3 mL/min,<br>140 bar, 45°C,<br>wavelength: 200-400 nm<br>(isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.06 (br d, J=7.2 Hz, 1H), 7.46 (br d, J=6.1 Hz, 1H), 7.30 - 7.11 (m, 2H), 7.09 - 7.00 (m, 1H), 6.93 (br d, J=7.6 Hz, 1H), 6.82 (br s, 1H), 6.52 (br t, J=9.2 Hz, 2H), 3.79 - 3.70 (m, 3H), 3.67 - 3.44 (m, 10H), 3.43 - 3.24 (m, 1H), 2.24 (br s, 1H), 2.06 - 1.95 (m, 1H) | 1.13<br>A<br>565.0    | A                                        |

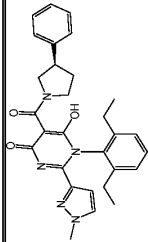
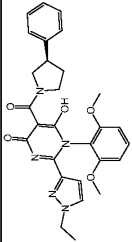


| Ex# | Structure                                                                           | Name                                                                                                                                       | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                                                         | <sup>1</sup> H NMR                                                                                                                                                                                                                                                               | LC/MS<br>Rt<br>(min)<br>Metho-<br>d<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|------------------------------------------------------|
| 279 |  | 2-(6-chloropyridin-3-yl)-5-[3-(2,4-difluorophenyl)pyrrolidin-1-yl]-1-carbonyl-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>2.53, 92.7%<br>Chiralpak IC, 4.6 x 250 mm,<br>5 micron;<br>mobile phase: 10% IPA/90%<br>CO <sub>2</sub> ;<br>Flow Conditions: 3 mL/min,<br>140 bar, 45°C,<br>wavelength: 200-400 nm<br>(isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.17 (br d, J=14.0 Hz, 1H), 7.70 - 7.56 (m, 1H), 7.47 (br d, J=9.2 Hz, 1H), 7.37 (br t, J=9.2 Hz, 1H), 7.29 - 7.15 (m, 2H), 7.03 (br s, 1H), 6.73 - 6.46 (m, 2H), 3.95 - 3.46 (m, 1H), 2.22 (br s, 1H), 2.05 - 1.91 (m, 1H) | 1.27<br>A<br>569.2                         | A                                                    |

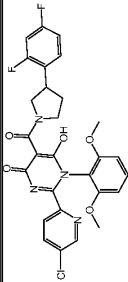
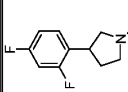
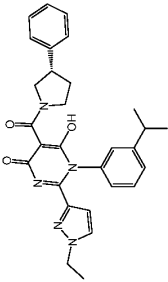
| Ex# | Structure                                                                           | Name                                                                                                                                       | Chiral amine intermediate with retention time                                                                                                                                                                                                         | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                    | LC/MS Rt (min) Method | hAPI cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 280 |  | 2-(5-chloropyridin-2-yl)-5-[3-(2,6-difluorophenyl)pyrrolidin-1-yl]-1-carbonyl-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>5.4, >99.7%<br>Welko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (600 MHz, DMSO-d <sub>6</sub> ) δ 8.42 - 8.23 (m, 1H), 7.98 - 7.85 (m, 1H), 7.50 (br dd, J=20.0, 8.1 Hz, 1H), 7.37 (br s, 1H), 7.27 - 7.16 (m, 1H), 7.10 (br d, J=8.5 Hz, 2H), 6.68 - 6.44 (m, 2H), 3.95 - 3.50 (m, 10H), 3.40 - 3.27 (m, 1H), 2.28 - 2.16 (m, 2H) | 1.29 A<br>569.2       | A                                        |

| Ex# | Structure                                                                           | Name                                                                                                                                       | Chiral amine intermediate with retention time                                                                                                                                                                                                         | <sup>1</sup> H NMR                                                                                                                                                                                                                                                | LC/MS Rt (min) Method | hAPI cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 281 |  | 2-(6-chloropyridin-3-yl)-5-[3-(2,6-difluorophenyl)pyrrolidin-1-yl]-1-carbonyl-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>5.4, >99.7%<br>Welko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.22 - 8.10 (m, 1H), 7.69 - 7.52 (m, 1H), 7.36 (br dd, J=14.6, 7.9 Hz, 2H), 7.28 - 7.17 (m, 1H), 7.10 (q, J=8.1 Hz, 2H), 6.65 - 6.51 (m, 2H), 3.78 - 3.54 (m, 10H), 3.51 - 3.31 (m, 1H), 2.32 - 2.10 (m, 2H) | 1.18<br>A<br>569.0    | A                                        |

| Ex# | Structure | Name                                                                                                                                   | Chiral amine intermediate<br>with retention time                                                                                                                                                               | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                    | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-----------|----------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 282 |           | 5-[3-(2,4-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-2-(5-methylpyridin-2-yl)-1,4-dihydropyrimidin-4-one | <p>2.53, 92.7%<br/>Chiralpak IC, 4.6 x 250 mm,<br/>5 micron;<br/>mobile phase: 10% IPA/90%<br/>CO<sub>2</sub>;<br/>Flow Conditions: 3 mL/min,<br/>140 bar, 45°C,<br/>wavelength: 200-400 nm<br/>(isomer 1)</p> | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.09 (br d, J=12.6 Hz, 1H), 7.63 - 7.41 (m, 2H), 7.34 (br d, J=7.9 Hz, 1H), 7.28 - 7.11 (m, 2H), 7.05 (br s, 1H), 6.61 - 6.43 (m, 2H), 3.89 - 3.70 (m, 1H), 3.68 - 3.31 (m, 10H), 2.33 - 2.15 (m, 4H), 2.00 (br d, J=4.6 Hz, 1H) | 1.16<br>A<br>549.1                    | A                                                    |

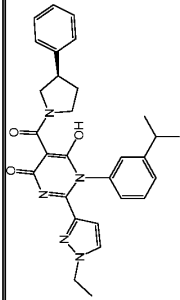
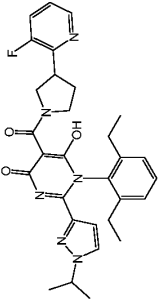
| Ex# | Structure                                                                           | Name                                                                                                                              | Chiral amine intermediate<br>with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                                             | LC/MS<br>Rt<br>(min)<br>Metho-<br>d<br>M+H | hAPI<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|------------------------------------------------------|
| 283 |  | 1-(2,6-diethylphenyl)-6-hydroxy-2-((1-methyl-1H-pyrazol-3-yl)-5-pyrazol-3-yl)-3-phenylpyrrolidine-1-carbonyl                      | R-isomer                                         | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.50 (br d, J=10.4 Hz, 1H), 7.40 - 7.19 (m, 6H), 7.19 - 7.07 (m, 2H), 5.62 (br s, 1H), 3.95 - 3.72 (m, 1H), 3.67 (br d, J=10.9 Hz, 7H), 2.37 - 2.15 (m, 6H), 1.14 - 0.81 (m, 6H)                                          | 1.27<br>A<br>498.0                         | A                                                    |
| 284 |  | 1-(2,6-dimethoxyphenyl)-2-((1-ethyl-1H-pyrazol-3-yl)-6-hydroxy-5-((3R)-3-phenylpyrrolidine-1-carbonyl)-1,4-dihydropyrimidin-4-one | R isomer                                         | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.56 (br d, J=9.3 Hz, 1H), 7.40 - 7.14 (m, 6H), 6.74 - 6.59 (m, 2H), 6.06 (br d, J=5.7 Hz, 1H), 4.06 - 3.82 (m, 2H), 3.78 - 3.45 (m, 10H), 3.44 - 3.21 (m, 1H), 2.25 (br s, 1H), 2.03 - 1.84 (m, 1H), 1.22 - 1.06 (m, 3H) | 1.09<br>A<br>516.0                         | A                                                    |

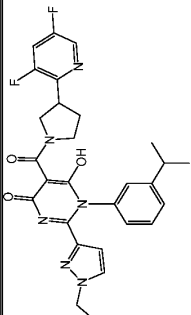
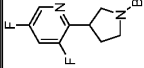
| Ex# | Structure | Name                                                                                         | Chiral amine intermediate with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                                      | LC/MS Rt (min) Method | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-----------|----------------------------------------------------------------------------------------------|-----------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 285 |           | 1-(2,6-diethylphenyl)-6-hydroxy-2-(1-methyl-1H-pyrazol-3-yl)-5-phenylpyrrolidine-1-carbonyl  | S isomer                                      | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.50 (br d, J=9.7 Hz, 1H), 7.41 - 7.20 (m, 6H), 7.19 - 7.06 (m, 2H), 5.61 (br s, 1H), 3.96 - 3.45 (m, 7H), 3.43 - 3.22 (m, 1H), 2.35 - 2.14 (m, 6H), 1.11 - 0.82 (m, 6H)                                           | 1.37 A 498.2          | A                                        |
| 286 |           | 1-(2,6-dimethoxyphenyl)-2-(1-ethyl-1H-pyrazol-3-yl)-6-hydroxy-5-phenylpyrrolidine-1-carbonyl | S isomer                                      | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.55 (br d, J=9.3 Hz, 1H), 7.36 - 7.17 (m, 6H), 6.73 - 6.57 (m, 2H), 6.06 (br d, J=6.6 Hz, 1H), 4.01 - 3.81 (m, 2H), 3.77 - 3.42 (m, 10H), 3.41 - 3.22 (m, 1H), 2.25 (br s, 1H), 1.91 (s, 1H), 1.20 - 1.06 (m, 3H) | 1.10 A 516.2          | A                                        |

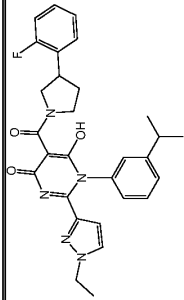
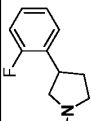
| Ex# | Structure                                                                            | Name                                                                                                                                  | Chiral amine intermediate with retention time                                                                                                                                                                                                                                   | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                 | LC/MS Rt (min) Method M+H | hAPI cAMP EC <sub>50</sub> Potency range |
|-----|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 287 |   | 2-(5-chloropyridin-2-yl)-5-[3-(2,4-difluorophenyl)pyrrolidin-1-carbonyl]-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>2.53, 92.7%<br>Chiralpak IC, 4.6 x 250 mm, 5 micron;<br>mobile phase: 10% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 3 mL/min, 140 bar, 45°C,<br>wavelength: 200-400 nm<br>(isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.26 - 8.18 (m, 1H), 7.81 (br d, J=5.8 Hz, 1H), 7.44 - 7.32 (m, 1H), 7.29 - 7.16 (m, 1H), 7.15 - 6.97 (m, 3H), 6.57 - 6.37 (m, 2H), 3.92 - 3.70 (m, 1H), 3.67 - 3.29 (m, 10H), 2.21 (br d, J=3.5 Hz, 1H), 2.01 - 1.92 (m, 1H) | 1.33<br>A<br>569.2        | A                                        |
| 288 |  | 2-(1-ethyl-1H-pyrazol-3-yl)-6-hydroxy-5-[(3S)-3-phenylpyrrolidine-1-carbonyl]-1-[3-(propan-2-yl)phenyl]-1,4-dihydropyrimidin-4-one    | S isomer                                                                                                                                                                                                                                                                        | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.58 (br d, J=10.1 Hz, 1H), 7.42 - 7.15 (m, 7H), 7.10 - 6.96 (m, 2H), 6.02 - 5.81 (m, 1H), 4.08 - 3.55 (m, 6H), 3.54 - 3.27 (m, 1H), 2.90 - 2.75 (m, 1H), 2.34 - 2.20 (m, 1H), 2.05 - 1.86 (m, 1H), 1.19 - 1.03 (m, 9H)       | 1.40<br>A<br>498.2        | A                                        |

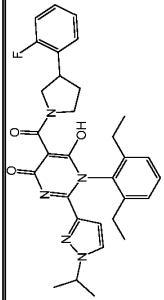
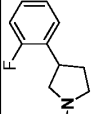
| Ex# | Structure | Name                                                                                                                      | Chiral amine intermediate with retention time                                                                                                                      | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                               | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-----------|---------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 289 |           | 1-(2,6-diethylphenyl)-6-hydroxy-5-[(3S)-3-phenylpyrrolidin-1-yl]-propan-2-yl)-1H-pyrazol-3-yl]-1,4-dihydropyrimidin-4-one | S isomer                                                                                                                                                           | <sup>1</sup> H NMR (600 MHz, DMSO-d <sub>6</sub> ) δ 7.62 (br d, J=10.9 Hz, 1H), 7.38 - 7.27 (m, 4H), 7.27 - 7.20 (m, 2H), 7.19 - 7.09 (m, 2H), 6.28 (br d, J=15.5 Hz, 1H), 4.38 - 4.23 (m, 2H), 3.98 - 3.50 (m, 3H), 3.47 - 3.26 (m, 1H), 2.36 - 2.14 (m, 5H), 2.01 - 1.87 (m, 1H), 1.13 - 1.04 (m, 6H), 1.01 - 0.85 (m, 6H)    | 1.52 A 526.3              | A                                        |
| 290 |           | 5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidin-1-yl]-propan-2-yl)-1H-pyrazol-3-yl]-1,4-dihydropyrimidin-4-one             | <br>7.6, >99.7%<br>Wheko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 27°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (600 MHz, DMSO-d <sub>6</sub> ) δ 8.54 - 8.39 (m, 1H), 8.13 - 7.96 (m, 1H), 7.60 (br d, J=9.5 Hz, 1H), 7.36 - 7.23 (m, 1H), 7.13 (br dd, J=12.1, 8.1 Hz, 2H), 6.26 (br d, J=18.6 Hz, 1H), 4.27 (br d, J=6.3 Hz, 2H), 3.96 - 3.43 (m, 4H), 2.34 - 2.06 (m, 6H), 1.07 (br d, J=4.0 Hz, 6H), 1.01 - 0.84 (m, 6H) | 1.54 A 579.1              | A                                        |

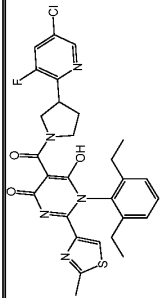
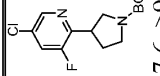


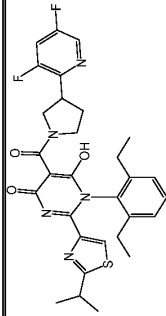
| Ex# | Structure                                                                           | Name                                                                                                                                              | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                        | <sup>1</sup> H NMR                                                                                                                                                                                                                                                       | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 291 |  | 2-(1-ethyl-1H-pyrazol-3-yl)-6-hydroxy-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-1-[3-(propan-2-yl)phenyl]-1,4-dihydropyrimidin-4-one                | R isomer                                                                                                                                                                                                                                                | <sup>1</sup> H NMR (600 MHz, DMSO-d <sub>6</sub> ) δ 7.58 (br d, J=11.9 Hz, 1H), 7.43 - 7.15 (m, 7H), 7.12 - 6.96 (m, 2H), 6.00 - 5.79 (m, 1H), 4.09 - 3.77 (m, 2H), 3.69 - 3.25 (m, 5H), 2.97 - 2.79 (m, 1H), 2.28 (br s, 1H), 2.04 - 1.88 (m, 1H), 1.23 - 0.99 (m, 9H) | 1.41<br>A<br>497.9                    | A                                                    |
| 292 |  | 1-(2,6-diethylphenyl)-5-[3-(3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-2-[1-(propan-2-yl)-1H-pyrazol-3-yl]-1,4-dihydropyrimidin-4-one | <br>9, 5, >99.8%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 10% IPA/90% CO <sub>2</sub> ,<br>Flow Conditions: 340 mL/min, 45°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (600 MHz, DMSO-d <sub>6</sub> ) δ 8.38 (br d, J=18.4 Hz, 1H), 7.85 - 7.55 (m, 2H), 7.46 - 7.01 (m, 4H), 6.62 - 6.43 (m, 1H), 4.40 - 3.78 (m, 2H), 3.78 - 3.41 (m, 4H), 2.38 - 2.02 (m, 6H), 1.16 (br t, J=7.3 Hz, 6H), 1.11 - 0.79 (m, 6H)            | 1.38<br>A<br>545.0                    | A                                                    |

| Ex# | Structure                                                                           | Name                                                                                                                                              | Chiral amine intermediate with retention time                                                                                                                                                                                                          | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                            | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 293 |  | 5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carboxyl]-2-(1-ethyl-1H-pyrazol-3-yl)-6-hydroxy-1-[3-(propan-2-yl)phenyl]-1,4-dihydropyrimidin-4-one | <br>6.3, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (600 MHz, DMSO-d <sub>6</sub> ) δ 8.31 (br d, J=9.7 Hz, 1H), 7.73 (q, J=10.0 Hz, 1H), 7.39 (br d, J=9.7 Hz, 1H), 7.17 - 7.00 (m, 2H), 6.90 - 6.73 (m, 2H), 5.78 (br d, J=17.6 Hz, 1H), 3.93 - 3.57 (m, 6H), 3.57 - 3.28 (m, 1H), 2.76 - 2.59 (m, 1H), 2.08 (br d, J=15.5 Hz, 1H), 2.04 - 1.88 (m, 1H), 1.02 - 0.89 (m, 9H) | 1.30 A 535.2              | A                                        |

| Ex# | Structure                                                                           | Name                                                                | Chiral amine intermediate with retention time                                                                                                                                                                                                                               | <sup>1</sup> H NMR                                                                                                                                                                                                                                            | LC/MS Rt (min) Method | hAPI cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 294 |  | 2-(1-ethyl-1H-pyrazol-3-yl)-5-fluorophenylpyrrolidine-1-carboxylate | <br>10.65, 99.5%<br>Chiralpak IF, 4.6 x 250 mm, 5 micron;<br>mobile phase: 15% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 2.0 mL/min, 150 bar, 40°C,<br>wavelength: 220 nm (Isomer 2) | <sup>1</sup> H NMR (600 MHz, DMSO-d <sub>6</sub> ) δ 9.16 - 8.93 (m, 3H), 8.75 - 8.50 (m, 5H), 8.26 (br s, 1H), 7.33 (br s, 1H), 4.05 - 3.65 (m, 2H), 3.53 - 3.20 (m, 5H), 3.00 - 2.86 (m, 1H), 2.14 - 2.00 (m, 1H), 1.94 - 1.77 (m, 1H), 1.35 - 1.07 (m, 9H) | 1.87 A 1031.1 (2M+H)  | A                                        |

| Ex# | Structure                                                                           | Name                                                                                                              | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                                                        | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                 | LC/MS<br>Rt<br>(min)<br>Metho<br>d<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|------------------------------------------------------|
| 295 |  | 1-(2,6-diethylphenyl)-5-[3-(2-fluorophenyl)pyrrolidin-1-yl]propan-2-yl-1H-pyrazol-3-yl-1,4-dihydropyrimidin-4-one | <br>10.65, 99.5%<br>Chiralpak IF, 4.6 x 250 mm,<br>5 micron;<br>mobile phase: 15% IPA/90%<br>CO <sub>2</sub> ;<br>Flow Conditions: 2.0<br>mL/min, 150 bar, 40°C,<br>wavelength: 220 nm (Isomer<br>2) | <sup>1</sup> H NMR (600 MHz, DMSO-d <sub>6</sub> ) δ 7.62 (br d, J=10.5 Hz, 1H), 7.37 (dt, J=14.6, 7.4 Hz, 1H), 7.34 - 7.25 (m, 2H), 7.23 - 7.09 (m, 4H), 6.28 (br d, J=15.1 Hz, 1H), 4.37 - 4.20 (m, 1H), 3.97 - 3.31 (m, 5H), 2.37 - 2.13 (m, 5H), 2.06 - 1.96 (m, 1H), 1.10 - 1.05 (m, 6H), 1.02 - 0.83 (m, 6H) | 1.56<br>A<br>544.2                        | A                                                    |

| Ex# | Structure                                                                           | Name                                                                                                                                                 | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                     | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 296 |  | 5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-1-(2,6-diethylphenyl)-6-hydroxy-2-(2-methyl-1,3-thiazol-4-yl)-1,4-dihydropyrimidin-4-one | <br>7.6, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 27°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.45 (br d, J=18.6 Hz, 1H), 8.01 (br t, J=9.8 Hz, 1H), 7.47 (br d, J=13.7 Hz, 1H), 7.30 - 7.17 (m, 1H), 7.05 (br dd, J=12.5, 7.6 Hz, 2H), 3.94 - 3.48 (m, 4H), 3.47 - 3.23 (m, 1H), 2.43 - 2.19 (m, 8H), 2.19 - 2.06 (m, 1H), 1.14 - 0.85 (m, 6H) | 1.45<br>A<br>568.0                    | A                                                    |

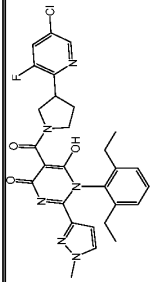
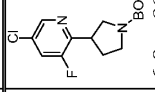
| Ex# | Structure                                                                           | Name                                                                                                                                                | Chiral amine intermediate with retention time                                                                                                                                                                                                          | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                   | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 297 |  | 1-(2,6-diethylphenyl)-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(propan-2-yl)-1,3-thiazol-4-yl]-1,4-dihydropyrimidin-4-one | <br>6.3, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.52 - 8.40 (m, 1H), 7.95 - 7.82 (m, 1H), 7.72 (br d, J=17.4 Hz, 1H), 7.24 - 7.09 (m, 1H), 6.99 (br dd, J=13.3, 7.2 Hz, 2H), 3.99 - 3.38 (m, 5H), 3.02 - 2.88 (m, 1H), 2.33 (dt, J=14.8, 7.2 Hz, 4H), 2.24 - 2.13 (m, 2H), 1.11 - 0.87 (m, 12H) | 1.58<br>A<br>580.3        | A                                        |

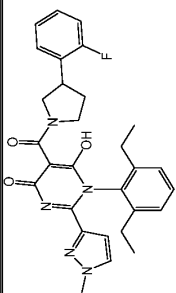
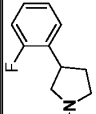
| Ex# | Structure | Name                                                                                                                                                              | Chiral amine intermediate with retention time                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                                                                                    | LC/MS Rt (min) Method M+H | hAPI cAMP EC <sub>50</sub> Potency range |
|-----|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 298 |           | 1-(2,6-diethylphenyl)-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidin-1-yl]pyrrolidine-1-carboxylate-2-(2-hydroxy-1-methyl-1,3-thiazol-4-yl)-1,4-dihydropyrimidin-4-one | <br>6.3, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.45 (br d, J=18.0 Hz, 1H), 7.92 - 7.84 (m, 1H), 7.47 (br d, J=14.0 Hz, 1H), 7.29 - 7.15 (m, 1H), 7.10 - 6.96 (m, 2H), 3.97 - 3.38 (m, 5H), 2.44 - 2.08 (m, 9H), 1.15 - 0.89 (m, 6H)                             | 1.37<br>A<br>552.3        | A                                        |
| 299 |           | 1-(2,6-diethylphenyl)-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidin-1-yl]pyrrolidine-1-carboxylate-2-(2-hydroxy-1-methyl-1,3-thiazol-4-yl)-1,4-dihydropyrimidin-4-one | S isomer                                                                                                                                                            | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.66 (br d, J=13.7 Hz, 1H), 7.39 - 7.18 (m, 5H), 7.17 - 7.08 (m, 1H), 6.97 (br dd, J=11.0, 7.6 Hz, 2H), 3.96 - 3.72 (m, 1H), 3.68 - 3.23 (m, 4H), 3.03 - 2.84 (m, 1H), 2.44 - 2.13 (m, 6H), 1.11 - 0.87 (m, 12H) | 1.73<br>A<br>543.3        | A                                        |

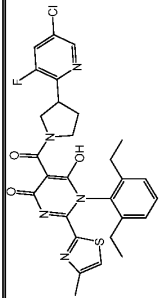
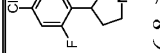
| Ex# | Structure | Name                                                                                                                             | Chiral amine intermediate with retention time                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                   | LC/MS Rt (min) Method M <sup>+</sup> H | hAPI cAMP EC <sub>50</sub> Potency range |
|-----|-----------|----------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|------------------------------------------|
| 300 |           | 1-(2,6-diethylphenyl)-5-[3-(5-fluoropyridin-2-yl)pyrrolidin-1-yl]pyrrolidine-1-carboxylate                                       | <br>7.7, >95.5%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 10% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 340 mL/min, 45°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.56 - 8.41 (m, 1H), 7.73 (br d, J=15.6 Hz, 1H), 7.70 - 7.60 (m, 1H), 7.53 - 7.37 (m, 1H), 7.23 - 7.09 (m, 1H), 6.99 (br dd, J=13.6, 7.2 Hz, 2H), 4.11 - 3.82 (m, 1H), 3.80 - 3.35 (m, 4H), 3.02 - 2.89 (m, 1H), 2.42 - 2.16 (m, 5H), 2.12 - 1.96 (m, 1H), 1.12 - 0.87 (m, 12H) | 1.51<br>A<br>562.3                     | A                                        |
| 301 |           | 1-(2,6-diethylphenyl)-6-hydroxy-2-(2-methyl-1,3-thiazol-4-yl)-5-[(3R)-3-phenylpyrrolidine-1-carboxyl]-1,4-dihydropyrimidin-4-one | R isomer                                                                                                                                                            | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.57 (br d, J=8.9 Hz, 1H), 7.41 - 7.18 (m, 6H), 7.15 - 7.04 (m, 2H), 4.04 - 3.85 (m, 1H), 3.82 - 3.30 (m, 4H), 2.44 - 2.14 (m, 8H), 2.03 - 1.84 (m, 1H), 1.11 - 0.86 (m, 6H)                                                                                                    | 1.44<br>A<br>515.4                     | A                                        |



| Ex# | Structure | Name                                                                                                                                                                            | Chiral amine intermediate with retention time                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                                                             | LC/MS Rt (min) Method M <sup>+</sup> H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|------------------------------------------|
| 302 |           | 1-(2,6-diethylphenyl)-5-[3-(3-fluoropyrrolidin-2-yl)pyrrolidin-6-yl]-1-carboxylate-2-hydroxy-2-(2-methyl-1,3-thiazol-4-yl)-1,4-dihydropyrimidin-4-one                           | <br>9.5, >99.8%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 10% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 340 mL/min, 45°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.35 (br d, J=3.7 Hz, 1H), 7.74 - 7.60 (m, 1H), 7.55 - 7.30 (m, 2H), 7.27 - 7.13 (m, 1H), 7.01 (br dd, J=17.5, 6.9 Hz, 2H), 3.95 - 3.42 (m, 5H), 2.44 - 2.06 (m, 9H), 1.10 - 0.85 (m, 6H) | 1.24<br>A<br>534.1                     | A                                        |
| 303 |           | 1-(2,6-diethylphenyl)-6-hydroxy-2-(2-methyl-1,3-thiazol-4-yl)-5-[(3S)-3-phenylpyrrolidin-1-yl]-1-carboxylate-2-hydroxy-2-(2-methyl-1,3-thiazol-4-yl)-1,4-dihydropyrimidin-4-one | S isomer                                                                                                                                                            | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.61 - 8.42 (m, 1H), 8.07 - 7.91 (m, 2H), 7.69 - 7.45 (m, 1H), 7.39 - 7.16 (m, 4H), 7.14 - 6.98 (m, 1H), 3.75 - 3.22 (m, 5H), 2.40 - 2.13 (m, 8H), 1.94 (s, 1H), 1.11 - 0.85 (m, 6H)      | 1.40<br>A<br>515.2                     | A                                        |

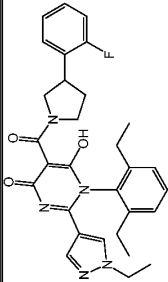
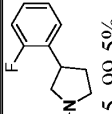
| Ex# | Structure                                                                           | Name                                                                                                                                               | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                     | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 304 |  | 5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidin-1-carbonyl]-1-(2,6-diethylphenyl)-6-hydroxy-2-(1-methyl-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one | <br>6.8, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 27°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.47 (br d, J=18.3 Hz, 1H), 8.15 - 7.95 (m, 1H), 7.44 (br d, J=10.4 Hz, 1H), 7.35 - 7.19 (m, 1H), 7.09 (br dd, J=14.6, 7.6 Hz, 2H), 5.65 (br d, J=5.6 Hz, 1H), 3.97 - 3.70 (m, 1H), 3.70 - 3.26 (m, 7H), 2.37 - 2.02 (m, 6H), 1.12 - 0.76 (m, 6H) | 1.33<br>A<br>551.2                    | A                                                    |

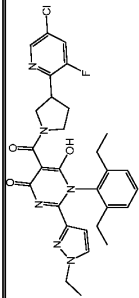
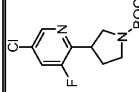
| Ex# | Structure                                                                           | Name                                                                                                                        | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                                                        | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                  | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 305 |  | 1-(2,6-diethylphenyl)-5-[(3-(2-fluorophenyl)pyrrolidin-1-yl)carbonyl]-6-hydroxy-1H-pyrazol-3-yl)-1,4-dihydropyrimidin-4-one | <br>10.65, 99.5%<br>Chiralpak IF, 4.6 x 250 mm,<br>5 micron;<br>mobile phase: 15% IPA/90%<br>CO <sub>2</sub> ;<br>Flow Conditions: 2.0<br>mL/min, 150 bar, 40°C,<br>wavelength: 220 nm (Isomer<br>2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.54 (br d, J=7.9 Hz, 1H), 7.38 (br d, J=7.0 Hz, 2H), 7.29 (br d, J=5.8 Hz, 1H), 7.24 - 7.04 (m, 4H), 5.59 (br s, 1H), 3.99 - 3.73 (m, 1H), 3.73 - 3.32 (m, 7H), 2.35 - 2.14 (m, 5H), 2.09 - 1.96 (m, 1H), 1.11 - 0.83 (m, 6H) | 1.27<br>A<br>516.3                    | A                                                    |

| Ex# | Structure                                                                           | Name                                                                                                                                          | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                                                       | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 306 |  | 5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidin-1-yl]-1-(2,6-diethylphenyl)-6-hydroxy-2-(4-methyl-1,3-thiazol-2-yl)-1,4-dihydropyrimidin-4-one | <br>6.8, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 27°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.47 (br d, J=19.9 Hz, 1H), 8.14 - 7.95 (m, 1H), 7.44 - 7.18 (m, 2H), 7.16 - 7.00 (m, 2H), 3.99 - 3.39 (m, 5H), 2.38 - 2.08 (m, 8H), 2.00 (br d, J=6.6 Hz, 1H), 1.10 - 0.82 (m, 6H) | 1.46<br>A<br>568.1                    | A                                                    |

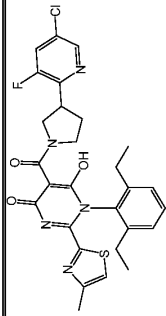
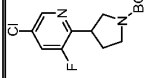
| Ex# | Structure | Name                                                                                                                                                                          | Chiral amine intermediate with retention time                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                                                                      | LC/MS Rt (min) Method M+H | hAPI cAMP EC <sub>50</sub> Potency range |
|-----|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 307 |           | 1-(2,6-diethylphenyl)-5-[(3-(2-(4-methyl-1,3-thiazol-2-yl)-1,4-dihydropyrimidin-4-yl)pyrrolidin-2-yl)fluoropyridin-2-yl]pyrrolidine-1-carboxylate                             | <br>9.5, >99.8%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 10% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 340 mL/min, 45°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.38 (br d, J=18.1 Hz, 1H), 7.78 - 7.61 (m, 1H), 7.51 - 7.22 (m, 3H), 7.20 - 7.02 (m, 2H), 3.97 - 3.54 (m, 4H), 3.54 - 3.27 (m, 1H), 2.34 - 2.09 (m, 5H), 2.08 - 1.91 (m, 4H), 1.14 - 0.78 (m, 6H) | 1.33<br>A<br>534.2        | A                                        |
| 308 |           | 1-(2,6-diethylphenyl)-2-(1-ethyl-1H-pyrazol-3-yl)-5-[(3-(2-(4-methyl-1,3-thiazol-2-yl)-1,4-dihydropyrimidin-4-yl)pyrrolidin-2-yl)fluoropyridin-2-yl]pyrrolidine-1-carboxylate | <br>9.5, >99.8%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 10% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 340 mL/min, 45°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.47 - 8.27 (m, 1H), 7.65 (br d, J=8.9 Hz, 1H), 7.53 (br s, 1H), 7.43 - 7.21 (m, 2H), 7.10 (br s, 2H), 5.97 (br s, 1H), 4.13 - 3.49 (m, 7H), 2.37 - 2.04 (m, 6H), 1.19 - 0.77 (m, 9H)              | 1.19<br>A<br>531.3        | A                                        |

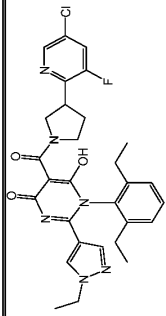
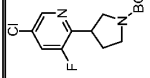
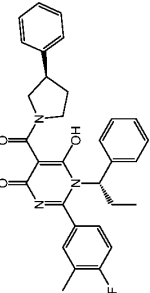
| Ex# | Structure | Name                                                                                                                             | Chiral amine intermediate<br>with retention time                                                                                                                                                  | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                       | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-----------|----------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 309 |           | 1-(2,6-diethylphenyl)-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidin-1-yl]-2-carbonyl-1-(1-ethyl-4-hydroxy-1,4-dihydropyrimidin-4-one | <p>6.3, &gt;99.7%<br/> Whelko, 5 x 50 cm, 10<br/> micron;<br/> mobile phase: 20% IPA/80%<br/> CO<sub>2</sub>;<br/> Flow Conditions: 350<br/> mL/min, 30°C, wavelength:<br/> 220 nm (isomer 2)</p> | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.45 (br d, J=18.6 Hz, 1H), 7.88 (q, J=9.4 Hz, 1H), 7.52 (br d, J=9.9 Hz, 1H), 7.34 - 7.20 (m, 1H), 7.10 (br dd, J=13.5, 7.6 Hz, 2H), 5.94 (br d, J=12.2 Hz, 1H), 4.04 - 3.67 (m, 6H), 3.55 (br d, J=18.0 Hz, 1H), 2.33 - 2.03 (m, 6H), 1.07 (q, J=6.9 Hz, 3H), 1.02 - 0.85 (m, 6H) | 1.30<br>A<br>549.1                    | A                                                    |

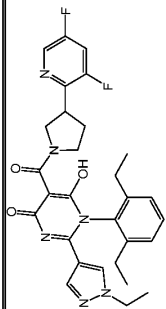
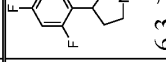
| Ex# | Structure                                                                           | Name                                                                                                                                | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                                                                 | <sup>1</sup> H NMR                                                                                                                                                                                                                                                              | LC/MS<br>Rt<br>(min)<br>Metho<br>d<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|------------------------------------------------------|
| 310 |  | 1-(2,6-diethylphenyl)-2-(1-ethyl-1H-pyrazol-4-yl)-5-[3-(2-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>Cbz-N<br>10.65, 99.5%<br>Chiralpak IF, 4.6 x 250 mm,<br>5 micron;<br>mobile phase: 15% IPA/90%<br>CO <sub>2</sub> ;<br>Flow Conditions: 2.0<br>mL/min, 150 bar, 40°C,<br>wavelength: 220 nm (Isomer<br>2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.58 - 7.34 (m, 2H), 7.34 - 7.23 (m, 3H), 7.22 - 7.05 (m, 3H), 6.46 (br d, J=14.0 Hz, 1H), 4.07 - 3.70 (m, 6H), 3.65 - 3.38 (m, 1H), 2.35 - 2.12 (m, 5H), 2.07 - 1.94 (m, 1H), 1.19 (q, J=6.6 Hz, 3H), 1.05 - 0.79 (m, 6H) | 1.40<br>A<br>530.1                        | A                                                    |

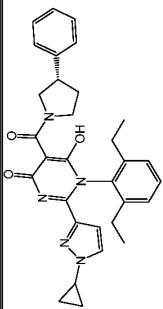
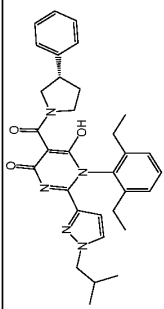
| Ex# | Structure                                                                           | Name                                                                                                                                               | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                         | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 311 |  | 5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-1-(2,6-diethylphenyl)-2-(1-ethyl-1H-pyrazol-3-yl)-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>7.6, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 27°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.45 (br d, J=18.6 Hz, 1H), 8.01 (br t, J=10.4 Hz, 1H), 7.62 - 7.44 (m, 1H), 7.36 - 7.20 (m, 1H), 7.17 - 7.01 (m, 2H), 5.92 (br d, J=11.5 Hz, 1H), 4.05 - 3.70 (m, 4H), 3.65 - 3.35 (m, 3H), 2.35 - 2.04 (m, 6H), 1.14 - 0.78 (m, 9H) | 1.40<br>A<br>565.1                    | A                                                    |

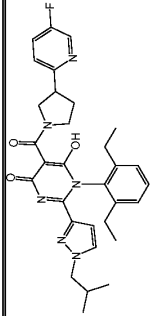
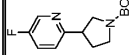


| Ex# | Structure                                                                           | Name                                                                                                                                                 | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                                                                                             | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 312 |  | 5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-1-(2,6-diethylphenyl)-6-hydroxy-2-(4-methyl-1,3-thiazol-2-yl)-1,4-dihydropyrimidin-4-one | <br>7.6, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 27°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.47 (br d, J=19.2 Hz, 1H), 8.11 - 7.98 (m, 1H), 7.45 (br d, J=8.2 Hz, 1H), 7.38 - 7.29 (m, 1H), 7.15 (br s, 2H), 3.97 - 3.52 (m, 4H), 3.49 - 3.30 (m, 1H), 2.33 - 2.08 (m, 5H), 2.08 - 1.98 (m, 4H), 1.09 - 0.81 (m, 6H) | 1.46<br>A<br>568.3                    | A                                                    |

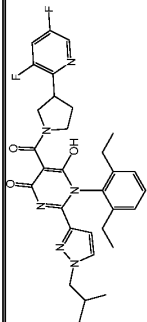
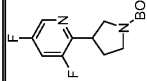
| Ex# | Structure                                                                            | Name                                                                                                                                      | Chiral amine intermediate with retention time                                                                                                                                                                                                          | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                     | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|--------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 313 |   | 5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-1,4-dimethyl-2-(1-ethyl-1H-pyrazol-4-yl)-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>7.6, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 27°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.44 (br d, J=16.5 Hz, 1H), 8.00 (br s, 1H), 7.53 (br s, 1H), 7.35 (br s, 2H), 7.25 (br s, 1H), 6.56 (br s, 1H), 3.99 (br d, J=6.1 Hz, 2H), 3.63 (br s, 4H), 3.49 (br d, J=6.1 Hz, 1H), 2.37 - 2.00 (m, 6H), 1.20 (br s, 3H), 1.05 - 0.75 (m, 6H) | 1.30<br>A<br>565.1        | A                                        |
| 314 |  | 2-(4-fluoro-3-methylphenyl)-6-hydroxy-1-[(1S)-1-phenylpropyl]-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-1,4-dihydropyrimidin-4-one          | R-isomer                                                                                                                                                                                                                                               | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.32 (br d, J=3.1 Hz, 6H), 7.28 - 7.09 (m, 7H), 3.94 - 3.80 (m, 1H), 3.73 - 3.24 (m, 4H), 3.22 - 3.10 (m, 1H), 2.45 - 2.15 (m, 6H), 2.00 - 1.84 (m, 1H), 0.88 - 0.71 (m, 3H)                                                                      | 1.70<br>A<br>512.0        | A                                        |

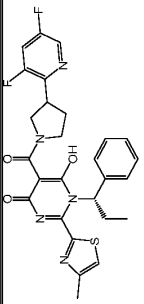
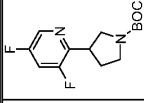
| Ex# | Structure                                                                           | Name                                                                                                                                          | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                                                                                                             | <sup>1</sup> H NMR                                                                                                                                                                                                                                                        | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 315 |  | 1-(2,6-diethylphenyl)-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-2-(1-ethyl-1H-pyrazol-4-yl)-6-hydroxy-1,4-dihydropyrimidin-4-one |  <p>6.3, &gt;99.7%<br/>         Welko, 5 x 50 cm, 10<br/>         micron;<br/>         mobile phase: 20% IPA/80%<br/>         CO<sub>2</sub>;<br/>         Flow Conditions: 350<br/>         mL/min, 30°C, wavelength:<br/>         220 nm (isomer 2)</p> | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.56 - 8.41 (m, 1H), 7.93 (br d, J=7.3 Hz, 1H), 7.54 (br s, 2H), 7.44 - 7.28 (m, 2H), 6.71 - 6.50 (m, 1H), 4.01 (br d, J=6.6 Hz, 2H), 3.92 - 3.26 (m, 5H), 2.35 - 1.97 (m, 6H), 1.21 (br s, 3H), 1.08 - 0.78 (m, 6H) | 1.27<br>A<br>548.9                    | A                                                    |

| Ex# | Structure                                                                            | Name                                                                                                                       | Chiral amine intermediate<br>with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                | LC/MS<br>Rt<br>(min)<br>Metho<br>d<br>M+H | hAPI<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|--------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|------------------------------------------------------|
| 316 |   | 2-(1-cyclopropyl-1H-pyrazol-3-yl)-1-(2,6-dihydroxy-3-phenyl)-5-(3-phenylpyrrolidine-1-carbonyl)-1,4-dihydropyrimidin-4-one | S isomer                                         | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.71 (br d, J=10.1 Hz, 1H), 7.37 - 7.27 (m, 4H), 7.27 - 7.18 (m, 2H), 7.18 - 7.04 (m, 2H), 6.25 (br d, J=11.3 Hz, 1H), 3.88 (br d, J=11.3 Hz, 1H), 3.79 - 3.36 (m, 4H), 3.35 - 3.14 (m, 1H), 2.39 - 2.13 (m, 5H), 2.00 - 1.85 (m, 1H), 1.07 - 0.83 (m, 6H), 0.74 (br s, 2H), 0.59 (br s, 2H) | 1.72<br>A<br>524.0                        | A                                                    |
| 317 |  | 1-(2,6-dihydroxy-3-phenyl)-5-(2-phenyl-1-cyclopropyl-3-yl)-1,4-dihydropyrimidin-4-one                                      | S isomer                                         | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.57 (br d, J=10.3 Hz, 1H), 7.40 - 7.18 (m, 6H), 7.17 - 7.03 (m, 2H), 6.04 (br d, J=7.9 Hz, 1H), 4.00 - 3.82 (m, 1H), 3.81 - 3.53 (m, 5H), 3.52 - 3.25 (m, 1H), 2.36 - 2.15 (m, 5H), 2.02 - 1.87 (m, 1H), 1.85 - 1.69 (m, 1H), 1.09 - 0.85 (m, 6H), 0.68 - 0.52 (m, 6H)                      | 1.72<br>A<br>540.1                        | B                                                    |

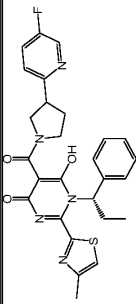
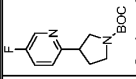
| Ex# | Structure                                                                           | Name                                                                                                                                                            | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                  | LC/MS<br>Rt<br>(min)<br>Method<br>M <sup>+</sup> H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|------------------------------------------------------|
| 318 |  | 1-(2,6-diethylphenyl)-5-[3-(5-fluoropyrrolidin-2-yl)pyrrolidin-1-yl]pyrrolidin-1-yl-1-carboxy-2-[1-(2-methylpropyl)-1H-pyrazol-3-yl]-1,4-dihydropyrimidin-4-one | <br>8.4, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 10% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 340 mL/min, 45°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.50 (br d, J=19.6 Hz, 1H), 7.80 - 7.58 (m, 2H), 7.53 - 7.38 (m, 1H), 7.38 - 7.27 (m, 1H), 7.24 - 7.04 (m, 2H), 6.04 (br d, J=9.3 Hz, 1H), 4.03 - 3.43 (m, 6H), 3.33 (br s, 1H), 2.37 - 2.15 (m, 5H), 2.15 - 1.97 (m, 1H), 1.90 - 1.60 (m, 1H), 1.10 - 0.82 (m, 6H), 0.60 (br d, J=5.7 Hz, 6H) | 1.51<br>A<br>559.4                                 | A                                                    |

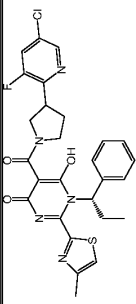
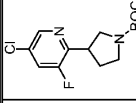
| Ex# | Structure | Name                                                                                                                                            | Chiral amine intermediate<br>with retention time                                                                                                                          | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                         | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 319 |           | 2-(1-cyclopropyl-1H-pyrazol-3-yl)-1-(2,6-diethylphenyl)-5-[3-(3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one | <p>9.5, &gt;99.8%<br/>Wheko, 5 x 50 cm, 10 micron;<br/>mobile phase: 10% IPA/90% CO<sub>2</sub>;<br/>Flow Conditions: 340 mL/min, 45°C, wavelength: 220 nm (isomer 2)</p> | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.55 - 8.27 (m, 1H), 7.86 - 7.58 (m, 2H), 7.53 - 7.24 (m, 2H), 7.19 - 6.90 (m, 2H), 6.43 - 6.11 (m, 1H), 3.96 - 3.41 (m, 4H), 3.38 - 3.16 (m, 2H), 2.35 - 1.92 (m, 6H), 1.11 - 0.85 (m, 6H), 0.80 - 0.67 (m, 2H), 0.65 - 0.43 (m, 2H) | 1.26<br>A<br>543.3                    | A                                                    |

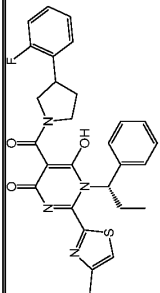
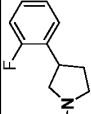
| Ex# | Structure                                                                           | Name                                                                                                                                                     | Chiral amine intermediate with retention time                                                                                                                                                                                                          | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                        | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 320 |  | 1-(2,6-diethylphenyl)-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-2-[1-(2-methylpropyl)-1H-pyrazol-3-yl]-1,4-dihydropyrimidin-4-one | <br>6.3, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.45 (br s, 1H), 8.03 - 7.85 (m, 1H), 7.50 (br s, 1H), 7.30 - 7.13 (m, 1H), 7.09 - 6.97 (m, 2H), 6.35 - 6.06 (m, 1H), 3.90 - 3.43 (m, 6H), 3.40 - 3.22 (m, 1H), 2.39 - 1.98 (m, 6H), 1.23 (br s, 1H), 1.14 - 0.76 (m, 6H), 0.55 (br d, J=5.8 Hz, 6H) | 1.61 A<br>577.3           | B                                        |

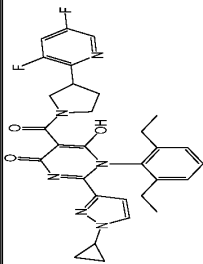
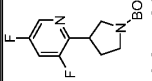
| Ex# | Structure                                                                           | Name                                                                                                                                                        | Chiral amine intermediate with retention time                                                                                                                                                                                                         | <sup>1</sup> H NMR                                                                                                                                                                                                                                            | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 321 |  | 5-[3-(3,5-difluoropyridin-2-yl)pyrrolidin-1-yl]pyrrolidine-1-carboxylic acid (4-methyl-1,3-thiazol-2-yl)-1-[(1S)-1-phenylpropyl]-1,4-dihydropyrimidin-4-one | <br>6.3, >99.7%<br>Welko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.43 (br s, 1H), 7.92 - 7.78 (m, 1H), 7.53 (br s, 1H), 7.35 - 6.99 (m, 4H), 6.85 - 6.65 (m, 1H), 3.84 - 3.40 (m, 5H), 3.39 - 3.21 (m, 1H), 2.44 - 2.28 (m, 4H), 2.22 - 1.98 (m, 3H), 0.94 - 0.78 (m, 3H) | 1.43 A 537.9              | A                                        |

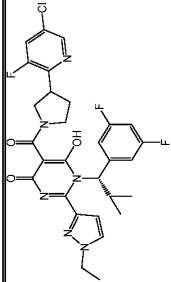
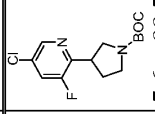


| Ex# | Structure                                                                           | Name                                                                                                                                          | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                                   | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                            | LC/MS<br>Rt<br>(min)<br>Metho<br>d<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|------------------------------------------------------|
| 322 |  | 5-[3-(5-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(4-methyl-1,3-thiazol-2-yl)-1-[(1S)-1-phenylpropyl]-1,4-dihydropyrimidin-4-one | <br>8.4, >99.7%<br>Whelko, 5 x 50 cm, 10<br>micron;<br>mobile phase: 10% IPA/90%<br>CO <sub>2</sub> ;<br>Flow Conditions: 340<br>mL/min, 45°C, wavelength:<br>220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) Shift 8.56 - 8.40 (m, 1H), 7.64 (br d, J=8.5 Hz, 1H), 7.56 (br s, 1H), 7.37 - 7.08 (m, 5H), 6.80 (br d, J=4.9 Hz, 1H), 3.92 - 3.72 (m, 1H), 3.67 - 3.30 (m, 4H), 3.29 - 3.18 (m, 1H), 2.40 (br s, 4H), 2.27 - 2.11 (m, 1H), 2.08 - 1.93 (m, 2H), 0.87 (br d, J=7.3 Hz, 3H) | 1.51<br>A<br>520.2                        | A                                                    |

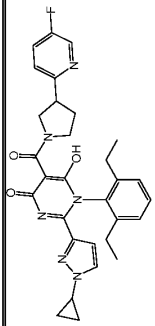
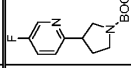
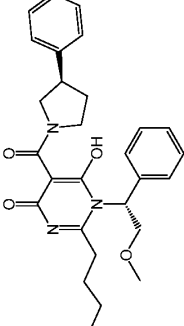
| Ex# | Structure                                                                           | Name                                                                                                                                                             | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                                                                                  | LC/MS<br>Rt<br>(min)<br>Metho<br>d<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|------------------------------------------------------|
| 323 |  | 5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidin-1-yl]pyrrolidine-1-carboxylic acid (4-methyl-1,3-thiazol-2-yl)-1-[(1S)-1-phenylpropyl]-1,4-dihydropyrimidin-4-one | <br>7.6, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 27°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.44 (br d, J=18.9 Hz, 1H), 8.00 (br d, J=10.1 Hz, 1H), 7.66 (br s, 1H), 7.36 - 7.10 (m, 4H), 7.06 - 6.89 (m, 1H), 3.62 (br s, 5H), 3.47 - 3.31 (m, 1H), 2.42 (br s, 3H), 2.31 - 2.01 (m, 4H), 0.87 (br s, 3H) | 1.64<br>A<br>554.1                        | A                                                    |

| Ex# | Structure                                                                           | Name                                                                                                                                    | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                                                            | <sup>1</sup> H NMR                                                                                                                                                                                                                               | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPI<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 324 |  | 5-[3-(2-fluorophenyl)pyrrolidine-1-carbonyl]-6-hydroxy-2-(4-methyl-1,3-thiazol-2-yl)-1-[(1S)-1-phenylpropyl]-1,4-dihydropyrimidin-4-one | <br>Cbz-10.65, 99.5%<br>Chiralpak IF, 4.6 x 250 mm,<br>5 micron;<br>mobile phase: 15% IPA/90%<br>CO <sub>2</sub> ;<br>Flow Conditions: 2.0<br>mL/min, 150 bar, 40°C,<br>wavelength: 220 nm (Isomer<br>2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.60 - 7.46 (m, 1H), 7.42 - 7.00 (m, 8H), 6.86 - 6.65 (m, 1H), 3.79 - 3.52 (m, 4H), 3.51 - 3.26 (m, 2H), 2.43 - 2.27 (m, 4H), 2.22 - 2.05 (m, 1H), 1.99 - 1.82 (m, 2H), 0.94 - 0.73 (m, 3H) | 1.58<br>A<br>519.1                    | A                                                    |

| Ex# | Structure                                                                           | Name                                                                                                                                                | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                      | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                       | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 325 |  | 2-(1-cyclopropyl-1H-pyrazol-3-yl)-1-(2,6-diethylphenyl)-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>6.3, >99.7%<br>Welko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.57 - 8.36 (m, 1H), 7.95 - 7.80 (m, 1H), 7.62 (br d, J=10.4 Hz, 1H), 7.33 - 7.16 (m, 1H), 7.06 (br dd, J=14.0, 7.3 Hz, 2H), 6.23 (br d, J=15.0 Hz, 1H), 3.99 - 3.53 (m, 5H), 3.45 (br s, 1H), 2.36 - 2.05 (m, 6H), 1.09 - 0.84 (m, 6H), 0.70 (br d, J=4.3 Hz, 2H), 0.57 (br s, 2H) | 1.32<br>A<br>561.0                    | A                                                    |

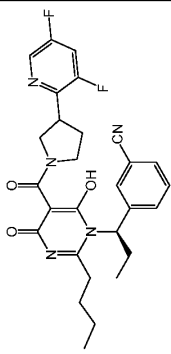
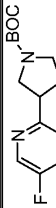
| Ex# | Structure                                                                           | Name                                                                                                                                                                               | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                       | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 326 |  | 5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidin-1-yl]-1-carboxylate-1-[(1S)-1-(3,5-difluorophenyl)-2-methylpropyl]-2-(1-ethyl-1H-pyrazol-3-yl)-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>7.6, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 27°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.58 - 8.37 (m, 1H), 8.12 - 7.88 (m, 2H), 7.36 - 7.06 (m, 2H), 7.03 - 6.72 (m, 1H), 5.95 (br d, J=8.5 Hz, 1H), 4.27 (br d, J=6.4 Hz, 2H), 3.83 - 3.34 (m, 5H), 3.25 (br s, 1H), 2.36 - 1.89 (m, 3H), 1.54 - 1.35 (m, 3H), 0.85 (br d, J=4.3 Hz, 6H) | 1.62<br>A<br>601.2                    | A                                                    |

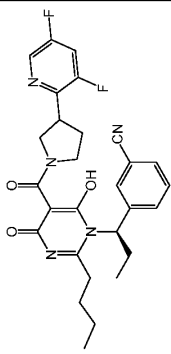
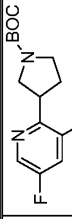
| Ex# | Structure | Name                                                                                                                                                                   | Chiral amine intermediate with retention time                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                   | LC/MS Rt (min) Metho d | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|------------------------------------------|
| 327 |           | 1-[(1S)-1-(3,5-difluorophenyl)-2-methylpropyl]-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-2-(1-ethyl-1H-pyrazol-3-yl)-6-hydroxy-1,4-dihydropyrimidin-2-one | <br>6.3, >99.7%<br>Wheiko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.46 (br d, J=13.2 Hz, 1H), 8.08 - 7.78 (m, 2H), 7.39 - 6.93 (m, 2H), 6.85 - 6.58 (m, 1H), 5.90 - 5.57 (m, 1H), 4.40 - 4.14 (m, 2H), 4.11 - 3.53 (m, 5H), 3.48 - 3.28 (m, 1H), 2.40 - 1.97 (m, 3H), 1.43 (q, J=7.4 Hz, 3H), 1.00 - 0.61 (m, 6H) | 1.63 A<br>585.2        | A                                        |

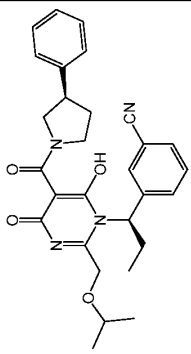
| Ex# | Structure                                                                            | Name                                                                                                                                                           | Chiral amine intermediate with retention time                                                                                                                                                                                                          | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                            | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|--------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 328 |   | 2-(1-cyclopropyl-1H-pyrazol-3-yl)-1-(2,6-diethylphenyl)-5-[3-(5-fluoropyridin-2-yl)pyrrolidin-2-yl]pyrrolidine-1-carboxyl-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>8.4, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 10% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 340 mL/min, 45°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.49 (br d, J=18.8 Hz, 1H), 7.88 - 7.59 (m, 2H), 7.56 - 7.37 (m, 1H), 7.34 - 7.18 (m, 1H), 7.16 - 6.90 (m, 2H), 6.23 (br d, J=15.9 Hz, 1H), 4.25 - 3.48 (m, 6H), 2.32 - 2.14 (m, 5H), 2.11 - 1.98 (m, 1H), 1.10 - 0.85 (m, 6H), 0.84 - 0.66 (m, 2H), 0.64 - 0.43 (m, 2H) | 1.26<br>A<br>543.1        | A                                        |
| 329 |  | 6-hydroxy-3-[(1R)-2-methoxy-1-phenylethyl]-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-2-propyl-3,4-dihydropyrimidin-4-one                                         |                                                                                                                                                                                                                                                        | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.47 - 6.93 (m, 10H), 5.71 - 5.09 (m, 1H), 4.39 - 3.72 (m, 2H), 3.44 - 2.63 (m, 4H), 2.59 - 2.48 (m, 6H), 1.96 - 1.28 (m, 3H), 2.34 - 1.22 (m, 1H), 1.04 - 0.27 (m, 3H)                                                                                                  | 1.38<br>A<br>462.2        | B                                        |

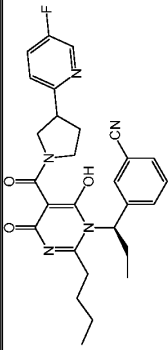
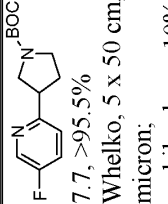
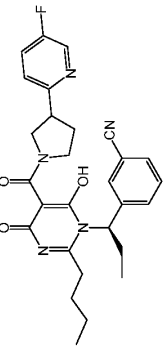
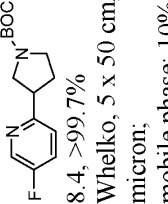
| Ex# | Structure | Name                                                                                                                                                             | Chiral amine intermediate<br>with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                          | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPI<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 330 |           | 6-hydroxy-3-<br>[(1R)-2-<br>methoxy-1-<br>phenylethyl]-5-<br>phenylpyrrolidi<br>ne-1-carbonyl]-<br>2-propyl-3,4-<br>dihydropyrimidi<br>n-4-one                   |                                                  | <sup>1</sup> H NMR (500 MHz, DMSO-<br>d <sub>6</sub> ) δ 7.36 - 7.16 (m, 10H),<br>5.76 - 5.35 (m, 1H), 4.40 -<br>3.48 (m, 2H), 3.44 - 2.63 (m,<br>4H), 2.59 - 2.48 (m, 6H), 1.96<br>- 1.28 (m, 2H), 1.73 - 1.27<br>(m, 2H), 1.04 - 0.59 (m, 3H)                                                             | 1.37<br>A<br>462.0                    | B                                                    |
| 331 |           | 3-[(1S)-1-(2-<br>butyl-4-<br>hydroxy-6-oxo-<br>5-[(3R)-3-<br>phenylpyrrolidi<br>ne-1-carbonyl]-<br>1,6-<br>dihydropyrimidi<br>n-1-<br>yl)propyl]benz<br>onitrile |                                                  | <sup>1</sup> H NMR (500 MHz, DMSO-<br>d <sub>6</sub> ) δ 7.75 (br s, 2H), 7.57 (br<br>s, 2H), 7.31 (br s, 3H), 7.26 -<br>7.05 (m, 2H), 5.50 - 5.31 (m,<br>1H), 3.91 (s, 5H), 2.88 (br d,<br>J=9.5 Hz, 2H), 2.23 (br d,<br>J=5.8 Hz, 2H), 1.92 (s, 2H),<br>1.74 - 1.25 (m, 4H), 0.89 (br<br>d, J=6.1 Hz, 6H) | 1.53<br>A<br>485.0                    | A                                                    |

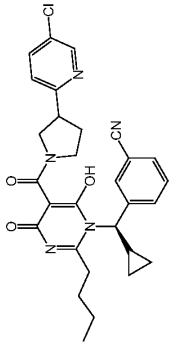
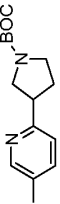


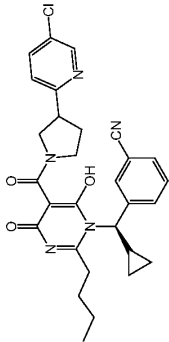
| Ex# | Structure                                                                           | Name                                                                                                                                    | Chiral amine intermediate with retention time                                                                                                                                                                                                        | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                                                               | LC/MS Rt (min) Method | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 332 |  | 3-[(1S)-1-{2-butyl-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidin-1-carbonyl]-4-hydroxy-6-oxo-1,6-dihydropyrimidin-1-yl}propyl]benz onitrile | <br>5.6, >99.7%<br>Welko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer-1) | <sup>1</sup> H NMR (METHANOL-d <sub>4</sub> , 500MHz, at 333K): δ = 8.29 (s, 1H), 7.67 (s, 1H), 7.61 (d, J=7.4 Hz, 2H), 7.52 (d, J=8.3 Hz, 1H), 7.41-7.48 (m, 1H), 3.83 (d, J=7.2 Hz, 2H), 3.71 (br. s., 2H), 3.56 (br. s., 1H), 2.78 (br. s., 2H), 2.54-2.62 (m, 1H), 2.47 (br. s., 1H), 2.20-2.34 (m, 2H), 1.68 (br. s., 1H), 1.32 (br. s., 2H), 1.02 (t, J=7.4 Hz, 3H), 0.87 ppm (br. s., 3H) | 1.33 A<br>522.3       | A                                        |

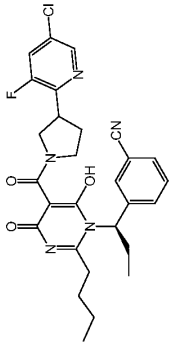
| Ex# | Structure                                                                           | Name                                                                                                                                     | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                     | <sup>1</sup> H NMR                                                                                                                                                                                                                      | LC/MS<br>Rt<br>(min)<br>Metho<br>d<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|------------------------------------------------------|
| 333 |  | 3-[(1S)-1-{2-butyl-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-4-hydroxy-6-oxo-1,6-dihydropyrimidin-1-yl}propyl]benz onitrile | <br>6.3, >99.7%<br>Welko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer-2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.41 (br. s., 1H), 7.86 (d, J=8.5 Hz, 1H), 7.33-7.77 (m, 4H), 5.36 (br. s., 1H), 2.61-3.79 (m, 5H), 1.79-2.25 (m, 4H), 1.48-1.72 (m, 2H), 1.11-1.43 (m, 2H), 0.23-0.96 ppm (m, 6H) | 1.33<br>A<br>522.1                        | A                                                    |

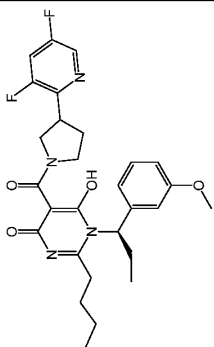
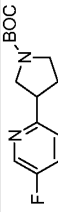
| Ex# | Structure                                                                           | Name                                                                                                                                       | Chiral amine intermediate<br>with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                      | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 334 |  | 3-[(1S)-1-{4-hydroxy-6-oxo-5-[(3R)-3-phenylpyrrolidine-1-carbonyl]-2-[(propan-2-yl)oxy)methyl]-1,6-dihydropyrimidin-1-yl}propyl]benzotrile |                                                  | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 6.92-7.93 (m, 9H), 5.27 (br. s., 1H), 4.13-4.75 (m, 2H), 3.09-3.38 (m, 2H), 2.32-2.46 (m, 2H), 2.06-2.26 (m, 1H), 1.68-1.94 (m, 2H), 0.97-1.15 (m, 6H), 0.88 ppm (d, J=7.1 Hz, 3H) | 1.41<br>A<br>501.1                    | A                                                    |

| Ex# | Structure                                                                            | Name                                                                                                                                                | Chiral amine intermediate with retention time                                                                                                                                                                                                          | <sup>1</sup> H NMR                                                                                                                                                                                                                                                              | LC/MS Rt (min) Method | hAPI cAMP EC <sub>50</sub> Potency range |
|-----|--------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 335 |   | 3-[(1S)-1-{2-butyl-5-[3-(5-fluoropyridin-2-yl)pyrrolidin-2-yl]pyrrolidin-1-carbonyl]-4-hydroxy-6-oxo-1,6-dihydropyrimidin-1-yl}propyl]benz onitrile | <br>7.7, >95.5%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 10% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 340 mL/min, 45°C, wavelength: 220 nm (isomer-1)  | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.47 (br. s., 1H), 7.27-7.92 (m, 6H), 6.63 and 5.28 (br. s., 1H), 3.10-4.20 (m, 3H), 2.61-2.92 (m, 2H), 2.40 (br. s., 1H), 1.96-2.25 (m, 3H), 1.58 (d, J=7.4 Hz, 2H), 1.16-1.43 (m, 2H), 0.85 ppm (dd, J=12.5, 6.8 Hz, 6H) | 1.52<br>A<br>504.3    | A                                        |
| 336 |  | 3-[(1S)-1-{2-butyl-5-[3-(5-fluoropyridin-2-yl)pyrrolidin-2-yl]pyrrolidin-1-carbonyl]-4-hydroxy-6-oxo-1,6-dihydropyrimidin-1-yl}propyl]benz onitrile | <br>8.4, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 10% IPA/90% CO <sub>2</sub> ;<br>Flow Conditions: 340 mL/min, 45°C, wavelength: 220 nm (isomer-2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.32-8.57 (m, 1H), 7.10-7.85 (m, 6H), 6.59 and 5.27 (br. s., 1H), 2.59-2.97 (m, 2H), 2.29-2.43 (m, 2H), 1.85-2.24 (m, 3H), 1.55 (br. s., 2H), 1.09-1.41 (m, 2H), 0.42-0.90 ppm (m, 6H)                                     | 1.30<br>A<br>504.4    | A                                        |

| Ex# | Structure                                                                           | Name                                                                                                                                         | Chiral amine intermediate with retention time                                                                                                                                                                                                         | <sup>1</sup> H NMR                                                                                                                                                                                                                           | LC/MS Rt (min) Method | hAPI cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 337 |  | 3-[(S)-{2-butyl-5-[3-(5-chloropyridin-2-yl)pyrrolidin-1-carbonyl]-4-hydroxy-6-oxo-1,6-dihydropyrimidin-1-yl}(cyclopropyl)methyl]benzonitrile | <br>6.8, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer-1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.52 (br. s., 1H), 7.05-8.16 (m, 6H), 5.85 and 4.56 (br. s., 1H), 2.58-2.81 (m, 2H), 1.95-2.42 (m, 3H), 1.12-1.77 (m, 3H), 0.66-1.12 (m, 5H), 0.57 (br. s., 3H), 0.29 ppm (br. s., 1H). | 1.41<br>A<br>532.4    | A                                        |

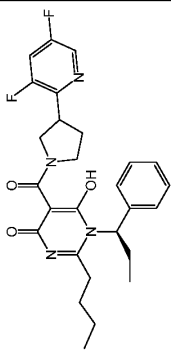
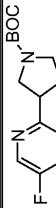
| Ex# | Structure                                                                           | Name                                                                                                                                         | Chiral amine intermediate with retention time                                                                                                                                                                                                         | <sup>1</sup> H NMR                                                                                                                                                                                                                          | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 338 |  | 3-[(S)-{2-butyl-5-[3-(5-chloropyridin-2-yl)pyrrolidin-1-carbonyl]-4-hydroxy-6-oxo-1,6-dihydropyrimidin-1-yl}(cyclopropyl)methyl]benzonitrile | <br>7.9, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer-2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.53 (br. s., 1H), 6.82-8.27 (m, 6H), 5.75 and 4.53 (br. s., 1H), 3.09-3.68 (m, 2H), 1.76-2.43 (m, 3H), 1.13-1.73 (m, 3H), 0.62-1.07 (m, 5H), 0.54 (br. s., 3H), 0.30 ppm (br. s., 1H) | 1.41 A<br>532.3           | A                                        |

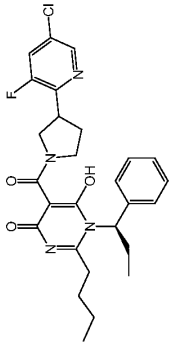
| Ex# | Structure                                                                           | Name                                                                                                                                         | Chiral amine intermediate with retention time                                                                                                                                                                                                         | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                          | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 339 |  | 3-[(1S)-1-{2-butyl-5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-4-hydroxy-6-oxo-1,6-dihydropyrimidin-1-yl}propyl]benz nitrile | <br>6.8, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 27°C, wavelength: 220 nm (isomer-1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.44 (br. s., 1H), 7.99 (d, J=9.2 Hz, 1H), 7.36-7.78 (m, 4H), 6.39-6.75 and 5.06-5.67 (m, 1H), 3.48 (m, 4H), 2.60-2.94 (m, 2H), 2.43 (br. s., 2H), 1.97-2.29 (m, 3H), 1.48-1.76 (m, 2H), 1.36 (br. s., 2H), 0.85 ppm (d, J=7.3 Hz, 6H) | 1.54 A 538.3              | A                                        |

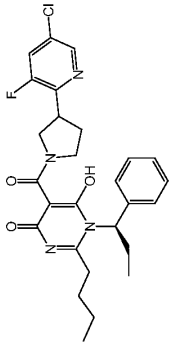
| Ex# | Structure                                                                           | Name                                                                                                                          | Chiral amine intermediate with retention time                                                                                                                                                                                                         | <sup>1</sup> H NMR                                                                                                                                                                                                                 | LC/MS Rt (min) Method | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 340 |  | 2-butyl-5-[(3,5-difluoropyridin-2-yl)pyrrolidin-1-yl]-6-hydroxy-3-[(1S)-1-(3-methoxyphenyl)propyl]-3,4-dihydropyrimidin-4-one | <br>5.6, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer-1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.43 (br. s., 1H), 7.85 (br. s., 1H), 7.25 (br. s., 1H), 6.43-6.98 (m, 3H), 3.64-3.05 (m, 7H), 2.59-3.03 (m, 2H), 1.98-2.43 (m, 4H), 0.95-1.78 (m, 4H), 0.20-0.88 ppm (m, 6H) | 1.62 A<br>527.0       | A                                        |

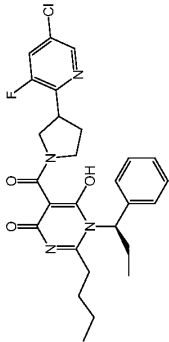


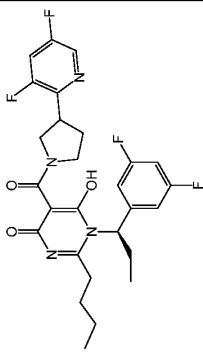
| Ex# | Structure | Name                                                                                                                                          | Chiral amine intermediate with retention time                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                                                               | LC/MS Rt (min) Method | hAPI cAMP EC <sub>50</sub> Potency range |
|-----|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 341 |           | 2-butyl-5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidin-1-carbonyl]-3-[(1S)-1-(3,5-difluorophenyl)propyl]-6-hydroxy-3,4-dihydropyrimidin-4-one | <br>7.6, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 27°C, wavelength: 220 nm (isomer-2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.39 (br. s., 1H), 7.95 (d, J=8.5 Hz, 1H), 6.75-7.37 (m, 3H), 6.50 and 5.21 (br. s., 1H), 3.87-2.97 (m, 5H), 2.56-2.91 (m, 2H), 2.02-2.41 (m, 4H), 1.15-1.62 (m, 4H), 0.50-0.93 ppm (m, 6H) | 1.76<br>A<br>549.2    | A                                        |
| 342 |           | 2-butyl-5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidin-1-carbonyl]-3-[(1S)-1-(3,5-difluorophenyl)propyl]-6-hydroxy-3,4-dihydropyrimidin-4-one | <br>6.8, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 27°C, wavelength: 220 nm (isomer-1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.43 (br. s., 1H), 7.99 (d, J=9.2 Hz, 1H), 6.79-7.38 (m, 3H), 6.62 and 5.28 (br. s., 1H), 3.05-4.12 (m, 7H), 2.59-2.96 (m, 2H), 1.94-2.45 (m, 4H), 0.94-1.74 (m, 4H), 0.44-0.90 ppm (m, 6H) | 1.69<br>A<br>549.3    | A                                        |

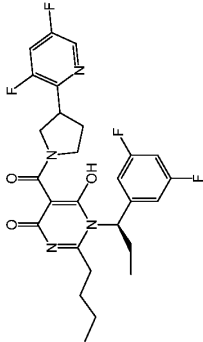
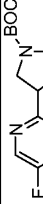
| Ex# | Structure                                                                           | Name                                                                                                          | Chiral amine intermediate with retention time                                                                                                                                                                                                         | <sup>1</sup> H NMR                                                                                                                                                                                                                 | LC/MS Rt (min) Method | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 343 |  | 2-butyl-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidin-1-yl]-6-hydroxy-3-phenylpropyl-1,3,4-dihydropyrimidin-4-one | <br>5.6, >99.7%<br>WHELKO, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer-1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.42 (br. s., 1H), 7.84 (br. s., 1H), 7.05-7.50 (m, 5H), 6.14-6.79 (m, 1H), 3.15 (s, 5H), 2.40 (br. s., 2H), 2.00-2.30 (m, 4H), 0.98 (d, J=6.2 Hz, 4H), 0.50-0.90 ppm (m, 6H) | 1.47 A 497.5          | A                                        |

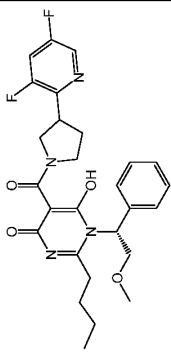
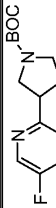
| Ex# | Structure                                                                           | Name                                                                                                                             | Chiral amine intermediate with retention time                                                                                                                                                                                                          | <sup>1</sup> H NMR                                                                                                                                                                                         | LC/MS Rt (min) Method | hAPI cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 344 |  | 2-butyl-5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-3-[(1S)-1-phenylpropyl]-3,4-dihydropyrimidin-4-one | <br>6.8, >99.7%<br>W helko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 27°C, wavelength: 220 nm (isomer-1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.35-8.53 (m, 1H), 7.96 (br. s., 1H), 6.99-7.46 (m, 5H), 2.51-4.14 (m, 5H), 2.36 (br. s., 2H), 1.93-2.22 (m, 4H), 0.91-1.79 (m, 4H), 0.86 ppm (m, 6H) | 1.67 A 513.2          | A                                        |

| Ex# | Structure                                                                           | Name                                                                                                                       | Chiral amine intermediate with retention time                                                                                                                                                                                                        | <sup>1</sup> H NMR                                                                                                                                                                                                    | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 345 |  | 2-butyl-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidin-1-carbonyl]-6-hydroxy-3-[(1S)-1-phenylpropyl]-3,4-dihydropyrimidin-4-one | <br>6.3, >99.7%<br>Welko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer-2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.43 (d, J=15.7 Hz, 1H), 7.85 (br. s., 1H), 7.15-7.41 (m, 5H), 2.61-3.55 (m, 5H), 2.42 (br. s., 2H), 1.94-2.27 (m, 4H), 0.94-1.77 (m, 4H), 0.60-0.90 ppm (m, 6H) | 1.56 A 497.0              | A                                        |

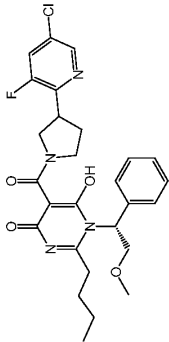
| Ex# | Structure                                                                           | Name                                                                                                                             | Chiral amine intermediate with retention time                                                                                                                                                                                                        | <sup>1</sup> H NMR                                                                                                                                                                                                       | LC/MS Rt (min) Method | hAPI cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 346 |  | 2-butyl-5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-3-[(1S)-1-phenylpropyl]-3,4-dihydropyrimidin-4-one | <br>7.6, >99.7%<br>Wheko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 27°C, wavelength: 220 nm (isomer-2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.44 (d, J=17.7 Hz, 1H), 7.99 (d, J=8.5 Hz, 1H), 7.10-7.47 (m, 5H), 2.59-3.87 (m, 5H), 2.40 (br s, 2H), 1.91-2.32 (m, 4H), 0.96-1.81 (m, 4H), 0.52-0.93 ppm (m, 6H) | 1.67 A 512.9          | A                                        |

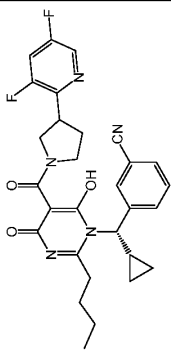
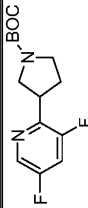
| Ex# | Structure                                                                           | Name                                                                                                                                      | Chiral amine intermediate with retention time                                                                                                                                                                                                        | <sup>1</sup> H NMR                                                                                                                                                                                                                     | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 347 |  | 2-butyl-3-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-3,4-dihydropyrimidin-4-one | <br>5.6, >99.7%<br>Welko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer-1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.39 (br. s., 1H), 7.75-8.02 (m, 1H), 7.05 (br. s., 1H), 6.82 (br. s., 2H), 6.55 and 5.23 (s, 1H), 2.57-3.85 (m, 5H), 1.91-2.38 (m, 5H), 0.91-1.69 (m, 5H), 0.43-0.88 ppm (m, 6H) | 1.50 A 533.4              | A                                        |

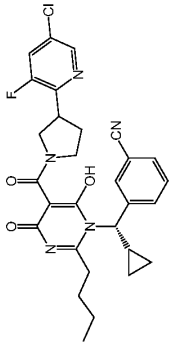
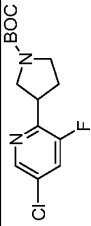
| Ex# | Structure                                                                           | Name                                                                                                                                      | Chiral amine intermediate with retention time                                                                                                                                                                                                         | <sup>1</sup> H NMR                                                                                                                                                                                                                               | LC/MS Rt (min) Method | hAPI cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 348 |  | 2-butyl-3-[(1S)-1-(3,5-difluorophenyl)propyl]-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-3,4-dihydropyrimidin-4-one | <br>6.3, >99.7%<br>WHELKO, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer-2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.15-8.58 (m, 1H), 7.82 (br. s., 1H), 6.99-7.27 (m, 1H), 6.69-6.94 (m, 2H), 6.30-6.62 and 4.97-5.36 (m, 1H), 2.59-3.69 (m, 7H), 2.10 (br. s., 4H), 0.91-1.68 (m, 4H), 0.48-0.86 ppm (m, 6H) | 1.50 A 533.4          | A                                        |

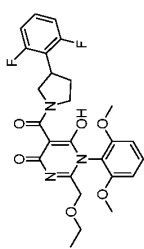
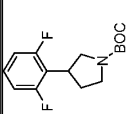
| Ex# | Structure                                                                           | Name                                                                                                                          | Chiral amine intermediate with retention time                                                                                                                                                                                                            | <sup>1</sup> H NMR                                                                                                                                                                                                                                         | LC/MS Rt (min) Method | hAPI cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 349 |  | 2-butyl-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidin-1-yl]-6-hydroxy-3-[(1R)-2-methoxy-1-phenylethyl]-3,4-dihydropyrimidin-4-one | <br>6.3, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm<br>(isomer-2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.38 (br. s., 1H), 7.84 (br. s., 1H), 6.92-7.38 (m, 5H), 5.17-5.70 (m, 1H), 4.21 (d, J=7.1 Hz, 2H), 2.93-3.74 (m, 8H), 2.68 (br. s., 2H), 1.95-2.30 (m, 2H), 0.93-1.68 (m, 4H), 0.77 ppm (br. s., 3H) | 1.44 A 513.4          | A                                        |



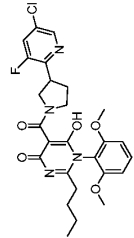
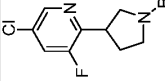
| Ex# | Structure                                                                           | Name                                                                                                                                      | Chiral amine intermediate with retention time                                                                                                                                                                                                         | <sup>1</sup> H NMR                                                                                                                                                                                                                                    | LC/MS Rt (min) Method | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 350 |  | 2-butyl-5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-3-[(1R)-2-methoxy-1-phenylethyl]-3,4-dihydropyrimidin-4-one | <br>6.8, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 27°C, wavelength: 220 nm (isomer-1) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.45 (br. s., 1H), 8.01 (br. s., 1H), 6.95-7.62 (m, 5H), 4.99-5.87 (m, 1H), 3.92-4.44 (m, 2H), 3.07-3.88 (m, 8H), 2.72 (br. s., 2H), 1.94-2.32 (m, 2H), 1.03-1.79 (m, 4H), 0.80 ppm (br. s., 3H) | 1.48 A<br>529.4       | A                                        |

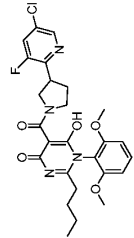
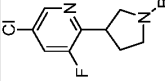
| Ex# | Structure                                                                           | Name                                                                                                                                              | Chiral amine intermediate with retention time                                                                                                                                                                                                            | <sup>1</sup> H NMR                                                                                                                                                                                                       | LC/MS Rt (min) Method | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 351 |  | 3-[(S)-{2-butyl-5-[3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carboxyl]-4-hydroxy-6-oxo-1,6-dihydropyrimidin-1-yl}(cyclopropyl)methyl]benzonitrile | <br>6.3, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm<br>(isomer-2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.33-8.48 (m, 1H), 7.15-7.98 (m, 5H), 5.83 and 4.57 (br. s., 1H), 2.58-4.01 (m, 5H), 1.85-2.30 (m, 3H), 1.16-1.71 (m, 4H), 0.64-1.05 (m, 5H), 0.17-0.61 ppm (m, 4H) | 1.49<br>A<br>534.1    | A                                        |

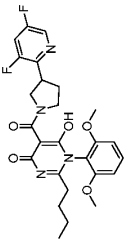
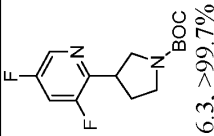
| Ex# | Structure                                                                           | Name                                                                                                                                      | Chiral amine intermediate with retention time                                                                                                                                                                                                         | <sup>1</sup> H NMR                                                                                                                                                                                                                                         | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 352 |  | 2-butyl-5-[3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl]-6-hydroxy-3-[(1R)-2-methoxy-1-phenylethyl]-3,4-dihydropyrimidin-4-one | <br>7.6, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ;<br>Flow Conditions: 350 mL/min, 27°C, wavelength: 220 nm (isomer-2) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.22-8.55 (m, 1H), 7.96 (d, J=9.7 Hz, 1H), 6.82-7.67 (m, 5H), 5.22-5.89 (m, 1H), 3.92-4.57 (m, 2H), 2.95-3.89 (m, 6H), 2.59-2.87 (m, 2H), 1.90-2.26 (m, 2H), 0.93-1.77 (m, 4H), 0.77 ppm (br. s., 3H) | 1.52<br>A<br>528.9        | A                                        |

| Ex# | Structure                                                                           | Name                                                                                                                            | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                | <sup>1</sup> H NMR                                                                                                                                                                                                                     | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 353 |  | 5-[3-(2,6-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-2-(ethoxy methyl)-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>5.9, >99.7%<br>Wheko, 5 x 50 cm, 10 micron; mobile phase: 20% IPA/80% CO <sub>2</sub> ; Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (400MHz, METHANOL-d <sub>4</sub> ) δ 7.55 - 7.46 (m, 1H), 7.38 - 7.25 (m, 1H), 6.98 (s, 2H), 6.88 - 6.72 (m, 2H), 4.13 (br. s., 2H), 3.93 - 3.67 (m, 1H), 3.45 (br. s., 2H), 2.48 - 2.20 (m, 2H), 1.12 (br. s., 3H) | 0.78<br>B<br>516.1                    | A                                                    |

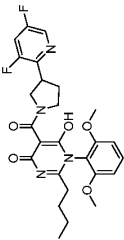
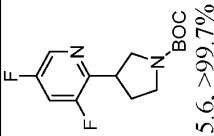
| Ex# | Structure | Name                                                                                                                            | Chiral amine intermediate with retention time                                                                                                                  | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                            | LC/MS Rt (min) Method M+H | hAPI cAMP EC <sub>50</sub> Potency range |
|-----|-----------|---------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 354 |           | 5-[3-(2,6-difluorophenyl)pyrrolidine-1-carbonyl]-1-(2,6-dimethoxyphenyl)-2-(ethoxy methyl)-6-hydroxy-1,4-dihydropyrimidin-4-one | <br>5.4, >99.7%,<br>Whelko, 5 x 50 cm, 10 micron; mobile phase: 20% IPA/80% CO <sub>2</sub> ; Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (400MHz, METHANOL-d <sub>4</sub> ) □ 7.55 - 7.46 (m, 1H), 7.38 - 7.25 (m, 1H), 6.98 (s, 2H), 6.88 - 6.72 (m, 2H), 4.13 (br. s., 2H), 3.93 - 3.67 (m, 1H), 3.45 (br. s., 2H), 2.48 - 2.20 (m, 2H), 1.12 (br. s., 3H)                                                        | 0.078<br>B<br>516.1       | A                                        |
| 355 |           | 2-butyl-5-(4-(2,3-dichlorobenzyl)piperazine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-6-hydroxy-1,4-dihydropyrimidin-4-one            |                                                                                                                                                                | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.76 (d, J=7.9 Hz, 1H), 7.65 (d, J=7.6 Hz, 1H), 7.52 - 7.43 (m, 2H), 6.85 (d, J=8.5 Hz, 2H), 4.42 (br. s., 2H), 3.76 (s, 6H), 2.51 (br. s., 8H), 2.27 (t, J=7.3 Hz, 2H), 1.48 - 1.38 (m, 2H), 1.21 - 1.08 (m, 2H), 0.70 (t, J=7.3 Hz, 3H) | 0.68<br>B<br>575.0        | A                                        |

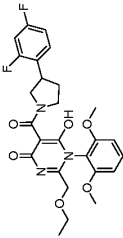
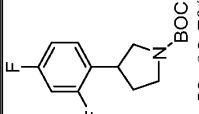
| Ex# | Structure                                                                           | Name                                                                                                                     | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                   | <sup>1</sup> H NMR                                                                                                                                                                                                                                                        | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 356 |  | 2-butyl-5-(3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-6-hydroxypyrimidin-4(1H)-one | <br>6.8, >99.7%<br>Wheko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ; Flow Conditions: 350 mL/min, 27°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 8.46 (br. s., 1H), 8.03 (d, J=9.0 Hz, 1H), 7.45 (br. s., 1H), 6.83 (d, J=7.5 Hz, 2H), 3.88 - 3.35 (m, 10H), 2.23 (d, J=6.5 Hz, 3H), 2.10 (br. s., 1H), 1.41 (br. s., 2H), 1.19 - 1.06 (m, 2H), 0.69 (d, J=6.5 Hz, 3H) | 0.96<br>B<br>531.0                    | A                                                    |

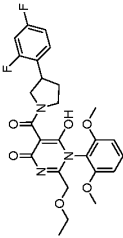
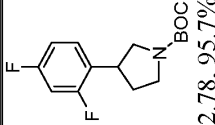
| Ex# | Structure                                                                           | Name                                                                                                                     | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                    | <sup>1</sup> H NMR                                                                                                                                                                                                                                                        | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 357 |  | 2-butyl-5-(3-(5-chloro-3-fluoropyridin-2-yl)pyrrolidine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-6-hydroxypyrimidin-4(1H)-one | <br>7.6, >99.7%<br>Whelko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ; Flow Conditions: 350 mL/min, 27°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 8.46 (br. s., 1H), 8.03 (d, J=9.0 Hz, 1H), 7.45 (br. s., 1H), 6.83 (d, J=7.5 Hz, 2H), 3.88 - 3.35 (m, 10H), 2.23 (d, J=6.5 Hz, 3H), 2.10 (br. s., 1H), 1.41 (br. s., 2H), 1.19 - 1.06 (m, 2H), 0.69 (d, J=6.5 Hz, 3H) | 0.96<br>B<br>531.0                    | A                                                    |

| Ex# | Structure                                                                           | Name                                                                                                                | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                   | <sup>1</sup> H NMR                                                                                                                                                                                                                           | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPI<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 358 |  | 2-butyl-5-(3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-6-hydroxypyrimidin-4(1H)-one | <br>6.3, >99.7%<br>Welko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ; Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 8.45 (br. s, 1H), 7.87 (br. s, 1H), 7.43 (br. s, 1H), 6.82 (br. s, 2H), 3.75 (br. s, 8H), 3.57 - 3.33 (m, 3H), 2.29 - 2.05 (m, 4H), 1.41 (br. s, 2H), 1.13 (br. s, 2H), 0.69 (br. s, 3H) | 0.80<br>B<br>515.1                    | A                                                    |



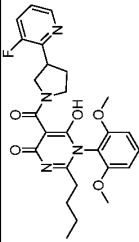
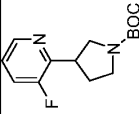
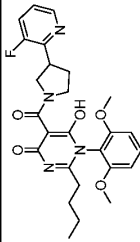
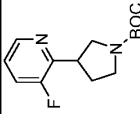
| Ex# | Structure                                                                           | Name                                                                                                          | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                     | <sup>1</sup> H NMR                                                                                                                                                                                                                           | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPI<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 359 |  | 2-butyl-5-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl-(2,6-dimethoxyphenyl)-6-hydroxypyrimidin-4(1H)-one | <br>5.6, >99.7%<br>W helko, 5 x 50 cm, 10 micron;<br>mobile phase: 20% IPA/80% CO <sub>2</sub> ; Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 8.45 (br. s, 1H), 7.87 (br. s, 1H), 7.43 (br. s, 1H), 6.82 (br. s, 2H), 3.75 (br. s, 8H), 3.57 - 3.33 (m, 3H), 2.29 - 2.05 (m, 4H), 1.41 (br. s, 2H), 1.13 (br. s, 2H), 0.69 (br. s, 3H) | 0.80<br>B<br>515.1                    | A                                                    |

| Ex# | Structure                                                                           | Name                                                                                                                    | Chiral amine intermediate with retention time                                                                                                                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                   | LC/MS Rt (min) Method | hAPI cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 360 |  | 5-(3-(2,4-difluorophenyl)pyrrolidine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-2-(ethoxy methyl)-6-hydroxypyrimidin-4(1H)-one | <br>2.53, 92.7%<br>Chiralpak IC, 4.6 x 250 mm, 5 micron; mobile phase: 10% IPA/90% CO <sub>2</sub> ; Flow Conditions: 3 mL/min, 140 bar, 45°C, wavelength: 200-400 nm (isomer 1) | <sup>1</sup> H NMR (500MHz, METHANOL-d <sub>4</sub> ) δ 8.04 - 7.32 (m, 2H), 7.14 - 6.68 (m, 4H), 4.13 (br. s., 2H), 3.84 (br. s., 13H), 2.44 - 2.29 (m, 1H), 2.20 - 2.09 (m, 1H), 1.13 (br. s., 3H) | 0.82<br>B<br>516.1    | A                                        |

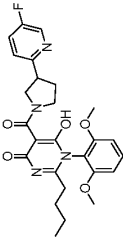
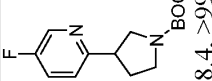
| Ex# | Structure                                                                           | Name                                                                                                                    | Chiral amine intermediate with retention time                                                                                                                                                                                                                       | <sup>1</sup> H NMR                                                                                                                                                                                   | LC/MS Rt (min) Method | hAPI cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 361 |  | 5-(3-(2,4-difluorophenyl)pyrrolidine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-2-(ethoxy methyl)-6-hydroxypyrimidin-4(1H)-one | <br>2.78, 95.7%<br>Chiralpak IC, 4.6 x 250 mm, 5 micron; mobile phase: 10% IPA/90% CO <sub>2</sub> ; Flow Conditions: 3 mL/min, 140 bar, 45°C, wavelength: 200-400 nm (isomer 2) | <sup>1</sup> H NMR (500MHz, METHANOL-d <sub>4</sub> ) δ 8.04 - 7.32 (m, 2H), 7.14 - 6.68 (m, 4H), 4.13 (br. s., 2H), 3.84 (br. s., 13H), 2.44 - 2.29 (m, 1H), 2.20 - 2.09 (m, 1H), 1.13 (br. s., 3H) | 0.82<br>B<br>516.1    | A                                        |

| Ex# | Structure | Name                                                                                                               | Chiral amine intermediate with retention time                                                                                                                           | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                          | LC/MS Rt (min) Method M <sup>+</sup> H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-----------|--------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|------------------------------------------|
| 362 |           | 2-(1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-6-hydroxy-4-oxo-1,4-dihydropyrimidin-5-yl)pyrrolidin-3-yl)benzonitrile | <br>Chiralpak IC, 4.6 x 250 mm, 5 micron; mobile phase: 15% IPA/0.1% DEA /85% CO <sub>2</sub> ; Flow Conditions: 2 mL/min, 150 bar, 45°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.86 - 7.78 (m, 1H), 7.70 - 7.63 (m, 1H), 7.61 - 7.53 (m, 1H), 7.50 - 7.38 (m, 2H), 6.86 - 6.74 (m, 2H), 3.95 (d, J=9.5 Hz, 2H), 3.78 - 3.35 (m, 10H), 3.35 - 3.20 (m, 2H), 2.40 - 2.26 (m, 1H), 2.06 (br. s., 1H), 1.02 - 0.90 (m, 3H) | 0.83 B<br>505.0                        | A                                        |
| 363 |           | 2-(1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-6-hydroxy-4-oxo-1,4-dihydropyrimidin-5-yl)pyrrolidin-3-yl)benzonitrile | <br>Chiralpak IC, 4.6 x 250 mm, 5 micron; mobile phase: 15% IPA/0.1% DEA /85% CO <sub>2</sub> ; Flow Conditions: 2 mL/min, 150 bar, 45°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.86 - 7.78 (m, 1H), 7.70 - 7.63 (m, 1H), 7.61 - 7.53 (m, 1H), 7.50 - 7.38 (m, 2H), 6.86 - 6.74 (m, 2H), 3.95 (d, J=9.5 Hz, 2H), 3.78 - 3.35 (m, 10H), 3.35 - 3.20 (m, 2H), 2.40 - 2.26 (m, 1H), 2.06 (br. s., 1H), 1.02 - 0.90 (m, 3H) | 0.83 B<br>505.0                        | A                                        |

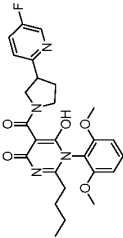
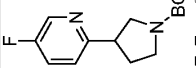
| Ex# | Structure | Name                                                                                                         | Chiral amine intermediate with retention time                                                                                                                                                | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                            | LC/MS Rt (min) Method | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-----------|--------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 364 |           | 2-(1-(2-butyl-1-(2,6-dimethoxyphenyl)-6-hydroxy-4-oxo-1,4-dihydropyrimidin-5-yl)pyrrolidin-3-yl)benzonitrile | <br>BOC<br>5.68, >99%<br>Chiralpak IC, 4.6 x 250 mm, 5 micron; mobile phase: 15% IPA/0.1% DEA /85% CO <sub>2</sub> ; Flow Conditions: 2 mL/min, 150 bar, 45°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.82 (t, J=6.1 Hz, 1H), 7.72 - 7.56 (m, 2H), 7.49 - 7.38 (m, 2H), 6.88 - 6.76 (m, 2H), 4.05 - 3.36 (m, 11H), 2.35 - 2.28 (m, 1H), 2.24 - 2.12 (m, 2H), 2.08 - 1.97 (m, 1H), 1.50 - 1.32 (m, 2H), 1.20 - 1.03 (m, 2H), 0.78 - 0.60 (m, 3H) | 0.80<br>B<br>503.0    | A                                        |
| 365 |           | 2-(1-(2-butyl-1-(2,6-dimethoxyphenyl)-6-hydroxy-4-oxo-1,4-dihydropyrimidin-5-yl)pyrrolidin-3-yl)benzonitrile | <br>BOC<br>4.87, >99%<br>Chiralpak IC, 4.6 x 250 mm, 5 micron; mobile phase: 15% IPA/0.1% DEA /85% CO <sub>2</sub> ; Flow Conditions: 2 mL/min, 150 bar, 45°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.82 (t, J=6.1 Hz, 1H), 7.72 - 7.56 (m, 2H), 7.49 - 7.38 (m, 2H), 6.88 - 6.76 (m, 2H), 4.05 - 3.36 (m, 11H), 2.35 - 2.28 (m, 1H), 2.24 - 2.12 (m, 2H), 2.08 - 1.97 (m, 1H), 1.50 - 1.32 (m, 2H), 1.20 - 1.03 (m, 2H), 0.78 - 0.60 (m, 3H) | 0.80<br>B<br>503.0    | A                                        |

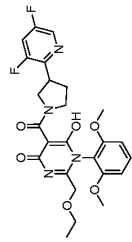
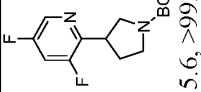
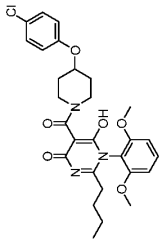
| Ex# | Structure                                                                            | Name                                                                                                   | Chiral amine intermediate with retention time                                                                                                                                                                                                     | <sup>1</sup> H NMR                                                                                                                                                                                                                                                   | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 366 |   | 2-butyl-1-(2,6-dimethoxyphenyl)-5-(3-(fluoropyridin-2-yl)pyrrolidin-2-yl)-6-hydroxypyrimidin-4(1H)-one | <br>9.5, >99.8%<br>Whelko, 5 x 50 cm, 10 micron; mobile phase: 10% IPA/90% CO <sub>2</sub> ; Flow Conditions: 340 mL/min, 45°C, wavelength: 220 nm (isomer 2)  | <sup>1</sup> H NMR (400MHz, METHANOL-d <sub>4</sub> ) δ 8.31 - 8.17 (m, 1H), 7.49 - 7.32 (m, 2H), 7.22 (dt, J=8.5, 4.2 Hz, 1H), 6.73 (d, J=8.4 Hz, 2H), 3.94 - 3.46 (m, 11H), 2.27 (d, J=7.9 Hz, 4H), 1.44 (br. s., 2H), 1.17 - 1.04 (m, 2H), 0.67 (t, J=7.4 Hz, 3H) | 0.77 B<br>497.3           | A                                        |
| 367 |  | 2-butyl-1-(2,6-dimethoxyphenyl)-5-(3-(fluoropyridin-2-yl)pyrrolidin-2-yl)-6-hydroxypyrimidin-4(1H)-one | <br>8.5, >99.8%<br>Whelko, 5 x 50 cm, 10 micron; mobile phase: 10% IPA/90% CO <sub>2</sub> ; Flow Conditions: 340 mL/min, 45°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (400MHz, METHANOL-d <sub>4</sub> ) δ 8.31 - 8.17 (m, 1H), 7.49 - 7.32 (m, 2H), 7.22 (dt, J=8.5, 4.2 Hz, 1H), 6.73 (d, J=8.4 Hz, 2H), 3.94 - 3.46 (m, 11H), 2.27 (d, J=7.9 Hz, 4H), 1.44 (br. s., 2H), 1.17 - 1.04 (m, 2H), 0.67 (t, J=7.4 Hz, 3H) | 0.77 B<br>497.3           | A                                        |

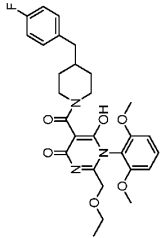
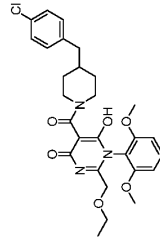
| Ex# | Structure | Name                                                                                                                              | Chiral amine intermediate with retention time                                                                                                                           | <sup>1</sup> H NMR                                                                                                                                                                                                                         | LC/MS Rt (min) Method | hAPI cAMP EC <sub>50</sub> Potency range |
|-----|-----------|-----------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------------------------|
| 368 |           | 2-(1-(2-(tert-butoxymethyl)-1-(2,6-dimethoxyphenyl)-6-hydroxy-4-oxo-1,4-dihydropyrimidine-5-carbonyl)pyrrolidin-3-yl)benzonitrile | <br>Chiralpak IC, 4.6 x 250 mm, 5 micron; mobile phase: 15% IPA/0.1% DEA /85% CO <sub>2</sub> ; Flow Conditions: 2 mL/min, 150 bar, 45°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.88 - 7.76 (m, 1H), 7.71 - 7.54 (m, 2H), 7.50 - 7.35 (m, 2H), 6.86 - 6.70 (m, 2H), 3.86 (br. s., 2H), 3.17 (s, 1H), 2.37 - 2.26 (m, 1H), 2.11 - 2.00 (m, 1H), 0.82 (d, J=14.6 Hz, 9H) | 0.83 B<br>533.1       | A                                        |
| 369 |           | 2-(1-(2-(tert-butoxymethyl)-1-(2,6-dimethoxyphenyl)-6-hydroxy-4-oxo-1,4-dihydropyrimidine-5-carbonyl)pyrrolidin-3-yl)benzonitrile | <br>Chiralpak IC, 4.6 x 250 mm, 5 micron; mobile phase: 15% IPA/0.1% DEA /85% CO <sub>2</sub> ; Flow Conditions: 2 mL/min, 150 bar, 45°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.88 - 7.76 (m, 1H), 7.71 - 7.54 (m, 2H), 7.50 - 7.35 (m, 2H), 6.86 - 6.70 (m, 2H), 3.86 (br. s., 2H), 3.17 (s, 1H), 2.37 - 2.26 (m, 1H), 2.11 - 2.00 (m, 1H), 0.82 (d, J=14.6 Hz, 9H) | 0.83 B<br>533.1       | A                                        |

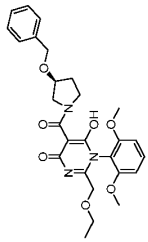
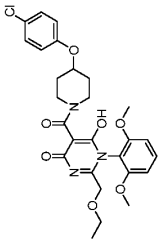
| Ex# | Structure                                                                           | Name                                                                                                     | Chiral amine intermediate with retention time                                                                                                                                                                                                     | <sup>1</sup> H NMR                                                                                                                                                                                                      | LC/MS Rt (min) Method M+H | hAPJ cAMP EC <sub>50</sub> Potency range |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 370 |  | 2-butyl-1-(2,6-dimethoxyphenyl)-5-(3-(5-fluoropyridin-2-yl)pyrrolidin-1-yl)-6-hydroxypyrimidin-4(1H)-one | <br>8.4, >99.7%<br>W helko, 5 x 50 cm, 10 micron; mobile phase: 10% IPA/90% CO <sub>2</sub> ; Flow Conditions: 340 mL/min, 45°C, wavelength: 220 nm (isomer 2) | <sup>1</sup> H NMR (400MHz, METHANOL-d <sub>4</sub> ) δ 8.30 (br. s., 1H), 7.33 (s, 3H), 6.80 - 6.67 (m, 2H), 3.81 - 3.44 (m, 11H), 2.28 (t, J=7.6 Hz, 4H), 1.43 (br. s., 2H), 1.18 - 1.03 (m, 2H), 0.74 - 0.56 (m, 3H) | 0.75<br>B<br>497.3        | A                                        |

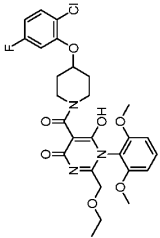
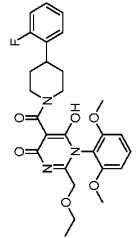


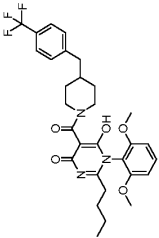
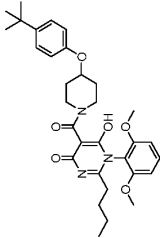
| Ex# | Structure                                                                           | Name                                                                                                     | Chiral amine intermediate<br>with retention time                                                                                                                                                                                                | <sup>1</sup> H NMR                                                                                                                                                                                                      | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPI<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 371 |  | 2-butyl-1-(2,6-dimethoxyphenyl)-5-(3-(5-fluoropyridin-2-yl)pyrrolidin-1-yl)-6-hydroxypyrimidin-4(1H)-one | <br>7.7, >95.5%<br>Whelko, 5 x 50 cm, 10 micron; mobile phase: 10% IPA/90% O <sub>2</sub> ; Flow Conditions: 340 mL/min, 45°C, wavelength: 220 nm (isomer 1) | <sup>1</sup> H NMR (400MHz, METHANOL-d <sub>4</sub> ) δ 8.30 (br. s., 1H), 7.33 (s, 3H), 6.80 - 6.67 (m, 2H), 3.81 - 3.44 (m, 11H), 2.28 (t, J=7.6 Hz, 4H), 1.43 (br. s., 2H), 1.18 - 1.03 (m, 2H), 0.74 - 0.56 (m, 3H) | 0.75<br>B<br>497.3                    | A                                                    |

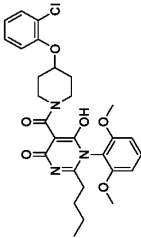
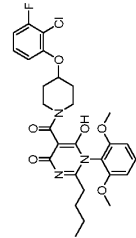
| Ex# | Structure                                                                            | Name                                                                                                                         | Chiral amine intermediate with retention time                                                                                                                                                                                                    | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                      | LC/MS Rt (min) Method M+H | hAPI cAMP EC <sub>50</sub> Potency range |
|-----|--------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------|
| 372 |   | 5-(3-(3,5-difluoropyridin-2-yl)pyrrolidine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-6-hydroxypyrimidin-4(1H)-one | <br>5.6, >99.7%<br>Whelko, 5 x 50 cm, 10 micron; mobile phase: 20% IPA/80% CO <sub>2</sub> ; Flow Conditions: 350 mL/min, 30°C, wavelength: 220 nm (isomer I) | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 8.46 (br d, J=4.6 Hz, 1H), 8.00 - 7.82 (m, 1H), 7.40 (br d, J=6.1 Hz, 1H), 6.88 - 6.73 (m, 2H), 4.07 - 3.44 (m, 11H), 3.26 (br s, 2H), 2.55 (s, 2H), 2.30 - 2.04 (m, 2H), 1.05 - 0.85 (m, 3H)                                                      |                           | A                                        |
| 373 |  | 2-butyl-5-(4-(4-chlorophenoxy)piperidine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-6-hydroxypyrimidin-4(1H)-one                    |                                                                                                                                                                                                                                                  | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.44 (t, J=8.5 Hz, 1H), 7.30 (br d, J=8.8 Hz, 2H), 7.00 (br d, J=8.8 Hz, 2H), 6.82 (d, J=8.5 Hz, 2H), 3.73 (s, 9H), 2.19 (br d, J=7.8 Hz, 2H), 1.91 (s, 4H), 1.64 - 1.46 (m, 2H), 1.46 - 1.37 (m, 2H), 1.20 - 1.06 (m, 2H), 0.69 (t, J=7.3 Hz, 3H) | 0.97<br>B<br>542.0        | A                                        |

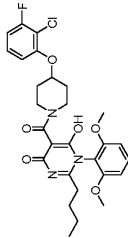
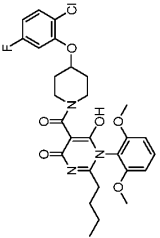
| Ex# | Structure                                                                            | Name                                                                                                            | Chiral amine intermediate<br>with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                         | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|--------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|--------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 374 |   | 1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-5-(4-(4-fluorobenzyl)pyridine-1-carbonyl)-6-hydroxypyrimidin-4(1H)-one |                                                  | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.43 (t, J=8.5 Hz, 1H), 7.22 - 7.15 (m, 2H), 7.11 - 7.04 (m, 2H), 6.80 (d, J=8.5 Hz, 2H), 3.92 (s, 2H), 3.72 (s, 6H), 3.30 - 3.22 (m, 2H), 2.55 (s, 3H), 2.46 (d, J=6.9 Hz, 2H), 1.76 - 1.65 (m, 1H), 1.61 - 1.44 (m, 2H), 1.18 - 0.99 (m, 2H), 0.96 (t, J=6.9 Hz, 4H) | 0.86<br>B<br>526.1                    | A                                                    |
| 375 |  | 5-(4-(4-chlorobenzyl)pyridine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-6-hydroxypyrimidin-4(1H)-one |                                                  | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.41 (br t, J=8.4 Hz, 1H), 7.30 (br d, J=8.1 Hz, 2H), 7.18 (br d, J=8.1 Hz, 2H), 6.79 (br d, J=8.5 Hz, 2H), 3.97 - 3.51 (m, 8H), 3.24 (br d, J=6.9 Hz, 2H), 2.55 (s, 4H), 2.48 - 2.43 (m, 2H), 1.90 (s, 2H), 1.74 - 1.62 (m, 1H), 1.60 - 1.33 (m, 2H), 0.95 (s, 3H)   | 0.95<br>B<br>542.0                    | A                                                    |

| Ex# | Structure                                                                            | Name                                                                                                               | Chiral amine intermediate<br>with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                             | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 376 |   | (S)-5-(3-(benzyloxy)pyrrolidine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-6-hydroxypyrimidin-4(1H)-one  |                                                  | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.43 (s, 1H), 7.37 - 7.25 (m, 5H), 6.81 (d, J=8.3 Hz, 2H), 4.52 - 4.40 (m, 2H), 4.21 - 4.12 (m, 1H), 3.93 (s, 2H), 3.74 (s, 6H), 3.57 - 3.21 (m, 6H), 2.03 - 1.92 (m, 2H), 0.97 (t, J=6.9 Hz, 3H)                                          | 1.58<br>B<br>509.2                    | A                                                    |
| 377 |  | 5-(4-(4-chlorophenoxy)piperidine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-6-hydroxypyrimidin-4(1H)-one |                                                  | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.47 - 7.36 (m, 1H), 7.34 - 7.27 (m, 2H), 7.01 (d, J=8.7 Hz, 2H), 6.79 (d, J=8.4 Hz, 2H), 4.60 (br. s., 1H), 3.89 (s, 2H), 3.73 (br. s., 6H), 3.36 - 3.16 (m, 2H), 2.55 (s, 3H), 1.91 (s, 3H), 1.67 - 1.47 (m, 2H), 0.97 (t, J=6.9 Hz, 3H) | 0.90<br>B<br>544.0                    | A                                                    |

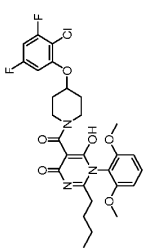
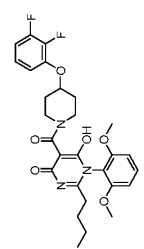
| Ex# | Structure                                                                            | Name                                                                                                                        | Chiral amine intermediate<br>with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                              | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPI<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|--------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 378 |   | 5-(4-(2-chloro-5-fluorophenoxy)piperidine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-6-hydroxypyrimidin-4(1H)-one |                                                  | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.50 - 7.36 (m, 1H), 7.23 (d, J=8.8 Hz, 1H), 6.87 - 6.74 (m, 3H), 4.81 - 4.66 (m, 1H), 3.88 (br s, 2H), 3.73 (s, 6H), 3.30 - 3.20 (m, 2H), 2.55 (s, 3H), 1.91 (s, 4H), 1.73 - 1.50 (m, 2H), 0.96 (br s, 3H) | 0.92<br>B<br>562.0                    | A                                                    |
| 379 |  | 1-(2,6-dimethoxyphenyl)-2-(ethoxymethyl)-5-(4-(2-fluorophenyl)piperidin-1-carbonyl)-6-hydroxypyrimidin-4(1H)-one            |                                                  | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.42 (s, 1H), 7.28 - 7.20 (m, 2H), 7.18 - 7.10 (m, 2H), 6.80 (d, J=8.5 Hz, 2H), 3.91 (s, 2H), 3.73 (br s, 6H), 3.51 - 2.98 (m, 6H), 1.82 - 1.46 (m, 5H), 0.97 (t, J=6.9 Hz, 3H)                             | 1.6<br>B<br>511.2                     | A                                                    |

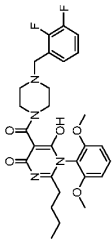
| Ex# | Structure                                                                            | Name                                                                                                                | Chiral amine intermediate<br>with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                              | LC/MS<br>Rt<br>(min)<br>Method<br>M <sup>+</sup> H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|------------------------------------------------------|
| 380 |   | 2-butyl-1-(2,6-dimethoxyphenyl)-6-hydroxy-5-(4-(4-(trifluoromethyl)benzyl)piperidine-1-carbonyl)pyrimidin-4(1H)-one |                                                  | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.63 (d, J=8.0 Hz, 2H), 7.51 - 7.31 (m, 3H), 6.84 (d, J=8.5 Hz, 2H), 3.82 - 3.68 (m, 5H), 2.58 (d, J=6.9 Hz, 2H), 2.55 (s, 2H), 2.21 (t, J=7.5 Hz, 2H), 1.84 - 1.71 (m, 1H), 1.62 - 1.36 (m, 4H), 1.23 (s, 3H), 1.20 - 0.96 (m, 4H), 0.70 (t, J=7.3 Hz, 3H) | 1.0<br>B<br>574.0                                  | A                                                    |
| 381 |  | 2-butyl-5-(4-(4-(tert-butyl)phenoxy)piperidine-1-carbonyl)-(2,6-dimethoxyphenyl)-6-hydroxypyrimidin-4(1H)-one       |                                                  | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.45 (s, 1H), 7.27 (d, J=8.6 Hz, 2H), 6.92 - 6.78 (m, 4H), 4.63 - 4.48 (m, 1H), 3.75 (s, 6H), 2.52 - 2.48 (m, 4H), 2.25 - 2.15 (m, 2H), 2.00 - 1.82 (m, 2H), 1.68 - 1.37 (m, 4H), 1.24 (s, 9H), 1.19 - 1.09 (m, 2H), 0.71 (s, 3H)                           | 1.1<br>B<br>564.1                                  | B                                                    |

| Ex# | Structure                                                                            | Name                                                                                                               | Chiral amine intermediate<br>with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                          | LC/MS<br>Rt<br>(min)<br>Method<br>M <sup>+</sup> H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|------------------------------------------------------|
| 382 |   | 2-butyl-5-(4-(2-chlorophenoxy)piperidine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-6-hydroxypyrimidin-4(1H)-one          |                                                  | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.52 - 7.36 (m, 2H), 7.33 - 7.16 (m, 2H), 6.96 (t, J=7.1 Hz, 1H), 6.87 - 6.76 (m, 2H), 4.79 - 4.63 (m, 1H), 3.75 (s, 6H), 2.21 (br s, 2H), 1.91 (s, 3H), 1.72 - 1.55 (m, 2H), 1.44 (br s, 2H), 1.23 (s, 3H), 1.15 (d, J=7.3 Hz, 2H), 0.71 (t, J=7.3 Hz, 3H)             | 0.94<br>B<br>542.0                                 | A                                                    |
| 383 |  | 2-butyl-5-(4-(2-chloro-3-fluorophenoxy)piperidine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-6-hydroxypyrimidin-4(1H)-one |                                                  | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.45 (t, J=8.4 Hz, 1H), 7.37 - 7.24 (m, 2H), 7.21 - 7.08 (m, 1H), 6.83 (d, J=8.5 Hz, 2H), 4.38 (br s, 1H), 3.74 (s, 8H), 3.17 (s, 2H), 2.25 - 2.17 (m, 2H), 1.96 - 1.85 (m, 2H), 1.76 - 1.56 (m, 2H), 1.47 - 1.37 (m, 2H), 1.18 - 1.09 (m, 2H), 0.69 (t, J=7.3 Hz, 3H) | 0.91<br>B<br>560.0                                 | A                                                    |

| Ex# | Structure                                                                            | Name                                                                                                               | Chiral amine intermediate<br>with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                      | LC/MS<br>Rt<br>(min)<br>Method<br>M <sup>+</sup> H | hAPI<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|--------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|------------------------------------------------------|
| 384 |   | 2-butyl-5-(4-(2-chloro-3-fluorophenoxy)piperidine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-6-hydroxypyrimidin-4(1H)-one |                                                  | <sup>1</sup> H NMR (500 MHz, DMSO-d <sub>6</sub> ) δ 7.46 (t, J=8.5 Hz, 1H), 7.37 - 7.29 (m, 1H), 7.15 - 7.08 (m, 1H), 6.99 (t, J=8.6 Hz, 1H), 4.79 (br s, 1H), 3.75 (s, 6H), 3.64 - 3.25 (m, 4H), 2.26 - 2.17 (m, 2H), 1.99 - 1.84 (m, 2H), 1.74 - 1.54 (m, 2H), 1.44 (br s, 2H), 1.23 (s, 3H), 0.71 (t, J=7.3 Hz, 4H) | 0.92<br>B<br>560.0                                 | A                                                    |
| 385 |  | 2-butyl-5-(4-(2-chloro-5-fluorophenoxy)piperidine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-6-hydroxypyrimidin-4(1H)-one |                                                  | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.55 - 7.35 (m, 2H), 7.28 - 7.05 (m, 1H), 6.93 - 6.63 (m, 3H), 4.76 (br s, 1H), 3.75 (s, 6H), 2.51 (br s, 4H), 2.26 - 2.14 (m, 2H), 1.99 - 1.85 (m, 2H), 1.73 - 1.53 (m, 2H), 1.51 - 1.37 (m, 2H), 1.23 - 1.07 (m, 2H), 0.70 (t, J=7.3 Hz, 3H)                      | 0.93<br>B<br>560.0                                 | A                                                    |

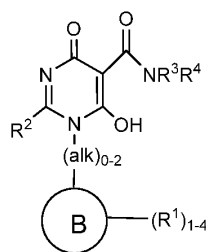


| Ex# | Structure                                                                             | Name                                                                                                       | Chiral amine intermediate<br>with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                                                                                                                       | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPJ<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|---------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|--------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 386 |    | 2-butyl-5-(4-(2-chloro-3,5-difluorophenoxy)piperidin-1-yl)-6-dimethoxyphenyl)-6-hydroxypyrimidin-4(1H)-one |                                                  | <sup>1</sup> H NMR (600MHz, DMSO-d <sub>6</sub> ) δ 7.45 (t, J=8.3 Hz, 1H), 7.17 (d, J=10.7 Hz, 1H), 7.05 (t, J=9.0 Hz, 1H), 6.84 (d, J=8.5 Hz, 2H), 4.87 - 4.73 (m, 1H), 3.75 (br. s., 6H), 3.53 - 3.21 (m, 5H), 2.29 - 2.12 (m, 2H), 1.98 - 1.84 (m, 2H), 1.74 - 1.54 (m, 2H), 1.49 - 1.33 (m, 2H), 1.15 (d, J=7.1 Hz, 2H), 0.71 (t, J=7.2 Hz, 3H)     | 0.93<br>B<br>577.9                    | A                                                    |
| 387 |  | 2-butyl-5-(4-(2-chloro-3,5-difluorophenoxy)piperidin-1-yl)-6-dimethoxyphenyl)-6-hydroxypyrimidin-4(1H)-one |                                                  | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.46 (t, J=8.5 Hz, 1H), 7.17 - 7.07 (m, 2H), 7.04 - 6.92 (m, 1H), 6.84 (d, J=8.5 Hz, 2H), 4.68 (br. s., 1H), 3.75 (s, 6H), 3.37 - 3.20 (m, 1H), 2.26 - 2.18 (m, 2H), 2.00 - 1.87 (m, 2H), 1.71 - 1.48 (m, 2H), 1.48 - 1.37 (m, 2H), 1.29 - 1.20 (m, 3H), 1.19 - 1.09 (m, 2H), 0.70 (t, J=7.3 Hz, 3H) | 0.88<br>B<br>544.0                    | A                                                    |

| Ex# | Structure                                                                           | Name                                                                                                         | Chiral amine intermediate<br>with retention time | <sup>1</sup> H NMR                                                                                                                                                                                                                                 | LC/MS<br>Rt<br>(min)<br>Method<br>M+H | hAPI<br>cAMP<br>EC <sub>50</sub><br>Potency<br>range |
|-----|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|--------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|------------------------------------------------------|
| 388 |  | 2-butyl-5-(4-(2,3-difluorobenzyl)piperazine-1-carbonyl)-1-(2,6-dimethoxyphenyl)-6-hydroxypyrimidin-4(1H)-one |                                                  | <sup>1</sup> H NMR (500MHz, DMSO-d <sub>6</sub> ) δ 7.55 - 7.42 (m, 2H), 7.38 - 7.28 (m, 2H), 6.85 (d, J=8.5 Hz, 2H), 4.32 - 4.14 (m, 2H), 3.75 (s, 6H), 2.51 (br. s., 8H), 2.26 (t, J=7.3 Hz, 2H), 1.41 (d, J=7.2 Hz, 2H), 0.69 (t, J=7.3 Hz, 3H) | 0.65<br>B<br>543.1                    | A                                                    |

## WHAT IS CLAIMED IS:

1. A compound of Formula (I):



5 (I)

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

alk is C<sub>1-6</sub> alkylene substituted with 0-5 R<sup>e</sup>;

ring B is independently selected from C<sub>3-6</sub> cycloalkyl, C<sub>3-6</sub> cycloalkenyl, aryl, bicyclic carbocyclyl, and 6-membered heteroaryl;

10 R<sup>1</sup>, at each occurrence, is independently selected from H, halogen, NO<sub>2</sub>, -(CH<sub>2</sub>)<sub>n</sub>OR<sup>b</sup>, (CH<sub>2</sub>)<sub>n</sub>S(O)<sub>p</sub>R<sup>c</sup>, -(CH<sub>2</sub>)<sub>n</sub>C(=O)R<sup>b</sup>, -(CH<sub>2</sub>)<sub>n</sub>NR<sup>a</sup>R<sup>a</sup>, -(CH<sub>2</sub>)<sub>n</sub>CN, - (CH<sub>2</sub>)<sub>n</sub>C(=O)NR<sup>a</sup>R<sup>a</sup>, -(CH<sub>2</sub>)<sub>n</sub>NR<sup>a</sup>C(=O)R<sup>b</sup>, -(CH<sub>2</sub>)<sub>n</sub>NR<sup>a</sup>C(=O)NR<sup>a</sup>R<sup>a</sup>, - (CH<sub>2</sub>)<sub>n</sub>NR<sup>a</sup>C(=O)OR<sup>b</sup>, -(CH<sub>2</sub>)<sub>n</sub>OC(=O)NR<sup>a</sup>R<sup>a</sup>, -(CH<sub>2</sub>)<sub>n</sub>C(=O)OR<sup>b</sup>, - (CH<sub>2</sub>)<sub>n</sub>S(O)<sub>p</sub>NR<sup>a</sup>R<sup>a</sup>, -(CH<sub>2</sub>)<sub>n</sub>NR<sup>a</sup>S(O)<sub>p</sub>NR<sup>a</sup>R<sup>a</sup>, -(CH<sub>2</sub>)<sub>n</sub>NR<sup>a</sup>S(O)<sub>p</sub>R<sup>c</sup>, C<sub>1-4</sub> alkyl substituted with 0-3 R<sup>e</sup>, -(CH<sub>2</sub>)<sub>n</sub>-C<sub>3-6</sub> carbocyclyl substituted with 0-3 R<sup>e</sup>, and - (CH<sub>2</sub>)<sub>n</sub>-heterocyclyl substituted with 0-3 R<sup>e</sup>;

15 R<sup>2</sup> is independently selected from C<sub>1-10</sub> alkyl substituted with 0-3 R<sup>e</sup>; C<sub>2-5</sub> alkenyl substituted with 0-3 R<sup>e</sup>, aryl substituted with 0-3 R<sup>e</sup>, heteroaryl substituted with 0-3 R<sup>e</sup>, and C<sub>3-6</sub> cycloalkyl substituted with 0-3 R<sup>e</sup>; provided when R<sup>2</sup> is C<sub>1-5</sub> alkyl, the carbon atoms and the groups attached thereto except the carbon atom attached to the pyrimidine ring may be replaced by O, N, and S;

R<sup>3</sup> is independently selected from H and C<sub>1-5</sub> alkyl;

20 R<sup>4</sup> is independently selected from -(CR<sup>7</sup>R<sup>7</sup>)<sub>n</sub>-R<sup>6</sup>, -(CR<sup>7</sup>R<sup>7</sup>)<sub>n</sub>OR<sup>6</sup>, -(CR<sup>7</sup>R<sup>7</sup>)<sub>n</sub>S(O)<sub>p</sub>R<sup>6</sup>, - (CR<sup>7</sup>R<sup>7</sup>)<sub>n</sub>C(=O)R<sup>6</sup>, -(CR<sup>7</sup>R<sup>7</sup>)<sub>n</sub>NR<sup>a</sup>R<sup>6</sup>, -(CR<sup>7</sup>R<sup>7</sup>)<sub>n</sub>NR<sup>a</sup>C(=O)R<sup>6</sup>, - (CR<sup>7</sup>R<sup>7</sup>)<sub>n</sub>S(O)<sub>p</sub>NR<sup>a</sup>R<sup>6</sup>, and -(CR<sup>7</sup>R<sup>7</sup>)<sub>n</sub>NR<sup>a</sup>S(O)<sub>p</sub>R<sup>6</sup>;

alternatively, R<sup>3</sup> and R<sup>4</sup> together with the nitrogen atom to which they are both attached form a heterocyclic ring or a spiro heterocyclic ring comprising carbon atoms and

- additional 1 to 4 heteroatoms selected from  $\text{NR}^{5a}$ , O, and S and substituted with 0-5  $\text{R}^5$ ;
- $\text{R}^5$ , at each occurrence, is independently selected from OH, halogen,  $-(\text{CR}^7\text{R}^7)_n\text{-R}^6$ ,  $-\text{OR}^6$ ,  $-\text{S(O)}_p\text{R}^6$ ,  $-\text{C(=O)R}^6$ ,  $-\text{NR}^a\text{R}^6$ ,  $-\text{C(=O)NR}^a\text{R}^6$ ,  $-\text{NR}^a\text{C(=O)R}^6$ ,  $-\text{NR}^a\text{C(=O)OR}^6$ , -
- 5  $\text{OC(=O)NR}^a\text{R}^6$ ,  $-\text{C(=O)OR}^6$ ,  $-\text{S(O)}_p\text{NR}^a\text{R}^6$ ,  $-\text{NR}^a\text{S(O)}_p\text{NR}^a\text{R}^6$ , and  $-\text{NR}^a\text{S(O)}_p\text{R}^6$ ;
- $\text{R}^{5a}$ , at each occurrence, is independently selected from  $-\text{C(=O)OR}^6$ ,  $\text{C(=O)NR}^a\text{R}^6$ , -  $(\text{CR}^7\text{R}^7)_n\text{-R}^6$ ,  $-\text{C(=O)-R}^6$ , and  $-\text{S(O)}_p\text{R}^6$ ;
- $\text{R}^6$ , at each occurrence, is independently selected from  $-(\text{CR}^7\text{R}^7)_n\text{-C}_{3-10}$  carbocyclyl and -  $(\text{CR}^7\text{R}^7)_n\text{-heteroaryl}$ , each substituted with 0-3  $\text{R}^8$ ;
- 10  $\text{R}^7$ , at each occurrence, is independently selected from H,  $\text{C}_{1-4}$  alkyl, and  $-(\text{CH}_2)_n\text{-C}_{3-12}$  carbocyclyl substituted with 0-3  $\text{R}^e$ ;
- $\text{R}^8$ , at each occurrence, is independently selected from H, halogen,  $-(\text{CH}_2)_n\text{OR}^b$ ,  $=\text{O}$ ,  $(\text{CH}_2)_n\text{S(O)}_p\text{R}^c$ ,  $-(\text{CH}_2)_n\text{C(=O)R}^b$ ,  $-(\text{CH}_2)_n\text{NR}^a\text{R}^a$ ,  $-(\text{CH}_2)_n\text{CN}$ , -  $(\text{CH}_2)_n\text{C(=O)NR}^a\text{R}^a$ ,  $-(\text{CH}_2)_n\text{NR}^a\text{C(=O)R}^b$ ,  $-(\text{CH}_2)_n\text{NR}^a\text{C(=O)NR}^a\text{R}^a$ , -
- 15  $(\text{CH}_2)_n\text{NR}^a\text{C(=O)OR}^b$ ,  $-(\text{CH}_2)_n\text{OC(=O)NR}^a\text{R}^a$ ,  $-(\text{CH}_2)_n\text{C(=O)OR}^b$ , -  $(\text{CH}_2)_n\text{S(O)}_p\text{NR}^a\text{R}^a$ ,  $-(\text{CH}_2)_n\text{NR}^a\text{S(O)}_p\text{NR}^a\text{R}^a$ ,  $-(\text{CH}_2)_n\text{NR}^a\text{S(O)}_p\text{R}^c$ ,  $\text{C}_{1-5}$  alkyl substituted with 0-3  $\text{R}^e$ ,  $-(\text{CH}_2)_n\text{-C}_{3-6}$  carbocyclyl substituted with 0-3  $\text{R}^e$ , and -  $(\text{CH}_2)_n\text{-heterocyclyl}$  substituted with 0-3  $\text{R}^e$ ;
- $\text{R}^a$ , at each occurrence, is independently selected from H,  $\text{C}_{1-6}$  alkyl substituted with 0-5  $\text{R}^e$ ,  $\text{C}_{2-6}$  alkenyl substituted with 0-5  $\text{R}^e$ ,  $\text{C}_{2-6}$  alkynyl substituted with 0-5  $\text{R}^e$ , -
- 20  $(\text{CH}_2)_n\text{-C}_{3-10}$  carbocyclyl substituted with 0-5  $\text{R}^e$ , and  $-(\text{CH}_2)_n\text{-heterocyclyl}$  substituted with 0-5  $\text{R}^e$ ; or  $\text{R}^a$  and  $\text{R}^a$  together with the nitrogen atom to which they are both attached form a heterocyclic ring substituted with 0-5  $\text{R}^e$ ;
- $\text{R}^b$ , at each occurrence, is independently selected from H,  $\text{C}_{1-6}$  alkyl substituted with 0-5  $\text{R}^e$ ,  $\text{C}_{2-6}$  alkenyl substituted with 0-5  $\text{R}^e$ ,  $\text{C}_{2-6}$  alkynyl substituted with 0-5  $\text{R}^e$ , -
- 25  $(\text{CH}_2)_n\text{-C}_{3-10}$  carbocyclyl substituted with 0-5  $\text{R}^e$ , and  $-(\text{CH}_2)_n\text{-heterocyclyl}$  substituted with 0-5  $\text{R}^e$ ;
- $\text{R}^c$ , at each occurrence, is independently selected from  $\text{C}_{1-6}$  alkyl substituted with 0-5  $\text{R}^e$ ,  $\text{C}_{2-6}$  alkenyl substituted with 0-5  $\text{R}^e$ ,  $\text{C}_{2-6}$  alkynyl substituted with 0-5  $\text{R}^e$ ,  $\text{C}_{3-6}$  carbocyclyl, and heterocyclyl;
- 30  $\text{R}^e$ , at each occurrence, is independently selected from F, Cl, Br, CN,  $\text{NO}_2$ ,  $=\text{O}$ ,  $\text{CO}_2\text{H}$ ,  $\text{C}_{1-6}$  alkyl substituted with 0-5  $\text{R}^e$ ,  $\text{C}_{2-6}$  alkenyl,  $\text{C}_{2-6}$  alkynyl,  $-(\text{CH}_2)_n\text{-C}_{3-6}$  cycloalkyl,

$-(CH_2)_n$ -C<sub>4-6</sub> heterocyclyl,  $-(CH_2)_n$ -aryl,  $-(CH_2)_n$ -heteroaryl,  $-(CH_2)_nOR^f$ ,  $-S(O)_pR^f$ ,  
 $-C(=O)NR^fR^f$ ,  $-NR^fC(=O)R^f$ ,  $-S(O)_pNR^fR^f$ ,  $-NR^fS(O)_pR^f$ ,  $-NR^fC(=O)OR^f$ ,  $-$   
 $OC(=O)NR^fR^f$  and  $-(CH_2)_nNR^fR^f$ ;

$R^f$ , at each occurrence, is independently selected from H, F, Cl, Br, CN, OH, C<sub>1-5</sub>alkyl  
 5 (optionally substituted with halogen and OH), C<sub>3-6</sub> 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<sub>1-4</sub>alkyl;

$n$ , at each occurrence, is independently selected from zero, 1, 2, 3, and 4; and

$p$ , at each occurrence, is independently selected from zero, 1, and 2.

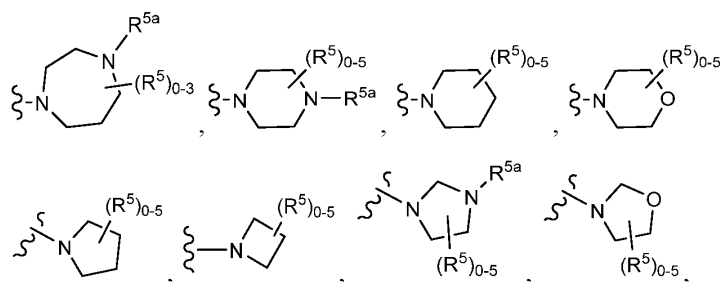
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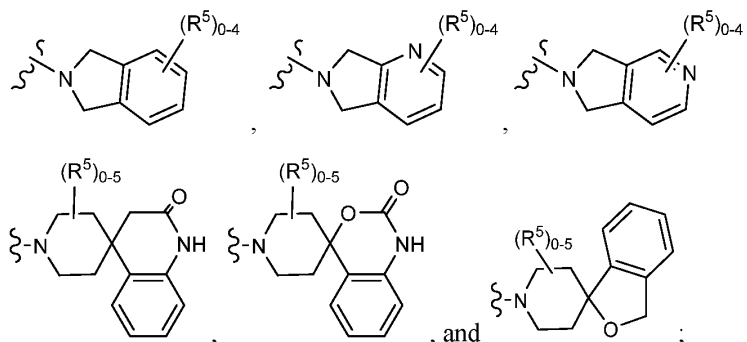
2. The compound according to claim 1, or a stereoisomer, an enantiomer, a  
 diastereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof, wherein:

$R^1$ , at each occurrence, is independently selected from H, F, Cl, Br, NO<sub>2</sub>,  $-(CH_2)_nOR^b$ ,  $-$   
 $(CH_2)_nC(=O)R^b$ ,  $-(CH_2)_nNR^aR^a$ ,  $-(CH_2)_nCN$ ,  $-(CH_2)_nC(=O)NR^aR^a$ ,  $-$   
 15  $(CH_2)_nNR^aC(=O)R^b$ , C<sub>1-4</sub> alkyl substituted with 0-3  $R^e$ , and C<sub>3-6</sub> cycloalkyl  
 substituted with 0-3  $R^e$ ;

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

20  $R^3$  and  $R^4$  together with the nitrogen atom to which they are both attached form a  
 heterocyclic ring or a spiro heterocyclic ring selected from





- $R^5$ , at each occurrence, is independently selected from OH,  $-(CR^7R^7)_n-R^6$ ,  $-OR^6$ ,  $-S(O)_pR^6$ ,  $-C(=O)R^6$ ,  $-NR^aR^6$ ,  $-C(=O)NR^aR^6$ ,  $-NR^aC(=O)R^6$ ,  $-NR^aC(=O)OR^6$ ,  $-OC(=O)NR^aR^6$ ,  $-C(=O)OR^6$ ,  $-S(O)_pNR^aR^6$ ,  $-NR^aS(O)_pNR^aR^6$ , and  $-NR^aS(O)_pR^6$ ;
- $R^{5a}$ , at each occurrence, is independently selected from  $-C(=O)OR^6$ ,  $-C(=O)NR^aR^6$ ,  $-(CR^7R^7)_n-R^6$ ,  $-C(=O)-R^6$ , and  $-S(O)_pR^6$ ;
- $R^6$ , at each occurrence, is independently selected from  $-(CR^7R^7)_n$ -aryl,  $-(CR^7R^7)_n$ -C<sub>3-6</sub> cycloalkyl, and  $-(CR^7R^7)_n$ -heteroaryl, each substituted with 0-3  $R^8$ ;
- $R^7$ , at each occurrence, is independently selected from H, C<sub>1-4</sub> alkyl, and  $-(CH_2)_n$ -C<sub>3-12</sub> carbocyclyl substituted with 0-3  $R^e$ ;
- $R^8$ , at each occurrence, 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<sub>1-4</sub> alkyl substituted with 0-3  $R^e$ ,  $(CH_2)_n$ -C<sub>3-6</sub> carbocyclyl substituted with 0-3  $R^e$ , and  $-(CH_2)_n$ -heterocyclyl substituted with 0-3  $R^e$ ;
- $R^a$ , at each occurrence, is independently selected from H, C<sub>1-6</sub> alkyl substituted with 0-5  $R^e$ ,  $-(CH_2)_n$ -C<sub>3-10</sub>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  $R^e$ ;
- $R^b$ , at each occurrence, is independently selected from H, C<sub>1-6</sub> alkyl substituted with 0-5  $R^e$ , C<sub>2-6</sub> alkenyl substituted with 0-5  $R^e$ , C<sub>2-6</sub> alkynyl substituted with 0-5  $R^e$ ,  $-(CH_2)_n$ -C<sub>3-10</sub>carbocyclyl substituted with 0-5  $R^e$ , and  $-(CH_2)_n$ -heterocyclyl substituted with 0-5  $R^e$ ;
- $R^e$ , at each occurrence, is independently selected from F, Cl, Br, CN, NO<sub>2</sub>, =O,  $-CO_2H$ , C<sub>1-6</sub> alkyl substituted with 0-5  $R^e$ , C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl,  $-(CH_2)_n$ -C<sub>3-6</sub> cycloalkyl,  $-(CH_2)_n$ -C<sub>4-6</sub> heterocyclyl,  $-(CH_2)_n$ -aryl,  $-(CH_2)_n$ -heteroaryl, -

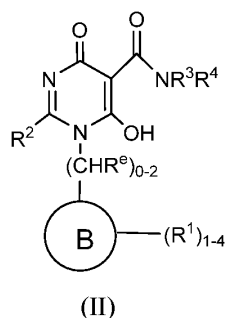
$(\text{CH}_2)_n\text{OR}^f$ ,  $-\text{S}(\text{O})_p\text{R}^f$ ,  $-\text{C}(=\text{O})\text{NR}^f\text{R}^f$ ,  $-\text{NR}^f\text{C}(=\text{O})\text{R}^f$ ,  $-\text{S}(\text{O})_p\text{NR}^f\text{R}^f$ ,  $-\text{NR}^f\text{S}(\text{O})_p\text{R}^f$ ,  $-\text{NR}^f\text{C}(=\text{O})\text{OR}^f$ ,  $-\text{OC}(=\text{O})\text{NR}^f\text{R}^f$  and  $-(\text{CH}_2)_n\text{NR}^f\text{R}^f$ ;

$\text{R}^f$ , at each occurrence, is independently selected from H, F, Cl, Br, CN, OH,  $\text{C}_{1-5}$ alkyl (optionally substituted with halogen and OH),  $\text{C}_{3-6}$  cycloalkyl, and phenyl;

5  $n$ , at each occurrence, is independently selected from zero, 1, 2, 3, and 4; and

$p$ , at each occurrence, is independently selected from zero, 1, and 2.

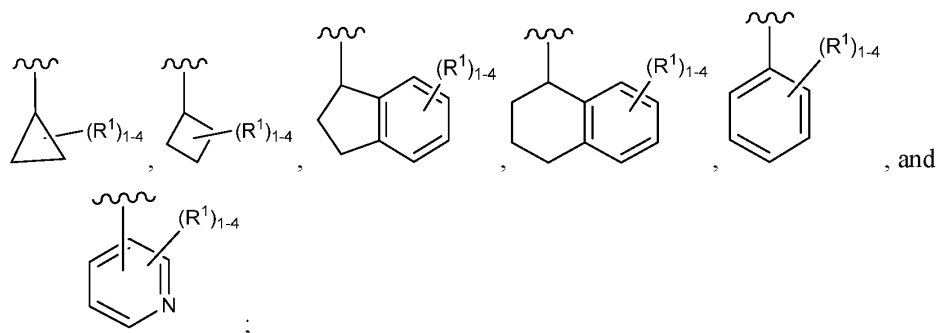
3. The compound according to claim 2 having Formula (II):



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

ring B is independently selected from



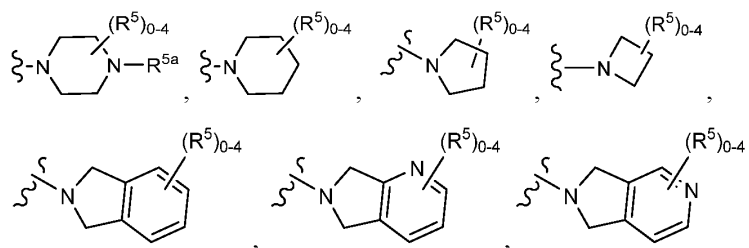
15

$\text{R}^1$ , at each occurrence, is independently selected from H, F, Cl, OH, CN,  $\text{C}_{1-4}$  alkyl,  $\text{OC}_{1-4}$  alkyl, and  $\text{C}_{3-6}$  cycloalkyl;

$\text{R}^2$  is independently selected from  $\text{C}_{1-5}$  alkyl substituted with 0-3  $\text{R}^e$ ;  $\text{C}_{2-5}$  alkenyl, aryl substituted with 0-3  $\text{R}^e$ , heteroaryl substituted with 0-3  $\text{R}^e$ ,  $\text{C}_{3-6}$  cycloalkyl,  $-(\text{CH}_2)_{1-4}\text{OC}_{1-5}$ alkyl, and  $-(\text{CH}_2)_{1-3}\text{OC}_{3-6}$ cycloalkyl;

20

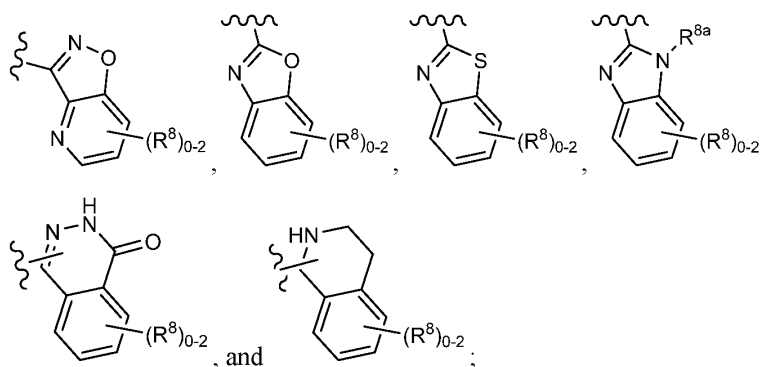
$\text{R}^3$  and  $\text{R}^4$  together with the nitrogen atom to which they are both attached form a heterocyclic ring selected from



- $R^5$ , at each occurrence, is independently selected from OH,  $-(CR^7R^7)_n-R^6$ ,  $-OR^6$ ,  $-S(O)_pR^6$ ,  $-C(=O)R^6$ ,  $-NR^aR^6$ ,  $-C(=O)NR^aR^6$ ,  $-NR^aC(=O)R^6$ ,  $-NR^aC(=O)OR^6$ ,  $-OC(=O)NR^aR^6$ ,  $-C(=O)OR^6$ ,  $-S(O)_pNR^aR^6$ ,  $-NR^aS(O)_pNR^aR^6$ , and  $-NR^aS(O)_pR^6$ ;
- $R^{5a}$  is independently selected from  $-C(=O)OR^6$ ,  $-C(=O)NR^aR^6$ ,  $-(CR^7R^7)_n-R^6$ ,  $-C(=O)-R^6$ , and  $-S(O)_pR^6$ ;
- $R^6$ , at each occurrence, is independently selected from  $-(CR^7R^7)_n$ -aryl,  $-(CR^7R^7)_n$ -C<sub>3-6</sub> cycloalkyl, and  $-(CR^7R^7)_n$ -heteroaryl, each substituted with 0-3  $R^8$ ;
- $R^7$ , at each occurrence, is independently selected from H, C<sub>1-4</sub> alkyl, and (CH<sub>2</sub>)<sub>n</sub>-C<sub>3-12</sub> carbocyclyl substituted with 0-3  $R^e$ ;
- $R^8$ , at each occurrence, 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,  $-(CH_2)_nC(=O)NR^aR^a$ , C<sub>1-4</sub> alkyl substituted with 0-3  $R^e$ ,  $-(CH_2)_n$ -C<sub>3-6</sub> carbocyclyl substituted with 0-3  $R^e$ , and  $-(CH_2)_n$ -heterocyclyl substituted with 0-3  $R^e$ ;
- $R^a$ , at each occurrence, is independently selected from H, C<sub>1-6</sub> alkyl substituted with 0-5  $R^e$ ,  $-(CH_2)_n$ -C<sub>3-10</sub>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  $R^e$ ;
- $R^b$ , at each occurrence, is independently selected from H, C<sub>1-6</sub> alkyl substituted with 0-5  $R^e$ , C<sub>2-6</sub> alkenyl substituted with 0-5  $R^e$ , C<sub>2-6</sub> alkynyl substituted with 0-5  $R^e$ ,  $-(CH_2)_n$ -C<sub>3-10</sub>carbocyclyl substituted with 0-5  $R^e$ , and  $-(CH_2)_n$ -heterocyclyl substituted with 0-5  $R^e$ ;
- $R^e$ , at each occurrence, is independently selected from F, Cl, Br, CN, NO<sub>2</sub>, =O, CO<sub>2</sub>H, C<sub>1-6</sub> alkyl (optionally substituted with F and Cl), OH, OCH<sub>3</sub>, OCF<sub>3</sub>,  $-(CH_2)_n$ -C<sub>3-6</sub> cycloalkyl,  $-(CH_2)_n$ -C<sub>4-6</sub> heterocyclyl,  $-(CH_2)_n$ -aryl,  $-(CH_2)_n$ -heteroaryl, and  $-(CH_2)_nOC_{1-4} alkyl; and$
- $n$ , at each occurrence, is independently selected from zero, 1, 2, 3, and 4.







$R^8$ , at each occurrence, is independently selected from H, F, Cl, Br,  $-\text{OCH}_3$ ,  $-\text{OCF}_3$ ,  $=\text{O}$ , CN,  $\text{CH}_3$ ,  $\text{CF}_3$ ,  $-(\text{CH}_2)_n\text{-aryl}$ ,  $-(\text{CH}_2)_n\text{-C}_{3-6}$  cycloalkyl substituted with 0-3  $R^e$ , and  $-(\text{CH}_2)_n\text{-heterocyclyl}$  substituted with 0-3  $R^e$ ;

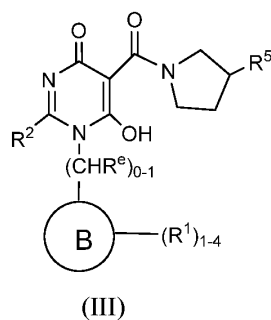
$R^{8a}$ , at each occurrence, is independently selected from H,  $\text{CH}_3$ , aryl substituted with 0-3  $R^e$ , and heterocyclyl substituted with 0-3  $R^e$ ;

$R^a$ , at each occurrence, is independently selected from H,  $\text{C}_{1-6}$  alkyl substituted with 0-5  $R^e$ ,  $-(\text{CH}_2)_n\text{-C}_{3-10}\text{carbocyclyl}$  substituted with 0-5  $R^e$ , and  $-(\text{CH}_2)_n\text{-heterocyclyl}$  substituted with 0-5  $R^e$ ;

$R^e$ , at each occurrence, is independently selected from F, Cl, Br, CN,  $\text{NO}_2$ ,  $=\text{O}$ ,  $\text{CO}_2\text{H}$ ,  $\text{C}_{1-6}$  alkyl (optionally substituted with F and Cl), OH,  $\text{OCH}_3$ ,  $\text{OCF}_3$ ,  $-(\text{CH}_2)_n\text{-C}_{3-6}$  cycloalkyl,  $-(\text{CH}_2)_n\text{-C}_{4-6}$  heterocyclyl,  $-(\text{CH}_2)_n\text{-aryl}$ ,  $-(\text{CH}_2)_n\text{-heteroaryl}$ , and  $-(\text{CH}_2)_n\text{OC}_{1-4}\text{alkyl}$ ; and

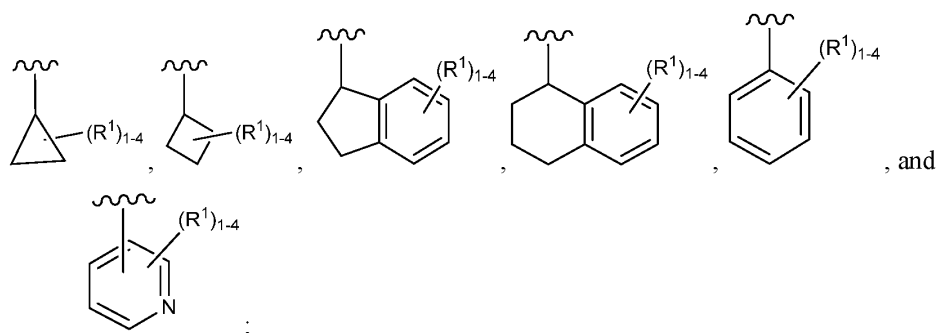
$n$ , at each occurrence, is independently selected from zero, 1, 2, and 3.

5. A compound according to claim 4, having Formula (III):



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

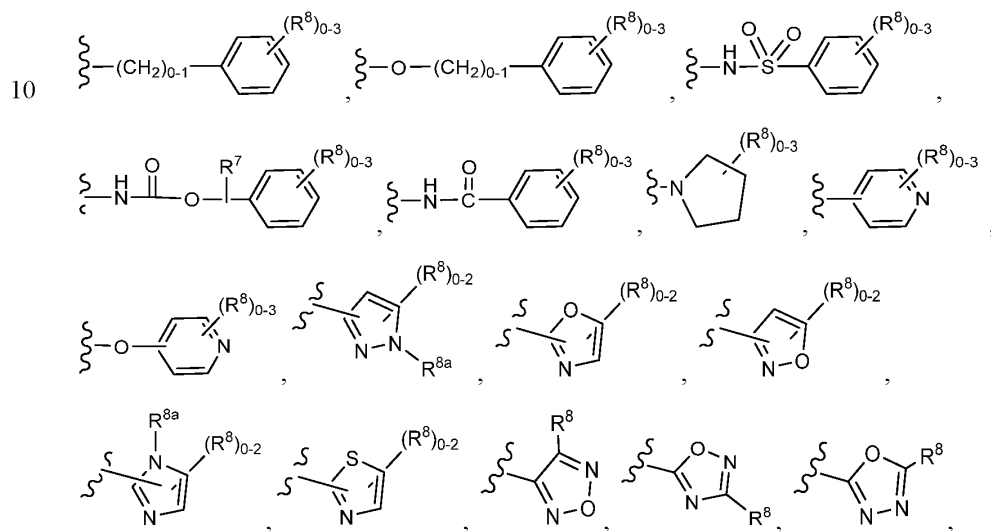
ring B is independently selected from

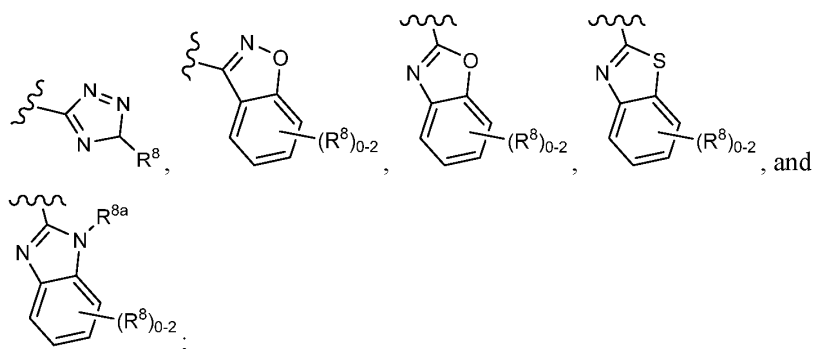


R<sup>1</sup>, at each occurrence, is independently selected from H, F, Cl, OH, CN, C<sub>1-4</sub> alkyl, and OC<sub>1-4</sub> alkyl;

R<sup>2</sup> is independently selected from C<sub>1-5</sub> alkyl substituted with 0-3 R<sup>e</sup>; C<sub>2-5</sub> alkenyl, phenyl substituted with 0-3 R<sup>e</sup>, 5- to 6-membered heteroaryl substituted with 0-3 R<sup>e</sup>, C<sub>3-6</sub> cycloalkyl, and CH<sub>2</sub>O(CH<sub>2</sub>)<sub>1-3</sub>CH<sub>3</sub>;

$R^5$  is independently at each occurrence, selected from OH,





$R^8$ , at each occurrence, is independently selected from H, F, Cl, Br,  $-\text{OCH}_3$ ,  $-\text{OCF}_3$ ,  $=\text{O}$ , CN,  $\text{CH}_3$ ,  $\text{CF}_3$ ,  $-\text{C}(=\text{O})\text{NH}_2$ ,  $-(\text{CH}_2)_n$ -aryl substituted with 0-3  $R^e$ ,  $-(\text{CH}_2)_n$ -C<sub>3-6</sub> cycloalkyl substituted with 0-3  $R^e$ , and  $-(\text{CH}_2)_n$ -heterocyclyl substituted with 0-3  $R^e$ ;

$R^{8a}$ , at each occurrence, is independently selected from H,  $\text{CH}_3$ , aryl substituted with 0-3  $R^e$ , and heterocyclyl substituted with 0-3  $R^e$ ;

$R^a$ , at each occurrence, is independently selected from H, C<sub>1-6</sub> alkyl substituted with 0-5  $R^e$ ,  $-(\text{CH}_2)_n$ -C<sub>3-10</sub>carbocyclyl substituted with 0-5  $R^e$ , and  $-(\text{CH}_2)_n$ -heterocyclyl substituted with 0-5  $R^e$ ;

$R^e$ , at each occurrence, is independently selected from F, Cl, Br, CN,  $\text{NO}_2$ ,  $=\text{O}$ ,  $\text{CO}_2\text{H}$ , C<sub>1-6</sub> alkyl (optionally substituted with F and Cl),  $-\text{OH}$ ,  $-\text{OCH}_3$ ,  $-\text{OCF}_3$ ,  $-(\text{CH}_2)_n$ -C<sub>3-6</sub> cycloalkyl,  $-(\text{CH}_2)_n$ -C<sub>4-6</sub> heterocyclyl,  $-(\text{CH}_2)_n$ -aryl,  $-(\text{CH}_2)_n$ -heteroaryl, and  $-(\text{CH}_2)_n\text{OC}_{1-4}\text{alkyl}$ ; and

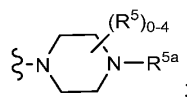
$n$ , at each occurrence, is independently selected from zero, 1, 2, and 3.

6. A compound according to claim 3, or a stereoisomer, an enantiomer, a diastereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof, wherein:

$R^1$ , at each occurrence, is independently selected from F, Cl,  $-\text{OH}$ ,  $-\text{CH}_2\text{CH}_3$ ,  $-\text{OCH}_3$ , and  $-\text{OCD}_3$ ;

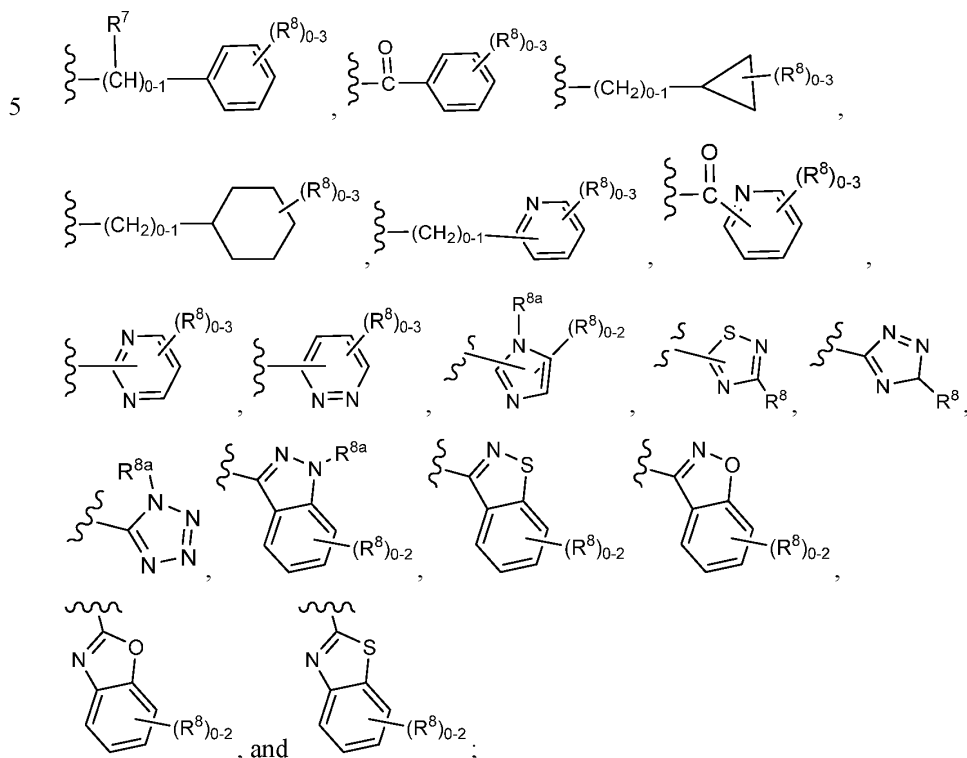
$R^2$  is independently selected from C<sub>1-5</sub> alkyl substituted with 0-3  $R^e$ , C<sub>2-5</sub> alkenyl, phenyl substituted with 0-3  $R^e$ , 5- to 6-membered heteroaryl substituted with 0-3  $R^e$ , C<sub>3-6</sub> cycloalkyl, and  $-\text{CH}_2\text{O}(\text{CH}_2)_{1-3}\text{CH}_3$ ;

$R^3$  and  $R^4$  together with the nitrogen atom to which they are both attached form



R<sup>5</sup>, at each occurrence, is independently at each occurrence, selected from -OH, F, and Cl;

$R^{5a}$ , at each occurrence, is independently selected from



- 10 R<sup>8</sup>, at each occurrence, is independently selected from H, F, Cl, Br, -OCH<sub>3</sub>, -O(CH<sub>2</sub>)<sub>1-3</sub>OCH<sub>3</sub>, -OCF<sub>3</sub>, =O, CN, CH<sub>3</sub>, CF<sub>3</sub>, -(CH<sub>2</sub>)<sub>n</sub>-aryl, -(CH<sub>2</sub>)<sub>n</sub>-C<sub>3-6</sub> cycloalkyl substituted with 0-3 R<sup>e</sup>, and -(CH<sub>2</sub>)<sub>n</sub>-heterocyclyl substituted with 0-3 R<sup>e</sup>;  
R<sup>8a</sup>, at each occurrence, is independently selected from H, CH<sub>3</sub>, aryl substituted with 0-3 R<sup>e</sup>, and heterocyclyl substituted with 0-3 R<sup>e</sup>;  
15 R<sup>a</sup>, at each occurrence, is independently selected from H, C<sub>1-6</sub> alkyl substituted with 0-5 R<sup>e</sup>, -(CH<sub>2</sub>)<sub>n</sub>-C<sub>3-10</sub>carbocyclyl substituted with 0-5 R<sup>e</sup>, and -(CH<sub>2</sub>)<sub>n</sub>-heterocyclyl substituted with 0-5 R<sup>e</sup>;  
R<sup>b</sup>, at each occurrence, is independently selected from H, C<sub>1-6</sub> alkyl substituted with 0-5 R<sup>e</sup>, C<sub>2-6</sub> alkenyl substituted with 0-5 R<sup>e</sup>, C<sub>2-6</sub> alkynyl substituted with 0-5 R<sup>e</sup>, -

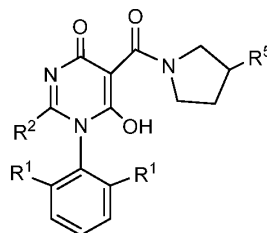
$(\text{CH}_2)_n\text{-C}_{3-10}\text{carbocyclyl}$  substituted with 0-5  $\text{R}^e$ , and  $(\text{CH}_2)_n\text{-heterocyclyl}$  substituted with 0-5  $\text{R}^e$ ;

- $\text{R}^e$ , at each occurrence, is independently selected from F, Cl, Br, CN,  $\text{NO}_2$ ,  $=\text{O}$ ,  $\text{CO}_2\text{H}$ ,  $\text{C}_{1-6}$  alkyl (optionally substituted with F and Cl), OH,  $\text{OCH}_3$ ,  $\text{OCF}_3$ ,  $(\text{CH}_2)_n\text{-C}_{3-6}$  cycloalkyl,  $(\text{CH}_2)_n\text{-C}_{4-6}$  heterocyclyl,  $(\text{CH}_2)_n\text{-aryl}$ , and  $(\text{CH}_2)_n\text{-heteroaryl}$ ; and  
 5  $n$ , at each occurrence, is independently selected from zero, 1, 2, and 3.

7. A compound according to claim 1, or a stereoisomer, an enantiomer, a diastereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof, wherein:
- 10  $\text{R}^1$ , at each occurrence, is independently selected from  $-\text{CH}_2\text{OH}$ ,  $-\text{OCH}_3$ ,  $-\text{OCH}_3$ ,  $-\text{OCF}_3$ ,  $\text{OCH}_2\text{Ph}$ ,  $-\text{C}(=\text{O})\text{NR}^a\text{R}^a$ ,  $-\text{NR}^a\text{R}^a$ ,  $\text{CH}_3$ ,  $\text{CH}_2\text{CH}_3$ ,  $\text{CH}(\text{CH}_3)_2$ , and cyclopropyl;
- $\text{R}^2$  is independently selected from  $\text{C}_{1-4}$  alkyl substituted with 0-3  $\text{R}^e$ ;  $\text{C}_{2-4}$  alkenyl, phenyl substituted with 0-3  $\text{R}^e$ , 5- to 6-membered heteroaryl substituted with 0-3  $\text{R}^e$ ,  $\text{C}_{3-6}$  cycloalkyl, and  $\text{CH}_2\text{O}(\text{CH}_2)_{1-3}\text{CH}_3$ ;
- 15  $\text{R}^3$  is independently selected from H and  $\text{C}_{1-4}$  alkyl;
- $\text{R}^4$  is independently selected from  $-(\text{CHR}^7)_{1-4}\text{-R}^6$ ,  $-(\text{CH}_2)_{1-3}\text{OR}^6$ ,  $-(\text{CH}_2)_{1-3}\text{NHR}^6$ , and  $-(\text{CH}_2)_{0-3}\text{NHC}(=\text{O})\text{R}^6$ ;
- $\text{R}^6$ , at each occurrence, is independently selected from  $-(\text{CR}^7\text{R}^7)_n\text{-aryl}$ ,  $-(\text{CR}^7\text{R}^7)_n\text{-C}_{3-6}$  cycloalkyl, and  $-(\text{CR}^7\text{R}^7)_n\text{-heteroaryl}$ , each substituted with 0-3  $\text{R}^8$ ;
- 20  $\text{R}^7$ , at each occurrence, is independently selected from H,  $\text{C}_{1-4}$  alkyl, and aryl;
- $\text{R}^8$ , at each occurrence, is independently selected from H, F, Cl,  $-\text{OR}^b$ ,  $-\text{NR}^a\text{R}^a$ ,  $\text{C}_{1-4}$  alkyl substituted with 0-3  $\text{R}^e$ , phenyl substituted with 0-3  $\text{R}^e$ , and heterocyclyl substituted with 0-3  $\text{R}^e$ ;
- $\text{R}^a$ , at each occurrence, is independently selected from H,  $\text{C}_{1-6}$  alkyl substituted with 0-5  $\text{R}^e$ ,  $(\text{CH}_2)_n\text{-phenyl}$  substituted with 0-5  $\text{R}^e$ , and  $(\text{CH}_2)_n\text{-heteroaryl}$  substituted with 0-5  $\text{R}^e$ ;
- 25  $\text{R}^b$ , at each occurrence, is independently selected from H,  $\text{C}_{1-6}$  alkyl substituted with 0-5  $\text{R}^e$ ,  $(\text{CH}_2)_n\text{-C}_{3-10}\text{carbocyclyl}$  substituted with 0-5  $\text{R}^e$ , and  $(\text{CH}_2)_n\text{-heterocyclyl}$  substituted with 0-5  $\text{R}^e$ ;
- 30  $\text{R}^e$ , at each occurrence, is independently selected from F, Cl, Br, CN,  $\text{NO}_2$ ,  $=\text{O}$ ,  $\text{CO}_2\text{H}$ ,  $\text{C}_{1-6}$  alkyl (optionally substituted with F and Cl), OH,  $\text{OCH}_3$ ,  $\text{OCF}_3$ ,  $(\text{CH}_2)_n\text{-C}_{3-6}$  cycloalkyl,  $(\text{CH}_2)_n\text{-C}_{4-6}$  heterocyclyl,  $(\text{CH}_2)_n\text{-aryl}$ ,  $(\text{CH}_2)_n\text{-heteroaryl}$ ; and

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

8. A compound according to claim 5, having Formula (IV):



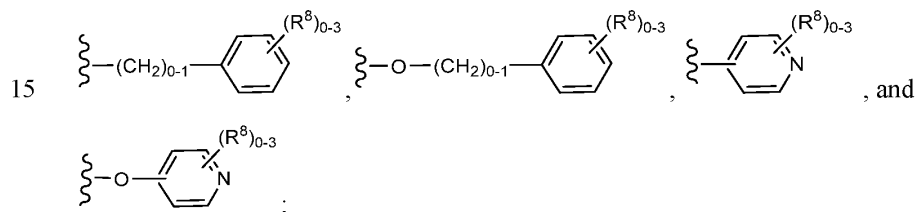
(IV)

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

R<sup>1</sup>, at each occurrence, is independently selected from F, Cl, OH, C<sub>1-4</sub> alkyl, and OC<sub>1-4</sub> alkyl;

10 R<sup>2</sup> is independently selected from -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CF<sub>3</sub>, -CH<sub>2</sub>-cyclopropyl, -CH<sub>2</sub>CH<sub>2</sub>-cyclopropyl, cyclobutyl, cyclopentyl, -CH<sub>2</sub>O(CH<sub>2</sub>)<sub>1-3</sub>CH<sub>3</sub>, -CH<sub>2</sub>OCH(CH<sub>3</sub>)<sub>2</sub>, phenyl substituted with 0-2 R<sup>e</sup>, and 5- to 6-membered heteroaryl substituted with 0-2 R<sup>e</sup>;

R<sup>5</sup>, at each occurrence, is independently selected from



R<sup>8</sup>, at each occurrence, is independently selected from F, Cl, Br, -OCH<sub>3</sub>, -OCF<sub>3</sub>, =O, CN, CH<sub>3</sub>, CF<sub>3</sub>, -C(=O)NH<sub>2</sub>, -(CH<sub>2</sub>)<sub>n</sub>-aryl substituted with 0-3 R<sup>e</sup>, -(CH<sub>2</sub>)<sub>n</sub>-C<sub>3-6</sub> cycloalkyl substituted with 0-3 R<sup>e</sup>, and -(CH<sub>2</sub>)<sub>n</sub>-heterocyclyl substituted with 0-3 R<sup>e</sup>;

20 R<sup>e</sup>, at each occurrence, is independently selected from F, Cl, Br, CN, NO<sub>2</sub>, =O, CO<sub>2</sub>H, C<sub>1-6</sub> alkyl (optionally substituted with F and Cl), OH, OCH<sub>3</sub>, OCF<sub>3</sub>, -(CH<sub>2</sub>)<sub>n</sub>-C<sub>3-6</sub> cycloalkyl, -(CH<sub>2</sub>)<sub>n</sub>-C<sub>4-6</sub> heterocyclyl, -(CH<sub>2</sub>)<sub>n</sub>-aryl, and -(CH<sub>2</sub>)<sub>n</sub>-heteroaryl; and

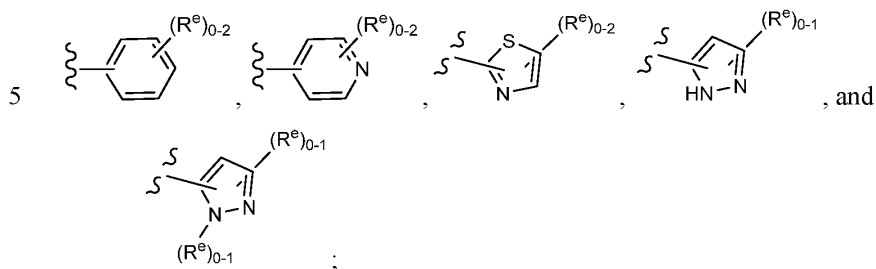
n is independently selected from zero, 1, 2, 3, and 4.

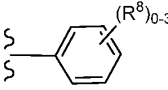
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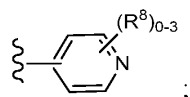
9. A compound according to claim 8, or a stereoisomer, an enantiomer, a diastereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof, wherein:

$R^1$  is both  $CH_2CH_3$  or both  $OCH_3$ ;

$R^2$  is independently selected from



$R^5$  is independently at each occurrence, selected from  and

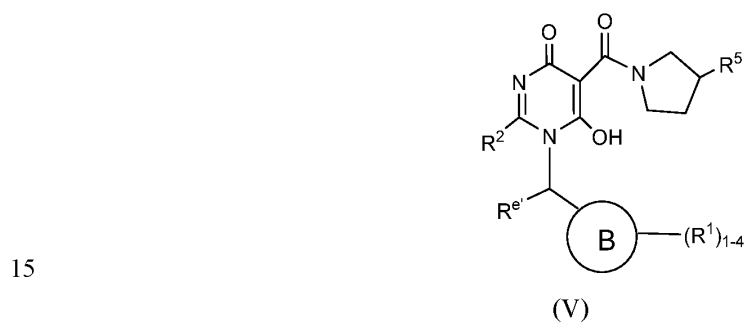


$R^8$ , at each occurrence, is independently selected from F, Cl, Br,  $-OCH_3$ ,  $-OCF_3$ , CN,

10  $CH_3$ , and  $CF_3$ ; and

$R^e$ , at each occurrence, is independently selected from F, Cl, Br,  $C_{1-3}$  alkyl, and cyclopropyl.

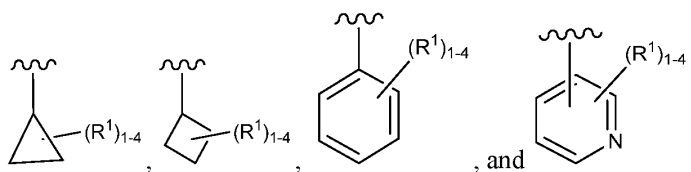
10. A compound according to claim 5, having Formula (V):



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

ring B is independently selected from





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

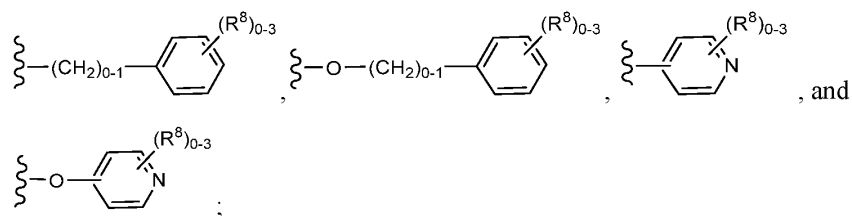
$R^2$  is independently selected from  $-CH_2CH_2CH_2CH_3$ ,  $-CH_2CH_2CH(CH_3)_2$ ,

$CH_2CH_2CH_2CF_3$ ,  $-CH_2$ -cyclopropyl,  $-CH_2CH_2$ -cyclopropyl, cyclobutyl,

5 cyclopentyl,  $CH_2O(CH_2)_{1-3}CH_3$ , and  $CH_2OCH(CH_3)_2$ , phenyl substituted with 0-2

$R^e$ , and 5- to 6-membered heteroaryl substituted with 0-2  $R^e$ ;

$R^5$ , at each occurrence, is independently selected from



10  $R^8$ , at each occurrence, is independently selected from F, Cl, Br,  $-OCH_3$ ,  $-OCF_3$ ,  $=O$ , CN,

$CH_3$ ,  $CF_3$ ,  $-C(=O)NH_2$ ,  $-(CH_2)_n$ -aryl substituted with 0-3  $R^e$ ,  $-(CH_2)_n$ - $C_{3-6}$

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

$R^e$ , at each occurrence, is independently selected from F, Cl, Br, CN,  $NO_2$ ,  $=O$ ,  $CO_2H$ ,  $C_{1-6}$

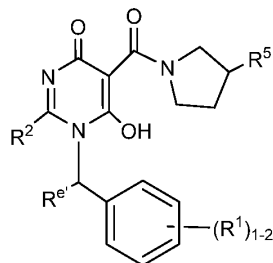
15  $alkyl$  (optionally substituted with F and Cl), OH,  $OCH_3$ ,  $OCF_3$ ,  $-(CH_2)_n$ - $C_{3-6}$

cycloalkyl,  $-(CH_2)_n$ - $C_{4-6}$  heterocyclyl,  $-(CH_2)_n$ -aryl, and  $-(CH_2)_n$ -heteroaryl;

$R^{e'}$  is independently selected from  $C_{1-2}$  alkyl,  $-CH_2OC_{1-2}$  alkyl, and cyclopropyl; and

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

20 11. A compound according to claim 10, having Formula (VI):

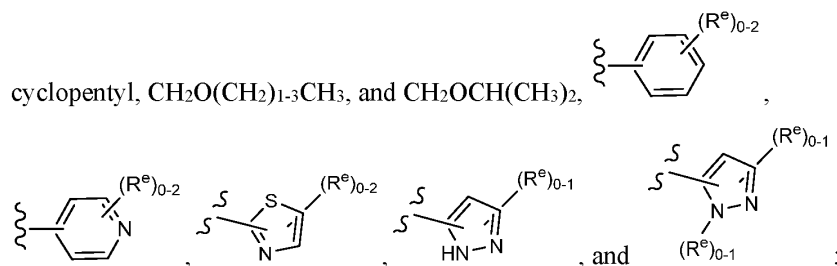


(VI)

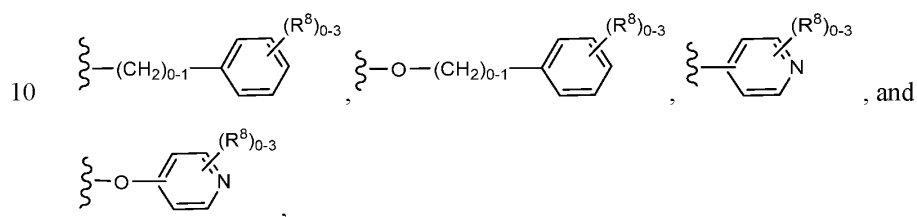
or a stereoisomer, an enantiomer, a diastereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof, wherein:

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

- 5  $R^2$  is independently selected from  $-CH_2CH_2CH_2CH_3$ ,  $-CH_2CH_2CH(CH_3)_2$ ,  $-CH_2CH_2CH_2CF_3$ ,  $-CH_2$ -cyclopropyl,  $-CH_2CH_2$ -cyclopropyl, cyclobutyl,



$R^5$ , at each occurrence, is independently selected from



$R^8$ , at each occurrence, is independently selected from F, Cl, Br,  $-OCH_3$ ,  $-OCF_3$ ,  $=O$ , CN,

$CH_3$ ,  $CF_3$ ,  $-C(=O)NH_2$ ,  $-(CH_2)_n$ -aryl substituted with 0-3  $R^e$ ,  $-(CH_2)_n$ - $C_{3-6}$

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

- 15  $R^e$ ;

$R^e$ , at each occurrence, is independently selected from F, Cl, Br, CN,  $NO_2$ ,  $=O$ ,  $-CO_2H$ ,

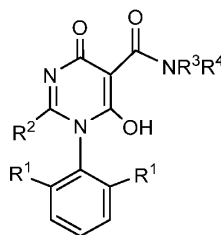
$C_{1-6}$  alkyl (optionally substituted with F and Cl),  $-OH$ ,  $-OCH_3$ ,  $-OCF_3$ ,  $-(CH_2)_n$ - $C_{3-6}$

cycloalkyl,  $-(CH_2)_n$ - $C_{4-6}$  heterocyclyl,  $-(CH_2)_n$ -aryl, and  $-(CH_2)_n$ -heteroaryl;

$R^e$  is independently selected from  $C_{1-2}$  alkyl,  $-CH_2OC_{1-2}$  alkyl, and cyclopropyl; and

- 20 n is independently selected from zero, 1, 2, 3, and 4.

12. A compound according to claim 3, having Formula (VII):



(VII)

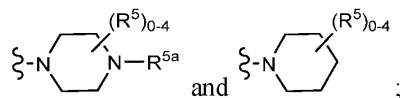
or a stereoisomer, an enantiomer, a diastereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof, wherein:

5  $R^1$ , at each occurrence, is independently selected from F, Cl, -OH, C<sub>1-2</sub> alkyl, and -OC<sub>1-2</sub> alkyl;

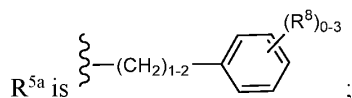
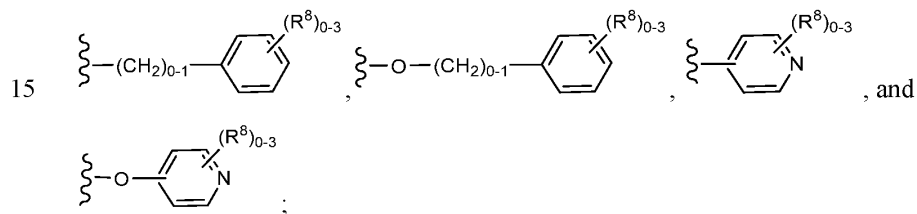
$R^2$  is independently selected from -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CF<sub>3</sub>, -CH<sub>2</sub>-cyclopropyl, -CH<sub>2</sub>CH<sub>2</sub>-cyclopropyl, cyclobutyl, cyclopentyl, -CH<sub>2</sub>O(CH<sub>2</sub>)<sub>1-3</sub>CH<sub>3</sub>, -CH<sub>2</sub>OCH(CH<sub>3</sub>)<sub>2</sub>, phenyl substituted with 0-2

10  $R^e$ , and 5- to 6-membered heteroaryl substituted with 0-2  $R^e$ ;

$R^3$  and  $R^4$  together with the nitrogen atom to which they are both attached form a heterocyclic ring selected from



$R^5$  is independently at each occurrence, selected from



$R^8$ , at each occurrence, is independently selected from F, Cl, Br, -OCH<sub>3</sub>, -OCF<sub>3</sub>, CN,

CH<sub>3</sub>, CF<sub>3</sub>, -C(=O)NH<sub>2</sub>, -(CH<sub>2</sub>)<sub>n</sub>-aryl substituted with 0-3  $R^e$ , -(CH<sub>2</sub>)<sub>n</sub>-C<sub>3-6</sub>

20 cycloalkyl substituted with 0-3  $R^e$ , and -(CH<sub>2</sub>)<sub>n</sub>-heterocyclyl substituted with 0-3  $R^e$ ;

R<sup>e</sup>, at each occurrence, is independently selected from F, Cl, Br, CN, NO<sub>2</sub>, =O, CO<sub>2</sub>H, C<sub>1-6</sub> alkyl (optionally substituted with F and Cl), -OH, -OCH<sub>3</sub>, -OCF<sub>3</sub>, -(CH<sub>2</sub>)<sub>n</sub>-C<sub>3-6</sub> cycloalkyl, -(CH<sub>2</sub>)<sub>n</sub>-C<sub>4-6</sub> heterocyclyl, -(CH<sub>2</sub>)<sub>n</sub>-aryl, and -(CH<sub>2</sub>)<sub>n</sub>-heteroaryl; and n is independently selected from zero, 1, 2, 3, and 4.

5

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

10

14. A pharmaceutical composition, comprising a pharmaceutically acceptable carrier and a compound of any one of claims 1-12, or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt thereof.

15

15. The compounds according to anyone of claims 1-12 or composition according to claim 13 for use in therapy.

20

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

25

17. The method of claim 16 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.