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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 February 2022 (17.02.2022)

WIPO | PCT

(10) International Publication Number
WO 2022/035923 A1

(51) International Patent Classification:

C07D 401/04 (2006.01)	*A61P 29/00* (2006.01)
C07D 401/14 (2006.01)	*A61P 37/00* (2006.01)
C07D 403/04 (2006.01)	*A61K 31/5377* (2006.01)
C07D 405/14 (2006.01)	*A61K 31/4439* (2006.01)
C07D 487/08 (2006.01)	*A61K 31/496* (2006.01)
C07D 487/04 (2006.01)	

(21) International Application Number:
PCT/US2021/045474

(22) International Filing Date:
11 August 2021 (11.08.2021)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/064,640 12 August 2020 (12.08.2020) US

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

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

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

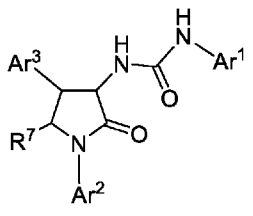
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

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

(54) Title: OXOPYRROLIDINE UREA FPR2 AGONISTS

(57) Abstract: The disclosure relates to compounds of Formula (I), which are formyl peptide 2 (FPR2) receptor agonists and/or formyl peptide 1 (FPR1) receptor agonists. The disclosure also provides compositions and methods of using the compounds, for example, for the treatment of atherosclerosis, heart failure, chronic obstructive pulmonary disease (COPD), and related diseases. (I)



(I)

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OXOPYRROLIDINE UREA FPR2 AGONISTS

CROSS REFERENCE TO RELATED APPLICATIONS

This application is entitled to priority pursuant to 35 U.S.C. §119(e) to U.S. provisional patent application Nos. 63/064,640, filed August 12, 2020, which is incorporated herein in its entirety.

BACKGROUND OF THE INVENTION

The present invention relates to novel oxopyrrolidine urea compounds, which are formyl peptide 2 (FPR2) receptor agonists and/or formyl peptide 1 (FPR1) receptor agonists, compositions containing them, and methods of using them, for example, for the treatment of atherosclerosis, heart failure, chronic obstructive pulmonary disease (COPD), and related diseases.

Formyl peptide receptor 2 (FPR2) belongs to a small group of seven-transmembrane domain, G protein-coupled receptors that are expressed in multiple human tissues including immune cells and are known to be important in host defense and inflammation. FPR2 shares significant sequence homology with FPR1 and FPR3 (Journal of Autoimmunity 85, 2017, 64-77). Collectively, these receptors bind a number of structurally diverse agonists, including N-formyl and nonformyl peptides which act as chemo attractants and activate phagocytes. The endogenous peptide Annexin A1 and its N-terminal fragments are examples of ligands that bind human FPR1 and FPR2. Fatty acids such as eicosanoid, lipoxin A4, which belongs to a class of small pro-resolution mediators (SPMs), has also been identified as an agonist for FPR2 (Ye RD., et al., Pharmacol. Rev., 2009, 61, 119-61).

Endogenous FPR2 pro-resolution ligands, such as lipoxin A_4 and Annexin A1, have been reported to trigger a wide array of cytoplasmatic cascades such as Gi coupling, Ca^{2+} mobilization and β-arrestin recruitment. (Int J Mol Sci. 2013 April; 14(4): 7193–7230). FPR2 regulates both innate and adaptive immune systems including neutrophils, macrophages, T-, and B-cells. In neutrophils, FPR2 ligands modulate movement, cytotoxicity and life span. In macrophages, agonism of FPR2 prevents apoptosis and enhances efferocytosis. (Chandrasekharan JA, Sharma-Walia N,. J. Inflamm. Res., 2015, 8, 181-92). The initiation of resolution of inflammation by FPR2 agonism is responsible

for enhancing anti-fibrotic wound healing and returning of the injured tissue to homeostasis (Romano M., et al., Eur. J. Pharmacol., 2015, 5, 49-63).

Chronic inflammation is part of the pathway of pathogenesis of many human diseases and stimulation of resolution pathways with FPR2 agonists may have both protective and reparative effects. Ischaemia-reperfusion (I/R) injury is a common feature of several diseases associated with high morbidity and mortality, such as myocardial infarction and stroke. Non-productive wound healing associated with cardiomyocyte death and pathological remodeling resulting from ischemia-reperfusion injury leads to scar formation, fibrosis, and progressive loss of heart function. FPR2 modulation is proposed to enhance myocardial wound healing post injury and diminish adverse myocardial remodeling (Kain V., et al., J. Mol. Cell. Cardiol., 2015, 84, 24-35). In addition, FPR2 pro-resolution agonists, in the central nervous system, may be useful therapeutics for the treatment of a variety of clinical I/R conditions, including stroke in brain (Gavins FN., Trends Pharmacol. Sci., 2010, 31, 266-76) and I/R induced spinal cord injury (Liu ZQ., et al., Int. J. Clin. Exp. Med., 2015, 8, 12826-33).

In addition to beneficial effects of targeting the FPR2 receptor with novel pro-resolution agonists for treatment of I/R induced injury therapeutic, utility of these ligands can also be applied to other diseases. In the cardiovascular system both the FPR2 receptor and its pro-resolution agonists were found to be responsible for atherogenic-plaque stabilization and healing (Petri MH., et al., Cardiovasc. Res., 2015, 105, 65-74; and Fredman G., et al., Sci. Trans. Med., 2015, 7(275);275ra20). FPR2 agonists also have been shown to be beneficial in preclinical models of chronic inflammatory human diseases, including: infectious diseases, psoriasis, dermatitis, inflammatory bowel syndrome, Crohn's disease, occular inflammation, sepsis, pain, metabolic/diabetes diseases, cancer, COPD, asthma and allergic diseases, cystic fibrosis, acute lung injury and fibrosis, rheumatoid arthritis and other joint diseases, Alzheimer's disease, kidney fibrosis, and organ transplantation (Romano M., et al., Eur. J. Pharmacol., 2015, 5, 49-63, Perrett, M., et al., Trends in Pharm. Sci., 2015, 36, 737-755).

SUMMARY OF THE INVENTION

The present invention provides novel oxopyrrolidine urea compounds, and their analogues thereof, which are useful as FPR2 agonists, including stereoisomers, tautomers, pharmaceutically acceptable salts, or solvates thereof.

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

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

The compounds of the invention may be used in the treatment and/or prophylaxis of multiple diseases or disorders associated with FPR2, such as inflammatory diseases, heart diseases, chronic airway diseases, cancers, septicemia, allergic symptoms, HIV retrovirus infection, circulatory disorders, neuroinflammation, nervous disorders, pains, prion diseases, amyloidosis, and immune disorders. The heart diseases are selected from the group consisting of angina pectoris, unstable angina, myocardial infarction, acute coronary disease, cardiac iatrogenic damage, and heart failure including, but not limited to, acute heart failure, chronic heart failure of ischemic and non-ischemic origin, systolic heart failure, diastolic heart failure, heart failure with reduced ejection fraction (HF_REF), and heart failure with preserved ejection fraction (HF_PEF).

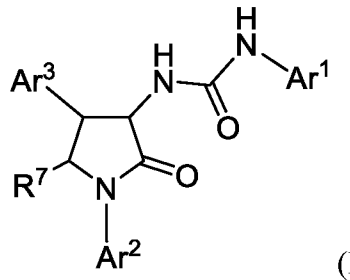
The compounds of the invention can be used alone, in combination with other compounds of the present invention, or in combination with one or more other agent(s).

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

DESCRIPTION OF THE INVENTION

The invention encompasses compounds of Formula (I), which are formyl peptide 2 (FPR2) receptor agonists and/or formyl peptide 1 (FPR1) receptor agonists, compositions containing them, and methods of using them, for example, in the treatment of atherosclerosis, heart failure, chronic obstructive pulmonary disease (COPD), and related diseases.

One aspect of the invention is a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

Ar^1 is cycloalkyl, cycloalkylalkyl, aryl or heterocycloalkyl, each substituted with 0-3 R^1;

Ar^2 is C_{3-6} cycloalkyl, aryl, or a 5- to 12-membered heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, $S(O)_p$, N, and NR^{2a}, and each substituted with 0-3 R^2;

Ar^3 is phenyl or pyridyl, each substituted with 1 R^{5a}, 1 R^{5b}, and 1 R^{5c};

R^1 is halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, or aryl substituted with 0-2 halo, C_{1-4} haloalkyl, or C_{1-4} alkoxy;

R^2 is oxo, cyano, halo, C_{1-6} alkyl substituted with 0-5 R^e, $-OR^b$, $-NR^3R^4$, $-NR^4C(O)R^b$, $-NR^4(CR^dR^d)_{0-1}C(O)NR^3R^4$, $(C_{1-4}$ alkyl$)_2(O)P-$, C_{3-6} cycloalkyl, aryl, or a 5 to 6-membered heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, $S(O)_p$, N, and NR^a;

R^{2a} is hydrogen, C_{1-4} alkyl substituted with 0-5 R^e, $-(CR^dR^d)_{1-4}-NR^3R^4$, $-(CR^dR^d)_{1-4}-OR^b$, $-(CR^dR^d)_{1-4}-C(O)NR^3R^4$, $-(CR^dR^d)_r-C_{3-6}$ cycloalkyl substituted with 0-5 R^e, $-(CR^dR^d)_r-$aryl substituted with 0-5 R^e, or $-(CR^dR^d)_r-$heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, $S(O)_p$, N, and NR^a and substituted with 0-5 R^e;

R^3 is hydrogen, C_{1-4} alkyl substituted with 0-5 R^e, C_{3-6} cycloalkyl substituted with 0-5 R^e, heteroaryl, or heterocycloalkyl comprising 1-4 heteroatoms selected from O, $S(O)_p$, N, and NR^8 and substituted with 0-5 R^e;

R^4 is hydrogen or C_{1-4} alkyl;

alternatively, R^3 and R^4 together with the nitrogen to which they are both attached form a 4 to 9-membered heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, $S(O)_p$, N, and NR^8 and substituted with 1-3 R^6;

R^{5a} is hydrogen or halo;

R^{5b} is hydrogen or halo;

R^{5c} is halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, or deuteroalkoxy;

R^6 is hydrogen, halo, oxo, hydroxy, or C_{1-4} alkyl substituted with 0-5 R^e;

R^7 is hydrogen or C_{1-4} alkyl;

R^8 is hydrogen, C_{1-4} alkyl, or $-S(O)_pR^c$;

R^a is hydrogen or C_{1-6} alkyl substituted with 0-5 R^e, C_{3-6} cycloalkyl substituted with 0-5 R^e, aryl substituted with 0-5 R^e, or heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, $S(O)_p$, N, NR^d and substituted with 0-5 R^e;

R^b is hydrogen, C_{1-6} alkyl substituted with 0-5 R^e, C_{3-6} cycloalkyl substituted with 0-5 R^e, aryl substituted with 0-5 R^e, or heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, $S(O)_p$, N, NR^d and substituted with 0-5 R^e;

R^c is C_{1-4} alkyl substituted with 0-5 R^e;

R^d is hydrogen or C_{1-4} alkyl substituted with 0-5 R^e;

R^e is halo, cyano, oxo, $-OR^g$,$-NR^gR^g$, $-C(O)NR^gR^g$, $-S(O)_pC_{1-4}$ alkyl, C_{1-6} alkyl substituted with 0-5 R^f, $-(CH_2)_r-C_{3-6}$ cycloalkyl substituted with 0-5 R^f, $-(CH_2)_r-$aryl substituted with 0-5 R^f, or $-(CH_2)_r-$heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, $S(O)_p$, N, and NR^g and substituted with 0-5 R^f;

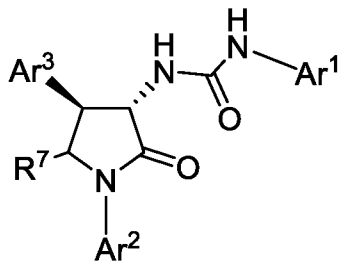
R^f is halo, cyano, hydroxy, C_{1-5} alkyl, C_{3-6} cycloalkyl, or phenyl;

R^g is hydrogen, C_{1-5} alkyl, C_{3-6} cycloalkyl, aryl, or heteroaryl or heterocycloalkyl; or R^g and R^g together with the nitrogen atom to which they are both attached form a heteroaryl or heterocycloalkyl;

p is zero, 1, or 2; and

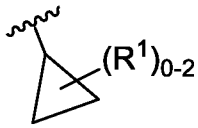
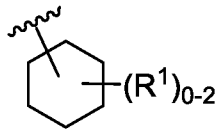
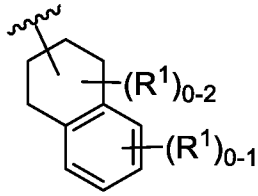
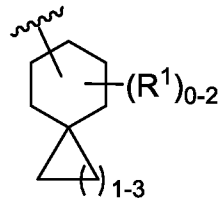
r is zero, 1, 2, 3, or 4.

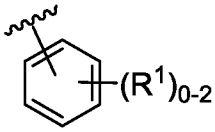
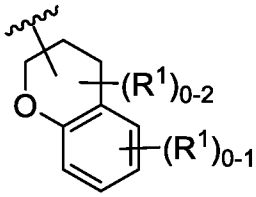
Another aspect of the invention is a compound of Formula (II):



(II)

or a pharmaceutically acceptable salt thereof, wherein:

Ar^1 is  ,  ,  ,  ,

 , or  ;

Ar^2 is C_{3-6} cycloalkyl, phenyl, a 5- to 6-membered heteroaryl or heterocycloalkyl comprising 1-2 N or NR^{2a}, each substituted with 0-2 R^2;

Ar^3 is phenyl substituted with 1 R^{5a}, 1 R^{5b}, and 1 R^{5c};

R^1 is halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, or phenyl substituted with 0-2 halo or C_{1-4} alkoxy;

R^2 is oxo, cyano, halo, C_{1-5} alkyl substituted with 0-5 R^e, $-OR^b$, $-NR^3R^4$, $-NR^4C(O)R^b$, $(C_{1-3}\text{ alkyl})_2(O)P-$, C_{3-6} cycloalkyl, aryl, or a 5- to 6-membered heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^a;

R^{2a} is hydrogen, C_{1-4} alkyl substituted with 0-4 R^e, $-(CHR^d)_{1-3}-C(O)NR^3R^4$, $-(CHR^d)_r-C_{3-6}$ cycloalkyl substituted with 0-4 R^e, $-(CHR^d)_r-$aryl substituted with 0-4 R^e, or $-(CHR^d)_r-$heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^a and substituted with 0-4 R^e;

R^3 is hydrogen, C_{1-4} alkyl substituted with 0-4 R^e, C_{3-6} cycloalkyl, or heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^8 and substituted with 0-4 R^e;

R^4 is hydrogen or C_{1-3} alkyl;

alternatively, R^3 and R^4 together with the nitrogen to which they are both attached form a 4- to 8-membered heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^8 and substituted with 1-3 R^6;

R^{5a} is hydrogen or halo;

R^{5b} is hydrogen or halo;

R^{5c} is halo, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} alkoxy;

R^6 is hydrogen, halo, oxo, hydroxy, or C_{1-4} alkyl substituted with 0-4 R^e;

R^7 is hydrogen or C_{1-3} alkyl;

R^8 is hydrogen, C_{1-3} alkyl, or $-S(O)_pR^c$;

R^a is hydrogen or C_{1-6} alkyl substituted with 0-5 R^e;

R^b is hydrogen, C_{1-6} alkyl substituted with 0-5 R^e, heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, NR^d and substituted with 0-5 R^e;

R^c is C_{1-3} alkyl substituted with 0-5 R^e;

R^d is hydrogen or C_{1-4} alkyl substituted with 0-1 $–OC_{1-4}$ alkyl;

R^e is halo, cyano, oxo, $-OR^g$, $–NR^gR^g$, $-C(O)NR^gR^g$, $-S(O)_pC_{1-4}$ alkyl, C_{1-4} alkyl substituted with 0-5 R^f, $–(CH_2)_r–C_{3-6}$ cycloalkyl substituted with 0-5 R^f, $–(CH_2)_r–$aryl substituted with 0-5 R^f, or $–(CH_2)_r–$heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^g and substituted with 0-5 R^f;

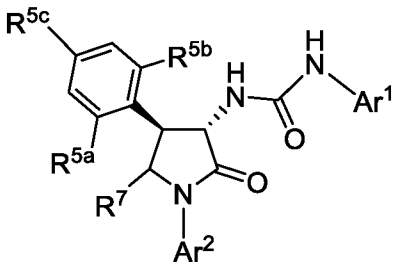
R^f is halo, cyano, hydroxy, C_{1-5} alkyl, or C_{3-6} cycloalkyl;

R^g is hydrogen, C_{1-5} alkyl, heteroaryl or heterocycloalkyl;

n is zero; and

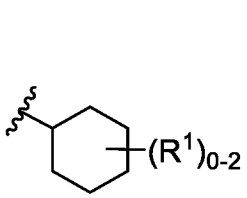
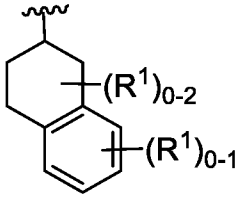
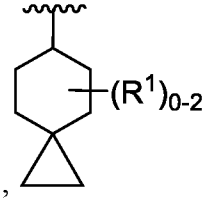
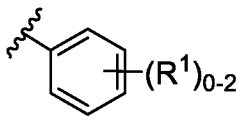
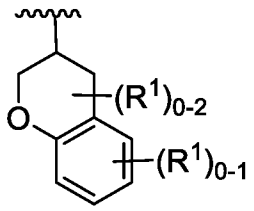
r is zero, 1, 2, or 3.

Another aspect of the invention is a compound of Formula (III):

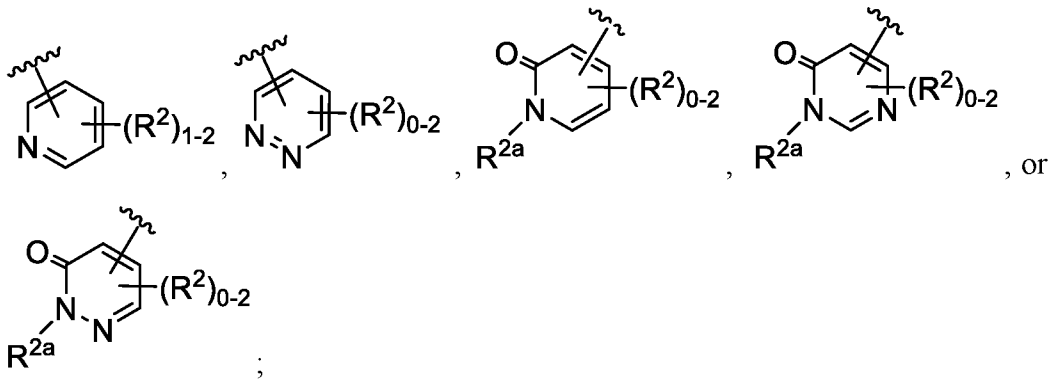


(III)

or a pharmaceutically acceptable salt thereof, wherein:

Ar^1 is  ,  ,  ,  ,  , or ;

Ar^2 is



;

R^1 is halo, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} haloalkyl, or C_{1-3} haloalkoxy;

R^2 is cyano, halo, C_{1-4} alkyl substituted with 0-5 R^e, $-OR^b$, $-NR^3R^4$, $-NR^4C(O)R^b$, $(C_{1-4}$ alkyl$)_2(O)P-$, C_{3-6} cycloalkyl, aryl, or a 5- to 6-membered heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^a;

R^{2a} is hydrogen, C_{1-4} alkyl substituted with 0-3 R^e, $-(CHR^d)_{1-2}$-$C(O)NR^3R^4$, $-(CH_2)_r$-C_{3-6} cycloalkyl substituted with 0-3 R^e, $-(CH_2)_r-$aryl substituted with 0-3 R^e, or $-(CH_2)_r-$heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^a and substituted with 0-3 R^e;

R^3 is hydrogen, C_{1-4} alkyl substituted with 0-3 R^e, C_{3-6} cycloalkyl, or heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^8 and substituted with 0-3 R^e;

R^4 is hydrogen or C_{1-2} alkyl;

alternatively, R^3 and R^4 together with the nitrogen to which they are both attached form a 4- to 8-membered heteroaryl or heterocycloalkyl comprising 1-3 heteroatoms selected from O, S, N, and NR^8 and substituted with 1-3 R^6;

R^{5a} is hydrogen or halo;

R^{5b} is hydrogen or halo;

R^{5c} is halo or C_{1-2} alkoxy;

R^6 is hydrogen, halo, oxo, hydroxy, or C_{1-4} alkyl substituted with 0-3 R^e;

R^7 is hydrogen or CH_3;

R^8 is hydrogen, C_{1-2} alkyl, or $-S(O)_2C_{1-4}$ alkyl;

R^a is hydrogen, C_{1-5} alkyl substituted with 0-4 R^e;

R^b is hydrogen, C_{1-5} alkyl substituted with 0-4 R^e, heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, NR^d and substituted with 0-4 R^e;

R^d is hydrogen or C_{1-3} alkyl substituted with 0-1 $-OC_{1-4}$ alkyl;

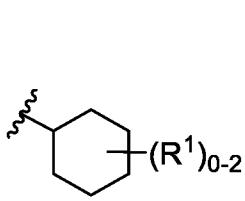
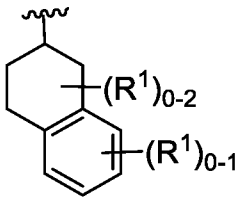
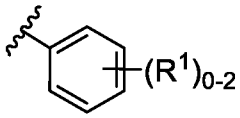
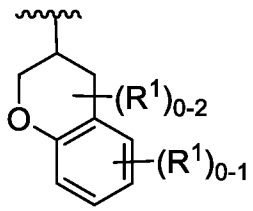
R^e is halo, cyano, oxo, -OR^g, –NR^gR^g, $C(O)NR^gR^g$, -$S(O)_pC_{1-4}$ alkyl, C_{1-4} alkyl substituted with 0-4 R^f, –$(CH_2)_r$–C_{3-6} cycloalkyl substituted with 0-4 R^f, –$(CH_2)_r$–aryl substituted with 0-4 R^f, or –$(CH_2)_r$–heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^g and substituted with 0-4 R^f;

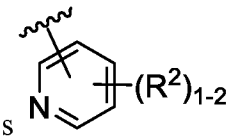
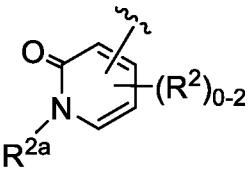
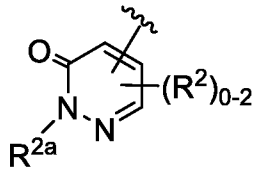
R^f is halo, cyano, hydroxy, or C_{1-5} alkyl;

R^g is hydrogen or C_{1-4} alkyl; and

r is zero, 1, or 2.

Another aspect of the invention is a compound of Formula (III), or a pharmaceutically acceptable salt thereof, wherein:

Ar^1 is  ,  ,  , or  ;

Ar^2 is  ,  , or  ;

R^1 is Cl, -CH_3, -CF_3, -OCH_3, -$OCHF_2$, or -OCF_3;

R^2 is cyano, halo, C_{1-4} alkyl substituted with 0-4 R^e, -OR^b, -NR^3R^4, -$NR^4C(O)R^b$, $(C_{1-2}$ alkyl$)_2(O)P$-, C_{3-6} cycloalkyl, heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^a;

R^{2a} is hydrogen, C_{1-4} alkyl substituted with 0-2 R^e, –$(CHR^d)_{1-2}$-$C(O)NR^3R^4$, –$(CH_2)_r$-C_{3-6} cycloalkyl substituted with 0-2 R^e, –$(CH_2)_r$–aryl substituted with 0-2 R^e, or –$(CH_2)_r$–heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^a and substituted with 0-2 R^e;

R^3 is hydrogen, C_{1-4} alkyl substituted with 0-3 R^e, or heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^8 and substituted with 0-3 R^e;

R^4 is hydrogen or C_{1-2} alkyl;

alternatively, R^3 and R^4 together with the nitrogen to which they are both attached form a 4- to 8-membered heteroaryl or heterocycloalkyl comprising 1-3 heteroatoms selected from O, S, N, and NR^8 and substituted with 1-3 R^6;

R^{5a} is hydrogen, F, or Cl;

R^{5b} is hydrogen, F, or Cl;

R^{5c} is Cl or $-OCH_3$;

R^6 is hydrogen, halo, oxo, hydroxy, or C_{1-3} alkyl substituted with 0-3 R^e;

R^7 is hydrogen or $-CH_3$;

R^8 is hydrogen, C_{1-2} alkyl, or $S(O)_2C_{1-3}$ alkyl;

R^a is hydrogen, C_{1-4} alkyl substituted with 0-3 R^e;

R^b is hydrogen, C_{1-4} alkyl substituted with 0-3 R^e, heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^d and substituted with 0-3 R^e;

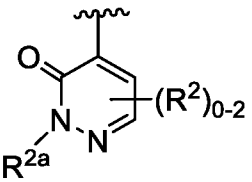
R^d is hydrogen or C_{1-2} alkyl substituted with 0-1 $-OC_{1-4}$ alkyl;

R^e is halo, cyano, oxo, $-OR^g$, $-NR^gR^g$, $-C(O)NR^gR^g$, $-S(O)_2C_{1-4}$ alkyl, C_{1-6} alkyl substituted with 0-3 R^f, C_{3-6} cycloalkyl substituted with 0-3 R^f, or heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^g and substituted with 0-3 R^f;

R^f is halo, cyano, hydroxy, or C_{1-4} alkyl; and

R^g is hydrogen or C_{1-3} alkyl.

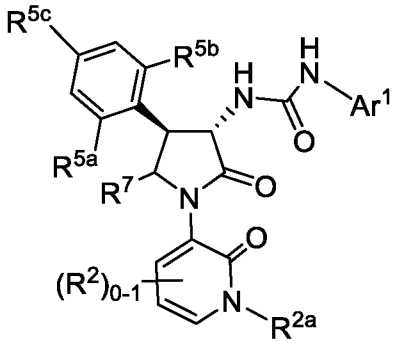
Another aspect of the invention is a compound of Formulae (I)-(III), or a pharmaceutically acceptable salt thereof, wherein:

Ar^2 is  ;

R^2 is F, Cl, CH_2OH, CH_3, CF_3, or CHF_2; and

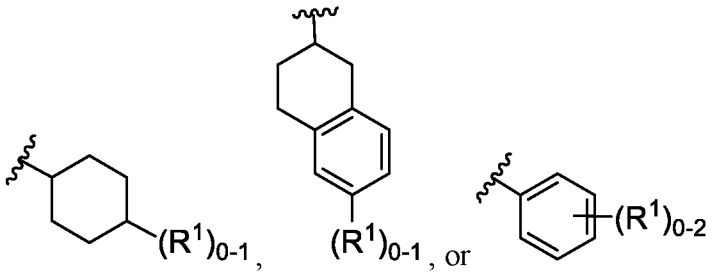
R^{2a} is $-CH_3$, $-CH_2CH_3$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CH_2CH_2OCH_3$, $-CH_2CH(OH)CF_3$, $-CH_2CH(OH)CH_3$, $-CH_2CH_2OH$, $-CH_2CH(CH_3)OH$, $-CH_2CH(CF_3)OH$, $-CH_2CH_2CF_3$, $-CH(CH_2OH)CH_2OCH_3$, $-CH(CH_2NH_2)OCH_3$, $-CH_2CH(CH_3)OCH_3$, or $-CH_2CH(CF_3)OCH_3$.

Another aspect of the invention is a compound of Formula (IV):



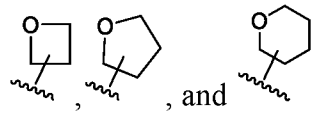
(IV)

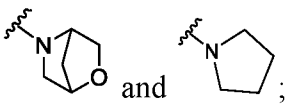
or a pharmaceutically acceptable salt thereof, wherein:

Ar^1 is  ;

R^1 is Cl, CH_3, $-CF_3$, $-CHF_2$, $-OCH_3$, $-OCHF_2$, or $-OCF_3$;

R^2 is cyano, F, Cl, $-CH_3$, $-OCH_3$, $-CF_3$, $-CHF_2$, $-CF_3$, or $-NHC(O)CH_3$;

R^{2a} is $-CH_3$, CHF_2, $-CH_2CH_3$, $-CH_2CN$, $-CH_2CHF_2$, $-CH_2CH_2OCH_3$, $-CH_2CH(OH)CF_3$, $-CH_2CH(OH)CH_3$, $-CH_2CH_2OH$, $-CF_2CH_2OH$, $-CH_2CH(CH_3)OH$, $-CH_2CH_2CF_3$, $-CH(CH_2OH)CH_2OCH_3$, $-CH(CH_2NH_2)OCH_3$, $-CH_2CH(CH_3)OCH_3$, $-CH_2CH(CF_3)OCH_3$, $-CH(CH_2NH_2)CH_2OCH_3$, $-CH(C(O)N(CH_3)_2)CH_2OCH_3$, $-CH_2C(CH_3)(CH_2OH)_2$, $-CH_2CH_2N(CH_3)_2$, $-CH_2CH_2S(O)_2C_{1-4}$ alkyl, $-CHR^dC(O)NR^3R^4$, $-(CH_2)_{0-1}$-C_{3-6} cycloalkyl, $-(CH_2)_{0-3}$-heterocycloalkyl selected from  ;

R^3 and R^4 together with the nitrogen to which they are both attached form a heterocycloalkyl selected from  ;

R^{5a} is hydrogen or F;

R^{5b} is hydrogen or F;

R^{5c} is Cl or $-OCH_3$;

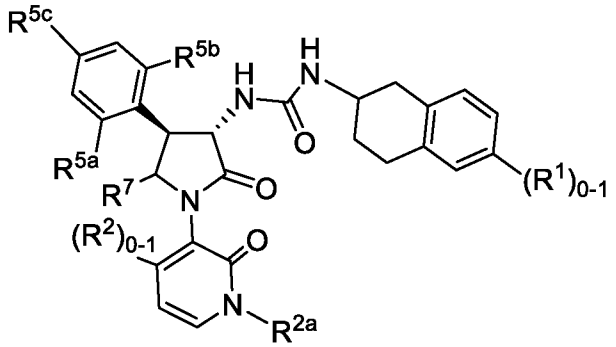
R^6 is hydrogen, oxo, halo, $-CH_3$, $-CHF_2$, $-CF_3$, or $-CH_2OH$;

R^7 is hydrogen or $-CH_3$;

R^8 is hydrogen, C_{1-2} alkyl, or $-S(O)_2C_{1-3}$ alkyl; and

R^d is $-CH_2OCH_3$.

Another aspect of the invention is a compound of Formula (V):

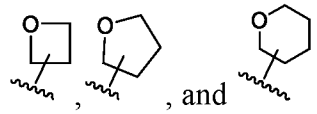


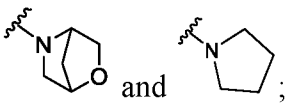
(V)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is Cl or $-OCH_3$;

R^2 is cyano, F, Cl, $-CH_3$, $-OCH_3$, $-CF_3$, $-CHF_2$, or $-CF_3$;

R^{2a} is $-CH_3$, CHF_2, $-CH_2CH_3$, $-CH_2CN$, $-CH_2CHF_2$, $-CH_2CH_2OCH_3$, $-CH_2CH(OH)CF_3$, $-CH_2CH(OH)CH_3$, $-CH_2CH_2OH$, $-CF_2CH_2OH$, $-CH_2CH(CH_3)OH$, $-CH_2CH_2CF_3$, $-CH(CH_2OH)CH_2OCH_3$, $-CH(CH_2NH_2)OCH_3$, $-CH_2CH(CH_3)OCH_3$, $-CH_2CH(CF_3)OCH_3$, $-CH(CH_2NH_2)CH_2OCH_3$, $-CH(C(O)N(CH_3)_2)CH_2OCH_3$, $-CH_2C(CH_3)(CH_2OH)_2$, $-CH_2CH_2N(CH_3)_2$, $-CH_2CH_2S(O)_2C_{1-4}$ alkyl, $-CHR^dC(O)NR^3R^4$, $-(CH_2)_{0-1}$-C_{3-6} cycloalkyl, $-(CH_2)_{0-3}$-heterocycloalkyl selected from  ;

R^3 and R^4 together with the nitrogen to which they are both attached form a heterocycloalkyl selected from  ;

R^{5a} is hydrogen or F;

R^{5b} is hydrogen or F;

R^{5c} is Cl or $-OCH_3$;

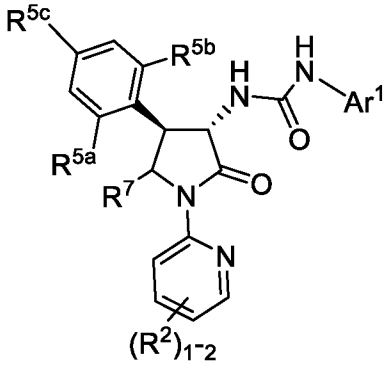
R^6 is hydrogen, oxo, halo, $-CH_3$, $-CHF_2$, $-CF_3$, or $-CH_2OH$;

R^7 is hydrogen or $-CH_3$;

R^8 is hydrogen, C_{1-2} alkyl, or $-S(O)_2C_{1-3}$ alkyl; and

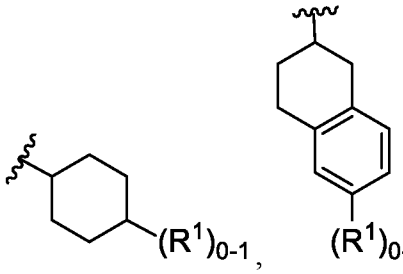
R^d is $-CH_2OCH_3$.

Another aspect of the invention is a compound of Formula (VI):

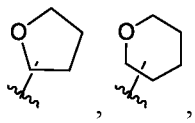


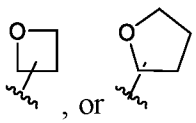
(VI)

or a pharmaceutically acceptable salt thereof, wherein:

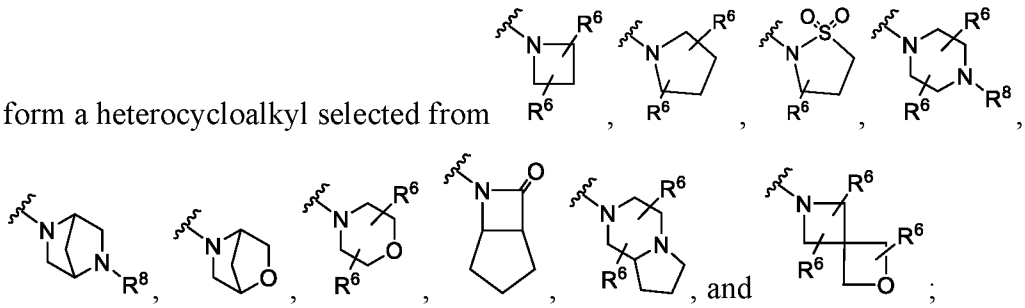
Ar^1 is  ;

R^1 is Cl, $-CF_3$, CHF_2, $-OCHF_2$, $-OCH_3$, or $-OCF_3$;

R^2 is cyano, F, Cl, $-CH_2OH$, $-CH_3$, $-CHF_2$, $-CF_3$, $-OCH_3$, $-OCH(CH_3)_2$, $-NR^3R^4$, $(CH_3)_2(O)P-$, C_{3-6} cycloalkyl,  ;

R^3 is hydrogen or C_{1-4} alkyl substituted with 0-3 R^e,  ;

R^4 is hydrogen;

alternatively, R^3 and R^4 together with the nitrogen to which they are both attached form a heterocycloalkyl selected from  ;

R^{5a} is hydrogen or F;

R^{5b} is hydrogen or F;

R^{5c} is Cl or $-OCH_3$

R^6 is hydrogen, halo, oxo, $-CH_3$, $-CH_2CH_3$, or $-CH_2OH$;

R^7 is hydrogen or $-CH_3$;

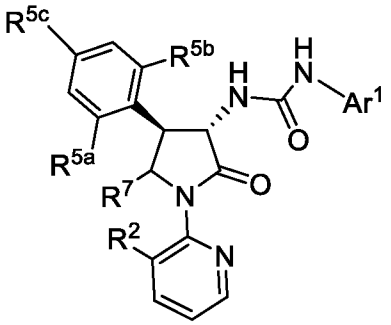
R^8 is hydrogen, C_{1-4} alkyl, or $-S(O)_2C_{1-3}$ alkyl; and

R^e is halo, $-OR^g$, $-C(O)NR^gR^g$, $-S(O)_2C_{1-4}$ alkyl, heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^g and substituted with 0-3 R^f;

R^f is halo, cyano, hydroxy, or C_{1-4} alkyl; and

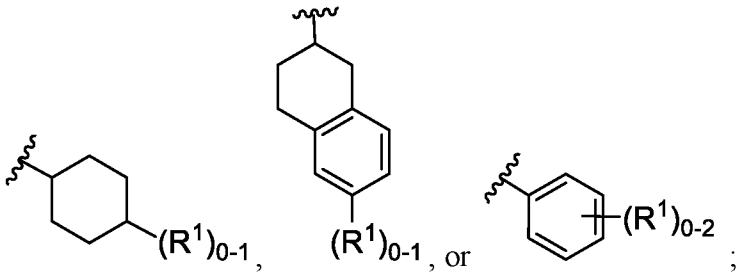
R^g is hydrogen or C_{1-3} alkyl.

Another aspect of the invention is a compound of Formula (VII):



(VII)

or a pharmaceutically acceptable salt thereof, wherein:

Ar^1 is  ;

R^1 is Cl, $-CF_3$, CHF_2, $-OCHF_2$, $-OCH_3$, or $-OCF_3$;

R^2 is F, Cl, $-CH_2OH$, $-CH_3$, $-CHF_2$, $-CF_3$, $-OCH_3$, or $-OCH(CH_3)_2$;

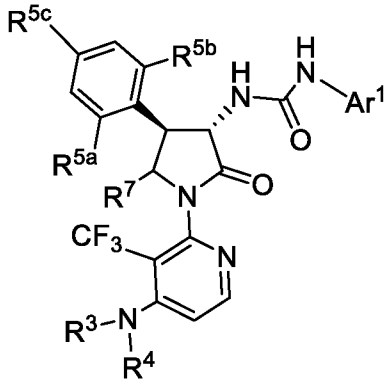
R^{5a} is hydrogen or F;

R^{5b} is hydrogen or F;

R^{5c} is Cl or $-OCH_3$; and

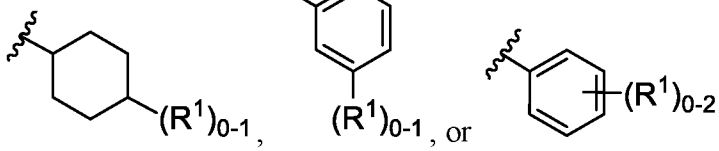
R^7 is hydrogen or $-CH_3$.

Another aspect of the invention is a compound of Formula (VIII):



(VIII)

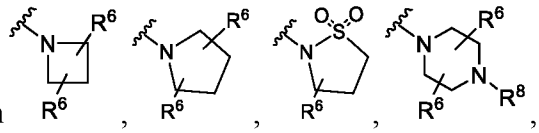
or a pharmaceutically acceptable salt thereof, wherein:

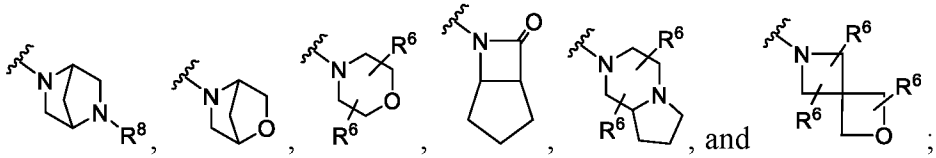
Ar^1 is  ;

R^1 is F, Cl, $-CF_3$, CHF_2, $-OCHF_2$, $-OCH_3$, or $-OCF_3$;

R^3 is hydrogen or C_{1-4} alkyl substituted with 0-2 R^e;

R^4 is hydrogen;

alternatively, R^3 and R^4 together with the nitrogen to which they are both attached form a heterocycloalkyl selected from  ,

 ;

R^{5a} is hydrogen or F;

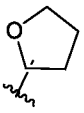
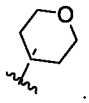
R^{5b} is hydrogen or F;

R^{5c} is Cl or $-OCH_3$;

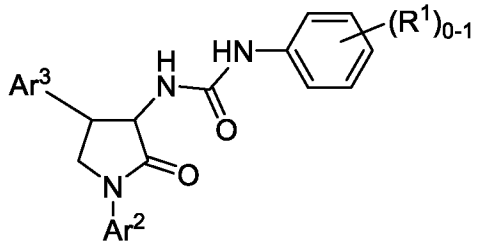
R^6 is hydrogen, halo, hydroxy, oxo, $-CH_3$, $-CH_2CH_3$, or $-CH_2OH$;

R^7 is hydrogen or $-CH_3$;

R^8 is hydrogen, C_{1-4} alkyl, or $-S(O)_2C_{1-3}$ alkyl; and

R^e is –OH, -OC_{1-4} alkyl, -$C(O)NHC_{1-4}$ alkyl, -$S(O)_2C_{1-4}$ alkyl,  ,  , or  .

Another aspect of the invention is a compound of Formula (IX):



(IX)

or a pharmaceutically acceptable salt thereof, wherein:

Ar^2 is pyridinyl or pyridinonyl, each substituted with 0-2 R^2;

Ar^3 is phenyl substituted with 3 R^5;

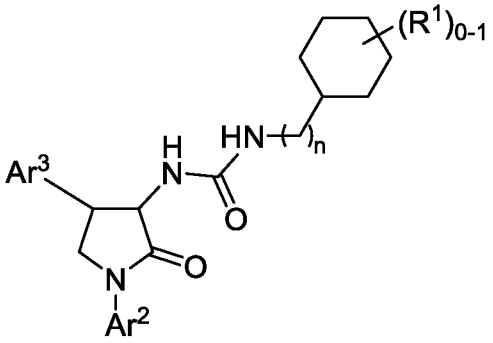
R^1 is halo, C_{1-4} haloalkyl, or C_{1-4} haloalkoxy;

R^2 is cyano, halo, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} haloalkyl, C_{3-6} cycloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy or NR^3R^4;

R^3 and R^4 together with the nitrogen to which they are both attached form a 4-6 membered heterocylic ring; and

R^5 is halo, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} alkoxy.

Another aspect of the invention is a compound of Formula (X):



(X)

or a pharmaceutically acceptable salt thereof, wherein:

Ar^2 is pyridinyl or pyridinonyl, each substituted with 0-2 R^2;

Ar^3 is phenyl substituted with 3 R^5;

R^1 is halo, C_{1-4} haloalkyl, or C_{1-4} haloalkoxy;

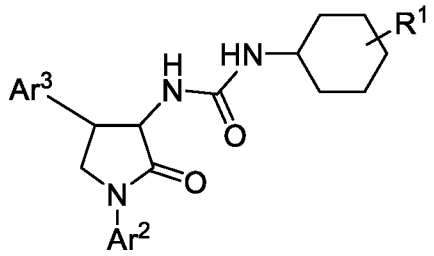
R^2 is cyano, halo, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} haloalkyl, C_{3-6} cycloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy or NR^3R^4;

R^3 and R^4 together with the nitrogen to which they are both attached form a 4-6 membered heterocylic ring;

R^5 is halo, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} alkoxy; and

n is zero or 1.

Another aspect of the invention is a compound of Formula (XI):



(XI)

or a pharmaceutically acceptable salt thereof, wherein:

Ar^2 is pyridinyl or pyridinonyl, each substituted with 0-2 R^2;

Ar^3 is phenyl substituted with 3 R^5;

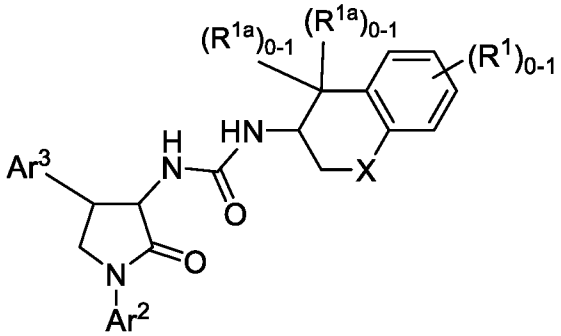
R^1 is halo, C_{1-4} haloalkyl, or C_{1-4} haloalkoxy;

R^2 is cyano, halo, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} haloalkyl, C_{3-6} cycloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy or NR^3R^4;

R^3 and R^4 together with the nitrogen to which they are both attached form a 4-6 membered heterocylic ring; and

R^5 is halo, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} alkoxy.

Another aspect of the invention is a compound of Formula (XII):



(XII)

or a pharmaceutically acceptable salt thereof, wherein:

Ar^2 is pyridinyl or pyridinonyl, each substituted with 0-2 R^2;

Ar^3 is phenyl substituted with 3 R^5;

X is CH_2 or O;

R^1 is halo, C_{1-4} haloalkyl, or C_{1-4} haloalkoxy;

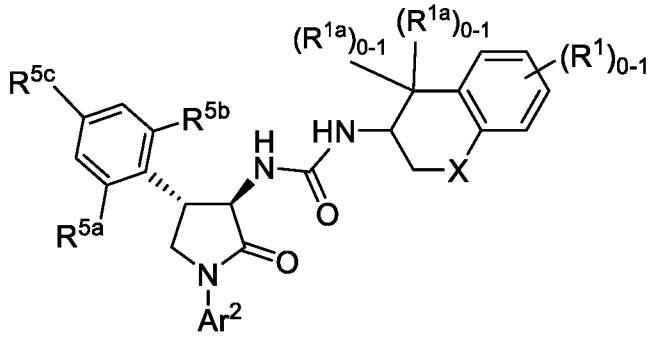
R^{1a} is methyl;

R^2 is cyano, halo, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} haloalkyl, C_{3-6} cycloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, or NR^3R^4;

R^3 and R^4 together with the nitrogen to which they are both attached form a 4-6 membered heterocylic ring; and

R^5 is halo, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} alkoxy.

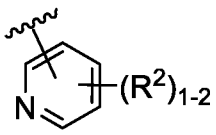
Another aspect of the invention is a compound of Formula (XIII):



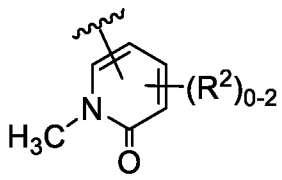
(XIII)

or a pharmaceutically acceptable salt thereof, wherein:

Ar^2 is



, or



;

X is CH_2 or O;

R^1 is halo, C_{1-4} haloalkyl, or C_{1-4} haloalkoxy

R^{1a} is methyl;

R^2 is cyano, halo, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} haloalkyl, C_{3-6} cycloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, NR^3R^4;

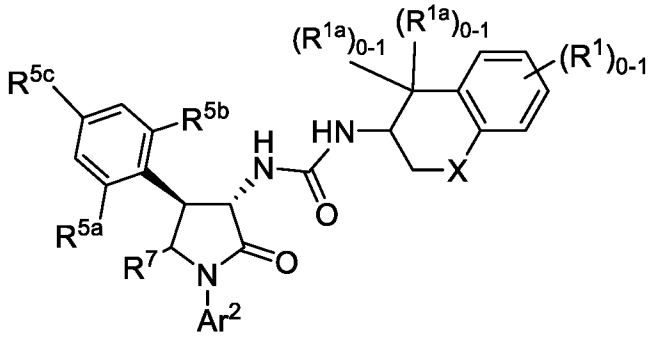
R^3 and R^4 together with the nitrogen to which they are both attached form a 4-6 membered heterocylic ring;

R^{5a} is halo;

R^{5b} is halo; and

R^{5c} is C_{1-2} alkoxy.

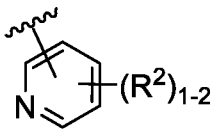
Another aspect of the invention is a compound of Formula (XIV):



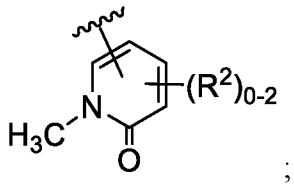
(XIV)

or a pharmaceutically acceptable salt thereof, wherein:

Ar^2 is



, or



;

X is CH_2 or O;

R^1 is halo, C_{1-4} haloalkyl, or C_{1-4} haloalkoxy;

R^{1a} is methyl;

R^2 is cyano, halo, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} haloalkyl, C_{3-6} cycloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, or NR^3R^4;

R^3 and R^4 together with the nitrogen to which they are both attached form a 4-6 membered heterocylic ring;

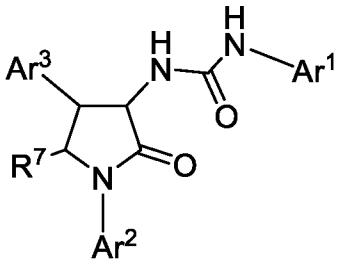
R^{5a} is halo;

R^{5b} is halo;

R^{5c} is C_{1-2} alkoxy; and

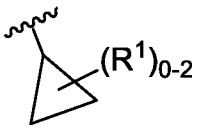
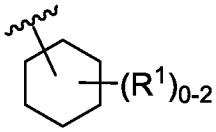
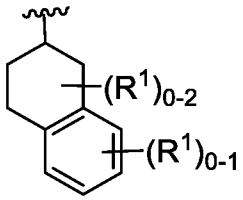
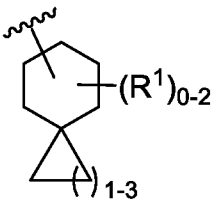
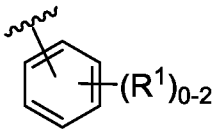
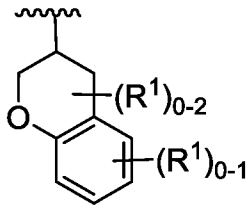
R^7 is hydrogen or methyl.

Another aspect of the invention is a compound of Formula (IIa):



(IIa)

or a pharmaceutically acceptable salt thereof, wherein:

Ar^1 is  ,  ,  ,  ,  , or  ;

Ar^2 is C_{3-6} cycloalkyl, phenyl, a 5- to 6-membered heteroaryl or heterocycloalkyl comprising 1-2 N or NR^{2a}, each substituted with 0-2 R^2;

Ar^3 is phenyl substituted with 1 R^{5a}, 1 R^{5b}, and 1 R^{5c};

R^1 is halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, or phenyl substituted with 0-2 halo or C_{1-4} alkoxy;

R^2 is oxo, cyano, halo, C_{1-5} alkyl substituted with 0-5 R^e, $-OR^b$, $-NR^3R^4$, $-NR^4C(O)R^b$, $(C_{1-3}\text{ alkyl})_2(O)P-$, C_{3-6} cycloalkyl, aryl, or a 5- to 6-membered heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^a;

R^{2a} is hydrogen, C_{1-4} alkyl substituted with 0-4 R^e, $-(CHR^d)_{1-3}$-$C(O)NR^3R^4$, $-(CHR^d)_r$-C_{3-6} cycloalkyl substituted with 0-4 R^e, $-(CHR^d)_r$–aryl substituted with 0-4 R^e, or $-(CHR^d)_r$–heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^a and substituted with 0-4 R^e;

R^3 is hydrogen, C_{1-4} alkyl substituted with 0-4 R^e, C_{3-6} cycloalkyl, or heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^8 and substituted with 0-4 R^e;

R^4 is hydrogen or C_{1-3} alkyl;

alternatively, R^3 and R^4 together with the nitrogen to which they are both attached form a 4- to 8-membered heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^8 and substituted with 1-3 R^6;

R^{5a} is hydrogen or halo;

R^{5b} is hydrogen or halo;

R^{5c} is halo, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} alkoxy;

R^6 is hydrogen, halo, oxo, hydroxy, or C_{1-4} alkyl substituted with 0-4 R^e;

R^7 is hydrogen or C_{1-3} alkyl;

R^8 is hydrogen, C_{1-3} alkyl, or $-S(O)_pR^c$;

R^a is hydrogen or C_{1-6} alkyl substituted with 0-5 R^e;

R^b is hydrogen, C_{1-6} alkyl substituted with 0-5 R^e, or heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, NR^d and substituted with 0-5 R^e;

R^c is C_{1-3} alkyl substituted with 0-5 R^e;

R^d is hydrogen or C_{1-4} alkyl substituted with 0-1 $-OC_{1-4}$ alkyl;

R^e is halo, cyano, oxo, $-OR^g$, $-NR^gR^g$, $-C(O)NR^gR^g$, $-S(O)_pC_{1-4}$ alkyl, C_{1-4} alkyl substituted with 0-5 R^f, $-(CH_2)_r-C_{3-6}$ cycloalkyl substituted with 0-5 R^f, $-(CH_2)_r-$aryl substituted with 0-5 R^f, or $-(CH_2)_r-$heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^g and substituted with 0-5 R^f;

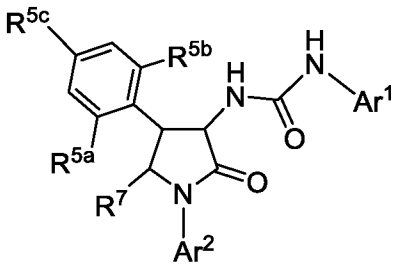
R^f is halo, cyano, hydroxy, C_{1-5} alkyl, or C_{3-6} cycloalkyl;

R^g is hydrogen, C_{1-5} alkyl, or heteroaryl or heterocycloalkyl;

n is zero; and

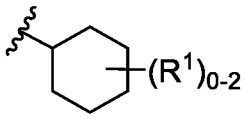
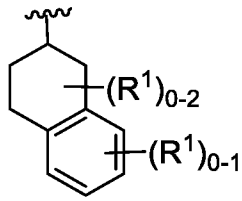
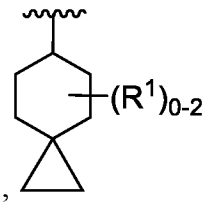
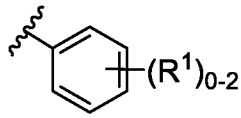
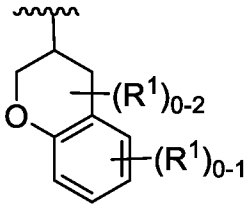
r is zero, 1, 2, or 3.

Another aspect of the invention is a compound of Formula (IIIa):

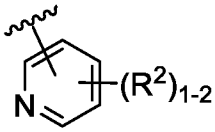
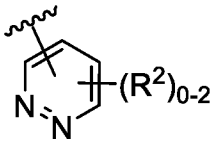
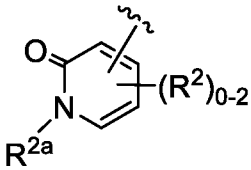
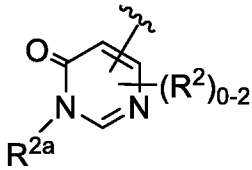


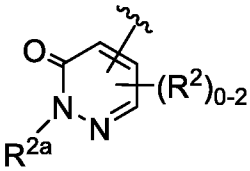
(IIIa)

or a pharmaceutically acceptable salt thereof, wherein:

Ar^1 is  ,  ,  ,  ,  , or ;

Ar^2 is

 ,  ,  ,  , or

 ;

R^1 is halo, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} haloalkyl, or C_{1-3} haloalkoxy;

R^2 is cyano, halo, C_{1-4} alkyl substituted with 0-5 R^e, $-OR^b$, $-NR^3R^4$, $-NR^4C(O)R^b$, $(C_{1-4}$ alkyl$)_2(O)P-$, C_{3-6} cycloalkyl, aryl, or a 5- to 6-membered heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^a;

R^{2a} is hydrogen, C_{1-4} alkyl substituted with 0-3 R^e, $-(CHR^d)_{1-2}-C(O)NR^3R^4$, $-(CH_2)_r-C_{3-6}$ cycloalkyl substituted with 0-3 R^e, $-(CH_2)_r-$aryl substituted with 0-3 R^e, or $-(CH_2)_r-$heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^a and substituted with 0-3 R^e;

R^3 is hydrogen, C_{1-4} alkyl substituted with 0-3 R^e, C_{3-6} cycloalkyl, or heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^8 and substituted with 0-3 R^e;

R^4 is hydrogen or C_{1-2} alkyl;

alternatively, R^3 and R^4 together with the nitrogen to which they are both attached form a 4- to 8-membered heteroaryl or heterocycloalkyl comprising 1-3 heteroatoms selected from O, S, N, and NR^8 and substituted with 1-3 R^6;

R^{5a} is hydrogen or halo;

R^{5b} is hydrogen or halo;

R^{5c} is halo or C_{1-2} alkoxy;

R^6 is hydrogen, halo, oxo, hydroxy, or C_{1-4} alkyl substituted with 0-3 R^e;

R^7 is hydrogen or CH_3;

R^8 is hydrogen, C_{1-2} alkyl, or $-S(O)_2C_{1-4}$ alkyl;

R^a is hydrogen, C_{1-5} alkyl substituted with 0-4 R^e;

R^b is hydrogen, C_{1-5} alkyl substituted with 0-4 R^e, heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, NR^d and substituted with 0-4 R^e;

R^d is hydrogen or C_{1-3} alkyl substituted with 0-1 $-OC_{1-4}$ alkyl;

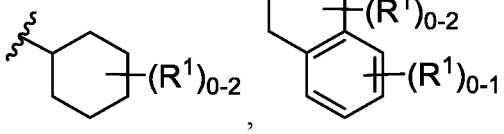
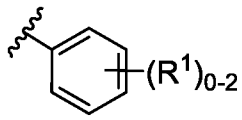
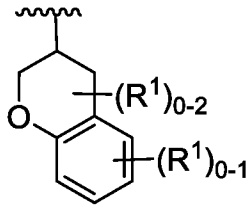
R^e is halo, cyano, oxo, $-OR^g$, $-NR^gR^g$, $C(O)NR^gR^g$, $-S(O)_pC_{1-4}$ alkyl, C_{1-4} alkyl substituted with 0-4 R^f, $-(CH_2)_r-C_{3-6}$ cycloalkyl substituted with 0-4 R^f, $-(CH_2)_r-$aryl substituted with 0-4 R^f, or $-(CH_2)_r-$heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^g and substituted with 0-4 R^f;

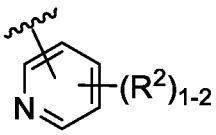
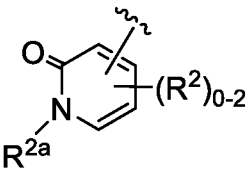
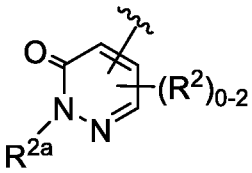
R^f is halo, cyano, hydroxy, or C_{1-5} alkyl;

R^g is hydrogen or C_{1-4} alkyl; and

r is zero, 1, or 2.

Another aspect of the invention is a compound of Formula (IIIa), or a pharmaceutically acceptable salt thereof, wherein:

Ar^1 is  , ,  , or  ;

Ar^2 is  ,  , or  ;

R^1 is Cl, $-CH_3$, $-CF_3$, $-OCH_3$, $-OCHF_2$, or $-OCF_3$;

R^2 is cyano, halo, C_{1-4} alkyl substituted with 0-4 R^e, -OR^b, -NR^3R^4, -$NR^4C(O)R^b$, $(C_{1-2}$ alkyl$)_2(O)P$-, C_{3-6} cycloalkyl, heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^a;

R^{2a} is hydrogen, C_{1-4} alkyl substituted with 0-2 R^e, $–(CHR^d)_{1-2}$-$C(O)NR^3R^4$, $–(CH_2)_r$-C_{3-6} cycloalkyl substituted with 0-2 R^e, $–(CH_2)_r$–aryl substituted with 0-2 R^e, or $–(CH_2)_r$–heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^a and substituted with 0-2 R^e;

R^3 is hydrogen, C_{1-4} alkyl substituted with 0-3 R^e, or heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^8 and substituted with 0-3 R^e;

R^4 is hydrogen or C_{1-2} alkyl;

alternatively, R^3 and R^4 together with the nitrogen to which they are both attached form a 4- to 8-membered heteroaryl or heterocycloalkyl comprising 1-3 heteroatoms selected from O, S, N, and NR^8 and substituted with 1-3 R^6;

R^{5a} is hydrogen, F, or Cl;

R^{5b} is hydrogen, F, or Cl;

R^{5c} is Cl or -OCH_3;

R^6 is hydrogen, halo, oxo, hydroxy, or C_{1-3} alkyl substituted with 0-3 R^e;

R^7 is hydrogen or -CH_3;

R^8 is hydrogen, C_{1-2} alkyl, or $S(O)_2C_{1-3}$ alkyl;

R^a is hydrogen, C_{1-4} alkyl substituted with 0-3 R^e;

R^b is hydrogen, C_{1-4} alkyl substituted with 0-3 R^e, heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^d and substituted with 0-3 R^e;

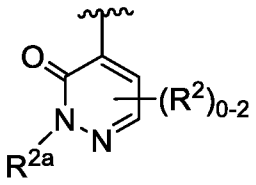
R^d is hydrogen or C_{1-2} alkyl substituted with 0-1 $–OC_{1-4}$ alkyl;

R^e is halo, cyano, oxo, -OR^g, $–NR^gR^g$, -$C(O)NR^gR^g$, -$S(O)_2C_{1-4}$ alkyl, C_{1-6} alkyl substituted with 0-3 R^f, C_{3-6} cycloalkyl substituted with 0-3 R^f, or heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^g and substituted with 0-3 R^f;

R^f is halo, cyano, hydroxy, or C_{1-4} alkyl; and

R^g is hydrogen or C_{1-3} alkyl.

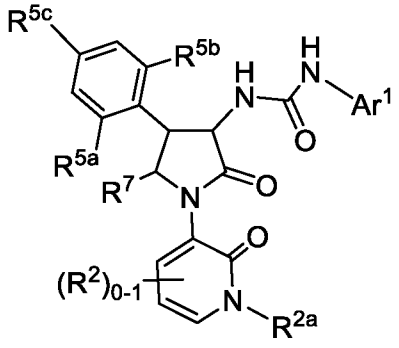
Another aspect of the invention is a compound of Formulae (IIa)-(IIIa), or a pharmaceutically acceptable salt thereof, wherein:

Ar^2 is  ;

R^2 is F, Cl, CH_2OH, CH_3, CF_3, or CHF_2; and

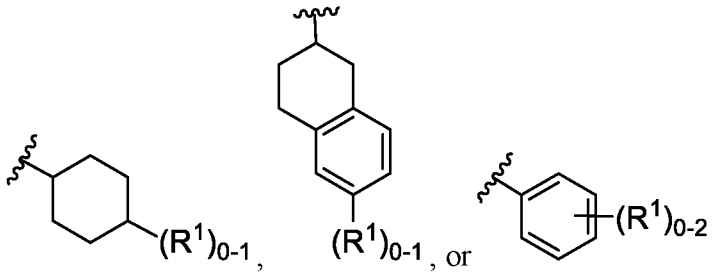
R^{2a} is $-CH_3$, $-CH_2CH_3$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CH_2CH_2OCH_3$, $-CH_2CH(OH)CF_3$, $-CH_2CH(OH)CH_3$, $-CH_2CH_2OH$, $-CH_2CH(CH_3)OH$, $-CH_2CH(CF_3)OH$, $-CH_2CH_2CF_3$, $-CH(CH_2OH)CH_2OCH_3$, $-CH(CH_2NH_2)OCH_3$, $-CH_2CH(CH_3)OCH_3$, or $-CH_2CH(CF_3)OCH_3$.

Another aspect of the invention is a compound of Formula (IVa):



(IVa)

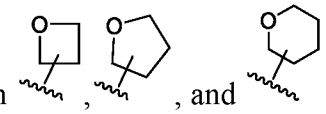
or a pharmaceutically acceptable salt thereof, wherein:

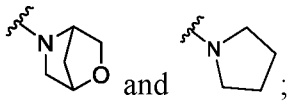
Ar^1 is  ;

R^1 is Cl, CH_3, $-CF_3$, $-CHF_2$, $-OCH_3$, $-OCHF_2$, or $-OCF_3$;

R^2 is cyano, F, Cl, $-CH_3$, $-OCH_3$, $-CF_3$, $-CHF_2$, $-CF_3$, or $-NHC(O)CH_3$;

R^{2a} is $-CH_3$, CHF_2, $-CH_2CH_3$, $-CH_2CN$, $-CH_2CHF_2$, $-CH_2CH_2OCH_3$, $-CH_2CH(OH)CF_3$, $-CH_2CH(OH)CH_3$, $-CH_2CH_2OH$, $-CF_2CH_2OH$, $-CH_2CH(CH_3)OH$, $-CH_2CH_2CF_3$, $-CH(CH_2OH)CH_2OCH_3$, $-CH(CH_2NH_2)OCH_3$, $-CH_2CH(CH_3)OCH_3$, $-CH_2CH(CF_3)OCH_3$, $-CH(CH_2NH_2)CH_2OCH_3$, $-CH(C(O)N(CH_3)_2)CH_2OCH_3$, $-CH_2C(CH_3)(CH_2OH)_2$, $-CH_2CH_2N(CH_3)_2$, $-CH_2CH_2S(O)_2C_{1\text{-}4}$ alkyl, $-CHR^dC(O)NR^3R^4$, -

$(CH_2)_{0-1}$-C_{3-6} cycloalkyl, -$(CH_2)_{0-3}$-heterocycloalkyl selected from  ;

R^3 and R^4 together with the nitrogen to which they are both attached form a heterocycloalkyl selected from  ;

R^{5a} is hydrogen or F;

R^{5b} is hydrogen or F;

R^{5c} is Cl or -OCH_3;

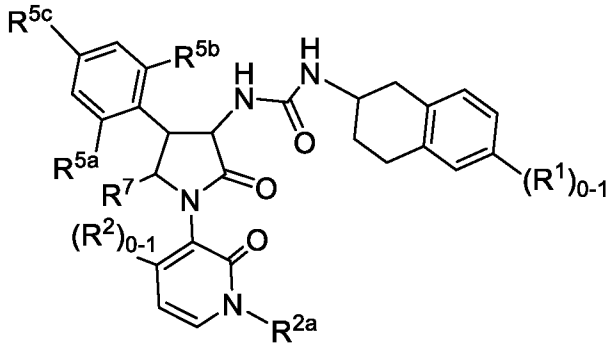
R^6 is hydrogen, oxo, halo, -CH_3, -CHF_2, -CF_3, or -CH_2OH;

R^7 is hydrogen or -CH_3;

R^8 is hydrogen, C_{1-2} alkyl, or -$S(O)_2C_{1-3}$ alkyl; and

R^d is -CH_2OCH_3.

Another aspect of the invention is a compound of Formula (Va):



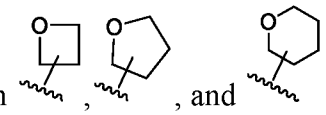
(Va)

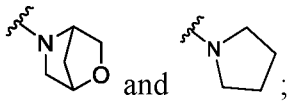
or a pharmaceutically acceptable salt thereof, wherein:

R^1 is Cl or -OCH_3;

R^2 is cyano, F, Cl, -CH_3, -OCH_3, -CF_3, -CHF_2, or -CF_3;

R^{2a} is -CH_3, CHF_2, -CH_2CH_3, -CH_2CN, -CH_2CHF_2, -$CH_2CH_2OCH_3$, -$CH_2CH(OH)CF_3$, -$CH_2CH(OH)CH_3$, -CH_2CH_2OH, -CF_2CH_2OH, -$CH_2CH(CH_3)OH$, -$CH_2CH_2CF_3$, -$CH(CH_2OH)CH_2OCH_3$, -$CH(CH_2NH_2)OCH_3$, -$CH_2CH(CH_3)OCH_3$, -$CH_2CH(CF_3)OCH_3$, -$CH(CH_2NH_2)CH_2OCH_3$, -$CH(C(O)N(CH_3)_2)CH_2OCH_3$, -$CH_2C(CH_3)(CH_2OH)_2$, -$CH_2CH_2N(CH_3)_2$, -$CH_2CH_2S(O)_2C_{1-4}$ alkyl, –$CHR^dC(O)NR^3R^4$, -

$(CH_2)_{0-1}$-C_{3-6} cycloalkyl, -$(CH_2)_{0-3}$-heterocycloalkyl selected from  ;

R^3 and R^4 together with the nitrogen to which they are both attached form a heterocycloalkyl selected from  ;

R^{5a} is hydrogen or F;

R^{5b} is hydrogen or F;

R^{5c} is Cl or -OCH_3;

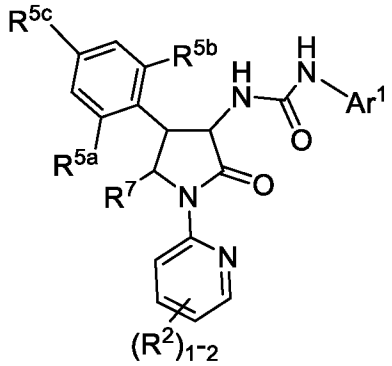
R^6 is hydrogen, oxo, halo, -CH_3, -CHF_2, -CF_3, or -CH_2OH;

R^7 is hydrogen or -CH_3;

R^8 is hydrogen, C_{1-2} alkyl, or -$S(O)_2C_{1-3}$ alkyl; and

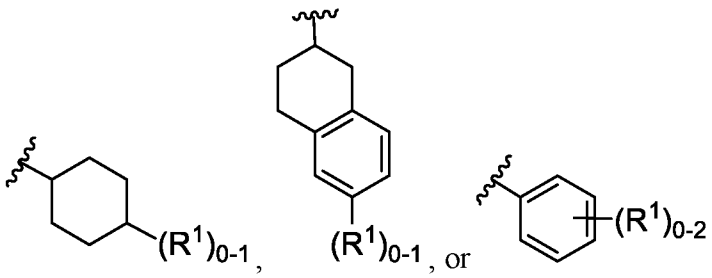
R^d is -CH_2OCH_3.

Another aspect of the invention is a compound of Formula (VIa):

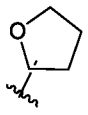
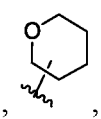
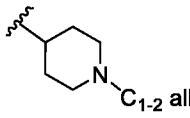


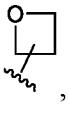
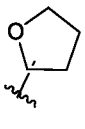
(VIa)

or a pharmaceutically acceptable salt thereof, wherein:

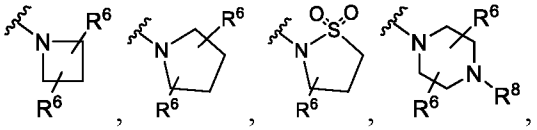
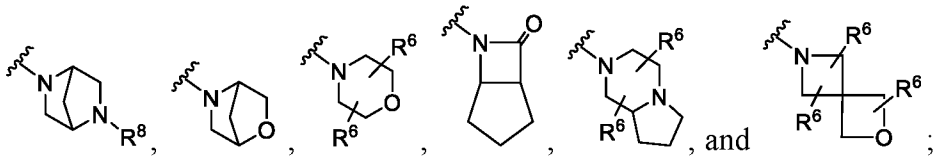
Ar^1 is  ;

R^1 is Cl, -CF_3, CHF_2, -$OCHF_2$, -OCH_3, or -OCF_3;

R^2 is cyano, F, Cl, -CH_2OH, -CH_3, -CHF_2, -CF_3, -OCH_3, -$OCH(CH_3)_2$, -NR^3R^4, $(CH_3)_2(O)P$-, C_{3-6} cycloalkyl,  ,  , or  ;

R^3 is hydrogen or C_{1-4} alkyl substituted with 0-3 R^e,  , or  ;

R^4 is hydrogen;

alternatively, R^3 and R^4 together with the nitrogen to which they are both attached form a heterocycloalkyl selected from  ,  , and ;

R^{5a} is hydrogen or F;

R^{5b} is hydrogen or F;

R^{5c} is Cl or -OCH_3;

R^6 is hydrogen, halo, oxo, -CH_3, -CH_2CH_3, or -CH_2OH;

R^7 is hydrogen or -CH_3;

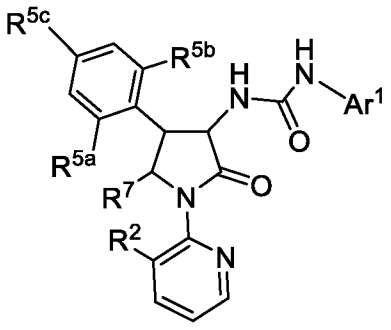
R^8 is hydrogen, C_{1-4} alkyl, or -$S(O)_2C_{1-3}$ alkyl; and

R^e is halo, -OR^g, -$C(O)NR^gR^g$, -$S(O)_2C_{1-4}$ alkyl, heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^g and substituted with 0-3 R^f;

R^f is halo, cyano, hydroxy, or C_{1-4} alkyl; and

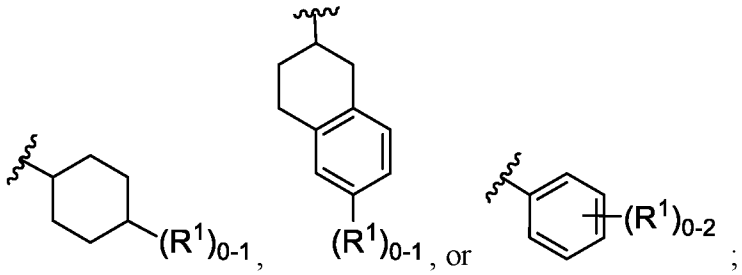
R^g is hydrogen or C_{1-3} alkyl.

Another aspect of the invention is a compound of Formula (VIIa):



(VIIa)

or a pharmaceutically acceptable salt thereof, wherein:

Ar^1 is  ;

R^1 is Cl, $-CF_3$, CHF_2, $-OCHF_2$, $-OCH_3$, or $-OCF_3$;

R^2 is F, Cl, $-CH_2OH$, $-CH_3$, $-CHF_2$, $-CF_3$, $-OCH_3$, or $-OCH(CH_3)_2$;

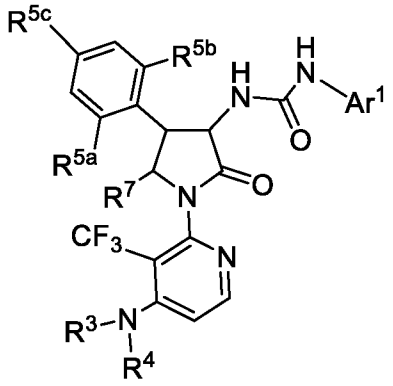
R^{5a} is hydrogen or F;

R^{5b} is hydrogen or F;

R^{5c} is Cl or $-OCH_3$; and

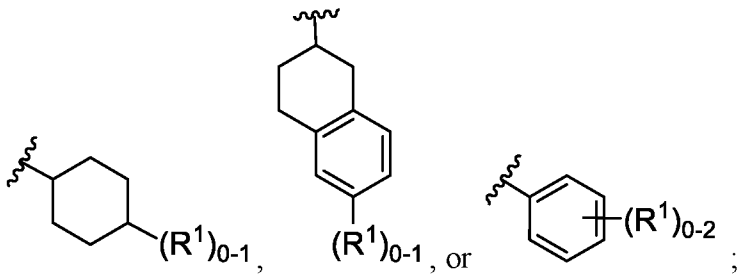
R^7 is hydrogen or $-CH_3$.

Another aspect of the invention is a compound of Formula (VIIIa):



(VIIIa)

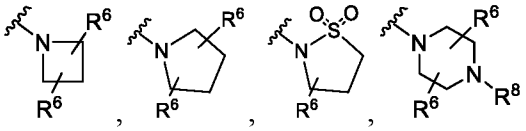
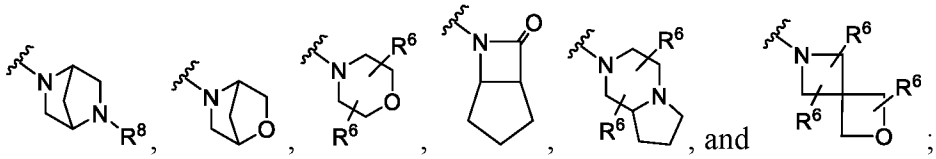
or a pharmaceutically acceptable salt thereof, wherein:

Ar^1 is  ;

R^1 is F, Cl, $-CF_3$, CHF_2, $-OCHF_2$, $-OCH_3$, or $-OCF_3$;

R^3 is hydrogen or C_{1-4} alkyl substituted with 0-2 R^e;

R^4 is hydrogen;

alternatively, R^3 and R^4 together with the nitrogen to which they are both attached form a heterocycloalkyl selected from  ,  , and ;

R^{5a} is hydrogen or F;

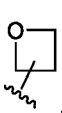
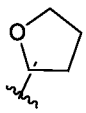
R^{5b} is hydrogen or F;

R^{5c} is Cl or $-OCH_3$;

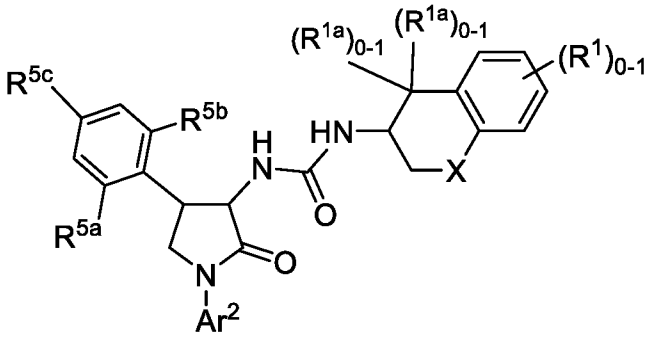
R^6 is hydrogen, halo, hydroxy, oxo, $-CH_3$, $-CH_2CH_3$, or $-CH_2OH$;

R^7 is hydrogen or $-CH_3$;

R^8 is hydrogen, C_{1-4} alkyl, or $-S(O)_2C_{1-3}$ alkyl; and

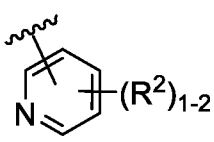
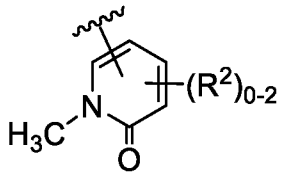
R^e is –OH, $-OC_{1-4}$ alkyl, $-C(O)NHC_{1-4}$ alkyl, $-S(O)_2C_{1-4}$ alkyl,  ,  , or  .

Another aspect of the invention is a compound of Formula (XIIIa):



(XIIIa)

or a pharmaceutically acceptable salt thereof, wherein:

Ar^2 is  , or  ;

X is CH_2 or O;

R^1 is halo, C_{1-4} haloalkyl, or C_{1-4} haloalkoxy

R^{1a} is methyl;

R^2 is cyano, halo, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} haloalkyl, C_{3-6} cycloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, NR^3R^4;

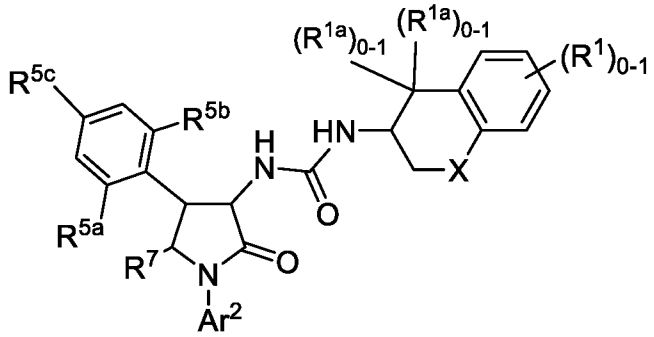
R^3 and R^4 together with the nitrogen to which they are both attached form a 4-6 membered heterocylic ring;

R^{5a} is halo;

R^{5b} is halo; and

R^{5c} is C_{1-2} alkoxy.

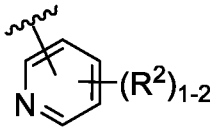
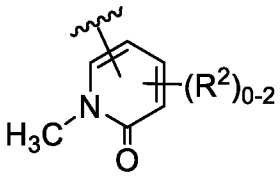
Another aspect of the invention is a compound of Formula (XIVa):



(XIVa)

or a pharmaceutically acceptable salt thereof, wherein:

Ar^2 is

 , or  ;

X is CH_2 or O;

R^1 is halo, C_{1-4} haloalkyl, or C_{1-4} haloalkoxy;

R^{1a} is methyl;

R^2 is cyano, halo, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} haloalkyl, C_{3-6} cycloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, or NR^3R^4;

R^3 and R^4 together with the nitrogen to which they are both attached form a 4-6 membered heterocylic ring;

R^{5a} is halo;

R^{5b} is halo;

R^{5c} is C_{1-2} alkoxy; and

R^7 is hydrogen or methyl.

For a compound of Formula (I), (II), (III), (IIIa), (IV), (IV2), (V), (Va), (VI), (VIa), (VII), (VIIa), (VIII), (VIIIa), (IX), (X), (XI), (XII), (XIII), (XIIIa), (XIV), or (XIVa), the scope of any instance of a variable substituent, including Ar^1, Ar^2, Ar^3, R^1 (R^{1a}), R^2, R^3, R^4, R^5 (R^{5a}, R^{5b}, and R^{5c}), R^6, R^7, R^a, R^b, R^c, R^d, R^e, R^f, and R^g, can be used independently with the scope of any other instance of a variable substituent. As such, the invention includes combinations of the different aspects.

Unless specified otherwise, these terms have the following meanings. "Alkyl" means a straight or branched alkyl group composed of 1 to 6 carbons. "Alkenyl" means a straight or branched alkyl group composed of 2 to 6 carbons with at least one double bond. "Alkynyl" means a straight or branched alkyl group composed of 2 to 6 carbons with at least one triple bond. "Cycloalkyl" means a monocyclic ring system composed of 3 to 7 carbons. Terms with a hydrocarbon moiety (e.g. alkoxy) include straight and branched isomers for the hydrocarbon portion. "Halo" includes fluoro, chloro, bromo, and iodo. "Haloalkyl" and "haloalkoxy" include all halogenated isomers from monohalo to perhalo. "Aryl" means a monocyclic or bicyclic aromatic hydrocarbon groups having 6 to 12 carbon atoms, or a bicyclic fused ring system wherein one or both of the rings is aromatic. Bicyclic fused ring systems consist of a phenyl group fused to a four- to seven-membered aromatic or non-aromatic carbocyclic ring. Representative examples of aryl groups include but are not limited to phenyl, indanyl, indenyl, naphthyl, and tetrahydronaphthyl. "Heteroaryl" means a 5 to 7 membered monocyclic or 8 to 11 membered bicyclic aromatic ring system with 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur. Where a bonding attachment location is not specified, the bonding may be attached at any appropriate location as understood by practitioners in the art. Combinations of substituents and bonding patterns are only those that result in stable compounds as understood by practitioners in the art. Parenthetic and multiparenthetic terms are intended to clarify bonding relationships to those skilled in the art. For example, a term such as ((R)alkyl) means an alkyl substituent further substituted with the substituent R.

As used herein, "heterocycloalkyl" refers to non-aromatic monocyclic or polycyclic heterocycles having one or more ring-forming heteroatoms selected from O, N,

or S. Heterocycloalkyl groups can also include spirocycles and bridged rings, e.g., a 5-8 membered bridged heterocycloalkyl ring optionally substituted with 0 to 2 additional heteroatoms independently selected from nitrogen, oxygen and sulfur. Example heterocycloalkyl groups include pyrrolidin-2-one, 1,3-isoxazolidin-2-one, pyranyl, tetrahydropuran, oxetanyl, azetidinyl, morpholine, thiomorpholino, piperazinyl, tetrahydrofuranyl, tetrahydrothienyl, piperidinyl, pyrrolidinyl, isoxazolidinyl, isothiazolidinyl, pyrazolidinyl, oxazolidinyl, thiazolidinyl, imidazolidinyl, azepanyl, benzazapene, azabicyclo[3.1.0]hexanyl, diazabicyclo[3.1.0]hexanyl, oxabicyclo[2.1.1]hexanyl, azabicyclo[2.2.1]heptanyl, diazabicyclo[2.2.1]heptanyl, azabicyclo[3.1.1]heptanyl, diazabicyclo[3.1.1]heptanyl, azabicyclo[3.2.1]octanyl, diazabicyclo[3.2.1]octanyl, oxabicyclo[2.2.2]octanyl, azabicyclo[2.2.2]octanyl, azaadamantanyl, diazaadamantanyl, oxa-adamantanyl, azaspiro[3.3]heptanyl, diazaspiro[3.3]heptanyl, oxa-azaspiro[3.3]heptanyl, azaspiro[3.4]octanyl, diazaspiro[3.4]octanyl, oxa-azaspiro[3.4]octanyl, azaspiro[2.5]octanyl, diazaspiro[2.5]octanyl, azaspiro[4.4]nonanyl, diazaspiro[4.4]nonanyl, oxa-azaspiro[4.4]nonanyl, azaspiro[4.5]decanyl, diazaspiro[4.5]decanyl, diazaspiro[4.4]nonanyl, oxa-diazaspiro[4.4]nonanyl, chormane and the like. Ring-forming carbon atoms and heteroatoms of a heterocycloalkyl group can be optionally substituted by oxo or sulfido (e.g., C(O), S(O), C(S), or $S(O)_2$, etc.). The heterocycloalkyl group can be attached through a ring-forming carbon atom or a ring-forming heteroatom. In some embodiments, the heterocycloalkyl group contains 0 to 3 double bonds. In some embodiments, the heterocycloalkyl group contains 0 to 2 double bonds. A heterocycloalkyl group containing a fused aromatic ring can be attached through any ring-forming atom including a ring-forming atom of the fused aromatic ring. In some embodiments, the heterocycloalkyl is a monocyclic or bicyclic 4-10 membered heterocycloalkyl having 1, 2, 3, or 4 heteroatoms independently selected from nitrogen, oxygen, or sulfur and having one or more oxidized ring members.

As used herein, "cycloalkyl" refers to non-aromatic cyclic hydrocarbons including cyclized alkyl and/or alkenyl groups. Cycloalkyl groups can include mono- or polycyclic (e.g., having 2, 3 or 4 fused rings) groups, spirocycles, and bridged rings. Ring-forming carbon atoms of a cycloalkyl group can be optionally substituted by oxo or sulfido (e.g., C(O) or C(S)). Also included in the definition of cycloalkyl are moieties that have one or

more aromatic rings fused (i.e., having a bond in common with) to the cycloalkyl ring, for example, benzo or thienyl derivatives of cyclopentane, cyclohexane, and the like. A cycloalkyl group containing a fused aromatic ring can be attached through any ring-forming atom including a ring-forming atom of the fused aromatic ring. Cycloalkyl groups can have 3, 4, 5, 6, 7, 8, 9, or 10 ring-forming carbons (C_{3-10}). In some embodiments, the cycloalkyl is a C_{3-10} monocyclic or bicyclic cyclocalkyl. In some embodiments, the cycloalkyl is a C_{3-7} monocyclic cyclocalkyl. In some embodiments, the cycloalkyl is a C_{4-10} spirocycle or bridged cycloalkyl. Example cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptatrienyl, norbomyl, norpinyl, norcamyl, cubane, adamantane, bicyclo[1.1.1]pentyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptanyl, bicyclo[3.1.1]heptanyl, bicyclo[2.2.2]octanyl, spiro[3.3]heptanyl, and the like. In some embodiments, cycloalkyl is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

"Cycloalkylalkyl" refers to an alkyl group that has at least one hydrogen atom substituted with a cycloalkyl group as herein defined.

The invention includes all pharmaceutically acceptable salt forms of the compounds. Pharmaceutically acceptable salts are those in which the counter ions do not contribute significantly to the physiological activity or toxicity of the compounds and as such function as pharmacological equivalents. These salts can be made according to common organic techniques employing commercially available reagents. Some anionic salt forms include acetate, acistrate, besylate, bromide, chloride, citrate, fumarate, glucouronate, hydrobromide, hydrochloride, hydroiodide, iodide, lactate, maleate, mesylate, nitrate, pamoate, phosphate, succinate, sulfate, tartrate, tosylate, and xinofoate. Some cationic salt forms include ammonium, aluminum, benzathine, bismuth, calcium, choline, diethylamine, diethanolamine, lithium, magnesium, meglumine, 4-phenylcyclohexylamine, piperazine, potassium, sodium, tromethamine, and zinc.

Some of the compounds of the invention exist in stereoisomeric forms including the structure below with the indicated carbon. The invention includes all stereoisomeric forms of the compounds including enantiomers and diastereomers. Methods of making and separating stereoisomers are known in the art. The invention includes all tautomeric forms of the compounds. The invention includes atropisomers and rotational isomers.

The invention is intended to include all isotopes of atoms occurring in the compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include deuterium and tritium. Isotopes of carbon include ^{13}C and ^{14}C. Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed. Such compounds may have a variety of potential uses, for example as standards and reagents in determining biological activity. In the case of stable isotopes, such compounds may have the potential to favorably modify biological, pharmacological, or pharmacokinetic properties.

BIOLOGICAL METHODS

N-formyl peptide receptors (FPRs) are a family of chemo attractant receptors that facilitate leukocyte response during inflammation. FPRs belong to the seven-transmembrane G protein-coupled receptor superfamily and are linked to inhibitory G-proteins (Gi). Three family members (FPR1, FPR2 and FPR3) have been identified in humans and are predominantly found in myeloid cells with varied distribution and have also been reported in multiple organs and tissues. After agonist binding, the FPRs activate a multitude of physiological pathways, such as intra cellular signaling transduction, Ca^{2+} mobilization and transcription. The family interacts with a diverse set of ligands that includes proteins, polypeptides and fatty acid metabolites which activate both pro-inflammatory and pro-resolution downstream responses. FPR2 and FPR1 Cyclic Adenosine Monophosphate (cAMP) Assays were used to measure the activity of the compounds in this patent.

FPR2 and FPR1 Cyclic Adenosine Monophosphate (cAMP) Assays. A mixture of forskolin (5 μM final for FPR2 or 10 μM final for FPR1) and IBMX (200 μM final) were added to 384-well Proxiplates (Perkin-Elmer) pre-dotted with test compounds in DMSO (1% final) at final concentrations in the range of 0.020 nM to 100 μM. Chinese Hamster Ovary cells (CHO) overexpressing human FPR1 or human FPR2 receptors were cultured in F-12 (Ham's) medium supplemented with 10% qualified FBS, 250 μg/ml zeocin and 300 μg/ml hygromycin (Life Technologies). Reactions were initiated by adding 2,000

human FPR2 cells per well or 4,000 human FPR1 cells per well in Dulbecco's PBS (with calcium and magnesium) (Life Technologies) supplemented with 0.1% BSA (Perkin-Elmer). The reaction mixtures were incubated for 30 min at room temperature. The level of intracellular cAMP was determined using the HTRF HiRange cAMP assay reagent kit (Cisbio) according to manufacturer's instruction. Solutions of cryptate conjugated anti-cAMP and d2 flurorophore-labelled cAMP were made in a supplied lysis buffer separately. Upon completion of the reaction, the cells were lysed with equal volume of the d2-cAMP solution and anti-cAMP solution. After a 1-h room temperature incubation, time-resolved fluorescence intensity was measured using the Envision (Perkin-Elmer) at 400 nm excitation and dual emission at 590 nm and 665 nm. A calibration curve was constructed with an external cAMP standard at concentrations ranging from 1 μM to 0.1 pM by plotting the fluorescent intensity ratio from 665 nm emission to the intensity from the 590 nm emission against cAMP concentrations. The potency and activity of a compound to inhibit cAMP production was then determined by fitting to a 4-parametric logistic equation from a plot of cAMP level versus compound concentrations.

The examples disclosed below were tested in the FPR2 and FPR1 cAMP assay described above and found having FPR2 and/or FPR1 agonist activity. Table 1 below lists EC_{50} values in the FPR2 and FPR1 cAMP assays measured for the following examples.

Table 1

Example	**hFPR2 cAMP2 EC_{50} (μM)**	**hFPR1 cAMP EC_{50} (μM)**
1	0.0148	6.8
2	0.020	0.04
3	0.006	0.02
4	0.0001	0.0054
5	0.0002	0.0000
6	0.0004	0.0001
7	0.0005	0.0007
8	0.0006	0.0005
9	0.0007	0.0060
10	0.0007	0.0005
11	0.0008	0.0001
12	0.0009	0.0008
13	0.0013	0.0000
14	0.0014	0.0008

Example	hFPR2 cAMP2 EC_{50} (μM)	hFPR1 cAMP EC_{50} (μM)
15	0.0015	0.0132
16	0.0017	0.0047
17	0.0017	0.0006
18	0.0018	0.0002
19	0.0019	0.0301
20	0.0026	0.0389
21	0.0015	0.0004
22	0.0027	0.0021
23	0.0028	0.0540
24	0.0028	0.0180
25	0.0028	1.6317
26	0.0028	NA
27	0.0029	0.0025
28	0.0033	0.0030
29	0.0033	0.0024
30	0.0036	2.5
31	0.0038	0.11
32	0.0039	1.2
33	0.0040	0.0042
34	0.0042	0.0003
35	0.0045	0.062
36	0.0026	0.010
37	0.0045	0.011
38	0.0045	0.0013
39	0.0048	0.021
40	0.0053	0.20
41	0.0056	0.0005
42	0.0058	0.0017
43	0.0060	0.0071
44	0.0062	>10
45	0.0067	0.5623
46	0.0071	0.0015
47	0.0073	>10
48	0.0074	0.60
49	0.0099	2.5
50	0.012	0.0012
51	0.012	0.0770
52	0.013	0.5934
53	0.013	0.0246

Example	hFPR2 cAMP2 EC_{50} (μM)	hFPR1 cAMP EC_{50} (μM)
54	0.019	0.0088
55	0.024	0.0005
56	0.024	3.9076
57	0.026	0.0012
58	0.029	0.2205
59	0.029	0.47
60	0.030	6.7
61	0.033	0.017
62	0.036	0.023
63	0.041	3.6
64	0.053	0.054
65	0.055	5.0
66	0.060	>10
67	0.097	>10
68	0.027	4.8
69	0.0052	1.8
70	0.033	1.2
71	0.054	1.1
72	0.025	>1
73	0.32	>1
74	0.026	>1
75	0.021	>1
76	0.023	>1
77	0.015	NA
78	0.050	0.10
79	0.0073	NA
80	0.011	0.001
81	0.0059	0.0015
82	0.0099	0.0008
83	0.0010	0.012
84	0.0014	0.0003
85	0.0044	0.0076
86	0.0014	0.0003
87	0.0032	0.0048
88	0.0091	>10
89	0.0071	0.0043
90	0.0040	0.0037
91	0.0077	0.78
92	0.044	>5

Example	hFPR2 cAMP2 EC_{50} (μM)	hFPR1 cAMP EC_{50} (μM)
93	0.014	1.7
94	0.0016	0.0012
95	0.004	0.0053
96	0.0046	3.4
97	0.0004	1.4
98	0.0072	>5
99	0.0062	0.73
100	0.0090	>10
101	0.0016	>10
102	0.0079	1.0
103	0.017	2.1
104	0.039	5.0
105	0.017	1.2
106	0.023	1.7
107	0.028	2.8
108	0.67	3.5
109	0.054	1.1

PHARMACEUTICAL COMPOSITIONS AND METHODS OF USE

The compounds of the present invention may be administered to mammals, preferably humans, for the treatment of a variety of conditions and disorders including atherosclerosis, heart failure, lung diseases including asthma, COPD, and cystic fibrosis; neuroinflammatory diseases including multiple sclerosis, Alzheimer's disease, and stroke; and chronic inflammatory diseases such as inflammatory bowel disease, rheumatoid arthritis, psoriasis, sepsis, and kidney fibrosis.

Unless otherwise specified, the following terms have the stated meanings. The term "subject" refers to any human or other mammalian species that could potentially benefit from treatment with a FPR2 and/or FPR1 agonist as understood by practioners in this field. Some subjects include human beings of any age with risk factors for cardiovascular disease. Common risk factors include age, sex, weight, family history, sleep apnea, alcohol or tobacco use, physical inactivity arrthymia or signs of insulin resistance such as acanthosis nigricans, hypertension, dyslipidemia, or polycystic ovary syndrome (PCOS). The term "patient" means a person suitable for therapy as determined by practitioners in the field. "Treating" or "treatment" cover the treatment of a patient or subject as understood by practitioners in this field. "Preventing" or "prevention" cover the preventive treatment (*i.e.*,

prophylaxis and/or risk reduction) of a subclinical disease-state in a patient or subject aimed at reducing the probability of the occurrence of a clinical disease-state as understood by practitioners in this field. 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. "Therapeutically effective amount" means an amount of a compound that is effective as understood by practitioners in this field.

Another aspect of the invention are pharmaceutical compositions comprising a therapeutically effective amount of a compound of Formula (I) in combination with a pharmaceutical carrier.

Another aspect of the invention are pharmaceutical compositions comprising a therapeutically effective amount of a compound of Formula (I) in combination with at least one other therapeutic agent and a pharmaceutical carrier.

"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, anti-bacterial agents, anti-fungal 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, L.V., Jr. et al., *Remington: The Science and Practice of Pharmacy* (2 Volumes), 22nd Edition, Pharmaceutical Press (2012).

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

Another aspect of the invention is a method for treating heart disease comprising administering a therapeutically effective amount of a compound of Formula (I) to a patient.

Another aspect of the invention is a method for treating heart disease wherein the heart disease is selected from the group consisting of angina pectoris, unstable angina, myocardial infarction, heart failure, acute coronary disease, acute heart failure, chronic heart failure, and cardiac iatrogenic damage.

It will be understood that treatment or prophylaxis of heart failure may involve treatment or prophylaxis of a cardiovascular event as well. Treatment or prophylaxis as referred to herein may refer to treatment or prophylaxis of certain negative symptoms or

conditions associated with or arising as a result of a cardiovascular event. By way of example, treatment or prophylaxis may involve reducing or preventing negative changes in fractional shortening, heart weight, lung weight, myocyte cross sectional area, pressure overload induced cardiac fibrosis, stress induced cellular senescence, and/or cardiac hypertrophy properties, or any combination thereof, associated with or arising as a result of a cardiovascular event. Treatment may be administered in preparation for or in response to a cardiovascular event to alleviate negative effects. Prevention may involve a pro-active or prophylactic type of treatment to prevent the cardiovascular event or to reduce the onset of negative effects of a cardiovascular event.

In one embodiment, the present invention provides the use of a compound of Formulae (I)-(XIVa) or a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition for the treatment or prophylaxis of heart failure, for example, heart failure results from hypertension, an ischemic heart disease, a non-ischemic heart disease, exposure to a cardiotoxic compound, myocarditis, Kawasaki's disease, Type I and Type II diabetes, thyroid disease, viral infection, gingivitis, drug abuse, alcohol abuse, pericarditis, atherosclerosis, vascular disease, hypertrophic cardiomyopathy, dilated cardiomyopathy, myocardial infarction, atrial fibrosis, left ventricular systolic dysfunction, left ventricular diastolic dysfunction, coronary bypass surgery, pacemaker implantation surgery, starvation, an eating disorder, muscular dystrophies, and a genetic defect. Preferably, the heart failure to be treated is diastolic heart failure, heart failure with reduced ejection fraction (HF_REF), heart failure with preserved ejection fraction (HF_PEF), acute heart failure, and chronic heart failure of ischemic and non-ischemic origin.

In one embodiment, the present invention provides the use of a compound of Formulae (I)-(XIVa) to treat systolic and/or diastolic dysfunction, wherein the compound is administered in a therapeutically effective amount to increase the ability of the cardiac muscle cells to contract and relax thereby increasing the filling and emptying of both the right and left ventricles, preferably, the left ventricle.

In another embodiment, the present invention provides the use of a compound of Formulae (I)-(XIVa) to treat heart failure wherein the compound is administered in a therapeutically effective amount to increase ejection fraction in the left ventricle.

In still another embodiment, the present invention provides the use of a compound of Formulae (I)-(XIVa) to treat heart failure wherein the compound is administered in a therapeutically effective amount to reduce fibrosis in heart tissue.

Another aspect of the invention is a method for treating heart disease wherein the treatment is post myocardial infarction.

Another aspect of the invention is a method for treating heart disease comprising administering a therapeutically effective amount of a compound of Formulae (I)-(XIVa) to a patient in conjuction with other therapeutic agents.

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

The 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 0.01 to about 5000 mg per day, preferably between about 0.1 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.

Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 2000 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.1-95% by weight based on the total weight of the composition. A typical capsule for oral administration contains at least one of the compounds of the present invention (250 mg), lactose (75 mg), and magnesium stearate (15 mg). The mixture is passed through a 60 mesh sieve and packed into a No. 1 gelatin capsule. A typical injectable preparation is produced by aseptically placing at least one of the compounds of the present invention (250 mg) into a vial, aseptically freeze-drying and sealing. For use, the contents of the vial are mixed with 2 mL of physiological saline, to produce an injectable preparation.

The compounds of the present invention may be employed in combination with other suitable therapeutic agents useful in the treatment of the aforementioned diseases or disorders including: 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-hypertensive agents, anti-obesity agents, anti-hyperlipidemic agents, anti-hypertriglyceridemic agents, anti-hypercholesterolemic agents, anti-restenotic agents, anti-pancreatic agents, lipid lowering agents, anorectic agents, memory enhancing agents, anti-dementia agents, cognition promoting agents, appetite suppressants, agents for treating heart failure, agents for treating peripheral arterial disease, agents for treating malignant tumors, and anti-inflammatory agents.

The compounds of the invention may be used with at least one of the following heart failure agents selected from loop diuretics, Angiotensin converting enzyme (ACE) inhibitors, Angiotensin II receptor blockers (ARBs), angiotensin receptor-neprilysin inhibitors (ARNI), beta blockers, mineralocorticoid receptor antagonists, nitroxyl donors, RXFP1 agonists, APJ agonists and cardiotonic agents. These agents include, but are not limited to furosemide, bumetanide, torsemide, sacubitrial-valsartan, thiazide diruetics, captopril, enalapril, lisinopril, carvedilol, metopolol, bisoprolol, serelaxin, spironolactone, eplerenone, ivabradine, candesartan, eprosartan, irbestarain, losartan, olmesartan, telmisartan, and valsartan.

The compounds of the present invention may be employed in combination with at least one of the following therapeutic agents in treating atherosclerosis: anti-hyperlipidemic agents, plasma HDL-raising agents, anti-hypercholesterolemic agents, cholesterol biosynthesis inhibitors (such as HMG CoA reductase inhibitors), LXR agonist, probucol, raloxifene, nicotinic acid, niacinamide, cholesterol absorption inhibitors, bile acid sequestrants (such as anion exchange resins, or quaternary amines (*e.g.*, cholestyramine or colestipol)), low density lipoprotein receptor inducers, clofibrate, fenofibrate, benzofibrate, cipofibrate, gemfibrizol, vitamin B_6, vitamin B_{12}, anti-oxidant vitamins, β-blockers, anti-diabetes agents, angiotensin II antagonists, angiotensin converting enzyme inhibitors, platelet aggregation inhibitors, fibrinogen receptor antagonists, aspirin and fibric acid derivatives.

The compounds of the present invention may be employed in combination at least one of the following therapeutic agents in treating cholesterol biosynthesis inhibitor, particularly an HMG-CoA reductase inhibitor. Examples of suitable HMG-CoA reductase inhibitors include, but are not limited to, lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, and rosuvastatin.

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

The compounds of the invention may be used in combination with at least one of the following anti-obesity agents selected from phenylpropanolamine, phentermine, diethylpropion, mazindol, fenfluramine, dexfenfluramine, phentiramine, β_3-adrenoreceptor agonist agents; sibutramine, gastrointestinal lipase inhibitors (such as orlistat), and leptins. Other agents used in treating obesity or obesity-related disorders include neuropeptide Y, enterostatin, cholecytokinin, bombesin, amylin, histamine H_3 receptors, dopamine D_2 receptor modulators, melanocyte stimulating hormone, corticotrophin releasing factor, galanin and gamma amino butyric acid (GABA).

The 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 FPR2. Such compounds may be provided in a commercial kit, for example, for use in pharmaceutical research involving FPR2 activity. For example, a compound of the present invention could be used as a reference in an assay to compare its known activity to a compound with an unknown activity. This would ensure the experimenter that the assay was being performed properly and provide a basis for comparison, especially if the test compound was a derivative of the reference compound. When developing new assays or protocols, compounds according to the present invention could be used to test their effectiveness. The compounds of the present invention may also be used in diagnostic assays involving FPR2.

The present invention also encompasses an article of manufacture. As used herein, article of manufacture is intended to include, but not be limited to, kits and packages. The article of manufacture of the present invention, comprises: (a) a first container; (b) a pharmaceutical composition located within the first container, wherein the composition, comprises a first therapeutic agent, comprising a compound of the present invention or a pharmaceutically acceptable salt form thereof; and, (c) a package insert stating that the pharmaceutical composition can be used for the treatment of dyslipidemias and the sequelae thereof. 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 of dyslipidemias and the sequelae thereof. The article of manufacture can further comprise: (d) a second container, wherein components (a) and (b) are located within the second container and component (c) is located within or outside of the second container. Located within the first and second containers means that the

respective container holds the item within its boundaries. The first container is a receptacle used to hold a pharmaceutical composition. This container can be for manufacturing, storing, shipping, and/or individual/bulk selling. First container is intended to cover a bottle, jar, vial, flask, syringe, tube (*e.g.*, for a cream preparation), or any other container used to manufacture, hold, store, or distribute a pharmaceutical product. The second container is one used to hold the first container and, optionally, the package insert. Examples of the second container include, but are not limited to, boxes (*e.g.*, cardboard or plastic), crates, cartons, bags (*e.g.*, paper or plastic bags), pouches, and sacks. The package insert can be physically attached to the outside of the first container via tape, glue, staple, or another method of attachment, or it can rest inside the second container without any physical means of attachment to the first container. Alternatively, the package insert is located on the outside of the second container. When located on the outside of the second container, it is preferable that the package insert is physically attached via tape, glue, staple, or another method of attachment. Alternatively, it can be adjacent to or touching the outside of the second container without being physically attached. The package insert is a label, tag, marker, etc. that recites information relating to the pharmaceutical composition located within the first container. The information recited will usually be determined by the regulatory agency governing the area in which the article of manufacture is to be sold (*e.g.*, the United States Food and Drug Administration). Preferably, the package insert specifically recites the indications for which the pharmaceutical composition has been approved. The package insert may be made of any material on which a person can read information contained therein or thereon. Preferably, the package insert is a printable material (*e.g.*, paper, plastic, cardboard, foil, adhesive-backed paper or plastic, etc.) on which the desired information has been formed (*e.g.*, printed or applied).

CHEMISTRY METHODS

Abbreviations as used herein, are defined as follows: "1x" for once, "2x" for twice, "3x" for thrice, " °C" for degrees Celsius, "aq" for aqueous, "Col" for column, "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, "nM" for nanomolar, "mol" for mole or moles, "mmol" for millimole or millimoles, "min" for minute or minutes, "h" for hour or hours, "rt" for room

temperature, "RT" for retention time, "ON" for overnight, "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, "mw" or "μwave" for microwave, "mp" for melting point, "Wt" for weight, "MS" or "Mass Spec" for mass spectrometry, "ESI" for electrospray ionization mass spectroscopy, "HR" for high resolution, "HRMS" for high resolution mass spectrometry, "LCMS" for liquid chromatography mass spectrometry, "HPLC" for high pressure liquid chromatography, "RP HPLC" for reverse phase HPLC, "TLC" or "tlc" for thin layer chromatography, "NMR" for nuclear magnetic resonance spectroscopy, "nOe" for nuclear Overhauser effect spectroscopy, "^{1}H" for proton, "δ " for delta, "s" for singlet, "d" for doublet, "t" for triplet, "q" for quartet, "m" for multiplet, "br" for broad, "Hz" for hertz, and "α", "β", "R", "S", "E", and "Z" are stereochemical designations familiar to one skilled in the art.

Ac	Acetic
AcOH	acetic acid
Acn (or MeCN)	Acetonitrile
Bn	Benzyl
Boc	*tert*-butyl carbonyl
Boc_2O	di-*tert*-butyl dicarbonate
Bu	Butyl
Dba as in $(Pd_2(dba)_3)$	dibenzylideneacetone
Cbz	Carboxybenzyl
DCM	Dichloromethane
DEA	Diethylamine
DIEA or DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	Dimethylformamide
DMSO	dimethyl sulfoxide
dppf	1,1′-bis(diphenylphosphino)ferrocene
Et	ethyl
EtOH	Ethanol

EtOAc	ethyl acetate
HATU	2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HBTU	2-(1*H*-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
i-Bu	Isobutyl
IPA	isopropyl alcohol
i-Pr	Isopropyl
LAH	lithium aluminum hydride
Me	Methyl
MeOH	Methanol
pet	Petroleum
Ph	Phenyl
Pr	Propyl
t-Bu	*tert*-butyl
TEA	Trimethylamine
TFA	trifluoroacetic acid
THF	Tetrahydrofuran
Ts	Tosyl

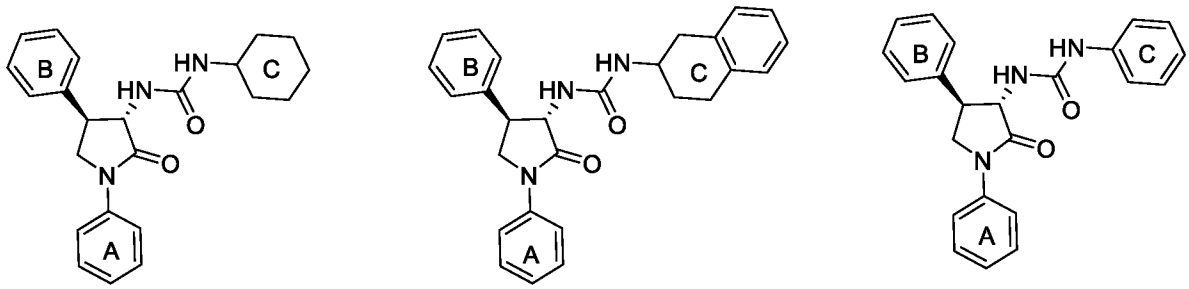
The disclosed compounds can be made by various methods known in the art including those of the following schemes and in the specific embodiments section. The structure numbering and variable numbering shown in the synthetic schemes are distinct from and should not be confused with the structure or variable numbering in the claims or the rest of the specification. The variables in the schemes are meant only to illustrate how to make some of the compounds of this invention.

The disclosure is not limited to the foregoing illustrative examples and the examples should be considered in all respects as illustrative and not restrictive, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced.

A consideration in the planning of any synthetic route in this field is the choice of the protecting group used for protection of the reactive functional groups present in the

compounds described in this invention. An authoritative account describing the many alternatives to the trained practitioner is Greene, T.W. et al., *Protecting Groups in Organic Synthesis*, 4th Edition, Wiley (2007)).

Compounds having the general Formula (I'), (II') or (III') wherein A, B and C correspond to Ar^2, Ar^3, and Ar^1, respectively, can be prepared by the following one or more of the synthetic Schemes.



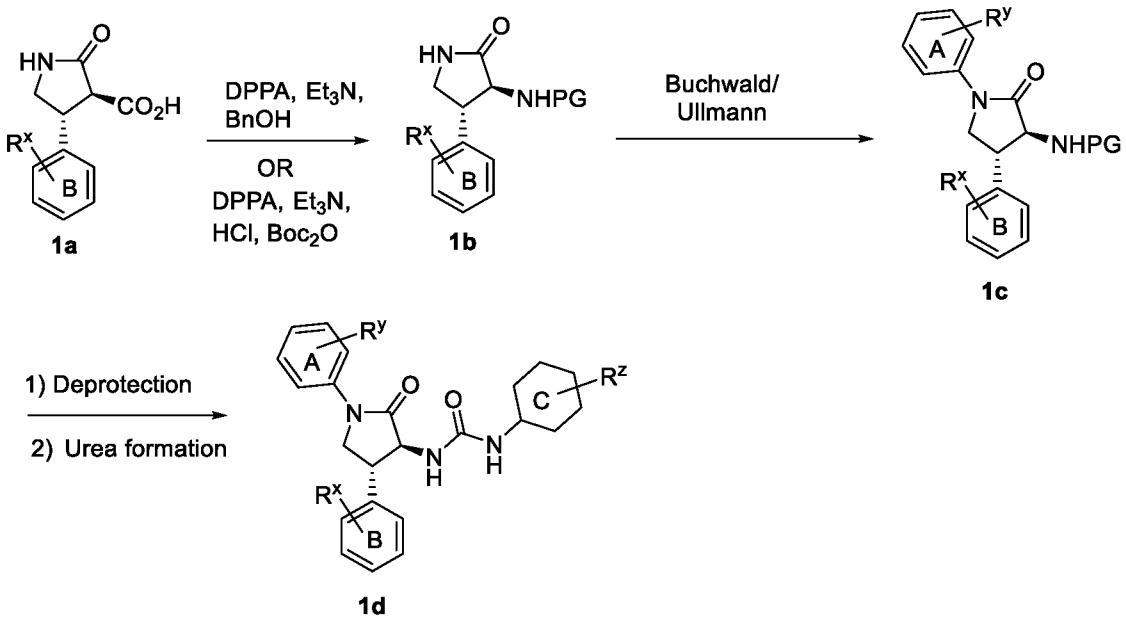
(I') (II') (III')

1-Arylpyrrolidinone compounds of this invention wherein rings A and B are substituted phenyl rings or heteroaryl rings can be prepared by the general route shown in Scheme 1. Compound **1a** was synthesized as per the procedure reported in the patent literature (WO2015079692). Compound **1b** where PG is a protecting group such as Boc or Cbz Compound was synthesized by Curtius rearrangement for example **1a** was treated with diphenylphosphoryl azide (DPPA) and a tertiary amine such as triethylamine (TEA). Subsequent addition of benzyl alcohol yielded Cbz protected compound **1b**. Copper or Pd-catalyzed coupling of **1b** to a substituted heteroaryl compounds in a suitable solvent such as butanol or dioxane or toluene, in the presence of a base such as potassium carbonate or cesium carbonate and a suitable ligand such as N,N'-dimethylethylenediamine, or Xanthphos can afford desired compounds **1c**. Suitable heteroaryl halides are either commercially available or can be readily obtained from the corresponding readily available starting materials by methods known to one skilled in the art. Additional methods for this transformation include other variations of Ullmann, Goldberg, and Buchwald copper-catalyzed amidation or Buchwald Pd-catalyzed C-N coupling depending on the nature of ring B, using methods known to one skilled in the art for these types of couplings (see for example Yin & Buchwald, Organic Lett. 2000, 2, 1101; Klapers et al., JACS, 2001, 123, 7727; Klapars et al., JACS, 2002, 124, 7421; Yin & Buchwald, JACS. 2002, 124, 6043; Kiyomor, Madoux & Buchwald, Tet. Lett., 1999, 40, 2657). Removal of the protecting group from **1c**, followed by condensation of the resulting free amine with a suitably

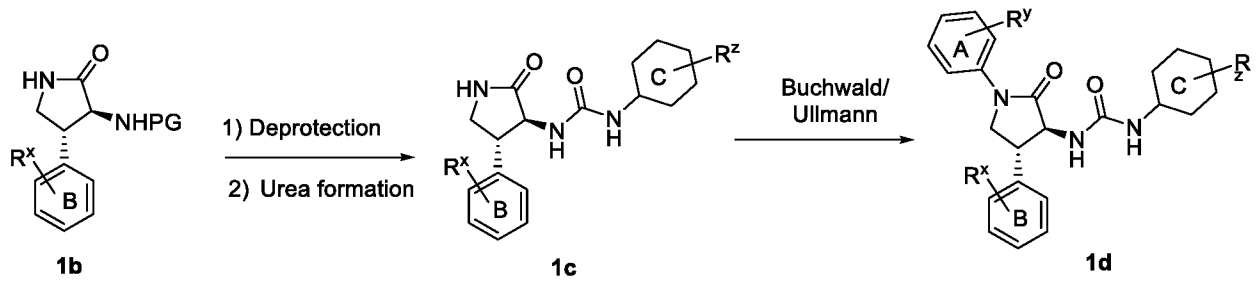
substituted aryl isocyanate or cycloalkyl isocyanate, or cycloakyl acids can provide ureas **1d**. Suitable isocyanates or cycloakyl acids are either commercially available or can be readily obtained by methods known to one skilled in the art.

Similarly, 1-arylpyrrolidinone compounds of this invention (Formula (I'), (II'), or (III')) wherein rings A and B are substituted phenyl rings or heteroaryl rings can be prepared by the general route shown in Scheme 2.

Scheme 1



Scheme 2



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

The following methods were used in the exemplified Examples, except where noted otherwise. Purification of intermediates and final products was carried out via either normal or reverse phase chromatography. Normal phase chromatography was carried out using prepacked SiO_2 cartridges eluting with either gradients of hexane and ethyl acetate or DCM and MeOH unless otherwise indicated. Reverse phase preparative HPLC was carried out using C18 columns with UV 220 nm or prep LCMS detection eluting with gradients of Solvent A (90% water, 10% MeOH, 0.1% TFA) and Solvent B (10% water, 90% MeOH, 0.1% TFA) or with gradients of Solvent A (95% water, 5% Acn, 0.1% TFA) and Solvent B (5% water, 95% Acn, 0.1% TFA) or with gradients of Solvent A (95% water, 2% Acn, 0.1% HCOOH) and Solvent B (98% Acn, 2% water, 0.1% HCOOH) or with gradients of Solvent A (95% water, 5% Acn, 10 mM NH_4OAc) and Solvent B (98% Acn, 2% water, 10 mM NH_4OAc) or with gradients of Solvent A (98% water, 2% Acn, 0.1% NH_4OH) and Solvent B (98% Acn, 2% water, 0.1% NH_4OH).

LC/MS Methods Employed in Characterization of Examples. Reverse phase analytical HPLC/MS was performed on a Waters Acquity system coupled with a Waters MICROMASS® ZQ Mass Spectrometer.

Method A: Linear gradient of 0 to 100% B over 3 min, with 0.75 min hold time at 100% B;

UV visualization at 220 nm
Column: Waters BEH C18 2.1 x 50 mm
Flow rate: 1.0 mL/min
Solvent A: 0.1% TFA, 95% water, 5% Acn
Solvent B: 0.1% TFA, 5% water, 95% Acn

Method B: Linear gradient of 0 to 100% B over 3 min, with 0.75 min hold time at 100% B;

UV visualization at 220 nm
Column: Waters BEH C18 2.1 x 50 mm
Flow rate: 1.0 mL/min
Solvent A: 10 mM ammonium acetate, 95% water, 5% Acn

Solvent B: 10 mM ammonium acetate, 5% water, 95% Acn

Analytical HPLC: Methods Employed in Characterization of Examples

Products were analyzed by reverse phase analytical HPLC: carried out on a Shimadzu Analytical HPLC: system running Discovery VP software. RT = retention time.

Method C: Ascentis Express C18, 2.1 x 50 mm, 2.7-µm particles; Solvent A: 95% water, 5% acetonitrile, 0.05% TFA; Solvent B: 95% acetonitrile, 5% water, 0.1% TFA; Temperature: 50 °C; Gradient: 0-100% B over 3 minutes, then a 1-minute hold at 100% B; Flow: 1.1 mL/min.

Method D: Ascentis Express C18, 2.1 x 50 mm, 2.7-µm particles; Solvent A: 95% water, 5% acetonitrile with 10 mM ammonium acetate; Solvent B: 95% acetonitrile, 5% water with 10 mM ammonium acetate; Temperature: 50 °C; Gradient: 0-100% B over 3 minutes, then a 1-minute hold at 100% B; Flow: 1.1 mL/min.

Method E: Kinetex biphenyl (4.6X100) mm, 2.6-µm particles; Solvent A: 95% buffer (0.05% TFA in water), 5% acetonitrile; Solvent B: 95% acetonitrile, 5% buffer (0.05% TFA in water); Temperature: 50 °C; Gradient: 0-100% B over 3 minutes, then a 1-minute hold at 100% B; Flow: 1.1 mL/min.

Method F: Ascentis Express C18, 2.1 x 50 mm, 2.7-µm particles; Solvent A: 95% water, 5% acetonitrile with 10 mM ammonium formate; Solvent B: 95% acetonitrile, 5% water with 10 mM ammonium formate; Temperature: 50 °C; Gradient: 0-100% B over 3 minutes, then a 1-minute hold at 100% B; Flow: 1.1 mL/min.

SFC and chiral purity methods

Method A: DAD-1: CHIRALPAK IA (250*4.6) mm, 5µm; DAD-2: CHIRALPAK IB (250*4.6) mm, 5µm. co-solvent: 0.2% ammonia in acetonitrile: methanol (1:1)

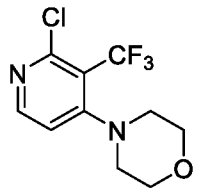
Method B: DAD-1: CHIRALPAK IC (250*4.6) mm, 5µm; DAD-2: CHIRALPAK ID (250*4.6) mm, 5µm. co-solvent: 0.2% ammonia in acetonitrile: methanol (1:1)

Method C: DAD-1: CHIRALPAK IE (250*4.6) mm, 5µm; DAD-2: CHIRALPAK IF (250*4.6) mm, 5µm. co-solvent: 0.2% ammonia in acetonitrile: methanol (1:1)

NMR Employed in Characterization of Examples. ^{1}H NMR spectra were obtained with Bruker or JEOL® Fourier transform spectrometers operating at frequencies as follows: ^{1}H NMR: 300 MHz (Bruker or JEOL®) or 400 MHz (Bruker or JEOL®) or 500

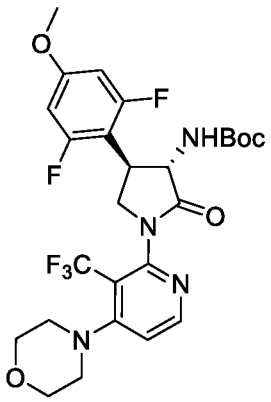
MHz (Bruker or JEOL®). ^{13}C NMR: 100 MHz (Bruker or JEOL®). Spectra data are reported in the format: chemical shift (multiplicity, coupling constants, and number of hydrogens). Chemical shifts are specified in ppm downfield of a tetramethylsilane internal standard (δ units, tetramethylsilane = 0 ppm) and/or referenced to solvent peaks, which in ^{1}H NMR spectra appear at 2.49 ppm for CD_2HSOCD_3, 3.30 ppm for CD_2HOD, 1.94 for CD_3CN, and 7.24 ppm for $CHCl_3$, and which in ^{13}C NMR spectra appear at 39.7 ppm for CD_3SOCD_3, 49.0 ppm for CD_3OD, and 77.0 ppm for $CDCl_3$. All ^{13}C NMR spectra were proton decoupled.

Intermediate 1: *4-(2-Chloro-3-(trifluoromethyl)pyridin-4-yl)morpholine*



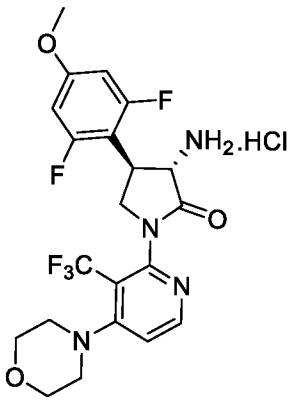
To a stirred solution of 2,4-dichloro-3-(trifluoromethyl)pyridine (500 mg, 2.3 mmol) in 1,2-dichloroethane (5 mL), were added morpholine (202 mg, 2.32 mmol), and Cs_2CO_3 (754 mg, 2.32 mmol). The reaction mixture was heated at 80 °C for 16 hours. Then, the reaction mixture was cooled, filtered through Celite pad and the filtrate was concentrated under reduced pressure to get the crude compound, which was purified by CombiFlash chromatography (24 g silica gel column; pet. ether-ethyl acetate as eluent). The desired product was eluted at 80-90% ethyl acetate in pet. ether. The pure fractions were evaporated under reduced pressure to get 4-(2-chloro-3-(trifluoromethyl)pyridin-4-yl)morpholine (200 mg, 0.75 mmol, 32 % yield) as a pale yellow solid. Two regioisomers were formed in 7:3 ratios. The structure of the major isomer was confirmed using NOE experiment. MS(ESI) m/z: 267.1 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.23 (d, J = 5.8 Hz, 1H), 6.85 (d, J = 5.8 Hz, 1H), 3.87 - 3.82 (m, 4H), 3.20 - 3.14 (m, 4H).

Intermediate-2: *tert-Butyl ((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(4-morpholino-3-(trifluoromethyl)pyridin-2-yl)-2-oxopyrrolidin-3-yl)carbamate*



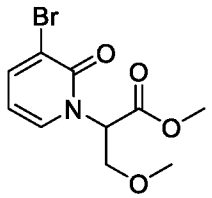
To a stirred solution of *tert*-butyl ((3*S*,4*R*)-4-(2,6-difluoro-4-methoxyphenyl)-2-oxopyrrolidin-3-yl)carbamate (200 mg, 0.584 mmol) in 1,4-dioxane (3 mL) at rt, were added 4-(2-chloro-3-(trifluoromethyl)pyridin-4-yl)morpholine (171 mg, 0.643 mmol), Cs_2CO_3 (381 mg, 1.17 mmol), and Xantphos (67.6 mg, 0.117 mmol). The reaction mixture was purged with nitrogen for 5 min and then charged with $Pd_2(dba)_3$ (54 mg, 0.058 mmol). The reaction mixture was again purged with nitrogen for 3 min and heated at 100 °C for 16 h. The brown color reaction mixture was cooled, filtered through Celite pad and the filtrate was concentrated under reduced pressure to give the crude compound, which was purified by silica gel chromatography (12 g silica gel column; pet. ether-ethyl acetate as eluent). The desired product was eluted at 80 % ethyl acetate in pet. ether. The pure fractions were evaporated under reduced pressure to afford *tert*-butyl ((3*S*,4*R*)-4-(2,6-difluoro-4-methoxyphenyl)-1-(4-morpholino-3-(trifluoromethyl)pyridin-2-yl)-2-oxopyrrolidin-3-yl)carbamate (200 mg, 0.35 mmol, 60 % yield) as a pale yellow solid. MS(ESI) m/z: 573.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ = 8.45 (d, J = 5.7 Hz, 1H), 7.34 (br s, 1H), 7.21 (d, J = 6.0 Hz, 1H), 6.87 - 6.77 (m, 2H), 4.57 - 4.43 (m, 1H), 4.35 - 4.16 (m, 1H), 4.13 - 3.95 (m, 2H), 3.79 (s, 3H), 3.86 - 3.62 (m, 4H), 3.32 - 3.01 (m, 4H), 1.33 (s, 9H).

Intermediate-3: *(3S,4R)-3-Amino-4-(2,6-difluoro-4-methoxyphenyl)-1-(4-morpholino-3-(trifluoromethyl)pyridin-2-yl)pyrrolidin-2-one, hydrochloride*



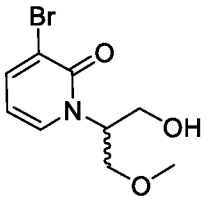
To a stirred solution of *tert*-butyl ((3*S*,4*R*)-4-(2,6-difluoro-4-methoxyphenyl)-1-(4-morpholino-3-(trifluoromethyl)pyridin-2-yl)-2-oxopyrrolidin-3-yl)carbamate (0.20 g, 0.35 mmol) in 1,4-dioxane (2 mL) at 0 °C, was added 4M HCl in 1,4-dioxane (0.87 mL, 3.5 mmol). The reaction mixture was stirred at room temperature for additional 3 hours, and concentrated under reduced pressure to get the crude compound which triturated with diethyl ether to afford (3*S*,4*R*)-3-amino-4-(2,6-difluoro-4-methoxyphenyl)-1-(4-morpholino-3-(trifluoromethyl)pyridin-2-yl)pyrrolidin-2-one,HCl (160 mg, 0.31 mmol, 90 % yield) as a pale yellow solid. MS(ESI) m/z: 473.3 $[M+H]^+$.

Intermediate 4: *Methyl 2-(3-bromo-2-oxopyridin-1(2H)-yl)-3-methoxypropanoate*



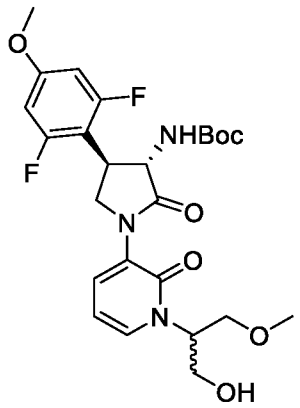
To a stirred solution of 3-bromopyridin-2(1H)-one (5.0 g, 29 mmol) in DMF (30 mL) at rt, were added K_2CO_3 (12 g, 86 mmol) and methyl 2-bromo-3-methoxypropanoate (5.8 mL, 43 mmol). Then, the reaction mixture was stirred at rt for additional 16 hours. The reaction mixture was cooled, filtered through Celite pad and the filtrate was concentrated under reduced pressure to give the crude compound, which was purified by silica gel chromatography (24 g silica gel column; pet. ether-ethyl acetate as eluent). The desired product was eluted at 60% ethyl acetate in pet. ether to give the methyl 2-(3-bromo-2-oxopyridin-1(2H)-yl)-3-methoxypropanoate (4.5 g, 16 mmol, 54% yield) as a white solid. MS(ESI) m/z: 290.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ = 7.97 (d, J = 7.0 Hz, 1H), 7.76 (d, J = 7.0 Hz, 1H), 6.33 - 6.17 (m, 1H), 5.51 - 5.38 (m, 1H), 4.10 - 3.97 (m, 1H), 3.94 - 3.84 (m, 1H), 3.67 (s, 3H), 3.35 - 3.27 (m, 1H), 3.25 (s, 3H).

Intermediate 5: *3-Bromo-1-(1-hydroxy-3-methoxypropan-2-yl)pyridin-2(1H)-one*



To a stirred solution of methyl 2-(3-bromo-2-oxopyridin-1(2H)-yl)-3-methoxypropanoate (1.0 g, 3.5 mmol) in MeOH (10 mL) at 0 °C was added sodium borohydride (0.2 g, 5.2 mmol). The reaction mixture was gradually warm up to rt over a period of 3 hours and quenched with water. Then, the reaction mixture was extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous NH_4Cl solution brine, dried over Na_2SO_4, and concentrated under reduced pressure to give the crude 3-bromo-1-(1-hydroxy-3-methoxypropan-2-yl)pyridin-2(1H)-one (0.85 g, 3.2 mmol, 94 % yield) as a white solid. MS(ESI) m/z: 262.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ = 7.90 - 7.87 (m, 1H), 7.74 - 7.71 (m, 1H), 6.21 - 6.16 (m, 1H), 5.05 - 4.99 (m, 2H), 3.78 - 3.55 (m, 4H), 3.22 (s, 3H).

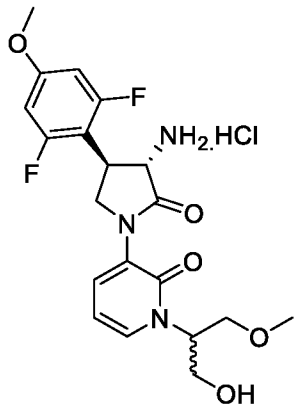
Intermediate 6: *tert-Butyl ((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-(1-hydroxy-3-methoxypropan-2-yl)-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)carbamate*



To a stirred solution of *tert*-butyl ((3*S*,4*R*)-4-(2,6-difluoro-4-methoxyphenyl)-2-oxopyrrolidin-3-yl)carbamate (250 mg, 0.73 mmol) in 1,4-dioxane (5 mL) at rt, were added 3-bromo-1-(1-hydroxy-3-methoxypropan-2-yl)pyridin-2(1H)-one (191 mg, 0.730 mmol), cesium carbonate (476 mg, 1.46 mmol), and *N*,*N*'-dimethylethylenediamine (0.016 mL, 0.15 mmol). The reaction mixture was purged with nitrogen for 5 min and then charged

with copper (I) iodide (14 mg, 0.073 mmol). The reaction mixture was again purged with nitrogen for 3 min and heated at 100 °C for 16 hours. The reaction mixture was cooled, filtered through Celite pad and the filtrate was concentrated under reduced pressure to give the crude compound, which was purified by silica gel chromatography chromatography (24 g silica gel column; pet. ether-ethyl acetate as eluent). The desired product was eluted at 75% ethyl acetate in pet. ether to afford the *tert*-butyl ((3*S*,4*R*)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-(1-hydroxy-3-methoxypropan-2-yl)-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)carbamate (250 mg, 0.48 mmol, 65 % yield) as a brown liquid. MS(ESI) m/z: 524.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ = 7.70 - 7.66 (m, 1H), 7.56 - 7.49 (m, 1H), 7.33 - 7.27 (m, 1H), 6.84 - 6.75 (m, 2H), 6.35 - 6.29 (m, 1H), 5.08 - 5.01 (m, 2H), 4.52 - 4.45 (m, 1H), 3.79 (s, 3H), 3.76 - 3.59 (m, 4H), 3.58 - 3.55 (m, 3H), 3.23 (s, 3H), 1.37 - 1.21 (m, 9H).

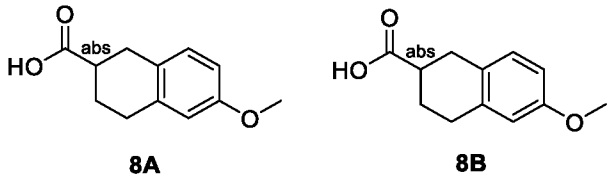
Intermediate 7: *3-((3S,4R)-3-Amino-4-(2,6-difluoro-4-methoxyphenyl)-2-oxopyrrolidin-1-yl)-1 (1-hydroxy-3-methoxypropan-2-yl)pyridin-2(1H)-one hydrochloride*



To a stirred solution of *tert*-butyl ((3*S*,4*R*)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-(1-hydroxy-3-methoxypropan-2-yl)-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)carbamate (250 mg, 0.48 mmol) in 1,4-dioxane (5 mL) at 0°C, was added 4M HCl solution in 1,4-dioxane (1.2 mL, 4.8 mmol). The reaction mixture was gradually warm up to room temperature over a period of 2 hours. Then, the reaction mixture was concentrated under reduced pressure to obtain gummy solid, which was further triturated with diethyl ether and dried under high vacuum to afford the 3-((3*S*,4*R*)-3-amino-4-(2,6-difluoro-4-methoxyphenyl)-2-oxopyrrolidin-1-yl)-1-(1-hydroxy-3-methoxypropan-2-yl)pyridin-

2(1H)-one hydrochloride (200 mg, 0.44 mmol, 91 % yield) as a brown solid. MS(ESI) m/z: 424.2 $[M+H]^+$.

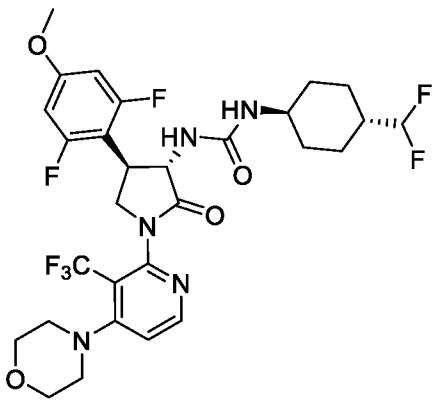
Intermediate 8: 6-methoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid



8A **8B**

Compound **8** was chiraly separated using chiral SFC. Enantiomer **8A** and **8B** were used in reaction. *SFC prep condition:* Column/dimensions: Whelk(R,R)(250 X 30) mm, 5µ; % CO_2: 90%, % Co-solvent: 10% of 4M methanolic ammonia in MeOH. Total flow: 14.0 g/min, back pressure: 100 bar, temperature: 30°C, UV: 220 nm; Retention time: peak 1 = 3.8 min and peak 2 = 4.9 min. *Enantiomer 8A:* ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.22 (br s, 1H), 7.00 (d, J = 8.3 Hz, 1H), 6.73 - 6.56 (m, 2H), 3.7 (s, 3H), 2.91 - 2.83 (m, 1H), 2.80 - 2.71 (m, 3H), 2.65 - 2.57 (m, 1H), 2.11 - 2.02 (m, 1H), 1.76 - 1.63 (m, 1H). *Enantiomer 8B:* ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.22 (br s, 1H), 7.00 (d, J = 8.3 Hz, 1H), 6.70 - 6.61 (m, 2H), 3.7 (s, 3H), 2.91 - 2.82 (m, 1H), 2.80 - 2.71 (m, 3H), 2.66 - 2.56 (m, 1H), 2.12 - 2.01 (m, 1H), 1.75 - 1.63 (m, 1H).

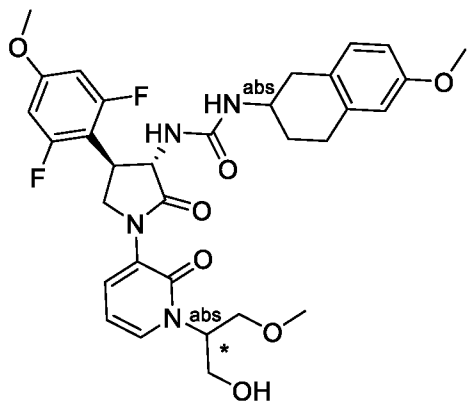
Example 1: *1-((3S,4R)-4-(2,6-Difluoro-4-methoxyphenyl)-1-(4-morpholino-3-(trifluoromethyl)pyridin-2-yl)-2-oxopyrrolidin-3-yl)-3-((1r,4S)-4-(difluoromethyl)cyclohexyl) urea*



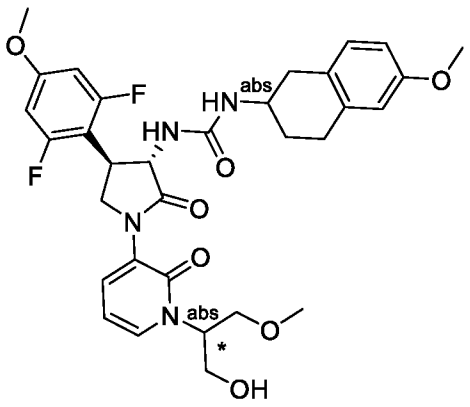
To a stirred solution of (1*R*,4*R*)-4-(difluoromethyl)cyclohexane-1-carboxylic acid (50 mg, 0.28 mmol) in toluene (5 mL) and acetonitrile (1 mL), were added TEA (0.043

mL, 0.309 mmol), and diphenylphosphoryl azide (0.067 mL, 0.31 mmol). The reaction mixture was stirred at rt for 3 hours, followed by 80 °C for 30 min. Then, the reaction mixture was cooled to rt, Intermediate 3 (80 mg, 0.17 mmol) was added, and the mixture was stirred at rt for additional 16 hours. The reaction mixture was filtered through Celite pad and evaporated under reduced pressure to afford the crude product as brown solid, which was purified *via* reverse phase HPLC to afford 1-((3*S*,4*R*)-4-(2,6-difluoro-4-methoxyphenyl)-1-(4-morpholino-3-(trifluoromethyl)pyridin-2-yl)-2-oxopyrrolidin-3-yl)-3-((1*r*,4*S*)-4-(difluoromethyl)cyclohexyl)urea (10 mg, 0.015 mmol, 5.3 % yield) as an off-white solid. MS(ESI) m/z: 643.3 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.49 - 8.35 (m, 1H), 7.20 (d, J = 5.6 Hz, 1H), 6.77 (d, J = 10.8 Hz, 2H), 6.36 - 6.20 (m, 1H), 6.04 - 5.92 (m, 1H), 5.84 (dt, J = 60.8, 4.0 Hz, 1H), 4.75 (dd, J = 11.0, 8.8 Hz, 1H), 4.33 - 4.08 (m, 1H), 4.07 - 3.91 (m, 1H), 3.78 (s, 3H), 3.76 - 3.57 (m, 5H), 3.27 - 3.06 (m, 5H), 1.91 - 1.79 (m, 1H), 1.77 - 1.58 (m, 4H), 1.19 - 0.94 (m, 4H).

Examples 2 and 3: *1-((3S,4R)-4-(2,6-Difluoro-4-methoxyphenyl)-1-(1-(1-hydroxy-3-methoxypropan-2-yl)-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)urea*



Diastereomer A



Diastereomer B

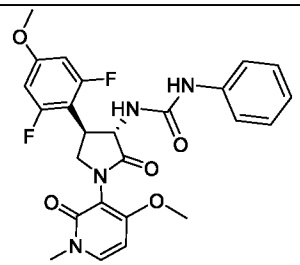
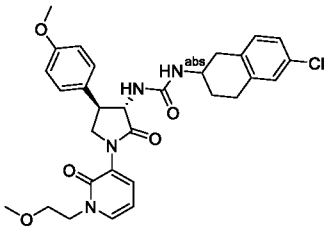
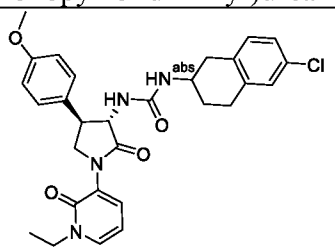
To a stirred solution of 6-methoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (70 mg, 0.34 mmol) (Intermediates 8A or 8B) in toluene (4 mL) and acetonitrile (1 mL), were added TEA (0.043 mL, 0.31 mmol), and diphenylphosphoryl azide (0.067 mL, 0.31 mmol). The reaction mixture was stirred at rt for 3 hours, followed by 80 °C for 30 min. Then, the reaction mixture was cooled to rt, Intermediate 7 (156 mg, 0.339 mmol) was added and the mixture was stirred at 60 °C for 6 hours. The reaction mixture was filtered

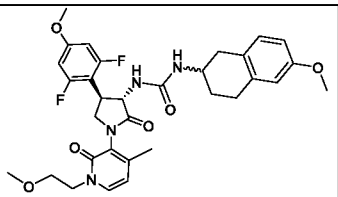
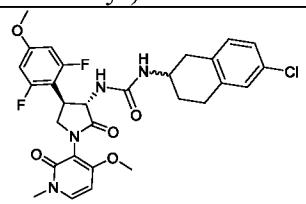
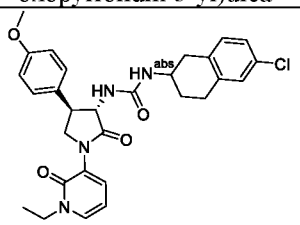
through Celite pad and evaporated under reduced pressure to afford the crude product as brown solid, which was purified *via* reverse phase HPLC followed by chiral SFC to afford 1-((3*S*,4*R*)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-(1-hydroxy-3-methoxypropan-2-yl)-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)urea (Example 2, *Diastereomer A*, 26 mg, 0.040 mmol, 13% yield) and 1-((3*S*,4*R*)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-(1-hydroxy-3-methoxypropan-2-yl)-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)urea (Example 3, *Diastereomer B*, 25 mg, 0.040 mmol, 13% yield). *SFC prep condition:* Column/dimensions: Chiralpak IC (250 X 21) mm, 5µ; % CO_2: 65%, % Co-solvent: 35% of 4M methanolic ammonia in MeOH. Total flow: 90.0g/min, back pressure: 100 bar, temperature: 35°C, UV: 222 nm; Retention time: peak 1 = 7.6 min and peak 2 = 10.1 min. Example 2, *Diastereomer A*: MS(ESI) m/z: 627.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ = 7.67 (dd, J = 7.0, 1.9 Hz, 1H), 7.52 (dd, J = 7.1, 1.9 Hz, 1H), 6.93 (d, J = 8.3 Hz, 1H), 6.78 (d, J = 10.9 Hz, 2H), 6.70 - 6.56 (m, 2H), 6.37 - 6.21 (m, 2H), 6.09 (d, J = 7.9 Hz, 1H), 5.05 (m, 2H), 4.73 (m, 1H), 3.95 - 3.88 (m, 1H), 3.86 - 3.77 (m, 5H), 3.77 - 3.70 (m, 3H), 3.69 (s, 3H), 3.68 - 3.59 (m, 2H), 3.23 (s, 3H), 2.85 - 2.71 (m, 3H), 2.44 (m, 1H), 1.93 - 1.81 (m, 1H), 1.62 - 1.51 (m, 1H). Example 3, *Diastereomer B*: MS(ESI) m/z: 627.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ = 7.67 (dd, J = 6.9, 1.9 Hz, 1H), 7.53 (dd, J = 7.2, 1.9 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 6.78 (d, J = 10.6 Hz, 2H), 6.67 (dd, J = 8.0, 3.1 Hz, 1H), 6.65 - 6.57 (m, 1H), 6.38 - 6.26 (m, 2H), 6.10 (d, J = 7.6 Hz, 1H), 5.05 (m, 2H), 4.79 - 4.68 (m, 1H), 3.93 - 3.78 (m, 3H), 3.79 (s, 3H), 3.77 - 3.70 (m, 3H),3.69 (s, 3H), 3.68 - 3.59 (m, 2H), 3.23 (s, 3H), 2.84 - 2.72 (m, 3H), 2.46 - 2.39 (m, 1H), 1.92 - 1.82 (m, 1H), 1.64 - 1.51 (m, 1H).

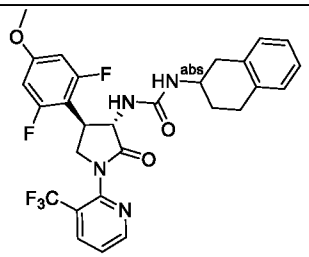
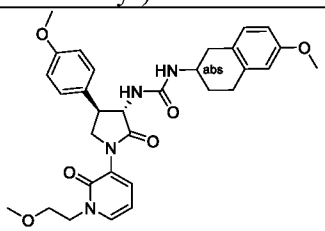
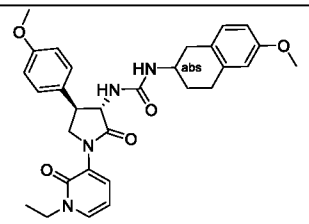
The following Examples in Table 2 were made by using the analogous procedures as shown for Examples 1-3.

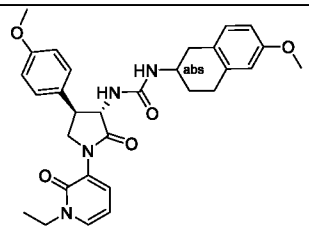
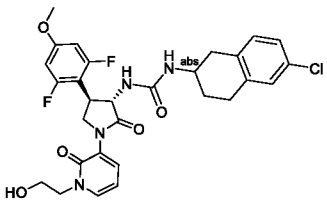
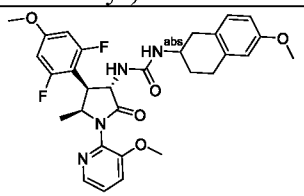
Table 2

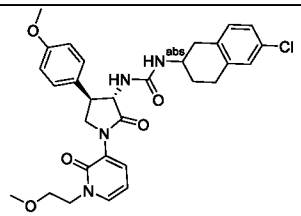
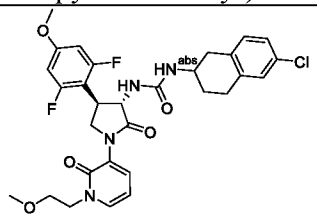
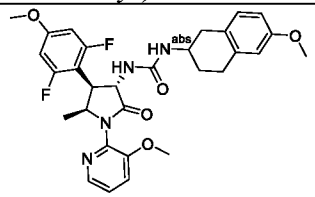
#	Structure	LCMS $(M+H)^+$	HPLC Method, RT (min) & Purity	^1H NMR

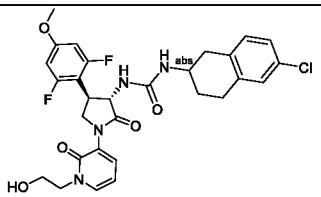
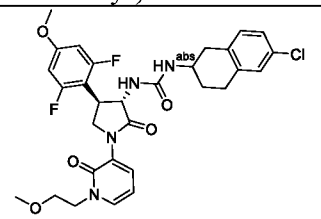
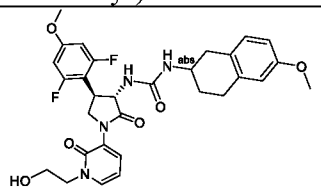
4	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(4-methoxy-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)-3-phenylurea	499.2	Method C RT = 1.37 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.54 - 8.49 (m, 1H), 7.85 - 7.78 (m, 1H), 7.39 - 7.28 (m, 2H), 7.26 - 7.16 (m, 2H), 6.94 - 6.86 (m, 1H), 6.80 - 6.75 (m, 2H), 6.72 - 6.64 (m, 1H), 6.40 - 6.34 (m, 1H), 4.98 - 4.81 (m, 1H), 3.89 - 3.85 (2s, 3H), 3.83 - 3.70 (m, 5H), 3.50 - 3.46 (m, 1H), 3.46 - 3.42 (2s, 3H). (mixture of interconvertible atropisomers)
5	 1-(6-chloro-1,2,3,4-tetrahydronaphthalen-2-yl)-3-((3S,4R)-1-(1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)-4-(4-methoxyphenyl)-2-oxopyrrolidin-3-yl)urea	565.3	Method D, RT = 1.74 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.64 - 7.60 (m, 1H), 7.57 - 7.52 (m, 1H), 7.36 - 7.25 (m, 2H), 7.20 - 7.03 (m, 3H), 6.98 - 6.84 (m, 2H), 6.35 - 6.20 (m, 2H), 6.06 (d, J = 7.8 Hz, 1H), 4.62 (dd, J = 11.5, 8.8 Hz, 1H), 4.14 - 4.10 (m, 2H), 3.98 (t, J = 8.7 Hz, 1H), 3.80 - 3.75 (m, 1H), 3.74 (s, 3H), 3.67 - 3.52 (m, 3H), 3.24 (s, 3H), 2.99 - 2.87 (m, 2H), 2.81 - 2.73 (m, 2H), 2.54 (s, 1H), 1.91 - 1.79 (m, 1H), 1.62 - 1.50 (m, 1H).
6	 1-(6-chloro-1,2,3,4-tetrahydronaphthalen-2-yl)-3-((3S,4R)-1-(1-ethyl-2-oxo-1,2-dihydropyridin-3-yl)-4-(4-methoxyphenyl)-2-oxopyrrolidin-3-yl)urea	535.2	Method D, RT = 1.75 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.76 - 7.65 (m, 1H), 7.59 - 7.48 (m, 1H), 7.40 - 7.26 (m, 2H), 7.20 - 7.01 (m, 3H), 6.98 - 6.85 (m, 2H), 6.38 - 6.28 (m, 1H), 6.26 (d, J = 8.6 Hz, 1H), 6.05 (d, J = 7.3 Hz, 1H), 4.62 (dd, J = 11.2, 8.8 Hz, 1H), 4.02 - 3.89 (m, 3H), 3.85 - 3.75 (m, 1H), 3.75 (s, 3H), 3.62 (t, J = 9.8 Hz, 1H), 3.53 - 3.40 (m, 1H), 2.95 - 2.91 (m, 1H), 2.82 - 2.69 (m, 2H), 2.58 - 2.54 (m, 1H), 1.83 (br d, J = 3.4 Hz, 1H), 1.63 - 1.50 (m, 1H), 1.23 (t, J = 7.1 Hz, 3H).

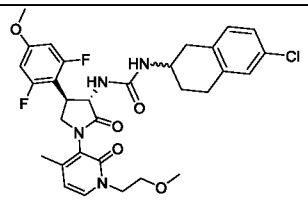
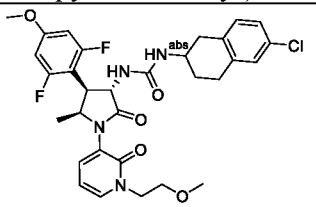
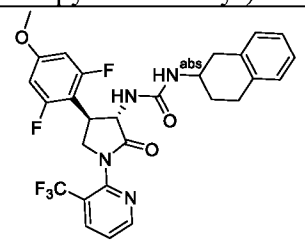
7	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-(2-methoxyethyl)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)urea	611.4	Method D RT = 1.69 min, 98.8%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.59 - 7.48 (m, 1H), 6.97 - 6.88 (m, 1H), 6.81 - 6.72 (m, 2H), 6.70 - 6.60 (m, 2H), 6.39 - 6.32 (m, 1H), 6.23 - 6.15 (m, 1H), 6.12 - 5.98 (m, 1H), 4.96 - 4.49 (m, 2H), 4.16 - 3.87 (m, 4H), 3.78 (s, 3H), 3.75 - 3.64 (m, 5H), 3.59 - 3.54 (m, 3H), 3.49 - 3.35 (m, 2H), 2.89 - 2.68 (m, 4H), 1.87 (s, 3H), 1.62 - 1.50 (m, 1H). (mixture of interconvertible atropisomers)
8	 1-(6-chloro-1,2,3,4-tetrahydronaphthalen-2-yl)-3-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(4-methoxy-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)urea	587.2	Method D RT = 1.70 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.83 - 7.77 (m, 1H), 7.21 - 7.09 (m, 2H), 7.09 - 6.97 (m, 1H), 6.79 - 6.74 (m, 2H), 6.43 - 6.21 (m, 2H), 6.09 - 5.93 (m, 1H), 4.95 - 4.72 (m, 1H), 3.85 (s, 3H), 3.78 (s, 3H), 3.75 - 3.66 (m, 2H), 3.47 - 3.37 (m, 4H), 2.95 - 2.81 (m, 1H), 2.81 - 2.69 (m, 2H), 2.48 - 2.40 (m, 2H), 1.87 - 1.73 (m, 1H), 1.63 - 1.45 (m, 1H). (mixture of interconvertible atropisomers)
9	 1-(6-chloro-1,2,3,4-tetrahydronaphthalen-2-yl)-3-((3S,4R)-1-(1-ethyl-2-oxo-1,2-dihydropyridin-3-yl)-4-(4-methoxyphenyl)-2-oxopyrrolidin-3-yl)urea	535.3	Method D, RT = 1.75 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.72 (dd, J = 6.8, 2.0 Hz, 1H), 7.52 (dd, J = 7.1, 2.0 Hz, 1H), 7.39 - 7.28 (m, 2H), 7.22 - 7.08 (m, 2H), 7.08 - 7.03 (m, 1H), 6.97 - 6.82 (m, 2H), 6.32 (t, J = 7.0 Hz, 1H), 6.27 (d, J = 9.0 Hz, 1H), 6.05 (d, J = 7.6 Hz, 1H), 4.62 (dd, J = 11.2, 9.0 Hz, 1H), 4.05 - 3.90 (m, 3H), 3.84 - 3.75 (m, 1H), 3.74 (s, 3H), 3.66 - 3.57 (m, 1H), 3.46 (dt, J = 10.7, 8.2 Hz, 1H), 2.95 - 2.73 (m, 4H), 1.96 - 1.82 (m, 1H), 1.68 - 1.55 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H).

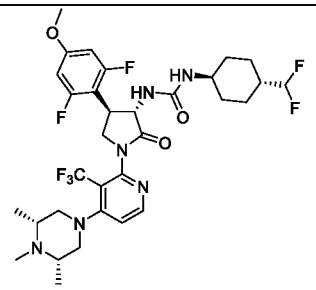
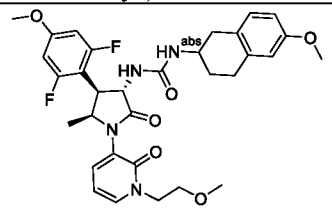
10	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-2-oxo-1-(3-(trifluoromethyl)pyridin-2-yl)pyrrolidin-3-yl)-3-(1,2,3,4-tetrahydronaphthalen-2-yl)urea	561.3	Method D, RT = 1.92 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.86 (d, J = 3.2 Hz, 1H), 8.36 (dd, J = 8.1, 1.2 Hz, 1H), 7.69 (dd, J = 7.5, 4.8 Hz, 1H), 7.12 - 6.99 (m, 4H), 6.85 - 6.71 (m, 2H), 6.42 (d, J = 9.0 Hz, 1H), 6.17 (d, J = 7.8 Hz, 1H), 4.86 - 4.78 (m, 1H), 4.11 - 3.99 (m, 1H), 3.94 - 3.87 (m, 2H), 3.79 (s, 3H), 3.76 - 3.68 (m, 1H), 2.96 - 2.89 (m, 1H), 2.79 - 2.71 (m, 2H), 2.58 - 2.55 (m, 1H), 1.87 - 1.76 (m, 1H), 1.61 - 1.47 (m, 1H).
11	 1-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-3-((3S,4R)-1-(1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)-4-(4-methoxyphenyl)-2-oxopyrrolidin-3-yl)urea	561.4	Method D, RT = 1.52 min, 94%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.61 (dd, J = 6.8, 2.0 Hz, 1H), 7.54 (dd, J = 7.3, 2.0 Hz, 1H), 7.32 (d, J = 8.8 Hz, 2H), 6.99 - 6.84 (m, 3H), 6.72 - 6.56 (m, 2H), 6.37 - 6.22 (m, 2H), 6.07 (d, J = 7.8 Hz, 1H), 4.62 (dd, J = 11.4, 8.9 Hz, 1H), 4.10 (t, J = 5.3 Hz, 2H), 3.98 (t, J = 8.6 Hz, 1H), 3.84 - 3.75 (m, 1H), 3.74 (s, 3H), 3.68 (s, 3H), 3.64 - 3.56 (m, 3H), 3.51 - 3.44 (m, 2H), 3.24 (s, 3H), 2.87 (m, 1H), 2.78 - 2.70 (m, 2H), 1.84 (m, 1H), 1.60 - 1.47 (m, 1H).
12	 1-((3S,4R)-1-(1-ethyl-2-oxo-1,2-dihydropyridin-3-yl)-4-(4-methoxyphenyl)-2-oxopyrrolidin-3-yl)-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)urea	531.3	Method D, RT = 1.52 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.71 (dd, J = 6.7, 1.8 Hz, 1H), 7.52 (dd, J = 7.3, 2.0 Hz, 1H), 7.37 - 7.21 (m, 2H), 7.01 - 6.77 (m, 3H), 6.73 - 6.57 (m, 2H), 6.42 - 6.20 (m, 2H), 6.01 (d, J = 7.6 Hz, 1H), 4.61 (dd, J = 11.1, 8.9 Hz, 1H), 4.02 - 3.88 (m, 4H), 3.74 (s, 3H), 3.68 (s, 3H), 3.65 - 3.65 (m, 1H), 3.50 - 3.44 (m, 1H), 2.88 - 2.71 (m, 3H), 2.43 (m, 1H), 1.94 - 1.79 (m, 1H), 1.64 - 1.50 (m, 1H), 1.23 (t, J = 7.1 Hz, 3H).

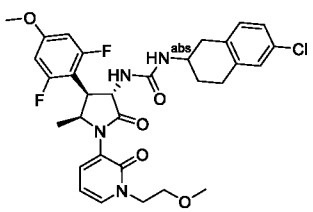
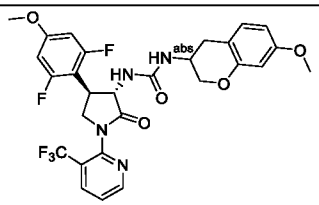
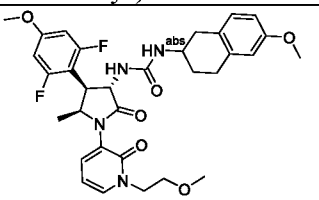
13	 1-((3S,4R)-1-(1-ethyl-2-oxo-1,2-dihydropyridin-3-yl)-4-(4-methoxyphenyl)-2-oxopyrrolidin-3-yl)-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)urea	531.3	Method D, RT = 1.52 min, 96%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.76 - 7.67 (m, 1H), 7.56 - 7.46 (m, 1H), 7.32 (d, J = 8.6 Hz, 2H), 7.04 - 6.81 (m, 3H), 6.73 - 6.58 (m, 2H), 6.32 (t, J = 7.0 Hz, 1H), 6.28 - 6.17 (m, 1H), 6.02 (d, J = 7.6 Hz, 1H), 4.62 (dd, J = 11.2, 9.0 Hz, 1H), 4.02 - 3.91 (m, 3H), 3.81 - 3.76 (m, 1H), 3.74 (s, 3H), 3.69 (s, 3H), 3.62 (t, J = 9.5 Hz, 1H), 3.52 - 3.39 (m, 1H), 2.93 - 2.82 (m, 1H), 2.74 (br t, J = 6.4 Hz, 2H), 2.45 (br d, J = 8.8 Hz, 1H), 1.87 - 1.77 (m, 1H), 1.61 - 1.50 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H).
14	 1-(6-chloro-1,2,3,4-tetrahydronaphthalen-2-yl)-3-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-(2-hydroxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)urea	587.3	Method D RT = 1.66 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.62 (dd, J = 6.6, 2.0 Hz, 1H), 7.54 (dd, J = 7.3, 2.0 Hz, 1H), 7.19 - 7.10 (m, 2H), 7.10 - 6.99 (m, 1H), 6.76 (d, J = 10.8 Hz, 2H), 6.36 (d, J = 8.6 Hz, 1H), 6.29 (t, J = 7.0 Hz, 1H), 6.22 (d, J = 7.3 Hz, 1H), 5.01 - 4.86 (m, 1H), 4.81 - 4.68 (m, 1H), 4.02 - 3.95 (m, 2H), 3.94 - 3.86 (m, 1H), 3.84 - 3.79 (m, 3H), 3.77 (s, 3H), 1.76 - 1.68 (m, 1H), 3.63 (br t, J = 5.4 Hz, 2H), 2.91 (dd, J = 16.4, 4.9 Hz, 1H), 2.82 - 2.70 (m, 2H), 1.86 - 1.77 (m, 1H), 1.60 - 1.43 (m, 1H).
15	 1-((3S,4S,5S)-4-(2,6-difluoro-4-methoxyphenyl)-1-(3-methoxypyridin-2-yl)-5-methyl-2-oxopyrrolidin-3-yl)-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)urea	567.3	Method D, RT = 1.76 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.08 (dd, J = 4.6, 1.5 Hz, 1H), 7.61 (dd, J = 8.3, 1.5 Hz, 1H), 7.39 (dd, J = 8.6, 4.6 Hz, 1H), 6.91 (d, J = 8.3 Hz, 1H), 6.85 - 6.73 (m, 2H), 6.71 - 6.56 (m, 2H), 6.31 (d, J = 8.6 Hz, 1H), 6.03 (d, J = 7.8 Hz, 1H), 5.19 (dd, J = 11.5, 8.6 Hz, 1H), 4.49 - 4.37 (m, 1H), 4.08 - 4.03 (m, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.75 - 3.69 (m, 1H), 3.68 (s, 3H), 2.85 - 2.71 (m, 3H), 2.41 (dd, J = 16.0, 8.6 Hz, 1H), 1.91 - 1.82 (m, 1H), 1.63 - 1.48 (m, 1H), 0.87 (d, J = 6.6 Hz, 3H).

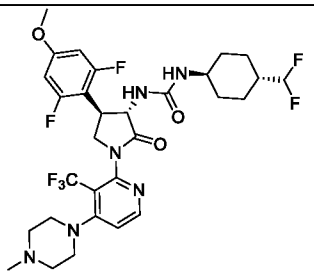
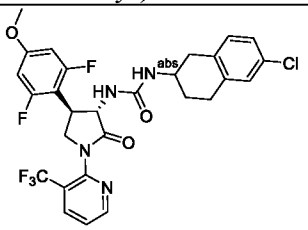
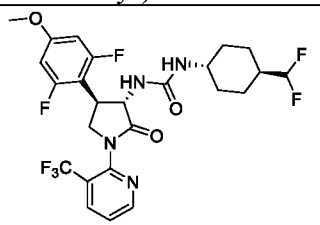
16	 1-(6-chloro-1,2,3,4-tetrahydronaphthalen-2-yl)-3-((3S,4R)-1-(1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)-4-(4-methoxyphenyl)-2-oxopyrrolidin-3-yl)urea	565.3	Method D, RT = 1.74 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.62 (dd, J = 6.7, 1.8 Hz, 1H), 7.54 (dd, J = 7.3, 1.8 Hz, 1H), 7.32 (d, J = 8.6 Hz, 2H), 7.19 - 7.09 (m, 2H), 7.09 - 7.01 (m, 1H), 6.96 - 6.83 (m, 2H), 6.37 - 6.23 (m, 2H), 6.07 (d, J = 7.6 Hz, 1H), 4.61 (dd, J = 11.4, 9.2 Hz, 1H), 4.10 (t, J = 5.4 Hz, 2H), 3.98 (t, J = 8.4 Hz, 1H), 3.81 - 3.75 (m, 1H), 3.74 (s, 3H), 3.67 - 3.51 (m, 4H), 3.50 - 3.43 (m, 1H), 3.24 (s, 3H), 2.96 - 2.85 (m, 1H), 2.84 - 2.73 (m, 2H), 1.96 - 1.84 (m, 1H), 1.67 - 1.54 (m, 1H).
17	 1-(6-chloro-1,2,3,4-tetrahydronaphthalen-2-yl)-3-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)urea	601.3	Method D, RT = 1.82 min, 100%	^{1}H NMR (400MHz, DMSO-d$_6$) δ = 7.63 (dd, J = 6.7, 2.1 Hz, 1H), 7.54 (dd, J = 7.3, 2.1 Hz, 1H), 7.19 - 7.10 (m, 2H), 7.10 - 7.01 (m, 1H), 6.77 (d, J = 10.8 Hz, 2H), 6.36 - 6.24 (m, 2H), 6.15 (d, J = 7.6 Hz, 1H), 4.75 (dd, J = 10.6, 8.4 Hz, 1H), 4.10 (t, J = 5.3 Hz, 2H), 3.95 - 3.85 (m, 1H), 3.82 - 3.79 (m, 2H), 3.78 (s, 3H), 3.75 - 3.66 (m, 1H), 3.58 (t, J = 5.4 Hz, 2H), 3.24 (s, 3H), 2.91 (dd, J = 16.3, 5.0 Hz, 1H), 2.81 - 2.69 (m, 2H), 2.55 - 2.51 (m, 1H), 1.86 - 1.76 (m, 1H), 1.60 - 1.48 (m, 1H).
18	 1-((3S,4S,5S)-4-(2,6-difluoro-4-methoxyphenyl)-1-(3-methoxypyridin-2-yl)-5-methyl-2-oxopyrrolidin-3-yl)-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)urea	567.3	Method D, RT = 1.75 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.08 (dd, J = 4.6, 1.5 Hz, 1H), 7.61 (dd, J = 8.3, 1.5 Hz, 1H), 7.39 (dd, J = 8.3, 4.6 Hz, 1H), 6.94 (d, J = 8.3 Hz, 1H), 6.85 - 6.72 (m, 2H), 6.69 - 6.54 (m, 2H), 6.30 (d, J = 8.8 Hz, 1H), 6.05 (d, J = 7.8 Hz, 1H), 5.23 - 5.15 (m, 1H), 4.47 - 4.38 (m, 1H), 4.07 - 4.02 (m, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.75 - 3.71 (m, 1H), 3.68 (s, 3H), 2.85 (dd, J = 15.5, 5.0 Hz, 1H), 2.76 - 2.69 (m, 2H), 2.47 - 2.43 (m, 1H), 1.87 - 1.78 (m, 1H), 1.57 - 1.48 (m, 1H), 0.87 (d, J = 6.6 Hz, 3H).

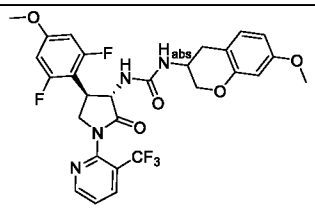
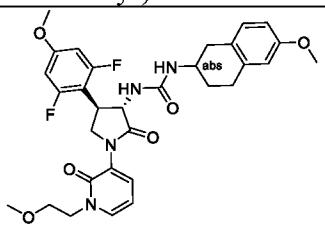
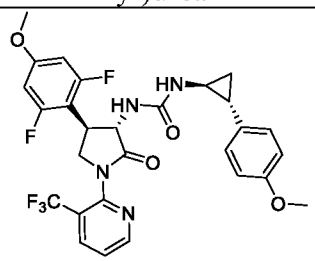
19	 1-(6-chloro-1,2,3,4-tetrahydronaphthalen-2-yl)-3-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-(2-hydroxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)urea	587.2	Method D RT = 1.66 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.62 (dd, J = 6.8, 2.0 Hz, 1H), 7.54 (dd, J = 7.2, 2.0 Hz, 1H), 7.18 - 7.09 (m, 2H), 7.08 - 7.00 (m, 1H), 6.82 - 6.68 (m, 2H), 6.36 (d, J = 8.6 Hz, 1H), 6.29 (t, J = 6.8 Hz, 1H), 6.20 (d, J = 7.6 Hz, 1H), 4.99 - 4.89 (m, 1H), 4.77 - 4.65 (m, 1H), 4.02 - 3.95 (m, 2H), 3.94 - 3.86 (m, 1H), 3.85 - 3.79 (m, 2H), 3.78 (s, 3H), 3.75 - 3.68 (m, 1H), 3.66 - 3.59 (m, 2H), 2.90 - 2.82 (m, 1H), 2.81 - 2.73 (m, 2H), 2.53 - 2.48 (m, 1H), 1.93 - 1.82 (m, 1H), 1.64 - 1.53 (m, 1H).
20	 1-(6-chloro-1,2,3,4-tetrahydronaphthalen-2-yl)-3-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)urea	601.3	Method D, RT = 1.82 min, 98%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ =7.63 (dd, J = 6.8, 2.0 Hz, 1H), 7.54 (dd, J = 7.2. 2.0 Hz, 1H), 7.20 - 7.10 (m, 2H), 7.08 - 7.02 (m, 1H), 6.77 (d, J = 10.8 Hz, 2H), 6.35 - 6.25 (m, 2H), 6.14 (d, J = 7.6 Hz, 1H), 4.79 - 4.69 (m, 1H), 4.10 (t, J = 5.4 Hz, 2H), 3.95 - 3.85 (m, 1H), 3.85 - 3.77 (m, 2H), 3.76 (s, 3H), 3.75 - 3.68 (m, 1H), 3.58 (t, J = 5.4 Hz, 2H), 3.24 (s, 3H), 2.91 - 2.71 (m, 3H), 2.50 - 2.45 (m, 1H), 1.64 - 1.52 (m, 1H), 1.13 - 1.04 (m, 1H).
21	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-(2-hydroxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)urea	583.3	Method D RT = 1.46 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ =7.62 (dd, J = 6.8, 2.0 Hz, 1H), 7.54 (dd, J = 7.2, 2.0 Hz, 1H), 6.92 (d, J = 8.3 Hz, 1H), 6.77 (d, J = 10.8 Hz, 2H), 6.70 - 6.57 (m, 2H), 6.35 - 6.25 (m, 2H), 6.11 (d, J = 7.8 Hz, 1H), 4.93 (br t, J = 4.9 Hz, 1H), 4.73 (t, J = 9.3 Hz, 1H), 3.98 (t, J = 5.4 Hz, 2H), 3.93 - 3.79 (m, 3H), 3.78 (s, 3H), 3.73 - 3.69 (m, 1H), 3.68 (s, 3H), 3.66 - 3.56 (m, 2H), 2.85 - 2.70 (m, 3H), 2.42 (dd, J = 15.8, 8.9 Hz, 1H), 1.94 - 1.78 (m, 1H), 1.63 - 1.49 (m, 1H).

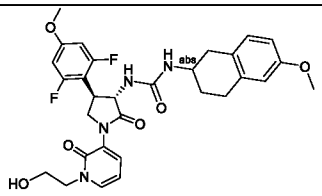
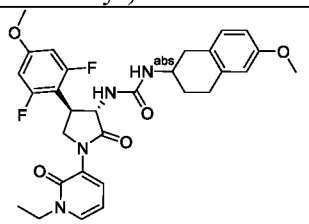
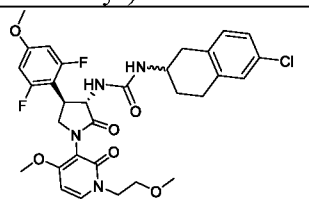
22	 1-(6-chloro-1,2,3,4-tetrahydronaphthalen-2-yl)-3-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-(2-methoxyethyl)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)urea	615.3	Method D RT = 1.86 min, 93.9%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.58 - 7.52 (m, 1H), 7.21 - 7.00 (m, 3H), 6.83 - 6.67 (m, 2H), 6.41 - 6.28 (m, 1H), 6.22 - 6.16 (m, 1H), 6.14 - 5.98 (m, 1H), 4.95 - 4.50 (m, 1H), 4.14 - 3.90 (m, 4H), 3.79 - 3.76 (2s, 3H), 3.76 - 3.65 (m, 1H), 3.59 - 3.51 (m, 2H), 3.46 - 3.37 (m, 1H), 3.25 - 3.19 (2s, 3H), 2.95 - 2.72 (m, 4H), 2.15 - 1.98 (m, 3H), 1.93 - 1.73 (m, 1H), 1.64 - 1.46 (m, 1H). (mixture of interconvertible atropisomers)
23	 1-(6-chloro-1,2,3,4-tetrahydronaphthalen-2-yl)-3-((3S,4S,5S)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)-5-methyl-2-oxopyrrolidin-3-yl)urea	615.3	Method D, RT = 1.88 min, 94%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.71 - 7.44 (m, 1H), 7.19 - 7.08 (m, 1H), 7.14 - 7.10 (m, 2H) 7.08 - 6.98 (m, 1H), 6.88 - 6.65 (m, 2H), 6.38 - 6.20 (m, 2H), 6.01 (d, J = 7.3 Hz, 1H), 5.11 (dd, J = 11.4, 8.7 Hz, 1H), 4.56 - 4.44 (m, 1H), 4.25 - 3.99 (m, 2H), 3.98 - 3.90 (m, 1H), 3.79 (s, 3H), 3.78 - 3.71 (m, 1H), 3.58 (t, J = 5.3 Hz, 2H), 3.24 (s, 3H), 2.93 - 2.83 (m, 1H), 2.81 - 2.69 (m, 2H), 2.50 - 2.45 (m, 1H), 1.93 - 1.80 (m, 1H), 1.66 - 1.34 (m, 1H), 0.88 (d, J = 6.6 Hz, 3H).
24	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-2-oxo-1-(3-(trifluoromethyl)pyridin-2-yl)pyrrolidin-3-yl)-3-(1,2,3,4-tetrahydronaphthalen-2-yl)urea	561.3	Method C, RT = 1.93 min, 94.64%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.86 (d, J = 3.2 Hz, 1H), 8.36 (dd, J = 8.1, 1.2 Hz, 1H), 7.69 (dd, J = 7.5, 4.8 Hz, 1H), 7.12 - 6.99 (m, 4H), 6.85 - 6.71 (m, 2H), 6.42 (d, J = 9.0 Hz, 1H), 6.17 (d, J = 7.8 Hz, 1H), 4.86 - 4.78 (m, 1H), 4.11 - 3.99 (m, 1H), 3.94 - 3.87 (m, 2H), 3.79 (s, 3H), 3.76 - 3.68 (m, 1H), 2.96 - 2.89 (m, 1H), 2.79 - 2.71 (m, 2H), 2.58 - 2.55 (m, 1H), 1.87 - 1.76 (m, 1H), 1.61 - 1.47 (m, 1H).

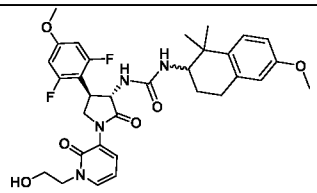
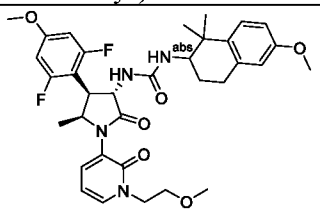
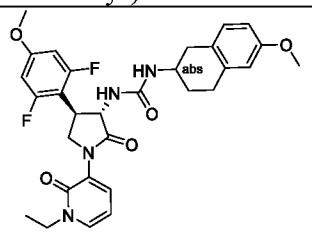
25	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-2-oxo-1-(3-(trifluoromethyl)pyridin-2-yl)pyrrolidin-3-yl)-3-(1,2,3,4-tetrahydronaphthalen-2-yl)urea	689.3	Method C, RT = 1.61 min, 93.34%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 9.58 - 9.40 (m, 1H), 8.59 - 8.43 (m, 1H), 7.42 - 7.29 (m, 1H), 6.82 - 6.75 (m, 2H), 6.37 - 6.20 (m, 1H), 5.84 (td, J = 60.8, 4.0 Hz, 1H), 4.80 - 4.68 (m, 1H), 4.36 - 4.27 (m, 1H), 4.22 -4.10 (m, 1H), 4.08 - 3.97 (m, 1H), 3.77 (2s, 3H), 3.71 - 3.66 (m, 1H), 3.51 - 3.36 (m, 2H), 3.23 - 3.06 (m, 4H), 2.91 (2s, 3H), 1.87 - 1.59 (m, 5H), 1.36 (s, 3H), 1.34 (s, 3H), 1.18 - 0.94 (m, 4H). (mixture of interconvertible atropisomers)
26	 1-((3S,4S,5S)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)-5-methyl-2-oxopyrrolidin-3-yl)-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)urea	611.3	Method D, RT = 1.68 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.65 (dd, J = 6.7, 2.1 Hz, 1H), 7.52 (dd, J = 7.1, 2.1 Hz, 1H), 6.93 (d, J = 8.3 Hz, 1H), 6.82 - 6.73 (m, 2H), 6.70 - 6.64 (m, 1H), 6.63 (d, J = 2.7 Hz, 1H), 6.37 - 6.25 (m, 2H), 5.99 (d, J = 7.8 Hz, 1H), 5.12 (dd, J = 11.4, 8.3 Hz, 1H), 4.57 - 4.46 (m, 1H), 4.18 (td, J = 13.6, 5.2 Hz, 1H), 4.04 (td, J = 13.6, 5.6 Hz, 1H), 3.93 (dd, J = 11.2, 8.1 Hz, 1H), 3.79 (s, 3H), 3.76 - 3.69 (m, 1H), 3.68 (s, 3H), 3.58 (t, J = 6.0 Hz, 2H), 3.24 (s, 3H), 2.85 (dd, J = 15.5, 5.3 Hz, 1H), 2.73 (br t, J = 6.0 Hz, 2H), 2.48 - 2.41 (m, 1H), 1.88 - 1.75 (m, 1H), 1.58 - 1.44 (m, 1H), 0.84 (d, J = 6.6 Hz, 3H).

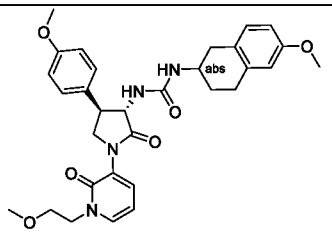
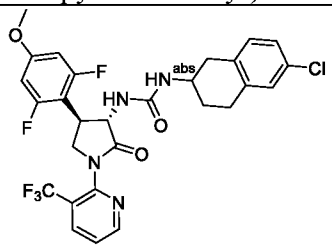
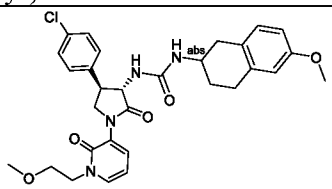
27	 1-(6-chloro-1,2,3,4-tetrahydronaphthalen-2-yl)-3-((3S,4S,5S)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)-5-methyl-2-oxopyrrolidin-3-yl)urea	615.3	Method D, RT = 1.88 min, 92%	^{1}H NMR (400 MHz, DMSO-d6) δ = 7.65 (dd, J = 6.7, 2.1 Hz, 1H), 7.52 (dd, J = 7.1, 2.1 Hz, 1H), 6.93 (d, J = 8.3 Hz, 1H), 6.82 - 6.73 (m, 2H), 6.70 - 6.64 (m, 1H), 6.63 (d, J = 2.7 Hz, 1H), 6.37 - 6.25 (m, 2H), 5.99 (d, J = 7.8 Hz, 1H), 5.12 (dd, J = 11.4, 8.3 Hz, 1H), 4.57 - 4.46 (m, 1H), 4.18 (td, J = 13.6, 5.2 Hz, 1H), 4.04 (td, J = 13.6, 5.6 Hz, 1H), 3.93 (dd, J = 11.2, 8.1 Hz, 1H), 3.79 (s, 3H), 3.76 - 3.69 (m, 1H), 3.58 (t, J = 5.4 Hz, 2H), 3.24 (s, 3H), 2.85 (dd, J = 15.5, 5.3 Hz, 1H), 2.73 (br t, J = 6.6 Hz, 2H), 2.48 - 2.41 (m, 1H), 1.88 - 1.75 (m, 1H), 1.58 - 1.44 (m, 1H), 0.84 (d, J = 7.1 Hz, 3H).
28	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-2-oxo-1-(3-(trifluoromethyl)pyridin-2-yl)pyrrolidin-3-yl)-3-(7-methoxychroman-3-yl)urea	593.2	Method E, RT = 8.91 min, 95.2%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.86 (d, J = 3.5 Hz, 1H), 8.36 (dd, J = 8.3, 1.8 Hz, 1H), 7.70 (dd, J = 8.3, 4.3 Hz, 1H), 6.96 (d, J = 8.5 Hz, 1H), 6.80 (d, J = 10.5 Hz, 2H), 6.58 (br d, J = 8.3 Hz, 1H), 6.46 (dd, J = 8.3, 2.8 Hz, 1H), 6.35 (d, J = 2.5 Hz, 1H), 6.22 (d, J = 7.5 Hz, 1H), 4.85 - 4.78 (m, 1H), 4.03 - 3.96 (m, 2H), 3.95 - 3.87 (m, 3H), 3.79 (s, 3H), 3.68 (s, 3H), 3.44 - 3.39 (m, 1H), 2.96 - 2.84 (m, 2H).
29	 1-((3S,4S,5S)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)-5-methyl-2-oxopyrrolidin-3-yl)-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)urea	611.3	Method D, RT = 1.68 min, 98%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.65 (dd, J = 6.8, 2.0 Hz, 1H), 7.53 (dd, J = 7.3, 2.0 Hz, 1H), 6.92 (d, J = 8.3 Hz, 1H), 6.84 - 6.71 (m, 2H), 6.70 - 6.60 (m, 2H), 6.37 - 6.22 (m, 2H), 5.96 (d, J = 7.6 Hz, 1H), 5.11 (dd, J = 11.2, 8.6 Hz, 1H), 4.56 - 4.46 (m, 1H), 4.22 - 4.13 (m, 1H), 4.04 (td, J = 13.7, 5.6 Hz, 1H), 3.94 (dd, J = 11.2, 8.1 Hz, 1H), 3.79 (s, 3H), 3.76 - 3.69 (m, 1H), 3.68 (s, 3H), 3.58 (t, J = 5.3 Hz, 2H), 3.24 (s, 3H), 2.85 - 2.69 (m, 3H), 2.41 (dd, J = 16.1, 8.3 Hz, 1H), 1.89 - 1.82 (m, 1H), 1.63 - 1.52 (m, 1H), 0.84 (d, J = 6.6 Hz, 3H).

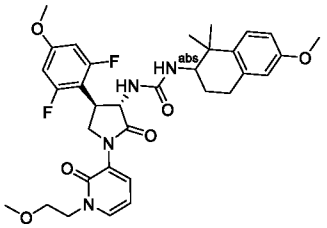
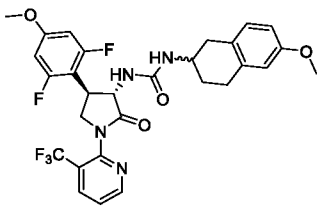
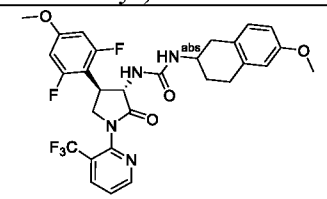
30	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(4-(4-methylpiperazin-1-yl)-3-(trifluoromethyl)pyridin-2-yl)-2-oxopyrrolidin-3-yl)-3-((1r,4S)-4-(difluoromethyl)cyclohexyl)urea	661.4	Method C, RT = 1.56 min, 93.13%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 9.97 - 9.91(m, 1H), 8.59 - 8.43 (m, 1H), 7.42 - 7.29 (m, 1H), 6.82 - 6.75 (m, 2H), 6.37 - 6.20 (m, 1H), 5.84 (td, J = 60.8, 4.0 Hz, 1H), 4.80 - 4.68 (m, 1H), 4.36 - 4.27 (m, 1H), 4.22 - 4.10 (m, 1H), 4.08 - 3.97 (m, 1H), 3.77 (s, 3H), 3.47 - 3.34 (m, 5H), 3.23 - 3.06 (m, 4H), 2.88 (s, 3H), 1.88 - 1.79 (m, 1H), 1.77 - 1.51 (m, 4H), 1.20 - 0.82 (m, 4H). (mixture of interconvertible atropisomers)
31	 1-(6-chloro-1,2,3,4-tetrahydronaphthalen-2-yl)-3-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-2-oxo-1-(3-(trifluoromethyl)pyridin-2-yl)pyrrolidin-3-yl)urea	595.2	Method C, RT = 2.07 min, 94.7%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.86 (dd, J = 4.9, 1.7 Hz, 1H), 8.36 (dd, J = 8.1, 1.7 Hz, 1H), 7.74 - 7.64 (m, 1H), 7.20 - 7.08 (m, 2H), 7.08 - 6.94 (m, 1H), 6.80 (d, J = 10.8 Hz, 2H), 6.41 (br d, J = 8.6 Hz, 1H), 6.16 (d, J = 7.8 Hz, 1H), 4.80 (dd, J = 10.5, 8.3 Hz, 1H), 4.07 - 3.84 (m, 3H), 3.79 (s, 3H), 3.76 - 3.61 (m, 1H), 2.94 - 2.81 (m, 2H) 2.80 -2.73 (m, 2H), 1.87 (br dd, J = 3.3, 2.6 Hz, 1H), 1.65 - 1.53 (m, 1H).
32	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-2-oxo-1-(3-(trifluoromethyl)pyridin-2-yl)pyrrolidin-3-yl)-3-((1r,4S)-4-(difluoromethyl)cyclohexyl)urea	563.2	Method D, RT = 1.82 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.86 (dd, J = 4.8, 1.6 Hz, 1H), 8.36 (dd, J = 8.1, 1.6 Hz, 1H), 7.70 (dd, J = 7.9, 4.8 Hz, 1H), 6.87 - 6.73 (m, 2H), 6.40 - 6.29 (m, 1H), 6.04 - 5.96 (m, 1H), 5.84 (dt, J = 60.8, 4.0 Hz, 1H), 4.78 (dd, J = 10.1, 8.7 Hz, 1H), 4.08 - 3.83 (m, 3H), 3.79 (s, 3H), 3.65 - 3.58 (m, 1H), 3.25 - 3.14 (m, 1H), 1.77 - 1.59 (m, 4H), 1.21 - 0.96 (m, 4H).

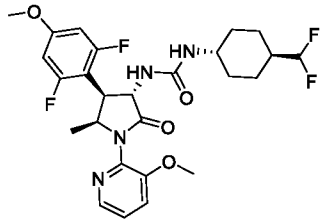
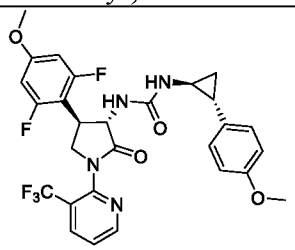
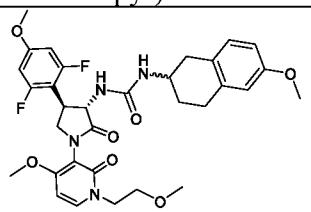
33	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-2-oxo-1-(3-(trifluoromethyl)pyridin-2-yl)pyrrolidin-3-yl)-3-(7-methoxychroman-3-yl)urea	593.2	Method E, RT = 7.41 min, 96.17%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.86 (d, J = 3.0 Hz, 1H), 8.38 - 8.34 (m, 1H), 7.71 (br d, J = 5.5 Hz, 1H), 6.96 - 6.91 (m, 1H), 6.79 (d, J = 11.0 Hz, 2H), 6.56 (br d, J = 8.5 Hz, 1H), 6.47 - 6.43 (m, 1H), 6.35 (d, J = 2.5 Hz, 1H), 6.19 (d, J = 7.5 Hz, 1H), 4.85 - 4.78 (m, 1H), 4.05 - 3.99 (m, 2H), 3.95 - 3.81 (m, 3H), 3.79 (s, 3H), 3.67 (s, 3H), 3.41 - 3.37 (m, 1H), 2.69 - 2.65 (m, 2H).
34	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)urea	597.4	Method D, RT = 2.32 min, 99%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.64 (dd, J = 6.5, 2.0 Hz, 1H), 7.55 (dd, J = 7.3, 2.0 Hz, 1H), 6.95 (d, J = 8.5 Hz, 1H), 6.78 (d, J = 11.0 Hz, 2H), 6.70 - 6.61 (m, 2H), 6.34 - 6.26 (m, 2H), 6.12 (d, J = 8.0 Hz, 1H), 4.76 (dd, J = 10.8, 8.8 Hz, 1H), 4.11 (t, J = 5.3 Hz, 2H), 3.95 - 3.87 (m, 1H), 3.86 - 3.76 (m, 5H), 3.73 - 3.67 (m, 4H), 3.63 - 3.55 (m, 2H), 3.27 (s, 3H), 2.90 - 2.81 (m, 1H), 2.76 - 2.70 (m, 2H), 2.49 - 2.45 (m, 1H), 1.86 - 1.75 (m, 1H), 1.59 - 1.47 (m, 1H).
35	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-2-oxo-1-(3-(trifluoromethyl)pyridin-2-yl)pyrrolidin-3-yl)-3-((1S,2R)-2-(4-methoxyphenyl)cyclopropyl)urea	577.2	Method D, RT = 1.83 min, 96.2%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.85 (dd, J = 4.9, 1.3 Hz, 1H), 8.36 (dd, J = 7.9, 1.3 Hz, 1H), 7.69 (dd, J = 7.8, 4.9 Hz, 1H), 7.00 (d, J = 8.8 Hz, 2H), 6.85 - 6.72 (m, 4H), 6.62 - 6.41 (m, 2H), 4.84 (t, J = 9.5 Hz, 1H), 4.07 - 3.91 (m, 2H), 3.91 - 3.81 (m, 1H), 3.78 (s, 3H), 3.70 (s, 3H), 3.56 -3.45 (m, 1H), 1.81 (dt, J = 7.8, 3.1 Hz, 1H), 1.00 - 0.89 (m, 2H).

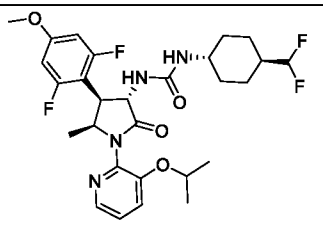
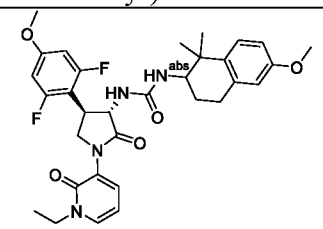
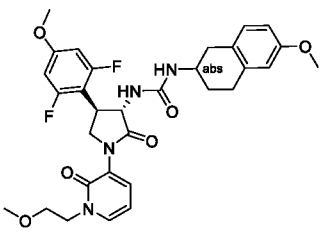
36	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-(2-hydroxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)urea	583.3	Method D RT = 1.46 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.62 (dd, J = 6.8, 2.0 Hz, 1H), 7.54 (dd, J = 7.2, 2.0 Hz, 1H), 6.94 (d, J = 8.6 Hz, 1H), 6.77 (d, J = 11.0 Hz, 2H), 6.71 - 6.55 (m, 2H), 6.37 - 6.22 (m, 2H), 6.14 (d, J = 7.6 Hz, 1H), 5.00 - 4.89 (m, 1H), 4.75 (dd, J = 10.5, 8.6 Hz, 1H), 4.03 - 3.94 (m, 2H), 3.93 - 3.85 (m, 1H), 3.84 - 3.74 (m, 6H), 3.74 - 3.68 (m, 4H), 3.63 (br t, J = 5.3 Hz, 2H), 2.85 (dd, J = 16.1, 4.6 Hz, 1H), 2.78 - 2.68 (m, 2H), 2.47 - 2.40 (m, 1H), 1.56 - 1.47 (m, 1H).
37	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-ethyl-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)urea	567.3	Method D, RT = 1.62 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.74 (dd, J = 6.8, 2.0 Hz, 1H), 7.54 (dd, J = 7.2, 2.0 Hz, 1H), 6.93 (d, J = 8.1 Hz, 1H), 6.83 - 6.72 (m, 2H), 6.70 - 6.58 (m, 2H), 6.38 - 6.23 (m, 2H), 6.10 (d, J = 7.8 Hz, 1H), 4.78 - 4.67 (m, 1H), 4.00 - 3.93 (m, 2H), 3.91 - 3.80 (m, 3H), 3.75 (s, 3H), 3.69 (s, 3H), 2.85 - 2.71 (m, 3H), 2.45 - 2.36 (m, 2H), 1.92 - 1.79 (m, 1H), 1.61 - 1.47 (m, 1H), 1.24 (t, J = 7.1 Hz, 3H).
38	 1-(6-chloro-1,2,3,4-tetrahydronaphthalen-2-yl)-3-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(4-methoxy-1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)urea	631.3	Method D RT = 1.78 min, 97.4%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.73- 7.69 (m, 1H), 7.22 - 7.09 (m, 2H), 7.09 - 6.94 (m, 1H), 6.78 - 6.74(m, 2H), 6.42 - 6.23 (m, 2H), 6.09 - 5.93 (m, 1H), 4.92 - 4.76 (m, 1H), 4.14 - 3.96 (m, 2H), 3.86 - 3.83 (2s, 3H), 3.81 - 3.60 (m, 6H), 3.57 - 3.51 (m, 2H), 3.46 - 3.38 (m, 1H), 3.27 - 3.22 (2s, 3H), 2.95 - 2.70 (m, 3H), 2.48 - 2.40 (m, 1H), 1.92 - 1.76 (m, 1H), 1.64 - 1.49 (m, 1H). (mixture of interconvertible atropisomers)

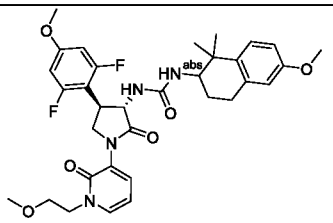
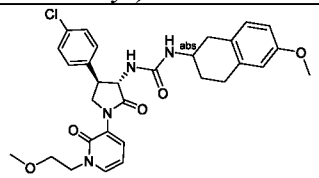
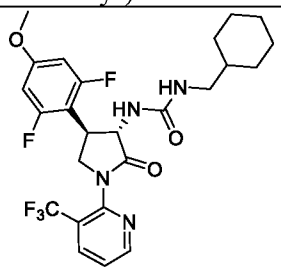
39	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-(2-hydroxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)-3-(6-methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)urea	611.4	Method D RT = 1.60 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.66 - 7.60 (m, 1H), 7.58 - 7.51 (m, 1H), 7.27 - 7.17 (m, 1H), 7.10 - 6.92 (m, 1H), 6.84 - 6.68 (m, 4H), 6.61 - 6.57 (2s, 1H), 5.60 - 5.55 (m, 1H), 4.95 - 4.86 (m, 1H), 4.79 - 4.64 (m, 1H), 3.99 (t, J = 5.5 Hz, 2H), 3.84 - 3.77 (m, 5H), 3.75 -3.68 (m, 4H), 3.66 - 3.60 (m, 3H), 2.80 - 2.72 (m, 2H), 1.85 - 1.60 (m, 2H), 1.19 - 1.10 (2s, 3H), 1.10 - 1.02 (2s, 3H). (mixture of interconvertible atropisomers)
40	 1-((3S,4S,5S)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)-5-methyl-2-oxopyrrolidin-3-yl)-3-(6-methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)urea	639.3	Method F, RT = 2.65 min, 99%	^{1}H NMR (400MHz, DMSO-d$_6$) δ = 7.65 (dd, J = 6.5, 2.0 Hz, 1H), 7.51 (dd, J = 7.0, 2.0 Hz, 1H), 7.22 (d, J = 9.0 Hz, 1H), 6.80 - 6.77 (m, 2H), 6.70 (dd, J = 8.8, 2.8 Hz, 1H), 6.57 (d, J = 2.5 Hz, 1H), 6.31 - 6.27 (m, 2H), 5.86 (d, J = 9.5 Hz, 1H), 5.06 (dd, J = 10.5, 8.5 Hz, 1H), 4.53 - 4.45 (m, 1H), 4.17 (dt, J = 13.7, 5.2 Hz, 1H), 4.03 (dt, J = 13.6, 5.8 Hz, 1H), 3.89 (dd, J = 10.8, 8.3 Hz, 1H), 3.79 (s, 3H), 3.71 - 3.65 (m, 4H), 3.58 (t, J = 5.3 Hz, 2H), 3.26 - 3.16 (m, 3H), 2.75 - 2.67 (m, 2H), 1.85 - 1.71 (m, 1H), 1.67 - 1.57 (m, 1H), 1.16 (s, 3H), 1.09 (s, 3H), 0.84 (d, J = 6.6 Hz, 3H).
41	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-ethyl-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)urea	567.3	Method D, RT = 1.62 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.74 (dd, J = 6.8, 2.0 Hz, 1H), 7.53 (dd, J = 7.3, 2.0 Hz, 1H), 6.95 (d, J = 8.6 Hz, 1H), 6.78 (d, J = 10.8 Hz, 2H), 6.70 - 6.59 (m, 2H), 6.40 - 6.24 (m, 2H), 6.12 (d, J = 7.6 Hz, 1H), 4.76 (dd, J = 10.9, 8.4 Hz, 1H), 4.01 - 3.86 (m, 3H), 3.84 - 3.78 (m, 2H), 3.76 (s, 3H), 3.69 (s, 3H), 2.85 (br dd, J = 16.5, 5.0 Hz, 1H), 2.78 - 2.69 (m, 2H), 2.46 - 2.39 (m, 2H), 1.86 - 1.76 (m, 1H), 1.58 - 1.45 (m, 1H), 1.23 (t, J = 7.2 Hz, 3H).

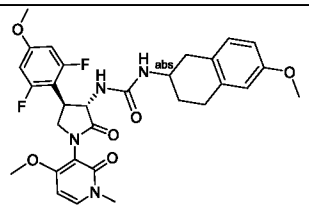
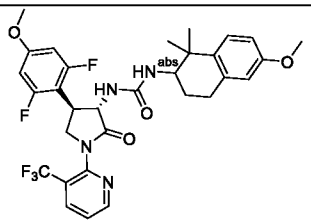
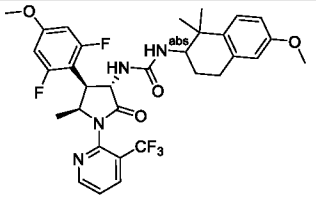
42	 1-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-3-((3S,4R)-1-(1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)-4-(4-methoxyphenyl)-2-oxopyrrolidin-3-yl)urea	561.3	Method D, RT = 1.52 min, 97%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.62 (dd, J = 6.8, 1.7 Hz, 1H), 7.58 - 7.49 (m, 1H), 7.36 - 7.25 (m, 2H), 6.98 - 6.87 (m, 3H), 6.70 - 6.58 (m, 2H), 6.36 - 6.22 (m, 2H), 6.04 - 5.92 (m, 1H), 4.61 (dd, J = 11.0, 9.5, Hz, 1H), 4.10 (br t, J = 5.1 Hz, 3H), 4.02 - 3.95 (m, 1H), 3.74 (s, 3H), 3.68 (s, 3H), 3.64 - 3.54 (m, 3H), 3.50 - 3.41 (m, 1H), 3.24 (s, 3H), 2.85 - 2.71 (m, 3H), 2.45 - 2.38 (m, 1H), 1.94 - 1.83 (m, 1H), 1.64 - 1.51 (m, 1H).
43	 1-(6-chloro-1,2,3,4-tetrahydronaphthalen-2-yl)-3-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-2-oxo-1-(3-(trifluoromethyl)pyridin-2-yl)pyrrolidin-3-yl)urea	595.2	Method D, RT = 2.07 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.86 (dd, J = 4.9, 1.7 Hz, 1H), 8.36 (dd, J = 8.1, 1.7 Hz, 1H), 7.74 - 7.64 (m, 1H), 7.20 - 7.08 (m, 2H), 7.08 - 6.94 (m, 1H), 6.80 (d, J = 10.8 Hz, 2H), 6.41 (br d, J = 8.6 Hz, 1H), 6.16 (d, J = 7.8 Hz, 1H), 4.80 (dd, J = 10.5, 8.3 Hz, 1H), 4.04 - 3.98 (m, 1H), 3.93 - 3.87 (m, 2H), 3.79 (s, 3H), 3.76 - 3.61 (m, 1H), 2.94 - 2.81 (m, 2H) 2.80 -2.73 (m, 2H), 1.87 (br dd, J = 3.3, 2.6 Hz, 1H), 1.65 - 1.53 (m, 1H).
44	 1-((3S,4R)-4-(4-chlorophenyl)-1-(1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)urea	564.3	Method D RT = 1.71 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ =7.62 (dd, J = 6.8, 2.0 Hz, 1H), 7.55 (dd, J = 7.3, 2.0 Hz, 1H), 7.49 - 7.36 (m, 4H), 6.95 (d, J = 8.3 Hz, 1H), 6.72 - 6.57 (m, 2H), 6.39 - 6.26 (m, 2H), 6.09 (d, J = 7.6 Hz, 1H), 4.66 (dd, J = 11.1, 8.7 Hz, 1H), 4.10 (t, J = 5.5 Hz, 2H), 4.06 - 3.97 (m, 1H), 3.77 - 3.74 (m, 1H), 3.69 (s, 3H), 3.70 - 3.62 (m, 1H), 3.60 - 3.48 (m, 3H), 3.24 (s, 3H), 2.87 (dd, J = 15.5, 5.0 Hz, 1H), 2.78 - 2.70 (m, 2H), 2.48 - 2.43 (m, 1H), 1.90 - 1.71 (m, 1H), 1.61 - 1.45 (m, 1H).

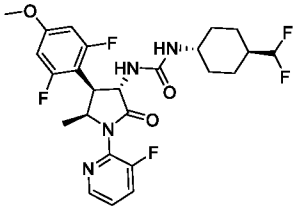
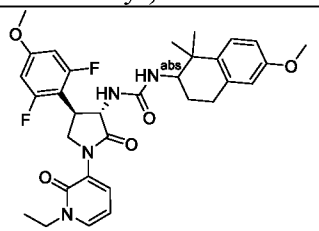
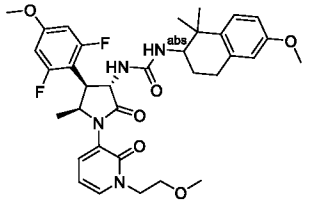
45	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)-3-(6-methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)urea	625.3	Method D, RT = 1.76 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.63 (dd, J = 6.8, 2.0 Hz, 1H), 7.54 (dd, J = 7.1, 2.0 Hz, 1H), 7.23 (d, J = 8.8 Hz, 1H), 6.77 (d, J = 10.8 Hz, 2H), 6.71 (dd, J = 8.7, 2.8 Hz, 1H), 6.58 (d, J = 2.7 Hz, 1H), 6.36 - 6.23 (m, 2H), 6.01 (d, J = 9.3 Hz, 1H), 4.67 - 4.63 (m, 1H), 4.10 (t, J = 5.3 Hz, 2H), 3.92 (br d, J = 0.7 Hz, 1H), 3.84 - 3.78 (m, 2H), 3.77 (s, 3H), 3.69 (s, 3H), 3.58 (t, J = 5.3 Hz, 3H), 3.24 (s, 3H), 2.73 (br t, J = 6.8 Hz, 2H), 1.79 - 1.69 (m, 1H), 1.66 - 1.57 (m, 1H), 1.17 (s, 3H), 1.11 (s, 3H).
46	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-2-oxo-1-(3-(trifluoromethyl)pyridin-2-yl)pyrrolidin-3-yl)-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)urea	591.3	Method D, RT = 1.89 min, 95.55%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.93 - 8.77 (m, 1H), 8.36 (dd, J = 7.9, 1.6 Hz, 1H), 7.70 (dd, J = 7.3, 4.9 Hz, 1H), 6.94 (t, J = 8.4 Hz, 1H), 6.86 - 6.75 (m, 2H), 6.73 - 6.58 (m, 2H), 6.42 (br d, J = 7.1 Hz, 1H), 6.20 - 6.08 (m, 1H), 4.88 - 4.76 (m, 1H), 4.08 - 3.81 (m, 2H), 3.79 (s, 3H), 3.78 - 3.72 (m, 1H), 3.70 (s, 3H), 2.95 - 2.67 (m, 4H), 2.46 - 2.36 (m, 1H), 1.92 - 1.73 (m, 1H), 1.66 - 1.44 (m, 1H).
47	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-2-oxo-1-(3-(trifluoromethyl)pyridin-2-yl)pyrrolidin-3-yl)-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)urea	591.2	Method E, RT = 4.48 min, 99%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.93 - 8.77 (m, 1H), 8.36 (dd, J = 7.9, 1.6 Hz, 1H), 7.70 (dd, J = 7.3, 4.9 Hz, 1H), 6.94 (t, J = 8.4 Hz, 1H), 6.86 - 6.75 (m, 2H), 6.73 - 6.58 (m, 2H), 6.42 (br d, J = 7.1 Hz, 1H), 6.20 - 6.08 (m, 1H), 4.88 - 4.76 (m, 1H), 4.08 - 3.81 (m, 2H), 3.79 (s, 3H), 3.78 - 3.72 (m, 1H), 3.70 (s, 3H), 2.95 - 2.67 (m, 4H), 2.46 - 2.36 (m, 1H), 1.92 - 1.73 (m, 1H), 1.66 - 1.44 (m, 1H).

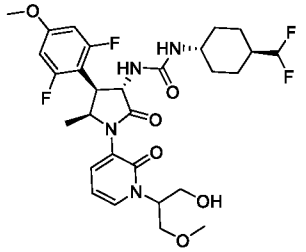
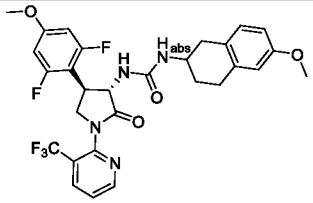
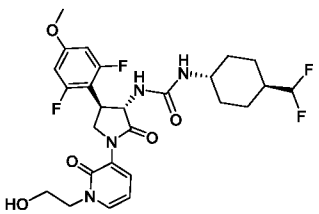
48	 1-((3S,4S,5S)-4-(2,6-difluoro-4-methoxyphenyl)-1-(3-methoxypyridin-2-yl)-5-methyl-2-oxopyrrolidin-3-yl)-3-((1r,4S)-4-(difluoromethyl)cyclohexyl)urea	539.3	Method D, RT = 1.66 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.08 (dd, J = 4.8, 1.3 Hz, 1H), 7.61 (dd, J = 8.4, 1.3 Hz, 1H), 7.39 (dd, J = 8.2, 4.8 Hz, 1H), 6.84 - 6.71 (m, 2H), 6.22 (d, J = 8.8 Hz, 1H), 5.89 - 5.87 (m, 1H), 5.83 (dt, J = 56.0, 4.0, Hz, 1H), 5.18 (dd, J = 11.4, 8.7 Hz, 1H), 4.48 - 4.38 (m, 1H), 4.08 - 4.03 (m, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 3.27 - 3.17 (m, 1H), 1.89 - 1.59 (m, 5H), 1.21 - 0.99 (m, 4H), 0.86 (d, J = 6.6 Hz, 3H).
49	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-2-oxo-1-(3-(trifluoromethyl)pyridin-2-yl)pyrrolidin-3-yl)-3-((1S,2R)-2-(4-methoxyphenyl)cyclopropyl)urea	577.2	Method D, RT = 1.83 min, 95.7%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.85 (dd, J = 4.9, 1.3 Hz, 1H), 8.36 (dd, J = 7.9, 1.3 Hz, 1H), 7.69 (dd, J = 4.9, 7.8 Hz, 1H), 7.00 (d, J = 8.8 Hz, 2H), 6.85 - 6.72 (m, 4H), 6.62 - 6.41 (m, 2H), 4.84 (t, J = 9.5 Hz, 1H), 4.07 - 3.91 (m, 2H), 3.91 - 3.81 (m, 1H), 3.78 (s, 3H), 3.70 (s, 3H), 3.56 - 3.45 (m, 1H), 1.84 - 1.79 (m, 1H), 1.00 - 0.89 (m, 2H).
50	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(4-methoxy-1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)urea	627.3	Method D RT = 1.59 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.72 - 7.68 (m, 1H), 6.95 - 6.91 (m, 1H), 6.76 (br d, J = 11.0 Hz, 2H), 6.70 - 6.58 (m, 2H), 6.43 - 6.21 (m, 2H), 6.06 - 5.90 (m, 1H), 4.93 - 4.75 (m, 1H), 4.14 - 3.99 (m, 2H), 3.88 - 3.82 (m, 3H), 3.80 - 3.77 (2s, 3H), 3.74 - 3.59 (m, 6H), 3.54 (t, J = 5.4 Hz, 2H), 3.47 - 3.35 (m, 1H), 3.26 - 3.22 (2s, 3H), 2.88 - 2.68 (m, 3H), 2.48 - 2.35 (m, 1H), 1.90 - 1.69 (m, 1H), 1.63 - 1.40 (m, 1H). (mixture of interconvertible atropisomers)

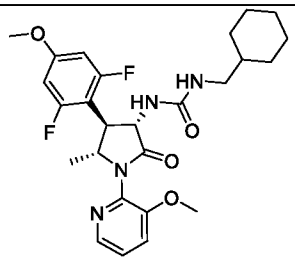
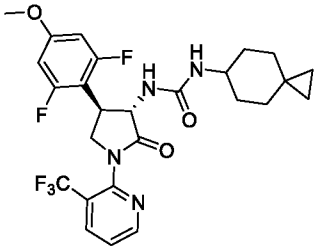
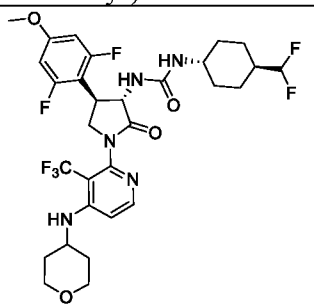
51	 1-((3S,4S,5S)-4-(2,6-difluoro-4-methoxyphenyl)-1-(3-isopropoxypyridin-2-yl)-5-methyl-2-oxopyrrolidin-3-yl)-3-((1r,4S)-4-(difluoromethyl)cyclohexyl)urea	567.3	Method D, RT = 1.86 min, 98%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.04 (dd, J = 4.6, 1.5 Hz, 1H), 7.59 (dd, J = 8.7, 1.5 Hz, 1H), 7.35 (dd, J = 8.3, 4.6 Hz, 1H), 6.85 - 6.66 (m, 2H), 6.22 (d, J = 8.3 Hz, 1H), 5.86 (d, J = 7.0 Hz, 1H) 5.83 (dt, J = 54.0, 4.0 Hz, 1H), 5.11 (dd, J = 11.1, 8.4 Hz, 1H), 4.68 (td, J = 12.0, 6.1 Hz, 1H), 4.42 - 4.30 (m, 1H), 4.04 (dd, J = 11.1, 8.2 Hz, 1H), 3.78 (s, 3H), 3.27 - 3.17 (m, 1H), 1.90 - 1.82 (m, 1H), 1.82 - 1.74 (m, 1H), 1.74 - 1.58 (m, 3H), 1.27 (d, J = 6.1 Hz, 3H), 1.25 (d, J = 6.1 Hz, 3H), 1.20 - 0.99 (m, 4H), 0.85 (d, J = 6.6 Hz, 3H).
52	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-ethyl-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)-3-(6-methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)urea	595.3	Method D, RT = 1.77 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.73 (dd, J = 7.0, 2.0 Hz, 1H), 7.53 (dd, J = 7.0, 2.0 Hz, 1H), 7.24 (d, J = 8.5 Hz, 1H), 6.78 (d, J = 10.5 Hz, 2H), 6.72 (dd, J = 8.8, 2.8 Hz, 1H), 6.59 (d, J = 3.0 Hz, 1H), 6.42 - 6.21 (m, 2H), 6.01 (d, J = 9.5 Hz, 1H), 4.66 (t, J = 9.3 Hz, 1H), 4.04 - 3.88 (m, 3H), 3.86 - 3.79 (m, 2H), 3.75 (s, 3H), 3.72 (s, 3H), 3.71 - 3.59 (m, 1H), 2.74 (m, 2H), 1.75 (m, 1H), 1.68 - 1.56 (m, 1H), 1.24 (t, J = 7.3 Hz, 3H), 1.18 (s, 3H), 1.11 (s, 3H).
53	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)urea	597.3	Method D, RT = 1.62 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.64 (dd, J = 6.8, 2.0 Hz, 1H), 7.55 (dd, J = 7.1, 2.0 Hz, 1H), 6.93 (d, J = 8.3 Hz, 1H), 6.78 (d, J = 10.8 Hz, 2H), 6.70 - 6.57 (m, 2H), 6.38 - 6.26 (m, 2H), 6.11 (d, J = 7.8 Hz, 1H), 4.73 (dd, J = 10.1, 8.7 Hz, 1H), 4.11 (t, J = 5.3 Hz, 2H), 3.94 - 3.80 (m, 3H), 3.79 (s, 3H), 3.73 - 3.66 (m, 4H), 3.59 (t, J = 5.4 Hz, 2H), 3.24 (s, 3H), 2.85 - 2.70 (m, 3H), 2.45 - 2.39(m, 1H), 1.93 - 1.81 (m, 1H), 1.65 - 1.48 (m, 1H).

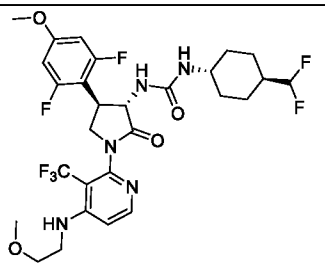
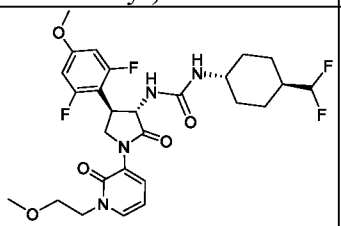
54	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)-3-(6-methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)urea	625.3	Method D, RT = 1.75 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.63 (dd, J = 6.8, 2.0 Hz, 1H), 7.55 (dd, J = 7.3, 2.0 Hz, 1H), 7.20 (d, J = 8.8 Hz, 1H), 6.79 - 6.65 (m, 3H), 6.58 (d, J = 2.9 Hz, 1H), 6.35 - 6.22 (m, 2H), 5.97 (d, J = 9.5 Hz, 1H), 4.74 (dd, J = 10.9 Hz, 1H), 4.10 (t, J = 5.3 Hz, 2H), 3.96 - 3.87 (m, 1H), 3.84 - 3.79 (m, 1H), 3.77 (s, 3H), 3.76 - 3.70 (m, 1H), 3.69 (s, 3H), 3.65 - 3.52 (m, 3H), 3.24 (s, 3H), 2.80 - 2.69 (m, 2H), 1.86 - 1.75 (m, 1H), 1.72 - 1.59 (m, 1H), 1.08 (s, 3H), 1.01 (s, 3H).
55	 1-((3S,4R)-4-(4-chlorophenyl)-1-(1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)urea	565.3	Method D RT = 1.71 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.62 (dd, J = 6.7, 2.1 Hz, 1H), 7.54 (dd, J = 7.2, 2.1 Hz, 1H), 7.49 - 7.35 (m, 4H), 6.93 (d, J = 8.3 Hz, 1H), 6.73 - 6.61 (m, 2H), 6.38 - 6.24 (m, 2H), 6.05 (d, J = 7.6 Hz, 1H), 4.65 (dd, J = 11.1, 8.9 Hz, 1H), 4.10 (br t, J = 5.4 Hz, 2H), 4.02 (t, J = 8.8 Hz, 1H), 3.79 - 3.61 (m, 5H), 3.60 - 3.48 (m, 3H), 3.23 (s, 3H), 2.89 - 2.68 (m, 3H), 2.47 - 2.38 (m, 1H), 1.94 - 1.84 (m, 1H), 1.67 - 1.53 (m, 1H).
56	 1-(cyclohexylmethyl)-3-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-2-oxo-1-(3-(trifluoromethyl)pyridin-2-yl)pyrrolidin-3-yl)urea	527.2	Method D, RT = 1.93 min, 98.3%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.86 (d, J = 3.4 Hz, 1H), 8.36 (d, J = 8.1 Hz, 1H), 7.69 (dd, J = 7.6, 5.7 Hz, 1H), 6.77 (br d, J = 11.0 Hz, 2H), 6.37 (br d, J = 8.8 Hz, 1H), 6.01 (t, J = 5.7 Hz, 1H), 4.85 - 4.73 (m, 1H), 4.05 - 3.99 (m, 1H), 3.98 - 3.84 (m, 2H), 3.78 (s, 3H), 2.78 - 2.70 (m, 2H), 1.36 - 0.98 (m, 5H), 0.92 - 0.71 (m, 6H).

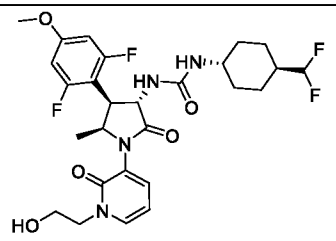
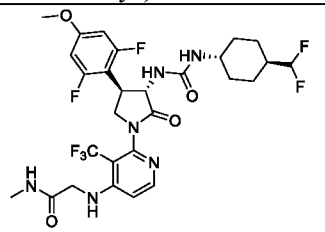
57	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(4-methoxy-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)urea	583.3	Method D RT = 1.51 min, 98.7%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.83 - 7.79 (m, 1H), 6.95 - 6.90 (m, 1H), 6.83 - 6.72 (m, 2H), 6.70 - 6.55 (m, 2H), 6.41 - 6.22 (m, 2H), 6.02 - 5.97 (m, 1H), 4.93 - 4.74 (m, 1H), 3.88 - 3.83 (2s, 3H), 3.79 - 3.77 (2s, 3H), 3.74 - 3.57 (m, 6H), 3.45 - 3.38 (m, 4H), 2.89 - 2.68 (m, 3H), 2.48 - 2.35 (m, 1H), 1.90 - 1.73 (m, 1H), 1.64 - 1.45 (m, 1H). (mixture of interconvertible atropisomers)
58	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-2-oxo-1-(3-(trifluoromethyl)pyridin-2-yl)pyrrolidin-3-yl)-3-(6-methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)urea	619.3	Method D, RT = 2.03 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.87 (dd, J = 4.8, 1.7 Hz, 1H), 8.37 (dd, J = 8.1, 1.7 Hz, 1H), 7.77 - 7.62 (m, 1H), 7.28 - 7.15 (m, 1H), 6.80 (d, J = 11.2 Hz, 2H), 6.77 - 6.67 (m, 1H), 6.59 (d, J = 2.9 Hz, 1H), 6.40 (d, J = 8.6 Hz, 1H), 5.98 (d, J = 9.5 Hz, 1H), 4.82 (dd, J = 10.8, 8.8 Hz, 1H), 4.04 - 3.88 (m, 3H), 3.78 (s, 3H), 3.69 (s, 3H), 3.70 - 3.60 (m, 1H), 2.80 - 2.70 (m, 2H), 1.84 - 1.70 (m, 1H), 1.73 - 1.61 (m, 1H), 1.08 (s, 3H), 1.02 (s, 3H).
59	 1-((3S,4S,5S)-4-(2,6-difluoro-4-methoxyphenyl)-5-methyl-2-oxo-1-(3-(trifluoromethyl)pyridin-2-yl)pyrrolidin-3-yl)-3-(6-methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)urea	633.3	Method F, RT = 3.17 min, 99%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.86 (dd, J = 4.8, 1.3 Hz, 1H), 8.35 (d, J = 8.3 Hz, 1H), 7.68 (dd, J = 7.0, 5.0 Hz, 1H), 7.23 (d, J = 9.0 Hz, 1H), 6.85 - 6.79 (m, 2H), 6.71 (dd, J = 8.8, 2.8 Hz, 1H), 6.58 (d, J = 2.5 Hz, 1H), 6.43 - 6.32 (m, 1H), 6.04 - 5.94 (m, 1H), 5.06 - 4.95 (m, 1H), 4.73 - 4.56 (m, 1H), 4.12 - 3.97 (m, 1H), 3.80 (s, 3H), 3.69 - 3.62 (m, 4H), 2.76 - 2.63 (m, 2H), 1.78 - 1.69 (m, 1H), 1.70 - 1.61 (m, 1H), 1.17 (s, 3H), 1.09 (s, 3H), 0.94 (br d, J = 6.0 Hz, 3H).

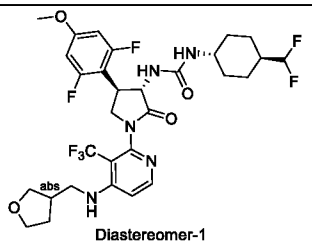
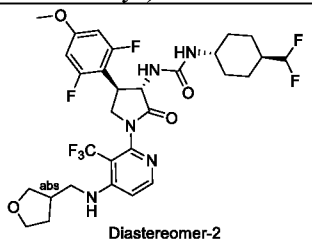
60	 1-((3S,4S,5S)-4-(2,6-difluoro-4-methoxyphenyl)-1-(3-fluoropyridin-2-yl)-5-methyl-2-oxopyrrolidin-3-yl)-3-((1r,4S)-4-(difluoromethyl)cyclohexyl)urea	527.3	Method D, RT = 1.73 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.37 (d, J = 4.6 Hz, 1H), 7.89 - 7.86 (m, 1H), 7.49-7.44 (m, 1H), 6.87 - 6.70 (m, 2H), 6.31 (d, J = 8.3 Hz, 1H), 5.99 - 5.97 (m, 1H), 5.83 (dt, J = 56.0, 4.0 Hz, 1H), 5.05 (dd, J = 10.5, 8.3 Hz, 1H), 4.75 - 4.61 (m, 1H), 4.15 (dd, J = 10.4, 8.7 Hz, 1H), 3.79 (s, 3H), 3.26 - 3.16 (m, 1H), 1.89 - 1.56 (m, 5H), 1.22 - 1.03 (m, 4H), 0.91 (d, J = 6.8 Hz, 3H).
61	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-ethyl-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)-3-(6-methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)urea	595.3	Method D, RT = 1.77 min, 98%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.74 (dd, J = 6.5, 2.0 Hz, 1H), 7.54 (dd, J = 7.0, 2.0 Hz, 1H), 7.21 (d, J = 8.5 Hz, 1H), 6.83 - 6.64 (m, 3H), 6.59 (d, J = 3.0 Hz, 1H), 6.42 - 6.22 (m, 2H), 5.96 (d, J = 9.5 Hz, 1H), 4.75 (dd, J = 11.0, 8.5 Hz, 1H), 4.05 - 3.88 (m, 3H), 3.84 - 3.80 (m, 1H), 3.79 (s, 3H), 3.78 - 3.70 (m, 1H), 3.70 (s, 3H), 3.63 (dt, J = 9.0, 3.0 Hz, 1H), 2.80 - 2.70 (m, 2H), 1.84 - 1.79 (m, 1H), 1.74 - 1.60 (m, 1H), 1.24 (t, J = 7.8 Hz, 3H), 1.08 (s, 3H), 1.02 (s, 3H).
62	 1-((3S,4S,5S)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)-5-methyl-2-oxopyrrolidin-3-yl)-3-(6-methoxy-1,1-dimethyl-1,2,3,4-tetrahydronaphthalen-2-yl)urea	639.3	Method F, RT = 2.65 min, 99%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.66 (dd, J = 6.5, 2.0 Hz, 1H), 7.53 (dd, J = 7.0, 2.0 Hz, 1H), 7.20 (d, J = 8.5 Hz, 1H), 6.80 - 6.69 (m, 3H), 6.59 (d, J = 2.5 Hz, 1H), 6.33 - 6.27 (m, 2H), 5.84 (d, J = 9.5 Hz, 1H), 5.07 (dd, J = 10.8, 8.3 Hz, 1H), 4.58 - 4.46 (m, 1H), 4.21 - 4.12 (m, 1H), 4.10 - 3.97 (m, 1H), 3.88 (dd, J = 11.0, 8.0 Hz, 1H), 3.79 (s, 3H), 3.69 (s, 3H), 3.70 - 3.58 (m, 1H), 3.58 (t, J = 5.3 Hz, 2H), 3.25 (s, 3H), 2.80 - 2.69 (m, 2H), 1.88 - 1.77 (m, 1H), 1.77 - 1.63 (m, 1H), 1.11 (s, 3H), 1.02 (s, 3H), 0.85 (d, J = 7.0 Hz, 3H).

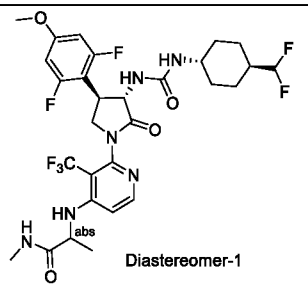
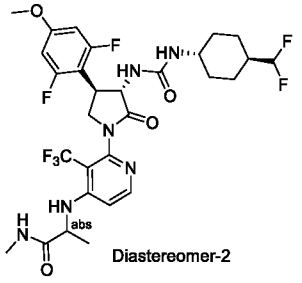
63	 1-((3S,4S,5S)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-(1-hydroxy-3-methoxypropan-2-yl)-2-oxo-1,2-dihydropyridin-3-yl)-5-methyl-2-oxopyrrolidin-3-yl)-3-((1r,4S)-4-(difluoromethyl)cyclohexyl)urea	612.2	Method D, RT = 1.47 min, 93%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.65 (dd, J = 6.7, 2.1 Hz, 1H), 7.48 (dd, J = 7.1, 2.1 Hz, 1H), 6.82 - 6.63 (m, 2H), 6.35 - 6.25 (m, 1H), 6.22 (br d, J = 8.6 Hz, 1H), 5.83 - 5.81 (m, 1H), 5.82 (dt, J = 56.0, 4.0 Hz, 1H), 5.15 - 4.96 (m, 3H), 4.55 - 4.45 (m, 1H), 3.93 (dd, J = 11.0, 8.1 Hz, 1H), 3.79 (s, 3H), 3.78 - 3.52 (m, 3H), 3.22 (s, 3H), 3.20 - 3.12 (m, 2H), 1.89 - 1.56 (m, 5H), 1.22 - 1.03 (m, 4H), 0.83 (br d, J = 6.8 Hz, 3H).
64	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-2-oxo-1-(3-(trifluoromethyl)pyridin-2-yl)pyrrolidin-3-yl)-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)urea	591.2	Method E, RT = 4.48 min, 99%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.93 - 8.77 (m, 1H), 8.36 (dd, J = 7.9, 1.6 Hz, 1H), 7.70 (dd, J = 7.3, 4.9 Hz, 1H), 6.94 (t, J = 8.4 Hz, 1H), 6.86 - 6.75 (m, 2H), 6.73 - 6.58 (m, 2H), 6.42 (br d, J = 7.1 Hz, 1H), 6.20 - 6.08 (m, 1H), 4.88 - 4.76 (m, 1H), 4.08 -3.99 (m, 1H), 3.97 - 3.81 (m, 1H), 3.79 (s, 3H), 3.75 - 3.71 (m, 1H), 3.70 (s, 3H), 2.95 - 2.67 (m, 4H), 2.46 - 2.36 (m, 1H), 1.92 - 1.73 (m, 1H), 1.66 - 1.44 (m, 1H).
65	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-(2-hydroxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)-3-((1r,4S)-4-(difluoromethyl)cyclohexyl)urea	555.3	Method D RT = 1.35 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.62 (dd, J = 6.6, 2.0 Hz, 1H), 7.53 (dd, J = 7.3, 2.0 Hz, 1H), 6.76 (d, J = 11.0 Hz, 2H), 6.29 (t, J = 7.1 Hz, 1H), 6.21 (br d, J = 8.6 Hz, 1H), 5.98 (d, J = 8 Hz, 1H), 5.83 (dt, J = 56.0, 4.0 Hz, 1H), 4.95 - 4.89 (m, 1H), 4.71 (t, J = 9.3 Hz, 1H), 3.98 (t, J = 5.5 Hz, 2H), 3.92 - 3.85 (m, 1H), 3.84 - 3.78 (m, 2H), 3.77 (s, 3H), 3.63 (t, J = 5.5 Hz, 2H), 3.25 - 3.14 (m, 1H), 1.88 - 1.57 (m, 5H), 1.22 - 1.01 (m, 4H).

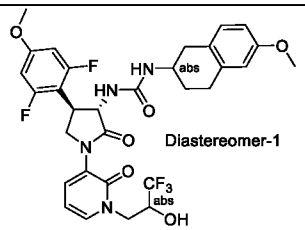
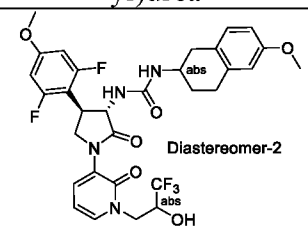
66	 1-(cyclohexylmethyl)-3-((3S,4S,5R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(3-methoxypyridin-2-yl)-5-methyl-2-oxopyrrolidin-3-yl)urea	503.3	Method D, RT = 1.79 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.09 (dd, J = 4.6, 1.5 Hz, 1H), 7.62 (dd, J = 8.3, 1.5 Hz, 1H), 7.41 (dd, J = 8.2, 4.8 Hz, 1H), 6.81 - 6.68 (m, 2H), 6.41 (d, J = 9.0 Hz, 1H), 5.95 (t, J = 6.1 Hz, 1H), 4.90 (dd, J = 11.2, 8.8 Hz, 1H), 4.28 - 4.17 (m, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 3.31 (t, J = 10.4 Hz, 1H), 2.79 - 2.74 (m, 2H), 1.68 - 1.49 (m, 5H), 1.30 - 1.21 (m, 1H), 1.19 - 1.01 (m, 3H), 0.93 (d, J = 6.1 Hz, 3H), 0.85 - 0.71 (m, 2H).
67	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-2-oxo-1-(3-(trifluoromethyl)pyridin-2-yl)pyrrolidin-3-yl)-3-(spiro[2.5]octan-6-yl)urea	539.3	Method D, RT = 1.93 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.86 (dd, J = 4.9, 1.2 Hz, 1H), 8.37 (dd, J = 8.1, 1.2 Hz, 1H), 7.70 (dd, J = 7.6, 4.4 Hz, 1H), 6.79 (d, J = 10.8 Hz, 2H), 6.31 (d, J = 8.3 Hz, 1H), 6.01 (d, J = 8.1 Hz, 1H), 4.79 (dd, J = 10.6, 8.7 Hz, 1H), 4.09 - 3.99 (m, 1H), 3.99 - 3.85 (m, 2H), 3.78 (s, 3H), 3.34 - 3.28 (m, 1H), 1.78 - 1.68 (m, 1H), 1.66 - 1.48 (m, 3H), 1.29 - 1.17 (m, 2H), 1.02 - 0.90 (m, 2H), 0.31 - 0.21 (m, 2H), 0.20 - 0.12 (m, 2H).
68	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-2-oxo-1-(4-((tetrahydro-2H-pyran-4-yl)amino)-3-(trifluoromethyl)pyridin-2-yl)pyrrolidin-3-yl)-3-((1r,4S)-4-(difluoromethyl)cyclohexyl)urea	662.4	Method C, RT = 1.66 min, 90.27%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.22 - 8.05 (m, 1H), 6.97 (d, J = 6.4 Hz, 1H), 6.80 - 6.75 (m, 2H), 6.34 - 6.18 (m, 1H), 6.02 - 5.65 (m, 3H), 4.80 - 4.71 (m, 1H), 4.26 - 3.98 (m, 1H), 3.93 - 3.83 (m, 2H), 3.79 - 3.71 (m, 4H), 3.70 - 3.56 (m, 2H), 3.48 - 3.36 (m, 2H), 3.23 - 3.06 (m, 1H), 1.92 - 1.58 (m, 9H), 1.20 - 0.97 (m, 4H). (mixture of interconvertible atropisomers)

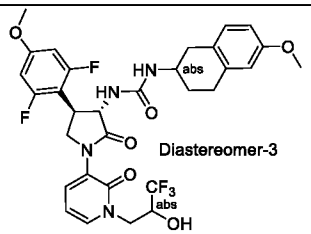
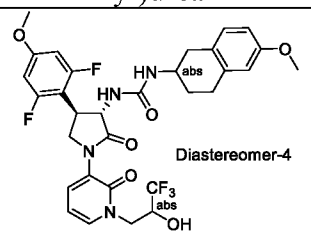
69	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(4-((2-methoxyethyl)amino)-3-(trifluoromethyl)pyridin-2-yl)-2-oxopyrrolidin-3-yl)-3-((1r,4S)-4-(difluoromethyl)cyclohexyl)urea	636.3	Method C, RT = 1.64 min, 90.79%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.20- 8.15 (m, 1H), 6.91 - 6.87 (m, 1H), 6.86 - 6.66 (m, 2H), 6.47 - 6.33 (m, 1H), 6.28 - 6.23 (m, 1H), 6.04 - 5.92 (m, 1H), 5.84 (dt, J = 60.8, 4.0 Hz, 1H), 4.82 - 4.65 (m, 1H), 4.26 - 4.03 (m, 1H), 3.96 - 3.84 (m, 1H), 3.78 (2s, 3H), 3.76 - 3.53 (m, 2H), 3.52 - 3.39 (m, 4H), 3.28 (s, 3H), 1.90 - 1.56 (m, 5H), 1.20 - 0.92 (m, 4H). (mixture of interconvertible atropisomers)
70	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)-3-((1r,4S)-4-(difluoromethyl)cyclohexyl)urea	569.3	Method D RT = 1.54 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.62 (dd, J = 7.0, 1.7 Hz, 1H), 7.54 (dd, J = 7.3, 1.7 Hz, 1H), 6.75 (d, J = 10.5 Hz, 2H), 6.36 - 6.19 (m, 2H), 5.98 (d, J = 8.0 Hz, 1H), 5.83 (dt, J = 56.4, 4.4 Hz, 1H), 4.80 - 4.64 (m, 1H), 4.10 (t, J = 5.3 Hz, 2H), 3.92 - 3.79 (m, 3H), 3.79 (s, 3H), 3.58 (t, J = 5.3 Hz, 2H), 3.24 (s, 3H), 3.22 - 3.14 (m, 1H), 1.90 - 1.80 (m, 1H), 1.79 - 1.61 (m, 4H), 1.19 - 0.95 (m, 4H).

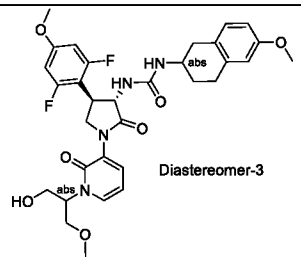
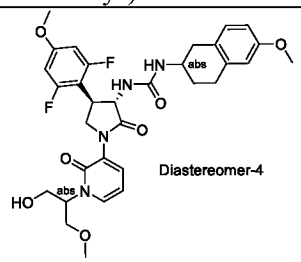
71	 1-((3S,4S,5S)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-(2-hydroxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)-5-methyl-2-oxopyrrolidin-3-yl)-3-((1r,4S)-4-(difluoromethyl)cyclohexyl)urea	569.3	Method D, RT = 1.41 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.64 (dd, J = 6.6, 2.0 Hz, 1H), 7.51 (dd, J = 6.6, 2.0 Hz, 1H), 6.76 (d, J = 11.5 Hz, 2H), 6.29 (t, J = 7.0 Hz, 1H), 6.21(d, J = 8.3 Hz, 1H), 5.97 - 5.68 (m, 2H), 5.10 (dd, J = 11.0, 8.6 Hz, 1H), 4.92 (br s, 1H), 4.56 - 4.44 (m, 1H), 4.10 - 4.00 (m, 1H), 3.98 - 3.86 (m, 2H), 3.78 (s, 3H), 3.68 - 3.59 (m, 2H), 3.24 - 3.18 (m, 1H), 1.91 - 1.57 (m, 5H), 1.21 - 0.96 (m, 4H), 0.84 (d, J = 6.6 Hz, 3H).
72	 2-((2-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-3-(3-((1r,4S)-4-(difluoromethyl)cyclohexyl)ureido)-2-oxopyrrolidin-1-yl)-3-(trifluoromethyl)pyridin-4-yl)amino)-N-methylacetamide	649.3	Method C, RT = 1.57 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.22 (br d, J = 5.9 Hz, 1H), 8.09 - 7.96 (m, 1H), 6.87 - 6.74 (m, 3H), 6.58 (d, J = 6.1 Hz, 1H), 6.39 - 6.22 (m, 1H), 6.05 - 5.90 (m, 1H), 5.83 (td, J = 56.0, 4.0 Hz, 1H), 4.86 - 4.69 (m, 1H), 4.21 - 4.09 (m, 2H), 3.91 (br d, J = 5.3 Hz, 2H), 3.81 - 3.78 (2s, 3H), 3.74 - 3.57 (m, 1H), 3.26 - 3.10 (m, 1H), 2.67 - 2.63 (2s, 3H), 1.93 - 1.80 (m, 1H), 1.80 - 1.56 (m, 4H), 1.21 - 0.92 (m, 4H). (mixture of interconvertible atropisomers)

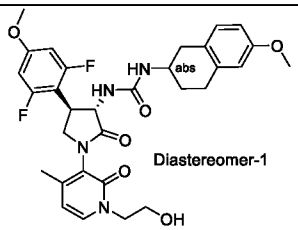
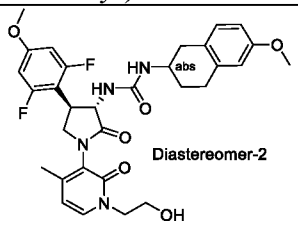
73	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-2-oxo-1-(4-(((tetrahydrofuran-3-yl)methyl)amino)-3-(trifluoromethyl)pyridin-2-yl)pyrrolidin-3-yl)-3-((1r,4S)-4-(difluoromethyl)cyclohexyl)urea	662.2	Method D, RT = 1.81 min, 93.6%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.17 (t, J = 5.9 Hz, 1H), 6.86 (d, J = 6.1 Hz, 1H), 6.81 - 6.65 (m, 3H), 6.29 (br t, J = 9.1 Hz, 1H), 6.05 - 5.90 (m, 1H), 5.83 (td, J = 56.0, 4.0 Hz, 1H), 4.83 - 4.67 (m, 1H), 4.26 - 4.06 (m, 1H), 3.96 - 3.84 (m, 1H), 3.82 - 3.74 (m, 4H), 3.71 - 3.57 (m, 3H), 3.52 - 3.48 (m, 1H), 3.28 - 3.12 (m, 4H), 1.98 - 1.81 (m, 2H), 1.79 - 1.56 (m, 5H), 1.21 - 0.96 (m, 4H). (mixture of interconvertible atropisomers)
74	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-2-oxo-1-(4-(((tetrahydrofuran-3-yl)methyl)amino)-3-(trifluoromethyl)pyridin-2-yl)pyrrolidin-3-yl)-3-((1r,4S)-4-(difluoromethyl)cyclohexyl)urea	662.2	Method D, RT = 1.81 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.17 (t, J = 5.9 Hz, 1H), 6.86 (d, J = 6.1 Hz, 1H), 6.81 - 6.65 (m, 3H), 6.29 (br t, J = 9.1 Hz, 1H), 6.05 - 5.90 (m, 1H), 5.83 (td, J = 56.0, 4.0 Hz, 1H), 4.83 - 4.67 (m, 1H), 4.26 - 4.06 (m, 1H), 3.96 - 3.84 (m, 1H), 3.82 - 3.74 (m, 4H), 3.71 - 3.57 (m, 3H), 3.52 - 3.48 (m, 1H), 3.28 - 3.12 (m, 4H), 1.98 - 1.81 (m, 2H), 1.79 - 1.56 (m, 5H), 1.21 - 0.96 (m, 4H). (mixture of interconvertible atropisomers)

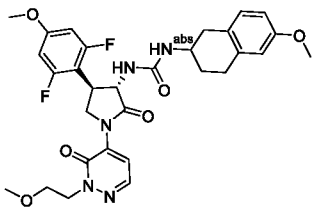
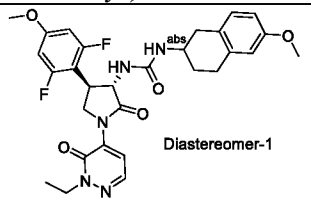
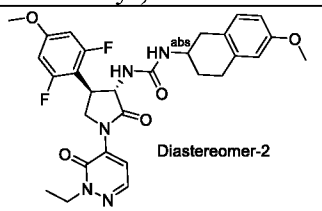
75	 2-((2-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-3-(3-((1r,4S)-4-(difluoromethyl)cyclohexyl)ureido)-2-oxopyrrolidin-1-yl)-3-(trifluoromethyl)pyridin-4-yl)amino)-N-methylpropanamide	663.3	Method D, RT = 1.65 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.29 - 8.19 (m, 2H), 6.82 - 6.74 (m, 2H), 6.67 (br d, J = 3.5 Hz, 1H), 6.39 - 6.27 (m, 2H), 6.05 - 5.90 (m, 1H), 5.83 (td, J = 56.0, 4.0 Hz, 1H), 4.79 - 4.71 (m, 1H), 4.27 - 3.97 (m, 2H), 3.81 (2s, 3H), 3.67 - 3.60 (m, 2H), 3.30 - 3.12 (m, 1H), 2.69 - 2.65 (2s, 3H), 1.95- 1.80 (m, 1H), 1.79 - 1.64 (m, 4H), 1.37 (2d, J = 6.1 Hz, 3H), 1.21 - 0.99 (m, 4H). (mixture of interconvertible atropisomers)
76	 2-((2-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-3-(3-((1r,4S)-4-(difluoromethyl)cyclohexyl)ureido)-2-oxopyrrolidin-1-yl)-3-(trifluoromethyl)pyridin-4-yl)amino)-N-methylpropanamide	663.3	Method D, RT = 1.66 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.29 - 8.19 (m, 2H), 6.82 - 6.74 (m, 2H), 6.67 (br d, J = 3.5 Hz, 1H), 6.39 - 6.27 (m, 2H), 6.05 - 5.90 (m, 1H), 5.83 (td, J = 56.0, 4.0 Hz, 1H), 4.79 - 4.71 (m, 1H), 4.27 - 3.97 (m, 2H), 3.81 (2s, 3H), 3.67 - 3.60 (m, 2H), 3.30 - 3.12 (m, 1H), 2.69 - 2.65 (2s, 3H), 1.95 - 1.80 (m, 1H), 1.79 - 1.64 (m, 4H), 1.41 - 1.32 (2d, J = 6.2 Hz, 3H), 1.21 - 0.99 (m, 4H). (mixture of interconvertible atropisomers)

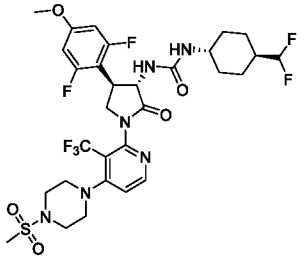
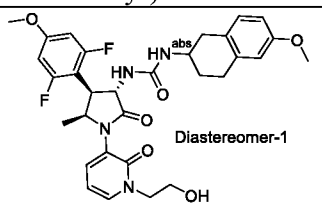
77	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-2-oxo-1-(2-oxo-1-(3,3,3-trifluoro-2-hydroxypropyl)-1,2-dihydropyridin-3-yl)pyrrolidin-3-yl)-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)urea	651.3	Method D, RT = 1.75 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.68 (dd, J = 6.8, 1.9 Hz, 1H), 7.62 (dd, J = 7.3, 1.9 Hz, 1H), 6.93 (d, J = 8.3 Hz, 1H), 6.78 (d, J = 10.8 Hz, 2H), 6.67 (dd, J = 8.3, 2.6 Hz, 1H), 6.64 (d, J = 2.6 Hz, 1H), 6.36 (t, J = 7.0 Hz, 1H), 6.31 (br d, J = 8.9 Hz, 1H), 6.11 (d, J = 7.6 Hz, 1H), 4.77 - 4.66 (m, 1H), 4.43 (m, 1H), 4.37 - 4.25 (m, 1H), 3.93 - 3.80 (m, 4H), 3.79 (s, 3H), 3.72 - 3.67 (m, 4H), 3.17 (br s, 1H), 2.85 - 2.71 (m, 3H), 2.42 (dd, J = 16.1, 8.9 Hz, 1H), 1.93 - 1.79 (m, 1H), 1.63 - 1.52 (m, 1H).
78	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-2-oxo-1-(2-oxo-1-(3,3,3-trifluoro-2-hydroxypropyl)-1,2-dihydropyridin-3-yl)pyrrolidin-3-yl)-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)urea	651.3	Method D, RT = 1.74 min, 97%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.67 (dd, J = 6.8, 2.1 Hz, 1H), 7.61 (dd, J = 7.2, 2.1 Hz, 1H), 6.98 - 6.74 (m, 3H), 6.69 - 6.60 (m, 2H), 6.40 - 6.26 (m, 2H), 6.12 (d, J = 7.8 Hz, 1H), 4.75 - 4.70 (m, 1H), 4.45 - 4.40 (m, 1H), 4.39 - 4.29 (m, 1H), 4.03 - 3.96 (m, 1H), 3.88 - 3.77 (m, 6H), 3.72 - 3.66 (m, 4H), 3.17 (br d, J = 4.5 Hz, 1H), 2.86 - 2.70 (m, 3H), 2.45 - 2.36 (m, 1H), 1.96 - 1.82 (m, 1H), 1.63 - 1.52 (m, 1H).

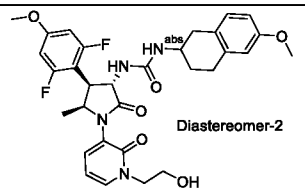
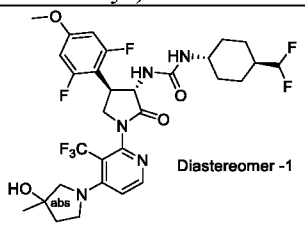
79	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-2-oxo-1-(2-oxo-1-(3,3,3-trifluoro-2-hydroxypropyl)-1,2-dihydropyridin-3-yl)pyrrolidin-3-yl)-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)urea	651.3	Method D, RT = 1.75 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.68 (dd, J = 6.8, 1.9 Hz, 1H), 7.61 (dd, J = 7.3, 1.9 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 6.77 (d, J = 10.8 Hz, 2H), 6.67 (dd, J = 8.4, 2.9 Hz, 1H), 6.64 (d, J = 2.5 Hz, 1H), 6.35 (t, J = 7.0 Hz, 2H), 6.17 (d, J = 7.8 Hz, 1H), 4.75 (m, 1H), 4.43 (m, 1H), 4.37 - 4.26 (m, 1H), 3.93 - 3.80 (m, 4H) 3.79 (s, 3H), 3.72 - 3.66 (m, 4H), 3.35 - 3.30 (m, 1H), 2.86 (m, 1H), 2.80 - 2.70 (m, 2H), 2.48 - 2.41 (m, 1H), 1.87 - 1.73 (m, 1H), 1.58 - 1.45 (m, 1H).
80	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-2-oxo-1-(2-oxo-1-(3,3,3-trifluoro-2-hydroxypropyl)-1,2-dihydropyridin-3-yl)pyrrolidin-3-yl)-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)urea	651.3	Method D, RT = 1.741 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.68 (dd, J = 6.9, 1.9 Hz, 1H), 7.60 (dd, J = 7.3, 1.9, Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 6.78 (d, J = 10.8 Hz, 2H), 6.67 (dd, J = 8.0, 3.3 Hz, 1H), 6.64 (d, J = 2.6 Hz, 1H), 6.40 - 6.30 (m, 2H), 6.17 (d, J = 4.0 Hz,, 1H), 4.80 - 4.72 (m, 1H), 4.43 (dd, J = 13.1, 2.9 Hz, 1H), 4.38 - 4.29 (m, 1H), 4.03 - 3.92 (m, 1H), 3.88 - 3.78 (m, 6H), 3.75 - 3.65 (m, 4H), 3.35 - 3.30 (m, 1H), 2.86 (m, 1H), 2.80 - 2.70 (m, 2H), 2.47 (m, 1H), 1.87 - 1.76 (m, 1H), 1.58 - 1.46 (m, 1H).

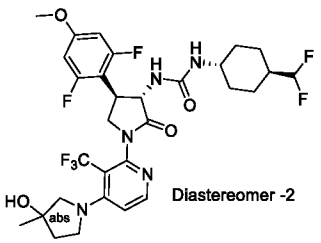
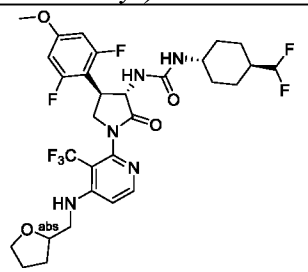
81	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-(1-hydroxy-3-methoxypropan-2-yl)-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)urea	627.3	Method D, RT = 1.56 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.67 (dd, J = 7.0, 2.0 Hz, 1H), 7.52 (dd, J = 7.3, 2.0 Hz, 1H), 6.95 (d, J = 8.5 Hz, 1H), 6.77 (d, J = 10.8 Hz, 2H), 6.67 (dd, J = 8.4, 0.3 Hz, 1H), 6.64 (d, J = 2.6 Hz, 1H), 6.39 - 6.23 (m, 2H), 6.12 (d, J = 7.8 Hz, 1H), 5.11 - 4.97 (m, 2H), 4.80 - 4.68 (m, 1H), 3.91 (d, J = 5.9 Hz, 1H), 3.84 - 3.76 (m, 5H), 3.76 - 3.68 (m, 3H), 3.69 (s, 3H), 3.65 - 3.58 (m, 2H), 3.23 (s, 3H), 2.86 (dd, J = 15.8, 4.6 Hz, 1H), 2.78 - 2.70 (m, 2H), 2.47 - 2.41 (m, 1H), 1.87 -1.74 (m, 1H), 1.53 (m, 1H).
82	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-(1-hydroxy-3-methoxypropan-2-yl)-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)urea	627.3	Method D, RT = 1.57 min, 97%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.67 (dd, J = 7.0, 2.0 Hz, 1H), 7.52 (dd, J = 7.3, 2.0 Hz, 1H), 6.95 (d, J = 8.5 Hz, 1H), 6.77 (d, J = 10.8 Hz, 2H), 6.67 (dd, J = 8.1, 2.8 Hz, 1H), 6.64 (d, J = 2.6 Hz, 1H), 6.35 - 6.23 (m, 2H), 6.11 (d, J = 8.0 Hz, 1H), 5.07 - 5.03 (m, 2H), 4.78 - 4.75 (m, 1H), 3.93 - 3.80 (m, 3H), 3.79 (s, 3H), 3.76 - 3.71 (m, 3H), 3.69 (s, 3H), 3.67 - 3.57 (m, 2H), 3.23 (s, 3H), 2.86 (dd, J = 15.8, 4.9 Hz, 1H), 2.76 - 2.70 (m, 2H), 2.47 - 2.40 (m, 1H), 1.87 - 1.75 (m, 1H), 1.59 - 1.47 (m, 1H).

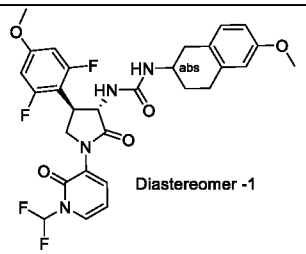
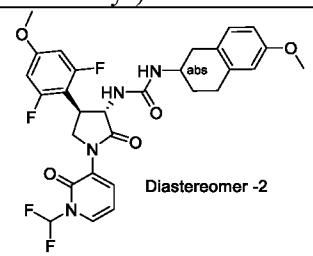
83	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-(2-hydroxyethyl)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)urea	597.3	Method D, RT = 1.61 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.57 - 7.52 (m, 1H), 6.95 - 6.90 (m, 1H), 6.80 - 6.77 (m, 2H), 6.71 - 6.52 (m, 2H), 6.44 - 6.28 (m, 1H), 6.21 - 6.17 (m, 1H), 6.12 - 5.84 (m, 1H), 4.95 - 4.49 (m, 2H), 4.15 - 3.88 (m, 4H), 3.79 (s, 3H), 3.72 - 3.66 (m, 4H), 3.64 - 3.57 (m, 2H), 3.46 - 3.38 (m, 1H), 2.88 - 2.71 (m, 3H), 2.46 - 2.38 (m, 1H), 2.18 - 1.98 (2s, 3H), 1.93 - 1.82 (m, 1H), 1.63 - 1.50 (m, 1H). (mixture of interconvertible atropisomers)
84	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-(2-hydroxyethyl)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)urea	597.3	Method D, RT = 1.67 min, 94%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.60 - 7.46 (m, 1H), 6.96 - 6.91 (m, 1H), 6.84 - 6.71 (m, 2H), 6.70 - 6.59 (m, 2H), 6.40 - 6.26 (m, 1H), 6.21 - 6.16 (m, 1H), 6.09 - 5.97 (m, 1H), 4.97 - 4.56 (m, 2H), 4.15 - 3.85 (m, 4H), 3.78 (s, 3H), 3.74 - 3.65 (m, 4H), 3.62 - 3.57 (m, 2H), 3.45 - 3.37 (m, 1H), 2.91 - 2.68 (m, 3H), 2.47 - 2.40 (m, 1H), 2.15 - 2.01 (2s, 3H), 1.85 - 1.74 (m, 1H), 1.60 - 1.43 (m, 1H). (mixture of interconvertible atropisomers)

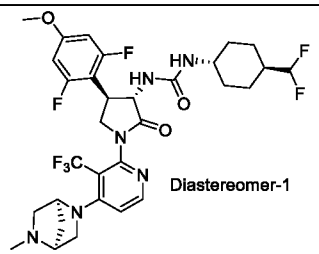
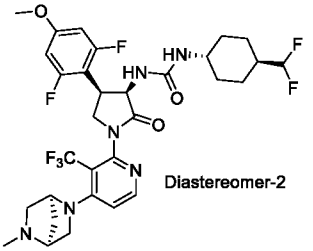
85	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(2-(2-methoxyethyl)-3-oxo-2,3-dihydropyridazin-4-yl)-2-oxopyrrolidin-3-yl)-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)urea	598.3	Method D, RT = 1.76 min, 98%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.99 (d, J = 4.6 Hz, 1H), 7.67 (d, J = 4.6 Hz, 1H), 6.93 (d, J = 8.6 Hz, 1H), 6.78 (d, J = 11.0 Hz, 2H), 6.69 - 6.58 (m, 2H), 6.33 (br d, J = 7.6 Hz, 1H), 6.20 (d, J = 7.8 Hz, 1H), 4.70 (dd, J = 11.2, 8.3 Hz, 1H), 4.26 (dt, J = 5.6, 2.1 Hz, 2H), 4.17- 4.08 (m, 2H), 3.89 (br d, J = 11.0 Hz, 1H), 3.79 (s, 3H), 3.71 - 3.66 (m, 5H), 3.23 (s, 3H), 3.17 (d, J = 5.1 Hz, 1H), 2.83 - 2.72 (m, 3H), 2.46 - 2.36 (m, 1H), 1.92 - 1.81 (m, 1H), 1.64 - 1.49 (m, 1H).
86	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(2-ethyl-3-oxo-2,3-dihydropyridazin-4-yl)-2-oxopyrrolidin-3-yl)-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)urea	568.3	Method D, RT = 1.83 min, 96%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.99 (d, J = 4.4 Hz, 1H), 7.67 (d, J = 4.6 Hz, 1H), 6.95 (d, J = 8.6 Hz, 1H), 6.78 (d, J = 10.8 Hz, 2H), 6.67 (dd, J = 8.2, 2.6 Hz, 1H), 6.63 (d, J = 2.7 Hz, 1H), 6.32 (d, J = 8.8 Hz, 1H), 6.22 (d, J = 7.8 Hz, 1H), 4.72 (dd, J = 11.2, 8.3 Hz, 1H), 4.19 - 4.06 (m, 4H), 3.91 - 3.84 (m, 1H), 3.79 (s, 3H), 3.69 (s, 3H), 3.17 (d, J = 5.1 Hz, 1H), 2.89 - 2.81 (m, 1H), 2.77 - 2.69 (m, 2H), 2.47 - 2.41 (m, 1H), 1.86 - 1.77 (m, 1H), 1.57 - 1.47 (m, 1H), 1.27 (t, J = 8.0 Hz, 3H).
87	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(2-ethyl-3-oxo-2,3-dihydropyridazin-4-yl)-2-oxopyrrolidin-3-yl)-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)urea	568.3	Method D, RT = 1.83 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.02 - 7.94 (m, 1H), 7.66 (d, J = 4.6 Hz, 1H), 6.92 (d, J = 8.6 Hz, 1H), 6.78 (d, J = 10.8 Hz, 2H), 6.71 - 6.64 (m, 1H), 6.63 (d, J = 2.7 Hz, 1H), 6.33 (dd, J = 8.8, 0.7 Hz 1H), 6.19 (d, J = 7.6 Hz, 1H), 4.69 (dd, J = 11.5, 8.3 Hz, 1H), 4.19 - 4.05 (m, 4H), 3.94 - 3.84 (m, 1H), 3.79 (s, 3H), 3.73 - 3.63 (m, 4H), 2.83 - 2.70 (m, 3H), 2.42 (dd, J = 15.8, 8.9 Hz, 1H), 1.92 - 1.82 (m, 1H), 1.64 - 1.51 (m, 1H), 1.26 (t, J = 8.0 Hz, 3H).

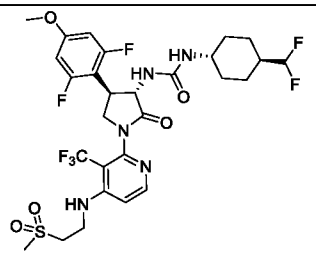
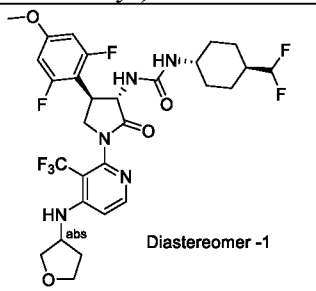
88	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(4-(4-(methylsulfonyl)piperazin-1-yl)-3-(trifluoromethyl)pyridin-2-yl)-2-oxopyrrolidin-3-yl)-3-((1r,4S)-4-(difluoromethyl)cyclohexyl)urea	725.3	Method D, RT = 1.90 min, 98.5%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.50 (d, J = 5.4 Hz, 1H), 7.27 (d, J = 5.9 Hz, 1H), 6.78 (br d, J = 11.0 Hz, 2H), 6.27 (td, J = 4.8, 2.5 Hz, 1H), 6.02 - 5.62 (m, 2H), 4.75 (br dd, J = 10.8, 9.0 Hz, 1H), 4.02 - 3.95 (m, 1H), 3.81 - 3.64 (m, 4H), 3.35 - 3.11 (m, 10H), 2.95 (s, 3H), 1.91 - 1.62 (m, 5H), 1.23 - 0.98 (m, 4H). (mixture of interconvertible atropisomers)
89	 1-((3S,4S,5S)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-(2-hydroxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)-5-methyl-2-oxopyrrolidin-3-yl)-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)urea	597.3	Method D, RT = 1.60 min, 96%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.64 (dd, J = 7.3, 2.0 Hz, 1H), 7.51 (dd, J = 7.3, 2.0 Hz, 1H), 6.96 - 6.91 (m, 1H), 6.77 (d, J = 11.2 Hz, 2H), 6.68 - 6.60 (m, 2H), 6.32 - 6.24 (m, 2H), 5.98 - 5.93 (m, 1H), 5.12 (dd, J = 11.1, 8.2 Hz, 1H), 4.95 - 4.92 (m, 1H), 4.54 - 4.48 (m, 1H), 4.10 - 4.00 (m, 1H), 3.99 - 3.89 (m, 2H), 3.79 (s, 3H), 3.75 - 3.69 (m, 1H), 3.68 (s, 3H), 3.66 - 3.58 (m, 2H), 2.81 (dd, J = 15.7, 4.6 Hz, 1H), 2.88 - 2.80 (m, 2H), 2.74 -2.68 (m, 1H), 1.89 - 1.80 (m, 1H), 1.55 - 1.50 (m, 1H), 0.85 (d, J = 7.1 Hz, 3H).

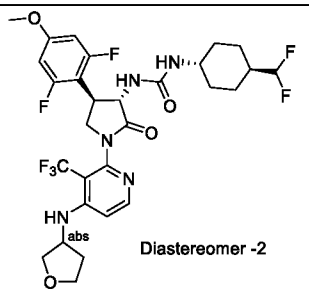
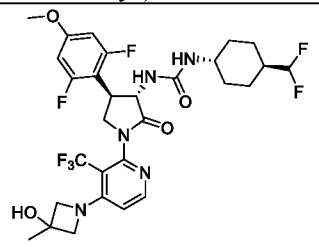
90	 1-((3S,4S,5S)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-(2-hydroxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)-5-methyl-2-oxopyrrolidin-3-yl)-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)urea	597.3	Method D, RT = 1.59 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.64 (dd, J = 6.6, 2.0 Hz, 1H), 7.51 (dd, J = 6.6, 2.0 Hz, 1H), 6.91 (d, J = 8.3 Hz, 1H), 6.81 - 6.72 (m, 2H), 6.69 - 6.58 (m, 2H), 6.36 - 6.24 (m, 2H), 5.98 (d, J = 7.3 Hz, 1H), 5.11 (dd, J = 11.1, 8.2 Hz, 1H), 5.0 - 4.95 (m, 1H), 4.56 - 4.42 (m, 1H), 4.10 - 4.00 (m, 1H), 3.99 - 3.89 (m, 2H), 3.79 (s, 3H), 3.75 - 3.69 (m, 1H), 3.68 (s, 3H), 3.66 - 3.58 (m, 2H), 2.81 (dd, J = 15.7, 4.6 Hz, 1H), 2.77 - 2.70 (m, 2H), 2.41 (dd, J = 15.9, 8.8 Hz, 1H), 1.91 - 1.78 (m, 1H), 1.60 - 1.52 (m, 1H), 0.84 (d, J = 7.1 Hz, 3H).
91	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(4-(3-hydroxy-3-methylpyrrolidin-1-yl)-3-(trifluoromethyl)pyridin-2-yl)-2-oxopyrrolidin-3-yl)-3-((1r,4S)-4-(difluoromethyl)cyclohexyl)urea	662.3	Method D, RT = 1.90 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.15 - 8.02 (m, 1H), 6.90 - 6.64 (m, 3H), 6.26 - 6.15 (m, 1H), 5.90 - 5.81 (m, 1H), 5.78 (td, J = 56.0, 4.0 Hz, 1H), 4.96 - 4.82 (m, 1H), 5.16 - 4.76 (m, 1H), 4.82 - 4.69 (m, 1H), 4.25 - 4.10 (m, 1H), 3.78 (s, 3H), 3.75 - 3.62 (m, 2H), 3.49 - 3.40 (m, 1H), 3.23 - 3.10 (m, 3H), 2.03 - 1.81 (m, 3H), 1.81 - 1.51 (m, 4H), 1.36 (s, 3H), 1.19 - 0.91 (m, 4H).

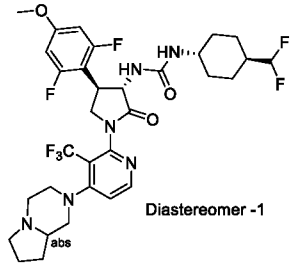
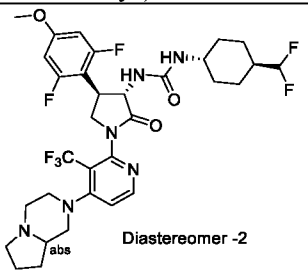
92	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(4-(3-hydroxy-3-methylpyrrolidin-1-yl)-3-(trifluoromethyl)pyridin-2-yl)-2-oxopyrrolidin-3-yl)-3-((1r,4S)-4-(difluoromethyl)cyclohexyl)urea	662.3	Method D, RT = 1.90 min, 98.1%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.15 - 8.02 (m, 1H), 6.90 - 6.64 (m, 3H), 6.26 - 6.15 (m, 1H), 5.90 - 5.81 (m, 1H), 5.78 (td, J = 56.0, 4.0 Hz, 1H), 4.96 - 4.82 (m, 1H), 4.76 (br dd, J = 10.5, 9.5 Hz, 1H), 4.25 - 4.10 (m, 1H), 3.78 (s, 3H), 3.75 - 57 (m, 2H), 3.49 - 3.40 (m, 1H), 3.23 - 3.10 (m, 4H), 2.03 - 1.81 (m, 3H), 1.81 - 1.51 (m, 4H), 1.36 (s, 3H), 1.19 - 0.91 (m, 4H).
93	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-2-oxo-1-(4-(((tetrahydrofuran-2-yl)methyl)amino)-3-(trifluoromethyl)pyridin-2-yl)pyrrolidin-3-yl)-3-((1r,4S)-4-(difluoromethyl)cyclohexyl)urea	662.3	Method D, RT = 1.99 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.16 (t, J = 5.4 Hz, 1H), 6.92 - 6.84 (m, 1H), 6.80 - 6.71 (m, 2H), 6.39 - 6.22 (m, 2H), 6.03 - 5.97 (m, 1H), 5.82 (td, J = 56.0, 4.0 Hz, 1H), 4.79 - 4.68 (m, 1H), 4.22 - 3.86 (m, 3H), 3.79 - 3.77 (2s, 3H), 3.76 - 3.57 (m, 3H), 3.50 - 3.38 (m, 2H), 3.19 - 3.09 (m, 2H), 1.97 - 1.78 (m, 4H), 1.76 - 1.62 (m, 4H), 1.19 - 0.96 (m, 4H). (mixture of interconvertible atropisomers)

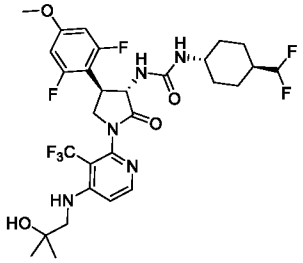
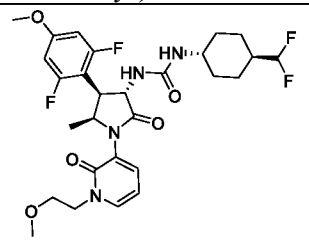
94	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-(difluoromethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)urea	589.3	Method D, RT = 1.85 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.89 (t, J = 60.0 Hz, 1H), 7.83 - 7.77 (m, 1H), 7.70 (dd, J = 7.1, 1.7 Hz, 1H), 6.94 (d, J = 8.3 Hz, 1H), 6.77 (d, J = 10.8 Hz, 2H), 6.71 - 6.60 (m, 2H), 6.53 (t, J = 7.2 Hz, 1H), 6.32 (d, J = 8.6 Hz, 1H), 6.15 (d, J = 7.6 Hz, 1H), 4.73 (t, J = 8.9 Hz, 1H), 3.95 - 3.80 (m, 3H), 3.78 (s, 3H), 3.75 - 3.70 (m, 1H), 3.69 (m, 3H), 2.85 (dd, J = 16.1, 4.9 Hz, 1H), 2.77 - 2.68 (m, 2H), 2.47 - 2.41 (m, 1H), 1.86 - 1.73 (m, 1H), 1.59 - 1.44 (m, 1H).
95	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-(difluoromethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)-3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)urea	589.3	Method D, RT = 1.85 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.89 (t, J = 60.0 Hz, 1H), 7.83 - 7.77 (m, 1H), 7.70 (dd, J = 7.1, 2.0 Hz, 1H), 6.92 (d, J = 8.8 Hz, 1H), 6.77 (d, J = 10.8 Hz, 2H), 6.71 - 6.60 (m, 2H), 6.53 (t, J = 7.2 Hz, 1H), 6.33 (br d, J = 8.3 Hz, 1H), 6.14 (d, J = 7.6 Hz, 1H), 4.74 - 4.62 (m, 1H), 3.94 - 3.81 (m, 3H), 3.78 (s, 3H), 3.73 - 3.7 (m, 1H), 3.69 (s, 3H), 2.85 - 2.71 (m, 3H), 2.46 - 2.36 (m, 1H), 1.92 - 1.81 (m, 1H), 1.60 - 1.51 (m, 1H).

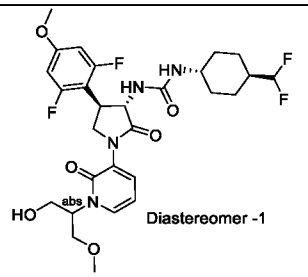
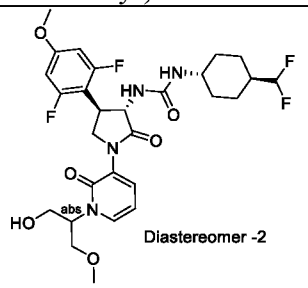
96	 Diastereomer-1 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(4-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)-3-(trifluoromethyl)pyridin-2-yl)-2-oxopyrrolidin-3-yl)-3-((1r,4S)-4-(difluoromethyl)cyclohexyl)urea	673.3	Method D, RT = 1.68 min, 98.1%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.20 - 8.06 (m, 1H), 7.02 - 6.83 (m, 1H), 6.78 (d, J = 10.8 Hz, 2H), 6.31 (br d, J = 8.3 Hz, 1H), 6.02 - 5.97 (m, 1H), 5.82 (td, J = 56.0, 4.0 Hz, 1H), 4.83 - 4.70 (m, 1H), 4.59 - 4.55 (m, 1H), 4.26 - 4.13 (m, 1H), 3.78 (s, 3H), 3.74 - 3.61 (m, 2H), 3.41 - 3.12 (m, 5H), 2.98 - 2.87 (m, 1H), 2.51 (br s, 3H), 2.20 - 2.04 (m, 1H), 2.01 - 1.94 (m, 1H), 1.91 - 1.80 (m, 1H), 1.79 - 1.61 (m, 4H), 1.20 - 0.95 (m, 4H).
97	 Diastereomer-2 1-((3R,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(4-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)-3-(trifluoromethyl)pyridin-2-yl)-2-oxopyrrolidin-3-yl)-3-((1r,4R)-4-(difluoromethyl)cyclohexyl)urea	673.3	Method D, RT = 1.82 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.32 (d, J = 5.1 Hz, 1H), 6.84 - 6.75 (m, 3H), 6.27 (br d, J = 8.3 Hz, 1H), 6.02 - 5.97 (m, 1H), 5.82 (td, J = 56.0, 4.0 Hz, 1H), 4.73 - 4.62 (m, 2H), 3.99- 3.80 (m, 2H), 3.79 (s, 3H), 3.63 - 3.37 (m, 3H), 3.28 - 3.15 (m, 3H), 2.80 - 2.70 (m, 2H), 2.28 (br s, 3H), 1.93 - 1.83 (m, 2H), 1.81 -1.65 (m, 4H), 1.25 - 0.99 (m, 4H).

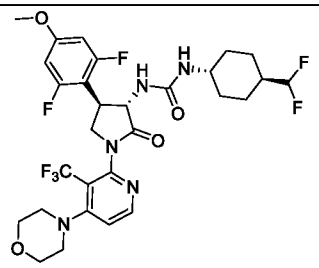
98	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(4-((2-(methylsulfonyl)ethyl)amino)-3-(trifluoromethyl)pyridin-2-yl)-2-oxopyrrolidin-3-yl)-3-((1r,4S)-4-(difluoromethyl)cyclohexyl)urea	684.3	Method D, RT = 1.86 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.33 - 8.13 (m, 1H), 6.86 (d, J = 6.1 Hz, 1H), 6.82 - 6.60 (m, 3H), 6.34 - 6.19 (m, 1H), 6.02 - 5.89 (m, 1H), 5.82 (td, J = 56.0, 4.0 Hz, 1H), 4.79 - 4.72 (m, 1H), 4.24 - 4.06 (m, 2H), 3.99 - 3.86 (m, 1H), 3.79 (s, 3H), 3.78 - 3.57 (m, 2H), 3.44 (t, J = 6.6 Hz, 2H), 3.23 - 3.12 (m, 1H), 3.07 (s, 3H), 1.92 - 1.82 (m, 1H), 1.79 - 1.55 (m, 4H), 1.19 - 1.03 (m, 4H).
99	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-2-oxo-1-(4-((tetrahydrofuran-3-yl)amino)-3-(trifluoromethyl)pyridin-2-yl)pyrrolidin-3-yl)-3-((1r,4S)-4-(difluoromethyl)cyclohexyl)urea	648.3	Method D, RT = 1.86 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.23 (d, J = 5.4 Hz, 1H), 6.88 (d, J = 5.9 Hz, 1H), 6.77 (dd, J = 10.9, 4.0 Hz, 2H), 6.34 - 6.17 (m, 1H), 6.04 - 5.91 (m, 2H), 5.82 (td, J = 56.0, 4.0 Hz, 1H), 4.80 - 4.68 (m, 1H), 4.33 - 4.07 (m, 2H), 3.96 - 3.82 (m, 3H), 3.78 - 3.59 (m, 6H), 3.21 - 3.09 (m, 1H), 2.30 - 2.19 (m, 1H), 2.02 - 1.81 (m, 2H), 1.80 - 1.61 (m, 4H), 1.20 - 0.95 (m, 4H). (mixture of interconvertible atropisomers)

100	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-2-oxo-1-(4-((tetrahydrofuran-3-yl)amino)-3-(trifluoromethyl)pyridin-2-yl)pyrrolidin-3-yl)-3-((1r,4S)-4-(difluoromethyl)cyclohexyl)urea	648.3	Method D, RT = 1.85 min, 95.44%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.22 (t, J = 5.6 Hz, 1H), 6.88 (d, J = 6.4 Hz, 1H), 6.81 - 6.61 (m, 2H), 6.34 - 6.17 (m, 1H), 6.04 - 5.91 (m, 2H), 5.82 (td, J = 56.0, 4.0 Hz, 1H), 4.81 - 4.67 (m, 1H), 4.33 - 4.01 (m, 2H), 3.95 - 3.81 (m, 3H), 3.79 - 3.57 (m, 6H), 3.20 - 3.15 (m, 1H), 2.32 - 2.16 (m, 1H), 2.03 - 1.81 (m, 2H), 1.80 - 1.54 (m, 4H), 1.20 - 0.95 (m, 4H). (mixture of interconvertible atropisomers)
101	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(4-(3-hydroxy-3-methylazetidin-1-yl)-3-(trifluoromethyl)pyridin-2-yl)-2-oxopyrrolidin-3-yl)-3-((1r,4S)-4-(difluoromethyl)cyclohexyl)urea	648.3	Method D, RT = 1.92 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.18 - 8.07 (m, 1H), 6.86 - 6.70 (m, 2H), 6.50 (d, J = 6.1 Hz, 1H), 6.37 - 6.28 (m, 1H), 6.02 - 5.78 (m, 1H), 5.82 (td, J = 56.0, 4.0 Hz, 1H), 5.74 (br s, 1H), 4.80 - 4.71 (m, 1H), 4.33 - 4.16 (m, 1H), 4.10 - 4.05 (m, 1H), 4.02 - 3.86 (m, 3H), 3.79 (s, 3H), 3.74 - 3.59 (m, 2H), 3.21 - 3.10 (m, 1H), 1.92 - 1.81 (m, 1H), 1.79 - 1.63 (m, 4H), 1.44 (s, 3H), 1.21 - 0.97 (m, 4H).

102	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-3-(trifluoromethyl)pyridin-2-yl)-2-oxopyrrolidin-3-yl)-3-((1r,4S)-4-(difluoromethyl)cyclohexyl)urea	687.3	Method D, RT = 2.06 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.37 (d, J = 5.9 Hz, 1H), 7.23 - 7.13 (m, 1H), 6.77 (d, J = 11.0 Hz, 2H), 6.41 - 6.25 (m, 1H), 6.02 - 5.89 (m, 1H), 5.82 (td, J = 56.0, 4.0 Hz, 1H), 4.81 - 4.65 (m, 1H), 4.32 - 3.92 (m, 3H), 3.80 (s, 3H), 3.79 - 3.55 (m, 2H), 3.52 - 3.44 (m, 1H), 3.22 - 3.12 (m, 2H), 3.09 - 2.93 (m, 3H), 2.89 - 2.70 (m, 1H), 2.30 - 1.95 (m, 3H), 1.89 - 1.59 (m, 6H), 1.40 - 1.25 (m, 1H), 1.19 - 0.93 (m, 4H).
103	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)-3-(trifluoromethyl)pyridin-2-yl)-2-oxopyrrolidin-3-yl)-3-((1r,4S)-4-(difluoromethyl)cyclohexyl)urea	687.3	Method D, RT = 2.06 min, 98.4%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.37 (d, J = 5.9 Hz, 1H), 7.23 - 7.13 (m, 1H), 6.77 (d, J = 11.0 Hz, 2H), 6.41 - 6.25 (m, 1H), 6.02 - 5.89 (m, 1H), 5.82 (td, J = 56.0, 4.0 Hz, 1H), 4.81 - 4.65 (m, 1H), 4.32 - 3.92 (m, 3H), 3.80 (s, 3H), 3.79 - 3.55 (m, 2H), 3.52 - 3.44 (m, 1H), 3.22 - 3.12 (m, 2H), 3.09 - 2.93 (m, 3H), 2.89 - 2.70 (m, 1H), 2.30 - 1.95 (m, 3H), 1.89 - 1.59 (m, 6H), 1.40 - 1.25 (m, 1H), 1.19 - 0.93 (m, 4H).

104	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(4-((2-hydroxy-2-methylpropyl)amino)-3-(trifluoromethyl)pyridin-2-yl)-2-oxopyrrolidin-3-yl)-3-((1r,4S)-4-(difluoromethyl)cyclohexyl)urea	650.3	Method D, RT = 1.8 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.20 (d, J = 5.9 Hz, 1H), 7.03 - 6.89 (m, 1H), 6.83 - 6.68 (m, 2H), 6.36 - 6.16 (m, 2H), 6.02 - 5.89 (m, 1H), 5.82 (td, J = 56.0, 4.0 Hz, 1H), 4.81 - 4.68 (m, 1H), 4.23 - 4.08 (m, 2H), 3.78 (s, 3H), 3.77 - 3.57 (m, 2H), 3.27 - 3.15 (m, 3H), 1.91 - 1.81 (m, 1H), 1.80 - 1.59 (m, 4H), 1.20 - 0.94 (m, 10H).
105	 1-((3S,4S,5S)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)-5-methyl-2-oxopyrrolidin-3-yl)-3-((1r,4S)-4-(difluoromethyl)cyclohexyl)urea	583.3	Method D, RT = 1.57 min, 92%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ =7.65 (dd, J = 6.7, 2.0 Hz, 1H), 7.52 (dd, J = 6.7, 2.0 Hz, 1H), 6.82 - 6.63 (m, 2H), 6.35 - 6.25 (m, 1H), 6.22 (br d, J = 8.6 Hz, 1H), 5.82 (dt, J = 56.0, 4.0 Hz, 1H), 5.81 - 5.79 (m, 1H), 5.10 (dd, J = 11.4, 8.7 Hz, 1H), 4.61 - 4.41 (m, 1H), 4.26 - 4.12 (m, 1H), 4.06 - 4.03 (m, 1H), 3.97-3.92 (m, 1H), 3.79 (s, 3H), 3.59 (t, J = 6.6 Hz, 2H), 3.27 (s, 3H), 3.24 - 3.18 (m, 1H), 1.90 - 1.56 (m, 5H), 1.24 - 0.96 (m, 4H), 0.83 (d, J = 6.8 Hz, 3H).

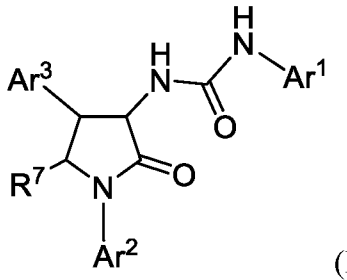
106	 Diastereomer -1 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-(1-hydroxy-3-methoxypropan-2-yl)-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)-3-((1r,4S)-4-(difluoromethyl)cyclohexyl)urea	599.3	Method D, RT = 1.48 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.70 - 7.58 (m, 1H), 7.52 (dd, J = 6.7, 1.6 Hz, 1H), 6.80 - 6.64 (m, 2H), 6.30 (t, J = 7.1 Hz, 1H), 6.26 - 6.19 (m, 1H), 5.99 - 5.93 (m, 1H), 5.83 (td, J = 56.0, 4.0 Hz, 1H), 5.08 - 4.97 (m, 2H), 4.75 - 4.65 (m, 1H), 3.90 - 3.79 (m, 3H), 3.78 (s, 3H), 3.76 - 3.57 (m, 4H), 3.23 (s, 3H), 3.22 - 3.17 (m, 1H), 1.89 - 1.81 (m, 1H), 1.82 - 1.59 (m, 4H), 1.20 - 1.01 (m, 4H).
107	 Diastereomer -2 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(1-(1-hydroxy-3-methoxypropan-2-yl)-2-oxo-1,2-dihydropyridin-3-yl)-2-oxopyrrolidin-3-yl)-3-((1r,4S)-4-(difluoromethyl)cyclohexyl)urea	599.3	Method D, RT = 1.49 min, 100%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 7.69 - 7.59 (m, 1H), 7.51 (dd, J = 6.7, 1.6 Hz, 1H), 6.80 - 6.63 (m, 2H), 6.31 (t, J = 7.1 Hz, 1H), 6.26 - 6.19 (m, 1H), 5.99 - 5.93 (m, 1H), 5.83 (td, J = 56.0, 4.0 Hz, 1H), 5.08 - 4.97 (m, 2H), 4.75 - 4.65 (m, 1H), 3.90 - 3.79 (m, 3H), 3.78 (s, 3H), 3.75 - 3.58 (m, 4H), 3.23 (s, 3H), 3.22 - 3.17 (m, 1H), 1.89 - 1.81 (m, 1H), 1.81 - 1.58 (m, 4H), 1.19 - 1.01 (m, 4H).

108	 1-((3S,4R)-4-(2,6-difluoro-4-methoxyphenyl)-1-(4-morpholino-3-(trifluoromethyl)pyridin-2-yl)-2-oxopyrrolidin-3-yl)-3-((1r,4S)-4-(difluoromethyl)cyclohexyl)urea	648.3	Method D, RT = 1.85 min, 98.5%	^{1}H NMR (400 MHz, DMSO-d$_6$) δ = 8.43 (d, J = 5.6 Hz, 1H), 7.18 (d, J = 5.9 Hz, 1H), 6.78 - 6.59 (m, 2H), 6.22 - 6.03 (m, 1H), 5.80 (td, J = 56.0, 4.0 Hz, 1H), 5.79 - 5.75 (m, 1H), 4.86 (dd, J = 9.9, 7.9 Hz, 1H), 4.32 - 4.22 (m, 1H), 4.15 - 4.02 (m, 2H), 3.83 (s, 3H), 3.81 - 3.62 (m, 4H), 3.19 - 3.08 (m, 5H), 1.87 - 1.75 (m, 1H), 1.75 - 1.55 (m, 4H), 1.20 - 0.94 (m, 4H).

It will be evident to one skilled in the art that the present disclosure is not limited to the foregoing illustrative examples, and that it can be embodied in other specific forms without departing from the essential attributes thereof. It is therefore desired that the examples be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, rather than to the foregoing examples, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

WE CLAIM:

1. A compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

Ar^1 is cycloalkyl, cycloalkylalkyl, aryl, or heterocycloalkyl, each substituted with 0-3 R^1;

Ar^2 is C_{3-6} cycloalkyl, aryl, or 5- to 12-membered heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, $S(O)_p$, N, and NR^{2a}, and each substituted with 0-3 R^2;

Ar^3 is phenyl or pyridyl, each substituted with 1 R^{5a}, 1 R^{5b}, and 1 R^{5c};

R^1 is halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, or aryl substituted with 0-2 halo, C_{1-4} haloalkyl, or C_{1-4} alkoxy;

R^2 is oxo, cyano, halo, C_{1-6} alkyl substituted with 0-5 R^e, $-OR^b$, $-NR^3R^4$, $-NR^4C(O)R^b$, $-NR^4(CR^dR^d)_{0-1}C(O)NR^3R^4$, $(C_{1-4}$ alkyl$)_2(O)P-$, C_{3-6} cycloalkyl, aryl, or a 5 to 6-membered heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, $S(O)_p$, N, and NR^a;

R^{2a} is hydrogen, C_{1-4} alkyl substituted with 0-5 R^e, $-(CR^dR^d)_{1-4}-NR^3R^4$, $-(CR^dR^d)_{1-4}-OR^b$, $-(CR^dR^d)_{1-4}-C(O)NR^3R^4$, $-(CR^dR^d)_r-C_{3-6}$ cycloalkyl substituted with 0-5 R^e, $-(CR^dR^d)_r-$aryl substituted with 0-5 R^e, $-(CR^dR^d)_r-$heteroaryl, or $-(CR^dR^d)_r-$heterocycloalkyl comprising 1-4 heteroatoms selected from O, $S(O)_p$, N, and NR^a and substituted with 0-5 R^e;

R^3 is hydrogen, C_{1-4} alkyl substituted with 0-5 R^e, C_{3-6} cycloalkyl substituted with 0-5 R^e, or heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, $S(O)_p$, N, and NR^8 and substituted with 0-5 R^e;

R^4 is hydrogen or C_{1-4} alkyl;

alternatively, R^3 and R^4 together with the nitrogen to which they are both attached form a 4 to 9-membered heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, $S(O)_p$, N, and NR^8 and substituted with 1-3 R^6;

R^{5a} is hydrogen or halo;

R^{5b} is hydrogen or halo;

R^{5c} is halo, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, or deuteroalkoxy;

R^6 is hydrogen, halo, oxo, hydroxy, or C_{1-4} alkyl substituted with 0-5 R^e;

R^7 is hydrogen or C_{1-4} alkyl;

R^8 is hydrogen, C_{1-4} alkyl, or $-S(O)_pR^c$;

R^a is hydrogen, C_{1-6} alkyl substituted with 0-5 R^e, C_{3-6} cycloalkyl substituted with 0-5 R^e, aryl substituted with 0-5 R^e, or heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, $S(O)_p$, N, NR^d and substituted with 0-5 R^e;

R^b is hydrogen, C_{1-6} alkyl substituted with 0-5 R^e, C_{3-6} cycloalkyl substituted with 0-5 R^e, aryl substituted with 0-5 R^e, or heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, $S(O)_p$, N, NR^d and substituted with 0-5 R^e;

R^c is C_{1-4} alkyl substituted with 0-5 R^e;

R^d is hydrogen or C_{1-4} alkyl substituted with 0-5 R^e;

R^e is halo, cyano, oxo, $-OR^g$,$-NR^gR^g$, $-C(O)NR^gR^g$, $-S(O)_pC_{1-4}$ alkyl, C_{1-6} alkyl substituted with 0-5 R^f, $-(CH_2)_r-C_{3-6}$ cycloalkyl substituted with 0-5 R^f, $-(CH_2)_r-$aryl substituted with 0-5 R^f, or $-(CH_2)_r-$heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, $S(O)_p$, N, and NR^g and substituted with 0-5 R^f;

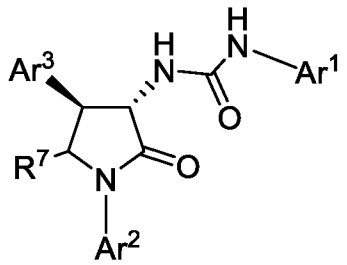
R^f is halo, cyano, hydroxy, C_{1-5} alkyl, C_{3-6} cycloalkyl, or phenyl;

R^g is hydrogen, C_{1-5} alkyl, C_{3-6} cycloalkyl, aryl, or heteroaryl or heterocycloalkyl; or R^g and R^g together with the nitrogen atom to which they are both attached form a heteroaryl or heterocycloalkyl;

p is zero, 1, or 2; and

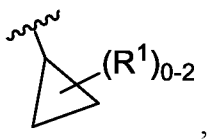
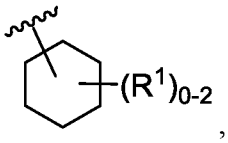
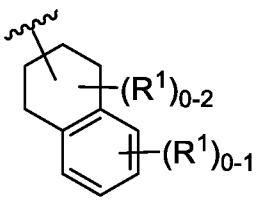
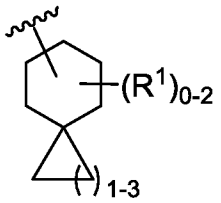
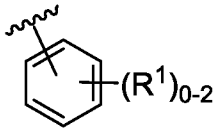
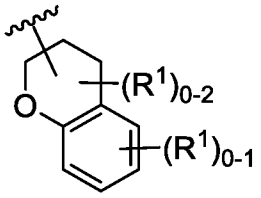
r is zero, 1, 2, 3, or 4.

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



(II)

or a pharmaceutically acceptable salt thereof, wherein:

Ar^1 is  ,  ,  ,  ,  , or  ;

Ar^2 is C_{3-6} cycloalkyl, phenyl, a 5- to 6-membered heteroaryl or heterocycloalkyl comprising 1-2 N or NR^{2a}, each substituted with 0-2 R^2;

Ar^3 is phenyl substituted with 1 R^{5a}, 1 R^{5b}, and 1 R^{5c};

R^1 is halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, or phenyl substituted with 0-2 halo, or C_{1-4} alkoxy;

R^2 is oxo, cyano, halo, C_{1-5} alkyl substituted with 0-5 R^e, $-OR^b$, $-NR^3R^4$, $-NR^4C(O)R^b$, $(C_{1-3}\text{ alkyl})_2(O)P-$, C_{3-6} cycloalkyl, aryl, or a 5- to 6-membered heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^a;

R^{2a} is hydrogen, C_{1-4} alkyl substituted with 0-4 R^e, $-(CHR^d)_{1-3}-C(O)NR^3R^4$, $-(CHR^d)_r-C_{3-6}$ cycloalkyl substituted with 0-4 R^e, $-(CHR^d)_r-$aryl substituted with 0-4 R^e, or $-(CHR^d)_r-$heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^a and substituted with 0-4 R^e;

R^3 is hydrogen, C_{1-4} alkyl substituted with 0-4 R^e, C_{3-6} cycloalkyl, or heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^8 and substituted with 0-4 R^e;

R^4 is hydrogen or C_{1-3} alkyl;

alternatively, R^3 and R^4 together with the nitrogen to which they are both attached form a 4- to 8-membered heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^8 and substituted with 1-3 R^6;

R^{5a} is hydrogen or halo;

R^{5b} is hydrogen or halo;

R^{5c} is halo, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{1-4} alkoxy;

R^6 is hydrogen, halo, oxo, hydroxy, or C_{1-4} alkyl substituted with 0-4 R^e;

R^7 is hydrogen or C_{1-3} alkyl;

R^8 is hydrogen, C_{1-3} alkyl, or $-S(O)_pR^c$;

R^a is hydrogen or C_{1-6} alkyl substituted with 0-5 R^e;

R^b is hydrogen, C_{1-6} alkyl substituted with 0-5 R^e, or heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, NR^d and substituted with 0-5 R^e;

R^c is C_{1-3} alkyl substituted with 0-5 R^e;

R^d is hydrogen or C_{1-4} alkyl substituted with 0-1 $-OC_{1-4}$ alkyl;

R^e is halo, cyano, oxo, $-OR^g$, $-NR^gR^g$, $-C(O)NR^gR^g$, $-S(O)_pC_{1-4}$ alkyl, C_{1-4} alkyl substituted with 0-5 R^f, $-(CH_2)_r-C_{3-6}$ cycloalkyl substituted with 0-5 R^f, $-(CH_2)_r-$aryl substituted with 0-5 R^f, or $-(CH_2)_r-$heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^g and substituted with 0-5 R^f;

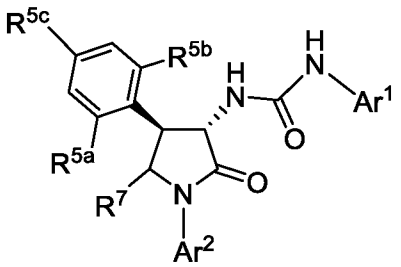
R^f is halo, cyano, hydroxy, C_{1-5} alkyl, or C_{3-6} cycloalkyl;

R^g is hydrogen, C_{1-5} alkyl, or heteroaryl or heterocycloalkyl;

n is zero; and

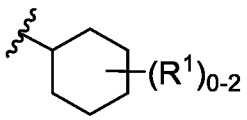
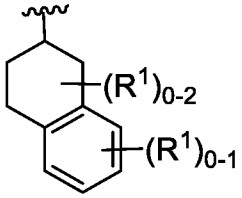
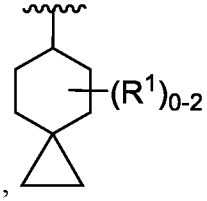
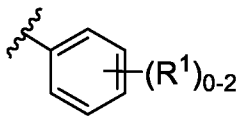
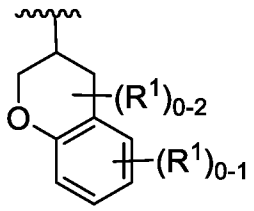
r is zero, 1, 2, or 3.

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

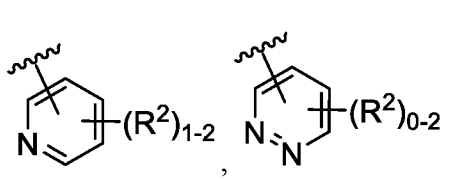


(III)

or a pharmaceutically acceptable salt thereof, wherein:

Ar^1 is  ,  ,  ,  ,  , or ;

Ar^2 is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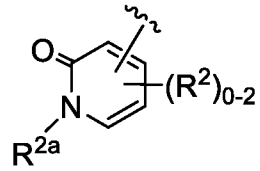
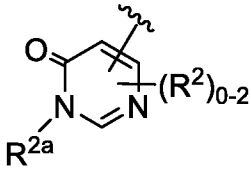
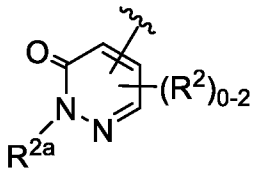
, 
, 
, or 
;

R^1 is halo, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} haloalkyl, or C_{1-3} haloalkoxy;

R^2 is cyano, halo, C_{1-4} alkyl substituted with 0-5 R^e, -OR^b, -NR^3R^4, -$NR^4C(O)R^b$, $(C_{1-4}$ alkyl$)_2(O)P$-, C_{3-6} cycloalkyl, aryl, or a 5- to 6-membered heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^a;

R^{2a} is hydrogen, C_{1-4} alkyl substituted with 0-3 R^e, –$(CHR^d)_{1-2}$-$C(O)NR^3R^4$, –$(CH_2)_r$-C_{3-6} cycloalkyl substituted with 0-3 R^e, –$(CH_2)_r$–aryl substituted with 0-3 R^e, or –$(CH_2)_r$–heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^a and substituted with 0-3 R^e;

R^3 is hydrogen, C_{1-4} alkyl substituted with 0-3 R^e, C_{3-6} cycloalkyl, or heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^8 and substituted with 0-3 R^e;

R^4 is hydrogen or C_{1-2} alkyl;

alternatively, R^3 and R^4 together with the nitrogen to which they are both attached form a 4- to 8-membered heteroaryl or heterocycloalkyl comprising 1-3 heteroatoms selected from O, S, N, and NR^8 and substituted with 1-3 R^6;

R^{5a} is hydrogen or halo;

R^{5b} is hydrogen or halo;

R^{5c} is halo or C_{1-2} alkoxy;

R^6 is hydrogen, halo, oxo, hydroxy, or C_{1-4} alkyl substituted with 0-3 R^e;

R^7 is hydrogen or CH_3;

R^8 is hydrogen, C_{1-2} alkyl, or -$S(O)_2C_{1-4}$ alkyl;

R^a is hydrogen, C_{1-5} alkyl substituted with 0-4 R^e;

R^b is hydrogen, C_{1-5} alkyl substituted with 0-4 R^e, heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, NR^d and substituted with 0-4 R^e;

R^d is hydrogen or C_{1-3} alkyl substituted with 0-1 –OC_{1-4} alkyl;

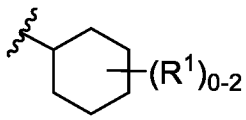
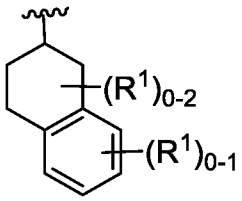
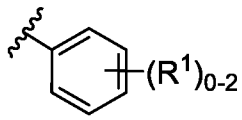
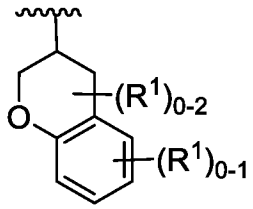
R^e is halo, cyano, oxo, -OR^g, –NR^gR^g, $C(O)NR^gR^g$, -$S(O)_pC_{1-4}$ alkyl, C_{1-4} alkyl substituted with 0-4 R^f, –$(CH_2)_r$–C_{3-6} cycloalkyl substituted with 0-4 R^f, –$(CH_2)_r$–aryl substituted with 0-4 R^f, or –$(CH_2)_r$–heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^g and substituted with 0-4 R^f;

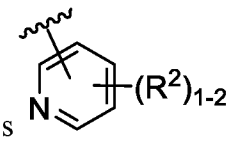
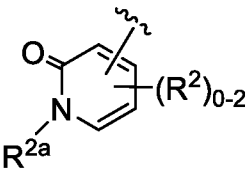
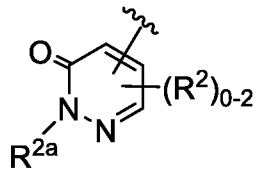
R^f is halo, cyano, hydroxy, or C_{1-5} alkyl;

R^g is hydrogen or C_{1-4} alkyl; and

r is zero, 1, or 2.

4. The compound of claim 3, or a pharmaceutically acceptable salt thereof, wherein:

Ar^1 is  ,  ,  , or  ;

Ar^2 is  ,  , or  ;

R^1 is Cl, -CH_3, -CF_3, -OCH_3, -$OCHF_2$, or -OCF_3;

R^2 is cyano, halo, C_{1-4} alkyl substituted with 0-4 R^e, -OR^b, -NR^3R^4, -$NR^4C(O)R^b$, $(C_{1-2}$ alkyl$)_2(O)P$-, C_{3-6} cycloalkyl, or heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^a;

R^{2a} is hydrogen, C_{1-4} alkyl substituted with 0-2 R^e, –$(CHR^d)_{1-2}$-$C(O)NR^3R^4$, –$(CH_2)_r$-C_{3-6} cycloalkyl substituted with 0-2 R^e, –$(CH_2)_r$–aryl substituted with 0-2 R^e, or –$(CH_2)_r$–heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^a and substituted with 0-2 R^e;

R^3 is hydrogen, C_{1-4} alkyl substituted with 0-3 R^e, or heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^8 and substituted with 0-3 R^e;

R^4 is hydrogen or C_{1-2} alkyl;

alternatively, R^3 and R^4 together with the nitrogen to which they are both attached form a 4- to 8-membered heteroaryl or heterocycloalkyl comprising 1-3 heteroatoms selected from O, S, N, and NR^8 and substituted with 1-3 R^6;

R^{5a} is hydrogen, F, or Cl;

R^{5b} is hydrogen, F, or Cl;

R^{5c} is Cl or $-OCH_3$;

R^6 is hydrogen, halo, oxo, hydroxy, or C_{1-3} alkyl substituted with 0-3 R^e;

R^7 is hydrogen or $-CH_3$;

R^8 is hydrogen, C_{1-2} alkyl, or $S(O)_2C_{1-3}$ alkyl;

R^a is hydrogen, C_{1-4} alkyl substituted with 0-3 R^e;

R^b is hydrogen, C_{1-4} alkyl substituted with 0-3 R^e, heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^d and substituted with 0-3 R^e;

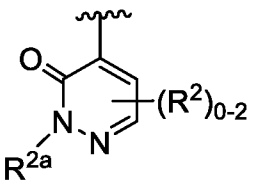
R^d is hydrogen or C_{1-2} alkyl substituted with 0-1 $-OC_{1-4}$ alkyl;

R^e is halo, cyano, oxo, $-OR^g$, $-NR^gR^g$, $-C(O)NR^gR^g$, $-S(O)_2C_{1-4}$ alkyl, C_{1-6} alkyl substituted with 0-3 R^f, C_{3-6} cycloalkyl substituted with 0-3 R^f, or heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^g and substituted with 0-3 R^f;

R^f is halo, cyano, hydroxy, or C_{1-4} alkyl; and

R^g is hydrogen or C_{1-3} alkyl.

5. The compound of claim 4, or a pharmaceutically acceptable salt thereof, wherein:

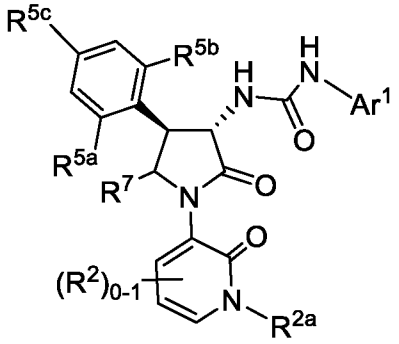
Ar^2 is  ;

R^2 is F, Cl, CH_2OH, CH_3, CF_3, or CHF_2; and

R^{2a} is $-CH_3$, $-CH_2CH_3$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CH_2CH_2OCH_3$, $-CH_2CH(OH)CF_3$, $-CH_2CH(OH)CH_3$, $-CH_2CH_2OH$, $-CH_2CH(CH_3)OH$, $-CH_2CH(CF_3)OH$, $-CH_2CH_2CF_3$, -

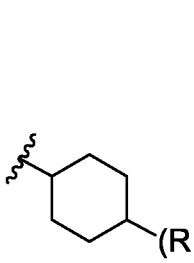
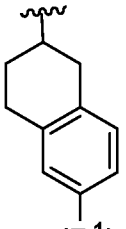
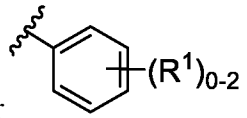
$CH(CH_2OH)CH_2OCH_3$, $-CH(CH_2NH_2)OCH_3$, $-CH_2CH(CH_3)OCH_3$, or $-CH_2CH(CF_3)OCH_3$.

6. The compound of claim 4, having Formula (IV):



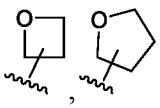
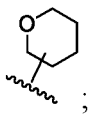
(IV)

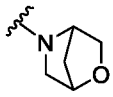
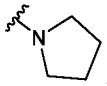
or a pharmaceutically acceptable salt thereof, wherein:

Ar^1 is  ,  , or  ;

R^1 is Cl, CH_3, $-CF_3$, $-CHF_2$, $-OCH_3$, $-OCHF_2$, or $-OCF_3$;

R^2 is cyano, F, Cl, $-CH_3$, $-OCH_3$, $-CF_3$, $-CHF_2$, $-CF_3$, or $-NHC(O)CH_3$;

R^{2a} is $-CH_3$, CHF_2, $-CH_2CH_3$, $-CH_2CN$, $-CH_2CHF_2$, $-CH_2CH_2OCH_3$, $-CH_2CH(OH)CF_3$, $-CH_2CH(OH)CH_3$, $-CH_2CH_2OH$, $-CF_2CH_2OH$, $-CH_2CH(CH_3)OH$, $-CH_2CH_2CF_3$, $-CH(CH_2OH)CH_2OCH_3$, $-CH(CH_2NH_2)OCH_3$, $-CH_2CH(CH_3)OCH_3$, $-CH_2CH(CF_3)OCH_3$, $-CH(CH_2NH_2)CH_2OCH_3$, $-CH(C(O)N(CH_3)_2)CH_2OCH_3$, $-CH_2C(CH_3)(CH_2OH)_2$, $-CH_2CH_2N(CH_3)_2$, $-CH_2CH_2S(O)_2C_{1\text{-}4}$ alkyl, $–CHR^dC(O)NR^3R^4$, $-(CH_2)_{0\text{-}1}$-$C_{3\text{-}6}$ cycloalkyl, $-(CH_2)_{0\text{-}3}$-heterocycloalkyl selected from  , and  ;

R^3 and R^4 together with the nitrogen to which they are both attached form a heterocycloalkyl selected from  and  ;

R^{5a} is hydrogen or F;

R^{5b} is hydrogen or F;

R^{5c} is Cl or $-OCH_3$;

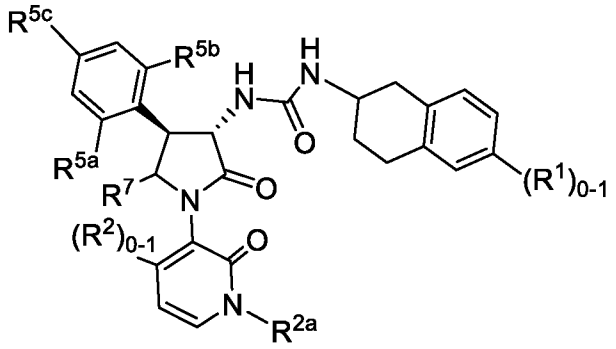
R^6 is hydrogen, oxo, halo, $-CH_3$, $-CHF_2$, $-CF_3$, or $-CH_2OH$;

R^7 is hydrogen or $-CH_3$;

R^8 is hydrogen, C_{1-2} alkyl, or $-S(O)_2C_{1-3}$ alkyl; and

R^d is $-CH_2OCH_3$.

7. The compound of claim 4, having Formula (V):

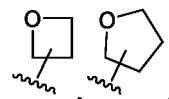
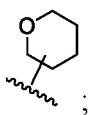


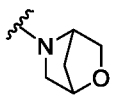
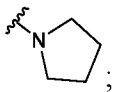
(V)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is Cl or $-OCH_3$;

R^2 is cyano, F, Cl, $-CH_3$, $-OCH_3$, $-CF_3$, $-CHF_2$, or $-CF_3$;

R^{2a} is $-CH_3$, CHF_2, $-CH_2CH_3$, $-CH_2CN$, $-CH_2CHF_2$, $-CH_2CH_2OCH_3$, $-CH_2CH(OH)CF_3$, $-CH_2CH(OH)CH_3$, $-CH_2CH_2OH$, $-CF_2CH_2OH$, $-CH_2CH(CH_3)OH$, $-CH_2CH_2CF_3$, $-CH(CH_2OH)CH_2OCH_3$, $-CH(CH_2NH_2)OCH_3$, $-CH_2CH(CH_3)OCH_3$, $-CH_2CH(CF_3)OCH_3$, $-CH(CH_2NH_2)CH_2OCH_3$, $-CH(C(O)N(CH_3)_2)CH_2OCH_3$, $-CH_2C(CH_3)(CH_2OH)_2$, $-CH_2CH_2N(CH_3)_2$, $-CH_2CH_2S(O)_2C_{1-4}$ alkyl, $-CHR^dC(O)NR^3R^4$, $-(CH_2)_{0-1}$-C_{3-6} cycloalkyl, $-(CH_2)_{0-3}$-heterocycloalkyl selected from  , and  ;

R^3 and R^4 together with the nitrogen to which they are both attached form a heterocycloalkyl selected from  and  ;

R^{5a} is hydrogen or F;

R^{5b} is hydrogen or F;

R^{5c} is Cl or $-OCH_3$;

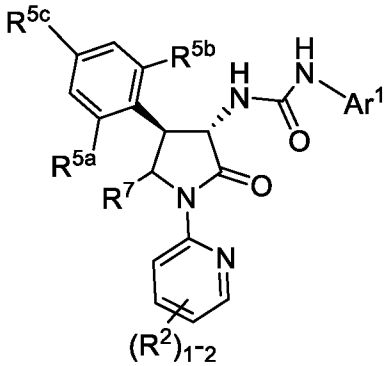
R^6 is hydrogen, oxo, halo, $-CH_3$, $-CHF_2$, $-CF_3$, or $-CH_2OH$;

R^7 is hydrogen or $-CH_3$;

R^8 is hydrogen, C_{1-2} alkyl, or $-S(O)_2C_{1-3}$ alkyl; and

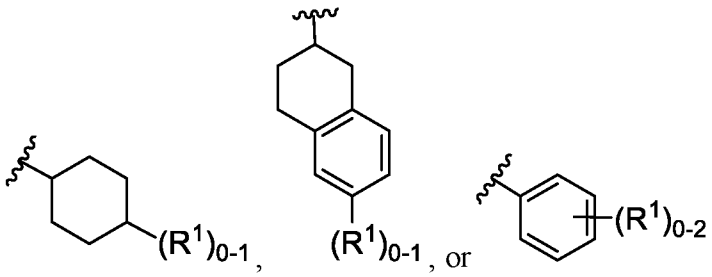
R^d is $-CH_2OCH_3$.

8. The compound of claim 4, having Formula (VI):

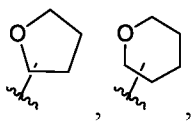


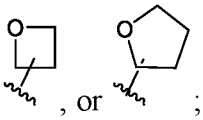
(VI)

or a pharmaceutically acceptable salt thereof, wherein:

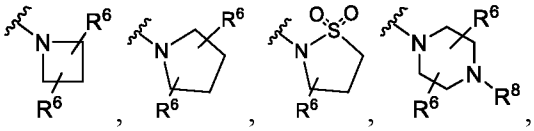
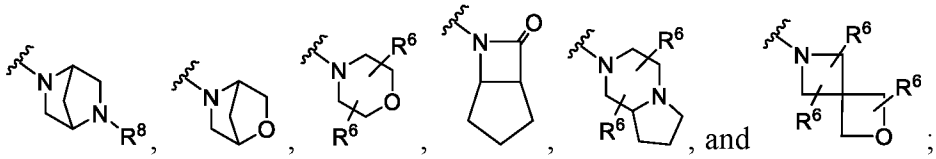
Ar^1 is  ;

R^1 is Cl, $-CF_3$, CHF_2, $-OCHF_2$, $-OCH_3$, or $-OCF_3$;

R^2 is cyano, F, Cl, $-CH_2OH$, $-CH_3$, $-CHF_2$, $-CF_3$, $-OCH_3$, $-OCH(CH_3)_2$, $-NR^3R^4$, $(CH_3)_2(O)P-$, C_{3-6} cycloalkyl,  ;

R^3 is hydrogen or C_{1-4} alkyl substituted with 0-3 R^e,  ;

R^4 is hydrogen;

alternatively, R^3 and R^4 together with the nitrogen to which they are both attached form a heterocycloalkyl selected from  ,  , and ;

R^{5a} is hydrogen or F;

R^{5b} is hydrogen or F;

R^{5c} is Cl or $-OCH_3$;

R^6 is hydrogen, halo, oxo, $-CH_3$, $-CH_2CH_3$, or $-CH_2OH$;

R^7 is hydrogen or $-CH_3$;

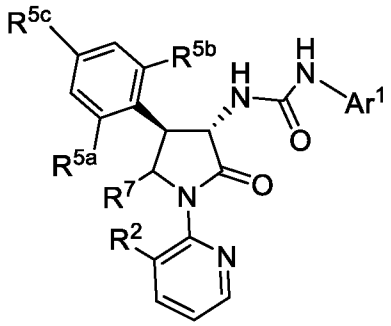
R^8 is hydrogen, C_{1-4} alkyl, or $-S(O)_2C_{1-3}$ alkyl; and

R^e is halo, $-OR^g$, $-C(O)NR^gR^g$, $-S(O)_2C_{1-4}$ alkyl, heteroaryl or heterocycloalkyl comprising 1-4 heteroatoms selected from O, S, N, and NR^g and substituted with 0-3 R^f;

R^f is halo, cyano, hydroxy, or C_{1-4} alkyl; and

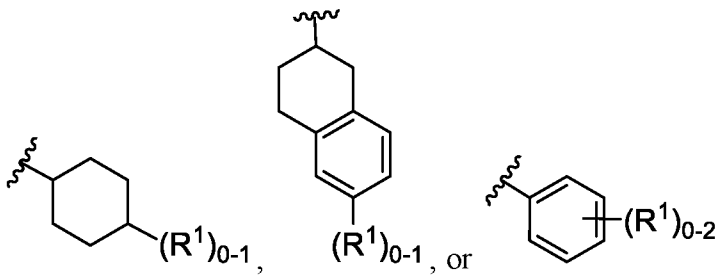
R^g is hydrogen or C_{1-3} alkyl.

9. The compound of claim 8, having Formula (VII):



(VII)

or a pharmaceutically acceptable salt thereof, wherein:

Ar^1 is  ;

R^1 is Cl, $-CF_3$, CHF_2, $-OCHF_2$, $-OCH_3$, or $-OCF_3$;

R^2 is F, Cl, -CH_2OH, -CH_3, -CHF_2, -CF_3, -OCH_3, or -$OCH(CH_3)_2$;

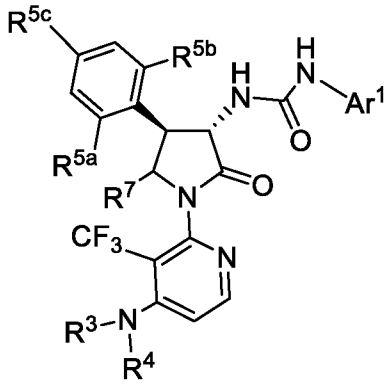
R^{5a} is hydrogen or F;

R^{5b} is hydrogen or F;

R^{5c} is Cl or -OCH_3; and

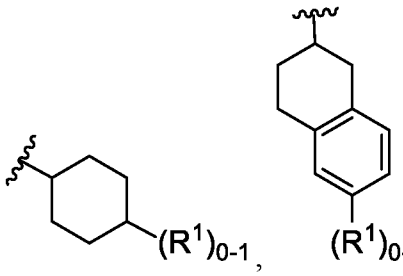
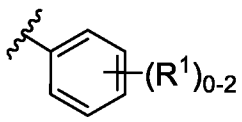
R^7 is hydrogen or -CH_3.

10. The compound of claim 8, having Formula (VIII):



(VIII)

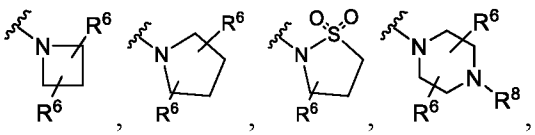
or a pharmaceutically acceptable salt thereof, wherein:

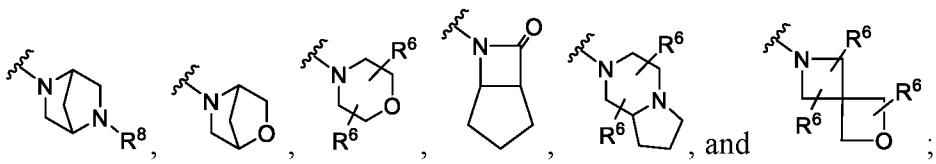
Ar^1 is  , , or  ;

R^1 is F, Cl, -CF_3, CHF_2, -$OCHF_2$, -OCH_3, or -OCF_3;

R^3 is hydrogen or C_{1-4} alkyl substituted with 0-2 R^e;

R^4 is hydrogen;

alternatively, R^3 and R^4 together with the nitrogen to which they are both attached form a heterocycloalkyl selected from  ,

 ;

R^{5a} is hydrogen or F;

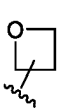
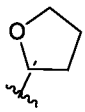
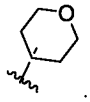
R^{5b} is hydrogen or F;

R^{5c} is Cl or $-OCH_3$;

R^6 is hydrogen, halo, hydroxy, oxo, $-CH_3$, $-CH_2CH_3$, or $-CH_2OH$;

R^7 is hydrogen or $-CH_3$;

R^8 is hydrogen, C_{1-4} alkyl, or $-S(O)_2C_{1-3}$ alkyl; and

R^e is –OH, $-OC_{1-4}$ alkyl, $-C(O)NHC_{1-4}$ alkyl, $-S(O)_2C_{1-4}$ alkyl,  ,  , or  .

11. A pharmaceutical composition comprising one or more compounds according to any one of claims 1-10 and a pharmaceutically acceptable carrier or diluent.

12. A method for the treatment or prophylaxis of inflammatory diseases, heart diseases, chronic airway diseases, cancers, septicemia, allergic symptoms, HIV retrovirus infection, circulatory disorders, neuroinflammation, nervous disorders, pains, prion diseases, amyloidosis, and immune disorders, comprising administering a therapeutically effective amount of a pharmaceutical composition of claim 11 to a patient in need thereof.

13. The method of claim 12 wherein the heart disease is selected from the group consisting of angina pectoris, unstable angina, myocardial infarction, heart failure, acute coronary disease, acute heart failure, chronic heart failure, and cardiac iatrogenic damage.

14. The method of claim 13, wherein the heart failure results from hypertension, an ischemic heart disease, a non-ischemic heart disease, exposure to a cardiotoxic compound, myocarditis, Kawasaki's disease, Type I and Type II diabetes, thyroid disease, viral infection, gingivitis, drug abuse, alcohol abuse, pericarditis, atherosclerosis, vascular disease, hypertrophic cardiomyopathy, dilated cardiomyopathy, myocardial infarction, atrial fibrosis, left ventricular systolic dysfunction, left ventricular diastolic dysfunction, coronary bypass surgery, pacemaker implantation surgery, starvation, an eating disorder, muscular dystrophies, and a genetic defect.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2021/045474

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/04 C07D401/14 C07D403/04 C07D405/14 C07D487/08
C07D487/04 A61P29/00 A61P37/00 A61K31/5377 A61K31/4439
A61K31/496

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2019/270704 A1 (SHIRUDE PRAVIN SUDHAKAR [IN] ET AL) 5 September 2019 (2019-09-05) paragraphs [0158], [0164]; tables 1,18,20-23	1-14
Y	WO 2018/227067 A1 (SQUIBB BRISTOL MYERS CO [US]) 13 December 2018 (2018-12-13) pages 12,13; claims 1,11-14; table 1	1-14
Y	WO 2020/112583 A1 (SQUIBB BRISTOL MYERS CO [US]) 4 June 2020 (2020-06-04) compounds of examples, Table 1 on page 8; pages 7, 8; claims 1, 7-10	1-14

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

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 November 2021	23/11/2021

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2021/045474

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