INHIBITORS OF GLYCOGEN SYNTHASE 1 (GYS1) AND METHODS OF USE THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 63/161,347 filed on March 15, 2021, and U.S. Provisional Application No. 63/266,572, filed January 09, 2022, the contents of which are incorporated herein by reference in their entireties.

BACKGROUND OF THE INVENTION

[0002] Pathological accumulation of glycogen is a hallmark of several devastating and chronic human diseases. For some of these disorders, the cellular etiology driving this aberrant accumulation has clear genetic underpinnings and for others the mechanistic driving force is more complex. Nonetheless, the consequence of elevated levels of glycogen is altered cellular homeostasis and impaired tissue function over time. The rate limiting enzyme in the glycogen synthesis pathway is the protein Glycogen Synthase (GYS). In humans there are two isoforms GYS1 & GYS2. The former is ubiquitously expressed but highly abundant in muscle cells, while the latter is expressed exclusively in liver. Glycogen synthesis ultimately begins with transport of glucose into cells via the GLUT transporter family of proteins. Conversion of glucose into glycogen follows along a well characterized biochemical conversion pathway to the step where GYS covalently links glucose molecules into long branches via α1,4-glycosidic linkages. The final spherical structure of glycogen results from the action of Glycogen Branching Enzyme (GBE) which introduces α1,6-linkage branch points along the strands. The result of this biochemical chain of events is the generation of an energy dense and highly soluble molecule that can be stored in the cytosol of cells for rapid catabolism into glucose energy when needed. An imbalance in the equilibrium of either glycogen synthesis or glycogenolysis can result in aberrant accumulation of cellular stores of glycogen. It has long been hypothesized that substrate reduction therapy targeted to inhibit glycogen synthase could be an effective treatment for diseases of glycogen storage. Indeed, substrate reduction therapy drugs have been very successful in modulating patient disease course in other storage disorders including Gaucher and Fabry diseases (Platt FM, Butters TD. Substrate Reduction Therapy. Lysosomal Storage Disorders, Springer US chapter 11, pgs 153-168, 2007; Shemesh E, et al. Enzyme replacement

and substrate reduction therapy for Gaucher disease. Cochrane Database of Systematic Reviews, Issue 3, 2015). It is the aim of this invention to inhibit glycogen synthase enzyme activity resulting in reduction of tissue glycogen stores with therapeutic benefit to patients suffering the consequences of aberrant cellular glycogen accumulation.

[0003] Pompe Disease is a rare genetic disorder caused by the pathological buildup of cellular glycogen due to loss of function (LOF) mutations in the lysosomal enzyme α-glucosidase (GAA). GAA catabolizes lysosomal glycogen and in its absence, glycogen builds up in lysosomes. This triggers a disease cascade beginning with lysosome and autophagosome dysfunction, leading ultimately to cell death and muscle atrophy over time (Raben N, et al. Autophagy and mitochondria in Pompe Disease: nothing is so new as what has long been forgotten. American Journal oMedical Genetics, vol. 160, 2012. van der Ploeg AT and Reuser AJJ, Pompe's Disease. Lancet vol. 372, 2008). In humans, the clinical manifestation of the disease results in a spectrum of severity and occurs at a prevalence of one in 40,000 live births (Meena NK, Raben N. Pompe disease: new developments in an old lysosomal storage disorder. Biomolecules, vol. 10, 2020). Infantile onset patients are born with cellular pathology and rapidly develop severe impairments including myopathy, heart defects, organomegaly, and hypotonia which collectively left untreated will take the child's life within a year. The later onset children may develop heart enlargement but are characterized consistently by the progressive loss of motor function, degeneration of skeletal muscle, and ultimate failure of the respiratory system leading to early death. Late onset adult Pompe patients exhibit normal heart function but develop progressive muscle weakness and respiratory decline then failure. The current standard of care for Pompe patients is enzyme replacement therapy (ERT) with recombinant human GAA. ERT treatment has been successful in slowing the rate of disease progression but in the majority of patients there remains incredible unmet need (Schoser B, et al. The humanistic burden of Pompe disease: are there still unmet needs? A systematic review. BMC Neurology, vol. 17, 2017). For over a decade, substrate reduction therapy targeting GYS1 has been hypothesized to be beneficial for the treatment of Pompe disease. In fact, three separate preclinical modalities have demonstrated that GYS1 genetic LOF in Pompe model mice effectively reduces tissue glycogen and improves mouse disease outcomes (Douillard-Guilloux G, et al. Modulation of glycogen synthesis by RNA interference: towards a new therapeutic approach for glycogenosis type II. Human Molecular Genetics, vol. 17, no. 24, 2008; Douillard-Guilloux G, et al.

Restoration of muscle functionality by genetic suppression of glycogen synthesis in a murine model of Pompe disease. Human Molecular Genetics, vol. 19, no. 4, 2010; Clayton NP, et al. Antisense oligonucleotide-mediated suppression of muscle glycogen synthase 1 synthesis as an approach for substrate reduction therapy of Pompe Disease. Molecular Therapy - Nucleic Acids, vol. 3, 2014). A small molecule GYS1 inhibitor could be used to address the current unmet needs for Pompe patients either as a single therapy or in combination with standard of care ERT.

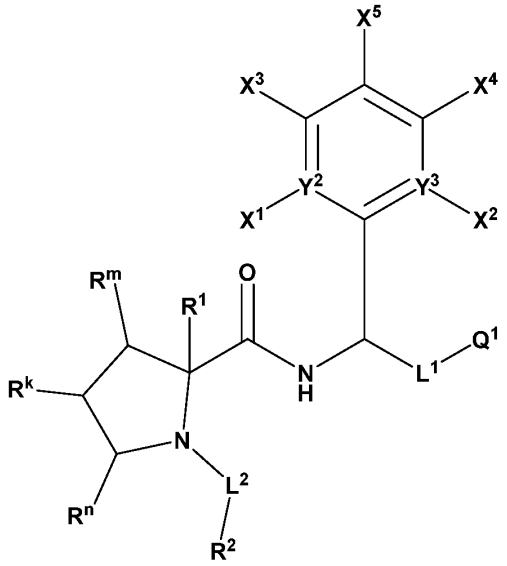
[0004] Pompe disease is only one of more than a dozen diseases caused by an inborn error of metabolism that result in aberrant build-up of glycogen in various tissues of the body. For some glycogen storage diseases (GSDs), specific dietary regimes effectively manage the disease but for others there are no clinically approved therapeutic interventions to modify disease course. Therefore, inhibition of glycogen synthesis and the concomitant reduction in tissue glycogen levels may be a viable treatment option for these patients. Cori disease, GSD III, is caused by mutations in the glycogen debranching enzyme (GDE) which results in pathological glycogen accumulation in the heart, skeletal muscle, and liver (Kishnani P, et al. Glycogen storage disease type III diagnosis and management guidelines. Genetics in Medicine, vol. 12, no. 7, 2010). While dietary management can be effective in ameliorating aspects of the disease there is currently no treatment to prevent the progressive myopathy in GSD III. Adult polyglucosan body disease (APBD) is an adult-onset disorder caused by loss of activity in the glycogen branching enzyme (GBE1). Deficiency in GBE results in accumulation of long strands of unbranched glycogen which precipitate in the cytosol generating polyglucosan bodies, and ultimately triggering neurological deficits in both the central and peripheral nervous systems. Genetic deletion of GYS1 in the APBD mouse model rescued deleterious accumulation of glycogen, improved life span, and neuromuscular function (Chown EE, et al. GYS1 or PPP1R3C deficiency rescues murine adult polyglucosan body disease. Annals of Clinical and Translational Neurology, vol. 7, no. 11, 2020). Lafora Disease (LD) is a very debilitating juvenile onset epilepsy disorder also characterized by accumulation of polyglucason bodies. Genetic cross of LD mouse models with GYS1 knock out (KO) mice resulted in rescue of disease phenotypes (Pedersen B, et al. Inhibiting glycogen synthesis prevents Lafora disease in a mouse model. Annals of Neurology, vol. 74, no. 2, 2013; Varea O, et al. Suppression of glycogen synthesis as a treatment for Lafora disease: establishing the window of opportunity. Neurobiology of Disease, 2020).

[0005] The reliance on high levels of glycogen by clear cell cancers has recently emerged as a novel therapeutic target. Ewing sarcoma (ES), clear cell renal cell carcinoma (ccRCC), glycogen rich clear cell carcinoma breast cancer (GRCC), acute myeloid leukemia (AML), and nonsmall-cell lung carcinoma (NSCLC) are all examples of cancers histopathologically defined by PAS+ abnormally high levels of cellular glycogen. Elevated transcriptional levels of GYS1 have been significantly correlated with poor disease outcomes in NSCLC (Giatromanolaki A, et al. Expression of enzymes related to glucose metabolism in non-small cell lung cancer and prognosis. Experimental Lung Research, vol. 43, no. 4-5, 2017) and AML (Falantes JF, et al. Overexpression of GYS1, MIF, and MYC is associated with adverse outcome and poor response to azacitidine in myelodysplastic syndromes and acute myeloid leukemia. Clinical Lymphoma, Myeloma & Leukemia, vol. 15, no. 4, 2015). Lentiviral knockdown of GYS1 in cultured myeloid leukemia cells potently inhibited in vitro cancer cell growth and in vivo tumorigenesis (Bhanot H, et al. Pathological glycogenesis through glycogen synthase I and suppression of excessive AMP kinase activity in myeloid leukemia cells. Leukemia, vol. 29, no. 7, 2015). Genetic knock-down of GYS1 in ccRCC cell models both suppresses tumor growth in vivo and increases the synthetic lethality of sunitinub (Chen S, et al. GYS1 induces glycogen accumulation and promotes tumor progression via the NF-kB pathway in clear cell renal carcinoma. Theranostics, vol. 10, no. 20, 2020).

[0006] Reduction of GYS1 enzyme activity and reduced cellular stores of glycogen in preclinical models of Pompe disease, APBD, LD, AML, ccRCC, and NSCLC all provide compelling evidence of the potential therapeutic benefit of inhibiting glycogen synthesis. It is the aim of this invention to inhibit glycogen synthase enzyme activity resulting in reduction of tissue glycogen stores with therapeutic benefit to patients suffering the consequences of accumulated cellular glycogen.

BRIEF SUMMARY OF THE INVENTION

[0007] In one aspect, provided herein is a compound of formula (I'):



(I'),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein:

Y^2 and Y^3 are each C, or

one of Y^2 and Y^3 is N and the other of Y^2 and Y^3 is C;

X^1 and X^2 are each independently H, $C_{1\text{-}6}$alkyl, or $C_{1\text{-}6}$alkoxy;

X^3 and X^4 are each independently H, halo, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, or 5-20 membered heteroaryl, wherein the $C_{1\text{-}6}$alkyl of X^3 and X^4 is optionally substituted with one of more halo;

X^5 is H, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, or $C_{3\text{-}10}$cycloalkyl;

either

(1) L^1 is absent; and

Q^1 is selected from (i) to (iv):

(i) phenyl, wherein the phenyl of Q^1 is substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, -NH_2, -NH-C(O)-(C_{1-6}alkyl), -NH-C(O)-(3-15 membered heterocyclyl), C_{3-10}cycloalkyl, or 5-20 membered heteroaryl, wherein

the C_{1-6}alkyl is optionally substituted with one or more halo, -NH-C(O)-NH(C_{1-6}alkyl), -NH-C(O)-C_{1-6}alkyl, or -NH-C(O)-C_{1-6}alkoxy,

the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl, and

the 5-20 membered heteroaryl is optionally substituted with one or more C_{1-6}alkyl,

(ii) 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of Q^1 is optionally substituted with one or more oxo, or C_{1-6}alkyl,

(iii) 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of Q^1 is optionally substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, -NH_2, or C_{3-10}cycloalkyl, wherein,

the C_{1-6}alkyl is optionally substituted with one or more halo, and

the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl, and

(iv) C_{3-10}cycloalkyl;

or

(2) L^1 is -CH_2-; and

Q^1 is C_{3-10}cycloalkyl;

L^2 is -C(O)- or -$S(O)_2$-

R^1 is H or C_{1-6}alkyl;

R^k is H, halo, -OH, -NH_2, or -NH-C(O)C_{1-6}alkyl;

R^m is H, -OH, or C_{1-6}alkyl;

R^n is H, C_{1-6}alkyl, or C_{3-10}cycloalkyl or R^n taken together with the carbon atom to which it is attached forms C_{3-5} cycloalkyl;

or R^k is taken together with either R^m or R^n, and the atoms to which they are attached, to form cyclopropyl; and

R^2 is selected from (i) to (vii):

(i) C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is optionally substituted with one or more R^a, wherein R^a is:

(a) -OH,

(b) cyano,

(c) C_{2-6}alkynyl,

(d) C_{6-20}aryl, wherein the C_{6-20}aryl of R^a is optionally substituted with one or more halo, cyano, C_{1-6}alkoxy, or -NH-C(O)-C_{1-6}alkyl,

(e) 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^a is optionally substituted with one or more R^c, wherein

R^c is halo, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, or -C(O)-C_{1-6}alkoxy, wherein

the C_{1-6}alkyl of R^c is optionally substituted with one or more halo or C_{2-6}alkynyl, and

the -C(O)-C_{1-6}alkoxy of R^c is optionally substituted with one or more halo,

(f) -N(R^c)(R^d), wherein R^c and R^d of N(Rc)(Rd) are, independently of each other, H, C_{1-6}alkyl,
-C(O)-C_{1-6}alkyl, -C(O)-C_{1-6}alkoxy, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -C(O)-(3-15 membered heterocyclyl), -CH_2-C(O)-NH_2, 3-15 membered heterocyclyl, or 5-20 membered heteroaryl, wherein

the C_{1-6}alkyl of R^c or R^d is optionally substituted with one or more -C(O)-NH_2,

the -C(O)-C_{1-6}alkyl of R^c or R^d is optionally substituted with one or more halo,

the 3-15 membered heterocyclyl and the 5-20 membered heteroaryl of R^c or R^d are independently optionally substituted with one or more C_{1-6}alkyl,

the -C(O)-(3-15 membered heterocyclyl) of R^c or R^d is optionally substituted with one or more halo, -C(O)-C_{1-6}alkoxy, or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, C_{1-6}alkoxy, or C_{3-10}cycloalkyl, and

the C_{1-6}alkyl of the -C(O)-N(C_{1-6}alkyl)$_2$ of R^c or R^d are, independently of each other, optionally substituted with one or more halo or C_{6-20}aryl,

(g) -O-R^e, wherein R^e is C_{1-6}alkyl, C_{6-20}aryl, -C(O)-(3-15 membered heterocyclyl), -C(O)-N-(C_{1-6}alkyl)$_2$, or 5-20 membered heteroaryl, wherein

the C_{1-6}alkyl of R^e is optionally substituted with one or more C_{1-6}alkoxy, wherein the C_{1-6}alkoxy is optionally substituted with one or more C_{2-6}alkynyl,

the C_{6-20}aryl of R^e is optionally substituted with one or more C_{1-6}alkyl, and

the -C(O)-(3-15 membered heterocyclyl) of R^e is optionally substituted with one or more C_{1-6}alkyl, C_{1-6}alkoxy, or -C(O)-C_{1-6}alkoxy, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, C_{1-6}alkoxy, or C_{3-10}cycloalkyl,

(h) -C(O)-R^e, wherein R^e of -C(O)-R^e is -NH_2, -OH, or 3-15 membered heterocyclyl, or

(i) -S(O)$_2$-R^f, wherein R^f is C_{1-6}alkyl or 3-15 membered heterocyclyl,

provided that, when R^2 is unsubstituted methyl, then either

(1) Q^1 is 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of Q^1 is optionally substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, -NH_2, C_{3-10}cycloalkyl, or -OH, and wherein Q^1 is not unsubstituted pyridyl, or

(2) Q^1 is phenyl, wherein the phenyl of Q^1 is substituted with

(i) at least one C_{3-6}alkyl, wherein the at least one C_{3-6}alkyl is optionally substituted with one or more halo, or

(ii) at least one C_{3-10}cycloalkyl, wherein the at least one C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl, or

(iii) at least one 5-20 membered heteroaryl, wherein the at least one 5-20 membered heteroaryl is optionally substituted with one or more C_{1-6}alkyl,

(ii) C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl of R^2 is optionally substituted with one or more R^q, wherein R^q is 5-20 membered heteroaryl or C_{6-20}aryl, wherein the C_{6-20}aryl of R^q is optionally substituted with one or more C_{1-6}alkoxy,

(iii) 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^2 is optionally substituted with one or more halo, oxo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, or 5-20 membered heteroaryl,

(iv) 5-20 membered heteroaryl or -(C_{1-4}alkyl)(5-20 membered heteroaryl), wherein the C_{1-4} alkyl is optionally substituted with one or more or more –OH, halo, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, and wherein the 5-20 membered heteroaryl is optionally substituted with one or more R^s, wherein

R^s is halo, C_{1-6}alkyl, C_{1-6}alkoxy, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, -NH-C(O)-C_{1-6}alkyl, C_{6-20}aryl, C_{3-10}cycloalkyl, 3-15 membered heterocyclyl, 5-20 membered heteroaryl, or -C(O)-C_{1-6}alkoxy, wherein

the C_{1-6}alkyl of R^s is optionally substituted with one or more halo, C_{1-6}alkoxy, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, -NH-C(O)C_{1-6}alkyl, or -NH-C(O)-C_{1-6}alkoxy, and

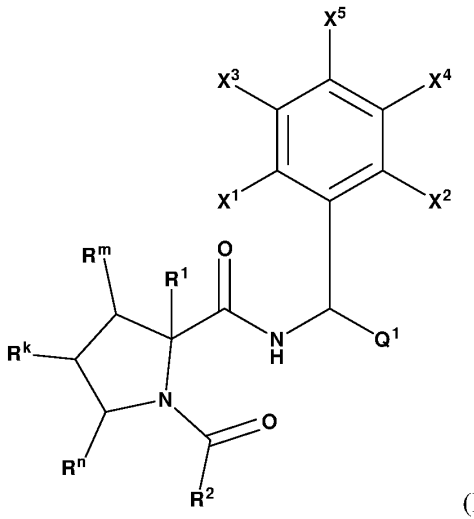
the 3-15-membered heterocyclyl of R^s is optionally substituted with one or more halo or -C(O)-C_{1-6}alkoxy,

(v) -N(R^g)(R^h), wherein R^g and R^h are independently H or C_{1-6}alkyl,

(vi) -C(O)-R^j, wherein R^j is C_{3-10}cycloalkyl, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, or -NH(5-20 membered heteroaryl), and

(vii) C_{6-20}aryl, wherein the C_{6-20}aryl of R^2 is optionally substituted with one or more 5-20 membered heteroaryl or -O-R^p, wherein R^p is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^p is optionally substituted with one or more -C(O)-C_{1-6}alkyl.

[0008] In one aspect, provided herein is a compound of formula (I):



(I),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein:

X^1 and X^2 are each independently H, C_{1-6}alkyl, or C_{1-6}alkoxy;

X^3 and X^4 are each independently H, halo, C_{1-6}alkyl, C_{1-6}alkoxy, or 5-20 membered heteroaryl;

X^5 is H, C_{1-6}alkyl, C_{1-6}alkoxy, or C_{3-10}cycloalkyl;

Q^1 is selected from (i) to (iii):

(i) phenyl, wherein the phenyl of Q^1 is substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, -NH_2, -NH-C(O)-(C_{1-6}alkyl), -NH-C(O)-(3-15 membered heterocyclyl), or C_{3-10}cycloalkyl, wherein

the C_{1-6}alkyl is optionally substituted with one or more halo, and

the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl,

(ii) 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of Q^1 is optionally substituted with one or more oxo, and

(iii) 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of Q^1 is optionally substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, $-NH_2$, or C_{3-10}cycloalkyl, wherein

the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl;

R^1 is H or C_{1-6}alkyl;

R^k is H, halo, -OH, $-NH_2$, or -NH-C(O)C_{1-6}alkyl;

R^m is H, -OH, or C_{1-6}alkyl;

R^n is H, C_{1-6}alkyl, or C_{3-10}cycloalkyl;

or R^k is taken together with either R^m or R^n, and the atoms to which they are attached, to form cyclopropyl; and

R^2 is selected from (i) to (vii):

(i) C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is optionally substituted with one or more R^a, wherein R^a is:

(a) -OH,

(b) cyano,

(c) C_{2-6}alkynyl,

(d) C_{6-20}aryl, wherein the C_{6-20}aryl of R^a is optionally substituted with one or more halo, cyano, C_{1-6}alkoxy, or -NH-C(O)-C_{1-6}alkyl,

(e) 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^a is optionally substituted with one or more R^b, wherein

R^b is halo, C_{1-6}alkyl, C_{1-6}alkoxy, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, C_{3-10}cycloalkyl, 3-15 membered heterocyclyl, or -C(O)-C_{1-6}alkoxy, wherein

the C_{1-6}alkyl of R^b is optionally substituted with one or more halo, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, -NH-C(O)C_{1-6}alkyl, or -NH-C(O)-C_{1-6}alkoxy, and

the 3-15-membered heterocyclyl of R^b is optionally substituted with one or more halo or -C(O)-C_{1-6}alkoxy,

(f) 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^a is optionally substituted with one or more R^c, wherein

R^c is halo, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, or -C(O)-C_{1-6}alkoxy, wherein

the C_{1-6}alkyl of R^c is optionally substituted with one or more halo or C_{2-6}alkynyl, and

the -C(O)-C_{1-6}alkoxy of R^c is optionally substituted with one or more halo,

(g) -N(R^c)(R^d), wherein R^c and R^d are, independently of each other, H, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-C_{1-6}alkoxy, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -C(O)-(3-15 membered heterocyclyl), -CH_2-C(O)-NH_2, 3-15 membered heterocyclyl, or 5-20 membered heteroaryl, wherein

the -C(O)-C_{1-6}alkyl of R^c or R^d is optionally substituted with one or more halo,

the 3-15 membered heterocyclyl and the 5-20 membered heteroaryl of R^c or R^d are independently optionally substituted with one or more C_{1-6}alkyl, and

the -C(O)-(3-15 membered heterocyclyl) of R^c or R^d is optionally substituted with one or more halo, -C(O)-C_{1-6}alkoxy, or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, C_{1-6}alkoxy, or C_{3-10}cycloalkyl,

(h) -O-R^e, wherein R^e is C_{1-6}alkyl, C_{6-20}aryl, -C(O)-(3-15 membered heterocyclyl), -C(O)-N-(C_{1-6}alkyl)$_2$, or 5-20 membered heteroaryl, wherein

the C_{1-6}alkyl of R^e is optionally substituted with one or more C_{1-6}alkoxy, wherein the C_{1-6}alkoxy is optionally substituted with one or more C_{2-6}alkynyl,

the C_{6-20}aryl of R^e is optionally substituted with one or more C_{1-6}alkyl, and

the -C(O)-(3-15 membered heterocyclyl) of R^e is optionally substituted with one or more C_{1-6}alkyl, C_{1-6}alkoxy, or -C(O)-C_{1-6}alkoxy, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, C_{1-6}alkoxy, or C_{3-10}cycloalkyl,

(i) -C(O)-R^e, wherein R^e is -NH_2, -OH, or 3-15 membered heterocyclyl, or

(j) -$S(O)_2$-R^f, wherein R^f is C_{1-6}alkyl or 3-15 membered heterocyclyl,

provided that, when R^2 is unsubstituted methyl, then either

(1) Q^1 is 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of Q^1 is substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, -NH_2, C_{3-10}cycloalkyl, or -OH, or

(2) Q^1 is phenyl, wherein the phenyl of Q^1 is substituted with at least one C_{3-6}alkyl or at least one C_{3-10}cycloalkyl, wherein the at least one C_{3-6}alkyl is optionally substituted with one or more halo, and the at least one C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl,

(ii) C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl of R^2 is optionally substituted with one or more R^q, wherein R^q is 5-20 membered heteroaryl or C_{6-20}aryl, wherein the C_{6-20}aryl of R^q is optionally substituted with one or more C_{1-6}alkoxy,

(iii) 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^2 is optionally substituted with one or more halo, oxo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, or 5-20 membered heteroaryl,

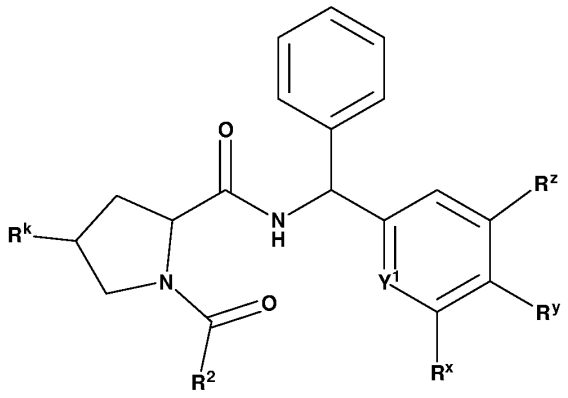
(iv) 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^2 is optionally substituted with one or more R^s, wherein R^s is C_{1-6}alkyl, C_{1-6}alkoxy, -NH-C(O)-C_{1-6}alkyl, C_{6-20}aryl, or 5-20 membered heteroaryl, wherein the C_{1-6}alkyl of R^s is optionally substituted with one or more C_{1-6}alkoxy,

(v) -N(R^g)(R^h), wherein R^g and R^h are independently H or C_{1-6}alkyl,

(vi) -C(O)-R^j, wherein R^j is C_{3-10}cycloalkyl, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, or -NH(5-20 membered heteroaryl), and

(vii) C_{6-20}aryl, wherein the C_{6-20}aryl of R^2 is optionally substituted with one or more 5-20 membered heteroaryl or -O-R^p, wherein R^p is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^p is optionally substituted with one or more -C(O)-C_{1-6}alkyl.

[0009] In one aspect, provided herein is a compound of formula (I-A):

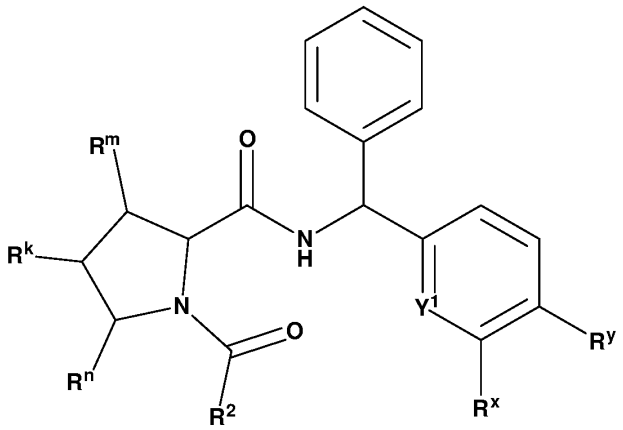


(I-A),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Y^1, R^2, R^k, R^x, R^y, and R^z are as defined elsewhere herein. In another

variation, Y^1, R^2, R^k, R^x, R^y, and R^z of formula (I-A) are as defined for a compound of formula (I') , or formula (I) elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

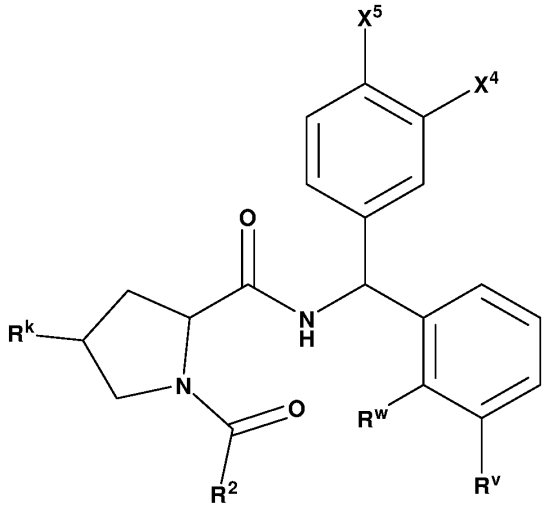
[0010] In one aspect, provided herein is a compound of formula (I-B):



(I-B),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Y^1, R^2, R^k, R^m, R^n, R^x, and R^y are as defined elsewhere herein. In another variation, Y^1, R^2, R^k, R^m, R^n, R^x, and R^y of formula (I-B) are as defined for a compound of formula (I'), or formula (I) elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

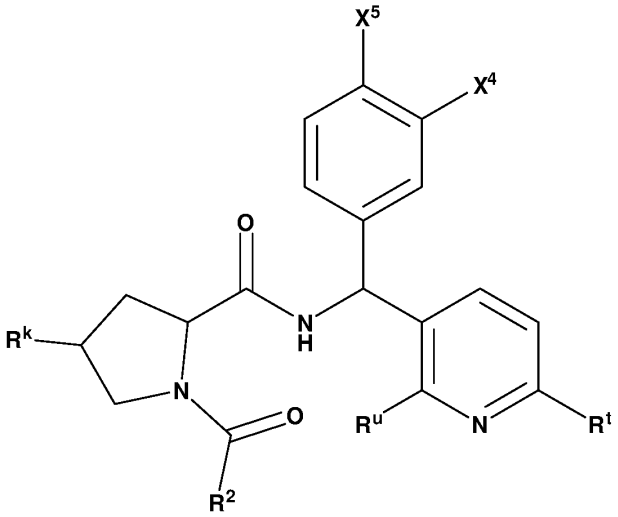
[0011] In one aspect, provided herein is a compound of formula (I-C):



(I-C),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X^4, X^5, R^2, R^k, R^v, and R^w are as defined elsewhere herein. In another variation, X^4, X^5, R^2, R^k, R^v, and R^w of formula (I-C) are as defined for a compound of formula (I') , or formula (I) elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

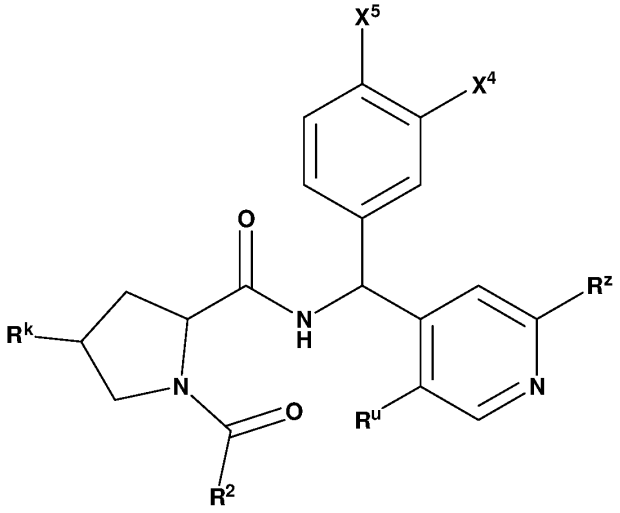
[0012] In one aspect, provided herein is a compound of formula (I-D):



(I-D),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X^4, X^5, R^2, R^k, R^u, and R^t are as defined elsewhere herein. In another variation, X^4, X^5, R^2, R^k, R^u, and R^t of formula (I-D) are as defined for a compound of formula (I'), or formula (I) elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

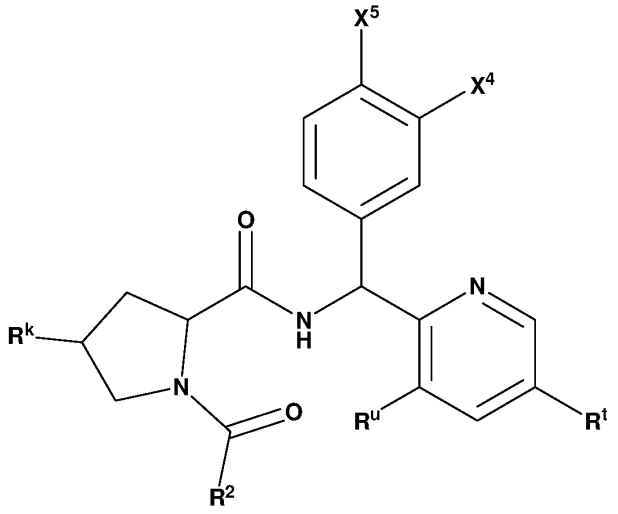
[0013] In one aspect, provided is a compound of formula (I'), wherein the compound is a compound of formula (I-D1):



(I-D1),

wherein X^4, X^5, R^2, R^k, R^u, and R^z of formula (I-D1) are as defined for a compound of formula (I') elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

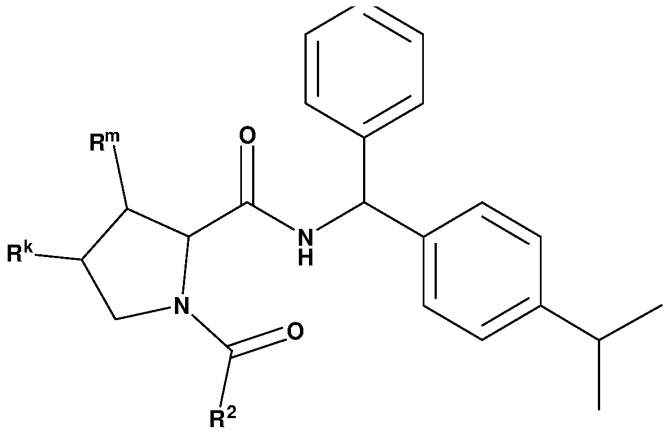
[0014] In one aspect, provided is a compound of formula (I'),, wherein the compound is a compound of formula (I-D1):



(I-D2),

wherein X^4, X^5, R^2, R^k, R^t, and R^u of formula (I-D2) are as defined for a compound of formula (I') elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

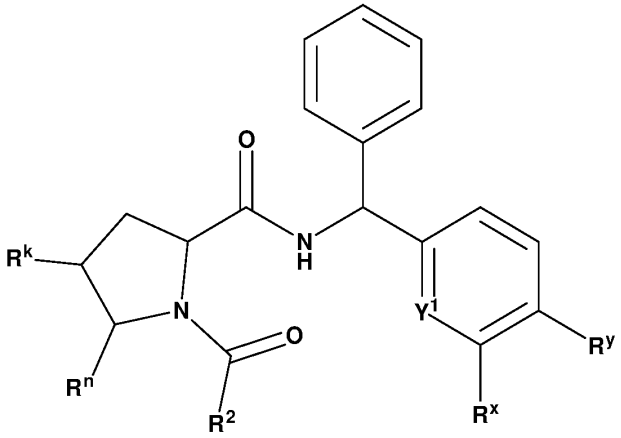
[0015] In one aspect, provided herein is a compound of formula (I-E):



(I-E),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2, R^k, and R^m are as defined elsewhere herein. In another variation, R^2, R^k, and R^m of formula (I-E) are as defined for a compound of formula (I'), or formula (I) elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

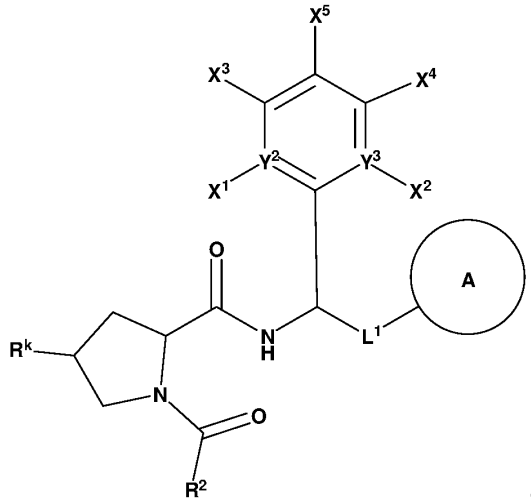
[0016] In one aspect, provided herein is a compound of formula (I-F):



(I-F),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Y^1, R^2, R^k, R^n, R^x, and R^y are as defined elsewhere herein. In another variation, R^2, R^k, and R^m of formula (I-F) are as defined for a compound of formula (I'), or formula (I) elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

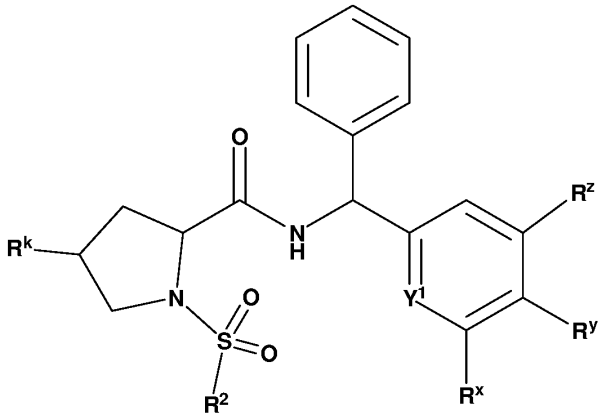
[0017] In one aspect, provided herein is a compound of formula (I') wherein the compound is of the formula (I-G):



(I-G),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein ring A, L^1, Y^2, Y^3, R^2, R^k, X^1, X^2, X^3, X^4, and X^5 are as defined elsewhere herein.

[0018] In one aspect, provided herein is a compound of formula (I') wherein the compound is of the formula (I-H):



(I-H),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Y^1, R^2, R^k, R^n, R^x, and R^y are as defined elsewhere herein.

[0019] In one aspect, provided herein is a pharmaceutical composition, comprising (i) a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and (ii) one or more pharmaceutically acceptable excipients. In another variation, provided herein is a pharmaceutical composition, comprising (i) a compound of formula (I'), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and (ii) one or more pharmaceutically acceptable excipients.

[0020] In one aspect, provided herein is a method of modulating GYS1 in a cell, comprising exposing the cell to (i) a composition comprising an effective amount of a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or (ii) a pharmaceutical composition, comprising a compound of formula (I), or any variation or embodiment thereof, or a

stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients. In another variation, provided herein is a method of modulating GYS1 in a cell, comprising exposing the cell to (i) a composition comprising an effective amount of a compound of formula (I'), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or (ii) a pharmaceutical composition, comprising a compound of formula (I'), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients.

[0021] In one aspect, provided herein is a method of inhibiting GYS1 in a cell, comprising exposing the cell to (i) a composition comprising an effective amount of a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or (ii) a pharmaceutical composition, comprising a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients. In another variation, provided herein is a method of inhibiting GYS1 in a cell, comprising exposing the cell to (i) a composition comprising an effective amount of a compound of formula (I'), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or (ii) a pharmaceutical composition, comprising a compound of formula (I'), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients.

[0022] In one aspect, provided herein is a method of reducing tissue glycogen stores in an individual in need thereof, comprising administering to the individual an effective amount of (i) a GYS1 inhibitor, or (ii) a pharmaceutical composition comprising a GYS1 inhibitor and one or more pharmaceutically acceptable excipients. In some embodiments, the GYS1 inhibitor is selective for GYS1 over GYS2. In some embodiments, the GYS1 inhibitor is greater than 500 or 1,000 or 1,500 or 1,700-fold selective for GYS1 over GYS2. In some embodiments, the GYS1 inhibitor is a small molecule.

[0023] In one aspect, provided herein is a method of reducing tissue glycogen stores in an individual in need thereof, comprising administering to the individual an effective amount

of (i) a composition comprising an effective amount of a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or (ii) a pharmaceutical composition, comprising a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients. In another variation, provided herein is a method of reducing tissue glycogen stores in an individual in need thereof, comprising administering to the individual an effective amount of (i) a composition comprising an effective amount of a compound of formula (I'), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or (ii) a pharmaceutical composition, comprising a compound of formula (I'), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients.

[0024] In one aspect, provided herein is a method of modulating GYS1 in a cell of an an individual in need thereof, comprising administering to the individual an effective amount of (i) a composition comprising an effective amount of a compound of formula (I), or formula (I') or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or (ii) a pharmaceutical composition, comprising a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients.

[0025] In one aspect, provided herein is a method of treating a GYS1-mediated disease, disorder, or condition in an individual in need thereof, comprising subjecting the individual to glycogen substrate reduction therapy. In some embodiments, the glycogen substrate reduction therapy comprises administration of a GYS1 inhibitor. In some embodiments, the GYS1 inhibitor is a small molecule. In some embodiments, the GYS1 inhibitor is selective for GYS1 over GYS2. In some embodiments, the GYS1 inhibitor is greater than 500 or 1,000 or 1,500 or 1,700-fold selective for GYS1 over GYS2.

[0026] In one aspect, provided herein is a method of treating a GYS1-mediated disease, disorder, or condition in an individual in need thereof, comprising administering to the

individual an effective amount of (i) a composition comprising an effective amount of a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or (ii) a pharmaceutical composition, comprising a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients. In another variation, provided herein is a method of treating a GYS1-mediated disease, disorder, or condition in an individual in need thereof, comprising administering to the individual an effective amount of (i) a composition comprising an effective amount of a compound of formula (I'), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or (ii) a pharmaceutical composition, comprising a compound of formula (I'), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients.

[0027] In one aspect, provided herein is a method of treating a glycogen storage disease, disorder, or condition in an individual in need thereof, comprising subjecting the individual to glycogen substrate reduction therapy. In some embodiments, the glycogen substrate reduction therapy comprises administration of a GYS1 inhibitor. In some embodiments, the GYS1 inhibitor is a small molecule. In some embodiments, the GYS1 inhibitor is selective for GYS1 over GYS2. In some embodiments, the GYS1 inhibitor is greater than 500 or 1,000 or 1,500 or 1,700-fold selective for GYS1 over GYS2.

[0028] In one aspect, provided herein is a kit, comprising (i) a composition comprising an effective amount of a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition, comprising a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients, and (ii) instructions for use in treating an GYS1-mediated disease, disorder, or condition in an individual in need thereof. In another variation, provided herein is a kit, comprising (i) a composition comprising an effective amount of a compound of formula (I'), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt

of any of the foregoing, or a pharmaceutical composition, comprising a compound of formula (I'), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients, and (ii) instructions for use in treating an GYS1-mediated disease, disorder, or condition in an individual in need thereof.

[0029] In some aspect, provided herein are methods of preparing a compound of formula (I) or (I'), or any embodiment or variation thereof, such as a compound of formula (I), (I-A), (I-A1), (I-A2), (I-A3), (I-A4), (I-B), (I-B1), (I-B2), (I-C), (I-D), (I-D1), (I-D2), (I-E), (I-F), (I-G), or (I-H) or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

BRIEF DESCRIPTION OF THE DRAWINGS

[0030] FIG. **1** depicts the pathway in which PPP1R3A Loss of Function (LoF) leads to reduction in muscle glycogen.

[0031] FIGS. **2A** and **2B** depict the association between PPP1R3A protein truncating variant (PTV) and left ventricular ejection (LVEF) (%) and left ventricle wall thickness (mm) in UK Biobank.

[0032] FIGS. **2C** and **2D** depict the association between PPP1R3A protein truncating variant (PTV) and exercise output (watts) and max heart rate (HR) exercise (bpm) in UK Biobank.

[0033] FIGS. **2E** and **2F** depict the association between PPP1R3A protein truncating variant (PTV) and PQ interval (ms) and QRS duration (ms) in UK Biobank.

[0034] FIGS. **2G** and **2H** depict the association between PPP1R3A protein truncating variant (PTV) and QT interval (ms) and serum glucose (mmol/L) in UK Biobank.

DETAILED DESCRIPTION OF THE INVENTION

[0035] "Individual" refers to mammals and includes humans and non-human mammals. Examples of individuals include, but are not limited to, mice, rats, hamsters, guinea pigs, pigs, rabbits, cats, dogs, goats, sheep, cows, and humans. In some embodiments, individual refers to a human.

[0036] As used herein, "about" a parameter or value includes and describes that parameter or value per se. For example, "about X" includes and describes X per se.

[0037] As used herein, an "at risk" individual is an individual who is at risk of developing a disease or condition. An individual "at risk" may or may not have a detectable disease or condition, and may or may not have displayed detectable disease prior to the treatment methods described herein. "At risk" denotes that an individual has one or more so-called risk factors, which are measurable parameters that correlate with development of a disease or condition and are known in the art. An individual having one or more of these risk factors has a higher probability of developing the disease or condition than an individual without these risk factor(s).

[0038] "Treatment" or "treating" is an approach for obtaining beneficial or desired results including clinical results. Beneficial or desired results may include one or more of the following: decreasing one or more symptom resulting from the disease or condition; diminishing the extent of the disease or condition; slowing or arresting the development of one or more symptom associated with the disease or condition (*e.g.*, stabilizing the disease or condition, preventing or delaying the worsening or progression of the disease or condition); and relieving the disease, such as by causing the regression of clinical symptoms (*e.g.*, ameliorating the disease state, enhancing the effect of another medication, delaying the progression of the disease, increasing the quality of life, and/or prolonging survival).

[0039] As used herein, "delaying" development of a disease or condition means to defer, hinder, slow, retard, stabilize and/or postpone development of the disease or condition. This delay can be of varying lengths of time, depending on the history of the disease and/or individual being treated. As is evident to one skilled in the art, a sufficient or significant delay

can, in effect, encompass prevention, in that the individual does not develop the disease or condition.

[0040] As used herein, the term "therapeutically effective amount" or "effective amount" intends such amount of a compound of the disclosure or a pharmaceutically salt thereof sufficient to effect treatment when administered to an individual. As is understood in the art, an effective amount may be in one or more doses, *e.g.*, a single dose or multiple doses may be required to achieve the desired treatment endpoint. An effective amount may be considered in the context of administering one or more therapeutic agents, and a single agent may be considered to be given in an effective amount if, in conjunction with one or more other agents, a desirable or beneficial result may be or is achieved.

[0041] As used herein, "unit dosage form" refers to physically discrete units, suitable as unit dosages, each unit containing a predetermined quantity of active ingredient, or compound, which may be in a pharmaceutically acceptable carrier.

[0042] As used herein, by "pharmaceutically acceptable" is meant a material that is not biologically or otherwise undesirable, *e.g.*, the material may be incorporated into a pharmaceutical composition administered to an individual without causing significant undesirable biological effects.

[0043] The term "alkyl", as used herein, refers to an unbranched or branched saturated univalent hydrocarbon chain. As used herein, alkyl has 1-20 carbons (*i.e.*, C_{1-20}alkyl), 1-16 carbons (*i.e.*, C_{1-16}alkyl), 1-12 carbons (*i.e.*, C_{1-12}alkyl), 1-10 carbons (*i.e.*, C_{1-10}alkyl), 1-8 carbons (*i.e.*, C_{1-8}alkyl), 1-6 carbons (*i.e.*, C_{1-6}alkyl), 1-4 carbons (*i.e.*, C_{1-4}alkyl), or 1-3 carbons (*i.e.*, C_{1-3}alkyl). Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, pentyl, 2-pentyl, *iso*-pentyl, *neo*-pentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl. When an alkyl residue having a specific number of carbons is named by chemical name or molecular formula, all positional isomers having that number of carbon atoms may be encompassed—for example, "butyl" includes *n*-butyl, *sec*-butyl, *iso*-butyl, and *tert*-butyl; and "propyl" includes *n*-propyl and *iso*-propyl. Certain commonly used alternative names may be used and will be understood by those of ordinary skill in the art. For instance, a divalent group, such as a divalent "alkyl" group, may be referred to as an "alkylene".

[0044] The term "alkenyl", as used herein, refers to a branched or unbranched univalent hydrocarbon chain comprising at least one carbon-carbon double bond. As used herein, alkenyl has 2-20 carbons (*i.e.*, C_{2-20}alkenyl), 2-16 carbons (*i.e.*, C_{2-16}alkenyl), 2-12 carbons (*i.e.*, C_{2-12}alkenyl), 2-10 carbons (*i.e.*, C_{2-10}alkenyl), 2-8 carbons (*i.e.*, C_{2-8}alkenyl), 2-6 carbons (*i.e.*, C_{2-6}alkenyl), 2-4 carbons (*i.e.*, C_{2-4}alkenyl), or 2-3 carbons (*i.e.*, C_{2-3}alkenyl). Examples of alkenyl include, but are not limited to, ethenyl, prop-1-enyl, prop-2-enyl 1,2-butadienyl, and 1,3-butadienyl. When an alkenyl residue having a specific number of carbons is named by chemical name or molecular formula, all positional isomers having that number of carbon atoms may be encompassed—for example, "propenyl" includes prop-1-enyl and prop-2-enyl. Certain commonly used alternative names may be used and will be understood by those of ordinary skill in the art. For instance, a divalent group, such as a divalent "alkenyl" group, may be referred to as an "alkenylene".

[0045] The term "alkynyl", as used herein, refers to a branched or unbranched univalent hydrocarbon chain comprising at least one carbon-carbon triple bond. As used herein, alkynyl has 2-20 carbons (*i.e.*, C_{2-20}alkynyl), 2-16 carbons (*i.e.*, C_{2-16}alkynyl), 2-12 carbons (*i.e.*, C_{2-12}alkynyl), 2-10 carbons (*i.e.*, C_{2-10}alkynyl), 2-8 carbons (*i.e.*, C_{2-8}alkynyl), 2-6 carbons (*i.e.*, C_{2-6}alkynyl), 2-4 carbons (*i.e.*, C_{2-4}alkynyl), or 2-3 carbons (*i.e.*, C_{2-3}alkynyl). Examples of alkynyl include, but are not limited to, ethynyl, prop-1-ynyl, prop-2-ynyl, but-1-ynyl, but-2-ynyl, and but-3-ynyl. When an alkynyl residue having a specific number of carbons is named by chemical name or molecular formula, all positional isomers having that number of carbon atoms may be encompassed—for example, "propynyl" includes prop-1-ynyl and prop-2-ynyl. Certain commonly used alternative names may be used and will be understood by those of ordinary skill in the art. For instance, a divalent group, such as a divalent "alkynyl" group, may be referred to as an "alkynylene".

[0046] The term "alkoxy", as used herein, refers to an -O-alkyl moiety. Examples of alkoxy groups include, but are not limited to, methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *tert*-butoxy, *sec*-butoxy, *n*-pentoxy, *n*-hexoxy, and 1,2-dimethylbutoxy.

[0047] The term "aryl", as used herein, refers to a fully unsaturated carbocyclic ring moiety. The term "aryl" encompasses monocyclic and polycyclic fused-ring moieties. As used herein, aryl encompasses ring moieties comprising, for example, 6 to 20 annular carbon atoms

(*i.e.*, C_{6-20}aryl), 6 to 16 annular carbon atoms (*i.e.*, C_{6-16}aryl), 6 to 12 annular carbon atoms (*i.e.*, C_{6-12}aryl), or 6 to 10 annular carbon atoms (*i.e.*, C_{6-10}aryl). Examples of aryl moieties include, but are not limited to, phenyl, naphthyl, fluorenyl, and anthryl.

[0048] The term "cycloalkyl", as used herein, refers to a saturated or partially unsaturated carbocyclic ring moiety. The term "cycloalkyl" encompasses monocyclic and polycyclic ring moieties, wherein the polycyclic moieties may be fused, branched, or spiro. Cycloalkyl includes cycloalkenyl groups, wherein the ring moiety comprises at least one annular double bond. Cycloalkyl includes any polycyclic carbocyclic ring moiety comprising at least one non-aromatic ring, regardless of the point of attachment to the remainder of the molecule. As used herein, cycloalkyl includes rings comprising, for example, 3 to 20 annular carbon atoms (*i.e.*, a C_{3-20}cycloalkyl), 3 to 16 annular carbon atoms (*i.e.*, a C_{3-16}cycloalkyl), 3 to 12 annular carbon atoms (*i.e.*, a C_{3-12}cycloalkyl), 3 to 10 annular carbon atoms (*i.e.*, a C_{3-10}cycloalkyl), 3 to 8 annular carbon atoms (*i.e.*, a C_{3-8}cycloalkyl), 3 to 6 annular carbon atoms (*i.e.*, a C_{3-6}cycloalkyl), or 3 to 5 annular carbon atoms (*i.e.*, a C_{3-5}cycloalkyl). Monocyclic cycloalkyl ring moieties include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic groups include, for example, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, adamantyl, norbonyl, decalinyl, 7,7-dimethyl -bicyclo [2.2.1]heptanyl, and the like. Still further, cycloalkyl also includes spiro cycloalkyl ring moieties, for example, spiro[2.5]octanyl, spiro[4.5]decanyl, or spiro [5.5]undecanyl.

[0049] The term "halo", as used herein, refers to atoms occupying groups VIIA of The Periodic Table and includes fluorine (fluoro), chlorine (chloro), bromine (bromo), and iodine (iodo).

[0050] The term "heteroaryl", as used herein, refers to an aromatic (fully unsaturated) ring moiety that comprises one or more annular heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur. The term "heteroaryl" includes both monocyclic and polycyclic fused-ring moieties. As used herein, a heteroaryl comprises, for example, 5 to 20 annular atoms (*i.e.*, a 5-20 membered heteroaryl), 5 to 16 annular atoms (*i.e.*, a 5-16 membered heteroaryl), 5 to 12 annular atoms (*i.e.*, a 5-12 membered heteroaryl), 5 to 10 annular atoms (*i.e.*, a 5-10 membered heteroaryl), 5 to 8 annular atoms (*i.e.*, a 5-8 membered heteroaryl), or 5 to 6 annular atoms (*i.e.*, a 5-6 membered heteroaryl). Any monocyclic or

polycyclic aromatic ring moiety comprising one or more annular heteroatoms is considered a heteroaryl, regardless of the point of attachment to the remainder of the molecule (*i.e.*, the heteroaryl moiety may be attached to the remainder of the molecule through any annular carbon or any annular heteroatom of the heteroaryl moiety). Examples of heteroaryl groups include, but are not limited to, acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzofuranyl, benzothiazolyl, benzothiadiazolyl, benzonaphthofuranyl, benzoxazolyl, benzothienyl (benzothiophenyl), benzotriazolyl, benzo[4,6]imidazo[l,2-a]pyridyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, isoquinolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl, phenazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, and triazinyl. Examples of the fused-heteroaryl rings include, but are not limited to, benzo[d]thiazolyl, quinolinyl, isoquinolinyl, benzo[b]thiophenyl, indazolyl, benzo[d]imidazolyl, pyrazolo[1,5-a]pyridinyl, and imidazo[1,5-a]pyridinyl, wherein the heteroaryl can be bound *via* either ring of the fused system.

[0051] The term "heterocyclyl", as used herein, refers to a saturated or partially unsaturated cyclic moiety that encompasses one or more annular heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur. The term "heterocyclyl" includes both monocyclic and polycyclic ring moieties, wherein the polycyclic ring moieties may be fused, bridged, or spiro. Any non-aromatic monocyclic or polycyclic ring moiety comprising at least one annular heteroatom is considered a heterocyclyl, regardless of the point of attachment to the remainder of the molecule (*i.e.*, the heterocyclyl moiety may be attached to the remainder of the molecule through any annular carbon or any annular heteroatom of the heterocyclyl moiety). Further, the term heterocyclyl is intended to encompass any polycyclic ring moiety comprising at least one annular heteroatom wherein the polycyclic ring moiety comprises at least one non-aromatic ring, regardless of the point of attachment to the remainder of the molecule. As used herein, a heterocyclyl comprises, for example, 3 to 20 annular atoms (*i.e.*, a 3-20 membered heterocyclyl), 3 to 16 annular atoms (*i.e.*, a 3-16 membered heterocyclyl), 3 to 12 annular atoms (*i.e.*, a 3-12 membered heterocyclyl), 3 to 10 annular atoms (*i.e.*, a 3-10 membered heterocyclyl), 3 to 8 annular atoms (*i.e.*, a 3-8 membered heterocyclyl), 3 to 6 annular

atoms (*i.e.*, a 3-6 membered heterocyclyl), 3 to 5 annular atoms (*i.e.*, a 3-5 membered heterocyclyl), 5 to 8 annular atoms (*i.e.*, a 5-8 membered heterocyclyl), or 5 to 6 annular atoms (*i.e.*, a 5-6 membered heterocyclyl). Examples of heterocyclyl groups include, *e.g.*, azetidinyl, azepinyl, benzodioxolyl, benzo[b][l,4]dioxepinyl, 1,4-benzodioxanyl, benzopyranyl, benzodioxinyl, benzopyranonyl, benzofuranonyl, dioxolanyl, dihydropyranyl, hydropyranyl, thienyl[l,3]dithianyl, decahydroisoquinolyl, furanonyl, imidazolinyl, imidazolidinyl, indolinyl, indolizinyl, isoindolinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, oxiranyl, oxetanyl, phenothiazinyl, phenoxazinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, tetrahydropyranyl, trithianyl, tetrahydroquinolinyl, thiophenyl (*i.e.*, thienyl), thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, and 1,1-dioxo-thiomorpholinyl. Examples of spiro heterocyclyl rings include, but are not limited to, bicyclic and tricyclic ring systems, such as oxabicyclo[2.2.2]octanyl, 2-oxa-7-azaspiro[3.5]nonanyl, 2-oxa-6-azaspiro[3.4]octanyl, and 6-oxa-1-azaspiro[3.3]heptanyl. Examples of fused heterocyclyl rings include, but are not limited to, 1,2,3,4-tetrahydroisoquinolinyl, 4,5,6,7-tetrahydrothieno[2,3-c]pyridinyl, indolinyl, and isoindolinyl, where the heterocyclyl can be bound via either ring of the fused system.

[0052] The term "oxo", as used herein, refers to a =O moiety.

[0053] The terms "optional" and "optionally", as used herein, mean that the subsequently described event or circumstance may or may not occur and that the description includes instances where the event or circumstance occurs and instances where it does not. Accordingly, the term "optionally substituted" infers that any one or more (*e.g.*, 1, 2, 1 to 5, 1 to 3, 1 to 2, etc.) hydrogen atoms on the designated atom or moiety or group may be replaced or not replaced by an atom or moiety or group other than hydrogen. By way of illustration and not limitation, the phrase "methyl optionally substituted with one or more chloro" encompasses -CH_3, -CH_2Cl, -$CHCl_2$, and -CCl_3 moieties.

[0054] It is understood that aspects and embodiments described herein as "comprising" include "consisting of" and "consisting essentially of" embodiments.

[0055] The term "pharmaceutically acceptable salt", as used herein, of a given compound refers to salts that retain the biological effectiveness and properties of the given compound and which are not biologically or otherwise undesirable. "Pharmaceutically acceptable salts" include, for example, salts with inorganic acids, and salts with an organic acid. In addition, if the compounds described herein are obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. *See*, *e.g.*, *Handbook of Pharmaceutical Salts Properties, Selection, and Use*, International Union of Pure and Applied Chemistry, John Wiley & Sons (2008), which is incorporated herein by reference. Those skilled in the art will recognize various synthetic methodologies that may be used to prepare nontoxic pharmaceutically acceptable addition salts. Pharmaceutically acceptable acid addition salts may be prepared from inorganic or organic acids. Salts derived from inorganic acids include, *e.g.*, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Salts derived from organic acids include, *e.g.*, acetic acid, propionic acid, gluconic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluene-sulfonic acid, salicylic acid, trifluoroacetic acid, and the like. Likewise, pharmaceutically acceptable base addition salts can be prepared from inorganic or organic bases. Salts derived from inorganic bases include, by way of example only, sodium, potassium, lithium, aluminum, ammonium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines. Specific examples of suitable amines include, by way of example only, isopropylamine, trimethyl amine, diethyl amine, tri(*iso*-propyl) amine, tri(*n*-propyl) amine, ethanolamine, 2-dimethylaminoethanol, piperazine, piperidine, morpholine, N-ethylpiperidine, and the like.

[0056] Isotopically labeled forms of the compounds depicted herein may be prepared. Isotopically labeled compounds have structures depicted herein, except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon,

nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, and ^{125}I, respectively. In some embodiments, a compound of formula (A) is provided wherein one or more hydrogen is replaced by deuterium or tritium.

[0057] Some of the compounds provided herein may exist as tautomers. Tautomers are in equilibrium with one another. By way of illustration, amide containing compounds may exist in equilibrium with imidic acid tautomers. Regardless of which tautomer is shown and regardless of the nature of the equilibrium among tautomers, the compounds of this disclosure are understood by one of ordinary skill in the art to comprise both amide and imidic acid tautomers. Thus, for example, amide-containing compounds are understood to include their imidic acid tautomers. Likewise, imidic-acid containing compounds are understood to include their amide tautomers.

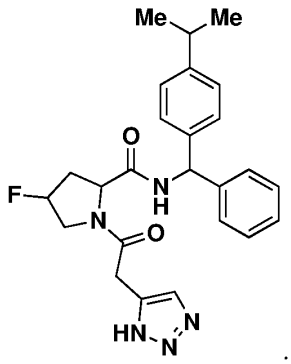
[0058] Also provided herein are prodrugs of the compounds depicted herein, or a pharmaceutically acceptable salt thereof. Prodrugs are compounds that may be administered to an individual and release, *in vivo*, a compound depicted herein as the parent drug compound. It is understood that prodrugs may be prepared by modifying a functional group on a parent drug compound in such a way that the modification is cleaved *in vitro* or *in vivo* to release the parent drug compound. *See*, *e.g.*, Rautio, J., Kumpulainen, H., Heimbach, T. et al. Prodrugs: design and clinical applications. *Nat Rev Drug Discov* 7, 255–270 (2008), which is incorporated herein by reference.

[0059] The compounds of the present disclosure, or their pharmaceutically acceptable salts, may include an asymmetric center and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)- (or as (D)- or (L)- for amino acids). The present disclosure is meant to include all such possible isomers, as well as their racemic and optically pure forms and mixtures thereof in any ratio. Optically active (+) and (-), (*R*)- and (*S*)-, or (D)- and (L)- isomers may be prepared using chiral synthons or chiral reagents, or may be resolved using conventional techniques, for example, chromatography and/or fractional crystallization. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or the resolution of the racemate (or the racemate of a salt or derivative) using, for

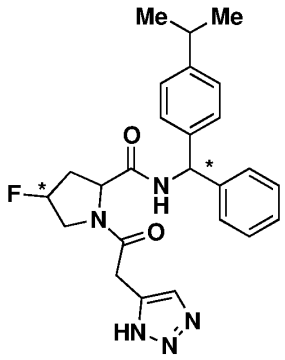
example, chiral high pressure liquid chromatography (HPLC), and chiral supercritical fluid chromatography (SFC). When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, unless specified otherwise, it is intended that the present disclosure includes both E and Z geometric isomers. Likewise, cis- and trans- are used in their conventional sense to describe relative spatial relationships.

[0060] A "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds, but having different three-dimensional structures, which are not interchangeable. The present disclosure contemplates various stereoisomers, or mixtures thereof, and includes "enantiomers," which refers to two stereoisomers whose structures are non-superimposable mirror images of one another. "Diastereomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror images of each other.

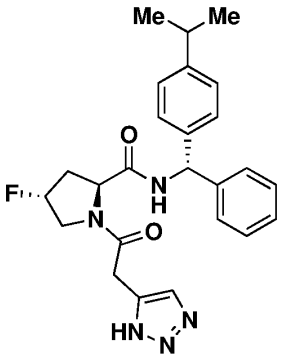
[0061] Where enantiomeric and/or diastereomeric forms exist of a given structure, flat bonds indicate that all stereoisomeric forms of the depicted structure may be present, *e.g.*,



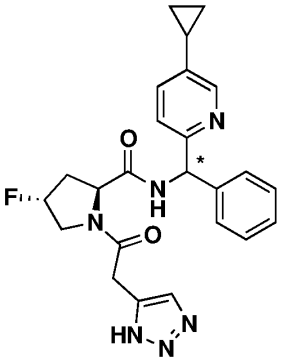
[0062] Where enantiomeric and/or diastereomeric forms exist of a given structure, flat bonds and the presence of a " * " symbol indicate that the composition is made up of at least 90%, by weight, of a single isomer with unknown stereochemistry, *e.g.*,



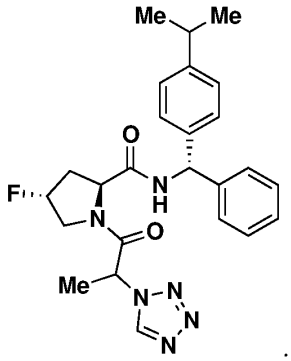
[0063] Where enantiomeric and/or diastereomeric forms exist of a given structure, wedged or hashed bonds indicate the composition is made up of at least 90%, by weight, of a single enantiomer or diastereomer with known stereochemistry, *e.g.*,



[0064] Where relevant, combinations of the above notation may be used. Exemplified species may contain stereogenic centers with known stereochemistry and stereogenic centers with unknown stereochemistry, stereochemistry, *e.g.*,

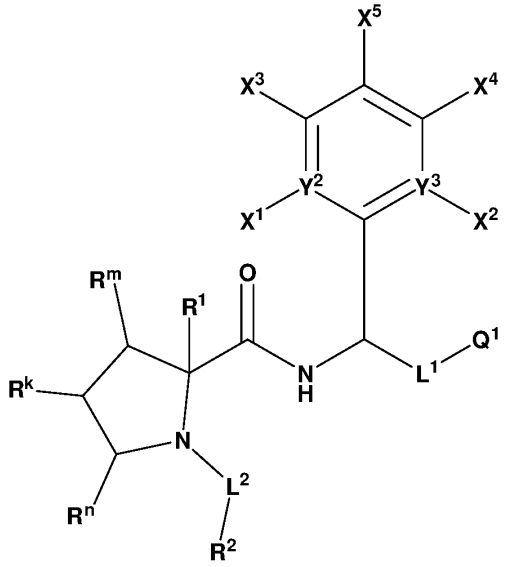


[0065] Where relevant, combinations of the above notation may be used. Exemplified species may contain stereogenic centers with known stereochemistry and stereogenic centers bearing a mixture of isomers, *e.g.*,



COMPOUNDS

[0066] In one aspect, provided herein is a compound of formula (I'):



(I'),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein:

Y^2 and Y^3 are each C, or

one of Y^2 and Y^3 is N and the other of Y^2 and Y^3 is C;

X^1 and X^2 are each independently H, C_{1-6}alkyl, or C_{1-6}alkoxy;

X^3 and X^4 are each independently H, halo, C_{1-6}alkyl, C_{1-6}alkoxy, or 5-20 membered heteroaryl, wherein the C_{1-6}alkyl of X^3 and X^4 is optionally substituted with one of more halo;

X^5 is H, C_{1-6}alkyl, C_{1-6}alkoxy, or C_{3-10}cycloalkyl;

either

(1) L^1 is absent; and

Q^1 is selected from (i) to (iv):

(i) phenyl, wherein the phenyl of Q^1 is substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, -NH_2, -NH-C(O)-(C_{1-6}alkyl), -NH-C(O)-(3-15 membered heterocyclyl), C_{3-10}cycloalkyl, or 5-20 membered heteroaryl, wherein

the C_{1-6}alkyl is optionally substituted with one or more halo, -NH-C(O)-NH(C_{1-6}alkyl), -NH-C(O)-C_{1-6}alkyl, or -NH-C(O)-C_{1-6}alkoxy,

the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl, and

the 5-20 membered heteroaryl is optionally substituted with one or more C_{1-6}alkyl,

(ii) 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of Q^1 is optionally substituted with one or more oxo, or C_{1-6}alkyl,

(iii) 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of Q^1 is optionally substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, -NH_2, or C_{3-10}cycloalkyl, wherein,

the C_{1-6}alkyl is optionally substituted with one or more halo, and

the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl, and

(iv) C_{3-10}cycloalkyl;

or

(2) L^1 is $-CH_2-$; and

Q^1 is C_{3-10}cycloalkyl;

L^2 is -C(O)- or $-S(O)_2-$

R^1 is H or C_{1-6}alkyl;

R^k is H, halo, -OH, $-NH_2$, or -NH-C(O)C_{1-6}alkyl;

R^m is H, -OH, or C_{1-6}alkyl;

R^n is H, C_{1-6}alkyl, or C_{3-10}cycloalkyl or R^n taken together with the carbon atom to which it is attached forms C_{3-5} cycloalkyl;

or R^k is taken together with either R^m or R^n, and the atoms to which they are attached, to form cyclopropyl; and

R^2 is selected from (i) to (vii):

(i) C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is optionally substituted with one or more R^a, wherein R^a is:

(a) -OH,

(b) cyano,

(c) C_{2-6}alkynyl,

(d) C_{6-20}aryl, wherein the C_{6-20}aryl of R^a is optionally substituted with one or more halo, cyano, C_{1-6}alkoxy, or -NH-C(O)-C_{1-6}alkyl,

(e) 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^a is optionally substituted with one or more R^c, wherein

R^c is halo, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, or -C(O)-C_{1-6}alkoxy, wherein

the C_{1-6}alkyl of R^c is optionally substituted with one or more halo or C_{2-6}alkynyl, and

the -C(O)-C_{1-6}alkoxy of R^c is optionally substituted with one or more halo,

(f) -N(R^c)(R^d), wherein R^c and R^d of N(Rc)(Rd) are, independently of each other, H, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-C_{1-6}alkoxy, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -C(O)-(3-15 membered heterocyclyl), -CH_2-C(O)-NH_2, 3-15 membered heterocyclyl, or 5-20 membered heteroaryl, wherein

the C_{1-6}alkyl of R^c or R^d is optionally substituted with one or more -C(O)-NH_2,

the -C(O)-C_{1-6}alkyl of R^c or R^d is optionally substituted with one or more halo,

the 3-15 membered heterocyclyl and the 5-20 membered heteroaryl of R^c or R^d are independently optionally substituted with one or more C_{1-6}alkyl,

the -C(O)-(3-15 membered heterocyclyl) of R^c or R^d is optionally substituted with one or more halo, -C(O)-C_{1-6}alkoxy, or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, C_{1-6}alkoxy, or C_{3-10}cycloalkyl, and

the C_{1-6}alkyl of the -C(O)-N(C_{1-6}alkyl)$_2$ of R^c or R^d are, independently of each other, optionally substituted with one or more halo or C_{6-20}aryl,

(g) -O-R^e, wherein R^e is C_{1-6}alkyl, C_{6-20}aryl, -C(O)-(3-15 membered heterocyclyl), -C(O)-N-(C_{1-6}alkyl)$_2$, or 5-20 membered heteroaryl, wherein

the C_{1-6}alkyl of R^e is optionally substituted with one or more C_{1-6}alkoxy, wherein the C_{1-6}alkoxy is optionally substituted with one or more C_{2-6}alkynyl,

the C_{6-20}aryl of R^e is optionally substituted with one or more C_{1-6}alkyl, and

the -C(O)-(3-15 membered heterocyclyl) of R^e is optionally substituted with one or more C_{1-6}alkyl, C_{1-6}alkoxy, or -C(O)-C_{1-6}alkoxy, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, C_{1-6}alkoxy, or C_{3-10}cycloalkyl,

(h) -C(O)-R^e, wherein R^e of -C(O)-R^e is -NH_2, -OH, or 3-15 membered heterocyclyl, or

(i) -$S(O)_2$-R^f, wherein R^f is C_{1-6}alkyl or 3-15 membered heterocyclyl,

provided that, when R^2 is unsubstituted methyl, then either

(1) Q^1 is 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of Q^1 is optionally substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, -NH_2, C_{3-10}cycloalkyl, or -OH, and wherein Q^1 is not unsubstituted pyridyl, or

(2) Q^1 is phenyl, wherein the phenyl of Q^1 is substituted with

(i) at least one C_{3-6}alkyl, wherein the at least one C_{3-6}alkyl is optionally substituted with one or more halo, or

(ii) at least one C_{3-10}cycloalkyl, wherein the at least one C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl, or

(iii) at least one 5-20 membered heteroaryl, wherein the at least one 5-20 membered heteroaryl is optionally substituted with one or more C_{1-6}alkyl,

(ii) C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl of R^2 is optionally substituted with one or more R^q, wherein R^q is 5-20 membered heteroaryl or C_{6-20}aryl, wherein the C_{6-20}aryl of R^q is optionally substituted with one or more C_{1-6}alkoxy,

(iii) 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^2 is optionally substituted with one or more halo, oxo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, or 5-20 membered heteroaryl,

(iv) 5-20 membered heteroaryl or -(C_{1-4}alkyl)(5-20 membered heteroaryl), wherein the C_{1-4} alkyl is optionally substituted with one or more or more –OH, halo, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, and wherein the 5-20 membered heteroaryl is optionally substituted with one or more R^s, wherein

R^s is halo, C_{1-6}alkyl, C_{1-6}alkoxy, $-NH_2$, $-NH(C_{1-6}alkyl)$, $-N(C_{1-6}alkyl)_2$, $-NH-C(O)-C_{1-6}$alkyl, C_{6-20}aryl, C_{3-10}cycloalkyl, 3-15 membered heterocyclyl, 5-20 membered heteroaryl, or $-C(O)-C_{1-6}$alkoxy, wherein

the C_{1-6}alkyl of R^s is optionally substituted with one or more halo, C_{1-6}alkoxy, $-NH_2$, $-NH(C_{1-6}alkyl)$, $-N(C_{1-6}alkyl)_2$, $-NH-C(O)C_{1-6}$alkyl, or $-NH-C(O)-C_{1-6}$alkoxy, and

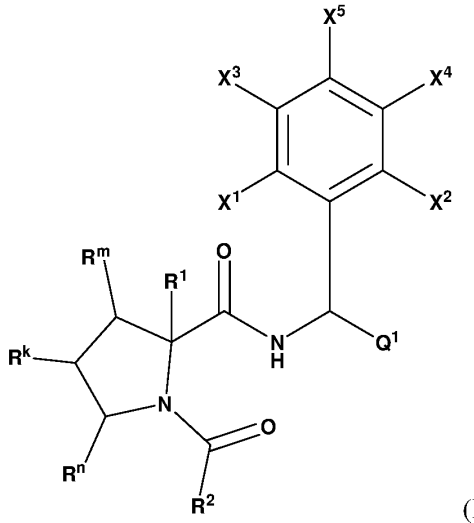
the 3-15-membered heterocyclyl of R^s is optionally substituted with one or more halo or $-C(O)-C_{1-6}$alkoxy,

(v) $-N(R^g)(R^h)$, wherein R^g and R^h are independently H or C_{1-6}alkyl,

(vi) $-C(O)-R^j$, wherein R^j is C_{3-10}cycloalkyl, $-NH(C_{1-6}alkyl)$, $-N(C_{1-6}alkyl)_2$, or -NH(5-20 membered heteroaryl), and

(vii) C_{6-20}aryl, wherein the C_{6-20}aryl of R^2 is optionally substituted with one or more 5-20 membered heteroaryl or $-O-R^p$, wherein R^p is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^p is optionally substituted with one or more $-C(O)-C_{1-6}$alkyl.

[0067] In one aspect, provided is a compound of formula (I):



(I),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein:

X^1 and X^2 are each independently H, C_{1-6}alkyl, or C_{1-6}alkoxy;

X^3 and X^4 are each independently H, halo, C_{1-6}alkyl, C_{1-6}alkoxy, or 5-20 membered heteroaryl;

X^5 is H, C_{1-6}alkyl, C_{1-6}alkoxy, or C_{3-10}cycloalkyl;

Q^1 is selected from (i) to (iii):

(i) phenyl, wherein the phenyl of Q^1 is substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, -NH_2, -NH-C(O)-(C_{1-6}alkyl), -NH-C(O)-(3-15 membered heterocyclyl), or C_{3-10}cycloalkyl, wherein

the C_{1-6}alkyl is optionally substituted with one or more halo, and

the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl,

(ii) 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of Q^1 is optionally substituted with one or more oxo, and

(iii) 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of Q^1 is optionally substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, -NH_2, or C_{3-10}cycloalkyl, wherein

the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl;

R^1 is H or C_{1-6}alkyl;

R^k is H, halo, -OH, -NH_2, or -NH-C(O)C_{1-6}alkyl;

R^m is H, -OH, or C_{1-6}alkyl;

R^n is H, C_{1-6}alkyl, or C_{3-10}cycloalkyl;

or R^k is taken together with either R^m or R^n, and the atoms to which they are attached, to form cyclopropyl; and

R^2 is selected from (i) to (vii):

(i) C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is optionally substituted with one or more R^a, wherein R^a is:

(a) -OH,

(b) cyano,

(c) C_{2-6}alkynyl,

(d) C_{6-20}aryl, wherein the C_{6-20}aryl of R^a is optionally substituted with one or more halo, cyano, C_{1-6}alkoxy, or -NH-C(O)-C_{1-6}alkyl,

(e) 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^a is optionally substituted with one or more R^b, wherein

R^b is halo, C_{1-6}alkyl, C_{1-6}alkoxy, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, C_{3-10}cycloalkyl, 3-15 membered heterocyclyl, or -C(O)-C_{1-6}alkoxy, wherein

the C_{1-6}alkyl of R^b is optionally substituted with one or more halo, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, -NH-C(O)C_{1-6}alkyl, or -NH-C(O)-C_{1-6}alkoxy, and

the 3-15-membered heterocyclyl of R^b is optionally substituted with one or more halo or -C(O)-C_{1-6}alkoxy,

(f) 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^a is optionally substituted with one or more R^c, wherein

R^c is halo, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, or -C(O)-C_{1-6}alkoxy, wherein

the C_{1-6}alkyl of R^c is optionally substituted with one or more halo or C_{2-6}alkynyl, and

the -C(O)-C_{1-6}alkoxy of R^c is optionally substituted with one or more halo,

(g) -$N(R^c)(R^d)$, wherein R^c and R^d are, independently of each other, H, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-C_{1-6}alkoxy, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -C(O)-(3-15 membered heterocyclyl), -CH_2-C(O)-NH_2, 3-15 membered heterocyclyl, or 5-20 membered heteroaryl, wherein

the -C(O)-C_{1-6}alkyl of R^c or R^d is optionally substituted with one or more halo,

the 3-15 membered heterocyclyl and the 5-20 membered heteroaryl of R^c or R^d are independently optionally substituted with one or more C_{1-6}alkyl, and

the -C(O)-(3-15 membered heterocyclyl) of R^c or R^d is optionally substituted with one or more halo, -C(O)-C_{1-6}alkoxy, or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, C_{1-6}alkoxy, or C_{3-10}cycloalkyl,

(h) -O-R^e, wherein R^e is C_{1-6}alkyl, C_{6-20}aryl, -C(O)-(3-15 membered heterocyclyl), -C(O)-N-(C_{1-6}alkyl)$_2$, or 5-20 membered heteroaryl, wherein

the C_{1-6}alkyl of R^e is optionally substituted with one or more C_{1-6}alkoxy, wherein the C_{1-6}alkoxy is optionally substituted with one or more C_{2-6}alkynyl,

the C_{6-20}aryl of R^e is optionally substituted with one or more C_{1-6}alkyl, and

the -C(O)-(3-15 membered heterocyclyl) of R^e is optionally substituted with one or more C_{1-6}alkyl, C_{1-6}alkoxy, or -C(O)-C_{1-6}alkoxy, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, C_{1-6}alkoxy, or C_{3-10}cycloalkyl,

(i) -C(O)-R^e, wherein R^e is -NH_2, -OH, or 3-15 membered heterocyclyl, or

(j) $-S(O)_2-R^f$, wherein R^f is C_{1-6}alkyl or 3-15 membered heterocyclyl,

provided that, when R^2 is unsubstituted methyl, then either

(1) Q^1 is 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of Q^1 is substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, $-NH_2$, C_{3-10}cycloalkyl, or -OH, or

(2) Q^1 is phenyl, wherein the phenyl of Q^1 is substituted with at least one C_{3-6}alkyl or at least one C_{3-10}cycloalkyl, wherein the at least one C_{3-6}alkyl is optionally substituted with one or more halo, and the at least one C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl,

(ii) C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl of R^2 is optionally substituted with one or more R^q, wherein R^q is 5-20 membered heteroaryl or C_{6-20}aryl, wherein the C_{6-20}aryl of R^q is optionally substituted with one or more C_{1-6}alkoxy,

(iii) 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^2 is optionally substituted with one or more halo, oxo, C_{1-6}alkyl, $-C(O)-C_{1-6}$alkyl, or 5-20 membered heteroaryl,

(iv) 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^2 is optionally substituted with one or more R^s, wherein R^s is C_{1-6}alkyl, C_{1-6}alkoxy, $-NH-C(O)-C_{1-6}$alkyl, C_{6-20}aryl, or 5-20 membered heteroaryl, wherein the C_{1-6}alkyl of R^s is optionally substituted with one or more C_{1-6}alkoxy,

(v) $-N(R^g)(R^h)$, wherein R^g and R^h are independently H or C_{1-6}alkyl,

(vi) $-C(O)-R^j$, wherein R^j is C_{3-10}cycloalkyl, $-NH(C_{1-6}$alkyl), $-N(C_{1-6}$alkyl$)_2$, or -NH(5-20 membered heteroaryl), and

(vii) C_{6-20}aryl, wherein the C_{6-20}aryl of R^2 is optionally substituted with one or more 5-20 membered heteroaryl or -O-R^p, wherein R^p is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^p is optionally substituted with one or more -C(O)-C_{1-6}alkyl.

[0068] Any embodiments provided herein of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof, are also, where applicable, embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

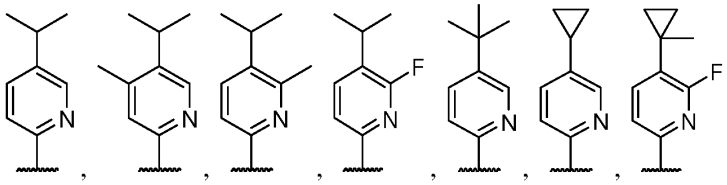
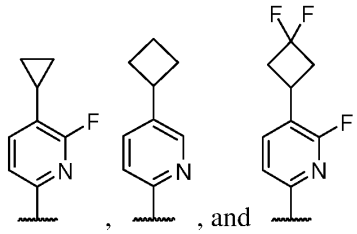
[0069] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^2 is -C(O) or -$S(O)_2$-. In some embodiments, L^2 is -C(O)-. In some embodiments, L^2 is -$S(O)_2$-.

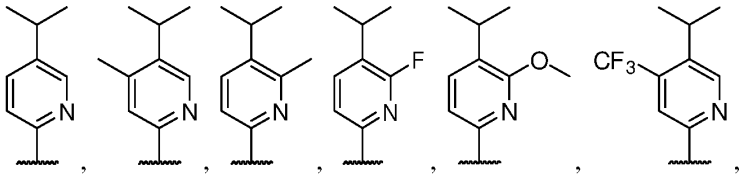
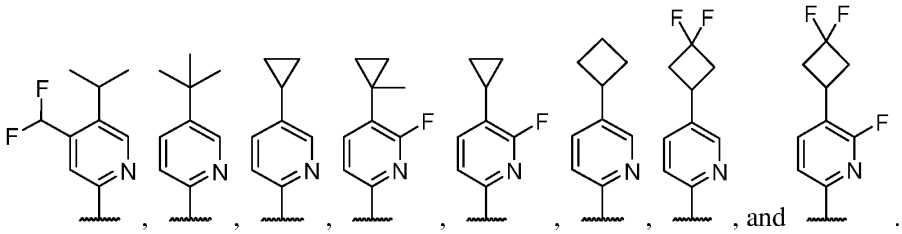
[0070] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, Q^1 is 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of Q^1 is optionally substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, -NH_2, or C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl is optionally substituted with one or more C_{1-6}alkyl or halo. In some embodiments, Q^1 is 5-6 membered heteroaryl, wherein the 5-6 membered heteroaryl of Q^1 is optionally substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, -NH_2, or C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl is optionally substituted with one or more C_{1-6}alkyl or halo. In some embodiments, Q^1 is pyridinyl, wherein the pyridinyl of Q^1 is optionally substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, -NH_2, or C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl is optionally substituted with one or more C_{1-6}alkyl or halo. In some embodiments, Q^1 is 2-pyridinyl or 3-pyridinyl, wherein the 2-pyridinyl or 3-pyridinyl of Q^1 is optionally substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, -NH_2, or C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl is optionally substituted with one or more C_{1-6}alkyl or halo. In some embodiments, Q^1 is 2-pyridinyl, wherein the 2-pyridinyl of Q^1 is optionally substituted with one or more halo, C_{1-6}alkyl, C_{1-6}alkoxy, -NH_2, or C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl is optionally substituted with one or more C_{1-6}alkyl or halo. In some embodiments Q^1 is 2-pyridinyl, wherein the 2-pyridinyl of Q^1 is optionally substituted with one or more halo, C_{1-6}alkyl, or C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl is optionally substituted with one or more

C_{1-6}alkyl or halo. In some embodiments, Q^1 is 2-pyridinyl, wherein the 2-pyridinyl of Q^1 is optionally substituted with one or more fluoro, chloro, methyl, *iso*-propyl, *tert*-butyl, cyclopropyl, or cyclobutyl, wherein the cyclopropyl and cyclobutyl are independently optionally substituted with one or more methyl or fluoro.

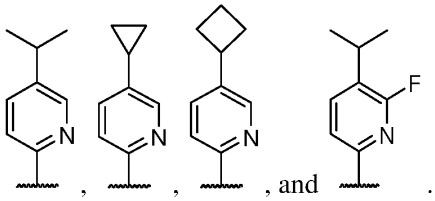
[0071] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, Q^1 is 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of Q^1 is optionally substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, $-NH_2$, or C_{3-10}cycloalkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, and the C_{3-10}cycloalkyl is optionally substituted with one or more C_{1-6}alkyl or halo. In some embodiments, Q^1 is 5-6 membered heteroaryl, wherein the 5-6 membered heteroaryl of Q^1 is optionally substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, $-NH_2$, or C_{3-10}cycloalkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, and the C_{3-10}cycloalkyl is optionally substituted with one or more C_{1-6}alkyl or halo. In some embodiments, Q^1 is pyridinyl, wherein the pyridinyl of Q^1 is optionally substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, $-NH_2$, or C_{3-10}cycloalkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, and the C_{3-10}cycloalkyl is optionally substituted with one or more C_{1-6}alkyl or halo. In some embodiments, Q^1 is 2-pyridinyl or 3-pyridinyl, wherein the 2-pyridinyl or 3-pyridinyl of Q^1 is optionally substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, $-NH_2$, or C_{3-10}cycloalkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, and the C_{3-10}cycloalkyl is optionally substituted with one or more C_{1-6}alkyl or halo. In some embodiments, Q^1 is 2-pyridinyl, wherein the 2-pyridinyl of Q^1 is optionally substituted with one or more halo, C_{1-6}alkyl, C_{1-6}alkoxy, $-NH_2$, or C_{3-10}cycloalkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, and the C_{3-10}cycloalkyl is optionally substituted with one or more C_{1-6}alkyl or halo. In some embodiments Q^1 is 2-pyridinyl, wherein the 2-pyridinyl of Q^1 is optionally substituted with one or more halo, C_{1-6}alkyl, C_{1-6}alkoxy, or C_{3-10}cycloalkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, and the C_{3-10}cycloalkyl is optionally substituted with one or more C_{1-6}alkyl or halo. In some embodiments, Q^1 is 2-pyridinyl, wherein the 2-pyridinyl of Q^1 is optionally substituted with one or more fluoro, chloro, methyl, *iso*-propyl, *tert*-butyl, cyclopropyl, cyclobutyl, or methoxy, wherein the methyl is optionally substituted with one

or more fluoro and the cyclopropyl and cyclobutyl are independently optionally substituted with one or more methyl or fluoro.

[0072] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, Q^1 is selected from the group consisting of  ,  , and .

[0073] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, Q^1 is selected from the group consisting of  ,  , and .

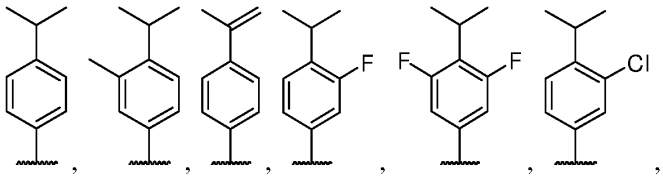
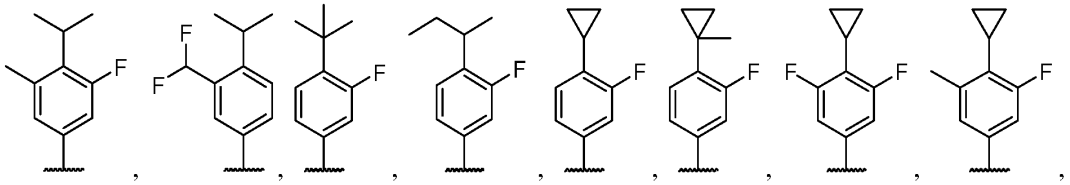
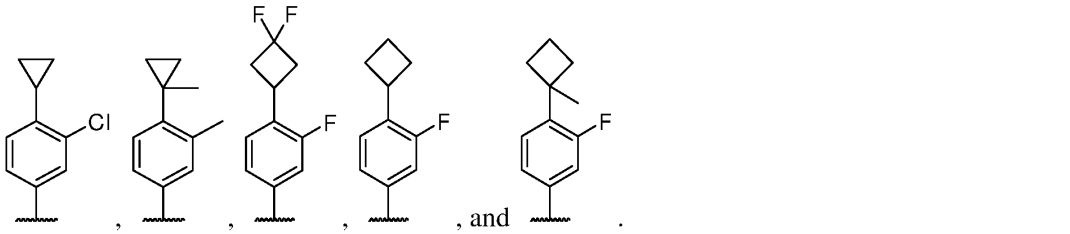
[0074] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, Q^1 is selected

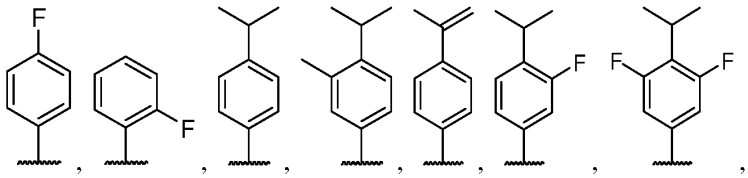
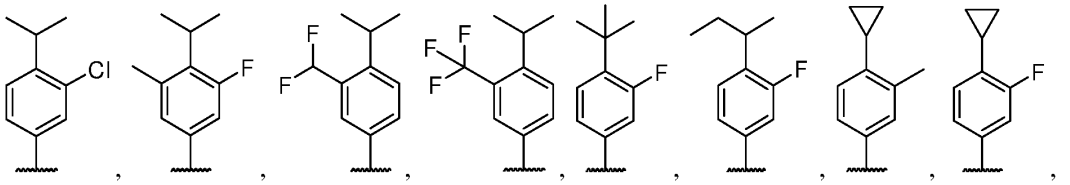
from the group consisting of  . In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

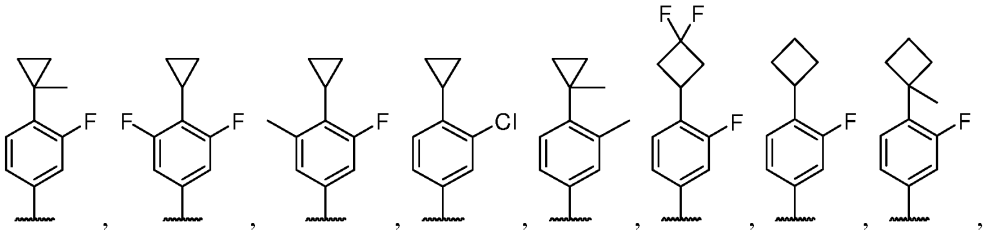
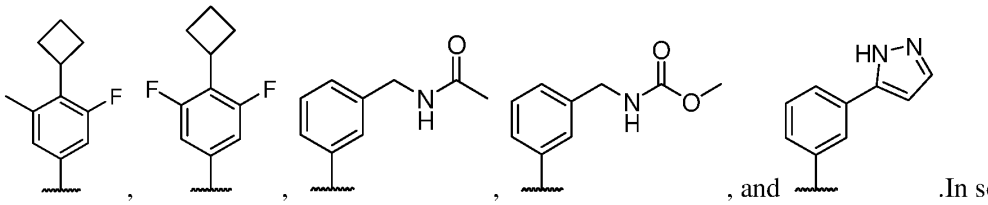
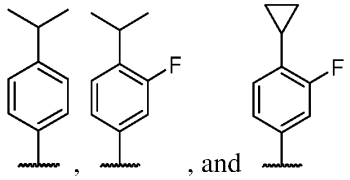
[0075] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, Q^1 is phenyl, wherein the phenyl of Q^1 is substituted with one or more halo, C_{1-6}alkyl, C_{2-6} alkenyl, $-NH_2$, -NH-C(O)-(C_{1-6}alkyl), -NH-C(O)-(3-15 membered heterocyclyl), or C_{3-10}cycloalkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, and the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl. In some embodiments, Q^1 is phenyl, wherein the phenyl of Q^1 is substituted with one or more halo, C_{1-6}alkyl, C_{2-6} alkenyl, or C_{3-10}cycloalkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, and the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl. In some embodiments, Q^1 is phenyl, wherein the phenyl of Q^1 is substituted with one or more fluoro, chloro, methyl, *iso*-propyl, *sec*-butyl, *tert*-butyl, prop-1-en-2-yl, cyclopropyl, or cyclobutyl, wherein the methyl, *iso*-propyl, *sec*-butyl, and *tert*-butyl are independently optionally substituted with one or more halo, and the cyclopropyl and cyclobutyl are independently optionally substituted with one or more fluoro or methyl. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

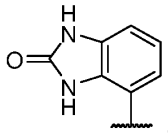
[0076] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, Q^1 is phenyl, wherein the phenyl of Q^1 is substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, $-NH_2$, -NH-C(O)-(C_{1-6}alkyl), -NH-C(O)-(3-15 membered heterocyclyl), C_{3-10}cycloalkyl, or 5-20 membered heteroaryl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, -NH-C(O)-NH(C_{1-6}alkyl), -NH-C(O)-C_{1-6}alkyl, or -NH-C(O)-C_{1-6}alkoxy, the C_{3-10}cycloalkyl is optionally

substituted with one or more halo or C_{1-6}alkyl, and the 5-20 membered heteroaryl is optionally substituted with one or more C_{1-6}alkyl.

[0077] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, Q^1 is selected from the group consisting of  ,  ,  , and .

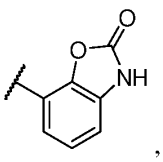
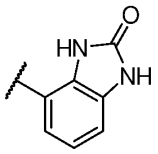
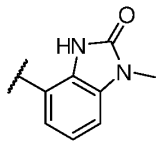
[0078] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, Q^1 is selected from the group consisting of  ,  .



, and .In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, Q^1 is selected from the group consisting of 
. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

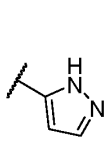
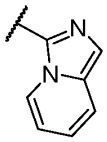
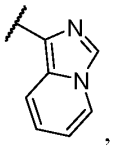
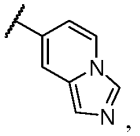
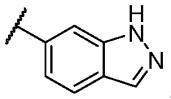
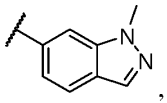
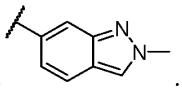
[0079] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, Q^1 is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of Q^1 is optionally substituted with one or more oxo. In some embodiments, Q^1 is 
. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0080] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, Q^1 is (i) 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of Q^1 is optionally substituted

with one or more oxo, or C_{1-6}alkyl, (ii) 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of Q^1 is optionally substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, $-NH_2$, or C_{3-10}cycloalkyl, wherein, the C_{1-6}alkyl is optionally substituted with one or more halo, and the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl, or (iii) C_{3-10}cycloalkyl.

[0081] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, Q^1 is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of Q^1 is optionally substituted with one or more oxo, or C_{1-6}alkyl,. In some embodiments Q^1 is selected from the group consisting of  ,  , and  .

[0082] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, Q^1 is 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of Q^1 is optionally substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, $-NH_2$, or C_{3-10}cycloalkyl, wherein, the C_{1-6}alkyl is optionally substituted with one or more halo, and the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl. In some embodiments Q^1 is 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of Q^1 is optionally substituted with one or more C_{1-6}alkyl. In some embodiments, is 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of Q^1 comprises one or more annular N. In some embodiments, is 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of Q^1 comprises two annular N. In some embodiments, is 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of Q^1 is monocyclic of bicyclic. In some embodiments, is 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of Q^1 is monocyclic. In some embodiments, is 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of Q^1 is bicyclic. In some embodiments Q^1 is selected

from the group consisting of  ,  ,  ,  ,  ,  , and  .

[0083] In some embodiments of a compound of formula (I'), (I-G), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, Q^1 is C_{3-10}cycloalkyl. In some embodiments, Q^1 is C_{3-6}cycloalkyl. In some embodiments Q^1 is cyclopropyl.

[0084] In some embodiments of a compound of formula (I'), (I-G), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, L^1 is absent or is $-CH_2-$. In some embodiments, L^1 is absent. In some embodiments, L^1 is $-CH_2-$. In some embodiments, L^1 is absent and Q^1 is C_{3-10}cycloalkyl. In some embodiments, L^1 is absent and Q^1 is C_{3-6}cycloalkyl. In some embodiments L^1 is absent and Q^1 is cyclopropyl. In some embodiments, L^1 is $-CH_2-$ and Q^1 is C_{3-10}cycloalkyl. In some embodiments, L^1 is $-CH_2-$ and Q^1 is C_{3-6}cycloalkyl. In some embodiments L^1 is $-CH_2-$ and Q^1 is cyclopropyl.

[0085] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, X^1, X^2, X^3, X^4, and X^5 are each H. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0086] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^1 is H or C_{1-6}alkyl. In some embodiments R^1 is H. In some ebodiments, R^1 is C_{1-3}alkyl. In some ebodiments, R^1 is methyl.

[0087] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^k is H, halo, -

OH, -NH_2, or -NH-C(O)C_{1-6}alkyl. In some embodiments, R^k is H. In some embodiments, R^k is halo. In some embodiments, R^k is F.

[0088] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^m is H, -OH, or C_{1-6}alkyl. In some embodiments R^m is H.

[0089] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^n is H, C_{1-6}alkyl, or C_{3-10}cycloalkyl. In some embodiments R^n is H.

[0090] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^m is H, R^n is H, and R^k is H, halo, -OH, -NH_2, or -NH-C(O)C_{1-6}alkyl. In some embodiments, R^m is H, R^n is H, and R^k is halo, -OH, or -NH_2. In some embodiments, R^m is H, R^n is H, and R^k is halo. In some embodiments, R^m is H, R^n is H, and R^k is fluoro. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0091] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^k is taken together with either R^m or R^n, and the atoms to which they are attached, to form cyclopropyl. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0092] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^n taken together with the carbon atom to which it is attached forms C_{3-5} cycloalkyl. In some embodiments, R^n taken together with the carbon atom to which it is attached forms cyclopropyl.

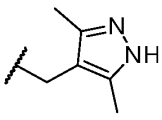
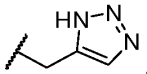
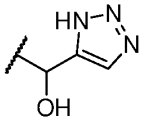
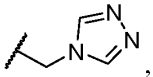
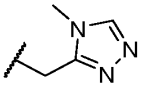
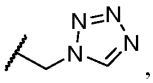
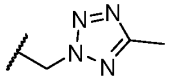
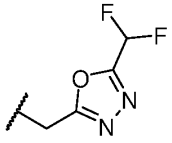
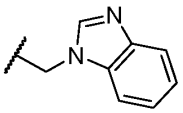
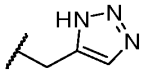
[0093] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^1 is H. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a

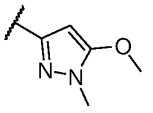
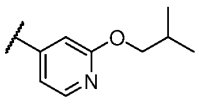
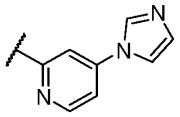
stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

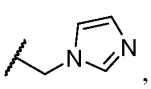
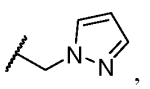
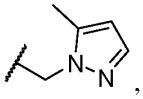
[0094] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is optionally substituted with one or more R^a. In some embodiments, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^a is optionally substituted with one or more R^b. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl of R^a is optionally substituted with one or more R^b. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl of R^a is optionally substituted with one or more C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, $-NH_2$, $-NH(C_{1-6}alkyl)$, $-N(C_{1-6}alkyl)_2$, $-NH-C(O)C_{1-6}$alkyl, or $-NH-C(O)-C_{1-6}$alkoxy. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl of R^a is optionally substituted with one or more methyl, wherein the methyl is optionally substituted with one or more fluoro.

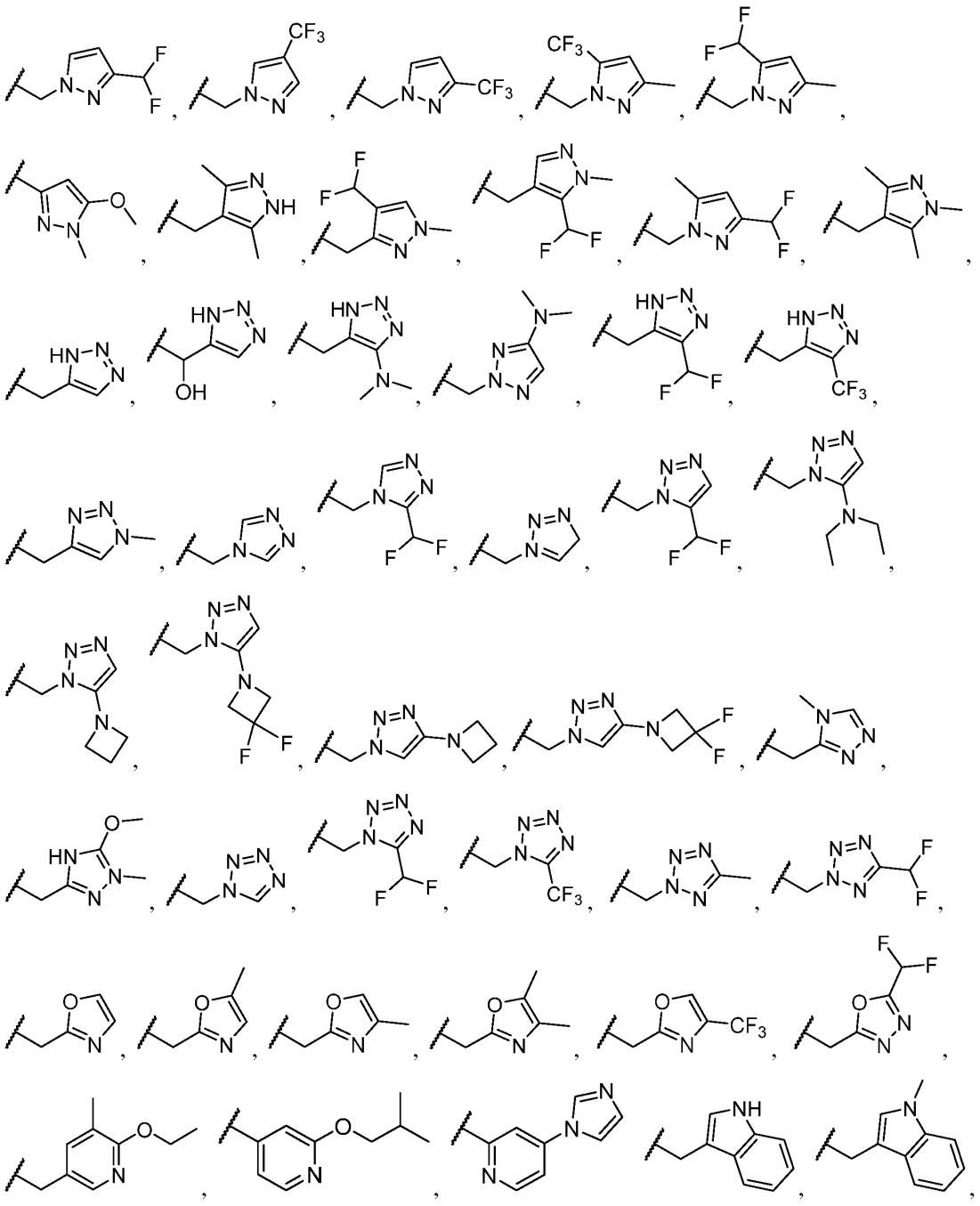
[0095] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is 5-20 membered heteroaryl or $-(C_{1-4}alkyl)$(5-20 membered heteroaryl), wherein the C_{1-4} alkyl is optionally substituted with one or more or more –OH, halo, $-NH_2$, $-NH(C_{1-6}alkyl)$, $-N(C_{1-6}alkyl)_2$, and wherein the 5-20 membered heteroaryl is optionally substituted with one or more R^s. In some embodiments, R^2 is 5-20 membered heteroaryl, wherein the C_{1-4} alkyl is optionally substituted with one or more or more –OH, halo, $-NH_2$, $-NH(C_{1-6}alkyl)$, $-N(C_{1-6}alkyl)_2$, and wherein the 5-20 membered heteroaryl is optionally substituted with one or more R^s. In some embodiments, R^2 is (methyl)(5-20 membered heteroaryl), wherein the methyl is optionally substituted with one or more or more –OH, halo, $-NH_2$, $-NH(C_{1-6}alkyl)$, $-N(C_{1-6}alkyl)_2$, and wherein the 5-20 membered heteroaryl is optionally substituted with one or more R^s. In some embodiments, R^s is halo, C_{1-6}alkyl, C_{1-6}alkoxy, $-NH_2$, $-NH(C_{1-6}alkyl)$, $-N(C_{1-6}alkyl)_2$, -NH-C(O)-

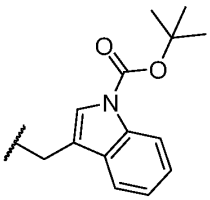
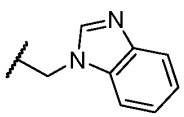
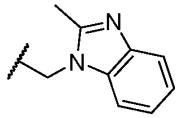
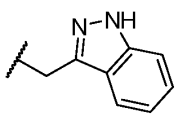
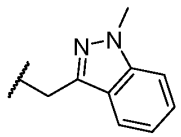
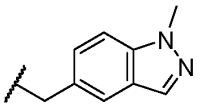
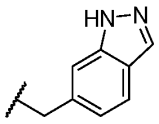
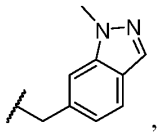
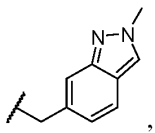
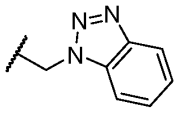
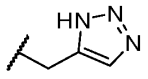
C_{1-6}alkyl, C_{6-20}aryl, C_{3-10}cycloalkyl, 3-15 membered heterocyclyl, 5-20 membered heteroaryl, or -C(O)-C_{1-6}alkoxy. In some embodiments, the C_{1-6}alkyl of R^s is optionally substituted with one or more halo, C_{1-6}alkoxy, $-NH_2$, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, -NH-C(O)C_{1-6}alkyl, or -NH-C(O)-C_{1-6}alkoxy, and the 3-15-membered heterocyclyl of R^s is optionally substituted with one or more halo or -C(O)-C_{1-6}alkoxy.

[0096] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  , and  . In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is  .

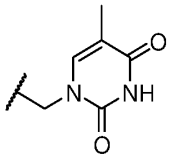
[0097] In some embodiments of a compound of formula (I'), (I-C), (I-D), (I-E), or (I-F), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is selected from the group consisting of  ,  , and  .

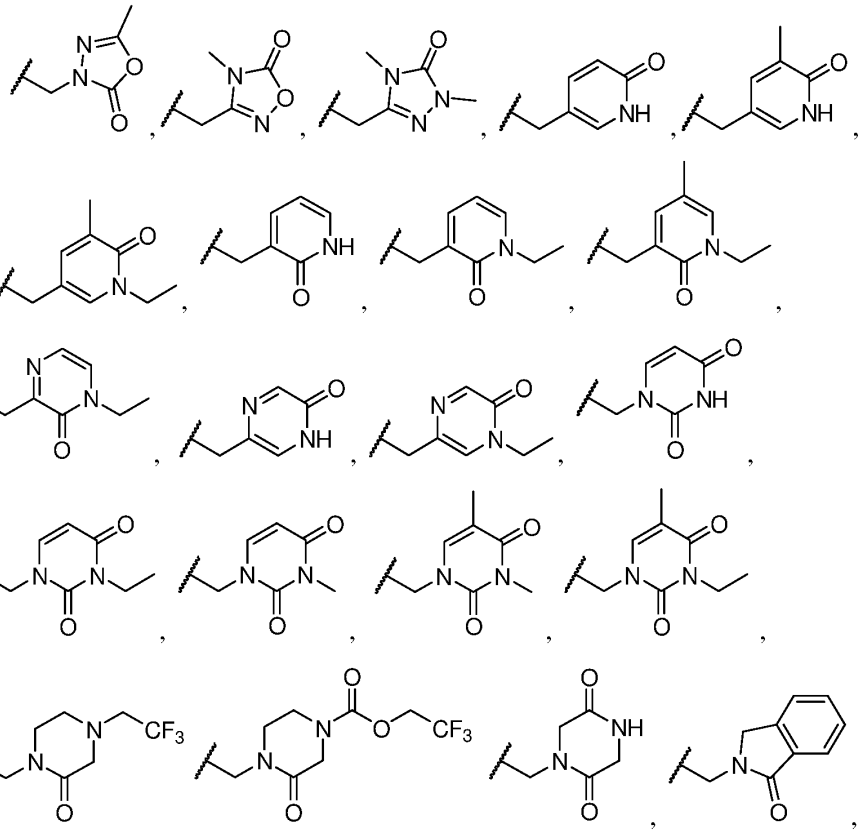
[0098] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is selected from the group consisting of  ,  ,  ,  ,

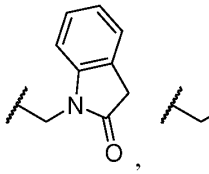
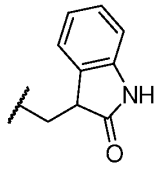
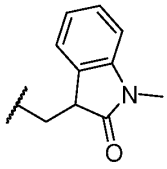
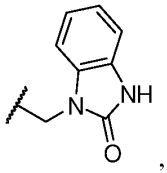
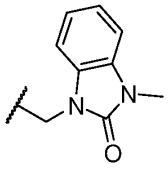
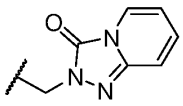
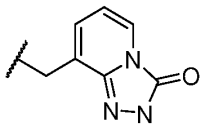
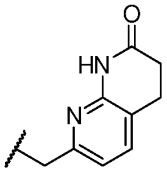











, and

. In some embodiments, R^2 is

.

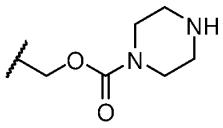
[0099] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is $C_{1\text{-}6}$alkyl, wherein the $C_{1\text{-}6}$alkyl of R^2 is substituted with one or more R^a, wherein R^a is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^a is optionally substituted with one or more R^c.

[0100] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^a is optionally substituted with one or more R^c. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-8 membered heterocyclyl, wherein the 3-8 membered heterocyclyl of R^a is optionally substituted with one or more R^c. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-8 membered heterocyclyl, wherein the 3-8 membered heterocyclyl of R^a is optionally substituted with one or more oxo or $C_{1\text{-}6}$alkyl. In some embodiments, R^2 is

. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

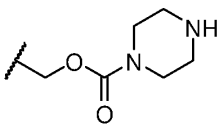
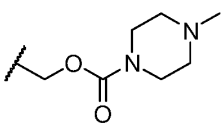
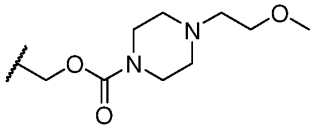
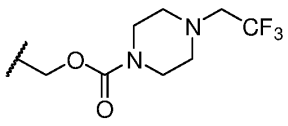
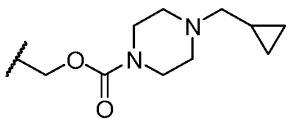
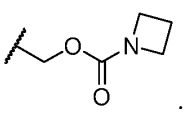
[0101] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-8 membered heterocyclyl, wherein the 3-8 membered heterocyclyl of R^a is optionally substituted with one or more R^c, wherein R^c is oxo, C_{1-6}alkyl, or -C(O)-C_{1-6}alkoxy, wherein the C_{1-6}alkyl of R^c is optionally substituted with one or more halo , and the -C(O)-C_{1-6}alkoxy of R^c is optionally substituted with one or more halo. In some embodiments, R^2 is selected from the group consisting of 

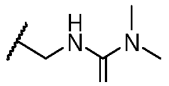

,

,

,

,

,

,

, and

.

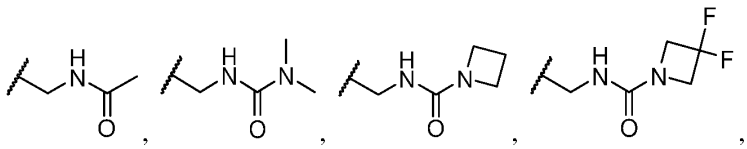
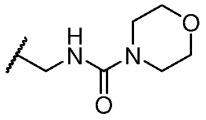
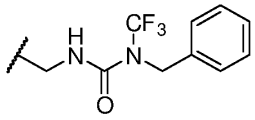
[0102] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e, wherein R^e is -C(O)-(3-15 membered heterocyclyl). In some embodiments, R^2 is

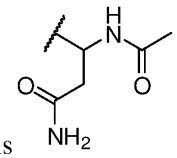

. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0103] In some embodiments of a compound of formula (I'), (I-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e, wherein R^e is -C(O)-(3-15 membered heterocyclyl) wherein the -C(O)-(3-15 membered heterocyclyl) of R^e is optionally substituted with one or more C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, C_{1-6}alkoxy, or C_{3-10}cycloalkyl. In some embodiments, R^2 is selected from the group consisting of


,

,

,

,

, and

.

[0104] In some embodiments of a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is -$N(R^c)(R^d)$. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -$N(R^c)(R^d)$. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -$N(R^c)(R^d)$, wherein one of R^c and R^d is H, and the other of R^c and R^d is -C(O)-$N(C_{1-6}alkyl)_2$. In some embodiments, R^2 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0105] In some embodiments of a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -$N(R^c)(R^d)$, wherein one of R^c and R^d is H, and the other of R^c and R^d, -C(O)-C_{1-6}alkyl, -C(O)-$N(C_{1-6}alkyl)_2$, or -C(O)-(3-15 membered heterocyclyl). In some embodiments, R^2 is selected from the group consisting of  ,  , and  .

[0106] In some embodiments of a compound of formula (I'), (I-A1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is ethyl, wherein the ethyl of R^2 is substituted with one or more R^a, wherein R^a is -$N(R^c)(R^d)$, wherein one of R^c and R^d is H, and the other of R^c and R^d , is -C(O)-C_{1-6}alkyl. In some embodiments, R^2 is  .

[0107] In some embodiments of a compound of formula (I'), (I-A1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, X^1 and X^2 are each independently H, C_{1-6}alkyl, or C_{1-6}alkoxy. In some embodiments, X^1 and X^2 are each H.

[0108] In some embodiments of a compound of formula (I'), (I-A1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, X^3 and X^4 are each independently H, halo, C_{1-6}alkyl, C_{1-6}alkoxy, or 5-20 membered heteroaryl, wherein the C_{1-6}alkyl of X^3 and X^4 is optionally substituted with one of more halo.

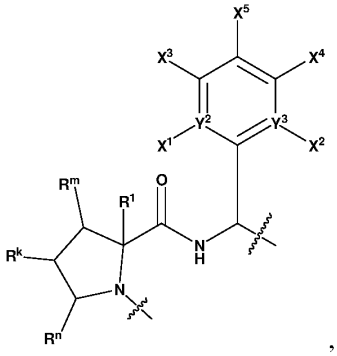
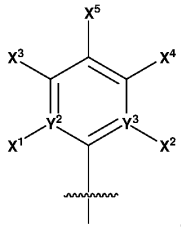
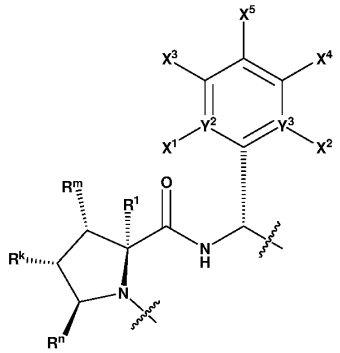
[0109] In some embodiments of a compound of formula (I'), (I-A1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, X^5 is H, C_{1-6}alkyl, C_{1-6}alkoxy, or C_{3-10}cycloalkyl. In some embodiments, X^5 is H, C_{1-4}alkyl, C_{1-3}alkoxy, or C_{3-6}cycloalkyl. In some embodiments, X^5 is H. In some embodiments, X^5 is isopropyl, n-butyl, iso-butyl or t-butyl.

[0110] In some embodiments of a compound of formula (I), X^1-X^5 are each H, and Q^1 is a 5-20 membered heteroaryl optionally substituted with one or more halo, C_{1-6}alkyl, -NH_2, or C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl. In some embodiments, X^1-X^5 are each H, and Q^1 is a 5-6 membered heteroaryl optionally substituted with one or more halo, C_{1-6}alkyl, -NH_2, or C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl. In some embodiments, X^1-X^5 are each H, and Q^1 is a pyridinyl optionally substituted with one or more halo, C_{1-6}alkyl, -NH_2, or C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl. In some embodiments, X^1-X^5 are each H, and Q^1 is a pyridinyl optionally substituted with one or more halo, C_{1-4}alkyl, -NH_2, or C_{3-4}cycloalkyl, wherein the C_{3-4}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl. In some embodiments of the foregoing, R^m is H and R^n is H. In some embodiments of the foregoing, R^1 is H. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

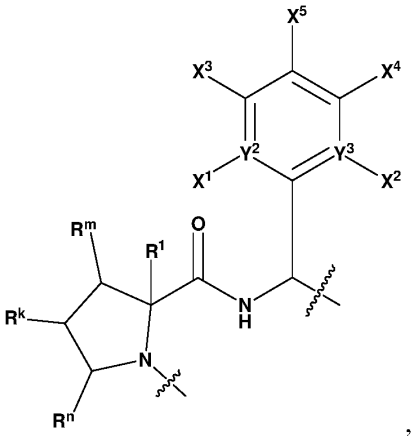
[0111] In some embodiments of a compound of formula (I), X^1-X^5 are each H, and Q^1 is phenyl substituted with one or more halo, C_{1-6}alkyl, C_{2-6} alkenyl, -NH_2, -NH-C(O)-(C_{1-6}alkyl), -NH-C(O)-(3-15 membered heterocyclyl), or C_{3-10}cycloalkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, and the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl. In some embodiments, X^1-X^5 are each H, and Q^1 is phenyl substituted with one or more halo, C_{1-6}alkyl, C_{2-6} alkenyl, -NH_2, -NH-C(O)-(C_{1-6}alkyl), -NH-C(O)-(3-10 membered heterocyclyl), or C_{3-10}cycloalkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, and the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl. In some embodiments, X^1-X^5 are each H, and Q^1 is phenyl substituted with one or more halo, C_{1-4}alkyl, C_{2-4} alkenyl, -NH_2, -NH-C(O)-(C_{1-4}alkyl), -NH-C(O)-(3-10 membered heterocyclyl), or C_{3-4}cycloalkyl, wherein the C_{1-4}alkyl is optionally substituted with one or more halo, and the C_{3-4}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

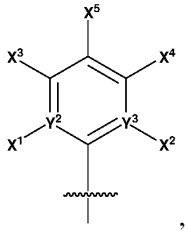
[0112] In some embodiments of the foregoing, R^1 is H. In some embodiments of the foregoing, R^m is H and R^n is H. In some embodiments of the foregoing, R^k is taken together with either R^m or R^n, and the atoms to which they are attached, to form cyclopropyl. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

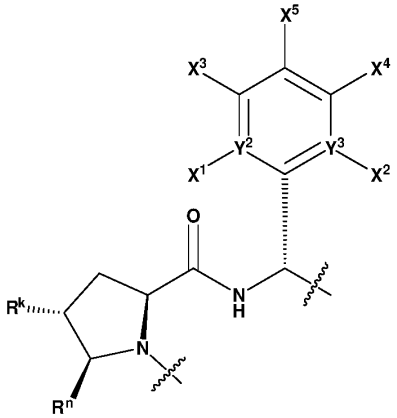
[0113] In some embodiments of a compound of formula (I') or (I), or any embodiment or variation thereof, such as a compound of formula (I-A), (I-A1), (I-A2), (I-A3), (I-A4), (I-B), (I-B1), (I-B2), (I-C), (I-D), (I-D1), (I-D2), (I-E), (I-F), (I-G), or (I-H), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing,

the moiety represented by  , with carbon atoms bearing moieties  , R^k, R^m, R^n, and R^1, has a stereochemical configuration of the formula  , wherein X^1, X^2, X^3, X^4, X^5, Y^2, Y^3, R^1, R^k, R^m, and R^n are as defined elsewhere herein.

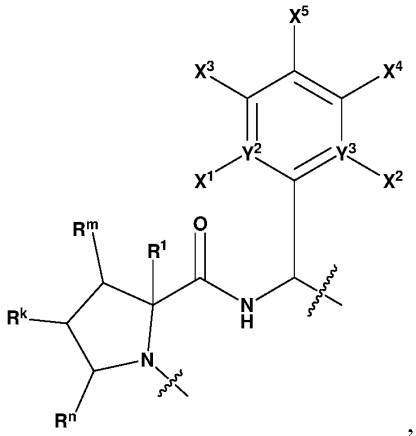
[0114] In some embodiments of a compound of formula (I') or (I), or any embodiment or variation thereof, such as a compound of formula (I-A), (I-A1), (I-A2), (I-A3), (I-A4), (I-B), (I-B1), (I-B2), (I-C), (I-D), (I-D1), (I-D2), (I-E), (I-F), (I-G), or (I-H), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing,

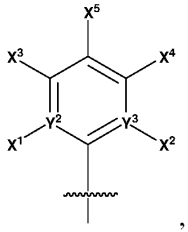
the moiety represented by  , with carbon atoms bearing

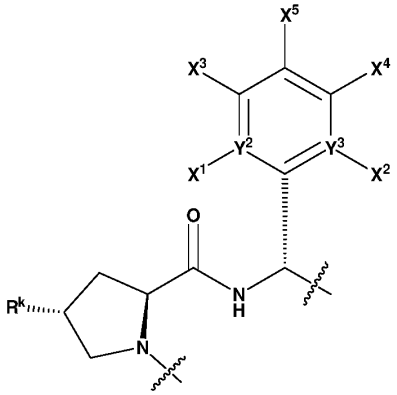
moieties  , R^k, R^m, R^n, and R^1, has a stereochemical configuration of the formula

 , wherein R^1 and R^m are both H, and X^1, X^2, X^3, X^4, X^5, Y^2, Y^3, R^k, and R^n are as defined elsewhere herein.

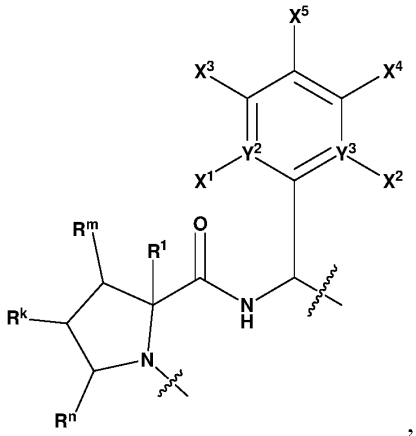
[0115] In some embodiments of a compound of formula (I') or (I), or any embodiment or variation thereof, such as a compound of formula (I-A), (I-A1), (I-A2), (I-A3), (I-A4), (I-B), (I-B1), (I-B2), (I-C), (I-D), (I-D1), (I-D2), (I-E), (I-F), (I-G), or (I-H), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing,

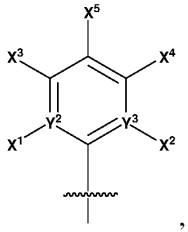
the moiety represented by  , with carbon atoms bearing

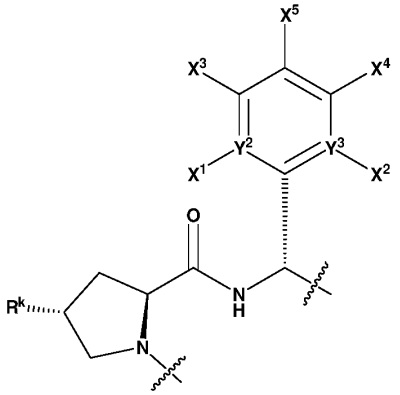
moieties  , R^k, R^m, R^n, and R^1, has a stereochemical configuration of the formula

 , wherein R^1, R^m, and R^n are each H, and X^1, X^2, X^3, X^4, X^5, Y^2, Y^3, and R^k are as defined elsewhere herein.

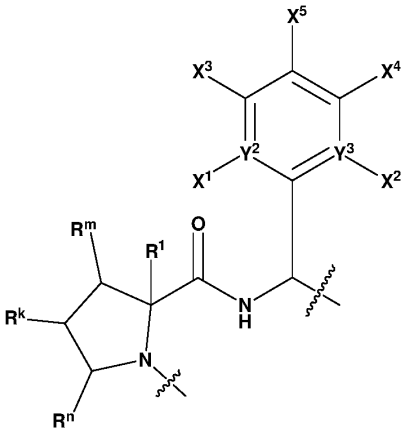
[0116] In some embodiments of a compound of formula (I') or (I), or any embodiment or variation thereof, such as a compound of formula (I-A), (I-A1), (I-A2), (I-A3), (I-A4), (I-B), (I-B1), (I-B2), (I-C), (I-D), (I-D1), (I-D2), (I-E), (I-F), (I-G), or (I-H), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing,

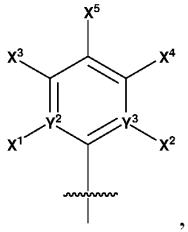
the moiety represented by  , with carbon atoms bearing

moieties  , R^k, R^m, R^n, and R^1, has a stereochemical configuration of the formula

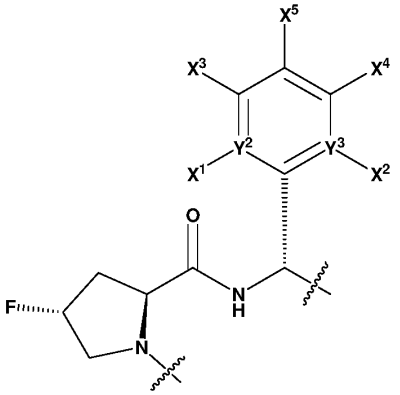
 , wherein R^1, R^m, and R^n are each H, R^k is halo or H , and X^1, X^2, X^3, X^4, X^5, Y^2, and Y^3 are as defined elsewhere herein. In some embodiments, the moiety R^k is fluoro.

[0117] In some embodiments of a compound of formula (I') or (I), or any embodiment or variation thereof, such as a compound of formula (I-A), (I-A1), (I-A2), (I-A3), (I-A4), (I-B), (I-B1), (I-B2), (I-C), (I-D), (I-D1), (I-D2), (I-E), (I-F), (I-G), or (I-H), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing,

the moiety represented by  with carbon atoms bearing

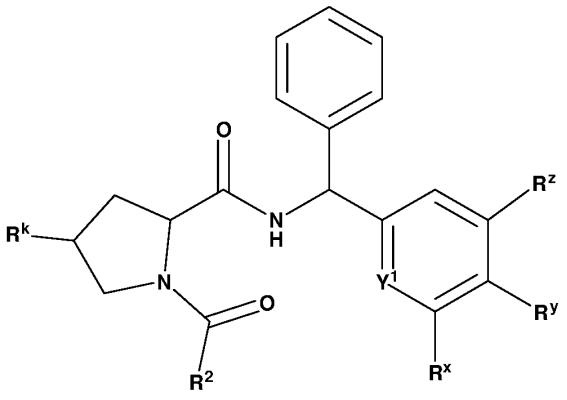


moieties , R^k, R^m, R^n, and R^1, has a stereochemical configuration of the formula



, wherein R^1, R^m, and R^n are each H, R^k is fluoro, and X^1, X^2, X^3, X^4, X^5, Y^2, and Y^3 are as defined elsewhere herein. In some embodiments Y^2 and Y^3 are each C. In some embodiments one Y^2 and Y^3 is C and the other of Y^2 and Y^3 is N.

[0118] In some embodiments, provided herein is a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (I-A):



(I-A),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Y^1 is CH or N; R^x and R^z are independently H, halo, C_{1-6}alkyl, or -NH_2, wherein, when Y^1 is CH, the C_{1-6}alkyl of R^x or R^z may be optionally substituted with one or more halo; and R^y is (i) C_{1-6}alkyl, (ii), C_{2-6}alkenyl, or (iii) C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl. In some variations, R^2, R^k, R^x, R^y, and R^z of formula (I-A1) are as defined for a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof, wherein Y^1 is CR^x or N; wherein, when the ring bearing R^x, R^y and R^z is phenyl, R^x, R^y and R^z is H, halo, C_{1-6}alkyl, C_{2-6}alkenyl, -NH_2, -NH-C(O)-(C_{1-6}alkyl), -NH-C(O)-(3-15 membered heterocyclyl), C_{3-10}cycloalkyl, or 5-20 membered heteroaryl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, -NH-C(O)-NH(C_{1-6}alkyl), -NH-C(O)-C_{1-6}alkyl, or -NH-C(O)-C_{1-6}alkoxy, the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl, and the 5-20 membered heteroaryl is optionally substituted with one or more C_{1-6}alkyl; and wherein when the ring bearing R^x, R^y and R^z is pyridyl, R^x, R^y and R^z are each indepdently H, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, -NH_2, or C_{3-10}cycloalkyl, wherein, the C_{1-6}alkyl is optionally substituted with one or more halo, and the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl.

[0119] In some embodiments of a compound of formula (I-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^x and R^z are independently H, fluoro, chloro, or methyl; and R^y is (i) isopropyl, (ii) isopropenyl, or (iii) C_{3-4}cycloalkyl, wherein the C_{3-4}cycloalkyl is optionally substituted with one or more fluoro or

methyl. In some embodiments, R^x and R^z are independently H, fluoro, chloro, or methyl; and R^y is (i) isopropyl or (ii) C_{3-4}cycloalkyl, wherein the C_{3-4}cycloalkyl is optionally substituted with one or more fluoro or methyl. In some embodiments, R^x is H, fluoro, chloro, or methyl; R^z is H; and R^y is (i) isopropyl, or (ii) C_{3-4}cycloalkyl, wherein the C_{3-4}cycloalkyl is optionally substituted with one or more fluoro or methyl. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

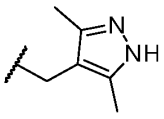
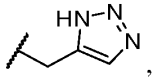
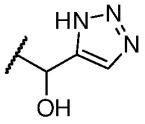
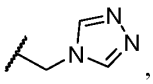
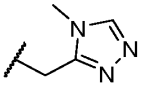
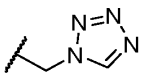
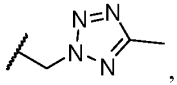
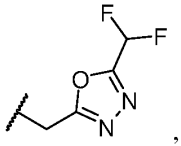
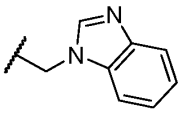
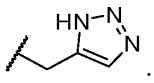
[0120] In some embodiments of a compound of formula (I'), (I-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^x is fluoro or methyl optionally substituted with one or more fluoro; R^y is (i) isopropyl (ii) isopropenyl or (iii) C_{3-4}cycloalkyl optionally substituted with one or more halo or C_{1-6}alkyl or (iv) butyl; and R^z is fluoro or methyl; provided that at least one of R^x and R^z is halo, CF_2 or CF_3.

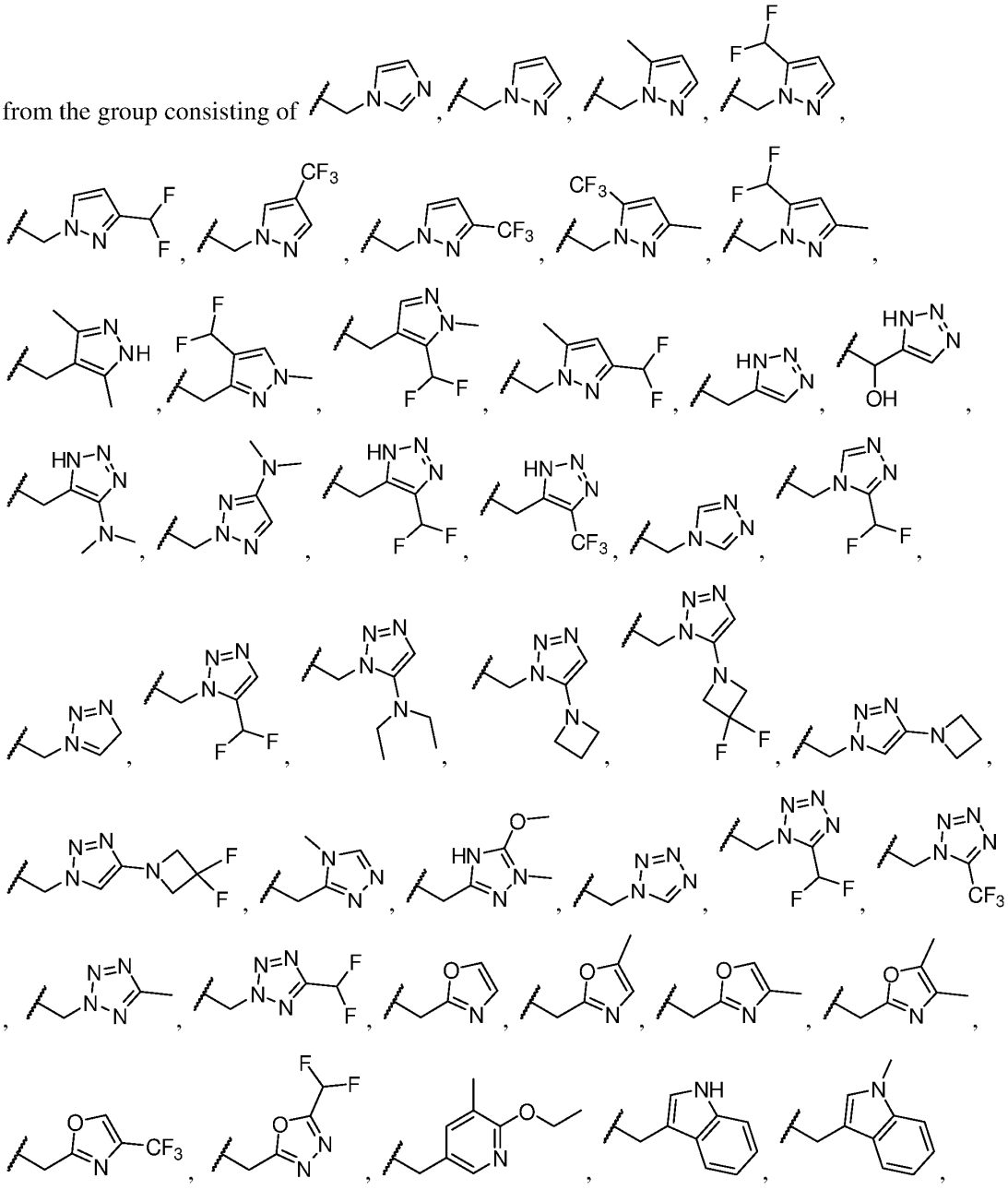
[0121] In some embodiments of a compound of formula (I-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^k is H or halo. In some embodiments of a compound of formula (I-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^k is H or fluoro. In some embodiments of a compound of formula (I-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^k is fluoro. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

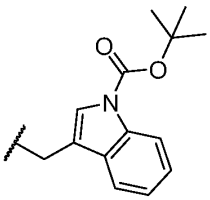
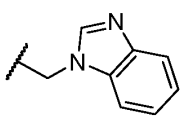
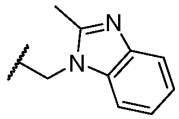
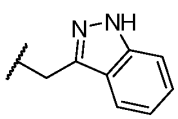
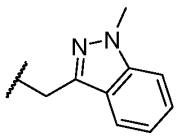
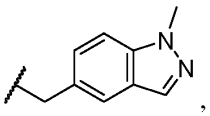
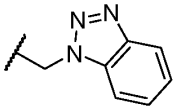
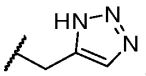
[0122] In some embodiments of a compound of formula (I-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is optionally substituted with one or more R^a. In some embodiments, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^a is optionally substituted with one or more R^b. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl of R^a is optionally substituted with one or more R^b. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein

R^a is -OH or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl of R^a is optionally substituted with one or more C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, -NH-C(O)C_{1-6}alkyl, or -NH-C(O)-C_{1-6}alkoxy. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl of R^a is optionally substituted with one or more methyl, wherein the methyl is optionally substituted with one or more fluoro.

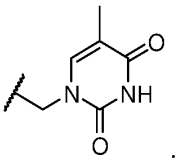
[0123] In some embodiments of a compound of formula (I'), (I-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is 5-20 membered heteroaryl or -(C_{1-4}alkyl)(5-20 membered heteroaryl), wherein the C_{1-4} alkyl is optionally substituted with one or more or more –OH, halo, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, and wherein the 5-20 membered heteroaryl is optionally substituted with one or more R^s. In some embodiments, R^s is halo, C_{1-6}alkyl, C_{1-6}alkoxy, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, -NH-C(O)-C_{1-6}alkyl, C_{6-20}aryl, C_{3-10}cycloalkyl, 3-15 membered heterocyclyl, 5-20 membered heteroaryl, or -C(O)-C_{1-6}alkoxy. In some embodiments, the C_{1-6}alkyl of R^s is optionally substituted with one or more halo, C_{1-6}alkoxy, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, -NH-C(O)C_{1-6}alkyl, or -NH-C(O)-C_{1-6}alkoxy, and the 3-15-membered heterocyclyl of R^s is optionally substituted with one or more halo or -C(O)-C_{1-6}alkoxy.

[0124] In some embodiments of a compound of formula (I-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  , and  . In some embodiments, R^2 is  .

[0125] In some embodiments of a compound of formula (I'), (I-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is selected from the group consisting of 

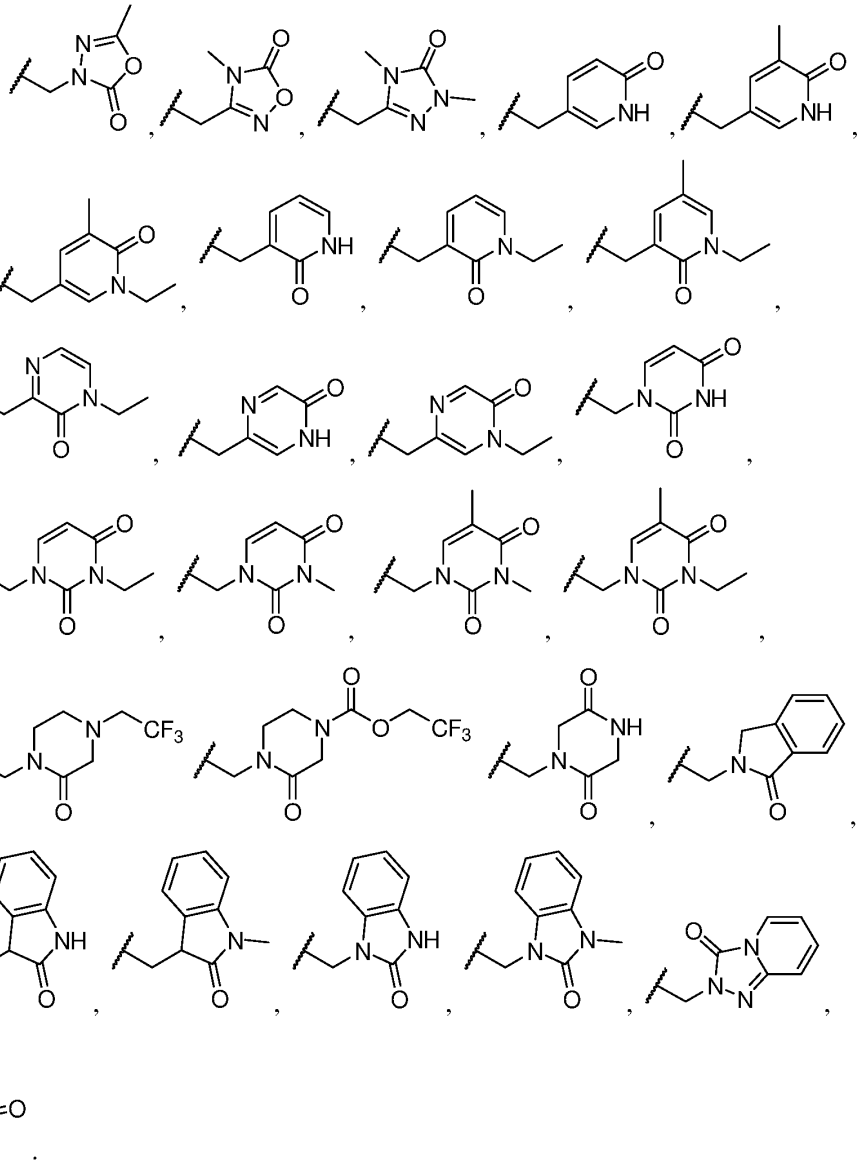
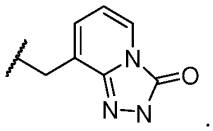









[0126] In some embodiments of a compound of formula (I-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^a is optionally substituted with one or more R^c. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^a is optionally substituted with one or more R^c. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-8 membered heterocyclyl, wherein the 3-8 membered heterocyclyl of R^a is optionally substituted with one or more R^c. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-8 membered heterocyclyl, wherein the 3-8 membered heterocyclyl of R^a is optionally substituted with one or more oxo or C_{1-6}alkyl. In some embodiments, R^2 is

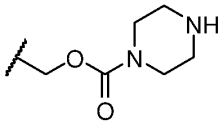


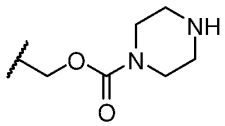
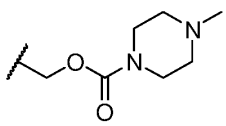
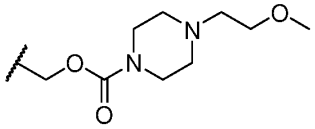
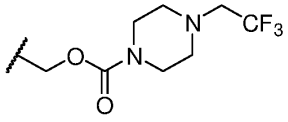
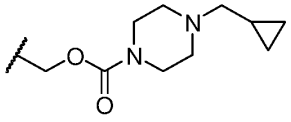
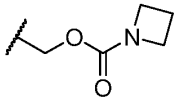
. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

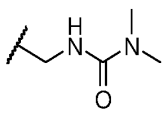
[0127] In some embodiments of a compound of formula (I'), (I-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-8 membered heterocyclyl, wherein the 3-8 membered heterocyclyl of R^a is optionally substituted with one or more R^c, wherein R^c is oxo, C_{1-6}alkyl, or -C(O)-C_{1-6}alkoxy, wherein the

C_{1-6}alkyl of R^c is optionally substituted with one or more halo , and the -C(O)-C_{1-6}alkoxy of R^c is optionally substituted with one or more halo. In some embodiments, R^2 is selected from the group consisting of 
and  .

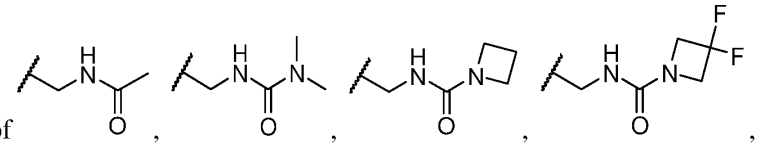
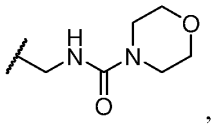
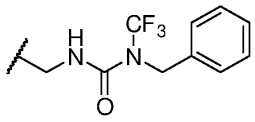
[0128] In some embodiments of a compound of formula (I-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein

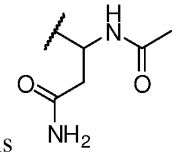
R^a is -O-R^e. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e, wherein R^e is -C(O)-(3-15 membered heterocyclyl). In some embodiments, R^2 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0129] In some embodiments of a compound of formula (I'), (I-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e, wherein R^e is -C(O)-(3-15 membered heterocyclyl) wherein the -C(O)-(3-15 membered heterocyclyl) of R^e is optionally substituted with one or more C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, C_{1-6}alkoxy, or C_{3-10}cycloalkyl. In some embodiments, R^2 is selected from the group consisting of  ,  ,  ,  ,  , and  .

[0130] In some embodiments of a compound of formula (I-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is -N(R^c)(R^d). In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -N(R^c)(R^d). In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -N(R^c)(R^d), wherein one of R^c and R^d is H, and the other of R^c and R^d is -C(O)-N(C_{1-6}alkyl)$_2$. In some embodiments, R^2 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I') or a

stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0131] In some embodiments of a compound of formula (I'), (I-A1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -$N(R^c)(R^d)$, wherein one of R^c and R^d is H, and the other of R^c and R^d, -C(O)-C_{1-6}alkyl, -C(O)-$N(C_{1-6}alkyl)_2$, or -C(O)-(3-15 membered heterocyclyl). In some embodiments, R^2 is selected from the group consisting of  ,  , and  .

[0132] In some embodiments of a compound of formula (I'), (I-A1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is ethyl, wherein the ethyl of R^2 is substituted with one or more R^a, wherein R^a is -$N(R^c)(R^d)$, wherein one of R^c and R^d is H, and the other of R^c and R^d , is -C(O)-C_{1-6}alkyl. In some embodiments, R^2 is  .

[0133] In some embodiments of a compound of formula (I-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, Y^1 is CH or N; R^x and R^z are independently H or halo; R^y is C_{1-6}alkyl or C_{3-10}cycloalkyl; R^k is H or halo; and R^2 is selected from (i) to (iii):

(i) C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is

(a) -OH,

(b) C_{6-20}aryl, wherein the C_{6-20}aryl of R^a is optionally substituted with one or more halo, cyano, C_{1-6}alkoxy, or -NH-C(O)-C_{1-6}alkyl,

(c) 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^a is optionally substituted with one or more R^c, wherein

R^c is halo, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, or -C(O)-C_{1-6}alkoxy, wherein

the C_{1-6}alkyl of R^c is optionally substituted with one or more halo or C_{2-6}alkynyl, and

the -C(O)-C_{1-6}alkoxy of R^c is optionally substituted with one or more halo,

(d) -N(R^c)(R^d), wherein R^c and R^d of N(Rc)(Rd) are, independently of each other, H, C_{1-6}alkyl,
-C(O)-C_{1-6}alkyl, -C(O)-C_{1-6}alkoxy, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -C(O)-(3-15 membered heterocyclyl), -CH_2-C(O)-NH_2, 3-15 membered heterocyclyl, or 5-20 membered heteroaryl, wherein

the C_{1-6}alkyl of R^c or R^d is optionally substituted with one or more -C(O)-NH_2,

the -C(O)-C_{1-6}alkyl of R^c or R^d is optionally substituted with one or more halo,

the 3-15 membered heterocyclyl and the 5-20 membered heteroaryl of R^c or R^d are independently optionally substituted with one or more C_{1-6}alkyl,

the -C(O)-(3-15 membered heterocyclyl) of R^c or R^d is optionally substituted with one or more halo, -C(O)-C_{1-6}alkoxy, or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, C_{1-6}alkoxy, or C_{3-10}cycloalkyl, and

the C_{1-6}alkyl of the -C(O)-N(C_{1-6}alkyl)$_2$ of R^c or R^d are, independently of each other, optionally substituted with one or more halo or C_{6-20}aryl,

(e) -O-R^e, wherein R^e is C_{1-6}alkyl, C_{6-20}aryl, -C(O)-(3-15 membered heterocyclyl), -C(O)-N-(C_{1-6}alkyl)$_2$, or 5-20 membered heteroaryl, wherein

the C_{1-6}alkyl of R^e is optionally substituted with one or more C_{1-6}alkoxy, wherein the C_{1-6}alkoxy is optionally substituted with one or more C_{2-6}alkynyl,

the C_{6-20}aryl of R^e is optionally substituted with one or more C_{1-6}alkyl, and

the -C(O)-(3-15 membered heterocyclyl) of R^e is optionally substituted with one or more C_{1-6}alkyl, C_{1-6}alkoxy, or -C(O)-C_{1-6}alkoxy, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, C_{1-6}alkoxy, or C_{3-10}cycloalkyl, or

(f) -C(O)-R^e, wherein R^e of -C(O)-R^e is $-NH_2$, -OH, or 3-15 membered heterocyclyl,

(ii) 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^2 is optionally substituted with one or more halo, oxo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, or 5-20 membered heteroaryl,

(iii) 5-20 membered heteroaryl or -(C_{1-4}alkyl)(5-20 membered heteroaryl), wherein the C_{1-4} alkyl is optionally substituted with one or more or more –OH, halo, $-NH_2$, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, and wherein the 5-20 membered heteroaryl is optionally substituted with one or more R^s, wherein

R^s is halo, C_{1-6}alkyl, C_{1-6}alkoxy, $-NH_2$, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, -NH-C(O)-C_{1-6}alkyl, C_{6-20}aryl, C_{3-10}cycloalkyl, 3-15 membered heterocyclyl, 5-20 membered heteroaryl, or -C(O)-C_{1-6}alkoxy, wherein

the C_{1-6}alkyl of R^s is optionally substituted with one or more halo, C_{1-6}alkoxy, $-NH_2$, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, -NH-C(O)C_{1-6}alkyl, or -NH-C(O)-C_{1-6}alkoxy, and

the 3-15-membered heterocyclyl of R^s is optionally substituted with one or more halo or -C(O)-C_{1-6}alkoxy.

[0134] In some embodiments of formula (I-A), Y^1 is CH or N; R^x and R^z are independently H or halo; R^y is C_{1-6}alkyl or C_{3-10}cycloalkyl; R^k is H or halo; R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a; R^a is

(a) -OH,

(b) C_{6-10}aryl optionally substituted with one or more halo, cyano, C_{1-3}alkoxy, or -NH-C(O)-C_{1-3}alkyl, or

(c) 3-15 membered heterocyclyl optionally substituted with one or more halo, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, or -C(O)-C_{1-6}alkoxy.

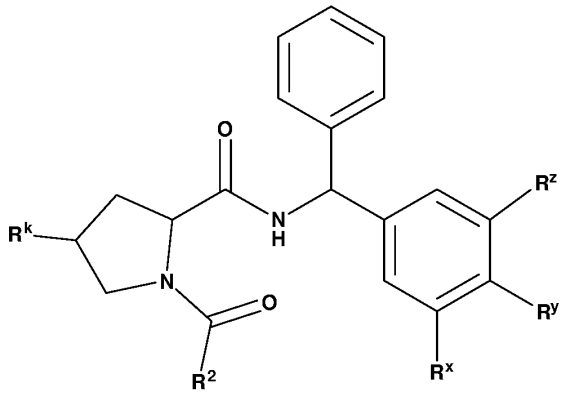
[0135] In some embodiments of formula (I-A), Y^1 is CH or N; R^x and R^z are independently H or halo; R^y is C_{1-3}alkyl or C_{3-5}cycloalkyl; R^k is halo; R^2 is C_{1-4}alkyl substituted with one or more R^a; R^a is

(a) -OH,

(b) C_{6-10}aryl optionally substituted with one or more halo, cyano, C_{1-3}alkoxy, or -NH-C(O)-C_{1-3}alkyl, or

(c) C_{3-8}heteroaryl optionally substituted with one or more halo, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, or -C(O)-C_{1-6}alkoxy.

[0136] In some embodiments, provided herein is a compound of formula (I) or formula (I-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein the compound is of formula (I-A1):



(I-A1),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^x and R^z are independently H, halo, C_{1-6}alkyl, or $-NH_2$, wherein the C_{1-6}alkyl is optionally substituted with one or more halo. In some embodiments, R^x is H, halo, or C_{1-6}alkyl; R^y is (i) C_{1-6}alkyl, (ii) C_{2-6}alkenyl, or (ii) C_{3-10}cycloalkyl; and R^z is H, halo or C_{1-6}alkyl. In

some embodiments, R^z is H. In some embodiments, at least one of R^x and R^z is halo. In some variations, R^2, R^k, R^x, R^y, and R^z of formula (I-A1) are as defined for a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof, wherein R^x, $R^y$and R^z are independently H, halo, C_{1-6}alkyl, C_{2-6}alkenyl, -NH_2, -NH-C(O)-(C_{1-6}alkyl), -NH-C(O)-(3-15 membered heterocyclyl), C_{3-10}cycloalkyl, or 5-20 membered heteroaryl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, -NH-C(O)-NH(C_{1-6}alkyl), -NH-C(O)-C_{1-6}alkyl, or -NH-C(O)-C_{1-6}alkoxy, the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl, and the 5-20 membered heteroaryl is optionally substituted with one or more C_{1-6}alkyl. In some embodiments, R^x is H, halo, or C_{1-6}alkyl optionally substituted with one or more halo; R^y is (i) C_{1-6}alkyl, (ii) C_{2-6}alkenyl, (iii) C_{3-10}cycloalkyl optionally substituted with one or more halo or C_{1-6}alkyl or (iv) butyl; and R^z is H, halo or C_{1-6}alkyl. In some embodiments, R^z is H. In some embodiments, at least one of R^x and R^z is halo or C_{1-6}alkyl optionally substituted with one or more halo.

[0137] In some embodiments of a compound of formula (I-A1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^x is fluoro or methyl; R^y is (i) isopropyl or (ii) C_{3-4}cycloalkyl; and R^z is fluoro or methyl; provided that at least one of R^x and R^z is halo. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0138] In some embodiments of a compound of formula (I'), (I-A1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^x is fluoro or methyl optionally substituted with one or more fluoro; R^y is (i) isopropyl (ii) C_{3-4}cycloalkyl optionally substituted with one or more halo or C_{1-6}alkyl or (iii) butyl; and R^z is fluoro or methyl; provided that at least one of R^x and R^z is halo, CF_2 or CF_3.

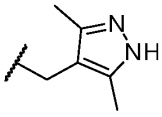
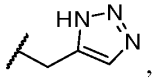
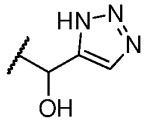
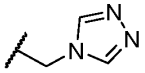
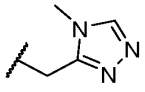
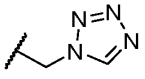
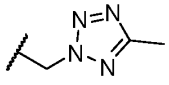
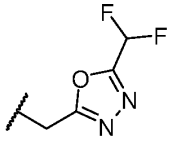
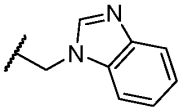
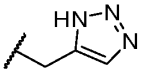
[0139] In some embodiments of a compound of formula (I-A1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^k is H or halo. In some embodiments of a compound of formula (I-A1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^k is H or fluoro. In some embodiments of a compound of formula (I-A1), or a stereoisomer or tautomer thereof, or a

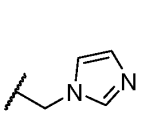
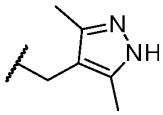
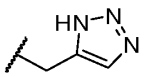
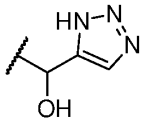
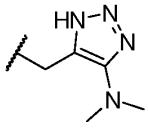
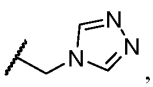
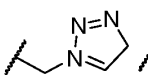
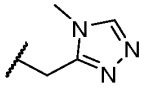
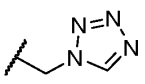
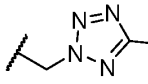
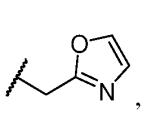
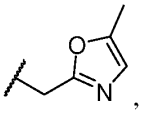
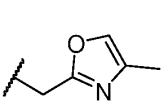
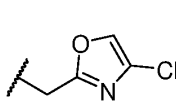
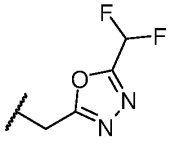
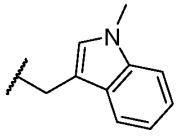
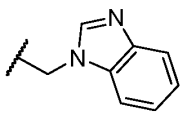
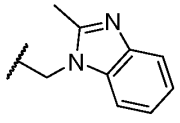
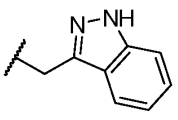
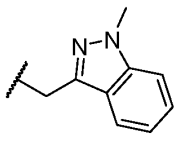
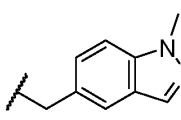
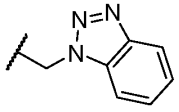
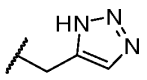
pharmaceutically acceptable salt of any of the foregoing, R^k is fluoro. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0140] In some embodiments of a compound of formula (I-A1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is optionally substituted with one or more R^a. In some embodiments, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^a is optionally substituted with one or more R^b. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl of R^a is optionally substituted with one or more R^b. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl of R^a is optionally substituted with one or more C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, $-NH_2$, $-NH(C_{1-6}alkyl)$, $-N(C_{1-6}alkyl)_2$, $-NH-C(O)C_{1-6}$alkyl, or $-NH-C(O)-C_{1-6}$alkoxy. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl of R^a is optionally substituted with one or more methyl, wherein the methyl is optionally substituted with one or more fluoro.

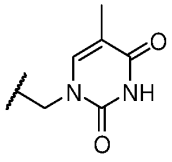
[0141] In some embodiments of a compound of formula (I'), (I-A1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is 5-20 membered heteroaryl or $-(C_{1-4}alkyl)$(5-20 membered heteroaryl), wherein the C_{1-4} alkyl is optionally substituted with one or more or more –OH, halo, $-NH_2$, $-NH(C_{1-6}alkyl)$, $-N(C_{1-6}alkyl)_2$, and wherein the 5-20 membered heteroaryl is optionally substituted with one or more R^s. In some embodiments, R^s is halo, C_{1-6}alkyl, C_{1-6}alkoxy, $-NH_2$, $-NH(C_{1-6}alkyl)$, $-N(C_{1-6}alkyl)_2$, $-NH-C(O)-C_{1-6}$alkyl, C_{6-20}aryl, C_{3-10}cycloalkyl, 3-15 membered heterocyclyl, 5-20 membered heteroaryl, or $-C(O)-C_{1-6}$alkoxy. In some embodiments, the C_{1-6}alkyl of R^s is optionally substituted with one or more halo, C_{1-6}alkoxy, $-NH_2$, $-NH(C_{1-6}alkyl)$, $-N(C_{1-6}alkyl)_2$, -NH-

C(O)C_{1-6}alkyl, or -NH-C(O)-C_{1-6}alkoxy, and the 3-15-membered heterocyclyl of R^s is optionally substituted with one or more halo or -C(O)-C_{1-6}alkoxy.

[0142] In some embodiments of a compound of formula (I-A1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  , and  . In some embodiments, R^2 is  .

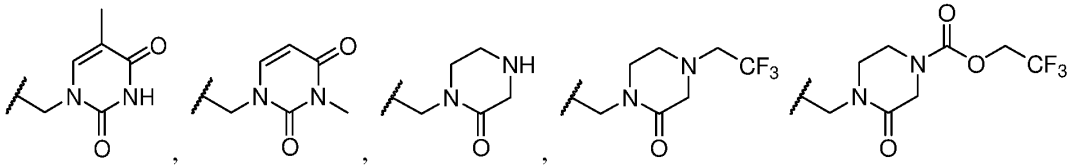
[0143] In some embodiments of a compound of formula (I'), (I-A1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  . In some embodiments, R^2 is  .

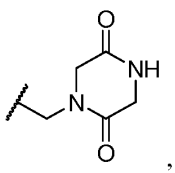
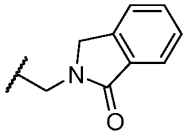
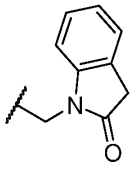
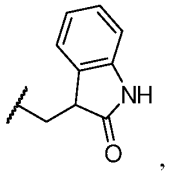
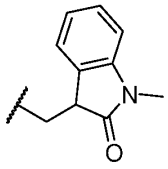
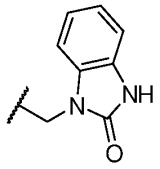
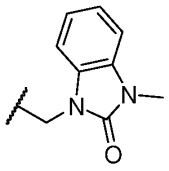
[0144] In some embodiments of a compound of formula (I-A1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^a is optionally substituted with one or more R^c. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^a is optionally substituted with one or more R^c. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-8 membered heterocyclyl, wherein the 3-8 membered heterocyclyl of R^a is optionally substituted with one or more R^c. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-8 membered heterocyclyl, wherein the 3-8 membered heterocyclyl of R^a is optionally substituted with one or more oxo or C_{1-6}alkyl. In some embodiments, R^2 is

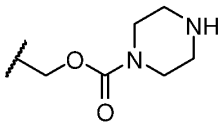


. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

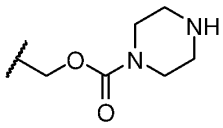
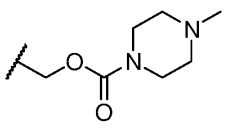
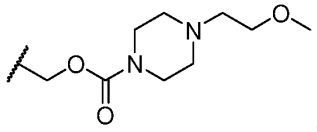
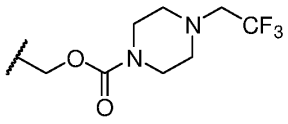
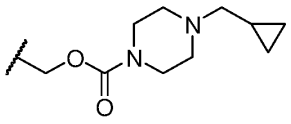
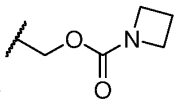
[0145] In some embodiments of a compound of formula (I'), (I-A1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-8 membered heterocyclyl, wherein the 3-8 membered heterocyclyl of R^a is optionally substituted with one or more R^c, wherein R^c is oxo, C_{1-6}alkyl, or -C(O)-C_{1-6}alkoxy, wherein the C_{1-6}alkyl of R^c is optionally substituted with one or more halo , and the -C(O)-C_{1-6}alkoxy of R^c is optionally substituted with one or more halo. In some embodiments, R^2 is

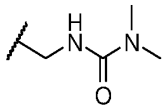


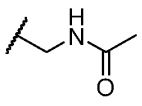
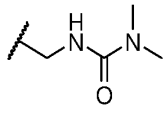
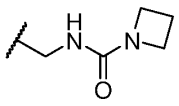
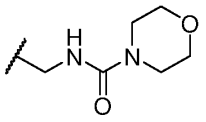






, or

.

[0146] In some embodiments of a compound of formula (I-A1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e, wherein R^e is -C(O)-(3-15 membered heterocyclyl). In some embodiments, R^2 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0147] In some embodiments of a compound of formula (I'), (I-A1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e, wherein R^e is -C(O)-(3-15 membered heterocyclyl) wherein the -C(O)-(3-15 membered heterocyclyl) of R^e is optionally substituted with one or more C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, C_{1-6}alkoxy, or C_{3-10}cycloalkyl. In some

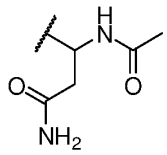
embodiments, R^2 is  ,  ,  ,  ,  , or  .

[0148] In some embodiments of a compound of formula (I-A1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is $C_{1\text{-}6}$alkyl, wherein the $C_{1\text{-}6}$alkyl of R^2 is substituted with one or more R^a, wherein R^a is $-N(R^c)(R^d)$. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is $-N(R^c)(R^d)$. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is $-N(R^c)(R^d)$, wherein one of R^c and R^d is H, and the other of R^c and R^d is $-C(O)-N(C_{1\text{-}6}alkyl)_2$. In some embodiments, R^2 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0149] In some embodiments of a compound of formula (I') (I-A1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is $-N(R^c)(R^d)$, wherein one of R^c and R^d is H, and the other of R^c and R^d, $-C(O)-C_{1\text{-}6}$alkyl, $-C(O)-N(C_{1\text{-}6}alkyl)_2$, or -C(O)-(3-15 membered heterocyclyl). In some embodiments, R^2 is  ,  ,  , or  .

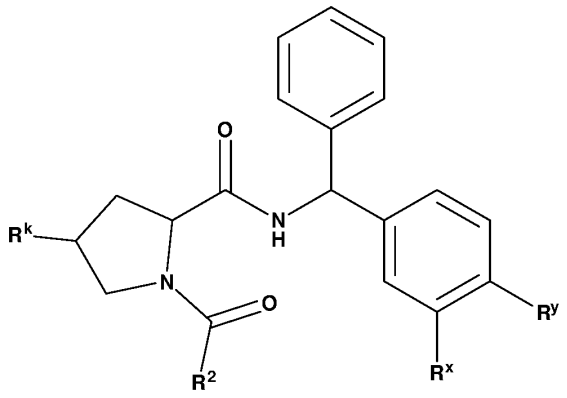
[0150] In some embodiments of a compound of formula (I') (I-A1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is ethyl,

wherein the ethyl of R^2 is substituted with one or more R^a, wherein R^a is $-N(R^c)(R^d)$, wherein one of R^c and R^d is H, and the other of R^c and R^d , is $-C(O)-C_{1-6}$alkyl. In some embodiments, R^2 is



.

[0151] In some embodiments, provided is a compound of formula (I) or formula (I-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is a compound of formula (I-A2):



(I-A2),

[0152] or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^x is H, halo, C_{1-6}alkyl, or $-NH_2$, wherein the C_{1-6}alkyl is optionally substituted with one or more halo; and R^y is (i) C_{1-6}alkyl, (ii), C_{2-6}alkenyl, or (iii) C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl. In some embodiments, R^x is H, halo, or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo; and R^y is (i), C_{1-6}alkyl, (ii) C_{2-6}alkenyl, or (iii) C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl. In some embodiments, R^x is H, halo, or C_{1-6}alkyl; and R^y is (i) C_{1-6}alkyl, (ii) C_{2-6}alkenyl, or (iii) C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl. In some variations, R^2, R^k, R^x, and R^y of formula (I-A2) are as defined for a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof, wherein R^x and R^y are each independently H, halo, C_{1-6}alkyl, C_{2-6}alkenyl, $-NH_2$, $-NH-C(O)-(C_{1-6}$alkyl), $-NH-C(O)-$(3-15

membered heterocyclyl), C_{3-10}cycloalkyl, or 5-20 membered heteroaryl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, -NH-C(O)-NH(C_{1-6}alkyl), -NH-C(O)-C_{1-6}alkyl, or -NH-C(O)-C_{1-6}alkoxy, the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl, and the 5-20 membered heteroaryl is optionally substituted with one or more C_{1-6}alkyl. In some embodiments, R^x is H, halo, or C_{1-6}alkyl optionally substituted with one or more halo; and R^y is (i) C_{1-6}alkyl, (ii) C_{3-10}cycloalkyl optionally substituted with one or more halo or C_{1-6}alkyl or (iii) butyl.

[0153] In some embodiments of a compound of formula (I-A2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^x is H, fluoro, chloro, or methyl, wherein the methyl is optionally substituted with one or more fluoro; and R^y is (i) isopropyl, (ii) isopropenyl, (iii) sec-butyl, (iv) tert-butyl, or (v) C_{3-4}cycloalkyl, wherein the C_{3-4}cycloalkyl is optionally substituted with one or more fluoro or methyl. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

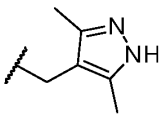
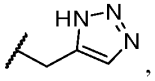
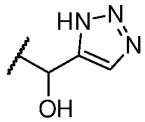
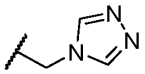
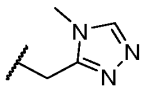
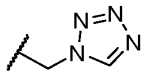
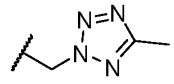
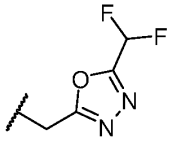
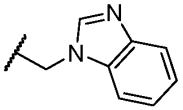
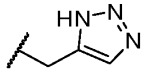
[0154] In some embodiments of a compound of formula (I'), (I-A2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^x is fluoro or methyl optionally substituted with one or more fluoro; and R^y is (i) isopropyl (ii) C_{3-4}cycloalkyl optionally substituted with one or more halo or C_{1-6}alkyl or (iii) butyl.

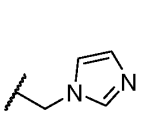
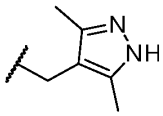
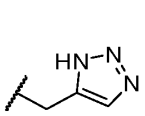
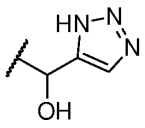
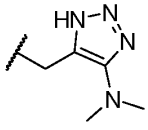
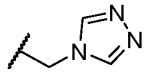
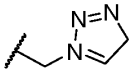
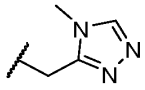
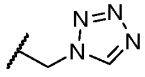
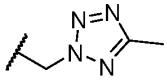
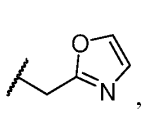
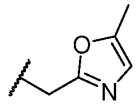
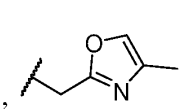
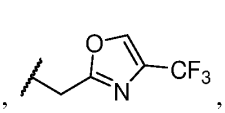
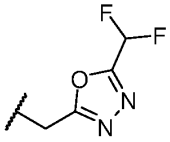
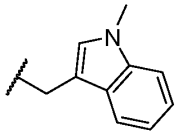
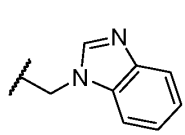
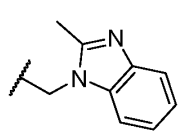
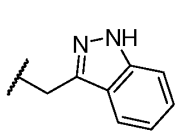
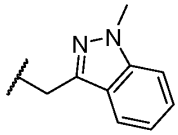
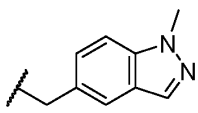
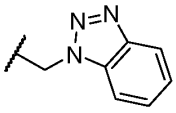
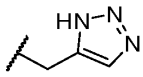
[0155] In some embodiments of a compound of formula (I-A2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^k is H or halo. In some embodiments of a compound of formula (I-A2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^k is H or fluoro. In some embodiments of a compound of formula (I-A2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^k is fluoro. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0156] In some embodiments of a compound of formula (I-A2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is optionally substituted with one or more R^a. In some embodiments, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^a is optionally substituted with one or more R^b. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl of R^a is optionally substituted with one or more R^b. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl of R^a is optionally substituted with one or more C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, $-NH_2$, $-NH(C_{1-6}alkyl)$, $-N(C_{1-6}alkyl)_2$, $-NH-C(O)C_{1-6}$alkyl, or $-NH-C(O)-C_{1-6}$alkoxy. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl of R^a is optionally substituted with one or more methyl, wherein the methyl is optionally substituted with one or more fluoro.

[0157] In some embodiments of a compound of formula (I'), (I-A2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is $-(C_{1-4}alkyl)$(5-20 membered heteroaryl), wherein the C_{1-4} alkyl is optionally substituted with one or more or more –OH, and wherein the 5-20 membered heteroaryl is optionally substituted with one or more R^s. In some embodiments, R^s is halo, C_{1-6}alkyl, C_{1-6}alkoxy, $-NH_2$, $-NH(C_{1-6}alkyl)$, $-N(C_{1-6}alkyl)_2$, $-NH-C(O)-C_{1-6}$alkyl, C_{6-20}aryl, C_{3-10}cycloalkyl, 3-15 membered heterocyclyl, 5-20 membered heteroaryl, or $-C(O)-C_{1-6}$alkoxy. In some embodiments, the C_{1-6}alkyl of R^s is optionally substituted with one or more halo, C_{1-6}alkoxy, $-NH_2$, $-NH(C_{1-6}alkyl)$, $-N(C_{1-6}alkyl)_2$, $-NH-C(O)C_{1-6}$alkyl, or $-NH-C(O)-C_{1-6}$alkoxy, and the 3-15-membered heterocyclyl of R^s is optionally substituted with one or more halo or $-C(O)-C_{1-6}$alkoxy.

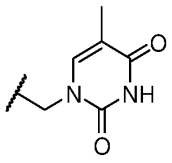
[0158] In some embodiments of a compound of formula (I-A2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is selected

from the group consisting of  ,  ,  ,  ,  ,  ,  ,  , and  . In some embodiments, R^2 is  .

[0159] In some embodiments of a compound of formula (I'), (I-A2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  . In some embodiments, R^2 is  .

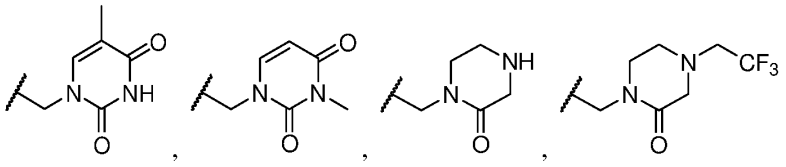
[0160] In some embodiments of a compound of formula (I-A2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is $C_{1\text{-}6}$alkyl, wherein the $C_{1\text{-}6}$alkyl of R^2 is substituted with one or more R^a, wherein R^a is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^a is optionally substituted with one or

more R^c. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^a is optionally substituted with one or more R^c. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-8 membered heterocyclyl, wherein the 3-8 membered heterocyclyl of R^a is optionally substituted with one or more R^c. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-8 membered heterocyclyl, wherein the 3-8 membered heterocyclyl of R^a is optionally substituted with one or more oxo or C_{1-6}alkyl. In some embodiments, R^2 is

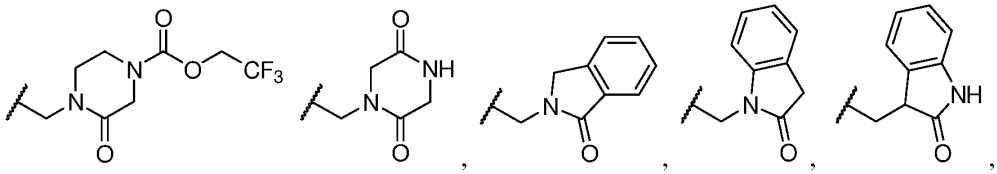


. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

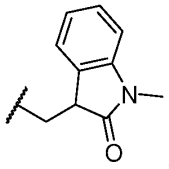
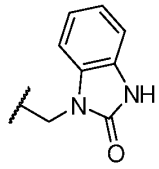
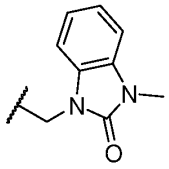
[0161] In some embodiments of a compound of formula (I'), (I-A2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-8 membered heterocyclyl, wherein the 3-8 membered heterocyclyl of R^a is optionally substituted with one or more R^c, wherein R^c is oxo, C_{1-6}alkyl, or -C(O)-C_{1-6}alkoxy, wherein the C_{1-6}alkyl of R^c is optionally substituted with one or more halo , and the -C(O)-C_{1-6}alkoxy of R^c is optionally substituted with one or more halo. In some embodiments, R^2 is selected from the group consisting of



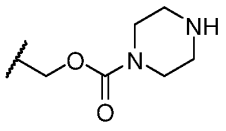
,



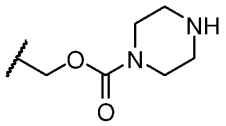
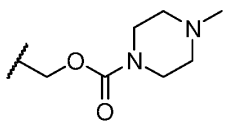
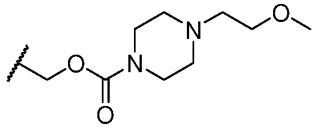
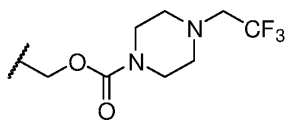
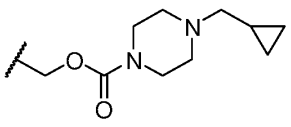
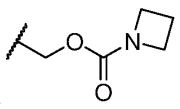
,

, , and .In some embodiments of a compound of formula (I-A2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e, wherein R^e is -C(O)-(3-15 membered heterocyclyl). In some embodiments, R^2 is

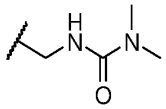


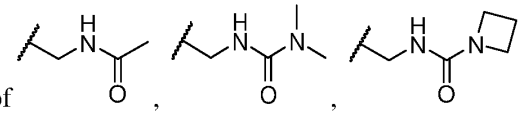
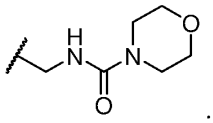
. In some embodiments of a compound of formula (I'), (I-A2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e, wherein R^e is -C(O)-(3-15 membered heterocyclyl)wherein the -C(O)-(3-15 membered heterocyclyl) of R^e is optionally substituted with one or more C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, C_{1-6}alkoxy, or C_{3-10}cycloalkyl. In some embodiments, R^2 is selected from the group consisting of

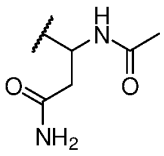







, , , , , and .

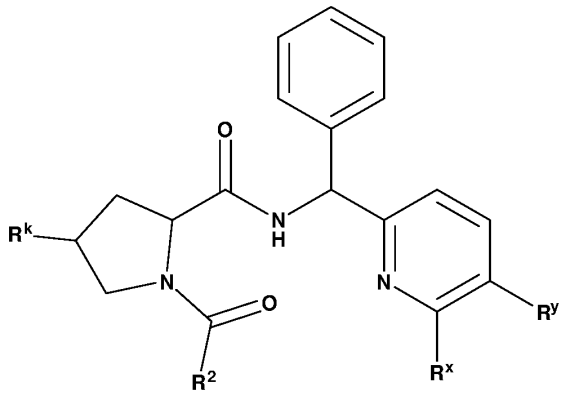
[0162] In some embodiments of a compound of formula (I-A2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is -N(R^c)(R^d). In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -N(R^c)(R^d). In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -N(R^c)(R^d), wherein one of R^c and R^d is H, and the other of



R^c and R^d is -C(O)-N(C_{1-6}alkyl)$_2$. In some embodiments, R^2 is . In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.In some embodiments of a compound of formula (I'), (I-A2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -N(R^c)(R^d), wherein one of R^c and R^d is H, and the other of R^c and R^d, -C(O)-C_{1-6}alkyl, -C(O)-N(C_{1-6}alkyl)$_2$, or -C(O)-(3-15 membered heterocyclyl). In some embodiments, R^2 is selected from the group consisting of  , and  .

[0163] In some embodiments of a compound of formula (I') (I-A2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is ethyl, wherein the ethyl of R^2 is substituted with one or more R^a, wherein R^a is -N(R^c)(R^d), wherein one of R^c and R^d is H, and the other of R^c and R^d , is -C(O)-C_{1-6}alkyl. In some embodiments, R^2 is  .

[0164] In some embodiments, provided herein is a compound of formula (I) or formula (I-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is a compound of formula (I-A3):



(I-A3),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^x is H, halo, C_{1-6}alkyl, or -NH_2, wherein the C_{1-6}alkyl is optionally substituted with one or more halo; and R^y is (i) C_{1-6}alkyl, (ii), C_{2-6}alkenyl, or (iii) C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl. In some embodiments, R^x is H, halo, C_{1-6}alkyl, or -NH_2; and R^y is (i) C_{1-6}alkyl or (ii) C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl. In some variations, R^2, R^k, R^x, and R^y of formula (I-A3) are as defined for a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof, wherein R^x and R^y are each independently H, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, -NH_2, or C_{3-10}cycloalkyl, wherein, the C_{1-6}alkyl is optionally substituted with one or more halo, and the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl,. In some embodiments, R^x is H, halo, C_{1-6}alkyl, or -NH_2; and R^y is (i) C_{1-6}alkyl or (ii) C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl.

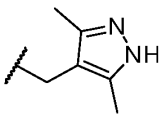
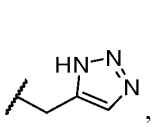
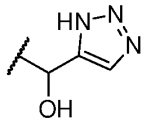
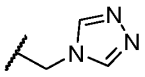
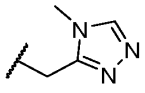
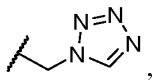
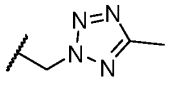
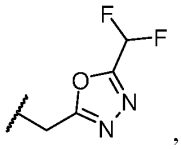
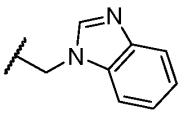
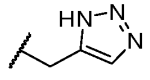
[0165] In some embodiments of a compound of formula (I-A3), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^x is H, fluoro, or methyl; and R^y is (i) H, (ii) isopropyl, (iii) tert-butyl, or (iv) C_{3-4}cycloalkyl, wherein the C_{3-4}cycloalkyl is optionally substituted with one or more fluoro or methyl. In some embodiments, R^x is H, fluoro, or methyl; and R^y is (i) isopropyl or (ii) C_{3-4}cycloalkyl, wherein the C_{3-4}cycloalkyl is optionally substituted with one or more fluoro or methyl. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation

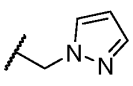
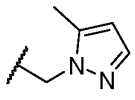
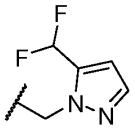
or embodiment thereof. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

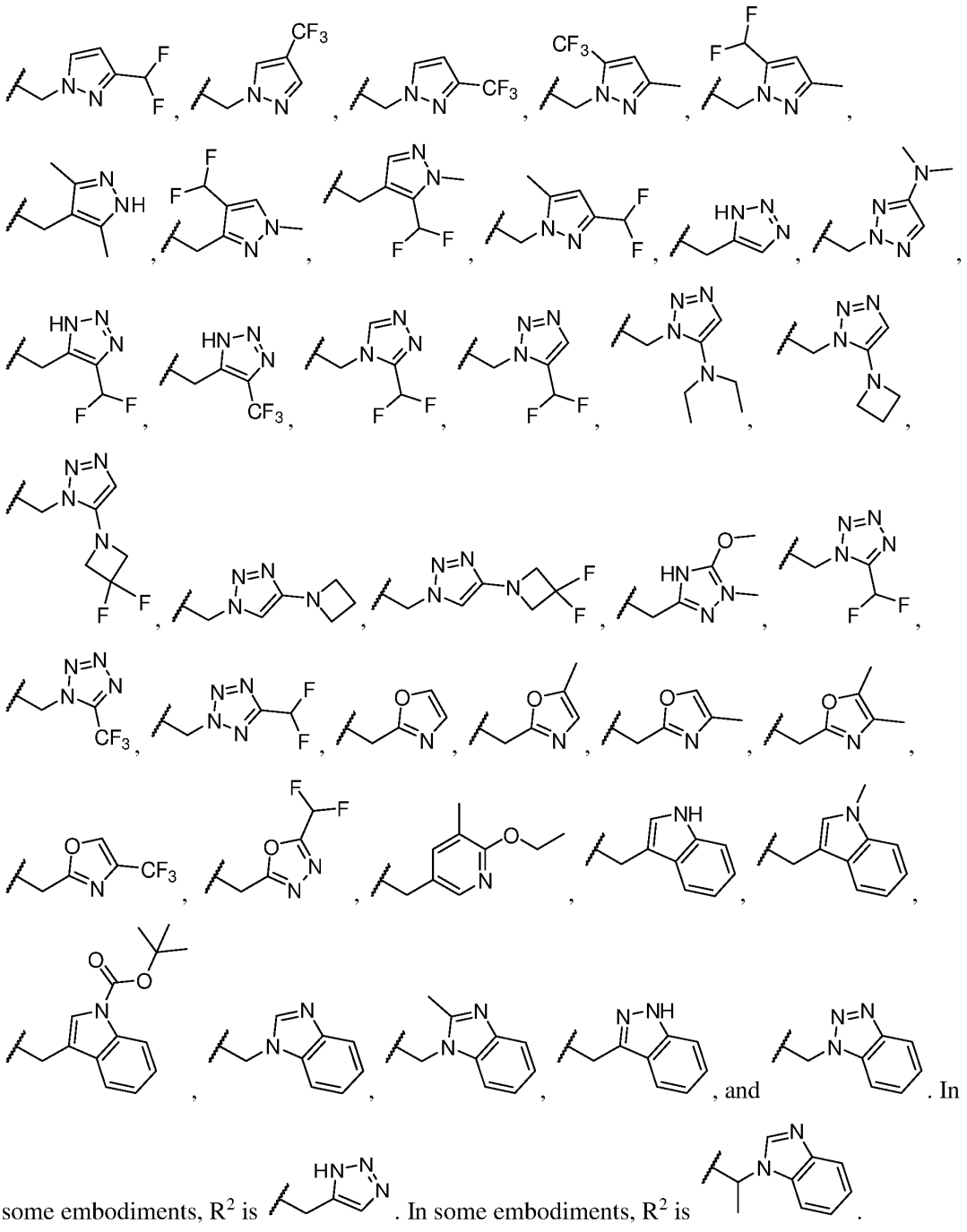
[0166] In some embodiments of a compound of formula (I-A3), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^k is H or halo. In some embodiments of a compound of formula (I-A3), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^k is H or fluoro. In some embodiments of a compound of formula (I-A3), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^k is fluoro. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0167] In some embodiments of a compound of formula (I-A3), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is $C_{1\text{-}6}$alkyl, wherein the $C_{1\text{-}6}$alkyl of R^2 is optionally substituted with one or more R^a. In some embodiments, R^2 is $C_{1\text{-}6}$alkyl, wherein the $C_{1\text{-}6}$alkyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^a is optionally substituted with one or more R^b. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl of R^a is optionally substituted with one or more R^b. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl of R^a is optionally substituted with one or more $C_{1\text{-}6}$alkyl, wherein the $C_{1\text{-}6}$alkyl is optionally substituted with one or more halo, $-NH_2$, $-NH(C_{1\text{-}6}alkyl)$, $-N(C_{1\text{-}6}alkyl)_2$, $-NH\text{-}C(O)C_{1\text{-}6}$alkyl, or $-NH\text{-}C(O)\text{-}C_{1\text{-}6}$alkoxy. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl of R^a is optionally substituted with one or more methyl, wherein the methyl is optionally substituted with one or more fluoro. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0168] In some embodiments of a compound of formula (I'), (I-A3), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is -(C_{1-4}alkyl)(5-20 membered heteroaryl), wherein the 5-20 membered heteroaryl is optionally substituted with one or more R^s. In some embodiments, R^s is halo, C_{1-6}alkyl, C_{1-6}alkoxy, $-NH_2$, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, -NH-C(O)-C_{1-6}alkyl, C_{6-20}aryl, C_{3-10}cycloalkyl, 3-15 membered heterocyclyl, 5-20 membered heteroaryl, or -C(O)-C_{1-6}alkoxy. In some embodiments, the C_{1-6}alkyl of R^s is optionally substituted with one or more halo, C_{1-6}alkoxy, $-NH_2$, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, -NH-C(O)C_{1-6}alkyl, or -NH-C(O)-C_{1-6}alkoxy, and the 3-15-membered heterocyclyl of R^s is optionally substituted with one or more halo or -C(O)-C_{1-6}alkoxy.

[0169] In some embodiments of a compound of formula (I-A3), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  , and  . In some embodiments, R^2 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

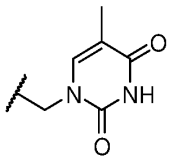
[0170] In some embodiments of a compound of formula (I'), (I-A3), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is selected from the group consisting of  ,  ,  , ,



some embodiments, R^2 is . In some embodiments, R^2 is .

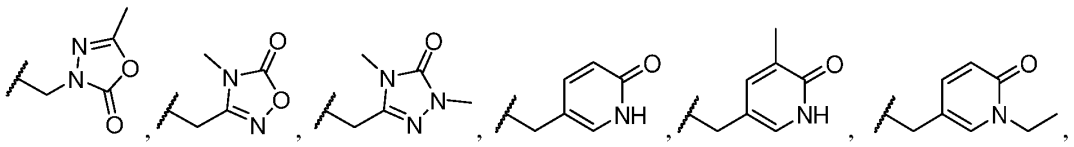
[0171] In some embodiments of a compound of formula (I-A3), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is $C_{1\text{-}6}$alkyl,

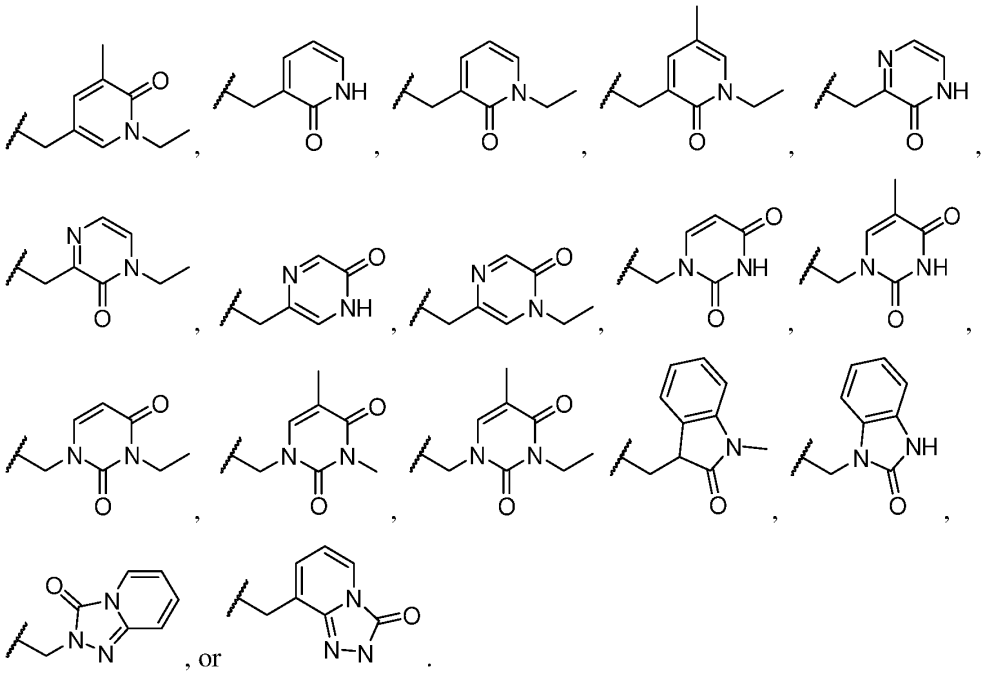
wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^a is optionally substituted with one or more R^c. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^a is optionally substituted with one or more R^c. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-8 membered heterocyclyl, wherein the 3-8 membered heterocyclyl of R^a is optionally substituted with one or more R^c. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-8 membered heterocyclyl, wherein the 3-8 membered heterocyclyl of R^a is optionally substituted with one or more oxo or C_{1-6}alkyl. In some embodiments, R^2 is

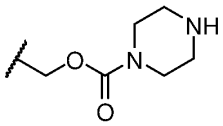


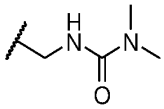
. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0172] In some embodiments of a compound of formula (I'), (I-A3), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-8 membered heterocyclyl, wherein the 3-8 membered heterocyclyl of R^a is optionally substituted with one or more R^c, wherein R^c is oxo, C_{1-6}alkyl, or -C(O)-C_{1-6}alkoxy, wherein the C_{1-6}alkyl of R^c is optionally substituted with one or more halo , and the -C(O)-C_{1-6}alkoxy of R^c is optionally substituted with one or more halo. In some embodiments, R^2 is

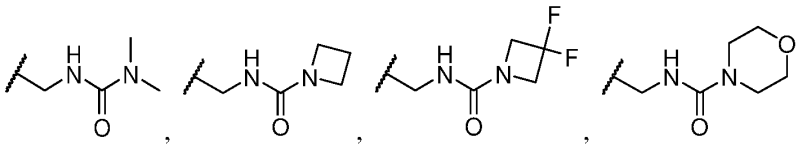


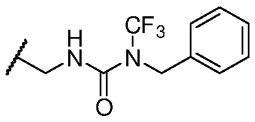


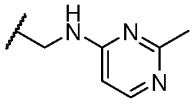
[0173] In some embodiments of a compound of formula (I-A3), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e, wherein R^e is -C(O)-(3-15 membered heterocyclyl). In some embodiments, R^2 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof. In some embodiments of a compound of formula (I-A3), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is -N(R^c)(R^d). In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -N(R^c)(R^d). In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -N(R^c)(R^d), wherein one of R^c and R^d is H, and the other of R^c and R^d

is -C(O)-N(C_{1-6}alkyl)$_2$. In some embodiments, R^2 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

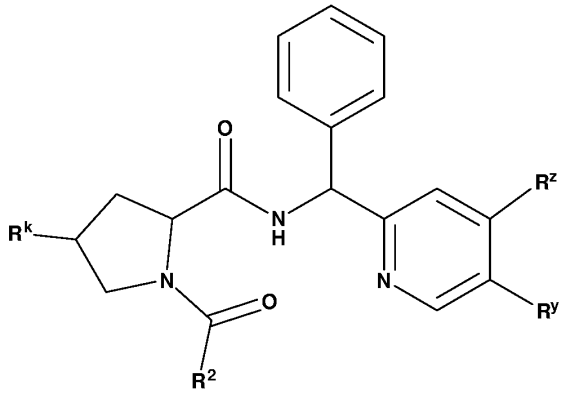
[0174] In some embodiments of a compound of formula (I'), (I-A3), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -N(R^c)(R^d), wherein one of R^c and R^d is H, and the other of R^c and R^d, -C(O)-C_{1-6}alkyl, -C(O)-N(C_{1-6}alkyl)$_2$, or -C(O)-(3-15 membered heterocyclyl), wherein the -C(O)-(3-15 membered heterocyclyl) of R^c or R^d is optionally substituted with one or more halo, -C(O)-C_{1-6}alkoxy, or C_{1-6}alkyl, and the C_{1-6}alkyl of the -C(O)-N(C_{1-6}alkyl)$_2$ of R^c or R^d are, independently of each other, optionally substituted with one or more halo or C_{6-20}aryl. In some embodiments, R^2 is

 , or

 .

[0175] In some embodiments of a compound of formula (I'), (I-A3), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -N(R^c)(R^d), wherein one of R^c and R^d is H, and the other of R^c and R^d is 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^c or R^d are independently optionally substituted with one or more C_{1-6}alkyl. In some embodiments, R^2 is  .

[0176] In some embodiments, provided herein is a compound of formula (I) or formula (I-A), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is a compound of formula (I-A4):



(I-A4),

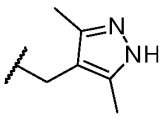
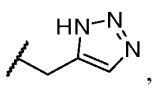
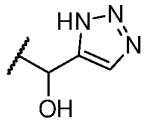
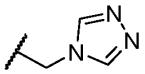
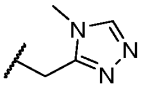
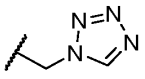
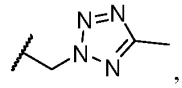
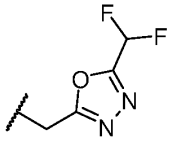
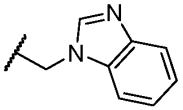
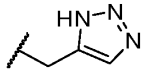
or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^z is H, halo, C_{1-6}alkyl, or $-NH_2$ and R^y is (i) C_{1-6}alkyl, (ii), C_{2-6}alkenyl, or (iii) C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl. In some embodiments, R^z is H, halo, or C_{1-6}alkyl; and R^y is (i) C_{1-6}alkyl, (ii), C_{2-6}alkenyl, or (iii) C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl. In some embodiments, R^z is H or C_{1-6}alkyl; and R^y is (i) C_{1-6}alkyl or (ii) C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl. In some embodiments of a compound of formula (I-A4), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^z is H or methyl; and R^y is (i) isopropyl, or (ii) C_{3-4}cycloalkyl. In some variations, R^2, R^k, R^y, and R^z of formula (I-A4) are as defined for a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof, wherein R^y and R^z are each independently H, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, $-NH_2$, or C_{3-10}cycloalkyl, wherein, the C_{1-6}alkyl is optionally substituted with one or more halo, and the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl. In some embodiments, R^z is H, halo, or C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^z is optionally substituted with one or more halo; and R^y is (i) C_{1-6}alkyl, (ii), or (ii) C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl. In some embodiments of a compound of formula (I-A4), or a stereoisomer or tautomer thereof, or a pharmaceutically

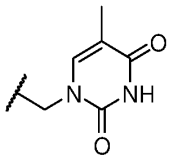
acceptable salt of any of the foregoing, R^z is H or methyl, wherein the methyl of R^z is optionally substituted with one or more halo; and R^y is (i) isopropyl, or (ii) C_{3-4}cycloalkyl.

[0177] In some embodiments of a compound of formula (I-A4), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^k is H or halo. In some embodiments of a compound of formula (I-A4), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^k is H or fluoro. In some embodiments of a compound of formula (I-A4), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^k is fluoro. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

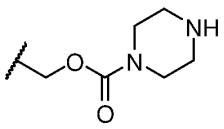
[0178] In some embodiments of a compound of formula (I-A4), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is optionally substituted with one or more R^a. In some embodiments, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^a is optionally substituted with one or more R^b. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl of R^a is optionally substituted with one or more R^b. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl of R^a is optionally substituted with one or more C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, $-NH_2$, $-NH(C_{1-6}alkyl)$, $-N(C_{1-6}alkyl)_2$, $-NH-C(O)C_{1-6}$alkyl, or $-NH-C(O)-C_{1-6}$alkoxy. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl of R^a is optionally substituted with one or more methyl, wherein the methyl is optionally substituted with one or more fluoro.

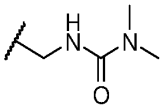
[0179] In some embodiments of a compound of formula (I-A4), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is selected

from the group consisting of  ,  ,  ,  ,  ,  ,  ,  , and  . In some embodiments, R^2 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

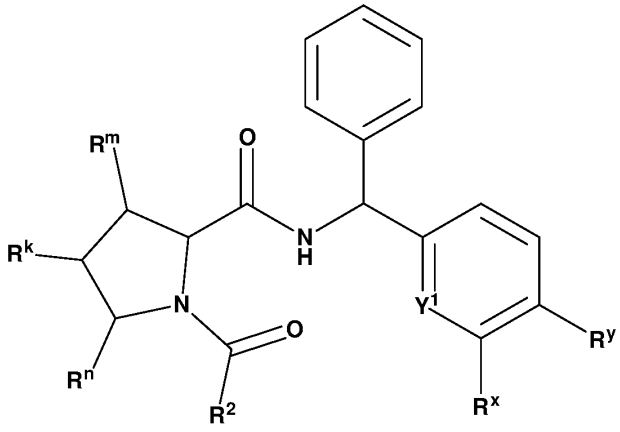
[0180] In some embodiments of a compound of formula (I-A4), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^a is optionally substituted with one or more R^c. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^a is optionally substituted with one or more R^c. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-8 membered heterocyclyl, wherein the 3-8 membered heterocyclyl of R^a is optionally substituted with one or more R^c. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-8 membered heterocyclyl, wherein the 3-8 membered heterocyclyl of R^a is optionally substituted with one or more oxo or C_{1-6}alkyl. In some embodiments, R^2 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0181] In some embodiments of a compound of formula (I-A4), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl,

wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e, wherein R^e is -C(O)-(3-15 membered heterocyclyl). In some embodiments, R^2 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0182] In some embodiments of a compound of formula (I-A4), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is -N(R^c)(R^d). In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -N(R^c)(R^d). In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -N(R^c)(R^d), wherein one of R^c and R^d is H, and the other of R^c and R^d is -C(O)-N(C_{1-6}alkyl)$_2$. In some embodiments, R^2 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0183] In some embodiments, provided herein is a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is a compound of formula (I-B):



(I-B),

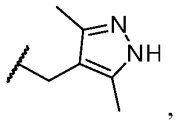
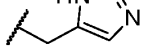
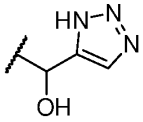
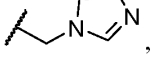
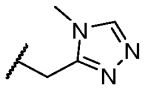
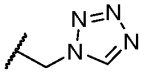
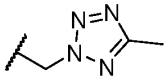
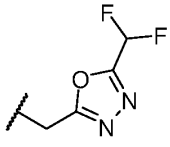
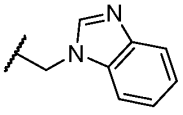
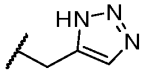
[0184] or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Y^1 is CH or N; R^x is H, halo, C_{1-6}alkyl, or -NH_2, wherein, when Y^1 is CH, the C_{1-6}alkyl of Rx may be optionally substituted with one or more halo; R^y is (i) C_{1-6}alkyl, (ii), C_{2-6}alkenyl, or (iii) C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C1-6alkyl; and Rk is taken together with either Rm or Rn, and the atoms to which they are attached, to form cyclopropyl. In some variations, Y^1, R^2, R^k, R^m, R^n, R^x, R^y, and R^z of formula (I-B) are as defined for a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof, wherein Y1 is CR^x or N; wherein, when the ring bearing R^x, and R^y is phenyl, R^x, and R^y are each independently H, halo, C_{1-6}alkyl, C_{2-6}alkenyl, -NH_2, -NH-C(O)-(C_{1-6}alkyl), -NH-C(O)-(3-15 membered heterocyclyl), C_{3-10}cycloalkyl, or 5-20 membered heteroaryl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, -NH-C(O)-NH(C_{1-6}alkyl), -NH-C(O)-C_{1-6}alkyl, or -NH-C(O)-C_{1-6}alkoxy, and the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl, and the 5-20 membered heteroaryl is optionally substituted with one or more C_{1-6}alkyl; and wherein when the ring bearing R^x, and R^y is pyridyl, R^x, and R^y are each independently H, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, -NH_2, or C_{3-10}cycloalkyl, wherein, the C_{1-6}alkyl is optionally substituted with one or more halo, and the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl.

[0185] In some embodiments of a compound of formula (I-B), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, Y^1 is CH or N; R^x is H, halo, C_{1-6}alkyl, or NH_2, wherein, when Y^1 is CH, the C_{1-6}alkyl of R^x may be optionally

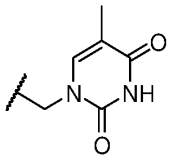
substituted with one or more halo; and R^y is (i) C_{1-6}alkyl, (ii), C_{2-6}alkenyl, or (iii) C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl. In some embodiments, Y^1 is CH or N; R^x is H or halo; R^y is C_{1-6}alkyl or C_{3-10}cycloalkyl; and R^k is taken together with either R^m or R^n, and the atoms to which they are attached, to form cyclopropyl. In some embodiments, Y^1 is CH or N; R^x is H or fluoro; R^y is (i) isopropyl or (ii) C_{3-4}cycloalkyl; and R^k is taken together with either R^m or R^n, and the atoms to which they are attached, to form cyclopropyl. In some embodiments, Y^1 is CH or N; R^x is H or fluoro; R^y is (i) isopropyl or (ii) C_{3-4}cycloalkyl; and R^k is taken together with R^m and the atoms to which they are attached to form cyclopropyl. In some embodiments, Y^1 is CH or N; R^x is H or fluoro; R^y is (i) isopropyl or (ii) C_{3-4}cycloalkyl; and R^k is taken together with R^n and the atoms to which they are attached to form cyclopropyl. In some embodiments, Y^1 is CH; R^x is H or fluoro; R^y is (i) isopropyl or (ii) C_{3-4}cycloalkyl; and R^k is taken together with R^n or R^n and the atoms to which they are attached to form cyclopropyl. In some embodiments, Y^1 is N; R^x is H or fluoro; R^y is (i) isopropyl or (ii) C_{3-4}cycloalkyl; and R^k is taken together with R^n or R^n and the atoms to which they are attached to form cyclopropyl. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

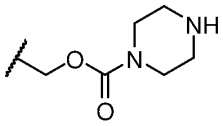
[0186] In some embodiments of a compound of formula (I-B), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is optionally substituted with one or more R^a. In some embodiments, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^a is optionally substituted with one or more R^b. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl of R^a is optionally substituted with one or more R^b. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl of R^a is optionally substituted with one or more C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, $-NH_2$, $-NH(C_{1-6}alkyl)$, $-N(C_{1-6}alkyl)_2$, $-NH-C(O)C_{1-6}$alkyl, or $-NH-C(O)-C_{1-6}$alkoxy. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-10 membered heteroaryl, wherein the 5-10 membered

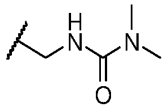
heteroaryl of R^a is optionally substituted with one or more methyl, wherein the methyl is optionally substituted with one or more fluoro. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0187] In some embodiments of a compound of formula (I-B), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  , and  . In some embodiments, R^2 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

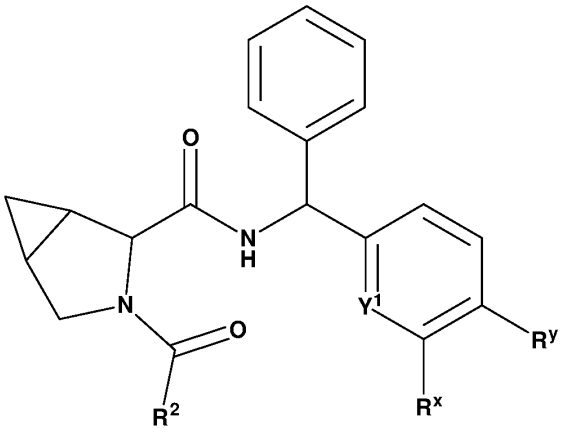
[0188] In some embodiments of a compound of formula (I-B), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is $C_{1\text{-}6}$alkyl, wherein the $C_{1\text{-}6}$alkyl of R^2 is substituted with one or more R^a, wherein R^a is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^a is optionally substituted with one or more R^c. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^a is optionally substituted with one or more R^c. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-8 membered heterocyclyl, wherein the 3-8 membered heterocyclyl of R^a is optionally substituted with one or more R^c. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-8 membered heterocyclyl, wherein the 3-8 membered heterocyclyl of R^a is optionally substituted with one or more oxo or $C_{1\text{-}6}$alkyl. In some embodiments, R^2 is


. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0189] In some embodiments of a compound of formula (I-B), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e, wherein R^e is -C(O)-(3-15 membered heterocyclyl). In some embodiments, R^2 is 
. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0190] In some embodiments of a compound of formula (I-B), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is -N(R^c)(R^d). In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -N(R^c)(R^d). In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -N(R^c)(R^d), wherein one of R^c and R^d is H, and the other of R^c and R^d is -C(O)-N(C_{1-6}alkyl)$_2$. In some embodiments, R^2 is 
. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0191] In some embodiments, provided here is a compound of formula (I) or formula (I-B), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is a compound of formula (I-B1):

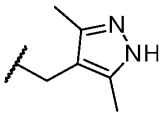
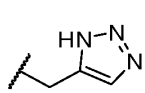
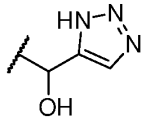
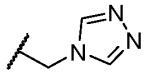
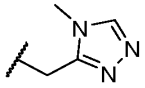
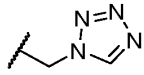
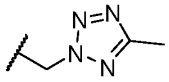
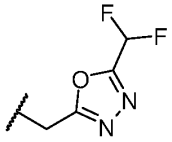
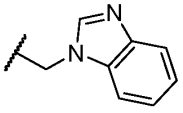


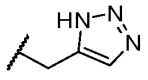
(I-B1),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Y^1 is CH or N; R^x is H or halo; and R^y is C_{1-6}alkyl or C_{3-10}cycloalkyl. In some embodiments, Y^1 is CH or N; R^x is H or fluoro; and R^y is (i) isopropyl or (ii) C_{3-4}cycloalkyl. In some embodiments, Y^1 is CH; R^x is H or fluoro; and R^y is (i) isopropyl or (ii) C_{3-4}cycloalkyl. In some embodiments, Y^1 is N; R^x is H or fluoro; and R^y is (i) isopropyl or (ii) C_{3-4}cycloalkyl. In some variations, Y^1, R^2, R^x, and R^y of formula (I-B1) are as defined for a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof, wherein Y^1 is CR^x or N; wherein, when the ring bearing R^x, and R^y is phenyl, R^x, and R^y are each independently H, halo, C_{1-6}alkyl, C_{2-6}alkenyl, -NH_2, -NH-C(O)-(C_{1-6}alkyl), -NH-C(O)-(3-15 membered heterocyclyl), C_{3-10}cycloalkyl, or 5-20 membered heteroaryl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, -NH-C(O)-NH(C_{1-6}alkyl), -NH-C(O)-C_{1-6}alkyl, or -NH-C(O)-C_{1-6}alkoxy, the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl, and the 5-20 membered heteroaryl is optionally substituted with one or more C_{1-6}alkyl; and wherein when the ring bearing R^x, and R^y is pyridyl, R^x, and R^y are each independently H, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, -NH_2, or C_{3-10}cycloalkyl, wherein, the C_{1-6}alkyl is optionally substituted with one or more halo, and the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl.. In some embodiments, Y^1 is CH or N; R^x is H or fluoro; and

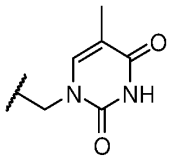
R^y is (i) isopropyl or (ii) C_{3-4}cycloalkyl. In some embodiments, Y^1 is CH; R^x is H or fluoro; and R^y is (i) isopropyl or (ii) C_{3-4}cycloalkyl. In some embodiments, Y^1 is N; R^x is H or fluoro; and R^y is (i) isopropyl or (ii) C_{3-4}cycloalkyl.

[0192] In some embodiments of a compound of formula (I-B1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is optionally substituted with one or more R^a. In some embodiments, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^a is optionally substituted with one or more R^b. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl of R^a is optionally substituted with one or more R^b. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl of R^a is optionally substituted with one or more C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, $-NH_2$, $-NH(C_{1-6}alkyl)$, $-N(C_{1-6}alkyl)_2$, $-NH-C(O)C_{1-6}$alkyl, or $-NH-C(O)-C_{1-6}$alkoxy. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl of R^a is optionally substituted with one or more methyl, wherein the methyl is optionally substituted with one or more fluoro. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

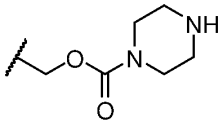
[0193] In some embodiments of a compound of formula (I-B1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  , and  . In some

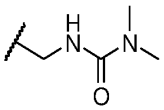
embodiments, R^2 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0194] In some embodiments of a compound of formula (I-B1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^a is optionally substituted with one or more R^c. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^a is optionally substituted with one or more R^c. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-8 membered heterocyclyl, wherein the 3-8 membered heterocyclyl of R^a is optionally substituted with one or more R^c. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-8 membered heterocyclyl, wherein the 3-8 membered heterocyclyl of R^a is optionally substituted with one or more oxo or C_{1-6}alkyl. In some embodiments, R^2 is

 . In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0195] In some embodiments of a compound of formula (I-B1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e, wherein R^e is -C(O)-(3-15 membered heterocyclyl). In

some embodiments, R^2 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0196] In some embodiments of a compound of formula (I-B1), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is $C_{1\text{-}6}$alkyl, wherein the $C_{1\text{-}6}$alkyl of R^2 is substituted with one or more R^a, wherein R^a is $-N(R^c)(R^d)$. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is $-N(R^c)(R^d)$. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is $-N(R^c)(R^d)$, wherein one of R^c and R^d is H, and the other of R^c and R^d is $-C(O)-N(C_{1\text{-}6}alkyl)_2$. In some embodiments, R^2 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

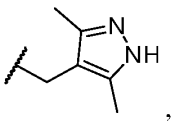
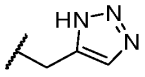
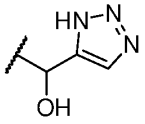
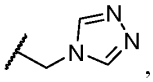
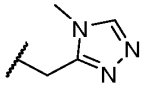
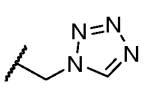
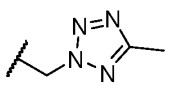
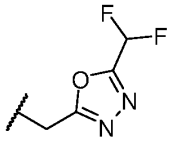
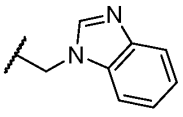
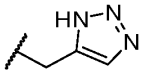
[0197] In some embodiments, provided herein is a compound of formula (I) or formula (I-B), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is a compound of formula (I-B2):

(I-B2),

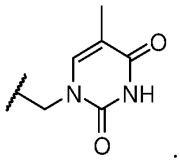
or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Y^1 is CH or N; R^x is H or halo; and R^y is C_{1-6}alkyl or C_{3-10}cycloalkyl. In some embodiments, Y^1 is CH or N; R^x is H or fluoro; and R^y is (i) isopropyl or (ii) C_{3-4}cycloalkyl. In some embodiments, Y^1 is CH; R^x is H or fluoro; and R^y is (i) isopropyl or (ii) C_{3-4}cycloalkyl. In some embodiments, Y^1 is N; R^x is H or fluoro; and R^y is (i) isopropyl or (ii) C_{3-4}cycloalkyl. In some variations, Y^1, R^2, R^x, and R^y of formula (I-B2) are as defined for a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof, wherein Y^1 is is CR^x or N; wherein, when the ring bearing R^x, and R^y is phenyl, R^x, and R^y are each independently H, halo, C_{1-6}alkyl, C_{2-6}alkenyl, $-NH_2$, -NH-C(O)-(C_{1-6}alkyl), -NH-C(O)-(3-15 membered heterocyclyl), C_{3-10}cycloalkyl, or 5-20 membered heteroaryl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, -NH-C(O)-NH(C_{1-6}alkyl), -NH-C(O)-C_{1-6}alkyl, or -NH-C(O)-C_{1-6}alkoxy, the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl, and the 5-20 membered heteroaryl is optionally substituted with one or more C_{1-6}alkyl; and wherein when the ring bearing R^x, and R^y is pyridyl, R^x, and R^y are each independently H, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, $-NH_2$, or C_{3-10}cycloalkyl, wherein, the C_{1-6}alkyl is optionally substituted with one or more halo, and the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl. In some embodiments, Y^1 is CH or N; R^x is H or fluoro; and R^y is (i) isopropyl or (ii) C_{3-4}cycloalkyl. In some embodiments, Y^1 is CH; R^x is H or fluoro; and R^y is (i) isopropyl or (ii) C_{3-4}cycloalkyl. In some embodiments, Y^1 is N; R^x is H or fluoro; and R^y is (i) isopropyl or (ii) C_{3-4}cycloalkyl.

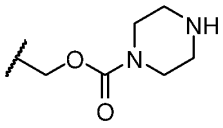
[0198] In some embodiments of a compound of formula (I-B2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is optionally substituted with one or more R^a. In some embodiments, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^a is optionally substituted with one or more R^b. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl of R^a is optionally substituted with one or more R^b. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl of R^a is

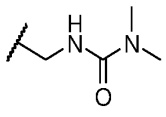
optionally substituted with one or more C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, -NH-C(O)C_{1-6}alkyl, or -NH-C(O)-C_{1-6}alkoxy. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl of R^a is optionally substituted with one or more methyl, wherein the methyl is optionally substituted with one or more fluoro. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0199] In some embodiments of a compound of formula (I-B2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  , and  . In some embodiments, R^2 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

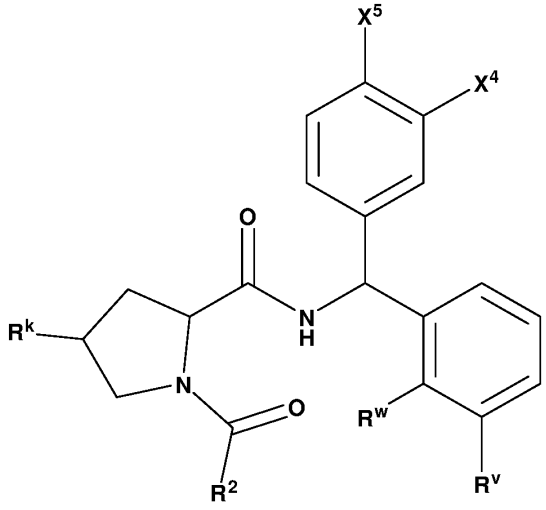
[0200] In some embodiments of a compound of formula (I-B2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^a is optionally substituted with one or more R^c. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^a is optionally substituted with one or more R^c. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-8 membered heterocyclyl, wherein the 3-8 membered heterocyclyl of R^a is optionally substituted with one or more R^c. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a,

wherein R^a is 3-8 membered heterocyclyl, wherein the 3-8 membered heterocyclyl of R^a is optionally substituted with one or more oxo or C_{1-6}alkyl. In some embodiments, R^2 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0201] In some embodiments of a compound of formula (I-B2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e, wherein R^e is -C(O)-(3-15 membered heterocyclyl). In some embodiments, R^2 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0202] In some embodiments of a compound of formula (I-B2), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is -N(R^c)(R^d). In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -N(R^c)(R^d). In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -N(R^c)(R^d), wherein one of R^c and R^d is H, and the other of R^c and R^d is -C(O)-N(C_{1-6}alkyl)$_2$. In some embodiments, R^2 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0203] In some embodiments, provided herein is a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is a compound of formula (I-C):

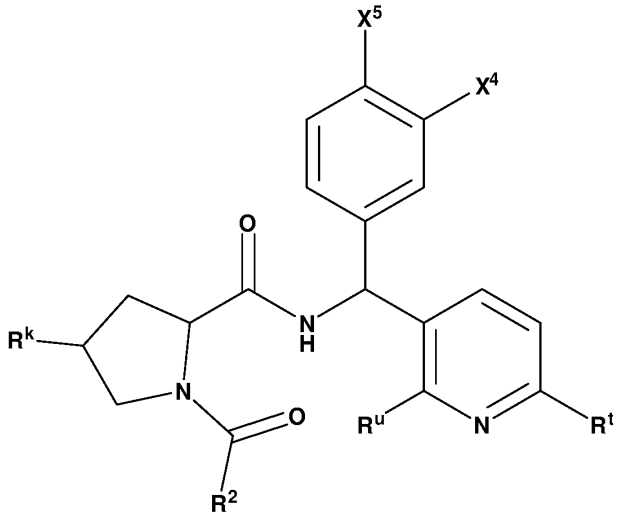


(I-C),

wherein X^5 is H, C_{1-6}alkyl, C_{1-6}alkoxy, or C_{3-10}cycloalkyl; X^4 is H, halo, C_{1-6}alkyl, C_{1-6}alkoxy, or 5-20 membered heteroaryl; R^v is $-NH_2$, -NH-C(O)-(C_{1-6}alkyl), or -NH-C(O)-(3-15 membered heterocyclyl); and R^w is H, $-NH_2$, -NH-C(O)-(C_{1-6}alkyl), or -NH-C(O)-(3-15 membered heterocyclyl). In some embodiments, X^5 is H or C_{1-6}alkyl; X^4 is H; R^v is $-NH_2$, -NH-C(O)-(C_{1-6}alkyl), or -NH-C(O)-(3-15 membered heterocyclyl); and R^w is H, $-NH_2$, -NH-C(O)-(C_{1-6}alkyl), or -NH-C(O)-(3-15 membered heterocyclyl). In some embodiments, R^w is H and R^v is -NH-C(O)C_{1-6}alkyl. In some embodiments, R^w is H and R^v is -NH-C(O)CH_3. In some variations, R^2, R^k, R^w, R^v, X^4 and X^5 of formula (I-C) are as defined for a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof, wherein X^5 is H, C_{1-6}alkyl, C_{1-6}alkoxy, or C_{3-10}cycloalkyl; X^4 is H, halo, C_{1-6}alkyl, C_{1-6}alkoxy, or 5-20 membered heteroaryl; R^v is $-NH_2$, -NH-C(O)-(C_{1-6}alkyl), or -NH-C(O)-(3-15 membered heterocyclyl); and R^w is H, $-NH_2$, -NH-C(O)-(C_{1-6}alkyl), or -NH-C(O)-(3-15 membered heterocyclyl). In some embodiments, X^5 is H or C_{1-6}alkyl; X^4 is H; R^v is $-NH_2$, -NH-C(O)-(C_{1-6}alkyl), or -NH-C(O)-(3-15 membered heterocyclyl); and R^w is H, $-NH_2$, -NH-C(O)-(C_{1-6}alkyl), or -NH-C(O)-(3-15 membered heterocyclyl). In some

embodiments, R^w is H and R^v is -NH-C(O)C_{1-6}alkyl. In some embodiments, R^w is H and R^v is -NH-C(O)CH_3.

[0204] In some embodiments, provided is a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is a compound of formula (I-D):

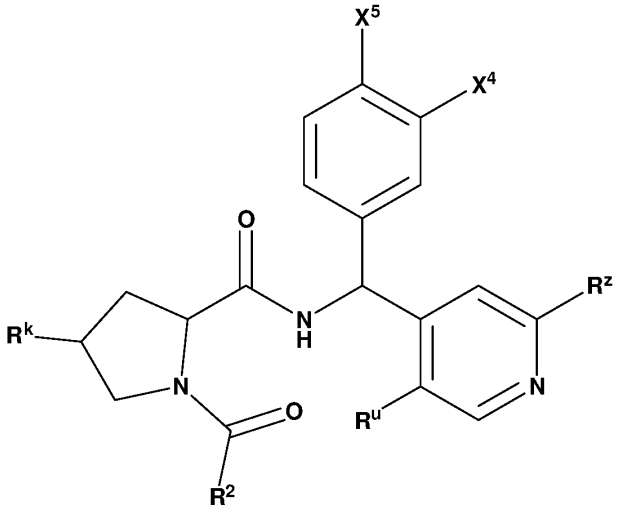


(I-D),

wherein X^5 is H, C_{1-6}alkyl, C_{1-6}alkoxy, or C_{3-10}cycloalkyl; X^4 is H, halo, C_{1-6}alkyl, C_{1-6}alkoxy, or 5-20 membered heteroaryl; and R^t and R^u are independently H, C_{1-6}alkoxy, or -NH_2. In some embodiments, X^5 is C_{1-6}alkyl; X^4 is H, halo, or C_{1-6}alkyl; and R^t and R^u are independently H or -NH_2. In some embodiments, at least one of R^t and R^u is -NH_2. In some embodiments, R^t is H and R^u is -NH_2. In some embodiments, R^t is -NH_2 and R^u is H. In some variations, R^2, R^k, R^t, R^u, X^4 and X^5 of formula (I-D) are as defined for a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof, wherein X^5 is H, C_{1-6}alkyl, C_{1-6}alkoxy, or C_{3-10}cycloalkyl, ; X^4 is H, halo, C_{1-6}alkyl, C_{1-6}alkoxy, or 5-20 membered heteroaryl; and R^t and R^u are independently H, C_{1-6}alkoxy, or -NH_2. In some embodiments, X^5 is C_{1-6}alkyl; X^4 is H, halo, or C_{1-6}alkyl; and R^t and R^u are independently H or -NH_2. In some embodiments, at least one of R^t and R^u is -NH_2. In some embodiments, R^t is H and R^u is -NH_2. In some embodiments, R^t is -NH_2 and R^u is H.

[0205] In some embodiments of a compound of formula (I-C) or (I-D), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^k is H or halo. In some embodiments of a compound of formula (I-C) or (I-D), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^k is H or fluoro. In some embodiments of a compound of formula (I-C) or (I-D), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^k is fluoro. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0206] In some embodiments, provided is a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is a compound of formula (I-D1):

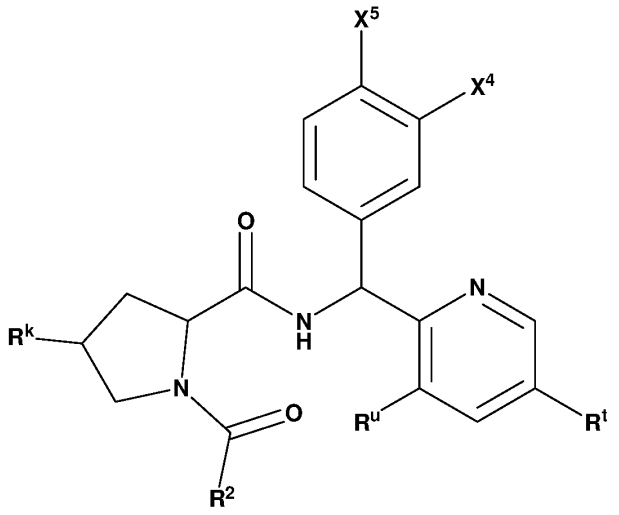


(I-D1),

wherein X^5 is H, C_{1-6}alkyl, C_{1-6}alkoxy, or C_{3-10}cycloalkyl; X^4 is H, halo, C_{1-6}alkyl, C_{1-6}alkoxy, or 5-20 membered heteroaryl; and R^t and R^u are independently H, C_{1-6}alkoxy, or $-NH_2$. In some embodiments, X^5 is C_{1-6}alkyl; X^4 is H, halo, or C_{1-6}alkyl; and R^u and R^z are independently H, halo or $-NH_2$. In some embodiments, at least one of R^u and R^z is $-NH_2$. In some embodiments, R^u is H and R^z is $-NH_2$. In some embodiments, R^u is $-NH_2$ and R^z is H. In some embodiments, at

least one of R^u and R^z is halo. In some embodiments, R^u is H and R^z is fluoro. In some embodiments, R^u is fluoro and R^z is H.

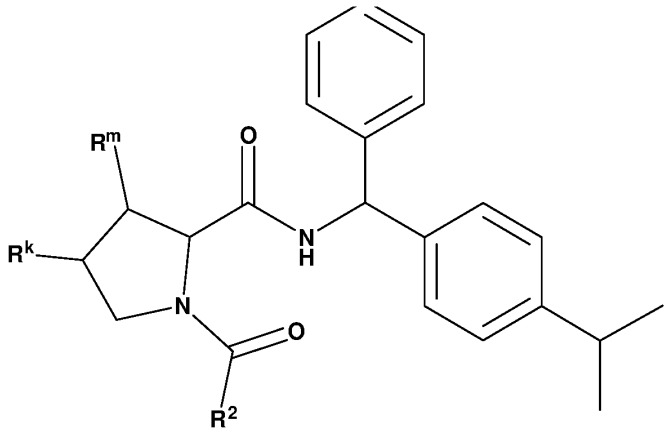
[0207] In some embodiments, provided is a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is a compound of formula (I-D2):



(I-D2),

wherein X^5 is H, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, or $C_{3\text{-}10}$cycloalkyl; X^4 is H, halo, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, or 5-20 membered heteroaryl, wherein the $C_{1\text{-}6}$alkyl of X^4 is optionally substituted with one of more halo; and R^t and R^u are independently H, $C_{1\text{-}6}$alkoxy, or $-NH_2$. In some embodiments, X^5 is $C_{1\text{-}6}$alkyl; X^4 is H, halo, or $C_{1\text{-}6}$alkyl; and R^u and R^z are independently H, halo or $-NH_2$. In some embodiments, at least one of R^u and R^z is $-NH_2$. In some embodiments, R^u is H and R^z is $-NH_2$. In some embodiments, R^u is $-NH_2$ and R^z is H. In some embodiments, at least one of R^u and R^z is halo. In some embodiments, R^u is H and R^z is fluoro. In some embodiments, R^u is fluoro and R^z is H.

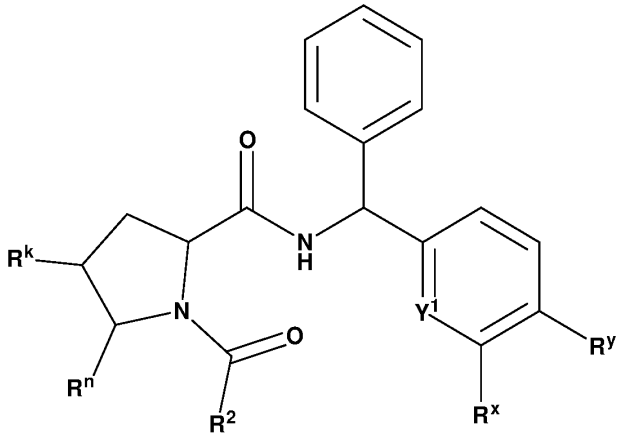
[0208] In some embodiments, provided is a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is a compound of formula (I-E):



(I-E),

wherein R^k and R^m are independently H, OH, $-NH_2$, or $-NH-C(O)C_{1-6}$alkyl. In some embodiments, R^k is H and R^m is H, OH, $-NH_2$, or $-NH-C(O)C_{1-6}$alkyl. In some embodiments, R^k is H and R^m is OH. In some embodiments, R^k is H, OH, $-NH_2$, or $-NH-C(O)C_{1-6}$alkyl, and R^m is H. In some embodiments, R^k is OH, $-NH_2$, or $-NH-C(O)C_{1-6}$alkyl, and R^m is H. In some embodiments, R^k is OH, $-NH_2$, or $-NH-C(O)CH_3$, and R^m is H. In some variations, R^2, R^k, and R^m of formula (I-E) are as defined for a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof, wherein R^k and R^m are independently H, OH, $-NH_2$, or $-NH-C(O)C_{1-6}$alkyl. In some embodiments, R^k is H and R^m is H, OH, $-NH_2$, or $-NH-C(O)C_{1-6}$alkyl. In some embodiments, R^k is H and R^m is OH. In some embodiments, R^k is H, OH, $-NH_2$, or $-NH-C(O)C_{1-6}$alkyl, and R^m is H. In some embodiments, R^k is OH, $-NH_2$, or $-NH-C(O)C_{1-6}$alkyl, and R^m is H. In some embodiments, R^k is OH, $-NH_2$, or $-NH-C(O)CH_3$, and R^m is H.

[0209] In some embodiments, provided is a compound of formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is a compound of formula (I-F):



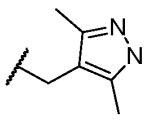
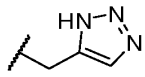
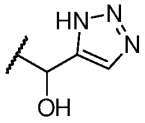
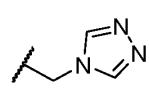
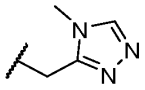
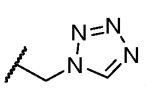
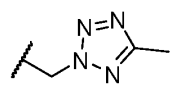
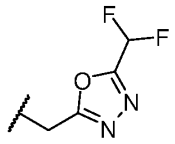
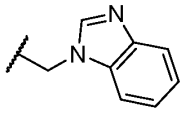
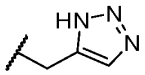
(I-F),

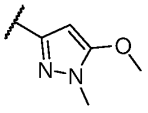
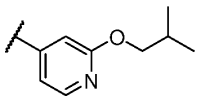
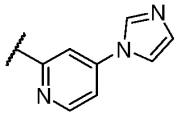
wherein Y^1 is CH or N; R^x is H, halo, C_{1-6}alkyl, or -NH_2, wherein, when Y^1 is CH, the C_{1-6}alkyl of R^x may be optionally substituted with one or more halo; R^y is (i) C_{1-6}alkyl, (ii), C_{2-6}alkenyl, or (iii) C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl; R^k is H, halo, -OH, -NH_2, or -NH-C(O)C_{1-6}alkyl; and R^n is H, C_{1-6}alkyl, or C_{3-10}cycloalkyl. In some embodiments, Y^1 is CH or N; R^x is H, halo, or C_{1-6}alkyl; R^y is (i) C_{1-6}alkyl, (ii), C_{2-6}alkenyl, or (iii) C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl; R^k is H, halo, -OH, -NH_2, or -NH-C(O)C_{1-6}alkyl; and R^n is H, C_{1-6}alkyl, or C_{3-10}cycloalkyl. In some variations, R^2, R^k, R^x, R^y, and R^z of formula (I-F) are as defined for a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof, wherein Y^1 is CH or N; R^x is H, halo, C_{1-6}alkyl, or -NH_2, wherein, when Y^1 is CH, the C_{1-6}alkyl of R^x may be optionally substituted with one or more halo; R^y is (i) C_{1-6}alkyl, (ii), C_{2-6}alkenyl or (iii) C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl; R^k is H, halo, -OH, -NH_2, or -NH-C(O)C_{1-6}alkyl; and R^n is H, C_{1-6}alkyl, or C_{3-10}cycloalkyl. In some embodiments, Y^1 is CH or N; R^x is H, halo, or C_{1-6}alkyl; R^y is (i) C_{1-6}alkyl, or (ii) C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl; R^k is H, halo, -OH, -NH_2, or -NH-C(O)C_{1-6}alkyl; and R^n is H, C_{1-6}alkyl, or C_{3-10}cycloalkyl.

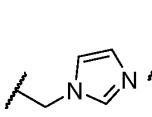
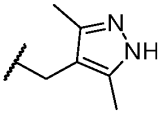
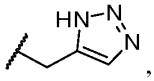
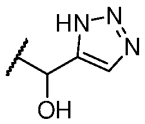
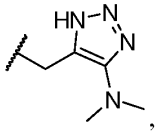
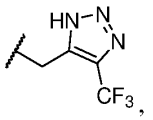
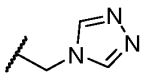
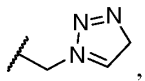
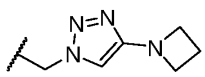
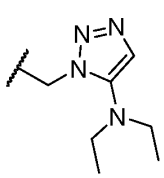
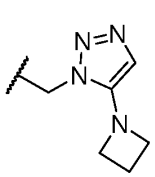
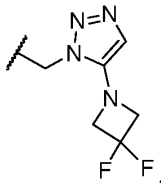
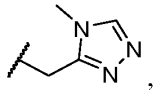
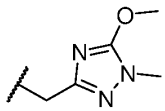
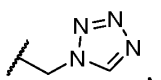
[0210] In some embodiments of a compound of formula (I-F), Y^1 is CH or N; R^x is H, halo, or C_{1-6}alkyl; R^y is (i) C_{1-6}alkyl, (ii), C_{2-6}alkenyl, or (iii) C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl; R^k is H or halo; and R^n is H, C_{1-6}alkyl, or C_{3-6}cycloalkyl. In some embodiments, Y^1 is N or CH, R^x is H or halo, R^y is C_{1-}

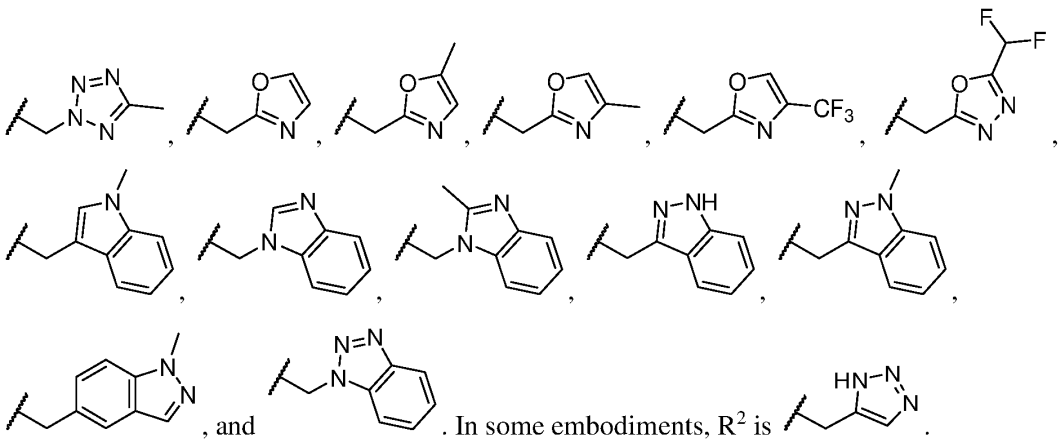
$_{6}$alkyl or C_{3-6}cycloalkyl, R^k is H or halo, and R^n is C_{1-6}alkyl or C_{3-6}cycloalkyl. In some embodiments, Y^1 is N or CH, R^x is H or fluoro, R^y is C_{1-6}alkyl or C_{3-6}cycloalkyl, R^k is H or fluoro, and R^n is C_{1-6}alkyl or C_{3-6}cycloalkyl. In some embodiments, Y^1 is N or CH, R^x is H or fluoro, R^y is C_{1-6}alkyl or C_{3-6}cycloalkyl, R^k is H or fluoro, and R^n is C_{1-6}alkyl or C_{3-6}cycloalkyl. In some embodiments, Y^1 is N or CH, R^x is H or fluoro, R^y is C_{1-6}alkyl or C_{3-6}cycloalkyl, R^k is H, and R^n is C_{1-6}alkyl or C_{3-6}cycloalkyl. In some embodiments, Y^1 is N or CH, R^x is H or fluoro, R^y is C_{1-3}alkyl or C_{3-6}cycloalkyl, R^k is H, and R^n is C_{1-3}lkyl or C_{3-6}cycloalkyl. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

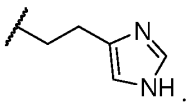
[0211] In some embodiments of a compound of formula (I-C), (I-D), (I-E), or (I-F), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is optionally substituted with one or more R^a. In some embodiments, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^a is optionally substituted with one or more R^b. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl of R^a is optionally substituted with one or more R^b. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl of R^a is optionally substituted with one or more C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, -NH-C(O)C_{1-6}alkyl, or -NH-C(O)-C_{1-6}alkoxy. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl of R^a is optionally substituted with one or more methyl, wherein the methyl is optionally substituted with one or more fluoro. In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

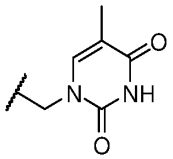
[0212] In some embodiments of a compound of formula (I-C), (I-D), (I-E), or (I-F), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  , and  . In some embodiments, R^2 is  .

[0213] In some embodiments of a compound of formula (I'), (I-C), (I-D), (I-E), or (I-F), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is selected from the group consisting of  ,  , and  .

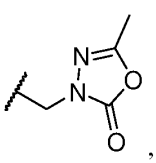
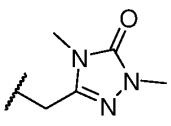
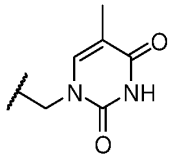
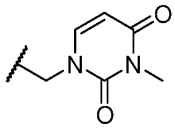
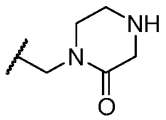
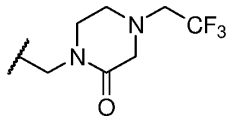
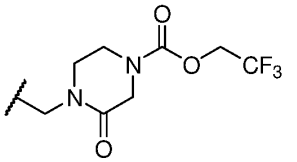
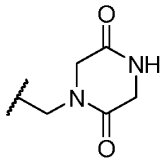
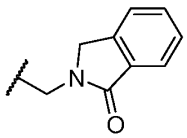
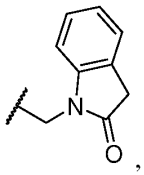
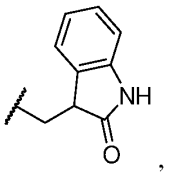
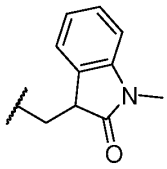
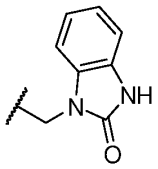
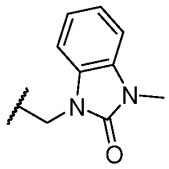
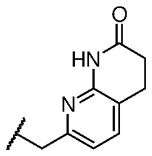
[0214] In some embodiments of a compound of formula (I'), (I-C), (I-D), (I-E), or (I-F), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  .

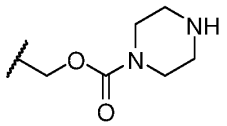


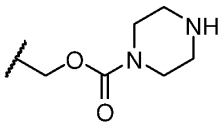
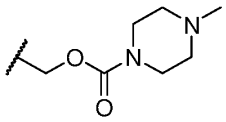
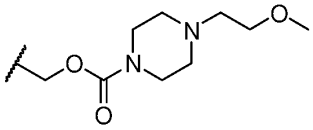
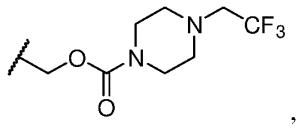
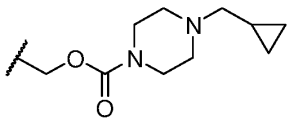
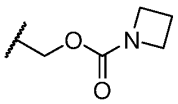
[0215] In some embodiments of a compound of formula (I'), (I-C), (I-D), (I-E), or (I-F), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is  .

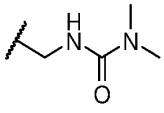
[0216] In some embodiments of a compound of formula (I-C), (I-D), (I-E), or (I-F), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^a is optionally substituted with one or more R^c. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^a is optionally substituted with one or more R^c. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-8 membered heterocyclyl, wherein the 3-8 membered heterocyclyl of R^a is optionally substituted with one or more R^c. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-8 membered heterocyclyl, wherein the 3-8 membered heterocyclyl of R^a is optionally substituted with one or more oxo or C_{1-6}alkyl. In some embodiments, R^2 is  . In some variations, the embodiments provided herein also

apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

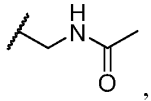
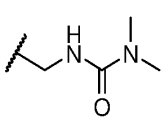
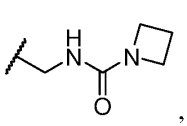
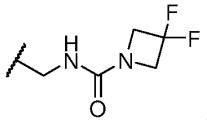
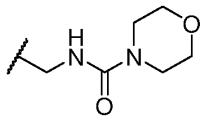
[0217] In some embodiments of a compound of formula (I') (I-C), (I-D), (I-E), or (I-F), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-8 membered heterocyclyl, wherein the 3-8 membered heterocyclyl of R^a is optionally substituted with one or more R^c, wherein R^c is oxo, C_{1-6}alkyl, or -C(O)-C_{1-6}alkoxy, wherein the C_{1-6}alkyl of R^c is optionally substituted with one or more halo , and the -C(O)-C_{1-6}alkoxy of R^c is optionally substituted with one or more halo. In some embodiments, R^2 is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  .

[0218] In some embodiments of a compound of formula (I-C), (I-D), (I-E), or (I-F), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e. In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e, wherein R^e is -C(O)-(3-15 membered heterocyclyl). In some embodiments, R^2 is  .

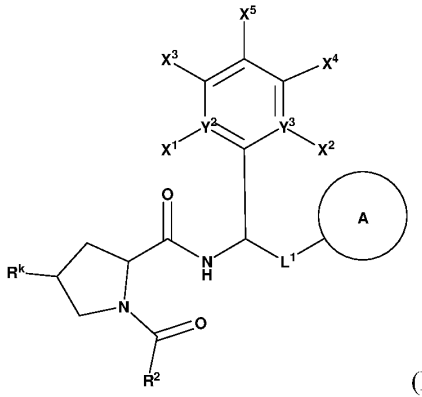
[0219] In some embodiments of a compound of formula (I'), (I-C), (I-D), (I-E), or (I-F), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e, wherein R^e is -C(O)-(3-15 membered heterocyclyl)wherein the -C(O)-(3-15 membered heterocyclyl) of R^e is optionally substituted with one or more C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, C_{1-6}alkoxy, or C_{3-10}cycloalkyl. In some embodiments, R^2 is selected from the group consisting of  ,  ,  ,  ,  , and  .

[0220] In some embodiments of a compound of formula (I-C), (I-D), (I-E), or (I-F), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is -N(R^c)(R^d). In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -N(R^c)(R^d). In some embodiments, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -N(R^c)(R^d), wherein one of R^c and R^d is H, and the other of R^c and R^d is -C(O)-N(C_{1-6}alkyl)$_2$. In some embodiments, R^2 is  . In some variations, the embodiments provided herein also apply to a compound of formula (I') or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or any variation or embodiment thereof.

[0221] In some embodiments of a compound of formula (I'), (I-C), (I-D), (I-E), or (I-F), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a

is -N(R^c)(R^d), wherein one of R^c and R^d is H, and the other of R^c and R^d, -C(O)-C_{1-6}alkyl, -C(O)-$N(C_{1-6}alkyl)_2$, or -C(O)-(3-15 membered heterocyclyl). In some embodiments, R^2 is  ,  ,  ,  , or  .

[0222] In some embodiments, provided herein is a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (I-G):



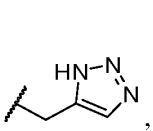
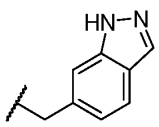
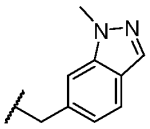
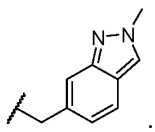
(I-G),

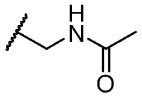
or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein ring A is (i) 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of ring A is optionally substituted with one or more oxo, (ii) 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of ring A is optionally substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, -NH_2, or C_{3-10}cycloalkyl, wherein, the C_{1-6}alkyl is optionally substituted with one or more halo, and the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl, or (iii) C_{3-10}cycloalkyl.

[0223] In some embodiments of a compound of formula (I'), (I-G), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, X^3 is H, fluoro or methyl optionally substituted with one or more fluoro; X^4 is (i) isopropyl (ii) C_{3-4}cycloalkyl optionally substituted with one or more halo or C_{1-6}alkyl or (iii) butyl; and R^z is fluoro or methyl; provided that at least one of X^3 and X^4 is halo, CF_2 or CF_3.

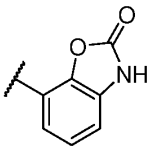
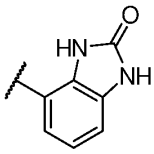
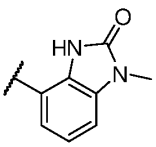
[0224] In some embodiments of a compound of formula (I'), (I-G), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^k is H or halo. In some embodiments of a compound of formula (I-G), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^k is H or fluoro. In some embodiments of a compound of formula (I-G), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^k is fluoro.

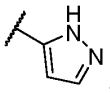
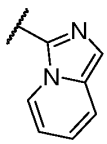
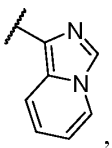
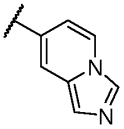
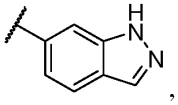
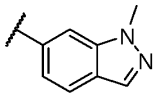
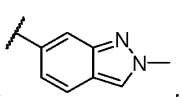
[0225] In some embodiments of a compound of formula (I'), (I-G), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is 5-20 membered heteroaryl or -(C_{1-4}alkyl)(5-20 membered heteroaryl), wherein the C_{1-4} alkyl is optionally substituted with one or more or more –OH, halo, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, and wherein the 5-20 membered heteroaryl is optionally substituted with one or more R^s. In some embodiments, R^s is halo, C_{1-6}alkyl, C_{1-6}alkoxy, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, -NH-C(O)-C_{1-6}alkyl, C_{6-20}aryl, C_{3-10}cycloalkyl, 3-15 membered heterocyclyl, 5-20 membered heteroaryl, or -C(O)-C_{1-6}alkoxy. In some embodiments, the C_{1-6}alkyl of R^s is optionally substituted with one or more halo, C_{1-6}alkoxy, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, -NH-C(O)C_{1-6}alkyl, or -NH-C(O)-C_{1-6}alkoxy, and the 3-15-membered heterocyclyl of R^s is optionally substituted with one or more halo or -C(O)-C_{1-6}alkoxy.

[0226] In some embodiments of a compound of formula (I'), (I-G), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is selected from the group consisting of  ,  ,  , and  .

[0227] In some embodiments of a compound of formula (I') (I-G), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -N(R^c)(R^d), wherein one of R^c and R^d is H, and the other of R^c and R^d, -C(O)-C_{1-6}alkyl, -C(O)-N(C_{1-6}alkyl)$_2$, or -C(O)-(3-15 membered heterocyclyl). In some embodiments, R^2 is  .

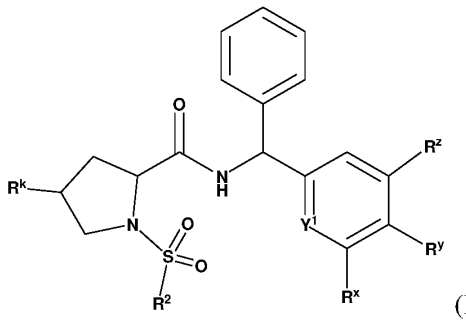
[0228] In some embodiments of a compound of formula (I') (I-G), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is (i) 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of ring A is optionally substituted with one or more oxo, or C_{1-6}alkyl, (ii) 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of ring A is optionally substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, $-NH_2$, or C_{3-10}cycloalkyl, wherein, the C_{1-6}alkyl is optionally substituted with one or more halo, and the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl, or (iii) C_{3-10}cycloalkyl.

[0229] In some embodiments of a compound of formula (I'), (I-G), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of ring A is optionally substituted with one or more oxo, or C_{1-6}alkyl,. In some embodiments ring A is selected from the group consisting of  ,  , and  .

[0230] In some embodiments of a compound of formula (I'), (I-G), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of ring A is optionally substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, $-NH_2$, or C_{3-10}cycloalkyl, wherein, the C_{1-6}alkyl is optionally substituted with one or more halo, and the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl. In some embodiments ring A is 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of ring A is optionally substituted with one or more C_{1-6}alkyl. In some embodiments ring A is selected from the group consisting of  ,  ,  ,  ,  ,  , and  .

[0231] In some embodiments of a compound of formula (I'), (I-G), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, ring A is C_{3-10}cycloalkyl. In some embodiments, ring A is C_{3-6}cycloalkyl. In some embodiments ring A is cyclopropyl.

[0232] In some embodiments, provided herein is a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of formula (I-H):



(I-H),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Y^1 is CR^x or N; wherein, when the ring bearing R^x, R^y and R^z is phenyl, R^x, R^y and R^z is H, halo, C_{1-6}alkyl, C_{2-6}alkenyl, -NH_2, -NH-C(O)-(C_{1-6}alkyl), -NH-C(O)-(3-15 membered heterocyclyl), C_{3-10}cycloalkyl, or 5-20 membered heteroaryl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, -NH-C(O)-NH(C_{1-6}alkyl), -NH-C(O)-C_{1-6}alkyl, or -NH-C(O)-C_{1-6}alkoxy, the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl, and the 5-20 membered heteroaryl is optionally substituted with one or more C_{1-6}alkyl; and wherein when the ring bearing R^x, R^y and R^z is pyridyl, R^x, R^y and R^z are each indepdently H, halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, -NH_2, or C_{3-10}cycloalkyl, wherein, the C_{1-6}alkyl is optionally substituted with one or more halo, and the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl.

[0233] In some embodiments, provided herein is a compound of formula (I), such as a compound of formula (I), (I-A), (I-A1), (I-A2), (I-A3), (I-A4), (I-B), (I-B1), (I-B2), (I-C), (I-D), (I-E), or (I-F), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is optionally substituted

with one or more R^a. In some embodiments, R^2 is C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl of R^2 is optionally substituted with one or more R^q. In other embodiments, R^2 is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^2 is optionally substituted with one or more halo, oxo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, or 5-20 membered heteroaryl. In some embodiments, R^2 is 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^2 is optionally substituted with one or more R^s. In some embodiments, R^2 is -N(R^g)(R^h), wherein R^g and R^h are independently H or C_{1-6}alkyl. In some embodiments, R^2 is -C(O)-R^j, wherein R^j is C_{3-10}cycloalkyl, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, or -NH(5-20 membered heteroaryl). In some embodiments, R^2 is C_{6-20}aryl, wherein the C_{6-20}aryl of R^2 is optionally substituted with one or more 5-20 membered heteroaryl or -O(R^p), wherein R^p is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^p is optionally substituted with one or more -C(O)-C_{1-6}alkyl.

[0234] In some embodiments, provided herein is a compound of formula (I'), such as a compound of formula (I), (I-A), (I-A1), (I-A2), (I-A3), (I-A4), (I-B), (I-B1), (I-B2), (I-C), (I-D), (I-D1), (I-D2), (I-E), (I-F), (I-G), or (I-H) or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is optionally substituted with one or more R^a. In some embodiments, R^2 is C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl of R^2 is optionally substituted with one or more R^q. In other embodiments, R^2 is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^2 is optionally substituted with one or more halo, oxo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, or 5-20 membered heteroaryl. In some embodiments, R^2 is 5-20 membered heteroaryl, or -(C_{1-4}alkyl)(5-20 membered heteroaryl), wherein the C_{1-4} alkyl is optionally substituted with one or more or more –OH, halo, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, and wherein the 5-20 membered heteroaryl is optionally substituted with one or more R^s. In some embodiments, R^2 is -N(R^g)(R^h), wherein R^g and R^h are independently H or C_{1-6}alkyl. In some embodiments, R^2 is -C(O)-R^j, wherein R^j is C_{3-10}cycloalkyl, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, or -NH(5-20 membered heteroaryl). In some embodiments, R^2 is C_{6-20}aryl, wherein the C_{6-20}aryl of R^2 is optionally substituted with one or more 5-20 membered heteroaryl or -O(R^p), wherein R^p is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^p is optionally substituted with one or more -C(O)-C_{1-6}alkyl.

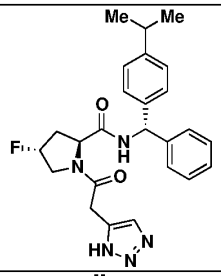
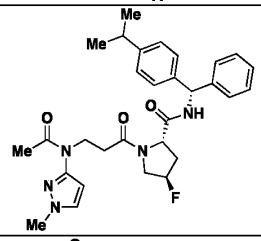
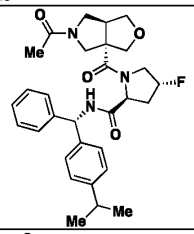
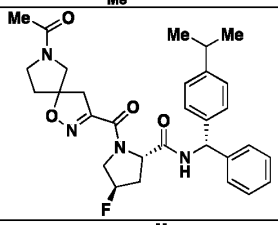
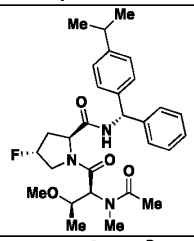
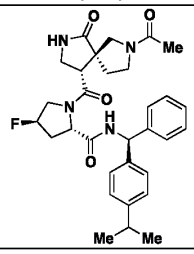
[0235] In some embodiments of a compound of formula (I), or formula (I'), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, the compound, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, is selected from Table 1.

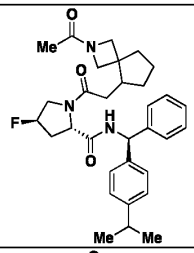
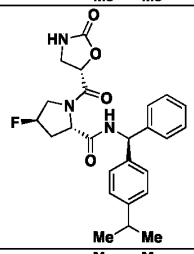
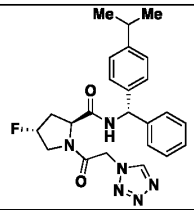
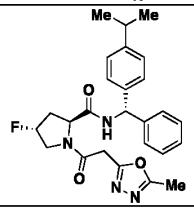
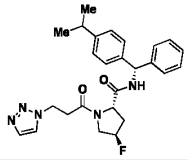
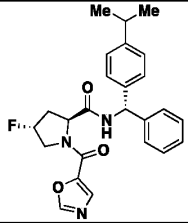
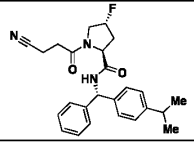
[0236] Compound Names included in Table 1 and for all intermediates and compounds were generated using ChemDraw® Professional software version 17.1.1.0 or Collaborative Drug Discovery Inc. (CDD) CDD Vault update #3.

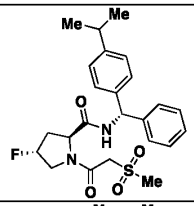
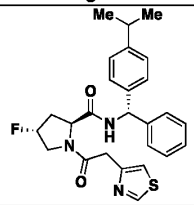
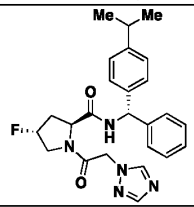
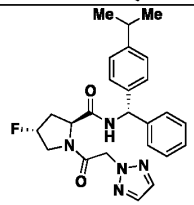
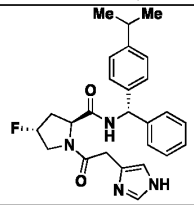
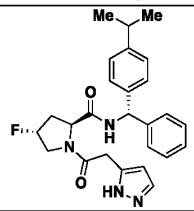
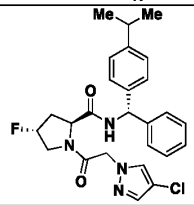
[0237] A Knime workflow was created to retrieve structures from an internal ChemAxon Compound Registry, generate the canonical smiles using RDKit Canon SMILES node, remove the stereochemistry using ChemAxon/Infocom MolConverter node, and name the structure using ChemAxon/Infocom Naming node. The following denotes the version of the Knime Analytics Platform and extensions utilized in the workflow:

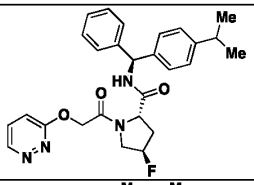
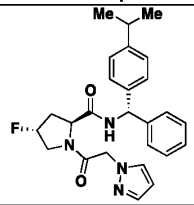
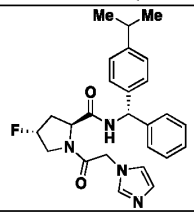
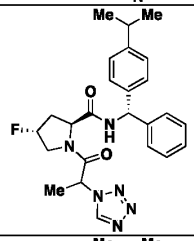
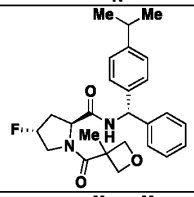
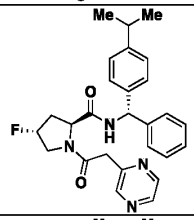
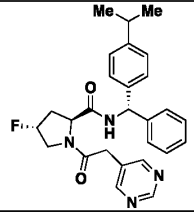
- Knime Analytics Platform 4.2.2
- RDKit Knime Integration 4.0.1.v202006261025 (this extension includes the RDKit Canon SMILES node)
- ChemAxon/Infocom Marvin Extensions Feature 4.3.0v202100 (this extension includes the MolConverter node)
- ChemAxon/Infocom JChem Extensions Feature 4.3.0v202100 (this extension includes the Naming node)

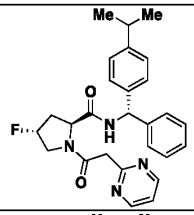
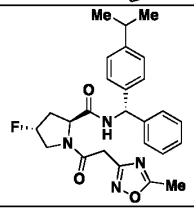
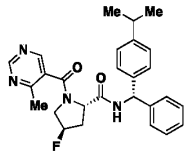
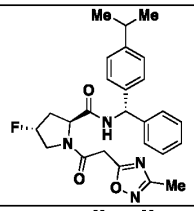
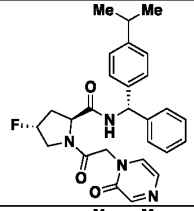
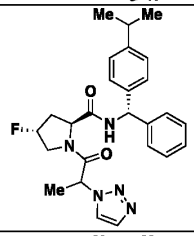
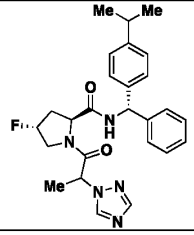
Table 1

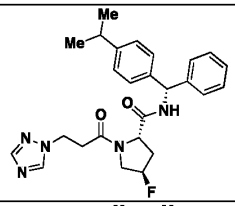
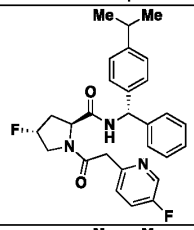
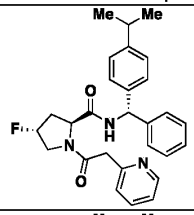
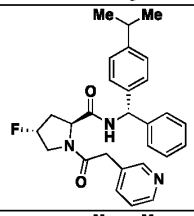
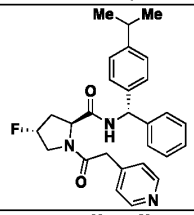
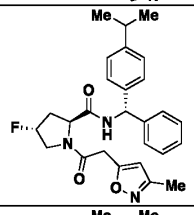
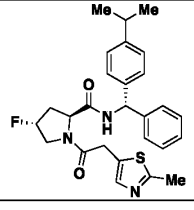
Compound No.	Structure	IUPAC
1		(2*S*,4*R*)-1-(2-(1*H*-1,2,3-triazol-5-yl)acetyl)-4-fluoro-*N*-((*S*)-(4-isopropylphenyl)(phenyl)methyl)pyrrolidine-2-carboxamide
2		(2S,4R)-4-fluoro-1-{3-[N-(1-methyl-1H-pyrazol-3-yl)acetamido]propanoyl}-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
3		(2S,4R)-1-[(3aS,6aS)-5-acetyl-hexahydro-1H-furo[3,4-c]pyrrole-3a-carbonyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
4		(2S,4R)-1-{7-acetyl-1-oxa-2,7-diazaspiro[4.4]non-2-ene-3-carbonyl}-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
5		(2S,4R)-4-fluoro-1-[(2S,3R)-3-methoxy-2-(N-methylacetamido)butanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
6		(2S,4R)-1-[(4S,5R)-7-acetyl-1-oxo-2,7-diazaspiro[4.4]nonane-4-carbonyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide

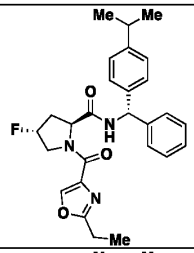
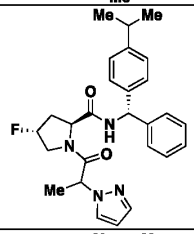
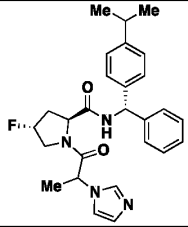
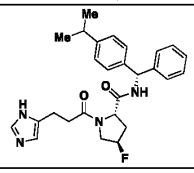
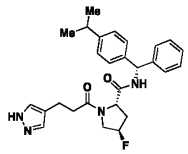
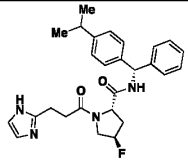
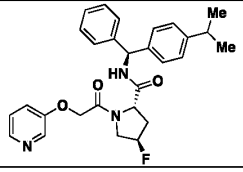
7		(2S,4R)-1-(2-{2-acetyl-2-azaspiro[3.4]octan-5-yl}acetyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
8		(2S,4R)-4-fluoro-1-[(5S)-2-oxo-1,3-oxazolidine-5-carbonyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
9		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(1H-1,2,3,4-tetrazol-1-yl)acetyl]pyrrolidine-2-carboxamide
10		(2S,4R)-4-fluoro-1-[2-(5-methyl-1,3,4-oxadiazol-2-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
11		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[3-(1H-1,2,3-triazol-1-yl)propanoyl]pyrrolidine-2-carboxamide
12		(2S,4R)-4-fluoro-1-(1,3-oxazole-5-carbonyl)-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
13		(2S,4R)-1-(3-cyanopropanoyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide

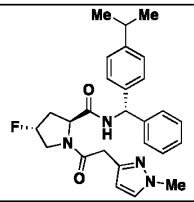
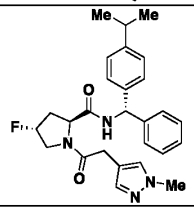
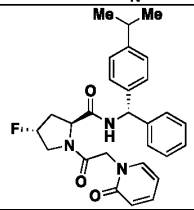
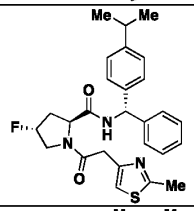
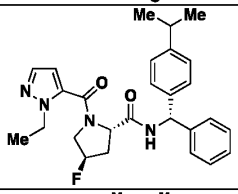
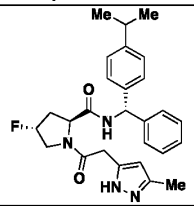
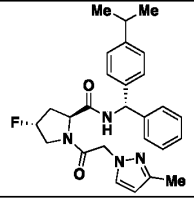
14		(2S,4R)-4-fluoro-1-(2-methanesulfonylacetyl)-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
15		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(1,3-thiazol-4-yl)acetyl]pyrrolidine-2-carboxamide
16		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(1H-1,2,4-triazol-1-yl)acetyl]pyrrolidine-2-carboxamide
17		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(2H-1,2,3-triazol-2-yl)acetyl]pyrrolidine-2-carboxamide
18		(2S,4R)-4-fluoro-1-[2-(1H-imidazol-4-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
19		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(1H-pyrazol-5-yl)acetyl]pyrrolidine-2-carboxamide
20		(2S,4R)-1-[2-(4-chloro-1H-pyrazol-1-yl)acetyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide

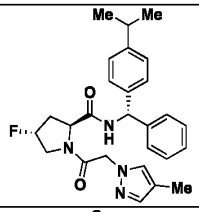
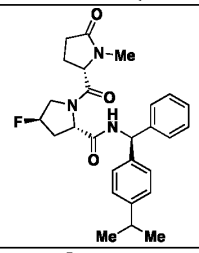
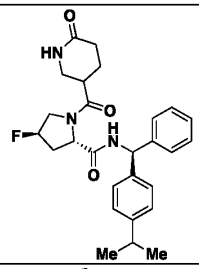
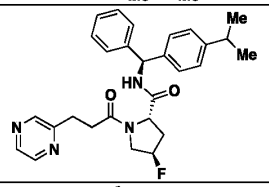
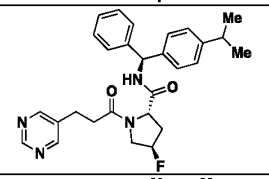
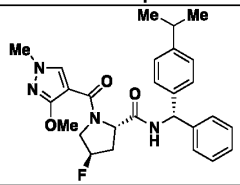
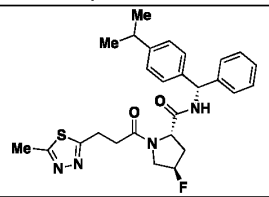
21		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(pyridazin-3-yloxy)acetyl]pyrrolidine-2-carboxamide
22		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(1H-pyrazol-1-yl)acetyl]pyrrolidine-2-carboxamide
23		(2S,4R)-4-fluoro-1-[2-(1H-imidazol-1-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
24		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(1H-1,2,3,4-tetrazol-1-yl)propanoyl]pyrrolidine-2-carboxamide
25		(2S,4R)-4-fluoro-1-(3-methyloxetane-3-carbonyl)-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
26		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(pyrazin-2-yl)acetyl]pyrrolidine-2-carboxamide
27		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(pyrimidin-5-yl)acetyl]pyrrolidine-2-carboxamide

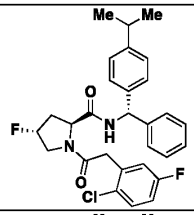
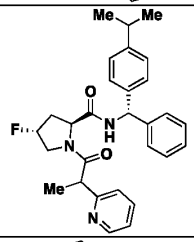
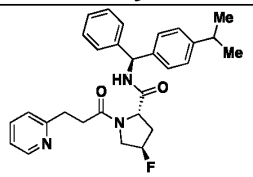
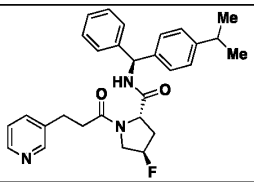
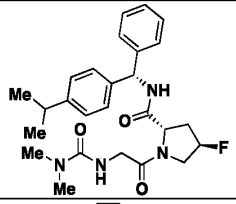
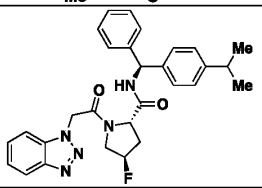
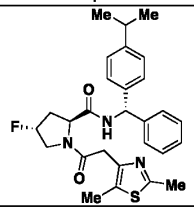
28		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(pyrimidin-2-yl)acetyl]pyrrolidine-2-carboxamide
29		(2S,4R)-4-fluoro-1-[2-(5-methyl-1,2,4-oxadiazol-3-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
30		(2S,4R)-4-fluoro-1-(4-methylpyrimidine-5-carbonyl)-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
31		(2S,4R)-4-fluoro-1-[2-(3-methyl-1,2,4-oxadiazol-5-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
32		(2S,4R)-4-fluoro-1-[2-(2-oxo-1,2-dihydropyrazin-1-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
33		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(1H-1,2,3-triazol-1-yl)propanoyl]pyrrolidine-2-carboxamide
34		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(1H-1,2,4-triazol-1-yl)propanoyl]pyrrolidine-2-carboxamide

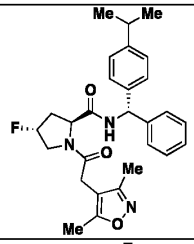
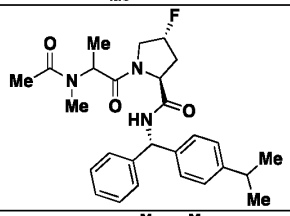
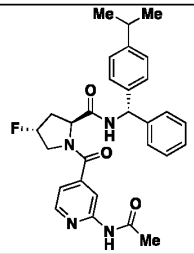
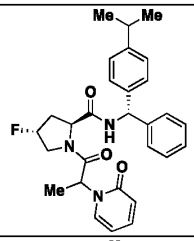
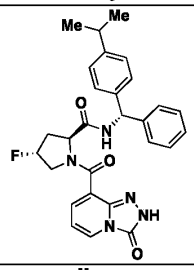
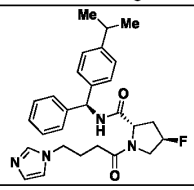
35		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[3-(1H-1,2,4-triazol-1-yl)propanoyl]pyrrolidine-2-carboxamide
36		(2S,4R)-4-fluoro-1-[2-(5-fluoropyridin-2-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
37		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(pyridin-2-yl)acetyl]pyrrolidine-2-carboxamide
38		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(pyridin-3-yl)acetyl]pyrrolidine-2-carboxamide
39		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(pyridin-4-yl)acetyl]pyrrolidine-2-carboxamide
40		(2S,4R)-4-fluoro-1-[2-(3-methyl-1,2-oxazol-5-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
41		(2S,4R)-4-fluoro-1-[2-(2-methyl-1,3-thiazol-5-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide

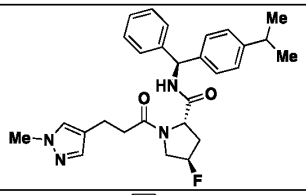
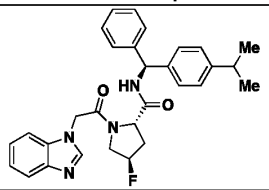
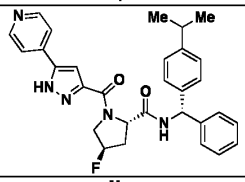
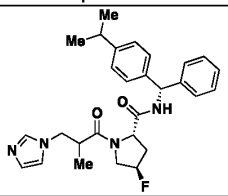
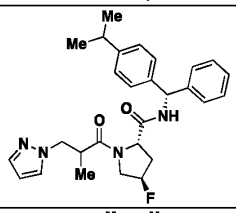
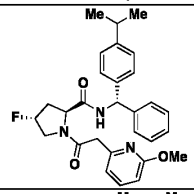
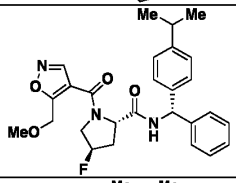
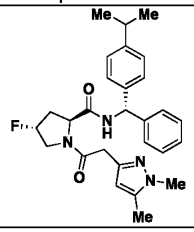
42		(2S,4R)-1-(2-ethyl-1,3-oxazole-4-carbonyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
43		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(1H-pyrazol-1-yl)propanoyl]pyrrolidine-2-carboxamide
44		(2S,4R)-4-fluoro-1-[2-(1H-imidazol-1-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
45		(2S,4R)-4-fluoro-1-[3-(1H-imidazol-5-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
46		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[3-(1H-pyrazol-4-yl)propanoyl]pyrrolidine-2-carboxamide
47		(2S,4R)-4-fluoro-1-[3-(1H-imidazol-2-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
48		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(pyridin-3-yloxy)acetyl]pyrrolidine-2-carboxamide

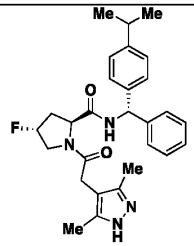
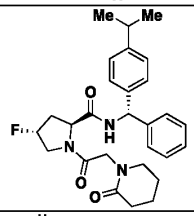
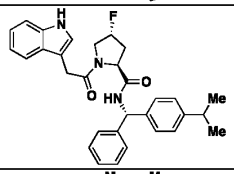
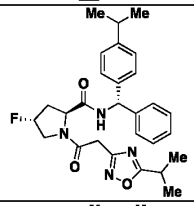
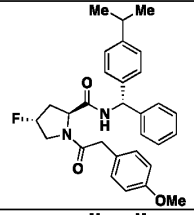
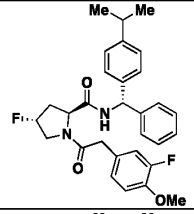
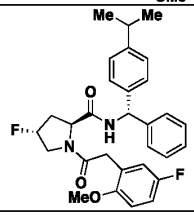
49		(2S,4R)-4-fluoro-1-[2-(1-methyl-1H-pyrazol-3-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
50		(2S,4R)-4-fluoro-1-[2-(1-methyl-1H-pyrazol-4-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
51		(2S,4R)-4-fluoro-1-[2-(2-oxo-1,2-dihydropyridin-1-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
52		(2S,4R)-4-fluoro-1-[2-(2-methyl-1,3-thiazol-4-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
53		(2S,4R)-1-(1-ethyl-1H-pyrazole-5-carbonyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
54		(2S,4R)-4-fluoro-1-[2-(3-methyl-1H-pyrazol-5-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
55		(2S,4R)-4-fluoro-1-[2-(3-methyl-1H-pyrazol-1-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide

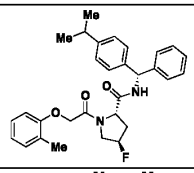
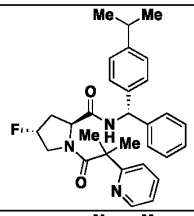
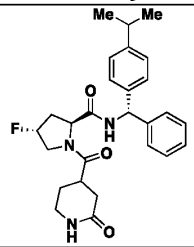
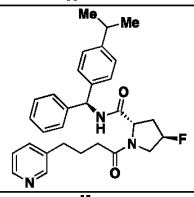
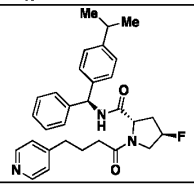
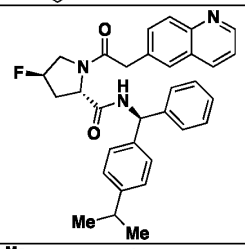
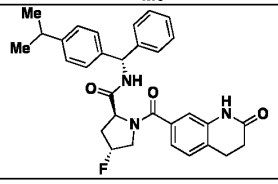
56		(2S,4R)-4-fluoro-1-[2-(4-methyl-1H-pyrazol-1-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
57		(2S,4R)-4-fluoro-1-[(2S)-1-methyl-5-oxopyrrolidine-2-carbonyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
58		(2S,4R)-4-fluoro-1-(6-oxopiperidine-3-carbonyl)-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
59		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[3-(pyrazin-2-yl)propanoyl]pyrrolidine-2-carboxamide
60		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[3-(pyrimidin-5-yl)propanoyl]pyrrolidine-2-carboxamide
61		(2S,4R)-4-fluoro-1-(3-methoxy-1-methyl-1H-pyrazole-4-carbonyl)-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
62		(2S,4R)-4-fluoro-1-[3-(5-methyl-1,3,4-thiadiazol-2-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide

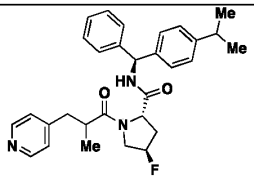
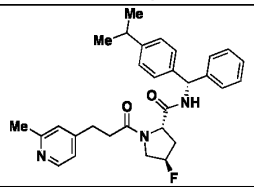
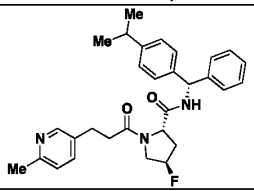
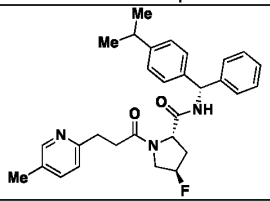
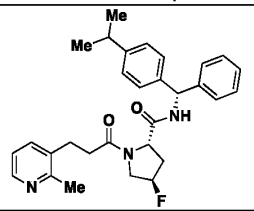
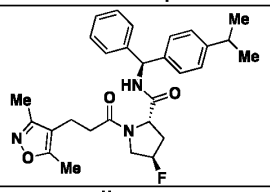
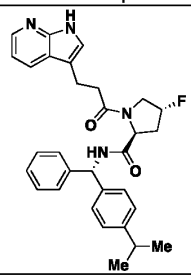
63		(2S,4R)-1-[2-(2-chloro-5-fluorophenyl)acetyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
64		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(pyridin-2-yl)propanoyl]pyrrolidine-2-carboxamide
65		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[3-(pyridin-2-yl)propanoyl]pyrrolidine-2-carboxamide
66		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[3-(pyridin-3-yl)propanoyl]pyrrolidine-2-carboxamide
67		(2S,4R)-1-{2-[(dimethylcarbamoyl)amino]acetyl}-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
68		(2S,4R)-1-[2-(1H-1,2,3-benzotriazol-1-yl)acetyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
69		(2S,4R)-1-[2-(2,5-dimethyl-1,3-thiazol-4-yl)acetyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide

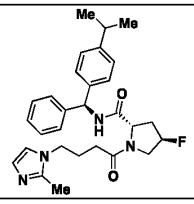
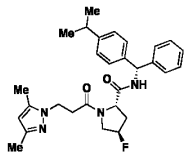
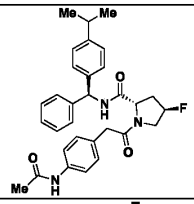
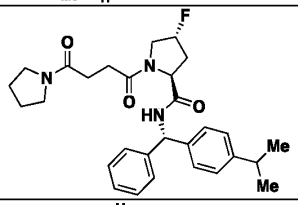
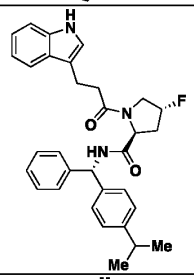
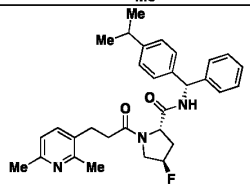
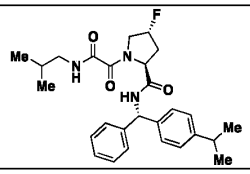
70		(2S,4R)-1-[2-(3,5-dimethyl-1,2-oxazol-4-yl)acetyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
71		(2S,4R)-4-fluoro-1-[2-(N-methylacetamido)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
72		(2S,4R)-1-(2-acetamidopyridine-4-carbonyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
73		(2S,4R)-4-fluoro-1-[2-(2-oxo-1,2-dihydropyridin-1-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
74		(2S,4R)-4-fluoro-1-{3-oxo-2H,3H-[1,2,4]triazolo[4,3-a]pyridine-8-carbonyl}-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
75		(2S,4R)-4-fluoro-1-[4-(1H-imidazol-1-yl)butanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide

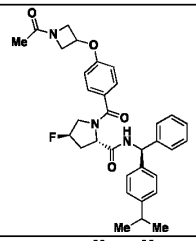
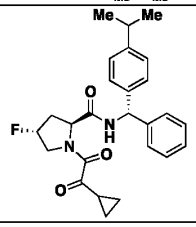
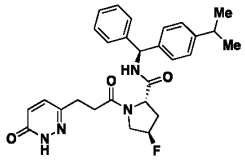
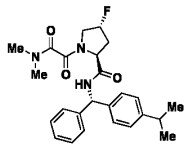
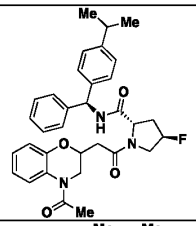
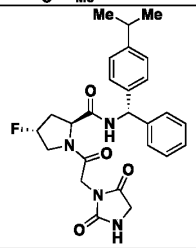
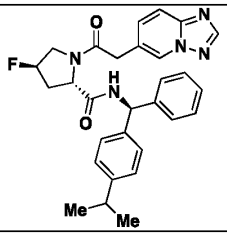
76		(2S,4R)-4-fluoro-1-[3-(1-methyl-1H-pyrazol-4-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
77		(2S,4R)-1-[2-(1H-1,3-benzodiazol-1-yl)acetyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
78		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[5-(pyridin-4-yl)-1H-pyrazole-3-carbonyl]pyrrolidine-2-carboxamide
79		(2S,4R)-4-fluoro-1-[3-(1H-imidazol-1-yl)-2-methylpropanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
80		(2S,4R)-4-fluoro-1-[2-methyl-3-(1H-pyrazol-1-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
81		(2S,4R)-4-fluoro-1-[2-(6-methoxypyridin-2-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
82		(2S,4R)-4-fluoro-1-[5-(methoxymethyl)-1,2-oxazole-4-carbonyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
83		(2S,4R)-1-[2-(1,5-dimethyl-1H-pyrazol-3-yl)acetyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide

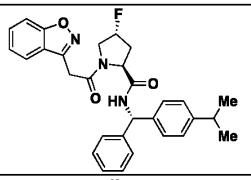
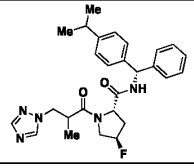
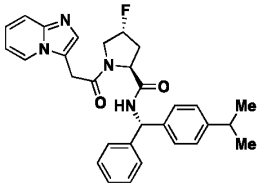
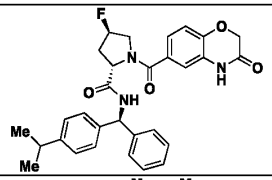
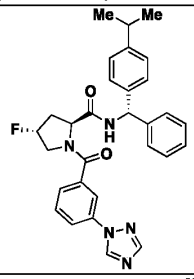
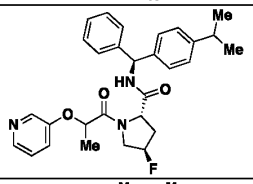
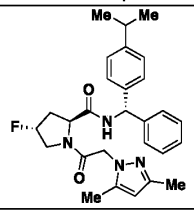
84		(2S,4R)-1-[2-(3,5-dimethyl-1H-pyrazol-4-yl)acetyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
85		(2S,4R)-4-fluoro-1-[2-(2-oxopiperidin-1-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
86		(2S,4R)-4-fluoro-1-[2-(1H-indol-3-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
87		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-{2-[5-(propan-2-yl)-1,2,4-oxadiazol-3-yl]acetyl}pyrrolidine-2-carboxamide
88		(2S,4R)-4-fluoro-1-[2-(4-methoxyphenyl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
89		(2S,4R)-4-fluoro-1-[2-(3-fluoro-4-methoxyphenyl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
90		(2S,4R)-4-fluoro-1-[2-(5-fluoro-2-methoxyphenyl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide

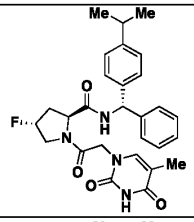
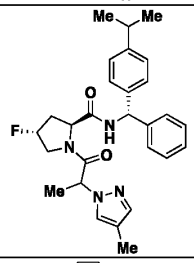
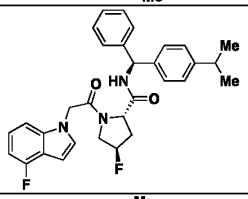
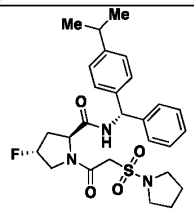
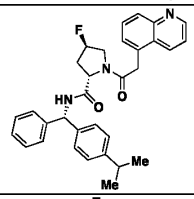
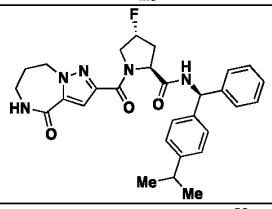
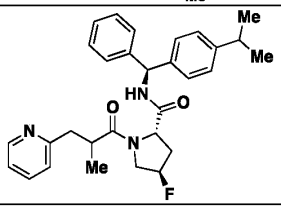
91		(2S,4R)-4-fluoro-1-[2-(2-methylphenoxy)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
92		(2S,4R)-4-fluoro-1-[2-methyl-2-(pyridin-2-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
93		(2S,4R)-4-fluoro-1-(2-oxopiperidine-4-carbonyl)-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
94		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[4-(pyridin-3-yl)butanoyl]pyrrolidine-2-carboxamide
95		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[4-(pyridin-4-yl)butanoyl]pyrrolidine-2-carboxamide
96		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(quinolin-6-yl)acetyl]pyrrolidine-2-carboxamide
97		(2S,4R)-4-fluoro-1-(2-oxo-1,2,3,4-tetrahydroquinoline-7-carbonyl)-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide

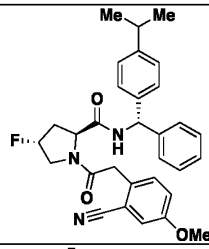
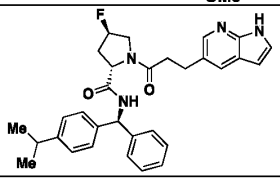
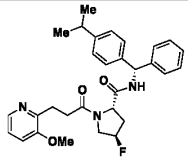
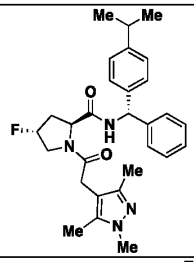
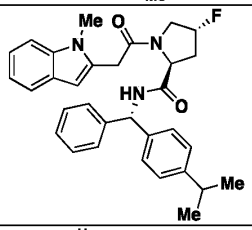
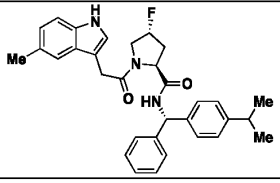
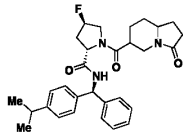
98		(2S,4R)-4-fluoro-1-[2-methyl-3-(pyridin-4-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
99		(2S,4R)-4-fluoro-1-[3-(2-methylpyridin-4-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
100		(2S,4R)-4-fluoro-1-[3-(6-methylpyridin-3-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
101		(2S,4R)-4-fluoro-1-[3-(5-methylpyridin-2-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
102		(2S,4R)-4-fluoro-1-[3-(2-methylpyridin-3-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
103		(2S,4R)-1-[3-(3,5-dimethyl-1,2-oxazol-4-yl)propanoyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
104		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-(3-{1H-pyrrolo[2,3-b]pyridin-3-yl}propanoyl)pyrrolidine-2-carboxamide

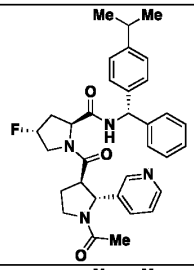
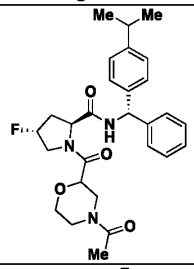
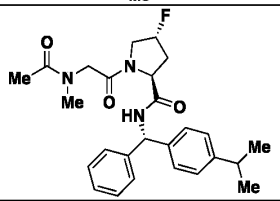
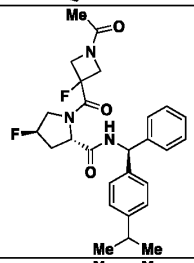
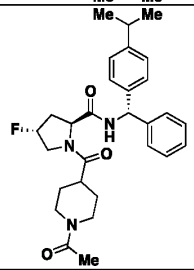
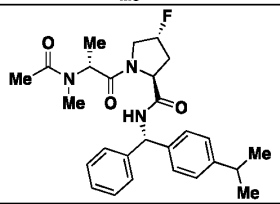
105		(2S,4R)-4-fluoro-1-[4-(2-methyl-1H-imidazol-1-yl)butanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
106		(2S,4R)-1-[3-(3,5-dimethyl-1H-pyrazol-1-yl)propanoyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
107		(2S,4R)-1-[2-(4-acetamidophenyl)acetyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
108		(2S,4R)-4-fluoro-1-[4-oxo-4-(pyrrolidin-1-yl)butanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
109		(2S,4R)-4-fluoro-1-[3-(1H-indol-3-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
110		(2S,4R)-1-[3-(2,6-dimethylpyridin-3-yl)propanoyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
111		(2S,4R)-4-fluoro-1-{[(2-methylpropyl)carbamoyl]carbonyl}-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide

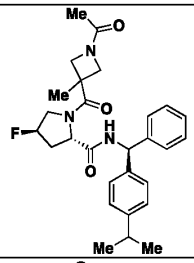
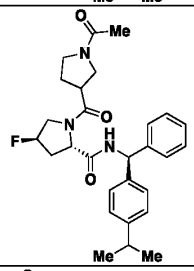
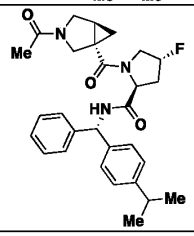
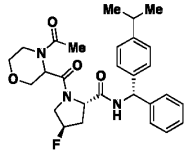
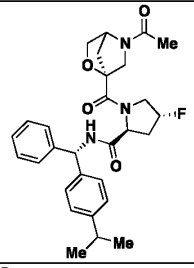
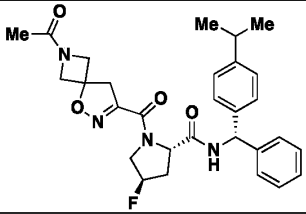
112		(2S,4R)-1-{4-[(1-acetylazetidin-3-yl)oxy]benzoyl}-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
113		(2S,4R)-1-(2-cyclopropyl-2-oxoacetyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
114		(2S,4R)-4-fluoro-1-[3-(6-oxo-1,6-dihydropyridazin-3-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
115		(2S,4R)-1-[(dimethylcarbamoyl)carbonyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
116		(2S,4R)-1-[2-(4-acetyl-3,4-dihydro-2H-1,4-benzoxazin-2-yl)acetyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
117		(2S,4R)-1-[2-(2,5-dioxoimidazolidin-1-yl)acetyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
118		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-(2-{[1,2,4]triazolo[1,5-a]pyridin-6-yl}acetyl)pyrrolidine-2-carboxamide

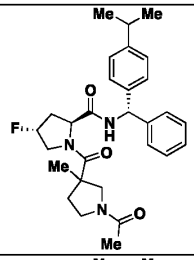
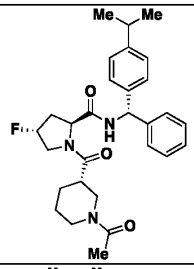
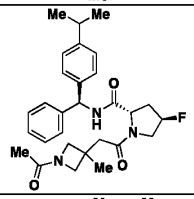
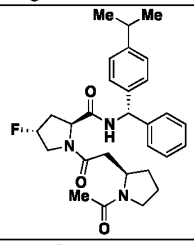
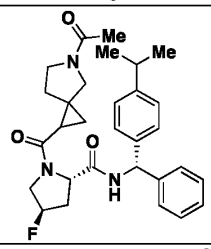
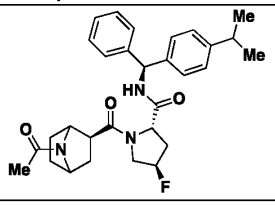
119		(2S,4R)-1-[2-(1,2-benzoxazol-3-yl)acetyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
120		(2S,4R)-4-fluoro-1-[2-methyl-3-(1H-1,2,4-triazol-1-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
121		(2S,4R)-4-fluoro-1-(2-{imidazo[1,2-a]pyridin-3-yl}acetyl)-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
122		(2S,4R)-4-fluoro-1-(3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carbonyl)-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
123		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[3-(1H-1,2,4-triazol-1-yl)benzoyl]pyrrolidine-2-carboxamide
124		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(pyridin-3-yloxy)propanoyl]pyrrolidine-2-carboxamide
125		(2S,4R)-1-[2-(3,5-dimethyl-1H-pyrazol-1-yl)acetyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide

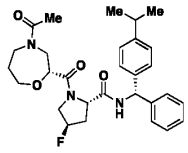
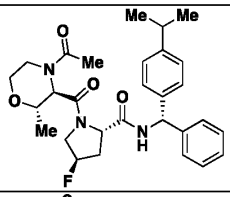
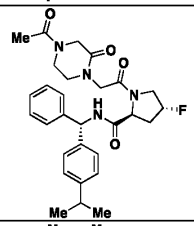
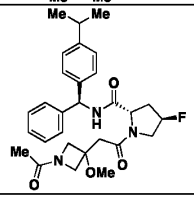
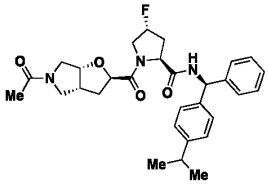
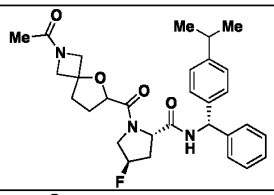
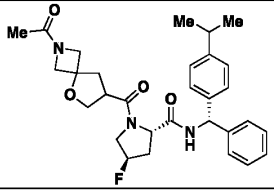
126		(2S,4R)-4-fluoro-1-[2-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
127		(2S,4R)-4-fluoro-1-[2-(4-methyl-1H-pyrazol-1-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
128		(2S,4R)-4-fluoro-1-[2-(4-fluoro-1H-indol-1-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
129		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(pyrrolidine-1-sulfonyl)acetyl]pyrrolidine-2-carboxamide
130		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(quinolin-5-yl)acetyl]pyrrolidine-2-carboxamide
131		(2S,4R)-4-fluoro-1-{4-oxo-4H,5H,6H,7H,8H-pyrazolo[1,5-a][1,4]diazepine-2-carbonyl}-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
132		(2S,4R)-4-fluoro-1-[2-methyl-3-(pyridin-2-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide

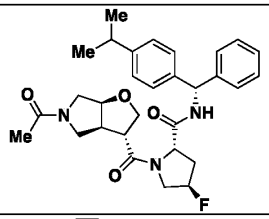
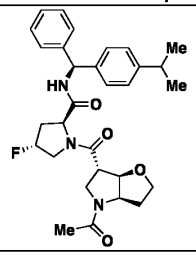
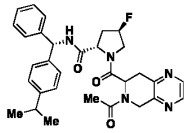
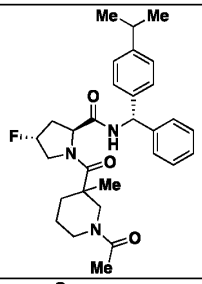
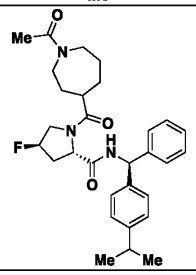
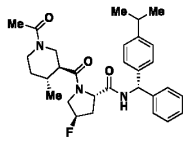
133		(2S,4R)-1-[2-(2-cyano-4-methoxyphenyl)acetyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
134		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-(3-{1H-pyrrolo[2,3-b]pyridin-5-yl}propanoyl)pyrrolidine-2-carboxamide
135		(2S,4R)-4-fluoro-1-[3-(3-methoxypyridin-2-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
136		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(1,3,5-trimethyl-1H-pyrazol-4-yl)acetyl]pyrrolidine-2-carboxamide
137		(2S,4R)-4-fluoro-1-[2-(1-methyl-1H-indol-2-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
138		(2S,4R)-4-fluoro-1-[2-(5-methyl-1H-indol-3-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
139		(2S,4R)-4-fluoro-1-(3-oxo-octahydroindolizine-6-carbonyl)-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide

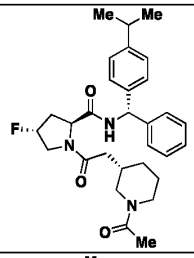
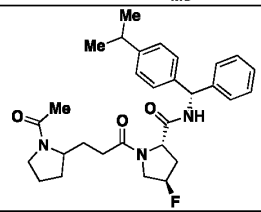
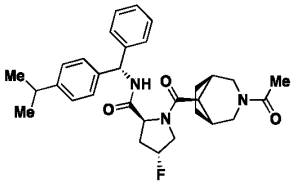
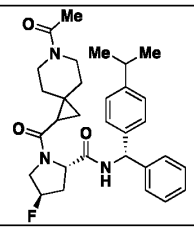
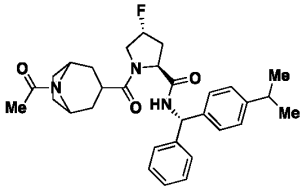
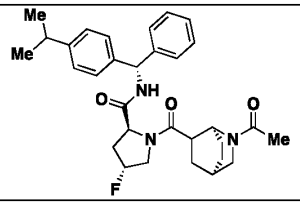
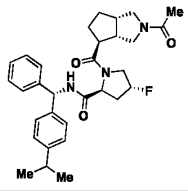
140		(2S,4R)-1-[(2R,3R)-1-acetyl-2-(pyridin-3-yl)pyrrolidine-3-carbonyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
141		(2S,4R)-1-(4-acetylmorpholine-2-carbonyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
142		(2S,4R)-4-fluoro-1-[2-(N-methylacetamido)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
143		(2S,4R)-1-(1-acetyl-3-fluoroazetidine-3-carbonyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
144		(2S,4R)-1-(1-acetylpiperidine-4-carbonyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
145		(2S,4R)-4-fluoro-1-[(2R)-2-(N-methylacetamido)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide

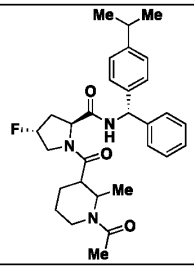
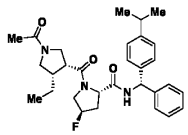
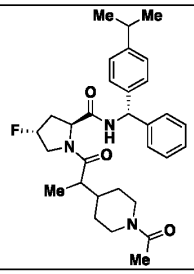
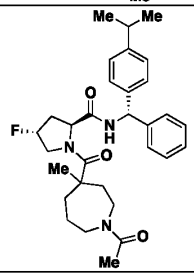
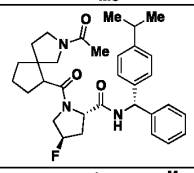
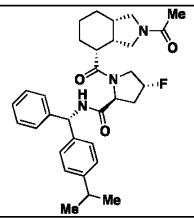
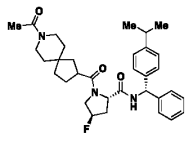
146		(2S,4R)-1-(1-acetyl-3-methylazetidine-3-carbonyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
147		(2S,4R)-1-(1-acetylpyrrolidine-3-carbonyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
148		(2S,4R)-1-[(1S,5S)-3-acetyl-3-azabicyclo[3.1.0]hexane-1-carbonyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
149		(2S,4R)-1-(4-acetylmorpholine-3-carbonyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
150		(2S,4R)-1-[(1S)-5-acetyl-2-oxa-5-azabicyclo[2.2.1]heptane-1-carbonyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
151		(2S,4R)-1-{2-acetyl-5-oxa-2,6-diazaspiro[3.4]oct-6-ene-7-carbonyl}-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide

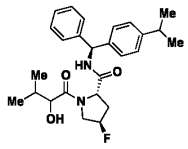
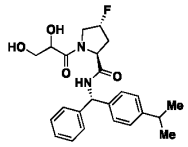
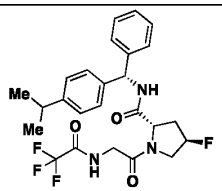
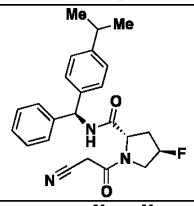
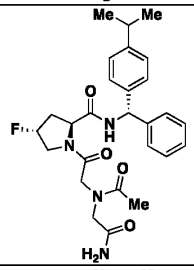
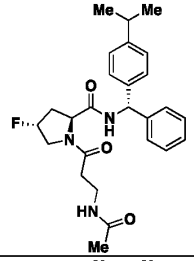
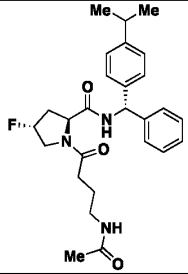
152		(2S,4R)-1-(1-acetyl-3-methylpyrrolidine-3-carbonyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
153		(2S,4R)-1-[(3S)-1-acetylpiperidine-3-carbonyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
154		(2S,4R)-1-[2-(1-acetyl-3-methylazetidin-3-yl)acetyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
155		(2S,4R)-1-{2-[(2R)-1-acetylpyrrolidin-2-yl]acetyl}-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
156		(2S,4R)-1-{5-acetyl-5-azaspiro[2.4]heptane-1-carbonyl}-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
157		(2S,4R)-1-[(2S)-7-acetyl-7-azabicyclo[2.2.1]heptane-2-carbonyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide

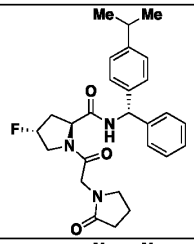
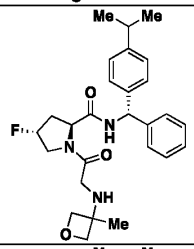
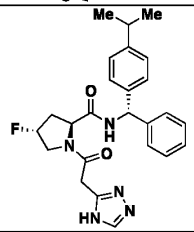
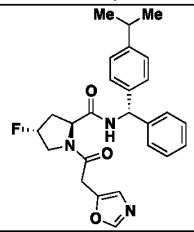
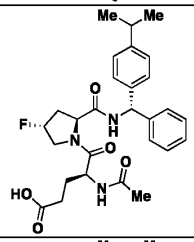
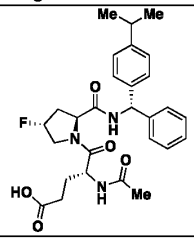
158		(2S,4R)-1-[(2R)-4-acetyl-1,4-oxazepane-2-carbonyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
159		(2S,4R)-1-[(2S,3R)-4-acetyl-2-methylmorpholine-3-carbonyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
160		(2S,4R)-1-[2-(4-acetyl-2-oxopiperazin-1-yl)acetyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
161		(2S,4R)-1-[2-(1-acetyl-3-methoxyazetidin-3-yl)acetyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
162		(2S,4R)-1-[(2R,3aR,6aR)-5-acetyl-hexahydro-2H-furo[2,3-c]pyrrole-2-carbonyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
163		(2S,4R)-1-{2-acetyl-5-oxa-2-azaspiro[3.4]octane-6-carbonyl}-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
164		(2S,4R)-1-{2-acetyl-5-oxa-2-azaspiro[3.4]octane-7-carbonyl}-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide

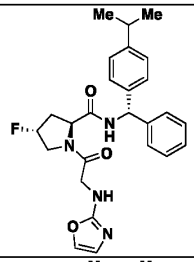
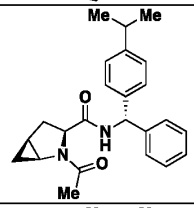
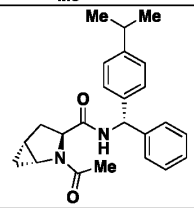
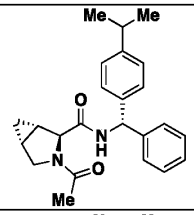
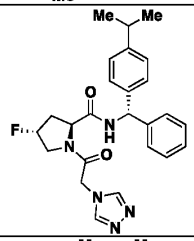
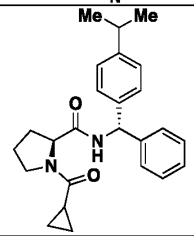
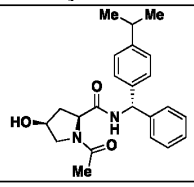
165		(2S,4R)-1-[(3R,3aS,6aS)-5-acetyl-hexahydro-2H-furo[2,3-c]pyrrole-3-carbonyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
166		(2S,4R)-1-[(3aR,6S,6aR)-4-acetyl-hexahydro-2H-furo[3,2-b]pyrrole-6-carbonyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
167		(2S,4R)-1-{6-acetyl-5H,6H,7H,8H-pyrido[3,4-b]pyrazine-7-carbonyl}-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
168		(2S,4R)-1-(1-acetyl-3-methylpiperidine-3-carbonyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
169		(2S,4R)-1-(1-acetylazepane-4-carbonyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
170		(2S,4R)-1-[(3S,4R)-1-acetyl-4-methylpiperidine-3-carbonyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide

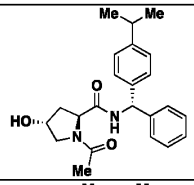
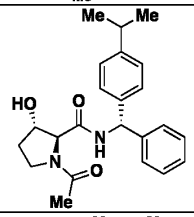
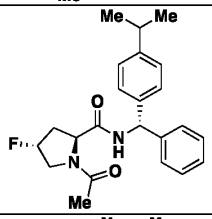
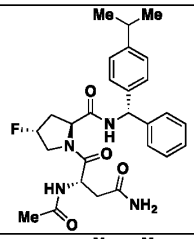
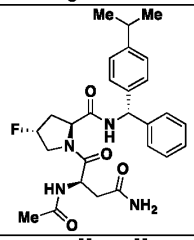
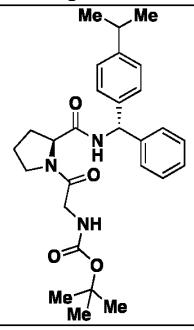
171		(2S,4R)-1-{2-[(3S)-1-acetylpiperidin-3-yl]acetyl}-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
172		(2S,4R)-1-[3-(1-acetylpyrrolidin-2-yl)propanoyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
173		(2S,4R)-1-[(1R,5S,8S)-3-acetyl-3-azabicyclo[3.2.1]octane-8-carbonyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
174		(2S,4R)-1-{6-acetyl-6-azaspiro[2.5]octane-1-carbonyl}-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
175		(2S,4R)-1-{8-acetyl-8-azabicyclo[3.2.1]octane-3-carbonyl}-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
176		(2S,4R)-1-[(1S,4R)-2-acetyl-2-azabicyclo[2.2.2]octane-6-carbonyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
177		(2S,4R)-1-[(3aS,4S,6aS)-2-acetyl-octahydrocyclopenta[c]pyrrole-4-carbonyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide

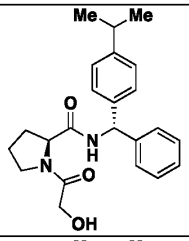
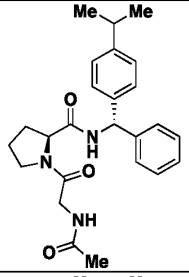
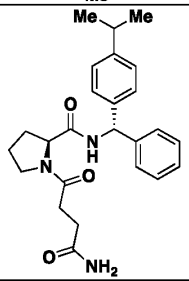
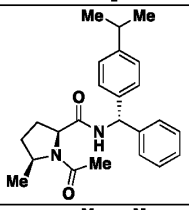
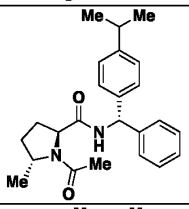
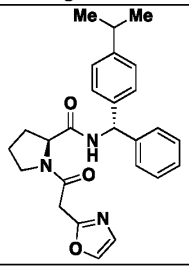
178		(2S,4R)-1-(1-acetyl-2-methylpiperidine-3-carbonyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
179		(2S,4R)-1-[(3R,4S)-1-acetyl-4-ethylpyrrolidine-3-carbonyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
180		(2S,4R)-1-[2-(1-acetylpiperidin-4-yl)propanoyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
181		(2S,4R)-1-(1-acetyl-4-methylazepane-4-carbonyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
182		(2S,4R)-1-{2-acetyl-2-azaspiro[4.4]nonane-6-carbonyl}-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
183		(2S,4R)-1-[(3aS,4R,7aS)-2-acetyl-octahydro-1H-isoindole-4-carbonyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
184		(2S,4R)-1-{8-acetyl-8-azaspiro[4.5]decane-2-carbonyl}-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide

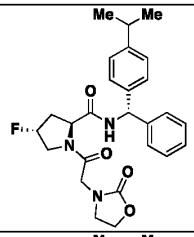
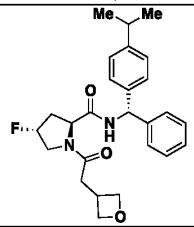
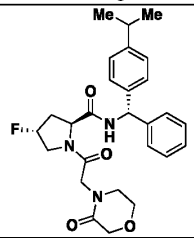
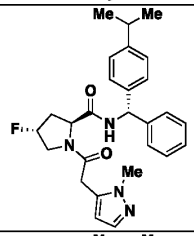
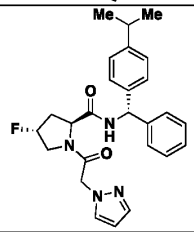
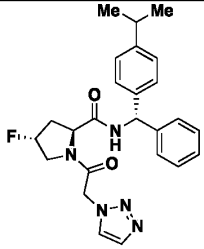
185		(2S,4R)-4-fluoro-1-(2-hydroxy-3-methylbutanoyl)-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
186		(2S,4R)-1-(2,3-dihydroxypropanoyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
187		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(2,2,2-trifluoroacetamido)acetyl]pyrrolidine-2-carboxamide
188		(2S,4R)-1-(2-cyanoacetyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
189		(2S,4R)-1-{2-[N-(carbamoylmethyl)acetamido]acetyl}-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
190		(2S,4R)-1-(3-acetamidopropanoyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
191		(2S,4R)-1-(4-acetamidobutanoyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide

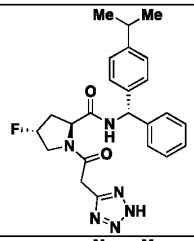
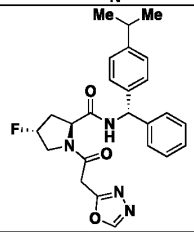
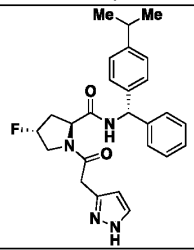
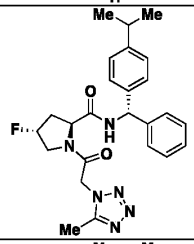
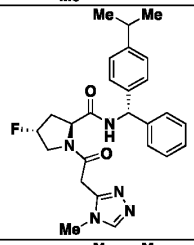
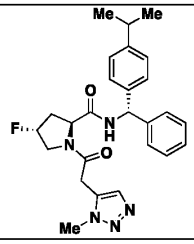
192		(2S,4R)-4-fluoro-1-[2-(2-oxopyrrolidin-1-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
193		(2S,4R)-4-fluoro-1-{2-[(3-methyloxetan-3-yl)amino]acetyl}-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
194		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(4H-1,2,4-triazol-3-yl)acetyl]pyrrolidine-2-carboxamide
195		(2S,4R)-4-fluoro-1-[2-(1,3-oxazol-5-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
196		(4S)-4-acetamido-5-[(2S,4R)-4-fluoro-2-{[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]carbamoyl}pyrrolidin-1-yl]-5-oxopentanoic acid
197		(4R)-4-acetamido-5-[(2S,4R)-4-fluoro-2-{[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]carbamoyl}pyrrolidin-1-yl]-5-oxopentanoic acid

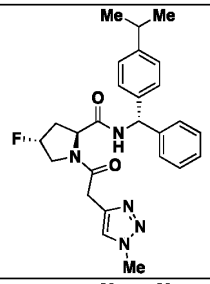
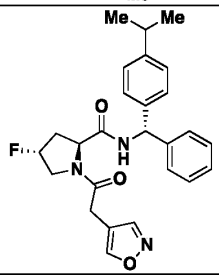
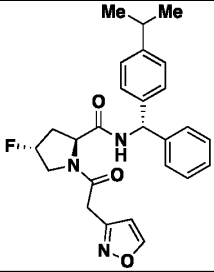
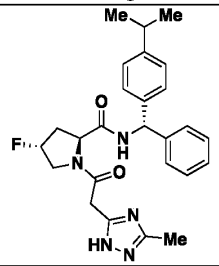
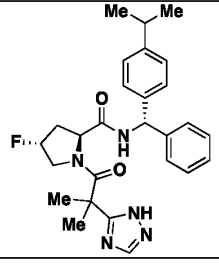
198		(2S,4R)-4-fluoro-1-{2-[(1,3-oxazol-2-yl)amino]acetyl}-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
199		(1S,3S,5S)-2-acetyl-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-2-azabicyclo[3.1.0]hexane-3-carboxamide
200		(1R,3S,5R)-2-acetyl-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-2-azabicyclo[3.1.0]hexane-3-carboxamide
201		(1S,2S,5R)-3-acetyl-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide
202		(2RS,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(4H-1,2,4-triazol-4-yl)acetyl]pyrrolidine-2-carboxamide
203		(2S)-1-cyclopropanecarbonyl-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
204		(2S,4S)-1-acetyl-4-hydroxy-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide

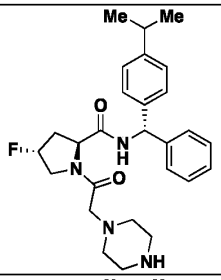
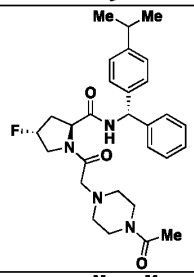
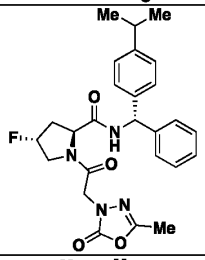
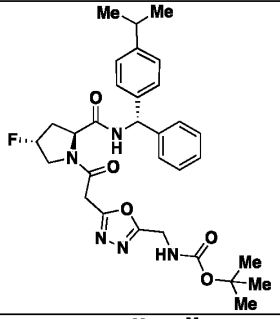
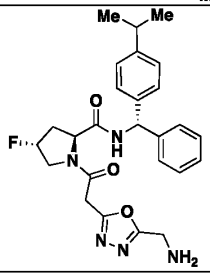
205		(2S,4R)-1-acetyl-4-hydroxy-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
206		(2S,3S)-1-acetyl-3-hydroxy-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
207		(2S,4R)-1-acetyl-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
208		(2S,4R)-1-[(2S)-3-carbamoyl-2-acetamidopropanoyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
209		(2S,4R)-1-[(2R)-3-carbamoyl-2-acetamidopropanoyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
210		tert-butyl N-{2-oxo-2-[(2S)-2-{[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]carbamoyl}pyrrolidin-1-yl]ethyl}carbamate

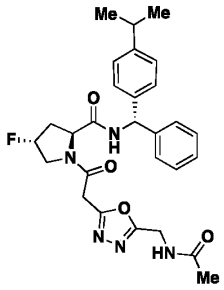
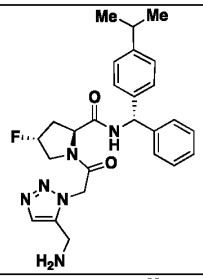
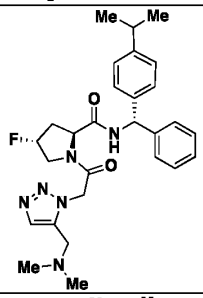
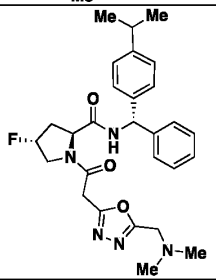
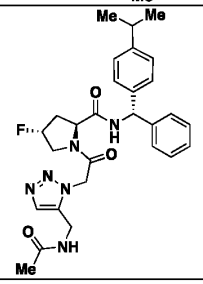
211		(2S)-1-(2-hydroxyacetyl)-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
212		(2S)-1-(2-acetamidoacetyl)-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
213		(2S)-1-(3-carbamoylpropanoyl)-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
214		(2S,5S)-1-acetyl-5-methyl-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
215		(2S,5R)-1-acetyl-5-methyl-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
216		(2S)-1-[2-(1,3-oxazol-2-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide

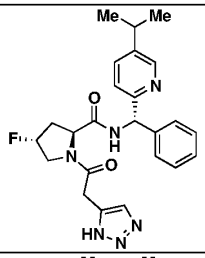
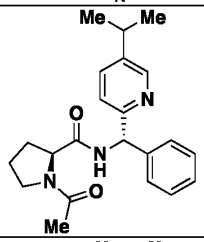
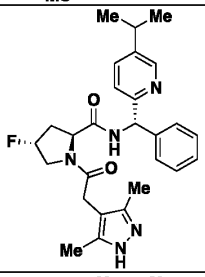
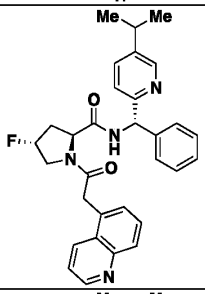
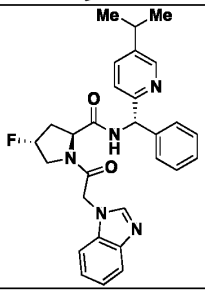
217		(2S,4R)-4-fluoro-1-[2-(2-oxo-1,3-oxazolidin-3-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
218		(2S,4R)-4-fluoro-1-[2-(oxetan-3-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
219		(2S,4R)-4-fluoro-1-[2-(3-oxomorpholin-4-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
220		(2S,4RS)-4-fluoro-1-[2-(1-methyl-1H-pyrazol-5-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
221		(2S,4RS)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(1H-pyrazol-1-yl)acetyl]pyrrolidine-2-carboxamide
222		(2RS,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(1H-1,2,3-triazol-1-yl)acetyl]pyrrolidine-2-carboxamide

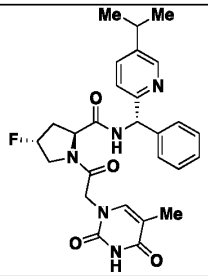
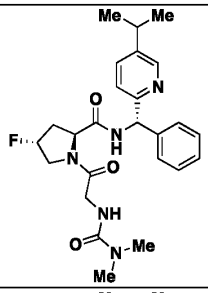
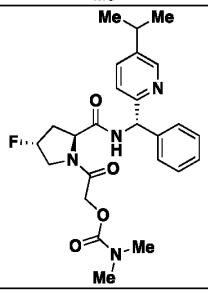
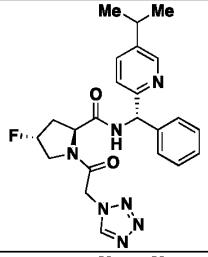
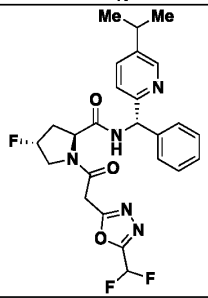
223		(2RS,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(2H-1,2,3,4-tetrazol-5-yl)acetyl]pyrrolidine-2-carboxamide
224		(2RS,4R)-4-fluoro-1-[2-(1,3,4-oxadiazol-2-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
225		(2RS,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(1H-pyrazol-3-yl)acetyl]pyrrolidine-2-carboxamide
226		(2RS,4R)-4-fluoro-1-[2-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
227		(2RS,4R)-4-fluoro-1-[2-(4-methyl-4H-1,2,4-triazol-3-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
228		(2RS,4R)-4-fluoro-1-[2-(1-methyl-1H-1,2,3-triazol-5-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide

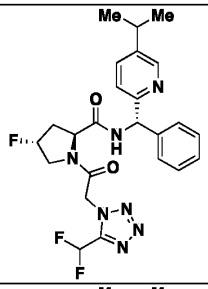
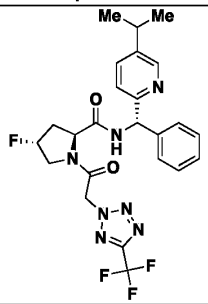
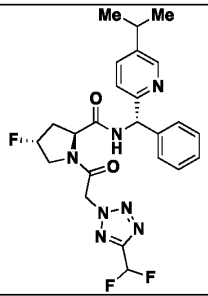
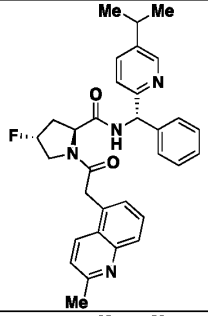
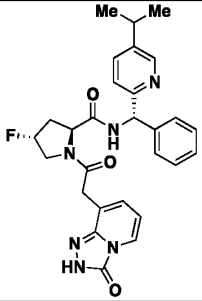
229		(2RS,4R)-4-fluoro-1-[2-(1-methyl-1H-1,2,3-triazol-4-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
230		(2S,4R)-4-fluoro-1-[2-(1,2-oxazol-4-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
231		(2S,4R)-4-fluoro-1-[2-(1,2-oxazol-3-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
232		(2S,4R)-4-fluoro-1-[2-(3-methyl-1H-1,2,4-triazol-5-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
233		(2S,4R)-4-fluoro-1-[2-methyl-2-(1H-1,2,4-triazol-5-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide

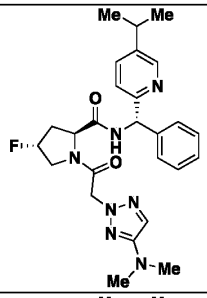
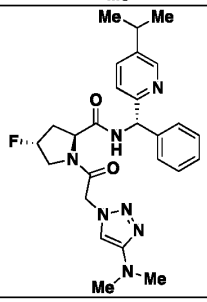
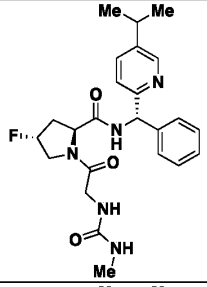
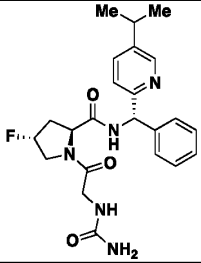
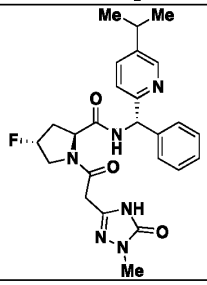
234		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(piperazin-1-yl)acetyl]pyrrolidine-2-carboxamide
235		(2S,4R)-1-[2-(4-acetylpiperazin-1-yl)acetyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
236		(2S,4R)-4-fluoro-1-[2-(5-methyl-2-oxo-2,3-dihydro-1,3,4-oxadiazol-3-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
237		tert-butyl N-[(5-{2-[(2S,4R)-4-fluoro-2-{[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl}-1,3,4-oxadiazol-2-yl)methyl]carbamate
238		(2S,4R)-1-{2-[5-(aminomethyl)-1,3,4-oxadiazol-2-yl]acetyl}-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide

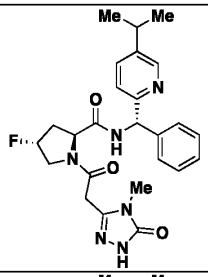
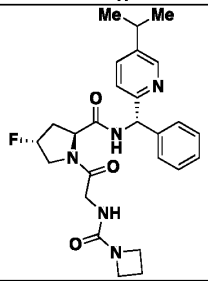
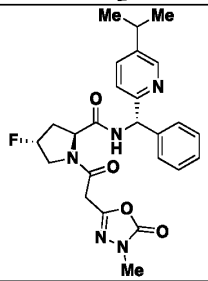
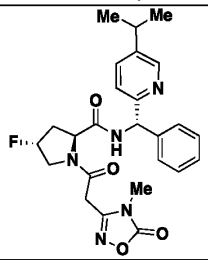
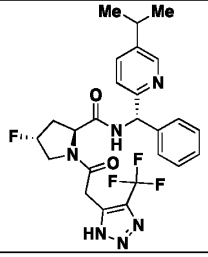
239		(2S,4R)-1-{2-[5-(acetamidomethyl)-1,3,4-oxadiazol-2-yl]acetyl}-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
240		(2S,4R)-1-{2-[5-(aminomethyl)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
241		(2S,4R)-1-(2-{5-[(dimethylamino)methyl]-1H-1,2,3-triazol-1-yl}acetyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
242		(2S,4R)-1-(2-{5-[(dimethylamino)methyl]-1,3,4-oxadiazol-2-yl}acetyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
243		(2S,4R)-1-{2-[5-(acetamidomethyl)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide

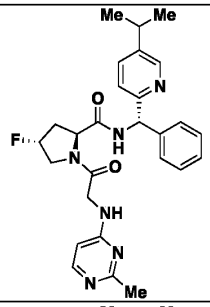
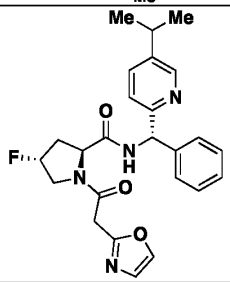
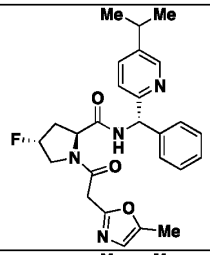
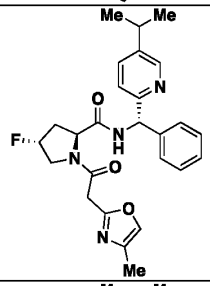
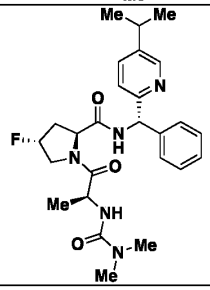
244		(2*S*,4*R*)-1-(2-(1*H*-1,2,3-triazol-5-yl)acetyl)-4-fluoro-*N*-((*S*)-(5-isopropylpyridin-2-yl)(phenyl)methyl)pyrrolidine-2-carboxamide
245		(2S)-1-acetyl-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide
246		(2S,4R)-1-[2-(3,5-dimethyl-1H-pyrazol-4-yl)acetyl]-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide
247		(2S,4R)-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]-1-[2-(quinolin-5-yl)acetyl]pyrrolidine-2-carboxamide
248		(2S,4R)-1-[2-(1H-1,3-benzodiazol-1-yl)acetyl]-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide

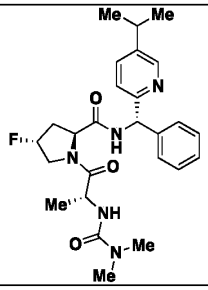
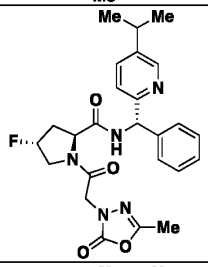
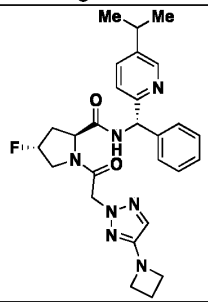
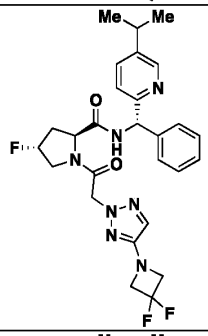
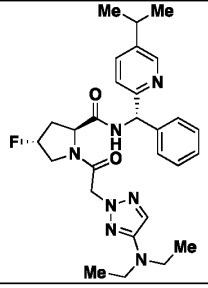
249		(2S,4R)-4-fluoro-1-[2-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide
250		(2S,4R)-1-{2-[(dimethylcarbamoyl)amino]acetyl}-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide
251		2-[(2S,4R)-4-fluoro-2-{[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl N,N-dimethylcarbamate
252		(2S,4R)-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]-1-[2-(1H-1,2,3,4-tetrazol-1-yl)acetyl]pyrrolidine-2-carboxamide
253		(2S,4R)-1-{2-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]acetyl}-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide

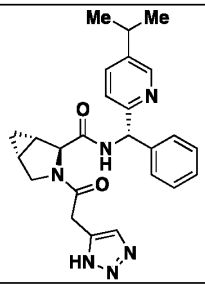
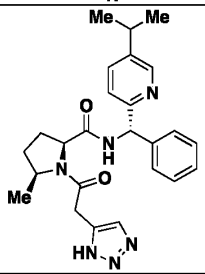
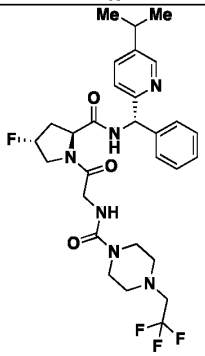
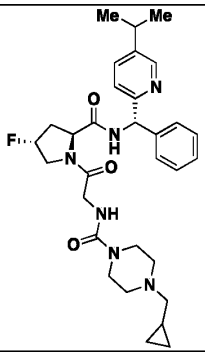
254		(2S,4R)-1-{2-[5-(difluoromethyl)-1H-1,2,3,4-tetrazol-1-yl]acetyl}-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide
255		(2S,4R)-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]-1-{2-[5-(trifluoromethyl)-2H-1,2,3,4-tetrazol-2-yl]acetyl}pyrrolidine-2-carboxamide
256		(2S,4R)-1-{2-[5-(difluoromethyl)-2H-1,2,3,4-tetrazol-2-yl]acetyl}-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide
257		(2S,4R)-4-fluoro-1-[2-(2-methylquinolin-5-yl)acetyl]-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide
258		(2S,4R)-4-fluoro-1-(2-{3-oxo-2H,3H-[1,2,4]triazolo[4,3-a]pyridin-8-yl}acetyl)-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide

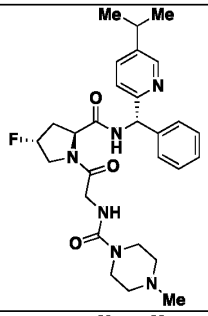
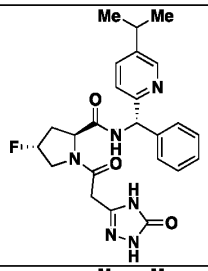
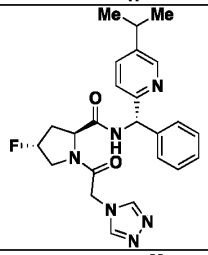
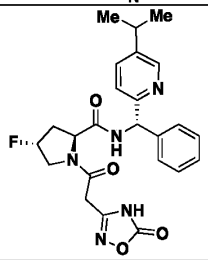
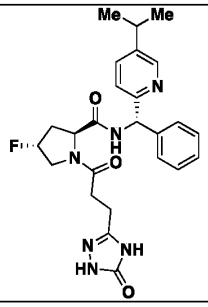
259		(2S,4R)-1-{2-[4-(dimethylamino)-2H-1,2,3-triazol-2-yl]acetyl}-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide
260		(2S,4R)-1-{2-[4-(dimethylamino)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide
261		(2S,4R)-4-fluoro-1-{2-[(methylcarbamoyl)amino]acetyl}-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide
262		(2S,4R)-1-[2-(carbamoylamino)acetyl]-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide
263		(2S,4R)-4-fluoro-1-[2-(1-methyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)acetyl]-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide

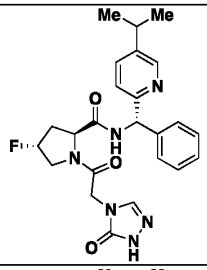
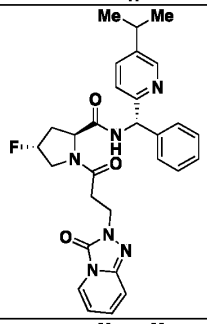
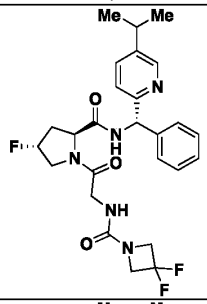
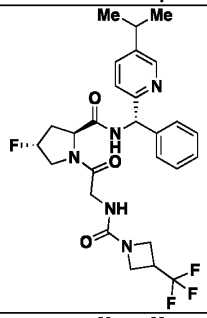
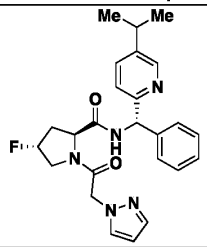
264		(2S,4R)-4-fluoro-1-[2-(4-methyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)acetyl]-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide
265		(2S,4R)-1-{2-[(azetidine-1-carbonyl)amino]acetyl}-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide
266		(2S,4R)-4-fluoro-1-[2-(4-methyl-5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)acetyl]-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide
267		(2S,4R)-4-fluoro-1-[2-(4-methyl-5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)acetyl]-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide
268		(2S,4R)-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]-1-{2-[4-(trifluoromethyl)-1H-1,2,3-triazol-5-yl]acetyl}pyrrolidine-2-carboxamide

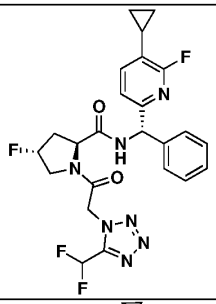
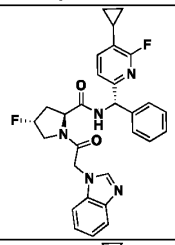
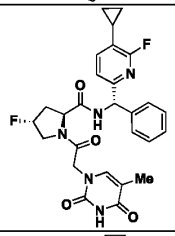
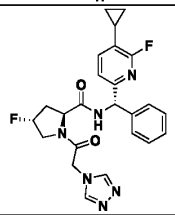
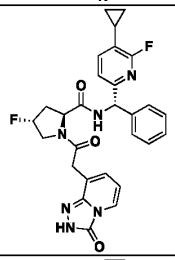
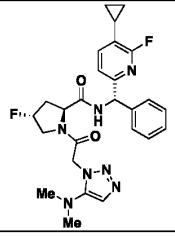
269		(2S,4R)-4-fluoro-1-{2-[(2-methylpyrimidin-4-yl)amino]acetyl}-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide
270		(2S,4R)-4-fluoro-1-[2-(1,3-oxazol-2-yl)acetyl]-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide
271		(2S,4R)-4-fluoro-1-[2-(5-methyl-1,3-oxazol-2-yl)acetyl]-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide
272		(2S,4R)-4-fluoro-1-[2-(4-methyl-1,3-oxazol-2-yl)acetyl]-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide
273		(2S,4R)-1-[(2S)-2-[(dimethylcarbamoyl)amino]propanoyl]-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide

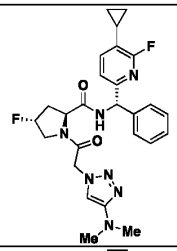
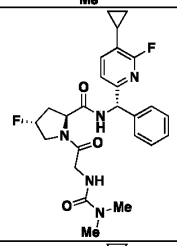
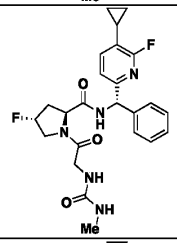
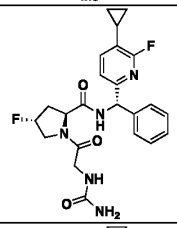
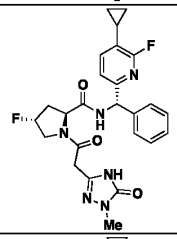
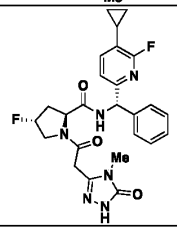
274		(2S,4R)-1-[(2R)-2-[(dimethylcarbamoyl)amino]propanoyl]-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide
275		(2S,4R)-4-fluoro-1-[2-(5-methyl-2-oxo-2,3-dihydro-1,3,4-oxadiazol-3-yl)acetyl]-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide
276		(2S,4R)-1-{2-[4-(azetidin-1-yl)-2H-1,2,3-triazol-2-yl]acetyl}-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide
277		(2S,4R)-1-{2-[4-(3,3-difluoroazetidin-1-yl)-2H-1,2,3-triazol-2-yl]acetyl}-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide
278		(2S,4R)-1-{2-[4-(diethylamino)-2H-1,2,3-triazol-2-yl]acetyl}-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide

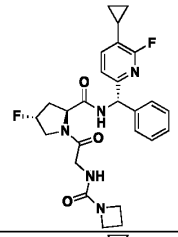
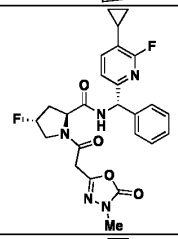
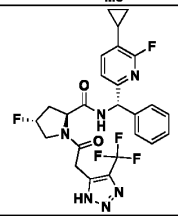
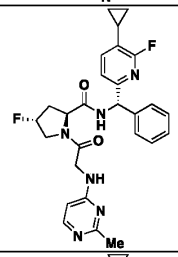
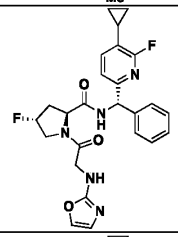
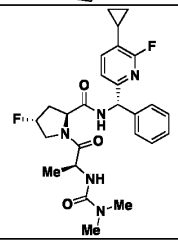
279		(1S,2S,5R)-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]-3-[2-(1H-1,2,3-triazol-5-yl)acetyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide
280		(2S,5S)-5-methyl-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
281		N-{2-[(2S,4R)-4-fluoro-2-{[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl}-4-(2,2,2-trifluoroethyl)piperazine-1-carboxamide
282		4-(cyclopropylmethyl)-N-{2-[(2S,4R)-4-fluoro-2-{[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl}piperazine-1-carboxamide

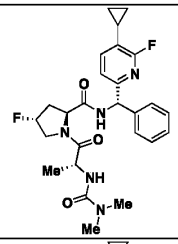
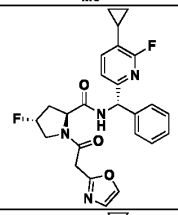
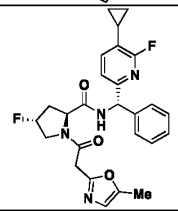
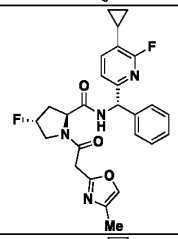
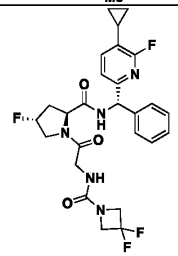
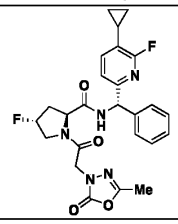
283		N-{2-[(2S,4R)-4-fluoro-2-{[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl}-4-methylpiperazine-1-carboxamide
284		(2S,4R)-4-fluoro-1-[2-(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)acetyl]-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide
285		(2S,4R)-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]-1-[2-(4H-1,2,4-triazol-4-yl)acetyl]pyrrolidine-2-carboxamide
286		(2S,4R)-4-fluoro-1-[2-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)acetyl]-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide
287		(2S,4R)-4-fluoro-1-[3-(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)propanoyl]-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide

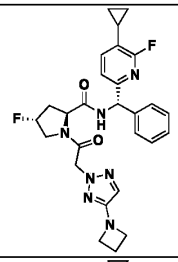
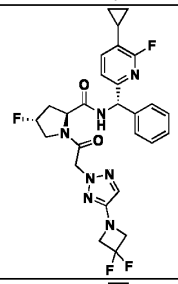
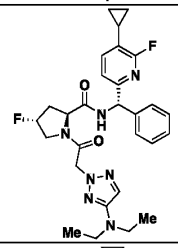
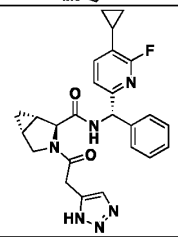
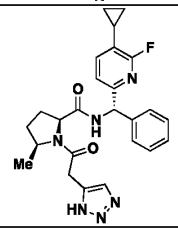
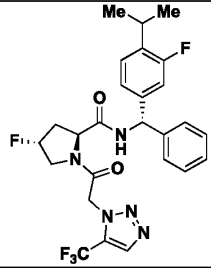
288		(2S,4R)-4-fluoro-1-[2-(5-oxo-4,5-dihydro-1H-1,2,4-triazol-4-yl)acetyl]-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide
289		(2S,4R)-4-fluoro-1-(3-{3-oxo-2H,3H-[1,2,4]triazolo[4,3-a]pyridin-2-yl}propanoyl)-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide
290		(2S,4R)-1-{2-[(3,3-difluoroazetidine-1-carbonyl)amino]acetyl}-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide
291		(2S,4R)-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]-1-(2-{[3-(trifluoromethyl)azetidine-1-carbonyl]amino}acetyl)pyrrolidine-2-carboxamide
292		(2S,4R)-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]-1-[2-(1H-pyrazol-1-yl)acetyl]pyrrolidine-2-carboxamide

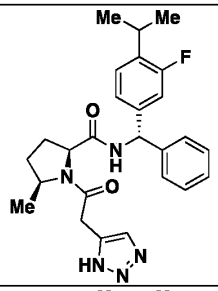
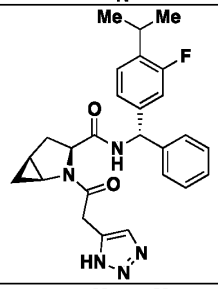
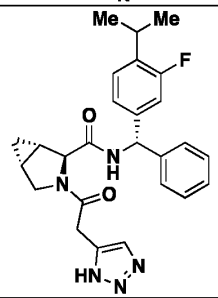
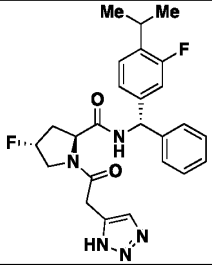
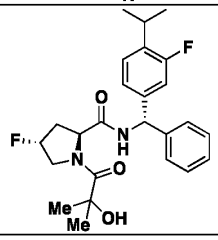
293		(2*S*,4*R*)-*N*-((*S*)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl)-1-(2-(5-(difluoromethyl)-1*H*-tetrazol-1-yl)acetyl)-4-fluoropyrrolidine-2-carboxamide
294		(2S,4R)-1-[2-(1H-1,3-benzodiazol-1-yl)acetyl]-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide
295		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]pyrrolidine-2-carboxamide
296		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(4H-1,2,4-triazol-4-yl)acetyl]pyrrolidine-2-carboxamide
297		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-(2-{3-oxo-2H,3H-[1,2,4]triazolo[4,3-a]pyridin-8-yl}acetyl)pyrrolidine-2-carboxamide
298		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[5-(dimethylamino)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide

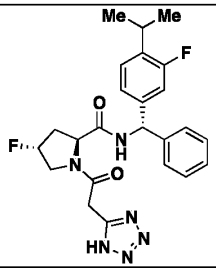
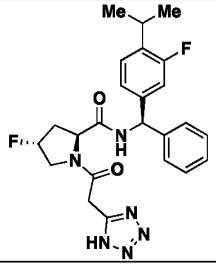
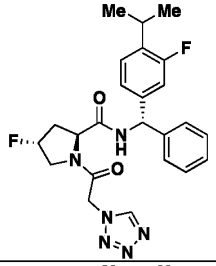
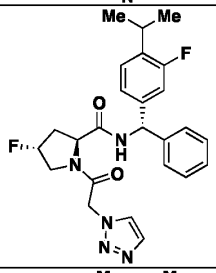
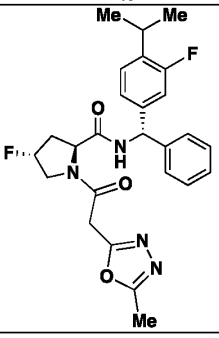
299		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[4-(dimethylamino)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide
300		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[(dimethylcarbamoyl)amino]acetyl}-4-fluoropyrrolidine-2-carboxamide
301		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-{2-[(methylcarbamoyl)amino]acetyl}pyrrolidine-2-carboxamide
302		(2S,4R)-1-[2-(carbamoylamino)acetyl]-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide
303		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(1-methyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)acetyl]pyrrolidine-2-carboxamide
304		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(4-methyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)acetyl]pyrrolidine-2-carboxamide

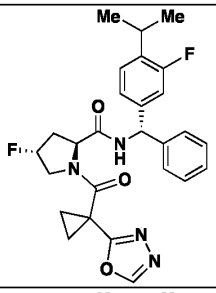
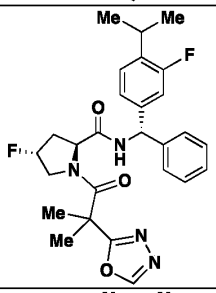
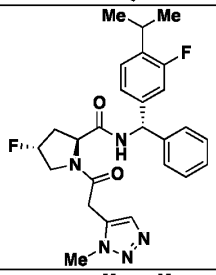
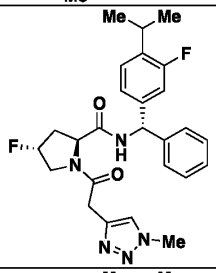
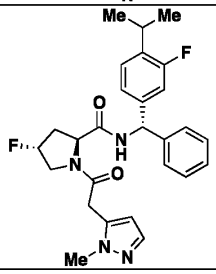
305		(2S,4R)-1-{2-[(azetidine-1-carbonyl)amino]acetyl}-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide
306		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(4-methyl-5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)acetyl]pyrrolidine-2-carboxamide
307		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-{2-[4-(trifluoromethyl)-1H-1,2,3-triazol-5-yl]acetyl}pyrrolidine-2-carboxamide
308		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-{2-[(2-methylpyrimidin-4-yl)amino]acetyl}pyrrolidine-2-carboxamide
309		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-{2-[(1,3-oxazol-2-yl)amino]acetyl}pyrrolidine-2-carboxamide
310		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[(2S)-2-[(dimethylcarbamoyl)amino]propanoyl]-4-fluoropyrrolidine-2-carboxamide

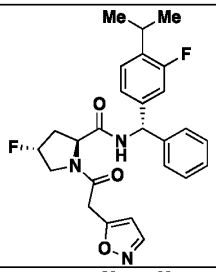
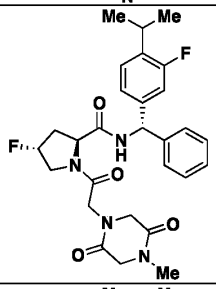
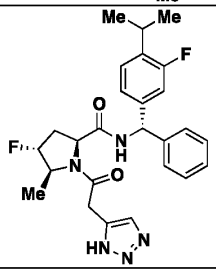
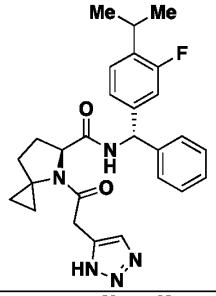
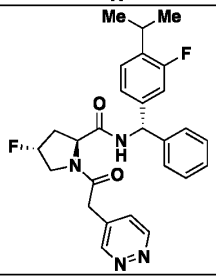
311		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[(2R)-2-[(dimethylcarbamoyl)amino]propanoyl]-4-fluoropyrrolidine-2-carboxamide
312		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide
313		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(5-methyl-1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide
314		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(4-methyl-1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide
315		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[(3,3-difluoroazetidine-1-carbonyl)amino]acetyl}-4-fluoropyrrolidine-2-carboxamide
316		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(5-methyl-2-oxo-2,3-dihydro-1,3,4-oxadiazol-3-yl)acetyl]pyrrolidine-2-carboxamide

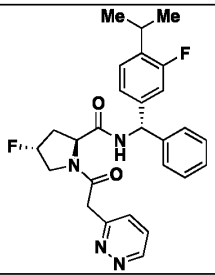
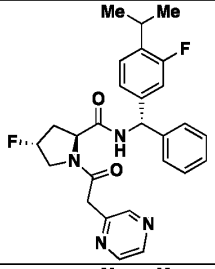
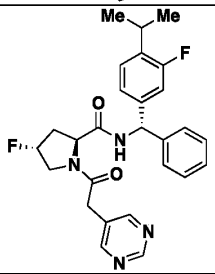
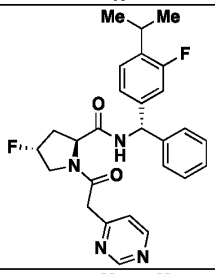
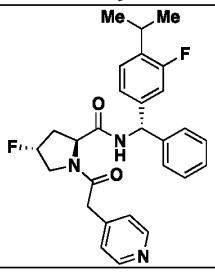
317		(2S,4R)-1-{2-[4-(azetidin-1-yl)-2H-1,2,3-triazol-2-yl]acetyl}-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide
318		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[4-(3,3-difluoroazetidin-1-yl)-2H-1,2,3-triazol-2-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide
319		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[4-(diethylamino)-2H-1,2,3-triazol-2-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide
320		(1S,2S,5R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-3-[2-(1H-1,2,3-triazol-5-yl)acetyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide
321		(2S,5S)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-5-methyl-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
322		(2*S*,4*R*)-4-fluoro-*N*-((*S*)-(3-fluoro-4-isopropylphenyl)(phenyl)methyl)-1-(2-(5-(trifluoromethyl)-1*H*-1,2,3-triazol-1-yl)acetyl)pyrrolidine-2-carboxamide

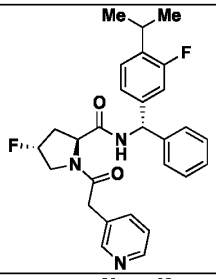
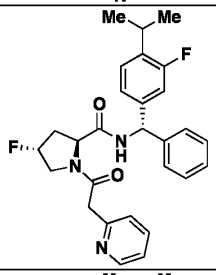
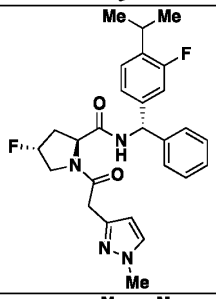
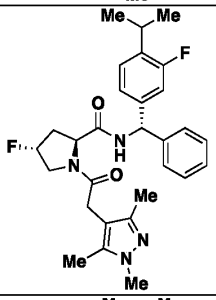
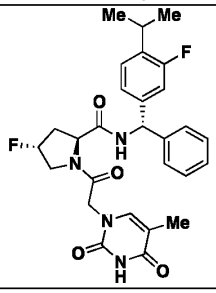
323		(2S,5S)-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-5-methyl-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
324		(1S,3S,5S)-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-2-[2-(1H-1,2,3-triazol-5-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carboxamide
325		(1S,2S,5R)-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-3-[2-(1H-1,2,3-triazol-5-yl)acetyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide
326		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
327		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-(2-hydroxy-2-methylpropanoyl)pyrrolidine-2-carboxamide

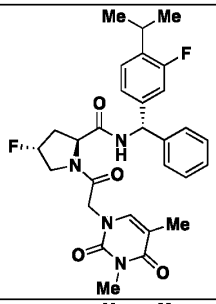
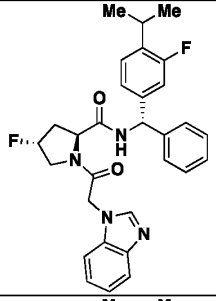
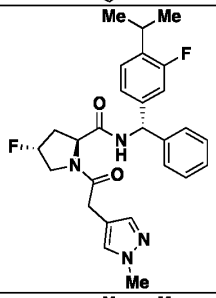
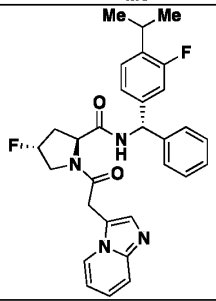
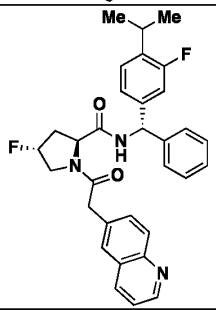
328		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(1H-1,2,3,4-tetrazol-5-yl)acetyl]pyrrolidine-2-carboxamide
329		(2S,4R)-4-fluoro-N-[(R)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(1H-1,2,3,4-tetrazol-5-yl)acetyl]pyrrolidine-2-carboxamide
330		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(1H-1,2,3,4-tetrazol-1-yl)acetyl]pyrrolidine-2-carboxamide
331		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(1H-1,2,3-triazol-1-yl)acetyl]pyrrolidine-2-carboxamide
332		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(5-methyl-1,3,4-oxadiazol-2-yl)acetyl]pyrrolidine-2-carboxamide

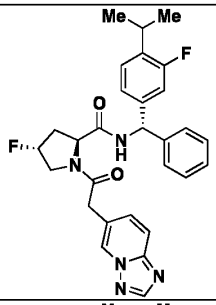
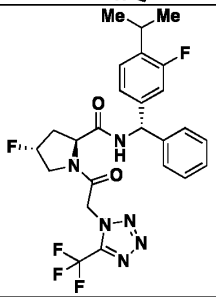
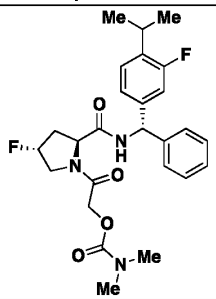
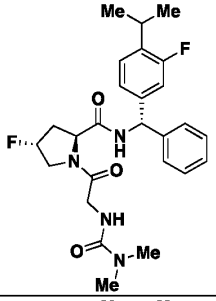
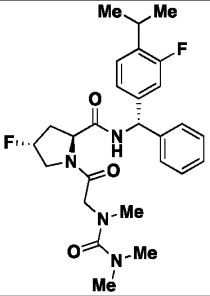
333		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[1-(1,3,4-oxadiazol-2-yl)cyclopropanecarbonyl]pyrrolidine-2-carboxamide
334		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-methyl-2-(1,3,4-oxadiazol-2-yl)propanoyl]pyrrolidine-2-carboxamide
335		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(1-methyl-1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
336		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(1-methyl-1H-1,2,3-triazol-4-yl)acetyl]pyrrolidine-2-carboxamide
337		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(1-methyl-1H-pyrazol-5-yl)acetyl]pyrrolidine-2-carboxamide

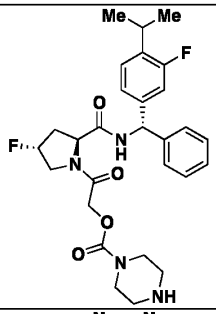
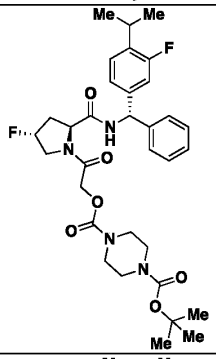
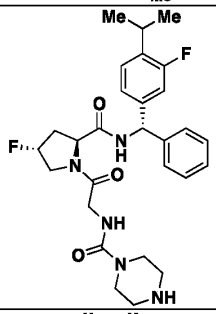
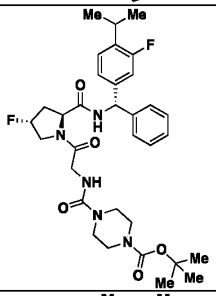
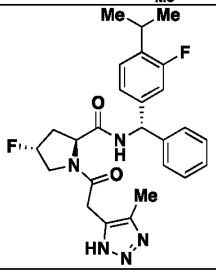
338		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(1,2-oxazol-5-yl)acetyl]pyrrolidine-2-carboxamide
339		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(4-methyl-2,5-dioxopiperazin-1-yl)acetyl]pyrrolidine-2-carboxamide
340		(2S,4R,5S)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-5-methyl-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
341		(5S)-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-4-[2-(1H-1,2,3-triazol-5-yl)acetyl]-4-azaspiro[2.4]heptane-5-carboxamide
342		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(pyridazin-4-yl)acetyl]pyrrolidine-2-carboxamide

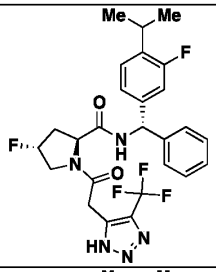
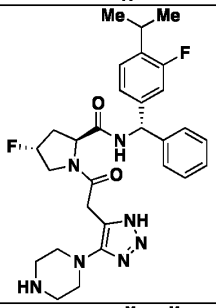
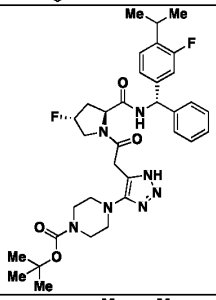
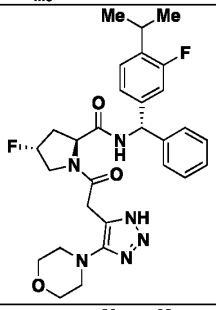
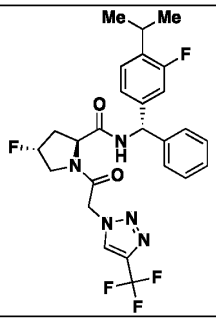
343		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(pyridazin-3-yl)acetyl]pyrrolidine-2-carboxamide
344		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(pyrazin-2-yl)acetyl]pyrrolidine-2-carboxamide
345		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(pyrimidin-5-yl)acetyl]pyrrolidine-2-carboxamide
346		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(pyrimidin-4-yl)acetyl]pyrrolidine-2-carboxamide
347		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(pyridin-4-yl)acetyl]pyrrolidine-2-carboxamide

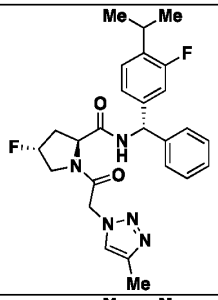
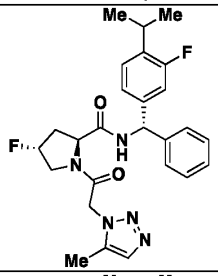
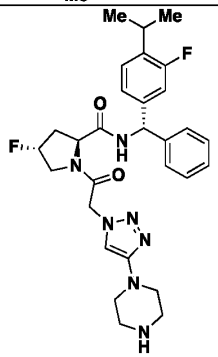
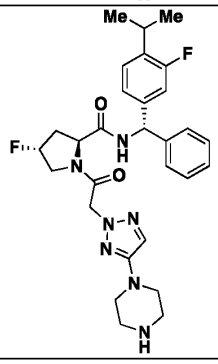
348		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(pyridin-3-yl)acetyl]pyrrolidine-2-carboxamide
349		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(pyridin-2-yl)acetyl]pyrrolidine-2-carboxamide
350		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(1-methyl-1H-pyrazol-3-yl)acetyl]pyrrolidine-2-carboxamide
351		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(1,3,5-trimethyl-1H-pyrazol-4-yl)acetyl]pyrrolidine-2-carboxamide
352		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]pyrrolidine-2-carboxamide

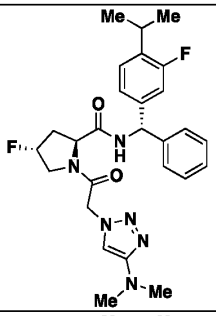
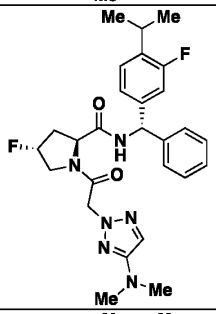
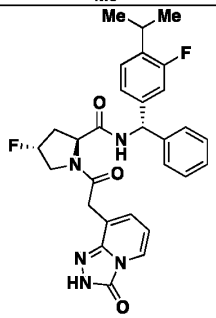
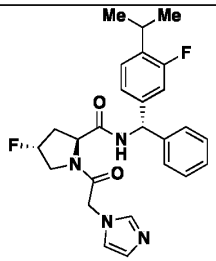
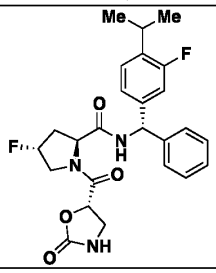
353		(2S,4R)-1-[2-(3,5-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]pyrrolidine-2-carboxamide
354		(2S,4R)-1-[2-(1H-1,3-benzodiazol-1-yl)acetyl]-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]pyrrolidine-2-carboxamide
355		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(1-methyl-1H-pyrazol-4-yl)acetyl]pyrrolidine-2-carboxamide
356		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-(2-{imidazo[1,2-a]pyridin-3-yl}acetyl)pyrrolidine-2-carboxamide
357		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(quinolin-6-yl)acetyl]pyrrolidine-2-carboxamide

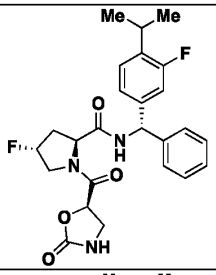
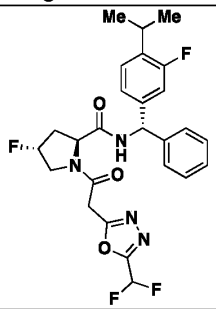
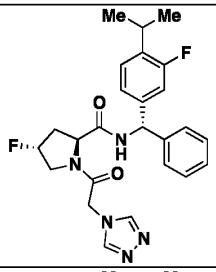
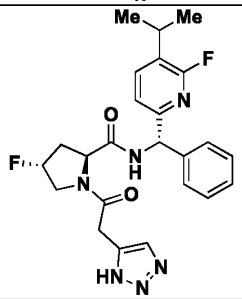
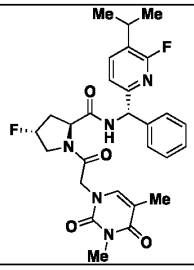
358		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-(2-{[1,2,4]triazolo[1,5-a]pyridin-6-yl}acetyl)pyrrolidine-2-carboxamide
359		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-{2-[5-(trifluoromethyl)-1H-1,2,3,4-tetrazol-1-yl]acetyl}pyrrolidine-2-carboxamide
360		2-[(2S,4R)-4-fluoro-2-{[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl N,N-dimethylcarbamate
361		(2S,4R)-1-{2-[(dimethylcarbamoyl)amino]acetyl}-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]pyrrolidine-2-carboxamide
362		(2S,4R)-1-{2-[(dimethylcarbamoyl)(methyl)amino]acetyl}-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]pyrrolidine-2-carboxamide

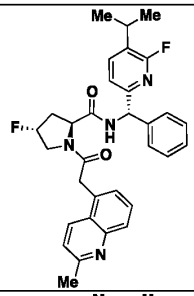
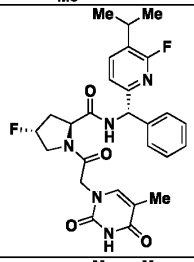
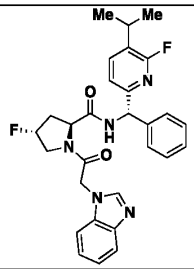
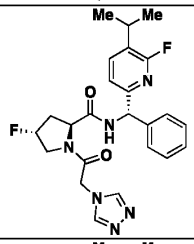
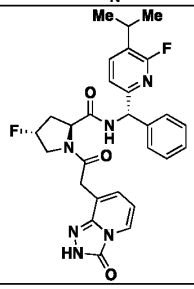
363		2-[(2S,4R)-4-fluoro-2-{[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl piperazine-1-carboxylate
364		1-tert-butyl 4-{2-[(2S,4R)-4-fluoro-2-{[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl} piperazine-1,4-dicarboxylate
365		N-{2-[(2S,4R)-4-fluoro-2-{[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl}piperazine-1-carboxamide
366		tert-butyl 4-({2-[(2S,4R)-4-fluoro-2-{[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl}carbamoyl)piperazine-1-carboxylate
367		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(4-methyl-1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

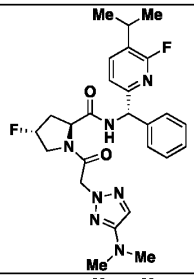
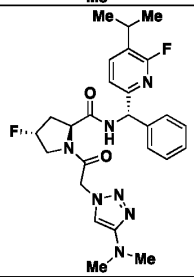
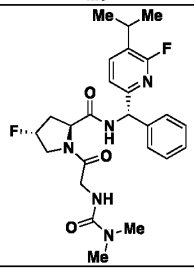
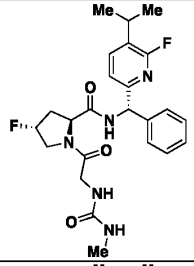
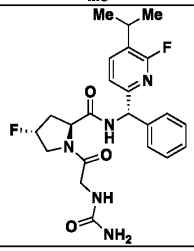
368		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-{2-[4-(trifluoromethyl)-1H-1,2,3-triazol-5-yl]acetyl}pyrrolidine-2-carboxamide
369		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-{2-[4-(piperazin-1-yl)-1H-1,2,3-triazol-5-yl]acetyl}pyrrolidine-2-carboxamide
370		tert-butyl 4-(5-{2-[(2S,4R)-4-fluoro-2-{[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl}-1H-1,2,3-triazol-4-yl)piperazine-1-carboxylate
371		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-{2-[4-(morpholin-4-yl)-1H-1,2,3-triazol-5-yl]acetyl}pyrrolidine-2-carboxamide
372		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-{2-[4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl]acetyl}pyrrolidine-2-carboxamide

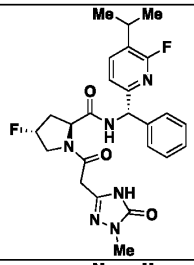
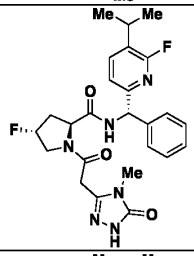
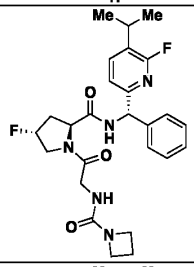
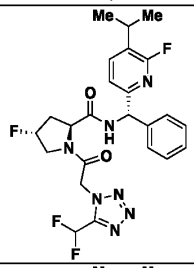
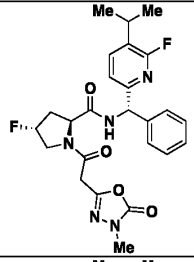
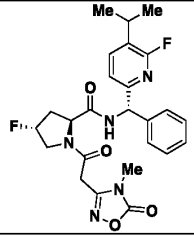
373		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(4-methyl-1H-1,2,3-triazol-1-yl)acetyl]pyrrolidine-2-carboxamide
374		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(5-methyl-1H-1,2,3-triazol-1-yl)acetyl]pyrrolidine-2-carboxamide
375		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-{2-[4-(piperazin-1-yl)-1H-1,2,3-triazol-1-yl]acetyl}pyrrolidine-2-carboxamide
376		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-{2-[4-(piperazin-1-yl)-2H-1,2,3-triazol-2-yl]acetyl}pyrrolidine-2-carboxamide

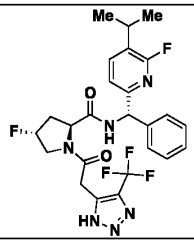
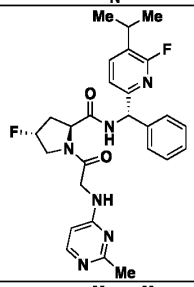
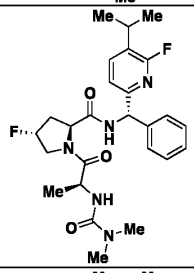
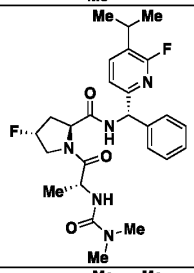
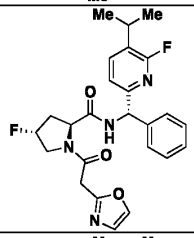
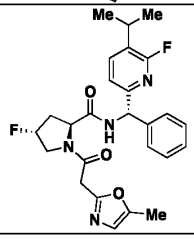
377		(2S,4R)-1-{2-[4-(dimethylamino)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]pyrrolidine-2-carboxamide
378		(2S,4R)-1-{2-[4-(dimethylamino)-2H-1,2,3-triazol-2-yl]acetyl}-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]pyrrolidine-2-carboxamide
379		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-(2-{3-oxo-2H,3H-[1,2,4]triazolo[4,3-a]pyridin-8-yl}acetyl)pyrrolidine-2-carboxamide
380		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(1H-imidazol-1-yl)acetyl]pyrrolidine-2-carboxamide
381		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[(5S)-2-oxo-1,3-oxazolidine-5-carbonyl]pyrrolidine-2-carboxamide

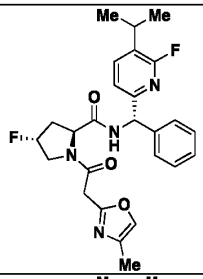
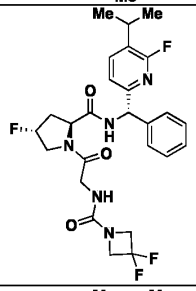
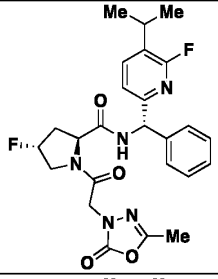
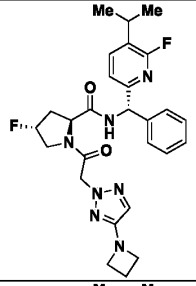
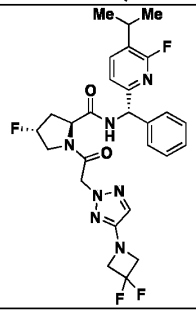
382		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[(5R)-2-oxo-1,3-oxazolidine-5-carbonyl]pyrrolidine-2-carboxamide
383		(2S,4R)-1-{2-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]acetyl}-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]pyrrolidine-2-carboxamide
384		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(4H-1,2,4-triazol-4-yl)acetyl]pyrrolidine-2-carboxamide
385		(2*S*,4*R*)-1-(2-(1*H*-1,2,3-triazol-5-yl)acetyl)-4-fluoro-*N*-((*S*)-(6-fluoro-5-isopropylpyridin-2-yl)(phenyl)methyl)pyrrolidine-2-carboxamide
386		(2S,4R)-1-[2-(3,5-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide

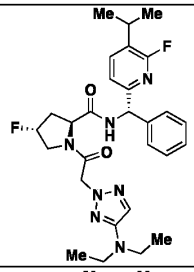
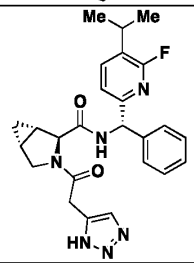
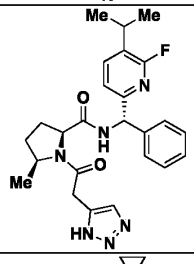
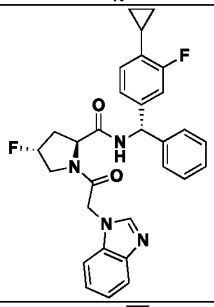
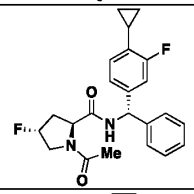
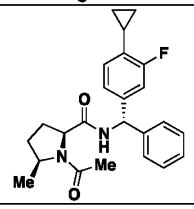
387		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(2-methylquinolin-5-yl)acetyl]pyrrolidine-2-carboxamide
388		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]pyrrolidine-2-carboxamide
389		(2S,4R)-1-[2-(1H-1,3-benzodiazol-1-yl)acetyl]-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide
390		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(4H-1,2,4-triazol-4-yl)acetyl]pyrrolidine-2-carboxamide
391		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-(2-{3-oxo-2H,3H-[1,2,4]triazolo[4,3-a]pyridin-8-yl}acetyl)pyrrolidine-2-carboxamide

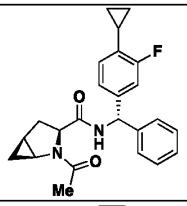
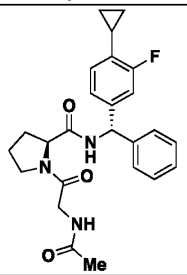
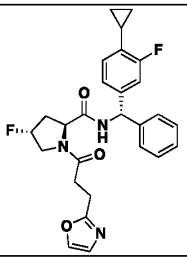
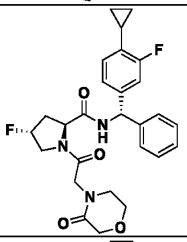
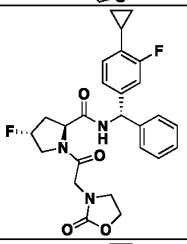
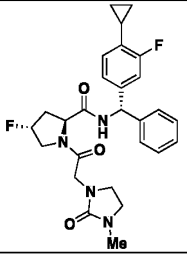
392		(2S,4R)-1-{2-[4-(dimethylamino)-2H-1,2,3-triazol-2-yl]acetyl}-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide
393		(2S,4R)-1-{2-[4-(dimethylamino)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide
394		(2S,4R)-1-{2-[(dimethylcarbamoyl)amino]acetyl}-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide
395		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-{2-[(methylcarbamoyl)amino]acetyl}pyrrolidine-2-carboxamide
396		(2S,4R)-1-[2-(carbamoylamino)acetyl]-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide

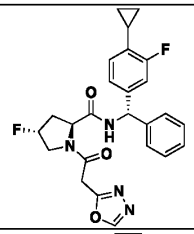
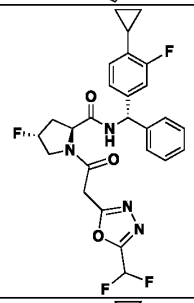
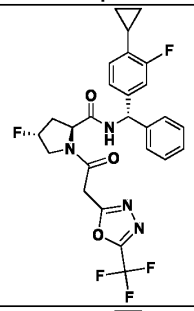
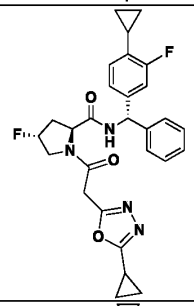
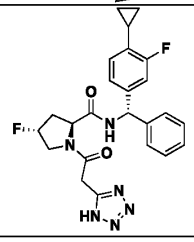
397		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(1-methyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)acetyl]pyrrolidine-2-carboxamide
398		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(4-methyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)acetyl]pyrrolidine-2-carboxamide
399		(2S,4R)-1-{2-[(azetidine-1-carbonyl)amino]acetyl}-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide
400		(2S,4R)-1-{2-[5-(difluoromethyl)-1H-1,2,3,4-tetrazol-1-yl]acetyl}-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide
401		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(4-methyl-5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)acetyl]pyrrolidine-2-carboxamide
402		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(4-methyl-5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)acetyl]pyrrolidine-2-carboxamide

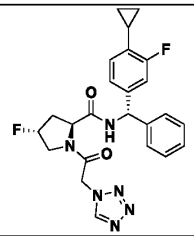
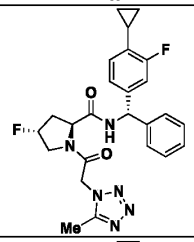
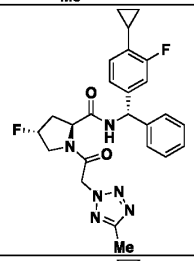
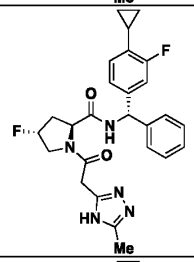
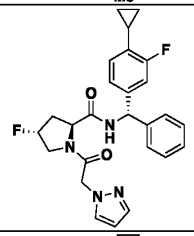
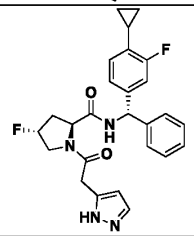
403		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-{2-[4-(trifluoromethyl)-1H-1,2,3-triazol-5-yl]acetyl}pyrrolidine-2-carboxamide
404		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-{2-[(2-methylpyrimidin-4-yl)amino]acetyl}pyrrolidine-2-carboxamide
405		(2S,4R)-1-[(2S)-2-[(dimethylcarbamoyl)amino]propanoyl]-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide
406		(2S,4R)-1-[(2R)-2-[(dimethylcarbamoyl)amino]propanoyl]-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide
407		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide
408		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(5-methyl-1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide

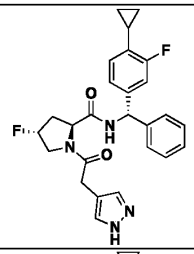
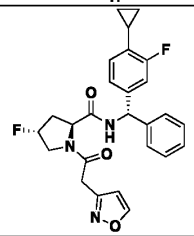
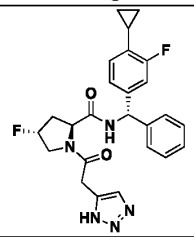
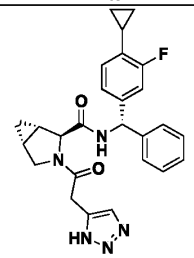
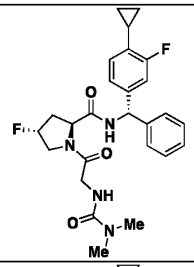
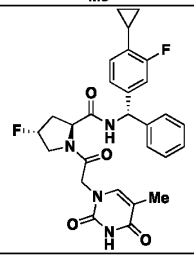
409		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(4-methyl-1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide
410		(2S,4R)-1-{2-[(3,3-difluoroazetidine-1-carbonyl)amino]acetyl}-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide
411		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(5-methyl-2-oxo-2,3-dihydro-1,3,4-oxadiazol-3-yl)acetyl]pyrrolidine-2-carboxamide
412		(2S,4R)-1-{2-[4-(azetidin-1-yl)-2H-1,2,3-triazol-2-yl]acetyl}-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide
413		(2S,4R)-1-{2-[4-(3,3-difluoroazetidin-1-yl)-2H-1,2,3-triazol-2-yl]acetyl}-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide

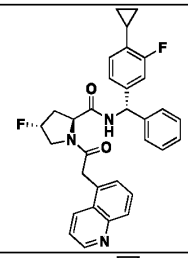
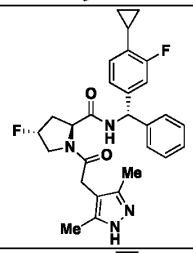
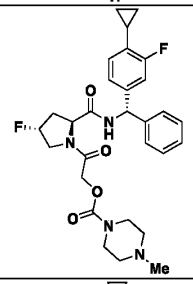
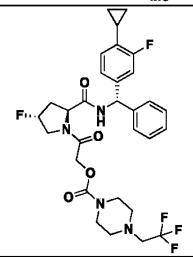
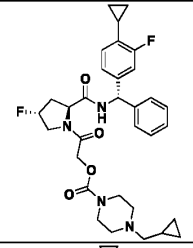
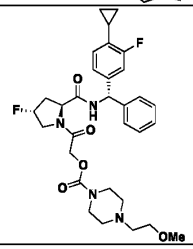
414		(2S,4R)-1-{2-[4-(diethylamino)-2H-1,2,3-triazol-2-yl]acetyl}-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide
415		(1S,2S,5R)-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-3-[2-(1H-1,2,3-triazol-5-yl)acetyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide
416		(2S,5S)-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-5-methyl-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
417		(2*S*,4*R*)-1-(2-(1*H*-benzo[*d*]imidazol-1-yl)acetyl)-*N*-((*S*)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl)-4-fluoropyrrolidine-2-carboxamide
418		(2S,4R)-1-acetyl-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide
419		(2S,5S)-1-acetyl-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-5-methylpyrrolidine-2-carboxamide

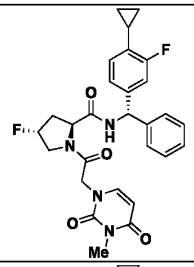
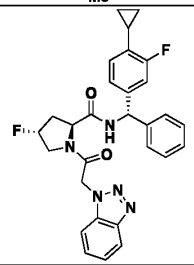
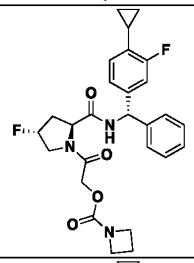
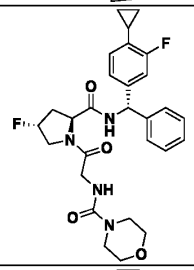
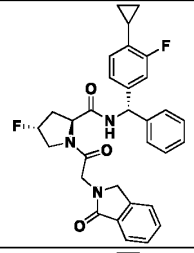
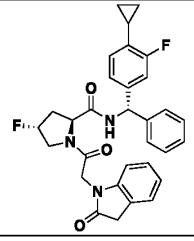
420		(1S,3S,5S)-2-acetyl-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-2-azabicyclo[3.1.0]hexane-3-carboxamide
421		(2S)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-1-(2-acetamidoacetyl)pyrrolidine-2-carboxamide
422		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[3-(1,3-oxazol-2-yl)propanoyl]pyrrolidine-2-carboxamide
423		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(3-oxomorpholin-4-yl)acetyl]pyrrolidine-2-carboxamide
424		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(2-oxo-1,3-oxazolidin-3-yl)acetyl]pyrrolidine-2-carboxamide
425		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(3-methyl-2-oxoimidazolidin-1-yl)acetyl]pyrrolidine-2-carboxamide

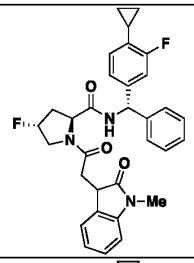
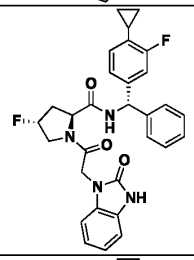
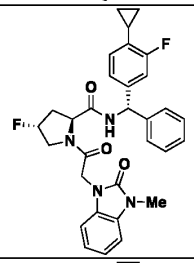
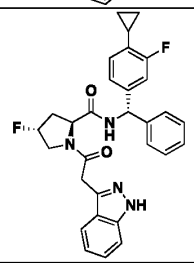
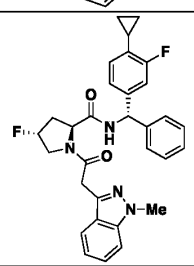
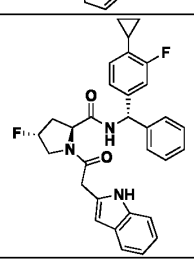
426		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1,3,4-oxadiazol-2-yl)acetyl]pyrrolidine-2-carboxamide
427		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-1-{2-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide
428		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-{2-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]acetyl}pyrrolidine-2-carboxamide
429		(2S,4R)-1-[2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)acetyl]-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide
430		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3,4-tetrazol-5-yl)acetyl]pyrrolidine-2-carboxamide

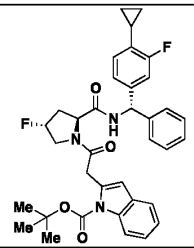
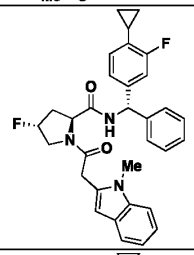
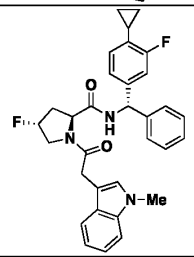
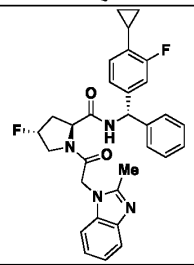
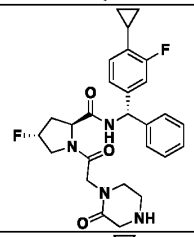
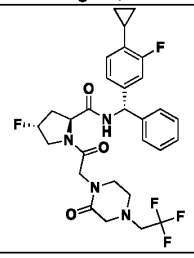
431		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3,4-tetrazol-1-yl)acetyl]pyrrolidine-2-carboxamide
432		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)acetyl]pyrrolidine-2-carboxamide
433		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(5-methyl-2H-1,2,3,4-tetrazol-2-yl)acetyl]pyrrolidine-2-carboxamide
434		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(5-methyl-4H-1,2,4-triazol-3-yl)acetyl]pyrrolidine-2-carboxamide
435		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-pyrazol-1-yl)acetyl]pyrrolidine-2-carboxamide
436		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-pyrazol-5-yl)acetyl]pyrrolidine-2-carboxamide

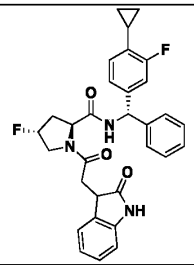
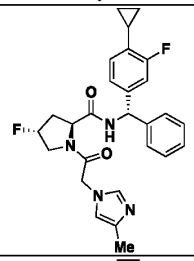
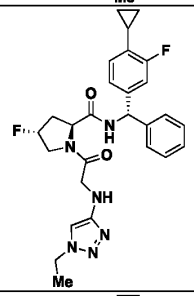
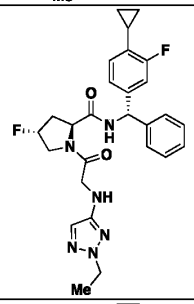
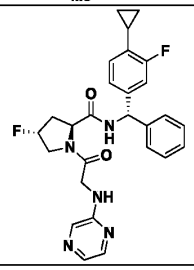
437		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-pyrazol-4-yl)acetyl]pyrrolidine-2-carboxamide
438		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1,2-oxazol-3-yl)acetyl]pyrrolidine-2-carboxamide
439		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
440		(1S,2S,5R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-3-[2-(1H-1,2,3-triazol-5-yl)acetyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide
441		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-1-{2-[(dimethylcarbamoyl)amino]acetyl}-4-fluoropyrrolidine-2-carboxamide
442		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]pyrrolidine-2-carboxamide

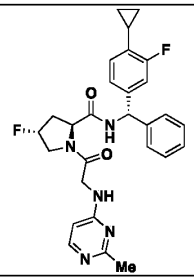
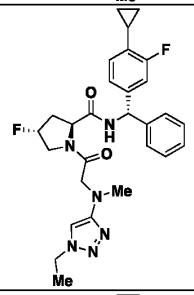
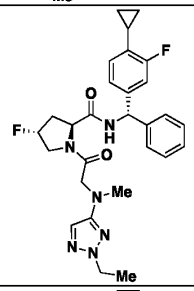
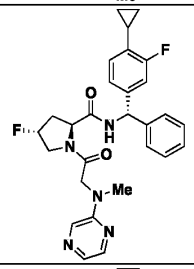
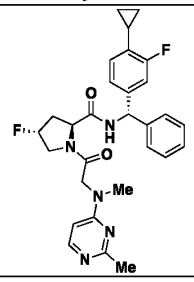
443		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(quinolin-5-yl)acetyl]pyrrolidine-2-carboxamide
444		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-1-[2-(3,5-dimethyl-1H-pyrazol-4-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide
445		2-[(2S,4R)-2-{[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]carbamoyl}-4-fluoropyrrolidin-1-yl]-2-oxoethyl 4-methylpiperazine-1-carboxylate
446		2-[(2S,4R)-2-{[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]carbamoyl}-4-fluoropyrrolidin-1-yl]-2-oxoethyl 4-(2,2,2-trifluoroethyl)piperazine-1-carboxylate
447		2-[(2S,4R)-2-{[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]carbamoyl}-4-fluoropyrrolidin-1-yl]-2-oxoethyl 4-(cyclopropylmethyl)piperazine-1-carboxylate
448		2-[(2S,4R)-2-{[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]carbamoyl}-4-fluoropyrrolidin-1-yl]-2-oxoethyl 4-(2-methoxyethyl)piperazine-1-carboxylate

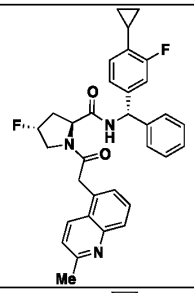
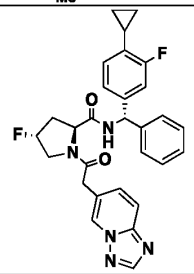
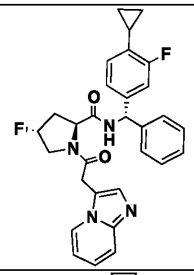
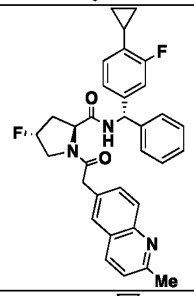
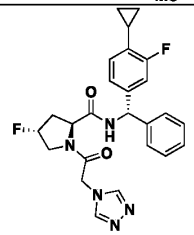
449		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]pyrrolidine-2-carboxamide
450		(2S,4R)-1-[2-(1H-1,2,3-benzotriazol-1-yl)acetyl]-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide
451		2-[(2S,4R)-2-{[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]carbamoyl}-4-fluoropyrrolidin-1-yl]-2-oxoethyl azetidine-1-carboxylate
452		N-{2-[(2S,4R)-2-{[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]carbamoyl}-4-fluoropyrrolidin-1-yl]-2-oxoethyl}morpholine-4-carboxamide
453		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1-oxo-2,3-dihydro-1H-isoindol-2-yl)acetyl]pyrrolidine-2-carboxamide
454		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(2-oxo-2,3-dihydro-1H-indol-1-yl)acetyl]pyrrolidine-2-carboxamide

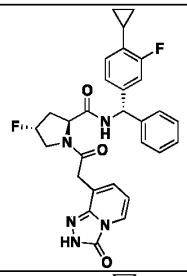
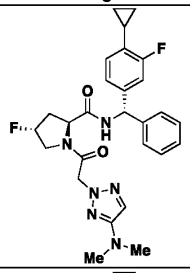
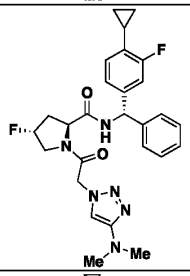
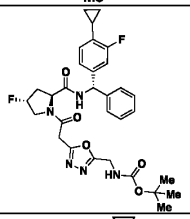
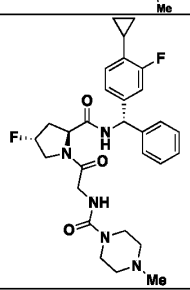
455		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl)acetyl]pyrrolidine-2-carboxamide
456		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)acetyl]pyrrolidine-2-carboxamide
457		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)acetyl]pyrrolidine-2-carboxamide
458		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-indazol-3-yl)acetyl]pyrrolidine-2-carboxamide
459		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1-methyl-1H-indazol-3-yl)acetyl]pyrrolidine-2-carboxamide
460		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-indol-2-yl)acetyl]pyrrolidine-2-carboxamide

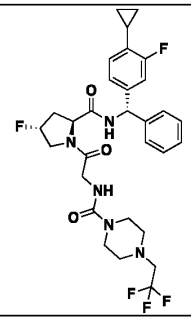
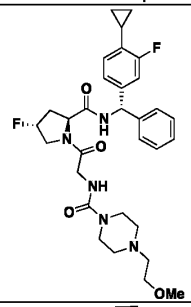
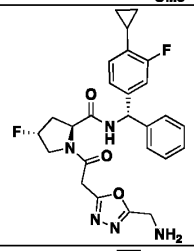
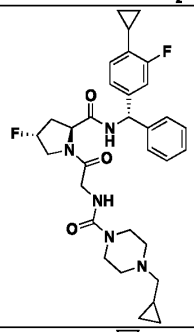
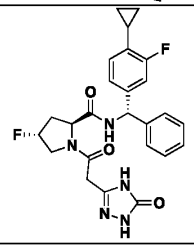
461		tert-butyl 2-{2-[(2S,4R)-2-{[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]carbamoyl}-4-fluoropyrrolidin-1-yl]-2-oxoethyl}-1H-indole-1-carboxylate
462		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1-methyl-1H-indol-2-yl)acetyl]pyrrolidine-2-carboxamide
463		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1-methyl-1H-indol-3-yl)acetyl]pyrrolidine-2-carboxamide
464		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(2-methyl-1H-1,3-benzodiazol-1-yl)acetyl]pyrrolidine-2-carboxamide
465		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(2-oxopiperazin-1-yl)acetyl]pyrrolidine-2-carboxamide
466		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-{2-[2-oxo-4-(2,2,2-trifluoroethyl)piperazin-1-yl]acetyl}pyrrolidine-2-carboxamide

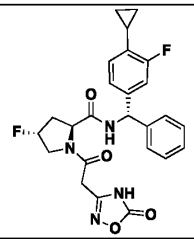
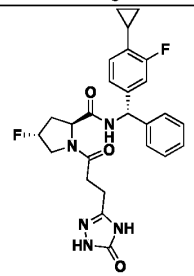
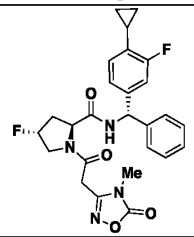
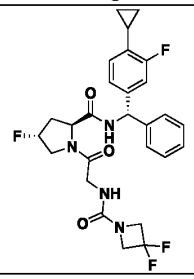
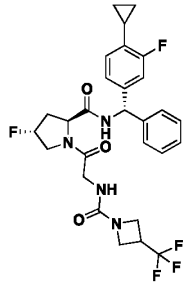
467		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(2-oxo-2,3-dihydro-1H-indol-3-yl)acetyl]pyrrolidine-2-carboxamide
468		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(4-methyl-1H-imidazol-1-yl)acetyl]pyrrolidine-2-carboxamide
469		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-1-{2-[(1-ethyl-1H-1,2,3-triazol-4-yl)amino]acetyl}-4-fluoropyrrolidine-2-carboxamide
470		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-1-{2-[(2-ethyl-2H-1,2,3-triazol-4-yl)amino]acetyl}-4-fluoropyrrolidine-2-carboxamide
471		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-{2-[(pyrazin-2-yl)amino]acetyl}pyrrolidine-2-carboxamide

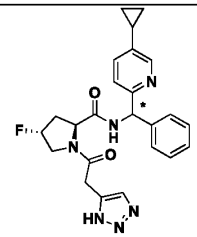
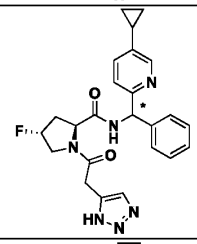
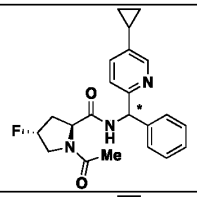
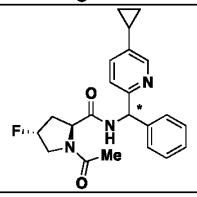
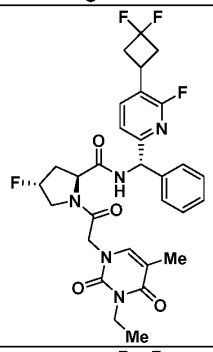
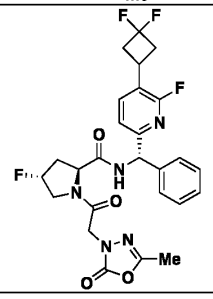
472		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-{2-[(2-methylpyrimidin-4-yl)amino]acetyl}pyrrolidine-2-carboxamide
473		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-1-{2-[(1-ethyl-1H-1,2,3-triazol-4-yl)(methyl)amino]acetyl}-4-fluoropyrrolidine-2-carboxamide
474		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-1-{2-[(2-ethyl-2H-1,2,3-triazol-4-yl)(methyl)amino]acetyl}-4-fluoropyrrolidine-2-carboxamide
475		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-{2-[methyl(pyrazin-2-yl)amino]acetyl}pyrrolidine-2-carboxamide
476		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-{2-[methyl(2-methylpyrimidin-4-yl)amino]acetyl}pyrrolidine-2-carboxamide

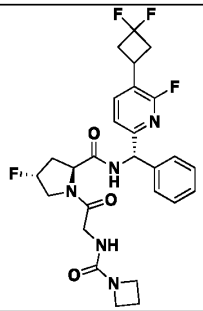
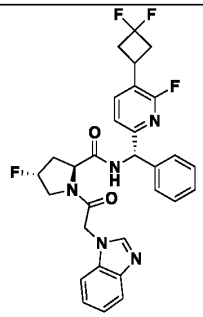
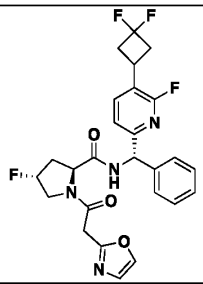
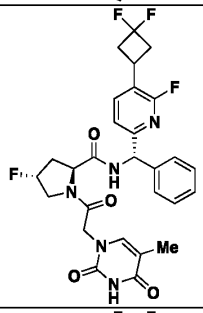
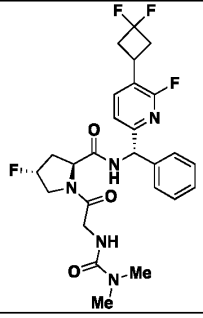
477		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(2-methylquinolin-5-yl)acetyl]pyrrolidine-2-carboxamide
478		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-(2-{[1,2,4]triazolo[1,5-a]pyridin-6-yl}acetyl)pyrrolidine-2-carboxamide
479		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-(2-{imidazo[1,2-a]pyridin-3-yl}acetyl)pyrrolidine-2-carboxamide
480		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(2-methylquinolin-6-yl)acetyl]pyrrolidine-2-carboxamide
481		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(4H-1,2,4-triazol-4-yl)acetyl]pyrrolidine-2-carboxamide

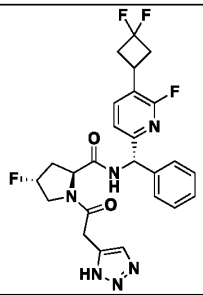
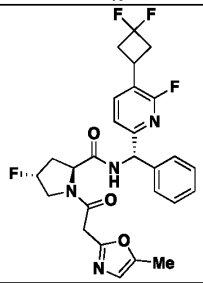
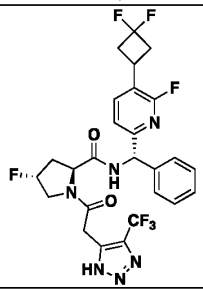
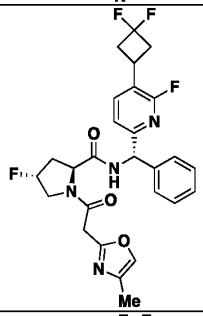
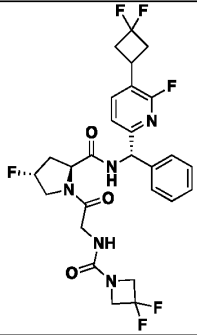
482		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-(2-{3-oxo-2H,3H-[1,2,4]triazolo[4,3-a]pyridin-8-yl}acetyl)pyrrolidine-2-carboxamide
483		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-1-{2-[4-(dimethylamino)-2H-1,2,3-triazol-2-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide
484		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-1-{2-[4-(dimethylamino)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide
485		tert-butyl N-[(5-{2-[(2S,4R)-2-{[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]carbamoyl}-4-fluoropyrrolidin-1-yl]-2-oxoethyl}-1,3,4-oxadiazol-2-yl)methyl]carbamate
486		N-{2-[(2S,4R)-2-{[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]carbamoyl}-4-fluoropyrrolidin-1-yl]-2-oxoethyl}-4-methylpiperazine-1-carboxamide

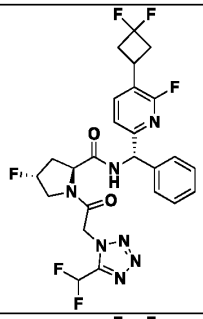
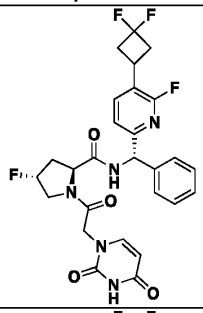
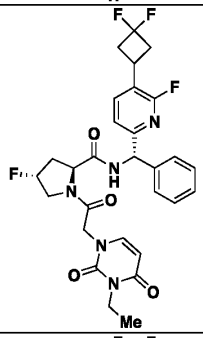
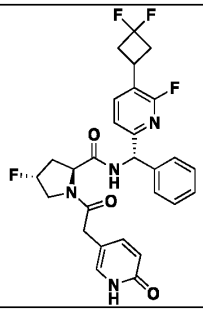
487		N-{2-[(2S,4R)-2-{[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]carbamoyl}-4-fluoropyrrolidin-1-yl]-2-oxoethyl}-4-(2,2,2-trifluoroethyl)piperazine-1-carboxamide
488		N-{2-[(2S,4R)-2-{[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]carbamoyl}-4-fluoropyrrolidin-1-yl]-2-oxoethyl}-4-(2-methoxyethyl)piperazine-1-carboxamide
489		(2S,4R)-1-{2-[5-(aminomethyl)-1,3,4-oxadiazol-2-yl]acetyl}-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide
490		N-{2-[(2S,4R)-2-{[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]carbamoyl}-4-fluoropyrrolidin-1-yl]-2-oxoethyl}-4-(cyclopropylmethyl)piperazine-1-carboxamide
491		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)acetyl]pyrrolidine-2-carboxamide

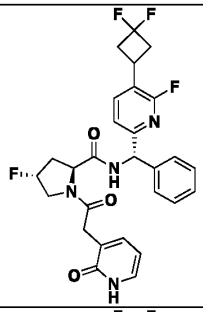
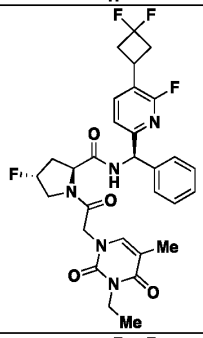
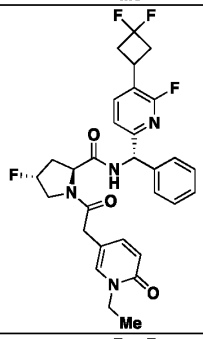
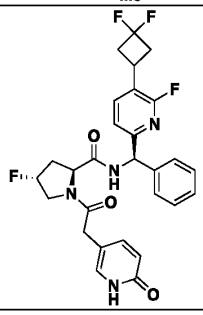
492		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)acetyl]pyrrolidine-2-carboxamide
493		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[3-(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)propanoyl]pyrrolidine-2-carboxamide
494		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(4-methyl-5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)acetyl]pyrrolidine-2-carboxamide
495		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-1-{2-[(3,3-difluoroazetidine-1-carbonyl)amino]acetyl}-4-fluoropyrrolidine-2-carboxamide
496		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-(2-{[3-(trifluoromethyl)azetidine-1-carbonyl]amino}acetyl)pyrrolidine-2-carboxamide

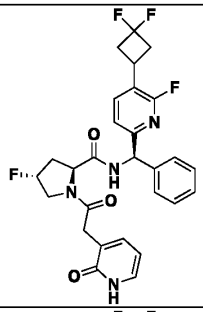
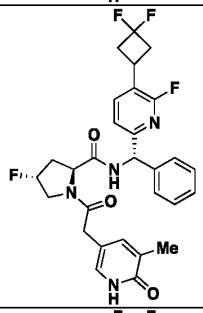
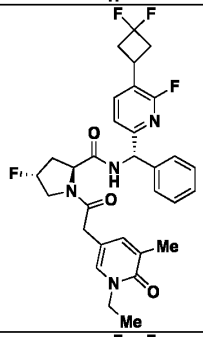
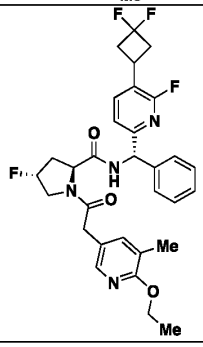
497		(2*S*,4*R*)-1-(2-(1*H*-1,2,3-triazol-5-yl)acetyl)-*N*-((*S*) or (*R*)-(5-cyclopropylpyridin-2-yl)(phenyl)methyl)-4-fluoropyrrolidine-2-carboxamide
498		(2*S*,4*R*)-1-(2-(1*H*-1,2,3-triazol-5-yl)acetyl)-*N*-((*R*) or (*S*)-(5-cyclopropylpyridin-2-yl)(phenyl)methyl)-4-fluoropyrrolidine-2-carboxamide
499		(2S,4R)-1-acetyl-N-[(S) or (*R*)-(5-cyclopropylpyridin-2-yl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide
500		(2S,4R)-1-acetyl-N-[(R) or (*S*)-(5-cyclopropylpyridin-2-yl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide (second eluting isomer)
501		(2*S*,4*R*)-*N*-((*S*)-(5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl)(phenyl)methyl)-1-(2-(3-ethyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)acetyl)-4-fluoropyrrolidine-2-carboxamide
502		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(5-methyl-2-oxo-2,3-dihydro-1,3,4-oxadiazol-3-yl)acetyl]pyrrolidine-2-carboxamide

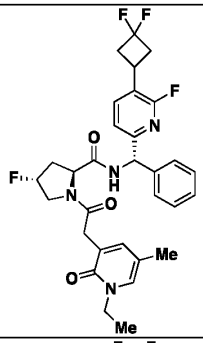
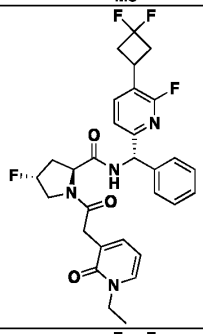
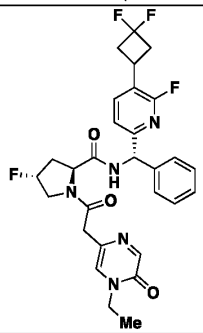
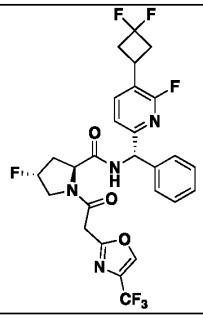
503		(2S,4R)-1-{2-[(azetidine-1-carbonyl)amino]acetyl}-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide
504		(2S,4R)-1-[2-(1H-1,3-benzodiazol-1-yl)acetyl]-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide
505		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide
506		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]pyrrolidine-2-carboxamide
507		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-1-{2-[(dimethylcarbamoyl)amino]acetyl}-4-fluoropyrrolidine-2-carboxamide

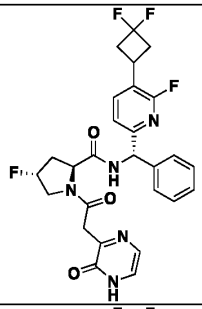
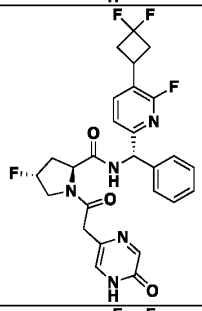
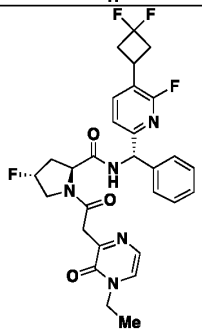
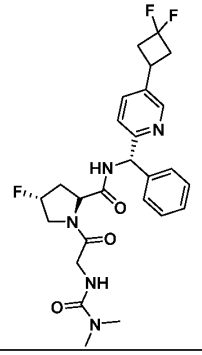
508		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
509		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(5-methyl-1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide
510		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-4-fluoro-1-{2-[4-(trifluoromethyl)-1H-1,2,3-triazol-5-yl]acetyl}pyrrolidine-2-carboxamide
511		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(4-methyl-1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide
512		(2S,4R)-1-{2-[(3,3-difluoroazetidine-1-carbonyl)amino]acetyl}-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide

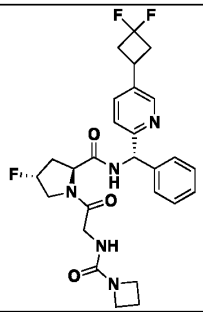
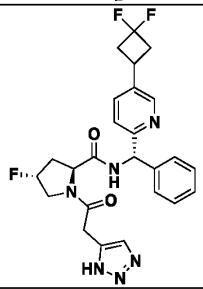
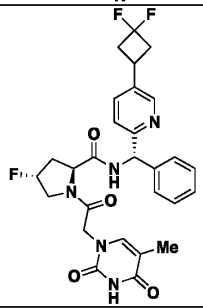
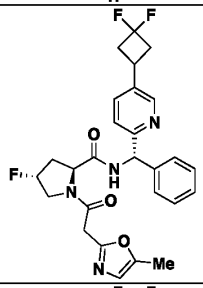
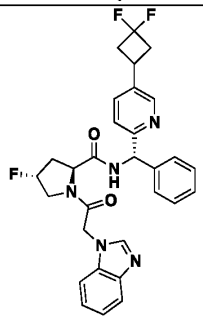
513		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-1-{2-[5-(difluoromethyl)-1H-1,2,3,4-tetrazol-1-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide
514		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-1-[2-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide
515		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-1-[2-(3-ethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide
516		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(6-oxo-1,6-dihydropyridin-3-yl)acetyl]pyrrolidine-2-carboxamide

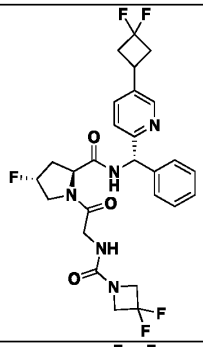
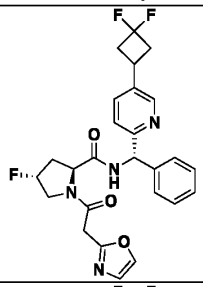
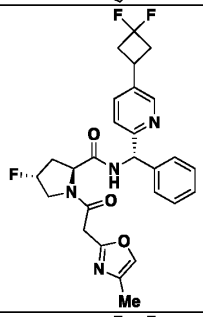
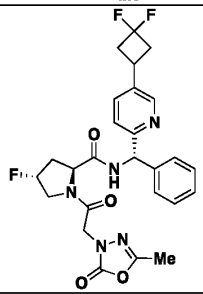
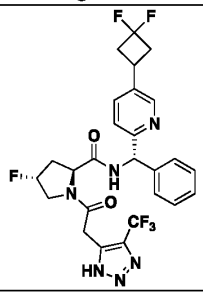
517		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(2-oxo-1,2-dihydropyridin-3-yl)acetyl]pyrrolidine-2-carboxamide
518		(2S,4R)-N-[(R)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-1-[2-(3-ethyl-5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide
519		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-1-[2-(1-ethyl-6-oxo-1,6-dihydropyridin-3-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide
520		(2S,4R)-N-[(R)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(6-oxo-1,6-dihydropyridin-3-yl)acetyl]pyrrolidine-2-carboxamide

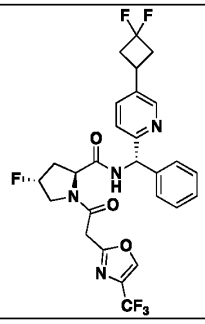
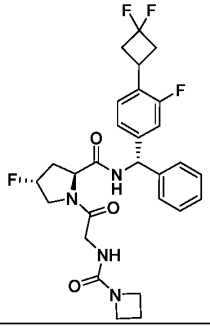
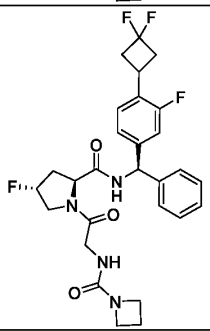
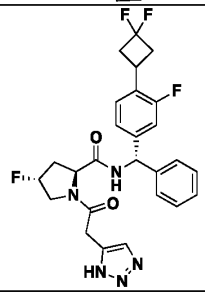
521		(2S,4R)-N-[(R)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(2-oxo-1,2-dihydropyridin-3-yl)acetyl]pyrrolidine-2-carboxamide
522		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)acetyl]pyrrolidine-2-carboxamide
523		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-1-[2-(1-ethyl-5-methyl-6-oxo-1,6-dihydropyridin-3-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide
524		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-1-[2-(6-ethoxy-5-methylpyridin-3-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide

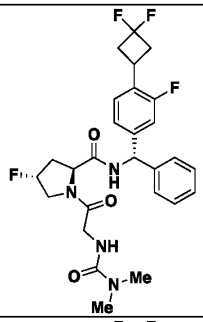
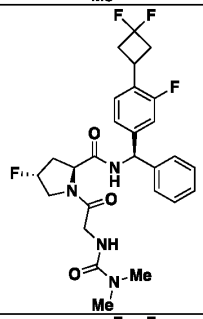
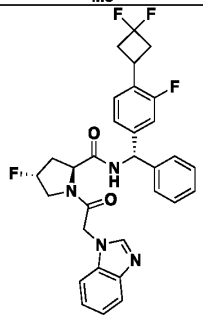
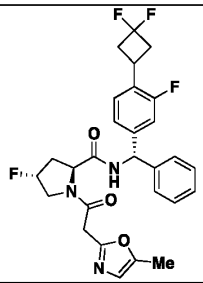
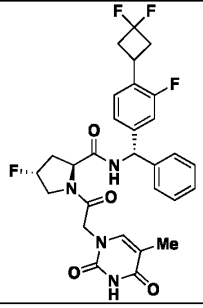
525		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-1-[2-(1-ethyl-5-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide
526		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-1-[2-(1-ethyl-2-oxo-1,2-dihydropyridin-3-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide
527		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-1-[2-(4-ethyl-5-oxo-4,5-dihydropyrazin-2-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide
528		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-4-fluoro-1-{2-[4-(trifluoromethyl)-1,3-oxazol-2-yl]acetyl}pyrrolidine-2-carboxamide

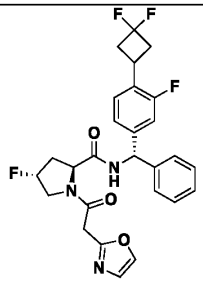
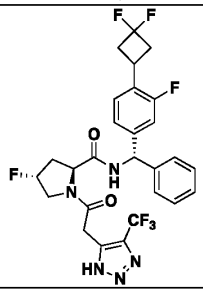
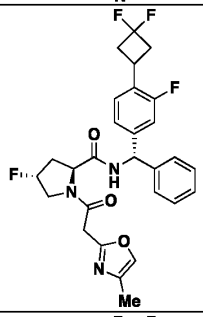
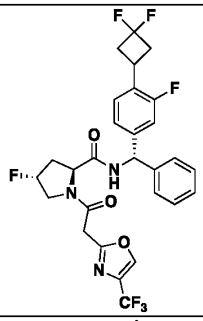
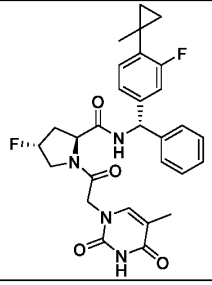
529		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(3-oxo-3,4-dihydropyrazin-2-yl)acetyl]pyrrolidine-2-carboxamide
530		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(5-oxo-4,5-dihydropyrazin-2-yl)acetyl]pyrrolidine-2-carboxamide
531		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-1-[2-(4-ethyl-3-oxo-3,4-dihydropyrazin-2-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide
532		(2*S*,4*R*)-*N*-((*S*)-(5-(3,3-difluorocyclobutyl)pyridin-2-yl)(phenyl)methyl)-1-((dimethylcarbamoyl)glycyl)-4-fluoropyrrolidine-2-carboxamide

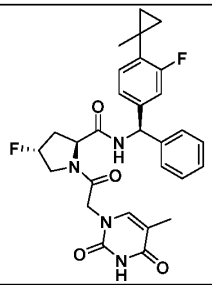
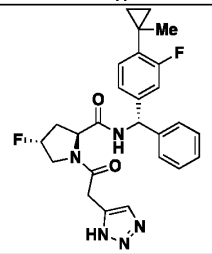
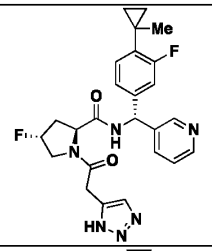
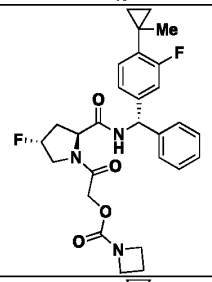
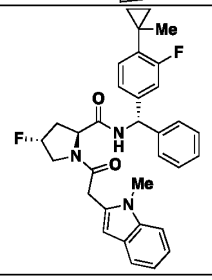
533		(2S,4R)-1-{2-[(azetidine-1-carbonyl)amino]acetyl}-N-[(S)-[5-(3,3-difluorocyclobutyl)pyridin-2-yl](phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide
534		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)pyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
535		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)pyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]pyrrolidine-2-carboxamide
536		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)pyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(5-methyl-1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide
537		(2S,4R)-1-[2-(1H-1,3-benzodiazol-1-yl)acetyl]-N-[(S)-[5-(3,3-difluorocyclobutyl)pyridin-2-yl](phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide

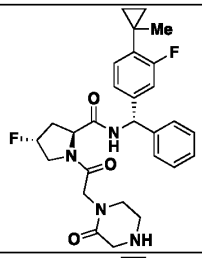
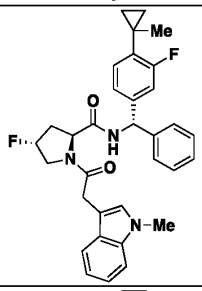
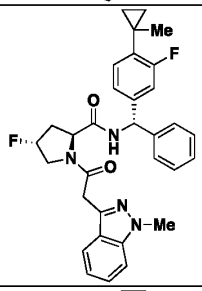
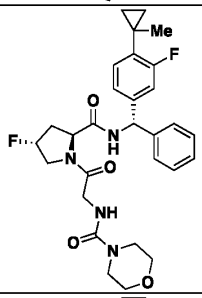
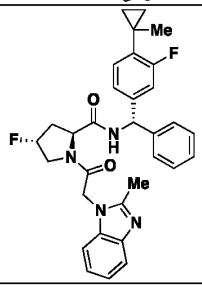
538		(2S,4R)-1-{2-[(3,3-difluoroazetidine-1-carbonyl)amino]acetyl}-N-[(S)-[5-(3,3-difluorocyclobutyl)pyridin-2-yl](phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide
539		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)pyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide
540		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)pyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(4-methyl-1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide
541		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)pyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(5-methyl-2-oxo-2,3-dihydro-1,3,4-oxadiazol-3-yl)acetyl]pyrrolidine-2-carboxamide
542		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)pyridin-2-yl](phenyl)methyl]-4-fluoro-1-{2-[4-(trifluoromethyl)-1H-1,2,3-triazol-5-yl]acetyl}pyrrolidine-2-carboxamide

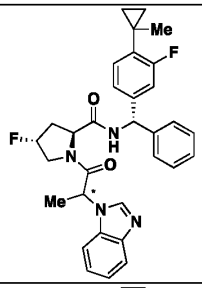
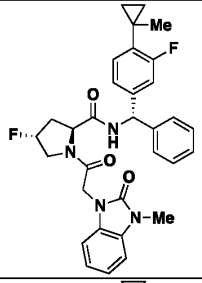
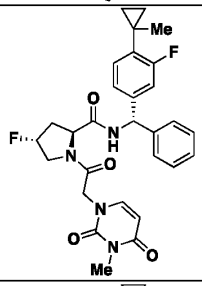
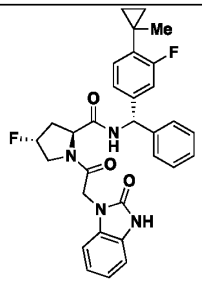
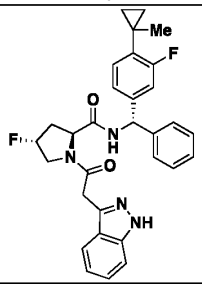
543		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)pyridin-2-yl](phenyl)methyl]-4-fluoro-1-{2-[4-(trifluoromethyl)-1,3-oxazol-2-yl]acetyl}pyrrolidine-2-carboxamide
544		(2*S*,4*R*)-1-((azetidine-1-carbonyl)glycyl)-*N*-((*S*)-(4-(3,3-difluorocyclobutyl)-3-fluorophenyl)(phenyl)methyl)-4-fluoropyrrolidine-2-carboxamide
545		(2*S*,4*R*)-1-((azetidine-1-carbonyl)glycyl)-*N*-((*R*)-(4-(3,3-difluorocyclobutyl)-3-fluorophenyl)(phenyl)methyl)-4-fluoropyrrolidine-2-carboxamide
546		(2S,4R)-N-[(S)-[4-(3,3-difluorocyclobutyl)-3-fluorophenyl](phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

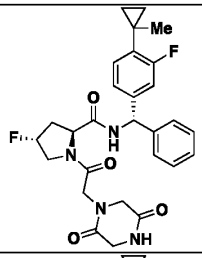
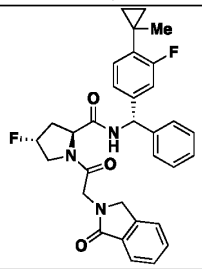
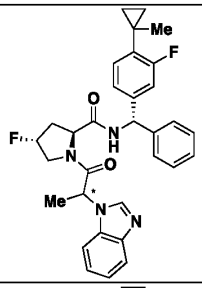
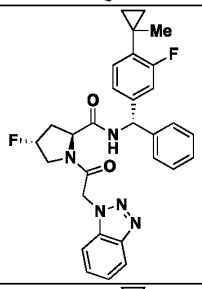
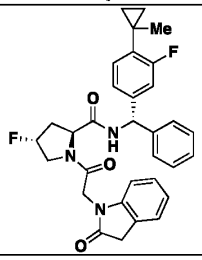
547		(2S,4R)-N-[(S)-[4-(3,3-difluorocyclobutyl)-3-fluorophenyl](phenyl)methyl]-1-{2-[(dimethylcarbamoyl)amino]acetyl}-4-fluoropyrrolidine-2-carboxamide
548		(2S,4R)-N-[(R)-[4-(3,3-difluorocyclobutyl)-3-fluorophenyl](phenyl)methyl]-1-{2-[(dimethylcarbamoyl)amino]acetyl}-4-fluoropyrrolidine-2-carboxamide
549		(2S,4R)-1-[2-(1H-1,3-benzodiazol-1-yl)acetyl]-N-[(S)-[4-(3,3-difluorocyclobutyl)-3-fluorophenyl](phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide
550		(2S,4R)-N-[(S)-[4-(3,3-difluorocyclobutyl)-3-fluorophenyl](phenyl)methyl]-4-fluoro-1-[2-(5-methyl-1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide
551		(2S,4R)-N-[(S)-[4-(3,3-difluorocyclobutyl)-3-fluorophenyl](phenyl)methyl]-4-fluoro-1-[2-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]pyrrolidine-2-carboxamide

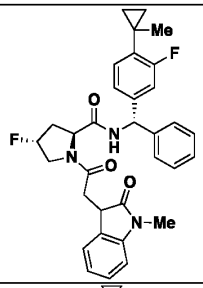
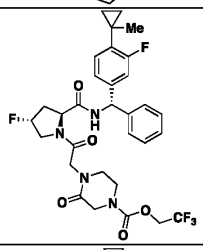
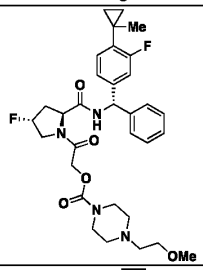
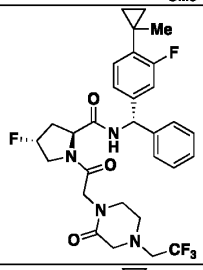
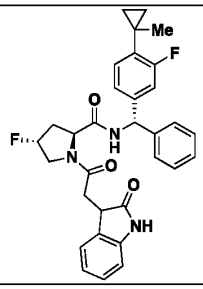
552		(2S,4R)-N-[(S)-[4-(3,3-difluorocyclobutyl)-3-fluorophenyl](phenyl)methyl]-4-fluoro-1-[2-(1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide
553		(2S,4R)-N-[(S)-[4-(3,3-difluorocyclobutyl)-3-fluorophenyl](phenyl)methyl]-4-fluoro-1-{2-[4-(trifluoromethyl)-1H-1,2,3-triazol-5-yl]acetyl}pyrrolidine-2-carboxamide
554		(2S,4R)-N-[(S)-[4-(3,3-difluorocyclobutyl)-3-fluorophenyl](phenyl)methyl]-4-fluoro-1-[2-(4-methyl-1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide
555		(2S,4R)-N-[(S)-[4-(3,3-difluorocyclobutyl)-3-fluorophenyl](phenyl)methyl]-4-fluoro-1-{2-[4-(trifluoromethyl)-1,3-oxazol-2-yl]acetyl}pyrrolidine-2-carboxamide
556		(2*S*,4*R*)-4-fluoro-*N*-((*S*)-(3-fluoro-4-(1-methylcyclopropyl)phenyl)(phenyl)methyl)-1-(2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)acetyl)pyrrolidine-2-carboxamide

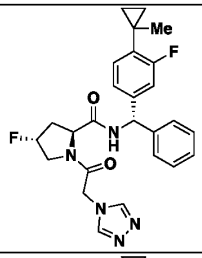
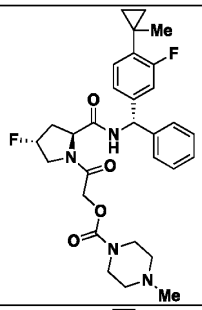
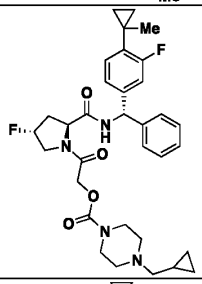
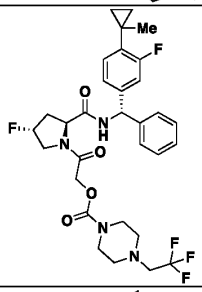
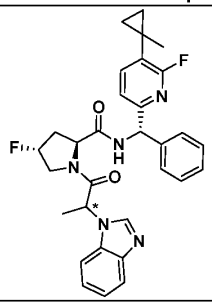
557		(2*S*,4*R*)-4-fluoro-*N*-((*R*)-(3-fluoro-4-(1-methylcyclopropyl)phenyl)(phenyl)methyl)-1-(2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)acetyl)pyrrolidine-2-carboxamide
558		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
559		(2S,4R)-4-fluoro-N-[(R)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](pyridin-3-yl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
560		2-[(2S,4R)-4-fluoro-2-{[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl azetidine-1-carboxylate
561		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]-1-[2-(1-methyl-1H-indol-2-yl)acetyl]pyrrolidine-2-carboxamide

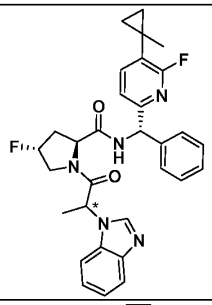
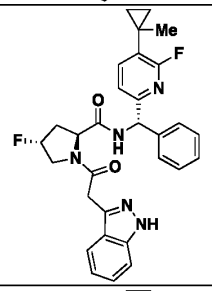
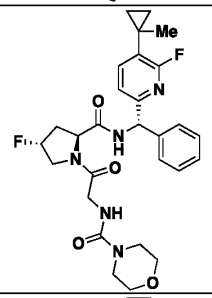
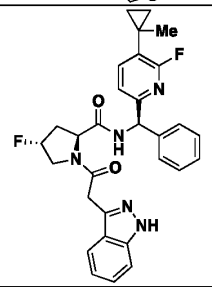
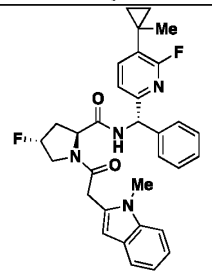
562		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]-1-[2-(2-oxopiperazin-1-yl)acetyl]pyrrolidine-2-carboxamide
563		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]-1-[2-(1-methyl-1H-indol-3-yl)acetyl]pyrrolidine-2-carboxamide
564		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]-1-[2-(1-methyl-1H-indazol-3-yl)acetyl]pyrrolidine-2-carboxamide
565		N-{2-[(2S,4R)-4-fluoro-2-{[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl}morpholine-4-carboxamide
566		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]-1-[2-(2-methyl-1H-1,3-benzodiazol-1-yl)acetyl]pyrrolidine-2-carboxamide

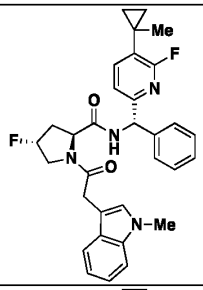
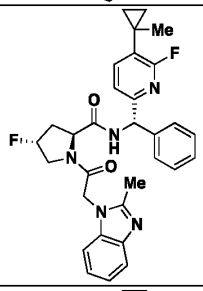
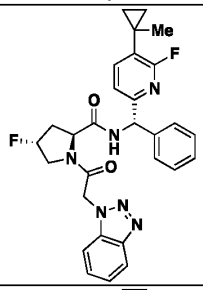
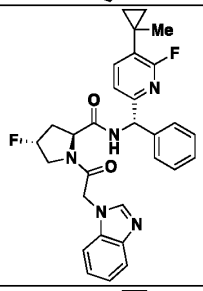
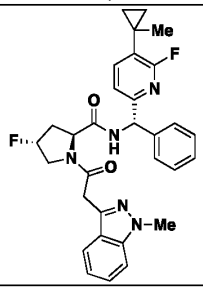
567		(2S,4R)-1-[(2R) or (2S)-2-(1H-1,3-benzodiazol-1-yl)propanoyl]-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]pyrrolidine-2-carboxamide
568		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]-1-[2-(3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)acetyl]pyrrolidine-2-carboxamide
569		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]-1-[2-(3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]pyrrolidine-2-carboxamide
570		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]-1-[2-(2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)acetyl]pyrrolidine-2-carboxamide
571		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]-1-[2-(1H-indazol-3-yl)acetyl]pyrrolidine-2-carboxamide

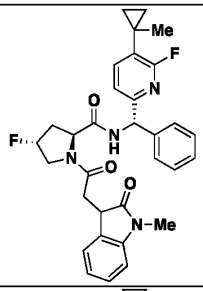
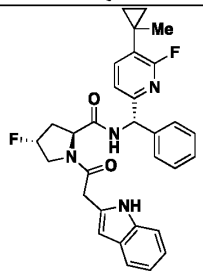
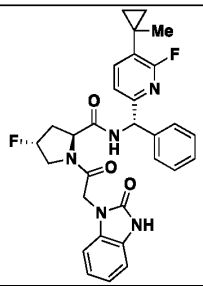
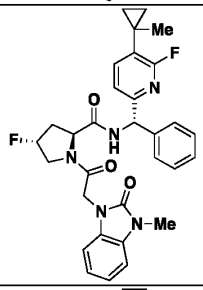
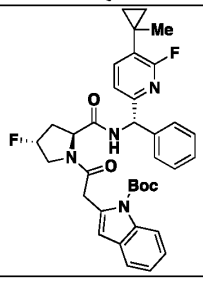
572		(2S,4R)-1-[2-(2,5-dioxopiperazin-1-yl)acetyl]-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]pyrrolidine-2-carboxamide
573		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]-1-[2-(1-oxo-2,3-dihydro-1H-isoindol-2-yl)acetyl]pyrrolidine-2-carboxamide
574		(2S,4R)-1-[(2S) or 2R)-2-(1H-1,3-benzodiazol-1-yl)propanoyl]-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]pyrrolidine-2-carboxamide
575		(2S,4R)-1-[2-(1H-1,2,3-benzotriazol-1-yl)acetyl]-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]pyrrolidine-2-carboxamide
576		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]-1-[2-(2-oxo-2,3-dihydro-1H-indol-1-yl)acetyl]pyrrolidine-2-carboxamide

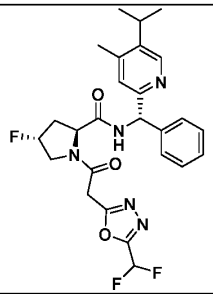
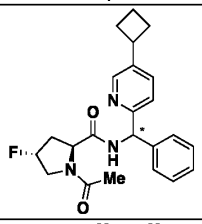
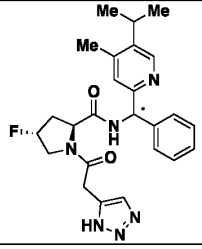
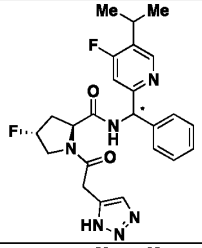
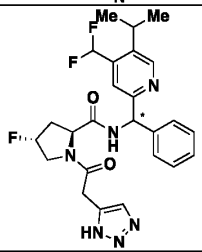
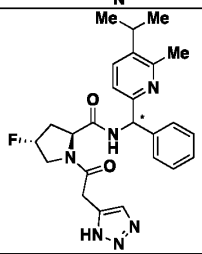
577		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]-1-[2-(1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl)acetyl]pyrrolidine-2-carboxamide
578		2,2,2-trifluoroethyl 4-{2-[(2S,4R)-4-fluoro-2-{[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl}-3-oxopiperazine-1-carboxylate
579		2-[(2S,4R)-4-fluoro-2-{[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl 4-(2-methoxyethyl)piperazine-1-carboxylate
580		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]-1-{2-[2-oxo-4-(2,2,2-trifluoroethyl)piperazin-1-yl]acetyl}pyrrolidine-2-carboxamide
581		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]-1-[2-(2-oxo-2,3-dihydro-1H-indol-3-yl)acetyl]pyrrolidine-2-carboxamide

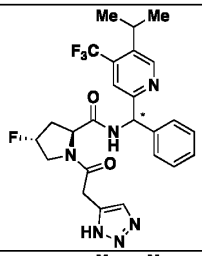
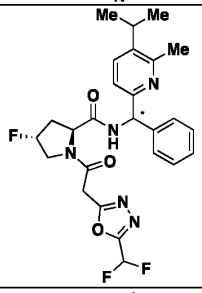
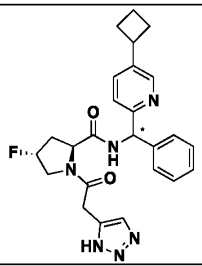
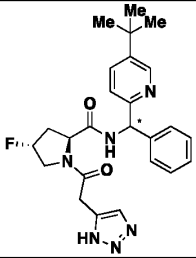
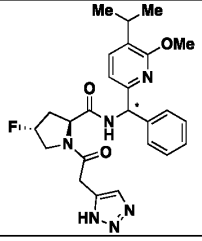
582		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]-1-[2-(4H-1,2,4-triazol-4-yl)acetyl]pyrrolidine-2-carboxamide
583		2-[(2S,4R)-4-fluoro-2-{[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl 4-methylpiperazine-1-carboxylate
584		2-[(2S,4R)-4-fluoro-2-{[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl 4-(cyclopropylmethyl)piperazine-1-carboxylate
585		2-[(2S,4R)-4-fluoro-2-{[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl 4-(2,2,2-trifluoroethyl)piperazine-1-carboxylate
586		(2*S*,4*R*)-1-((*R*) or (*S*)-2-(1*H*-benzo[*d*]imidazol-1-yl)propanoyl)-4-fluoro-*N*-((*S*)-(6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl)(phenyl)methyl)pyrrolidine-2-carboxamide

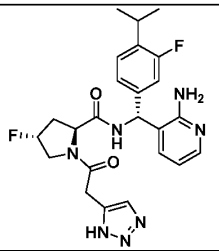
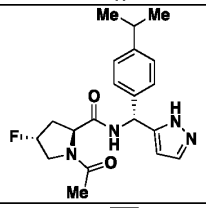
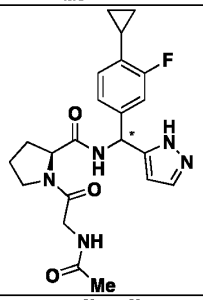
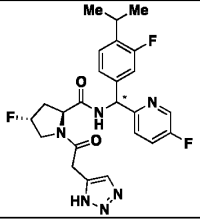
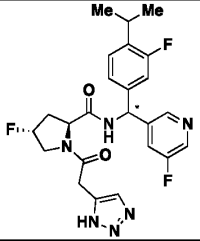
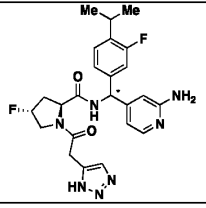
587		(2*S*,4*R*)-1-((*S*) or (*R*)-2-(1*H*-benzo[*d*]imidazol-1-yl)propanoyl)-4-fluoro-*N*-((*S*)-(6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl)(phenyl)methyl)pyrrolidine-2-carboxamide
588		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl]-1-[2-(1H-indazol-3-yl)acetyl]pyrrolidine-2-carboxamide
589		N-{2-[(2S,4R)-4-fluoro-2-{[(S)-[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl}morpholine-4-carboxamide
590		(2S,4R)-4-fluoro-N-[(R)-[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl]-1-[2-(1H-indazol-3-yl)acetyl]pyrrolidine-2-carboxamide
591		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl]-1-[2-(1-methyl-1H-indol-2-yl)acetyl]pyrrolidine-2-carboxamide

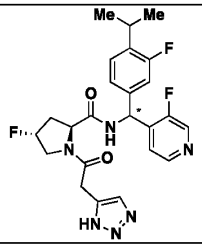
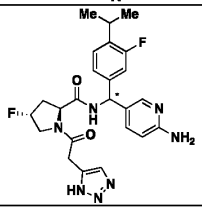
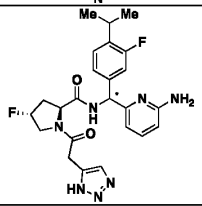
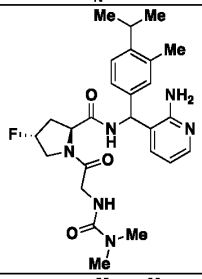
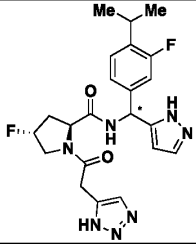
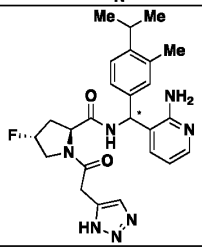
592		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl]-1-[2-(1-methyl-1H-indol-3-yl)acetyl]pyrrolidine-2-carboxamide
593		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl]-1-[2-(2-methyl-1H-1,3-benzodiazol-1-yl)acetyl]pyrrolidine-2-carboxamide
594		(2S,4R)-1-[2-(1H-1,2,3-benzotriazol-1-yl)acetyl]-4-fluoro-N-[(S)-[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide
595		(2S,4R)-1-[2-(1H-1,3-benzodiazol-1-yl)acetyl]-4-fluoro-N-[(S)-[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide
596		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl]-1-[2-(1-methyl-1H-indazol-3-yl)acetyl]pyrrolidine-2-carboxamide

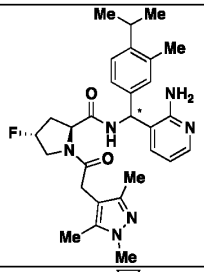
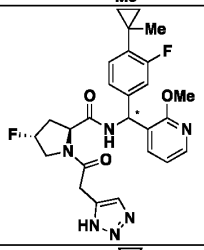
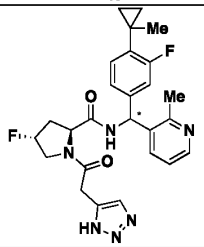
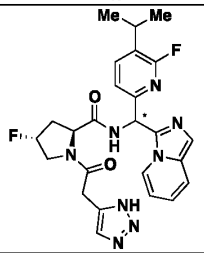
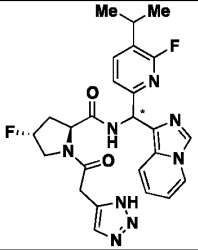
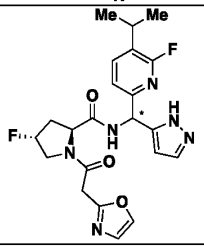
597		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl]-1-[2-(1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl)acetyl]pyrrolidine-2-carboxamide
598		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl]-1-[2-(1H-indol-2-yl)acetyl]pyrrolidine-2-carboxamide
599		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl]-1-[2-(2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)acetyl]pyrrolidine-2-carboxamide
600		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl]-1-[2-(3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)acetyl]pyrrolidine-2-carboxamide
601		tert-butyl 2-{2-[(2S,4R)-4-fluoro-2-{[(S)-[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl}-1H-indole-1-carboxylate

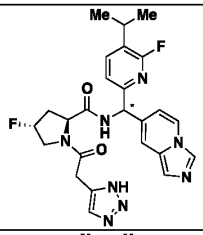
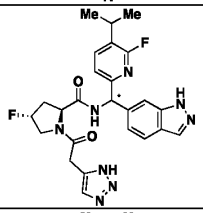
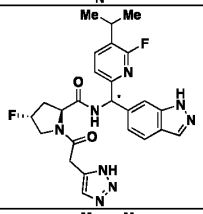
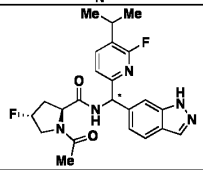
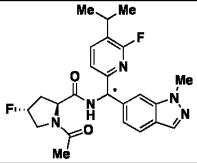
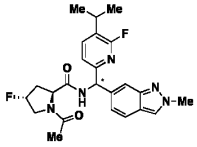
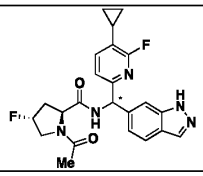
602		(2*S*,4*R*)-1-(2-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)acetyl)-4-fluoro-*N*-((*S*)-(5-isopropyl-4-methylpyridin-2-yl)(phenyl)methyl)pyrrolidine-2-carboxamide
603		(2S,4R)-1-acetyl-N-[(S) or (R)-(5-cyclobutylpyridin-2-yl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide
604		(2S,4R)-4-fluoro-N-[(S) or (R)-[4-methyl-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
605		(2S,4R)-4-fluoro-N-[(S) or (R)-[4-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
606		(2S,4R)-N-[(S) or (R)-[4-(difluoromethyl)-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
607		(2S,4R)-4-fluoro-N-[(S) or (R)-[6-methyl-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

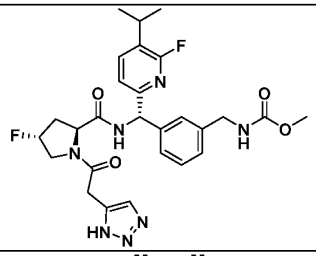
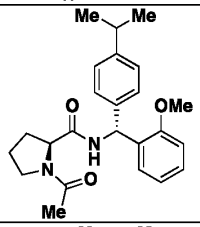
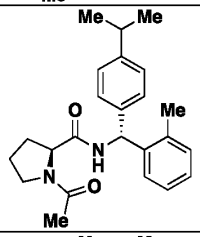
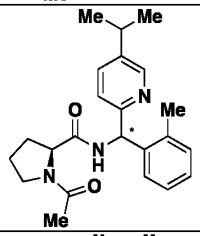
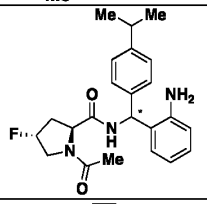
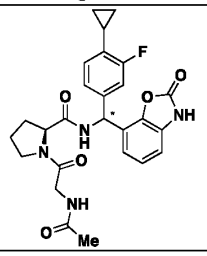
608		(2S,4R)-4-fluoro-N-[(S) or (R)-phenyl[5-(propan-2-yl)-4-(trifluoromethyl)pyridin-2-yl]methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
609		(2S,4R)-1-{2-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]acetyl}-4-fluoro-N-[(S) or (R)-[6-methyl-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide
610		(2S,4R)-N-[(S) or (R)-(5-cyclobutylpyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
611		(2S,4R)-N-[(S) or (R)-(5-tert-butylpyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
612		(2S,4R)-4-fluoro-N-[(S) or (R)-[6-methoxy-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

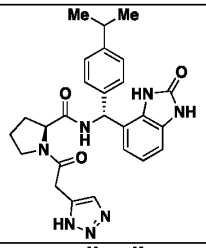
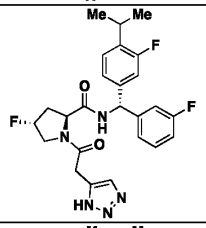
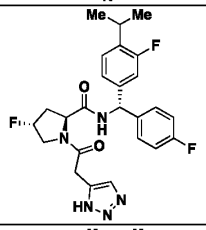
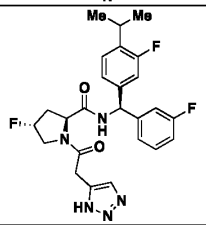
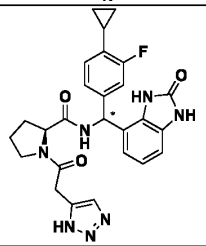
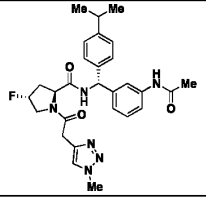
613		(2*S*,4*R*)-1-(2-(1*H*-1,2,3-triazol-5-yl)acetyl)-*N*-((*R*)-(2-aminopyridin-3-yl)(3-fluoro-4-isopropylphenyl)methyl)-4-fluoropyrrolidine-2-carboxamide
614		(2S,4R)-1-acetyl-4-fluoro-N-[(S)-[4-(propan-2-yl)phenyl](1H-pyrazol-5-yl)methyl]pyrrolidine-2-carboxamide
615		(2S)-N-[(R) or (S)-(4-cyclopropyl-3-fluorophenyl)(1H-pyrazol-5-yl)methyl]-1-(2-acetamidoacetyl)pyrrolidine-2-carboxamide
616		(2S,4R)-4-fluoro-N-[(R) or (S)-[3-fluoro-4-(propan-2-yl)phenyl](5-fluoropyridin-2-yl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
617		(2S,4R)-4-fluoro-N-[(R) or (S)-[3-fluoro-4-(propan-2-yl)phenyl](5-fluoropyridin-3-yl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
618		(2S,4R)-N-[(S) or (R)-(2-aminopyridin-4-yl)[3-fluoro-4-(propan-2-yl)phenyl]methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

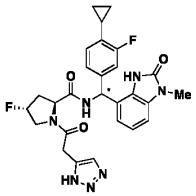
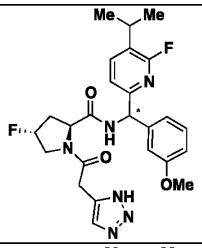
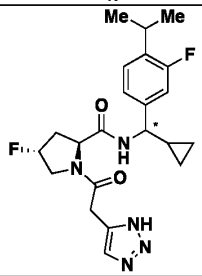
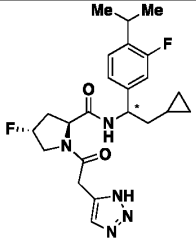
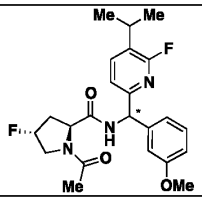
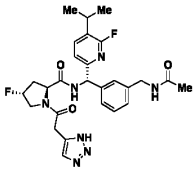
619		(2S,4R)-4-fluoro-N-[(R) or (S)-[3-fluoro-4-(propan-2-yl)phenyl](3-fluoropyridin-4-yl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
620		(2S,4R)-N-[(R) or (S)-(6-aminopyridin-3-yl)[3-fluoro-4-(propan-2-yl)phenyl]methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
621		(2S,4R)-N-[(R) or (S)-(6-aminopyridin-2-yl)[3-fluoro-4-(propan-2-yl)phenyl]methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
622		(2S,4R)-N-[(R) or (S)-(2-aminopyridin-3-yl)[3-methyl-4-(propan-2-yl)phenyl]methyl]-1-{2-[(dimethylcarbamoyl)amino]acetyl}-4-fluoropyrrolidine-2-carboxamide
623		(2S,4R)-4-fluoro-N-[(R) or (S)-[3-fluoro-4-(propan-2-yl)phenyl](1H-pyrazol-5-yl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
624		(2S,4R)-N-[(R) or (S)-(2-aminopyridin-3-yl)[3-methyl-4-(propan-2-yl)phenyl]methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

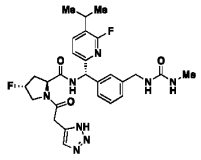
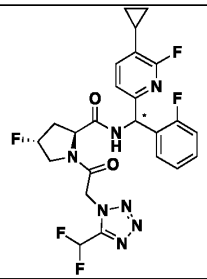
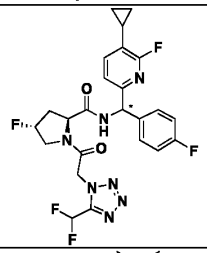
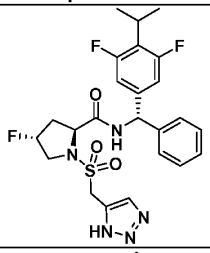
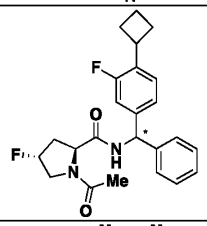
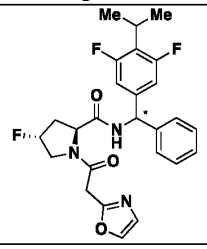
625		(2S,4R)-N-[(R) or (S)-(2-aminopyridin-3-yl)[3-methyl-4-(propan-2-yl)phenyl]methyl]-4-fluoro-1-[2-(1,3,5-trimethyl-1H-pyrazol-4-yl)acetyl]pyrrolidine-2-carboxamide
626		(2S,4R)-4-fluoro-N-[(R) or (S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](2-methoxypyridin-3-yl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
627		(2S,4R)-4-fluoro-N-[(R) or (S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](2-methylpyridin-3-yl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
628		(2S,4R)-4-fluoro-N-[(R) or (S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl]({imidazo[1,5-a]pyridin-3-yl})methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
629		(2S,4R)-4-fluoro-N-[(S) or (R)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl]({imidazo[1,5-a]pyridin-1-yl})methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
630		(2S,4R)-4-fluoro-N-[(S) or (R)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](1H-pyrazol-5-yl)methyl]-1-[2-(1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide

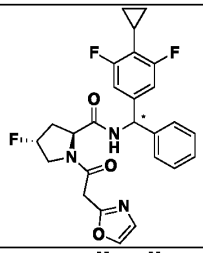
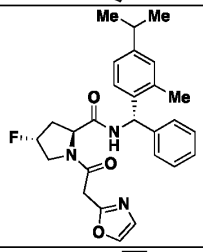
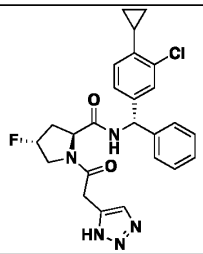
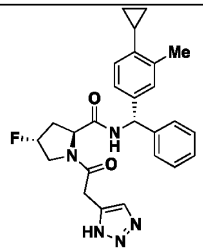
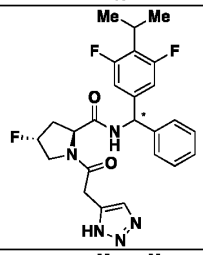
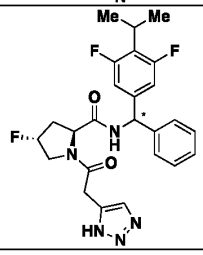
631		(2S,4R)-4-fluoro-N-[(S) or (R)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl]({imidazo[1,5-a]pyridin-7-yl})methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
632		(2S,4R)-4-fluoro-N-[(S) or (R)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](1H-indazol-6-yl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
633		(2S,4R)-4-fluoro-N-[(R) or (S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](1H-indazol-6-yl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
634		(2S,4R)-1-acetyl-4-fluoro-N-[(S) or (R)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](1H-indazol-6-yl)methyl]pyrrolidine-2-carboxamide
635		(2S,4R)-1-acetyl-4-fluoro-N-[(S) or (R)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](1-methyl-1H-indazol-6-yl)methyl]pyrrolidine-2-carboxamide
636		(2S,4R)-1-acetyl-4-fluoro-N-[(S) or (R)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](2-methyl-2H-indazol-6-yl)methyl]pyrrolidine-2-carboxamide
637		(2S,4R)-1-acetyl-N-[(S) or (R)-(5-cyclopropyl-6-fluoropyridin-2-yl)(1H-indazol-6-yl)methyl]-4-fluoropyrrolidine-2-carboxamide

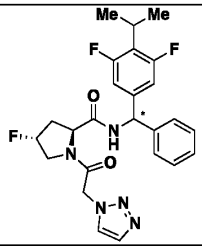
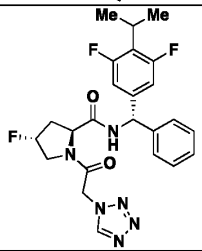
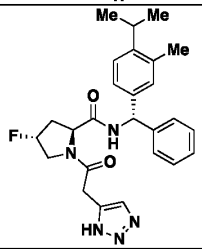
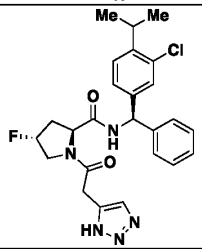
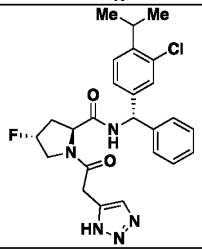
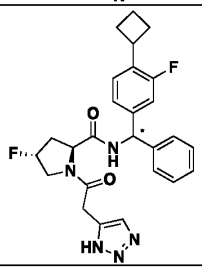
638		methyl (3-((*S*)-((2*S*,4*R*)-1-(2-(1*H*-1,2,3-triazol-5-yl)acetyl)-4-fluoropyrrolidine-2-carboxamido)(6-fluoro-5-isopropylpyridin-2-yl)methyl)benzyl)carbamate
639		(2S)-1-acetyl-N-[(R)-(2-methoxyphenyl)[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
640		(2S)-1-acetyl-N-[(R)-(2-methylphenyl)[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
641		(2S)-1-acetyl-N-[(S) or (R)-(2-methylphenyl)[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide
642		(2S,4R)-1-acetyl-N-[(R) or (S)-(2-aminophenyl)[4-(propan-2-yl)phenyl]methyl]-4-fluoropyrrolidine-2-carboxamide
643		(2S)-N-[(R) or (S)-(4-cyclopropyl-3-fluorophenyl)(2-oxo-2,3-dihydro-1,3-benzoxazol-7-yl)methyl]-1-(2-acetamidoacetyl)pyrrolidine-2-carboxamide

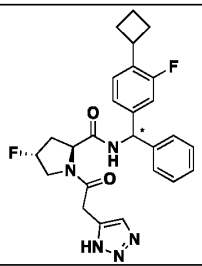
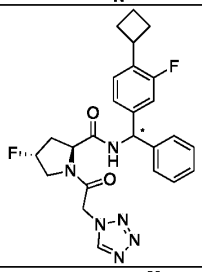
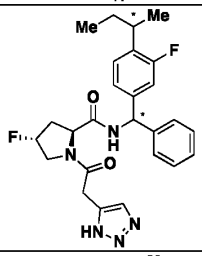
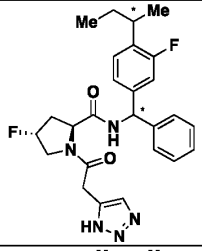
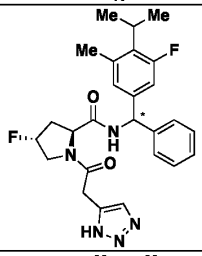
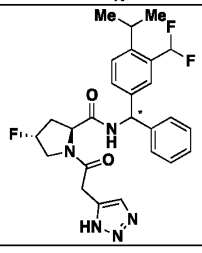
644		(2S)-N-[(R)-(2-oxo-2,3-dihydro-1H-1,3-benzodiazol-4-yl)[4-(propan-2-yl)phenyl]methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
645		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](3-fluorophenyl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
646		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](4-fluorophenyl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
647		(2S,4R)-4-fluoro-N-[(R)-[3-fluoro-4-(propan-2-yl)phenyl](3-fluorophenyl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
648		(2S)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(2-oxo-2,3-dihydro-1H-1,3-benzodiazol-4-yl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
649		(2S,4R)-N-[(R)-(3-acetamidophenyl)[4-(propan-2-yl)phenyl]methyl]-4-fluoro-1-[2-(1-methyl-1H-1,2,3-triazol-4-yl)acetyl]pyrrolidine-2-carboxamide

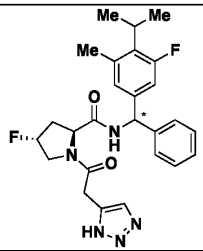
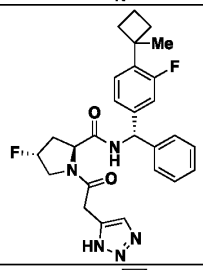
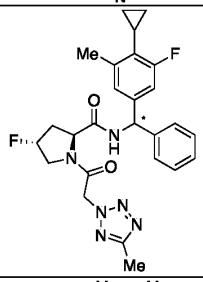
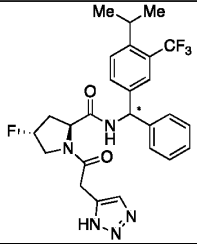
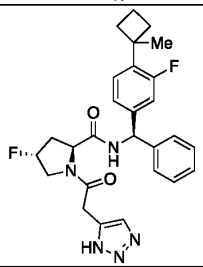
650		(2S,4R)-N-[(R) or (S)-(4-cyclopropyl-3-fluorophenyl)(1-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-4-yl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
651		(2S,4R)-4-fluoro-N-[(S) or (R)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](3-methoxyphenyl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
652		(2S,4R)-N-[(S) or (R)-cyclopropyl[3-fluoro-4-(propan-2-yl)phenyl]methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
653		(2S,4R)-N-[(1S) or (1R)-2-cyclopropyl-1-[3-fluoro-4-(propan-2-yl)phenyl]ethyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
654		(2S,4R)-1-acetyl-4-fluoro-N-[(S) or (R)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](3-methoxyphenyl)methyl]pyrrolidine-2-carboxamide
655		(2S,4R)-N-[(S)-[3-(acetamidomethyl)phenyl][6-fluoro-5-(propan-2-yl)pyridin-2-yl]methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

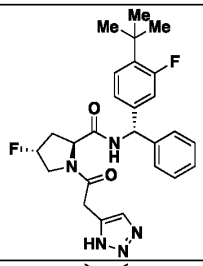
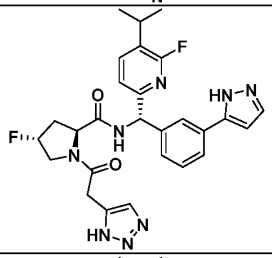
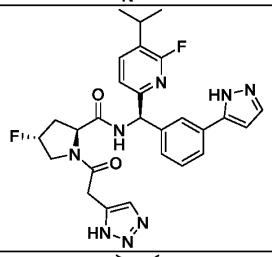
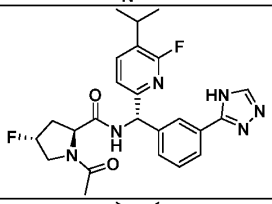
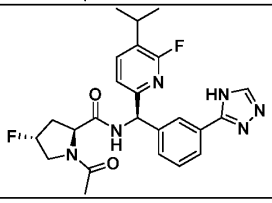
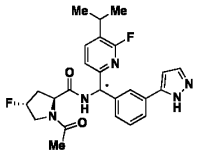
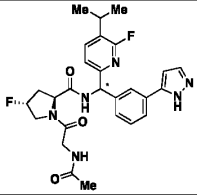
656		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](3-{[(methylcarbamoyl)amino]methyl}phenyl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
657		(2S,4R)-N-[(S) or (R)-(5-cyclopropyl-6-fluoropyridin-2-yl)(2-fluorophenyl)methyl]-1-{2-[5-(difluoromethyl)-1H-1,2,3,4-tetrazol-1-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide
658		(2S,4R)-N-[(S) or (R)-(5-cyclopropyl-6-fluoropyridin-2-yl)(4-fluorophenyl)methyl]-1-{2-[5-(difluoromethyl)-1H-1,2,3,4-tetrazol-1-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide
659		(2*S*,4*R*)-1-(((1*H*-1,2,3-triazol-5-yl)methyl)sulfonyl)-*N*-((*S*)-(3,5-difluoro-4-isopropylphenyl)(phenyl)methyl)-4-fluoropyrrolidine-2-carboxamide
660		(2S,4R)-1-acetyl-N-[(S) or (R)-(4-cyclobutyl-3-fluorophenyl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide
661		(2S,4R)-N-[(S) or (R)-[3,5-difluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-4-fluoro-1-[2-(1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide

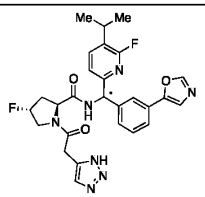
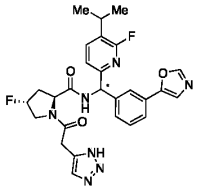
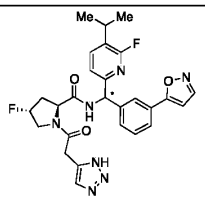
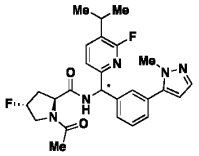
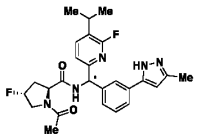
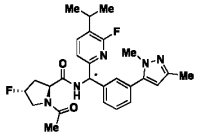
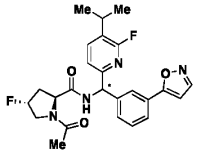
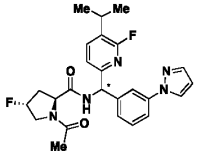
662		(2S,4R)-N-[(S)-(4-cyclopropyl-3,5-difluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide
663		(2S,4R)-4-fluoro-N-[(S)-[2-methyl-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide
664		(2S,4R)-N-[(S)-(3-chloro-4-cyclopropylphenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
665		(2S,4R)-N-[(S)-(4-cyclopropyl-3-methylphenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
666		(2S,4R)-N-[(R) or (S)-[3,5-difluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
667		(2S,4R)-N-[(S) or (R)-[3,5-difluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

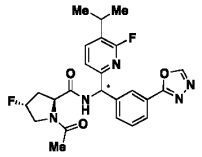
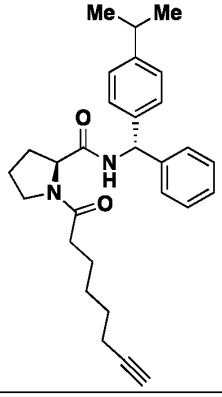
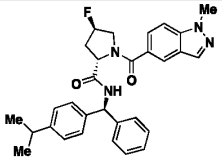
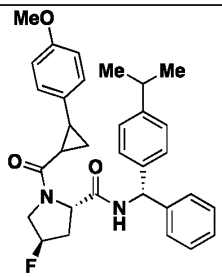
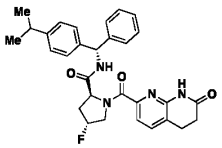
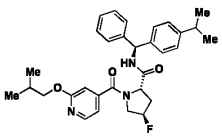
668		(2S,4R)-N-[(S) or (R)-[3,5-difluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-1-yl)acetyl]pyrrolidine-2-carboxamide
669		(2S,4R)-N-[(S)-[3,5-difluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3,4-tetrazol-1-yl)acetyl]pyrrolidine-2-carboxamide
670		(2S,4R)-4-fluoro-N-[(S)-[3-methyl-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
671		(2S,4R)-N-[(R)-[3-chloro-4-(propan-2-yl)phenyl](phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
672		(2S,4R)-N-[(S)-[3-chloro-4-(propan-2-yl)phenyl](phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
673		(2S,4R)-N-[(R) or (S)-(4-cyclobutyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

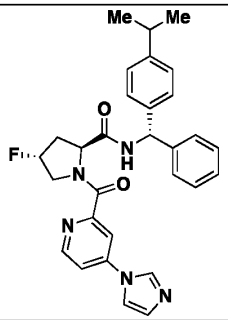
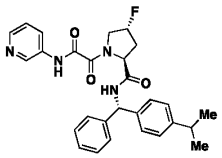
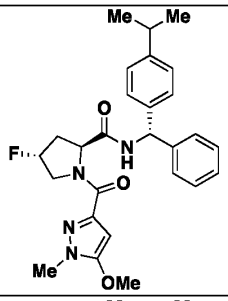
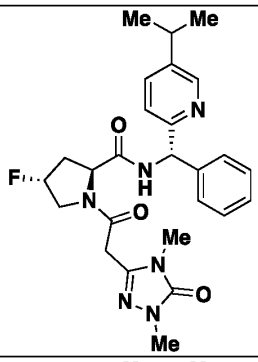
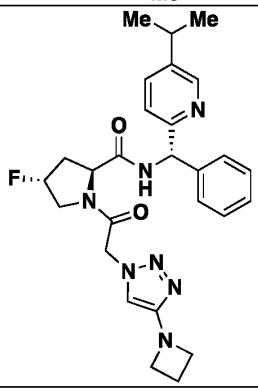
674		(2S,4R)-N-[(S) or (R)-(4-cyclobutyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
675		(2S,4R)-N-[(S) or (R)-(4-cyclobutyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3,4-tetrazol-1-yl)acetyl]pyrrolidine-2-carboxamide
676		(2S,4R)-N-[(R) or (S)-{4-[(2R) or (2S)-butan-2-yl]-3-fluorophenyl}(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
677		(2S,4R)-N-[(S) or (R)-{4-[(2R) or (2S)-butan-2-yl]-3-fluorophenyl}(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
678		(2S,4R)-4-fluoro-N-[(R) or (S)-[3-fluoro-5-methyl-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
679		(2S,4R)-N-[(S)-[3-(difluoromethyl)-4-(propan-2-yl)phenyl](phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

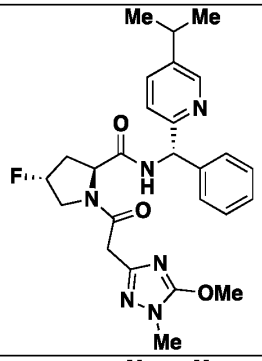
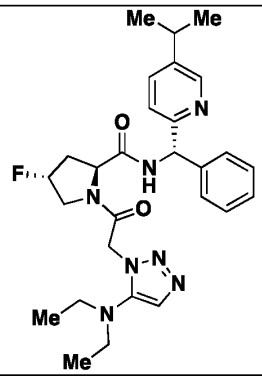
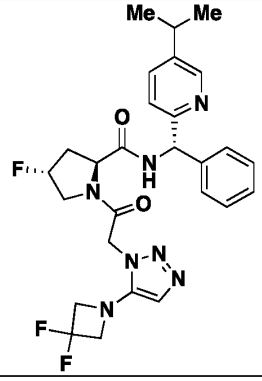
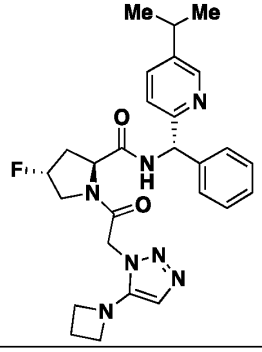
680		(2S,4R)-4-fluoro-N-[(S) or (R)-[3-fluoro-5-methyl-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
681		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclobutyl)phenyl](phenyl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
682		(2S,4R)-N-[(S) or (R)-(4-cyclopropyl-3-fluoro-5-methylphenyl)(phenyl)methyl]-4-fluoro-1-[2-(5-methyl-2H-1,2,3,4-tetrazol-2-yl)acetyl]pyrrolidine-2-carboxamide
683		(2S,4R)-4-fluoro-N-[(S) or (R)-phenyl[4-(propan-2-yl)-3-(trifluoromethyl)phenyl]methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
684		(2S,4R)-4-fluoro-N-[(R)-[3-fluoro-4-(1-methylcyclobutyl)phenyl](phenyl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

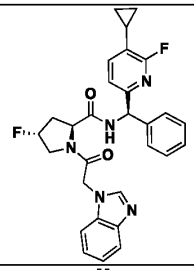
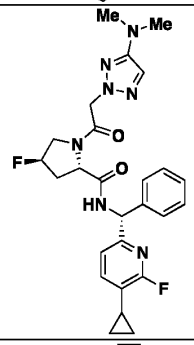
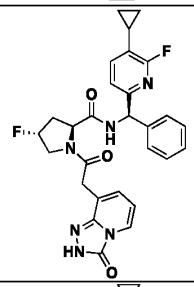
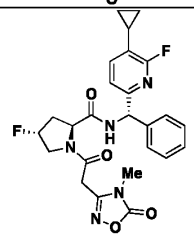
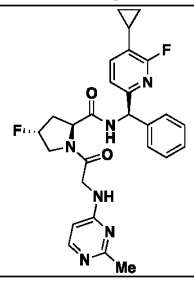
685		(2S,4R)-N-[(S)-(4-tert-butyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
686		(2*S*,4*R*)-1-(2-(1*H*-1,2,3-triazol-5-yl)acetyl)-*N*-((*S*)-(3-(1*H*-pyrazol-5-yl)phenyl)(6-fluoro-5-isopropylpyridin-2-yl)methyl)-4-fluoropyrrolidine-2-carboxamide
687		(2*S*,4*R*)-1-(2-(1*H*-1,2,3-triazol-5-yl)acetyl)-*N*-((*R*)-(3-(1*H*-pyrazol-5-yl)phenyl)(6-fluoro-5-isopropylpyridin-2-yl)methyl)-4-fluoropyrrolidine-2-carboxamide
688		(2*S*,4*R*)-*N*-((*S*) or (*R*)-(3-(4*H*-1,2,4-triazol-3-yl)phenyl)(6-fluoro-5-isopropylpyridin-2-yl)methyl)-1-acetyl-4-fluoropyrrolidine-2-carboxamide
689		(2*S*,4*R*)-*N*-((*R*) or (*S*)-(3-(4*H*-1,2,4-triazol-3-yl)phenyl)(6-fluoro-5-isopropylpyridin-2-yl)methyl)-1-acetyl-4-fluoropyrrolidine-2-carboxamide
690		(2S,4R)-1-acetyl-4-fluoro-N-[(S) or (R)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl][3-(1H-pyrazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide
691		(2S,4R)-1-(2-acetamidoacetyl)-4-fluoro-N-[(S) or (R)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl][3-(1H-pyrazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide

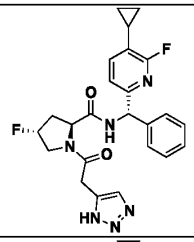
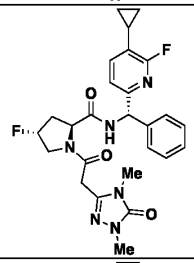
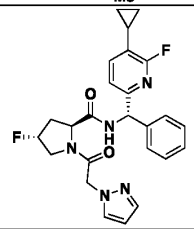
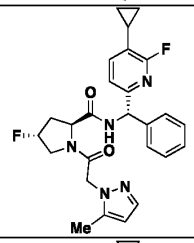
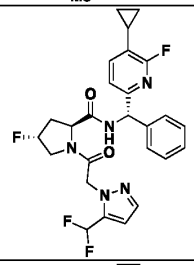
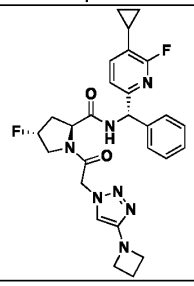
692		(2S,4R)-4-fluoro-N-[(R) or (S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl][3-(1,3-oxazol-5-yl)phenyl]methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
693		(2S,4R)-4-fluoro-N-[(S) or (R)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl][3-(1,3-oxazol-5-yl)phenyl]methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
694		(2S,4R)-4-fluoro-N-[(S) or (R)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl][3-(1,2-oxazol-5-yl)phenyl]methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
695		(2S,4R)-1-acetyl-4-fluoro-N-[(S) or (R)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl][3-(1-methyl-1H-pyrazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide
696		(2S,4R)-1-acetyl-4-fluoro-N-[(S) or (R)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl][3-(3-methyl-1H-pyrazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide
697		(2S,4R)-1-acetyl-N-[(S) or (R)-[3-(1,3-dimethyl-1H-pyrazol-5-yl)phenyl][6-fluoro-5-(propan-2-yl)pyridin-2-yl]methyl]-4-fluoropyrrolidine-2-carboxamide
698		(2S,4R)-1-acetyl-4-fluoro-N-[(S) or (R)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl][3-(1,2-oxazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide
699		(2S,4R)-1-acetyl-4-fluoro-N-[(S) or (R)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl][3-(1H-pyrazol-1-yl)phenyl]methyl]pyrrolidine-2-carboxamide

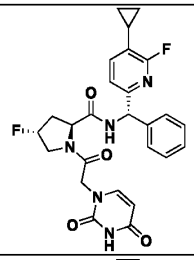
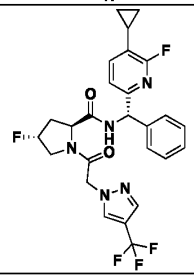
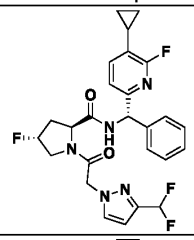
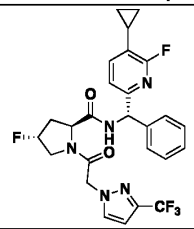
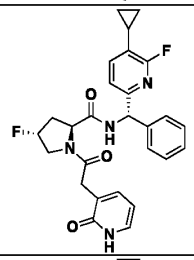
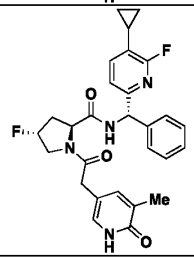
700		(2S,4R)-1-acetyl-4-fluoro-N-[(S) or (R)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl][3-(1,3,4-oxadiazol-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
701		(2S)-1-(oct-7-ynoyl)-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
702		(2S,4R)-4-fluoro-1-(1-methyl-1H-indazole-5-carbonyl)-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
703		(2S,4R)-4-fluoro-1-[2-(4-methoxyphenyl)cyclopropanecarbonyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
704		(2S,4R)-4-fluoro-1-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridine-2-carbonyl)-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
705		(2S,4R)-4-fluoro-1-[2-(2-methylpropoxy)pyridine-4-carbonyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide

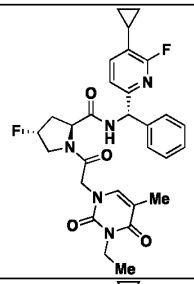
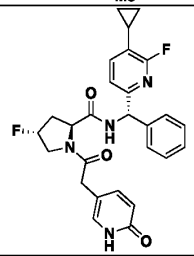
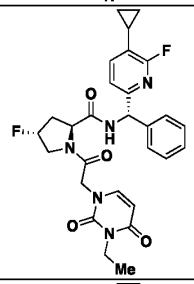
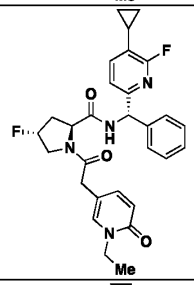
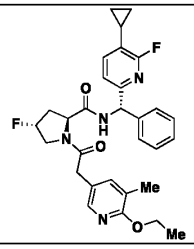
707		(2S,4R)-4-fluoro-1-[4-(1H-imidazol-1-yl)pyridine-2-carbonyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
708		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-{[(pyridin-3-yl)carbamoyl]carbonyl}pyrrolidine-2-carboxamide
709		(2S,4R)-4-fluoro-1-(5-methoxy-1-methyl-1H-pyrazole-3-carbonyl)-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide
710		(2S,4R)-1-[2-(1,4-dimethyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)acetyl]-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide
711		(2S,4R)-1-{2-[4-(azetidin-1-yl)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide

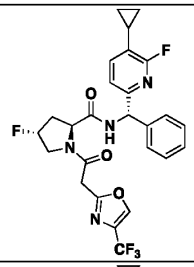
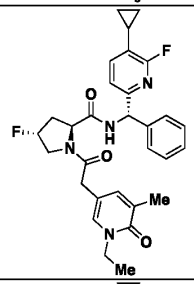
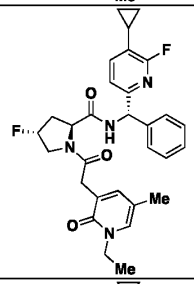
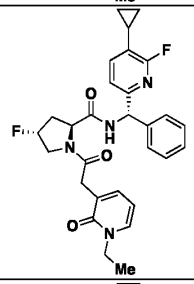
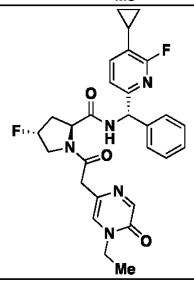
712		(2S,4R)-4-fluoro-1-[2-(5-methoxy-1-methyl-1H-1,2,4-triazol-3-yl)acetyl]-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide
713		(2S,4R)-1-{2-[5-(diethylamino)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide
714		(2S,4R)-1-{2-[5-(3,3-difluoroazetidin-1-yl)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide
715		(2S,4R)-1-{2-[5-(azetidin-1-yl)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide

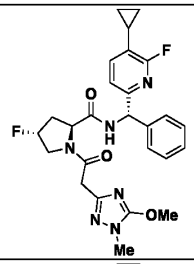
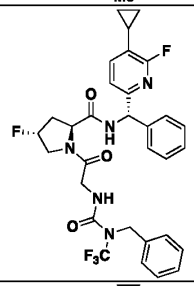
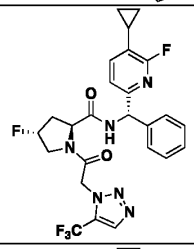
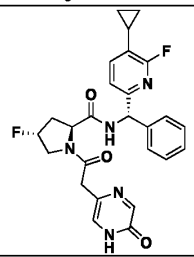
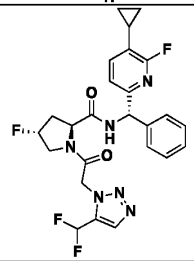
716		(2S,4R)-1-[2-(1H-1,3-benzodiazol-1-yl)acetyl]-N-[(R)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide
717		(2S,4R)-N-[(R)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[4-(dimethylamino)-2H-1,2,3-triazol-2-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide
718		(2S,4R)-N-[(R)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-(2-{3-oxo-2H,3H-[1,2,4]triazolo[4,3-a]pyridin-8-yl}acetyl)pyrrolidine-2-carboxamide
719		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(4-methyl-5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)acetyl]pyrrolidine-2-carboxamide
720		(2S,4R)-N-[(R)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-{2-[(2-methylpyrimidin-4-yl)amino]acetyl}pyrrolidine-2-carboxamide

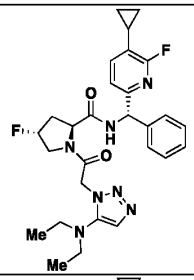
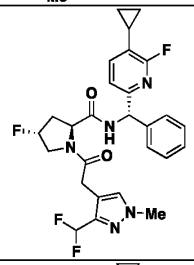
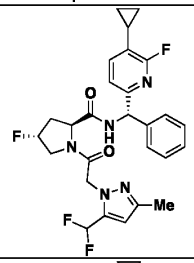
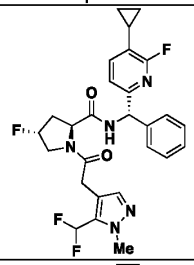
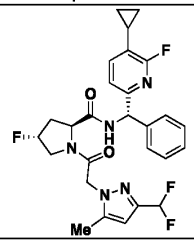
721		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
722		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[2-(1,4-dimethyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide
723		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(1H-pyrazol-1-yl)acetyl]pyrrolidine-2-carboxamide
724		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(5-methyl-1H-pyrazol-1-yl)acetyl]pyrrolidine-2-carboxamide
725		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[5-(difluoromethyl)-1H-pyrazol-1-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide
726		(2S,4R)-1-{2-[4-(azetidin-1-yl)-1H-1,2,3-triazol-1-yl]acetyl}-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide

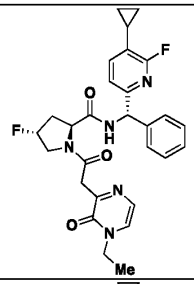
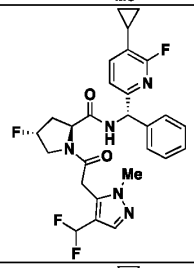
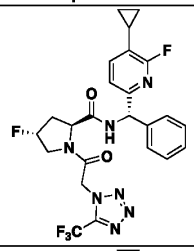
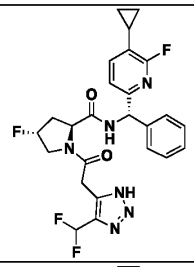
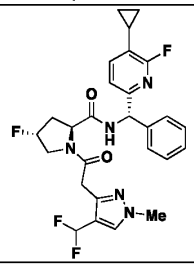
727		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[2-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide
728		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-{2-[4-(trifluoromethyl)-1H-pyrazol-1-yl]acetyl}pyrrolidine-2-carboxamide
729		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[3-(difluoromethyl)-1H-pyrazol-1-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide
730		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-{2-[3-(trifluoromethyl)-1H-pyrazol-1-yl]acetyl}pyrrolidine-2-carboxamide
731		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(2-oxo-1,2-dihydropyridin-3-yl)acetyl]pyrrolidine-2-carboxamide
732		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)acetyl]pyrrolidine-2-carboxamide

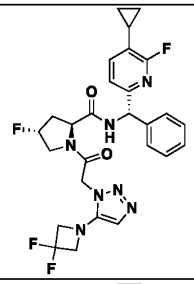
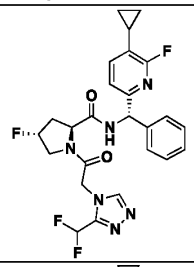
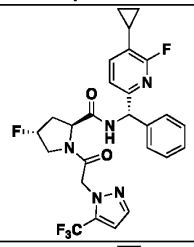
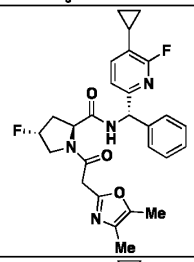
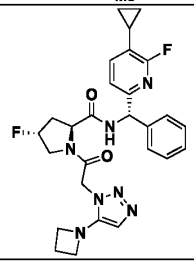
733		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[2-(3-ethyl-5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide
734		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(6-oxo-1,6-dihydropyridin-3-yl)acetyl]pyrrolidine-2-carboxamide
735		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[2-(3-ethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide
736		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[2-(1-ethyl-6-oxo-1,6-dihydropyridin-3-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide
737		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[2-(6-ethoxy-5-methylpyridin-3-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide

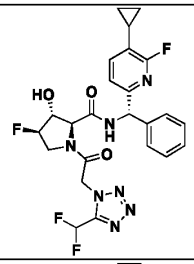
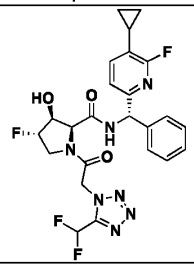
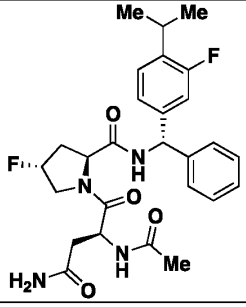
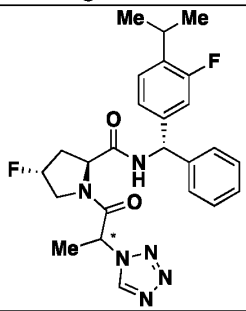
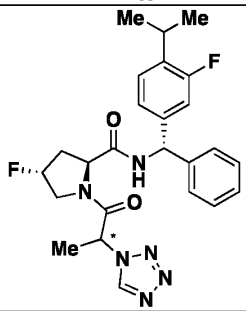
738		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-{2-[4-(trifluoromethyl)-1,3-oxazol-2-yl]acetyl}pyrrolidine-2-carboxamide
739		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[2-(1-ethyl-5-methyl-6-oxo-1,6-dihydropyridin-3-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide
740		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[2-(1-ethyl-5-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide
741		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[2-(1-ethyl-2-oxo-1,2-dihydropyridin-3-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide
742		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[2-(4-ethyl-5-oxo-4,5-dihydropyrazin-2-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide

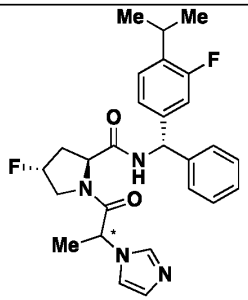
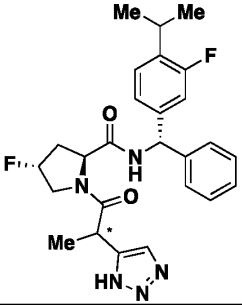
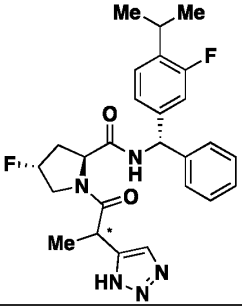
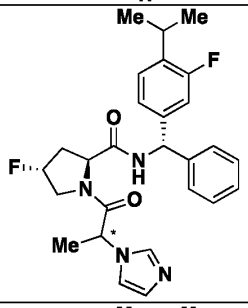
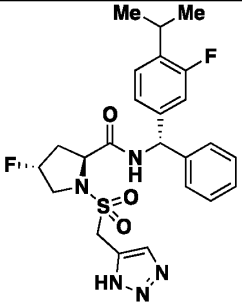
743		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(5-methoxy-1-methyl-1H-1,2,4-triazol-3-yl)acetyl]pyrrolidine-2-carboxamide
744		(2S,4R)-1-(2-{[benzyl(trifluoromethyl)carbamoyl]amino}acetyl)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide
745		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-{2-[5-(trifluoromethyl)-1H-1,2,3-triazol-1-yl]acetyl}pyrrolidine-2-carboxamide
746		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(5-oxo-4,5-dihydropyrazin-2-yl)acetyl]pyrrolidine-2-carboxamide
747		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[5-(difluoromethyl)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide

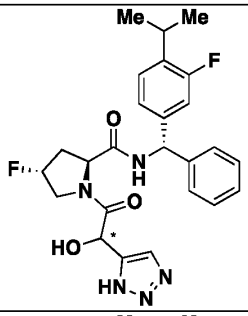
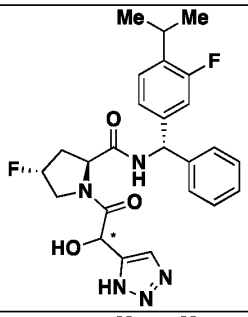
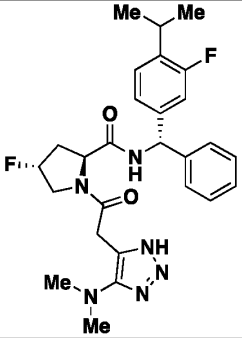
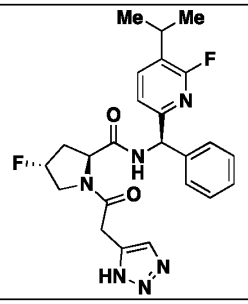
748		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[5-(diethylamino)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide
749		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide
750		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[5-(difluoromethyl)-3-methyl-1H-pyrazol-1-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide
751		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[5-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide
752		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[3-(difluoromethyl)-5-methyl-1H-pyrazol-1-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide

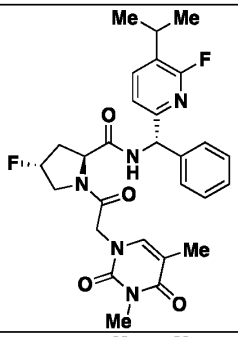
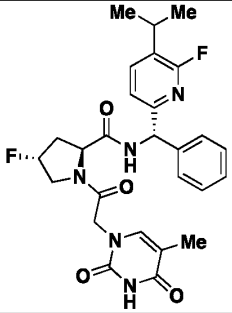
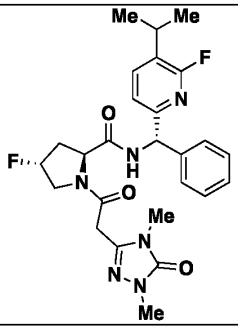
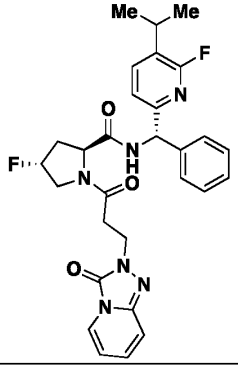
753		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[2-(4-ethyl-3-oxo-3,4-dihydropyrazin-2-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide
754		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[4-(difluoromethyl)-1-methyl-1H-pyrazol-5-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide
755		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-{2-[5-(trifluoromethyl)-1H-1,2,3,4-tetrazol-1-yl]acetyl}pyrrolidine-2-carboxamide
756		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[4-(difluoromethyl)-1H-1,2,3-triazol-5-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide
757		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[4-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide

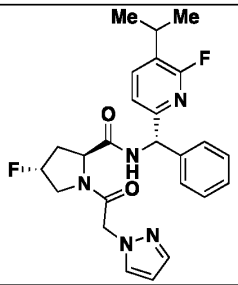
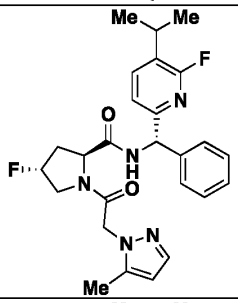
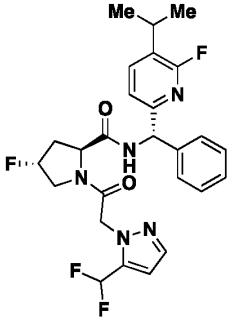
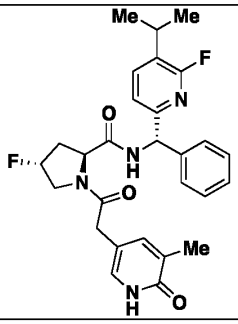
758		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[5-(3,3-difluoroazetidin-1-yl)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide
759		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[3-(difluoromethyl)-4H-1,2,4-triazol-4-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide
760		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-{2-[5-(trifluoromethyl)-1H-pyrazol-1-yl]acetyl}pyrrolidine-2-carboxamide
761		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[2-(4,5-dimethyl-1,3-oxazol-2-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide
762		(2S,4R)-1-{2-[5-(azetidin-1-yl)-1H-1,2,3-triazol-1-yl]acetyl}-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide

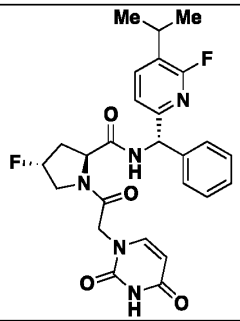
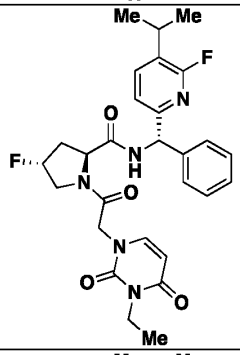
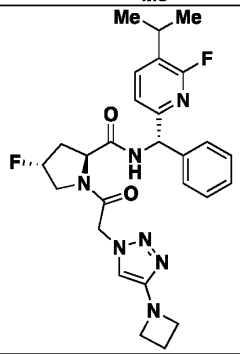
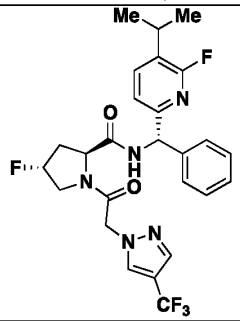
763		(2S,3R,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[5-(difluoromethyl)-1H-1,2,3,4-tetrazol-1-yl]acetyl}-4-fluoro-3-hydroxypyrrolidine-2-carboxamide
764		(2S,3S,4S)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[5-(difluoromethyl)-1H-1,2,3,4-tetrazol-1-yl]acetyl}-4-fluoro-3-hydroxypyrrolidine-2-carboxamide
765		(2S,4R)-1-[(2S)-3-carbamoyl-2-acetamidopropanoyl]-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]pyrrolidine-2-carboxamide
766		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[(2R) or (2S)-2-(1H-1,2,3,4-tetrazol-1-yl)propanoyl]pyrrolidine-2-carboxamide
767		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[(2S) or (2R)-2-(1H-1,2,3,4-tetrazol-1-yl)propanoyl]pyrrolidine-2-carboxamide

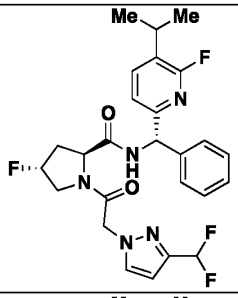
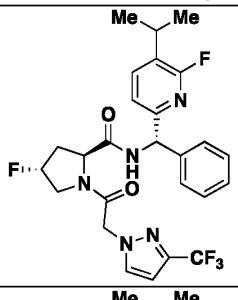
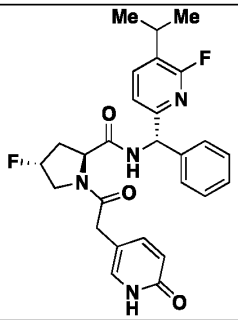
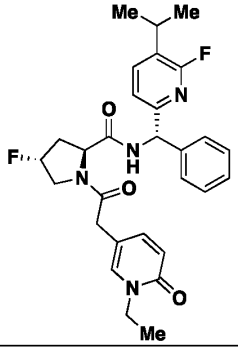
768		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[(2R) or (2S)-2-(1H-imidazol-1-yl)propanoyl]pyrrolidine-2-carboxamide
769		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[(2R) or (2S)-2-(1H-1,2,3-triazol-5-yl)propanoyl]pyrrolidine-2-carboxamide
770		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[(2S) or (2R)-2-(1H-1,2,3-triazol-5-yl)propanoyl]pyrrolidine-2-carboxamide
771		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[(2S) or (2R)-2-(1H-imidazol-1-yl)propanoyl]pyrrolidine-2-carboxamide
772		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[(1H-1,2,3-triazol-5-yl)methanesulfonyl]pyrrolidine-2-carboxamide

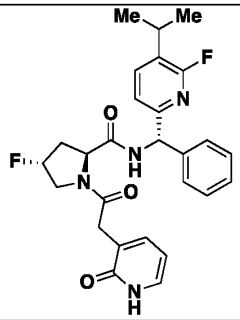
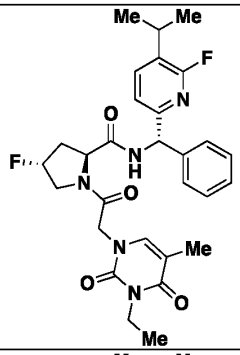
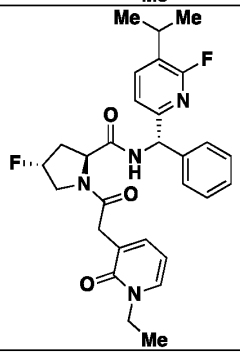
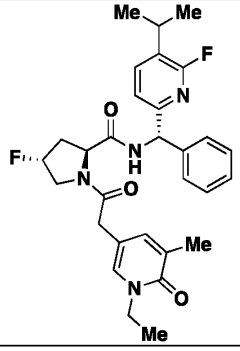
773		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[(2R) or (2S)-2-hydroxy-2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
774		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[(2S) or (2R)-2-hydroxy-2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
775		(2S,4R)-1-{2-[4-(dimethylamino)-1H-1,2,3-triazol-5-yl]acetyl}-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]pyrrolidine-2-carboxamide
776		(2S,4R)-4-fluoro-N-[(R*)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

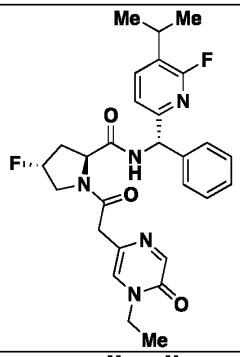
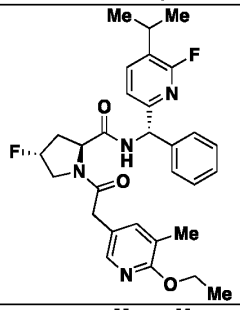
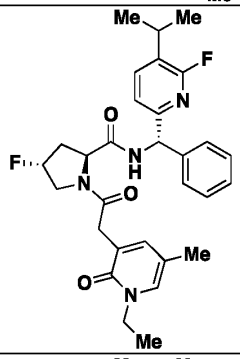
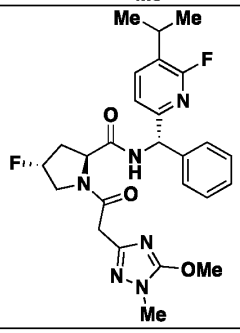
777		(2S,4R)-1-[2-(3,5-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-4-fluoro-N-[(R*)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide
778		(2S,4R)-4-fluoro-N-[(R*)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]pyrrolidine-2-carboxamide
779		(2S,4R)-1-[2-(1,4-dimethyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)acetyl]-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide
780		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-(3-{3-oxo-2H,3H-[1,2,4]triazolo[4,3-a]pyridin-2-yl}propanoyl)pyrrolidine-2-carboxamide

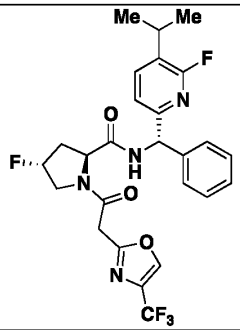
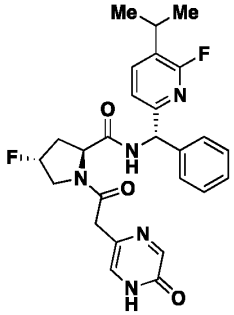
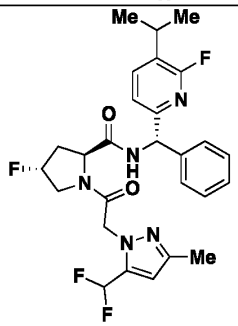
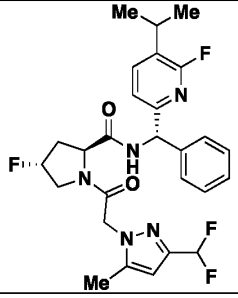
781		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(1H-pyrazol-1-yl)acetyl]pyrrolidine-2-carboxamide
782		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(5-methyl-1H-pyrazol-1-yl)acetyl]pyrrolidine-2-carboxamide
783		(2S,4R)-1-{2-[5-(difluoromethyl)-1H-pyrazol-1-yl]acetyl}-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide
784		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)acetyl]pyrrolidine-2-carboxamide

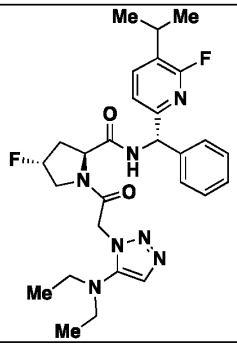
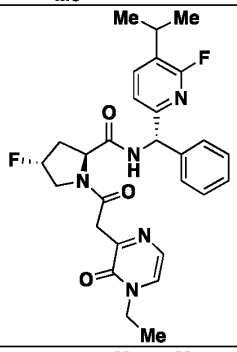
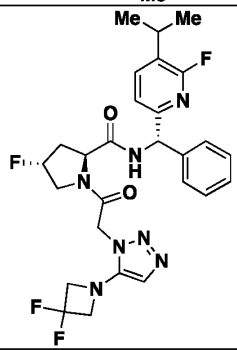
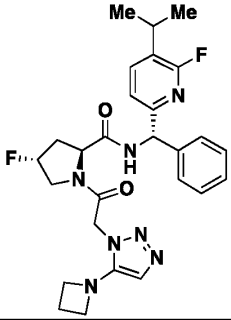
785		(2S,4R)-1-[2-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide
786		(2S,4R)-1-[2-(3-ethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide
787		(2S,4R)-1-{2-[4-(azetidin-1-yl)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide
788		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-{2-[4-(trifluoromethyl)-1H-pyrazol-1-yl]acetyl}pyrrolidine-2-carboxamide

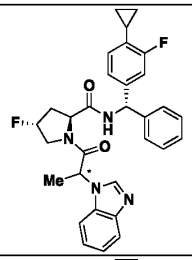
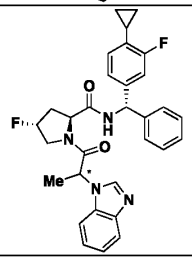
789		(2S,4R)-1-{2-[3-(difluoromethyl)-1H-pyrazol-1-yl]acetyl}-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide
790		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-{2-[3-(trifluoromethyl)-1H-pyrazol-1-yl]acetyl}pyrrolidine-2-carboxamide
791		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(6-oxo-1,6-dihydropyridin-3-yl)acetyl]pyrrolidine-2-carboxamide
792		(2S,4R)-1-[2-(1-ethyl-6-oxo-1,6-dihydropyridin-3-yl)acetyl]-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide

793		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(2-oxo-1,2-dihydropyridin-3-yl)acetyl]pyrrolidine-2-carboxamide
794		(2S,4R)-1-[2-(3-ethyl-5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide
795		(2S,4R)-1-[2-(1-ethyl-2-oxo-1,2-dihydropyridin-3-yl)acetyl]-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide
796		(2S,4R)-1-[2-(1-ethyl-5-methyl-6-oxo-1,6-dihydropyridin-3-yl)acetyl]-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide

797		(2S,4R)-1-[2-(4-ethyl-5-oxo-4,5-dihydropyrazin-2-yl)acetyl]-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide
798		(2S,4R)-1-[2-(6-ethoxy-5-methylpyridin-3-yl)acetyl]-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide
799		(2S,4R)-1-[2-(1-ethyl-5-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetyl]-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide
800		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(5-methoxy-1-methyl-1H-1,2,4-triazol-3-yl)acetyl]pyrrolidine-2-carboxamide

801		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-{2-[4-(trifluoromethyl)-1,3-oxazol-2-yl]acetyl}pyrrolidine-2-carboxamide
802		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(5-oxo-4,5-dihydropyrazin-2-yl)acetyl]pyrrolidine-2-carboxamide
803		(2S,4R)-1-{2-[5-(difluoromethyl)-3-methyl-1H-pyrazol-1-yl]acetyl}-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide
804		(2S,4R)-1-{2-[3-(difluoromethyl)-5-methyl-1H-pyrazol-1-yl]acetyl}-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide

805		(2S,4R)-1-{2-[5-(diethylamino)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide
806		(2S,4R)-1-[2-(4-ethyl-3-oxo-3,4-dihydropyrazin-2-yl)acetyl]-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide
807		(2S,4R)-1-{2-[5-(3,3-difluoroazetidin-1-yl)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide
808		(2S,4R)-1-{2-[5-(azetidin-1-yl)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide

809		(2S,4R)-1-[(2S) or (2R)-2-(1H-1,3-benzodiazol-1-yl)propanoyl]-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide
810		(2S,4R)-1-[(2R) or (2S)-2-(1H-1,3-benzodiazol-1-yl)propanoyl]-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide

[0238] In some embodiments, provided herein is a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, the compound, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, is selected from the group consisting of:

1-cyclopropanecarbonyl-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-acetyl-4-hydroxy-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-acetyl-3-hydroxy-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-acetyl-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-acetyl-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide;
1-(3-carbamoyl-2-acetamidopropanoyl)-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
tert-butyl N-{2-oxo-2-[2-({phenyl[4-(propan-2-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]ethyl}carbamate;
1-(2-hydroxyacetyl)-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-(2-acetamidoacetyl)-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-acetyl-N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide;
1-(3-carbamoylpropanoyl)-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;

1-acetyl-N-[(5-cyclopropylpyridin-2-yl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide;
2-acetyl-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-2-azabicyclo[3.1.0]hexane-3-carboxamide;
1-{2-[N-(carbamoylmethyl)acetamido]acetyl}-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-acetyl-5-methyl-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-[2-(1,3-oxazol-2-yl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[2-(4H-1,2,4-triazol-3-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-1-{2-[(3-methyloxetan-3-yl)amino]acetyl}-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-acetamido-5-[4-fluoro-2-({phenyl[4-(propan-2-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-5-oxopentanoic acid;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide;
1-(3-acetamidopropanoyl)-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(2-oxopyrrolidin-1-yl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(1,3-oxazol-5-yl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-(4-acetamidobutanoyl)-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
2-acetyl-N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-2-azabicyclo[3.1.0]hexane-3-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-1-(2-acetamidoacetyl)pyrrolidine-2-carboxamide;
3-acetyl-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-3-azabicyclo[3.1.0]hexane-2-carboxamide;
4-fluoro-1-[2-(2-oxo-1,3-oxazolidin-3-yl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;

4-fluoro-1-[2-(oxetan-3-yl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(3-oxomorpholin-4-yl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-acetyl-N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-5-methylpyrrolidine-2-carboxamide;
4-fluoro-1-[2-(1-methyl-1H-pyrazol-5-yl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-pyrazol-1-yl)acetyl]pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(3-oxomorpholin-4-yl)acetyl]pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(5-methyl-4H-1,2,4-triazol-3-yl)acetyl]pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[3-(1,3-oxazol-2-yl)propanoyl]pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3,4-tetrazol-1-yl)acetyl]pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(2-oxo-1,3-oxazolidin-3-yl)acetyl]pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-pyrazol-5-yl)acetyl]pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3,4-tetrazol-5-yl)acetyl]pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1,2-oxazol-3-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[2-(1H-pyrazol-1-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[2-(1H-1,2,3-triazol-1-yl)acetyl]pyrrolidine-2-carboxamide;

4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[2-(2H-1,2,3,4-tetrazol-5-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(1,3,4-oxadiazol-2-yl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-pyrazol-4-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-1-{2-[(1,3-oxazol-2-yl)amino]acetyl}-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(3-methyl-2-oxoimidazolidin-1-yl)acetyl]pyrrolidine-2-carboxamide;
1-[2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)acetyl]-N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-{2-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]acetyl}pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-1-{2-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[3-(1H-1,2,4-triazol-1-yl)propanoyl]pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(1-methyl-1H-pyrazol-4-yl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[2-(1H-1,2,3,4-tetrazol-1-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[2-(pyridazin-3-yloxy)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-1-(1-methyl-5-oxopyrrolidine-2-carbonyl)-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-[2-(2-chloro-5-fluorophenyl)acetyl]-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;

4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[4-(pyridin-3-yl)butanoyl]pyrrolidine-2-carboxamide;
4-fluoro-1-(3-oxo-octahydroindolizine-6-carbonyl)-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-(2-oxopiperidine-4-carbonyl)-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-[2-(2-cyano-4-methoxyphenyl)acetyl]-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-{3-oxo-2H,3H-[1,2,4]triazolo[4,3-a]pyridine-8-carbonyl}-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[4-(1H-imidazol-1-yl)butanoyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[2-(pyrimidin-5-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-1-(4-methylpyrimidine-5-carbonyl)-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(2-oxo-1,2-dihydropyridin-1-yl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-[3-(3,5-dimethyl-1,2-oxazol-4-yl)propanoyl]-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(3-fluoro-4-methoxyphenyl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-(1,3-oxazole-5-carbonyl)-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[4-(pyridin-4-yl)butanoyl]pyrrolidine-2-carboxamide;
1-[(dimethylcarbamoyl)carbonyl]-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;

4-fluoro-1-[2-(1H-imidazol-1-yl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[2-(1H-pyrazol-5-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-1-[2-methyl-3-(1H-1,2,4-triazol-1-yl)propanoyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(5-fluoropyridin-2-yl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(5-methyl-1H-indol-3-yl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-[2-(4-acetamidophenyl)acetyl]-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(1H-imidazol-4-yl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[3-(pyridin-3-yl)propanoyl]pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(4-methoxyphenyl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-[2-(1,5-dimethyl-1H-pyrazol-3-yl)acetyl]-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[3-(2-methylpyridin-3-yl)propanoyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[2-(pyrimidin-2-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[3-(pyrazin-2-yl)propanoyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[2-(2H-1,2,3-triazol-2-yl)acetyl]pyrrolidine-2-carboxamide;
1-[3-(2,6-dimethylpyridin-3-yl)propanoyl]-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;

1-[2-(1H-1,2,3-benzotriazol-1-yl)acetyl]-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[2-(1,3,5-trimethyl-1H-pyrazol-4-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[2-(pyridin-3-yloxy)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-1-[3-(1H-imidazol-5-yl)propanoyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[3-(5-methyl-1,3,4-thiadiazol-2-yl)propanoyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-[3-(3,5-dimethyl-1H-pyrazol-1-yl)propanoyl]-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-(3-cyanopropanoyl)-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-{2-[(dimethylcarbamoyl)amino]acetyl}-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(5-methyl-1,2,4-oxadiazol-3-yl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(1-methyl-1H-indol-2-yl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[3-(5-methylpyridin-2-yl)propanoyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-(2-ethyl-1,3-oxazole-4-carbonyl)-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(2-methyl-1,3-thiazol-4-yl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[2-(pyrazin-2-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-1-[2-methyl-3-(1H-pyrazol-1-yl)propanoyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;

4-fluoro-1-[3-(1H-indol-3-yl)propanoyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-methyl-3-(pyridin-4-yl)propanoyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(4-fluoro-1H-indol-1-yl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-{4-oxo-4H,5H,6H,7H,8H-pyrazolo[1,5-a][1,4]diazepine-2-carbonyl}-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-{2-[5-(propan-2-yl)-1,2,4-oxadiazol-3-yl]acetyl}pyrrolidine-2-carboxamide;
4-fluoro-1-(6-oxopiperidine-3-carbonyl)-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[2-(pyrrolidine-1-sulfonyl)acetyl]pyrrolidine-2-carboxamide;
1-[2-(1,2-benzoxazol-3-yl)acetyl]-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-(2-{[1,2,4]triazolo[1,5-a]pyridin-6-yl}acetyl)pyrrolidine-2-carboxamide;
1-[2-(1H-1,3-benzodiazol-1-yl)acetyl]-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[2-(1H-pyrazol-1-yl)propanoyl]pyrrolidine-2-carboxamide;
4-fluoro-1-[3-(3-methoxypyridin-2-yl)propanoyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(1H-imidazol-1-yl)propanoyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-[2-(3,5-dimethyl-1,2-oxazol-4-yl)acetyl]-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(1-methyl-1H-pyrazol-3-yl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;

4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[3-(1H-1,2,3-triazol-1-yl)propanoyl]pyrrolidine-2-carboxamide;
4-fluoro-1-[3-(1H-imidazol-2-yl)propanoyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(2-methylphenoxy)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(3-methyl-1,2-oxazol-5-yl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-(3-methyloxetane-3-carbonyl)-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-[2-(4-chloro-1H-pyrazol-1-yl)acetyl]-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-(1-ethyl-1H-pyrazole-5-carbonyl)-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[2-(pyridin-2-yl)propanoyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[3-(pyrimidin-5-yl)propanoyl]pyrrolidine-2-carboxamide;
4-fluoro-1-(3-methoxy-1-methyl-1H-pyrazole-4-carbonyl)-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(5-methyl-1,3,4-oxadiazol-2-yl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[3-(1H-pyrazol-4-yl)propanoyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[2-(1,3-thiazol-4-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-1-[4-(2-methyl-1H-imidazol-1-yl)butanoyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-(2-{imidazo[1,2-a]pyridin-3-yl}acetyl)-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;

4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[3-(pyridin-2-yl)propanoyl]pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(3-methyl-1,2,4-oxadiazol-5-yl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-[2-(3,5-dimethyl-1H-pyrazol-1-yl)acetyl]-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[3-(6-methylpyridin-3-yl)propanoyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-(3-{1H-pyrrolo[2,3-b]pyridin-3-yl}propanoyl)pyrrolidine-2-carboxamide;
4-fluoro-1-(2-oxo-1,3-oxazolidine-5-carbonyl)-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(4-methyl-1H-pyrazol-1-yl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[3-(1-methyl-1H-pyrazol-4-yl)propanoyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[2-(1H-1,2,4-triazol-1-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[5-(pyridin-4-yl)-1H-pyrazole-3-carbonyl]pyrrolidine-2-carboxamide;
4-fluoro-1-[3-(2-methylpyridin-4-yl)propanoyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-(2-hydroxy-3-methylbutanoyl)-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-(3-{1H-pyrrolo[2,3-b]pyridin-5-yl}propanoyl)pyrrolidine-2-carboxamide;
4-fluoro-1-[4-oxo-4-(pyrrolidin-1-yl)butanoyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[2-(quinolin-6-yl)acetyl]pyrrolidine-2-carboxamide;

4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[2-(pyridin-4-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[2-(2,2,2-trifluoroacetamido)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[2-(pyridin-3-yloxy)propanoyl]pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(1H-indol-3-yl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-(2-cyclopropyl-2-oxoacetyl)-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(5-fluoro-2-methoxyphenyl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(6-methoxypyridin-2-yl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(2-oxo-1,2-dihydropyridin-1-yl)propanoyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[2-(pyridin-3-yl)acetyl]pyrrolidine-2-carboxamide;
1-[2-(3,5-dimethyl-1H-pyrazol-4-yl)acetyl]-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-[2-(2,5-dioxoimidazolidin-1-yl)acetyl]-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-[2-(2,5-dimethyl-1,3-thiazol-4-yl)acetyl]-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-methyl-3-(pyridin-2-yl)propanoyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(2-oxo-1,2-dihydropyrazin-1-yl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(N-methylacetamido)propanoyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;

4-fluoro-1-[2-methyl-2-(pyridin-2-yl)propanoyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(2-oxopiperidin-1-yl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[2-(quinolin-5-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[3-(1H-1,2,4-triazol-1-yl)benzoyl]pyrrolidine-2-carboxamide;
4-fluoro-1-{[(2-methylpropyl)carbamoyl]carbonyl}-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[2-(1H-1,2,3,4-tetrazol-1-yl)propanoyl]pyrrolidine-2-carboxamide;
4-fluoro-1-(2-oxo-1,2,3,4-tetrahydroquinoline-7-carbonyl)-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(2-methyl-1,3-thiazol-5-yl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[3-(6-oxo-1,6-dihydropyridazin-3-yl)propanoyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(4-methyl-1H-pyrazol-1-yl)propanoyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[2-(pyridin-2-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(3-methyl-1H-pyrazol-1-yl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-(3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carbonyl)-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-(2-acetamidopyridine-4-carbonyl)-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[2-(1H-pyrazol-3-yl)acetyl]pyrrolidine-2-carboxamide;

N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-3-[2-(1H-1,2,3-triazol-5-yl)acetyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)acetyl]pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1,3,4-oxadiazol-2-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide;
N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-2-[2-(1H-1,2,3-triazol-5-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carboxamide;
N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-5-methyl-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-(2-hydroxy-2-methylpropanoyl)pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-[2-(1H-1,2,3,4-tetrazol-5-yl)acetyl]pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(5-methyl-2H-1,2,3,4-tetrazol-2-yl)acetyl]pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-3-[2-(1H-1,2,3-triazol-5-yl)acetyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-[2-(1H-1,2,3-triazol-1-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-[2-(1H-1,2,3,4-tetrazol-1-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[2-(4H-1,2,4-triazol-4-yl)acetyl]pyrrolidine-2-carboxamide;

4-fluoro-1-[2-(4-methyl-4H-1,2,4-triazol-3-yl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(1-methyl-1H-1,2,3-triazol-5-yl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(1-methyl-1H-1,2,3-triazol-4-yl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(1,2-oxazol-4-yl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(1,2-oxazol-3-yl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(3-methyl-1H-1,2,4-triazol-5-yl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-[2-(1-methyl-1H-pyrazol-5-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-[2-(1-methyl-1H-pyrazol-3-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-[2-(1-methyl-1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-[2-(pyridin-2-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-[2-(5-methyl-1,3,4-oxadiazol-2-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-[2-(pyridin-3-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-[2-(pyrimidin-4-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-[2-(pyrimidin-5-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-[2-(pyrazin-2-yl)acetyl]pyrrolidine-2-carboxamide;

4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-[2-(4-methyl-2,5-dioxopiperazin-1-yl)acetyl]pyrrolidine-2-carboxamide;
1-(2-cyanoacetyl)-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-(2-methanesulfonylacetyl)-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[2-(1H-1,2,3-triazol-1-yl)propanoyl]pyrrolidine-2-carboxamide;
1-(4-acetylmorpholine-2-carbonyl)-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-[2-(4-acetyl-3,4-dihydro-2H-1,4-benzoxazin-2-yl)acetyl]-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-[2-(4-acetyl-2-oxopiperazin-1-yl)acetyl]-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-(1-acetylpiperidine-4-carbonyl)-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-(2,3-dihydroxypropanoyl)-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-{8-acetyl-8-azaspiro[4.5]decane-2-carbonyl}-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[3-(1H-imidazol-1-yl)-2-methylpropanoyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-{6-acetyl-6-azaspiro[2.5]octane-1-carbonyl}-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-(1-acetyl-3-methylpyrrolidine-3-carbonyl)-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(N-methylacetamido)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-{2-acetyl-5-oxa-2,6-diazaspiro[3.4]oct-6-ene-7-carbonyl}-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;

1-[1-acetyl-2-(pyridin-3-yl)pyrrolidine-3-carbonyl]-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[5-(methoxymethyl)-1,2-oxazole-4-carbonyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-{6-acetyl-5H,6H,7H,8H-pyrido[3,4-b]pyrazine-7-carbonyl}-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[2-(1H-1,2,4-triazol-1-yl)propanoyl]pyrrolidine-2-carboxamide;
1-{5-acetyl-5-azaspiro[2.4]heptane-1-carbonyl}-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-[3-(1-acetylpyrrolidin-2-yl)propanoyl]-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-{4-[(1-acetylazetidin-3-yl)oxy]benzoyl}-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[3-methoxy-2-(N-methylacetamido)butanoyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-[2-(1-acetylpyrrolidin-2-yl)acetyl]-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-{7-acetyl-1-oxa-2,7-diazaspiro[4.4]non-2-ene-3-carbonyl}-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-{5-acetyl-hexahydro-1H-furo[3,4-c]pyrrole-3a-carbonyl}-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-(1-acetylpyrrolidine-3-carbonyl)-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(3-methyl-1H-pyrazol-5-yl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-{5-acetyl-2-oxa-5-azabicyclo[2.2.1]heptane-1-carbonyl}-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-[2-(1-acetylpiperidin-4-yl)propanoyl]-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;

4-fluoro-1-[2-methyl-2-(1H-1,2,4-triazol-5-yl)propanoyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-[2-methyl-2-(1,3,4-oxadiazol-2-yl)propanoyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-[2-(pyridin-4-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-(2-{imidazo[1,2-a]pyridin-3-yl}acetyl)pyrrolidine-2-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-[2-(1H-imidazol-1-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-[2-(1,3,5-trimethyl-1H-pyrazol-4-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-[2-(1,2-oxazol-5-yl)acetyl]pyrrolidine-2-carboxamide;
1-{2-[(dimethylcarbamoyl)amino]acetyl}-4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}pyrrolidine-2-carboxamide;
N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-4-[2-(1H-1,2,3-triazol-5-yl)acetyl]-4-azaspiro[2.4]heptane-5-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-(2-{[1,2,4]triazolo[1,5-a]pyridin-6-yl}acetyl)pyrrolidine-2-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-[2-(quinolin-6-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-[2-(1-methyl-1H-pyrazol-4-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-[2-(piperazin-1-yl)acetyl]pyrrolidine-2-carboxamide;
1-(1-acetyl-3-methylpiperidine-3-carbonyl)-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-(1-acetyl-4-methylazepane-4-carbonyl)-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;

1-(1-acetylazepane-4-carbonyl)-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-(1-acetylpiperidine-3-carbonyl)-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-(4-acetylmorpholine-3-carbonyl)-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-(2-{2-acetyl-2-azaspiro[3.4]octan-5-yl}acetyl)-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-{2-acetyl-2-azaspiro[4.4]nonane-6-carbonyl}-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-{2-acetyl-2-azabicyclo[2.2.2]octane-6-carbonyl}-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-[2-(1-acetylpiperidin-3-yl)acetyl]-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-(4-acetyl-1,4-oxazepane-2-carbonyl)-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-(1-acetyl-4-methylpiperidine-3-carbonyl)-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-(4-acetyl-2-methylmorpholine-3-carbonyl)-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-{5-acetyl-hexahydro-2H-furo[2,3-c]pyrrole-3-carbonyl}-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-{3-acetyl-3-azabicyclo[3.1.0]hexane-1-carbonyl}-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-{2-acetyl-octahydrocyclopenta[c]pyrrole-4-carbonyl}-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-{8-acetyl-8-azabicyclo[3.2.1]octane-3-carbonyl}-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-(1-acetyl-3-methylazetidine-3-carbonyl)-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;

1-{5-acetyl-hexahydro-2H-furo[2,3-c]pyrrole-2-carbonyl}-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-{3-acetyl-3-azabicyclo[3.2.1]octane-8-carbonyl}-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-(2-acetyl-octahydro-1H-isoindole-4-carbonyl)-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-{7-acetyl-7-azabicyclo[2.2.1]heptane-2-carbonyl}-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-{2-acetyl-5-oxa-2-azaspiro[3.4]octane-7-carbonyl}-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-[2-(1-acetyl-3-methylazetidin-3-yl)acetyl]-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-{2-acetyl-5-oxa-2-azaspiro[3.4]octane-6-carbonyl}-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-(1-acetyl-2-methylpiperidine-3-carbonyl)-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-{3-[N-(1-methyl-1H-pyrazol-3-yl)acetamido]propanoyl}-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-(1-acetyl-3-fluoroazetidine-3-carbonyl)-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-[2-(1-acetyl-3-methoxyazetidin-3-yl)acetyl]-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-{4-acetyl-hexahydro-2H-furo[3,2-b]pyrrole-6-carbonyl}-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-(1-acetyl-4-ethylpyrrolidine-3-carbonyl)-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-{7-acetyl-1-oxo-2,7-diazaspiro[4.4]nonane-4-carbonyl}-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-[1-(1,3,4-oxadiazol-2-yl)cyclopropanecarbonyl]pyrrolidine-2-carboxamide;

2-[4-fluoro-2-({[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}carbamoyl)pyrrolidin-1-yl]-2-oxoethyl N,N-dimethylcarbamate;
1-[2-(1H-1,3-benzodiazol-1-yl)acetyl]-4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}pyrrolidine-2-carboxamide;
1-[2-(1H-1,3-benzodiazol-1-yl)acetyl]-N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide;
2-[4-fluoro-2-({phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}carbamoyl)pyrrolidin-1-yl]-2-oxoethyl N,N-dimethylcarbamate;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-[2-(1-methyl-1H-1,2,3-triazol-4-yl)acetyl]pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-[2-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]pyrrolidine-2-carboxamide;
1-{2-[(dimethylcarbamoyl)amino]acetyl}-4-fluoro-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-1-{2-[(dimethylcarbamoyl)amino]acetyl}-4-fluoropyrrolidine-2-carboxamide;
4-fluoro-1-[2-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}-1-[2-(quinolin-5-yl)acetyl]pyrrolidine-2-carboxamide;
tert-butyl 4-({2-[4-fluoro-2-({[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}carbamoyl)pyrrolidin-1-yl]-2-oxoethyl}carbamoyl)piperazine-1-carboxylate;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-1-[2-(3,5-dimethyl-1H-pyrazol-4-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide;
N-{2-[4-fluoro-2-({[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}carbamoyl)pyrrolidin-1-yl]-2-oxoethyl}piperazine-1-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(quinolin-5-yl)acetyl]pyrrolidine-2-carboxamide;

4-fluoro-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}-1-[2-(1H-1,2,3,4-tetrazol-1-yl)acetyl]pyrrolidine-2-carboxamide;
1-[2-(4-acetylpiperazin-1-yl)acetyl]-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(5-methyl-2-oxo-2,3-dihydro-1,3,4-oxadiazol-3-yl)acetyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-[2-(3,5-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide;
1-{2-[(dimethylcarbamoyl)(methyl)amino]acetyl}-4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-(2-oxo-1,3-oxazolidine-5-carbonyl)pyrrolidine-2-carboxamide;
2-[4-fluoro-2-({[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}carbamoyl)pyrrolidin-1-yl]-2-oxoethyl piperazine-1-carboxylate;
1-[2-(3,5-dimethyl-1H-pyrazol-4-yl)acetyl]-4-fluoro-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide;
1-tert-butyl 4-{2-[4-fluoro-2-({[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}carbamoyl)pyrrolidin-1-yl]-2-oxoethyl} piperazine-1,4-dicarboxylate;
1-{2-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]acetyl}-4-fluoro-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide;
1-[2-(1H-1,3-benzodiazol-1-yl)acetyl]-4-fluoro-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide;
1-{2-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]acetyl}-4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}pyrrolidine-2-carboxamide;
tert-butyl N-({5-[2-(2-{[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]carbamoyl}-4-fluoropyrrolidin-1-yl)-2-oxoethyl]-1,3,4-oxadiazol-2-yl}methyl)carbamate;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-[2-(pyridazin-4-yl)acetyl]pyrrolidine-2-carboxamide;

4-fluoro-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}-1-{2-[5-(trifluoromethyl)-2H-1,2,3,4-tetrazol-2-yl]acetyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-5-methyl-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-[2-(pyridazin-3-yl)acetyl]pyrrolidine-2-carboxamide;
N-[(5-cyclopropylpyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(2-oxopiperazin-1-yl)acetyl]pyrrolidine-2-carboxamide;
N-[2-(2-{[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]carbamoyl}-4-fluoropyrrolidin-1-yl)-2-oxoethyl]-4-methylpiperazine-1-carboxamide;
N-[2-(2-{[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]carbamoyl}-4-fluoropyrrolidin-1-yl)-2-oxoethyl]-4-(2,2,2-trifluoroethyl)piperazine-1-carboxamide;
N-{2-[4-fluoro-2-({phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}carbamoyl)pyrrolidin-1-yl]-2-oxoethyl}-4-(2,2,2-trifluoroethyl)piperazine-1-carboxamide;
N-[2-(2-{[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]carbamoyl}-4-fluoropyrrolidin-1-yl)-2-oxoethyl]-4-(2-methoxyethyl)piperazine-1-carboxamide;
1-{2-[5-(aminomethyl)-1,3,4-oxadiazol-2-yl]acetyl}-N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-[2-(5-methyl-1H-1,2,3-triazol-1-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-[2-(4-methyl-1H-1,2,3-triazol-1-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-{2-[4-(piperazin-1-yl)-2H-1,2,3-triazol-2-yl]acetyl}pyrrolidine-2-carboxamide;
N-[2-(2-{[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]carbamoyl}-4-fluoropyrrolidin-1-yl)-2-oxoethyl]-4-(cyclopropylmethyl)piperazine-1-carboxamide;
4-(cyclopropylmethyl)-N-{2-[4-fluoro-2-({phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}carbamoyl)pyrrolidin-1-yl]-2-oxoethyl}piperazine-1-carboxamide;

N-{2-[4-fluoro-2-({phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}carbamoyl)pyrrolidin-1-yl]-2-oxoethyl}-4-methylpiperazine-1-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-[2-(4-methyl-1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-{2-[4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl]acetyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(2-methylquinolin-5-yl)acetyl]-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide;
tert-butyl N-[(5-{2-[4-fluoro-2-({phenyl[4-(propan-2-yl)phenyl]methyl}carbamoyl)pyrrolidin-1-yl]-2-oxoethyl}-1,3,4-oxadiazol-2-yl)methyl]carbamate;
1-{2-[5-(aminomethyl)-1,3,4-oxadiazol-2-yl]acetyl}-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-{2-[4-(dimethylamino)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}pyrrolidine-2-carboxamide;
tert-butyl 4-(5-{2-[4-fluoro-2-({[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}carbamoyl)pyrrolidin-1-yl]-2-oxoethyl}-1H-1,2,3-triazol-4-yl)piperazine-1-carboxylate;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-(2-{3-oxo-2H,3H-[1,2,4]triazolo[4,3-a]pyridin-8-yl}acetyl)pyrrolidine-2-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-{2-[5-(trifluoromethyl)-1H-1,2,3-triazol-1-yl]acetyl}pyrrolidine-2-carboxamide;
1-{2-[4-(dimethylamino)-2H-1,2,3-triazol-2-yl]acetyl}-4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}pyrrolidine-2-carboxamide;
1-[2-(3,5-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}pyrrolidine-2-carboxamide;
1-{2-[5-(difluoromethyl)-2H-1,2,3,4-tetrazol-2-yl]acetyl}-4-fluoro-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide;
1-{2-[5-(acetamidomethyl)-1,3,4-oxadiazol-2-yl]acetyl}-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
1-{2-[5-(aminomethyl)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;

1-(2-{5-[(dimethylamino)methyl]-1H-1,2,3-triazol-1-yl}acetyl)-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-{2-[4-(piperazin-1-yl)-1H-1,2,3-triazol-5-yl]acetyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-{2-[4-(morpholin-4-yl)-1H-1,2,3-triazol-5-yl]acetyl}pyrrolidine-2-carboxamide;
1-(2-{5-[(dimethylamino)methyl]-1,3,4-oxadiazol-2-yl}acetyl)-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-[2-(4H-1,2,4-triazol-4-yl)acetyl]pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(4H-1,2,4-triazol-4-yl)acetyl]pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-indazol-3-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-{2-[5-(trifluoromethyl)-1H-1,2,3,4-tetrazol-1-yl]acetyl}pyrrolidine-2-carboxamide;
1-[2-(1H-1,2,3-benzotriazol-1-yl)acetyl]-N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)acetyl]pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)acetyl]pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1-oxo-2,3-dihydro-1H-isoindol-2-yl)acetyl]pyrrolidine-2-carboxamide;
N-[2-(2-{[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]carbamoyl}-4-fluoropyrrolidin-1-yl)-2-oxoethyl]morpholine-4-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1-methyl-1H-indol-3-yl)acetyl]pyrrolidine-2-carboxamide;

N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1-methyl-1H-indol-2-yl)acetyl]pyrrolidine-2-carboxamide;
2-(2-{[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]carbamoyl}-4-fluoropyrrolidin-1-yl)-2-oxoethyl azetidine-1-carboxylate;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1-methyl-1H-indazol-3-yl)acetyl]pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(2-oxo-2,3-dihydro-1H-indol-1-yl)acetyl]pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(2-methyl-1H-1,3-benzodiazol-1-yl)acetyl]pyrrolidine-2-carboxamide;
1-{2-[5-(acetamidomethyl)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)acetyl]-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)acetyl]pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)acetyl]pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl)acetyl]pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(4-methyl-1H-imidazol-1-yl)acetyl]pyrrolidine-2-carboxamide;
1-{2-[5-(difluoromethyl)-1H-1,2,3,4-tetrazol-1-yl]acetyl}-4-fluoro-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide;
2-(2-{[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]carbamoyl}-4-fluoropyrrolidin-1-yl)-2-oxoethyl 4-(cyclopropylmethyl)piperazine-1-carboxylate;
2-(2-{[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]carbamoyl}-4-fluoropyrrolidin-1-yl)-2-oxoethyl 4-methylpiperazine-1-carboxylate;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(2-oxo-2,3-dihydro-1H-indol-3-yl)acetyl]pyrrolidine-2-carboxamide;

N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-(2-{imidazo[1,2-a]pyridin-3-yl}acetyl)pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-(2-{[1,2,4]triazolo[1,5-a]pyridin-6-yl}acetyl)pyrrolidine-2-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-{2-[4-(trifluoromethyl)-1H-1,2,3-triazol-5-yl]acetyl}pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-{2-[(pyrazin-2-yl)amino]acetyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-{2-[4-(piperazin-1-yl)-1H-1,2,3-triazol-1-yl]acetyl}pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-1-{2-[(2-ethyl-2H-1,2,3-triazol-4-yl)amino]acetyl}-4-fluoropyrrolidine-2-carboxamide;
4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}-1-[2-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-1-{2-[(1-ethyl-1H-1,2,3-triazol-4-yl)amino]acetyl}-4-fluoropyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(2-methylquinolin-6-yl)acetyl]pyrrolidine-2-carboxamide;
2-(2-{[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]carbamoyl}-4-fluoropyrrolidin-1-yl)-2-oxoethyl 4-(2-methoxyethyl)piperazine-1-carboxylate;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-{2-[2-oxo-4-(2,2,2-trifluoroethyl)piperazin-1-yl]acetyl}pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-{2-[methyl(2-methylpyrimidin-4-yl)amino]acetyl}pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(2-methylquinolin-5-yl)acetyl]pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-{2-[(2-methylpyrimidin-4-yl)amino]acetyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(4-methyl-5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)acetyl]-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide;

N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-{2-[methyl(pyrazin-2-yl)amino]acetyl}pyrrolidine-2-carboxamide;
4-fluoro-1-(2-{3-oxo-2H,3H-[1,2,4]triazolo[4,3-a]pyridin-8-yl}acetyl)-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide;
2-(2-{[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]carbamoyl}-4-fluoropyrrolidin-1-yl)-2-oxoethyl 4-(2,2,2-trifluoroethyl)piperazine-1-carboxylate;
N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(4H-1,2,4-triazol-4-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}-1-[2-(4H-1,2,4-triazol-4-yl)acetyl]pyrrolidine-2-carboxamide;
1-[2-(1H-1,3-benzodiazol-1-yl)acetyl]-N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide;
1-[2-(1H-1,3-benzodiazol-1-yl)acetyl]-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-1-{2-[4-(dimethylamino)-2H-1,2,3-triazol-2-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-1-{2-[4-(dimethylamino)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide;
1-{2-[4-(dimethylamino)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoro-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-(2-{3-oxo-2H,3H-[1,2,4]triazolo[4,3-a]pyridin-8-yl}acetyl)pyrrolidine-2-carboxamide;
4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}-1-(2-{3-oxo-2H,3H-[1,2,4]triazolo[4,3-a]pyridin-8-yl}acetyl)pyrrolidine-2-carboxamide;
4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}-1-[2-(2-methylquinolin-5-yl)acetyl]pyrrolidine-2-carboxamide;
tert-butyl 2-[2-(2-{[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]carbamoyl}-4-fluoropyrrolidin-1-yl)-2-oxoethyl]-1H-indole-1-carboxylate;
1-{2-[4-(dimethylamino)-2H-1,2,3-triazol-2-yl]acetyl}-4-fluoro-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide;

N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-indol-2-yl)acetyl]pyrrolidine-2-carboxamide;
1-[2-(carbamoylamino)acetyl]-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}pyrrolidine-2-carboxamide;
1-{2-[4-(dimethylamino)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-1-{2-[(2-ethyl-2H-1,2,3-triazol-4-yl)(methyl)amino]acetyl}-4-fluoropyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-1-{2-[(1-ethyl-1H-1,2,3-triazol-4-yl)(methyl)amino]acetyl}-4-fluoropyrrolidine-2-carboxamide;
N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]pyrrolidine-2-carboxamide;
N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[4-(dimethylamino)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide;
1-{2-[4-(dimethylamino)-2H-1,2,3-triazol-2-yl]acetyl}-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}pyrrolidine-2-carboxamide;
N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[5-(dimethylamino)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}-1-[2-(4H-1,2,4-triazol-4-yl)acetyl]pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[3-(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)propanoyl]pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(4-methyl-5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)acetyl]-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide;
1-{2-[(dimethylcarbamoyl)amino]acetyl}-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-{2-[(methylcarbamoyl)amino]acetyl}-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide;

4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}-1-{2-[(2-methylpyrimidin-4-yl)amino]acetyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}-1-{2-[(methylcarbamoyl)amino]acetyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}-1-[2-(4-methyl-5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)acetyl]pyrrolidine-2-carboxamide;
1-{2-[(azetidine-1-carbonyl)amino]acetyl}-4-fluoro-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide;
1-{2-[(azetidine-1-carbonyl)amino]acetyl}-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-{2-[(2-methylpyrimidin-4-yl)amino]acetyl}-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide;
N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[(dimethylcarbamoyl)amino]acetyl}-4-fluoropyrrolidine-2-carboxamide;
1-[2-(carbamoylamino)acetyl]-4-fluoro-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(4-methyl-5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)acetyl]-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[3-(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)propanoyl]-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide;
1-[2-(carbamoylamino)acetyl]-N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide;
1-{2-[(azetidine-1-carbonyl)amino]acetyl}-N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide;
N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-{2-[(methylcarbamoyl)amino]acetyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(1-methyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)acetyl]-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}-1-[2-(4-methyl-5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)acetyl]pyrrolidine-2-carboxamide;

N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-{2-[(2-methylpyrimidin-4-yl)amino]acetyl}pyrrolidine-2-carboxamide;
N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(4-methyl-5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)acetyl]pyrrolidine-2-carboxamide;
N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(1,3-oxazol-2-yl)acetyl]-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide;
N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[5-(difluoromethyl)-1H-1,2,3,4-tetrazol-1-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide;
1-{2-[5-(difluoromethyl)-1H-1,2,3,4-tetrazol-1-yl]acetyl}-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}pyrrolidine-2-carboxamide;
N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(1-methyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}-1-[2-(1-methyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}-1-{2-[4-(trifluoromethyl)-1H-1,2,3-triazol-5-yl]acetyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}-1-{2-[4-(trifluoromethyl)-1H-1,2,3-triazol-5-yl]acetyl}pyrrolidine-2-carboxamide;
1-{2-[(dimethylcarbamoyl)amino]propanoyl}-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}pyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-1-{2-[(3,3-difluoroazetidine-1-carbonyl)amino]acetyl}-4-fluoropyrrolidine-2-carboxamide;
N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-(2-{[3-(trifluoromethyl)azetidine-1-carbonyl]amino}acetyl)pyrrolidine-2-carboxamide;
N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-{2-[4-(trifluoromethyl)-1H-1,2,3-triazol-5-yl]acetyl}pyrrolidine-2-carboxamide;
N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[(dimethylcarbamoyl)amino]propanoyl}-4-fluoropyrrolidine-2-carboxamide;

4-fluoro-1-[2-(5-methyl-1,3-oxazol-2-yl)acetyl]-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide;
1-{2-[(dimethylcarbamoyl)amino]propanoyl}-4-fluoro-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}-1-[2-(5-methyl-1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide;
N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(5-methyl-1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}-1-[2-(1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(5-oxo-4,5-dihydro-1H-1,2,4-triazol-4-yl)acetyl]-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-(3-{3-oxo-2H,3H-[1,2,4]triazolo[4,3-a]pyridin-2-yl}propanoyl)-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide;
1-{2-[(3,3-difluoroazetidine-1-carbonyl)amino]acetyl}-4-fluoro-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}-1-(2-{[3-(trifluoromethyl)azetidine-1-carbonyl]amino}acetyl)pyrrolidine-2-carboxamide;
4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}-1-[2-(4-methyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)acetyl]pyrrolidine-2-carboxamide;
1-{2-[(3,3-difluoroazetidine-1-carbonyl)amino]acetyl}-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(4-methyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)acetyl]-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide;
N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[(3,3-difluoroazetidine-1-carbonyl)amino]acetyl}-4-fluoropyrrolidine-2-carboxamide;
N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}-3-[2-(1H-1,2,3-triazol-5-yl)acetyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;
5-methyl-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide;

N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(4-methyl-1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide;
N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-(2-{3-oxo-2H,3H-[1,2,4]triazolo[4,3-a]pyridin-8-yl}acetyl)pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(4-methyl-1,3-oxazol-2-yl)acetyl]-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide;
N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(4-methyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}-1-[2-(4-methyl-1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}-1-[2-(1H-pyrazol-1-yl)acetyl]pyrrolidine-2-carboxamide;
1-{2-[4-(3,3-difluoroazetidin-1-yl)-2H-1,2,3-triazol-2-yl]acetyl}-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}pyrrolidine-2-carboxamide;
1-{2-[4-(diethylamino)-2H-1,2,3-triazol-2-yl]acetyl}-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}pyrrolidine-2-carboxamide;
N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}-5-methyl-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide;
1-{2-[4-(3,3-difluoroazetidin-1-yl)-2H-1,2,3-triazol-2-yl]acetyl}-4-fluoro-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide;
N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-{2-[(1,3-oxazol-2-yl)amino]acetyl}pyrrolidine-2-carboxamide;
N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}-3-[2-(1H-1,2,3-triazol-5-yl)acetyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide;
N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[4-(3,3-difluoroazetidin-1-yl)-2H-1,2,3-triazol-2-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide;
1-{2-[4-(diethylamino)-2H-1,2,3-triazol-2-yl]acetyl}-4-fluoro-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide;
N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[4-(diethylamino)-2H-1,2,3-triazol-2-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide;

N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-5-methyl-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide;
1-{2-[4-(azetidin-1-yl)-2H-1,2,3-triazol-2-yl]acetyl}-4-fluoro-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide;
1-{2-[4-(azetidin-1-yl)-2H-1,2,3-triazol-2-yl]acetyl}-N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide;
1-{2-[4-(azetidin-1-yl)-2H-1,2,3-triazol-2-yl]acetyl}-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}pyrrolidine-2-carboxamide;
4-fluoro-1-[2-(5-methyl-2-oxo-2,3-dihydro-1,3,4-oxadiazol-3-yl)acetyl]-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide;
N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(5-methyl-2-oxo-2,3-dihydro-1,3,4-oxadiazol-3-yl)acetyl]pyrrolidine-2-carboxamide;
4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}-1-[2-(5-methyl-2-oxo-2,3-dihydro-1,3,4-oxadiazol-3-yl)acetyl]pyrrolidine-2-carboxamide; and
N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-3-[2-(1H-1,2,3-triazol-5-yl)acetyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide,
N-{[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl}-4-fluoro-1-[2-(5-methyl-2-oxo-2,3-dihydro-1,3,4-oxadiazol-3-yl)acetyl]pyrrolidine-2-carboxamide
1-{2-[(azetidine-1-carbonyl)amino]acetyl}-N-{[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl}-4-fluoropyrrolidine-2-carboxamide
1-[2-(1H-1,3-benzodiazol-1-yl)acetyl]-N-{[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl}-4-fluoropyrrolidine-2-carboxamide
N-{[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl}-4-fluoro-1-[2-(1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide
N-{[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl}-4-fluoro-1-[2-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]pyrrolidine-2-carboxamide
N-{[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl}-1-{2-[(dimethylcarbamoyl)amino]acetyl}-4-fluoropyrrolidine-2-carboxamide
N-{[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl}-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

N-{[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl}-4-fluoro-1-[2-(5-methyl-1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide

N-{[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl}-4-fluoro-1-{2-[4-(trifluoromethyl)-1H-1,2,3-triazol-5-yl]acetyl}pyrrolidine-2-carboxamide

N-{[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl}-4-fluoro-1-[2-(4-methyl-1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide

1-{2-[(3,3-difluoroazetidine-1-carbonyl)amino]acetyl}-N-{[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl}-4-fluoropyrrolidine-2-carboxamide

N-{[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl}-1-{2-[5-(difluoromethyl)-1H-1,2,3,4-tetrazol-1-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide

N-{[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl}-1-[2-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide

N-{[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl}-1-[2-(3-ethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide

N-{[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl}-4-fluoro-1-[2-(6-oxo-1,6-dihydropyridin-3-yl)acetyl]pyrrolidine-2-carboxamide

N-{[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl}-4-fluoro-1-[2-(2-oxo-1,2-dihydropyridin-3-yl)acetyl]pyrrolidine-2-carboxamide

N-{[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl}-1-[2-(3-ethyl-5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide

N-{[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl}-1-[2-(1-ethyl-6-oxo-1,6-dihydropyridin-3-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide

N-{[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl}-4-fluoro-1-[2-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)acetyl]pyrrolidine-2-carboxamide

N-{[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl}-1-[2-(1-ethyl-5-methyl-6-oxo-1,6-dihydropyridin-3-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide

N-{[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl}-1-[2-(6-ethoxy-5-methylpyridin-3-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide

N-{[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl}-1-[2-(1-ethyl-5-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide

N-{[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl}-1-[2-(1-ethyl-2-oxo-1,2-dihydropyridin-3-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide

N-{[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl}-1-[2-(4-ethyl-5-oxo-4,5-dihydropyrazin-2-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide

N-{[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl}-4-fluoro-1-{2-[4-(trifluoromethyl)-1,3-oxazol-2-yl]acetyl}pyrrolidine-2-carboxamide

N-{[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl}-4-fluoro-1-[2-(3-oxo-3,4-dihydropyrazin-2-yl)acetyl]pyrrolidine-2-carboxamide

N-{[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl}-4-fluoro-1-[2-(5-oxo-4,5-dihydropyrazin-2-yl)acetyl]pyrrolidine-2-carboxamide

N-{[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl}-1-[2-(4-ethyl-3-oxo-3,4-dihydropyrazin-2-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide

N-{[5-(3,3-difluorocyclobutyl)pyridin-2-yl](phenyl)methyl}-1-{2-[(dimethylcarbamoyl)amino]acetyl}-4-fluoropyrrolidine-2-carboxamide

1-{2-[(azetidine-1-carbonyl)amino]acetyl}-N-{[5-(3,3-difluorocyclobutyl)pyridin-2-yl](phenyl)methyl}-4-fluoropyrrolidine-2-carboxamide

N-{[5-(3,3-difluorocyclobutyl)pyridin-2-yl](phenyl)methyl}-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

N-{[5-(3,3-difluorocyclobutyl)pyridin-2-yl](phenyl)methyl}-4-fluoro-1-[2-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]pyrrolidine-2-carboxamide

N-{[5-(3,3-difluorocyclobutyl)pyridin-2-yl](phenyl)methyl}-4-fluoro-1-[2-(5-methyl-1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide

1-[2-(1H-1,3-benzodiazol-1-yl)acetyl]-N-{[5-(3,3-difluorocyclobutyl)pyridin-2-yl](phenyl)methyl}-4-fluoropyrrolidine-2-carboxamide

1-{2-[(3,3-difluoroazetidine-1-carbonyl)amino]acetyl}-N-{[5-(3,3-difluorocyclobutyl)pyridin-2-yl](phenyl)methyl}-4-fluoropyrrolidine-2-carboxamide

N-{[5-(3,3-difluorocyclobutyl)pyridin-2-yl](phenyl)methyl}-4-fluoro-1-[2-(1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide

N-{[5-(3,3-difluorocyclobutyl)pyridin-2-yl](phenyl)methyl}-4-fluoro-1-[2-(4-methyl-1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide

N-{[5-(3,3-difluorocyclobutyl)pyridin-2-yl](phenyl)methyl}-4-fluoro-1-[2-(5-methyl-2-oxo-2,3-dihydro-1,3,4-oxadiazol-3-yl)acetyl]pyrrolidine-2-carboxamide

N-{[5-(3,3-difluorocyclobutyl)pyridin-2-yl](phenyl)methyl}-4-fluoro-1-{2-[4-(trifluoromethyl)-1H-1,2,3-triazol-5-yl]acetyl}pyrrolidine-2-carboxamide

N-{[5-(3,3-difluorocyclobutyl)pyridin-2-yl](phenyl)methyl}-4-fluoro-1-{2-[4-(trifluoromethyl)-1,3-oxazol-2-yl]acetyl}pyrrolidine-2-carboxamide

1-{2-[(azetidine-1-carbonyl)amino]acetyl}-N-{[4-(3,3-difluorocyclobutyl)-3-fluorophenyl](phenyl)methyl}-4-fluoropyrrolidine-2-carboxamide

N-{[4-(3,3-difluorocyclobutyl)-3-fluorophenyl](phenyl)methyl}-1-{2-[(dimethylcarbamoyl)amino]acetyl}-4-fluoropyrrolidine-2-carboxamide

1-[2-(1H-1,3-benzodiazol-1-yl)acetyl]-N-{[4-(3,3-difluorocyclobutyl)-3-fluorophenyl](phenyl)methyl}-4-fluoropyrrolidine-2-carboxamide

N-{[4-(3,3-difluorocyclobutyl)-3-fluorophenyl](phenyl)methyl}-4-fluoro-1-[2-(5-methyl-1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide

N-{[4-(3,3-difluorocyclobutyl)-3-fluorophenyl](phenyl)methyl}-4-fluoro-1-[2-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]pyrrolidine-2-carboxamide

N-{[4-(3,3-difluorocyclobutyl)-3-fluorophenyl](phenyl)methyl}-4-fluoro-1-[2-(1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide

N-{[4-(3,3-difluorocyclobutyl)-3-fluorophenyl](phenyl)methyl}-4-fluoro-1-{2-[4-(trifluoromethyl)-1H-1,2,3-triazol-5-yl]acetyl}pyrrolidine-2-carboxamide

N-{[4-(3,3-difluorocyclobutyl)-3-fluorophenyl](phenyl)methyl}-4-fluoro-1-[2-(4-methyl-1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide

N-{[4-(3,3-difluorocyclobutyl)-3-fluorophenyl](phenyl)methyl}-4-fluoro-1-{2-[4-(trifluoromethyl)-1,3-oxazol-2-yl]acetyl}pyrrolidine-2-carboxamide

4-fluoro-N-{[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl}-1-[2-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]pyrrolidine-2-carboxamide

4-fluoro-N-{[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl}-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

4-fluoro-N-{[3-fluoro-4-(1-methylcyclopropyl)phenyl](pyridin-3-yl)methyl}-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

2-[4-fluoro-2-({[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl}carbamoyl)pyrrolidin-1-yl]-2-oxoethyl azetidine-1-carboxylate

4-fluoro-N-{[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl}-1-[2-(1-methyl-1H-indol-2-yl)acetyl]pyrrolidine-2-carboxamide

4-fluoro-N-{[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl}-1-[2-(2-oxopiperazin-1-yl)acetyl]pyrrolidine-2-carboxamide

4-fluoro-N-{[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl}-1-[2-(1-methyl-1H-indol-3-yl)acetyl]pyrrolidine-2-carboxamide

4-fluoro-N-{[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl}-1-[2-(1-methyl-1H-indazol-3-yl)acetyl]pyrrolidine-2-carboxamide

N-{2-[4-fluoro-2-({[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl}carbamoyl)pyrrolidin-1-yl]-2-oxoethyl}morpholine-4-carboxamide

4-fluoro-N-{[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl}-1-[2-(2-methyl-1H-1,3-benzodiazol-1-yl)acetyl]pyrrolidine-2-carboxamide

1-[2-(1H-1,3-benzodiazol-1-yl)propanoyl]-4-fluoro-N-{[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl}pyrrolidine-2-carboxamide

4-fluoro-N-{[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl}-1-[2-(3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)acetyl]pyrrolidine-2-carboxamide

4-fluoro-N-{[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl}-1-[2-(3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]pyrrolidine-2-carboxamide

4-fluoro-N-{[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl}-1-[2-(2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)acetyl]pyrrolidine-2-carboxamide

4-fluoro-N-{[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl}-1-[2-(1H-indazol-3-yl)acetyl]pyrrolidine-2-carboxamide

1-[2-(2,5-dioxopiperazin-1-yl)acetyl]-4-fluoro-N-{[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl}pyrrolidine-2-carboxamide

4-fluoro-N-{[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl}-1-[2-(1-oxo-2,3-dihydro-1H-isoindol-2-yl)acetyl]pyrrolidine-2-carboxamide

1-[2-(1H-1,2,3-benzotriazol-1-yl)acetyl]-4-fluoro-N-{[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl}pyrrolidine-2-carboxamide

4-fluoro-N-{[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl}-1-[2-(2-oxo-2,3-dihydro-1H-indol-1-yl)acetyl]pyrrolidine-2-carboxamide

4-fluoro-N-{[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl}-1-[2-(1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl)acetyl]pyrrolidine-2-carboxamide

2,2,2-trifluoroethyl 4-{2-[4-fluoro-2-({[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl}carbamoyl)pyrrolidin-1-yl]-2-oxoethyl}-3-oxopiperazine-1-carboxylate

2-[4-fluoro-2-({[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl}carbamoyl)pyrrolidin-1-yl]-2-oxoethyl 4-(2-methoxyethyl)piperazine-1-carboxylate

4-fluoro-N-{[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl}-1-{2-[2-oxo-4-(2,2,2-trifluoroethyl)piperazin-1-yl]acetyl}pyrrolidine-2-carboxamide

4-fluoro-N-{[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl}-1-[2-(2-oxo-2,3-dihydro-1H-indol-3-yl)acetyl]pyrrolidine-2-carboxamide

4-fluoro-N-{[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl}-1-[2-(4H-1,2,4-triazol-4-yl)acetyl]pyrrolidine-2-carboxamide

2-[4-fluoro-2-({[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl}carbamoyl)pyrrolidin-1-yl]-2-oxoethyl 4-methylpiperazine-1-carboxylate

2-[4-fluoro-2-({[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl}carbamoyl)pyrrolidin-1-yl]-2-oxoethyl 4-(cyclopropylmethyl)piperazine-1-carboxylate

2-[4-fluoro-2-({[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl}carbamoyl)pyrrolidin-1-yl]-2-oxoethyl 4-(2,2,2-trifluoroethyl)piperazine-1-carboxylate

1-[2-(1H-1,3-benzodiazol-1-yl)propanoyl]-4-fluoro-N-{[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl}pyrrolidine-2-carboxamide

4-fluoro-N-{[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl}-1-[2-(1H-indazol-3-yl)acetyl]pyrrolidine-2-carboxamide

N-{2-[4-fluoro-2-({[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl}carbamoyl)pyrrolidin-1-yl]-2-oxoethyl}morpholine-4-carboxamide

4-fluoro-N-{[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl}-1-[2-(1-methyl-1H-indol-2-yl)acetyl]pyrrolidine-2-carboxamide

4-fluoro-N-{[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl}-1-[2-(1-methyl-1H-indol-3-yl)acetyl]pyrrolidine-2-carboxamide

4-fluoro-N-{[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl}-1-[2-(2-methyl-1H-1,3-benzodiazol-1-yl)acetyl]pyrrolidine-2-carboxamide

1-[2-(1H-1,2,3-benzotriazol-1-yl)acetyl]-4-fluoro-N-{[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl}pyrrolidine-2-carboxamide

1-[2-(1H-1,3-benzodiazol-1-yl)acetyl]-4-fluoro-N-{[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl}pyrrolidine-2-carboxamide

4-fluoro-N-{[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl}-1-[2-(1-methyl-1H-indazol-3-yl)acetyl]pyrrolidine-2-carboxamide

4-fluoro-N-{[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl}-1-[2-(1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl)acetyl]pyrrolidine-2-carboxamide

4-fluoro-N-{[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl}-1-[2-(1H-indol-2-yl)acetyl]pyrrolidine-2-carboxamide

4-fluoro-N-{[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl}-1-[2-(2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)acetyl]pyrrolidine-2-carboxamide

4-fluoro-N-{[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl}-1-[2-(3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)acetyl]pyrrolidine-2-carboxamide

tert-butyl 2-{2-[4-fluoro-2-({[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl}carbamoyl)pyrrolidin-1-yl]-2-oxoethyl}-1H-indole-1-carboxylate

1-{2-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]acetyl}-4-fluoro-N-{[4-methyl-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}pyrrolidine-2-carboxamide

1-acetyl-N-[(5-cyclobutylpyridin-2-yl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide

4-fluoro-N-{[4-methyl-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

4-fluoro-N-{[4-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

N-{[4-(difluoromethyl)-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

4-fluoro-N-{[6-methyl-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

4-fluoro-N-{phenyl[5-(propan-2-yl)-4-(trifluoromethyl)pyridin-2-yl]methyl}-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

1-{2-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]acetyl}-4-fluoro-N-{[6-methyl-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}pyrrolidine-2-carboxamide
N-[(5-cyclobutylpyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
N-[(5-tert-butylpyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
4-fluoro-N-{[6-methoxy-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
N-[(2-aminopyridin-3-yl)[3-fluoro-4-(propan-2-yl)phenyl]methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

N-[(4-cyclopropyl-3-fluorophenyl)(1H-pyrazol-5-yl)methyl]-1-(2-acetamidoacetyl)pyrrolidine-2-carboxamide
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](5-fluoropyridin-2-yl)methyl}-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](5-fluoropyridin-3-yl)methyl}-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
N-[(2-aminopyridin-4-yl)[3-fluoro-4-(propan-2-yl)phenyl]methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](3-fluoropyridin-4-yl)methyl}-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
N-[(6-aminopyridin-3-yl)[3-fluoro-4-(propan-2-yl)phenyl]methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
N-[(6-aminopyridin-2-yl)[3-fluoro-4-(propan-2-yl)phenyl]methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
N-[(2-aminopyridin-3-yl)[3-methyl-4-(propan-2-yl)phenyl]methyl]-1-{2-[(dimethylcarbamoyl)amino]acetyl}-4-fluoropyrrolidine-2-carboxamide
4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](1H-pyrazol-5-yl)methyl}-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
N-[(2-aminopyridin-3-yl)[3-methyl-4-(propan-2-yl)phenyl]methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

N-[(2-aminopyridin-3-yl)[3-methyl-4-(propan-2-yl)phenyl]methyl]-4-fluoro-1-[2-(1,3,5-trimethyl-1H-pyrazol-4-yl)acetyl]pyrrolidine-2-carboxamide

4-fluoro-N-{[3-fluoro-4-(1-methylcyclopropyl)phenyl](2-methoxypyridin-3-yl)methyl}-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

4-fluoro-N-{[3-fluoro-4-(1-methylcyclopropyl)phenyl](2-methylpyridin-3-yl)methyl}-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl]({imidazo[1,5-a]pyridin-3-yl})methyl}-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl]({imidazo[1,5-a]pyridin-1-yl})methyl}-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](1H-pyrazol-5-yl)methyl}-1-[2-(1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide

4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl]({imidazo[1,5-a]pyridin-7-yl})methyl}-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](1H-indazol-6-yl)methyl}-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

1-acetyl-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](1H-indazol-6-yl)methyl}pyrrolidine-2-carboxamide

1-acetyl-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](1-methyl-1H-indazol-6-yl)methyl}pyrrolidine-2-carboxamide

1-acetyl-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](2-methyl-2H-indazol-6-yl)methyl}pyrrolidine-2-carboxamide

1-acetyl-N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(1H-indazol-6-yl)methyl]-4-fluoropyrrolidine-2-carboxamide

methyl N-({3-[({4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidin-2-yl}formamido)[6-fluoro-5-(propan-2-yl)pyridin-2-yl]methyl]phenyl}methyl)carbamate

1-acetyl-N-[(2-methoxyphenyl)[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide

1-acetyl-N-[(2-methylphenyl)[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide

1-acetyl-N-[(2-methylphenyl)[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide

N-[(4-cyclopropyl-3-fluorophenyl)(2-oxo-2,3-dihydro-1,3-benzoxazol-7-yl)methyl]-1-(2-acetamidoacetyl)pyrrolidine-2-carboxamide

N-[(2-oxo-2,3-dihydro-1H-1,3-benzodiazol-4-yl)[4-(propan-2-yl)phenyl]methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](3-fluorophenyl)methyl}-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](4-fluorophenyl)methyl}-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

N-[(4-cyclopropyl-3-fluorophenyl)(2-oxo-2,3-dihydro-1H-1,3-benzodiazol-4-yl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

N-[(3-acetamidophenyl)[4-(propan-2-yl)phenyl]methyl]-4-fluoro-1-[2-(1-methyl-1H-1,2,3-triazol-4-yl)acetyl]pyrrolidine-2-carboxamide

N-[(4-cyclopropyl-3-fluorophenyl)(1-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-4-yl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](3-methoxyphenyl)methyl}-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

N-{cyclopropyl[3-fluoro-4-(propan-2-yl)phenyl]methyl}-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

N-{2-cyclopropyl-1-[3-fluoro-4-(propan-2-yl)phenyl]ethyl}-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

1-acetyl-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](3-methoxyphenyl)methyl}pyrrolidine-2-carboxamide

N-{[3-(acetamidomethyl)phenyl][6-fluoro-5-(propan-2-yl)pyridin-2-yl]methyl}-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](3-{[(methylcarbamoyl)amino]methyl}phenyl)methyl}-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(2-fluorophenyl)methyl]-1-{2-[5-(difluoromethyl)-1H-1,2,3,4-tetrazol-1-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide

N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(4-fluorophenyl)methyl]-1-{2-[5-(difluoromethyl)-1H-1,2,3,4-tetrazol-1-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide

N-{[3,5-difluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-4-fluoro-1-[(1H-1,2,3-triazol-5-yl)methanesulfonyl]pyrrolidine-2-carboxamide

1-acetyl-N-[(4-cyclobutyl-3-fluorophenyl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide
N-{[3,5-difluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-4-fluoro-1-[2-(1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide
N-[(4-cyclopropyl-3,5-difluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide
4-fluoro-N-{[2-methyl-4-(propan-2-yl)phenyl](phenyl)methyl}-1-[2-(1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide
N-[(3-chloro-4-cyclopropylphenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
N-[(4-cyclopropyl-3-methylphenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
N-{[3,5-difluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
N-{[3,5-difluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-4-fluoro-1-[2-(1H-1,2,3-triazol-1-yl)acetyl]pyrrolidine-2-carboxamide
N-{[3,5-difluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-4-fluoro-1-[2-(1H-1,2,3,4-tetrazol-1-yl)acetyl]pyrrolidine-2-carboxamide
4-fluoro-N-{[3-methyl-4-(propan-2-yl)phenyl](phenyl)methyl}-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
N-{[3-chloro-4-(propan-2-yl)phenyl](phenyl)methyl}-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
N-[(4-cyclobutyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
N-[(4-cyclobutyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3,4-tetrazol-1-yl)acetyl]pyrrolidine-2-carboxamide
N-{[4-(butan-2-yl)-3-fluorophenyl](phenyl)methyl}-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
4-fluoro-N-{[3-fluoro-5-methyl-4-(propan-2-yl)phenyl](phenyl)methyl}-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide
N-{[3-(difluoromethyl)-4-(propan-2-yl)phenyl](phenyl)methyl}-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

4-fluoro-N-{[3-fluoro-4-(1-methylcyclobutyl)phenyl](phenyl)methyl}-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

N-[(4-cyclopropyl-3-fluoro-5-methylphenyl)(phenyl)methyl]-4-fluoro-1-[2-(5-methyl-2H-1,2,3,4-tetrazol-2-yl)acetyl]pyrrolidine-2-carboxamide

4-fluoro-N-{phenyl[4-(propan-2-yl)-3-(trifluoromethyl)phenyl]methyl}-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

N-[(4-tert-butyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl][3-(1H-pyrazol-5-yl)phenyl]methyl}-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

1-acetyl-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl][3-(4H-1,2,4-triazol-3-yl)phenyl]methyl}pyrrolidine-2-carboxamide

1-acetyl-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl][3-(1H-pyrazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide

1-(2-acetamidoacetyl)-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl][3-(1H-pyrazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide

4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl][3-(1,3-oxazol-5-yl)phenyl]methyl}-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl][3-(1,2-oxazol-5-yl)phenyl]methyl}-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

1-acetyl-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl][3-(1-methyl-1H-pyrazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide

1-acetyl-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl][3-(3-methyl-1H-pyrazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide

1-acetyl-N-{[3-(1,3-dimethyl-1H-pyrazol-5-yl)phenyl][6-fluoro-5-(propan-2-yl)pyridin-2-yl]methyl}-4-fluoropyrrolidine-2-carboxamide

1-acetyl-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl][3-(1,2-oxazol-5-yl)phenyl]methyl}pyrrolidine-2-carboxamide

1-acetyl-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl][3-(1H-pyrazol-1-yl)phenyl]methyl}pyrrolidine-2-carboxamide

1-acetyl-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl][3-(1,3,4-oxadiazol-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide

1-(oct-7-ynoyl)-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide

4-fluoro-1-(1-methyl-1H-indazole-5-carbonyl)-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide

4-fluoro-1-[2-(4-methoxyphenyl)cyclopropanecarbonyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide

4-fluoro-1-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridine-2-carbonyl)-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide

4-fluoro-1-[2-(2-methylpropoxy)pyridine-4-carbonyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide

4-fluoro-1-[3-(1H-imidazol-4-yl)propanoyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide

4-fluoro-1-[4-(1H-imidazol-1-yl)pyridine-2-carbonyl]-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide

4-fluoro-N-{phenyl[4-(propan-2-yl)phenyl]methyl}-1-{[(pyridin-3-yl)carbamoyl]carbonyl}pyrrolidine-2-carboxamide

4-fluoro-1-(5-methoxy-1-methyl-1H-pyrazole-3-carbonyl)-N-{phenyl[4-(propan-2-yl)phenyl]methyl}pyrrolidine-2-carboxamide

1-[2-(1,4-dimethyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)acetyl]-4-fluoro-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide

1-{2-[4-(azetidin-1-yl)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoro-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide

4-fluoro-1-[2-(5-methoxy-1-methyl-1H-1,2,4-triazol-3-yl)acetyl]-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide

1-{2-[5-(diethylamino)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoro-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide

1-{2-[5-(3,3-difluoroazetidin-1-yl)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoro-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide

1-{2-[5-(azetidin-1-yl)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoro-N-{phenyl[5-(propan-2-yl)pyridin-2-yl]methyl}pyrrolidine-2-carboxamide

N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-(2-{3-oxo-2H,3H-[1,2,4]triazolo[4,3-a]pyridin-8-yl}acetyl)pyrrolidine-2-carboxamide

N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(4-methyl-5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)acetyl]pyrrolidine-2-carboxamide

N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[2-(1,4-dimethyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide

N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(1H-pyrazol-1-yl)acetyl]pyrrolidine-2-carboxamide

N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(5-methyl-1H-pyrazol-1-yl)acetyl]pyrrolidine-2-carboxamide

N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[5-(difluoromethyl)-1H-pyrazol-1-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide

1-{2-[4-(azetidin-1-yl)-1H-1,2,3-triazol-1-yl]acetyl}-N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide

N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[2-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide

N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-{2-[4-(trifluoromethyl)-1H-pyrazol-1-yl]acetyl}pyrrolidine-2-carboxamide

N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[3-(difluoromethyl)-1H-pyrazol-1-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide

N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-{2-[3-(trifluoromethyl)-1H-pyrazol-1-yl]acetyl}pyrrolidine-2-carboxamide

N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(2-oxo-1,2-dihydropyridin-3-yl)acetyl]pyrrolidine-2-carboxamide

N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)acetyl]pyrrolidine-2-carboxamide

N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[2-(3-ethyl-5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide

N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(6-oxo-1,6-dihydropyridin-3-yl)acetyl]pyrrolidine-2-carboxamide
N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[2-(3-ethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide
N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[2-(1-ethyl-6-oxo-1,6-dihydropyridin-3-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide
N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[2-(6-ethoxy-5-methylpyridin-3-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide
N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-{2-[4-(trifluoromethyl)-1,3-oxazol-2-yl]acetyl}pyrrolidine-2-carboxamide
N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[2-(1-ethyl-5-methyl-6-oxo-1,6-dihydropyridin-3-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide
N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[2-(1-ethyl-5-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide
N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[2-(1-ethyl-2-oxo-1,2-dihydropyridin-3-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide
N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[2-(4-ethyl-5-oxo-4,5-dihydropyrazin-2-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide
N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(5-methoxy-1-methyl-1H-1,2,4-triazol-3-yl)acetyl]pyrrolidine-2-carboxamide
1-(2-{[benzyl(trifluoromethyl)carbamoyl]amino}acetyl)-N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide
N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-{2-[5-(trifluoromethyl)-1H-1,2,3-triazol-1-yl]acetyl}pyrrolidine-2-carboxamide
N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(5-oxo-4,5-dihydropyrazin-2-yl)acetyl]pyrrolidine-2-carboxamide
N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[5-(difluoromethyl)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide
N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[5-(diethylamino)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide

N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide

N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[5-(difluoromethyl)-3-methyl-1H-pyrazol-1-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide

N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[5-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide

N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[3-(difluoromethyl)-5-methyl-1H-pyrazol-1-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide

N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[2-(4-ethyl-3-oxo-3,4-dihydropyrazin-2-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide

N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[4-(difluoromethyl)-1-methyl-1H-pyrazol-5-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide

N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-{2-[5-(trifluoromethyl)-1H-1,2,3,4-tetrazol-1-yl]acetyl}pyrrolidine-2-carboxamide

N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[4-(difluoromethyl)-1H-1,2,3-triazol-5-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide

N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[4-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide

N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[5-(3,3-difluoroazetidin-1-yl)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide

N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[3-(difluoromethyl)-4H-1,2,4-triazol-4-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide

N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-{2-[5-(trifluoromethyl)-1H-pyrazol-1-yl]acetyl}pyrrolidine-2-carboxamide

N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[2-(4,5-dimethyl-1,3-oxazol-2-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide

1-{2-[5-(azetidin-1-yl)-1H-1,2,3-triazol-1-yl]acetyl}-N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide

N-[(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[5-(difluoromethyl)-1H-1,2,3,4-tetrazol-1-yl]acetyl}-4-fluoro-3-hydroxypyrrolidine-2-carboxamide

1-(3-carbamoyl-2-acetamidopropanoyl)-4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}pyrrolidine-2-carboxamide

4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-[2-(1H-1,2,3,4-tetrazol-1-yl)propanoyl]pyrrolidine-2-carboxamide

4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-[2-(1H-imidazol-1-yl)propanoyl]pyrrolidine-2-carboxamide

4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-[2-(1H-1,2,3-triazol-5-yl)propanoyl]pyrrolidine-2-carboxamide

4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-[(1H-1,2,3-triazol-5-yl)methanesulfonyl]pyrrolidine-2-carboxamide

4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}-1-[2-hydroxy-2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

1-{2-[4-(dimethylamino)-1H-1,2,3-triazol-5-yl]acetyl}-4-fluoro-N-{[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl}pyrrolidine-2-carboxamide

4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide

1-[2-(3,5-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}pyrrolidine-2-carboxamide

4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}-1-[2-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]pyrrolidine-2-carboxamide

1-[2-(1,4-dimethyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)acetyl]-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}pyrrolidine-2-carboxamide

4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}-1-(3-{3-oxo-2H,3H-[1,2,4]triazolo[4,3-a]pyridin-2-yl}propanoyl)pyrrolidine-2-carboxamide

4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}-1-[2-(1H-pyrazol-1-yl)acetyl]pyrrolidine-2-carboxamide

4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}-1-[2-(5-methyl-1H-pyrazol-1-yl)acetyl]pyrrolidine-2-carboxamide

1-{2-[5-(difluoromethyl)-1H-pyrazol-1-yl]acetyl}-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}pyrrolidine-2-carboxamide

4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}-1-[2-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)acetyl]pyrrolidine-2-carboxamide

1-[2-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}pyrrolidine-2-carboxamide

1-[2-(3-ethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}pyrrolidine-2-carboxamide

1-{2-[4-(azetidin-1-yl)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}pyrrolidine-2-carboxamide

4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}-1-{2-[4-(trifluoromethyl)-1H-pyrazol-1-yl]acetyl}pyrrolidine-2-carboxamide

1-{2-[3-(difluoromethyl)-1H-pyrazol-1-yl]acetyl}-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}pyrrolidine-2-carboxamide

4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}-1-{2-[3-(trifluoromethyl)-1H-pyrazol-1-yl]acetyl}pyrrolidine-2-carboxamide

4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}-1-[2-(6-oxo-1,6-dihydropyridin-3-yl)acetyl]pyrrolidine-2-carboxamide

1-[2-(1-ethyl-6-oxo-1,6-dihydropyridin-3-yl)acetyl]-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}pyrrolidine-2-carboxamide

4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}-1-[2-(2-oxo-1,2-dihydropyridin-3-yl)acetyl]pyrrolidine-2-carboxamide

1-[2-(3-ethyl-5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}pyrrolidine-2-carboxamide

1-[2-(1-ethyl-2-oxo-1,2-dihydropyridin-3-yl)acetyl]-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}pyrrolidine-2-carboxamide

1-[2-(1-ethyl-5-methyl-6-oxo-1,6-dihydropyridin-3-yl)acetyl]-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}pyrrolidine-2-carboxamide

1-[2-(4-ethyl-5-oxo-4,5-dihydropyrazin-2-yl)acetyl]-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}pyrrolidine-2-carboxamide

1-[2-(6-ethoxy-5-methylpyridin-3-yl)acetyl]-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}pyrrolidine-2-carboxamide

1-[2-(1-ethyl-5-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetyl]-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}pyrrolidine-2-carboxamide
4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}-1-[2-(5-methoxy-1-methyl-1H-1,2,4-triazol-3-yl)acetyl]pyrrolidine-2-carboxamide
4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}-1-{2-[4-(trifluoromethyl)-1,3-oxazol-2-yl]acetyl}pyrrolidine-2-carboxamide
4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}-1-[2-(5-oxo-4,5-dihydropyrazin-2-yl)acetyl]pyrrolidine-2-carboxamide
1-{2-[5-(difluoromethyl)-3-methyl-1H-pyrazol-1-yl]acetyl}-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}pyrrolidine-2-carboxamide
1-{2-[3-(difluoromethyl)-5-methyl-1H-pyrazol-1-yl]acetyl}-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}pyrrolidine-2-carboxamide
1-{2-[5-(diethylamino)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}pyrrolidine-2-carboxamide
1-[2-(4-ethyl-3-oxo-3,4-dihydropyrazin-2-yl)acetyl]-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}pyrrolidine-2-carboxamide
1-{2-[5-(3,3-difluoroazetidin-1-yl)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}pyrrolidine-2-carboxamide
1-{2-[5-(azetidin-1-yl)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoro-N-{[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl}pyrrolidine-2-carboxamide
1-[2-(1H-1,3-benzodiazol-1-yl)propanoyl]-N-[(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide
or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

METHODS OF TREATMENT

[0239] Provided herein is a method of modulating GYS1 in a cell, comprising exposing the cell to (i) a composition comprising an effective amount of a GYS1 inhibitor, or (ii) a pharmaceutical composition, comprising an effective amount of a GYS1 inhibitor, and one or more pharmaceutically acceptable excipients. In some embodiments, the GYS1 inhibitor is a small molecule. In some embodiments, the GYS1 inhibitor is selective for GYS1 over GYS2. In

some embodiments, the GYS1 inhibitor is greater than 500 or 1,000 or 1,500 or 1,700-fold selective for GYS1 over GYS2.

[0240] Provided herein is a method of modulating GYS1 in a cell, comprising exposing the cell to (i) a composition comprising an effective amount of a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or (ii) a pharmaceutical composition, comprising an effective amount of a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients.

[0241] Provided herein is a method of inhibiting GYS1 in a cell, comprising exposing the cell to (i) a composition comprising an effective amount of a GYS1 inhibitor, or (ii) a pharmaceutical composition, comprising an effective amount of a GYS1 inhibitor, and one or more pharmaceutically acceptable excipients. In some embodiments, the GYS1 inhibitor is a small molecule. In some embodiments, the GYS1 inhibitor is selective for GYS1 over GYS2. In some embodiments, the GYS1 inhibitor is greater than 500 or 1,000 or 1,500 or 1,700-fold selective for GYS1 over GYS2.

[0242] Provided herein is a method of inhibiting GYS1 in a cell, comprising exposing the cell to (i) a composition comprising an effective amount of a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or (ii) a pharmaceutical composition, comprising an effective amount of a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients.

[0243] Provided herein is a method of reducing tissue glycogen stores in an individual in need thereof, comprising administering to the individual an effective amount of (i) a GYS1 inhibitor, or (ii) a pharmaceutical composition, comprising a GYS1 inhibitor, and one or more pharmaceutically acceptable excipients. In some embodiments, the GYS1 inhibitor is a small molecule. In some embodiments, the GYS1 inhibitor is selective for GYS1 over GYS2. In some embodiments, the GYS1 inhibitor is greater than 500 or 1,000 or 1,500 or 1,700-fold

selective for GYS1 over GYS2. In some embodiments, the individual has a GYS1-mediated disease, disorder, or condition is selected from the group consisting of Pompe disease, Cori disease (GSD III), adult polyglucosan body disease (APBD), and Lafora disease. In some embodiments, the GYS1-mediated disease, disorder, or condition is cancer. In some embodiments, the GYS1-mediated disease, disorder, or condition is selected from the group consisting of Ewing sarcoma (ES), clear cell renal cell carcinoma (ccRCC), glycogen rich clear cell carcinoma (GRCC) breast cancer, non-small-cell lung carcinoma (NSCLC), and acute myeloid leukemia (AML). In some embodiments, the GYS1-mediated disease, disorder, or condition is Pompe disease. In some embodiments, the GYS1-mediated disease, disorder, or condition is late-onset Pompe disease (LOPD).

[0244] Provided herein is a method of reducing tissue glycogen stores in an individual in need thereof, comprising administering to the individual (i) a composition comprising an effective amount of a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or (ii) a pharmaceutical composition, comprising an effective amount of a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients.

[0245] Provided herein is a method of reducing tissue glycogen stores in an individual in need thereof, comprising administering to the individual (i) a composition comprising an effective amount of a compound of formula (I'), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or (ii) a pharmaceutical composition, comprising an effective amount of a compound of formula (I'), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients.

[0246] Provided herein is a method of inhibiting glycogen synthesis in an individual in need thereof, comprising administering to the individual an effective amount of (i) a GYS1 inhibitor, or (ii) a pharmaceutical composition, comprising a GYS1 inhibitor, and one or more pharmaceutically acceptable excipients. In certain embodiments the GYS1 inhibitor is a

compound of formula (I'), (I) or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients. In some embodiments, the pharmaceutical composition is (i) a composition comprising an effective amount of a compound of formula (I'), (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or (ii) a pharmaceutical composition, comprising an effective amount of a compound of formula (I'), (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients. In some embodiments, the compounds and/or compositions inhibit the hGYS enzyme, and subsequently, the glycogen synthesis in cells.

[0247] Provided herein is a method of treating a GYS1-mediated disease, disorder, or condition in an individual in need thereof, comprising subjecting the individual to glycogen substrate reduction therapy. In some embodiments, glycogen substrate reduction therapy reduces glycogen stores. In some embodiments, glycogen substrate reduction therapy comprises administering to the individual an effective amount of (i) a GYS1 inhibitor, or (ii) a pharmaceutical composition comprising a GYS1 inhibitor, and one or more pharmaceutically acceptable excipients. In some embodiments, the GYS1 inhibitor is a small molecule. In some embodiments, the GYS1 inhibitor is selective for GYS1 over GYS2. In some embodiments, the GYS1 inhibitor is greater than 500 or 1,000 or 1,500 or 1,700-fold selective for GYS1 over GYS2. In some embodiments, the GYS1-mediated disease, disorder, or condition is selected from the group consisting of Pompe disease, Cori disease (GSD III), adult polyglucosan body disease (APBD), and Lafora disease. In some embodiments, the GYS1-mediated disease, disorder, or condition is cancer. In some embodiments, the GYS1-mediated disease, disorder, or condition is selected from the group consisting of Ewing sarcoma (ES), clear cell renal cell carcinoma (ccRCC), glycogen rich clear cell carcinoma (GRCC) breast cancer, non-small-cell lung carcinoma (NSCLC), and acute myeloid leukemia (AML). In some embodiments, the GYS1-mediated disease, disorder, or condition is Pompe disease.

[0248] Provided herein is a method of treating a GYS1-mediated disease, disorder, or condition in an individual in need thereof, comprising administering to the individual (i) a composition comprising an effective amount of a compound of formula (I), or any variation or

embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or (ii) a pharmaceutical composition, comprising an effective amount of a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients. In some embodiments, the GYS1-mediated disease, disorder, or condition is selected from the group consisting of Pompe disease, Cori disease (GSD III), adult polyglucosan body disease (APBD), and Lafora disease. In some embodiments, the GYS1-mediated disease, disorder, or condition is cancer. In some embodiments, the GYS1-mediated disease, disorder, or condition is selected from the group consisting of Ewing sarcoma (ES), clear cell renal cell carcinoma (ccRCC), glycogen rich clear cell carcinoma (GRCC) breast cancer, non-small-cell lung carcinoma (NSCLC), and acute myeloid leukemia (AML).

[0249] Provided herein is a method of treating a glycogen storage disease, disorder, or condition in an individual in need thereof, comprising subjecting the individual to glycogen substrate reduction therapy. In some embodiments, glycogen substrate reduction therapy reduces glycogen stores. In some embodiments, glycogen substrate reduction therapy comprises administering to the individual an effective amount of (i) a GYS1 inhibitor, or (ii) a pharmaceutical composition comprising a GYS1 inhibitor, and one or more pharmaceutically acceptable excipients. In some embodiments, the GYS1 inhibitor is a small molecule. In some embodiments, the GYS1 inhibitor is selective for GYS1 over GYS2. In some embodiments, the GYS1 inhibitor is greater than 500 or 1,000 or 1,500 or 1,700-fold selective for GYS1 over GYS2. In some embodiments, the level of glycogen in the individual is reduced upon treatment. In some embodiments, the level of glycogen in muscle is reduced. In some embodiments, the level of glycogen is skeletal muscle is reduced. In some embodiments, the level of glycogen is reduced at least 10%, at least 20%, at least 30% or at least 50% upon administration of the compound. In some embodiments, the compounds provided herein are effective for treating a lysosomal disorder. In some embodiments, the glycogen storage disease, disorder, or condition is selected from the group consisting of Pompe disease, Cori disease (GSD III), adult polyglucosan body disease (APBD), and Lafora disease. In some embodiments, the glycogen storage disease, disorder, or condition is Pompe disease. In some embodiments, the individual has late onset Pompe Disease. In some embodiments, the GYS1 inhibitor comprises a

compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt thereof.

[0250] Provided herein is a method of treating a glycogen storage disease, disorder, or condition in an individual in need thereof, comprising administering to the individual (i) a composition comprising an effective amount of a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or (ii) a pharmaceutical composition, comprising an effective amount of a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients. In some embodiments, the level of glycogen in the individual is reduced upon treatment. In some embodiments, the level of glycogen in muscle is reduced. In some embodiments, the level of glycogen is skeletal muscle is reduced. In some embodiments, the level of glycogen is reduced at least 10%, at least 20%, at least 30% or at least 50% upon administration of the compound. In some embodiments, the compounds provided herein are effective for treating a lysosomal disorder. In some embodiments, the glycogen storage disease, disorder, or condition is selected from the group consisting of Pompe disease, Cori disease (GSD III), adult polyglucosan body disease (APBD), and Lafora disease.

[0251] Provided herein is a method of treating Pompe disease in an individual in need thereof, comprising administering to the individual (i) a composition comprising an effective amount of a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or (ii) a pharmaceutical composition, comprising an effective amount of a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients. In some embodiments, the individual has infant onset Pompe disease. In some embodiments, the individual has non-classic infant-onset Pompe disease. In some embodiments, the individual has late-onset Pompe disease. In some embodiments, the individual has a deficiency in acid alfa glucosidase (GAA). In some embodiments, the individual has reduced expression of GAA.

[0252] In some embodiments, the compounds provided herein reduce and/or eliminate one or more symptoms associated with Pompe disease. In some embodiments, the compounds reduce and/or eliminate weak muscles, poor muscle tone, enlarged liver, failure to grow and gain weight, trouble breathing, feeding problems, infections in the respiratory system, problems with hearing, motor skill delay, heart enlargement, tiredness, lung infection, frequent falling, or irregular heartbeat. In some embodiments, the compounds herein delay progression of Pompe disease.

[0253] In some embodiments, the compounds provided herein increase the lifespan of the individual. In some embodiments, the lifespan is increased at least 5, at least 10, or at least 20 years upon treatment.

[0254] In some embodiments, the compounds provided herein prevent, reduce, or delay muscle weakness. In some embodiments, muscle weakness is determined by manual muscle testing, sit to stand test, heel-raise test, hand-held dynamometry, or hand grip dynamometry. In some embodiments, strength is graded according to the following scale: 0: No visible muscle contraction; 1: Visible muscle contraction with no or trace movement; 2: Limb movement, but not against gravity; 3: Movement against gravity but not resistance; 4: Movement against at least some resistance supplied by the examiner; 5: Full strength.

[0255] Also provided herein is a method of inhibiting a GYS1 enzyme in an individual comprising administering an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof to the individual. In some embodiments the GYS1 enzyme is human GYS1 (hGYS1). In some embodiments, the compounds provided herein are inhibit GYS1 at a concentration of less than 10 μM, less than 1 μM, less than 0.5 μM, or less than 0.1 μM. In some embodiments, the compounds provided herein inhibit GYS1 at a concentration of 1-10 μM, 0.01 to 1 μM, or 0.01 to 10 μM.

[0256] In some embodiments, the compounds have an IC_{50} of less than 10 nM, less than 10 μM, less than 1 μM, less than 0.5 μM, or less than 0.1 μM. In some embodiments, the compounds provided herein have an IC_{50} of 1 to 10 nM, 1 to 10 μM, 0.01 to 1 μM, 0.01 to 10 μM, or 0.001 to 0.01 μM.

[0257] In some embodiments, glycogen synthesis is inhibited upon administration of a compound provided herein. In some embodiments, glycogen synthesis is reduced at least 10%, at least 20%, at least 40% or at least 50% upon administration.

[0258] In some embodiments, the individual receiving treatment is a juvenile human or an infant. In some embodiments, the individual is less than 10 years old, less than 9 years old, less than 8 years old, less than 7 years old, less than 6 years old, less than 5 years old, less than 4 years old, less than 3 years old, less than 2 years old, or less than one year old.

[0259] In some embodiments, the methods further comprise enzyme replacement therapy (ERT). Exemplary ERTs include alglucosidase alfa (human recombinant alpha-glucosidase (human GAA)) and those described in Byrne BJ et al (2011). Pompe disease: design, methodology, and early findings from the Pompe Registry. Mol Genet Metab 103: 1-11 (herein incorporated by reference in its entirety). In some embodiments, the ERT is selected from the group consisting of Myozyme and Lumizyme. In some embodiments, the ERT is Myozyme. In some embodiments, the ERT is Lumizyme. In some embodiments, the individual has an advanced glycogen storage disease. In some embodiments, the individual has late onset Pompe Disease. Thus, provided herein is a method of treating a GYS1-mediated disease, disorder, or condition in an individual in need thereof, comprising subjecting the individual to (a) glycogen substrate reduction therapy, such as administering to the individual an effective amount of (i) a GYS1 inhibitor, or (ii) a pharmaceutical composition comprising a GYS1 inhibitor, and one or more pharmaceutically acceptable excipients and (b) enzyme replacement therapy. In some embodiments, the GYS1-mediated disease, disorder, or condition is Pompe disease, such as late-onset Pompe disease. In some embodiments, the GYS1 inhibitor is a small molecule. In some embodiments, the GYS1 inhibitor is selective for GYS1 over GYS2. In some embodiments, the GYS1 inhibitor is greater than 500 or 1,000 or 1,500 or 1,700-fold selective for GYS1 over GYS2. In some embodiments, the GYS1 inhibitor is a compound of formula (I) or a pharmaceutically acceptable salt thereof.

[0260] In some embodiments, the individual has a mutation in the GAA gene. In some embodiments, the mutation reduces the level of GAA protein. In some embodiments, the mutation is a loss-of-function mutation. In some embodiments, the mutation is a missense

mutation. In some embodiments, the mutation is a deletion. In some embodiments, the mutation is a recessive mutation. In some embodiments, the mutation is a splicing variant.

[0261] In some embodiments of the foregoing, the administration is oral administration.

KITS

[0262] The present disclosure further provides kits for carrying out the methods of the invention. The kits may comprise a compound or pharmaceutically acceptable salt thereof as described herein and suitable packaging. The kits may comprise one or more containers comprising any compound described herein. In one aspect, a kit includes a compound of the disclosure or a pharmaceutically acceptable salt thereof, and a label and/or instructions for use of the compound in the treatment of a disease or disorder described herein. The kits may comprise a unit dosage form of the compound.

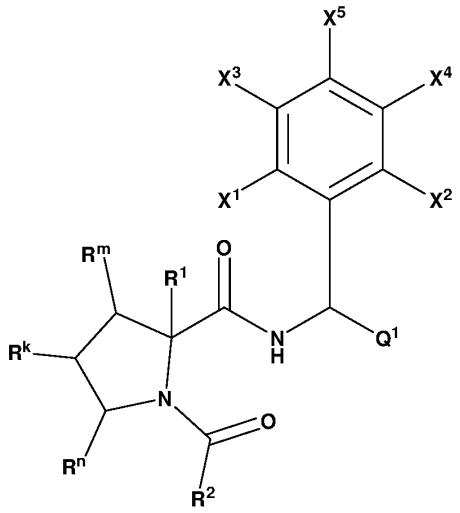
[0263] Provided herein are kits, comprising (i) a composition comprising an effective amount of a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and (ii) instructions for use in treating an GYS1-mediated disease, disorder, or condition in an individual in need thereof. Also provided herein are kits, comprising (i) a pharmaceutical composition comprising an effective amount of a compound of formula (I), or any variation or embodiment thereof, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and one or more pharmaceutically acceptable excipients; and (ii) instructions for use in treating an GYS1-mediated disease, disorder, or condition in an individual in need thereof

[0264] Articles of manufacture are also provided, wherein the article of manufacture comprises a compound of formula (I), or any variation or embodiment thereof, as described elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, in a suitable container. Also provided herein are articles of manufacture, comprising a pharmaceutical composition comprising a compound of formula (I), or any variation or embodiment thereof, as described elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, in a suitable container. The container may be a vial, jar, ampoule, preloaded syringe, or intravenous bag.

ENUMERATED EMBODIMENTS

[0265] The following enumerated embodiments are also contemplated:

[0266] Embodiment 1. A compound of formula (I):



(I),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein:

X^1 and X^2 are each independently H, C_{1-6}alkyl, or C_{1-6}alkoxy;

X^3 and X^4 are each independently H, halo, C_{1-6}alkyl, C_{1-6}alkoxy, or 5-20 membered heteroaryl;

X^5 is H, C_{1-6}alkyl, C_{1-6}alkoxy, or C_{3-10}cycloalkyl;

Q^1 is selected from (i) to (iii):

(i) phenyl, wherein the phenyl of Q^1 is substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, $-NH_2$, -NH-C(O)-(C_{1-6}alkyl), -NH-C(O)-(3-15 membered heterocyclyl), or C_{3-}

$_{10}$cycloalkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, and the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl,

(ii) 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of Q^1 is optionally substituted with one or more oxo, and

(iii) 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of Q^1 is optionally substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, $-NH_2$, or C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl;

R^1 is H or C_{1-6}alkyl;

R^k is H, halo, -OH, $-NH_2$, or -NH-C(O)C_{1-6}alkyl;

R^m is H, -OH, or C_{1-6}alkyl;

R^n is H, C_{1-6}alkyl, or C_{3-10}cycloalkyl;

or R^k is taken together with either R^m or R^n, and the atoms to which they are attached, to form cyclopropyl; and

R^2 is selected from (i) to (vii):

(i) C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is optionally substituted with one or more R^a, wherein R^a is:

(a) -OH,

(b) cyano,

(c) C_{2-6}alkynyl,

(d) C_{6-20}aryl, wherein the C_{6-20}aryl of R^a is optionally substituted with one or more halo, cyano, C_{1-6}alkoxy, or -NH-C(O)-C_{1-6}alkyl,

(e) 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^a is optionally substituted with one or more R^b, wherein

R^b is halo, C_{1-6}alkyl, C_{1-6}alkoxy, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, C_{3-10}cycloalkyl, 3-15 membered heterocyclyl, or -C(O)-C_{1-6}alkoxy, wherein

the C_{1-6}alkyl of R^b is optionally substituted with one or more halo, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, -NH-C(O)C_{1-6}alkyl, or -NH-C(O)-C_{1-6}alkoxy, and

the 3-15-membered heterocyclyl of R^b is optionally substituted with one or more halo or -C(O)-C_{1-6}alkoxy,

(f) 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^a is optionally substituted with one or more R^c, wherein

R^c is halo, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, or -C(O)-C_{1-6}alkoxy, wherein

the C_{1-6}alkyl of R^c is optionally substituted with one or more halo or C_{2-6}alkynyl, and

the -C(O)-C_{1-6}alkoxy of R^c is optionally substituted with one or more halo,

(g) -N(R^c)(R^d), wherein R^c and R^d are, independently of each other, H, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-C_{1-6}alkoxy, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -C(O)-(3-15 membered heterocyclyl), -CH_2-C(O)-NH_2, 3-15 membered heterocyclyl, or 5-20 membered heteroaryl, wherein

the -C(O)-C_{1-6}alkyl of R^c or R^d is optionally substituted with one or more halo,

the 3-15 membered heterocyclyl and the 5-20 membered heteroaryl of R^c or R^d are independently optionally substituted with one or more C_{1-6}alkyl, and

the -C(O)-(3-15 membered heterocyclyl) of R^c or R^d is optionally substituted with one or more halo, -C(O)-C_{1-6}alkoxy, or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, C_{1-6}alkoxy, or C_{3-10}cycloalkyl,

(h) -O-R^e, wherein R^e is C_{1-6}alkyl, C_{6-20}aryl, -C(O)-(3-15 membered heterocyclyl), -C(O)-N-(C_{1-6}alkyl)$_2$, or 5-20 membered heteroaryl, wherein

the C_{1-6}alkyl of R^e is optionally substituted with one or more C_{1-6}alkoxy, wherein the C_{1-6}alkoxy is optionally substituted with one or more C_{2-6}alkynyl,

the C_{6-20}aryl of R^e is optionally substituted with one or more C_{1-6}alkyl, and

the -C(O)-(3-15 membered heterocyclyl) of R^e is optionally substituted with one or more C_{1-6}alkyl, C_{1-6}alkoxy, or -C(O)-C_{1-6}alkoxy, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, C_{1-6}alkoxy, or C_{3-10}cycloalkyl,

(i) -C(O)-R^e, wherein R^e is -NH_2, -OH, or 3-15 membered heterocyclyl, or

(j) -$S(O)_2$-R^f, wherein R^f is C_{1-6}alkyl or 3-15 membered heterocyclyl,

provided that, when R^2 is unsubstituted methyl, then either

(1) Q^1 is 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of Q^1 is substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, -NH_2, C_{3-10}cycloalkyl, or -OH, or

(2) Q^1 is phenyl, wherein the phenyl of Q^1 is substituted with at least one C_{3-6}alkyl or at least one C_{3-10}cycloalkyl, wherein the at least one C_{3-6}alkyl is optionally substituted with one or more halo, and the at least one C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl,

(ii) C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl of R^2 is optionally substituted with one or more R^q, wherein R^q is 5-20 membered heteroaryl or C_{6-20}aryl, wherein the C_{6-20}aryl of R^q is optionally substituted with one or more C_{1-6}alkoxy,

(iii) 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^2 is optionally substituted with one or more halo, oxo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, or 5-20 membered heteroaryl,

(iv) 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^2 is optionally substituted with one or more R^s, wherein R^s is C_{1-6}alkyl, C_{1-6}alkoxy, -NH-C(O)-C_{1-6}alkyl, C_{6-20}aryl, or 5-20 membered heteroaryl, wherein the C_{1-6}alkyl of R^s is optionally substituted with one or more C_{1-6}alkoxy,

(v) -N(R^g)(R^h), wherein R^g and R^h are independently H or C_{1-6}alkyl,

(vi) -C(O)-R^j, wherein R^j is C_{3-10}cycloalkyl, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, or -NH(5-20 membered heteroaryl), and

(vii) C_{6-20}aryl, wherein the C_{6-20}aryl of R^2 is optionally substituted with one or more 5-20 membered heteroaryl or -O-R^p, wherein R^p is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^p is optionally substituted with one or more -C(O)-C_{1-6}alkyl.

[0267] Embodiment 2. The compound of embodiment 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Q^1 is 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of Q^1 is optionally substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, -NH_2, or C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl is optionally substituted with one or more C_{1-6}alkyl or halo.

[0268] Embodiment 3. The compound of embodiment 1 or embodiment 2, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Q^1 is 5-6 membered heteroaryl, wherein the 5-6 membered heteroaryl of Q^1 is optionally substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, -NH_2, or C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl is optionally substituted with one or more C_{1-6}alkyl or halo.

[0269] Embodiment 4. The compound of any one of embodiments 1-3, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing,

wherein Q^1 is pyridinyl, wherein the pyridinyl of Q^1 is optionally substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, -NH_2, or C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl is optionally substituted with one or more C_{1-6}alkyl or halo.

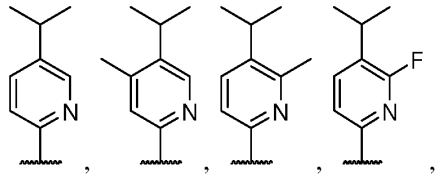
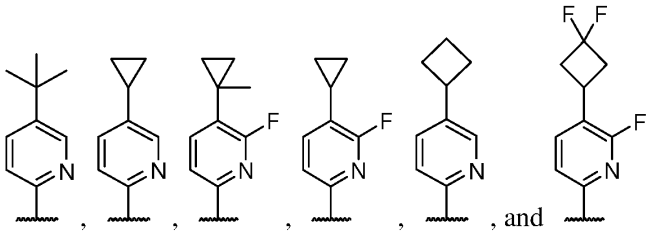
[0270] Embodiment 5. The compound of any one of embodiments 1-4, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Q^1 is 2-pyridinyl or 3-pyridinyl, wherein the 2-pyridinyl or 3-pyridinyl of Q^1 is optionally substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, -NH_2, or C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl is optionally substituted with one or more C_{1-6}alkyl or halo.

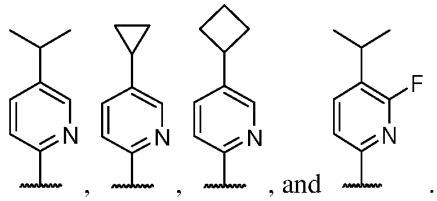
[0271] Embodiment 6. The compound of any one of embodiments 1-5, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Q^1 is 2-pyridinyl, wherein the 2-pyridinyl of Q^1 is optionally substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, -NH_2, or C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl is optionally substituted with one or more C_{1-6}alkyl or halo.

[0272] Embodiment 7. The compound of any one of embodiments 1-6, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Q^1 is 2-pyridinyl, wherein the 2-pyridinyl of Q^1 is optionally substituted with one or more halo, C_{1-6}alkyl, or C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl is optionally substituted with one or more C_{1-6}alkyl or halo.

[0273] Embodiment 8. The compound of any one of embodiments 1-7, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Q^1 is 2-pyridinyl, wherein the 2-pyridinyl of Q^1 is optionally substituted with one or more fluoro, chloro, methyl, *iso*-propyl, *tert*-butyl, cyclopropyl, or cyclobutyl, wherein the cyclopropyl and cyclobutyl are independently optionally substituted with one or more methyl or fluoro.

[0274] Embodiment 9. The compound of any one of embodiments 1-8, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing,

wherein Q^1 is selected from the group consisting of  ,  , and .

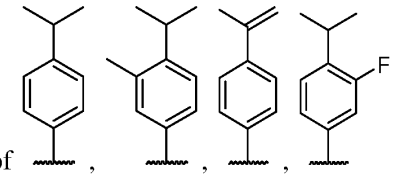
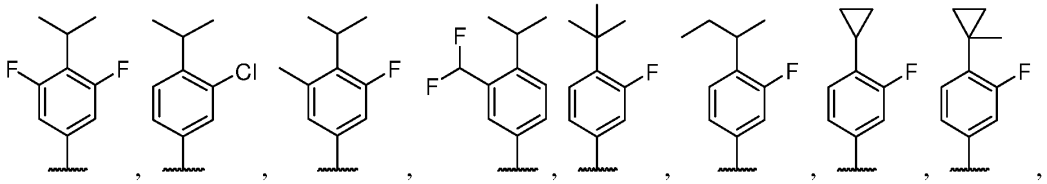
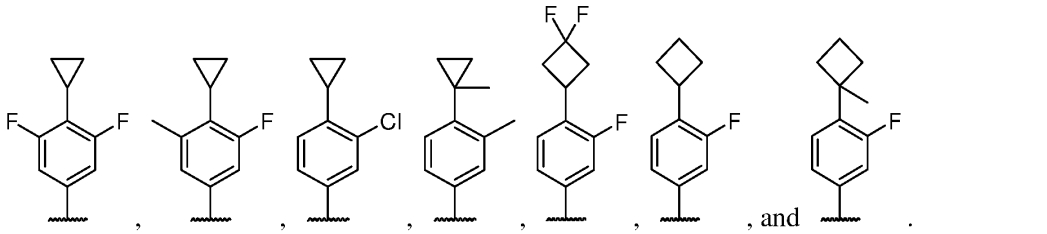
[0275] Embodiment 10. The compound of any one of embodiments 1-9, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Q^1 is selected from the group consisting of  , , , and .

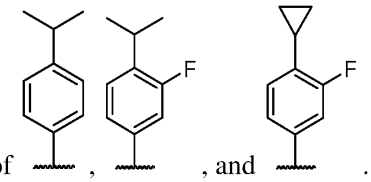
[0276] Embodiment 11. The compound of embodiment 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Q^1 is phenyl, wherein the phenyl of Q^1 is substituted with one or more halo, C_{1-6}alkyl, C_{2-6} alkenyl, -NH_2, -NH-C(O)-(C_{1-6}alkyl), -NH-C(O)-(3-15 membered heterocyclyl), or C_{3-10}cycloalkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, and the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl.

[0277] Embodiment 12. The compound of embodiment 1 or embodiment 11, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Q^1 is phenyl, wherein the phenyl of Q^1 is substituted with one or more halo, C_{1-6}alkyl, C_{2-6} alkenyl, or C_{3-10}cycloalkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, and the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl.

[0278] Embodiment 13. The compound of any one of embodiments 1, 11 and 12, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing,

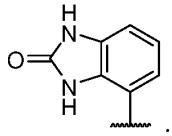
wherein Q^1 is phenyl, wherein the phenyl of Q^1 is substituted with one or more fluoro, chloro, methyl, *iso*-propyl, *sec*-butyl, *tert*-butyl, prop-1-en-2-yl, cyclopropyl, or cyclobutyl, wherein the methyl, *iso*-propyl, *sec*-butyl, and *tert*-butyl are independently optionally substituted with one or more halo, and the cyclopropyl and cyclobutyl are independently optionally substituted with one or more fluoro or methyl.

[0279] Embodiment 14. The compound of any one of embodiments 1 and 11-13, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Q^1 is selected from the group consisting of  ,  ,  , and .

[0280] Embodiment 15. The compound of any one of embodiments 1 and 11-13, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Q^1 is selected from the group consisting of  , , and .

[0281] Embodiment 16. The compound of embodiment 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Q^1 is 3-

15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of Q^1 is optionally substituted with one or more oxo.

[0282] Embodiment 17. The compound of embodiment 1 or embodiment 16, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Q^1 is  .

[0283] Embodiment 18. The compound of any one of embodiments 1-17, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X^1, X^2, X^3, X^4, and X^5 are each H.

[0284] Embodiment 19. The compound of any one of embodiments 1-18, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^m is H, R^n is H, and R^k is H, halo, -OH, $-NH_2$, or -NH-C(O)C_{1-6}alkyl.

[0285] Embodiment 20. The compound of any one of embodiments 1-19, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^m is H, R^n is H, and R^k is halo, -OH, or $-NH_2$.

[0286] Embodiment 21. The compound of any one of embodiments 1-20, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^m is H, R^n is H, and R^k is halo.

[0287] Embodiment 22. The compound of any one of embodiments 1-21, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^m is H, R^n is H, and R^k is fluoro.

[0288] Embodiment 23. The compound of any one of embodiments 1-18, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^k is taken together with either R^m or R^n, and the atoms to which they are attached, to form cyclopropyl.

[0289] Embodiment 24. The compound of any one of embodiments 1-23, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is H.

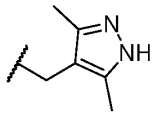
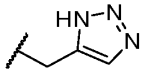
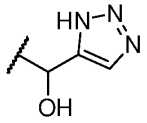
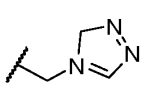
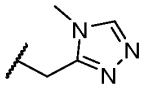
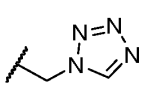
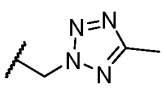
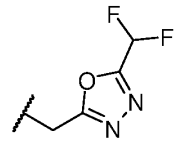
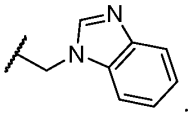
[0290] Embodiment 25. The compound of any one of embodiments 1-24, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is optionally substituted with one or more R^a.

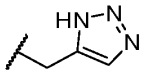
[0291] Embodiment 26. The compound of any one of embodiments 1-25, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^a is optionally substituted with one or more R^b.

[0292] Embodiment 27. The compound of any one of embodiments 1-26, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl of R^a is optionally substituted with one or more R^b.

[0293] Embodiment 28. The compound of any one of embodiments 1-27, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl of R^a is optionally substituted with one or more C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, $-NH_2$, $-NH(C_{1-6}alkyl)$, $-N(C_{1-6}alkyl)_2$, $-NH-C(O)C_{1-6}$alkyl, or $-NH-C(O)-C_{1-6}$alkoxy.

[0294] Embodiment 29. The compound of any one of embodiments 1-28, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl of R^a is optionally substituted with one or more methyl, wherein the methyl is optionally substituted with one or more fluoro.

[0295] Embodiment 30. The compound of any one of embodiments 1-29, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  , and  .

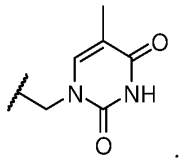
[0296] Embodiment 31. The compound of any one of embodiments 1-30, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is  .

[0297] Embodiment 32. The compound of any one of embodiments 1-25, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^a is optionally substituted with one or more R^c.

[0298] Embodiment 33. The compound of any one of embodiments 1-25 and 32, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^a is optionally substituted with one or more R^c.

[0299] Embodiment 34. The compound of any one of embodiments 1-25, 32, and 33, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-8 membered heterocyclyl, wherein the 3-8 membered heterocyclyl of R^a is optionally substituted with one or more R^c.

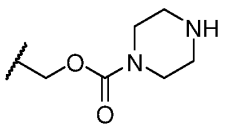
[0300] Embodiment 35. The compound of any one of embodiments 1-25 and 32-34, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-8 membered heterocyclyl, wherein the 3-8 membered heterocyclyl of R^a is optionally substituted with one or more oxo or C_{1-6}alkyl.

[0301] Embodiment 36. The compound of any one of embodiments 1-25 and 32-35, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is  .

[0302] Embodiment 37. The compound of any one of embodiments 1-25, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e.

[0303] Embodiment 38. The compound of any one of embodiments 1-25 and 37, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e.

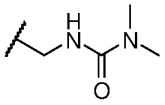
[0304] Embodiment 39. The compound of any one of embodiments 1-25, 37, and 38, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e, wherein R^e is -C(O)-(3-15 membered heterocyclyl).

[0305] Embodiment 40. The compound of any one of embodiments 1-25 and 37-39, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is  .

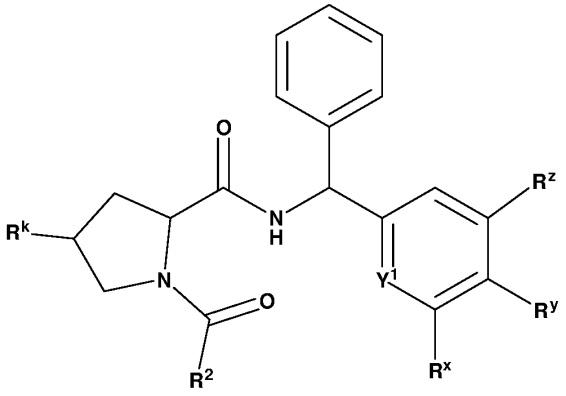
[0306] Embodiment 41. The compound of any one of embodiments 1-25, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is $-N(R^c)(R^d)$.

[0307] Embodiment 42. The compound of any one of embodiments 1-25 and 41, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is $-N(R^c)(R^d)$.

[0308] Embodiment 43. The compound of any one of embodiments 1-25, 41, and 42, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is $-N(R^c)(R^d)$, wherein one of R^c and R^d is H, and the other of R^c and R^d is $-C(O)-N(C_{1-6}alkyl)_2$.

[0309] Embodiment 44. The compound of any one of embodiments 1-25 and 41-43, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is  .

[0310] Embodiment 45. The compound of embodiment 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is of formula (I-A):



(I-A),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein

Y^1 is CH or N;

R^x and R^z are independently H, halo, C_{1-6}alkyl, or $-NH_2$, wherein, when Y^1 is CH, the C_{1-6}alkyl of R^x or R^z may be optionally substituted with one or more halo; and

R^y is (i) C_{1-6}alkyl, (ii) C_{2-6}alkenyl, or (iii) C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl.

[0311] Embodiment 46. The compound of embodiment 1 or embodiment 45, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^x is H, fluoro, or methyl, and

R^y is (i) isopropyl, or (ii) C_{3-4}cycloalkyl, wherein the C_{3-4}cycloalkyl is optionally substituted with one or more fluoro or methyl.

[0312] Embodiment 47. The compound of any one of embodiments 1, 45, and 46, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^k is H or halo.

[0313] Embodiment 48. The compound of any one of embodiments 1-24, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is optionally substituted with one or more R^a.

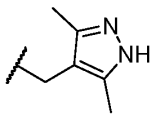
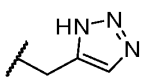
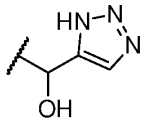
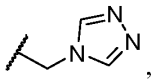
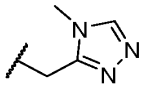
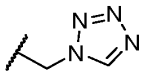
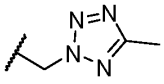
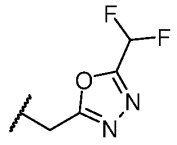
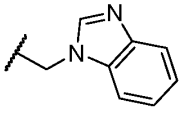
[0314] Embodiment 49. The compound of any one of embodiments 1 and 45-48, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of R^a is optionally substituted with one or more R^b.

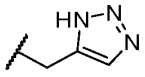
[0315] Embodiment 50. The compound of any one of embodiments 1 and 45-49, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl of R^a is optionally substituted with one or more R^b.

[0316] Embodiment 51. The compound of any one of embodiments 1 and 45-50, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl of R^a is optionally substituted with one or more C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, $-NH_2$, $-NH(C_{1-6}alkyl)$, $-N(C_{1-6}alkyl)_2$, -NH-C(O)C_{1-6}alkyl, or -NH-C(O)-C_{1-6}alkoxy.

[0317] Embodiment 52. The compound of any one of embodiments 1 and 45-51, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -OH or 5-10 membered heteroaryl, wherein the 5-10 membered heteroaryl of R^a is optionally substituted with one or more methyl, wherein the methyl is optionally substituted with one or more fluoro.

[0318] Embodiment 53. The compound of any one of embodiments 1 and 45-52, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing,

wherein R^2 is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  , and  .

[0319] Embodiment 54. The compound of any one of embodiments 1 and 45-53, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is  .

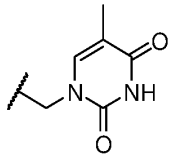
[0320] Embodiment 55. The compound of any one of embodiments 1 and 45-48, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is $C_{1\text{-}6}$alkyl, wherein the $C_{1\text{-}6}$alkyl of R^2 is substituted with one or more R^a, wherein R^a is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^a is optionally substituted with one or more R^c.

[0321] Embodiment 56. The compound of any one of embodiments 1, 45-48, and 55, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^a is optionally substituted with one or more R^c.

[0322] Embodiment 57. The compound of any one of embodiments 1, 45-48, 55, and 56, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-8 membered heterocyclyl, wherein the 3-8 membered heterocyclyl of R^a is optionally substituted with one or more R^c.

[0323] Embodiment 58. The compound of any one of embodiments 1, 45-48, and 55-57, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the

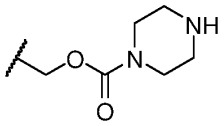
foregoing, wherein R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-8 membered heterocyclyl, wherein the 3-8 membered heterocyclyl of R^a is optionally substituted with one or more oxo or C_{1-6}alkyl.

[0324] Embodiment 59. The compound of any one of embodiments 1, 45-48, and 55-58, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is  .

[0325] Embodiment 60. The compound of any one of embodiments 1 and 45-48, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e.

[0326] Embodiment 61. The compound of any one of embodiments 1, 45-48, and 60, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e.

[0327] Embodiment 62. The compound of any one of embodiments 1, 45-48, 60, and 61, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e, wherein R^e is -C(O)-(3-15 membered heterocyclyl).

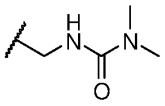
[0328] Embodiment 63. The compound of any one of embodiments 1, 45-48, and 60-62, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is  .

[0329] Embodiment 64. The compound of any one of embodiments 1, 45-48, and 60-63, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the

foregoing, wherein R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is $-N(R^c)(R^d)$.

[0330] Embodiment 65. The compound of any one of embodiments 1, 45-48, and 60-64, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is $-N(R^c)(R^d)$.

[0331] Embodiment 66. The compound of any one of embodiments 1, 45-48, and 60-65, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is $-N(R^c)(R^d)$, wherein one of R^c and R^d is H, and the other of R^c and R^d is $-C(O)-N(C_{1-6}alkyl)_2$.

[0332] Embodiment 67. The compound of any one of embodiments 1, 45-48, and 60-66, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is  .

[0333] Embodiment 68. The compound of embodiment 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, is selected from Table 1.

[0334] Embodiment 69. A pharmaceutical composition comprising (i) a compound of any one of embodiments 1-68, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and (ii) one or more pharmaceutically acceptable excipients.

[0335] Embodiment 70. A method of modulating GYS1 in a cell, comprising exposing the cell to a composition comprising an effective amount of a compound of any one or

embodiments 1-68, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition of embodiment 69.

[0336] Embodiment 71. A method of inhibiting GYS1 in a cell, comprising exposing the cell to a composition comprising an effective amount of a compound of any one or embodiments 1-68, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition of embodiment 69.

[0337] Embodiment 72. A method of reducing tissue glycogen stores in an individual in need thereof, comprising administering to the individual an effective amount of a compound of any one of embodiments 1-68, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition of embodiment 69.

[0338] Embodiment 73. A method of treating a GYS1-mediated disease, disorder, or condition in an individual in need thereof, comprising administering to the individual an effective amount of a compound of any one of embodiments 1-68, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition of embodiment 69.

[0339] Embodiment 74. The method of embodiment 73, wherein the disease, disorder, or condition is a glycogen storage disorder (GSD).

[0340] Embodiment 75. The method of embodiment 73 or embodiment 74, wherein the disease, disorder, or condition is selected from the group consisting of Pompe disease, Cori disease (GSD III), adult polyglucosan body disease (APBD), and Lafora disease.

[0341] Embodiment 76. The method of any one of embodiments 73-75, wherein the disease, disorder, or condition is Pompe disease.

[0342] Embodiment 77. The method of embodiment 73, wherein the disease, disorder, or condition is cancer.

[0343] Embodiment 78. The method of embodiment 73 or embodiment 77, wherein the disease, disorder, or condition is selected from the group consisting of Ewing sarcoma (ES),

clear cell renal cell carcinoma (ccRCC), glycogen rich clear cell carcinoma (GRCC) breast cancer, non-small-cell lung carcinoma (NSCLC), and acute myeloid leukemia (AML).

[0344] Embodiment 79. The method of embodiment 73, wherein the individual has a GAA mutation.

[0345] Embodiment 80. The method of embodiment 79, wherein the GAA mutation is a loss-of-function mutation.

[0346] Embodiment 81. A kit, comprising (i) a compound of any one of embodiments 1-68, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition of embodiment 69, and (ii) instructions for use in treating an GYS1-mediated disease, disorder, or condition in an individual in need thereof.

[0347] Embodiment 82. The kit of embodiment 81, wherein the disease, disorder, or condition is a glycogen storage disorder (GSD).

[0348] Embodiment 83. The kit of embodiment 81 or embodiment 82, wherein the disease, disorder, or condition is selected from the group consisting of Pompe disease, Cori disease (GSD III), adult polyglucosan body disease (APBD), and Lafora disease.

[0349] Embodiment 84. The kit of any one of embodiments 81-83, wherein the disease, disorder, or condition is Pompe disease.

[0350] Embodiment 85. The kit of embodiment 81, wherein the disease, disorder, or condition is cancer.

[0351] Embodiment 86. The kit of embodiment 81 or embodiment 85, wherein the disease, disorder, or condition is selected from the group consisting of Ewing sarcoma (ES), clear cell renal cell carcinoma (ccRCC), glycogen rich clear cell carcinoma (GRCC) breast cancer, non-small-cell lung carcinoma (NSCLC), and acute myeloid leukemia (AML).

[0352] Embodiment 87. The kit of embodiment 81, wherein the individual has a GAA mutation.

[0353] Embodiment 88. The kit of embodiment 87, wherein the GAA mutation is a loss-of-function mutation.

[0354] Embodiment 89. A method of modulating GYS1 in a cell, comprising exposing the cell to a composition comprising an effective amount of a GYS1 modulator, or a pharmaceutical composition comprising a GYS1 modulator.

[0355] Embodiment 90. A method of inhibiting GYS1 in a cell, comprising exposing the cell to a composition comprising an effective amount of a GYS1 inhibitor, or a pharmaceutical composition comprising a GYS1 inhibitor.

[0356] Embodiment 91. A method of reducing tissue glycogen stores in an individual in need thereof, comprising administering to the individual an effective amount of a GYS1 inhibitor, or a pharmaceutical composition comprising a GYS1 inhibitor.

[0357] Embodiment 92. A method of treating a GYS1-mediated disease, disorder, or condition in an individual in need thereof, comprising subjecting the individual to glycogen substrate reduction therapy.

[0358] Embodiment 93. The method of embodiment 92, wherein the disease, disorder, or condition is a glycogen storage disorder (GSD).

[0359] Embodiment 94. The method of embodiment 92 or embodiment 93, wherein the disease, disorder, or condition is selected from the group consisting of Pompe disease, Cori disease (GSD III), adult polyglucosan body disease (APBD), and Lafora disease.

[0360] Embodiment 95. The method of any one of embodiments 92-94, wherein the disease, disorder, or condition is Pompe disease.

[0361] Embodiment 96. The method of embodiment 92, wherein the disease, disorder, or condition is cancer.

[0362] Embodiment 97. The method of embodiment 92 or embodiment 96, wherein the disease, disorder, or condition is selected from the group consisting of Ewing sarcoma (ES),

clear cell renal cell carcinoma (ccRCC), glycogen rich clear cell carcinoma (GRCC) breast cancer, non-small-cell lung carcinoma (NSCLC), and acute myeloid leukemia (AML).

[0363] Embodiment 98. The method of embodiment 92, wherein the individual has a GAA mutation.

[0364] Embodiment 99. The method of embodiment 98, wherein the GAA mutation is a loss-of-function mutation.

[0365] Embodiment 100. The method of any one of embodiments 89-91 wherein the GYS1 inhibitor is selective for GYS1 over GYS2.

[0366] Embodiment 101. The method of embodiment 100, wherein the GYS1 inhibitor is greater than 500 or 1,000 or 1,500 or 1,700-fold selective for GYS1 over GYS2.

[0367] Embodiment 102. The method of any one of embodiments 92-99 wherein the glycogen substrate reduction therapy comprises administering to the individual a GYS1 inhibitor.

[0368] Embodiment 103. The method of embodiment 102, wherein the GYS1 inhibitor is a small molecule.

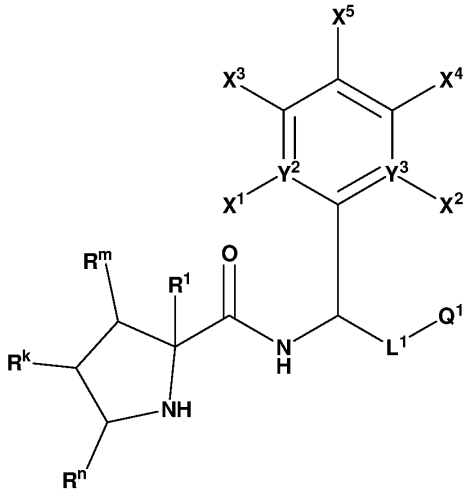
[0369] Embodiment 104. The method of embodiment 103, wherein the GYS1 inhibitor is selective for GYS1 over GYS2.

[0370] Embodiment 105. The method of embodiment 104, wherein the GYS1 inhibitor is greater than 500 or 1,000 or 1,500 or 1,700-fold selective for GYS1 over GYS2.

METHODS OF PREPARING

[0371] The present disclosure further provides processes for preparing the compounds of present invention. In some aspect, provided herein are processes of preparing a compound of formula (I') or formula (I), or any embodiment or variation thereof, such as a compound of formula (I-A), (I-B), (I-C), (I-D), (I-D1), (I-D2), (I-E), (I-F), (I-G), (I-H) or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing.

[0372] In some embodiments, a process for preparing a compound of formula (I') or formula (I), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, comprises reacting a compound of formula (I'-1):



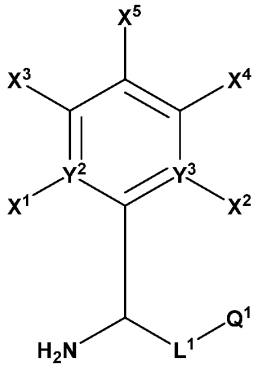
(I'-1),

or a salt thereof, with a compound of formula R^2COOH in the presence of a coupling reagent.

[0373] In some embodiments, the coupling reagent comprises EDCCl, TCFH, or T3P. In some embodiments, the process further comprises the presence of a base. In some embodiments, the base comprises an amine. In some embodiments, the amine is DMAP, NMM, or a trialkylamine.

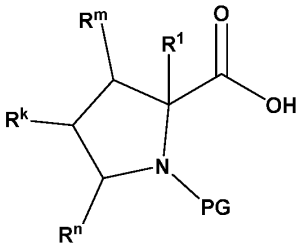
[0374] In some embodiments, a process for preparing a compound of formula (I'), or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, comprises

(a) reacting a compound of formula (I'-2):



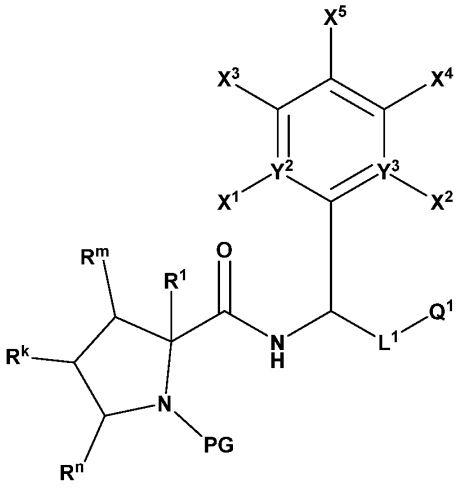
(I'-2),

or a salt thereof, with a compound of formula (I'-3):



(I'-3), wherein PG is a protecting group,

in the presence of a coupling reagent to provide a compound of formula I'-4:



(I'-4),

followed by

(b) contacting the compound of formula (I'-4) with an acid to provide a compound of formula (I').

[0375] In some embodiments, the protecting group is an oxycarbonyl group. In some embodiments the protecting group is a tert-butoxycarbonyl.

[0376] In some embodiments, the coupling reagent comprises EDCCl, TCFH, or T3P. In some embodiments, the process further comprises the presence of a base. In some embodiments, the base comprises an amine. In some embodiments, the amine is DMAP, NMM, or a trialkylamine.

[0377] In some embodiments the acid is HCl or TFA.

EXAMPLES

[0378] The following synthetic reaction schemes, which are detailed in the Schemes and Examples, are merely illustrative of some of the methods by which the compounds of the present disclosure, or an embodiment or aspect thereof, can be synthesized. Various modifications to these synthetic reaction schemes can be made, as will be apparent to those of ordinary skill in the art.

[0379] The starting materials and the intermediates of the synthetic reaction schemes can be isolated and purified if desired using conventional techniques, including, but not limited to, filtration, distillation, crystallization, chromatography, and the like. Such materials can be characterized using conventional means, including physical constants and spectral data.

[0380] Although certain exemplary embodiments are depicted and described herein, the compounds of the present disclosure, or any variation or embodiment thereof, may be prepared using appropriate starting materials according to the methods described generally herein and/or by methods available to one of ordinary skill in the art.

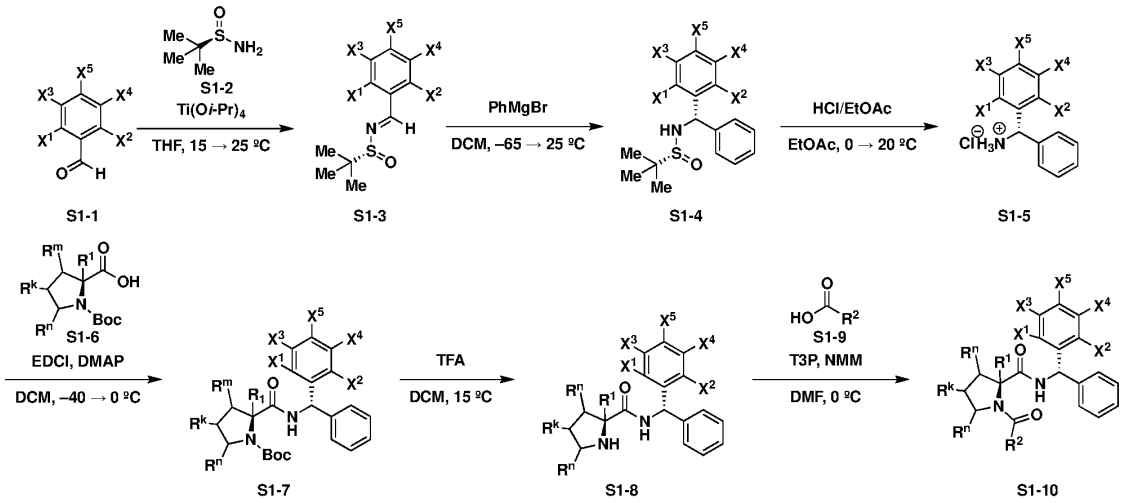
Synthetic Examples

[0381] As depicted in the Schemes and Examples below, in certain exemplary embodiments, compounds of formula (I), or any variation or embodiment thereof, as described

elsewhere herein, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, are prepared according to the general procedures. The general methods below, and other methods known to synthetic chemists of ordinary skill in the art, can be applied to all formulae, variations, embodiments, and species described herein.

Schemes

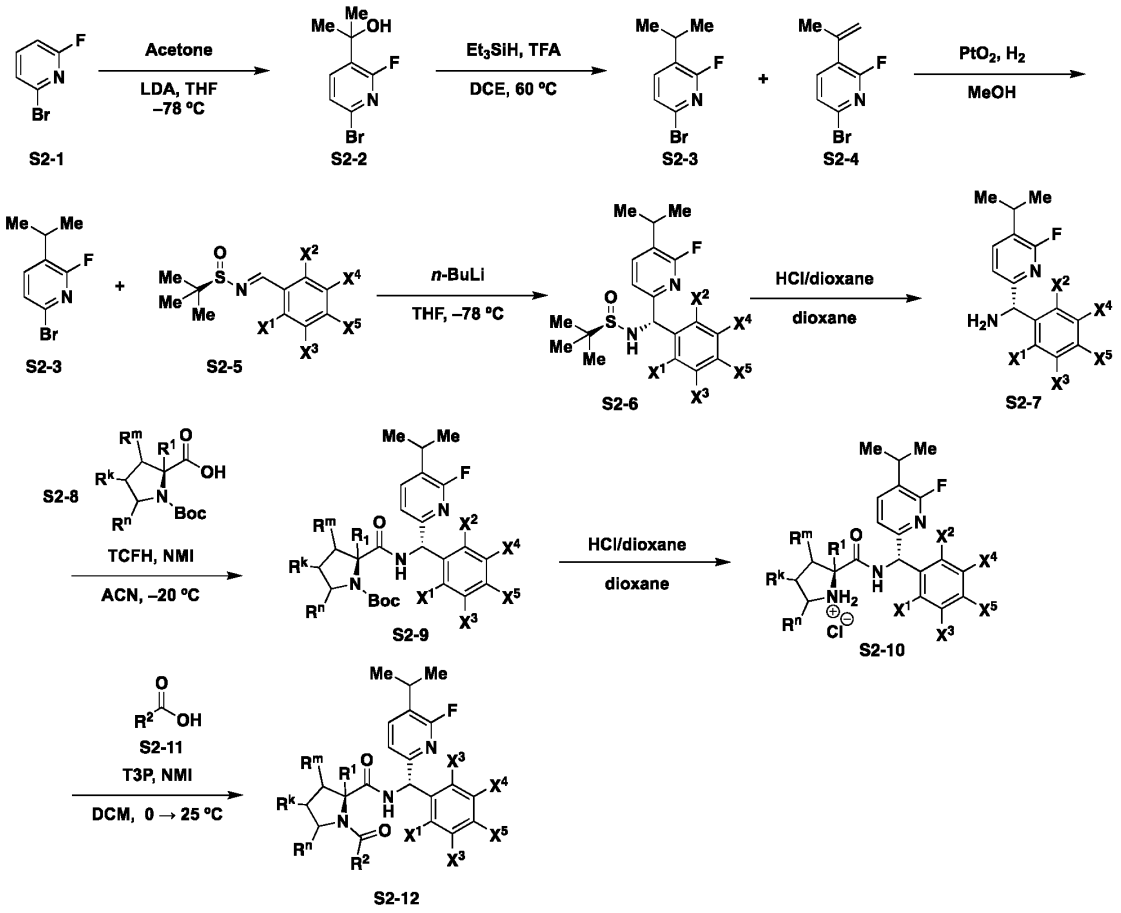
Scheme 1



[0382] Compounds of the formula **S1-10** may be prepared according to the general synthetic scheme outlined in **Scheme 1.**

[0383] Condensation of a chiral sulfinamide such as **S1-2** with an aldehyde such as **S1-1** provides sulfinimine **S1-3**. Addition of a reagent such as phenylmagnesium bromide at low temperature, followed by warming to ambient temperature provides benzhydryl sulfinamide **S1-4**. Sulfinamide **S1-3** can be converted to the corresponding amine hydrochloride salt upon treatment with HCl in a solvent such as EtOAc. Amide bond formation between **S1-5** and a substituted proline analog such as **S1-6** may be achieved with a carbodiimide reagent such as EDCI and DMAP as a catalyst. Removal of the *N*-Boc group of **S1-7** via treatment with a protic acid such as trifluoroacetic acid gives rise to amines such as **S1-8.** Proline amides such as **S1-10** may then be generated by coupling with a carboxylic acid such as **S1-9** using a coupling agent such as T3P and NMM as a base.

Scheme 2

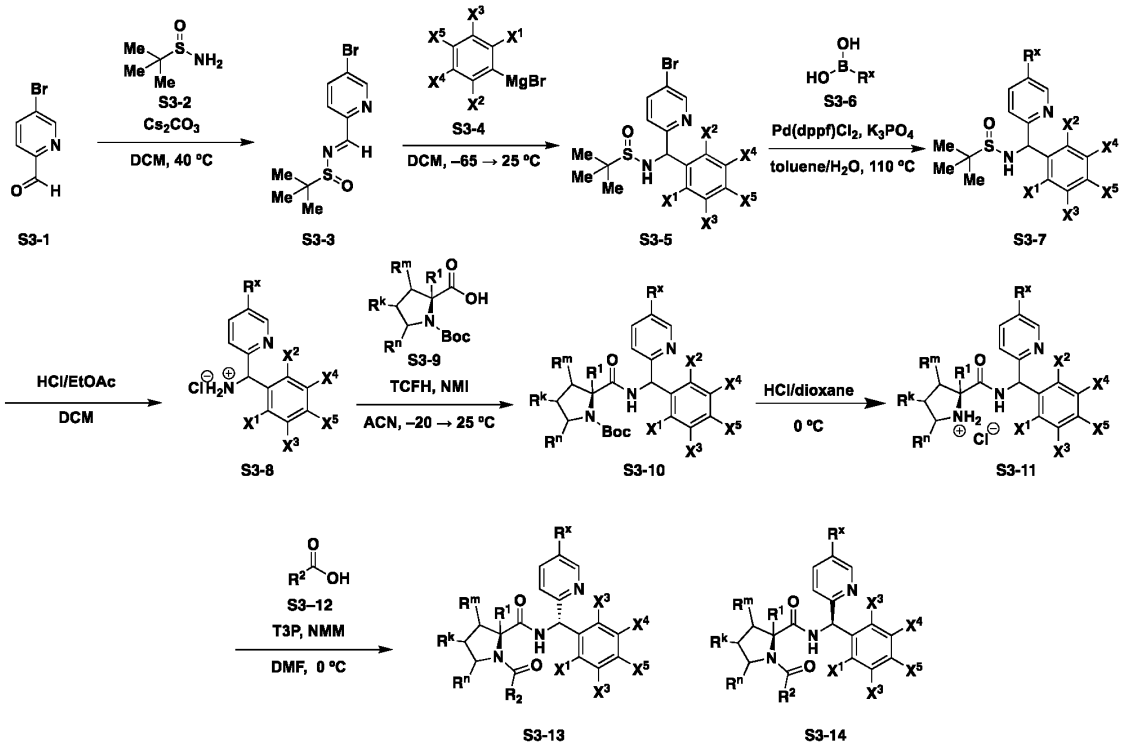


[0384] Compounds of the formula **S2-12** may be prepared according to the general synthetic scheme outlined in **Scheme 2.**

[0385] Directed *ortho*-metalation of pyridine **S2-1** with an amide base such as LDA in an aprotic solvent such as THF at –78 °C followed by reaction with a ketone such as acetone can generate pyridine **S2-2**. Treatment of **S2-2** with a reducing agent such as triethyl silane and a protic acid such as trifluoroacetic acid generates a mixture of compounds, **S2-3** and **S2-4**. This mixture can be converted to **S2-3** by reduction with hydrogen gas and a metal catalyst such as PtO_2. Metal-halogen exchange can be affected by treatment of **S2-3** at –78 °C with *n*-butyllithium, and the pyridyllithium intermediate may then be reacted with sulfinimine **S2-5** to

generate **S2-6**. Treatment with a protic acid such as HCl generates the amine **S2-7**. Coupling of amine **S2-7** with proline derivative **S2-8** using TCFH and *N*-methylimidazole base gives rise to **S2-9**. Removal of the proline N-Boc group by treatment with a protic acid such as HCl, in an aprotic solvent such as 1,4-dioxane, provides amine **S2-10**. Amine **S2-10** may then be reacted with carboxylic acid **S2-11** to generate **S2-12**, using methods described in **Scheme 1.**

Scheme 3

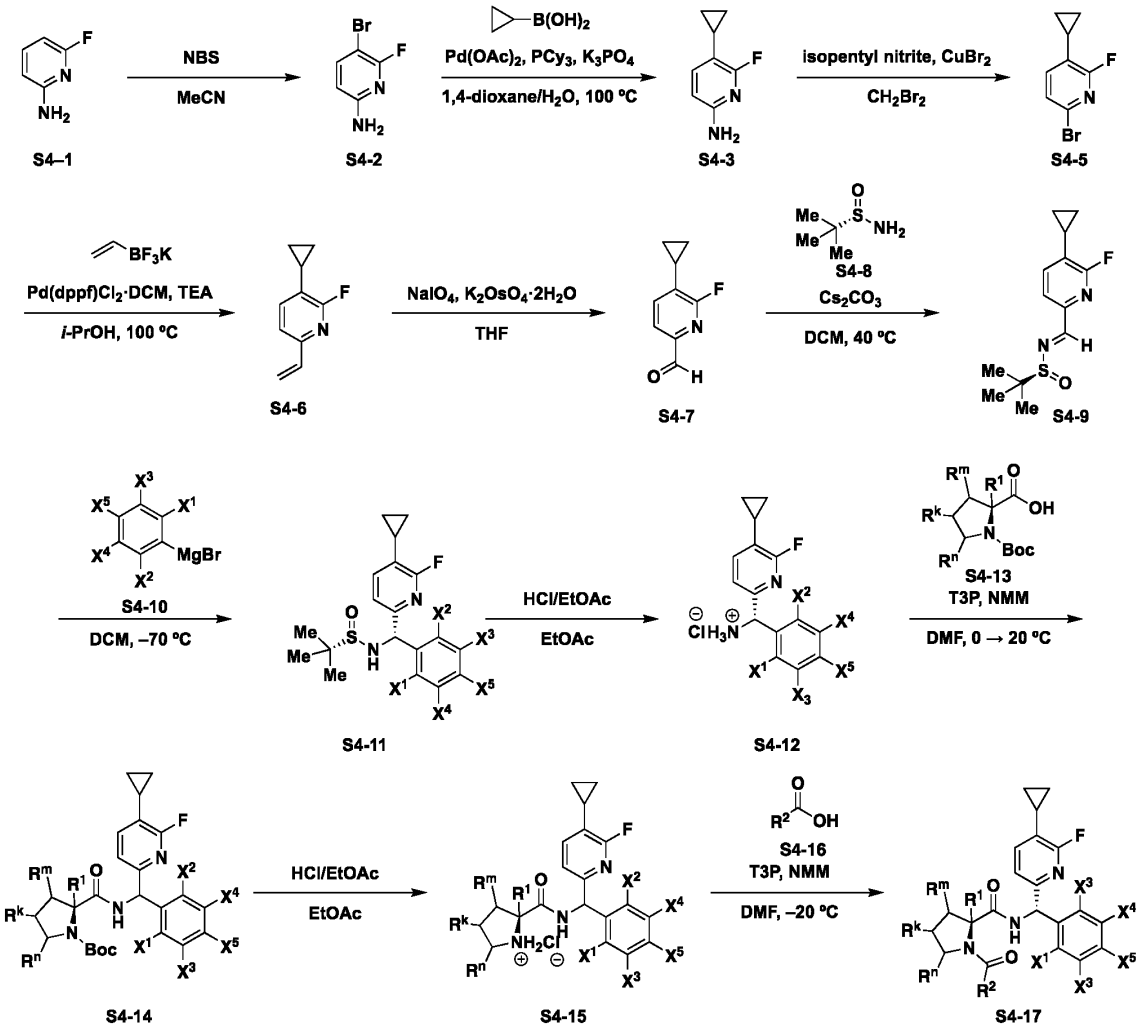


[0386] Compounds of the formulae **S3-13** and **S3-14** may be prepared according to the general synthetic scheme outlined in **Scheme 3.**

[0387] Condensation of racemic sulfinimide **S3-2** with pyridyl aldehyde **S3-1** generates sulfinimine **S3-3**. Reaction with arylmagnesium bromide **S3-4** generates **S3-5**, as a racemate. A Suzuki cross-coupling of **S3-5** with a boronic acid such as **S3-6** using a palladium catalyst such as Pd(dppf)Cl_2 and an inorganic base such as K_3PO_4 generates compound **S3-7**.

Treatment of **S3-7** with a protic acid such as HCl in an aprotic solvent mixture such as EtOAc/DCM provides amine **S3-8**. **S3-8** may then be coupled with carboxylic acid **S3-9** and processed to compounds **S3-13** and **S3-14** using methods outlined in Scheme 1. If desired, mixtures of stereoisomers may be further purified to provide **S3-13** and **S3-14** as single isomers, using methods such as reverse-phase HPLC or chiral SFC.

Scheme 4

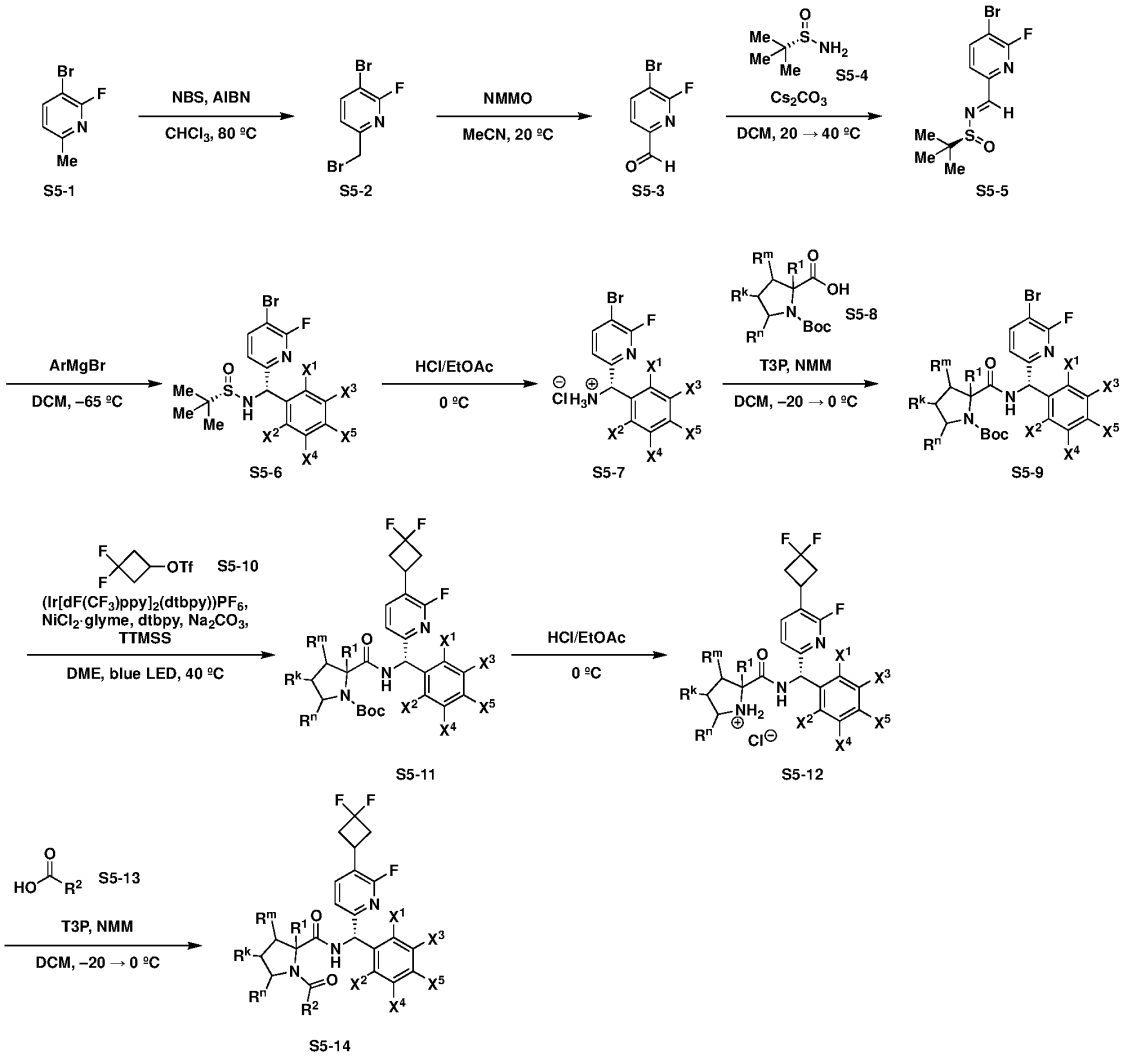


[0388] Compounds of the formula **S4-17** may be prepared according to the general synthetic scheme outlined in **Scheme 4.**

[0389] Reaction of pyridine **S3-1** with an electrophilic brominating agent such as NBS gives pyridine **S4-2**. Suzuki cross-coupling with cyclopropylboronic acid, using a catalyst such as palladium acetate, a ligand such as tricyclohexyl phosphine, and an inorganic base such K_3PO_4 in a mixed solvent system such as 1,4-dioxane and water, provides **S4-3**. Conversion of **S4-3** to pyridyl bromide **S4-5** can be achieved with a Sandmeyer reaction under the action of

isopentyl nitrite and cupric bromide in dibromomethane solvent. Suzuki cross coupling of potassium vinyltrifluoroborate with **S4-6** using a palladium catalyst such as $Pd(dppf)Cl_2$ and an inorganic base such as K_3PO_4. Oxidative cleavage of olefin **S4-6** with $NaIO_4$ and $K_2OsO_4{\cdot}2H_2O$ in a THF generates aldehyde **S4-7**. Condensation with sulfinimide **S4-8** generates sulfinimine **S4-9**. Reaction of **S4-9** with aryl Grignard reagent **S4-10** in a solvent such as DCM at low temperature gives rise to **S4-11**. Cleavage of sulfinimide **S4-11** with a HCl in EtOAc generates amine salt **S4-12**. **S4-12** may then be joined with carboxylic acid **S4-13** using a coupling agent such as T3P and a base such as NMM in DMF to produce **S4-14**. Removal of the *N*-Boc group with HCl in EtOAc generates amine **S4-15**, which may then be processed to **S4-17** using the procedure described in **Scheme 3**.

Scheme 5

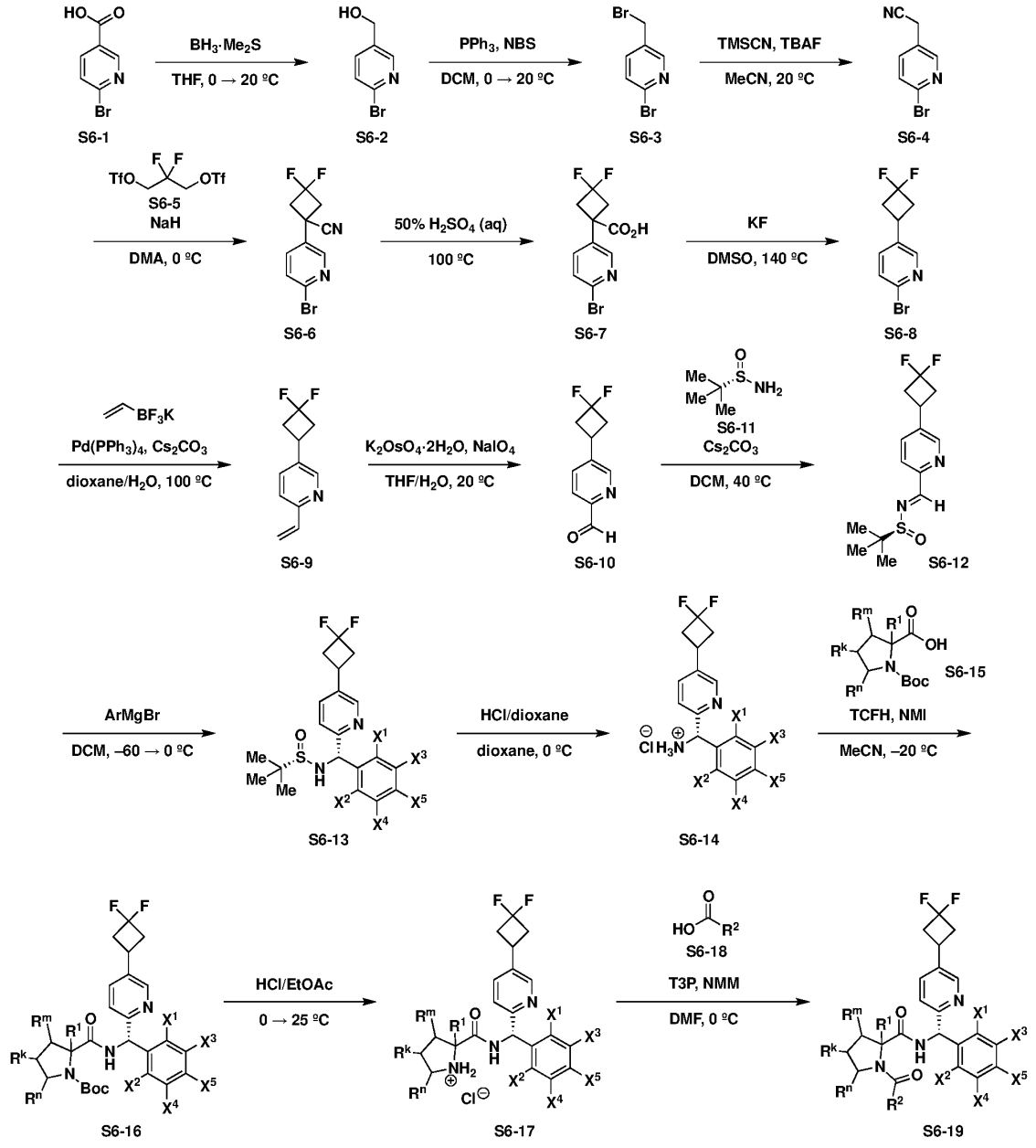


[0390] Compounds of the general formula **S5-14** can be prepared according to the general scheme outlined in **Scheme 5**.

[0391] Radical bromination of **S5-1** with NBS and catalytic AIBN provides **S5-2**. Oxidation under the action NMMO gives aldehyde **S5-3**. Condensation of aldehyde with sulfinimide **S5-4** using an inorganic base such as cesium carbonate provide sulfinimine **S5-5** . Addition of an aryl Grignard reagent such as phenylmagnesium bromide at low temperature provides **S5-6**. Cleavage of the sulfinimide to generate a primary amine salt can be achieved upon treatment with a protic acid such as HCl in a solvent such as EtOAc. Amide bond

formation with proline derivative **S5-8** proceeds as previously described to give **S5-9**. Photoredox coupling of triflate **S5-10** with **S5-9** using an iridium photocatalyst such as $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$, a nickel co-catalyst such as $NiCl_2$•glyme, a ligand such as 4,4-di-*tert*-butyl-2,2-bipyridyl, sodium carbonate as base, and tris(trimethylsilyl)silane and blue LED gives cyclobutyl adduct **S5-11**. Removal of the proline Boc protecting group with HCl in EtOAc, followed by amide bond formation under the action of T3P and NMM in DCM gives compounds of formula **S5-14**.

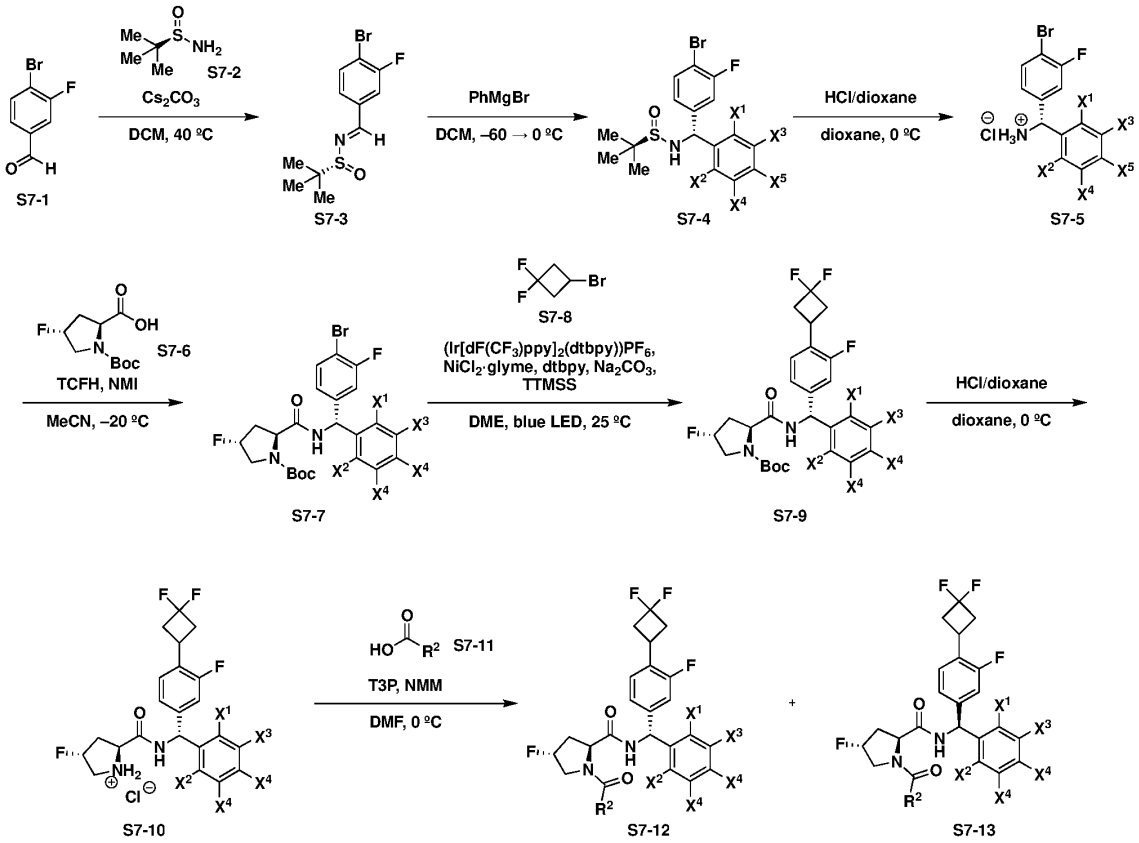
Scheme 6



[0392] Compounds of the general formula **S6-19** can be prepared according to the general scheme outlined in **Scheme 6**.

[0393] Reduction of carboxylic acid **S6-1** with borane-methylsulfide complex gives alcohol **S6-2**. Conversion of **S6-2** to alkyl bromide **S6-3** is achieved by treatment with triphenylphosphine and NBS in a solvent such as DCM. Selective displacement of the primary bromide can be achieved upon reaction with TMSCN and TBAF in acetonitrile to provide **S6-4**. Double alkylation of nitrile **S6-4** with a di-triflate such as **S6-5** gives rise to cyclobutane **S6-6** . Hydrolysis of the nitrile on treatment with sulfuric acid at elevated temperature gives acid **S6-7**. Decarboxylation can be achieved by reaction with KF in DMSO at high temperature to provide **S6-8**. Suzuki-type cross coupling with potassium vinyltrifluoroborate, a palladium catalyst such as tetrakis triphenylphosphine palladium(0) and a base such as cesium carbonate generates **S6-9**. Lemieux-Johnson oxidation of **S6-9** gives aldehyde **S6-10**, which may then be condensed with sulfinimide **S6-11** under conditions previously described to give **S6-12**. Addition of an aryl Grignard reagent such as phenylmagnesium bromide to **S6-12** gives **S6-13**. Generation of primary amine salt **S6-14** may occur upon treatment with HCl in dioxane. Coupling of **S6-14** with proline derivative **S6-15** using chloro-*N*,*N*,*N*',*N*'-tetramethylformamidinium hexafluorophosphate (TCFH) and *N*-methylimidazole (NMI) gives **S6-16**. Boc deprotection and proline amide bond formation as described in **Scheme 5** gives compounds of formula **S6-19**.

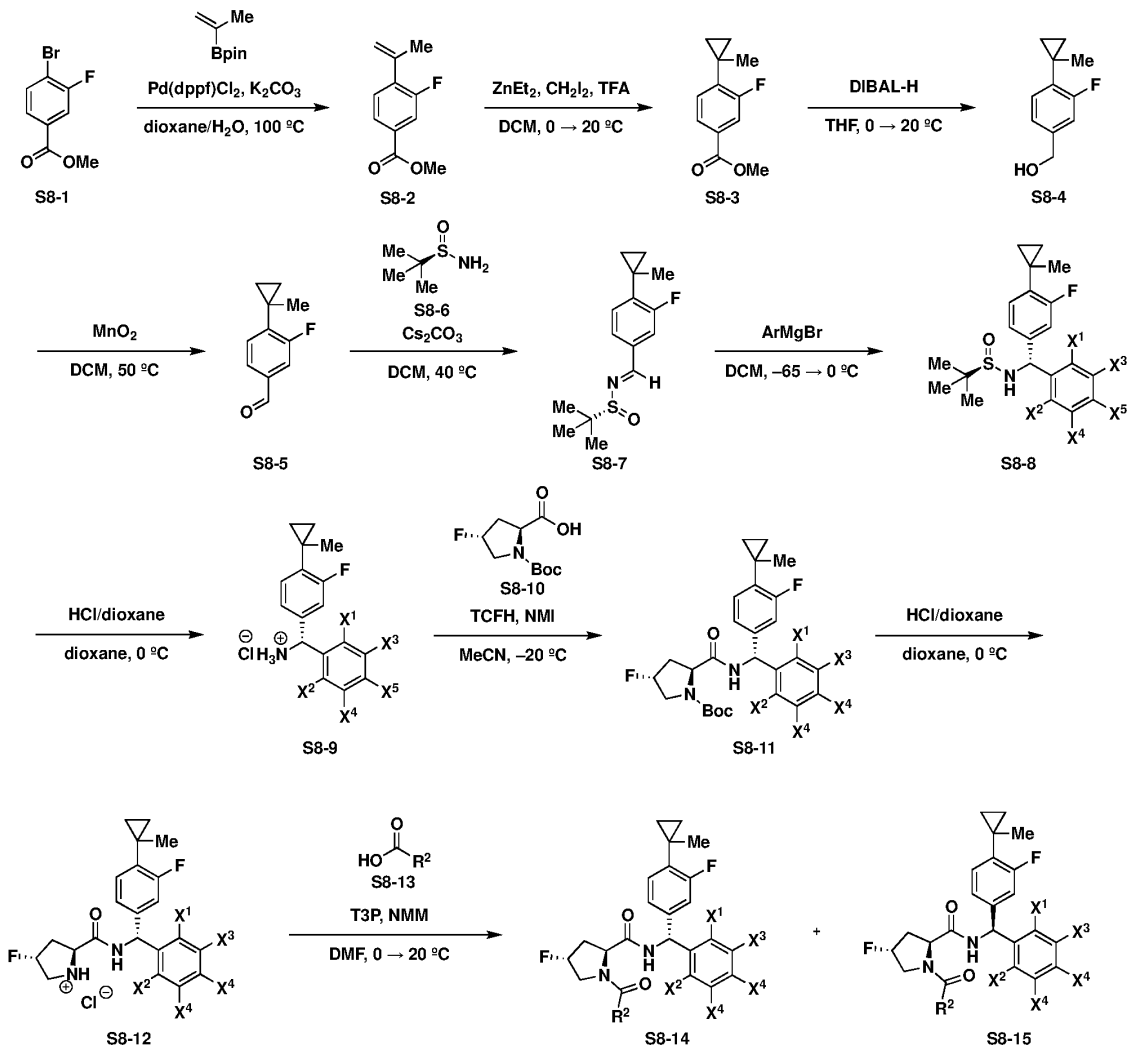
Scheme 7



[0394] Compounds of the general formulae **S7-12** and **S7-13** can be prepared according to the general scheme outlined in **Scheme 7**.

[0395] Condensation of sulfinimide **S7-2** with aldehyde **S7-1** as previously described, followed by addition of an aryl Grignard reagent such as phenylmagnesium bromide, gives **S7-4**. Generation of the amine salt and coupling with proline derivative **S7-6** may be achieved under conditions previously described. Photoredox coupling of cyclobutyl bromide **S7-8** under conditions like those described in **Scheme 5** gives **S7-9**. As previously described, Boc deprotection and amide bond formation generates compounds of formula **S7-12**. A minor stereoisomer such as **S7-13** may also be isolated at this stage.

Scheme 8

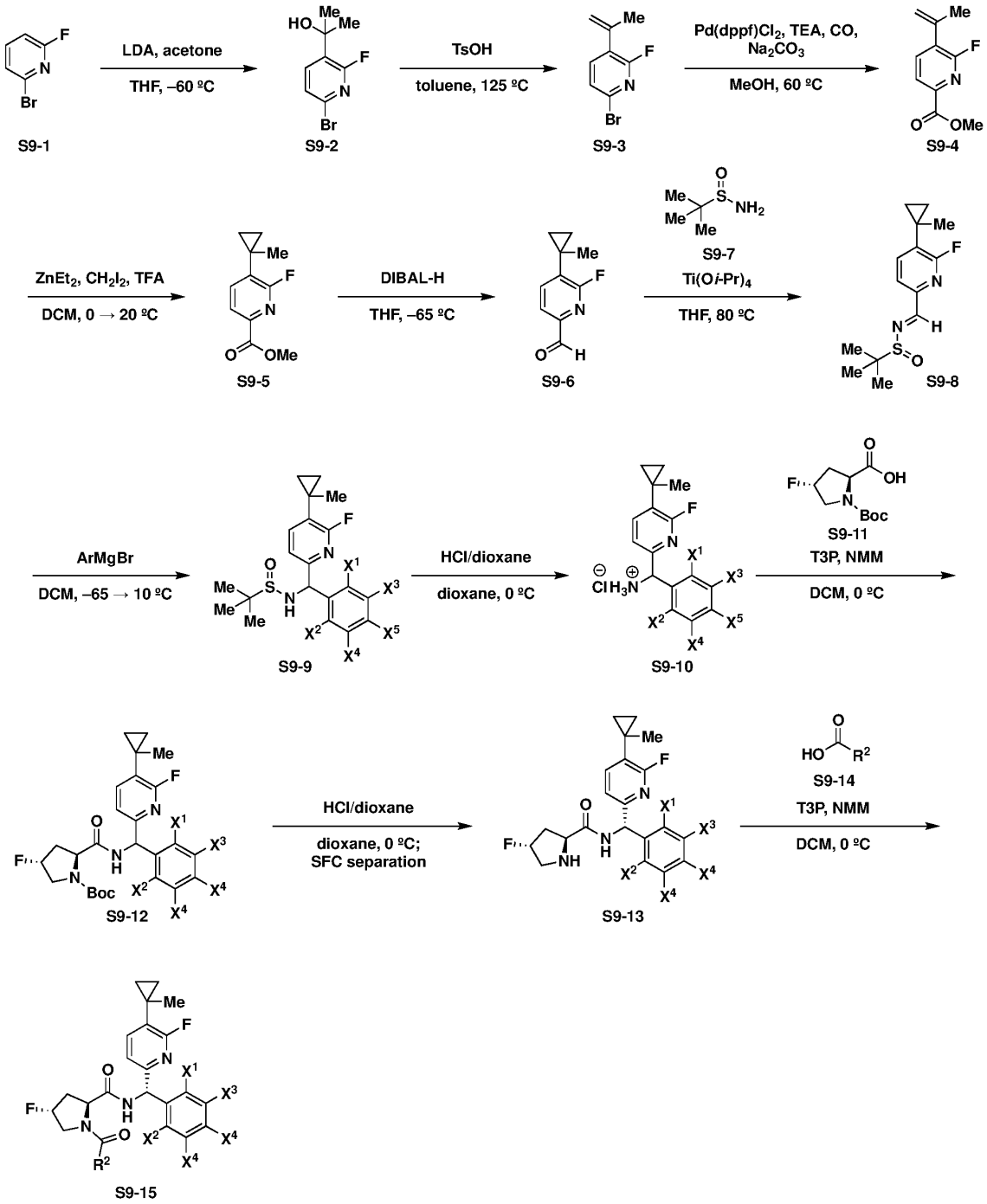


[0396] Compounds of the general formula3 **S8-14** and **S8-15** can be prepared according to the general scheme outlined in **Scheme 8**.

[0397] An alternative generation of benzhydryl fragments begins with cross-coupling of **S8-1** with isopropenylboronic acid pinacol ester with a catalyst such as [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride and potassium carbonate as base in a mixed dioxane/water solvent at elevated temperature gives **S8-2**. Simmons-Smith cyclopropanation gives **S8-3**. Reduction of ester **S8-3** with DIBAL-H, followed by oxidation with MnO_2 gives aldehyde **S8-5**. Aldehyde **S8-5** may then be processed over several steps

previously described to give compounds of formula **S8-14**. Minor diastereomers which could not be separated in previous steps may be isolated at this stage, giving **S8-15**.

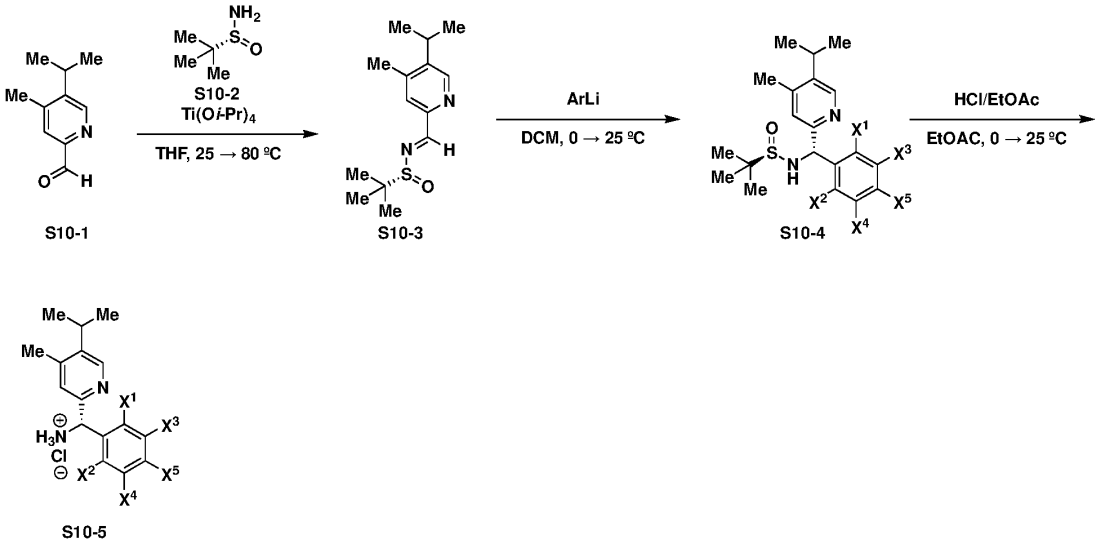
Scheme 9



[0398] Compounds of the general formula **S9-15** can be prepared according to the general scheme outlined in **Scheme 9**.

[0399] An alternative approach to cyclopropane containing analogs begins with directed metalation of **S9-1** with LDA and reaction with acetone to generate **S9-2**. Dehydration under the action of a protic acid such as *p*-toluene sulfonic acid in toluene at elevated temperature generates olefin **S9-3**. Cyclopropanation under conditions described in **Scheme 8** gives **S9-5**. Partial reduction of **S9-5** to aldehyde **S9-6** can be achieved with DIBAL-H in THF at low temperature. Condensation of aldehyde **S9-6** with racemic sulfinimide **S9-7** gives **S9-8**. Addition of a Grignard reagent and deprotection under conditions previously described gives amine salt **S9-10** as a racemate. Coupling with proline derivative **S9-11** under standard conditions and Boc deprotection generates an intermediate which can be further purified by chiral SFC to give amine **S9-13** as a single isomer. Conversion to compounds of formula **S9-15** occurs under conditions previous described. If the R^2 substituent bears stereogenic atoms that are mixtures, additional purification by chiral SFC may be utilized to generate single isomer analogs.

Scheme 10

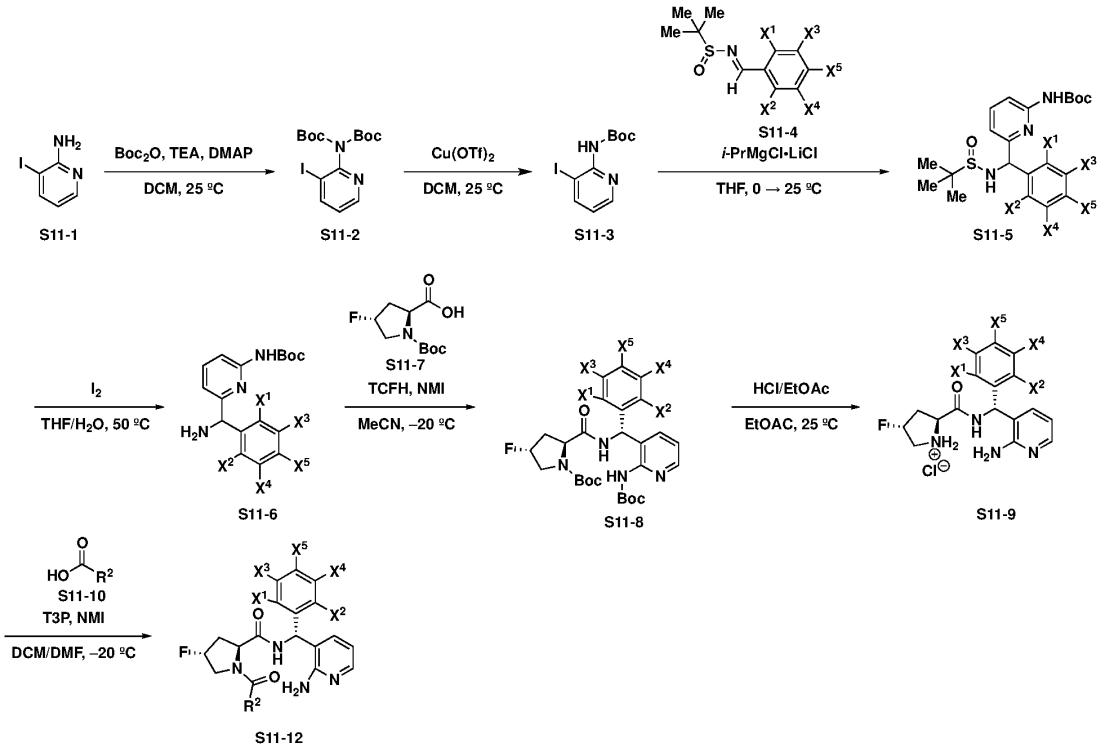


[0400] Compounds of the general formula **S10-5** can be prepared according to the general scheme outlined in **Scheme 10.**

[0401] An alternative approach to compounds of formula **S10-5** starts with condensation of pyridine **S10-1** with sulfinimide **S10-2**. Addition of an aryllithium reagent such

as phenyllithium provides **S10-4**. Deprotection under standard conditions gives amine salts of formula **S10-5**, which may be further elaborated as described in the **Schemes 1-9** and **Schemes 11-15**.

Scheme 11

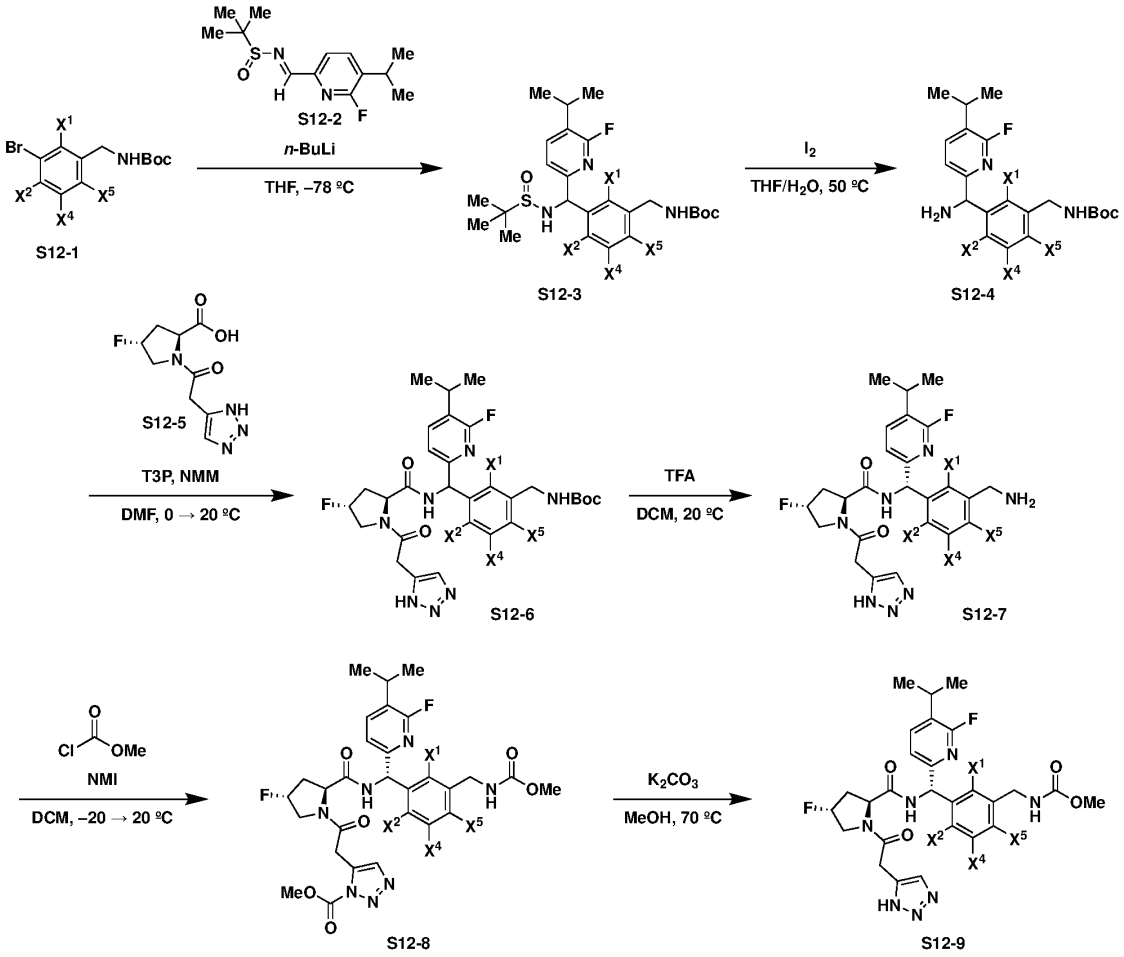


[0402] Compounds of the general formula **S11-12** can be prepared according to the general scheme outlined in **Scheme 11.**

[0403] Yet another alternative approach to amine intermediates such as S11-6 starts with pyridine S11-1. Bis-carbamate formation, followed by treatment copper (II) triflate gives pyridine S11-3. Conversion of S11-3 to the corresponding Grignard reagent with isopropylmagnesium chloride-lithium chloride complex followed by addition to a racemic sulfinimine such as S11-4 gives S11-5. Selective cleavage of the sulfinamide may occur on reaction with iodine at elevated temperature. Coupling with proline derivative S11-7 and further processing to generate compounds of formula S11-12 occurs as previously described. If

necessary, mixtures of stereoisomers may be further purified using chiral SFC, to generate compounds as single isomers.

Scheme 12

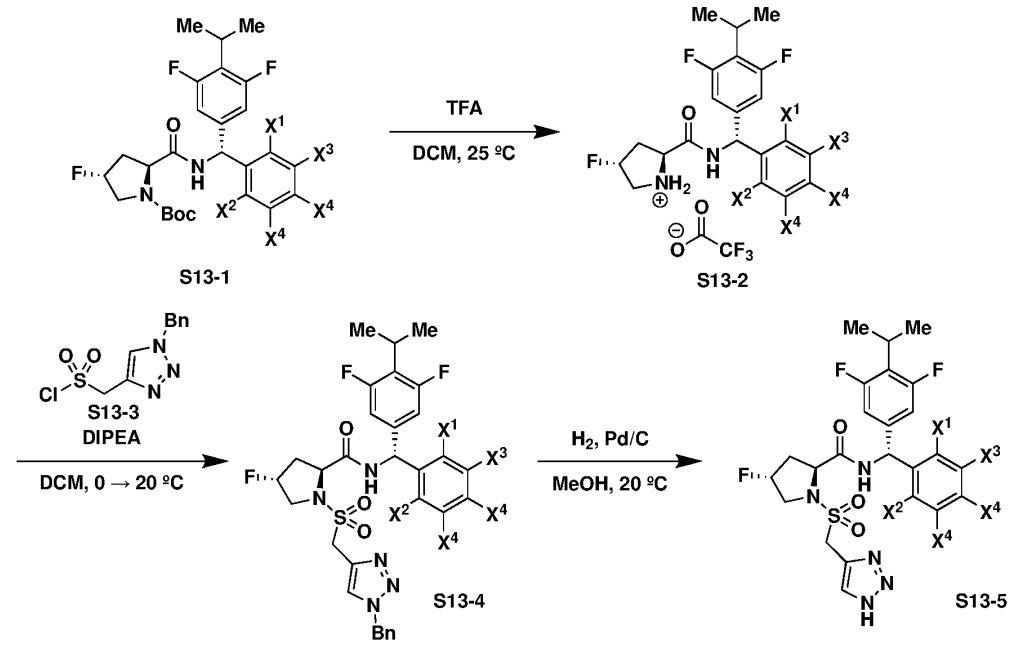


[0404] Compounds of the general formula **S12-9** can be prepared according to the general scheme outlined in **Scheme 12.**

[0405] An alternative sequence enabling late-stage elaboration of the benzhydryl moieties begins with lithiation of S12-1 and addition of sulfinimine S12-2. Oxidative cleavage with iodine generates S12-4. Coupling with proline derivative S12-5 generates S12-6. Cleavage of the Boc group with TFA generates amine S12-7. Treatment with an acylating agent such as

methyl chloroformate and NMI as base gives bis-carbamate S12-8. Selective cleavage of the triazole carbamate moiety can be achieved by reaction with potassium carbonate and methanol at elevated temperature, to generate compounds of formula S12-9.

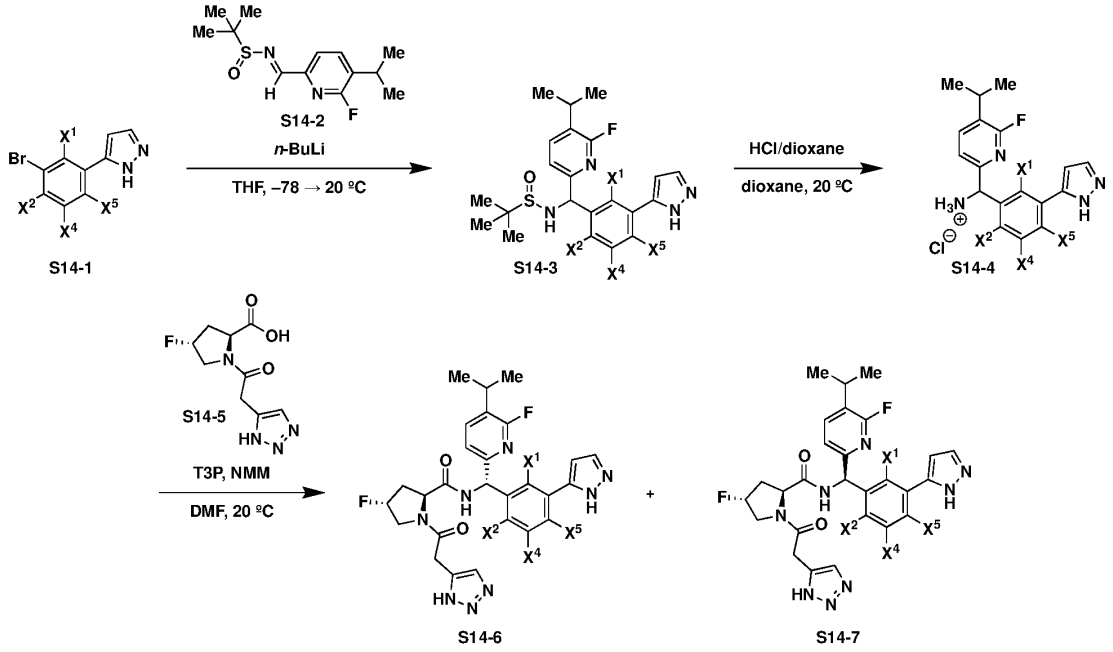
Scheme 13



[0406] Compounds of the general formula **S13-5** can be prepared according to the general scheme outlined in **Scheme 13.**

[0407] Sulfonamides of formula S13-5 can be generated starting from S13-1. Boc cleavage as previously described gives S13-2. Reaction of S13-2 with sulfonyl chloride S13-3 using a tertiary amine base such as DIPEA gives S13-4. Cleavage of the triazole *N*-benzyl group occurs under standard hydrogenation conditions to give S13-5.

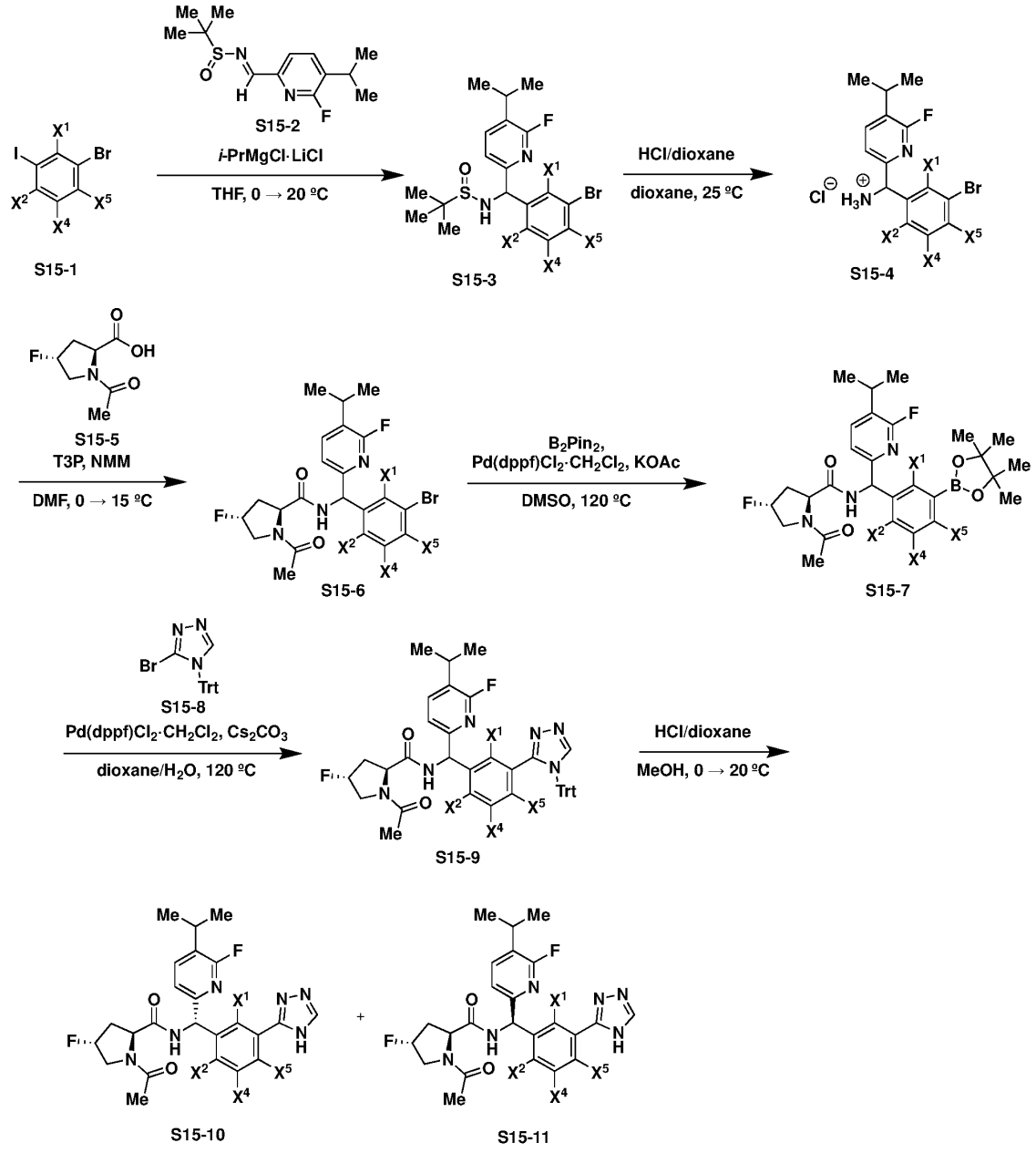
Scheme 14



[0408] Compounds of the general formulae **S14-6** and **S14-7** can be prepared according to the general scheme outlined in **Scheme 14.**

[0409] Bromobenzene analogs bearing heterocycles such as pyrazoles can undergo metalation using an excess of *n*-BuLi and addition to sulfinimines such as S14-2 to give adducts such as S14-3. Conversion to the amine HCl salt can occur under previously described conditions. Coupling with proline derivative S14-5 under previously described conditions gives compounds of formulae S14-6 and S14-7, which can be isolated as single isomers using methods such as reverse phase prep-HPLC or chiral SFC.

Scheme 15



[0410] Compounds of the general formula **S15-10** and **S15-11** can be prepared according to the general scheme outlined in **Scheme 15.**

[0411] An alternative strategy that enables late-stage elaboration to generate compounds of formulae S15-10 and S15-11 begins by selective metal-halogen exchange with

S15-1 and addition to sulfinimine S15-2 to generate S15-3. Generation of the amine HCl salt and coupling to proline derivative S15-5 under conditions previously described gives S15-6. S16-6 may then undergo palladium catalyzed borylation to generate boronate ester S15-7. Suzuki-type cross coupling under conditions previously described, using an aryl or heteroaryl bromide such as S15-8 gives S15-9. Cleavage of the trityl protecting from the triazole moiety under protic acid conditions gives compounds of formula S15-10 and S15-11, which can be isolated as single isomers using methods such as flash column chromatography, reverse phase HPLC, or chiral SFC.

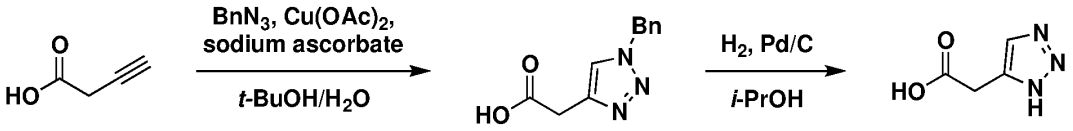
[0412] Abbreviations used are those conventional in the art and are in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics,* 75th Ed. The following examples are intended to be illustrative only and not limiting in any way.

Docket No.: 792752000240

°C	degrees Celsius
µL	microliter
$[M+XX]^+$	observed mass
AC_{50}	half-maximal activity concentration
ACN	acetonitrile
app	apparent (NMR)
$BH_3 \cdot THF$	borane-tetrahydrofuran complex
BBr_3	boron tribromide
Calc'd	calculated
Cbz-Cl	benzyl chloroformate
CO_2	carbon dioxide
Cs_2CO_3	cesium carbonate
d	deuterated (NMR solvents)
d	doublet (NMR)
dd	doublet of doublets (NMR)
DCM	dichloromethane
DIAD	diisopropyl azodicarboxylate
DMF	*N*,*N*-dimethylformamide
EC_{50}	half-maximal effective concentration
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ESI	electrospray ionization
EtOAc	ethyl acetate
EtOH	ethanol
eq	equivalents
g	grams
h	hours
H	hydrogen
HCl	hydrochloric acid
HPLC	high-performance liquid chromatography
IC_{50}	half-maximal inhibitory concentration
In vacuo	in a vacuum
IUPAC	International Union of Pure and Applied Chemistry
MHz	megahertz
J	J-coupling value (NMR)
K_2CO_3	potassium carbonate
LDA	lithium diisopropylamide
LiHMDS	lithium bis(trimethylsilyl)amide
MeOH	Methanol
MeCN	acetonitrile
m	multiplet (NMR)
mg	milligrams
min	minutes
mL	milliliter
mmol	millimole
mM	millimolar
M	molarity or molar
MS	mass spectrometry
MsCl	methanesulfonyl chloride
MTBE	methyl *tert*-butyl ether
n/a	not applicable
NBS	N-bromosuccinimide
NH_4	ammonium
NH_4OH	ammonium hydroxide
NH_4HCO_3	ammonium bicarbonate
Na_2SO_4	sodium sulfate
$NaBH_3CN$	sodium cyanoborohydride
NMI	N-methylimidazole
NMM	N-methylmorpholine
NMR	nuclear magnetic resonance
NaOH	sodium hydroxide
PCy_3	Tricyclohexylphosphine
$PdCl_2(dppf)$	[1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)
pH	potential of hydrogen
PPh_3	triphenyl phosphine
s	singlet (NMR)

SFC	super fluid chromatography
t	triplet (NMR)
T3P	Propanephosphonic acid anhydride
TBAB	tetrabutylammonium bromide
TEA	triethylamine
TFA	trifluoroacetic acid
TFCH	N,N,N′,N′-tetramethylchloroformamidinium hexafluorophosphate
THF	tetrahydrofuran
TMSCl	trimethylsilyl chloride
wt. %	weight percent

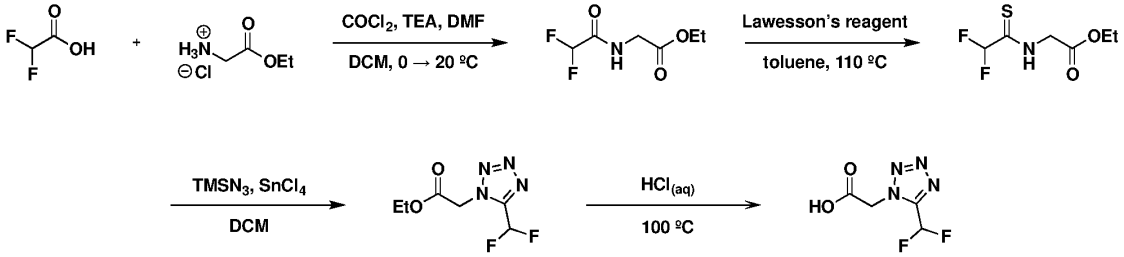
Intermediate A-1: Synthesis of 2-(1*H*-1,2,3-triazol-5-yl)acetic acid



[0413] Step a: To a mixture of but-3-ynoic acid (7.5 g, 89.2 mmol, 1 eq), $Cu(OAc)_2$ (1.62 g, 8.92 mmol, 0.1 eq) and sodium ascorbate (3.53 g, 17.8 mmol, 0.2 eq) in H_2O (75 mL) and *t*-BuOH (75 mL) at 0 °C was added, in portions, benzyl azide (BnN_3, 13.9 g, 93.7 mmol, 90% purity, 1.05 eq). The resulting mixture was warmed to 25 °C and stirred for 12 h. The mixture was then filtered and the solids were washed with water (2 x 20 mL) and dried under reduced pressure to afford 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)acetic acid. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{11}H_{11}N_3O_2$: 218.1; found 218.1.

[0414] Step b: A suspension of 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)acetic acid (5 g, 23 mmol, 1 eq) and Pd/C (2.45 g, 10% wt. %) in *i*-PrOH (300 mL) was stirred under H_2 (50 psi) at 25 °C for 5 h. The reaction mixture was then filtered through a pad of Celite, and the filter cake was washed with CH_2Cl_2 (3 x 30 mL). The filtrate was concentrated under reduced pressure to give 2-(1*H*-1,2,3-triazol-5-yl)acetic acid. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_4H_5N_3O_2$: 128.1; found 128.1.

Intermediate A-2: Synthesis of 2-(5-(difluoromethyl)-1*H*-tetrazol-1-yl)acetic acid



[0415] Step a: To a solution of 2,2-difluoroacetic acid (50.0 g, 520 mmol, 1.00 eq) in dry DCM (200 mL) at 0 °C was added a catalytic amount of DMF (4 mL) and oxalyl dichloride (66.1 g, 520 mmol, 45.6 mL, 1.00 eq), sequentially. The resulting mixture was warmed to 20 °C and stirred for 1 h. The reaction mixture was then cooled to 0 °C and a solution of 2-ethoxy-2-oxoethan-1-aminium chloride (80.0 g, 573 mmol, 1.10 eq), TEA (105 g, 1.04 mol, 2.00 eq) and

DMAP (7.37 g, 52.1 mmol, 0.10 eq) in DCM (500 mL) was added. The reaction mixture was warmed to 20 °C and stirred for 1 h. The reaction mixture was then quenched with water (100 mL) and extracted with dichloromethane (3 x 200 mL). The combined organic extracts were washed with brine (500 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude residue was purified by column chromatography to give ethyl (2,2-difluoroacetyl)glycinate. This compound was carried forward to the next step without further characterization.

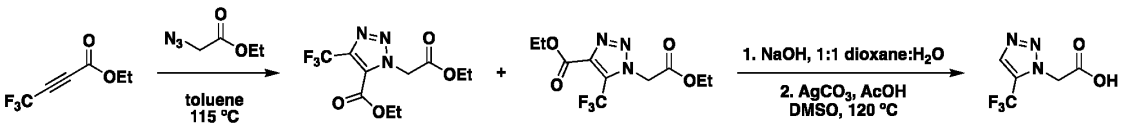
[0416] Step b: To a solution of ethyl (2,2-difluoroacetyl)glycinate (25.0 g, 138 mmol, 1.00 eq) in toluene (250 mL) at 25 °C was added 2,4-bis(4-methoxyphenyl)-2,4-dithioxo-1,3,2λ^5,4λ^5-dithiadiphosphetane (Lawesson's reagent, 67.0 g, 165 mmol, 1.20 eq) under N_2. The resulting mixture was warmed to 110 °C and stirred for 1 h. The reaction mixture was then cooled to 25 °C, and poured into water (300 mL) and NaOCl (~10% aqueous, 100 mL). The resulting mixture was extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were washed with brine (2 x 200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude residue was purified by column chromatography to give ethyl (2,2-difluoroethanethioyl)glycinate. This compound was carried forward to the next step without further characterization.

[0417] Step c: To a mixture of ethyl (2,2-difluoroethanethioyl)glycinate (12.5 g, 63.4 mmol, 1.00 eq) and azido(trimethyl)silane (14.6 g, 127 mmol, 2.00 eq) in DCM (120 mL) at 0 °C under N_2 was added $SnCl_4$ (41.2 g, 158 mmol, 2.50 eq). The resulting mixture was warmed to 25 °C and stirred for 2 h. The reaction mixture was then cooled to 0 °C and quenched by addition of saturated aqueous $NaHCO_3$ (200 mL). The resulting biphasic mixture was extracted with DCM (2 x 100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude residue was purified by silica gel chromatography to give ethyl 2-(5-(difluoromethyl)-1*H*-tetrazol-1-yl)acetate. This compound was carried forward to the next step without further characterization.

[0418] Step d: Ethyl 2-(5-(difluoromethyl)-1*H*-tetrazol-1-yl)acetate (6.50 g, 31.5 mmol, 1.00 eq) was dissolved in aqueous HCl (6 M, 65 mL) at 20 °C. The resulting mixture was warmed to 100 °C and stirred for 20 h. The reaction mixture was then concentrated under

reduced pressure to give 2-(5-(difluoromethyl)-1*H*-tetrazol-1-yl)acetic acid. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_4H_4F_2N_4O_2$: 179.0; found 179.0.

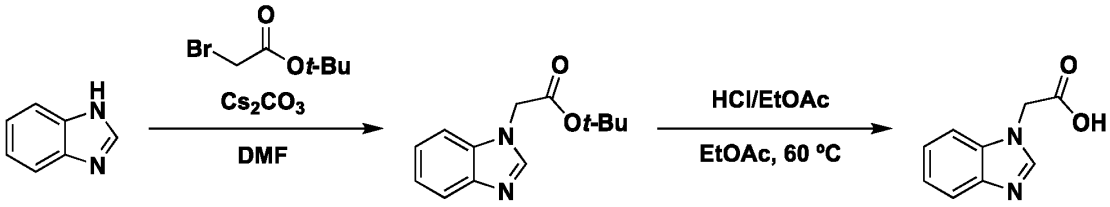
Intermediate A-3: Synthesis of 2-(5-(trifluoromethyl)-1*H*-1,2,3-triazol-1-yl)acetic acid



[0419] Step a: To a solution of ethyl 2-azidoacetate (200 mg, 94% purity, 1.5 mmol, 1 eq) in toluene (5 mL) was added ethyl 4,4,4-trifluorobut-2-ynoate (500 mg, 3.0 mmol, 2 eq). The mixture was warmed to 115 °C and stirred for 16 h. The reaction mixture was then cooled to 0 °C, quenched with MeOH (10 mL) and concentrated under reduced pressure. The resulting crude residue was purified by column chromatography to give a mixture of ethyl 1-(2-ethoxy-2-oxoethyl)-4-(trifluoromethyl)-1*H*-1,2,3-triazole-5-carboxylate and ethyl 1-(2-ethoxy-2-oxoethyl)-5-(trifluoromethyl)-1H-1,2,3-triazole-4-carboxylate. This compound was carried forward to the next step without further characterization.

[0420] Step b: To a mixture of ethyl 1-(2-ethoxy-2-oxoethyl)-4-(trifluoromethyl)-1H-1,2,3-triazole-5-carboxylate and ethyl 1-(2-ethoxy-2-oxoethyl)-5-(trifluoromethyl)-1H-1,2,3-triazole-4-carboxylate (220.00 mg, 745 µmol, 1 eq) in 1:1 dioxane:H_2O (4 mL) at 25 °C was added NaOH (60 mg, 1.1 mmol, 1.5 eq). The resulting mixture was stirred at for 16 h. The reaction mixture was then quenched with HCl (6 M, 1 mL) in H_2O (10 mL) and extracted with DCM (3 x 20 mL). The aqueous phase was lyophilized to afford a crude solid, which was immediately dissolved in DMSO (3 mL). To the resulting mixture was added Ag_2CO_3 (140 mg, 508 µmol, 0.5 eq), followed by AcOH (6 mg, 100 µmol, 0.1 eq). The mixture was warmed to 130 °C and stirred for 16 h. The reaction mixture was then quenched with H_2O (30 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (2 x 15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude residue was purified by prep-HPLC to give 2-(5-(trifluoromethyl)-1H-1,2,3-triazol-1-yl) acetic acid. LC-MS (ESI): m/z: $[M - H]^-$ calculated for $C_5H_4F_3N_3O_2$: 194.0; found 194.1.

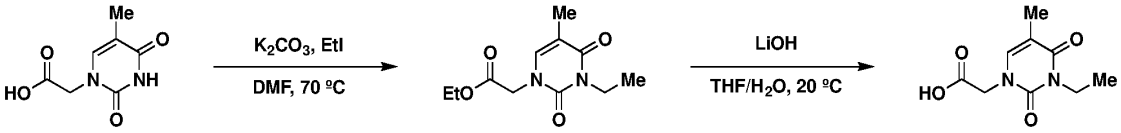
Intermediate A-4: Synthesis of 2-(1*H*-benzo[*d*]imidazol-1-yl)acetic acid



[0421] Step a: To a solution of 1*H*-benzo[*d*]imidazole (10.0 g, 84.6 mmol, 1 eq) in DMF (100 mL) was added Cs_2CO_3 (33.1 g, 102 mmol, 1.2 eq) and tert-butyl 2-bromoacetate (18.2 g, 93.1 mmol, 1.1 eq). The mixture was stirred at 25 °C for 2 h. The reaction mixture was then filtered and the filtrate was diluted with EtOAc (200 mL). The combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude residue was purified by column chromatography to give compound *tert*-butyl 2-(1*H*-benzo[*d*]imidazol-1-yl)acetate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{13}H_{16}N_2O_2$: 233.1; found 233.1.

[0422] Step b: To a solution of *tert*-butyl 2-(1*H*-benzo[*d*]imidazol-1-yl)acetate (16.8 g, 72.3 mmol, 1 eq) in EtOAc (100 mL) was added HCl/EtOAc (4 M, 200 mL). The mixture was warmed to 60 °C and stirred for 2 h. The reaction mixture was then concentrated under reduced pressure. The resulting crude product was triturated with petroleum ether at 25 °C for 10 min and filtered to give 2-(1*H*-benzo[*d*]imidazol-1-yl)acetic acid. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_9H_8N_2O_2$: 177.1; found 177.0.

Intermediate A-5: Synthesis of 2-(3-ethyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)acetic acid

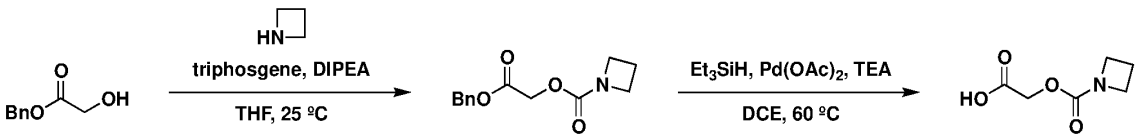


[0423] Step a: To a mixture of iodoethane (1.27 g, 8.15 mmol, 3 eq) and 2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)acetic acid (500 mg, 2.72 mmol, 1 eq) in DMF (6 mL) at 20 °C under N_2 was added K_2CO_3 (1.88 g, 13.5 mmol, 5 eq) in one portion. The resulting

mixture was warmed to 70 °C and stirred for 2 h. After this time, the reaction mixture was cooled to 0 °C, and the reaction was quenched by addition H_2O (30 mL). The resulting biphasic mixture was then extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a crude residue that was purified by column chromatography to obtain ethyl 2-(3-ethyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)acetate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{11}H_{16}N_2O_4$: 241.1; found 241.1.

[0424] Step b: To a solution of ethyl 2-(3-ethyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)acetate (450 mg, 1.87 mmol, 1 eq) in THF (5 mL) and H_2O (5 mL) at 20 °C under N_2 was added LiOH (89.7 mg, 3.75 mmol, 2 *eq*) in one portion. The resulting mixture was stirred at 20 °C for 2 h. After this time, the reaction mixture was diluted with H_2O (20 mL), and the pH of the solution was adjusted to pH = 3 by addition of aqueous HCl (2M). The resulting mixture was then extracted with EtOAc (3 x 10 mL). The combined organic extracts were then washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to obtain 2-(3-ethyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)acetic acid. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_9H_{12}N_2O_4$: 213.1; found 213.1.

Intermediate A-6: Synthesis of 2-((azetidine-1-carbonyl)oxy)acetic acid



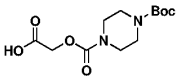
[0425] Step a: To a solution of benzyl 2-hydroxyacetate (0.96 g, 5.78 mmol, 821 µL, 1 eq) in THF (10 mL) at 0 °C was added triphosgene (686 mg, 2.31 mmol, 0.4 eq) followed by DIPEA (2.09 g, 16.2 mmol, 2.82 mL, 2.8 eq), and the resulting mixture was stirred at 0 °C for 0.5 h before it was warmed to 25 °C and stirred for 0.5 h. A solution of azetidine (330 mg, 5.78 mmol, 390 µL, 1 eq) in THF (10 mL) and DIPEA (1.05 g, 8.09 mmol, 1.41 mL, 1.4 eq) were then added, and the resulting mixture was stirred at 25 °C for 12 h. The reaction mixture was then diluted with saturated aqueous $NaHCO_3$ (20 mL), and the resulting biphasic mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The

crude residue obtained was purified by column chromatography to give 2-(benzyloxy)-2-oxoethyl azetidine-1-carboxylate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{13}H_{15}NO_4$: 250.1; found 250.2.

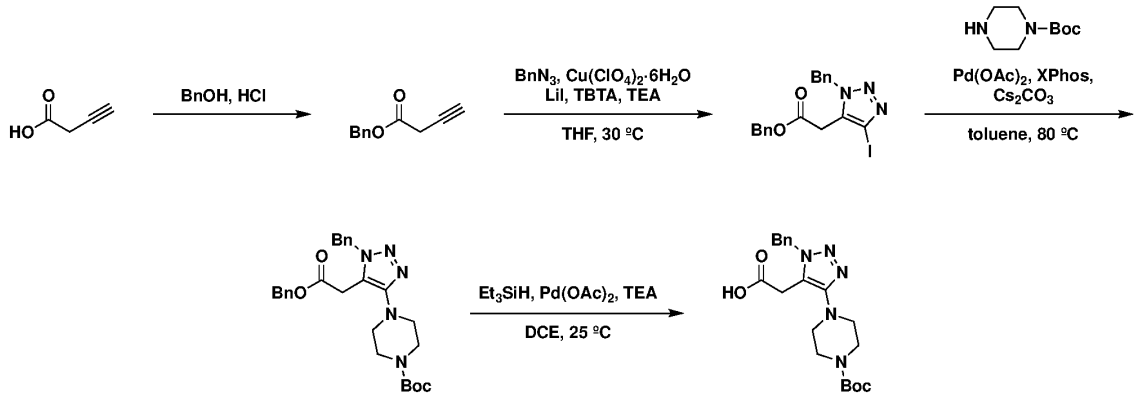
[0426] Step b: To a mixture of 2-(benzyloxy)-2-oxoethyl azetidine-1-carboxylate (250 mg, 1.00 mmol, 1 eq) in DCE (5 mL) at 25 ºC under N_2 was added TEA (20.3 mg, 200 µmol, 27.9 µL, 0.2 eq), $Pd(OAc)_2$ (56.3 mg, 251 µmol, 0.25 eq) and Et_3SiH (233 mg, 2.01 mmol, 320 µL, 2 eq). The resulting mixture was stirred at 60 ºC for 2 h before it was filtered through a pad of Celite. The filtrate was then concentrated under reduced pressure to give 2-((azetidine-1-carbonyl)oxy)acetic acid. LC-MS (ESI): m/z: $[M - H]^-$ calculated for $C_6H_9NO_4$: 158.0; found 158.1.

[0427] The following compounds in Table B-1 were synthesized using procedures similar to Intermediate A-6 using the appropriate starting materials.

Table B-1

Intermediate No.	Structure	IUPAC	Exact mass (g/mol)	LCMS, Found $[M + H]^+$
B-1-1		2-((4-(*tert*-butoxycarbonyl)piperazine-1-carbonyl)oxy)acetic acid	288.1	189.1 $[M - Boc + H]^+$

Intermediate A-7: Synthesis of 2-(1-benzyl-4-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)-1*H*-1,2,3-triazol-5-yl)acetic acid



[0428] Step a: To a mixture of but-3-ynoic acid (5.00 g, 59.5 mmol, 1.00 eq) in benzyl alcohol (19.3 g, 178 mmol, 18.6 mL, 3.00 eq) at 25 °C was added aqueous HCl (12 M, 297 µL, 37.0% purity, 0.06 eq) in one portion. The resulting mixture was stirred at 25 °C for 16 h. The reaction mixture was then quenched by addition of H_2O (30 mL) at 25 °C, and the resulting biphasic mixture was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give benzyl but-3-ynoate. This compound was carried forward to the next step without further characterization.

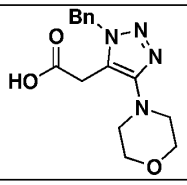
[0429] Step b: To a mixture of benzyl azide (3.00 g, 22.5 mmol, 1.00 eq) in THF (45 mL) at 25 °C under N_2 was added LiI (12.1 g, 90.1 mmol, 3.46 mL, 4.00 eq), copper (II) perchlorate hexahydrate (16.7 g, 45.1 mmol, 2.00 eq), and tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (TBTA, 1.20 g, 2.25 mmol, 0.100 eq) in one portion. The resulting mixture was stirred at 25 °C for 5 min before TEA (2.28 g, 22.5 mmol, 3.14 mL, 1.00 eq) and benzyl but-3-ynoate (4.32 g, 24.8 mmol, 1.10 eq) were added, and the resulting mixture was stirred at 30 °C for 6 h. The reaction mixture was then quenched by addition H_2O (30 mL), and the resulting biphasic mixture was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give benzyl 2-(1-benzyl-4-iodo-1*H*-1,2,3-triazol-5-yl)acetate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{18}H_{16}IN_3O_2$: 434.0; found 434.1.

[0430] Step c: To a mixture of *tert*-butyl piperazine-1-carboxylate (645 mg, 3.46 mmol, 5.00 eq) and benzyl 2-(1-benzyl-4-iodo-1*H*-1,2,3-triazol-5-yl)acetate (300 mg, 693 µmol, 1.00 eq) in toluene (10 mL) at 25 ºC under N_2 was added XPhos (83.0 mg, 173 µmol, 0.250 eq), $Pd(OAc)_2$ (34.0 mg, 152 µmol, 0.220 eq) and Cs_2CO_3 (677 mg, 2.08 mmol, 3.00 eq) in one portion. The resulting mixture was stirred at 80 ºC for 6 h. The reaction mixture was then filtered, and the filtrate was concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give *tert*-butyl 4-(1-benzyl-5-(2-(benzyloxy)-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl)piperazine-1-carboxylate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{27}H_{33}N_5O_4$: 492.2; found 492.3.

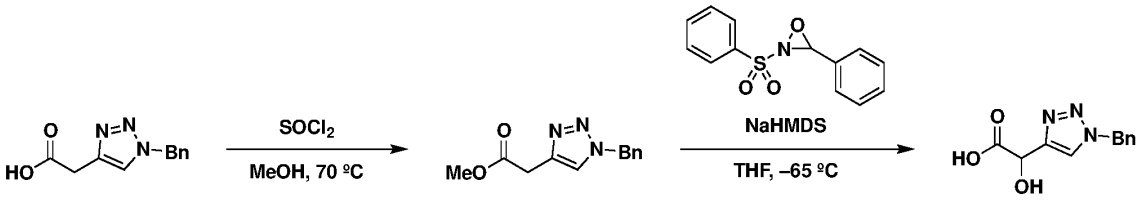
[0431] Step d: To a mixture of *tert*-butyl 4-(1-benzyl-5-(2-(benzyloxy)-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl)piperazine-1-carboxylate (200 mg, 406 µmol, 1.00 eq) in DCE (5 mL) at 25 ºC under N_2 were added TEA (8.0 mg, 81.3 µmol, 11.3 µL, 0.2 eq), Et_3SiH (95.0 mg, 813 µmol, 130 µL, 2.00 eq), $Pd(OAc)_2$ (23.0 mg, 102 µmol, 0.250 eq) in one portion. The resulting mixture was stirred at 25 ºC for 60 min before it was quenched by addition H_2O (10 mL). The resulting biphasic mixture was then extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give 2-(1-benzyl-4-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)-1*H*-1,2,3-triazol-5-yl)acetic acid. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{20}H_{27}N_5O_4$: 402.2; found 402.3.

[0432] The following compounds in Table B-2 were synthesized using procedures similar to Intermediate A-7 using the appropriate starting materials.

Table B-2

Intermediate No.	Structure	IUPAC	Exact mass (g/mol)	LCMS, Found $[M + H]^+$
B-2-1		2-(1-benzyl-4-morpholino-1*H*-1,2,3-triazol-5-yl)acetic acid	302.1	303.2

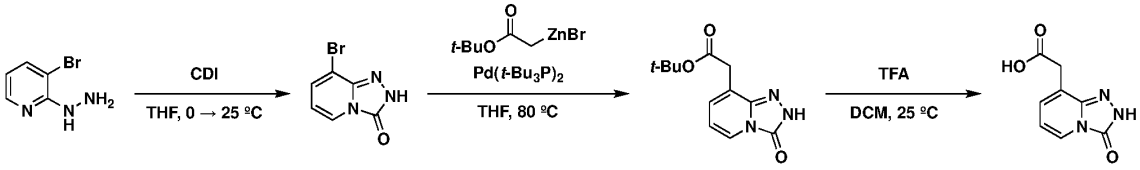
Intermediate A-8: Synthesis of 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-2-hydroxyacetic acid



[0433] Step a: To a solution of 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)acetic acid (2.00 g, 9.21 mmol, 1 eq) in MeOH (20 mL) at 25 °C was added $SOCl_2$ (109.54 mg, 920.71 µmol, 66.79 µL, 0.1 eq). The resulting mixture was warmed to 70 °C and stirred for 3 h. The reaction mixture was then quenched with water (20 mL), and the resulting biphasic mixture was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give methyl 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)acetate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{12}H_{13}N_3O_2$: 232.1; found 232.1.

[0434] Step b: To a solution of methyl 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)acetate (500 mg, 2.16 mmol, 1 eq) and 3-phenyl-2-(phenylsulfonyl)-1,2-oxaziridine (847.45 mg, 3.24 mmol, 1.5 eq) in THF (5 mL) at –65 °C under N_2 was added NaHMDS (1 M in THF, 3.24 mL, 1.5 eq) in THF (5 mL) in a dropwise manner. The resulting mixture was stirred at –65 °C for 2 h. The reaction mixture was adjusted to pH = 7 by addition of saturated aqueous NH_4Cl solution. The resulting biphasic solution was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by prep-HPLC to give 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-2-hydroxyacetic acid. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{11}H_{11}N_3O_3$: 234.1; found 234.1.

Intermediate A-9: Synthesis of 2-(3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-*a*]pyridin-8-yl)acetic acid

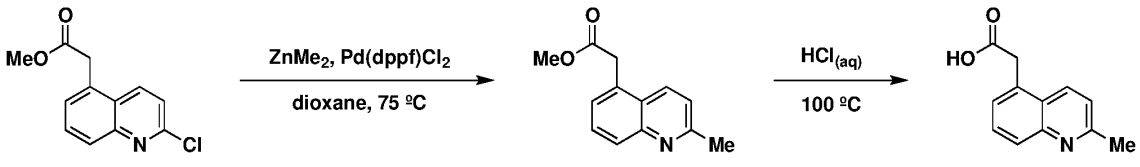


[0435] Step a: To a solution of 3-bromo-2-hydrazineylpyridine (2 g, 10.6 mmol, 1 eq) in THF (20 mL) at 0 ºC was added CDI (2.24 g, 13.8 mmol, 1.3 eq). The resulting mixture was warmed to 25 ºC and stirred for 2 h. The mixture was then poured into water (20 mL), resulting in the precipitation of a solid. The mixture was then filtered, and the filter cake was washed with water. The washed solid was then dried under reduced pressure to give 8-bromo-[1,2,4]triazolo[4,3-*a*]pyridin-3(2*H*)-one. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_6H_4BrN_3O$: 214.0; found 213.9.

[0436] Step b: To a mixture of 8-bromo-[1,2,4]triazolo[4,3-*a*]pyridin-3(2*H*)-one (500 mg, 2.34 mmol, 1 eq) and Pd(*t*-$Bu_3P)_2$ (239 mg, 467 µmol, 0.2 eq) in THF (30 mL) was added (2-(*tert*-butoxy)-2-oxoethyl)zinc(II) bromide (1 M in THF, 14.02 mL, 6 eq). The resulting mixture was degassed and purged with N_2, and then the mixture was warmed to 80 ºC and stirred for 2 h under N_2 atmosphere. The mixture was then filtered, and H_2O (10 mL) was added to the filtrate. The resulting biphasic mixture was extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine (2 x 15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give *tert*-butyl 2-(3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-*a*]pyridin-8-yl)acetate. LC-MS (ESI): m/z: $[M - H]^-$ calculated for $C_{12}H_{15}N_3O_3$: 248.1; found 248.1.

[0437] Step c: To a solution of *tert*-butyl 2-(3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-*a*]pyridin-8-yl)acetate (50 mg, 201 µmol, 1 eq) in DCM (2 mL) was added TFA (1.54 g, 13.5 mmol, 1 mL, 67.3 eq). The resulting mixture was stirred at 25 ºC for 15 h. The mixture was then concentrated under reduced pressure to give 2-(3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-*a*]pyridin-8-yl)acetic acid. LC-MS (ESI): m/z: $[M - CO_2H - H]^-$ calculated for $C_8H_7N_3O_3$: 148.1; found 148.2.

Intermediate A-10: Synthesis of 2-(2-methylquinolin-5-yl)acetic acid

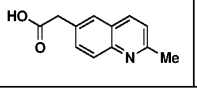


[0438] Step a: To a mixture of methyl 2-(2-chloroquinolin-5-yl)acetate (200 mg, 849 µmol, 1 eq) and dimethylzinc (1 M in toluene, 2.55 mL, 3.00 eq) in dioxane (2 mL) at 25 ºC under N_2 was added Pd(dppf)Cl_2 (124 mg, 170 µmol, 0.20 eq) in one portion. The mixture was then degassed and charged with N_2. The reaction mixture was then warmed to 75 ºC and stirred for 1 h. The reaction mixture was then cooled to 25 ºC and poured into water (10 mL). The resulting biphasic mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give methyl 2-(2-methylquinolin-5-yl)acetate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{13}H_{13}NO_2$: 216.1; found 216.1.

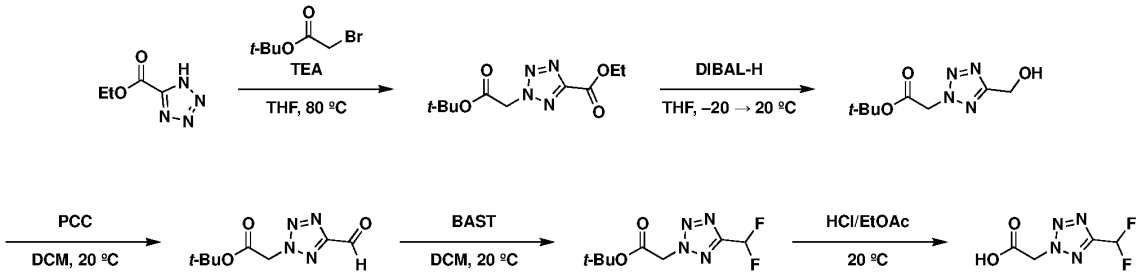
[0439] Step b: Methyl 2-(2-methylquinolin-5-yl)acetate (90 mg, 418 µmol, 1.00 eq) was added to aqueous HCl (6 M, 0.5 mL) in one portion at 25 ºC. The reaction mixture was then warmed to 100 ºC and stirred for 16 h. The reaction mixture was then concentrated under reduced pressure to give 2-(2-methylquinolin-5-yl)acetic acid. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{12}H_{11}NO_2$: 202.1; found 202.1.

[0440] The following compounds in Table B-3 were synthesized using procedures similar to Intermediate A-10 using the appropriate starting materials.

Table B-3

Intermediate No.	Structure	IUPAC	Exact mass (g/mol)	LCMS, Found $[M + H]^+$
B-3-1		2-(2-methylquinolin-6-yl)acetic acid	201.1	202.2

Intermediate A-11: Synthesis of 2-(5-(difluoromethyl)-2*H*-tetrazol-2-yl)acetic acid



[0441] Step a: A mixture of ethyl 1*H*-tetrazole-5-carboxylate (25.0 g, 175 mmol, 1.00 eq), *tert*-butyl 2-bromoacetate (37.7 g, 193 mmol, 28.5 mL, 1.10 eq) and TEA (26.7 g, 263 mmol, 36.7 mL, 1.50 eq) in THF (250 mL) was warmed to 80 °C and stirred for 1 h. The reaction mixture was then cooled and quenched with water (200 mL), and the resulting biphasic mixture was extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were washed with brine (400 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give ethyl 2-(2-(*tert*-butoxy)-2-oxoethyl)-2*H*-tetrazole-5-carboxylate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{10}H_{16}N_4O_4$: 257.1; found 257.1.

[0442] Step b: To a solution of ethyl 2-(2-(*tert*-butoxy)-2-oxoethyl)-2*H*-tetrazole-5-carboxylate (35.0 g, 136 mmol, 1.00 eq) in THF (180 mL) at –20 °C under N_2 was added DIBAL-H (1 M in THF, 273 mL, 2.00 eq) in a dropwise manner. The mixture was then warmed to 20 °C and stirred for 1 h. The mixture was then cooled to 0 °C and quenched with water (300 mL) before it was stirred for 10 min. The resulting biphasic mixture was extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give *tert*-butyl 2-(5-(hydroxymethyl)-2*H*-tetrazol-2-yl)acetate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_8H_{14}N_4O_3$: 215.1; found 215.1.

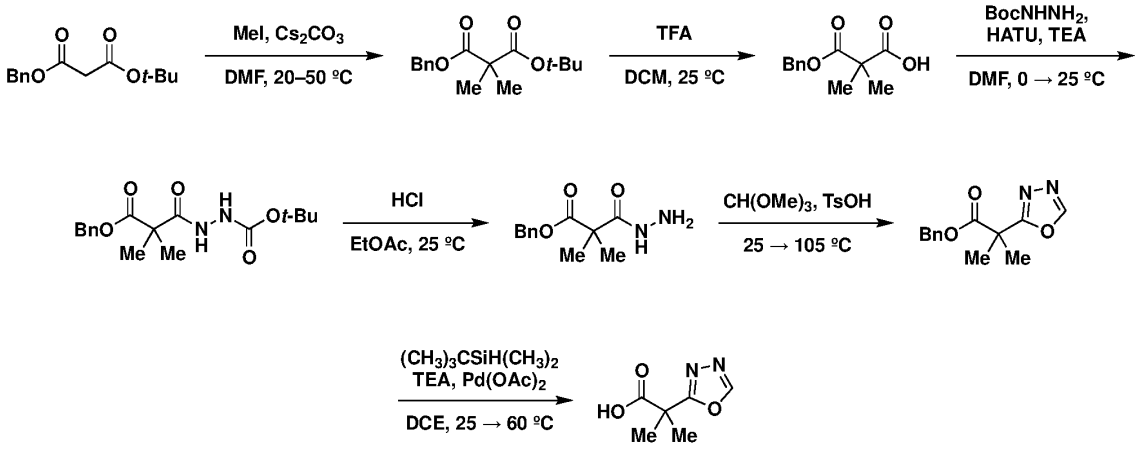
[0443] Step c: To a solution of *tert*-butyl 2-(5-(hydroxymethyl)-2*H*-tetrazol-2-yl)acetate (2.00 g, 9.34 mmol, 1.00 eq) in DCM (20 mL) at 20 °C was added PCC (4.02 g, 18.6 mmol, 2.00 eq) and silica gel (4.00 g). The resulting mixture was stirred at 20 °C for 40 h. The reaction mixture was then diluted with water (20 mL), and the resulting biphasic mixture was extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The

crude residue obtained was purified by column chromatography to give *tert*-butyl 2-(5-formyl-2*H*-tetrazol-2-yl)acetate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_8H_{12}N_4O_3$: 213.1; found 213.1.

[0444] Step d: To a solution of *tert*-butyl 2-(5-formyl-2*H*-tetrazol-2-yl)acetate (400 mg, 1.88 mmol, 1.00 eq) in DCM (4 mL) at 20 °C was added BAST (1.25 g, 5.64 mmol, 1.24 mL, 3.00 eq). The resulting mixture was stirred for 1 h. The mixture was then diluted with water (10 mL), and the resulting biphasic mixture was extracted with ethyl acetate (2 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give *tert*-butyl 2-(5-(difluoromethyl)-2*H*-tetrazol-2-yl)acetate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_8H_{12}F_2N_4O_2$: 235.1; found 235.1.

[0445] Step e: A solution of *tert*-butyl 2-(5-(difluoromethyl)-2*H*-tetrazol-2-yl)acetate (200 mg, 853 µmol, 1.00 eq) in HCl/EtOAc (4 M, 3 mL) was stirred at 20 °C for 16 h. The reaction mixture was then concentrated under reduced pressure to give 2-(5-(difluoromethyl)-2*H*-tetrazol-2-yl)acetic acid. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_4H_4F_2N_4O_2$: 179.0; found 179.0.

Intermediate A-12: Synthesis of 2-methyl-2-(1,3,4-oxadiazol-2-yl)propanoic acid



[0446] Step a: To a solution of benzyl *tert*-butyl malonate (4.5 g, 17.9 mmol, 1 eq) in DMF (40 mL) at 20 °C was added Cs_2CO_3 (14.6 g, 44.9 mmol, 2.5 eq) and iodomethane (10.2 g,

71.9 mmol, 4.48 mL, 4 eq). The resulting mixture was then warmed to 50 °C and stirred for 2 h. The reaction mixture was then cooled to 0 °C and quenched by addition of H_2O (30 mL). The resulting biphasic mixture was then extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine (3 x 50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 1-benzyl 3-(*tert*-butyl) 2,2-dimethylmalonate, which was carried forward to the next step without further characterization.

[0447] Step b: To a solution of 1-benzyl 3-(*tert*-butyl) 2,2-dimethylmalonate (4.6 g, 16.5 mmol, 1 eq) in DCM (40 mL) at 25 °C was added TFA (15.0 g, 132 mmol, 9.8 mL, 8.00 eq), and the resulting mixture was stirred at 25 °C for 2 h. The reaction mixture was then concentrated under reduced pressure to give 3-(benzyloxy)-2,2-dimethyl-3-oxopropanoic acid. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{12}H_{14}O_4$: 223.1; found 223.1.

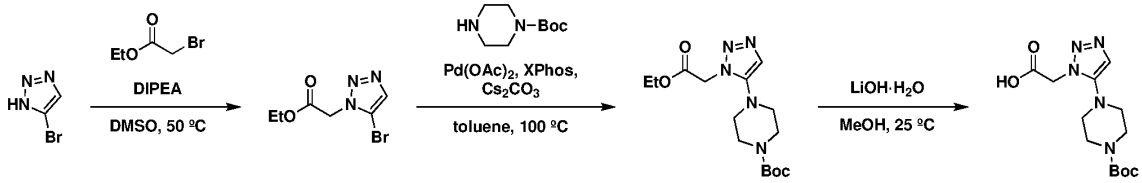
[0448] Step c: To a solution of 3-(benzyloxy)-2,2-dimethyl-3-oxopropanoic acid (1 g, 4.50 mmol, 1 eq) and *tert*-butyl hydrazinecarboxylate (654 mg, 4.95 mmol, 1.1 eq) in DMF (10 mL) at 0 °C was added triethylamine (1.37 g, 13.5 mmol, 1.88 mL, 3 eq) and HATU (1.88 g, 4.95 mmol, 1.1 eq). The resulting mixture was warmed to 25 °C and stirred for 2 h. The reaction mixture was then quenched by addition of H_2O (30 mL), and the resulting biphasic mixture was then extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (40 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give *tert*-butyl 2-(3-(benzyloxy)-2,2-dimethyl-3-oxopropanoyl)hydrazine-1-carboxylate, which was carried forward to the next step without further characterization.

[0449] Step d: To a solution of *tert*-butyl 2-(3-(benzyloxy)-2,2-dimethyl-3-oxopropanoyl)hydrazine-1-carboxylate (1 g, 2.97 mmol, 1 eq) in EtOAc (20 mL) at 25 °C was added HCl in EtOAc (4 M, 17.4 mL, 23.6 eq). The resulting mixture was stirred at 25 °C for 2 h. The reaction mixture was then concentrated under reduced pressure to give benzyl 3-hydrazineyl-2,2-dimethyl-3-oxopropanoate, which was carried forward to the next step without further characterization.

[0450] Step e: To a solution of benzyl 3-hydrazineyl-2,2-dimethyl-3-oxopropanoate (0.7 g, 2.50 mmol, 1 eq) in trimethoxymethane (10 mL) at 25 °C was added 4-methylbenzenesulfonic acid (43.0 mg, 249 µmol, 0.1 eq). The resulting mixture was warmed to 105 °C and stirred for 12 h. The reaction mixture was then cooled and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give benzyl 2-methyl-2-(1,3,4-oxadiazol-2-yl)propanoate, which was carried forward to the next step without further characterization.

[0451] Step f: To a solution of benzyl 2-methyl-2-(1,3,4-oxadiazol-2-yl)propanoate (0.4 g, 1.62 mmol, 1 eq), TEA (32.8 mg, 324 µmol, 45.2 µL, 0.2 eq) and *tert*-butyldimethylsilane (378 mg, 3.25 mmol, 2 eq) in DCE (5 mL) at 25 °C under N_2 was added $Pd(OAc)_2$ (91.2 mg, 406 µmol, 0.25 eq). The resulting mixture was warmed to 60 °C and stirred for 4 h. The reaction mixture was then filtered through a pad of Celite, and the pad was washed with EtOAc (2 x 200 mL). The combined filtrates were concentrated under reduced pressure, and the crude residue obtained was purified by prep-HPLC to give 2-methyl-2-(1,3,4-oxadiazol-2-yl)propanoic acid. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_6H_8N_2O_3$: 157.0; found 157.1.

Intermediate A-13: Synthesis of 2-(5-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)-1*H*-1,2,3-triazol-1-yl)acetic acid



[0452] Step a: To a solution of 5-bromo-1*H*-1,2,3-triazole (2.0 g, 13.5 mmol, 1 eq) and ethyl 2-bromoacetate (3.39 g, 20.3 mmol, 2.2 mL, 1.5 eq) in DMSO (15 mL) was added DIPEA (5.24 g, 40.6 mmol, 7.06 mL, 3 eq). The resulting mixture was warmed to 50 °C and stirred for 4 h. The reaction mixture was then cooled to 0 °C and quenched by addition of H_2O (20 mL), and the resulting biphasic mixture was then extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with H_2O (20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue

obtained was purified by column chromatography to give ethyl 2-(5-bromo-1*H*-1,2,3-triazol-1-yl)acetate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_6H_8BrN_3O_2$: 234.0; found 234.0.

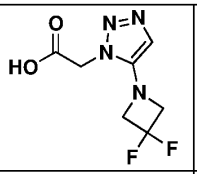
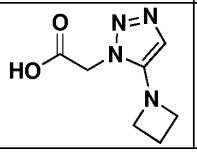
[0453] Step b: To a mixture of ethyl 2-(5-bromo-1*H*-1,2,3-triazol-1-yl)acetate (250 mg, 1.07 mmol, 1 eq), *tert*-butyl piperazine-1-carboxylate (1 g, 5.4 mmol, 5 eq), Cs_2CO_3 (1.1 g, 3.2 mmol, 3 eq), and XPhos (113 mg, 0.12 eq) in toluene (10 mL) was added $Pd(OAc)_2$ (60 mg, 0.12 eq). The resulting mixture was then degassed and placed under an N_2 atmosphere. The reaction mixture was then warmed to 100 °C and stirred for 16 h. The reaction mixture was then cooled to room temperature and filtered through a pad of Celite, and the filter cake was washed with toluene (2 x 10 mL). The combined filtrates were then concentrated under reduced pressure, and the crude residue obtained was purified by column chromatography to give *tert*-butyl 4-(1-(2-ethoxy-2-oxoethyl)-1*H*-1,2,3-triazol-5-yl)piperazine-1-carboxylate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{15}H_{25}N_5O_4$: 340.2; found 340.1.

[0454] Step c: To a solution of *tert*-butyl 4-(1-(2-ethoxy-2-oxoethyl)-1*H*-1,2,3-triazol-5-yl)piperazine-1-carboxylate (95 mg, 280 µmol, 1 eq) in MeOH (4 mL) was added $LiOH•H_2O$ (23.5 mg, 560 µmol, 2 eq), and the resulting mixture was stirred at 25 °C for 2 h. The reaction mixture was then concentrated under reduced pressure, and the residue obtained was dissolved in H_2O (5 mL). The resulting aqueous solution was extracted with EtOAc (2 x 5 mL), and then the aqueous phase was adjusted to pH 5–6 with aqueous HCl (3 M). The resulting aqueous solution was then extracted with EtOAc (2 x 6 mL), and the combined organic extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give 2-(5-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)-1*H*-1,2,3-triazol-1-yl)acetic acid. LC-MS (ESI): m/z: $[M - t\text{-Bu} + H]^+$ calculated for $C_{13}H_{21}N_5O_4$: 256.1; found 256.0.

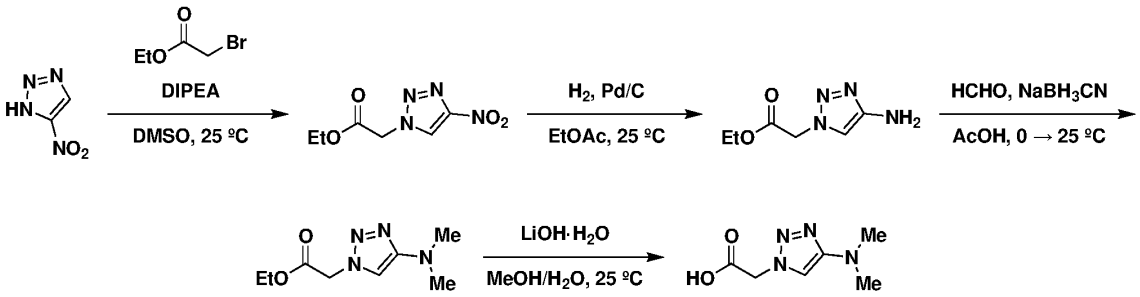
[0455] The following compounds in Table B-4 were synthesized using procedures similar to Intermediate A-13 using the appropriate starting materials.

Table B-4

Intermediate No.	Structure	IUPAC	Exact mass (g/mol)	LCMS, Found $[M + H]^+$

B-4-1		2-(5-(3,3-difluoroazetidin-1-yl)-1*H*-1,2,3-triazol-1-yl)acetic acid	218.1	219.0
B-4-2		2-(5-(azetidin-1-yl)-1*H*-1,2,3-triazol-1-yl)acetic acid	182.1	183.2

Intermediate A-14: Synthesis of 2-(4-(dimethylamino)-1*H*-1,2,3-triazol-1-yl)acetic acid



[0456] Step a: To a mixture of 5-nitro-1*H*-1,2,3-triazole (11.3 g, 99.1 mmol, 1 eq) and ethyl 2-bromoacetate (24.8 g, 149 mmol, 16.4 mL, 1.5 eq) in DMSO (100 mL) at 25 ºC was added DIPEA (38.4 g, 297 mmol, 51.8 mL, 3 eq), and the resulting mixture was stirred at 25 ºC for 3 h. The reaction mixture was then cooled to 0 ºC and quenched by addition of H_2O (100 mL), and the resulting biphasic mixture was then extracted with EtOAc (2 x 70 mL). The combined organic extracts were washed with H_2O (50 mL) and brine (2 x 50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give ethyl 2-(4-nitro-1*H*-1,2,3-triazol-1-yl)acetate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_6H_8N_4O_4$: 201.0; found 201.0.

[0457] Step b: To a solution of ethyl 2-(4-nitro-1*H*-1,2,3-triazol-1-yl)acetate (11 g, 54.9 mmol, 1 eq) in EtOAc (300 mL) was added Pd/C (1.5 g, 10% purity) under N_2. The suspension was then degassed under vacuum and placed under an H_2 atmosphere. The resulting mixture was then stirred under H_2 (15 psi) at 25 ºC for 8 h. The mixture was then filtered, and

the filtrate was concentrated under reduced pressure to give ethyl 2-(4-amino-1*H*-1,2,3-triazol-1-yl)acetate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_6H_{10}N_4O_2$: 171.1; found 171.1.

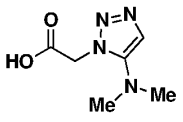
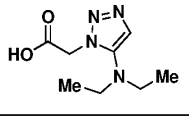
[0458] Step c: A mixture of ethyl 2-(4-amino-1*H*-1,2,3-triazol-1-yl)acetate (8 g, 47.0 mmol, 1 eq) and paraformaldehyde (14.1 g, 470 mmol, 10 eq) in AcOH (100 mL) was stirred at 25 ºC for 60 min. The reaction mixture was then cooled to 0 ºC before $NaBH_3CN$ (8.86 g, 141 mmol, 3 eq) was added in one portion. The resulting mixture was warmed to 25 ºC and stirred for 15 h. The reaction mixture was then cooled to 0 ºC and quenched by addition H_2O (100 mL). The pH of the resulting mixture was adjusted to pH = 6 using aqueous NaOH (4 M) before it was filtered. The filtrate was then extracted with EtOAc (2 x 150 mL). The combined organic extracts were washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give ethyl 2-(4-(dimethylamino)-1*H*-1,2,3-triazol-1-yl)acetate, which was carried forward to the next step without further characterization.

[0459] Step d: To a solution of ethyl 2-(4-(dimethylamino)-1*H*-1,2,3-triazol-1-yl)acetate (7 g, 35.3 mmol, 1 eq) in MeOH (70 mL) and H_2O (20 mL) at 25 ºC was added $LiOH•H_2O$ (2.96 g, 70.6 mmol, 2 eq). The resulting mixture was stirred at 25 ºC for 2 h. The reaction mixture was then concentrated under reduced pressure. The aqueous solution obtained was then adjusted to pH 5–6 using aqueous HCl (3 M), and the resulting mixture was concentrated under reduced pressure. The crude residue obtained was purified by prep-HPLC to give 2-(4-(dimethylamino)-1*H*-1,2,3-triazol-1-yl)acetic acid. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_6H_{10}N_4O_2$: 171.1; found 171.1.

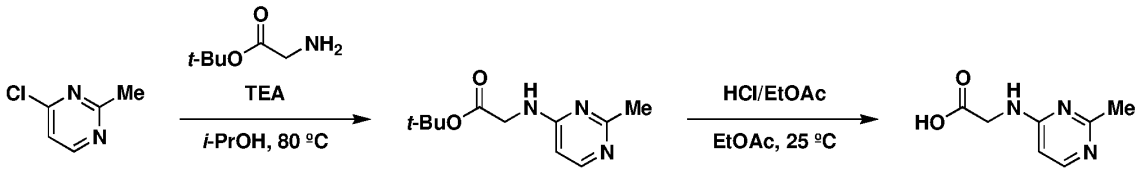
[0460] The following compounds in Table B-5 were synthesized using procedures similar to Intermediate A-14 using the appropriate starting materials.

Table B-5

Intermediate No.	Structure	IUPAC	Exact mass (g/mol)	LCMS, Found $[M + H]^+$

B-5-1		2-(5-(dimethylamino)-1*H*-1,2,3-triazol-1-yl)acetic acid	170.1	171.1
B-5-2		2-(5-(diethylamino)-1*H*-1,2,3-triazol-1-yl)acetic acid	198.1	199.0

Intermediate A-15: Synthesis of (2-methylpyrimidin-4-yl)glycine

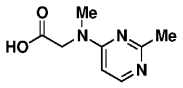


[0461] Step a: To a solution of 4-chloro-2-methylpyrimidine (300 mg, 2.33 mmol, 1 eq) in *i*-PrOH (3.00 mL) at 25 ºC was added TEA (708 mg, 7.00 mmol, 3 eq) and *tert*-butyl 2-aminoacetate (367 mg, 2.80 mmol, 1.2 eq). The resulting mixture was warmed to 80 ºC and stirred for 2 h. The reaction mixture was then quenched by addition H_2O (10 mL), and the resulting biphasic mixture was then extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give *tert*-butyl (2-methylpyrimidin-4-yl)glycinate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{11}H_{17}N_3O_2$: 224.1; found 224.1.

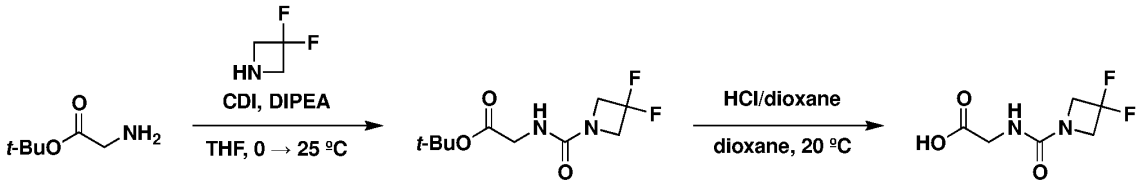
[0462] Step b: To a solution of *tert*-butyl (2-methylpyrimidin-4-yl)glycinate (310 mg, 1.39 mmol, 1 eq) in EtOAc (1.00 mL) was added HCl in EtOAc (4 M, 3 mL, 8.64 eq). The resulting mixture was stirred at 25 ºC for 4 h. The reaction mixture was then concentrated under reduced pressure to give (2-methylpyrimidin-4-yl)glycine. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_7H_9N_3O_2$: 168.1; found 168.1.

[0463] The following compounds in Table B-6 were synthesized using procedures similar to Intermediate A-15 using the appropriate starting materials.

Table B-6

Intermediate No.	Structure	IUPAC	Exact mass (g/mol)	LCMS, Found [M + H]$^+$
B-6-1		*N*-methyl-*N*-(2-methylpyrimidin-4-yl)glycine	181.1	182.1

Intermediate A-16: Synthesis of (3,3-difluoroazetidine-1-carbonyl)glycine

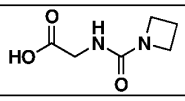


[0464] Step a: To a solution of *tert*-butyl 2-aminoacetate (1.00 g, 7.62 mmol, 1 eq) in THF (10 mL) at 0 °C under N_2 was added CDI (1.36 g, 8.39 mmol, 1.1 eq) and DIPEA (2.96 g, 22.9 mmol, 3 eq). The resulting mixture was stirred at 0 °C for 1 h. 3,3-difluoroazetidine (987 mg, 7.62 mmol, 1 eq, HCl salt) was then added, and the resulting mixture was warmed to 60 °C and stirred for 1 h. The reaction mixture was then diluted with H_2O (50 mL) and filtered. The filter cake was washed with H_2O (20 mL), and the washed solid was dried under reduced pressure to give *tert*-butyl (3,3-difluoroazetidine-1-carbonyl)glycinate. LC-MS (ESI): m/z: [M – *t*-Bu + H + H]$^+$ calculated for $C_{10}H_{16}F_2N_2O_3$: 195.0; found 195.0.

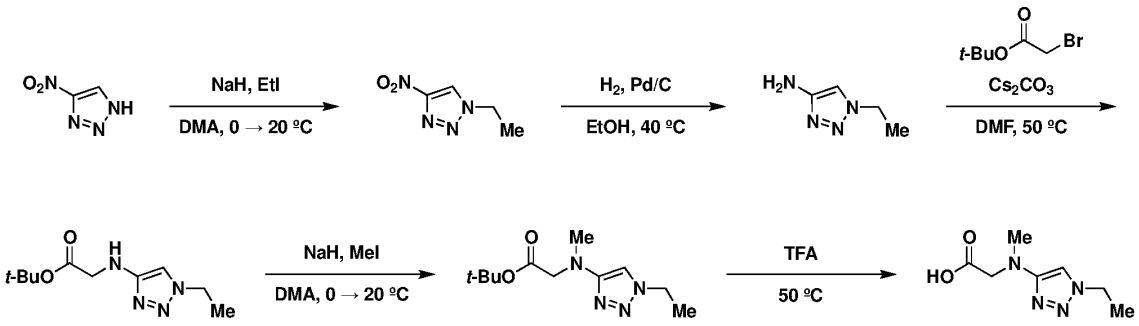
[0465] Step b: A solution *tert*-butyl (3,3-difluoroazetidine-1-carbonyl)glycinate (1.3 g, 5.19 mmol, 1 eq) in HCl in dioxane (4 M, 30 mL) was stirred at 20 °C for 1 h. The reaction mixture was then concentrated under reduced pressure, and the crude residue obtained was triturated with MTBE (20 mL) to give (3,3-difluoroazetidine-1-carbonyl)glycine. LC-MS (ESI): m/z: [M + H]$^+$ calculated for $C_6H_8F_2N_2O_3$: 195.0; found 195.0.

[0466] The following compounds in Table B-7 were synthesized using procedures similar to Intermediate A-16 using the appropriate starting materials.

Table B-7

Intermediate No.	Structure	IUPAC	Exact mass (g/mol)	LCMS, Found [M + H]$^+$
B-7-1		(azetidine-1-carbonyl)glycine	158.1	159.1

Intermediate A-17: Synthesis of *N*-(1-ethyl-1*H*-1,2,3-triazol-4-yl)-*N*-methylglycine



[0467] Step a: To a solution of 4-nitro-1*H*-1,2,3-triazole (4.00 g, 35.1 mmol, 1 eq) in DMA (80 mL) at 0 ºC was added NaH (1.47 g, 36.8 mmol, 60% purity, 1.05 eq). The resulting mixture was stirred at 0 ºC for 0.5 h. EtI (8.20 g, 52.6 mmol, 4.21 mL, 1.5 eq) was then added in one portion, and the resulting mixture was warmed to 20 ºC and stirred for 3 h. The reaction mixture was then quenched with H_2O (150 mL), and the resulting biphasic mixture was extracted with EtOAc (2 x 50 mL). The combined organic extracts were concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 1-ethyl-4-nitro-1*H*-1,2,3-triazole. LC-MS (ESI): m/z: [M + H]$^+$ calculated for $C_4H_6N_4O_2$: 143.0; found 143.1.

[0468] Step b: A mixture of 1-ethyl-4-nitro-1*H*-1,2,3-triazole 1.6 g, 11.3 mmol, 1 eq) and Pd/C (400 mg, 10% purity) in EtOH (20 mL) was degassed with H_2. The degassed mixture was then warmed to 40 ºC and stirred under H_2 (50 psi) for 3 h. The reaction mixture was then cooled and filtered, and the filtrate was concentrated under reduced pressure to give 1-ethyl-1*H*-1,2,3-triazol-4-amine, which was carried forward to the next step without further purification or characterization.

[0469] Step c: A mixture of 1-ethyl-1*H*-1,2,3-triazol-4-amine (600 mg, 5.35 mmol, 1 eq) and Cs_2CO_3 (1.74 g, 5.35 mmol, 1 eq) in DMF (3 mL) was stirred at 25 °C for 0.5 h before *tert*-butyl 2-bromoacetate (1.15 g, 5.89 mmol, 1.1 eq) was added in one portion, and the resulting mixture was warmed to 50 °C and stirred for 12 h. The reaction mixture was then quenched with H_2O (10 mL) and extracted with EtOAc (2 x 20 mL). The organic extracts were concentrated under reduced pressure, and the crude residue obtained was purified by column chromatography to give *tert*-butyl (1-ethyl-1*H*-1,2,3-triazol-4-yl)glycinate. LC-MS (ESI): m/z: $[M - t\text{-Bu} + H + H]^+$ calculated for $C_{10}H_{18}N_4O_2$: 171.1; found 171.1.

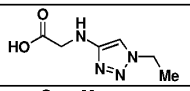
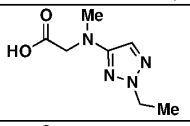
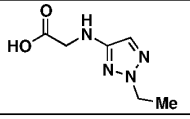
[0470] Step d: To a solution of *tert*-butyl (1-ethyl-1*H*-1,2,3-triazol-4-yl)glycinate (280 mg, 1.24 mmol, 1 eq) in DMA (2 mL) at 0 °C was added NaH (49 mg, 1.24 mmol, 60% purity, 1 eq), and the resulting mixture was stirred at 0 °C for 0.5 h. CH_3I (175 mg, 1.24 mmol, 1 eq) was then added, and the resulting mixture was warmed to 20 °C and stirred for 3 h. The mixture was then quenched with H_2O (10 mL), and the biphasic mixture was extracted with EtOAc (2 x 10 mL). The organic extracts were concentrated under reduced pressure, and the crude residue obtained was purified by prep-TLC to give *tert*-butyl *N*-(1-ethyl-1*H*-1,2,3-triazol-4-yl)-*N*-methylglycinate. LC-MS (ESI): m/z: $[M - t\text{-Bu} + H + H]^+$ calculated for $C_{11}H_{20}N_4O_2$: 185.1; found 185.1.

[0471] Step e: A solution of *tert*-butyl *N*-(1-ethyl-1*H*-1,2,3-triazol-4-yl)-*N*-methylglycinate (130 mg, 541 µmol, 1 eq) in TFA (2.00 g, 17.56 mmol, 32.5 eq) was stirred at 50 °C for 1 h. The reaction mixture was then cooled and concentrated under reduced pressure to give *N*-(1-ethyl-1*H*-1,2,3-triazol-4-yl)-*N*-methylglycine, which was used without any additional purification. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_7H_{12}N_4O_2$: 185.1; found 185.2.

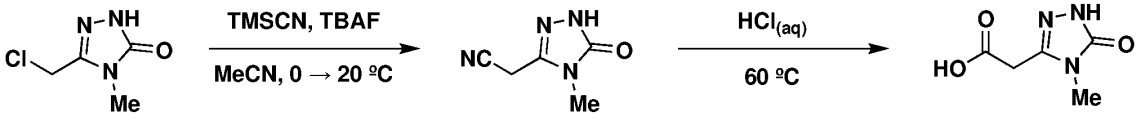
[0472] The following compounds in Table B-8 were synthesized using procedures similar to Intermediate A-17 using the appropriate starting materials.

Table B-8

Intermediate No.	Structure	IUPAC	Exact mass (g/mol)	LCMS, Found $[M + H]^+$

B-8-1		(1-ethyl-1*H*-1,2,3-triazol-4-yl)glycine	170.1	171.1
B-8-2		*N*-(2-ethyl-2*H*-1,2,3-triazol-4-yl)-*N*-methylglycine	184.1	185.1
B-8-3		(2-ethyl-2*H*-1,2,3-triazol-4-yl)glycine	170.1	171.1

Intermediate A-18: Synthesis of 2-(4-methyl-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)acetic acid

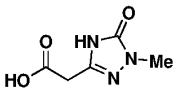


[0473] Step a: To a solution of 5-(chloromethyl)-4-methyl-2,4-dihydro-3*H*-1,2,4-triazol-3-one (100 mg, 678 µmol, 1 eq) in MeCN (2 mL) at 0 ºC was added TMSCN (100 mg, 1.02 mmol, 127 µL, 1.5 eq) and TBAF (1 M in THF, 1.02 mL, 1.5 eq). The resulting mixture was warmed to 20 ºC and stirred for 3 h. The reaction mixture was then quenched with H_2O (5 mL) and extracted with EtOAc (2 x 10 mL). The organic extracts were then concentrated under reduced pressure to give 2-(4-methyl-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)acetonitrile. LC-MS (ESI): m/z: $[M - H]^-$ calculated for $C_5H_6N_4O$: 137.0; found 137.2.

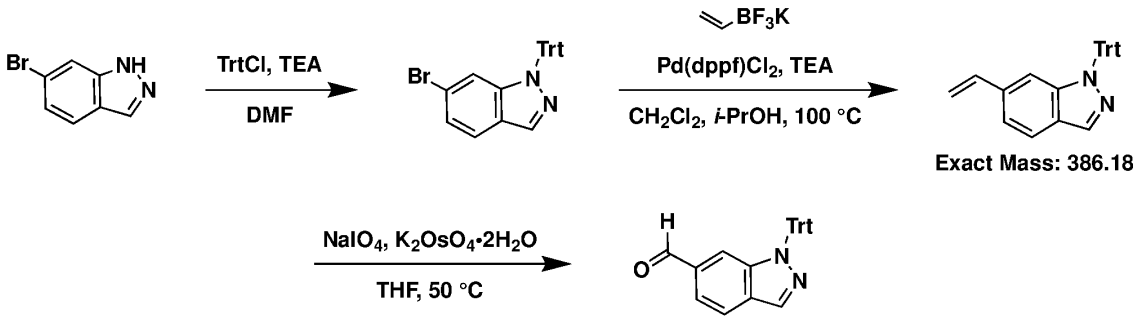
[0474] Step b: A mixture of 2-(4-methyl-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)acetonitrile (30 mg, 217 µmol, 1 eq) in aqueous HCl (12 M, 7.60 mL) was stirred at 60 ºC for 1 h. The mixture was then concentrated under reduced pressure to give 2-(4-methyl-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)acetic acid. LC-MS (ESI): m/z: $[M - H]^-$ calculated for $C_5H_7N_3O_3$: 156.0; found 156.2.

[0475] The following compounds in Table B-9 were synthesized using procedures similar to Intermediate A-18 using the appropriate starting materials.

Table B-9

Intermediate No.	Structure	IUPAC	Exact mass (g/mol)	LCMS, Found [M + H]$^+$
B-9-1		2-(1-methyl-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)acetic acid	157.0	156.1 [M – H]$^-$

Intermediate A-19: Synthesis of 1-trityl-1H-indazole-6-carbaldehyde



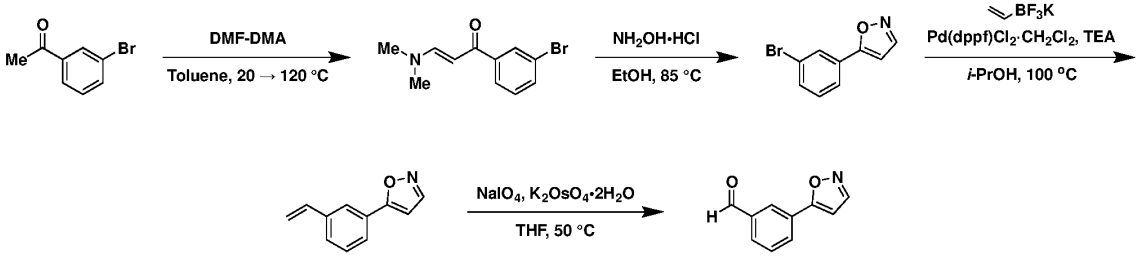
[0476] Step a: To a solution of 6-bromo-1*H*-indazole (8 g, 40.6 mmol, 1 eq) in DMF (50 mL) was added trityl chloride (TrtCl, 12.4 g, 44.6 mmol, 1.1 eq) and TEA (7.06 mL, 50.7 mmol, 1.25 eq). The resulting mixture was stirred at 25 ºC for 16 h. The reaction mixture was then diluted with water, and the resulting biphasic mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was triturated with MTBE (30 mL) and filtered to give 6-bromo-1-trityl-1*H*-indazole, which was carried forward to the next step without further purification or characterization.

[0477] Step b: To a mixture of 6-bromo-1-trityl-1*H*-indazole (16.7 g, 38.0 mmol, 1 eq), potassium vinyltrifluoroborate (10.1 g, 76.0 mmol, 2 eq) and TEA (15.8 mL, 14.0 mmol , 3 eq) in *i*-PrOH (160 mL), was added $Pd(dppf)Cl_2•CH_2Cl_2$ (1.55 g, 1.90 mmol, 0.05 eq) under N_2. The resulting mixture was then degassed and placed under an N_2 atmosphere. The reaction mixture was then warmed to 100 ºC and stirred for 2 h under N_2. After cooling, the mixture was filtered, and the filter cake was washed with ethyl acetate (3 x 100 mL). The combined filtrates were concentrated, and the crude residue obtained was purified by column chromatography to

give 1-trityl-6-vinyl-1*H*-indazole LC-MS (ESI): m/z: $[2M+Na]^+$ calculated for $C_{28}H_{22}N_2$: 795.4; found 795.3.

[0478] Step c: To a solution of 1-trityl-6-vinyl-1*H*-indazole (14.2 g, 36.7 mmol, 1 eq) in THF:H_2O (5:1) (300 mL) at 0 °C was added $NaIO_4$ (31.4 g, 146 mmol, 4 eq) and K_2OsO_4•$2H_2O$ (676 mg, 1.84 mmol, 0.05 eq). The resulting mixture was warmed to 50 °C and stirred for 1 h. The reaction mixture was then cooled to 25 °C and quenched with sat. aq. $Na_2S_2O_3$ (100 mL). The resulting mixture was extracted with ethyl acetate (3 x 100 mL), and the combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography to give 1-trityl-1*H*-indazole-6-carbaldehyde.

Intermediate A-20: Synthesis of 3-(isoxazol-5-yl)benzaldehyde



[0479] Step a: To a solution of 1-(3-bromophenyl)ethan-1-one (18.5 g, 92.9 mmol, 1 eq) in toluene (150 mL) was added *N*,*N*-dimethylformamide dimethyl acetal (37 mL, 346 mmol, 3.7 eq) at 20 °C. The resulting mixture was warmed to 120 °C and stirred for 1 h. The reaction mixture was then cooled to 20 °C and quenched with water (100 mL), and the resulting biphasic mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give (*E*)-1-(3-bromophenyl)-3-(dimethylamino)prop-2-en-1-one. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{11}H_{12}BrNO$: 254.1; found 254.1.

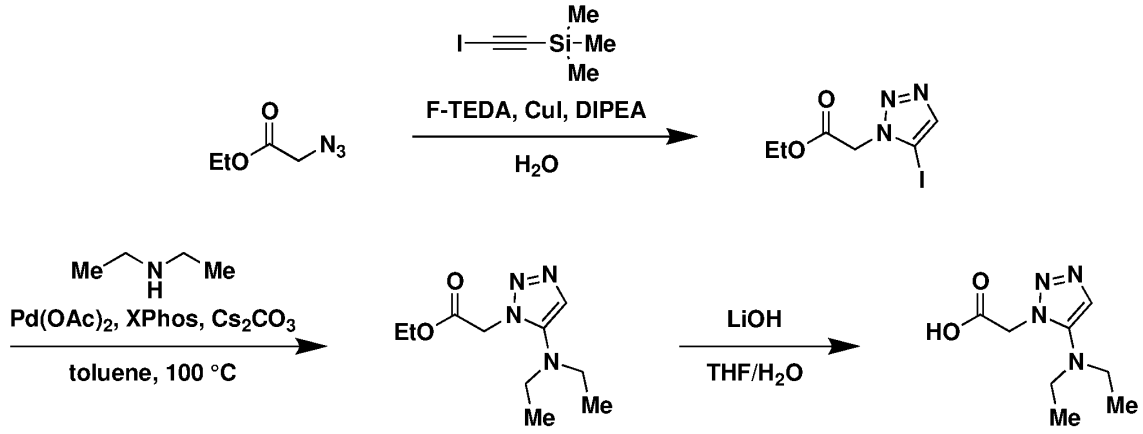
[0480] Step b: To a solution of (*E*)-1-(3-bromophenyl)-3-(dimethylamino)prop-2-en-1-one (8 g, 31.4 mmol, 1 eq) in EtOH (50 mL) was added NH_2OH•HCl (2.63 g, 37.7 mmol, 1.2 eq). The resulting mixture was warmed to 85 °C and stirred for 2 h. The reaction mixture was

then cooled to 25 °C and quenched with water (50 mL), and the resulting biphasic mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 5-(3-bromophenyl)isoxazole. LC-MS (ESI): m/z: $[M + H]^+$ calculated for C_9H_6BrNO: 224.0; found 224.1.

[0481] Step c: To a mixture of 5-(3-bromophenyl)isoxazole (8 g, 28.5 mmol, 1 eq), potassium vinyltrifluoroborate (7.65 g, 57.1 mmol, 2 eq) and TEA (11.9 mL, 85.6 mmol, 3 eq) in *i*-PrOH (50 mL) was added $Pd(dppf)Cl_2 \bullet CH_2Cl_2$ (1.17 g, 1.43 mmol, 0.05 eq) under N_2. The resulting mixture was degassed and placed under N_2, and the reaction mixture was then warmed to 100 °C and stirred for 1 h. The reaction mixture was then cooled, quenched with water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 5-(3-vinylphenyl)isoxazole. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{11}H_9NO$: 172.1; found 172.1.

[0482] Step d: To a solution of 5-(3-vinylphenyl)isoxazole (1.8 g, 10.5 mmol, 1 eq) in THF (50 mL) and H_2O (10 mL) was added $NaIO_4$ (9.00 g, 42.0 mmol, 4 eq) and potassium osmate dihydrate (194 mg, 525 μmol, 0.05 eq). The resulting mixture was warmed to 50 °C and stirred for 1 h. The reaction mixture was then cooled and quenched with water (50 mL), and the resulting biphasic mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 3-(isoxazol-5-yl)benzaldehyde. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{10}H_7NO_2$: 174.0; found 174.0.

Intermediate A-21: Synthesis of 2-(5-(diethylamino)-1*H*-1,2,3-triazol-1-yl)acetic acid



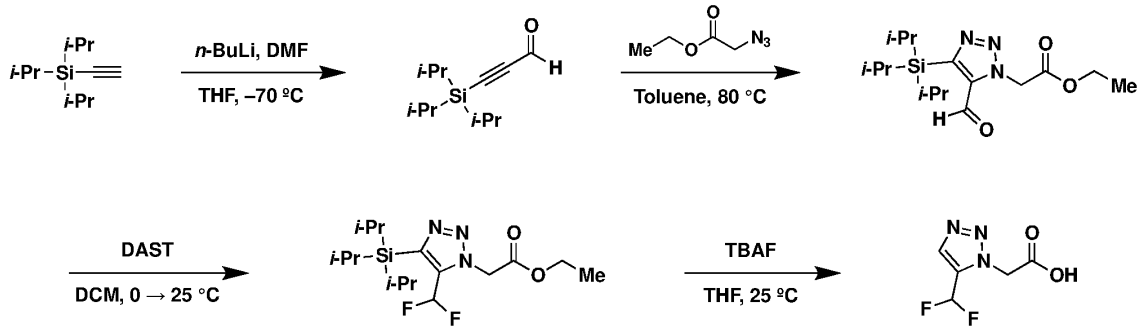
[0483] Step a: A mixture of ethyl 2-azidoacetate (8 g, 61.9 mmol, 7.08 mL, 1 eq), (iodoethynyl)trimethylsilane (15.2 g, 68.1 mmol, 1.1 eq), copper iodide (1.18 g, 6.20 mmol, 0.1 eq), DIPEA (16.0 g, 123 mmol, 21.5 mL, 2 eq) and 1-(chloromethyl)-4-fluoro-1,4-diazabicyclo[2.2.2]octane-1,4-diium ditetrafluoroborate (F-TEDA, 32.9 g, 92.9 mmol, 1.5 eq) in H_2O (80 mL) was degassed and placed under an N_2 atmosphere. The reaction mixture was then stirred for 16 h. The reaction mixture was then diluted with water and extracted with EtOAc (2 x 200 mL). The combined organic extracts were washed with brine (300 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give ethyl 2-(5-iodo-1*H*-1,2,3-triazol-1-yl)acetate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_6H_8IN_3O_2$: 282.0; found 281.9.

[0484] Step b: To a solution of ethyl 2-(5-iodo-1*H*-1,2,3-triazol-1-yl)acetate (700 mg, 2.49 mmol, 1 eq) in toluene (5 mL) was added *N*-ethylethanamine (911 mg, 12.4 mmol, 5 eq) and Cs_2CO_3 (1.62 g, 4.98 mmol, 2 eq). The resulting mixture was degassed and placed under an N_2 atmosphere, and then XPhos (949 mg, 1.99 mmol, 0.8 eq) and $Pd(OAc)_2$ (112 mg, 498 µmol, 0.2 eq) were added. The resulting mixture was then degassed and placed under an N_2 atmosphere, warmed to 100 °C, and stirred for 16 h. After cooling, the reaction mixture was concentrated under reduced pressure. Water (15 mL) was added, and the resulting mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give ethyl 2-(5-

(diethylamino)-1*H*-1,2,3-triazol-1-yl)acetate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{10}H_{18}N_4O_2$: 227.1; found 227.2.

[0485] Step c: To a solution of ethyl 2-(5-(diethylamino)-1*H*-1,2,3-triazol-1-yl)acetate (200 mg, 883 µmol, 1 eq) in THF (2 mL) at 0 ºC was added LiOH (23.3 mg, 972 µmol, 4.85 mL,1.1 eq) in water (0.5 mL), and the resulting mixture was warmed to 25 ºC and stirred for 1 h. The reaction mixture was then concentrated under reduced pressure. The crude residue obtained was purified by prep-HPLC to give 2-(5-(diethylamino)-1*H*-1,2,3-triazol-1-yl)acetic acid. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_8H_{14}N_4O_2$: 199.1; found 199.2.

Intermediate A-22: Synthesis of 2-(5-(difluoromethyl)-1*H*-1,2,3-triazol-1-yl)acetic acid



[0486] Step a: To a solution of ethynyltriisopropylsilane (15 g, 82.3 mmol, 18.5 mL, 1 eq) in THF (200 mL) at –70 ºC was added *n*-BuLi (2.5 M in hexane, 29.6 mL, 0.9 eq) in a dropwise manner. After 30 min, DMF (10.8 g, 148 mmol, 11.39 mL, 1.8 eq) was added in a dropwise manner, and the resulting mixture was warmed to room temperature and stirred for 30 min. The reaction mixture was then quenched with water (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 3-(triisopropylsilyl)propiolaldehyde.

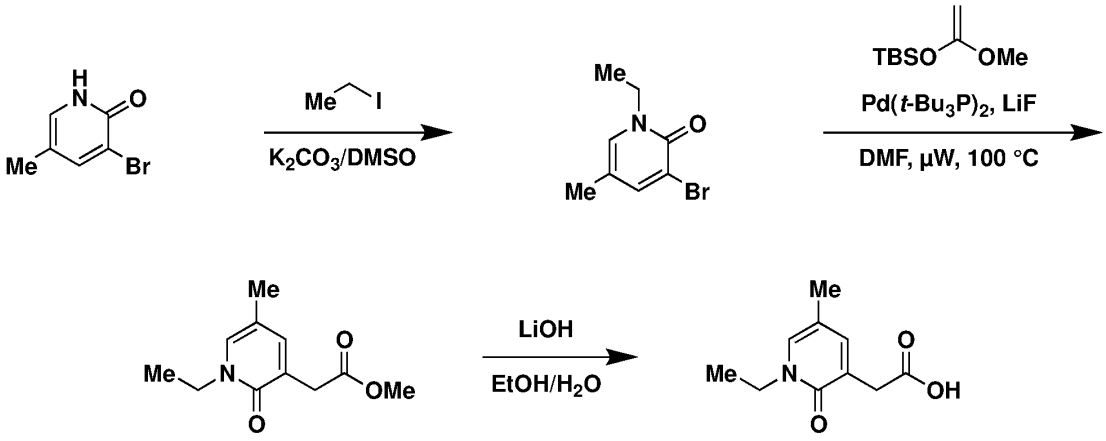
[0487] Step b: To a solution of ethyl 2-azidoacetate (2.56 g, 19.8 mmol, 1 eq) in toluene (60 mL) was added 3-(triisopropylsilyl)propiolaldehyde (5 g, 23.8 mmol, 1.2 eq). The resulting mixture was then warmed to 80 ºC and stirred for 16 h. After cooling, the reaction mixture was concentrated under reduced pressure. The crude residue obtained was purified by

column chromatography to give ethyl 2-(5-formyl-4-(triisopropylsilyl)-1*H*-1,2,3-triazol-1-yl)acetate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{16}H_{29}N_3O_3Si$: 340.2; found 340.3.

[0488] Step c: To a solution of ethyl 2-(5-formyl-4-(triisopropylsilyl)-1*H*-1,2,3-triazol-1-yl)acetate (4.5 g, 13.3 mmol, 1 eq) in DCM (40 mL) at 0 ºC was added DAST (5.34 g, 33.1 mmol, 2.5 eq) dropwise in a dropwise manner. The resulting mixture was warmed to room temperature and stirred for 16 h. The reaction mixture was then slowly added into ice-water (50 mL), and the resulting biphasic mixture was extracted with DCM (3 x 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and filtered, concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give ethyl 2-(5-(difluoromethyl)-4-(triisopropylsilyl)-1*H*-1,2,3-triazol-1-yl)acetate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{16}H_{29}F_2N_3O_2Si$: 362.2; found 362.3.

[0489] Step d: To a solution of 2-(5-(difluoromethyl)-4-(triisopropylsilyl)-1*H*-1,2,3-triazol-1-yl)acetate (1 g, 2.77 mmol, 1 eq) in THF (20 mL) was added TBAF (1.45 g, 5.53 mmol, 2 eq). The resulting mixture was stirred at 25 ºC for 16 h. The reaction mixture was then poured into ice-water (20 mL), and the resulting biphasic mixture was extracted with EtOAc (2 x 20 mL). The water phase was adjusted to pH 3–4 with aqueous HCl (2N) and then extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure to give 2-(5-(difluoromethyl)-1*H*-1,2,3-triazol-1-yl)acetic acid. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_5H_5F_2N_3O_2$: 178.0; found 178.0.

Intermediate A-23: Synthesis of 2-(1-ethyl-5-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetic acid

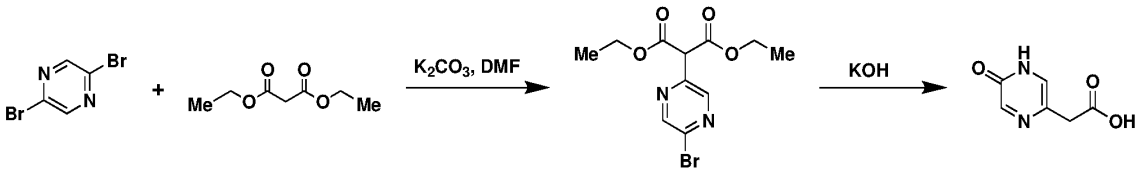


[0490] Step a: To a solution of 3-bromo-5-methylpyridin-2(1*H*)-one (5 g, 26.6 mmol, 1 eq) and K_2CO_3 (7.35 g, 53.2 mmol, 2 eq) in DMSO (30 mL) was added iodoethane (5.39 g, 34.6 mmol, 1.3 eq). The resulting mixture was warmed to 40 °C and stirred for 4 h. The reaction mixture was then cooled and quenched with H_2O (30 mL), and the resulting biphasic mixture was then extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 3-bromo-1-ethyl-5-methylpyridin-2(1H)-one. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_8H_{10}BrNO$: 216.0; found 216.1.

[0491] Step b: A mixture of 3-bromo-1-ethyl-5-methylpyridin-2(1*H*)-one (0.1 g, 462 µmol, 1 eq), *tert*-butyl((1-methoxyvinyl)oxy)dimethylsilane (261 mg, 1.39 mmol, 3 eq), LiF (72.0 mg, 2.78 mmol, 6 eq), and bis(tri-*tert*-butylphosphine)palladium(0) (23.6 mg, 46.2 µmol, 0.1 eq) in DMF (4 mL) was degassed and placed under an N_2 atmosphere. The reaction mixture was then warmed to 100 °C under in a microwave and stirred for 2 h. The reaction mixture was then cooled and quenched with H_2O (10 mL), and the resulting biphasic mixture was extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give methyl 2-(1-ethyl-5-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{11}H_{15}NO_3$: 210.1; found 210.1.

[0492] Step c: To a solution of methyl 2-(1-ethyl-5-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetate (0.25 g, 1.19 mmol, 1 eq) in EtOH (3 mL) was added a solution of $LiOH•H_2O$ (100 mg, 2.39 mmol, 2 eq) in H_2O (1 mL). The resulting mixture was stirred for 2 h and then concentrated under reduced pressure. The crude residue obtained was purified by prep-HPLC to give 2-(1-ethyl-5-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetic acid. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{10}H_{13}NO_3$: 196.1; found 196.2.

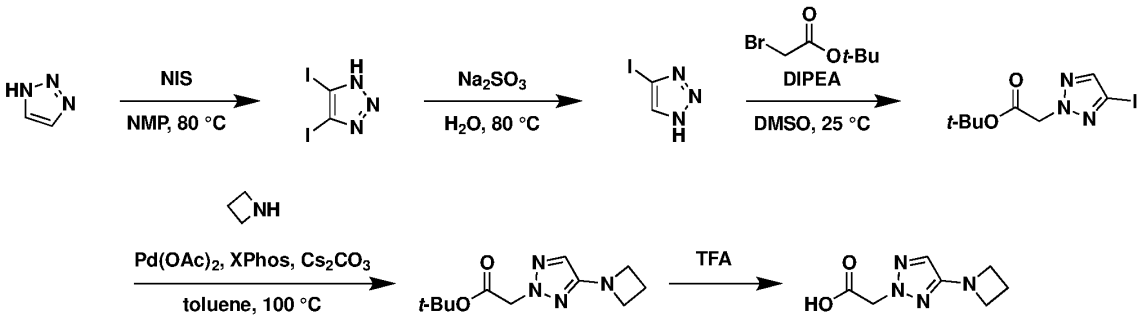
Intermediate A-24: Synthesis of 2-(5-oxo-4,5-dihydropyrazin-2-yl)acetic acid



[0493] Step a: To a solution of 2,5-dibromopyrazine (2 g, 8.41 mmol, 1 eq) in DMF (20 mL) was added K_2CO_3 (1.51 g, 10.9 mmol, 1.3 eq) and diethyl propanedioate (1.62 g, 10.1 mmol, 1.52 mL, 1.2 eq). The resulting mixture was warmed to 110 °C and stirred for 4 h. The reaction mixture was then cooled and diluted with H_2O (10 mL). The resulting biphasic mixture was extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (2 x 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give diethyl 2-(5-bromopyrazin-2-yl)malonate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{11}H_{13}BrN_2O_4$: 317.0; found 317.0.

[0494] Step b: Diethyl 2-(5-bromopyrazin-2-yl)malonate (700 mg, 2.21 mmol, 1 eq) was added to aqueous KOH (10 M, 7 mL), and the resulting mixture was warmed to 120 °C and stirred for 16 h. The reaction mixture was then cooled to room temperature, and the pH was adjusted to pH = 1 with aqueous HCl (6 N). The reaction mixture was then concentrated under reduced pressure, and the crude residue obtained was purified by prep-HPLC to give 2-(5-oxo-4,5-dihydropyrazin-2-yl)acetic acid. LC-MS (ESI): m/z: $[M - H]^-$ calculated for $C_6H_6N_2O_3$: 153.0; found 153.1.

Intermediate A-25: Synthesis of 2-(4-(azetidin-1-yl)-2*H*-1,2,3-triazol-2-yl)acetic acid



[0495] Step a: A mixture of 1*H*-1,2,3-triazole (10 g, 144 mmol, 1 eq) and *N*-iodosuccinimide (81.4 g, 361 mmol, 2.5 *eq*) in NMP (100 mL) under N_2 atmosphere was warmed to 80 °C and stirred for 1 h. The reaction mixture was then cooled to 0 °C and quenched with saturated aqueous Na_2SO_3 (15 mL). The resulting precipitate was collected by filtration. The solid was then diluted with H_2O (50 mL), and the resulting mixture was extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give 4,5-diiodo-1*H*-1,2,3-triazole. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_2HI_2N_3$: 321.8; found 321.8.

[0496] Step b: A mixture of 5-diiodo-1*H*-1,2,3-triazole (4 g, 12.4 mmol, 1 eq) and Na_2SO_3 (4.71 g, 37.4 mmol, 3 eq) in H_2O (40 mL) under N_2 atmosphere was warmed to 80 °C and stirred for 2 h. The reaction mixture was then cooled and diluted with H_2O (20 mL). The resulting biphasic mixture was extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give 4-iodo-1*H*-1,2,3-triazole, which was carried forward without further purification. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_2H_2IN_3$: 195.9; found 195.9.

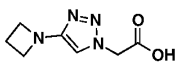
[0497] Step c: To a mixture of 4-iodo-1*H*-1,2,3-triazole (2 g, 10.2 mmol, 1 eq) and *tert*-butyl 2-bromoacetate (5 g, 25.6 mmol, 2.50 eq) in DMSO (20 mL) under N_2 atmosphere was added DIPEA (3.98 g, 30.7 mmol, 3 eq). The resulting mixture was stirred at 25 °C for 16 h. The reaction mixture was then quenched with H_2O (30 mL), and the resulting biphasic mixture was extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give *tert*-butyl 2-(4-iodo-2*H*-1,2,3-triazol-2-yl)acetate, which was carried forward to the next step without further characterization.

[0498] Step d: To a solution of *tert*-butyl 2-(4-iodo-2*H*-1,2,3-triazol-2-yl)acetate (1 g, 3.24 mmol, 1 eq) in dry toluene (25 mL) was added azetidine (923 mg, 16.2 mmol, 5 eq), Cs_2CO_3 (3.16 g, 9.71 mmol, 3 eq), and XPhos (1.23 g, 2.59 mmol, 0.8 eq) at 25 ºC, The resulting mixture was then degassed and placed under an N_2 atmosphere before $Pd(OAc)_2$ (145 mg, 647 µmol, 0.2 eq) was added. The resulting mixture was then degassed, placed under an N_2 atmosphere, warmed to 100 ºC, and stirred for 16 h. The reaction mixture was then cooled, and water (30 mL) was added. The resulting biphasic mixture was then extracted with ethyl acetate (3 x 30mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give *tert*-butyl 2-(4-(azetidin-1-yl)-2*H*-1,2,3-triazol-2-yl)acetate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{11}H_{18}N_4O_2$: 239.1; found 239.2.

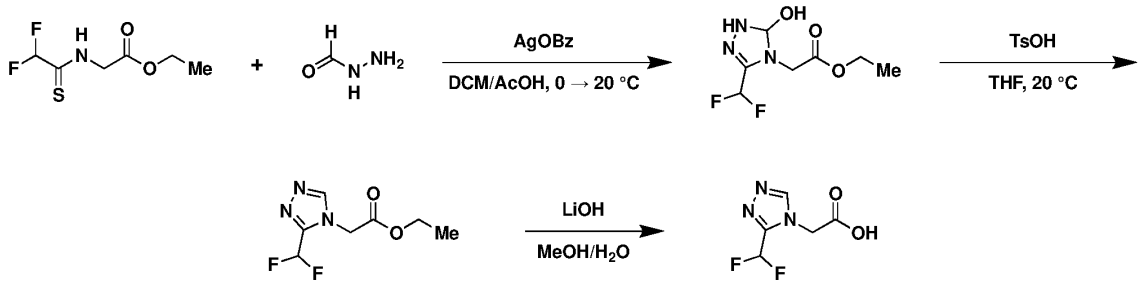
[0499] Step e: A solution of *tert*-butyl 2-(4-(azetidin-1-yl)-2*H*-1,2,3-triazol-2-yl)acetate (370 mg, 1.55 mmol, 1 eq) in TFA (3 mL, 40.5 mmol) was stirred at 25 ºC for 1 h. The mixture was then concentrated under reduced pressure, and the crude residue obtained was triturated with MTBE (3 mL) to give 2-(4-(azetidin-1-yl)-2*H*-1,2,3-triazol-2-yl)acetic acid**.** LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_7H_{10}N_4O_2$: 183.1; found 183.2.

[0500] The following compounds in Table B-10 were synthesized using procedures similar to Intermediate A-25 using the appropriate starting materials.

Table B-10

Intermediate No.	Structure	IUPAC	Exact mass (g/mol)	LCMS, Found $[M + H]^+$
B-10-1		2-(4-(azetidin-1-yl)-1*H*-1,2,3-triazol-1-yl)acetic acid	182.1	183.2

Intermediate A-26: Synthesis of 2-(3-(difluoromethyl)-4*H*-1,2,4-triazol-4-yl)acetic acid



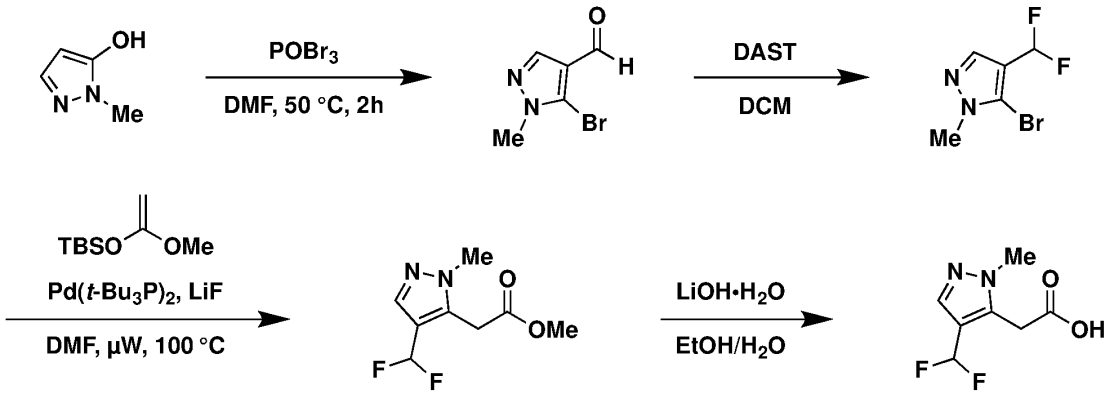
[0501] Step a: To a solution of ethyl (2,2-difluoroethanethioyl)glycinate (2 g, 9.29 mmol, 1 eq) and formic hydrazide (669 mg, 11.1 mmol, 1.2 eq) in DCM (100 mL) at 0 ºC was added silver benzoate (4.26 g, 18.5 mmol, 2 eq) and AcOH (1.67 g, 27.8 mmol, 3 eq). The resulting mixture was then warmed to 20 ºC and stirred for 16 h. The reaction mixture was then filtered, and the filtrate was quenched by addition of ice-water (100 mL). The resulting biphasic mixture was then extracted with DCM (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give ethyl 2-(3-(difluoromethyl)-5-hydroxy-1,5-dihydro-4*H*-1,2,4-triazol-4-yl)acetate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_7H_{11}F_2N_3O_3$: 224.1; found 224.0.

[0502] Step b: A mixture of ethyl 2-(3-(difluoromethyl)-5-hydroxy-1,5-dihydro-4*H*-1,2,4-triazol-4-yl)acetate (1 g, 4.48 mmol, 1 eq) and 4-methylbenzenesulfonic acid (77.1 mg, 448 µmol, 0.1 eq) in THF (20 mL) was stirred at 20 ºC for 16 hours under N_2. The reaction mixture was then concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give ethyl 2-(3-(difluoromethyl)-4*H*-1,2,4-triazol-4-yl)acetate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_7H_9F_2N_3O_2$: 206.1; found 206.0.

[0503] Step c: To a solution of ethyl 2-(3-(difluoromethyl)-4*H*-1,2,4-triazol-4-yl)acetate (100 mg, 487 µmol, 1 eq) in H_2O (1 mL) and MeOH (5 mL) was added LiOH•H_2O (40.9 mg, 974 µmol, 2 eq) at 20 ºC. The resulting mixture was then stirred at 20 ºC for 2 h. The reaction mixture was then concentrated under reduced pressure to remove MeOH. The resulting mixture was then adjusted to pH 3–4 using aqueous HCl (1 M), and the aqueous mixture was then extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (50 mL), dried over with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to

give 2-(3-(difluoromethyl)-4*H*-1,2,4-triazol-4-yl)acetic acid. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_5H_5F_2N_3O_2$: 178.0; found 178.1.

Intermediate A-27: Synthesis of 2-(4-(difluoromethyl)-1-methyl-1*H*-pyrazol-5-yl)acetic acid



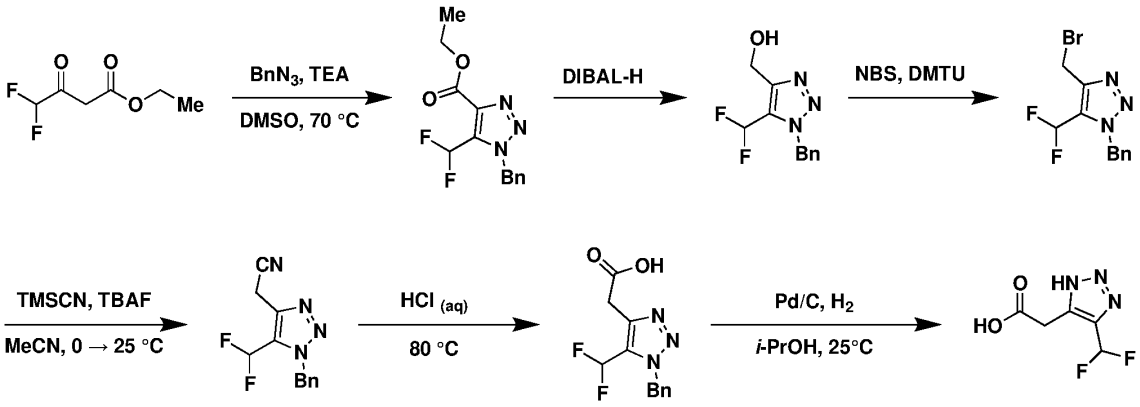
[0504] Step a: To a solution of $POBr_3$ (81.8 g, 285 mmol, 29.0 mL, 7 eq) in DMF (40 mL) at 0 °C was added 1-methyl-1*H*-pyrazol-5-ol (4 g, 40.7 mmol, 1 eq). The resulting mixture was warmed to 50 °C and stirred for 2 h. After cooling, the reaction mixture was quenched by addition saturated aq. Na_2CO_3 (100 mL) at 0 °C. The resulting biphasic mixture was extracted with EtOAc (2 x 250 mL). The combined organic extracts were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 5-bromo-1-methyl-1*H*-pyrazole-4-carbaldehyde. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_5H_5BrN_2O$: 189.0; found 188.9.

[0505] Step b: To a solution of 5-bromo-1-methyl-pyrazole-4-carbaldehyde (2.5 g, 13.2 mmol, 1 eq) in DCM (20 mL) at 0 °C was added DAST (8.53 g, 52.9 mmol, 4 eq) in a dropwise manner. The resulting mixture was warmed to 20 °C and stirred for 12 h. The reaction mixture was then cooled to 0 °C and quenched by addition H_2O (30 mL). The resulting biphasic mixture was extracted with DCM (3 x 10 mL). The combined organic extracts were washed with brine (30 mL), dried over with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 5-bromo-4-(difluoromethyl)-1-methyl-1*H*-pyrazole. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_5H_5BrF_2N_2$: 211.0; found 210.9.

[0506] Step c: To a solution of 5-bromo-4-(difluoromethyl)-1-methyl-1*H*-pyrazole (200 mg, 947 µmol, 1 eq) in DMF (2 mL) was added lithium fluoride (147 mg, 5.69 mmol, 6 eq) and *tert-tert*-butyl((1-methoxyvinyl)oxy)dimethylsilane (535 mg, 2.84 mmol, 3 eq). The resulting mixture was then degassed and placed under an N_2 atmosphere. Bis(tri-*tert*-butylphosphine)palladium(0) (48.4 mg, 94.7 µmol, 0.1 eq) was then added, and the resulting mixture was warmed to 100 °C using a microwave and stirred for 1.5 h. After cooling, the reaction mixture was then quenched by addition of H_2O (15 mL). The resulting biphasic mixture was then filtered and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give methyl 2-(4-(difluoromethyl)-1-methyl-1*H*-pyrazol-5-yl)acetate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_8H_{10}F_2N_2O_2$: 205.1; found 205.1.

[0507] Step d: To a solution of methyl 2-(4-(difluoromethyl)-1-methyl-1*H*-pyrazol-5-yl)acetate (75 mg, 367 µmol, 1 eq) in EtOH (1 mL) and H_2O (0.5 mL) was added $LiOH•H_2O$ (30.8 mg, 734 µmol, 2 eq), and the resulting mixture was stirred at 20 °C for 1 h. The reaction mixture was then quenched by addition of H_2O (5 mL), and the resulting biphasic mixture was extracted with EtOAc (2 x 5 mL). The aqueous phase pH was then adjusted to pH 3–4 with aqueous HCl (1M), and the aqueous phase was extracted with EtOAc (2 x 5 mL). The second set of organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give 2-(4-(difluoromethyl)-1-methyl-1*H*-pyrazol-5-yl)acetic acid. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_7H_8F_2N_2O_2$: 190.0; found 190.1.

Intermediate A-28: Synthesis of 2-(4-(difluoromethyl)-1*H*-1,2,3-triazol-5-yl)acetic acid



[0508] Step a: A mixture of compound ethyl 4,4-difluoro-3-oxobutanoate (12.0 g, 72.2 mmol, 1 eq), TEA (21.9 g, 217 mmol, 30.1 mL, 3 eq) and azidomethylbenzene (9.62 g, 72.2 mmol, 1 eq) in DMSO (100 mL) was heated and stirred at 70 °C for 16 h. After cooling the mixture was poured into ice-water (100 mL) and extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with aqueous HCl (0.5 M, 100 mL) and brine (200 mL), dried over anhydrous Na_2SO_4 filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography to give ethyl 1-benzyl-5-(difluoromethyl)-1*H*-1,2,3-triazole-4-carboxylate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{13}H_{13}F_2N_3O_2$: 282.2; found 282.2.

[0509] Step b: To a mixture of ethyl 1-benzyl-5-(difluoromethyl)-1*H*-1,2,3-triazole-4-carboxylate (3.00 g, 10.7 mmol, 1 eq) in THF (100 mL) was added DIBAL-H (1 M in THF, 64.0 mL, 6 eq) at 0 °C The resulting mixture was warmed to 25 °C and stirred for 1 h. The mixture was quenched by addition of sat. aq. NH_4Cl (10 mL), and the pH was adjusted to 5 with aqueous HCl (4M) and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash silica gel chromatography to give (1-benzyl-5-(difluoromethyl)-1*H*-1,2,3-triazol-4-yl)methanol LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{11}H_{11}F_2N_3O$: 240.1; found 240.1.

[0510] Step c: To a solution of compound (1-benzyl-5-(difluoromethyl)-1*H*-1,2,3-triazol-4-yl)methanol (2.00 g, 8.36 mmol, 1 eq) and 1,3-dimethylthiourea (DMTU, 392 mg, 3.76 mmol, 0.45 eq) in DCM (20 mL) was added NBS (2.23 g, 12.5 mmol, 1.5 eq) at 0 °C. The

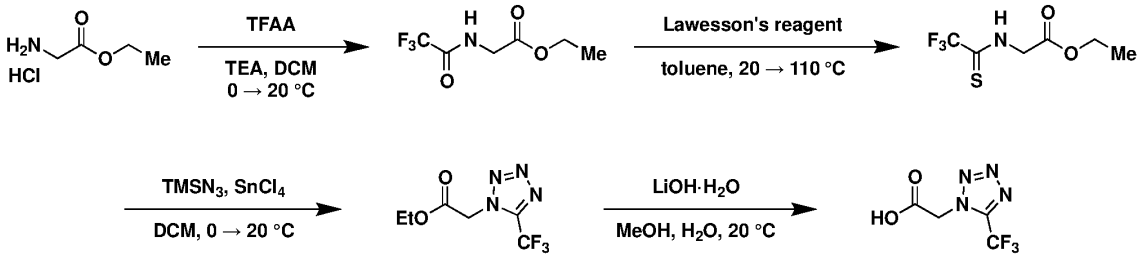
resulting mixture was warmed to 25 °C and stirred for 2 h. The mixture was quenched with H_2O (50 mL) and extracted with DCM (2 x 50 mL). The combined organic layers were washed with brine (80 mL), dried over with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography to give 1-benzyl-4-(bromomethyl)-5-(difluoromethyl)-1*H*-1,2,3-triazole. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{11}H_{10}BrN_3$: 301.9; found 301.9.

[0511] Step d: To a solution of compound 1-benzyl-4-(bromomethyl)-5-(difluoromethyl)-1*H*-1,2,3-triazole (800 mg, 2.65 mmol, 1 eq) and TMSCN (276 mg, 2.78 mmol, 1.05 eq) in MeCN (20 mL) was added TBAF (1 M, 3.97 mL, 1.5 eq) at 0 °C. The resulting mixture was warmed to 25 °C and stirred for 30 min. The mixture was quenched by addition of sat. aq. $NaHCO_3$ (30 mL) and extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with brine (20 mL), dried over with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography to obtain 2-(1-benzyl-5-(difluoromethyl)-1*H*-1,2,3-triazol-4-yl)acetonitrile. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{12}H_{10}F_2N_4$: 249.0; found 249.0.

[0512] Step e: A mixture of 2-(1-benzyl-5-(difluoromethyl)-1H-1,2,3-triazol-4-yl)acetonitrile (880 mg, 3.55 mmol, 1 eq) in concentrated HCl (20 mL) was stirred at 80 °C for 2 h. After cooling, the mixture was concentrated under reduced pressure. The resulting residue was washed with THF (40 mL) and filtered. The filtrate was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give 2-(1-benzyl-5-(difluoromethyl)-1*H*-1,2,3-triazol-4-yl)acetic acid. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{12}H_{11}F_2N_3O_2$: 268.0; found 268.0.

[0513] Step f: To a solution of 2-(1-benzyl-5-(difluoromethyl)-1*H*-1,2,3-triazol-4-yl)acetic acid (300 mg, 1.12 mmol, 1 eq) and concentrated HCl (11.4 mg, 112 µmol, 0.1 eq) in *i*-PrOH (10 mL) was added Pd/C (100 mg, 10% purity) under N_2. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (50 psi) at 25 °C for 16 h. The reaction mixture was filtered through a pad of celite and concentrated under reduced pressure to give 2-(4-(difluoromethyl)-1*H*-1,2,3-triazol-5-yl)acetic acid. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_5H_5F_2N_3O_2$: 178.0; found 178.0.

Intermediate A-29: Synthesis of 2-(5-(trifluoromethyl)-1*H*-tetrazol-1-yl)acetic acid



[0514] Step a: To a solution of ethyl glycinate hydrochloride (10 g, 71.6 mmol, 1 eq) in DCM (100 mL) at 0 °C was added trifluoroacetic anhydride (22.5 g, 107 mmol, 14.9 mL, 1.5 eq) and TEA (36.2 g, 358 mmol, 5 eq). The mixture was then warmed to 20 °C and stirred for 3 h. The reaction mixture was then poured into H_2O (100 mL), and the resulting biphasic mixture was extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried over with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give ethyl (2,2,2-trifluoroacetyl)glycinate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_6H_8F_3NO_3$: 200.0; found 200.0.

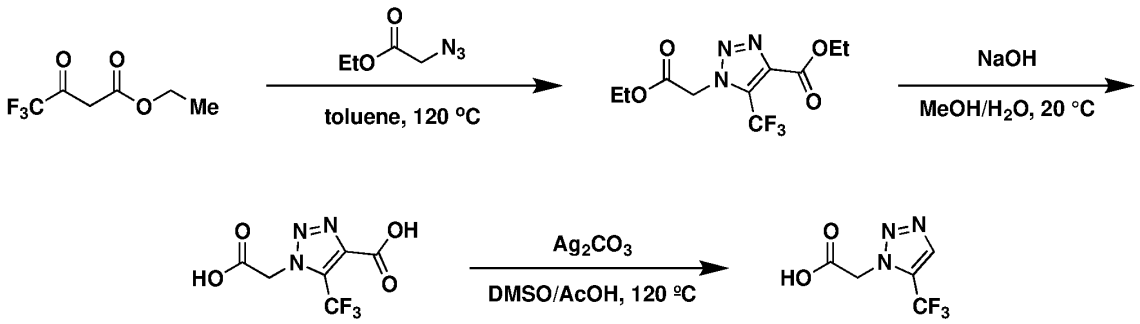
[0515] Step b: To a solution of ethyl (2,2,2-trifluoroacetyl)glycinate (11 g, 55.2 mmol, 1 eq) in toluene (200 mL) at 20 °C was added Lawesson's reagent (26.8 g, 66.2 mmol, 1.2 eq). The reaction mixture was then warmed to 110 °C and stirred for 1 h. After cooling to 20 °C, the reaction mixture was poured into H_2O (100 mL), and the resulting biphasic mixture was extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried over with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give ethyl (2,2,2-trifluoroethanethioyl)glycinate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_6H_8F_3NO_2S$: 216.0; found 215.9.

[0516] Step c: To a mixture of ethyl (2,2,2-trifluoroethanethioyl)glycinate (2 g, 9.29 mmol, 1 eq) and $TMSN_3$ (2.14 g, 18.5 mmol, 2.44 mL, 2 eq) in DCM (40 mL) at 0 °C under a N_2 atmosphere was added $SnCl_4$ (6.05 g, 23.2 mmol, 2.71 mL, 2.5 eq). The reaction mixture was then warmed to 20 °C and stirred for 16 h. The reaction mixture was then cooled to 0 °C and quenched by slow addition of saturated aq. $NaHCO_3$ (200 mL). The resulting biphasic mixture was extracted with EtOAc (2 x 200 mL). The combined organic extracts were dried over

anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give ethyl 2-(5-(trifluoromethyl)-1*H*-tetrazol-1-yl)acetate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_6H_7F_3N_4O_2$: 225.0; found 225.0.

[0517] Step d: To a solution of ethyl 2-(5-(trifluoromethyl)-1*H*-tetrazol-1-yl)acetate (500 mg, 2.23 mmol, 1 eq) in MeOH (10 mL) and H_2O (1 mL) at 20 °C was added $LiOH•H_2O$ (187 mg, 4.46 mmol, 2 eq). The resulting mixture was stirred at 20 °C for 16 h. The reaction mixture was then adjusted to pH 3–4 with aqueous HCl (1M) and stirred for 5 min. The resulting mixture was then filtered and concentrated under reduced pressure to give 2-(5-(trifluoromethyl)-1*H*-tetrazol-1-yl)acetic acid which was used without further purification. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_4H_3F_3N_4O_2$: 197.0; found 196.9.

Intermediate A-30: Synthesis of 2-(5-(trifluoromethyl)-1*H*-1,2,3-triazol-1-yl)acetic acid



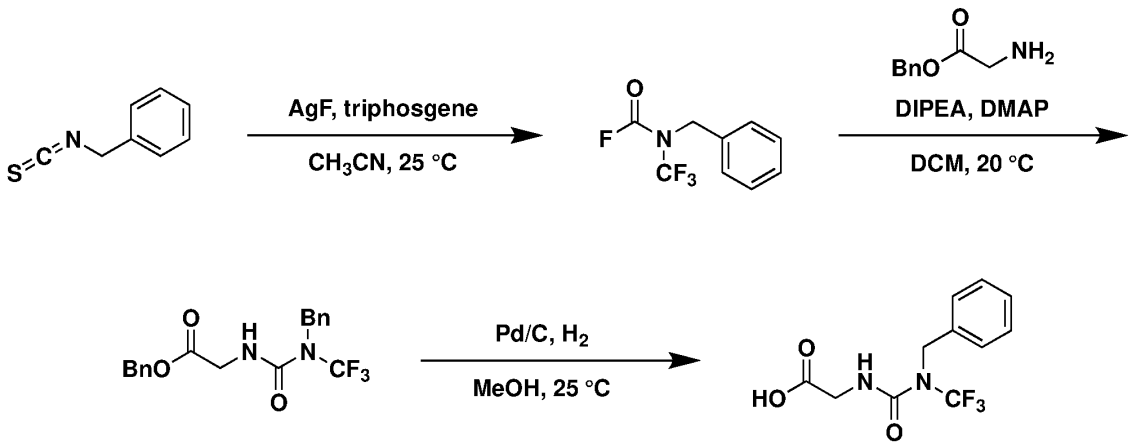
[0518] Step a: A mixture of ethyl 4,4,4-trifluoro-3-oxobutanoate (1.00 g, 5.43 mmol, 1 eq) and ethyl 2-azidoacetate (701 mg, 5.43 mmol, 1 eq) in toluene (10 mL) was warmed to 120 °C and stirred for 16 h. After cooling, the reaction mixture was concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give ethyl 1-(2-ethoxy-2-oxoethyl)-5-(trifluoromethyl)-1*H*-1,2,3-triazole-4-carboxylate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{10}H_{12}F_3N_3O_4$: 296.1; found 296.1.

[0519] Step b: A mixture of ethyl 1-(2-ethoxy-2-oxoethyl)-5-(trifluoromethyl)-1*H*-1,2,3-triazole-4-carboxylate (300 mg, 1.02 mmol, 1 eq) and NaOH (203 mg, 5.08 mmol, 5 eq) in H_2O (1 mL) and MeOH (10 mL) was stirred at 20 °C for 2 h. The reaction mixture was then acidified to pH = 2 with concentrated aq. HCl (12 N). The reaction mixture was concentrated

under reduced pressure to give 1-(carboxymethyl)-5-(trifluoromethyl)-1*H*-1,2,3-triazole-4-carboxylic acid. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_6H_4F_3N_3O_4$: 240.0; found 240.1.

[0520] Step c: A mixture of 1-(carboxymethyl)-5-(trifluoromethyl)-1*H*-1,2,3-triazole-4-carboxylic acid (250 mg, 1.05 mmol, 1 eq) and Ag_2CO_3 (28.8 mg, 104 µmol, 0.1 eq) in DMSO (1 mL) and AcOH (6.28 mg, 104 µmol, 0.1 eq) was warmed to 120 ºC and stirred for 16 h. After cooling, the reaction mixture was acidified to pH = 2 with concentrated aq. HCl (12 N). The reaction mixture was then concentrated under reduced pressure. The crude residue obtained was purified by prep-HPLC to give 2-(5-(trifluoromethyl)-1*H*-1,2,3-triazol-1-yl)acetic acid. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_5H_4F_3N_3O_2$: 196.0; found 196.1.

Intermediate A-31: Synthesis of (benzyl(trifluoromethyl)carbamoyl)glycine



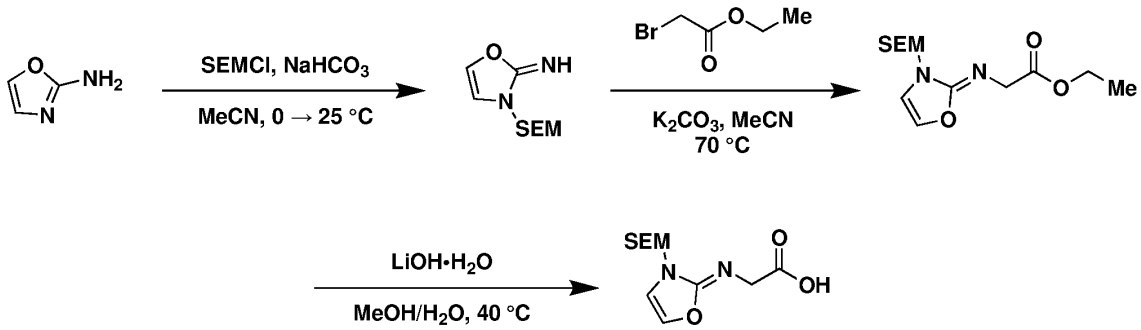
[0521] Step a. To a solution of AgF (1.02 g, 8.04 mmol, 6 eq) in CH_3CN (10 mL) at 0 ºC under an atmosphere of N_2 was added (isothiocyanatomethyl)benzene (0.2 g, 1.34 mmol, 177 µL, 1 eq) in a dropwise manner. Triphosgene (199 mg, 670 µmol, 0.5 eq) was then added. The resulting reaction mixture was warmed to 25 ºC and stirred for 16 h. The reaction mixture was then added to MTBE (20 mL) and stirred for 10 min. The precipitate generated was filtered to give benzyl (trifluoromethyl)carbamic fluoride, which was carried forward to the next step without further purification or characterization.

[0522] Step b. To as solution of benzyl (trifluoromethyl)carbamic fluoride (0.3 g, 1.36 mmol, 1 eq) in DCM (5 mL) was added benzyl glycinate (448 mg, 2.71 mmol, 2 eq),

DIPEA (526 mg, 4.07 mmol, 3 eq), and DMAP (16 mg, 136 µmol, 0.1 eq). The resulting reaction mixture was stirred at 20 °C for 16 h. The reaction was then quenched with water (20 mL), and the resulting biphasic mixture was extracted with DCM (3 x 20 mL). The combined organic extracts were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give benzyl (benzyl(trifluoromethyl)carbamoyl)glycinate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{18}H_{17}F_3N_2O_3$: 367.1; found 367.1.

[0523] Step c. To a solution of benzyl (benzyl(trifluoromethyl)carbamoyl)glycinate (150 mg, 409 µmol, 1 eq) in MeOH (3 mL) was added Pd/C (50 mg, 40.9 µmol, 10% purity, 0.1 eq). The resulting mixture was stirred at 25 °C for 16 h under H_2 (15 psi). The reaction mixture was then filtered and concentrated under reduced pressure to give (benzyl(trifluoromethyl)carbamoyl)glycine. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{11}H_{11}F_3N_2O_3$: 277.1; found 277.1.

Intermediate A-32: Synthesis of 2-(5-(trifluoromethyl)-1*H*-pyrazol-1-yl)acetic acid

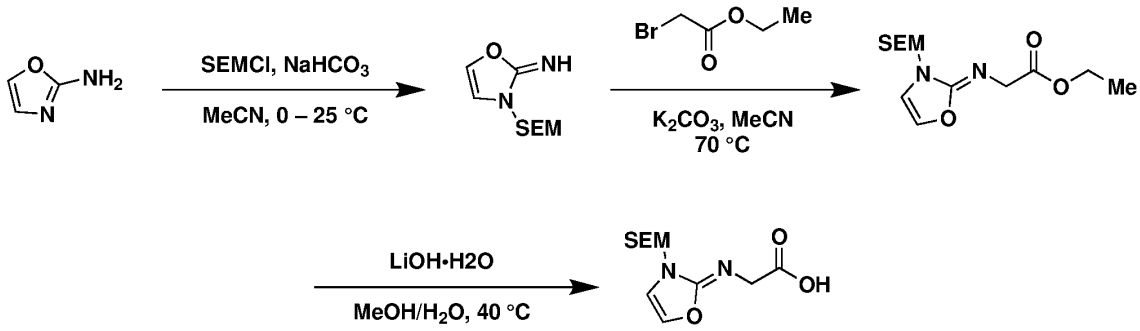


[0524] Step a: To a solution of ethyl aminoglycinate hydrochloride (3 g, 19.4 mmol, 1 eq) in EtOH (30 mL) was added NaOH (776 mg, 19.4 mmol, 1 eq) and ethyl (*Z*)-2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate (5.13 g, 21.4 mmol, 254 µL, 1.1 eq). The reaction was then stirred at 25 °C for 2 h. The reaction mixture was then concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give ethyl 1-(2-ethoxy-2-oxoethyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{11}H_{13}F_3N_2O_4$: 295.1; found 295.2.

[0525] Step b: A mixture of ethyl 1-(2-ethoxy-2-oxoethyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylate (3.5 g, 11.9 mmol, 1 eq) and LiOH•H_2O (3.49 g, 83.2 mmol, 7 eq) in THF (20 mL) and H_2O (20 mL) at 25 °C was stirred for 12 h. The reaction mixture was then extracted with EtOAc (50 mL). The combined organic extracts were washed with water (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 1-(carboxymethyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_7H_5F_3N_2O_4$: 239.0; found 239.1.

[0526] Step c: A mixture of 1-(carboxymethyl)-5-(trifluoromethyl)-1*H*-pyrazole-4-carboxylic acid (400 mg, 1.68 mmol, 1 eq), Cu_2O (24.0 mg, 168 µmol, 17.2 µL, 0.1 eq) and 1,10-phenantholine (30.3 mg, 168 µmol, 0.1 eq) in NMP (3 mL) were warmed to 150 °C and stirred for 3 h. The reaction mixture was then concentrated under reduced pressure. The crude residue obtained was purified by prep-HPLC to give 2-(5-(trifluoromethyl)-1*H*-pyrazol-1-yl)acetic acid. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_6H_5F_3N_2O_2$: 195.0; found 195.0.

Intermediate A-33: Synthesis of (*Z*)-2-((3-((2-(trimethylsilyl)ethoxy)methyl)oxazol-2(3*H*)-ylidene)amino)acetic acid



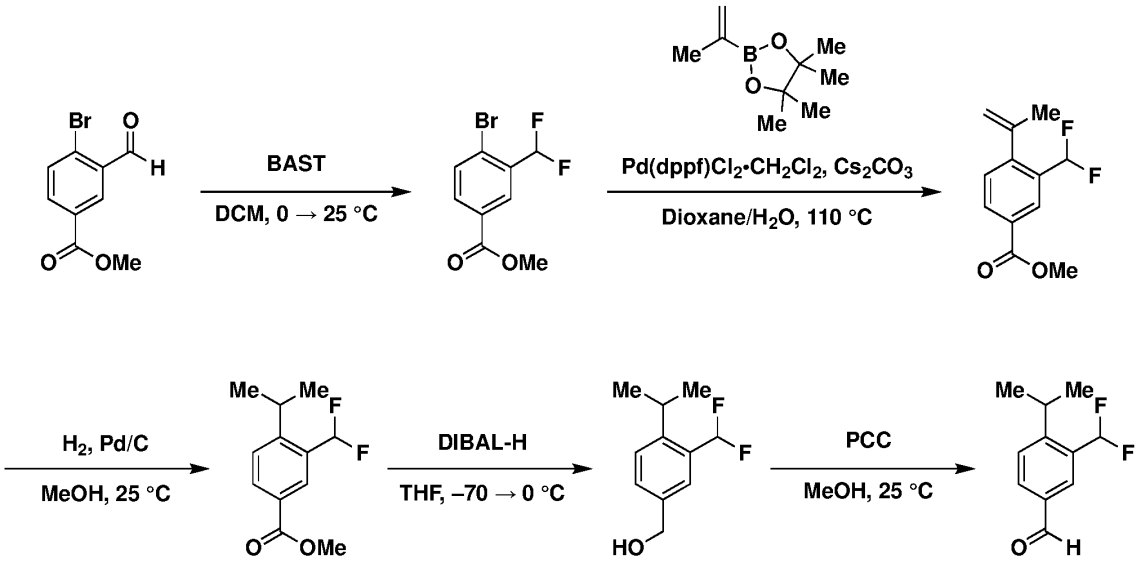
[0527] Step a: To a mixture of oxazol-2-amine (640 mg, 7.61 mmol, 1 eq) and $NaHCO_3$ (639 mg, 7.61 mmol, 296 µL, 1 eq) in MeCN (20 mL) at 0 °C under N_2 was added SEMCl (1.27 g, 7.61 mmol, 1.35 mL, 1 eq). The resulting mixture was warmed to 25 °C and stirred for 16 h. The reaction mixture was then quenched with H_2O (10 mL), and resulting biphasic mixture was extracted with EtOAc (2 x 30 mL). The combined organic extracts were washed with brine (20 mL), dried over with anhydrous Na_2SO_4, filtered, and concentrated under

reduced pressure to give 3-((2-(trimethylsilyl)ethoxy)methyl)oxazol-2(3*H*)-imine, which was carried forward to the next step without further purification or characterization.

[0528] Step b: A mixture of 3-((2-(trimethylsilyl) ethoxy) methyl) oxazol-2(3*H*)-imine (1.4 g, 6.53 mmol, 1 eq), K_2CO_3 (1.81 g, 13 mmol, 2 eq) and ethyl 2-bromoacetate (1.64 g, 9.80 mmol, 1.08 mL, 1.5 eq) in MeCN (50 mL) was warmed to 70 ºC and stirred for 3 h. After cooling, the reaction was quenched with H_2O (20 mL), and the resulting biphasic mixture was extracted with EtOAc (2 x 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crud residue obtained was purified by column chromatography to give ethyl (*Z*)-2-((3-((2-(trimethylsilyl)ethoxy)methyl)oxazol-2(3*H*)-ylidene)amino)acetate, which was carried forward to the next step without further characterization.

[0529] Step 3: A mixture of ethyl (*Z*)-2-((3-((2-(trimethylsilyl)ethoxy)methyl)oxazol-2(3*H*)-ylidene)amino)acetate (500 mg, 1.66 mmol, 1 eq) and $LiOH•H_2O$ (210 mg, 4.99 mmol, 3 eq) in MeOH (8 mL) and H_2O (1 mL) was stirred at 40 ºC for 1 h. After cooling, the reaction was diluted with H_2O (10 mL). The pH of the resulting solution was adjusted to pH = 5 using aqueous HCl (4M). The resulting mixture was extracted with EtOAc (2 x 30 mL). The combined organic extracts were washed with brine (10 mL), dried over with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give (*Z*)-2-((3-((2-(trimethylsilyl)ethoxy)methyl)oxazol-2(3*H*)-ylidene)amino)acetic acid. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{11}H_{20}N_2O_4Si$: 273.1; found 273.1.

Intermediate A-34: Synthesis of 3-(difluoromethyl)-4-isopropylbenzaldehyde



[0530] Step a: To a solution of methyl 4-bromo-3-formylbenzoate (4.50 g, 18.5 mmol, 1 eq) in DCM (45 mL) at 0 °C was added 1,1,1-trifluoro-*N*,*N*-bis(2-methoxyethyl)-λ^4-sulfanamine (BAST, 10.5 mL, 48.1 mmol, 2.6 eq). The mixture was warmed to 25 °C and stirred for 40 min. The mixture was then poured into ice-water (50 mL) and stirred for 5 min. Saturated aqueous $NaHCO_3$ was then added to adjust the pH to 8. The resulting biphasic mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with brine (3 x 30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give methyl 4-bromo-3-(difluoromethyl)benzoate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_9H_7BrF_2O_2$: 265.0; found 264.9.

[0531] Step b: To a mixture of methyl 4-bromo-3-(difluoromethyl)benzoate (4.30 g, 16.2 mmol, 1 eq), 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (3.27 g, 19.5 mmol, 1.20 eq), and Cs_2CO_3 (10.6 g, 32.5 mmol, 2.00 eq) in dioxane (43 mL) and H_2O (4 mL) at 25 °C under N_2 was added $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (1.32 g, 1.62 mmol, 0.10 eq). The resulting mixture was then degassed and then charged with N_2. The mixture was then warmed to 110 °C and stirred for 30 min. After cooling to room temperature, the mixture was poured into water (20 mL) and stirred for 5 min. The resulting biphasic mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried over Na_2SO_4, filtered, and concentrated under reduce pressure. The crude residue obtained was

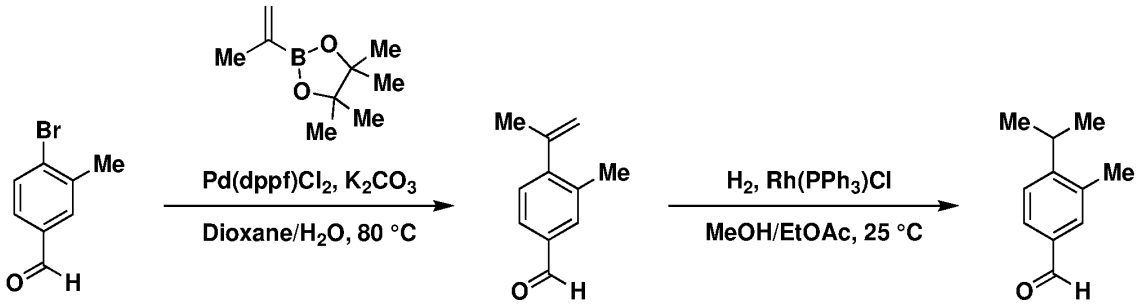
purified by column chromatography to give methyl 3-(difluoromethyl)-4-(prop-1-en-2-yl)benzoate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{12}H_{12}F_2O_2$: 227.1; found 227.1.

[0532] Step c: To a solution of methyl 3-(difluoromethyl)-4-(prop-1-en-2-yl)benzoate (2.40 g, 10.6 mmol, 1.00 eq) in MeOH (30 mL) at 25 °C was added Pd/C (1.12 g, 1.06 mmol, 10% purity, 0.1 eq) under N_2. The suspension was then degassed under vacuum and purged with H_2. The reaction mixture was then stirred under H_2 (15 psi) at 25 °C for 1 h. The reaction mixture was then filtered and concentrated under reduced pressure to give methyl 3-(difluoromethyl)-4-isopropylbenzoate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{12}H_{14}F_2O_2$: 229.1; found 229.1.

[0533] Step d: To a solution of methyl 3-(difluoromethyl)-4-isopropylbenzoate (2.35 g, 10.3 mmol, 1 eq) in THF (30 mL) at –70 °C under N_2 was added DIBAL-H (1 M in THF, 20.6 mL, 2.00 eq) dropwise. The reaction mixture was then stirred at –70 °C for 2 h under N_2. The reaction mixture was the warmed to 0 °C and quenched by addition of water (20 mL). The resulting biphasic mixture was then filtered and extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were washed with brine (2 x 20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give (3-(difluoromethyl)-4-isopropylphenyl)methanol. LC-MS (ESI): m/z: $[M - OH]^+$ calculated for $C_{11}H_{14}F_2O$: 183.1; found 183.1.

[0534] Step e: To a mixture of (3-(difluoromethyl)-4-isopropylphenyl)methanol (1.80 g, 8.99 mmol, 1.00 eq) and silica gel (2.91 g) in DCM (20 mL) at 25 °C under N_2 was added PCC (2.91 g, 13.48 mmol, 1.50 eq). The resulting mixture was stirred at 25 °C for 30 min. The reaction mixture was then filtered and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 3-(difluoromethyl)-4-isopropylbenzaldehyde. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{11}H_{12}F_2O$: 199.1; found 199.1.

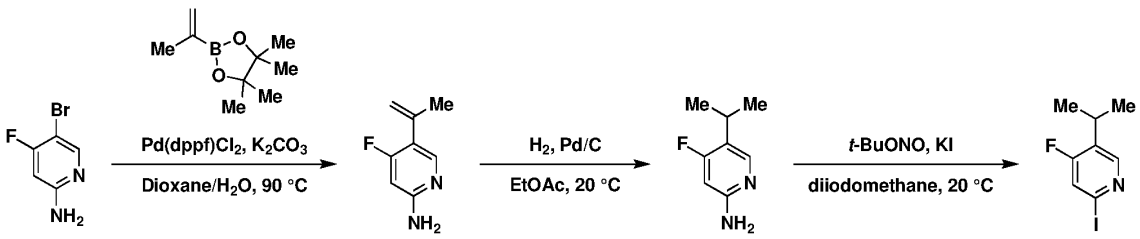
Intermediate A-35: Synthesis of 4-isopropyl-3-methylbenzaldehyde



[0535] Step a: To a mixture of 4-bromo-3-methylbenzaldehyde (5 g, 25.1 mmol, 1 eq), 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (8.44 g, 50.2 mmol, 2 eq), and K_2CO_3 (10.4 g, 75.4 mmol, 3 eq) in dioxane (60 mL) and H_2O (6 mL) was added $Pd(dppf)Cl_2$ (551 mg, 754 μmol, 0.03 eq). The resulting mixture was degassed and purged with N_2, and then the mixture was warmed to 80 ºC and stirred for 16 h under N_2 atmosphere. The reaction mixture was then filtered, and the filtrate was concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 3-methyl-4-(prop-1-en-2-yl)benzaldehyde (4 g, crude). LC-MS (ESI): m/z: $[M+H]^+$ calculated for $C_{11}H_{12}O$: 161.1; found 161.1.

[0536] Step b: To a solution of 3-methyl-4-(prop-1-en-2-yl)benzaldehyde (4 g, 25.0 mmol, 1 eq) in EtOAc (40 mL) and MeOH (20 mL) was added $Rh(PPh_3)Cl$ (1.15 g, 1.25 mmol, 0.05 eq) under argon. The resulting suspension was then degassed under vacuum and placed under an H_2 atmosphere. The resulting mixture was then stirred under H_2 (15 psi) at 25 ºC for 16 h. The mixture was then filtered, and the filtrate was concentrated under reduced pressure to give 4-isopropyl-3-methylbenzaldehyde. LC-MS (ESI): m/z: $[M+H]^+$ calculated for $C_{11}H_{14}O$: 163.1; found 163.1.

Intermediate A-36: Synthesis of 4-fluoro-2-iodo-5-isopropylpyridine

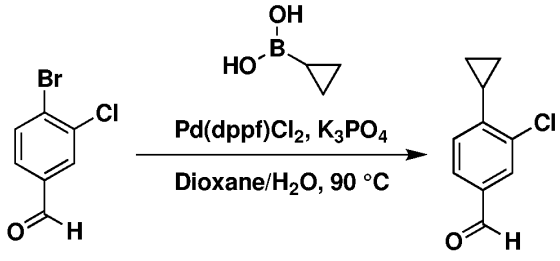


[0537] Step a: To a mixture of 5-bromo-4-fluoropyridin-2-amine (3 g, 15.7 mmol, 1 eq), 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (3.96 g, 23.5 mmol, 1.5 eq), and K_2CO_3 (6.51 g, 47.1 mmol, 3 eq) in H_2O (3 mL) and dioxane (30 mL) was added $Pd(dppf)Cl_2$ (460 mg, 629 µmol, 0.04). The resulting mixture was degassed and purged with N_2, and then the mixture was warmed to 90 °C and stirred for 16 h under N_2 atmosphere. The reaction mixture was then filtered, and the filtrate was concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 4-fluoro-5-(prop-1-en-2-yl)pyridin-2-amine. LC-MS (ESI): m/z: $[M+H]^+$ calculated for $C_8H_9FN_2$: 153.; found 153.2.

[0538] Step b: To a solution of 4-fluoro-5-(prop-1-en-2-yl)pyridin-2-amine (2.2 g, 14.4 mmol, 1 eq) in EtOAc (50 mL) was added Pd/C (1 g, 10% purity) under N_2. The suspension was then degassed under vacuum and placed under an H_2 atmosphere. The resulting mixture was then stirred under H_2 (20 psi) at 20 °C for 16 h. The mixture was then filtered, and the filtrate was concentrated under reduced pressure to give 4-fluoro-5-isopropylpyridin-2-amine. LC-MS (ESI): m/z: $[M+H]^+$ calculated for $C_8H_{11}FN_2$: 155.1; found 155.0.

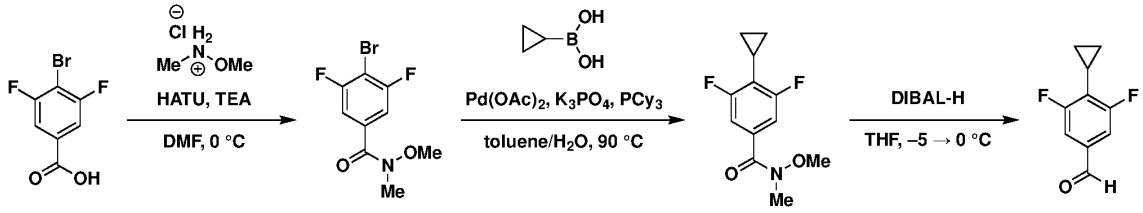
[0539] Step c: To a mixture of 4-fluoro-5-isopropylpyridin-2-amine (2 g, 12.9 mmol, 1 eq) and KI (21.5 g, 129 mmol, 10 eq) in diiodomethane (69.4 g, 259 mmol, 20.9 mL, 20 eq) was added *t*-BuONO (6.69 g, 64.8 mmol, 5 eq). The resulting mixture was degassed and purged with N_2, and then the mixture was stirred for 16 h under N_2 atmosphere at 20 °C. The reaction mixture was then filtered, and the filtrate was concentrated under reduced pressure. The crude residue was purified by column chromatography to give 4-fluoro-2-iodo-5-isopropylpyridine. LC-MS (ESI): m/z: $[M+H]^+$ calculated for C_8H_9FIN: 266.0; found 265.9.

Intermediate A-37: 3-chloro-4-cyclopropylbenzaldehyde



[0540] Step a: To a mixture of cyclopropylboronic acid (2.30 g, 26.7 mmol, 1.30 eq), 4-bromo-3-chlorobenzaldehyde (4.5 g, 20.5 mmol, 1.00 eq), and K_3PO_4 (10.0 g, 47.1 mmol, 2.30 eq) in dioxane (40.0 mL) and H_2O (4.00 mL) was added $Pd(dppf)Cl_2$ (750 mg, 1.02 mmol, 0.05 eq). The resulting mixture was degassed and purged with N_2, and then the mixture was warmed to 90 °C and stirred for 16 h under N_2 atmosphere. The reaction mixture was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 3-chloro-4-cyclopropylbenzaldehyde. LC-MS (ESI): m/z: $[M+H]^+$ calculated for $C_{10}H_9ClO$: 181.0; found 181.1.

Intermediate A-38: 4-cyclopropyl-3,5-difluorobenzaldehyde



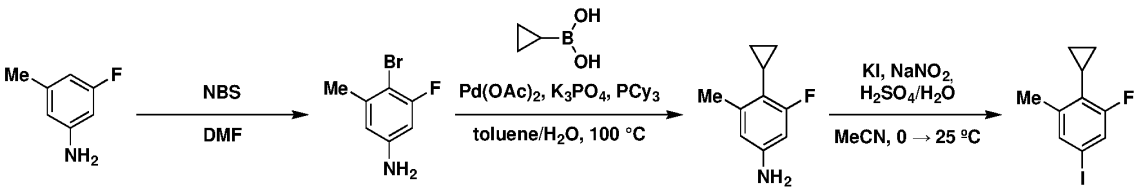
[0541] Step a: To a solution of 4-bromo-3,5-difluorobenzoic acid (2.7 g, 11.4 mmol, 1 eq), Et_3N (3.46 g, 34.2 mmol, 4.76 mL, 3 eq) and *N,O*-dimethylhydroxylammonium chloride (1.33 g, 13.7 mmol, 1.2 eq) in DMF (25 mL) at 0 °C was added HATU (4.55 g, 11.9 mmol, 1.05 eq). The resulting mixture was stirred at 0 °C for 1 h. The reaction was then quenched by addition of H_2O (80 mL) at 0 °C, and the resulting biphasic mixture was then extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (80 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 4-bromo-3,5-difluoro-*N*-methoxy-*N*-methylbenzamide. This compound was carried forward to the next step without further characterization.

[0542] Step b: To a mixture of 4-bromo-3,5-difluoro-*N*-methoxy-*N*-methylbenzamide (3.15 g, 11.3 mmol, 1 eq), cyclopropylboronic acid (1.45 g, 16.8 mmol, 1.5 eq), K_3PO_4 (7.16 g, 33.7 mmol, 3 eq), and PCy_3 (315 mg, 1.12 mmol, 0.1 eq) in toluene (60 mL) and H_2O (6 mL) was added $Pd(OAc)_2$ (253 mg, 1.12 mmol, 0.1 eq). The resulting mixture was degassed and purged with N_2, and the resulting mixture was warmed to 90 °C and stirred for 12 h under N_2

atmosphere. The reaction mixture was then filtered, and the filtrate was concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 4-cyclopropyl-3,5-difluoro-*N*-methoxy-*N*-methylbenzamide. This compound was carried forward to the next step without further characterization.

[0543] Step c: To a solution of 4-cyclopropyl-3,5-difluoro-*N*-methoxy-*N*-methylbenzamide (2.50 g, 10.4 mmol, 1 eq) in THF (20 mL) at –5 ºC under N_2 was added DIBAL-H (1 M in THF, 13.47 mL, 1.3 eq). The resulting mixture was then warmed to 0 ºC and stirred for 3 h. The reaction mixture was then poured into ice-water (20 mL), adjusted to pH = 7 with aq. HCl (4M), and extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine (40 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 4-cyclopropyl-3,5-difluorobenzaldehyde.

Intermediate A-39: 2-cyclopropyl-1-fluoro-5-iodo-3-methylbenzene



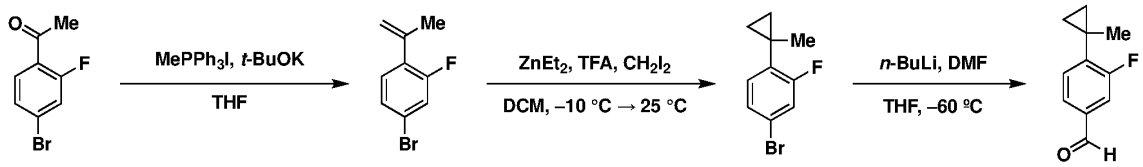
[0544] Step a: To a solution of 3-fluoro-5-methylaniline (15.0 g, 120 mmol, 1.00 eq) in DMF (100 mL) at 0 ºC was added NBS (21.5 g, 121 mmol, 1.01 eq). The resulting mixture was stirred at 0 ºC for 0.5 h. The reaction mixture was then warmed to 25 ºC and stirred for 1 h. The reaction mixture was then diluted with water (100 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 4-bromo-3-fluoro-5-methylaniline. LC-MS (ESI): m/z: $[M+H]^+$ calculated for C_7H_7BrFN: 204.0; found 204.0.

[0545] Step b: To a solution of 4-bromo-3-fluoro-5-methylaniline (8.0 g, 39.2 mmol, 1.00 eq), tricyclohexylphosphine (2.20 g, 7.84 mmol, 0.20 eq), cyclopropylboronic acid (4.04 g, 47.0 mmol, 1.20 eq), and K_3PO_4 (25.0 g, 118 mmol, 3.00 eq) in toluene (160 mL) and H_2O (32

mL) was added $Pd(OAc)_2$ (880 mg, 3.92 mmol, 0.10 eq). The resulting mixture was degassed and purged with N_2. The reaction mixture was then warmed to 100 °C and stirred for 16 h under N_2. After cooling to the room temperature, the reaction mixture was extracted with ethyl acetate (3 x 80 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 4-cyclopropyl-3-fluoro-5-methylaniline. LC-MS (ESI): m/z: $[M+H]^+$ calculated for $C_{10}H_{12}FN$: 166.1; found 166.1.

[0546] Step c: To a solution of 4-cyclopropyl-3-fluoro-5-methylaniline (4.00 g, 24.21 mmol, 1 eq) in MeCN (40 mL) was added a solution of H_2SO_4 (18 M, 3.36 mL, 98% purity, 2.50 eq) in H_2O (40 mL). After stirring 10 min, the reaction mixture was cooled to 0 °C, and a solution of $NaNO_2$ (3.34 g, 48.4 mmol, 2.00 eq) in H_2O (40 mL) was added over 20 min. A solution of KI (16.1 g, 96.8 mmol, 4.00 eq) in H_2O (40 mL) was then added to the reaction mixture at 0 °C. The reaction mixture was then warmed to 25 °C and stirred under N_2 atmosphere or 0.5 h. The reaction mixture was then extracted with ethyl acetate (3 x 600 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 2-cyclopropyl-1-fluoro-5-iodo-3-methylbenzene.

Intermediate A-40: 3-fluoro-4-(1-methylcyclopropyl)benzaldehyde



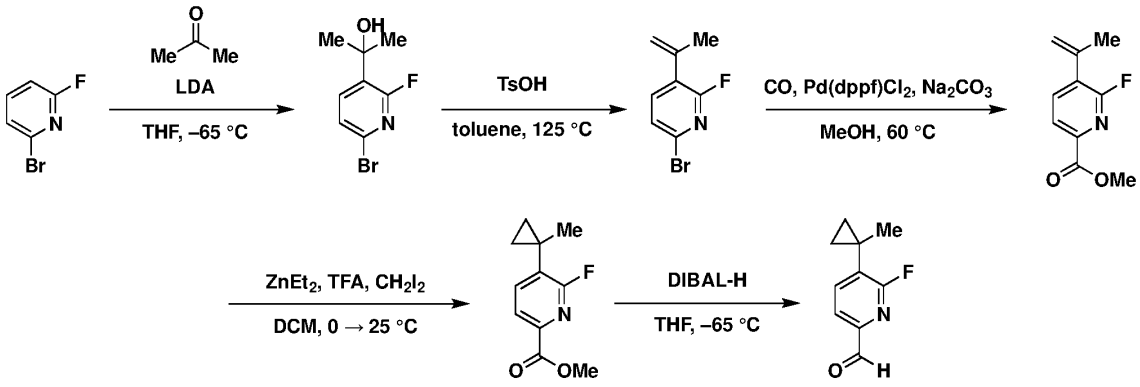
[0547] Step a: To a solution of methyltriphenylphosphonium iodide (14.0 g, 34.6 mmol, 1.5 eq) in THF (50.0 mL) was added *t*-BuOK (3.88 g, 34.6 mmol, 1.5 eq). The resulting mixture was stirred at 25 °C for 30 min. To this mixture was added a solution of 1-(4-bromo-2-fluorophenyl)ethan-1-one (5.00 g, 23.0 mmol, 1 eq) in THF (5.00 mL) at 25 °C. The resulting mixture was stirred at 25 °C for 16 h. The reaction mixture was then cooled to 0 °C and quenched by addition H_2O (100 mL), and the resulting biphasic mixture was extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried

over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 4-bromo-2-fluoro-1-(prop-1-en-2-yl)benzene, which was carried forward to the next step without further characterization.

[0548] Step b: To a solution of $ZnEt_2$ (1 M in hexane, 18.6 mL, 4 eq) in DCM (5.00 mL) at 0 °C under N_2 atmosphere was added TFA (2.12 g, 18.6 mmol, 1.38 mL, 4 eq). The resulting mixture was stirred at 0 °C for 30 min before CH_2I_2 (4.98 g, 18.6 mmol, 1.50 mL, 4 eq) in DCM (5.00 mL) was added dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 30 min before 4-bromo-2-fluoro-1-(prop-1-en-2-yl)benzene (1.00 g, 4.65 mmol, 1 eq) in DCM (5.00 mL) was added dropwise at 0 °C. The resulting mixture was then warmed to 25 °C and stirred for 16 h. The reaction mixture was then cooled to 0 °C and quenched by addition of aq. HCl (1N, 50 mL). The resulting biphasic mixture was extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 4-bromo-2-fluoro-1-(1-methylcyclopropyl)benzene, which was carried forward to the next step without further characterization.

[0549] Step c: To a solution of 4-bromo-2-fluoro-1-(1-methylcyclopropyl)benzene (5 g, 21.8 mmol, 1 eq) in THF (80 mL) at –60 °C under N_2 atmosphere was added *n*-BuLi (2.5 M in hexane, 8.72 mL, 1 eq). After 30 min, DMF (4.79 g, 65.4 mmol, 3 eq) was added dropwise at –60 °C. The resulting mixture was allowed to warm to 25 °C and stirred for 2 h. The reaction mixture was then cooled to 0 °C and quenched by addition saturated aqueous NH_4Cl (150 mL). The resulting biphasic mixture was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography to give 3-fluoro-4-(1-methylcyclopropyl)benzaldehyde. LC-MS (ESI): m/z: $[M+H]^+$ calculated for $C_{11}H_{11}FO$: 179.1; found 179.1.

Intermediate A-41: 6-fluoro-5-(1-methylcyclopropyl)picolinaldehyde



[0550] Step a: To a solution of 2-bromo-6-fluoropyridine (12.5 g, 71.0 mmol, 1.00 eq) in THF (125 mL) at –65 °C under N_2 atmosphere was added LDA (2 M in THF, 35.5 mL, 1.00 eq) in a dropwise manner. The reaction mixture was stirred at –65 °C for 0.5 h before acetone (6.19 g, 106 mmol, 1.50 eq) was added in a dropwise manner at –65 °C. The reaction mixture was then stirred at –65 °C for 0.5 h before it was warmed to 0 °C, quenched by addition of H_2O (60 mL), and stirred for 5 min. The resulting biphasic mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 2-(6-bromo-2-fluoropyridin-3-yl)propan-2-ol. LC-MS (ESI): m/z: $[M+H]^+$ calculated for C_8H_9BrFNO: 234.0; found 234.0.

[0551] Step b: To a solution of 2-(6-bromo-2-fluoropyridin-3-yl)propan-2-ol (13.5 g, 57.7 mmol, 1.00 eq) in toluene (135 mL)was added TsOH (1.99 g, 11.5 mmol, 0.2 eq). The reaction mixture was then warmed to 125 °C and stirred for 16 h. The reaction mixture was then filtered and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 6-bromo-2-fluoro-3-(prop-1-en-2-yl)pyridine. LC-MS (ESI): m/z: $[M+H]^+$ calculated for C_8H_7BrFN: 216.0; found 215.9.

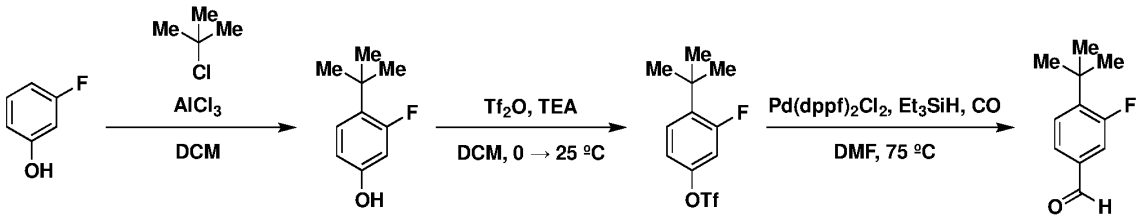
[0552] Step c: To a solution of 6-bromo-2-fluoro-3-(prop-1-en-2-yl)pyridine (6.50 g, 30.1 mmol, 1.00 eq) in MeOH (65 mL) was added TEA (6.09 g, 60.1 mmol, 2.00 eq) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (2.46 g, 3.01 mmol, 0.10 eq). The reaction mixture was then placed under a CO atmosphere (50 psi), warmed to 60 °C, and stirred for 1.5 h. The reaction mixture was then concentrated under reduced pressure. The crude residue obtained was purified by column

chromatography to give methyl 6-fluoro-5-(prop-1-en-2-yl)picolinate. LC-MS (ESI): m/z: $[M+H]^+$ calculated for $C_{10}H_{10}FNO_2$: 196.1; found 196.1.

[0553] Step d: To a solution of $ZnEt_2$ (1 M in hexane, 102 mL, 5.00 eq) at 0 °C was added TFA (102 mmol, 7.6 mL, 5.00 eq) in DCM (24 mL) in a dropwise manner. The resulting mixture was stirred at 0 °C for 30 min before CH_2I_2 (27.4 g, 102mmol, 5.0 eq) in DCM (22 mL) was added in a dropwise manner. The resulting mixture was stirred at 0 °C for 30 min before methyl 6-fluoro-5-(prop-1-en-2-yl)picolinate (4 g, 20 mmol, 1.0 eq) in DCM (12 mL) was added in a dropwise manner at 0 °C. The resulting mixture was then warmed to 25 °C and stirred for 15 h. The reaction mixture was then cooled to 0 °C and quenched by addition of saturated aq. NH_4Cl (100 ml). The resulting biphasic mixture was then extracted with ethyl acetate (3 x 500 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by prep-HPLC to give methyl 6-fluoro-5-(1-methylcyclopropyl)picolinate. LC-MS (ESI): m/z: $[M+H]^+$ calculated for $C_{11}H_{12}FNO_2$: 210.1; found 210.1.

[0554] Step e: A solution of methyl 6-fluoro-5-(1-methylcyclopropyl)picolinate (1.25 g, 5.97 mmol, 1 eq) in THF (12.5 mL) was degassed and purged with N_2. The resulting solution was cooled to –65 °C, and then DIBAL-H (1 M in THF, 11.95 mL, 2 eq) was added in a dropwise manner. The resulting mixture was stirred at –65 °C for 2 h. The reaction mixture was then warmed to 0 °C and quenched by addition of water (20 mL). The resulting biphasic mixture was then filtered and extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were washed with brine (2 x 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 6-fluoro-5-(1-methylcyclopropyl)picolinaldehyde. LC-MS (ESI): m/z: $[M+H]^+$ calculated for $C_{10}H_{10}FNO$: 180.1; found 180.1.

Intermediate A-42: 4-(*tert*-butyl)-3-fluorobenzaldehyde



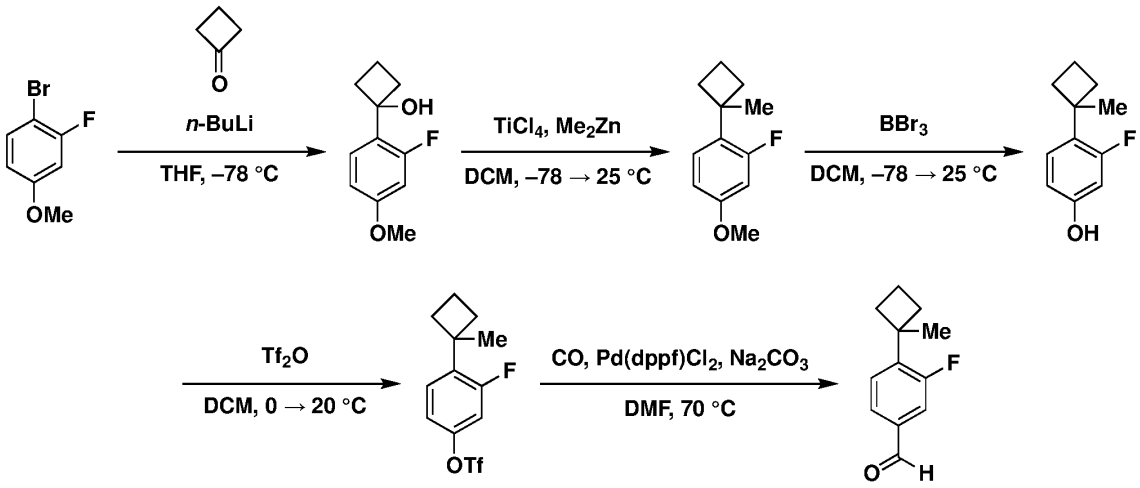
[0555] Step a: To a mixture of 3-fluorophenol (10.0 g, 89.20 mmol, 8.20 mL, 1 eq) and $AlCl_3$ (4.76 g, 35.7 mmol,1.95 mL, 0.4 eq) in DCM (150 mL) under N_2 was added 2-chloro-2-methyl-propane (12.4 g, 134 mmol, 14.8 mL, 1.5 eq) in a dropwise manner. The resulting mixture was stirred at 25 ºC for 16 h. The reaction mixture was then quenched with water (50 mL), and the resulting biphasic mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with water (3 x 50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 4-(*tert*-butyl)-3-fluorophenol. LC-MS (ESI): m/z: $[M+H]^+$ calculated for $C_{10}H_{13}FO$: 169.1; found 169.1.

[0556] Step b: To a solution of 4-(*tert*-butyl)-3-fluorophenol (3.80 g, 22.6 mmol, 1 eq) and TEA (6.86 g, 67.8 mmol, 9.43 mL, 3 eq) in DCM (15 mL) at 0 ºC was added Tf_2O (3.19 g, 11.3 mmol, 1.86 mL, 0.5 eq) in a dropwise manner. The resulting mixture was warmed to 25 ºC and stirred for 2 h. The reaction was then diluted with H_2O (5 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 4-(*tert*-butyl)-3-fluorophenyl trifluoromethanesulfonate. LC-MS (ESI): m/z: $[M+H]^+$ calculated for $C_{11}H_{12}F_4O_3S$: 301.0; found 301.1.

[0557] Step c: To a solution of 4-(*tert*-butyl)-3-fluorophenyl trifluoromethanesulfonate (2.00 g, 6.66 mmol, 1 eq), Et_3SiH (1.55 g, 13.3 mmol, 2.13 mL, 2 eq), and Na_2CO_3 (1.41 g, 13.3 mmol, 2 eq) in DMF (15 mL) under N_2 atmosphere was added $Pd(dppf)Cl_2$ (487 mg, 666 µmol, 0.1 eq). The resulting mixture was placed under CO atmosphere (50 psi), warmed to 75 ºC, and stirred for 5 h. The reaction mixture was then diluted with H_2O (20 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated

under reduced pressure. The crude residue obtained was purified by column chromatography to give 4-(*tert*-butyl)-3-fluorobenzaldehyde. LC-MS (ESI): m/z: $[M+H]^+$ calculated for $C_{11}H_{13}FO$: 181.1; found 181.1.

Intermediate A-43: 3-fluoro-4-(1-methylcyclobutyl)benzaldehyde



[0558] Step a: To a solution of 1-bromo-2-fluoro-4-methoxybenzene (23.0 g, 112 mmol, 1 eq) in THF (200 mL) at –78 ºC under N_2 atmosphere was added *n*-BuLi (2.5 M in hexane, 50 mL, 125.0 mmol, 1.1 eq). The resulting mixture was stirred at –78 ºC for 1 h before cyclobutanone (7.86 g, 112 mmol, 8.3 mL, 1 eq) was added in a dropwise manner. The resulting mixture was stirred at –78 ºC for 2 h. The reaction was then quenched by addition of saturated aqueous NH_4Cl (200 mL), and the resulting biphasic mixture was extracted with ethyl acetate (2 x 300 mL). The combined organic extracts were washed with water (50 mL) and brine (3 x 250 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 1-(2-fluoro-4-methoxyphenyl)cyclobutan-1-ol. This compound was carried forward to the next step without further characterization.

[0559] Step b: To a solution of 1-(2-fluoro-4-methoxyphenyl)cyclobutan-1-ol (5 g, 25.4 mmol, 1 eq) in DCM (40 mL) at –78 ºC was added titanium tetrachloride (9.6 g, 50.9 mmol, 9.67 mL, 2 eq), and the resulting mixture was stirred at –78 ºC for 1 h. A solution of dimethylzinc (1 M in heptane, 76.45 mL, 3 eq) was added at –78 ºC in a dropwise manner. The

resulting mixture was warmed to 25 °C and stirred for 1 h. The reaction mixture was then poured into ice-water (30 mL), and the resulting biphasic mixture was extracted with DCM (50 mL). The organic extracts were then washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 2-fluoro-4-methoxy-1-(1-methylcyclobutyl)benzene. This compound was carried forward to the next step without further characterization.

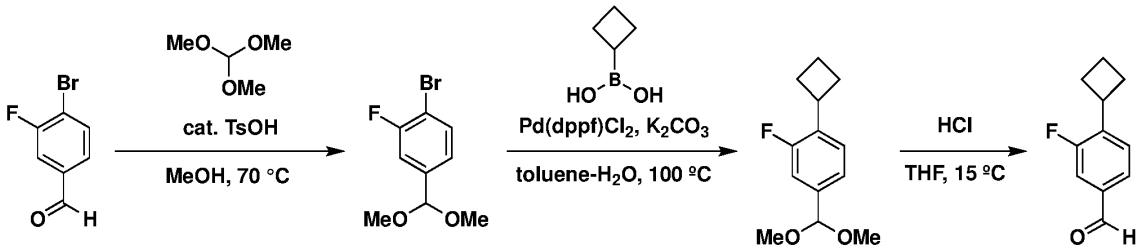
[0560] Step c: To a solution of 2-fluoro-4-methoxy-1-(1-methylcyclobutyl)benzene (1.5 g, 7.7 mmol, 1 eq) in DCM (2 mL) at –78 °C was added BBr_3 (1 M, 23.17 mL, 3 eq). The resulting mixture was stirred at –78 °C for 0.5 h. The reaction mixture was then warmed to 25 °C and stirred for 1 h. The reaction mixture was then quenched by addition of H_2O (100 mL), and the resulting biphasic mixture was extracted with DCM (2 x 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 3-fluoro-4-(1-methylcyclobutyl)phenol. This compound was carried forward to the next step without further characterization.

[0561] Step d: To a solution of 3-fluoro-4-(1-methylcyclobutyl)phenol (1.3 g, 7.2 mmol, 1 eq) and TEA (1.4 g, 14.4 mmol, 2.01 mL, 2 eq) in DCM (15 mL) at 0 °C was added Tf_2O (2.44 g, 8.66 mmol, 1.43 mL, 1.2 eq). The resulting mixture was stirred at 0 °C for 1 h. The reaction mixture was then warmed to 20 °C and stirred for 1 h. The reaction mixture was then diluted with DCM (22 ml) and washed with H_2O (20 mL). The organic solution was then dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 3-fluoro-4-(1-methylcyclobutyl)phenyl trifluoromethanesulfonate. This compound was carried forward to the next step without further characterization.

[0562] Step e: To a solution of 3-fluoro-4-(1-methylcyclobutyl)phenyl trifluoromethanesulfonate (2.2 g, 7.0 mmol, 1 eq), Na_2CO_3 (1.49 g, 14.09 mmol, 2 eq), and TESH (1.64 g, 14.1 mmol, 2.25 mL, 2 eq) in DMF (40 mL) was added $Pd(dppf)Cl_2$ (515 mg, 704 µmol, 0.1 eq). The resulting mixture was then placed under CO atmosphere (50 psi), warmed to 70 °C, and stirred for 4 h. The reaction mixture was then cooled to 20 °C and diluted with ethyl acetate (50 mL). The organic solution was then washed with H_2O (20 mL), dried over anhydrous

Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 3-fluoro-4-(1-methylcyclobutyl)benzaldehyde.

Intermediate A-44: 4-cyclobutyl-3-fluorobenzaldehyde

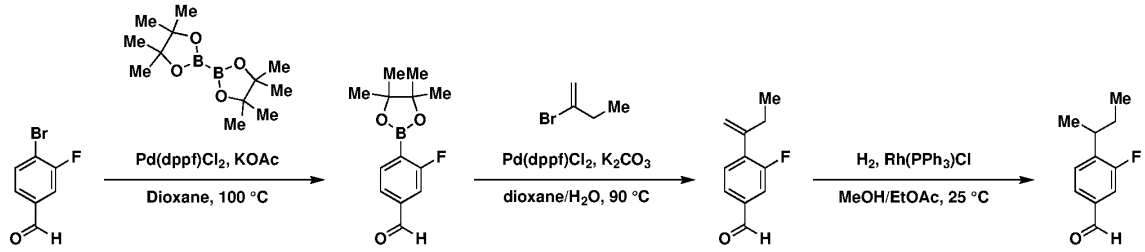


[0563] Step a: To a solution of 4-bromo-3-fluorobenzaldehyde (5 g, 24.63 mmol, 1 eq) and 4-methylbenzenesulfonic acid (848 mg, 4.93 mmol, 0.2 eq) in MeOH (50 mL) was added trimethyl orthoformate (5.23 g, 49.3 mmol, 5.40 mL, 2 eq). The resulting mixture was warmed to 70 ºC and stirred for 1 h. The reaction mixture was then poured into ice-water (150 mL) and stirred for 3 min. The resulting biphasic mixture was extracted with ethyl acetate (3 x 80 mL). The combined organic extracts were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give 1-bromo-4-(dimethoxymethyl)-2-fluorobenzene. LC-MS (ESI): m/z: $[M - OMe]^+$ calculated for $C_9H_{10}BrFO_2$: 217.0; found 217.0.

[0564] Step b: To a solution of 1-bromo-4-(dimethoxymethyl)-2-fluorobenzene (1.4 g, 5.62 mmol, 1 eq), cyclobutylboronic acid (5.62 g, 56.2 mmol, 10 eq), and K_2CO_3 (1.55 g, 11.2 mmol, 2 eq) in toluene (12 mL) and H_2O (3 mL) under N_2 was added $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (918 mg, 1.12 mmol, 0.2 eq). The resulting mixture was warmed to 100 ºC and stirred for 1 h. The reaction mixture was then poured into ice-water and stirred for 3 min. The resulting biphasic mixture was extracted with ethyl acetate (3 x 80 mL). The combined organic extracts were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 1-cyclobutyl-4-(dimethoxymethyl)-2-fluorobenzene, which was carried forward to the next step without further characterization.

[0565] Step c: To a solution of 1-cyclobutyl-4-(dimethoxymethyl)-2-fluorobenzene (1 g, 4.46 mmol, 1 eq) in THF (5 mL) at 15 °C was added aq. HCl (1 M, 10.00 mL, 2.24 eq). The resulting mixture was stirred at 15 °C for 1 h. The mixture was poured into ice-water (30 mL) and stirred for 2 min. The resulting biphasic mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give 4-cyclobutyl-3-fluorobenzaldehyde, which was used without further purification. LC-MS (ESI): m/z: $[M+H]^+$ calculated for $C_{11}H_{11}FO$: 179.1; found 179.1.

Intermediate A-45: 4-(*sec*-butyl)-3-fluorobenzaldehyde



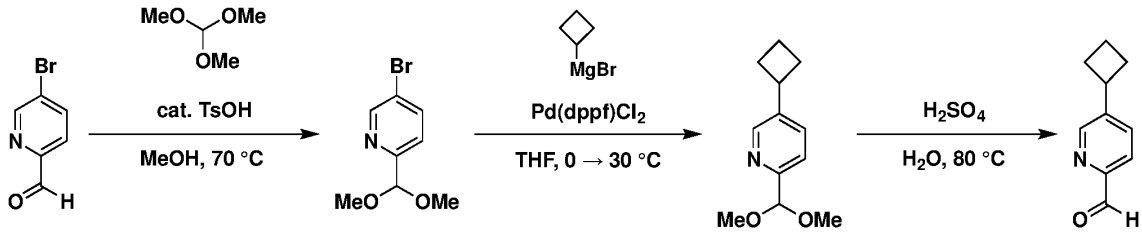
[0566] Step a: To a mixture of 4-bromo-3-fluorobenzaldehyde (5.00 g, 24.6 mmol, 1 eq), KOAc (6.04 g, 61.6 mmol, 2.5 eq), and bis(pinacolato)diboron (7.51 g, 29.6 mmol, 1.2 eq) in dioxane (50 mL) was added $Pd(dppf)Cl_2$ (1.80 g, 2.46 mmol, 0.1 eq). The resulting mixture was degassed and purged with N_2. The reaction mixture was then warmed to 100 °C and stirred for 3 h. The reaction mixture was then filtered, and the filter cake was washed with 10:1 EtOAc/MeOH (3 x 200 mL). The combined filtrate and washes were concentrated under reduced pressure. The crude residue obtained was poured into H_2O (100 mL), adjusted to pH = 10 with sat. aqueous Na_2CO_3, and extracted with ethyl acetate (3 x 100 mL). The organic extracts were discarded. The aqueous phase was then adjusted to pH = 4 with aq. HCl (4M) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give 3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde, which was carried forward to the next step without further characterization.

[0567] Step b: To a mixture of 3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (3.00 g, 12.0 mmol, 1 eq), 2-bromobut-1-ene (1.62 g, 12.0 mmol, 1 eq), and

K_2CO_3 (3.32 g, 24.0 mmol, 2 eq) in dioxane (60 mL) and H_2O (6 mL) was added $Pd(dppf)Cl_2$ (439 mg, 600 µmol, 0.05 eq). The reaction was degassed and purged with N_2. The resulting mixture was then warmed to 90 °C and stirred for 16 h. The reaction mixture was then cooled, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 4-(but-1-en-2-yl)-3-fluorobenzaldehyde, which was carried forward to the next step without further characterization.

[0568] Step c: To a solution of 4-(but-1-en-2-yl)-3-fluorobenzaldehyde (1.70 g, 9.54 mmol, 1 eq) in MeOH (20 mL) and ethyl acetate (20 mL) was added $Rh(PPh_3)_3Cl$ (883 mg, 954 µmol, 0.1 eq) under N_2. The resulting suspension was degassed under vacuum and purged with H_2. The resulting mixture was then stirred under H_2 (15 psi) at 25 °C for 2 h. The reaction mixture was then filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 4-(*sec*-butyl)-3-fluorobenzaldehyde. LC-MS (ESI): m/z: $[M+H]^+$ calculated for $C_{11}H_{13}FO$: 181.1; found 181.1.

Intermediate A-46: 5-cyclobutylpicolinaldehyde

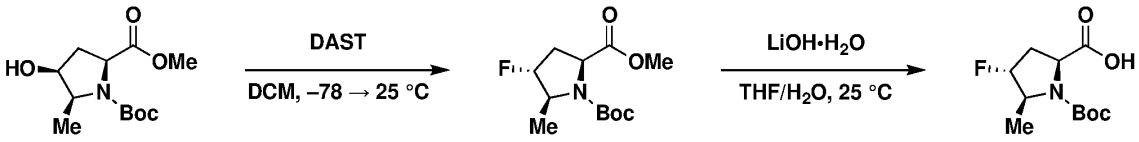


[0569] Step a: To a solution of 5-bromopicolinaldehyde (20 g, 107.52 mmol, 1 eq) and trimethyl orthoformate (22.8 g, 215.05 mmol, 23.6 mL, 2 eq) in MeOH (50 mL) at 0 °C was added 4-methylbenzenesulfonic acid (3.70 g, 21.50 mmol, 0.2 eq) in MeOH (5 mL). The resulting mixture was warmed to 70 °C and stirred for 1 h. The reaction solution was then cooled and quenched with sat. aqueous $NaHCO_3$ to reach pH = 7. The resulting biphasic mixture was then extracted with EtOAc (2 x 200 mL). The combined organic extracts were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give 5-bromo-2-(dimethoxymethyl)pyridine. LC-MS (ESI): m/z: $[M - OMe]^+$ calculated for $C_8H_{10}BrNO_2$: 200.0; found 200.1.

[0570] Step b: To a mixture of 5-bromo-2-(dimethoxymethyl)pyridine (2.5 g, 10.77 mmol, 1 eq) and $Pd(dppf)Cl_2$ (394 mg, 538.62 µmol, 0.05 eq) in THF (2 mL) at 0 °C was added cyclobutylmagnesium bromide (0.5 M, 86.2 mL, 4 eq). The resulting mixture was warmed to 30 °C and stirred for 16 h. The reaction mixture was then diluted with water and extracted with EtOAc (150 mL). The organic extracts were washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 5-cyclobutyl-2-(dimethoxymethyl)pyridine, which was carried forward to the next step without further characterization.

[0571] Step c: To a solution of 5-cyclobutyl-2-(dimethoxymethyl)pyridine (0.9 g, 4.34 mmol, 1 eq) in H_2O (9 mL) was added H_2SO_4 (5 M, 1.04 mL, 1.2 eq). The resulting mixture was warmed to 80 °C and stirred for 2 h. The reaction mixture was then adjusted to pH = 7 with sat. aqueous $NaHCO_3$. The resulting biphasic mixture was then extracted with EtOAc (80 mL). The organic extracts were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give 5-cyclobutylpicolinaldehyde. LC-MS (ESI): m/z: $[M+H]^+$ calculated for $C_{10}H_{11}NO$: 162.1; found 162.1.

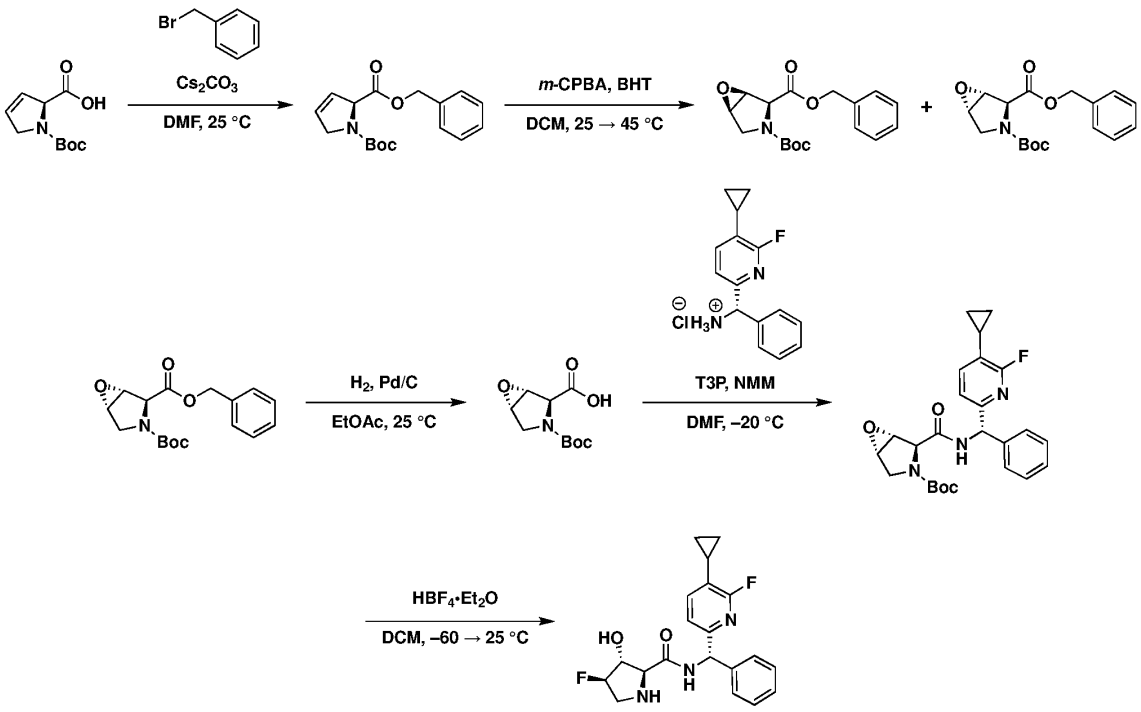
Intermediate A-47: (2*S*,4*R*,5*S*)-1-(*tert*-butoxycarbonyl)-4-fluoro-5-methylpyrrolidine-2-carboxylic acid



[0572] Step a: To a mixture of 1-(*tert*-butyl) 2-methyl (2*S*,4*S*,5*S*)-4-hydroxy-5-methylpyrrolidine-1,2-dicarboxylate (150 mg, 0.57 mmol, 1 eq) in DCM (4 mL) at –78 °C under N_2 atmosphere was added DAST (466 mg, 2.89 mmol, 5 eq) in a dropwise manner. The resulting mixture was warmed to 25 °C and stirred for 16 h. The reaction mixture was then diluted with H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give 1-(*tert*-butyl) 2-methyl (2*S*,4*R*,5*S*)-4-fluoro-5-methylpyrrolidine-1,2-dicarboxylate, which was carried forward to the next step without further characterization.

[0573] Step b: To a mixture of 1-(*tert*-butyl) 2-methyl (2*S*,4*R*,5*S*)-4-fluoro-5-methylpyrrolidine-1,2-dicarboxylate (40 mg, 0.15 mmol, 1 eq) in THF (2 mL) at 25 °C was added a solution of LiOH•H_2O (7 mg, 0.16 mmol, 1.1 eq) in H_2O (2 mL). The resulting mixture was stirred at 25 °C for 1 hr. The reaction mixture was then concentrated under reduced pressure. The crude residue was then diluted with water (3 mL) and washed with MTBE (3 x 5 mL). The aqueous phase was then adjusted to pH = 4 with aq. HCl (1 N) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give (2*S*,4*R*,5*S*)-1-(*tert*-butoxycarbonyl)-4-fluoro-5-methylpyrrolidine-2-carboxylic acid. LC-MS (ESI): m/z: $[M - H]^-$ calculated for $C_{11}H_{18}FNO_4$: 246.1; found 246.2.

Intermediate A-48: (2*S*,3*RS*,4*RS*)-*N*-((*S*)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl)-4-fluoro-3-hydroxypyrrolidine-2-carboxamide



[0574] Step a: To a mixture of (*S*)-1-(*tert*-butoxycarbonyl)-2,5-dihydro-1*H*-pyrrole-2-carboxylic acid (9 g, 42.2 mmol, 1 eq) and Cs_2CO_3 (15.1 g, 46.4 mmol, 1.1 eq) in DMF (100 mL) at 0 °C was added BnBr (8.66 g, 50.6 mmol, 1.2 eq) in a dropwise manner. The resulting

suspension was degassed under vacuum and purged with N_2. The reaction mixture was then warmed to 25 °C and stirred for 12 h. The reaction mixture was then quenched with H_2O (100 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 2-benzyl 1-(*tert*-butyl) (*S*)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate. LC-MS (ESI): m/z: $[M - t\text{-Bu} + H + H]^+$ calculated for $C_{17}H_{21}NO_4$: 248.1; found 248.1.

[0575] Step b: To a solution of 2-benzyl 1-(*tert*-butyl) (*S*)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate (4.7 g, 15.5 mmol, 1 eq) and BHT (341 mg, 1.55 mmol, 0.1 eq) in DCM (200 mL) at 25 °C was added 3-chloroperbenzoic acid (31.5 g, 154 mmol, 85% purity, 10 eq). The reaction was warmed to 45 °C and stirred for 12 h. After cooling to 25 °C, the reaction was quenched with saturated aqueous $Na_2S_2O_3$, and the resulting biphasic mixture extracted with DCM (2 x 200 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography and prep-HPLC to give 2-benzyl 3-(*tert*-butyl) (1*S*,2*S*,5*R*)-6-oxa-3-azabicyclo[3.1.0]hexane-2,3-dicarboxylate and 2-benzyl 3-(*tert*-butyl) (1*R*,2*S*,5*S*)-6-oxa-3-azabicyclo[3.1.0]hexane-2,3-dicarboxylate as separate diastereomers. LC-MS (ESI): m/z: $[M - t\text{-Bu} + H + H]^+$ calculated for $C_{17}H_{21}NO_5$: 264.1; found 264.0.

[0576] Step c: To a solution of 2-benzyl 3-(*tert*-butyl) (1*R*,2*S*,5*S*)-6-oxa-3-azabicyclo[3.1.0]hexane-2,3-dicarboxylate (600 mg, 1.88 mmol, 1 eq) in EtOAc (15 mL) was added Pd/C (500 mg, 1.88 mmol, 10% purity, 1.00 eq) under N_2. The resulting suspension was degassed under vacuum and purged with H_2. The resulting mixture was stirred under H_2 (15 psi) at 25 °C for 2 h. The reaction mixture was then filtered and concentrated under reduced pressure to give (1*R*,2*S*,5*S*)-3-(*tert*-butoxycarbonyl)-6-oxa-3-azabicyclo[3.1.0]hexane-2-carboxylic acid. LC-MS (ESI): m/z: $[M - t\text{-Bu} + H + H]^+$ calculated for $C_{10}H_{15}NO_5$ 174.0; found 174.1.

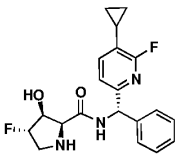
[0577] Step d: To a solution of (1*R*,2*S*,5*S*)-3-(*tert*-butoxycarbonyl)-6-oxa-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (430 mg, 1.88 mmol, 1 eq), (*S*)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methanaminium chloride (522 mg, 1.88 mmol, 1 eq), and *N*-methylmorpholine (NMM, 948 mg, 9.38 mmol, 5 eq) in DMF (5 mL) at –20 °C was added 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide (T3P, 1.43 g, 2.25 mmol, 50% purity,

1.2 eq). The resulting mixture was stirred at –20 ºC for 1 h. The reaction mixture was then quenched with H_2O (10 mL), and the resulting biphasic mixture was extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give *tert*-butyl (1*R*,2*S*,5*S*)-2-(((*S*)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl)carbamoyl)-6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate. LC-MS (ESI): m/z: $[M+H]^+$ calculated for $C_{25}H_{28}FN_3O_4$: 454.2; found 454.2.

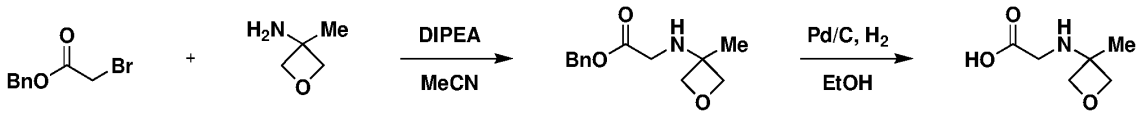
[0578] Step e: To a solution of *tert*-butyl (1*R*,2*S*,5*S*)-2-(((*S*)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl)carbamoyl)-6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate (430 mg, 0.95 mmol, 1 eq) in DCM (12 mL) at –60 ºC was added tetrafluoroboric acid diethyl ether complex (2.15 g, 6.64 mmol, 50% purity, 7 eq) in a dropwise manner. The resulting mixture was allowed to warm to 25 ºC and stirred for 12 h. The mixture was adjusted to pH = 7 with saturated aqueous $NaHCO_3$ and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by prep-TLC to give (2*S*,3*RS*,4*RS*)-*N*-((*S*)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl)-4-fluoro-3-hydroxypyrrolidine-2-carboxamide. LC-MS (ESI): m/z: $[M+H]^+$ calculated for $C_{20}H_{21}F_2N_3O_2$: 374.2; found 374.3.

[0579] The following compounds in Table B-11 were synthesized using procedures similar to Intermediate A-48 using the appropriate starting materials.

Table B-11

Intermediate No.	Structure	IUPAC	Exact mass (g/mol)	LCMS, Found $[M + H]^+$
B-11-1		(2*S*,3*RS*,4*RS*)-*N*-((*S*)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl)-4-fluoro-3-hydroxypyrrolidine-2-carboxamide	373.2	374.1

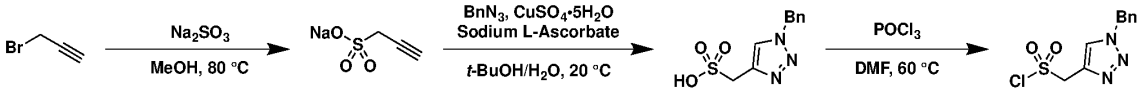
Intermediate A-49: (3-methyloxetan-3-yl)glycine



[0580] Step a: To a solution of 3-methyloxetan-3-amine (500 mg, 5.74 mmol, 1 eq) in MeCN (10 mL) at 30 °C was added benzyl 2-bromoacetate (2.63 g, 11.5 mmol, 2 eq) and DIPEA (1.48 g, 11.5 mmol, 2 eq) in a dropwise manner. The resulting mixture was stirred at 30 °C for 16 h under N_2. The reaction mixture was then diluted with H_2O (20 mL), and the resulting biphasic mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give benzyl (3-methyloxetan-3-yl)glycinate. LC-MS (ESI): m/z: $[M+H]^+$ calculated for $C_{13}H_{17}NO_3$: 236.1; found 236.1.

[0581] Step b: To a solution of benzyl (3-methyloxetan-3-yl)glycinate (100 mg, 425 µmol, 1 eq) in EtOH (2 mL) at 20 °C was added Pd/C (452 mg, 10% purity). The resulting mixture was stirred at 20 °C for 5 h under H_2 (15 Psi). The reaction mixture was then filtered, and the filtrate was concentrated under reduced pressure to give (3-methyloxetan-3-yl)glycine. LC-MS (ESI): m/z: $[M-H]^-$ calculated for $C_6H_{11}NO_3$: 144.1; found 144.1.

Intermediate A-50: (1-benzyl-1*H*-1,2,3-triazol-4-yl)methanesulfonyl chloride

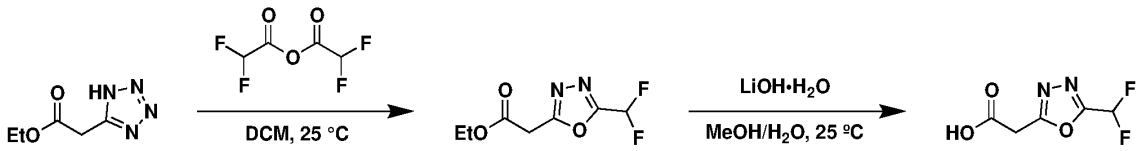


[0582] Step a: A mixture of 3-bromoprop-1-yne (25 g, 168 mmol, 80% purity, 1 eq) and Na_2SO_3 (25.4 g, 201 mmol, 1.2 eq) in MeOH (200 mL) was warmed to 80 °C and stirred for 16 h. The reaction mixture was then filtered, and the filtrate was concentrated under reduced pressure. The crude residue obtained was purified by re-crystallization from acetone to obtain sodium prop-2-yne-1-sulfonate, which was carried forward to the next step without further characterization.

[0583] Step b: To a mixture of sodium prop-2-yne-1-sulfonate (2 g, 14.0 mmol, 1 eq), sodium L-ascorbate (557 mg, 2.81 mmol, 0.2 eq), and $CuSO_4 \cdot 5H_2O$ (351 mg, 1.41 mmol, 0.1 eq) in H_2O (10 mL) and *t*-BuOH (10 mL) at 20 °C was added benzyl azide (BnN_3, 1.97 g, 14.7 mmol, 1.05 eq). The resulting mixture was stirred at 20 °C for 16 h. The reaction mixture was then filtered, and the filtrate was concentrated under reduced pressure. The crude residue obtained was purified by prep-HPLC to give (1-benzyl-1*H*-1,2,3-triazol-4-yl)methanesulfonic acid. LC-MS (ESI): m/z: $[M-H]^-$ calculated for $C_{10}H_{11}N_3O_3S$: 254.0; found 254.0.

[0584] Step c: To a mixture of (1-benzyl-1*H*-1,2,3-triazol-4-yl)methanesulfonic acid (300 mg, 947 µmol, 80% purity, 1 eq) in $POCl_3$ (7.26 g, 47.4 mmol, 4.4 mL, 50 eq) was added DMF (6.93 mg, 94.8 µmol, 0.1 eq). The resulting mixture was the warmed to 60 °C and stirred for 2 h. The mixture was then concentrated under reduced pressure to give (1-benzyl-1*H*-1,2,3-triazol-4-yl)methanesulfonyl chloride, which was used without further purification or characterization.

Intermediate A-51: 2-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)acetic acid

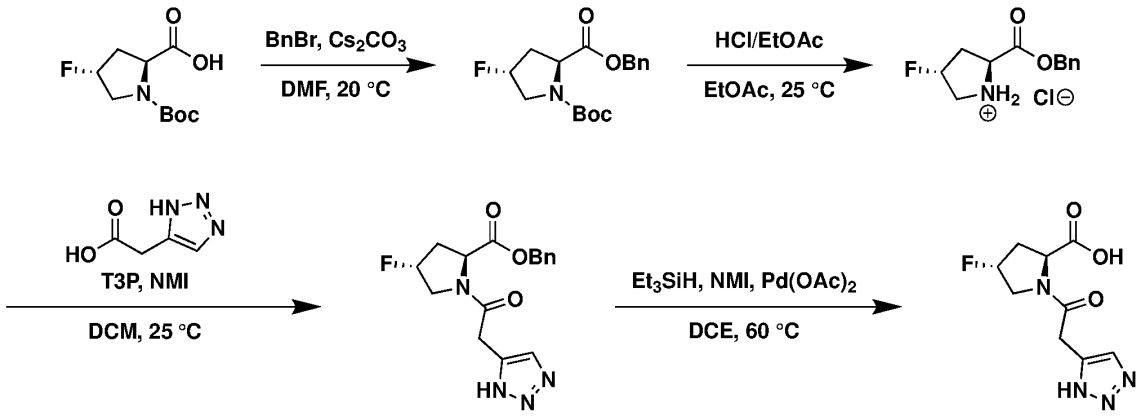


[0585] Step a: To a solution of ethyl 2-(1*H*-tetrazol-5-yl)acetate (1.0 g, 6.40 mmol, 1 eq) in DCM (10 mL) was added 2,2-difluoroacetic anhydride (1.45 g, 8.33 mmol, 1.3 eq). The resulting mixture was stirred at 25 °C for 16 h before it was poured into ice water (20 mL). The resulting biphasic mixture was extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give ethyl 2-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)acetate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_7H_8F_2N_2O_3$: 207.0; found 207.0.

[0586] Step b: To a solution of ethyl 2-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)acetate (60 mg, 291 µmol, 1 eq) in MeOH (1 mL) and H_2O (1 mL) was added $LiOH \cdot H_2O$ (13.4 mg, 320 µmol, 1.1 eq). The resulting mixture was stirred at 25 °C for 3 h. The reaction

mixture was then poured into ice-water (5 mL), and the pH was adjusted to pH = 3 with aqueous HCl (3M). The resulting biphasic mixture was extracted with EtOAc (3 x 5mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give 2-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)acetic acid. LC-MS (ESI): m/z: [M – H]$^-$ calculated for $C_5H_4F_2N_2O_3$: 177.0; found 177.1.

Intermediate A-52: (2*S*,4*R*)-1-(2-(1*H*-1,2,3-triazol-5-yl)acetyl)-4-fluoropyrrolidine-2-carboxylic acid



[0587] Step a: To a solution of (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (10.0 g, 42.9 mmol, 1 eq) and benzyl bromide (8.80 g, 51.5 mmol, 6.11 mL, 1.2 eq) in DMF (50 mL) at 20 °C was added Cs_2CO_3 (21.0 g, 64.3 mmol, 1.5 eq). The resulting mixture was stirred at 20 °C for 12 h before the reaction was quenched by addition of ice-water (100 mL). The resulting biphasic mixture was extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was triturated with petroleum ether to give 2-benzyl 1-(*tert*-butyl) (2*S*,4*R*)-4-fluoropyrrolidine-1,2-dicarboxylate. LC-MS (ESI): m/z: [M + Na]$^+$ calculated for $C_{17}H_{22}FNO_4$: 346.1; found 346.2.

[0588] Step b: To a solution of 2-benzyl 1-(*tert*-butyl) (2*S*,4*R*)-4-fluoropyrrolidine-1,2-dicarboxylate (12.7 g, 39.3 mmol, 1 eq) in EtOAc (50 mL) at 0 °C was added HCl in EtOAc (4 M, 180 mL). The resulting mixture was warmed to 25 °C and stirred for 30 min. The reaction mixture was then filtered, and the filter cake was washed with petroleum ether (3 x 50 mL) to

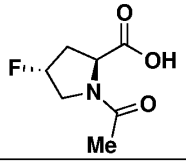
give (2*S*,4*R*)-2-((benzyloxy)carbonyl)-4-fluoropyrrolidin-1-ium chloride. LC-MS (ESI): m/z: [M + H]$^+$ calculated for $C_{12}H_{14}FNO_2$: 224.1; found 224.1.

[0589] Step c: To a mixture of (2*S*,4*R*)-2-((benzyloxy)carbonyl)-4-fluoropyrrolidin-1-ium chloride (9.55 g, 36.8 mmol, 1 eq), 2-(1*H*-1,2,3-triazol-5-yl)acetic acid (5.61 g, 44.1 mmol, 1.2 eq) and *N*-methylimidazole (NMI, 15.1 g, 184 mmol, 5 eq) in DCM (45 mL) at 0 ºC was added T3P (35.1 g, 55.1 mmol, 50% purity, 1.5 eq). The resulting mixture was warmed to 25 ºC and stirred for 2 h. The reaction mixture was then quenched by addition of H_2O (80 mL), and the resulting biphasic mixture was extracted with EtOAc (3 x 80 mL). The combined organic extracts were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was triturated with EtOAc to give benzyl (2*S*,4*R*)-1-(2-(1*H*-1,2,3-triazol-5-yl)acetyl)-4-fluoropyrrolidine-2-carboxylate. LC-MS (ESI): m/z: [M+H]$^+$ calculated for $C_{16}H_{17}FN_4O_3$: 333.1; found 333.1.

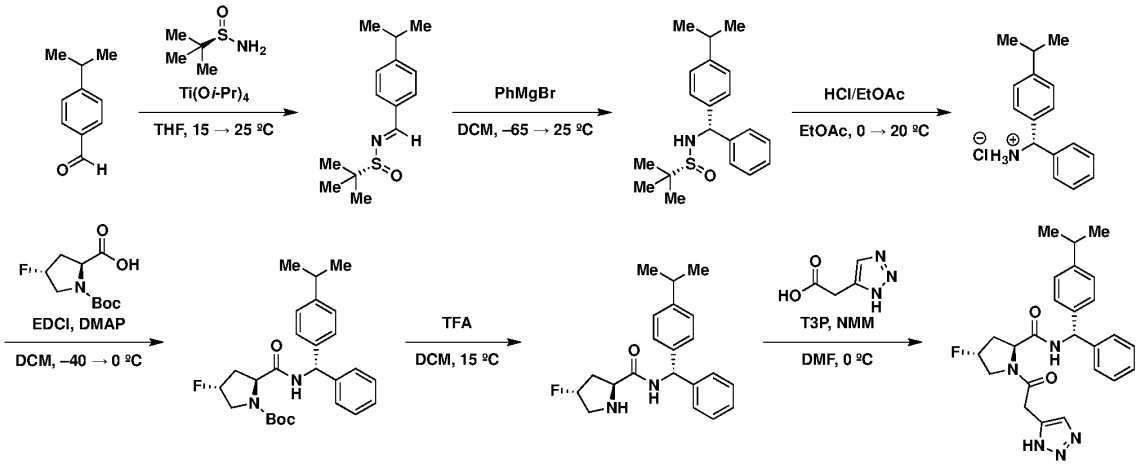
[0590] Step d: To a mixture of benzyl (2*S*,4*R*)-1-(2-(1*H*-1,2,3-triazol-5-yl)acetyl)-4-fluoropyrrolidine-2-carboxylate (6.60 g, 19.9 mmol, 1 eq), Et_3SiH (4.62 g, 39.7 mmol, 6.34 mL, 2 eq), and *N*-methylimidazole (NMI, 326 mg, 3.97 mmol, 0.2 eq) in DCE (132 mL) at 25 ºC under N_2 was added $Pd(OAc)_2$ (1.11 g, 4.96 mmol, 0.25 eq). The resulting mixture was warmed to 60 ºC and stirred for 6 h. The reaction mixture was then filtered, and the filter cake was washed with EtOAc (3 x 50 mL). The combined filtrates were concentrated under reduced pressure to give (2*S*,4*R*)-1-(2-(1*H*-1,2,3-triazol-5-yl)acetyl)-4-fluoropyrrolidine-2-carboxylic acid. LC-MS (ESI): m/z: [M + H]$^+$ calculated for $C_9H_{11}FN_4O_3$: 243.1; found 243.1.

[0591] The following compounds in Table B-12 were synthesized using procedures similar to Intermediate A-52 using the appropriate starting materials.

Table B-12

Intermediate No.	Structure	IUPAC	Exact mass (g/mol)	LCMS, Found [M + H]$^+$
B-12-1		(2*S*,4*R*)-1-acetyl-4-fluoropyrrolidine-2-carboxylic acid	175.1	176.0

Example S-1: Synthesis of (2*S*,4*R*)-1-(2-(1*H*-1,2,3-triazol-5-yl)acetyl)-4-fluoro-*N*-((*S*)-(4-isopropylphenyl)(phenyl)methyl)pyrrolidine-2-carboxamide (Compound 1)



[0592] Step a: To a mixture of 4-isopropylbenzaldehyde (25 g, 169 mmol, 25.6 mL, 1 eq) and (*R*)-2-methylpropane-2-sulfinamide (22.5 g, 186 mmol, 1.1 eq) in THF (150 mL) at 15 ºC under N_2 was added Ti(O*i*Pr)$_4$ (76.9 g, 337 mmol, 2 eq). The system was degassed and then charged with nitrogen three times. The mixture was then warmed to 25 ºC and stirred for 16 h under N_2. The reaction was then quenched by addition of H_2O (200 mL) at 0 ºC and stirred for 20 min. The resulting mixture was then filtered, and the filter cake was washed with ethyl acetate (2 x 200 mL). The filtrate was then extracted with ethyl acetate (2 x 200 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl (200 mL) and brine (200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography to give (*R*,*E*)-*N*-(4-isopropylbenzylidene)-2-methylpropane-2-sulfinamide. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{14}H_{21}NOS$: 252.1; found 252.1.

[0593] Step b: To a solution of (*R*,*E*)-*N*-(4-isopropylbenzylidene)-2-methylpropane-2-sulfinamide (150 g, 596 mmol, 1.00 eq) in DCM (1500 mL) at –65 ºC was added phenylmagnesium bromide (3.00 M in Et_2O, 358 mL, 1073 mmol, 1.80 eq). The reaction

mixture was warmed to 25 °C and stirred for 30 h. The reaction mixture was then cooled to 0 °C and quenched with saturated aqueous NH_4Cl (2000 mL). The organic phase was isolated and the solvent was removed under reduced pressure to give (*R*)-*N*-((*S*)-(4-isopropylphenyl)(phenyl)methyl)-2-methylpropane-2-sulfinamide, which was used in the next step without further purification. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{20}H_{27}NOS$: 330.2; found 330.3.

[0594] Step c: To a solution of (*R*)-*N*-((*S*)-(4-isopropylphenyl)(phenyl)methyl)-2-methylpropane-2-sulfinamide (15 g, 45.5 mmol, 1 eq) in EtOAc (100 mL) at 0 °C was added HCl/EtOAc (4 M, 100 mL). The resulting mixture was then warmed to 20 °C and stirred for 1 h. The reaction mixture was then concentrated under reduced pressure. The resulting crude residue was washed with MTBE (2 x 80 mL), and the resulting solid was collected by filtration. The solid obtained was dried under reduced pressure to give (*S*)-(4-isopropylphenyl)(phenyl)methanaminium chloride. LC-MS (ESI): m/z: $[M - NH_2]^+$ calculated for $C_{16}H_{19}N$: 209.1; found 209.1.

[0595] Step d: To a solution of (*S*)-(4-isopropylphenyl)(phenyl)methanaminium chloride (15 g, 57.4 mmol, 1 eq) in DCM (150 mL) was added (2*S*,4*R*)-1-*tert*-butoxycarbonyl-4-fluoro-pyrrolidine-2-carboxylic acid (14.7 g, 63.1 mmol, 1.1 eq), DMAP (7.0 g, 57.4 mmol, 1 eq), and EDCI (11.0 g, 57.3 mmol, 1 eq) sequentially at –40 °C. The reaction mixture was warmed over 30 min and stirred at 0 °C for 2 h. The reaction was then quenched with H_2O (50 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give *tert*-butyl (2*S*,4*R*)-4-fluoro-2-(((*S*)-(4-isopropylphenyl)(phenyl)methyl)carbamoyl)pyrrolidine-1-carboxylate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{26}H_{33}FN_2O_3$: 441.3; found 441.3.

[0596] Step e: To a solution of *tert*-butyl (2*S*,4*R*)-4-fluoro-2-(((*S*)-(4-isopropylphenyl)(phenyl)methyl)carbamoyl)pyrrolidine-1-carboxylate (24 g, 54.47 mmol, 1 eq) in DCM (240 mL) at 15 °C was added TFA (120 mL) in a dropwise manner. The resulting mixture was stirred at 15 °C for 1 h before the reaction mixture was adjusted to pH 5–6 with aq. $NaHCO_3$ (1 M) and extracted with ethyl acetate (3 x 150 mL). The combined organic extracts were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated

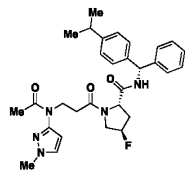
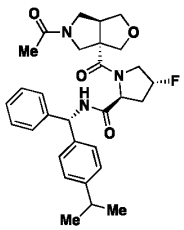
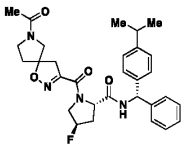
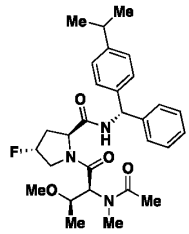
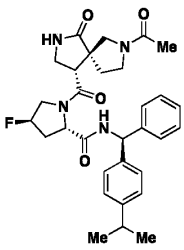
under reduced pressure to give (2*S*,4*R*)-4-fluoro-*N*-((*S*)-(4-isopropylphenyl)(phenyl)methyl)pyrrolidine-2-carboxamide. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{21}H_{25}FN_2O$: 341.2; found 341.1.

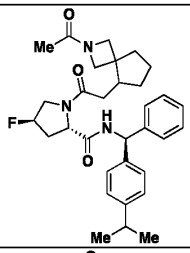
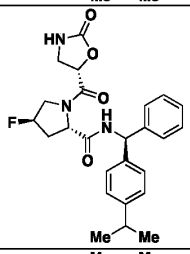
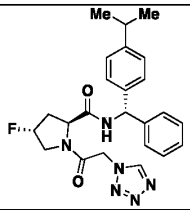
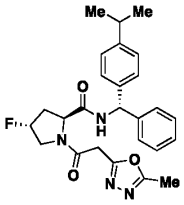
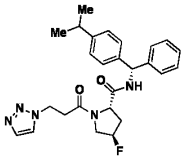
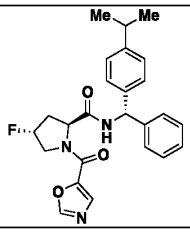
[0597] Step f: To a solution of (2*S*,4*R*)-4-fluoro-*N*-((*S*)-(4-isopropylphenyl)(phenyl)methyl)pyrrolidine-2-carboxamide (6.5 g, 19.1 mmol, 1 eq) and 2-(1*H*-1,2,3-triazol-5-yl)acetic acid (Intermediate A-1, 3.64 g, 28.6 mmol, 1.5 eq) in DMF (65 mL) at 0 ºC was added NMM (5.79 g, 57.3 mmol, 3 eq) and T3P (18.2 g, 28.6 mmol, 50% in EtOAc, 1.5 eq). The resulting mixture was stirred at 0 ºC for 1 h. The reaction mixture was then poured into H_2O (200 mL) and extracted with EtOAc (2 x 200 mL). The combined organic extracts were washed with brine (200 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography and SFC to give (2*S*,4*R*)-1-(2-(1*H*-1,2,3-triazol-5-yl)acetyl)-4-fluoro-*N*-((*S*)-(4-isopropylphenyl)(phenyl)methyl)pyrrolidine-2-carboxamide. ^{1}H NMR (3:1 rotamer ratio, asterisk denotes distinct minor rotamer peaks, obscured peaks not reported, 400 MHz, DMSO-d_6) δ 14.77 (br s, 1H), 9.25* (d, *J* = 8.2 Hz, 1H), 8.87 (d, *J* = 8.4 Hz, 1H), 7.98 – 7.41 (m, 1H), 7.35 – 7.26 (m, 4H), 7.26 – 7.11 (m, 5H), 6.11* (d, *J* = 8.1 Hz, 1H), 6.03 (d, *J* = 8.3 Hz, 1H), 5.48 – 5.22 (m, 1H), 4.82* (t, *J* = 8.1 Hz, 1H), 4.58 (t, *J* = 8.4 Hz, 1H), 4.13 – 3.88 (m, 1H), 3.88 – 3.66 (m, 3H), 3.55 – 3.38* (m, 1H), 2.92 – 2.62 (m, 1H), 2.47 – 2.35 (m, 1H), 2.28 – 1.89 (m, 1H), 1.18 (d, *J* = 7.0, 1.4 Hz, 6H). LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{25}H_{28}FN_5O_2$: 450.2; found 450.1.

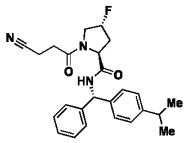
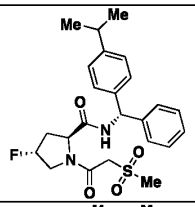
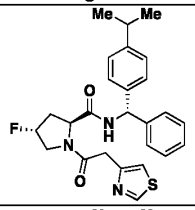
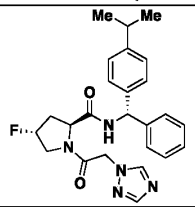
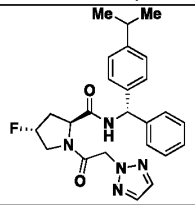
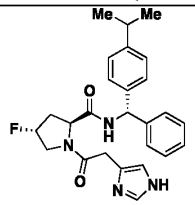
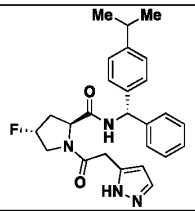
[0598] The following compounds in Table T-1 were synthesized using procedures similar to Compound 1 using the appropriate starting materials.

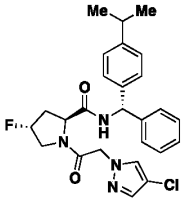
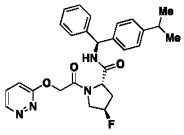
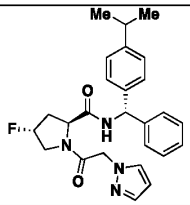
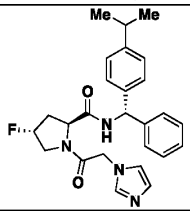
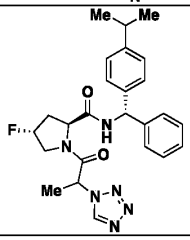
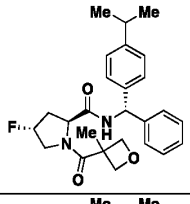
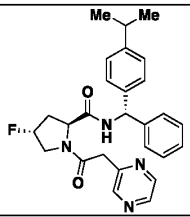
Table T-1

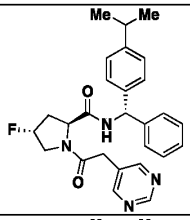
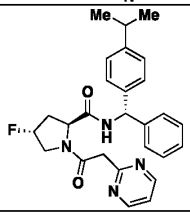
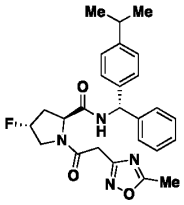
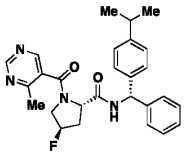
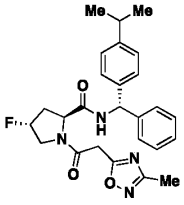
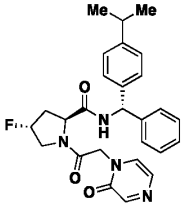
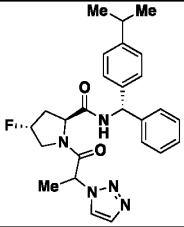
Compound No.	Structure	IUPAC	Exact mass (g/mol)	LCMS, Found $[M + H]^+$

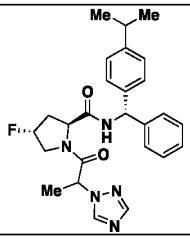
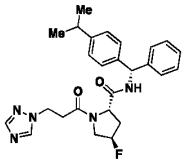
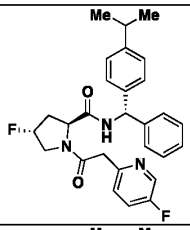
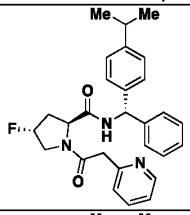
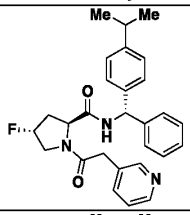
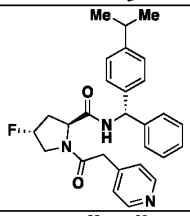
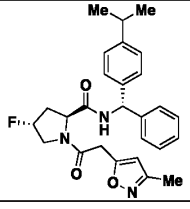
2		(2S,4R)-4-fluoro-1-{3-[N-(1-methyl-1H-pyrazol-3-yl)acetamido]propanoyl}-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	533.3	534.3
3		(2S,4R)-1-[(3aS,6aS)-5-acetyl-hexahydro-1H-furo[3,4-c]pyrrole-3a-carbonyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	521.3	522.3
4		(2S,4R)-1-{7-acetyl-1-oxa-2,7-diazaspiro[4.4]non-2-ene-3-carbonyl}-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	534.3	535.2
5		(2S,4R)-4-fluoro-1-[(2S,3R)-3-methoxy-2-(N-methylacetamido)butanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	511.3	512.3
6		(2S,4R)-1-[(4S,5R)-7-acetyl-1-oxo-2,7-diazaspiro[4.4]nonane-4-carbonyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	548.3	549.3

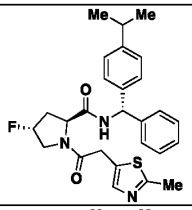
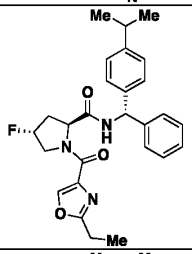
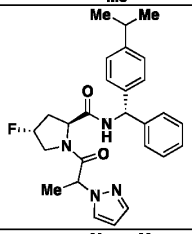
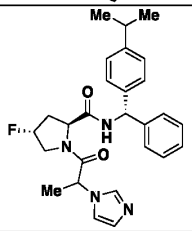
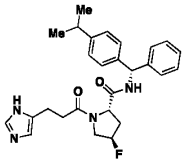
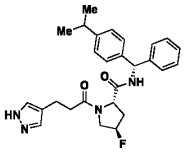
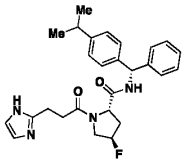
7		(2S,4R)-1-(2-{2-acetyl-2-azaspiro[3.4]octan-5-yl}acetyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	533.3	534.3
8		(2S,4R)-4-fluoro-1-[(5S)-2-oxo-1,3-oxazolidine-5-carbonyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	453.2	454.3
9		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(1H-1,2,3,4-tetrazol-1-yl)acetyl]pyrrolidine-2-carboxamide	450.2	451.3
10		(2S,4R)-4-fluoro-1-[2-(5-methyl-1,3,4-oxadiazol-2-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	464.2	465.2
11		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[3-(1H-1,2,3-triazol-1-yl)propanoyl]pyrrolidine-2-carboxamide	463.2	464.3
12		(2S,4R)-4-fluoro-1-(1,3-oxazole-5-carbonyl)-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	435.2	436.1

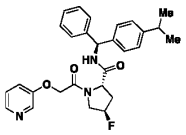
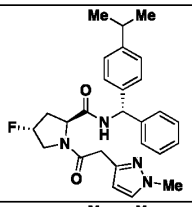
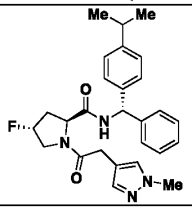
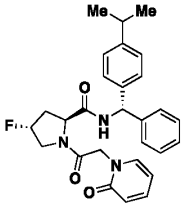
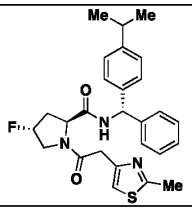
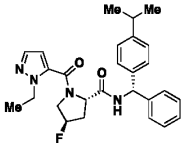
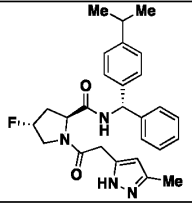
13		(2S,4R)-1-(3-cyanopropanoyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	421.2	422.3
14		(2S,4R)-4-fluoro-1-(2-methanesulfonylacetyl)-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	460.2	461.1
15		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(1,3-thiazol-4-yl)acetyl]pyrrolidine-2-carboxamide	465.2	466.2
16		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(1H-1,2,4-triazol-1-yl)acetyl]pyrrolidine-2-carboxamide	449.2	450.2
17		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(2H-1,2,3-triazol-2-yl)acetyl]pyrrolidine-2-carboxamide	449.2	450.3
18		(2S,4R)-4-fluoro-1-[2-(1H-imidazol-4-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	448.2	449.2
19		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(1H-pyrazol-5-yl)acetyl]pyrrolidine-2-carboxamide	448.2	449.3

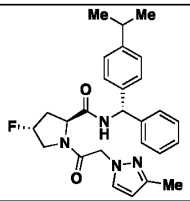
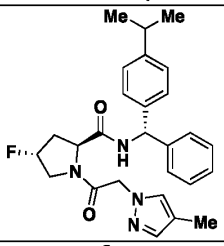
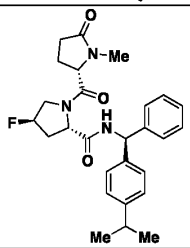
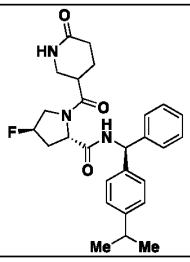
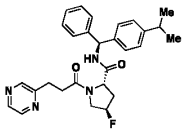
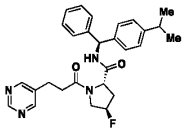
20		(2S,4R)-1-[2-(4-chloro-1H-pyrazol-1-yl)acetyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	482.2	483.2
21		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(pyridazin-3-yloxy)acetyl]pyrrolidine-2-carboxamide	476.2	477.1
22		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(1H-pyrazol-1-yl)acetyl]pyrrolidine-2-carboxamide	448.2	449.3
23		(2S,4R)-4-fluoro-1-[2-(1H-imidazol-1-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	448.2	449.3
24		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(1H-1,2,3,4-tetrazol-1-yl)propanoyl]pyrrolidine-2-carboxamide	464.2	465.3
25		(2S,4R)-4-fluoro-1-(3-methyloxetane-3-carbonyl)-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	438.2	439.3
26		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(pyrazin-2-yl)acetyl]pyrrolidine-2-carboxamide	460.2	461.2

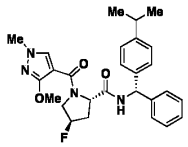
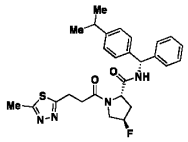
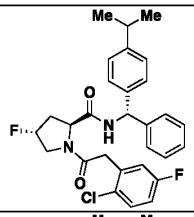
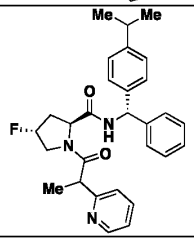
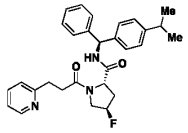
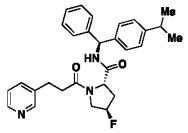
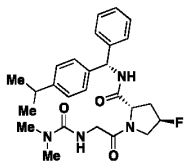
27		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(pyrimidin-5-yl)acetyl]pyrrolidine-2-carboxamide	460.2	461.2
28		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(pyrimidin-2-yl)acetyl]pyrrolidine-2-carboxamide	460.2	461.2
29		(2S,4R)-4-fluoro-1-[2-(5-methyl-1,2,4-oxadiazol-3-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	464.2	465.2
30		(2S,4R)-4-fluoro-1-(4-methylpyrimidine-5-carbonyl)-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	460.2	461.1
31		(2S,4R)-4-fluoro-1-[2-(3-methyl-1,2,4-oxadiazol-5-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	464.2	465.2
32		(2S,4R)-4-fluoro-1-[2-(2-oxo-1,2-dihydropyrazin-1-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	476.2	477.0
33		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(1H-1,2,3-triazol-1-yl)propanoyl]pyrrolidine-2-carboxamide	463.2	464.1

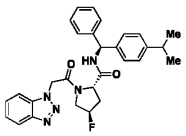
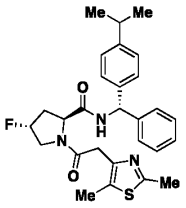
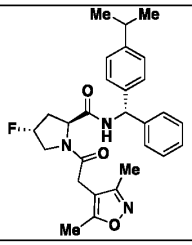
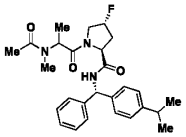
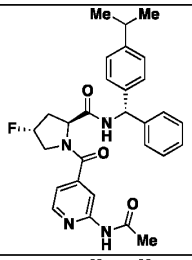
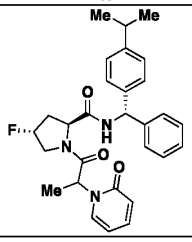
34		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(1H-1,2,4-triazol-1-yl)propanoyl]pyrrolidine-2-carboxamide	463.2	464.3
35		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[3-(1H-1,2,4-triazol-1-yl)propanoyl]pyrrolidine-2-carboxamide	463.2	464.2
36		(2S,4R)-4-fluoro-1-[2-(5-fluoropyridin-2-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	477.2	478.3
37		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(pyridin-2-yl)acetyl]pyrrolidine-2-carboxamide	459.2	460.3
38		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(pyridin-3-yl)acetyl]pyrrolidine-2-carboxamide	459.2	460.3
39		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(pyridin-4-yl)acetyl]pyrrolidine-2-carboxamide	459.2	460.3
40		(2S,4R)-4-fluoro-1-[2-(3-methyl-1,2-oxazol-5-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	463.2	464.4

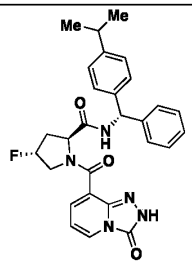
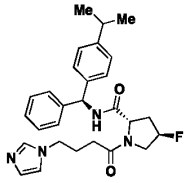
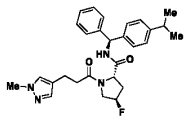
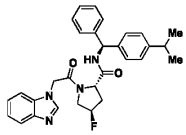
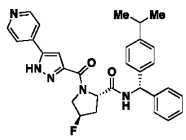
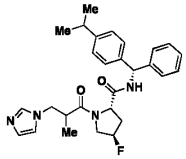
41		(2S,4R)-4-fluoro-1-[2-(2-methyl-1,3-thiazol-5-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	479.2	480.3
42		(2S,4R)-1-(2-ethyl-1,3-oxazole-4-carbonyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	463.2	464.3
43		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(1H-pyrazol-1-yl)propanoyl]pyrrolidine-2-carboxamide	462.2	463.3
44		(2S,4R)-4-fluoro-1-[2-(1H-imidazol-1-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	462.2	463.3
45		(2S,4R)-4-fluoro-1-[3-(1H-imidazol-5-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	462.2	463.2
46		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[3-(1H-pyrazol-4-yl)propanoyl]pyrrolidine-2-carboxamide	462.2	463.3
47		(2S,4R)-4-fluoro-1-[3-(1H-imidazol-2-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	462.2	463.2

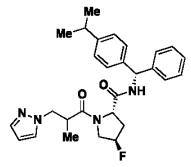
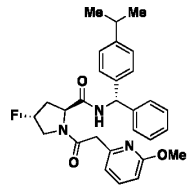
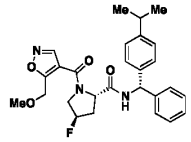
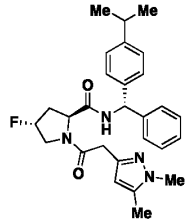
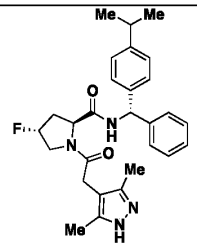
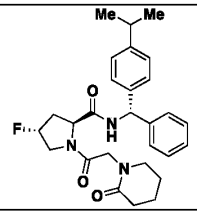
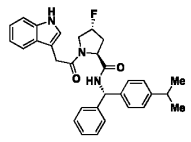
48		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(pyridin-3-yloxy)acetyl]pyrrolidine-2-carboxamide	475.2	476.3
49		(2S,4R)-4-fluoro-1-[2-(1-methyl-1H-pyrazol-3-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	462.2	463.3
50		(2S,4R)-4-fluoro-1-[2-(1-methyl-1H-pyrazol-4-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	462.2	463.3
51		(2S,4R)-4-fluoro-1-[2-(2-oxo-1,2-dihydropyridin-1-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	475.2	476.3
52		(2S,4R)-4-fluoro-1-[2-(2-methyl-1,3-thiazol-4-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	479.2	480.3
53		(2S,4R)-1-(1-ethyl-1H-pyrazole-5-carbonyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	462.2	463.3
54		(2S,4R)-4-fluoro-1-[2-(3-methyl-1H-pyrazol-5-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	462.2	463.3

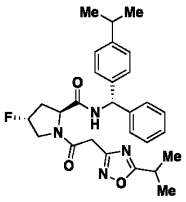
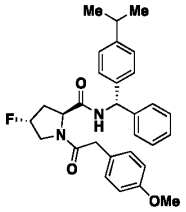
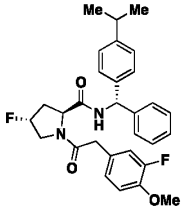
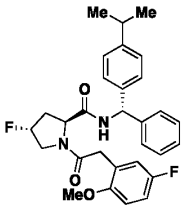
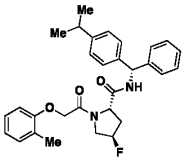
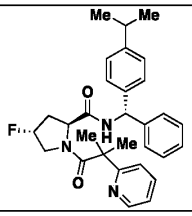
55		(2S,4R)-4-fluoro-1-[2-(3-methyl-1H-pyrazol-1-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	462.2	463.3
56		(2S,4R)-4-fluoro-1-[2-(4-methyl-1H-pyrazol-1-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	462.2	463.3
57		(2S,4R)-4-fluoro-1-[(2S)-1-methyl-5-oxopyrrolidine-2-carbonyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	465.2	466.3
58		(2S,4R)-4-fluoro-1-(6-oxopiperidine-3-carbonyl)-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	465.2	466.2
59		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[3-(pyrazin-2-yl)propanoyl]pyrrolidine-2-carboxamide	474.2	475.2
60		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[3-(pyrimidin-5-yl)propanoyl]pyrrolidine-2-carboxamide	474.2	475.2

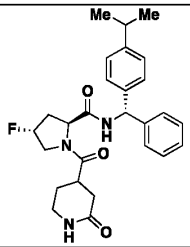
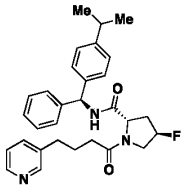
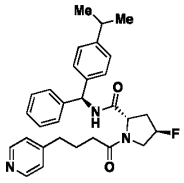
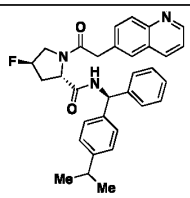
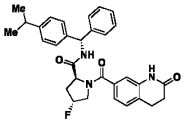
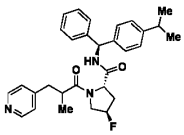
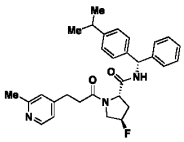
61		(2S,4R)-4-fluoro-1-(3-methoxy-1-methyl-1H-pyrazole-4-carbonyl)-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	478.2	479.3
62		(2S,4R)-4-fluoro-1-[3-(5-methyl-1,3,4-thiadiazol-2-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	494.2	495.2
63		(2S,4R)-1-[2-(2-chloro-5-fluorophenyl)acetyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	510.2	511.3
64		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(pyridin-2-yl)propanoyl]pyrrolidine-2-carboxamide	473.2	474.3
65		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[3-(pyridin-2-yl)propanoyl]pyrrolidine-2-carboxamide	473.2	474.3
66		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[3-(pyridin-3-yl)propanoyl]pyrrolidine-2-carboxamide	473.2	474.3
67		(2S,4R)-1-{2-[(dimethylcarbamoyl)amino]acetyl}-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	468.3	469.3

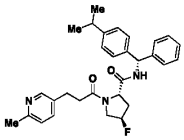
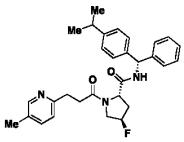
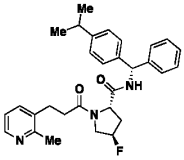
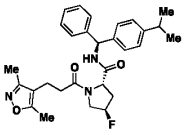
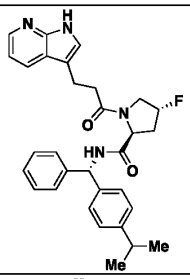
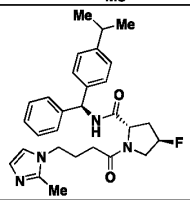
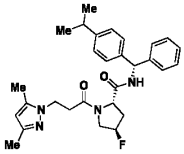
68		(2S,4R)-1-[2-(1H-1,2,3-benzotriazol-1-yl)acetyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	499.2	500.3
69		(2S,4R)-1-[2-(2,5-dimethyl-1,3-thiazol-4-yl)acetyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	493.2	494.3
70		(2S,4R)-1-[2-(3,5-dimethyl-1,2-oxazol-4-yl)acetyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	477.2	478.3
71		(2S,4R)-4-fluoro-1-[2-(N-methylacetamido)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	467.3	468.3
72		(2S,4R)-1-(2-acetamidopyridine-4-carbonyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	502.2	503.3
73		(2S,4R)-4-fluoro-1-[2-(2-oxo-1,2-dihydropyridin-1-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	489.2	490.3

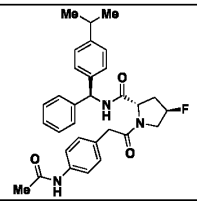
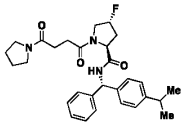
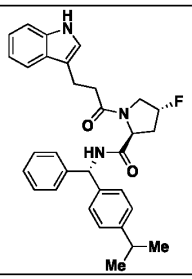
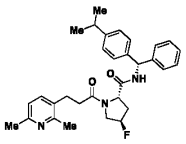
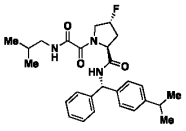
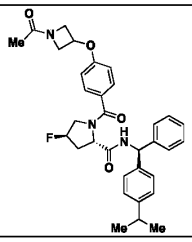
74		(2S,4R)-4-fluoro-1-{3-oxo-2H,3H-[1,2,4]triazolo[4,3-a]pyridine-8-carbonyl}-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	501.2	502.2
75		(2S,4R)-4-fluoro-1-[4-(1H-imidazol-1-yl)butanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	476.3	477.4
76		(2S,4R)-4-fluoro-1-[3-(1-methyl-1H-pyrazol-4-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	476.3	477.3
77		(2S,4R)-1-[2-(1H-1,3-benzodiazol-1-yl)acetyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	498.2	499.3
78		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[5-(pyridin-4-yl)-1H-pyrazole-3-carbonyl]pyrrolidine-2-carboxamide	511.2	512.3
79		(2S,4R)-4-fluoro-1-[3-(1H-imidazol-1-yl)-2-methylpropanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	476.3	477.3

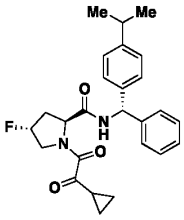
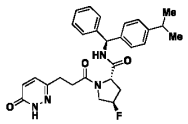
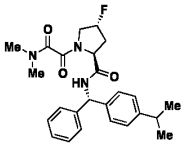
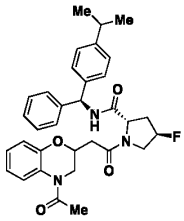
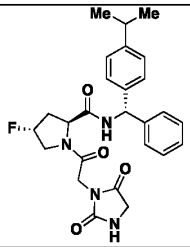
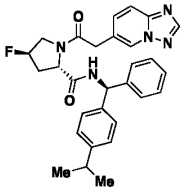
80		(2S,4R)-4-fluoro-1-[2-methyl-3-(1H-pyrazol-1-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	476.3	477.3
81		(2S,4R)-4-fluoro-1-[2-(6-methoxypyridin-2-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	489.2	490.3
82		(2S,4R)-4-fluoro-1-[5-(methoxymethyl)-1,2-oxazole-4-carbonyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	479.2	480.2
83		(2S,4R)-1-[2-(1,5-dimethyl-1H-pyrazol-3-yl)acetyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	476.3	477.3
84		(2S,4R)-1-[2-(3,5-dimethyl-1H-pyrazol-4-yl)acetyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	476.3	477.3
85		(2S,4R)-4-fluoro-1-[2-(2-oxopiperidin-1-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	479.3	480.3
86		(2S,4R)-4-fluoro-1-[2-(1H-indol-3-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	497.2	498.3

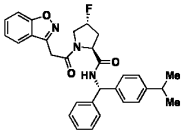
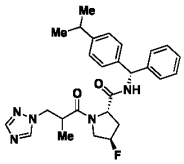
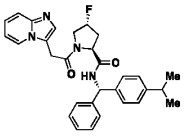
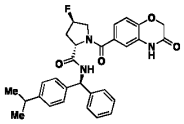
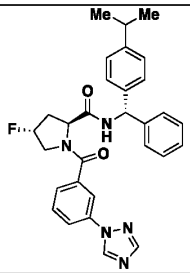
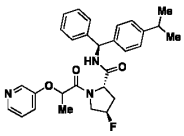
87		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-{2-[5-(propan-2-yl)-1,2,4-oxadiazol-3-yl]acetyl}pyrrolidine-2-carboxamide	492.3	493.3
88		(2S,4R)-4-fluoro-1-[2-(4-methoxyphenyl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	488.2	489.3
89		(2S,4R)-4-fluoro-1-[2-(3-fluoro-4-methoxyphenyl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	506.2	507.3
90		(2S,4R)-4-fluoro-1-[2-(5-fluoro-2-methoxyphenyl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	506.2	507.3
91		(2S,4R)-4-fluoro-1-[2-(2-methylphenoxy)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	488.2	489.3
92		(2S,4R)-4-fluoro-1-[2-methyl-2-(pyridin-2-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	487.3	488.3

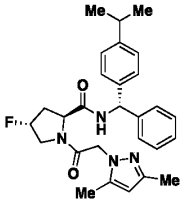
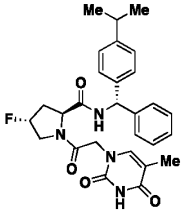
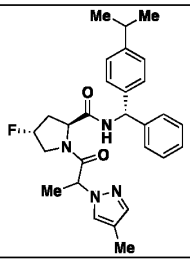
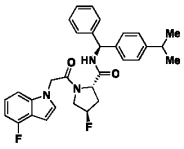
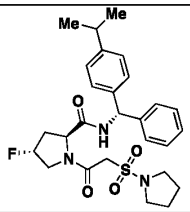
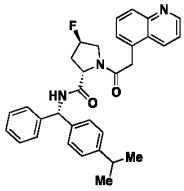
93		(2S,4R)-4-fluoro-1-(2-oxopiperidine-4-carbonyl)-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	465.2	466.1
94		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[4-(pyridin-3-yl)butanoyl]pyrrolidine-2-carboxamide	487.3	488.3
95		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[4-(pyridin-4-yl)butanoyl]pyrrolidine-2-carboxamide	487.3	488.3
96		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(quinolin-6-yl)acetyl]pyrrolidine-2-carboxamide	509.2	510.3
97		(2S,4R)-4-fluoro-1-(2-oxo-1,2,3,4-tetrahydroquinoline-7-carbonyl)-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	513.2	514.3
98		(2S,4R)-4-fluoro-1-[2-methyl-3-(pyridin-4-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	487.3	488.3
99		(2S,4R)-4-fluoro-1-[3-(2-methylpyridin-4-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	487.3	488.3

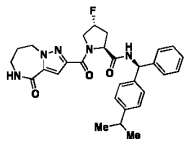
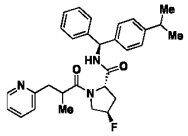
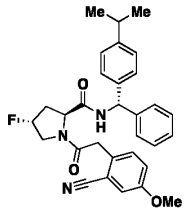
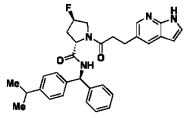
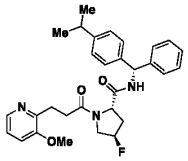
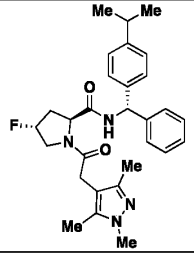
100		(2S,4R)-4-fluoro-1-[3-(6-methylpyridin-3-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	487.3	488.3
101		(2S,4R)-4-fluoro-1-[3-(5-methylpyridin-2-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	487.3	488.3
102		(2S,4R)-4-fluoro-1-[3-(2-methylpyridin-3-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	487.3	488.3
103		(2S,4R)-1-[3-(3,5-dimethyl-1,2-oxazol-4-yl)propanoyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	491.3	492.3
104		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-(3-{1H-pyrrolo[2,3-b]pyridin-3-yl}propanoyl)pyrrolidine-2-carboxamide	512.3	513.3
105		(2S,4R)-4-fluoro-1-[4-(2-methyl-1H-imidazol-1-yl)butanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	490.3	491.3
106		(2S,4R)-1-[3-(3,5-dimethyl-1H-pyrazol-1-yl)propanoyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	490.3	491.3

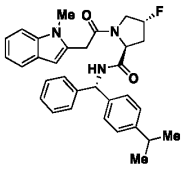
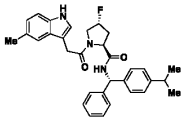
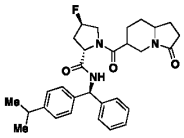
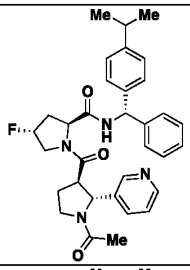
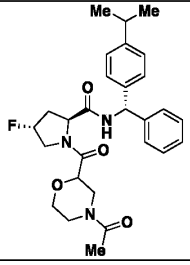
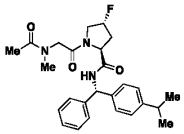
107		(2S,4R)-1-[2-(4-acetamidophenyl)acetyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	515.3	516.3
108		(2S,4R)-4-fluoro-1-[4-oxo-4-(pyrrolidin-1-yl)butanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	493.3	494.3
109		(2S,4R)-4-fluoro-1-[3-(1H-indol-3-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	511.3	512.3
110		(2S,4R)-1-[3-(2,6-dimethylpyridin-3-yl)propanoyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	501.3	502.3
111		(2S,4R)-4-fluoro-1-{[(2-methylpropyl)carbamoyl]carbonyl}-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	467.3	468.3
112		(2S,4R)-1-{4-[(1-acetylazetidin-3-yl)oxy]benzoyl}-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	557.3	558.3

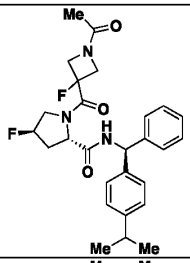
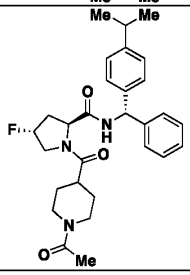
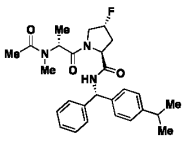
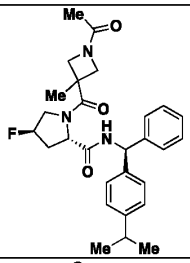
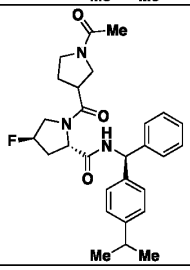
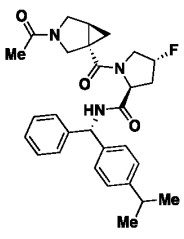
113		(2S,4R)-1-(2-cyclopropyl-2-oxoacetyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	436.2	437.3
114		(2S,4R)-4-fluoro-1-[3-(6-oxo-1,6-dihydropyridazin-3-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	490.2	491.2
115		(2S,4R)-1-[(dimethylcarbamoyl)carbonyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	439.2	440.2
116		(2S,4R)-1-[2-(4-acetyl-3,4-dihydro-2H-1,4-benzoxazin-2-yl)acetyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	557.3	558.3
117		(2S,4R)-1-[2-(2,5-dioxoimidazolidin-1-yl)acetyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	480.2	481.1
118		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-(2-{[1,2,4]triazolo[1,5-a]pyridin-6-yl}acetyl)pyrrolidine-2-carboxamide	499.2	500.3

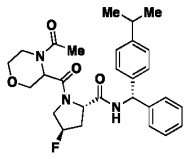
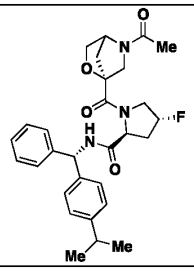
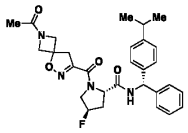
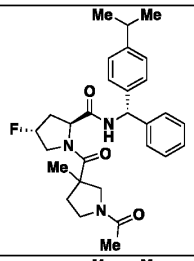
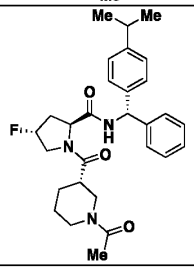
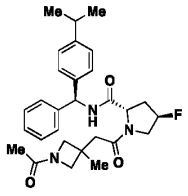
119		(2S,4R)-1-[2-(1,2-benzoxazol-3-yl)acetyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	499.2	500.3
120		(2S,4R)-4-fluoro-1-[2-methyl-3-(1H-1,2,4-triazol-1-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	477.3	478.1
121		(2S,4R)-4-fluoro-1-(2-{imidazo[1,2-a]pyridin-3-yl}acetyl)-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	498.2	499.3
122		(2S,4R)-4-fluoro-1-(3-oxo-3,4-dihydro-2H-1,4-benzoxazine-6-carbonyl)-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	515.2	516.3
123		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[3-(1H-1,2,4-triazol-1-yl)benzoyl]pyrrolidine-2-carboxamide	511.2	512.3
124		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(pyridin-3-yloxy)propanoyl]pyrrolidine-2-carboxamide	489.2	490.3

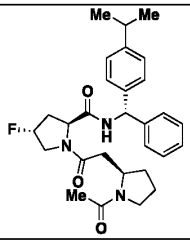
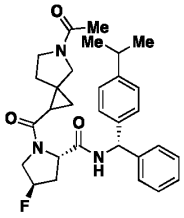
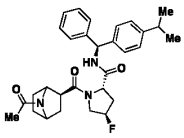
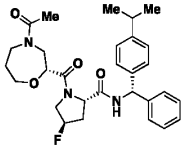
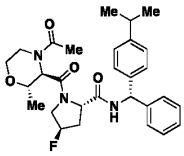
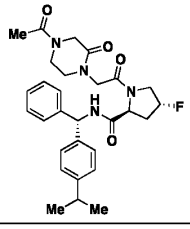
125		(2S,4R)-1-[2-(3,5-dimethyl-1H-pyrazol-1-yl)acetyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	476.3	477.4
126		(2S,4R)-4-fluoro-1-[2-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	506.2	507.3
127		(2S,4R)-4-fluoro-1-[2-(4-methyl-1H-pyrazol-1-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	476.3	477.4
128		(2S,4R)-4-fluoro-1-[2-(4-fluoro-1H-indol-1-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	515.2	516.3
129		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(pyrrolidine-1-sulfonyl)acetyl]pyrrolidine-2-carboxamide	515.2	516.3
130		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(quinolin-5-yl)acetyl]pyrrolidine-2-carboxamide	509.2	510.3

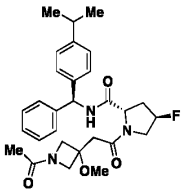
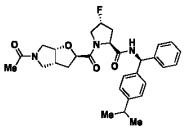
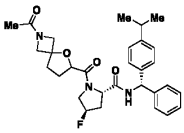
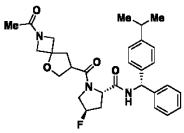
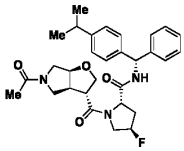
131		(2S,4R)-4-fluoro-1-{4-oxo-4H,5H,6H,7H,8H-pyrazolo[1,5-a][1,4]diazepine-2-carbonyl}-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	517.2	518.2
132		(2S,4R)-4-fluoro-1-[2-methyl-3-(pyridin-2-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	487.3	488.3
133		(2S,4R)-1-[2-(2-cyano-4-methoxyphenyl)acetyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	513.2	514.3
134		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-(3-{1H-pyrrolo[2,3-b]pyridin-5-yl}propanoyl)pyrrolidine-2-carboxamide	512.3	513.3
135		(2S,4R)-4-fluoro-1-[3-(3-methoxypyridin-2-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	503.3	504.3
136		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(1,3,5-trimethyl-1H-pyrazol-4-yl)acetyl]pyrrolidine-2-carboxamide	490.3	491.3

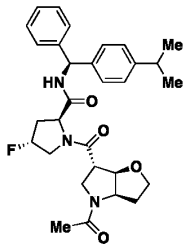
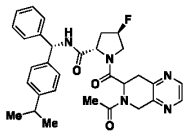
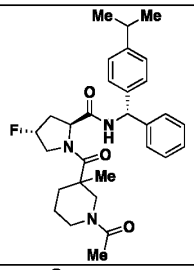
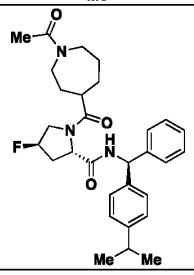
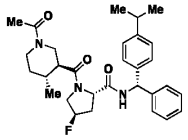
137		(2S,4R)-4-fluoro-1-[2-(1-methyl-1H-indol-2-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	511.3	512.3
138		(2S,4R)-4-fluoro-1-[2-(5-methyl-1H-indol-3-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	511.3	512.3
139		(2S,4R)-4-fluoro-1-(3-oxo-octahydroindolizine-6-carbonyl)-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	505.3	506.3
140		(2S,4R)-1-[(2R,3R)-1-acetyl-2-(pyridin-3-yl)pyrrolidine-3-carbonyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	556.3	557.2
141		(2S,4R)-1-(4-acetylmorpholine-2-carbonyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	495.3	496.3
142		(2S,4R)-4-fluoro-1-[2-(N-methylacetamido)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	453.2	454.3

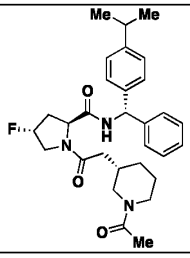
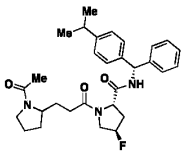
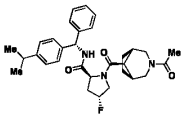
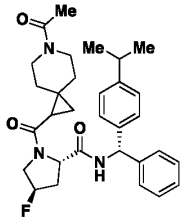
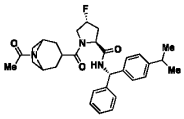
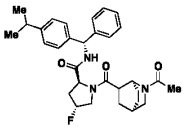
143		(2S,4R)-1-(1-acetyl-3-fluoroazetidine-3-carbonyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	483.2	484.3
144		(2S,4R)-1-(1-acetylpiperidine-4-carbonyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	493.3	494.2
145		(2S,4R)-4-fluoro-1-[(2R)-2-(N-methylacetamido)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	467.3	468.3
146		(2S,4R)-1-(1-acetyl-3-methylazetidine-3-carbonyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	479.3	480.3
147		(2S,4R)-1-(1-acetylpyrrolidine-3-carbonyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	479.3	480.2
148		(2S,4R)-1-[(1S,5S)-3-acetyl-3-azabicyclo[3.1.0]hexane-1-carbonyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	491.3	492.3

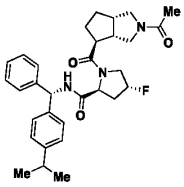
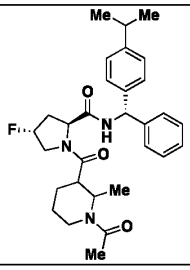
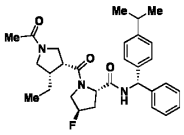
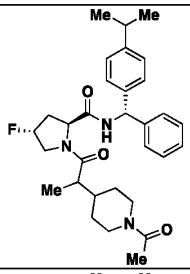
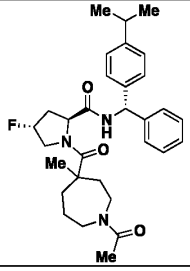
149		(2S,4R)-1-(4-acetylmorpholine-3-carbonyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	495.3	496.3
150		(2S,4R)-1-[(1S)-5-acetyl-2-oxa-5-azabicyclo[2.2.1]heptane-1-carbonyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	507.3	508.3
151		(2S,4R)-1-{2-acetyl-5-oxa-2,6-diazaspiro[3.4]oct-6-ene-7-carbonyl}-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	520.2	521.3
152		(2S,4R)-1-(1-acetyl-3-methylpyrrolidine-3-carbonyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	493.3	494.3
153		(2S,4R)-1-[(3S)-1-acetylpiperidine-3-carbonyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	493.3	494.3
154		(2S,4R)-1-[2-(1-acetyl-3-methylazetidin-3-yl)acetyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	493.3	494.1

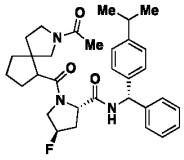
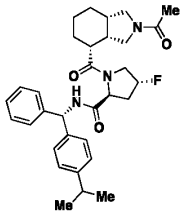
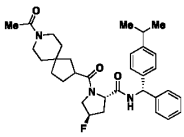
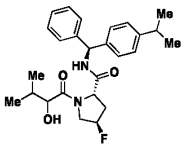
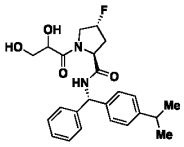
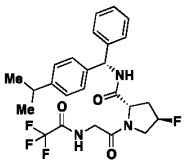
155		(2S,4R)-1-{2-[(2R)-1-acetylpyrrolidin-2-yl]acetyl}-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	493.3	494.3
156		(2S,4R)-1-{5-acetyl-5-azaspiro[2.4]heptane-1-carbonyl}-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	505.3	506.2
157		(2S,4R)-1-[(2S)-7-acetyl-7-azabicyclo[2.2.1]heptane-2-carbonyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	505.3	506.3
158		(2S,4R)-1-[(2R)-4-acetyl-1,4-oxazepane-2-carbonyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	509.3	510.2
159		(2S,4R)-1-[(2S,3R)-4-acetyl-2-methylmorpholine-3-carbonyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	509.3	510.3
160		(2S,4R)-1-[2-(4-acetyl-2-oxopiperazin-1-yl)acetyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	522.3	523.3

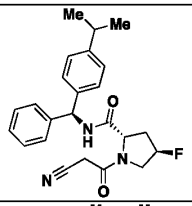
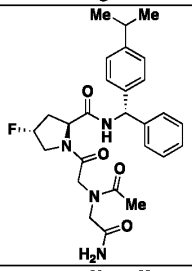
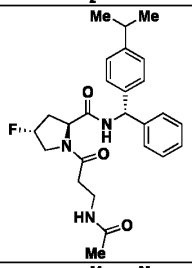
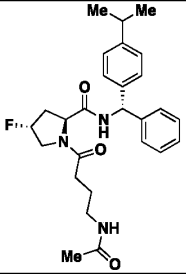
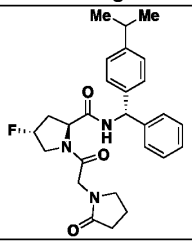
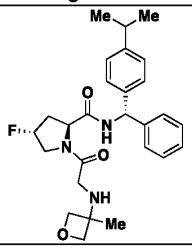
161		(2S,4R)-1-[2-(1-acetyl-3-methoxyazetidin-3-yl)acetyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	509.3	510.3
162		(2S,4R)-1-[(2R,3aR,6aR)-5-acetyl-hexahydro-2H-furo[2,3-c]pyrrole-2-carbonyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	521.3	522.2
163		(2S,4R)-1-{2-acetyl-5-oxa-2-azaspiro[3.4]octane-6-carbonyl}-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	521.3	522.2
164		(2S,4R)-1-{2-acetyl-5-oxa-2-azaspiro[3.4]octane-7-carbonyl}-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	521.3	522.2
165		(2S,4R)-1-[(3R,3aS,6aS)-5-acetyl-hexahydro-2H-furo[2,3-c]pyrrole-3-carbonyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	521.3	522.3

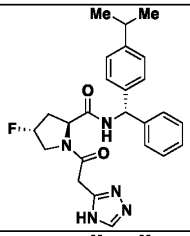
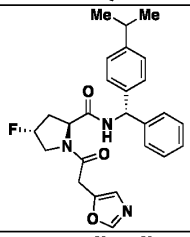
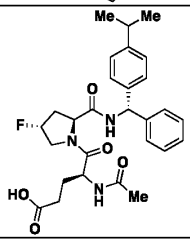
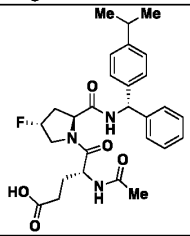
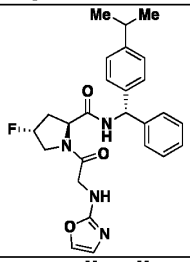
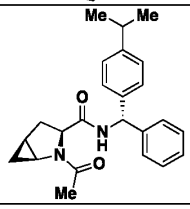
166		(2S,4R)-1-[(3aR,6S,6aR)-4-acetyl-hexahydro-2H-furo[3,2-b]pyrrole-6-carbonyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	521.3	522.3
167		(2S,4R)-1-{6-acetyl-5H,6H,7H,8H-pyrido[3,4-b]pyrazine-7-carbonyl}-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	543.3	544.2
168		(2S,4R)-1-(1-acetyl-3-methylpiperidine-3-carbonyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	507.3	508.3
169		(2S,4R)-1-(1-acetylazepane-4-carbonyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	507.3	508.2
170		(2S,4R)-1-[(3S,4R)-1-acetyl-4-methylpiperidine-3-carbonyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	507.3	508.3

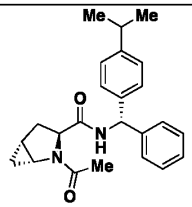
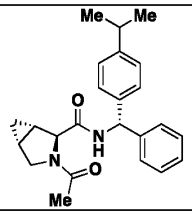
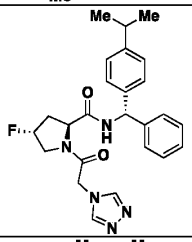
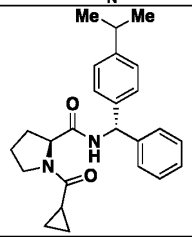
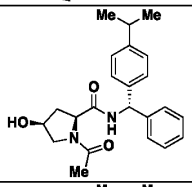
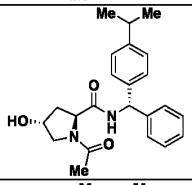
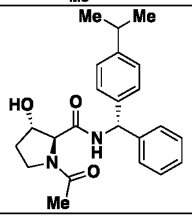
171		(2S,4R)-1-{2-[(3S)-1-acetylpiperidin-3-yl]acetyl}-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	507.3	508.2
172		(2S,4R)-1-[3-(1-acetylpyrrolidin-2-yl)propanoyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	507.3	508.3
173		(2S,4R)-1-[(1R,5S,8S)-3-acetyl-3-azabicyclo[3.2.1]octane-8-carbonyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	519.3	520.3
174		(2S,4R)-1-{6-acetyl-6-azaspiro[2.5]octane-1-carbonyl}-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	519.3	520.2
175		(2S,4R)-1-{8-acetyl-8-azabicyclo[3.2.1]octane-3-carbonyl}-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	519.3	520.2
176		(2S,4R)-1-[(1S,4R)-2-acetyl-2-azabicyclo[2.2.2]octane-6-carbonyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	519.3	520.3

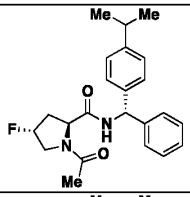
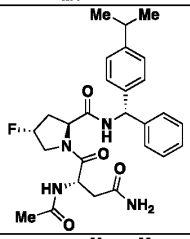
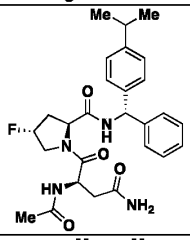
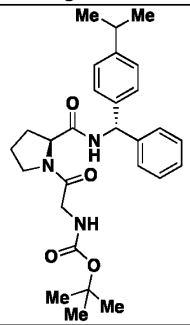
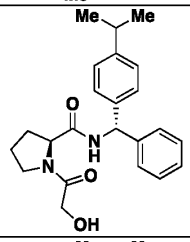
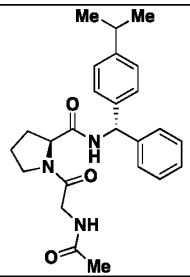
177		(2S,4R)-1-[(3aS,4S,6aS)-2-acetyl-octahydrocyclopenta[c]pyrrole-4-carbonyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	519.3	520.3
178		(2S,4R)-1-(1-acetyl-2-methylpiperidine-3-carbonyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	507.3	508.3
179		(2S,4R)-1-[(3R,4S)-1-acetyl-4-ethylpyrrolidine-3-carbonyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	507.3	508.3
180		(2S,4R)-1-[2-(1-acetylpiperidin-4-yl)propanoyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	521.3	522.3
181		(2S,4R)-1-(1-acetyl-4-methylazepane-4-carbonyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	521.3	522.2

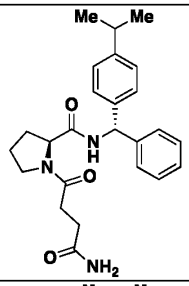
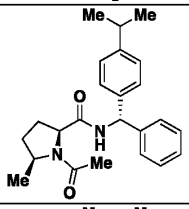
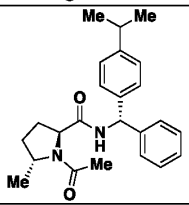
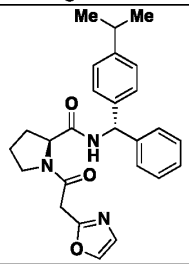
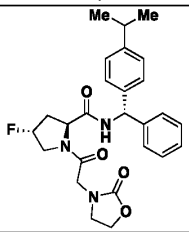
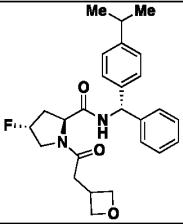
182		(2S,4R)-1-{2-acetyl-2-azaspiro[4.4]nonane-6-carbonyl}-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	533.3	534.3
183		(2S,4R)-1-[(3aS,4R,7aS)-2-acetyl-octahydro-1H-isoindole-4-carbonyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	533.3	534.0
184		(2S,4R)-1-{8-acetyl-8-azaspiro[4.5]decane-2-carbonyl}-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	547.3	548.3
185		(2S,4R)-4-fluoro-1-(2-hydroxy-3-methylbutanoyl)-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	440.2	441.3
186		(2S,4R)-1-(2,3-dihydroxypropanoyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	428.2	429.3
187		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(2,2,2-trifluoroacetamido)acetyl]pyrrolidine-2-carboxamide	493.2	494.1

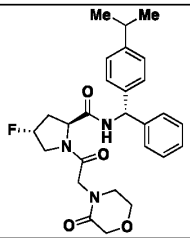
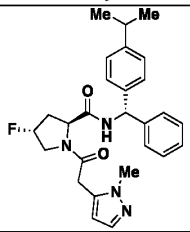
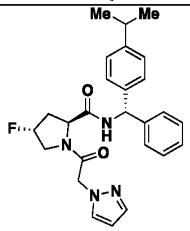
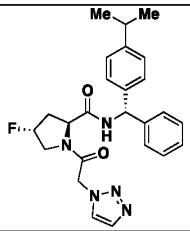
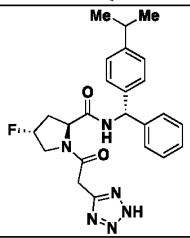
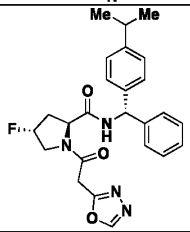
188		(2S,4R)-1-(2-cyanoacetyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	407.2	408.1
189		(2S,4R)-1-{2-[N-(carbamoylmethyl)acetamido]acetyl}-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	496.2	497.1
190		(2S,4R)-1-(3-acetamidopropanoyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	453.2	454.1
191		(2S,4R)-1-(4-acetamidobutanoyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	467.3	468.3
192		(2S,4R)-4-fluoro-1-[2-(2-oxopyrrolidin-1-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	465.2	466.2
193		(2S,4R)-4-fluoro-1-{2-[(3-methyloxetan-3-yl)amino]acetyl}-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	467.3	468.1

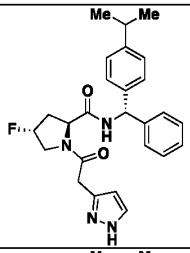
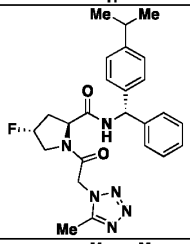
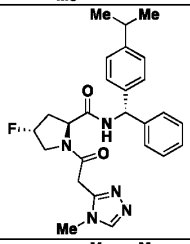
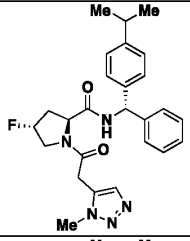
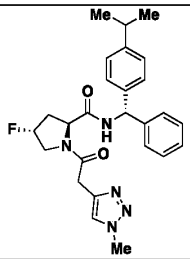
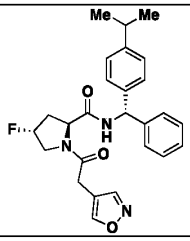
194		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(4H-1,2,4-triazol-3-yl)acetyl]pyrrolidine-2-carboxamide	449.2	450.2
195		(2S,4R)-4-fluoro-1-[2-(1,3-oxazol-5-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	449.2	450.2
196		(4S)-4-acetamido-5-[(2S,4R)-4-fluoro-2-{[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]carbamoyl}pyrrolidin-1-yl]-5-oxopentanoic acid	511.2	512.3
197		(4R)-4-acetamido-5-[(2S,4R)-4-fluoro-2-{[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]carbamoyl}pyrrolidin-1-yl]-5-oxopentanoic acid	511.2	512.3
198		(2S,4R)-4-fluoro-1-{2-[(1,3-oxazol-2-yl)amino]acetyl}-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	464.2	465.1
199		(1S,3S,5S)-2-acetyl-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-2-azabicyclo[3.1.0]hexane-3-carboxamide	376.2	377.1

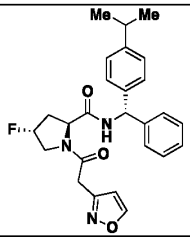
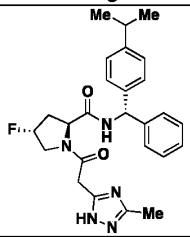
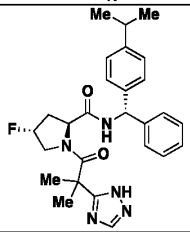
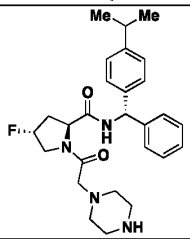
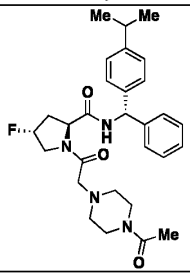
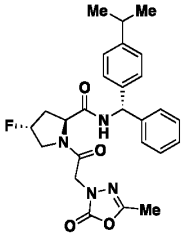
200		(1R,3S,5R)-2-acetyl-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-2-azabicyclo[3.1.0]hexane-3-carboxamide	376.2	377.1
201		(1S,2S,5R)-3-acetyl-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide	376.2	377.1
202		(2RS,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(4H-1,2,4-triazol-4-yl)acetyl]pyrrolidine-2-carboxamide	449.2	450.3
203		(2S)-1-cyclopropanecarbonyl-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	390.2	391.3
204		(2S,4S)-1-acetyl-4-hydroxy-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	380.2	381.2
205		(2S,4R)-1-acetyl-4-hydroxy-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	380.2	381.3
206		(2S,3S)-1-acetyl-3-hydroxy-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	380.2	381.1

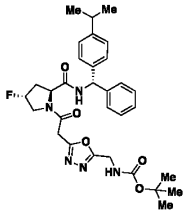
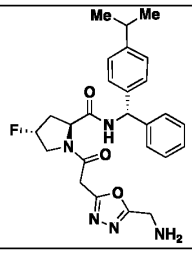
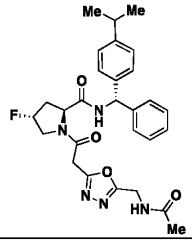
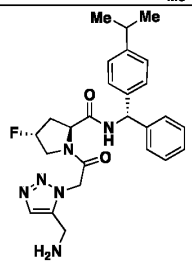
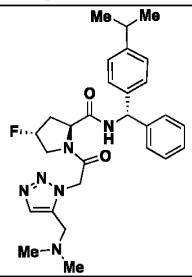
207		(2S,4R)-1-acetyl-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	382.2	422.2
208		(2S,4R)-1-[(2S)-3-carbamoyl-2-acetamidopropanoyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	496.2	383.3
209		(2S,4R)-1-[(2R)-3-carbamoyl-2-acetamidopropanoyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	496.2	497.1
210		tert-butyl N-{2-oxo-2-[(2S)-2-{[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]carbamoyl}pyrrolidin-1-yl]ethyl}carbamate	479.3	497.2
211		(2S)-1-(2-hydroxyacetyl)-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	380.2	381.2
212		(2S)-1-(2-acetamidoacetyl)-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	421.2	422.2

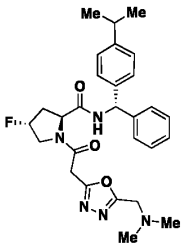
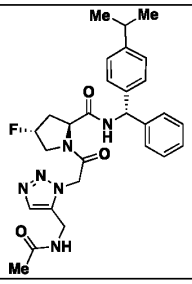
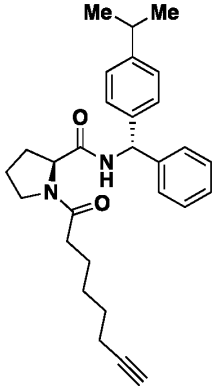
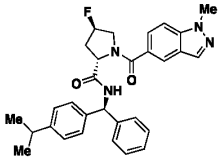
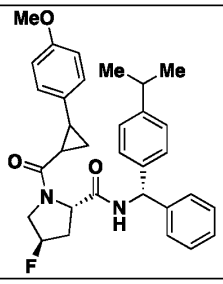
213		(2S)-1-(3-carbamoylpropanoyl)-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	421.2	422.3
214		(2S,5S)-1-acetyl-5-methyl-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	378.2	379.2
215		(2S,5R)-1-acetyl-5-methyl-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	378.2	379.2
216		(2S)-1-[2-(1,3-oxazol-2-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	431.2	432.3
217		(2S,4R)-4-fluoro-1-[2-(2-oxo-1,3-oxazolidin-3-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	467.2	468.1
218		(2S,4R)-4-fluoro-1-[2-(oxetan-3-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	438.2	439.3

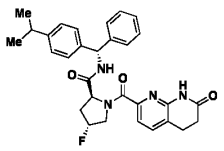
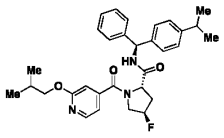
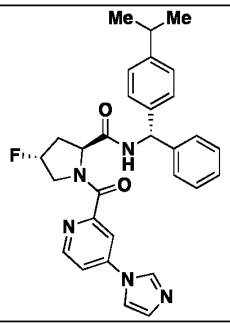
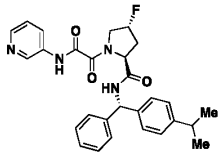
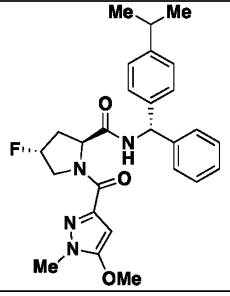
219		(2S,4R)-4-fluoro-1-[2-(3-oxomorpholin-4-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	481.2	482.2
220		(2S,4RS)-4-fluoro-1-[2-(1-methyl-1H-pyrazol-5-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	462.2	463.2
221		(2S,4RS)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(1H-pyrazol-1-yl)acetyl]pyrrolidine-2-carboxamide	448.2	449.9
222		(2RS,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(1H-1,2,3-triazol-1-yl)acetyl]pyrrolidine-2-carboxamide	449.2	450.1
223		(2RS,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(2H-1,2,3,4-tetrazol-5-yl)acetyl]pyrrolidine-2-carboxamide	450.2	451.2
224		(2RS,4R)-4-fluoro-1-[2-(1,3,4-oxadiazol-2-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	450.2	451.1

225		(2RS,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(1H-pyrazol-3-yl)acetyl]pyrrolidine-2-carboxamide	448.2	449.2
226		(2RS,4R)-4-fluoro-1-[2-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	464.2	465.3
227		(2RS,4R)-4-fluoro-1-[2-(4-methyl-4H-1,2,4-triazol-3-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	463.2	464.3
228		(2RS,4R)-4-fluoro-1-[2-(1-methyl-1H-1,2,3-triazol-5-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	463.2	464.3
229		(2RS,4R)-4-fluoro-1-[2-(1-methyl-1H-1,2,3-triazol-4-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	463.2	464.2
230		(2S,4R)-4-fluoro-1-[2-(1,2-oxazol-4-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	449.2	450.3

231		(2S,4R)-4-fluoro-1-[2-(1,2-oxazol-3-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	449.2	450.3
232		(2S,4R)-4-fluoro-1-[2-(3-methyl-1H-1,2,4-triazol-5-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	463.2	464.2
233		(2S,4R)-4-fluoro-1-[2-methyl-2-(1H-1,2,4-triazol-5-yl)propanoyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	477.3	478.2
234		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-[2-(piperazin-1-yl)acetyl]pyrrolidine-2-carboxamide	466.3	467.2
235		(2S,4R)-1-[2-(4-acetylpiperazin-1-yl)acetyl]-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	508.3	509.3
236		(2S,4R)-4-fluoro-1-[2-(5-methyl-2-oxo-2,3-dihydro-1,3,4-oxadiazol-3-yl)acetyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	480.2	481.1

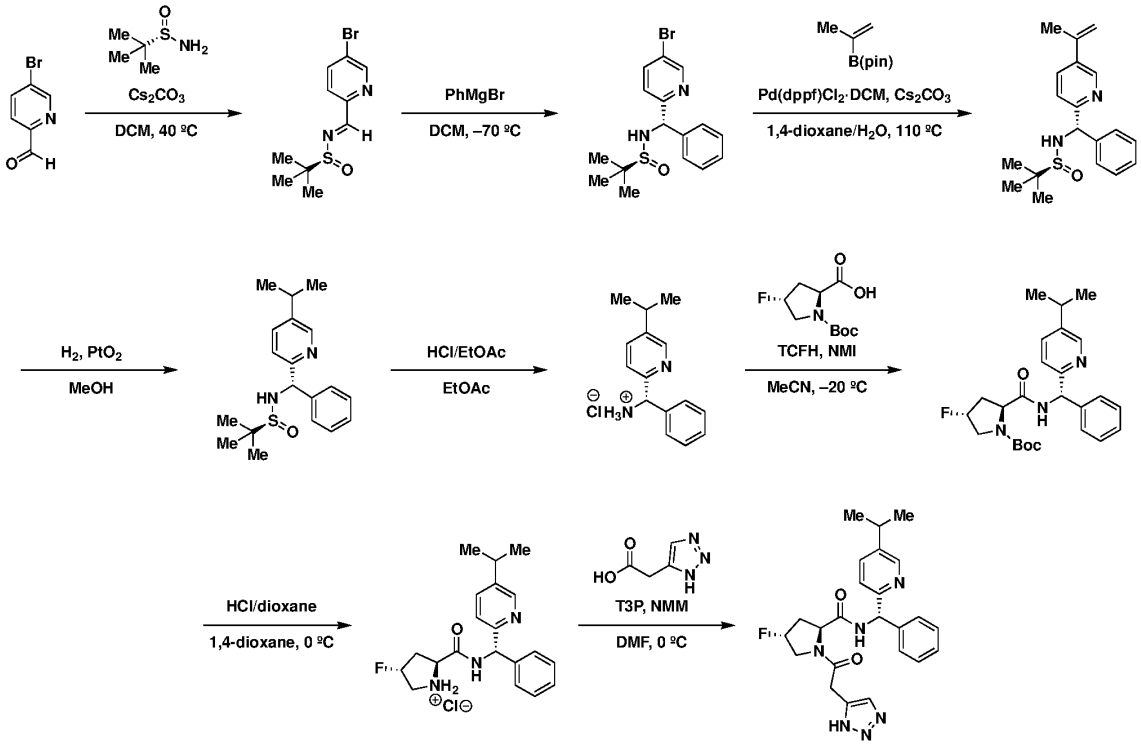
237		tert-butyl N-[(5-{2-[(2S,4R)-4-fluoro-2-{[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl}-1,3,4-oxadiazol-2-yl)methyl]carbamate	579.3	580.3
238		(2S,4R)-1-{2-[5-(aminomethyl)-1,3,4-oxadiazol-2-yl]acetyl}-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	479.2	480.2
239		(2S,4R)-1-{2-[5-(acetamidomethyl)-1,3,4-oxadiazol-2-yl]acetyl}-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	521.2	522.2
240		(2S,4R)-1-{2-[5-(aminomethyl)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	478.2	479.2
241		(2S,4R)-1-(2-{5-[(dimethylamino)methyl]-1H-1,2,3-triazol-1-yl}acetyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	506.3	507.2

242		(2S,4R)-1-(2-{5-[(dimethylamino)methyl]-1,3,4-oxadiazol-2-yl}acetyl)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	507.3	508.2
243		(2S,4R)-1-{2-[5-(acetamidomethyl)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	520.3	521.2
701		(2S)-1-(oct-7-ynoyl)-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	444.3	445.5
702		(2S,4R)-4-fluoro-1-(1-methyl-1H-indazole-5-carbonyl)-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	498.2	499.3
703		(2S,4R)-4-fluoro-1-[2-(4-methoxyphenyl)cyclopropanecarbonyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	514.3	515.3

704		(2S,4R)-4-fluoro-1-(7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridine-2-carbonyl)-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	514.2	515.3
705		(2S,4R)-4-fluoro-1-[2-(2-methylpropoxy)pyridine-4-carbonyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	517.3	518.3
707		(2S,4R)-4-fluoro-1-[4-(1H-imidazol-1-yl)pyridine-2-carbonyl]-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	511.2	512.3
708		(2S,4R)-4-fluoro-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]-1-{[(pyridin-3-yl)carbamoyl]carbonyl}pyrrolidine-2-carboxamide	488.2	489.2
709		(2S,4R)-4-fluoro-1-(5-methoxy-1-methyl-1H-pyrazole-3-carbonyl)-N-[(S)-phenyl[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	478.2	479.3

Example S-2: Synthesis of (2*S*,4*R*)-1-(2-(1*H*-1,2,3-triazol-5-yl)acetyl)-4-fluoro-*N*-((*S*)-(5-isopropylpyridin-2-yl)(phenyl)methyl)pyrrolidine-2-carboxamide

(Compound 244)



[0599] Step a: To a solution of 5-bromopicolinaldehyde (15 g, 80.6 mmol, 1 eq) in DCM (150 mL) at 25 °C was added (*S*)-2-methylpropane-2-sulfinamide (10.8 g, 88.7 mmol, 1.1 eq) and Cs_2CO_3 (28.9 g, 88.7 mmol, 1.1 eq). The resulting mixture was degassed and charged with nitrogen three times before it was warmed to 40 °C and stirred 2 h under N_2 atmosphere. After cooling to room temperature, the reaction mixture was filtered and concentrated under reduced pressure. The resulting crude residue was purified by column chromatography to give (*S*,*E*)-*N*-((5-bromopyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{10}H_{13}BrN_2OS$: 289.0; found 289.0.

[0600] Step b: A solution of (*S*,*E*)-*N*-((5-bromopyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide (20 g, 69.2 mmol, 1 eq) in DCM (100 mL) was degassed with N_2 and cooled to –70 °C. To the cooled solution was added PhMgBr (3 M in Et_2O, 27.7 mL, 1.2 eq) in a dropwise manner. The resulting reaction mixture was stirred at –70 °C for 2 h, warmed to room temperature, and stirred for another 1 h. The reaction mixture then was quenched with water (150 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with brine (3 x 50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated

under reduced pressure. The resulting crude residue was purified by column chromatography to give (*S*)-*N*-((*S*)-(5-bromopyridin-2-yl)(phenyl)methyl)-2-methylpropane-2-sulfinamide. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{16}H_{19}BrN_2OS$: 367.0; found 367.0.

[0601] Step c: To a solution of (*S*)-*N*-((*S*)-(5-bromopyridin-2-yl)(phenyl)methyl)-2-methylpropane-2-sulfinamide (23 g, 62.6 mmol, 1 eq) in 1,4-dioxane (150 mL) and water (40 mL) at 25 °C was added 2-isopropenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (15.8 g, 93.9 mmol, 1.5 eq), Cs_2CO_3 (40.8 g, 125 mmol, 2 eq) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (5.11 g, 6.26 mmol, 0.1 eq). The resulting mixture was degassed and charged with nitrogen three times, and the reaction mixture was warmed to 110 °C and stirred for 8 h. After cooling, the reaction mixture was concentrated under reduced pressure, and water (150 mL) was added. The resulting mixture was extracted with ethyl acetate (3 x 150 mL). The combined organic extracts were washed with brine (3 x 100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude residue was purified by column chromatography to give (*S*)-2-methyl-*N*-((*S*)-phenyl(5-(prop-1-en-2-yl)pyridin-2-yl)methyl)propane-2-sulfinamide. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{19}H_{24}N_2OS$: 329.2; found 329.2.

[0602] Step d: To a solution of (*S*)-2-methyl-*N*-((*S*)-phenyl(5-(prop-1-en-2-yl)pyridin-2-yl)methyl)propane-2-sulfinamide (11.5 g, 35 mmol, 1eq) in MeOH (80 mL) at 25 °C was added PtO_2 (795 mg, 3.50 mmol, 0.1 eq). The system was degassed and charged with hydrogen three times, and the reaction mixture was stirred under H_2 atmosphere (15 psi) at 25 °C for 2 h. The mixture was then filtered through a pad of Celite, and the filter cake was washed with MeOH (2 x 30 mL). The filtrate was then concentrated under reduced pressure to give (*S*)-*N*-((*S*)-(5-isopropylpyridin-2-yl)(phenyl)methyl)-2-methylpropane-2-sulfinamide, which was used directly for the next step without further purification. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{19}H_{26}N_2OS$: 331.2; found 331.2.

[0603] Step e: To a solution of (*S*)-*N*-((*S*)-(5-isopropylpyridin-2-yl)(phenyl)methyl)-2-methylpropane-2-sulfinamide (12.0 g, 36.3 mmol, 1 eq) in EtOAc (20 mL) at 25 °C was added HCl/EtOAc (4 M, 109 mL, 436 mmol, 12.0 eq). The resulting mixture was stirred for 1 h before it was filtered. The filter cake was then washed with petroleum ether, and the collected solid dried under reduced pressure to give (*S*)-(5-isopropylpyridin-2-yl)(phenyl)methanamine hydrochloride. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{15}H_{18}N_2$: 227.2; found 227.2.

[0604] Step f: To a solution of (*S*)-(5-isopropylpyridin-2-yl)(phenyl)methanamine hydrochloride (5.00 g, 19.0 mmol, 1 eq, HCl salt) in MeCN (70 mL) at –20 °C under N_2 atmosphere was added 1-methyl-1*H*-imidazole (NMI, 4.69 g, 57.1 mmol, 3 eq) and (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (4.9 g, 20.1 mmol, 1.1 eq), and the resulting mixture was stirred for 10 min. To this mixture was added chloro-*N*,*N*,*N*',*N*'-tetramethylformamidinium hexafluorophosphate (TCFH, 5.87 g, 20.9 mmol, 1.1 eq) in portions. The resulting reaction mixture was stirred at –20 °C for 3 h under N_2 atmosphere. The reaction mixture was then quenched with H_2O (30 mL), and the resulting biphasic mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were washed with brine (3 x 30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude residue was purified by column chromatography to give *tert*-butyl (2*S*,4*R*)-4-fluoro-2-(((*S*)-(5-isopropylpyridin-2-yl)(phenyl)methyl)carbamoyl)pyrrolidine-1-carboxylate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{25}H_{32}FN_3O_3$: 442.2; found 442.3.

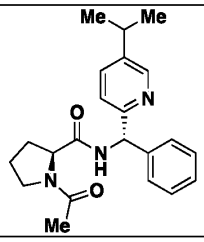
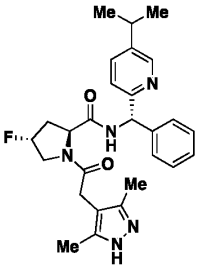
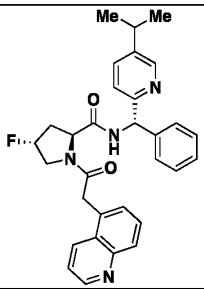
[0605] Step g: To a solution of *tert*-butyl (2*S*,4*R*)-4-fluoro-2-(((*S*)-(5-isopropylpyridin-2-yl)(phenyl)methyl)carbamoyl)pyrrolidine-1-carboxylate (3.9 g, 8.8 mmol) in 1,4-dioxane (5 mL) at 0 °C was added HCl/dioxane (4 M, 50 mL), and the resulting mixture was stirred at 0 °C for 2 h. The reaction mixture was then concentrated at low temperature under reduced pressure. The resulting solid was washed with MTBE (3 x 10 mL), collected via filtration, and dried under reduced pressure to give (2*S*,4*R*)-4-fluoro-2-(((*S*)-(5-isopropylpyridin-2-yl)(phenyl)methyl)carbamoyl)pyrrolidin-1-ium chloride. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{20}H_{24}FN_3O$: 342.2; found 342.2.

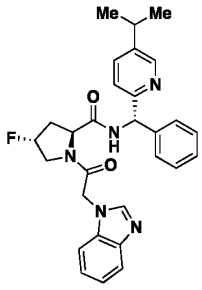
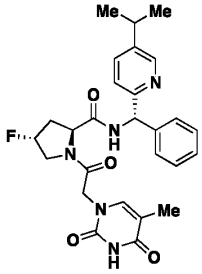
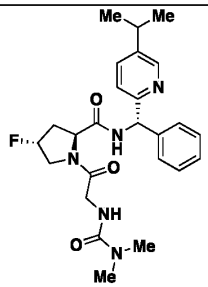
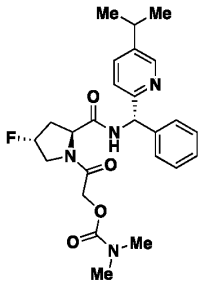
[0606] Step h: To a solution of (2*S*,4*R*)-4-fluoro-2-(((*S*)-(5-isopropylpyridin-2-yl)(phenyl)methyl)carbamoyl)pyrrolidin-1-ium chloride (2.50 g, 6.62 mmol, 1 eq, HCl), 4-methylmorpholine (NMM, 2.01 g, 19.9 mmol, 3 eq), and 2-(1*H*-1,2,3-triazol-5-yl)acetic acid (Intermediate A-1, 1.26 g, 9.92 mmol, 1.5 eq) in DMF (30 mL) at 0 °C was added T3P (50% in ethyl acetate, 8.42 g, 13.3 mmol, 2 eq). The resulting mixture was then stirred at 0 °C for 2 h under N_2 atmosphere. The reaction mixture was then quenched by addition of H_2O (60 mL) at 0 °C, and the biphasic mixture was extracted with DCM (3 x 15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was then purified by prep-HPLC to give (2*S*,4*R*)-1-(2-(1*H*-1,2,3-triazol-5-

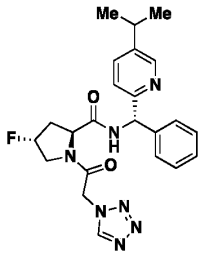
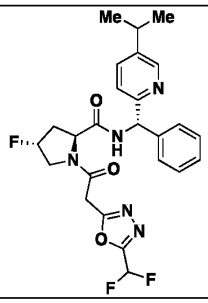
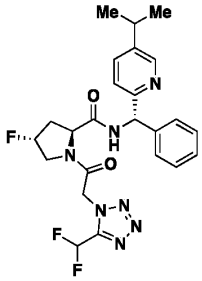
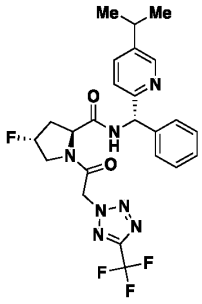
yl)acetyl)-4-fluoro-*N*-((*S*)-(5-isopropylpyridin-2-yl)(phenyl)methyl)pyrrolidine-2-carboxamide. ^{1}H NMR (2.4:1 rotamer ratio, asterisk denotes distinct minor rotamer peaks, obscured peaks not reported, 400 MHz, DMSO-d_6) δ 15.17 – 14.54 (m, 1H), 9.32* (d, J = 8.0 Hz, 1H), 8.90 (d, J = 8.3 Hz, 1H), 8.43* (d, J = 2.3 Hz, 1H), 8.39 (d, J = 2.3 Hz, 1H), 7.71 – 7.59 (m, 1H), 7.40 – 7.15 (m, 6H), 6.14* (d, J = 7.9 Hz, 1H), 6.05 (d, J = 8.2 Hz, 1H), 5.50 – 5.21 (m, 1H), 4.99 – 4.88* (m, 1H), 4.64 (t, J = 8.3 Hz, 1H), 4.14 – 3.63 (m, 3H), 3.55 – 3.36* (m, 1H), 2.99 – 2.83 (m, 1H), 2.76 – 2.59* (m, 1H), 2.47 – 2.35 (m, 1H), 2.27 – 1.90 (m, 1H), 1.20 (d, J = 7.0, 1.3 Hz, 6H). LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{24}H_{27}FN_6O_2$: 451.2; found 451.3.

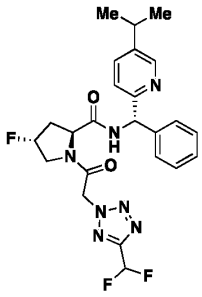
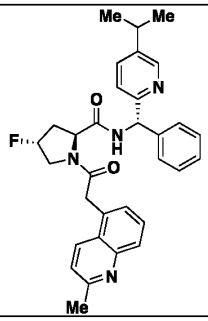
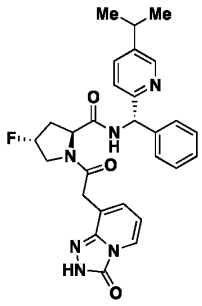
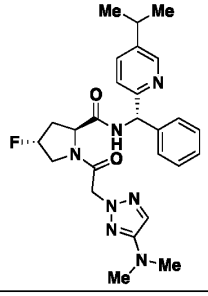
[0607] The following compounds in Table T-2 were synthesized using procedures similar to Compound 244 using the appropriate starting materials.

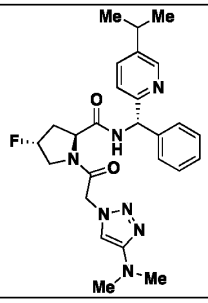
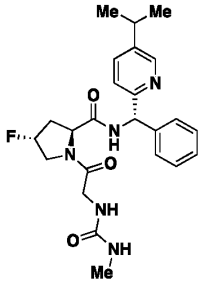
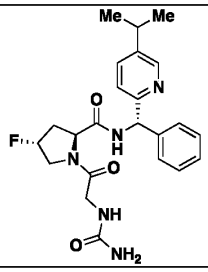
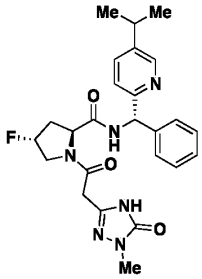
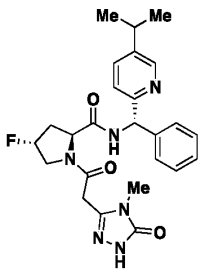
Table T-2

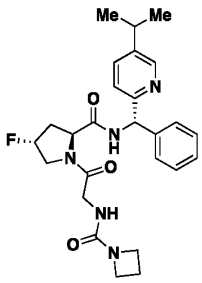
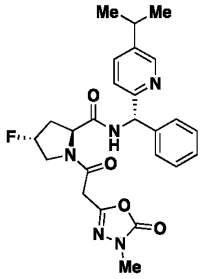
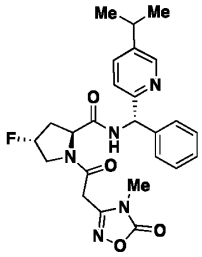
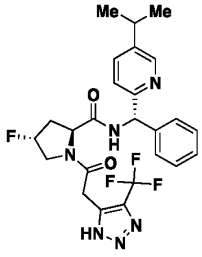
Compound No.	Structure	IUPAC	Exact mass (g/mol)	LCMS, Found $[M + H]^+$
245		(2S)-1-acetyl-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	365.2	366.3
246		(2S,4R)-1-[2-(3,5-dimethyl-1H-pyrazol-4-yl)acetyl]-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	477.3	478.1
247		(2S,4R)-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]-1-[2-(quinolin-5-yl)acetyl]pyrrolidine-2-carboxamide	510.2	511.2

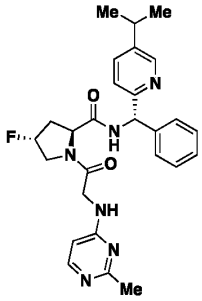
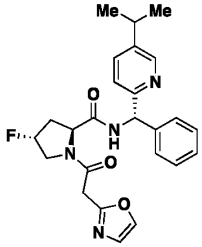
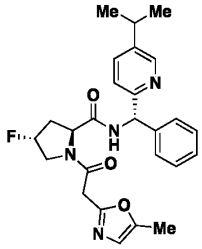
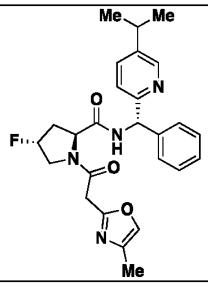
248		(2S,4R)-1-[2-(1H-1,3-benzodiazol-1-yl)acetyl]-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	499.2	500.1
249		(2S,4R)-4-fluoro-1-[2-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	507.2	508.2
250		(2S,4R)-1-{2-[(dimethylcarbamoyl)amino]acetyl}-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	469.2	470.3
251		2-[(2S,4R)-4-fluoro-2-{[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl N,N-dimethylcarbamate	470.2	471.1

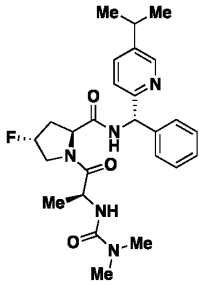
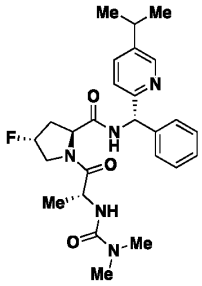
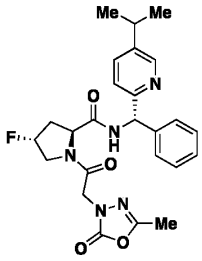
252		(2S,4R)-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]-1-[2-(1H-1,2,3,4-tetrazol-1-yl)acetyl]pyrrolidine-2-carboxamide	451.2	452.2
253		(2S,4R)-1-{2-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]acetyl}-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	501.2	502.1
254		(2S,4R)-1-{2-[5-(difluoromethyl)-1H-1,2,3,4-tetrazol-1-yl]acetyl}-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	501.2	502.3
255		(2S,4R)-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]-1-{2-[5-(trifluoromethyl)-2H-1,2,3,4-tetrazol-2-yl]acetyl}pyrrolidine-2-carboxamide	519.2	520.2

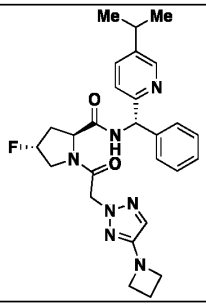
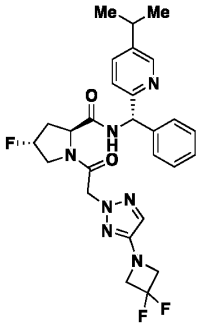
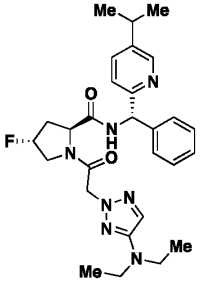
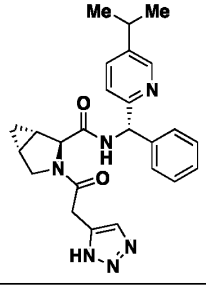
256		(2S,4R)-1-{2-[5-(difluoromethyl)-2H-1,2,3,4-tetrazol-2-yl]acetyl}-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	501.2	502.2
257		(2S,4R)-4-fluoro-1-[2-(2-methylquinolin-5-yl)acetyl]-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	524.3	525.3
258		(2S,4R)-4-fluoro-1-(2-{3-oxo-2H,3H-[1,2,4]triazolo[4,3-a]pyridin-8-yl}acetyl)-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	516.2	517.3
259		(2S,4R)-1-{2-[4-(dimethylamino)-2H-1,2,3-triazol-2-yl]acetyl}-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	493.3	494.3

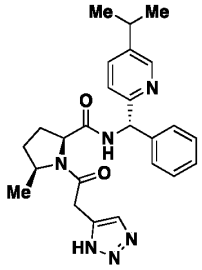
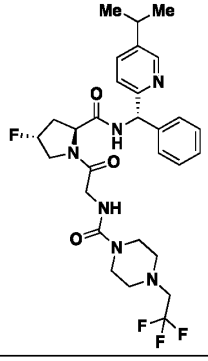
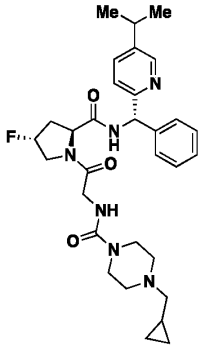
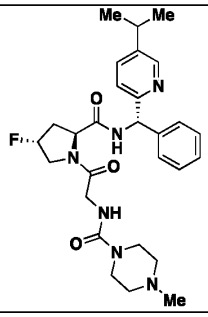
260		(2S,4R)-1-{2-[4-(dimethylamino)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	493.3	494.2
261		(2S,4R)-4-fluoro-1-{2-[(methylcarbamoyl)amino]acetyl}-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	455.2	456.2
262		(2S,4R)-1-[2-(carbamoylamino)acetyl]-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	441.2	442.1
263		(2S,4R)-4-fluoro-1-[2-(1-methyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)acetyl]-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	480.2	481.3
264		(2S,4R)-4-fluoro-1-[2-(4-methyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)acetyl]-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	480.2	481.2

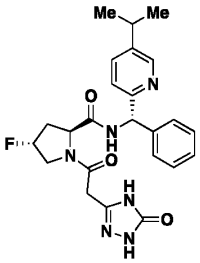
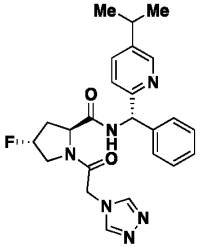
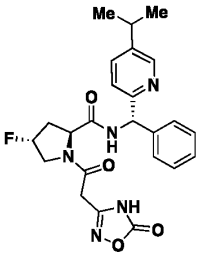
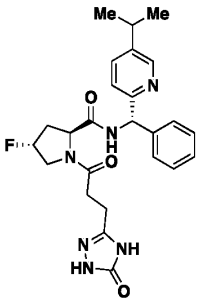
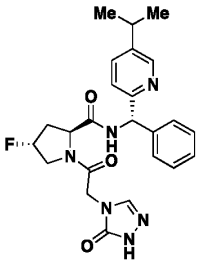
265		(2S,4R)-1-{2-[(azetidine-1-carbonyl)amino]acetyl}-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	481.2	482.2
266		(2S,4R)-4-fluoro-1-[2-(4-methyl-5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)acetyl]-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	481.2	482.3
267		(2S,4R)-4-fluoro-1-[2-(4-methyl-5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)acetyl]-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	481.2	482.3
268		(2S,4R)-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]-1-{2-[4-(trifluoromethyl)-1H-1,2,3-triazol-5-yl]acetyl}pyrrolidine-2-carboxamide	518.2	519.3

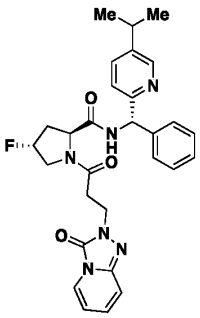
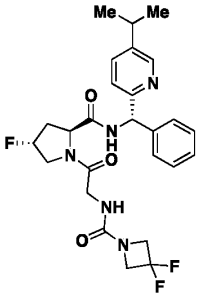
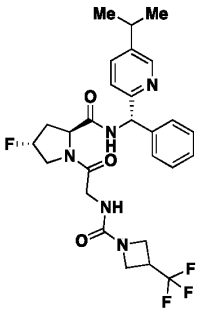
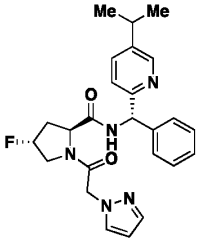
269		(2S,4R)-4-fluoro-1-{2-[(2-methylpyrimidin-4-yl)amino]acetyl}-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	490.2	491.2
270		(2S,4R)-4-fluoro-1-[2-(1,3-oxazol-2-yl)acetyl]-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	450.2	451.3
271		(2S,4R)-4-fluoro-1-[2-(5-methyl-1,3-oxazol-2-yl)acetyl]-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	464.2	465.2
272		(2S,4R)-4-fluoro-1-[2-(4-methyl-1,3-oxazol-2-yl)acetyl]-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	464.2	465.2

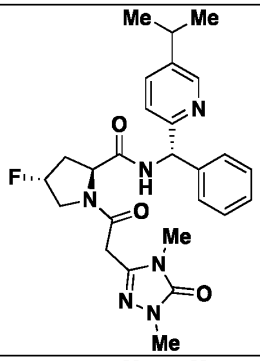
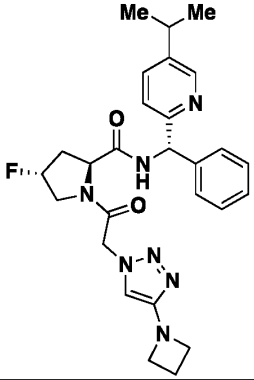
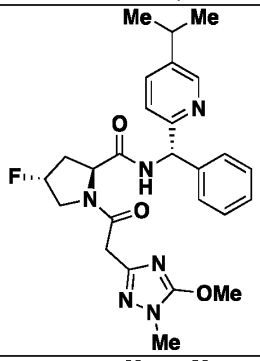
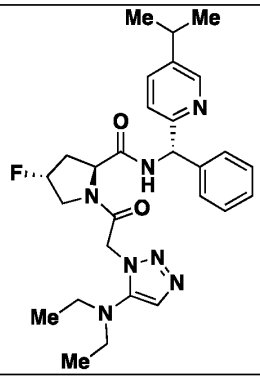
273		(2S,4R)-1-[(2S)-2-[(dimethylcarbamoyl)amino]propanoyl]-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	483.3	484.3
274		(2S,4R)-1-[(2R)-2-[(dimethylcarbamoyl)amino]propanoyl]-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	483.3	484.3
275		(2S,4R)-4-fluoro-1-[2-(5-methyl-2-oxo-2,3-dihydro-1,3,4-oxadiazol-3-yl)acetyl]-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	481.2	482.3

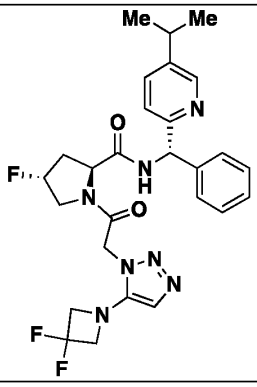
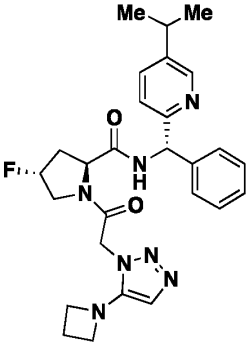
276		(2S,4R)-1-{2-[4-(azetidin-1-yl)-2H-1,2,3-triazol-2-yl]acetyl}-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	505.3	506.3
277		(2S,4R)-1-{2-[4-(3,3-difluoroazetidin-1-yl)-2H-1,2,3-triazol-2-yl]acetyl}-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	541.2	542.3
278		(2S,4R)-1-{2-[4-(diethylamino)-2H-1,2,3-triazol-2-yl]acetyl}-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	521.3	522.5
279		(1S,2S,5R)-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]-3-[2-(1H-1,2,3-triazol-5-yl)acetyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide	444.2	445.4

280		(2S,5S)-5-methyl-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide	446.2	447.3
281		N-{2-[(2S,4R)-4-fluoro-2-{[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl}-4-(2,2,2-trifluoroethyl)piperazine-1-carboxamide	592.3	593.2
282		4-(cyclopropylmethyl)-N-{2-[(2S,4R)-4-fluoro-2-{[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl}piperazine-1-carboxamide	564.3	565.5
283		N-{2-[(2S,4R)-4-fluoro-2-{[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl}-4-methylpiperazine-1-carboxamide	524.3	525.3

284		(2S,4R)-4-fluoro-1-[2-(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)acetyl]-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	466.2	467.0
285		(2S,4R)-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]-1-[2-(4H-1,2,4-triazol-4-yl)acetyl]pyrrolidine-2-carboxamide	450.2	451.3
286		(2S,4R)-4-fluoro-1-[2-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)acetyl]-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	467.2	468.2
287		(2S,4R)-4-fluoro-1-[3-(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)propanoyl]-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	480.2	481.0
288		(2S,4R)-4-fluoro-1-[2-(5-oxo-4,5-dihydro-1H-1,2,4-triazol-4-yl)acetyl]-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	466.2	467.2

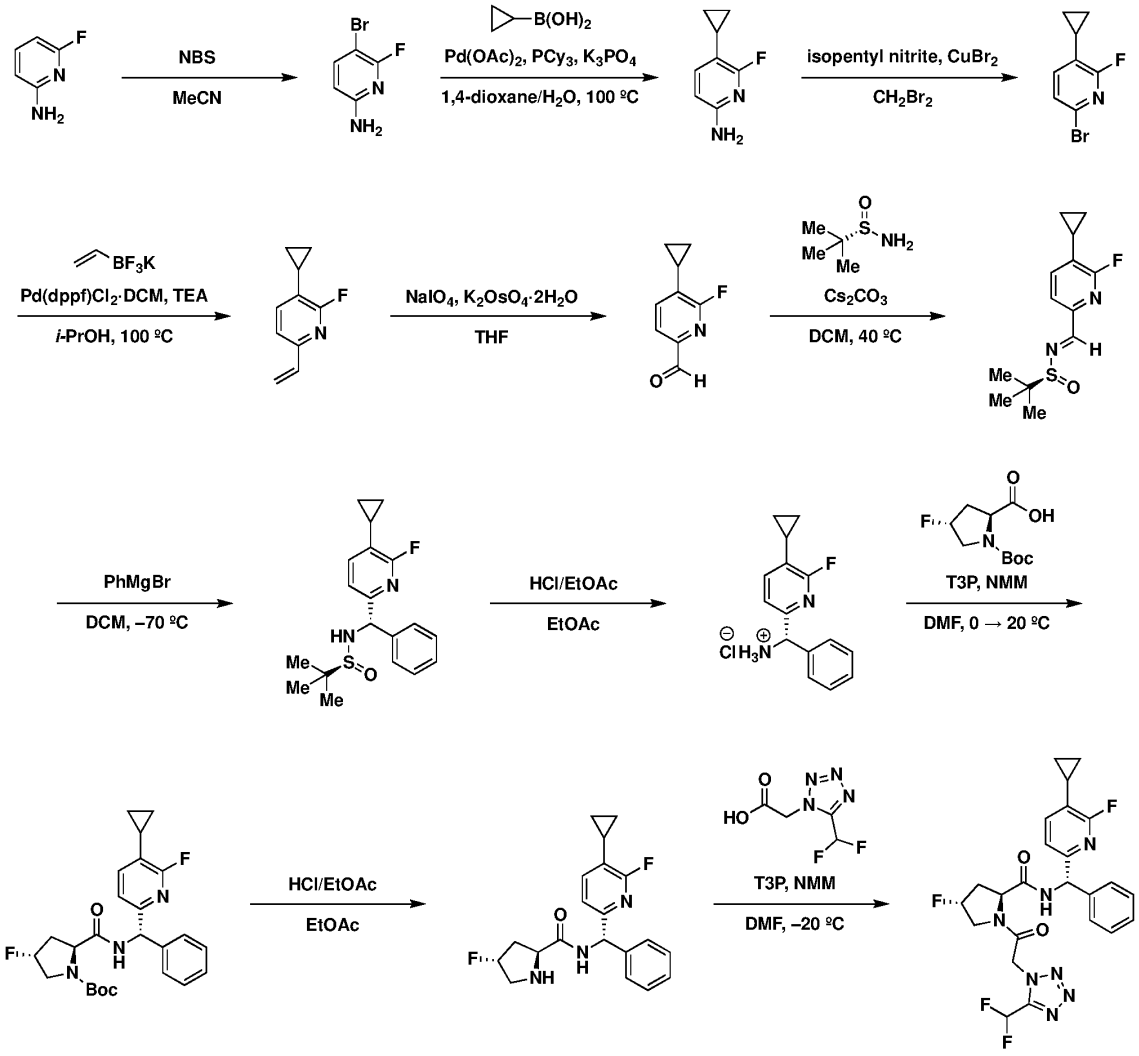
289		(2S,4R)-4-fluoro-1-(3-{3-oxo-2H,3H-[1,2,4]triazolo[4,3-a]pyridin-2-yl}propanoyl)-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	530.2	531.2
290		(2S,4R)-1-{2-[(3,3-difluoroazetidine-1-carbonyl)amino]acetyl}-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	517.2	517.2
291		(2S,4R)-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]-1-(2-{[3-(trifluoromethyl)azetidine-1-carbonyl]amino}acetyl)pyrrolidine-2-carboxamide	549.2	549.2
292		(2S,4R)-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]-1-[2-(1H-pyrazol-1-yl)acetyl]pyrrolidine-2-carboxamide	449.2	449.2

710		(2S,4R)-1-[2-(1,4-dimethyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)acetyl]-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	494.2	495.3
711		(2S,4R)-1-{2-[4-(azetidin-1-yl)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	505.3	506.3
712		(2S,4R)-4-fluoro-1-[2-(5-methoxy-1-methyl-1H-1,2,4-triazol-3-yl)acetyl]-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	494.2	495.3
713		(2S,4R)-1-{2-[5-(diethylamino)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	521.3	522.3

714		(2S,4R)-1-{2-[5-(3,3-difluoroazetidin-1-yl)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	541.2	542.3
715		(2S,4R)-1-{2-[5-(azetidin-1-yl)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoro-N-[(S)-phenyl[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide	505.2	506.3

Example S-3: Synthesis of (2*S*,4*R*)-*N*-((*S*)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl)-1-(2-(5-(difluoromethyl)-1*H*-tetrazol-1-yl)acetyl)-4-fluoropyrrolidine-2-carboxamide

(Compound 293)



[0608] Step a: In four parallel reactions, 6-fluoropyridin-2-amine (125 g, 1.11 mol, 1 eq) in MeCN (1.2 L) at 0 ºC under N_2 was treated with NBS (209 g, 1.17 mmol, 1.05 eq) in MeCN (1.2 L). The reaction mixtures were stirred at 20 ºC for 2 h. The four parallel reactions were combined, and the resulting mixture was concentrated under reduced pressure. The resulting crude residue was purified by column chromatography to give 5-bromo-6-fluoropyridin-2-amine. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_5H_4BrFN_2$: 190.9; found 191.0.

[0609] Step b: To a mixture of 5-bromo-6-fluoropyridin-2-amine (200 g, 1.04 mol, 1 eq) and cyclopropylboronic acid (226 g, 2.63 mol, 2.5 eq) in 1,4-dioxane (2 L) and H_2O (200 mL) under N_2 were added K_3PO_4 (666 g, 3.14 mol, 3 eq), PCy_3 (58.6 g, 209 mmol, 0.2 eq), and $Pd(OAc)_2$ (11.7g, 52.3 mmol, 0.05 eq). The system was then degassed and charged with nitrogen three times. The reaction mixture was warmed to 100 ºC and stirred for 12 h. The reaction mixture was then cooled to room temperature and filtered through Celite. The resulting filtrate was diluted with H_2O (2 L) and then extracted with EtOAc (3 x 500 mL). The combined organic extracts were washed with brine (2 x 300 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 5-cyclopropyl-6-fluoropyridin-2-amine. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_8H_9FN_2$: 153.1; found 153.0.

[0610] Step c: To a mixture of 5-cyclopropyl-6-fluoropyridin-2-amine (120 g, 788 mmol, 1 eq) in dibromomethane (564 mL) under N_2 was added isopentyl nitrite (110 g, 946 mmol, 127 mL, 1.2 eq). To the resulting mixture was added $CuBr_2$ (211 g, 946 mmol, 44.3 mL, 1.2 eq) over 0.5 h. The final mixture was then degassed and charged with nitrogen three times before stirring at 20 ºC for 16 h. The reaction mixture was then filtered, and the filtrate was diluted with H_2O (500 mL) and extracted with EtOAc (3 x 300 mL). The combined organic extracts were washed with brine (300 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 6-bromo-3-cyclopropyl-2-fluoropyridine. LC-MS (ESI): m/z: $[M + H]^+$ calculated for C_8H_7BrFN: 216.0; found 216.1.

[0611] Step d: To a mixture of 6-bromo-3-cyclopropyl-2-fluoropyridine (90 g, 416 mmol, 1 eq) and trifluoro(vinyl)-λ4-borane, potassium salt (83.7 g, 624 mmol, 1.5 eq) in *i*-PrOH (900 mL) at 20 ºC under N_2 was added TEA (126 g, 1.25 mol, 3 eq) and $Pd(dppf)Cl_2$•DCM (17 g, 20.8 mmol, 0.05 eq). The resulting mixture was degassed and charged with nitrogen three times. The reaction mixture was then warmed to 100 ºC and stirred for 2 h. The reaction mixture was then cooled to room temperature and filtered. The filtrate was diluted with H_2O (500 mL) and extracted with EtOAc (3 x 300 mL). The combined organic extracts were washed with brine (300 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was then purified by column chromatography to give 3-cyclopropyl-2-

fluoro-6-vinylpyridine. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{10}H_{10}FN$: 164.1; found 164.1.

[0612] Step e: To a mixture of 3-cyclopropyl-2-fluoro-6-vinylpyridine (47 g, 288 mmol, 1 eq) in THF (800 mL) and H_2O (160 mL) at 20 °C under N_2 was added $NaIO_4$ (246 g, 1.15 mol, 4 eq) and $K_2OsO_4 \cdot 2H_2O$ (2.12 g, 5.76 mmol, 0.02 eq). The resulting mixture was degassed and charged with nitrogen three times before stirring for 2 h. The reaction mixture was then filtered, and the filtrate was diluted with H_2O (500 mL), and extracted with EtOAc (3 × 300 mL). The combined organic extracts were washed with brine (300 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude residue was purified by column chromatography to give 5-cyclopropyl-6-fluoropicolinaldehyde. LC-MS (ESI): m/z: $[M + H]^+$ calculated for C_9H_8FNO: 166.1; found 166.2.

[0613] Step f: To a mixture of 5-cyclopropyl-6-fluoropicolinaldehyde (38 g, 230 mmol, 1 eq) and (*S*)-2-methylpropane-2-sulfinamide (30.6 g, 253 mmol, 1.1 eq) in DCM (200 mL) at 20 °C under N_2 was added Cs_2CO_3 (82.4 g, 253 mmol, 1.1 eq). The system was then degassed and charged with nitrogen three times. The resulting mixture was then warmed to 40 °C and stirred for 12 h. The reaction solution was then diluted with H_2O (300 mL) and extracted with DCM (3 x 200 mL). The combined organic extracts were washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude residue was then purified by column chromatography to give (*S*,*E*)-*N*-((5-cyclopropyl-6-fluoropyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{13}H_{17}FN_2OS$: 269.1; found 269.2.

[0614] Step g: To a solution of (*S*,*E*)-*N*-((5-cyclopropyl-6-fluoropyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide (58 g, 216 mmol, 1 eq) in dry DCM (600 mL) at –70 °C under nitrogen was added PhMgBr (3 M in Et_2O, 93.6 mL, 281 mmol, 1.3 eq) in a dropwise manner. The resulting reaction mixture was stirred at –70 °C for 1 h. The reaction mixture was then quenched with saturated aqueous NH_4Cl solution (500 mL), warmed to room temperature, and extracted with EtOAc (3 × 200 mL). The combined organic extracts were washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give

(*S*)-*N*-((*S*)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl)-2-methylpropane-2-sulfinamide. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{19}H_{23}FN_2OS$: 347.2; found 347.3.

[0615] Step h: To a solution of (*S*)-*N*-((*S*)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl)-2-methylpropane-2-sulfinamide (74 g, 213 mmol, 1 eq) in EtOAc (100 mL) at 0 °C under N_2 was added HCl/EtOAc (4 M, 740 mL, 2940 mmol, 13.8 eq). The resulting mixture was then warmed 20 °C and stirred for 1 h. The reaction mixture was then concentrated under reduced pressure, and the crude residue obtained was triturated with MTBE (500 mL). The resulting solid was collected by filtration and dried under reduced pressure to give (*S*)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methanaminium chloride. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{15}H_{15}FN_2$: 243.1; found 243.2.

[0616] Step i: To a mixture of (*S*)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methanaminium chloride (56 g, 200 mmol, 1 eq) and (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (60.9 g, 261 mmol, 1.3 eq) in DMF (500 mL) at 0 °C under N_2 was added *N*-methylmorpholine (NMM, 101 g, 1.00 mol, 110 mL, 5 eq) and T3P (50% in ethyl acetate, 166 g, 261 mmol, 155 mL, 1.3 eq). The resulting mixture was degassed and charged with nitrogen three times, warmed to 20 °C and stirred 1 h. The reaction mixture was then diluted with H_2O (200 mL) and extracted with EtOAc (3 × 300 mL). The combined organic extracts were washed with brine (500 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give *tert*-butyl (2*S*,4*R*)-2-(((*S*)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{25}H_{29}F_2N_3O_3$: 458.2; found 458.2.

[0617] Step j: To a solution of *tert*-butyl (2*S*,4*R*)-2-(((*S*)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate (90 g, 196 mmol, 1 eq) in EtOAc (100 mL) at 0 °C under N_2 was added HCl/EtOAc (4 M, 900 mL, 18.3 eq). The resulting mixture was warmed to 20 °C and stirred for 1 h. The reaction mixture was then concentrated under reduced pressure, and the resulting crude residue was added to H_2O (100 mL). The resulting mixture was cooled to 0 °C, adjusted to pH = 7–8 with saturated aqueous $NaHCO_3$ and extracted with EtOAc (3 × 200 mL). The combined organic extracts were washed with brine (100 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced

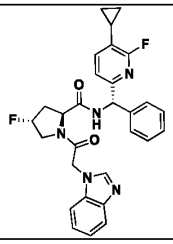
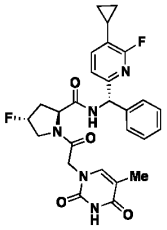
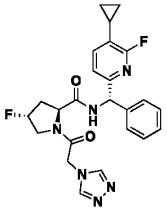
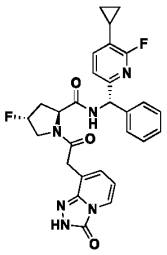
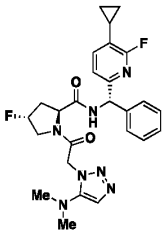
pressure. The resulting crude material was then triturated with *i*-PrOH (500 mL), and the resulting solid was isolated via filtration. The solid obtained was dried under reduced pressure to give (2*S*,4*R*)-*N*-((*S*)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl)-4-fluoropyrrolidine-2-carboxamide. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{20}H_{21}F_2N_3O$: 358.2; found 358.3.

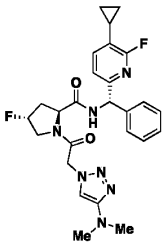
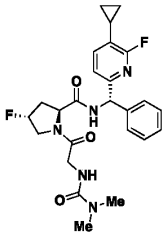
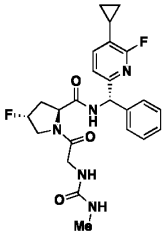
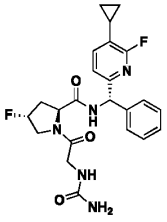
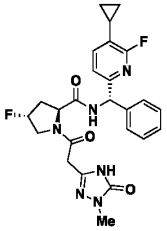
[0618] Step k: To a mixture of 2-(5-(difluoromethyl)-1*H*-tetrazol-1-yl)acetic acid (Intermediate A-2, 4.53 g, 25.5 mmol, 1.30 eq) and (2*S*,4*R*)-*N*-((*S*)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl)-4-fluoropyrrolidine-2-carboxamide (7 g, 19.6 mmol, 1.00 eq) in DMF (70 mL) at –20 °C was added *N*-methylmorpholine (11.2 g, 117 mmol, 6 eq) and T3P (50% in ethyl acetate, 25.0 g, 39.1 mmol, 2.00 eq). The reaction mixture was then warmed to –10 °C and stirred for 2 h. The reaction mixture was then quenched with water (100 mL) and extracted with dichloromethane (2 x 100 mL). The combined organic extracts were washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by prep-HPLC to give (2*S*,4*R*)-*N*-((*S*)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl)-1-(2-(5-(difluoromethyl)-1*H*-tetrazol-1-yl)acetyl)-4-fluoropyrrolidine-2-carboxamide. ^{1}H NMR (4.2:1 rotamer ratio, asterisk denotes distinct minor rotamer peaks, obscured peaks not reported, 400 MHz, DMSO-d_6) δ 9.29* (d, J = 7.7 Hz, 1H), 8.92 (d, J = 8.0 Hz, 1H), 7.65 – 7.17 (m, 8H), 6.11* (d, J = 7.7 Hz, 1H), 6.03 – 5.66 (m, 3H), 5.60 – 5.23 (m, 1H), 5.10 – 4.92* (m, 2H), 4.65 (t, J = 8.4 Hz, 1H), 4.17 – 3.76 (m, 2H), 3.61 – 3.40* (m, 1H), 2.92 – 2.75* (m, 1H), 2.15 – 1.89 (m, 2H), 1.03 – 0.91 (m, 2H), 0.82 – 0.69 (m, 2H). LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{24}H_{23}F_4N_7O_2$: 518.2; found 518.1.

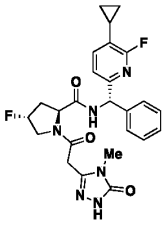
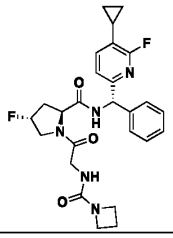
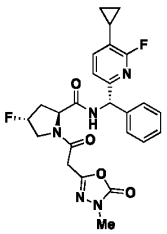
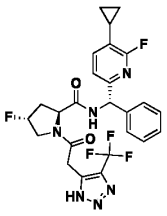
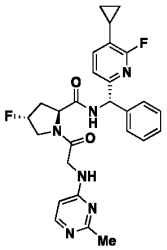
[0619] The following compounds in Table T-3 were synthesized using procedures similar to Compound 293 using the appropriate starting materials.

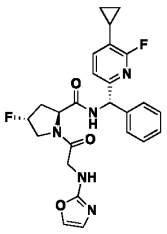
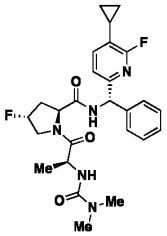
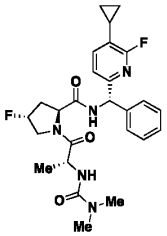
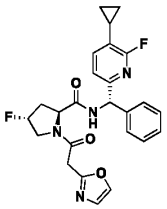
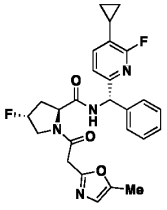
Table T-3

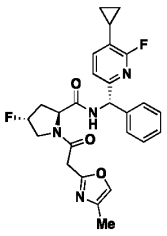
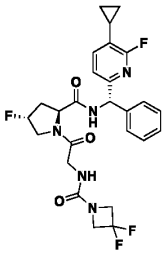
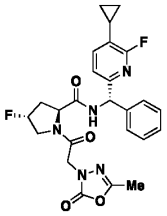
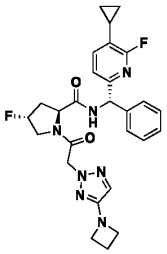
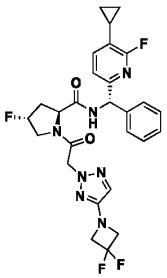
Compound No.	Structure	IUPAC	Exact mass (g/mol)	LCMS, Found [M + H]$^+$

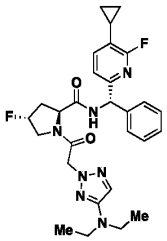
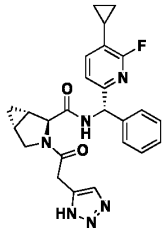
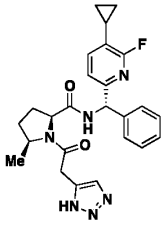
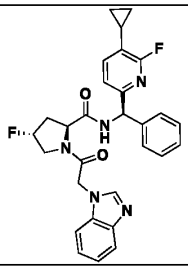
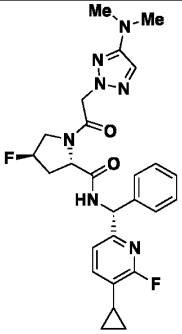
294		(2S,4R)-1-[2-(1H-1,3-benzodiazol-1-yl)acetyl]-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide	515.2	516.2
295		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]pyrrolidine-2-carboxamide	523.2	524.3
296		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(4H-1,2,4-triazol-4-yl)acetyl]pyrrolidine-2-carboxamide	466.2	467.2
297		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-(2-{3-oxo-2H,3H-[1,2,4]triazolo[4,3-a]pyridin-8-yl}acetyl)pyrrolidine-2-carboxamide	532.2	533.3
298		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[5-(dimethylamino)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide	509.2	510.2

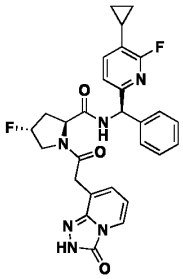
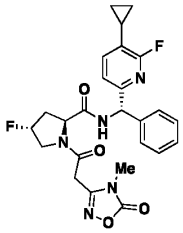
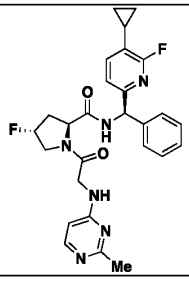
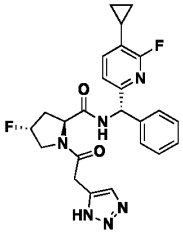
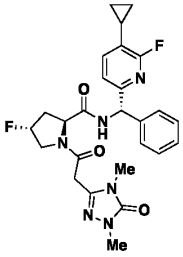
299		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[4-(dimethylamino)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide	509.2	510.2
300		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[(dimethylcarbamoyl)amino]acetyl}-4-fluoropyrrolidine-2-carboxamide	485.2	486.2
301		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-{2-[(methylcarbamoyl)amino]acetyl}pyrrolidine-2-carboxamide	471.2	472.2
302		(2S,4R)-1-[2-(carbamoylamino)acetyl]-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide	457.2	458.3
303		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(1-methyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)acetyl]pyrrolidine-2-carboxamide	496.2	497.3

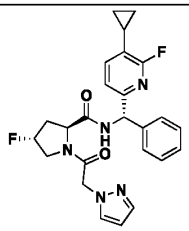
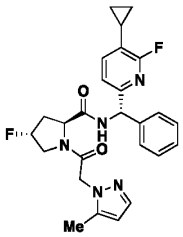
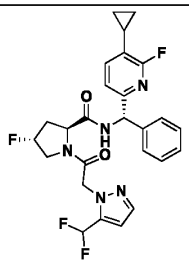
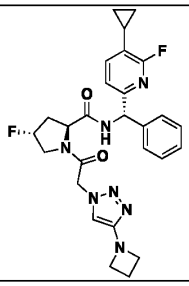
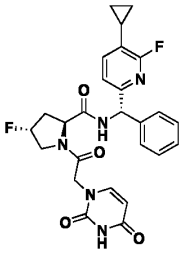
304		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(4-methyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)acetyl]pyrrolidine-2-carboxamide	496.2	497.1
305		(2S,4R)-1-{2-[(azetidine-1-carbonyl)amino]acetyl}-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide	497.2	498.2
306		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(4-methyl-5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)acetyl]pyrrolidine-2-carboxamide	497.2	498.2
307		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-{2-[4-(trifluoromethyl)-1H-1,2,3-triazol-5-yl]acetyl}pyrrolidine-2-carboxamide	534.2	535.1
308		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-{2-[(2-methylpyrimidin-4-yl)amino]acetyl}pyrrolidine-2-carboxamide	506.2	507.3

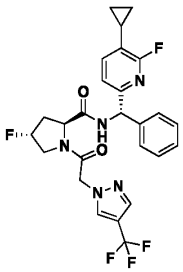
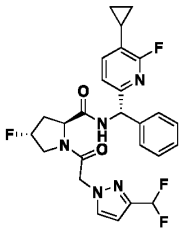
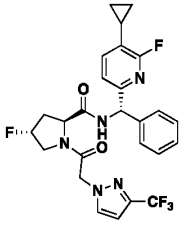
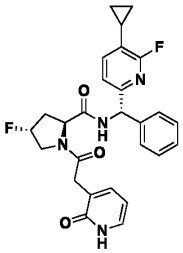
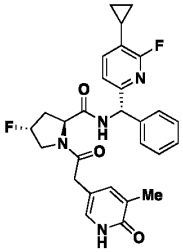
309		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-{2-[(1,3-oxazol-2-yl)amino]acetyl}pyrrolidine-2-carboxamide	481.2	482.4
310		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[(2S)-2-[(dimethylcarbamoyl)amino]propanoyl]-4-fluoropyrrolidine-2-carboxamide	499.2	500.3
311		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[(2R)-2-[(dimethylcarbamoyl)amino]propanoyl]-4-fluoropyrrolidine-2-carboxamide	499.2	500.3
312		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide	466.2	467.2
313		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(5-methyl-1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide	480.2	481.3

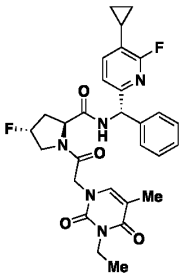
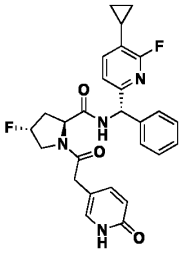
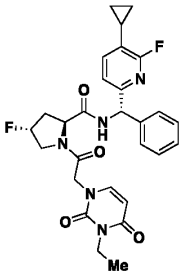
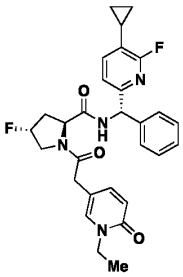
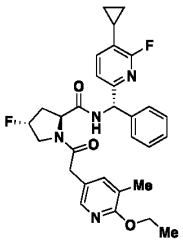
314		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(4-methyl-1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide	480.2	481.2
315		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[(3,3-difluoroazetidine-1-carbonyl)amino]acetyl}-4-fluoropyrrolidine-2-carboxamide	533.2	534.3
316		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(5-methyl-2-oxo-2,3-dihydro-1,3,4-oxadiazol-3-yl)acetyl]pyrrolidine-2-carboxamide	497.2	498.2
317		(2S,4R)-1-{2-[4-(azetidin-1-yl)-2H-1,2,3-triazol-2-yl]acetyl}-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide	521.2	522.3
318		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[4-(3,3-difluoroazetidin-1-yl)-2H-1,2,3-triazol-2-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide	557.2	558.2

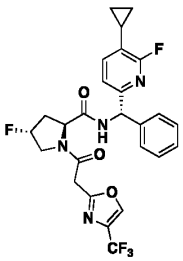
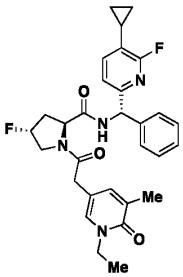
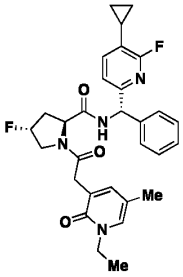
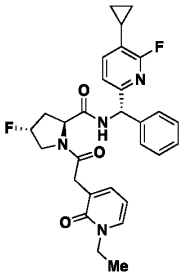
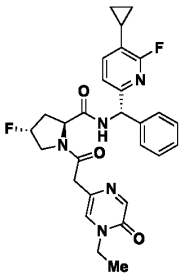
319		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[4-(diethylamino)-2H-1,2,3-triazol-2-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide	537.3	538.4
320		(1S,2S,5R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-3-[2-(1H-1,2,3-triazol-5-yl)acetyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide	460.2	461.3
321		(2S,5S)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-5-methyl-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide	462.2	463.1
716		(2S,4R)-1-[2-(1H-1,3-benzodiazol-1-yl)acetyl]-N-[(R)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide	515.2	516.3
717		(2S,4R)-N-[(R)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[4-(dimethylamino)-2H-1,2,3-triazol-2-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide	509.2	510.2

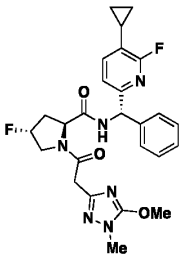
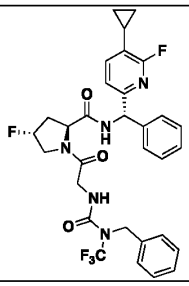
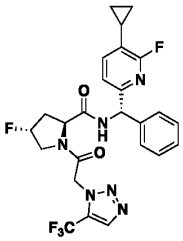
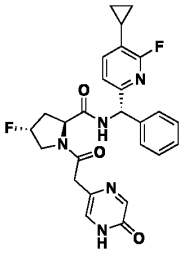
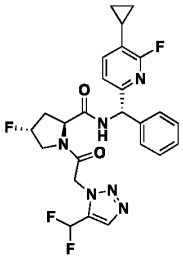
718		(2S,4R)-N-[(R)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-(2-{3-oxo-2H,3H-[1,2,4]triazolo[4,3-a]pyridin-8-yl}acetyl)pyrrolidine-2-carboxamide	532.2	533.2
719		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(4-methyl-5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)acetyl]pyrrolidine-2-carboxamide	497.2	498.2
720		(2S,4R)-N-[(R)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-{2-[(2-methylpyrimidin-4-yl)amino]acetyl}pyrrolidine-2-carboxamide	506.2	507.3
721		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide	466.2	467.1
722		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[2-(1,4-dimethyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide	510.2	511.3

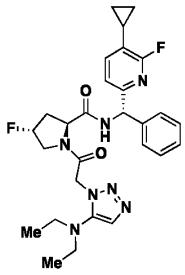
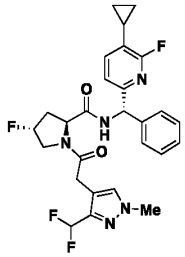
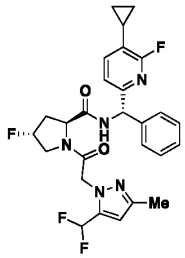
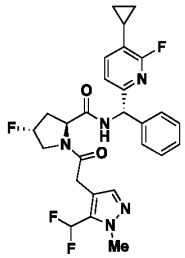
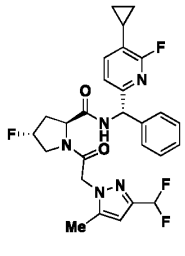
723		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(1H-pyrazol-1-yl)acetyl]pyrrolidine-2-carboxamide	465.2	466.1
724		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(5-methyl-1H-pyrazol-1-yl)acetyl]pyrrolidine-2-carboxamide	479.2	480.1
725		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[5-(difluoromethyl)-1H-pyrazol-1-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide	515.2	516.3
726		(2S,4R)-1-{2-[4-(azetidin-1-yl)-1H-1,2,3-triazol-1-yl]acetyl}-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide	521.2	522.3
727		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[2-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide	509.2	510.1

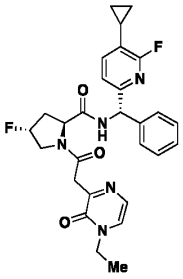
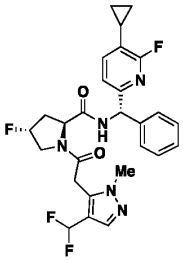
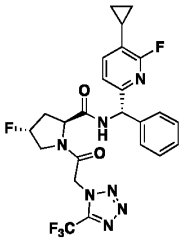
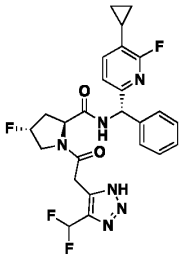
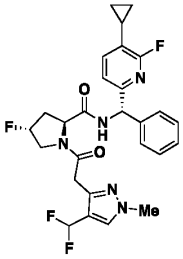
728		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-{2-[4-(trifluoromethyl)-1H-pyrazol-1-yl]acetyl}pyrrolidine-2-carboxamide	533.2	534.1
729		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[3-(difluoromethyl)-1H-pyrazol-1-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide	515.2	516.1
730		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-{2-[3-(trifluoromethyl)-1H-pyrazol-1-yl]acetyl}pyrrolidine-2-carboxamide	533.2	534.3
731		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(2-oxo-1,2-dihydropyridin-3-yl)acetyl]pyrrolidine-2-carboxamide	492.2	515.3
732		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)acetyl]pyrrolidine-2-carboxamide	506.2	507.1

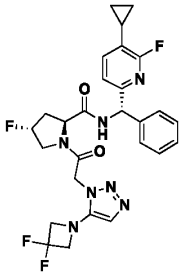
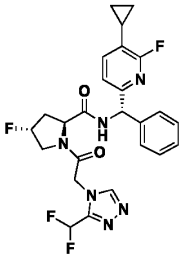
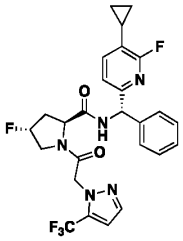
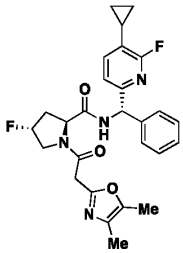
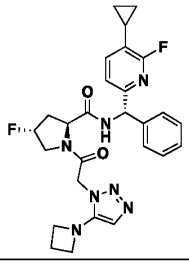
733		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[2-(3-ethyl-5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide	551.2	552.1
734		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(6-oxo-1,6-dihydropyridin-3-yl)acetyl]pyrrolidine-2-carboxamide	492.2	493.2
735		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[2-(3-ethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide	537.2	538.1
736		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[2-(1-ethyl-6-oxo-1,6-dihydropyridin-3-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide	520.2	521.4
737		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[2-(6-ethoxy-5-methylpyridin-3-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide	534.2	535.2

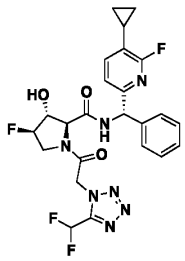
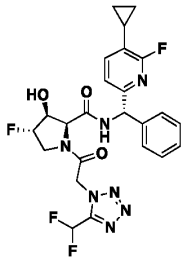
738		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-{2-[4-(trifluoromethyl)-1,3-oxazol-2-yl]acetyl}pyrrolidine-2-carboxamide	534.2	535.1
739		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[2-(1-ethyl-5-methyl-6-oxo-1,6-dihydropyridin-3-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide	534.2	535.2
740		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[2-(1-ethyl-5-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide	534.2	535.2
741		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[2-(1-ethyl-2-oxo-1,2-dihydropyridin-3-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide	520.2	521.2
742		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[2-(4-ethyl-5-oxo-4,5-dihydropyrazin-2-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide	521.2	522.2

743		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(5-methoxy-1-methyl-1H-1,2,4-triazol-3-yl)acetyl]pyrrolidine-2-carboxamide	510.2	511.3
744		(2S,4R)-1-(2-{[benzyl(trifluoromethyl)carbamoyl]amino}acetyl)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide	615.2	616.3
745		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-{2-[5-(trifluoromethyl)-1H-1,2,3-triazol-1-yl]acetyl}pyrrolidine-2-carboxamide	534.2	535.1
746		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(5-oxo-4,5-dihydropyrazin-2-yl)acetyl]pyrrolidine-2-carboxamide	493.2	494.3
747		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[5-(difluoromethyl)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide	516.2	517.3

748		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[5-(diethylamino)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide	537.3	538.3
749		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide	529.2	530.3
750		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[5-(difluoromethyl)-3-methyl-1H-pyrazol-1-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide	529.2	530.2
751		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[5-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide	529.2	530.3
752		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[3-(difluoromethyl)-5-methyl-1H-pyrazol-1-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide	529.2	530.3

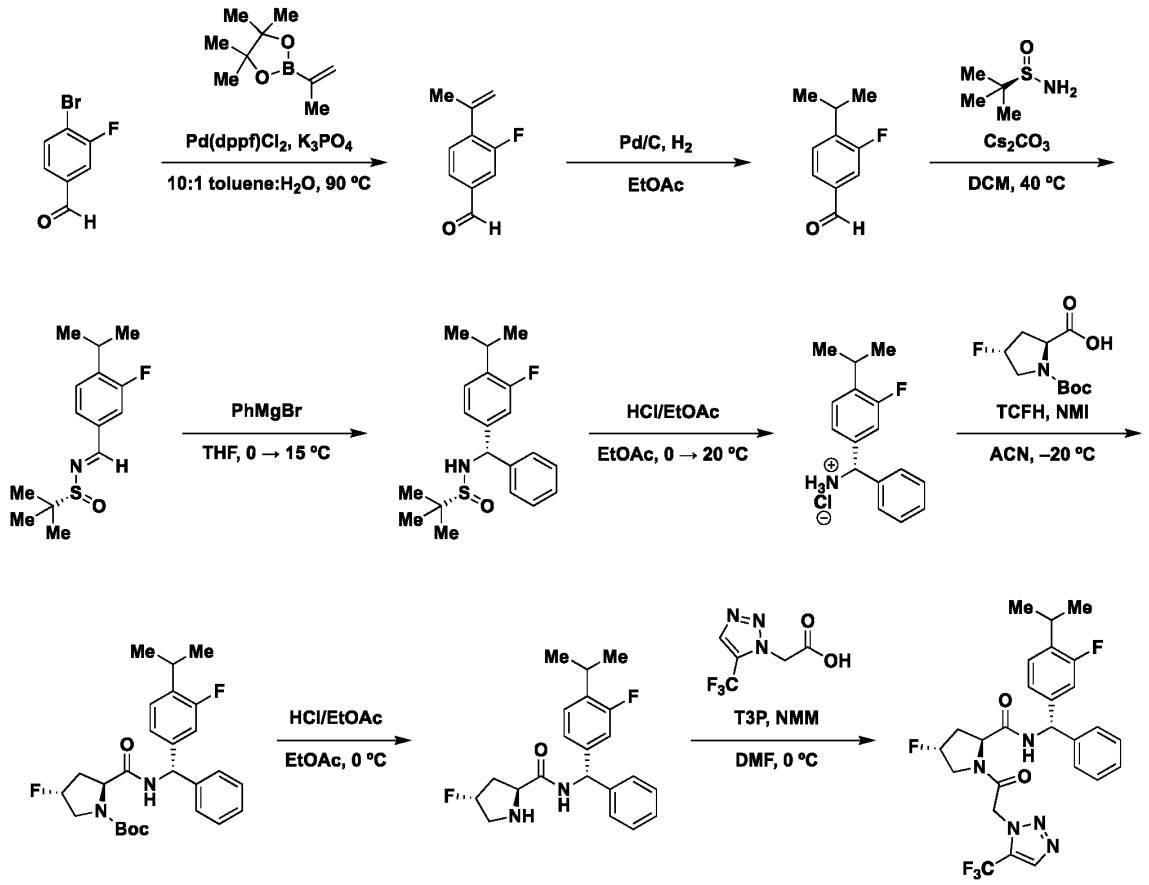
753		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[2-(4-ethyl-3-oxo-3,4-dihydropyrazin-2-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide	521.2	522.2
754		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[4-(difluoromethyl)-1-methyl-1H-pyrazol-5-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide	529.2	530.2
755		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-{2-[5-(trifluoromethyl)-1H-1,2,3,4-tetrazol-1-yl]acetyl}pyrrolidine-2-carboxamide	535.2	536.1
756		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[4-(difluoromethyl)-1H-1,2,3-triazol-5-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide	516.2	517.2
757		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[4-(difluoromethyl)-1-methyl-1H-pyrazol-3-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide	529.2	530.2

758		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[5-(3,3-difluoroazetidin-1-yl)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide	557.2	558.3
759		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[3-(difluoromethyl)-4H-1,2,4-triazol-4-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide	516.2	517.2
760		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoro-1-{2-[5-(trifluoromethyl)-1H-pyrazol-1-yl]acetyl}pyrrolidine-2-carboxamide	533.2	534.2
761		(2S,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-[2-(4,5-dimethyl-1,3-oxazol-2-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide	494.2	495.1
762		(2S,4R)-1-{2-[5-(azetidin-1-yl)-1H-1,2,3-triazol-1-yl]acetyl}-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide	521.2	522.3

763		(2S,3R,4R)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[5-(difluoromethyl)-1H-1,2,3,4-tetrazol-1-yl]acetyl}-4-fluoro-3-hydroxypyrrolidine-2-carboxamide	533.2	534.2
764		(2S,3S,4S)-N-[(S)-(5-cyclopropyl-6-fluoropyridin-2-yl)(phenyl)methyl]-1-{2-[5-(difluoromethyl)-1H-1,2,3,4-tetrazol-1-yl]acetyl}-4-fluoro-3-hydroxypyrrolidine-2-carboxamide	533.2	534.1

Example S-4: Synthesis of (2*S*,4*R*)-4-fluoro-*N*-((*S*)-(3-fluoro-4-isopropylphenyl)(phenyl)methyl)-1-(2-(5-(trifluoromethyl)-1*H*-1,2,3-triazol-1-yl)acetyl)pyrrolidine-2-carboxamide

(Compound 322)



[0620] Step a: To a mixture of 4-bromo-3-fluoro-benzaldehyde (200 g, 985 mmol, 1.00 eq) and 2-isopropenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (215 g, 1.28 mol, 1.30 eq) in toluene (3.70 L) and H_2O (410 mL) at 25 °C under N_2 was added $Pd(dppf)Cl_2$ (36.0 g, 49.3 mmol, 0.05 eq) and K_3PO_4 (418 g, 1.97 mol, 2.00 eq). The mixture was warmed to 90 °C and stirred for 12 h. The reaction mixture was then filtered, and the filtrate was concentrated under reduced pressure. The resulting crude residue was purified by column chromatography to give 3-fluoro-4-isopropenyl-benzaldehyde. The compound was carried forward to the next step without further characterization.

[0621] Step b: To a solution of 3-fluoro-4-isopropenyl-benzaldehyde (124 g, 755 mmol, 1.00 eq) in EtOAc (1.20 L) under N_2 was added Pd/C (85.0 g, 10 wt. %). The suspension was degassed and purged with H_2 several times. The mixture was stirred at 25 °C under H_2 (15

psi) for 1 h. The reaction mixture was then filtered, and the filtrate was concentrated under reduced pressure. The resulting crude residue was purified by column chromatography to give 3-fluoro-4-isopropyl-benzaldehyde. The compound was carried forward to the next step without further characterization.

[0622] Step c: To a mixture of 3-fluoro-4-isopropyl-benzaldehyde (80.0 g, 481 mmol, 1.00 eq) and (*R*)-2-methylpropane-2-sulfinamide (64.2 g, 523 mmol, 1.10 eq) in DCM (450 mL) at 25 ºC was added Cs_2CO_3 (173 g, 530 mmol, 1.10 eq). The mixture was warmed to 40 ºC and stirred for 16 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography to obtain (*R*,*E*)-*N*-(3-fluoro-4-isopropylbenzylidene)-2-methylpropane-2-sulfinamide. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{14}H_{20}FNOS$: 270.1; found 270.0.

[0623] Step d: To a solution of (*R*,*E*)-*N*-(3-fluoro-4-isopropylbenzylidene)-2-methylpropane-2-sulfinamide (30.0 g, 111 mmol, 1.00 eq) in DCM (400 mL) –65 ºC under N_2 was added, dropwise, a solution of phenylmagnesium bromide (3 M in Et_2O, 55.7 mL, 1.50 eq) over a period of 30 min. The reaction mixture was stirred at –65 ºC for 6 h, then warmed to 25 ºC and stirred for an additional 6 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with water (3 x 30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude residue was purified by column chromatography to obtain (*R*)-*N*-((*S*)-(3-fluoro-4-isopropylphenyl)(phenyl)methyl)-2-methylpropane-2-sulfinamide. The compound was carried forward to the next step without further characterization.

[0624] Step e: To a mixture of (*R*)-*N*-((*S*)-(3-fluoro-4-isopropylphenyl)(phenyl)methyl)-2-methylpropane-2-sulfinamide (35.0 g, 101mmol, 1.00 eq) in DCM (300 mL) at 25 ºC was added HCl/EtOAc (4 M, 50.4 mL, 2.00 eq), and the mixture was stirred for 2 h. The reaction mixture was filtered and the solid so obtained was set aside. The filtrate was concentrated under reduced pressure and the resulting residue was combined with the previously obtained solid. The mixture was dissolved in MTBE (200 mL) and filtered, and the filtrate was concentrated under reduced pressure to give (*S*)-(3-fluoro-4-isopropylphenyl)(phenyl)methanaminium chloride. The compound was carried forward to the next step without further characterization.

[0625] Step f: To a solution of (*S*)-(3-fluoro-4-isopropylphenyl)(phenyl)methanaminium chloride (600 mg, 2.14 mmol, 1 eq), and 1-methylimidazole (880 mg, 10.7 mmol, 5 eq) in CH_3CN (10 mL) at –20 °C was added (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (600 mg, 2.57 mmol, 1.2 eq). After 10 min, chloro-*N*,*N*,*N*',*N*'-tetramethylformamidinium hexafluorophosphate (TCFH, 722 mg, 2.57 mmol, 1.2 eq) was added at –20 °C, and the resulting mixture was stirred for 2 h. The reaction mixture was warmed to 25 °C, quenched with H_2O (30 mL), and extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude residue was purified by column chromatography to afford *tert*-butyl (2*S*,4*R*)-4-fluoro-2-(((*S*)-(3-fluoro-4-isopropylphenyl)(phenyl)methyl)carbamoyl)pyrrolidine-1-carboxylate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{26}H_{32}F_2N_2O_3$: 459.2; found 459.1.

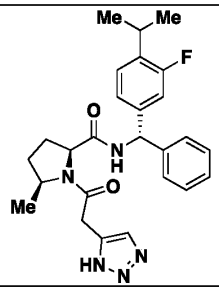
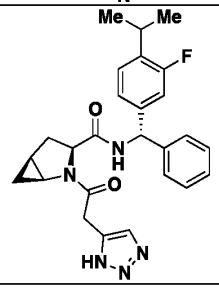
[0626] Step g: To a mixture of *tert*-butyl (2*S*,4*R*)-4-fluoro-2-(((*S*)-(3-fluoro-4-isopropylphenyl)(phenyl)methyl)carbamoyl)pyrrolidine-1-carboxylate (0.8 g, 1.74 mmol, 1 eq) in EtOAc (3 mL) at 0 °C was added 4M HCl/EtOAc (10 mL). The resulting mixture was stirred at 0 °C for 2 h. The reaction was then concentrated directly at low temperature under reduced pressure. The solid so obtained was washed with MTBE (3 x 10 mL), filtered, and dried under reduced pressure to give (2*S*,4*R*)-4-fluoro-*N*-((*S*)-(3-fluoro-4-isopropylphenyl)(phenyl)methyl)pyrrolidine-2-carboxamide. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{21}H_{24}F_2N_2O$: 359.2; found 359.1

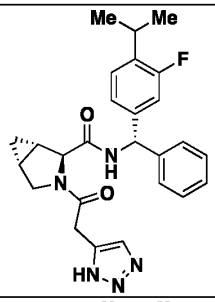
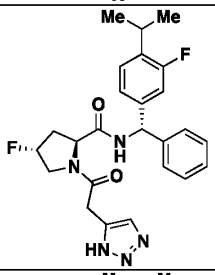
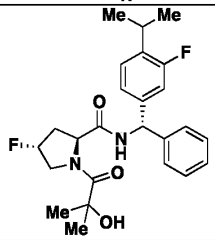
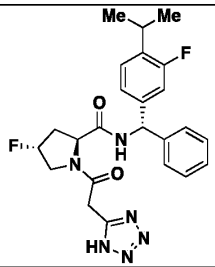
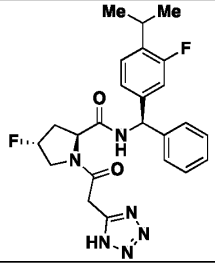
[0627] Step h: To a mixture of (2*S*,4*R*)-4-fluoro-*N*-((*S*)-(3-fluoro-4-isopropylphenyl)(phenyl)methyl)pyrrolidine-2-carboxamide (50 mg, 139 µmol, 1 eq), 4-methylmorpholine (28.22 mg, 279 µmol, 2 *eq*) and 2-(5-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)acetic acid (Intermediate A-3, 32.8 mg, 167 µmol, 1.2 eq) in DMF (3 mL) was added T3P (267 mg, 418 µmol, 50% in EtOAc, 3 eq) at –20 °C. The mixture was stirred at –20 °C for 2 h under N_2 atmosphere. The reaction mixture was then quenched with H_2O (20 mL) at 0 °C and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC to give (2*S*,4*R*)-4-fluoro-*N*-((*S*)-(3-fluoro-4-isopropylphenyl)(phenyl)methyl)-1-(2-(5-(trifluoromethyl)-1*H*-1,2,3-triazol-1-

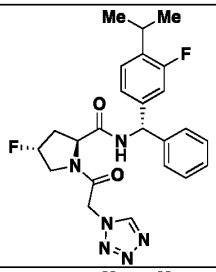
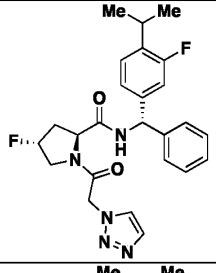
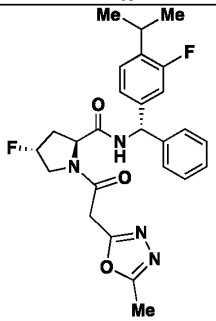
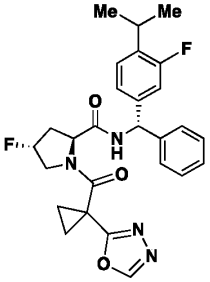
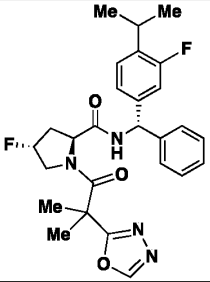
yl)acetyl)pyrrolidine-2-carboxamide. ^{1}H NMR (3.9:1 rotamer ratios, asterisk denotes minor rotamer peaks, obscured peaks not reported, 400 MHz, DMSO-d_6) δ 9.25* (d, J = 8.0 Hz, 1H), 8.89 (d, J = 8.2 Hz, 1H), 8.51 – 8.44 (m, 1H), 7.38 – 7.18 (m, 6H), 7.15 – 6.93 (m, 2H), 6.14* (d, J = 8.0 Hz, 1H), 6.01 (d, J = 8.2 Hz, 1H), 5.88 – 5.79 (m, 1H), 5.79 – 5.70* (m, 1H), 5.64 – 5.55 (m, 1H), 5.56 – 5.24 (m, 1H), 4.97 – 4.81* (m, 1H), 4.57 (t, J = 8.4 Hz, 1H), 4.22 – 4.09 (m, 1H), 4.00 – 3.76 (m, 1H), 3.58 – 3.40* (m, 1H), 3.18 – 3.05 (m, 1H), 2.92 – 2.77* (m, 1H), 2.30 – 1.91 (m, 1H), 1.22 – 1.15 (m, 6H). LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{26}H_{26}F_5N_5O_2$: 536.2; found 536.2.

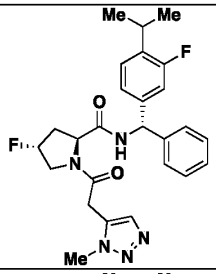
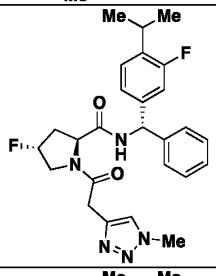
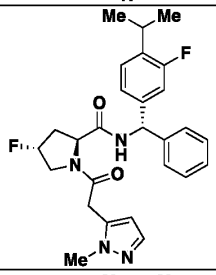
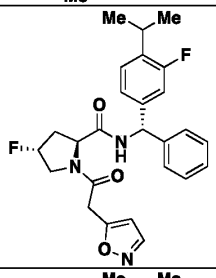
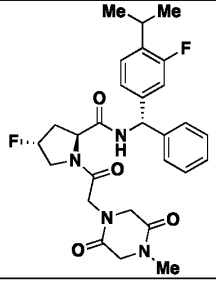
[0628] The following compounds in Table T-4 were synthesized using procedures similar to Compound 322 using the appropriate starting materials.

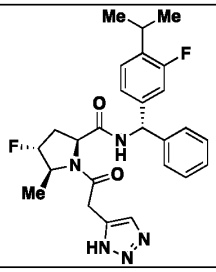
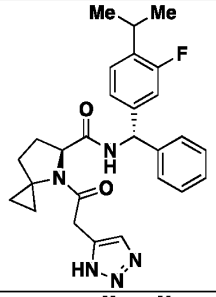
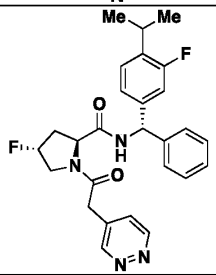
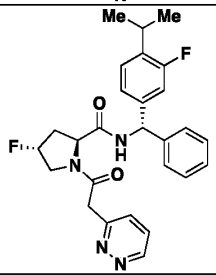
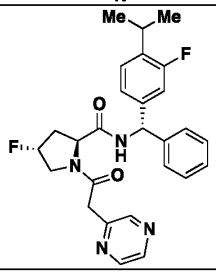
Table T-4

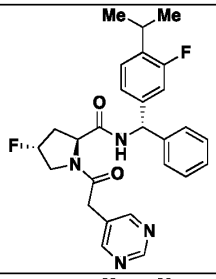
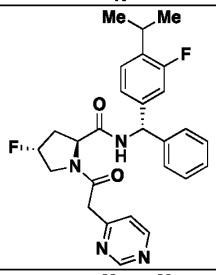
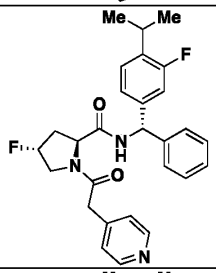
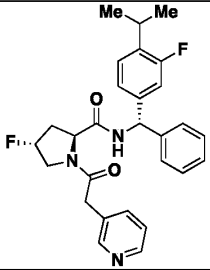
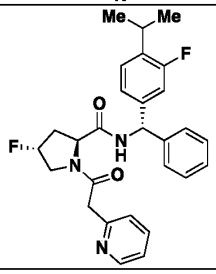
Compound No.	Structure	IUPAC	Exact mass (g/mol)	LCMS, Found [M + H]$^+$
323		(2S,5S)-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-5-methyl-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide	463.2	464.2
324		(1S,3S,5S)-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-2-[2-(1H-1,2,3-triazol-5-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carboxamide	461.2	462.1

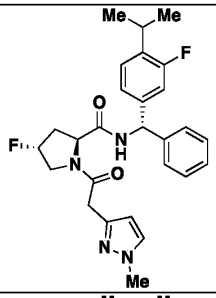
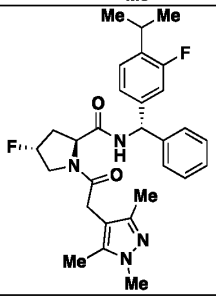
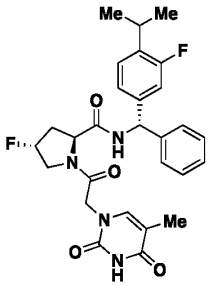
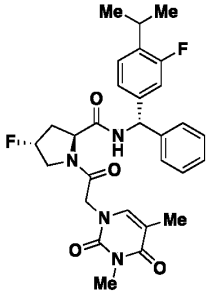
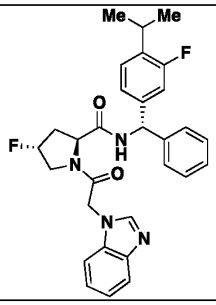
325		(1S,2S,5R)-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-3-[2-(1H-1,2,3-triazol-5-yl)acetyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide	461.2	462.1
326		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide	467.2	468.1
327		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-(2-hydroxy-2-methylpropanoyl)pyrrolidine-2-carboxamide	444.2	445.1
328		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(1H-1,2,3,4-tetrazol-5-yl)acetyl]pyrrolidine-2-carboxamide	468.2	469.1
329		(2S,4R)-4-fluoro-N-[(R)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(1H-1,2,3,4-tetrazol-5-yl)acetyl]pyrrolidine-2-carboxamide	468.2	469.1

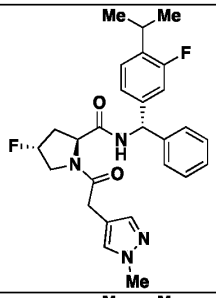
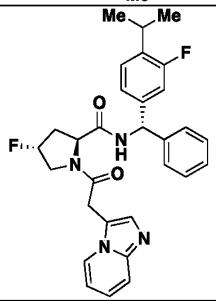
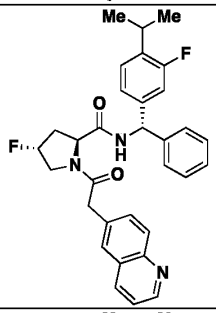
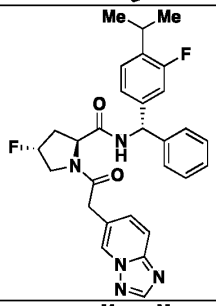
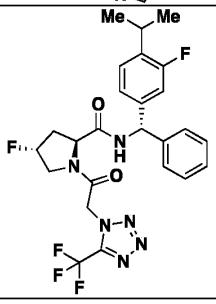
330		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(1H-1,2,3,4-tetrazol-1-yl)acetyl]pyrrolidine-2-carboxamide	468.2	469.1
331		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(1H-1,2,3-triazol-1-yl)acetyl]pyrrolidine-2-carboxamide	467.2	468.1
332		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(5-methyl-1,3,4-oxadiazol-2-yl)acetyl]pyrrolidine-2-carboxamide	482.2	493.1
333		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[1-(1,3,4-oxadiazol-2-yl)cyclopropanecarbonyl]pyrrolidine-2-carboxamide	494.2	495.1
334		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-methyl-2-(1,3,4-oxadiazol-2-yl)propanoyl]pyrrolidine-2-carboxamide	496.2	497.1

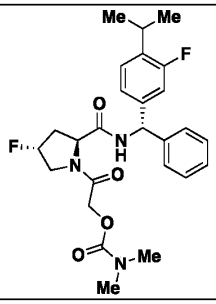
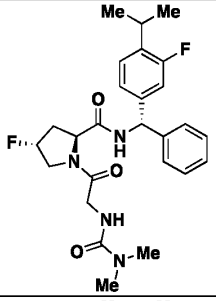
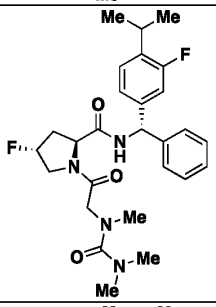
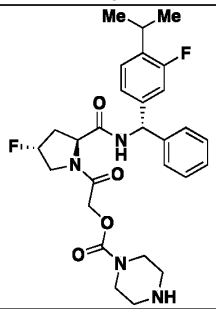
335		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(1-methyl-1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide	481.2	480.1
336		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(1-methyl-1H-1,2,3-triazol-4-yl)acetyl]pyrrolidine-2-carboxamide	481.2	482.1
337		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(1-methyl-1H-pyrazol-5-yl)acetyl]pyrrolidine-2-carboxamide	480.2	481.3
338		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(1,2-oxazol-5-yl)acetyl]pyrrolidine-2-carboxamide	467.2	468.1
339		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(4-methyl-2,5-dioxopiperazin-1-yl)acetyl]pyrrolidine-2-carboxamide	526.2	527.1

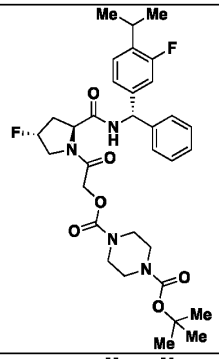
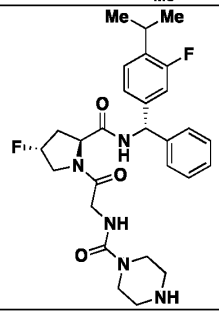
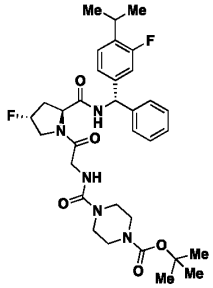
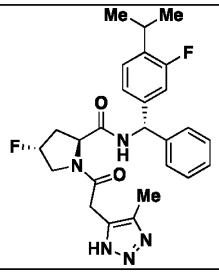
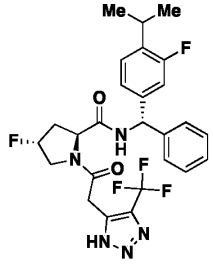
340		(2S,4R,5S)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-5-methyl-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide	481.2	482.2
341		(5S)-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-4-[2-(1H-1,2,3-triazol-5-yl)acetyl]-4-azaspiro[2.4]heptane-5-carboxamide	475.2	476.1
342		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(pyridazin-4-yl)acetyl]pyrrolidine-2-carboxamide	478.2	479.3
343		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(pyridazin-3-yl)acetyl]pyrrolidine-2-carboxamide	478.2	479.1
344		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(pyrazin-2-yl)acetyl]pyrrolidine-2-carboxamide	478.2	479.2

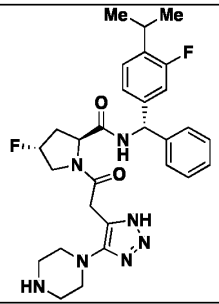
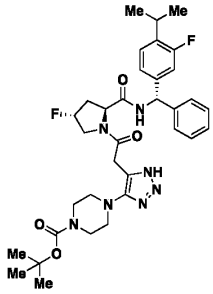
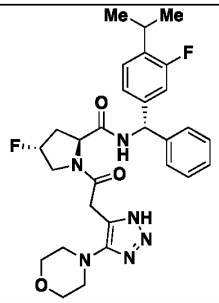
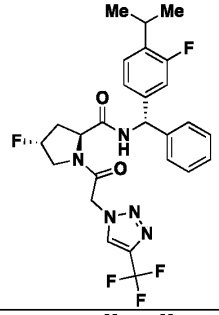
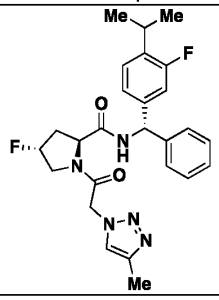
345		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(pyrimidin-5-yl)acetyl]pyrrolidine-2-carboxamide	478.2	479.1
346		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(pyrimidin-4-yl)acetyl]pyrrolidine-2-carboxamide	478.2	479.2
347		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(pyridin-4-yl)acetyl]pyrrolidine-2-carboxamide	477.2	478.2
348		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(pyridin-3-yl)acetyl]pyrrolidine-2-carboxamide	477.2	478.2
349		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(pyridin-2-yl)acetyl]pyrrolidine-2-carboxamide	477.2	478.1

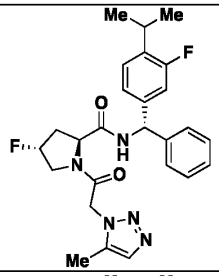
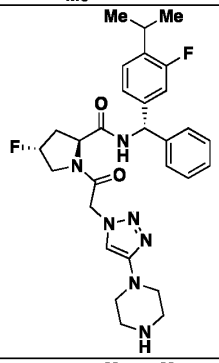
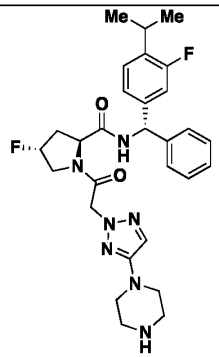
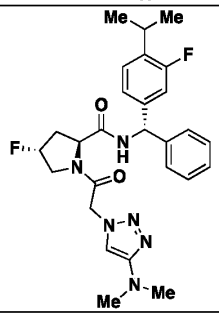
350		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(1-methyl-1H-pyrazol-3-yl)acetyl]pyrrolidine-2-carboxamide	480.2	481.3
351		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(1,3,5-trimethyl-1H-pyrazol-4-yl)acetyl]pyrrolidine-2-carboxamide	508.3	509.3
352		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]pyrrolidine-2-carboxamide	524.2	525.0
353		(2S,4R)-1-[2-(3,5-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]pyrrolidine-2-carboxamide	538.2	539.1
354		(2S,4R)-1-[2-(1H-1,3-benzodiazol-1-yl)acetyl]-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]pyrrolidine-2-carboxamide	516.2	517.2

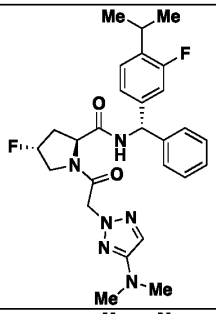
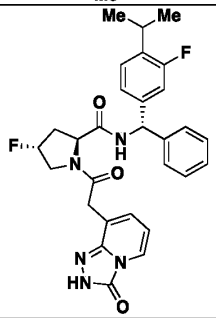
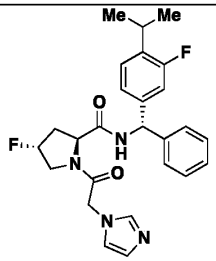
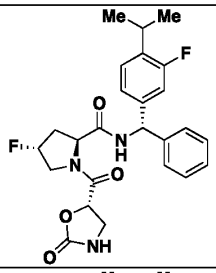
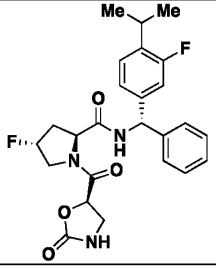
355		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(1-methyl-1H-pyrazol-4-yl)acetyl]pyrrolidine-2-carboxamide	480.2	481.1
356		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-(2-{imidazo[1,2-a]pyridin-3-yl}acetyl)pyrrolidine-2-carboxamide	516.2	517.1
357		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(quinolin-6-yl)acetyl]pyrrolidine-2-carboxamide	527.2	528.1
358		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-(2-{[1,2,4]triazolo[1,5-a]pyridin-6-yl}acetyl)pyrrolidine-2-carboxamide	517.2	518.1
359		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-{2-[5-(trifluoromethyl)-1H-1,2,3,4-tetrazol-1-yl]acetyl}pyrrolidine-2-carboxamide	536.2	559.2 [M + Na]$^+$

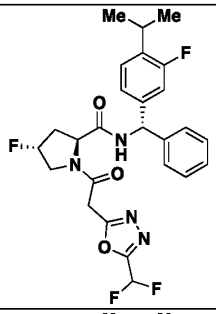
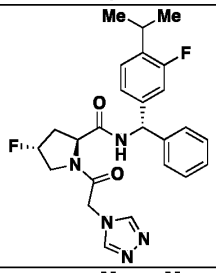
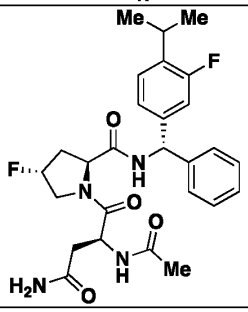
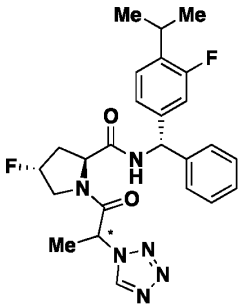
360		2-[(2S,4R)-4-fluoro-2-{[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl N,N-dimethylcarbamate	487.2	488.1
361		(2S,4R)-1-{2-[(dimethylcarbamoyl)amino]acetyl}-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]pyrrolidine-2-carboxamide	486.2	487.1
362		(2S,4R)-1-{2-[(dimethylcarbamoyl)(methyl)amino]acetyl}-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]pyrrolidine-2-carboxamide	500.3	501.2
363		2-[(2S,4R)-4-fluoro-2-{[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl piperazine-1-carboxylate	528.3	529.3

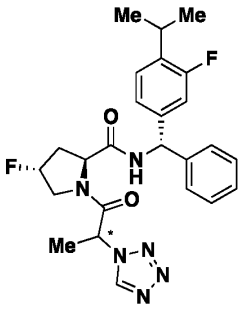
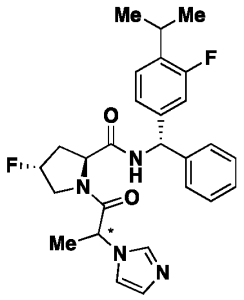
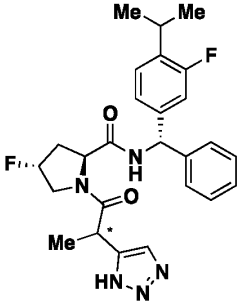
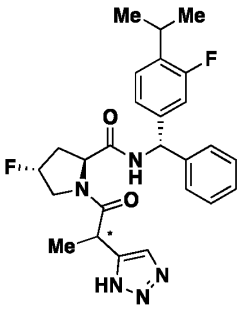
364		1-tert-butyl 4-{2-[(2S,4R)-4-fluoro-2-{[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl}piperazine-1,4-dicarboxylate	628.3	529.3 [M - Boc+1]$^+$
365		N-{2-[(2S,4R)-4-fluoro-2-{[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl}piperazine-1-carboxamide	527.3	528.1
366		tert-butyl 4-({2-[(2S,4R)-4-fluoro-2-{[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl}carbamoyl)piperazine-1-carboxylate	627.3	628.3
367		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(4-methyl-1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide	481.2	482.2
368		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-{2-[4-(trifluoromethyl)-1H-1,2,3-triazol-5-yl]acetyl}pyrrolidine-2-carboxamide	535.2	536.3

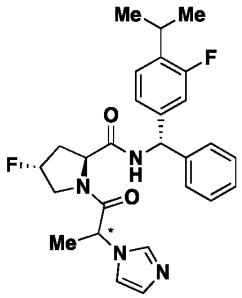
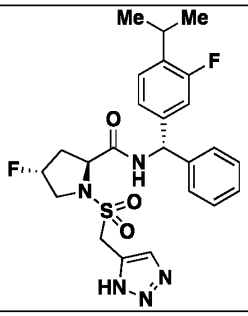
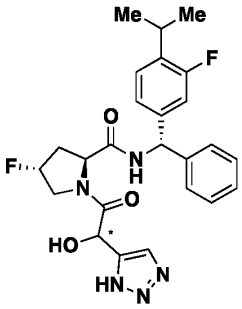
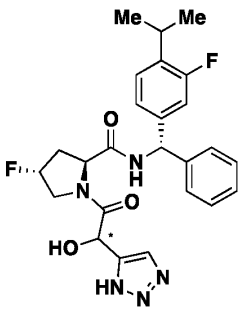
369		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-{2-[4-(piperazin-1-yl)-1H-1,2,3-triazol-5-yl]acetyl}pyrrolidine-2-carboxamide	551.3	552.3
370		tert-butyl 4-(5-{2-[(2S,4R)-4-fluoro-2-{[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl}-1H-1,2,3-triazol-4-yl)piperazine-1-carboxylate	651.3	652.4
371		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-{2-[4-(morpholin-4-yl)-1H-1,2,3-triazol-5-yl]acetyl}pyrrolidine-2-carboxamide	552.3	553.3
372		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-{2-[4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl]acetyl}pyrrolidine-2-carboxamide	535.2	558.0 [M + Na]$^+$
373		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(4-methyl-1H-1,2,3-triazol-1-yl)acetyl]pyrrolidine-2-carboxamide	481.2	482.2

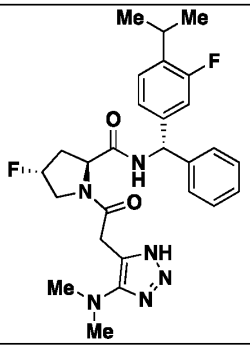
374		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(5-methyl-1H-1,2,3-triazol-1-yl)acetyl]pyrrolidine-2-carboxamide	481.2	482.2
375		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-{2-[4-(piperazin-1-yl)-1H-1,2,3-triazol-1-yl]acetyl}pyrrolidine-2-carboxamide	551.3	552.3
376		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-{2-[4-(piperazin-1-yl)-2H-1,2,3-triazol-2-yl]acetyl}pyrrolidine-2-carboxamide	551.3	552.3
377		(2S,4R)-1-{2-[4-(dimethylamino)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]pyrrolidine-2-carboxamide	510.3	511.2

378		(2S,4R)-1-{2-[4-(dimethylamino)-2H-1,2,3-triazol-2-yl]acetyl}-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]pyrrolidine-2-carboxamide	510.3	511.2
379		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-(2-{3-oxo-2H,3H-[1,2,4]triazolo[4,4,3-a]pyridin-8-yl}acetyl)pyrrolidine-2-carboxamide	533.2	534.2
380		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(1H-imidazol-1-yl)acetyl]pyrrolidine-2-carboxamide	466.2	467.2
381		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[(5S)-2-oxo-1,3-oxazolidine-5-carbonyl]pyrrolidine-2-carboxamide	471.2	489.2 [M + NH_4]$^+$
382		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[(5R)-2-oxo-1,3-oxazolidine-5-carbonyl]pyrrolidine-2-carboxamide	471.2	472.2

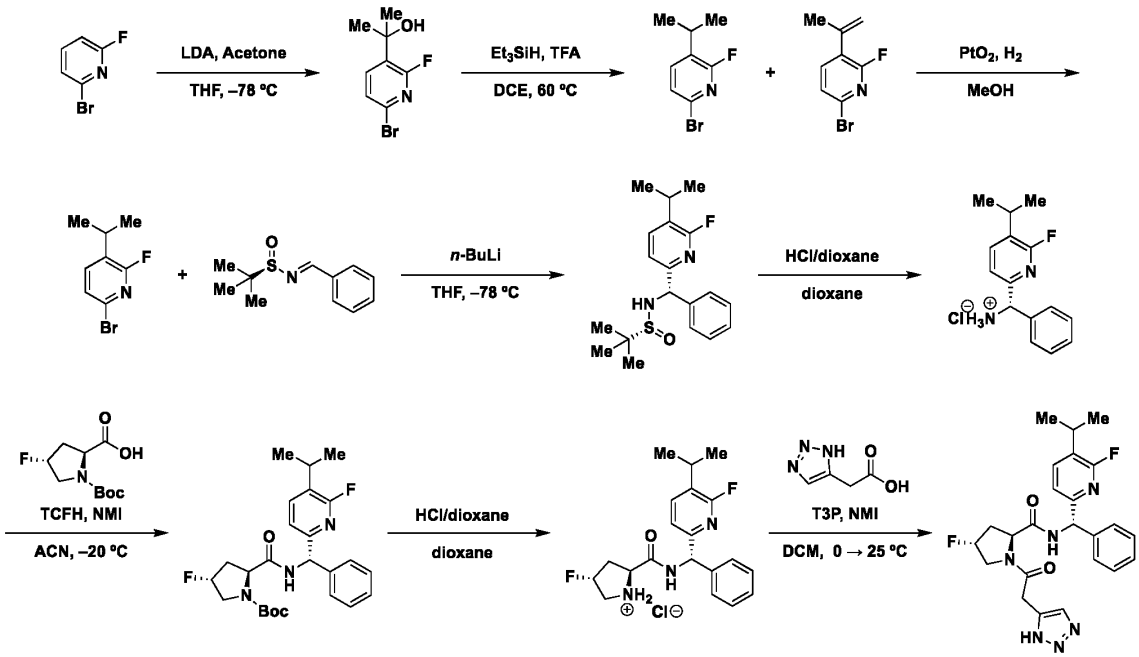
383		(2S,4R)-1-{2-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]acetyl}-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]pyrrolidine-2-carboxamide	518.2	519.1
384		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(4H-1,2,4-triazol-4-yl)acetyl]pyrrolidine-2-carboxamide	467.2	467.9
765		(2S,4R)-1-[(2S)-3-carbamoyl-2-acetamidopropanoyl]-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]pyrrolidine-2-carboxamide	514.2	515.2
766		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[(2R) or (2S)-2-(1H-1,2,3,4-tetrazol-1-yl)propanoyl]pyrrolidine-2-carboxamide (column: DAICEL CHIRALPAK AD-3, second-eluting isomer)	482.2	483.2

767		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[(2S) or (2R)-2-(1H-1,2,3,4-tetrazol-1-yl)propanoyl]pyrrolidine-2-carboxamide (column: DAICEL CHIRALPAK AD-3, first-eluting isomer)	482.2	483.2
768		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[(2R) or (2S)-2-(1H-imidazol-1-yl)propanoyl]pyrrolidine-2-carboxamide (column: DAICEL CHIRALPAK IG-3, first-eluting isomer)	480.2	481.2
769		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[(2R) or (2S)-2-(1H-1,2,3-triazol-5-yl)propanoyl]pyrrolidine-2-carboxamide (column: Phenomenex Luna C18, first-eluting isomer)	481.2	482.1
770		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[(2S) or (2R)-2-(1H-1,2,3-triazol-5-yl)propanoyl]pyrrolidine-2-carboxamide (column: Phenomenex Luna C18, second-eluting isomer)	481.2	482.1

771		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[(2S) or (2R)-2-(1H-imidazol-1-yl)propanoyl]pyrrolidine-2-carboxamide (column: DAICEL CHIRALPAK IG-3, second-eluting isomer)	480.2	481.2
772		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[(1H-1,2,3-triazol-5-yl)methanesulfonyl]pyrrolidine-2-carboxamide	503.2	504.1
773		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[(2R) or (2S)-2-hydroxy-2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide (column: DAICEL CHIRALPAK AD-3, first-eluting isomer)	483.2	484.2
774		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[(2S) or (2R)-2-hydroxy-2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide (column: DAICEL CHIRALPAK AD-3, second-eluting isomer)	483.2	484.2

775		(2S,4R)-1-{2-[4-(dimethylamino)-1H-1,2,3-triazol-5-yl]acetyl}-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](phenyl)methyl]pyrrolidine-2-carboxamide	510.3	511.3

Example S-5: Synthesis of (2*S*,4*R*)-1-(2-(1*H*-1,2,3-triazol-5-yl)acetyl)-4-fluoro-*N*-((*S*)-(6-fluoro-5-isopropylpyridin-2-yl)(phenyl)methyl)pyrrolidine-2-carboxamide (Compound 385)



[0629] Step a: To a solution of 2-bromo-6-fluoropyridine (50 g, 284 mmol, 1 eq) in THF (500 mL) at –78 °C was added LDA (2 M in THF, 142 mL, 1 eq) in a dropwise manner. The resulting mixture was stirred at –78 °C for 30 min. To this mixture was added acetone (24.7 g, 426 mmol, 1.5 eq) in a dropwise manner, and the resulting reaction mixture was stirred at –78 °C for 1.5 h. The reaction mixture was then cooled to 0 °C and quenched by dropwise addition of

water (500 mL), and the resulting mixture was extracted with EtOAc (2 x 500 mL). The combined organic extracts were washed with brine (2 x 200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude residue was purified by column chromatography to give 2-(6-bromo-2-fluoropyridin-3-yl)propan-2-ol. LC-MS (ESI): m/z: $[M + H]^+$ calculated for C_8H_9BrFNO: 234.0; found 234.0.

[0630] Step b: To a solution of 2-(6-bromo-2-fluoropyridin-3-yl)propan-2-ol (60 g, 256 mmol, 1 eq) in DCE (500 mL) at 25 °C was added Et_3SiH (149 g, 1.28 mol, 5 eq) and TFA (292 g, 2.56 mol, 10 eq). The reaction mixture was then warmed to 60 °C and stirred for 15 h. After cooling, the mixture was concentrated under reduced pressure. The resulting residue was poured into ice-water (300 mL) and adjusted to pH = 7 by addition of saturated aqueous Na_2CO_3 solution. The resulting biphasic mixture was extracted with EtOAc (3 x 500 mL). The combined organic extracts were washed with brine (3 x 300 mL), dried over anhydrous Na_2SO_4, and filtered. The filtrate was then concentrated under reduced pressure, and the resulting crude residue was purified by column chromatography to give a mixture of 6-bromo-2-fluoro-3-isopropylpyridine and 6-bromo-2-fluoro-3-(prop-1-en-2-yl)pyridine. LC-MS (ESI): m/z: $[M + H]^+$ calculated for C_8H_9BrFN: 218.0; found 218.1. $[M + H]^+$ calculated for C_8H_7BrFN: 216.0; found 215.9.

[0631] Step c: To a solution of 6-bromo-2-fluoro-3-isopropylpyridine and 6-bromo-2-fluoro-3-(prop-1-en-2-yl)pyridine (58 g, crude) in MeOH (500 mL) at 25 °C was added PtO_2 (4.17 g, 18.3 mmol). The resulting mixture was degassed and purged with H_2. The reaction mixture was then stirred at 25 °C under H_2 atmosphere (50 psi) for 12 h. The reaction mixture was then filtered through a pad of Celite, and the filter cake was washed with MeOH (2 x 200 mL). The combined filtrate was concentrated under reduced pressure, and the resulting crude residue was purified by column chromatography to give 6-bromo-2-fluoro-3-isopropylpyridine. LC-MS (ESI): m/z: $[M + H]^+$ calculated for C_8H_9BrFN: 218.0; found 218.1.

[0632] Step d: To a solution of 6-bromo-2-fluoro-3-isopropylpyridine (32.0 g, 146 mmol, 1 eq) in THF (250 mL) at –78 °C was added *n*-BuLi (2.5 M in hexane, 88.0 mL, 1.5 eq) in a dropwise manner. The resulting mixture was stirred at –78 °C for 30 min. To this mixture was added (*R*,*E*)-*N*-benzylidene-2-methylpropane-2-sulfinamide (30.7 g, 146 mmol, 1 eq) as a solution in THF (250 mL) in a dropwise manner. The resulting mixture was then stirred at –78

°C for 4 h. The reaction mixture was then poured into ice-water (500 mL) and extracted with EtOAc (3 x 500 mL). The combined organic extracts were washed with brine (300 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude residue was purified by column chromatography followed by prep-HPLC to give (*R*)-*N*-((*S*)-(6-fluoro-5-isopropylpyridin-2-yl)(phenyl)methyl)-2-methylpropane-2-sulfinamide. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{19}H_{25}FN_2OS$: 349.2; found 349.2.

[0633] Step e: To a solution of (*R*)-*N*-((*S*)-(6-fluoro-5-isopropylpyridin-2-yl)(phenyl)methyl)-2-methylpropane-2-sulfinamide (12.0 g, 34.4 mmol, 1 eq) in dioxane (10 mL) at 0 °C was added HCl/dioxane (4 M, 500 mL). The reaction mixture was warmed to 25 °C and stirred for 2 h. The reaction mixture was concentrated under reduced pressure to give (*S*)-(6-fluoro-5-isopropylpyridin-2-yl)(phenyl)methanaminium chloride, which was used in the next step without further purification. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{15}H_{17}FN_2$: 245.1; found 245.2.

[0634] Step f: To a mixture of (*S*)-(6-fluoro-5-isopropylpyridin-2-yl)(phenyl)methanaminium chloride (11 g, crude, 1 eq) and (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (10.0 g, 43.1 mmol, 1.1 eq) in CH_3CN (200 mL) at –20 °C was added 1-methylimidazole (NMI, 48.2 g, 587 mmol, 46.8 mL, 15 eq) and chloro-*N*,*N*,*N*',*N*'-tetramethylformamidinium hexafluorophosphate (TCFH, 12.1 g, 43.1 mmol, 1.1 eq). The reaction mixture was then stirred at –20 °C for 2 h. The reaction mixture was then poured into H_2O (500 mL) and extracted with EtOAc (3 x 500 mL). The combined organic extracts were washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude residue was purified by column chromatography to give *tert*-butyl (2*S*,4*R*)-4-fluoro-2-(((*S*)-(6-fluoro-5-isopropylpyridin-2-yl)(phenyl)methyl)carbamoyl)pyrrolidine-1-carboxylate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{25}H_{31}F_2N_3O_3$: 460.2; found 460.2.

[0635] Step g: To a solution of *tert*-butyl (2*S*,4*R*)-4-fluoro-2-(((*S*)-(6-fluoro-5-isopropylpyridin-2-yl)(phenyl)methyl)carbamoyl)pyrrolidine-1-carboxylate (14.0 g, 30.4 mmol, 1 eq) in dioxane (50 mL) at 25 °C was added HCl/dioxane (4 M, 300 mL, 45.9 eq), and the resulting mixture was stirred at 25 °C for 2 h. The reaction mixture was then concentrated under

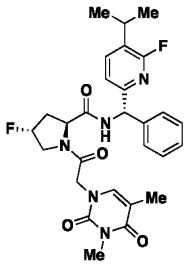
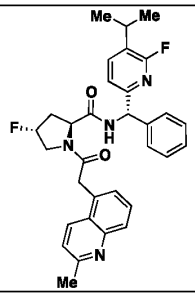
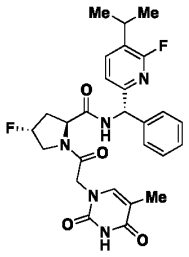
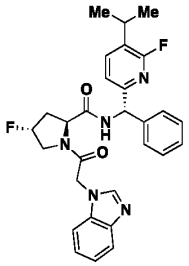
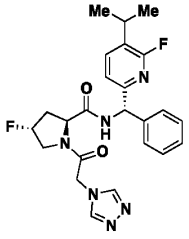
reduced pressure to give (2*S*,4*R*)-4-fluoro-*N*-((*S*)-(6-fluoro-5-isopropylpyridin-2-yl)(phenyl)methyl)pyrrolidine-2-carboxamide hydrochloride. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{20}H_{23}F_2N_3O$: 360.2; found 360.1.

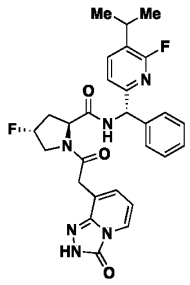
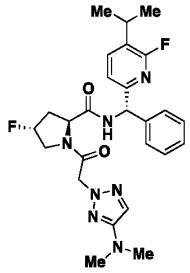
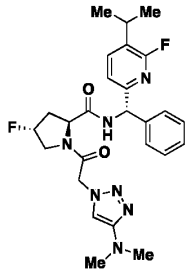
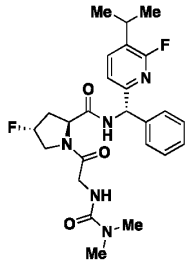
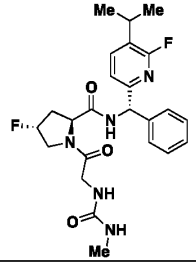
[0636] Step h: To a mixture of (2*S*,4*R*)-4-fluoro-*N*-((*S*)-(6-fluoro-5-isopropylpyridin-2-yl)(phenyl)methyl)pyrrolidine-2-carboxamide hydrochloride (8 g, 22.2 mmol, 1 eq) and 2-(1*H*-1,2,3-triazol-5-yl)acetic acid (Intermediate A-1, 3.39 g, 26.7 mmol, 1.2 eq) in DCM (200 mL) at 0 ºC was added 1-methylimidazole (NMI, 27.4 g, 333 mmol, 15 eq) and T3P (17.0 g, 26.7 mmol, 15.8 mL, 50% in EtOAc, 1.2 eq). The reaction mixture was then warmed to 25 ºC and stirred for 12 h. The reaction mixture was then poured into H_2O (200 mL) and extracted with EtOAc (3 x 200 mL). The combined organic extracts were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude residue was purified by column chromatography followed by prep-HPLC to give (2*S*,4*R*)-1-(2-(1*H*-1,2,3-triazol-5-yl)acetyl)-4-fluoro-*N*-((*S*)-(6-fluoro-5-isopropylpyridin-2-yl)(phenyl)methyl)pyrrolidine-2-carboxamide. ^{1}H NMR (3:1 rotamer ratio, asterisk denotes distinct minor rotamer peaks, obscured peaks not reported, 400 MHz, DMSO-d_6) δ 14.71 (br s, 1H), 9.30* (d, *J* = 7.8 Hz, 1H), 8.92 (d, *J* = 8.1 Hz, 1H), 7.92 – 7.80 (m, 1H), 7.67 (s, 1H), 7.54* (s, 1H), 7.40 – 7.18 (m, 6H), 6.09* (d, *J* = 7.8 Hz, 1H), 5.98 (d, *J* = 8.1 Hz, 1H), 5.48 – 5.20 (m, 1H), 4.90* (t, *J* = 8.0 Hz, 1H), 4.62 (t, *J* = 8.3 Hz, 1H), 4.12 – 3.63 (m, 3H), 3.12 – 2.95 (m, 1H), 2.79 – 2.61* (m, 1H), 2.28 – 1.91 (m, 1H), 1.24 – 1.16 (m, 6H). LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{24}H_{26}F_2N_6O_2$: 469.2; found 469.3.

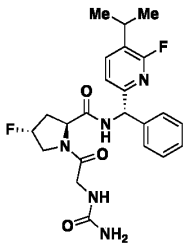
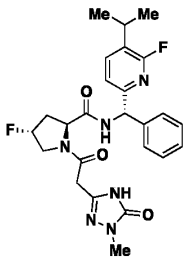
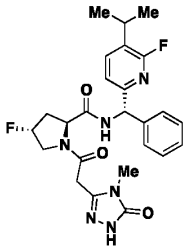
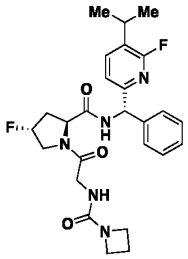
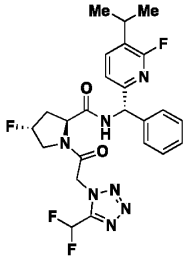
[0637] The following compounds in Table T-5 were synthesized using procedures similar to Compound 385 using the appropriate starting materials.

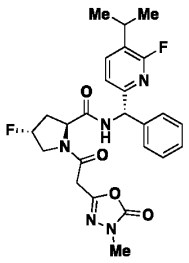
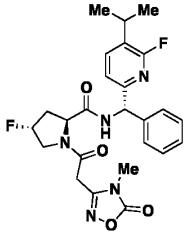
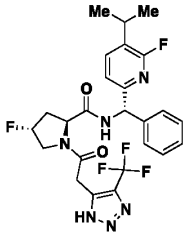
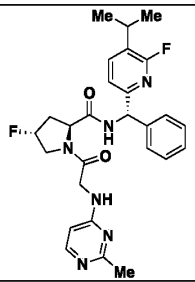
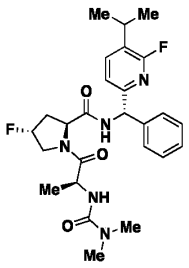
Table T-5

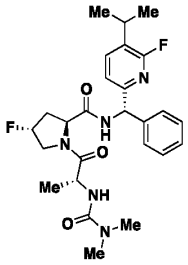
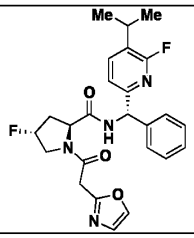
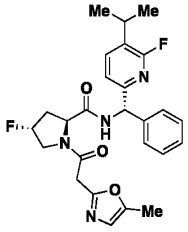
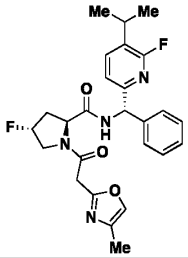
Compound No.	Structure	IUPAC	Exact mass (g/mol)	LCMS, Found $[M + H]^+$

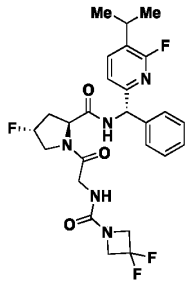
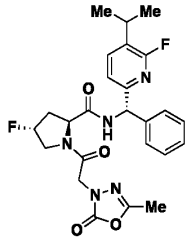
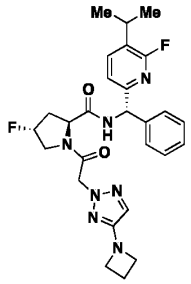
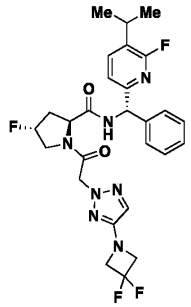
386		(2S,4R)-1-[2-(3,5-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide	539.2	540.1
387		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(2-methylquinolin-5-yl)acetyl]pyrrolidine-2-carboxamide	542.2	543.2
388		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]pyrrolidine-2-carboxamide	525.2	526.3
389		(2S,4R)-1-[2-(1H-1,3-benzodiazol-1-yl)acetyl]-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide	517.2	518.3
390		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(4H-1,2,4-triazol-4-yl)acetyl]pyrrolidine-2-carboxamide	468.2	469.2

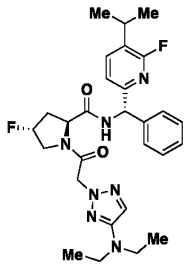
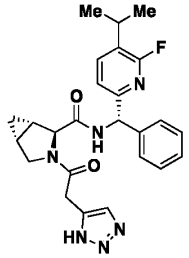
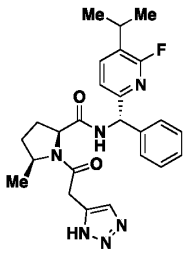
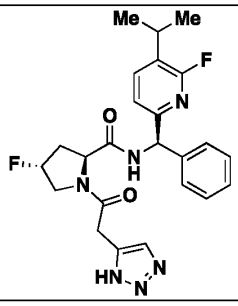
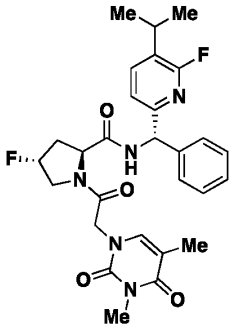
391		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-(2-{3-oxo-2H,3H-[1,2,4]triazolo[4,3-a]pyridin-8-yl}acetyl)pyrrolidine-2-carboxamide	534.2	535.2
392		(2S,4R)-1-{2-[4-(dimethylamino)-2H-1,2,3-triazol-2-yl]acetyl}-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide	511.3	512.3
393		(2S,4R)-1-{2-[4-(dimethylamino)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide	511.3	512.2
394		(2S,4R)-1-{2-[(dimethylcarbamoyl)amino]acetyl}-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide	487.2	488.3
395		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-{2-[(methylcarbamoyl)amino]acetyl}pyrrolidine-2-carboxamide	473.2	474.2

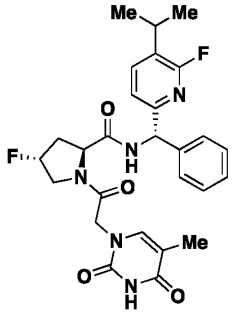
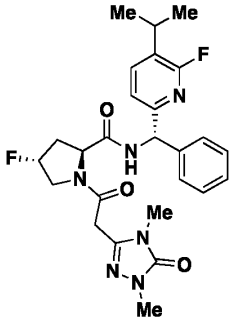
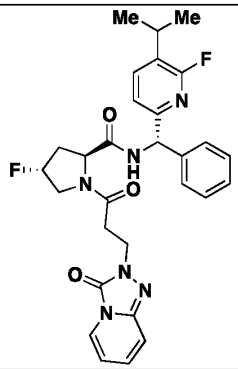
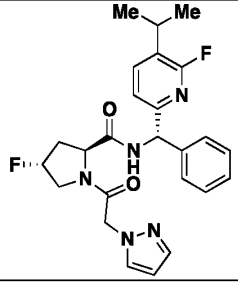
396		(2S,4R)-1-[2-(carbamoylamino)acetyl]-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide	459.2	460.1
397		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(1-methyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)acetyl]pyrrolidine-2-carboxamide	498.2	499.4
398		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(4-methyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)acetyl]pyrrolidine-2-carboxamide	498.2	499.2
399		(2S,4R)-1-{2-[(azetidine-1-carbonyl)amino]acetyl}-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide	499.2	500.3
400		(2S,4R)-1-{2-[5-(difluoromethyl)-1H-1,2,3,4-tetrazol-1-yl]acetyl}-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide	519.2	520.1

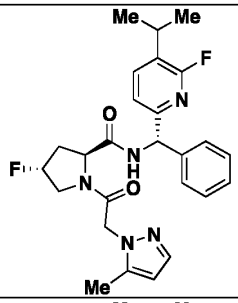
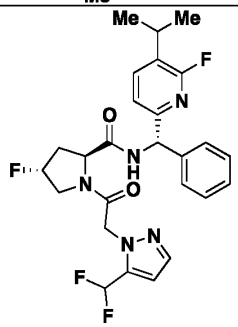
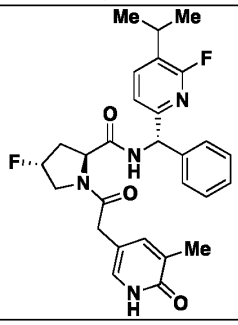
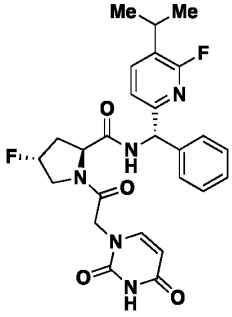
401		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(4-methyl-5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)acetyl]pyrrolidine-2-carboxamide	499.2	500.3
402		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(4-methyl-5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)acetyl]pyrrolidine-2-carboxamide	499.2	500.2
403		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-{2-[4-(trifluoromethyl)-1H-1,2,3-triazol-5-yl]acetyl}pyrrolidine-2-carboxamide	536.2	537.1
404		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-{2-[(2-methylpyrimidin-4-yl)amino]acetyl}pyrrolidine-2-carboxamide	508.2	509.3
405		(2S,4R)-1-[(2S)-2-[(dimethylcarbamoyl)amino]propanoyl]-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide	501.3	502.4

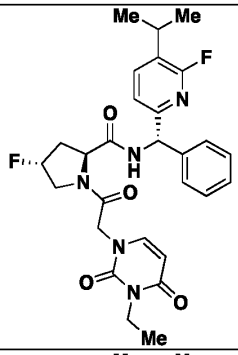
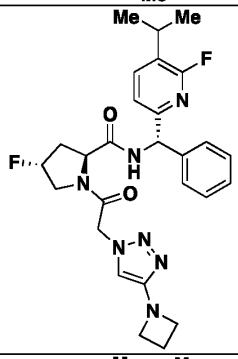
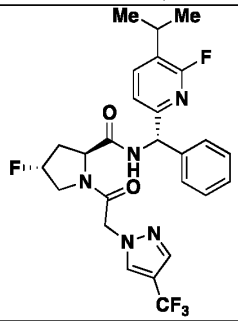
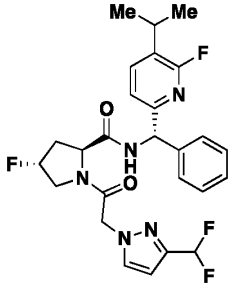
406		(2S,4R)-1-[(2R)-2-[(dimethylcarbamoyl) amino]propanoyl]-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide	501.3	502.4
407		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide	468.2	469.2
408		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(5-methyl-1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide	482.2	483.1
409		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(4-methyl-1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide	482.2	483.3

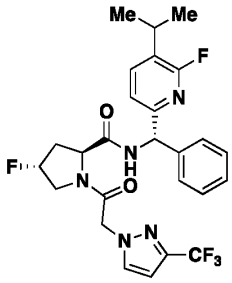
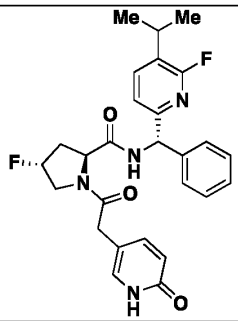
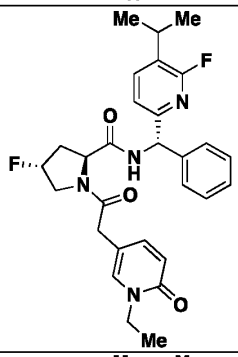
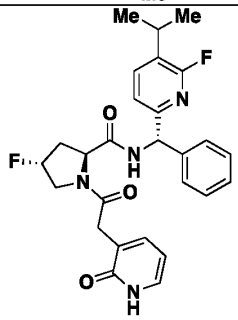
410		(2S,4R)-1-{2-[(3,3-difluoroazetidine-1-carbonyl)amino]acetyl}-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide	535.2	536.2
411		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(5-methyl-2-oxo-2,3-dihydro-1,3,4-oxadiazol-3-yl)acetyl]pyrrolidine-2-carboxamide	499.2	500.2
412		(2S,4R)-1-{2-[4-(azetidin-1-yl)-2H-1,2,3-triazol-2-yl]acetyl}-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide	523.3	524.3
413		(2S,4R)-1-{2-[4-(3,3-difluoroazetidin-1-yl)-2H-1,2,3-triazol-2-yl]acetyl}-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide	559.2	560.3

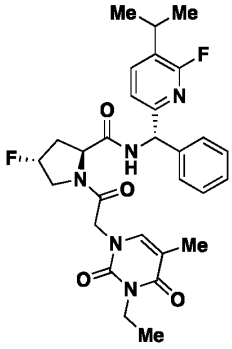
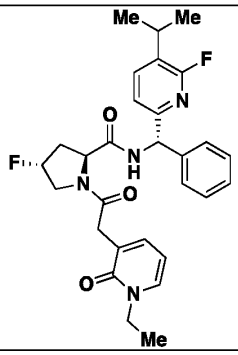
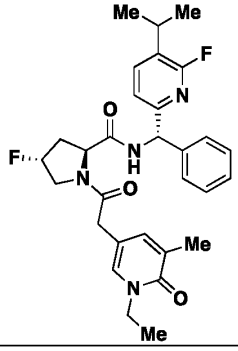
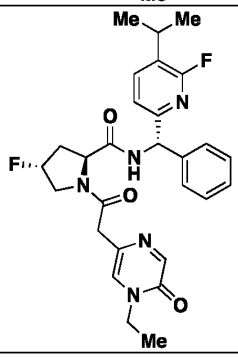
414		(2S,4R)-1-{2-[4-(diethylamino)-2H-1,2,3-triazol-2-yl]acetyl}-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide	539.3	540.4
415		(1S,2S,5R)-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-3-[2-(1H-1,2,3-triazol-5-yl)acetyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide	462.2	463.4
416		(2S,5S)-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-5-methyl-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide	464.2	465.4
776		(2S,4R)-4-fluoro-N-[(R*)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide	468.2	469.2
777		(2S,4R)-1-[2-(3,5-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-4-fluoro-N-[(R*)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide	539.2	540.1

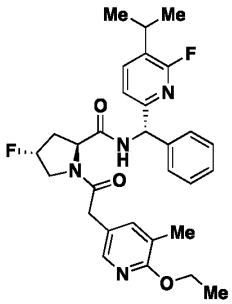
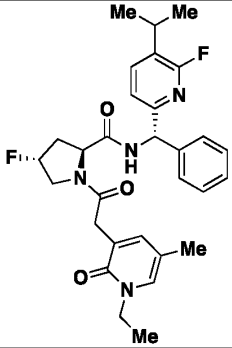
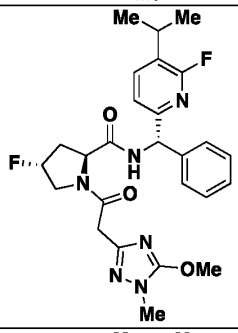
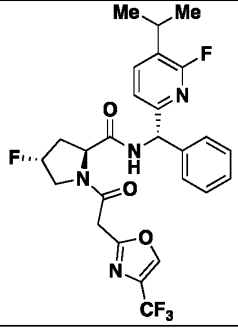
778		(2S,4R)-4-fluoro-N-[(R*)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]pyrrolidine-2-carboxamide	525.2	526.3
779		(2S,4R)-1-[2-(1,4-dimethyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)acetyl]-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide	512.2	513.3
780		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-(3-{3-oxo-2H,3H-[1,2,4]triazolo[4,3-a]pyridin-2-yl}propanoyl)pyrrolidine-2-carboxamide	548.2	549.2
781		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(1H-pyrazol-1-yl)acetyl]pyrrolidine-2-carboxamide	467.2	468.1

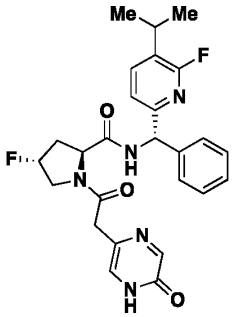
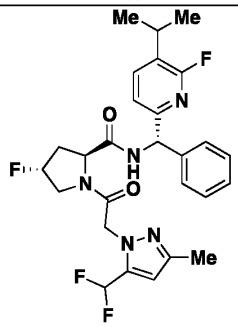
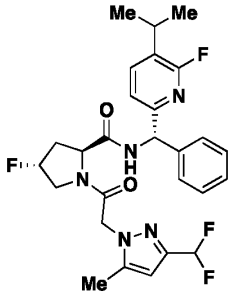
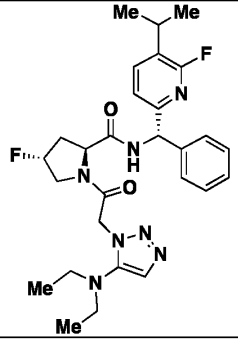
782		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(5-methyl-1H-pyrazol-1-yl)acetyl]pyrrolidine-2-carboxamide	481.2	482.2
783		(2S,4R)-1-{2-[5-(difluoromethyl)-1H-pyrazol-1-yl]acetyl}-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide	517.2	518.2
784		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(5-methyl-6-oxo-1,6-dihydropyridin-3-yl)acetyl]pyrrolidine-2-carboxamide	508.2	509.1
785		(2S,4R)-1-[2-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide	511.2	512.1

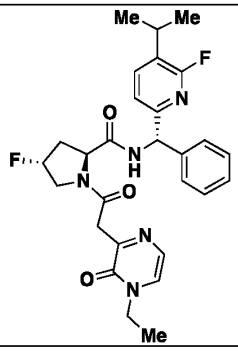
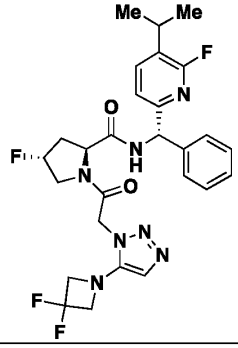
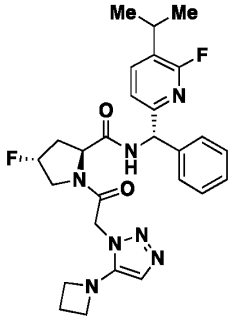
786		(2S,4R)-1-[2-(3-ethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide	539.2	540.2
787		(2S,4R)-1-{2-[4-(azetidin-1-yl)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide	523.3	524.3
788		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-{2-[4-(trifluoromethyl)-1H-pyrazol-1-yl]acetyl}pyrrolidine-2-carboxamide	535.2	536.2
789		(2S,4R)-1-{2-[3-(difluoromethyl)-1H-pyrazol-1-yl]acetyl}-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide	517.2	518.2

790		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-{2-[3-(trifluoromethyl)-1H-pyrazol-1-yl]acetyl}pyrrolidine-2-carboxamide	535.2	559.1 [M + Na]
791		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(6-oxo-1,6-dihydropyridin-3-yl)acetyl]pyrrolidine-2-carboxamide	494.2	495.2
792		(2S,4R)-1-[2-(1-ethyl-6-oxo-1,6-dihydropyridin-3-yl)acetyl]-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide	522.2	523.4
793		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(2-oxo-1,2-dihydropyridin-3-yl)acetyl]pyrrolidine-2-carboxamide	494.2	495.3

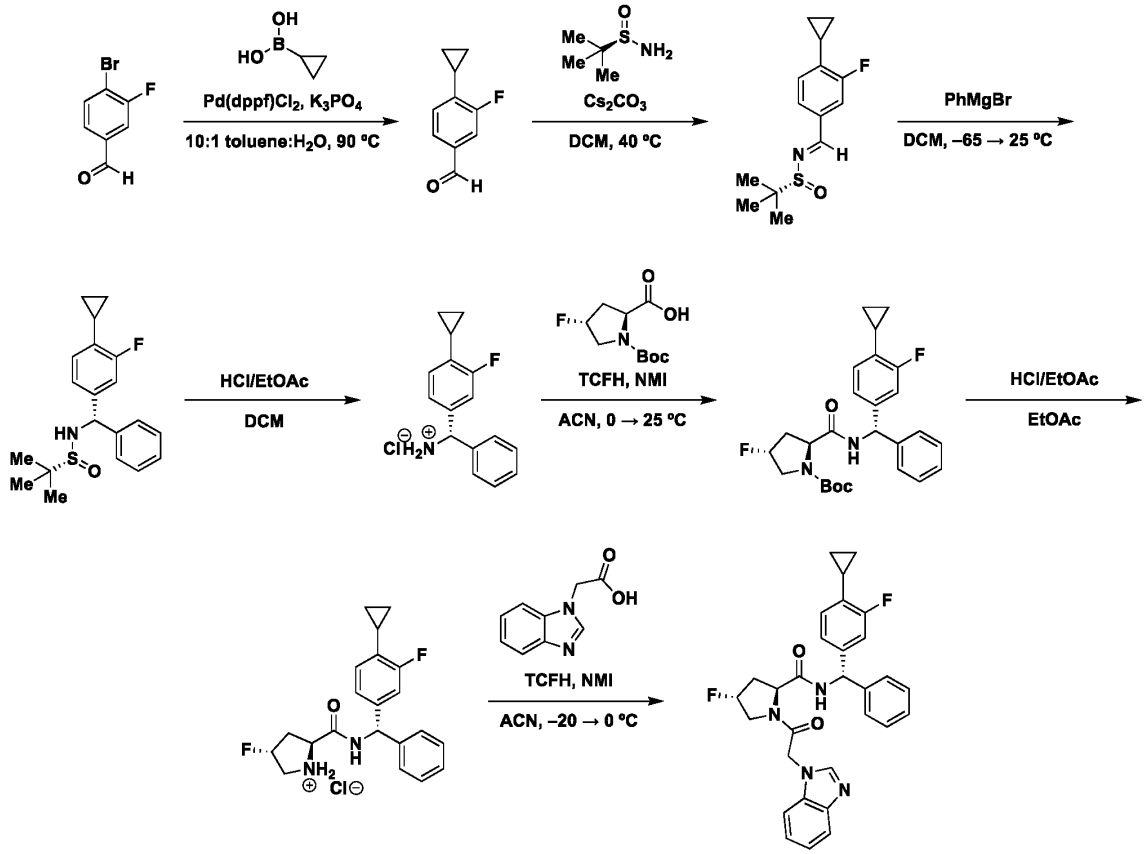
794		(2S,4R)-1-[2-(3-ethyl-5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide	553.3	554.2
795		(2S,4R)-1-[2-(1-ethyl-2-oxo-1,2-dihydropyridin-3-yl)acetyl]-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide	522.2	523.3
796		(2S,4R)-1-[2-(1-ethyl-5-methyl-6-oxo-1,6-dihydropyridin-3-yl)acetyl]-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide	536.3	537.2
797		(2S,4R)-1-[2-(4-ethyl-5-oxo-4,5-dihydropyrazin-2-yl)acetyl]-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide	523.2	524.3

798		(2S,4R)-1-[2-(6-ethoxy-5-methylpyridin-3-yl)acetyl]-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide	536.3	537.2
799		(2S,4R)-1-[2-(1-ethyl-5-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetyl]-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide	536.3	537.2
800		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(5-methoxy-1-methyl-1H-1,2,4-triazol-3-yl)acetyl]pyrrolidine-2-carboxamide	512.2	513.4
801		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-{2-[4-(trifluoromethyl)-1,3-oxazol-2-yl]acetyl}pyrrolidine-2-carboxamide	536.2	537.3

802		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl][phenyl)methyl]-1-[2-(5-oxo-4,5-dihydropyrazin-2-yl)acetyl]pyrrolidine-2-carboxamide	495.2	496.3
803		(2S,4R)-1-{2-[5-(difluoromethyl)-3-methyl-1H-pyrazol-1-yl]acetyl}-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide	531.2	532.3
804		(2S,4R)-1-{2-[3-(difluoromethyl)-5-methyl-1H-pyrazol-1-yl]acetyl}-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide	531.2	532.3
805		(2S,4R)-1-{2-[5-(diethylamino)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide	539.3	540.2

806		(2S,4R)-1-[2-(4-ethyl-3-oxo-3,4-dihydropyrazin-2-yl)acetyl]-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide	523.2	524.3
807		(2S,4R)-1-{2-[5-(3,3-difluoroazetidin-1-yl)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide	559.2	560.3
808		(2S,4R)-1-{2-[5-(azetidin-1-yl)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide	523.2	524.1

Example S-6: Synthesis of (2*S*,4*R*)-1-(2-(1*H*-benzo[*d*]imidazol-1-yl)acetyl)-*N*-((*S*)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl)-4-fluoropyrrolidine-2-carboxamide (Compound 417)



[0638] Step a: To a solution of 4-bromo-3-fluorobenzaldehyde (150 g, 738 mmol, 1.00 eq) in toluene (2.00 L) and H_2O (240 mL) under nitrogen atmosphere was added cyclopropylboronic acid (82.5 g, 960 mmol, 1.30 eq), K_3PO_4 (360 g, 1.70 mol, 2.30 eq) and $Pd(dppf)Cl_2$ (27.0 g, 36.9 mmol, 0.05 eq). The resulting mixture was degassed and purged with N_2, warmed to 90 °C, and stirred for 16 h. The reaction mixture was then filtered through Celite, and the solvent was removed under reduced pressure. The resulting crude material was purified by column chromatography to give 4-cyclopropyl-3-fluorobenzaldehyde, which was carried forward to the next step without further characterization.

[0639] Step b: To a solution of 4-cyclopropyl-3-fluorobenzaldehyde (146 g, 889 mmol, 1.00 eq) in DCM (1320 mL) under nitrogen atmosphere was added (*R*)-2-methylpropane-2-sulfinamide (118 g, 978 mmol, 1.10 eq), and Cs_2CO_3 (318 g, 978 mmol, 1.10 eq). The resulting mixture was warmed to 40 °C and stirred for 16 h. The reaction mixture was then

filtered, and the filtrate was concentrated under reduced pressure. The resulting crude material was purified by column chromatography to give (*R*,*E*)-*N*-(4-cyclopropyl-3-fluorobenzylidene)-2-methylpropane-2-sulfinamide, which was carried forward to the next step without further characterization.

[0640] Step c: To a solution of (*R*,*E*)-*N*-(4-cyclopropyl-3-fluorobenzylidene)-2-methylpropane-2-sulfinamide (47.7 g, 178 mmol, 1.00 eq) in DCM (477 mL) at –65 °C under N_2 was added phenylmagnesium bromide (3 M in Et_2O, 77.3 mL, 1.30 eq) in a dropwise manner. The resulting mixture was stirred while warming to 25 °C over 4 h. The reaction mixture was then quenched with saturated aqueous NH_4Cl (500 mL). The resulting biphasic mixture was extracted with EtOAc (3 x 500 mL). The organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude material was purified by column chromatography to give (*R*)-*N*-((*S*)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl)-2-methylpropane-2-sulfinamide, which was carried forward to the next step without further characterization.

[0641] Step d: To a solution of (*R*)-*N*-((*S*)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl)-2-methylpropane-2-sulfinamide (81.6 g, 236 mmol, 1.00 eq) in DCM (1632 mL) at 25 °C was added HCl/EtOAc (4 M, 147 mL, 2.50 eq) in one portion. The resulting mixture was stirred for 2 h. The mixture was then filtered, and the solid obtained was set aside. The filtrate was then concentrated under reduced pressure, and the resulting material was suspended in MTBE (800 mL) and filtered. The solids obtained from both filtrations were combined and dissolved in aqueous Na_2CO_3 (0.5 N, 1.00 L) and DCM (1.00 L). The isolated organic layer was washed with water (500 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give (*S*)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methanaminium chloride, which was carried forward to the next step without further characterization.

[0642] Step e: To a mixture of (*S*)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methanaminium chloride (12.5 g, 51.8 mmol, 1 eq) and (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (13.2 g, 56.9 mmol, 1.1 eq) in MeCN (125 mL) at 0 °C was added 1-methylimidazole (NMI, 12.7 g, 155 mmol, 12.3 mL, 3 eq) and chloro-*N*,*N*,*N*',*N*'-tetramethylformamidinium hexafluorophosphate (TCFH, 17.4 g, 62.1 mmol,

1.2 eq). The resulting mixture was warmed to 25 °C and stirred for 2 h under N_2 atmosphere. The reaction mixture was then quenched with H_2O (50 mL) and extracted with EtOAc (200 mL). The combined organic extracts were washed with brine (200 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude residue was purified by column chromatography to give *tert*-butyl (2*S*,4*R*)-2-(((*S*)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{26}H_{30}F_2N_2O_3$: 457.2; found 457.1.

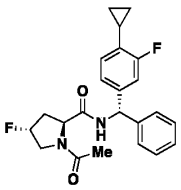
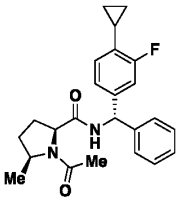
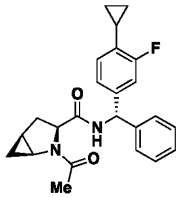
[0643] Step f: To a solution of *tert*-butyl (2*S*,4*R*)-2-(((*S*)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate (15.0 g, 32.8 mmol, 1 eq) in EtOAc (50 mL) was added HCl/EtOAc (4 M, 50 mL, 6.09 eq), and the resulting mixture was stirred at 25 °C for 2 h under N_2 atmosphere. MTBE (50 mL) was then added to the reaction mixture, which was then stirred for 10 min. The reaction mixture was then filtered and the filter cake was dried under reduced pressure to give (2*S*,4*R*)-*N*-((*S*)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl)-4-fluoropyrrolidine-2-carboxamide hydrochloride. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{21}H_{22}F_2N_2O$: 357.2; found 357.2.

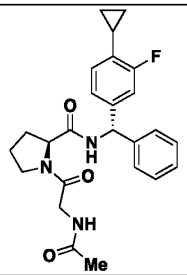
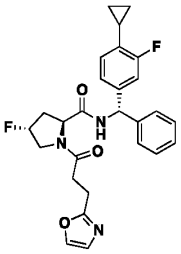
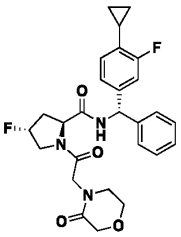
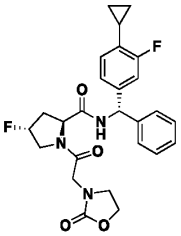
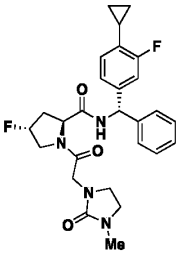
[0644] Step g: To a mixture of (2*S*,4*R*)-*N*-((*S*)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl)-4-fluoropyrrolidine-2-carboxamide hydrochloride (3.50 g, 8.91 mmol, 1 eq) and 2-(1*H*-benzo[*d*]imidazol-1-yl)acetic acid (Intermediate A-4, 2.46 g, 11.6 mmol, 1.3 eq) in MeCN (35 mL) at –20 °C was added 1-methylimidazole (NMI, 5.85 g, 71.3 mmol, 8 eq), and chloro-*N*,*N*,*N*′,*N*′-tetramethylformamidinium hexafluorophosphate (TCFH, 3.25 g, 11.6 mmol, 1.3 eq). The resulting mixture was then warmed to 0 °C and stirred for 2 h. The reaction mixture was then quenched by addition of H_2O (100 mL), and the resulting biphasic mixture was extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography followed by prep-HPLC to give (2*S*,4*R*)-1-(2-(1*H*-benzo[*d*]imidazol-1-yl)acetyl)-*N*-((*S*)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl)-4-fluoropyrrolidine-2-carboxamide (5.16 g). ^{1}H NMR (6.4:1 rotamer ratio, asterisk denotes distinct minor rotamer peaks, obscured peaks not reported, 400 MHz, methanol-d_4) δ 8.09 (s, 1H), 7.91* (s, 1H), 7.73 – 7.61 (m, 1H), 7.51 – 7.42 (m, 1H), 7.37 – 7.05 (m, 7H), 7.03 – 6.83 (m, 3H), 6.27* (s, 1H), 6.06 (s, 1H), 5.52 – 5.03 (m, 3H), 4.74 – 4.65

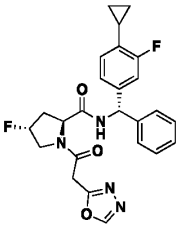
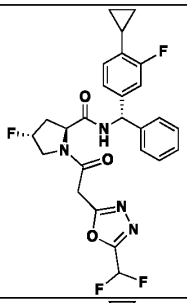
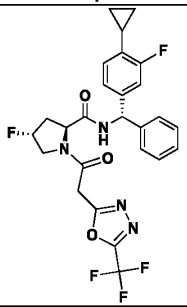
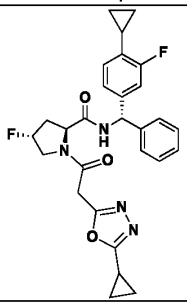
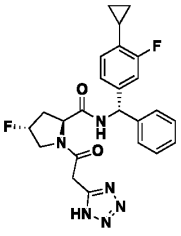
(m, 1H), 4.62 – 4.48* (m, 1H), 4.23 – 3.82 (m, 2H), 3.61* (ddd, *J* = 37.1, 13.8, 3.2 Hz, 0H), 2.97 – 2.81* (m, 1H), 2.67 – 2.49 (m, 1H), 2.46 – 2.26* (m, 1H), 2.25 – 1.96 (m, 2H), 0.99 – 0.92 (m, 2H), 0.72 – 0.65 (m, 2H). LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{30}H_{28}F_2N_4O_2$: 515.2; found 515.4.

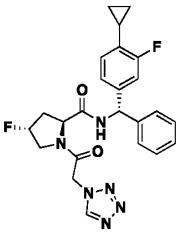
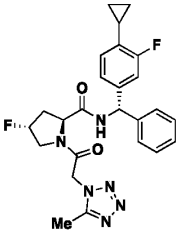
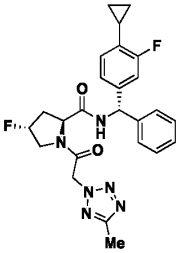
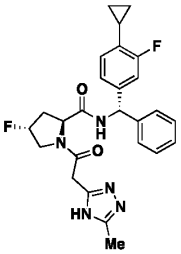
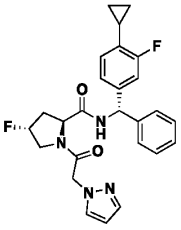
[0645] The following compounds in Table T-6 were synthesized using procedures similar to Compound 417 using the appropriate starting materials.

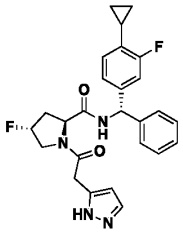
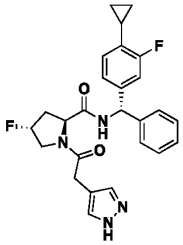
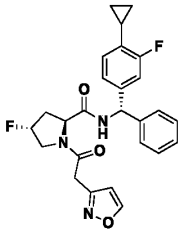
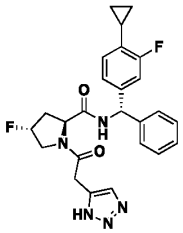
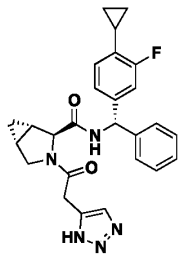
Table T-6

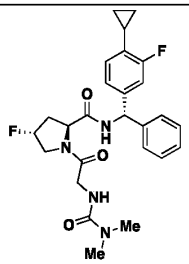
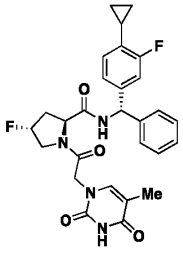
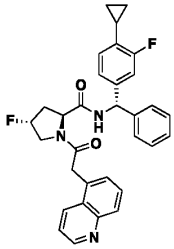
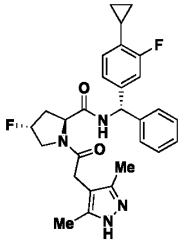
Compound No.	Structure	IUPAC	Exact mass (g/mol)	LCMS, Found $[M + H]^+$
418		(2S,4R)-1-acetyl-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide	398.2	399.2
419		(2S,5S)-1-acetyl-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-5-methylpyrrolidine-2-carboxamide	394.2	395.2
420		(1S,3S,5S)-2-acetyl-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-2-azabicyclo[3.1.0]hexane-3-carboxamide	392.2	393.1

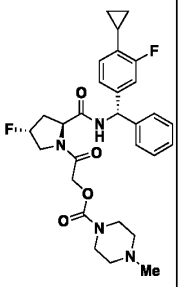
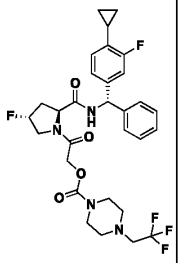
421		(2S)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-1-(2-acetamidoacetyl)pyrrolidine-2-carboxamide	437.2	438.1
422		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[3-(1,3-oxazol-2-yl)propanoyl]pyrrolidine-2-carboxamide	479.2	480.1
423		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(3-oxomorpholin-4-yl)acetyl]pyrrolidine-2-carboxamide	497.2	498.1
424		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(2-oxo-1,3-oxazolidin-3-yl)acetyl]pyrrolidine-2-carboxamide	483.2	484.1
425		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(3-methyl-2-oxoimidazolidin-1-yl)acetyl]pyrrolidine-2-carboxamide	496.2	497.1

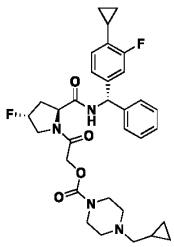
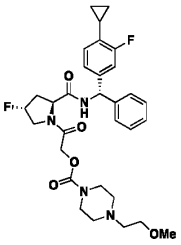
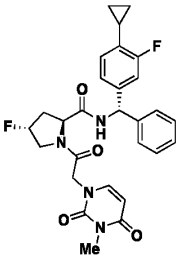
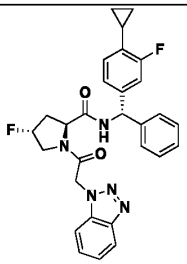
426		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1,3,4-oxadiazol-2-yl)acetyl]pyrrolidine-2-carboxamide	466.2	467.1
427		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-1-{2-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide	516.2	517.1
428		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-{2-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]acetyl}pyrrolidine-2-carboxamide	534.2	535.2
429		(2S,4R)-1-[2-(5-cyclopropyl-1,3,4-oxadiazol-2-yl)acetyl]-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide	506.2	507.1
430		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3,4-tetrazol-5-yl)acetyl]pyrrolidine-2-carboxamide	466.2	467.1

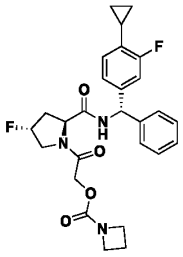
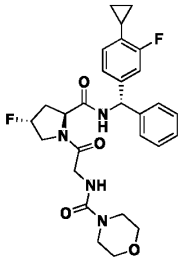
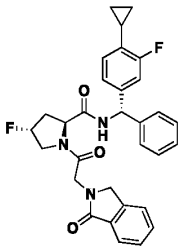
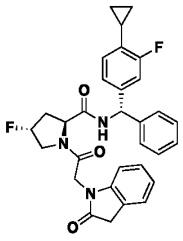
431		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3,4-tetrazol-1-yl)acetyl]pyrrolidine-2-carboxamide	466.2	467.2
432		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)acetyl]pyrrolidine-2-carboxamide	480.2	481.2
433		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(5-methyl-2H-1,2,3,4-tetrazol-2-yl)acetyl]pyrrolidine-2-carboxamide	480.2	481.1
434		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(5-methyl-4H-1,2,4-triazol-3-yl)acetyl]pyrrolidine-2-carboxamide	479.2	480.1
435		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-pyrazol-1-yl)acetyl]pyrrolidine-2-carboxamide	464.2	465.1

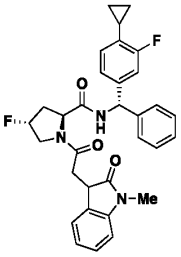
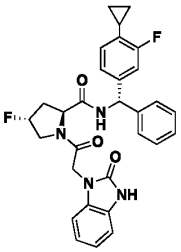
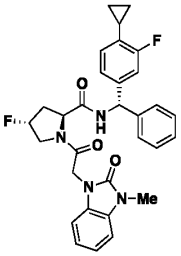
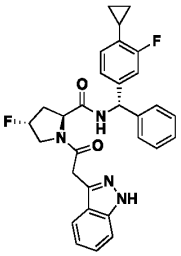
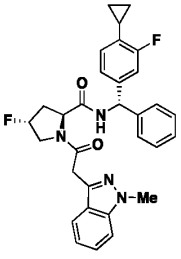
436		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-pyrazol-5-yl)acetyl]pyrrolidine-2-carboxamide	464.2	465.3
437		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-pyrazol-4-yl)acetyl]pyrrolidine-2-carboxamide	464.2	465.1
438		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1,2-oxazol-3-yl)acetyl]pyrrolidine-2-carboxamide	465.2	466.1
439		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide	465.2	466.1
440		(1S,2S,5R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-3-[2-(1H-1,2,3-triazol-5-yl)acetyl]-3-azabicyclo[3.1.0]hexane-2-carboxamide	459.2	460.1

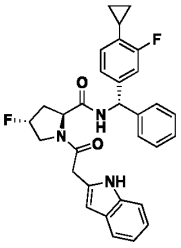
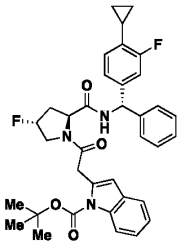
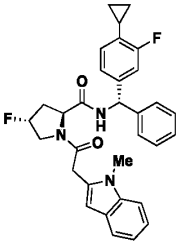
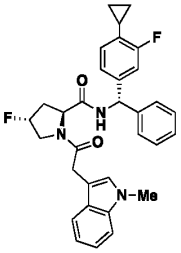
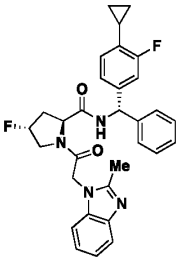
441		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-1-{2-[(dimethylcarbamoyl)amino]acetyl}-4-fluoropyrrolidine-2-carboxamide	484.2	485.1
442		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]pyrrolidine-2-carboxamide	522.2	523.2
443		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(quinolin-5-yl)acetyl]pyrrolidine-2-carboxamide	525.2	526.2
444		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-1-[2-(3,5-dimethyl-1H-pyrazol-4-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide	492.2	493.2

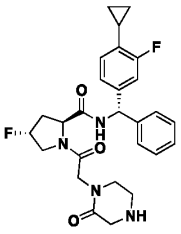
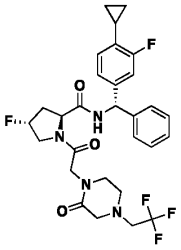
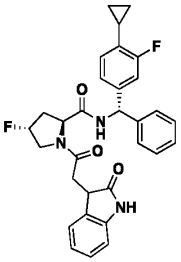
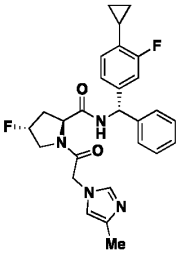
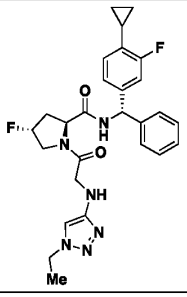
445		2-[(2S,4R)-2-{[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]carbamoyl}-4-fluoropyrrolidin-1-yl]-2-oxoethyl 4-methylpiperazine-1-carboxylate	540.3	541.3
446		2-[(2S,4R)-2-{[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]carbamoyl}-4-fluoropyrrolidin-1-yl]-2-oxoethyl 4-(2,2,2-trifluoroethyl)piperazine-1-carboxylate	608.2	609.2

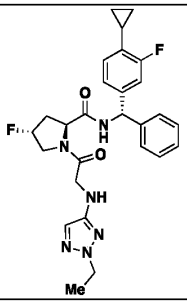
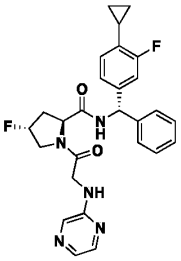
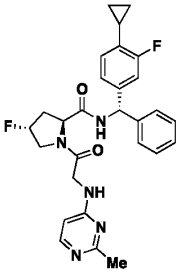
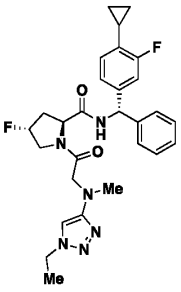
447		2-[(2S,4R)-2-{[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]carbamoyl}-4-fluoropyrrolidin-1-yl]-2-oxoethyl 4-(cyclopropylmethyl)piperazine-1-carboxylate	580.3	581.3
448		2-[(2S,4R)-2-{[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]carbamoyl}-4-fluoropyrrolidin-1-yl]-2-oxoethyl 4-(2-methoxyethyl)piperazine-1-carboxylate	584.3	585.3
449		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]pyrrolidine-2-carboxamide	522.2	523.2
450		(2S,4R)-1-[2-(1H-1,2,3-benzotriazol-1-yl)acetyl]-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide	515.2	516.3

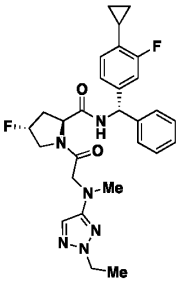
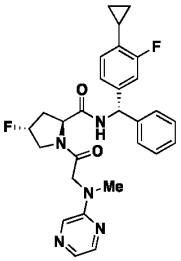
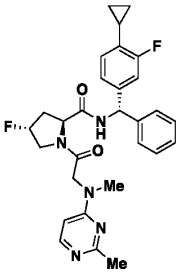
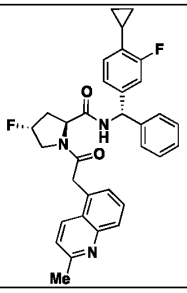
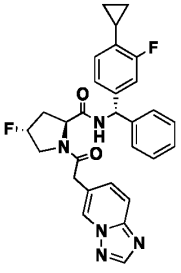
451		2-[(2S,4R)-2-{[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]carbamoyl}-4-fluoropyrrolidin-1-yl]-2-oxoethyl azetidine-1-carboxylate	497.2	498.3
452		N-{2-[(2S,4R)-2-{[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]carbamoyl}-4-fluoropyrrolidin-1-yl]-2-oxoethyl}morpholine-4-carboxamide	526.2	527.3
453		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1-oxo-2,3-dihydro-1H-isoindol-2-yl)acetyl]pyrrolidine-2-carboxamide	529.2	530.2
454		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(2-oxo-2,3-dihydro-1H-indol-1-yl)acetyl]pyrrolidine-2-carboxamide	529.2	530.1

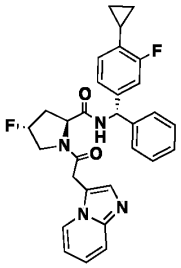
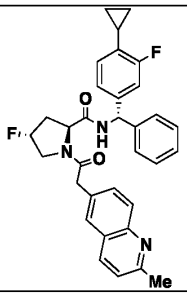
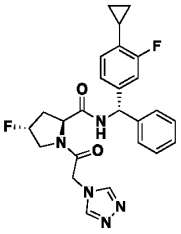
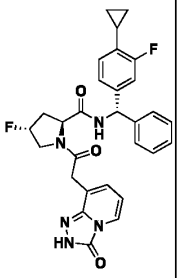
455		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl)acetyl]pyrrolidine-2-carboxamide	543.2	544.3
456		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)acetyl]pyrrolidine-2-carboxamide	530.2	531.2
457		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)acetyl]pyrrolidine-2-carboxamide	544.2	545.2
458		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-indazol-3-yl)acetyl]pyrrolidine-2-carboxamide	514.2	515.1
459		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1-methyl-1H-indazol-3-yl)acetyl]pyrrolidine-2-carboxamide	528.2	529.2

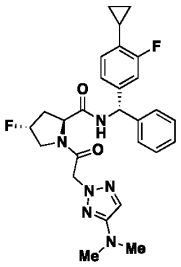
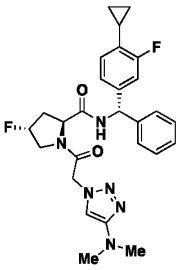
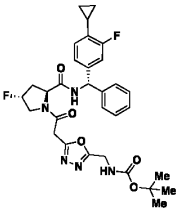
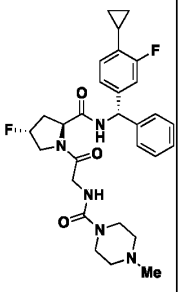
460		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-indol-2-yl)acetyl]pyrrolidine-2-carboxamide	513.2	514.3
461		tert-butyl 2-{2-[(2S,4R)-2-{[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]carbamoyl}-4-fluoropyrrolidin-1-yl]-2-oxoethyl}-1H-indole-1-carboxylate	613.3	514.3 [M – Boc + H]$^+$
462		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1-methyl-1H-indol-2-yl)acetyl]pyrrolidine-2-carboxamide	527.2	528.3
463		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1-methyl-1H-indol-3-yl)acetyl]pyrrolidine-2-carboxamide	527.2	528.2
464		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(2-methyl-1H-1,3-benzodiazol-1-yl)acetyl]pyrrolidine-2-carboxamide	528.2	529.3

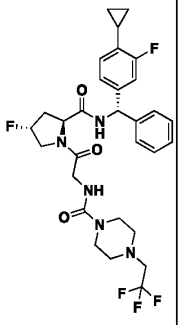
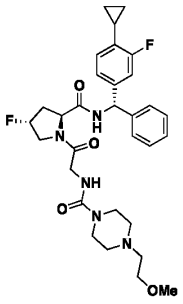
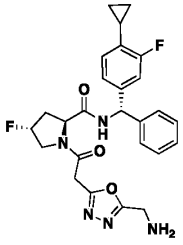
465		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(2-oxopiperazin-1-yl)acetyl]pyrrolidine-2-carboxamide	496.2	497.2
466		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-{2-[2-oxo-4-(2,2,2-trifluoroethyl)piperazin-1-yl]acetyl}pyrrolidine-2-carboxamide	578.2	579.2
467		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(2-oxo-2,3-dihydro-1H-indol-3-yl)acetyl]pyrrolidine-2-carboxamide	529.2	530.2
468		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(4-methyl-1H-imidazol-1-yl)acetyl]pyrrolidine-2-carboxamide	478.2	479.2
469		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-1-{2-[(1-ethyl-1H-1,2,3-triazol-4-yl)amino]acetyl}-4-fluoropyrrolidine-2-carboxamide	508.2	509.3

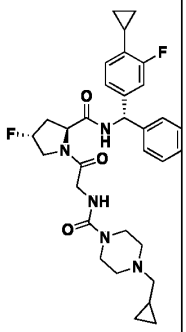
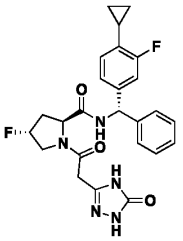
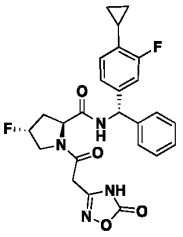
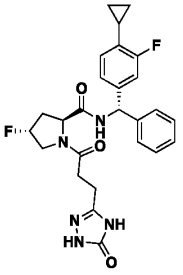
470		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-1-{2-[(2-ethyl-2H-1,2,3-triazol-4-yl)amino]acetyl}-4-fluoropyrrolidine-2-carboxamide	508.2	509.3
471		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-{2-[(pyrazin-2-yl)amino]acetyl}pyrrolidine-2-carboxamide	491.2	492.2
472		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-{2-[(2-methylpyrimidin-4-yl)amino]acetyl}pyrrolidine-2-carboxamide	505.2	506.3
473		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-1-{2-[(1-ethyl-1H-1,2,3-triazol-4-yl)(methyl)amino]acetyl}-4-fluoropyrrolidine-2-carboxamide	522.3	523.2

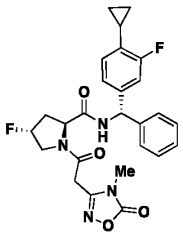
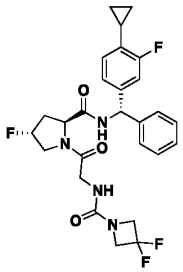
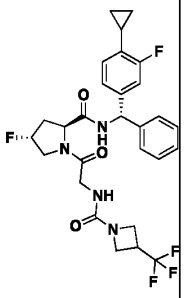
474		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-1-{2-[(2-ethyl-2H-1,2,3-triazol-4-yl)(methyl)amino]acetyl}-4-fluoropyrrolidine-2-carboxamide	522.3	523.2
475		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-{2-[methyl(pyrazin-2-yl)amino]acetyl}pyrrolidine-2-carboxamide	505.2	506.1
476		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-{2-[methyl(2-methylpyrimidin-4-yl)amino]acetyl}pyrrolidine-2-carboxamide	519.2	520.3
477		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(2-methylquinolin-5-yl)acetyl]pyrrolidine-2-carboxamide	539.2	540.2
478		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-(2-{[1,2,4]triazolo[1,5-a]pyridin-6-yl}acetyl)pyrrolidine-2-carboxamide	515.2	516.3

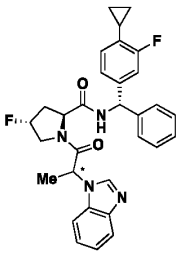
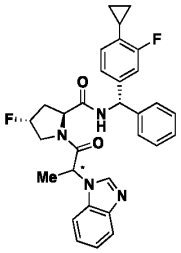
479		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-(2-{imidazo[1,2-a]pyridin-3-yl}acetyl)pyrrolidine-2-carboxamide	514.2	515.3
480		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(2-methylquinolin-6-yl)acetyl]pyrrolidine-2-carboxamide	539.2	540.2
481		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(4H-1,2,4-triazol-4-yl)acetyl]pyrrolidine-2-carboxamide	465.2	466.3
482		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-(2-{3-oxo-2H,3H-[1,2,4]triazolo[4,3-a]pyridin-8-yl}acetyl)pyrrolidine-2-carboxamide	531.2	532.2

483		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-1-{2-[4-(dimethylamino)-2H-1,2,3-triazol-2-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide	508.2	509.2
484		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-1-{2-[4-(dimethylamino)-1H-1,2,3-triazol-1-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide	508.2	509.2
485		tert-butyl N-[(5-{2-[(2S,4R)-2-{[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]carbamoyl}-4-fluoropyrrolidin-1-yl]-2-oxoethyl}-1,3,4-oxadiazol-2-yl)methyl]carbamate	595.3	596.3
486		N-{2-[(2S,4R)-2-{[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]carbamoyl}-4-fluoropyrrolidin-1-yl]-2-oxoethyl}-4-methylpiperazine-1-carboxamide	539.3	540.2

487		N-{2-[(2S,4R)-2-{[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]carbamoyl}-4-fluoropyrrolidin-1-yl]-2-oxoethyl}-4-(2,2,2-trifluoroethyl)piperazine-1-carboxamide	607.3	608.2
488		N-{2-[(2S,4R)-2-{[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]carbamoyl}-4-fluoropyrrolidin-1-yl]-2-oxoethyl}-4-(2-methoxyethyl)piperazine-1-carboxamide	583.3	584.2
489		(2S,4R)-1-{2-[5-(aminomethyl)-1,3,4-oxadiazol-2-yl]acetyl}-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide	495.2	496.1

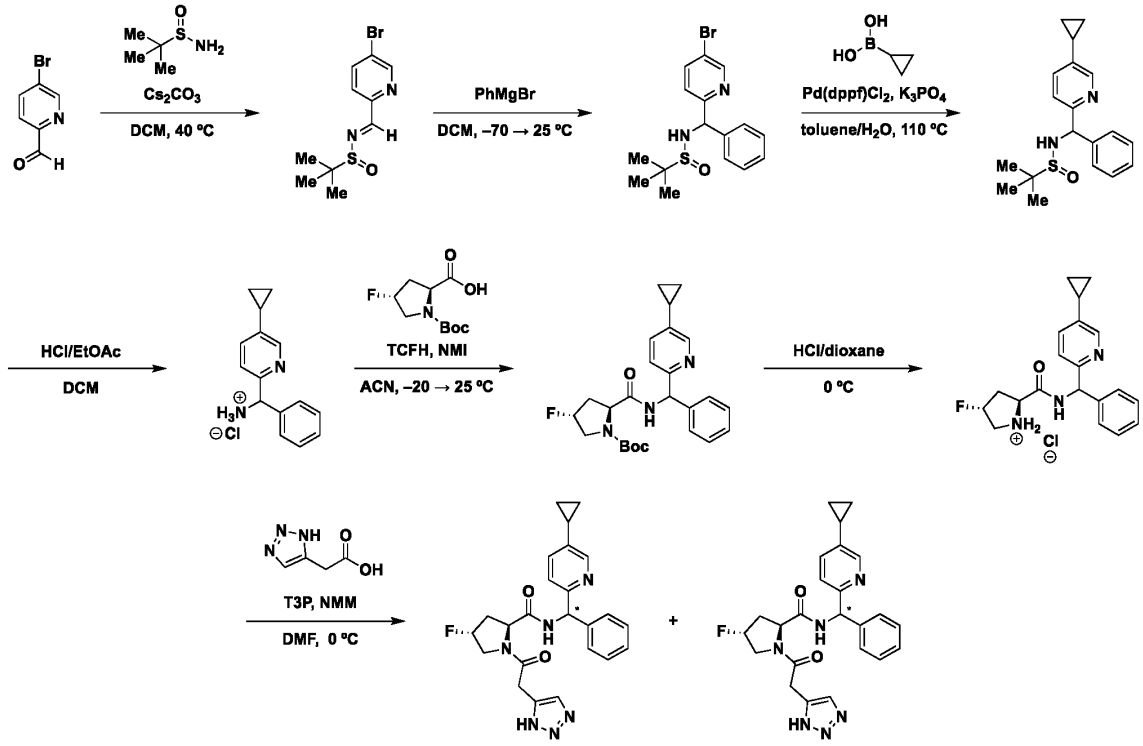
490		N-{2-[(2S,4R)-2-{[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]carbamoyl}-4-fluoropyrrolidin-1-yl]-2-oxoethyl}-4-(cyclopropylmethyl)piperazine-1-carboxamide	579.3	580.2
491		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)acetyl]pyrrolidine-2-carboxamide	481.2	482.3
492		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)acetyl]pyrrolidine-2-carboxamide	482.2	483.1
493		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[3-(5-oxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)propanoyl]pyrrolidine-2-carboxamide	495.2	496.2

494		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(4-methyl-5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)acetyl]pyrrolidine-2-carboxamide	496.2	497.1
495		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-1-{2-[(3,3-difluoroazetidine-1-carbonyl)amino]acetyl}-4-fluoropyrrolidine-2-carboxamide	532.2	533.1
496		(2S,4R)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-(2-{[3-(trifluoromethyl)azetidine-1-carbonyl]amino}acetyl)pyrrolidine-2-carboxamide	564.2	565.2

809		(2S,4R)-1-[(2S) or (2R)-2-(1H-1,3-benzodiazol-1-yl)propanoyl]-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide (column: DAICEL CHIRALPAK AD, second-eluting isomer)	528.2	529.2
810		(2S,4R)-1-[(2R) or (2S)-2-(1H-1,3-benzodiazol-1-yl)propanoyl]-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide (column: DAICEL CHIRALPAK AD, first-eluting isomer)	528.2	529.3

Example S-7: Synthesis of (2*S*,4*R*)-1-(2-(1*H*-1,2,3-triazol-5-yl)acetyl)-*N*-((*S*) or (*R*)-(5-cyclopropylpyridin-2-yl)(phenyl)methyl)-4-fluoropyrrolidine-2-carboxamide and (2*S*,4*R*)-1-(2-(1*H*-1,2,3-triazol-5-yl)acetyl)-*N*-((*R*) or (*S*)-(5-cyclopropylpyridin-2-yl)(phenyl)methyl)-4-fluoropyrrolidine-2-carboxamide

(Compound 497 & Compound 498)



[0646] Step a: To a solution of 5-bromopicolinaldehyde (5.00 g 26.9 mmol, 1 eq) in DCM (50 mL) at 25 °C was added 2-methylpropane-2-sulfinamide (3.58 g 29.6 mmol, 1.1 eq) and Cs_2CO_3 (9.63 g 29.6 mmol, 1.1 eq). The system was degassed and charged with nitrogen, and the reaction mixture was warmed to 40 °C and stirred for 2 h under N_2 atmosphere. After cooling, the reaction solution was filtered and concentrated under reduced pressure. The resulting crude residue was purified by column chromatography to give (*E*)-*N*-((5-bromopyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{10}H_{13}BrN_2OS$: 289.0; found 289.1.

[0647] Step b: A solution of (*E*)-*N*-((5-bromopyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide (7.5 g, 25.9 mmol, 1 eq) in DCM (80 mL) was degassed and charged with nitrogen three times and cooled to –70 °C. To the cooled solution was added PhMgBr (3 M in Et_2O, 10.4 mL, 1.2 eq) in a dropwise manner under N_2 atmosphere. The reaction mixture was then stirred at –70 °C for 2 h, warmed to room temperature, and stirred for another 1 h under N_2 atmosphere. The reaction mixture was then quenched with water (100 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with

brine (3 x 50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude residue was purified by column chromatography to give *N*-((5-bromopyridin-2-yl)(phenyl)methyl)-2-methylpropane-2-sulfinamide. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{16}H_{19}BrN_2OS$: 367.0; found 367.1.

[0648] Step c: To a solution of *N*-((5-bromopyridin-2-yl)(phenyl)methyl)-2-methylpropane-2-sulfinamide (9.00 g, 24.5 mmol, 1 eq) in toluene (200 mL) and H_2O (20 mL) at 25 °C was added cyclopropylboronic acid (16.8 g, 196 mmol, 8 eq), K_3PO_4 (15.6 g, 73.5 mmol, 3 eq) and $Pd(dppf)Cl_2.CH_2Cl_2$ (2.00 g, 2.45 mmol, 0.1 eq). The reaction mixture was degassed and purged with nitrogen three times, warmed to 110 °C, and stirred for 16 h under N_2 atmosphere. After cooling, the reaction mixture was concentrated under reduced pressure. To the resulting residue was added water (150 mL), and the biphasic mixture was extracted with ethyl acetate (3 x 150 mL). The combined organic extracts were washed with brine (3 x 100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography to give *N*-((5-cyclopropylpyridin-2-yl)(phenyl)methyl)-2-methylpropane-2-sulfinamide. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{19}H_{24}N_2OS$: 329.2; found 329.2.

[0649] Step d: To a solution of *N*-((5-cyclopropylpyridin-2-yl)(phenyl)methyl)-2-methylpropane-2-sulfinamide (5 g, 15.2 mmol, 1 eq) in ethyl acetate (10 mL) at 0 °C under N_2 atmosphere was added HCl in ethyl acetate (4 M, 20 mL). The reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was then filtered, and the solid obtained was dried under reduced pressure to give (5-cyclopropylpyridin-2-yl)(phenyl)methanamine hydrochloride, which was used without further purification. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{15}H_{16}N_2$: 225.1; found 225.2.

[0650] Step e: To a solution of (5-cyclopropylpyridin-2-yl)(phenyl)methanamine hydrochloride (3.50 g, 13.4 mmol, 1 eq) in CH_3CN (30 mL) at –20 °C under N_2 atmosphere was added 1-methyl-1H-imidazole (NMI, 4.69 g, 57.1 mmol, 3 eq) and (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (3.76 g, 16.1 mmol, 1.2 eq). After stirring for 10 min, *N,N,N',N'*- tetramethylchloroformamidinium hexafluorophosphate (4.52 g, 16.1 mmol, 1.2 eq) was added in portions. The reaction mixture was then stirred at –20 °C for 2 h under N_2 atmosphere. The reaction mixture was then quenched with H_2O (30 mL) and extracted

with ethyl acetate (3 x 30 mL). The combined organic extracts were washed with brine (3 x 30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude residue was purified by column chromatography to give *tert*-butyl (2*S*,4*R*)-2-(((5-cyclopropylpyridin-2-yl)(phenyl)methyl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{25}H_{30}FN_3O_3$: 440.2; found 440.3.

[0651] Step f: To a solution of *tert*-butyl (2*S*,4*R*)-2-(((5-cyclopropylpyridin-2-yl)(phenyl)methyl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate (7 g, crude) in 1,4-dioxane (5 mL) at 0 °C was added HCl/dioxane (4 M, 50 mL). The resulting mixture was stirred at 0 °C for 4 h. The reaction was then concentrated under reduced pressure. The resulting solid was washed with MTBE (3 x 10 mL) and dried under reduced pressure to give (2*S*,4*R*)-*N*-((5-cyclopropylpyridin-2-yl)(phenyl)methyl)-4-fluoropyrrolidine-2-carboxamide hydrochloride (6.5 g). LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{20}H_{22}FN_3O$: 340.2; found 340.2.

[0652] Step g: To a solution of (2*S*,4*R*)-*N*-((5-cyclopropylpyridin-2-yl)(phenyl)methyl)-4-fluoropyrrolidine-2-carboxamide hydrochloride (6.50 g, 17.3 mmol, 1 eq) in DMF (50 mL) at 0 °C was added 4-methylmorpholine (NMM, 7.00 g, 69.2 mmol, 4 eq), 2-(1*H*-1,2,3-triazol-5-yl)acetic acid (2.63 g, 20.8 mmol, 1.2 eq), and T3P (27.5 g, 43.2 mmol, 50% in ethyl acetate, 2.5 eq). The reaction mixture was then stirred at 0 °C for 2 h under N_2 atmosphere. The reaction mixture was then quenched with H_2O (60 mL) at 0 °C and extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with brine (70 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography and chiral SFC (column: REGIS (s,s) WHELK-O1 (250mm x 50mm,10 μm); mobile phase: [Phase A: CO_2, Phase B: 0.1%$NH_{3(aq)}$ in EtOH]; isocratic at 40% B, 3.4 min) to give (2*S*,4*R*)-1-(2-(1*H*-1,2,3-triazol-5-yl)acetyl)-*N*-((*S*) or (*R*)-(5-cyclopropylpyridin-2-yl)(phenyl)methyl)-4-fluoropyrrolidine-2-carboxamide (Compound 497; first-eluting isomer) and (2*S*,4*R*)-1-(2-(1*H*-1,2,3-triazol-5-yl)acetyl)-*N*-((*R*) or (*S*)-(5-cyclopropylpyridin-2-yl)(phenyl)methyl)-4-fluoropyrrolidine-2-carboxamide (Compound 498; second-eluting isomer).

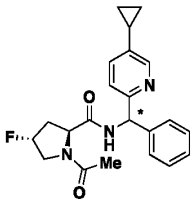
[0653] First-eluting isomer (Compound 497): ^1H NMR (4.4:1 rotamer ratio, asterisk denotes distinct minor rotamer peaks, obscured peaks not reported, 400 MHz, methanol-d_4) δ 8.30 – 8.21 (m, 1H), 7.55 – 7.39 (m, 2H), 7.38 – 7.14 (m, 5H), 6.18* (s, 1H), 6.09 (s, 1H), 5.44 –

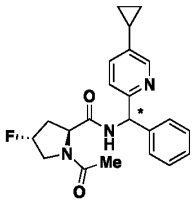
5.18 (m, 1H), 4.70 (t, 1H), 4.15 – 4.02 (m, 1H), 3.97 – 3.75 (m, 3H), 3.70 – 3.50* (m, 2H), 2.85 – 2.70* (m, 1H), 2.65 – 2.50 (m, 1H), 2.37 – 2.06 (m, 1H), 2.00 – 1.84 (m, 1H), 1.08 – 0.95 (m, 2H), 0.75 – 0.62 (m, 2H). LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{26}H_{25}FN_6O_2$: 449.2; found 449.2.

[0654] Second-eluting isomer (Compound 498): ^{1}H NMR (4.4:1 rotamer ratio, asterisk denotes distinct minor rotamer peaks, obscured peaks not reported, 400 MHz, methanol-d_4) δ 8.30 – 8.21 (m, 1H), 7.53 – 7.39 (m, 2H), 7.38 – 7.17 (m, 6H), 6.18* (s, 1H), 6.09 (s, 1H), 5.44 – 5.18 (m, 1H), 4.70 (t, J = 9.3, 7.7 Hz, 1H), 4.15 – 4.02 (m, 1H), 3.98 – 3.75 (m, 3H), 3.68 – 3.51* (m, 2H), 2.85 – 2.69* (m, 1H), 2.65 – 2.50 (m, 1H), 2.38 – 2.05 (m, 1H), 2.00 – 1.83 (m, 1H), 1.08 – 0.95 (m, 2H), 0.79 – 0.60 (m, 2H). LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{26}H_{25}FN_6O_2$: 449.2; found 449.1.

[0655] The following compounds in Table T-7 were synthesized using procedures similar to Compound 497 and Compound 498 using the appropriate starting materials.

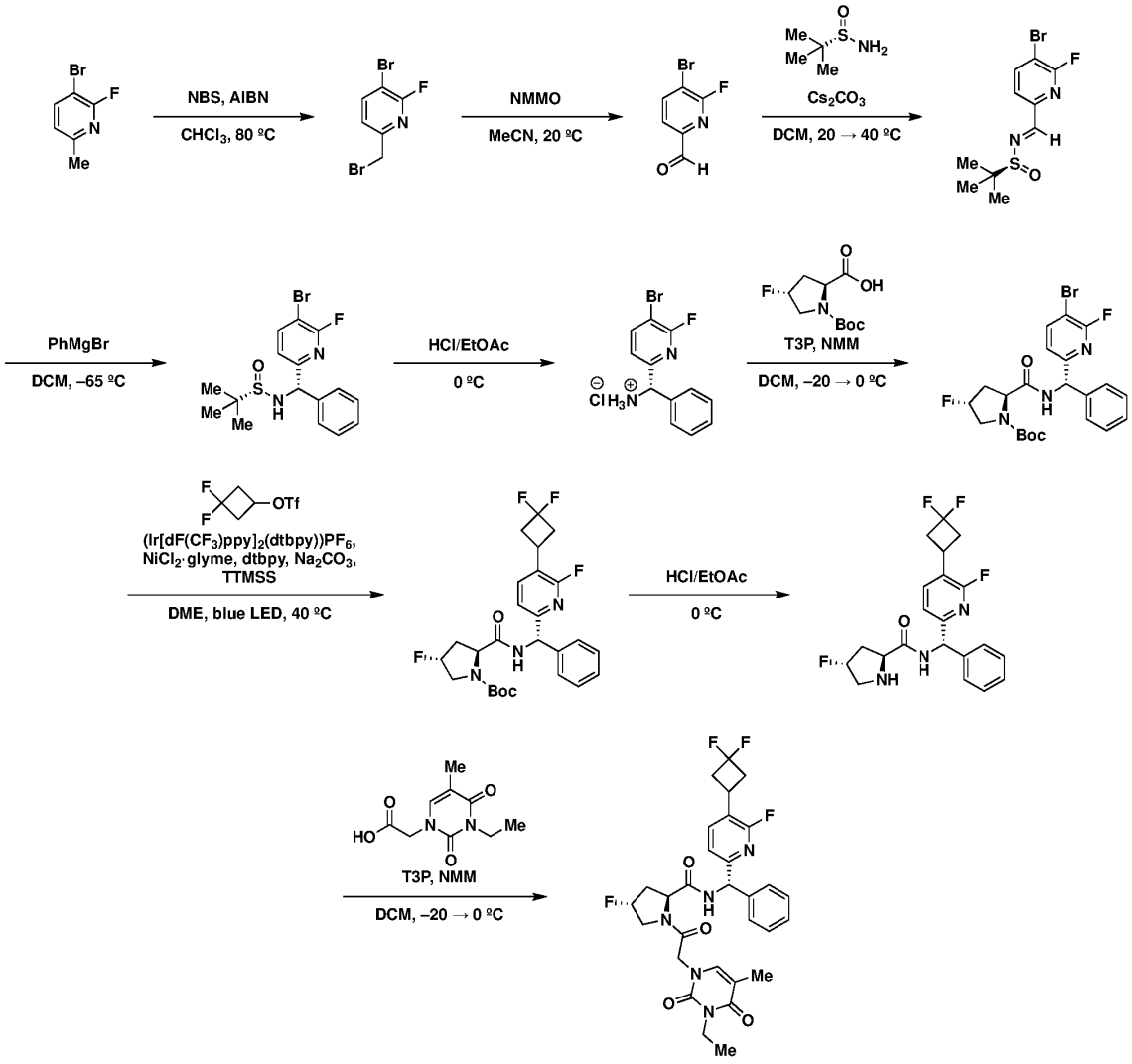
Table T-7

Compound No.	Structure	IUPAC	Exact mass (g/mol)	LCMS, Found $[M + H]^+$
499		(2*S*,4*R*)-1-acetyl-*N*-[(*S*) or (*R*)-(5-cyclopropylpyridin-2-yl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, first-eluting isomer)	381.2	382.2

500		(2*S*,4*R*)-1-acetyl-*N*-[(*R*) or (*S*)-(5-cyclopropylpyridin-2-yl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, second-eluting isomer)	381.2	382.4

Example S-8: Synthesis of (2*S*,4*R*)-*N*-((*S*)-(5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl)(phenyl)methyl)-1-(2-(3-ethyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)acetyl)-4-fluoropyrrolidine-2-carboxamide

(Compound 501)



[0656] Step a: To a solution of 3-bromo-2-fluoro-6-methylpyridine (9.00 g, 47.3 mmol, 1.00 eq) in $CHCl_3$ (90 mL) at 25 °C under N_2 was added *N*-bromosuccinimide (NBS, 10.1 g, 56.8 mmol, 1.20 eq) and azodiisobutyronitrile (AIBN, 777 mg, 4.74 mmol, 0.1 eq). The resulting mixture was warmed to 80 °C and stirred for 5 h. At this time, the reaction mixture was cooled to room temperature and poured into water (200 mL). The resulting biphasic mixture was extracted with dichloromethane (2 x 100 mL). The combined organic extracts were washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to obtain 3-bromo-6-

(bromomethyl)-2-fluoropyridine. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_6H_4Br_2FN$: 267.9; found 267.9

[0657] Step b: To a solution of 3-bromo-6-(bromomethyl)-2-fluoropyridine (13.0 g, 38.6 mmol, 80% purity, 1.00 eq) in MeCN (130 mL) at 20 °C under N_2 was added *N*-methylmorpholine *N*-oxide (NMMO, 9.06 g, 77.3 mmol, 8.16 mL, 2.00 eq). The resulting mixture was stirred at 20 °C for 2 h. The reaction mixture was then poured into water (200 mL) and extracted with dichloromethane (2 x 100 mL). The combined organic phases were washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to obtain 5-bromo-6-fluoropicolinaldehyde.

[0658] Step c: To a mixture of 5-bromo-6-fluoropicolinaldehyde (5.00 g, 24.5 mmol, 1.00 eq) and (*S*)- 2-methylpropane-2-sulfinamide (3.27 g, 26.9 mmol, 1.10 eq) in DCM (50 mL) at 20 °C under N_2 was added Cs_2CO_3 (8.78 g, 26.9 mmol, 1.10 eq). The resulting mixture was stirred for 10 min before it was warmed 40 °C and stirred for 2 h. The reaction mixture was then cooled to room temperature and poured into water (50 mL). The resulting biphasic mixture was extracted with dichloromethane (2 x 50 mL). The combined organic extracts were washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to obtain (*S*,*E*)-*N*-((5-bromo-6-fluoropyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide.

[0659] Step d: To a solution of (*S*,*E*)-*N*-((5-bromo-6-fluoropyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide (7.04 g, 22.9 mmol, 1.00 eq) in DCM (70 mL) –65 °C under N_2 was added in a dropwise manner phenylmagnesium bromide (5.41 g, 29.8 mmol, 1.30 eq). The resulting mixture was stirred at –65 °C for 1 h. The reaction mixture was then poured into water (100 mL) at room temperature. The resulting biphasic mixture was extracted with dichloromethane (2 x 100). The combined organic extracts were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to obtain (*S*)-*N*-((*S*)-(5-bromo-6-fluoropyridin-2-yl)(phenyl)methyl)-2-methylpropane-2-sulfinamide, which was carried forward to the next step without further characterization.

[0660] Step e: To a solution of (*S*)-*N*-((*S*)-(5-bromo-6-fluoropyridin-2-yl)(phenyl)methyl)-2-methylpropane-2-sulfinamide (7.50 g, 19.4 mmol, 1.00 eq) in EtOAc (30 mL) at 0 ºC was added HCl/EtOAc (30 mL). The resulting mixture was stirred at 0 ºC for 1 h. The reaction mixture was then concentrated under reduce pressure to obtain (*S*)-(5-bromo-6-fluoropyridin-2-yl)(phenyl)methanamine hydrochloride (6.18 g). LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{12}H_{10}BrFN_2$: 281.0; found: 281.0.

[0661] Step f: To a mixture of (*S*)-(5-bromo-6-fluoropyridin-2-yl)(phenyl)methanamine hydrochloride (0.5 g, 1.78 mmol, 1.00 eq) and (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (456 mg, 1.96 mmol, 1.10 eq) in DMF (5 mL) at –20 ºC was added *N*-methylmorpholine (NMM, 5.34 mmol, 3.00 eq) and 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide (T3P, 3.56 mmol, 2.12 mL, 50% purity, 2.00 eq). The resulting mixture was allowed to warm to 0 ºC and stirred for 1 h. The reaction mixture was then poured into water (20 mL) at room temperature. The resulting biphasic mixture was extracted with dichloromethane (2 x 50 mL). The combined organic phases were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give *tert*-butyl (2*S*,4*R*)-2-(((*S*)-(5-bromo-6-fluoropyridin-2-yl)(phenyl)methyl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate (0.7 g). LC-MS (ESI): m/z: $[M - t\text{-Bu} + H + H]^+$ calculated for $C_{22}H_{24}BrF_2N_3O_3$: 440.0; found: 440.1.

[0662] Step g: To a solution of *tert*-butyl (2*S*,4*R*)-2-(((*S*)-(5-bromo-6-fluoropyridin-2-yl)(phenyl)methyl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate (700 mg, 1.41 mmol, 1.00 eq) and 3-bromo-1,1-difluorocyclobutane (482 mg, 2.82 mmol, 2.00 *eq*) in 1,2-Dimethoxyethane (DME, 12 mL) at 25 ºC under N_2 was added nickel(II) chloride ethylene glycol dimethyl ether complex ($NiCl_2$•glyme, 3.1 mg, 14.1 µmol, 0.01 eq), 4,4-di-*tert*-butyl-2,2-bipyridyl (dtbpy, 3.79 mg, 14.1 µmol, 0.01 eq), Na_2CO_3 (298 mg, 2.82 mmol, 2.00 *eq*), tris(trimethylsilyl)silane (TTMSS, 350 mg, 1.41 mmol, 1 eq) and $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ (CAS: 870987-63-6, 15.8 mg, 14.1 µmol, 0.01 eq) in one portion. The resulting mixture was stirred for 16 h under N_2 at 25 ºC under a 34W blue LED. The reaction mixture was then filtered and concentrated under reduced pressure to give a crude residue that was purified by column chromatography to give *tert*-butyl (2*S*,4*R*)-2-(((S)-(5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-

yl)(phenyl)methyl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate. LC-MS (ESI): m/z: [M – *t*-Bu + H + H]$^+$ calculated for $C_{26}H_{29}F_4N_3O_3$: 452.1; found: 452.1.

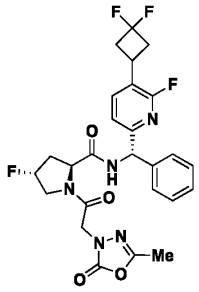
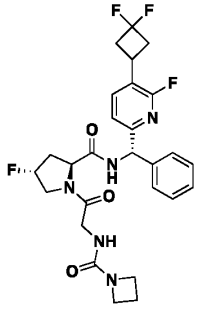
[0663] Step h: To a solution of *tert*-butyl (2*S*,4*R*)-2-(((*S*)-(5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl)(phenyl)methyl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate (173 mg, 341 µmol, 1.00 eq) in EtOAc (1 mL) at 0 ºC was added HCl/EtOAc (4 M, 2 mL). The resulting mixture was stirred at 0 ºC for 2 h. The reaction mixture was then concentrated under reduced pressure to give a crude residue. This residue was diluted in DCM (20 mL) and adjusted to pH = 7 with saturated aqueous $NaHCO_3$ solution. The reaction mixture was then extracted with DCM (3 x 45 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give (2S,4R)-N-((S)-(5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl)(phenyl)methyl)-4-fluoropyrrolidine-2-carboxamide. LC-MS (ESI): m/z: [M + H]$^+$ calculated for $C_{21}H_{21}F_4N_3O$: 408.2; found: 408.2.

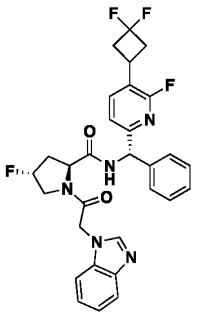
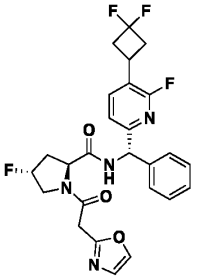
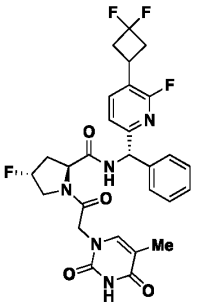
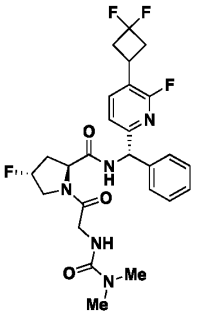
[0664] Step i: To a mixture of (2*S*,4*R*)-*N*-((*S*)-(5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl)(phenyl)methyl)-4-fluoropyrrolidine-2-carboxamide (80.0 mg, 196 µmol, 1 eq) and 2-(3-ethyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)acetic acid (62.5 mg, 295 µmol, 1.5 eq) in DMF (3 mL) at 0 ºC under N_2 was added 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide (T3P, 250 mg, 393 µmol, 50% purity, 2 eq) and *N*-methylmorpholine (NMM, 79.5 mg, 785 µmol, 4 eq) in one portion. The resulting mixture was stirred at 0 ºC for 1 h. The reaction was then allowed to warm to 20 ºC and stirred 1 h. The reaction mixture was then diluted with H_2O (20 mL) at 20 ºC and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by prep-HPLC to obtain (2*S*,4*R*)-*N*-((*S*)-(5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl)(phenyl)methyl)-1-(2-(3-ethyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)acetyl)-4-fluoropyrrolidine-2-carboxamide. ^{1}H NMR (4.3:1 rotamer ratio, asterisk denotes distinct minor rotamer peaks, obscured peaks not reported, 400 MHz, methanol-d_4) δ 7.88 – 7.78 (m, 1H), 7.44 – 7.37* (m, 2H), 7.37 – 7.18 (m, 7H), 7.06* (d, *J* = 1.3 Hz, 1H), 6.19* (s, 1H), 6.08 (s, 1H), 5.50 – 5.18 (m, 1H), 4.92 – 4.77 (m, 1H), 4.76 – 4.68 (m, 1H), 4.58* (d, *J* = 16.3 Hz, 1H), 4.48 (d, *J* = 16.7 Hz, 1H), 4.15 – 3.77 (m, 4H), 3.53 – 3.43 (m, 1H), 3.06 – 2.91 (m, 2H), 2.86 – 2.55 (m,

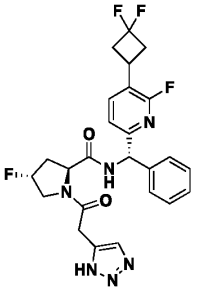
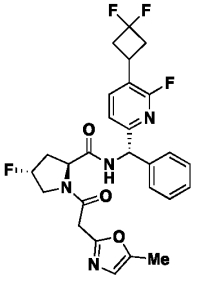
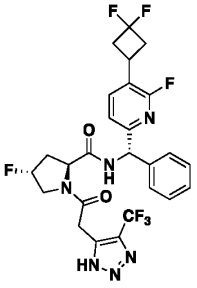
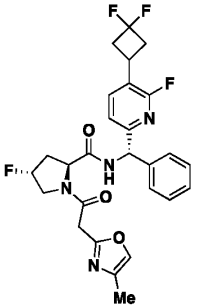
3H), 2.27 – 2.07 (m, 1H), 1.92 – 1.84 (m, 3H), 1.16 (t, J = 7.0 Hz, 3H). LC-MS (ESI): m/z: [M + H]$^+$ calculated for $C_{30}H_{31}F_4N_5O_4$: 602.2; found: 602.3.

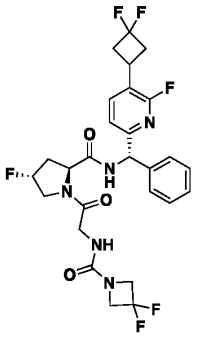
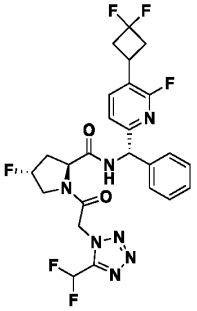
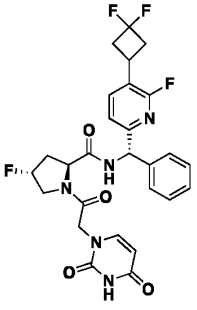
[0665] The following compounds in Table T-8 were synthesized using procedures similar to Compound 501 using the appropriate starting materials.

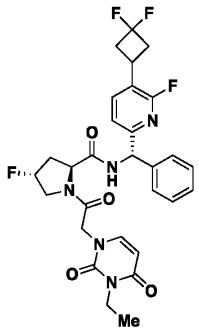
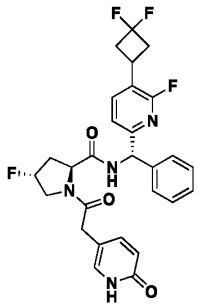
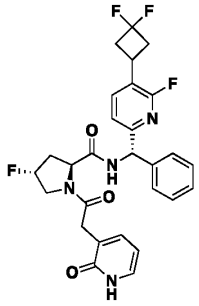
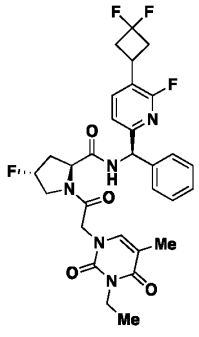
Table T-8

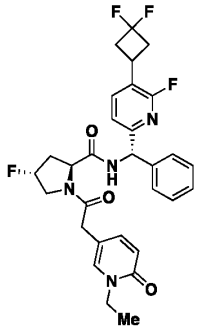
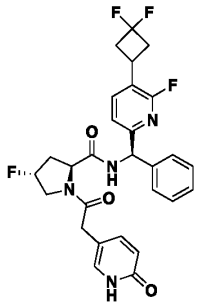
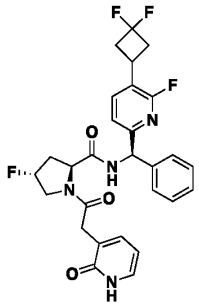
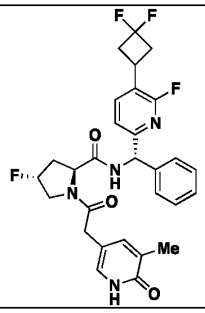
Compound No.	Structure	IUPAC	Exact mass (g/mol)	LCMS, Found [M + H]$^+$
502		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(5-methyl-2-oxo-2,3-dihydro-1,3,4-oxadiazol-3-yl)acetyl]pyrrolidine-2-carboxamide	547.2	548.30
503		(2S,4R)-1-{2-[(azetidine-1-carbonyl)amino]acetyl}-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide	547.2	548.30

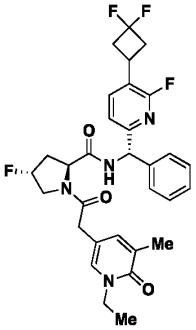
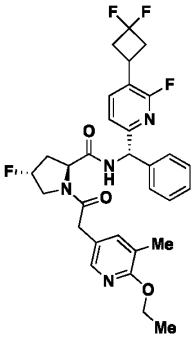
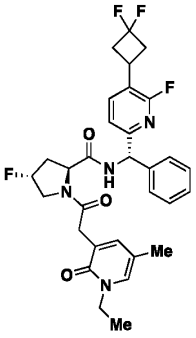
504		(2S,4R)-1-[2-(1H-1,3-benzodiazol-1-yl)acetyl]-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide	565.2	566.20
505		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide	516.2	517.10
506		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]pyrrolidine-2-carboxamide	573.2	574.1
507		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-1-{2-[(dimethylcarbamoyl)amino]acetyl}-4-fluoropyrrolidine-2-carboxamide	535.2	536.3

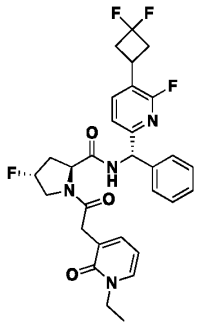
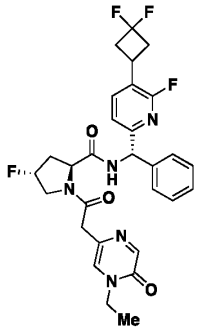
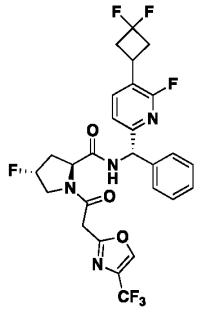
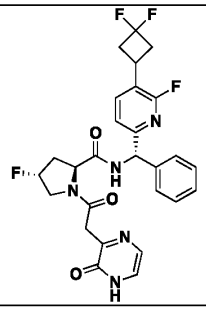
508		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide	516.2	517.2
509		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(5-methyl-1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide	530.2	531.2
510		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-4-fluoro-1-{2-[4-(trifluoromethyl)-1H-1,2,3-triazol-5-yl]acetyl}pyrrolidine-2-carboxamide	584.2	585.2
511		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(4-methyl-1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide	530.2	531.2

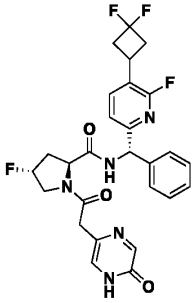
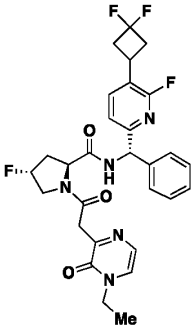
512		(2S,4R)-1-{2-[(3,3-difluoroazetidine-1-carbonyl)amino]acetyl}-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide	583.2	584.3
513		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-1-{2-[5-(difluoromethyl)-1H-1,2,3,4-tetrazol-1-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide	567.2	568.1
514		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-1-[2-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide	559.2	560.1

515		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-1-[2-(3-ethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide	587.2	588.2
516		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(6-oxo-1,6-dihydropyridin-3-yl)acetyl]pyrrolidine-2-carboxamide	542.2	543.3
517		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(2-oxo-1,2-dihydropyridin-3-yl)acetyl]pyrrolidine-2-carboxamide	542.2	543.3
518		(2S,4R)-N-[(R)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-1-[2-(3-ethyl-5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]-4-	601.2	602.3

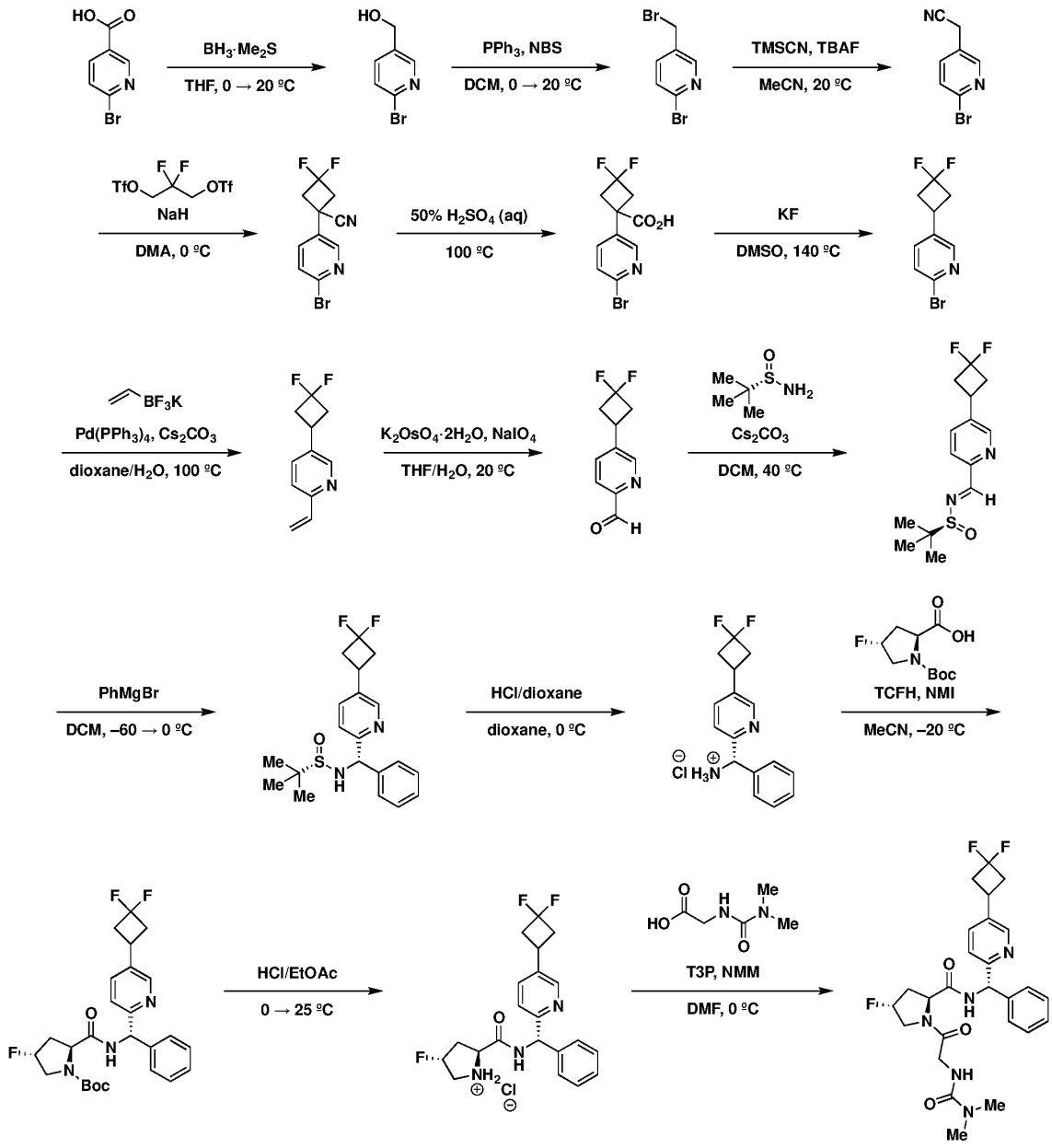
		fluoropyrrolidine-2-carboxamide		
519		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-1-[2-(1-ethyl-6-oxo-1,6-dihydropyridin-3-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide	570.2	571.3
520		(2S,4R)-N-[(R)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(6-oxo-1,6-dihydropyridin-3-yl)acetyl]pyrrolidine-2-carboxamide	542.2	543.3
521		(2S,4R)-N-[(R)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(2-oxo-1,2-dihydropyridin-3-yl)acetyl]pyrrolidine-2-carboxamide	542.2	543.3
522		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(5-methyl-6-oxo-1,6-dihydropyridin-3-	556.2	557.2

		yl)acetyl]pyrrolidine-2-carboxamide		
523		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-1-[2-(1-ethyl-5-methyl-6-oxo-1,6-dihydropyridin-3-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide	584.2	585.2
524		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-1-[2-(6-ethoxy-5-methylpyridin-3-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide	584.2	585.2
525		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-1-[2-(1-ethyl-5-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide	584.2	585.2

526		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-1-[2-(1-ethyl-2-oxo-1,2-dihydropyridin-3-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide	570.2	571.2
527		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-1-[2-(4-ethyl-5-oxo-4,5-dihydropyrazin-2-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide	571.2	572.3
528		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-4-fluoro-1-{2-[4-(trifluoromethyl)-1,3-oxazol-2-yl]acetyl}pyrrolidine-2-carboxamide	584.2	585.1
529		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(3-oxo-3,4-dihydropyrazin-2-	543.2	544.3

		yl)acetyl]pyrrolidine-2-carboxamide		
530		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(5-oxo-4,5-dihydropyrazin-2-yl)acetyl]pyrrolidine-2-carboxamide	543.2	544.3
531		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)-6-fluoropyridin-2-yl](phenyl)methyl]-1-[2-(4-ethyl-3-oxo-3,4-dihydropyrazin-2-yl)acetyl]-4-fluoropyrrolidine-2-carboxamide	571.2	572.3

Example S-9: Synthesis of (2*S*,4*R*)-*N*-((*S*)-(5-(3,3-difluorocyclobutyl)pyridin-2-yl)(phenyl)methyl)-1-((dimethylcarbamoyl)glycyl)-4-fluoropyrrolidine-2-carboxamide (Compound 532)



[0666] Step a: To a solution of 6-bromonicotinic acid (40 g, 198 mmol, 1 eq) in THF (400 mL) at 0 °C under N_2 was added BH_3•Me_2S (10 M, 59.40 mL, 3 eq). The mixture was then warmed to 20 °C and stirred for 3 h. The reaction mixture was then cooled to 0°C, quenched with MeOH (200 mL), H_2O (100 mL), and saturated aqueous K_2CO_3 (100 mL), sequentially. The resulting biphasic mixture was then extracted with EtOAc (3 x 200 mL), and the combined

organic extracts were washed with water, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give (6-bromopyridin-3-yl)methanol. LC-MS (ESI): m/z: $[M + H]^+$ calculated for C_6H_6BrNO: 188.0; found: 188.0.

[0667] Step b: To a solution of (6-bromopyridin-3-yl)methanol (16.2 g, 86.3 mmol, 1 eq) and PPh_3 (26.0 g, 99.7 mmol, 1.15 eq) in DCM (150 mL) at 0 ºC was added *N*-bromosuccinimide (NBS, 17.7 g, 99.7 mmol, 1.15 eq). The resulting mixture was then allowed to warm to 20 ºC and stirred for 3 h. The reaction mixture was then quenched by addition H_2O (200 mL) at 20ºC, and the resulting biphasic mixture was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (400 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 2-bromo-5-(bromomethyl)pyridine. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_6H_5Br_2N$: 249.9; found: 249.9.

[0668] Step c: To a solution of trimethylsilyl cyanide (TMSCN, 12.5 g, 126 mmol, 15.7 mL, 1 eq) in CH_3CN (30 mL) at 0 ºC was added tetrabutylammonium fluoride (TBAF, 1 M, 126 mL, 1.5 eq), and the resulting mixture was stirred for 0.5 h at 0 ºC. 2-bromo-5-(bromomethyl)pyridine (21.1 g, 84.9 mmol, 1 eq) in CH_3CN (100 mL) was then added to the reaction mixture, and the resulting mixture was warmed to 20 ºC and stirred for 0.5 h. The reaction mixture was then cooled to 0 ºC and quenched by addition H_2O (150 mL). The resulting biphasic mixture was then extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 2-(6-bromopyridin-3-yl)acetonitrile. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_7H_5BrN_2$: 197.0; found: 197.0.

[0669] Step d: To a solution of 2-(6-bromopyridin-3-yl)acetonitrile (13.5 g, 68.5 mmol, 1 eq) in dimethylacetamide (DMA, 130 mL) at 0 ºC under N_2 was added NaH (5.48 g, 137 mmol, 60% purity, 2 eq). The resulting mixture was stirred at 0 ºC for 30 min, and then [2,2-difluoro-3-(trifluoromethylsulfonyloxy)propyl] trifluoromethanesulfonate (30.9 g, 82.2 mmol, 1.2 eq) was added to the reaction mixture. The resulting mixture was then stirred at 0 ºC for 1 h. The reaction mixture was then quenched by addition ice-water (100 mL) at 0ºC The

resulting biphasic mixture was extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 1-(6-bromopyridin-3-yl)-3,3-difluorocyclobutane-1-carbonitrile. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{10}H_7BrF_2N_2$: 273.0; found: 273.0.

[0670] Step e: A mixture of 1-(6-bromopyridin-3-yl)-3,3-difluorocyclobutane-1-carbonitrile (2.34 g, 8.57 mmol, 1 eq) in aqueous H_2SO_4 (40 mL, 50%) was warmed to 100 °C and stirred 16 h. The reaction mixture was then cooled to 0 °C and adjusted to pH = 6 with saturated aqueous K_2CO_3 at 0 °C. The resulting mixture was then extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give 1-(6-bromopyridin-3-yl)-3,3-difluorocyclobutane-1-carboxylic acid. The crude residue obtained was used for next step without further purification. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{10}H_8BrF_2NO_2$: 292.0; found: 292.0.

[0671] Step f: A mixture of 1-(6-bromopyridin-3-yl)-3,3-difluorocyclobutane-1-carboxylic acid (2.30 g, 7.87 mmol, 1 eq) and KF (2.29 g, 39.4 mmol, 5 eq) in DMSO (10 mL) was warmed to 140 °C and stirred for 3 h. The mixture was then cooled to room temperature and poured into ice-water (50 mL). The resulting biphasic mixture was extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 2-bromo-5-(3,3-difluorocyclobutyl)pyridine. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_9H_8BrF_2N$: 248.0; found: 248.1.

[0672] Step g: A mixture of 2-bromo-5-(3,3-difluorocyclobutyl)pyridine (6 g, 24.1 mmol, 1 eq), potassium vinyltrifluoroborate (4.86 g, 36.2 mmol, 1.5 eq), Cs_2CO_3 (15.7 g, 48.3 mmol, 2 eq), and $Pd(PPh_3)_4$ (2 g, 1.73 mmol, 0.07 eq) in dioxane (100 mL) and H_2O (10 mL) was de-gassed, placed under N_2, warmed to 100 °C, and stirred for 16 h. The reaction mixture was concentrated in vacuum to obtain 5-(3,3-difluorocyclobutyl)-2-vinylpyridine, which was used directly in the next step without further purification or characterization.

[0673] Step h: To a solution of 5-(3,3-difluorocyclobutyl)-2-vinylpyridine (4 g, 20.4 mmol, 1 eq) in THF (100 mL) and H_2O (30 mL) at 0 °C was added $NaIO_4$ (17.5 g, 81.9 mmol, 4 eq) and $K_2OsO_4 \cdot 2H_2O$ (377 mg, 1.02 mmol, 0.05 eq). The mixture was allowed to warm to 20 °C and stirred at 20°C for 16 h. The reaction mixture was then filtered, and the biphasic mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic phase was washed with brine (30 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 5-(3,3-difluorocyclobutyl)picolinaldehyde. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{10}H_9F_2NO$: 198.0; found:198.0.

[0674] Step i: A mixture of 5-(3,3-difluorocyclobutyl)picolinaldehyde (2.5 g, 12.6 mmol, 1 eq), (S)-2-methylpropane-2-sulfinamide (1.69 g, 13.9 mmol, 1.1 eq), and Cs_2CO_3 (6.20 g, 19.0 mmol, 1.5 eq) in DCM (50 mL) was warmed to 40 °C and stirred for 1 h. The reaction mixture was then filtered, and the filtrate was concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to obtain (*S*,*E*)-*N*-((5-(3,3-difluorocyclobutyl)pyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{14}H_{18}F_2N_2OS$: 301.1; found: 301.1.

[0675] Step j: To a stirring solution of (*S*,*E*)-*N*-((5-(3,3-difluorocyclobutyl)pyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide (3.50 g, 11.6 mmol, 1 eq) in DCM (50 mL) at –60 °C was added phenylmagnesium bromide (3 M, 5.83 mL, 1.5 eq) in a dropwise manner. The mixture was then allowed to warm to 0 °C and stirred for 2 h. The reaction mixture was then quenched with saturated aqueous NH_4Cl (30 mL) at 0 °C. The resulting biphasic mixture was then extracted with DCM (2 x 30 mL). The combined organic extracts were washed with brine (80 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to obtain (*S*)-*N*-[(*S*)-[5-(3,3-difluorocyclobutyl)-2-pyridyl]-phenyl-methyl]-2-methyl-propane-2-sulfinamide. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{20}H_{24}F_2N_2OS$: 379.2; found: 379.2.

[0676] Step k: To a mixture of (*S*)-*N*-[(*S*)-[5-(3,3-difluorocyclobutyl)-2-pyridyl]-phenyl-methyl]-2-methyl-propane-2-sulfinamide (4.0 g, 10.5 mmol, 1 eq) in dioxane (20 mL) at 0 °C was added HCl/dioxane (4 M, 30 mL, 11.3 eq). The resulting mixture was stirred at 0 °C for 1 h The reaction mixture was then concentrated under reduced pressure to give (*S*)-(5-(3,3-

difluorocyclobutyl)pyridin-2-yl)(phenyl)methanaminium chloride, which was used in the next step without further purification. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{16}H_{16}F_2N_2$: 275.1; found: 275.2.

[0677] Step l: To a mixture of (*S*)-(5-(3,3-difluorocyclobutyl)pyridin-2-yl)(phenyl)methanaminium chloride (3.09 g, 10.3 mmol, 1 eq) and (2*S*,4*R*)-1-tert-butoxycarbonyl-4-fluoro-pyrrolidine-2-carboxylic acid (2.88 g, 12.3 mmol, 1.2 eq) in MeCN (50 mL) at –20 ºC under N_2 was added 1-methylimidazole (NMI, 2.54 g, 30.8 mmol, 3 eq) and chloro-*N*,*N*,*N*',*N*'-tetramethylformamidinium hexafluorophosphate (TCFH, 3.47 g, 12.3 mmol, 1.2 *eq*). The resulting mixture was stirred at –20 ºC for 1 h. The reaction was then quenched with H_2O (100 mL), and the resulting biphasic mixture was extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give *tert*-butyl (2*S*,4*R*)-2-(((*S*)-(5-(3,3-difluorocyclobutyl)pyridin-2-yl)(phenyl)methyl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{26}H_{30}F_3N_3O_3$: 490.2; found: 490.3

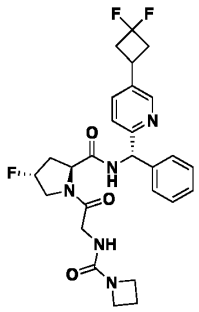
[0678] Step m: To a solution of *tert*-butyl (2*S*,4*R*)-2-(((*S*)-(5-(3,3-difluorocyclobutyl)pyridin-2-yl)(phenyl)methyl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate (5.00 g, 10.2 mmol, 1 eq) in EtOAc (30 mL) at 0 ºC was added HCl/EtOAc (4 M, 30mL) in a dropwise manner. The reaction was then allowed to warm to 25 ºC and stirred for 1 h. The reaction mixture was then concentrated under reduced pressure. The crude residue obtained was triturated with *i*-PrOH/EtOH (ratio=4:1, 150 mL) to give (2*S*,4*R*)-2-(((*S*)-(5-(3,3-difluorocyclobutyl)pyridin-2-yl)(phenyl)methyl)carbamoyl)-4-fluoropyrrolidin-1-ium chloride. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{21}H_{22}F_3N_3O$: 390.2; found: 390.3.

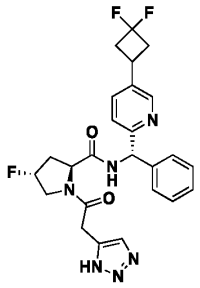
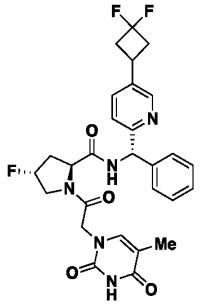
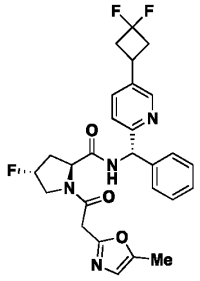
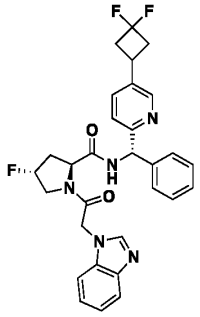
[0679] Step n: To a solution of (2*S*,4*R*)-2-(((*S*)-(5-(3,3-difluorocyclobutyl)pyridin-2-yl)(phenyl)methyl)carbamoyl)-4-fluoropyrrolidin-1-ium chloride (80 mg, 205 µmol, 1 eq) and (dimethylcarbamoyl)glycine (36.0 mg, 246 µmol, 1.2 eq) in DCM (3 mL) at 0 ºC was added *N*-methylmorpholine (NMM, 104 mg, 1.03 mmol, 5 eq) and 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide (T3P, 196 mg, 308 µmol, 50% purity, 1.5 eq). The resulting mixture was stirred at 0 ºC for 2 h. The reaction mixture was then poured into water (10 mL) at 0 ºC and stirred for 10 min. The biphasic mixture was then extracted with ethyl

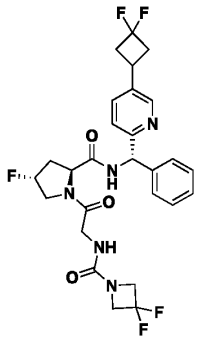
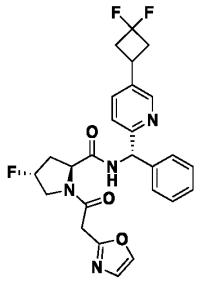
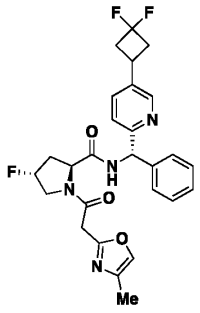
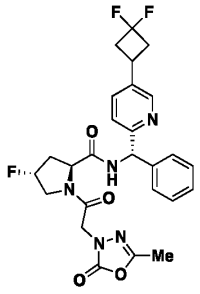
acetate (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by prep-HPLC to give (2*S*,4*R*)-*N*-((*S*)-(5-(3,3-difluorocyclobutyl)pyridin-2-yl)(phenyl)methyl)-1-((dimethylcarbamoyl)glycyl)-4-fluoropyrrolidine-2-carboxamide. ^{1}H NMR (2.3:1 rotamer ratio, asterisk denotes minor rotamer peaks, obscured peaks not reported, 400 MHz, DMSO-d_6) δ 9.27* (d, J = 7.9 Hz, 1H), 8.88 (d, J = 8.4 Hz, 1H), 8.50 – 8.41 (m, 1H), 7.80 – 7.71 (m, 1H), 7.48 – 7.40 (m, 1H), 7.37 – 7.18 (m, 4H), 6.46 (t, J = 5.5 Hz, 1H), 6.35* (t, J = 5.6 Hz, 1H), 6.16 – 6.05 (m, 1H), 5.46 – 5.18 (m, 1H), 4.85* (t, J = 8.0 Hz, 1H), 4.60 (t, J = 8.3 Hz, 1H), 4.03 – 3.83 (m, 2H), 3.75 – 3.57 (m, 2H), 3.51 – 3.22 (m, 4H), 3.06 – 2.91 (m, 2H), 2.84 – 2.68 (m, 4H), 2.23 – 1.85 (m, 2H). LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{26}H_{30}F_3N_5O_3$: 518.2; found: 518.4.

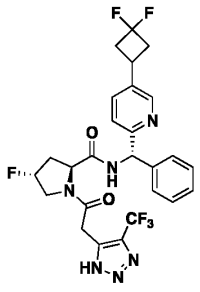
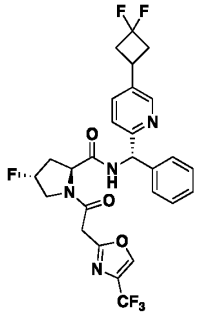
[0680] The following compounds in Table T-9 were synthesized using procedures similar to Compound 532 using the appropriate starting materials.

Table T-9

Compound No.	Structure	IUPAC	Exact mass (g/mol)	LCMS, Found $[M + H]^+$
533		(2S,4R)-1-{2-[(azetidine-1-carbonyl)amino]acetyl}-N-[(S)-[5-(3,3-difluorocyclobutyl)pyridin-2-yl](phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide	529.2	530.2

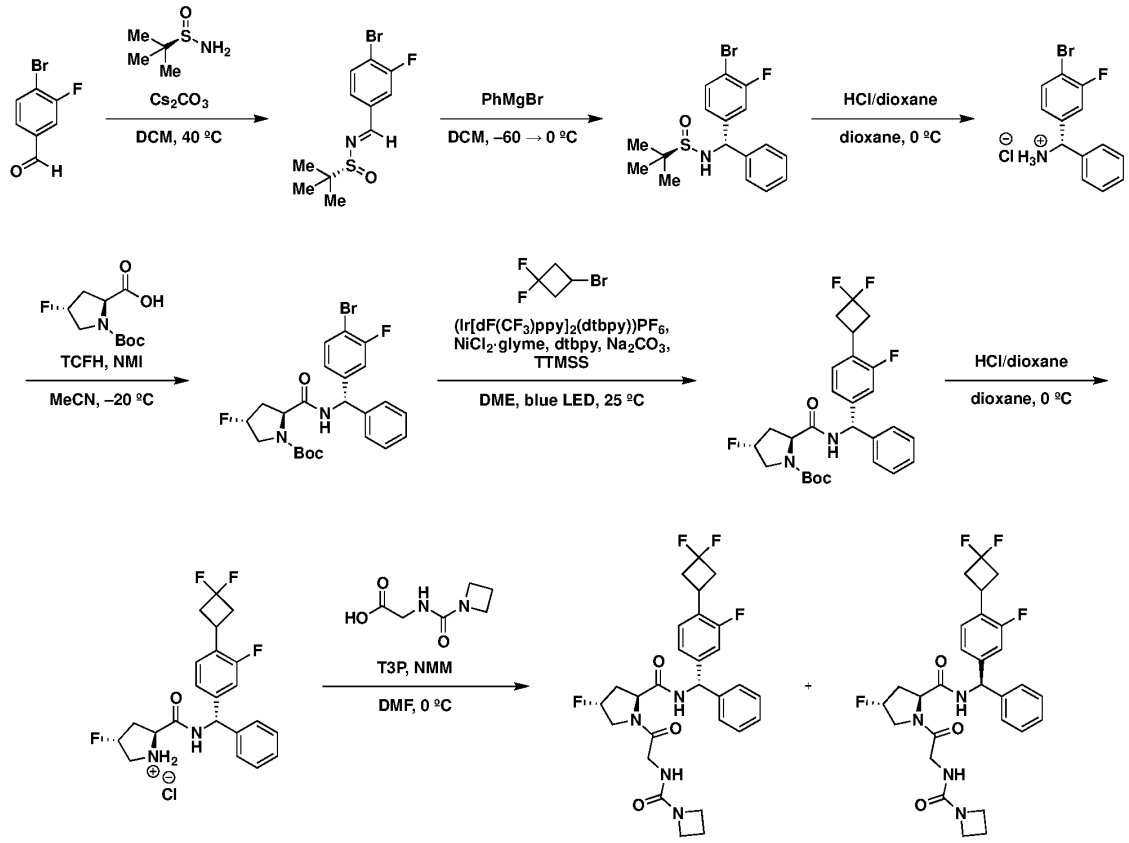
534		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)pyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide	498.2	499.3
535		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)pyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]pyrrolidine-2-carboxamide	555.2	556.4
536		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)pyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(5-methyl-1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide	512.2	513.1
537		(2S,4R)-1-[2-(1H-1,3-benzodiazol-1-yl)acetyl]-N-[(S)-[5-(3,3-difluorocyclobutyl)pyridin-2-yl](phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide	547.2	548.1

538		(2S,4R)-1-{2-[(3,3-difluoroazetidine-1-carbonyl)amino]acetyl}-N-[(S)-[5-(3,3-difluorocyclobutyl)pyridin-2-yl](phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide	565.2	566.2
539		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)pyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide	498.2	499.4
540		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)pyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(4-methyl-1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide	512.2	513.4
541		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)pyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(5-methyl-2-oxo-2,3-dihydro-1,3,4-oxadiazol-3-yl)acetyl]pyrrolidine-2-carboxamide	529.2	530.2

542		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)pyridin-2-yl](phenyl)methyl]-4-fluoro-1-{2-[4-(trifluoromethyl)-1H-1,2,3-triazol-5-yl]acetyl}pyrrolidine-2-carboxamide	566.2	567.1
543		(2S,4R)-N-[(S)-[5-(3,3-difluorocyclobutyl)pyridin-2-yl](phenyl)methyl]-4-fluoro-1-{2-[4-(trifluoromethyl)-1,3-oxazol-2-yl]acetyl}pyrrolidine-2-carboxamide	566.2	567.1

Example S-10: Synthesis of (2*S*,4*R*)-1-((azetidine-1-carbonyl)glycyl)-*N*-((*S*)-(4-(3,3-difluorocyclobutyl)-3-fluorophenyl)(phenyl)methyl)-4-fluoropyrrolidine-2-carboxamide and (2*S*,4*R*)-1-((azetidine-1-carbonyl)glycyl)-*N*-((*R*)-(4-(3,3-difluorocyclobutyl)-3-fluorophenyl)(phenyl)methyl)-4-fluoropyrrolidine-2-carboxamide

(Compounds 544 and 545)



[0681] Step a: A mixture of 4-bromo-3-fluorobenzaldehyde (25 g, 123 mmol, 1 eq), (*R*)-2-methylpropane-2-sulfinamide (16.4 g, 135 mmol, 1.1 eq) and Cs_2CO_3 (60.1 g, 184 mmol, 1.5 eq) in DCM (150 mL) at 40 °C was stirred for 1 h. The reaction mixture was then filtered, and the filtrate was concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give (*R*,*E*)-*N*-(4-bromo-3-fluorobenzylidene)-2-methylpropane-2-sulfinamide (37 g). LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{11}H_{13}BrFNOS$: 306.0; found: 305.9.

[0682] Step b: To a solution of (*R*,*E*)-*N*-(4-bromo-3-fluorobenzylidene)-2-methylpropane-2-sulfinamide (37 g, 120 mmol, 1 eq) in DCM (150 mL) at –60 °C was added phenylmagnesium bromide (3 M, 48.3 mL, 1.2 eq) in a dropwise manner. The resulting mixture was and stirred at –60 °C for 1 h before it was warmed to 0 °C and stirred for 1 h. The reaction mixture was then quenched by addition of saturated aqueous NH_4Cl (300 mL) at 0 °C. The resulting biphasic mixture was extracted with EtOAc (3 x 150 mL). The combined organic

extracts were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to obtain (*R*)-*N*-((*S*)-(4-bromo-3-fluorophenyl)(phenyl)methyl)-2-methylpropane-2-sulfinamide. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{17}H_{19}BrFNOS$: 384.0; found: 383.9.

[0683] Step c: To a mixture of (*R*)-*N*-((*S*)-(4-bromo-3-fluorophenyl)(phenyl)methyl)-2-methylpropane-2-sulfinamide (45 g, 117 mmol, 1 eq) in dioxane (200 mL) at 0 ºC was added HCl/dioxane (4 M, 500 mL). The resulting mixture was stirred at 0 ºC for 2 h. The reaction mixture was then filtered, and the white solid was washed with petroleum ether (3 x 50 mL). The washed solid was then dried under reduced pressure. The residue obtained was triturated with 2-methoxy-2-methylpropane to obtain (*S*)-(4-bromo-3-fluorophenyl)(phenyl)methanaminium chloride. LC-MS (ESI): m/z: $[M - NH_2]^+$ calculated for $C_{13}H_{11}BrFN$: 263.0; found: 263.0.

[0684] Step d: To a solution of (*S*)-(4-bromo-3-fluorophenyl)(phenyl)methanaminium chloride (20 g, 63.1 mmol, 1 eq), (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (17.6 g, 75.8 mmol, 1.2 eq) in CH_3CN (300 mL) at –20 ºC was added *N*-methylimidazole (NMI, 25.9 g, 315 mmol, 5 eq) and chloro-*N*,*N*,*N*′,*N*′-tetramethylformamidinium hexafluorophosphate (TCFH, 19.5 g, 69.4 mmol, 1.1 eq). The resulting mixture was then stirred at –20 ºC for 1 h. The reaction mixture was then quenched by addition H_2O (500 mL) at 20 ºC and extracted with EtOAc (3 x 200 mL). The combined organic extracts were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to obtain *tert*-butyl (2*S*,4*R*)-2-(((*S*)-(4-bromo-3-fluorophenyl)(phenyl)methyl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{23}H_{25}BrF_2N_2O_3$: 495.1; found: 495.0.

[0685] Step e: To a solution of *tert*-butyl (2*S*,4*R*)-2-(((*S*)-(4-bromo-3-fluorophenyl)(phenyl)methyl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate (5 g, 10.0 mmol, 1 eq) in dimethylacetamide (DME, 10 mL) at 25 ºC under N_2 was added 3-bromo-1,1-difluoro-cyclobutane (2.59 g, 15.1 mmol, 1.5 eq), nickel(II) chloride ethylene glycol dimethyl ether complex ($NiCl_2$•glyme, 11.0 mg, 50.4 µmol, 0.005 eq), 4,4-di-*tert*-butyl-2,2-bipyridyl (dtbpy,

13.5 mg, 50.4 μmol, 0.005 eq), Na_2CO_3 (2.14 g, 20.1 mmol, 2 eq), tris(trimethylsilyl)silane (TTMSS, 2.51 g, 10.0 mmol, 3.11 mL, 1 eq) and (Ir[dF(CF_3)ppy]$_2$(dtbpy))PF_6 (113 mg, 100 μmol, 0.01 eq). The resulting mixture was stirred under N_2 at 25°C under 34 W blue LED for 16 h. The reaction mixture was then filtered ,and the filtrate was concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give *tert*-butyl (2*S*,4*R*)-2-(((*S*)-(4-(3,3-difluorocyclobutyl)-3-fluorophenyl)(phenyl)methyl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{27}H_{30}F_4N_2O_3$: 507.2; found: 507.2.

[0686] Step f: To a mixture of *tert*-butyl (2*S*,4*R*)-2-(((*S*)-(4-(3,3-difluorocyclobutyl)-3-fluorophenyl)(phenyl)methyl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate (2.5 g, 4.94 mmol, 1 eq) in dioxane (20 mL) at 0 °C was added HCl/dioxane (4 M, 20 mL), and the resulting mixture was stirred at 0 °C for 1 h. The reaction mixture was then concentrated under reduced pressure, and the crude residue obtained was recrystallized from isopropanol (20 mL) to give (2*S*,4*R*)-2-(((*S*)-(4-(3,3-difluorocyclobutyl)-3-fluorophenyl)(phenyl)methyl)carbamoyl)-4-fluoropyrrolidin-1-ium chloride. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{22}H_{22}F_4N_2O$: 407.2; found: 407.1.

[0687] Step g: To a solution of (2*S*,4*R*)-2-(((*S*)-(4-(3,3-difluorocyclobutyl)-3-fluorophenyl)(phenyl)methyl)carbamoyl)-4-fluoropyrrolidin-1-ium chloride (130 mg, 294 μmol, 1 eq) in DMF (1 mL) at 0 °C was added 2-(azetidine-1-carboxamido)acetic acid (68.6 mg, 352 μmol, 1.2 eq, HCl salt), *N*-methylmorpholine (NMM, 178 mg, 1.76 mmol, 6 eq) and 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide (T3P, 374 mg, 587 μmol, 50% purity, 2 eq). The resulting mixture was stirred at 0 °C for 2 h. The reaction mixture was then quenched by addition of H_2O (10 mL). The resulting biphasic mixture was then extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with saturated aqueous NaCl (3 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by prep-HPLC to give a mixture of (2*S*,4*R*)-1-((azetidine-1-carbonyl)glycyl)-*N*-((*S*)-(4-(3,3-difluorocyclobutyl)-3-fluorophenyl)(phenyl)methyl)-4-fluoropyrrolidine-2-carboxamide and (2*S*,4*R*)-1-((azetidine-1-carbonyl)glycyl)-*N*-((*R*)-(4-(3,3-difluorocyclobutyl)-3-fluorophenyl)(phenyl)methyl)-4-fluoropyrrolidine-2-carboxamide. This purified mixture was then separated using chiral SFC to give (2*S*,4*R*)-1-((azetidine-1-

carbonyl)glycyl)-*N*-((*S*)-(4-(3,3-difluorocyclobutyl)-3-fluorophenyl)(phenyl)methyl)-4-fluoropyrrolidine-2-carboxamide (major isomer, Compound 544) and (2*S*,4*R*)-1-((azetidine-1-carbonyl)glycyl)-*N*-((*R*)-(4-(3,3-difluorocyclobutyl)-3-fluorophenyl)(phenyl)methyl)-4-fluoropyrrolidine-2-carboxamide (minor isomer, Compound 545).

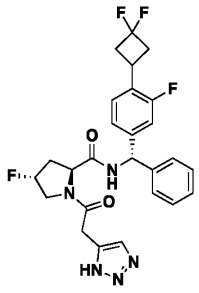
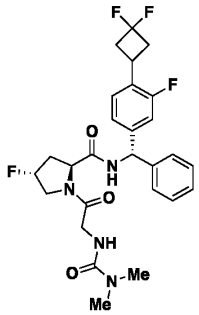
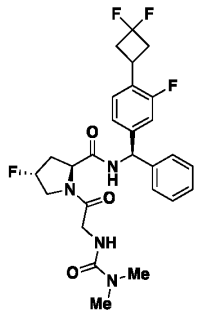
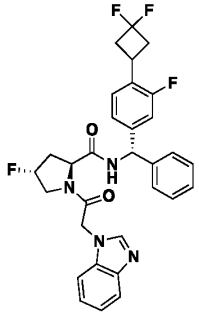
[0688] Major isomer (Compound 544): ^{1}H NMR (3:1 rotamer ratio, asterisk denotes minor rotamer peaks, obscured peaks not reported, 400 MHz, DMSO-d_6) δ 9.22 (d, J = 8.1 Hz, 0H), 8.85 (d, J = 8.5 Hz, 1H), 7.42 – 7.21 (m, 7H), 7.18 – 7.04 (m, 3H), 6.40 (t, J = 5.7 Hz, 1H), 6.28 (t, J = 5.8 Hz, 0H), 6.14 – 6.03 (m, 1H), 5.47 – 5.19 (m, 2H), 4.72 (t, J = 8.1 Hz, 0H), 4.52 (t, J = 8.4 Hz, 1H), 4.02 – 3.58 (m, 11H), 3.55 – 3.43 (m, 1H), 3.05 – 2.90 (m, 2H), 2.83 – 2.64 (m, 2H), 2.48 – 2.36 (m, 1H), 2.18 – 2.05 (m, 3H), 2.04 – 1.83 (m, 1H). LC-MS (ESI): m/z: [M + H]$^+$ calculated for $C_{28}H_{30}F_4N_4O_3$: 547.2; found 547.3.

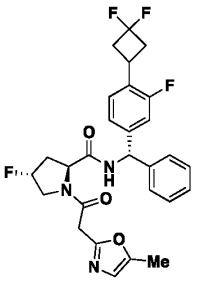
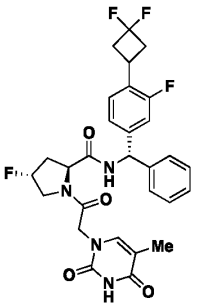
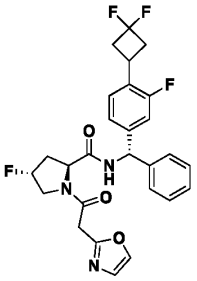
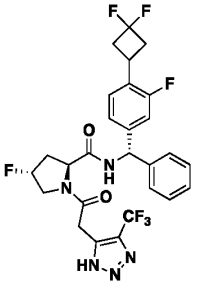
[0689] Minor isomer (Compound 545): ^{1}H NMR (2.6:1 rotamer ratio, asterisk denotes minor rotamer peaks, obscured peaks not reported, 400 MHz, DMSO-d_6) δ 9.22* (d, J = 8.2 Hz, 1H), 8.89 (d, J = 8.6 Hz, 1H), 7.41 – 7.08 (m, 7H), 6.38 (t, J = 5.7 Hz, 1H), 6.28* (t, J = 5.8 Hz, 1H), 6.14 – 6.03 (m, 1H), 5.48 – 5.20 (m, 1H), 4.72* (t, J = 8.1 Hz, 1H), 4.53 (t, J = 8.4 Hz, 1H), 4.01 – 3.70 (m, 5H), 3.69 – 3.59 (m, 1H), 3.55 – 3.43 (m, 1H), 3.05 – 2.90 (m, 2H), 2.83 – 2.67 (m, 2H), 2.46 – 2.35 (m, 1H), 2.18 – 2.06 (m, 2H), 2.07 – 1.85 (m, 1H). LC-MS (ESI): m/z: [M + H]$^+$ calculated for $C_{28}H_{30}F_4N_4O_3$: 547.2; found 547.3.

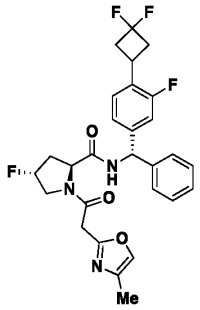
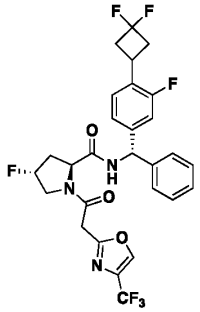
[0690] The following compounds in Table T-10 were synthesized using procedures similar to Compounds 544 and 545 using the appropriate starting materials.

Table T-10

Compound No.	Structure	IUPAC	Exact mass (g/mol)	LCMS, Found [M + H]$^+$

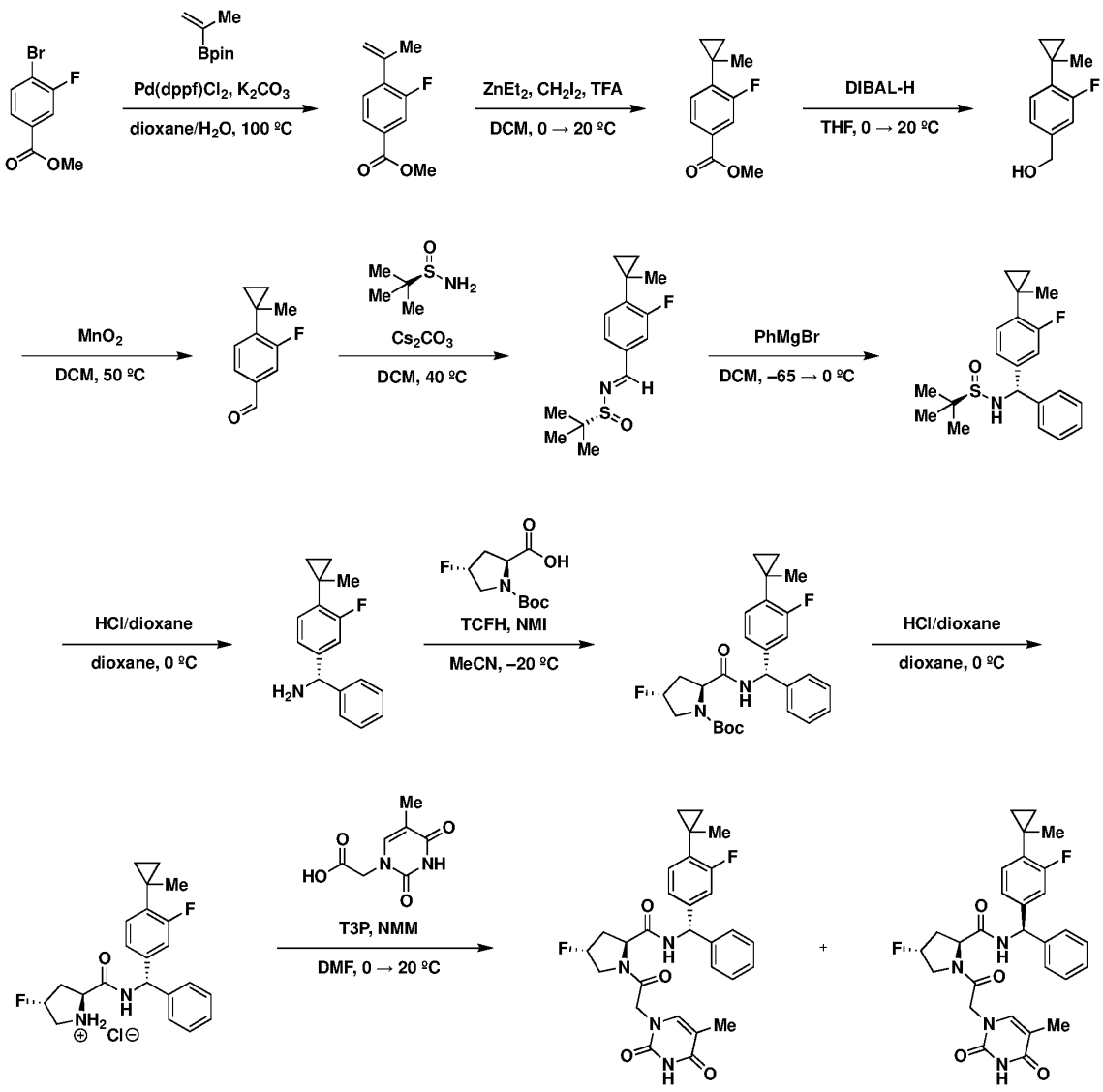
546		(2S,4R)-N-[(S)-[4-(3,3-difluorocyclobutyl)-3-fluorophenyl](phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide	515.2	516.3
547		(2S,4R)-N-[(S)-[4-(3,3-difluorocyclobutyl)-3-fluorophenyl](phenyl)methyl]-1-{2-[(dimethylcarbamoyl)amino]acetyl}-4-fluoropyrrolidine-2-carboxamide	534.2	535.2
548		(2S,4R)-N-[(R)-[4-(3,3-difluorocyclobutyl)-3-fluorophenyl](phenyl)methyl]-1-{2-[(dimethylcarbamoyl)amino]acetyl}-4-fluoropyrrolidine-2-carboxamide	534.2	535.2
549		(2S,4R)-1-[2-(1H-1,3-benzodiazol-1-yl)acetyl]-N-[(S)-[4-(3,3-difluorocyclobutyl)-3-fluorophenyl](phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide	564.2	565.1

550		(2S,4R)-N-[(S)-[4-(3,3-difluorocyclobutyl)-3-fluorophenyl](phenyl)methyl]-4-fluoro-1-[2-(5-methyl-1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide	529.2	530.1
551		(2S,4R)-N-[(S)-[4-(3,3-difluorocyclobutyl)-3-fluorophenyl](phenyl)methyl]-4-fluoro-1-[2-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)acetyl]pyrrolidine-2-carboxamide	572.2	488.3
552		(2S,4R)-N-[(S)-[4-(3,3-difluorocyclobutyl)-3-fluorophenyl](phenyl)methyl]-4-fluoro-1-[2-(1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide	515.2	516.4
553		(2S,4R)-N-[(S)-[4-(3,3-difluorocyclobutyl)-3-fluorophenyl](phenyl)methyl]-4-fluoro-1-{2-[4-(trifluoromethyl)-1H-1,2,3-triazol-5-yl]acetyl}pyrrolidine-2-carboxamide	583.2	584.2

554		(2S,4R)-N-[(S)-[4-(3,3-difluorocyclobutyl)-3-fluorophenyl](phenyl)methyl]-4-fluoro-1-[2-(4-methyl-1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide	529.2	530.2
555		(2S,4R)-N-[(S)-[4-(3,3-difluorocyclobutyl)-3-fluorophenyl](phenyl)methyl]-4-fluoro-1-{2-[4-(trifluoromethyl)-1,3-oxazol-2-yl]acetyl}pyrrolidine-2-carboxamide	583.2	584.1

Example S-11: Synthesis of (2*S*,4*R*)-4-fluoro-*N*-((*S*)-(3-fluoro-4-(1-methylcyclopropyl)phenyl)(phenyl)methyl)-1-(2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)acetyl)pyrrolidine-2-carboxamide and (2*S*,4*R*)-4-fluoro-*N*-((*R*)-(3-fluoro-4-(1-methylcyclopropyl)phenyl)(phenyl)methyl)-1-(2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)acetyl)pyrrolidine-2-carboxamide

(Compounds 556 and 557)



[0691] Step a: To a solution of methyl 4-bromo-3-fluoro-benzoate (25.0 g, 107 mmol, 1 eq) and 2-isopropenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (36.0 g, 214 mmol, 2 eq) in dioxane (200 mL) and H_2O (10 mL) under N_2 was added K_2CO_3 (44.4 g, 321 mmol, 3 eq) and $Pd(dppf)Cl_2$ (3.15 g, 4.30 mmol, 0.04 eq). The reaction was then warmed to 100 ºC and stirred for 16 h under N_2. The reaction mixture was then cooled to 0 ºC and quenched by addition H_2O (100 mL). The resulting biphasic mixture was then extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with H_2O (2 x 50 mL) and brine (2 x 50 mL),

dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give methyl 3-fluoro-4-(prop-1-en-2-yl)benzoate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{11}H_{11}FO_2$: 195.1; found: 195.1.

[0692] Step b: To a solution of $ZnEt_2$ (1 M in hexane, 154 mL, 2.50 eq) in DCM (100 mL) at 0 °C was dropwise added TFA (18.3 g, 160 mmol, 2.61 *eq*) in DCM (30 ml) over 15 min. Diiodomethane (41.3 g, 154 mmol, 12.4 mL, 2.50 eq) in DCM (30 mL) was then dropwise added at 0 °C. After 15 min, methyl 3-fluoro-4-(prop-1-en-2-yl)benzoate (12 g, 61.7 mmol, 1 eq) in DCM (30 mL) was added dropwise at 0 °C. The reaction mixture was then allowed to warm to 20 °C and stirred for 16 h. The reaction was then poured into saturated aqueous NH_4Cl (200 mL) at 0 °C and stirred for 10 min. The biphasic mixture was then extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give methyl 3-fluoro-4-(1-methylcyclopropyl)benzoate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{12}H_{13}FO_2$: 209.1; found: 209.1.

[0693] Step c: To a solution of methyl 3-fluoro-4-(1-methylcyclopropyl)benzoate (12 g, 46.1 mmol, 18.1 mL, 80% purity, 1 eq) in THF (100 mL) at 0 °C was added diisobutylaluminum hydride (DIBAL-H, 1 M in THF, 138 mL, 3 eq). The reaction was then allowed to warm to 20 °C and stirred for 2 h. The reaction mixture was then poured into saturated aqueous NH_4Cl (100 mL) at 0 °C and stirred for 10 min. The biphasic mixture was then extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give (3-fluoro-4-(1-methylcyclopropyl)phenyl)methanol, which was carried into the next step without further purification. LC-MS (ESI): m/z: $[M - H_2O]^+$ calculated for $C_{11}H_{13}FO$: 163.1; found: 163.1.

[0694] Step d: To a solution of (3-fluoro-4-(1-methylcyclopropyl)phenyl)methanol (8 g, 44.3 mmol, 1 eq) in DCM (150 mL) at 25 °C was added MnO_2 (57.8 g, 665 mmol, 15 eq). The resulting mixture was warmed to 50 °C and stirred for 16 h. The reaction mixture was then poured into H_2O (100 mL) at 0 °C, and the resulting biphasic mixture was extracted with DCM (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried

over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give 3-fluoro-4-(1-methylcyclopropyl)benzaldehyde, which was carried into the next step without further purification. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{11}H_{11}FO$: 179.1; found: 179.1.

[0695] Step e: To a mixture of 3-fluoro-4-(1-methylcyclopropyl)benzaldehyde (10 g, 56.1 mmol, 1 eq) and (*R*)-2-methylpropane-2-sulfinamide (7.48 g, 61.7 mmol, 1.1 eq) in DCM (150 mL) at 25 °C was added Cs_2CO_3 (27.4 g, 84.1 mmol, 1.5 eq). The resulting mixture was warmed to 40 °C and stirred for 1 h. The reaction mixture was then poured into H_2O (50 mL) at 0 °C, and the resulting biphasic mixture was extracted with DCM (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give (*R*,*E*)-*N*-(3-fluoro-4-(1-methylcyclopropyl)benzylidene)-2-methylpropane-2-sulfinamide. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{15}H_{20}FNOS$: 282.1; found: 282.0.

[0696] Step f: To a solution of (*R*,*E*)-*N*-(3-fluoro-4-(1-methylcyclopropyl)benzylidene)-2-methylpropane-2-sulfinamide (13 g, 46.2 mmol, 1 eq) in DCM (150 mL) at –60 °C was added phenylmagnesium bromide (3 M, 18.4 mL, 1.2 eq) in a dropwise manner. The resulting mixture was stirred at –60 °C for 1 h. The reaction mixture was then allowed to warm to 0 °C and stirred for 1 h. The reaction mixture was then quenched by addition of saturated aqueous NH_4Cl (100 mL) at 0 °C, and the resulting biphasic mixture was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give (*R*)-*N*-((*S*)-(3-fluoro-4-(1-methylcyclopropyl)phenyl)(phenyl)methyl)-2-methylpropane-2-sulfinamide. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{21}H_{26}FNOS$: 360.2; found: 360.1.

[0697] Step g: To a mixture of (*R*)-*N*-((*S*)-(3-fluoro-4-(1-methylcyclopropyl)phenyl)(phenyl)methyl)-2-methylpropane-2-sulfinamide (15 g, 41.7 mmol, 1 eq) in dioxane (100 mL) at 0 °C was added HCl/dioxane (4 M, 150 mL), and the resulting mixture was stirred at 0 °C for 1h. The reaction mixture was filtered and the filter cake was washed with petroleum ether (3 x 50 mL). The filter cake was then added to saturated aqueous $NaHCO_3$ (200 mL) and stirred for 20 min. The resulting biphasic mixture was then extracted

with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure obtain (*S*)-(3-fluoro-4-(1-methylcyclopropyl)phenyl)(phenyl)methanamine. LC-MS (ESI): m/z: $[M - NH_2]^+$ calculated for $C_{17}H_{18}FN$: 240.1; found: 240.0.

[0698] Step h: To a solution of (*S*)-(3-fluoro-4-(1-methylcyclopropyl)phenyl)(phenyl)methanamine (1.2 g, 4.70 mmol, 1 eq) and (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (1.32 g, 5.64 mmol, 1.2 eq) in CH_3CN (20 mL) at –20 °C was added *N*-methylimidazole (NMI, 1.93 g, 23.5 mmol, 1.87 mL, 5 eq) and chloro-*N*,*N*,*N*′,*N*′-tetramethylformamidinium hexafluorophosphate (TCFH, 1.58 g, 5.64 mmol, 1.2 eq). The resulting mixture was stirred at –20 °C for 1 h. The reaction mixture was then warmed to 0 °C and quenched with H_2O (50 mL). The resulting biphasic mixture was extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give *tert*-butyl (2*S*,4*R*)-4-fluoro-2-(((*S*)-(3-fluoro-4-(1-methylcyclopropyl)phenyl)(phenyl)methyl)carbamoyl)pyrrolidine-1-carboxylate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{27}H_{32}F_2N_2O_3$: 471.2; found: 471.1.

[0699] Step i: To a solution of *tert*-butyl (2*S*,4*R*)-4-fluoro-2-(((*S*)-(3-fluoro-4-(1-methylcyclopropyl)phenyl)(phenyl)methyl)carbamoyl)pyrrolidine-1-carboxylate (2 g, 4.25 mmol, 1 eq) in dioxane (10 mL) at 0 °C was added HCl/dioxane (4M, 20 mL). The resulting mixture was stirred at 0 °C for 1 h. The reaction mixture was then concentrated under reduced pressure to give (2*S*,4*R*)-4-fluoro-2-(((*S*)-(3-fluoro-4-(1-methylcyclopropyl)phenyl)(phenyl)methyl)carbamoyl)pyrrolidin-1-ium chloride. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{22}H_{24}F_2N_2O$: 371.2; found: 371.1.

[0700] Step j: To a solution of (2*S*,4*R*)-4-fluoro-2-(((*S*)-(3-fluoro-4-(1-methylcyclopropyl)phenyl)(phenyl)methyl)carbamoyl)pyrrolidin-1-ium chloride (100 mg, 270 µmol, 1 eq) in DMF (1.00 mL) at 0 °C was added 2-(5-methyl-2,4-dioxo-pyrimidin-1-yl)acetic acid (64.6 mg, 351 µmol, 1.3 eq), *N*-methylmorpholine (NMM, 149 mg, 1.47 mmol, 6 eq) and 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide (T3P, 344 mg, 540 µmol, 50% purity, 2 eq), and the resulting mixture was stirred at 0 °C for 1 h. The reaction was then allowed to warm to 20 °C and for 15 h. The reaction mixture was then quenched by addition of H_2O (10

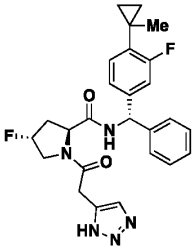
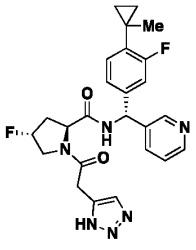
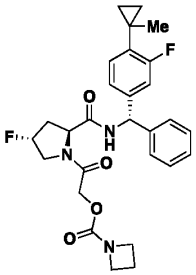
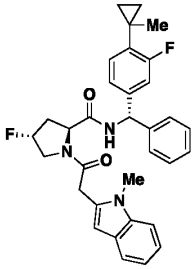
mL), and the resulting biphasic mixture was extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with saturated aqueous NaCl (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained residue was purified by prep-HPLC to give (2*S*,4*R*)-4-fluoro-*N*-((*S*)-(3-fluoro-4-(1-methylcyclopropyl)phenyl)(phenyl)methyl)-1-(2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)acetyl)pyrrolidine-2-carboxamide (major isomer, Compound 556) and (2*S*,4*R*)-4-fluoro-*N*-((*R*)-(3-fluoro-4-(1-methylcyclopropyl)phenyl)(phenyl)methyl)-1-(2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)acetyl)pyrrolidine-2-carboxamide (minor isomer, compound 557).

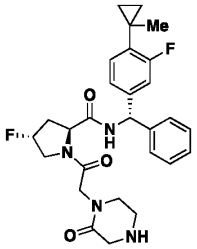
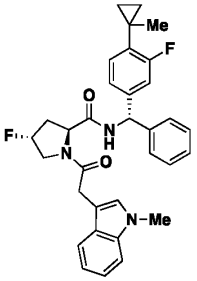
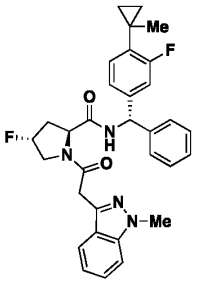
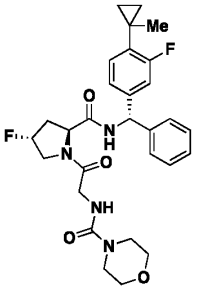
[0701] Major isomer (Compound 556): ^{1}H NMR (3.1:1 rotamer ratio, asterisk denotes minor rotamer peaks, obscured peaks not reported, 400 MHz, DMSO-d_6) δ 11.30 (br s, 1H), 9.26* (d, J = 8.0 Hz, 1H), 8.86 (d, J = 8.2 Hz, 1H), 7.38 – 7.20 (m, 7H), 7.11 – 7.02* (m, 2H), 7.02 – 6.93 (m, 2H), 6.10* (d, J = 7.9 Hz, 1H), 6.01 (d, J = 8.2 Hz, 1H), 5.52 – 5.22 (m, 1H), 4.77* (t, J = 8.2 Hz, 1H), 4.66 (d, J = 16.8 Hz, 1H), 4.58 – 4.41 (m, 2H), 4.06 – 3.89 (m, 1H), 3.82 – 3.65 (m, 1H), 3.53 – 3.36* (m, 1H), 2.82 – 2.68* (m, 1H), 2.27 – 2.09* (m, 1H), 2.09 – 1.88 (m, 1H), 1.78 – 1.70 (m, 3H), 1.31 – 1.25 (m, 3H), 0.77 – 0.63 (m, 4H). LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{29}H_{30}F_2N_4O_4$: 537.2; found 537.3.

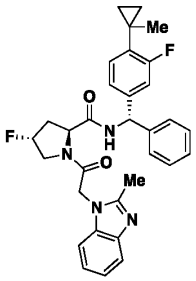
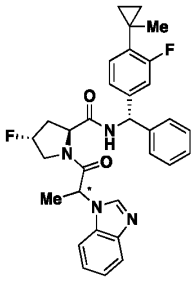
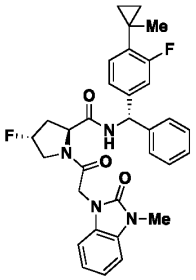
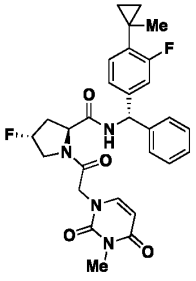
[0702] Minor isomer (compound 557): ^{1}H NMR (3.3:1 rotamer ratio, asterisk denotes minor rotamer peaks, obscured peaks not reported, 400 MHz, DMSO-d_6) δ 11.30 (br s, 1H), 9.27* (d, J = 8.1 Hz, 1H), 8.89 (d, J = 8.3 Hz, 1H), 7.41 – 7.20 (m, 6H), 7.17 – 6.94 (m, 2H), 6.11* (d, J = 8.0 Hz, 1H), 6.01 (d, J = 8.2 Hz, 1H), 5.54 – 5.21 (m, 1H), 4.77* (t, J = 8.2 Hz, 1H), 4.68 (d, J = 16.8 Hz, 1H), 4.54 (t, J = 8.1 Hz, 1H), 4.45 (d, J = 16.9 Hz, 1H), 4.05 – 3.86 (m, 1H), 3.83 – 3.65 (m, 1H), 3.53 – 3.36* (m, 1H), 2.25 – 1.87 (m, 1H), 1.78 – 1.70 (m, 3H), 1.30 – 1.21 (m, 3H), 0.75 – 0.62 (m, 4H). LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{29}H_{30}F_2N_4O_4$: 537.2; found 537.3.

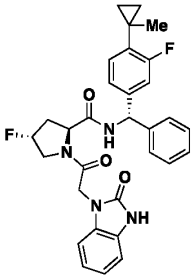
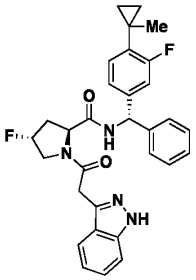
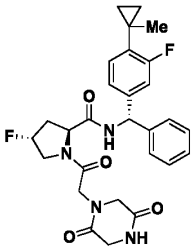
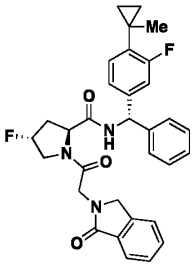
[0703] The following compounds in Table T-11 were synthesized using procedures similar to Compounds 556 and 557 using the appropriate starting materials.

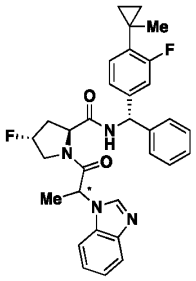
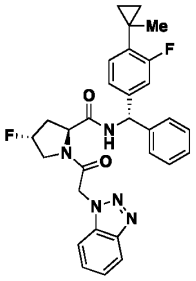
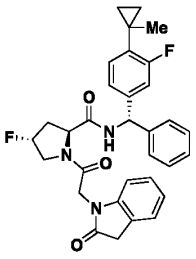
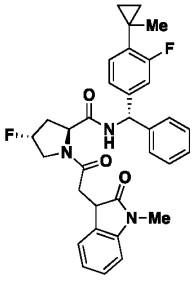
Table T-11

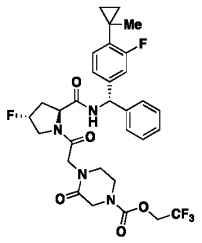
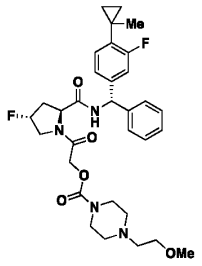
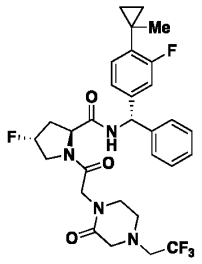
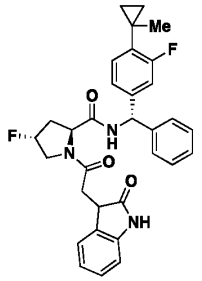
Compound No.	Structure	IUPAC	Exact mass (g/mol)	LCMS, Found [M + H]+
558		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide	479.2	480.2
559		(2S,4R)-4-fluoro-N-[(R)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](pyridin-3-yl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide	480.2	481.3
560		2-[(2S,4R)-4-fluoro-2-{[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl azetidine-1-carboxylate	511.2	512.3
561		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]-1-[2-(1-methyl-1H-indol-2-yl)acetyl]pyrrolidine-2-carboxamide	541.3	542.3

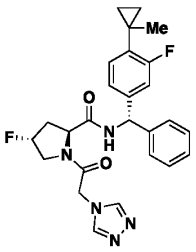
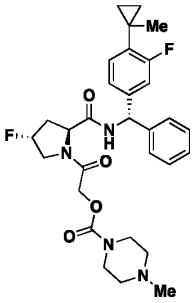
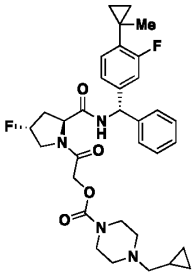
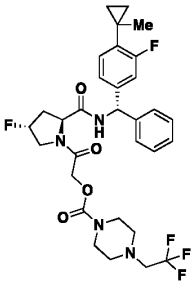
562		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]-1-[2-(2-oxopiperazin-1-yl)acetyl]pyrrolidine-2-carboxamide	510.2	511.3
563		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]-1-[2-(1-methyl-1H-indol-3-yl)acetyl]pyrrolidine-2-carboxamide	541.3	542.3
564		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]-1-[2-(1-methyl-1H-indazol-3-yl)acetyl]pyrrolidine-2-carboxamide	542.2	543.1
565		N-{2-[(2S,4R)-4-fluoro-2-{[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl}morpholine-4-carboxamide	540.3	541.3

566		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]-1-[2-(2-methyl-1H-1,3-benzodiazol-1-yl)acetyl]pyrrolidine-2-carboxamide	542.2	543.3
567		(2S,4R)-1-[(2R) or (2S)-2-(1H-1,3-benzodiazol-1-yl)propanoyl]-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]pyrrolidine-2-carboxamide (column: DAICEL CHIRALPAK IG-3, first-eluting isomer)	542.2	543.3
568		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]-1-[2-(3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)acetyl]pyrrolidine-2-carboxamide	558.2	559.3
569		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]-1-[2-(3-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-	536.2	537.2

		yl)acetyl]pyrrolidine-2-carboxamide		
570		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]-1-[2-(2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)acetyl]pyrrolidine-2-carboxamide	544.2	545.3
571		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]-1-[2-(1H-indazol-3-yl)acetyl]pyrrolidine-2-carboxamide	528.2	529.1
572		(2S,4R)-1-[2-(2,5-dioxopiperazin-1-yl)acetyl]-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]pyrrolidine-2-carboxamide	524.2	525.2
573		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]-1-[2-(1-oxo-2,3-dihydro-1H-isoindol-2-yl)acetyl]pyrrolidine-2-carboxamide	543.2	544.1

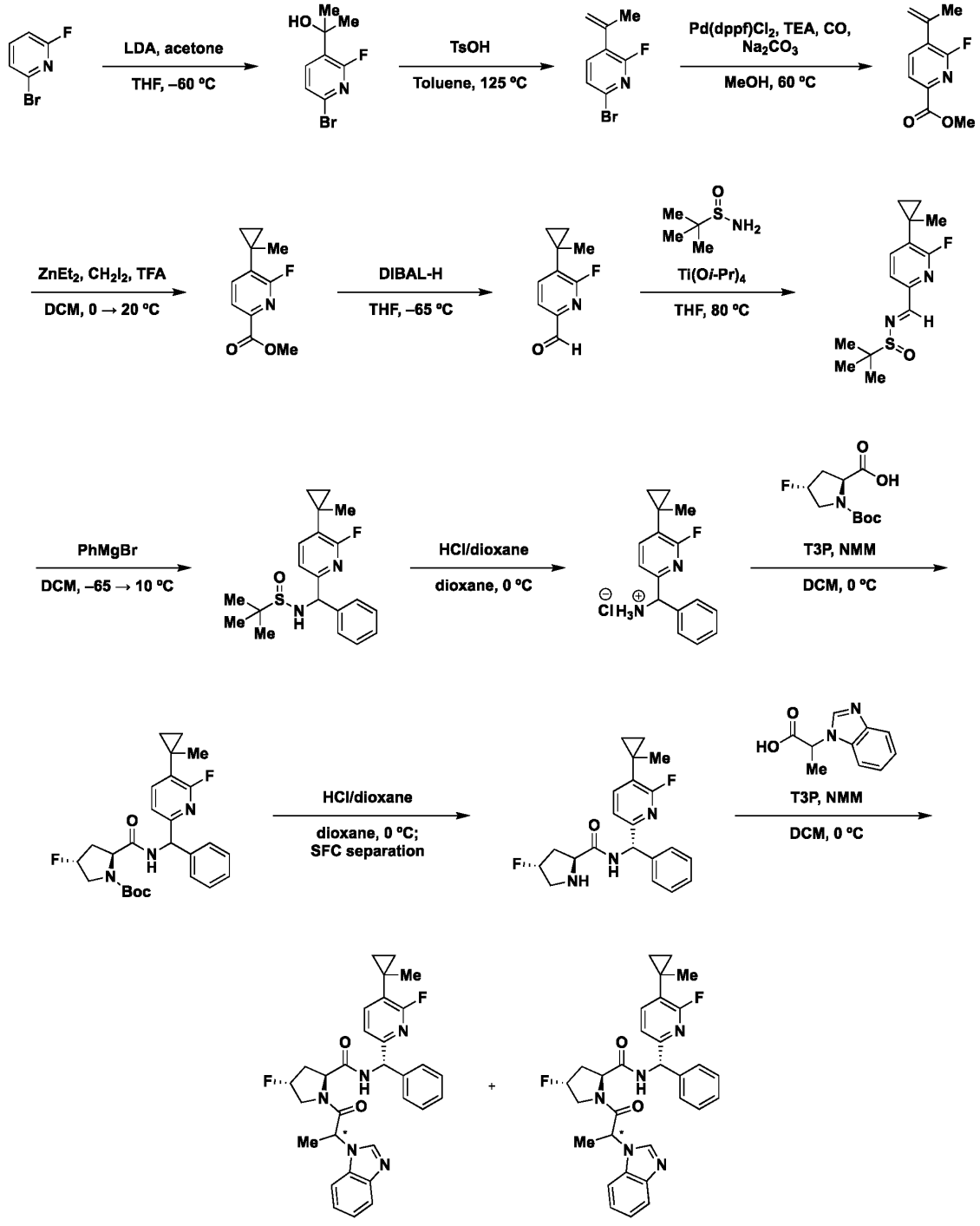
574		(2S,4R)-1-[(2S) or 2R)-2-(1H-1,3-benzodiazol-1-yl)propanoyl]-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]pyrrolidine-2-carboxamide (column: DAICEL CHIRALPAK IG-3, second-eluting isomer)	542.2	543.3
575		(2S,4R)-1-[2-(1H-1,2,3-benzotriazol-1-yl)acetyl]-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]pyrrolidine-2-carboxamide	529.2	530.1
576		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]-1-[2-(2-oxo-2,3-dihydro-1H-indol-1-yl)acetyl]pyrrolidine-2-carboxamide	543.2	544.2
577		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]-1-[2-(1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl)acetyl]pyrrolidine-2-carboxamide	557.2	558.3

578		2,2,2-trifluoroethyl 4-{2-[(2S,4R)-4-fluoro-2-{[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl}-3-oxopiperazine-1-carboxylate	636.2	637.2
579		2-[(2S,4R)-4-fluoro-2-{[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl 4-(2-methoxyethyl)piperazine-1-carboxylate	598.3	599.2
580		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]-1-{2-[2-oxo-4-(2,2,2-trifluoroethyl)piperazin-1-yl]acetyl}pyrrolidine-2-carboxamide	592.2	593.2
581		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]-1-[2-(2-oxo-2,3-dihydro-1H-indol-3-yl)acetyl]pyrrolidine-2-carboxamide	543.2	544.2

582		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]-1-[2-(4H-1,2,4-triazol-4-yl)acetyl]pyrrolidine-2-carboxamide	479.2	480.3
583		2-[(2S,4R)-4-fluoro-2-{[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl 4-methylpiperazine-1-carboxylate	554.3	555.3
584		2-[(2S,4R)-4-fluoro-2-{[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl 4-(cyclopropylmethyl)piperazine-1-carboxylate	594.3	595.3
585		2-[(2S,4R)-4-fluoro-2-{[(S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](phenyl)methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl 4-(2,2,2-trifluoroethyl)piperazine-1-carboxylate	622.3	623.3

Example S-12: Synthesis of (2*S*,4*R*)-1-((*S*) or (*R*)-2-(1*H*-benzo[*d*]imidazol-1-yl)propanoyl)-4-fluoro-*N*-((*S*)-(6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl)(phenyl)methyl)pyrrolidine-2-carboxamide and (2*S*,4*R*)-1-((*R*) or (*S*)-2-(1*H*-benzo[*d*]imidazol-1-yl)propanoyl)-4-fluoro-*N*-((*S*)-(6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl)(phenyl)methyl)pyrrolidine-2-carboxamide

(Compounds 586 and 587)



[0704] Step a: To a solution of 2-bromo-6-fluoropyridine (12.5 g, 71.0 mmol, 1.00 eq) in THF (125 mL) at –60 °C under N_2 was added lithium diisopropylamide (LDA, 2 M in

THF, 35.5 mL, 1.00 eq) in a dropwise manner. The resulting mixture was stirred at –60 ºC for 0.5 h. Acetone (6.19 g, 106 mmol, 1.50 eq) was then added in a dropwise manner at –60 ºC. The resulting mixture was then stirred at –60 ºC for 0.5 h. The reaction was then allowed to warm to 0 ºC, quenched by addition of H_2O (60 mL), and stirred for 10 min. The resulting biphasic mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 2-(6-bromo-2-fluoropyridin-3-yl)propan-2-ol. LC-MS (ESI): m/z: $[M + H]^+$ calculated for C_8H_9BrFNO: 234.0; found: 234.0.

[0705] Step b: To a solution of 2-(6-bromo-2-fluoropyridin-3-yl)propan-2-ol (13.5 g, 57.7 mmol, 1.00 eq) in toluene (135 mL) at 25 ºC was added TsOH (1.99 g, 11.5 mmol, 0.20 eq) in a dropwise manner. The reaction mixture was the warmed to 125 ºC and stirred for 16 h. The reaction mixture was then cooled to 0 ºC and quenched by addition of H_2O (50 mL). The resulting biphasic mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 6-bromo-2-fluoro-3-(prop-1-en-2-yl)pyridine. LC-MS (ESI): m/z: $[M + H]^+$ calculated for C_8H_7BrFN: 216.0; found: 216.0.

[0706] Step c: To a solution of 6-bromo-2-fluoro-3-(prop-1-en-2-yl)pyridine (6.5 g, 30.1 mmol, 1.00 eq) in MeOH (65 mL) was added TEA (6.09 g, 60.17 mmol, 2.00 eq) and $Pd(dppf)Cl_2$ (2.46 g, 3.01 mmol, 0.10 eq). The reaction mixture was then placed under an atmosphere of CO (50 psi), warmed to 60 ºC, and stirred for 2 h. The reaction mixture was then concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give methyl 6-fluoro-5-(prop-1-en-2-yl)picolinate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{10}H_{10}FNO_2$: 196.1; found: 196.1.

[0707] Step d: To a solution of $ZnEt_2$ (1 M in hexane, 102 mL, 5.00 eq) at 0 ºC was added TFA (102 mmol, 7.6 mL, 5.00 eq) in DCM (24 mL) in a dropwise manner. The resulting mixture was stirred at 0 ºC for 0.5 h. CH_2I_2 (27.4 g, 102 mmol, 5.00 eq) in DCM (22 mL) was then added in a dropwise manner at 0 ºC, and the resulting mixture was stirred at 0 ºC for 0.5 h. Methyl 6-fluoro-5-(prop-1-en-2-yl)picolinate (4 g, 20 mmol, 1.00 eq) in DCM (12 mL) was then

added in a dropwise manner at 0 ºC. The resulting mixture was then allowed to warm to 20 ºC and stirred for 15 h. The reaction mixture was then quenched by addition of saturated aqueous NH_4Cl (100 ml) at 0 ºC, and the resulting biphasic mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was obtained was purified by column chromatography and prep-HPLC to give methyl 6-fluoro-5-(1-methylcyclopropyl)picolinate (2.56 g). LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{11}H_{12}FNO_2$: 210.1; found: 210.1.

[0708] Step e: A solution of 6-fluoro-5-(1-methylcyclopropyl)picolinate (1.25 g, 5.97 mmol, 1 eq) in THF (12.5 mL) was degassed and purged with N_2 and cooled to –65 ºC. To this solution was added diisobutylaluminium hydride (DIBAL-H, 1 M in THF, 11.9 mL, 2 eq) in a dropwise manner. The resulting mixture was stirred at –65 ºC for 2 h. The reaction mixture was then warmed to 0 ºC and quenched by addition water (50 mL). The resulting biphasic mixture was then filtered and extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give 6-fluoro-5-(1-methylcyclopropyl)picolinaldehyde. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{10}H_{10}FNO$: 180.1; found: 180.1.

[0709] Step f: To a mixture of 6-fluoro-5-(1-methylcyclopropyl)picolinaldehyde (0.8 g, 4.46 mmol, 1 eq) and 2-methylpropane-2-sulfinamide (1.08 g, 8.93 mmol, 2 eq) in THF (8 mL) at 25 ºC under N_2 was added $Ti(O\textit{i}\text{-}Pr)_4$ (2.54 g, 8.93 mmol, 2.64 mL, 2 eq). The resulting mixture was warmed to 80 ºC and stirred for 2 h. The reaction mixture was then poured into ice-water (15 mL) and stirred for 10 min. The resulting biphasic mixture was extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with brine (2 x 30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give (*E*)-*N*-((6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{14}H_{19}FN_2OS$: 283.1; found: 283.1.

[0710] Step g: To a solution of (*E*)-*N*-((6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide (1.15 g, 4.07 mmol, 1 eq) in DCM (11.5 mL) at –

60 °C was added phenylmagnesium bromide (3 M in diethyl ether, 2.04 mL, 1.5 eq) in a dropwise manner. The resulting mixture was stirred at –60 °C for 1 h before it was warmed to 10 °C and stirred for 1 h. The reaction mixture was then poured into saturated aqueous NH_4Cl (30 mL) and stirred for 10 min. The resulting biphasic mixture was then extracted with DCM (2 x 50 mL). The combined organic extracts were washed with brine (2 x 30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give *N*-((6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl)(phenyl)methyl)-2-methylpropane-2-sulfinamide. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{20}H_{25}FN_2OS$: 361.2; found: 361.2.

[0711] Step h: To a solution of *N*-((6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl)(phenyl)methyl)-2-methylpropane-2-sulfinamide (1.45 g, 4.02 mmol, 1 eq) in dioxane (3 mL) at 0 °C was added HCl/dioxane (4 M, 6.44 mL, 6.41 eq), and the resulting mixture was stirred at 0 °C for 1 h. The reaction mixture was then concentrated under reduced pressure. The crude residue was then triturated with methyl *tert*-butyl ether (10 mL) at 25 °C for 10 min and filtered. The filter cake was dried under reduced pressure to give (6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl)(phenyl)methanaminium chloride. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{16}H_{17}FN_2$: 257.1; found: 257.2.

[0712] Step i: To a mixture of (6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl)(phenyl)methanaminium chloride (1.20 g, 4.1 mmol, 1 eq) and (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (1.15 g, 4.92 mmol, 1.2 eq) in DCM (20 mL) at 25 °C under N_2 was added *N*-methylmorpholine (NMM, 1.24 g, 12.3 mmol, 1.35 mL, 3 eq). The resulting mixture was cooled to –20 °C before 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide (T3P, 5.22 g, 8.20 mmol, 4.88 mL, 50% purity, 2 eq) was added in a dropwise manner. The resulting mixture was stirred at –20 °C for 1 h before the reaction mixture was poured into ice-water (15 mL) and stirred for 10 min. The aqueous phase was extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were washed with brine (3 x 15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give *tert*-butyl (2*S*,4*R*)-4-fluoro-2-(((6-fluoro-5-(1-methylcyclopropyl)pyridin-2-

yl)(phenyl)methyl)carbamoyl)pyrrolidine-1-carboxylate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{26}H_{31}F_2N_3O_3$: 472.2; found: 472.2.

[0713] Step j: To a solution of *tert*-butyl (2*S*,4*R*)-4-fluoro-2-(((6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl)(phenyl)methyl)carbamoyl)pyrrolidine-1-carboxylate (3.8 g, 8.06 mmol, 1 eq) in dioxane (20 mL) at 0 °C was added HCl/dioxane (4 M, 20 mL). The resulting mixture was then stirred at 0 °C for 1 h. The reaction mixture was then concentrated under reduced pressure. The crude product was added diluted with saturated aqueous $NaHCO_3$, and the aqueous phase was extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with brine (2 x 30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by SFC (column: REGIS(S,S)WHELK-O1) to give (2*S*,4*R*)-4-fluoro-*N*-((*S*)-(6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl)(phenyl)methyl)pyrrolidine-2-carboxamide and (2*S*,4*R*)-4-fluoro-*N*-((*R*)-(6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl)(phenyl)methyl)pyrrolidine-2-carboxamide as separate diastereomers. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{21}H_{23}F_2N_3O$: 372.2; found: 372.2.

[0714] Step k: To a mixture of 2-(1*H*-benzo[*d*]imidazol-1-yl)propanoic acid (80.0 mg, 421 µmol, 1.00 eq) and (2*S*,4*R*)-4-fluoro-*N*-((*S*)-(6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl)(phenyl)methyl)pyrrolidine-2-carboxamide (156 mg, 421 µmol, 1.00 eq) in DCM (2 mL) at –20 °C under N_2 was added *N*-methylmorpholine (NMM, 421 µmol, 46.2 µL, 1.00 eq) and 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide (T3P, 841 µmol, 500 µL, 50% purity, 2.00 eq). The resulting mixture was warmed to 0 °C and stirred for 1 h. The reaction was then quenched by addition H_2O (10 mL) at 0 °C. The resulting biphasic mixture was then extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by prep-HPLC followed by SCF (column: REGIS (R,R)WHELK-O1) to give (2*S*,4*R*)-1-((*R*) or (*S*)-2-(1*H*-benzo[*d*]imidazol-1-yl)propanoyl)-4-fluoro-*N*-((*S*)-(6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl)(phenyl)methyl)pyrrolidine-2-carboxamide (Compound 587; first-eluting isomer) and (2*S*,4*R*)-1-((*S*) or (*R*)-2-(1*H*-benzo[*d*]imidazol-1-yl)propanoyl)-4-fluoro-*N*-((*S*)-(6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl)(phenyl)methyl)pyrrolidine-2-carboxamide (Compound 586; second-eluting isomer).

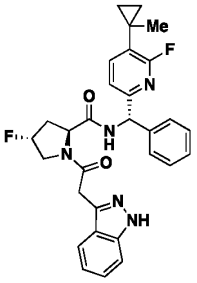
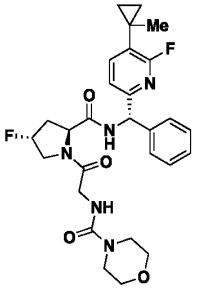
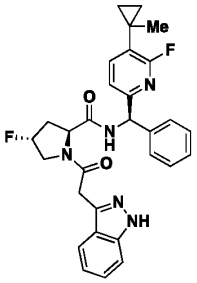
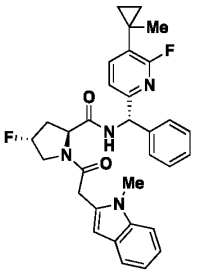
[0715] First-eluting isomer (Compound 587): ^{1}H NMR (4:1 rotamer ratio, asterisk denotes minor rotamer peaks, obscured peaks not reported, 400 MHz, DMSO-d_6) δ 9.61* (d, J = 8.3 Hz, 1H), 8.94 (d, J = 7.8 Hz, 1H), 8.25 (s, 1H), 7.90 – 7.81* (m, 1H), 7.81 – 7.70 (m, 1H), 7.70 – 7.55 (m, 2H), 7.52 – 7.42 (m, 1H), 7.39 – 7.11 (m, 7H), 6.19* (d, J = 8.0 Hz, 1H), 5.95 (d, J = 7.7 Hz, 1H), 5.72 – 5.66 (m, 1H), 5.43 – 5.17 (m, 1H), 5.12 – 5.02* (m, 1H), 4.71 (t, J = 8.4 Hz, 1H), 4.09 – 3.97 (m, 1H), 2.03 – 1.79 (m, 2H), 1.59 – 1.53 (m, 3H), 1.32 – 1.22 (m, 3H), 0.83 – 0.62 (m, 4H). LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{31}H_{31}F_2N_5O_2$: 544.2; found 544.2.

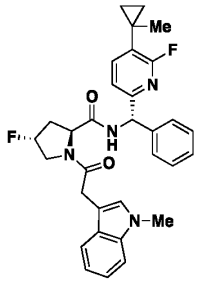
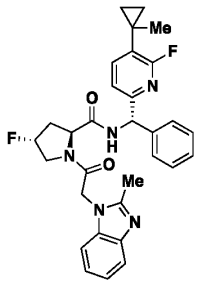
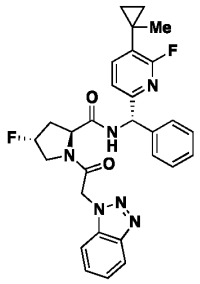
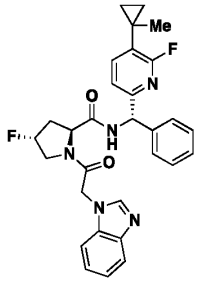
[0716] Second-eluting isomer (Compound 586): ^{1}H NMR (4.4:1 rotamer ratio, asterisk denotes minor rotamer peaks, obscured peaks not reported, 400 MHz, DMSO-d_6) δ 9.55* (d, J = 8.0 Hz, 1H), 8.90 (d, J = 8.0 Hz, 1H), 8.34 (s, 1H), 8.23* (s, 1H), 7.84 (dd, J = 10.1, 7.5 Hz, 1H), 7.69 – 7.62 (m, 1H), 7.57* (d, J = 8.0 Hz, 1H), 7.52 – 7.43 (m, 1H), 7.39 – 7.15 (m, 7H), 7.14 – 7.07* (m, 1H), 6.95* (d, J = 4.1 Hz, 1H), 6.17* (d, J = 8.0 Hz, 1H), 6.00 (d, J = 7.9 Hz, 1H), 5.70 (q, J = 7.0 Hz, 1H), 5.54 – 5.24 (m, 1H), 5.08* (t, J = 7.9 Hz, 1H), 4.88* (q, J = 7.1 Hz, 1H), 4.62 (t, J = 8.4 Hz, 1H), 4.27 (dd, J = 20.4, 12.6 Hz, 1H), 3.97 – 3.74 (m, 1H), 3.57 – 3.39* (m, 1H), 2.87 – 2.71* (m, 1H), 2.14 – 1.92 (m, 1H), 1.79 – 1.68 (m, 3H), 1.30 – 1.26 (m, 3H), 0.81 – 0.67 (m, 4H). LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{31}H_{31}F_2N_5O_2$: 544.2; found 544.2.

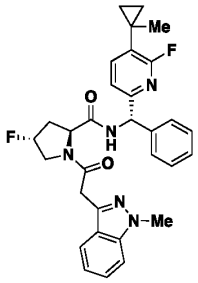
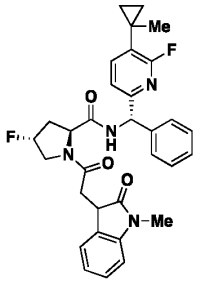
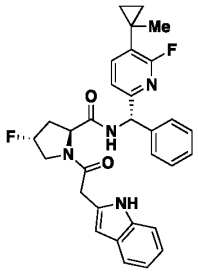
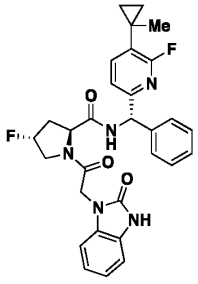
[0717] The following compounds in Table T-12 were synthesized using procedures similar to Compound 586 and Compound 587 using the appropriate starting materials.

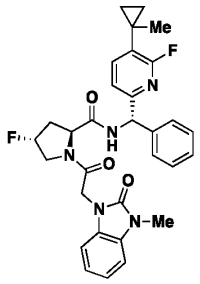
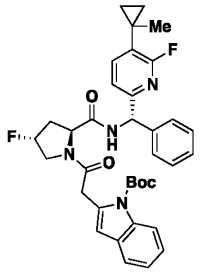
Table T-12

Compound No.	Structure	IUPAC	Exact mass (g/mol)	LCMS, Found $[M + H]^+$

588		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl]-1-[2-(1H-indazol-3-yl)acetyl]pyrrolidine-2-carboxamide	529.2	530.3
589		N-{2-[(2S,4R)-4-fluoro-2-{[(S)-[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl}morpholine-4-carboxamide	541.3	542.3
590		(2S,4R)-4-fluoro-N-[(R)-[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl]-1-[2-(1H-indazol-3-yl)acetyl]pyrrolidine-2-carboxamide	529.2	530.3
591		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl]-1-[2-(1-methyl-1H-indol-2-yl)acetyl]pyrrolidine-2-carboxamide	542.2	543.2

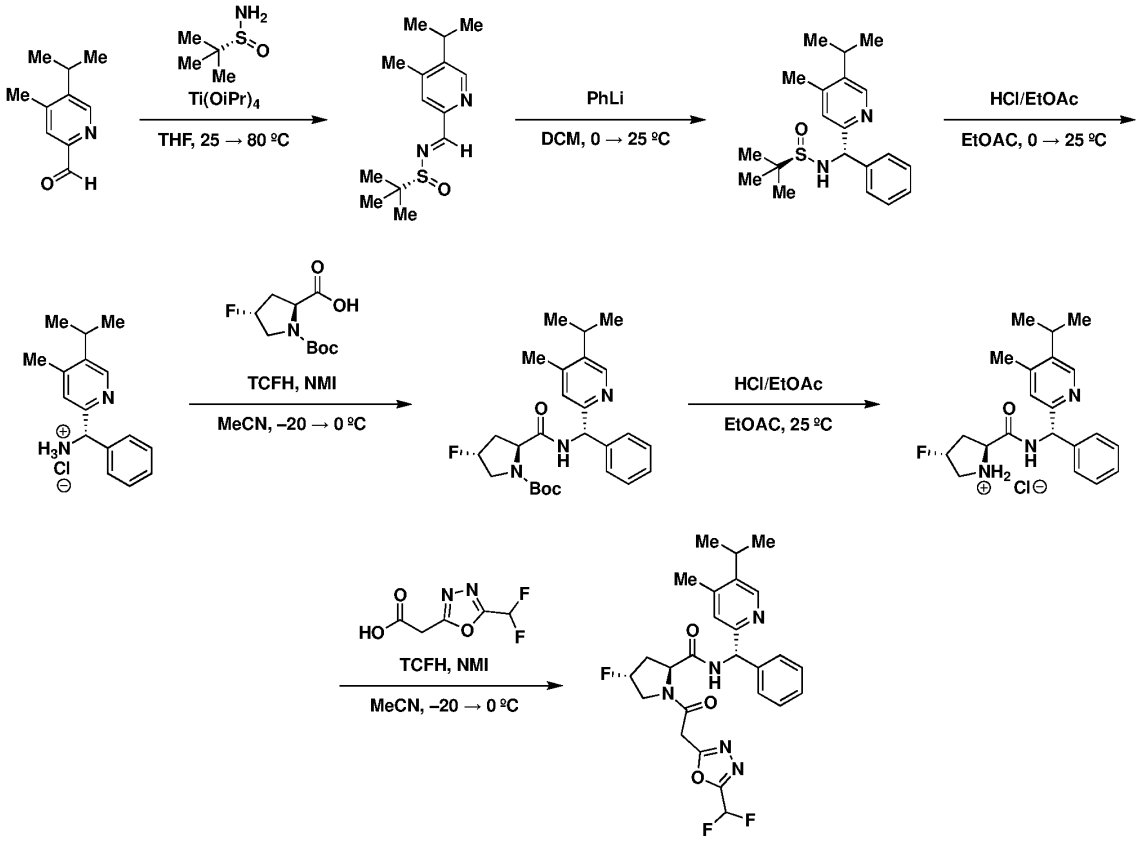
592		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl]-1-[2-(1-methyl-1H-indol-3-yl)acetyl]pyrrolidine-2-carboxamide	542.2	543.2
593		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl]-1-[2-(2-methyl-1H-1,3-benzodiazol-1-yl)acetyl]pyrrolidine-2-carboxamide	543.2	544.3
594		(2S,4R)-1-[2-(1H-1,2,3-benzotriazol-1-yl)acetyl]-4-fluoro-N-[(S)-[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide	530.2	531.3
595		(2S,4R)-1-[2-(1H-1,3-benzodiazol-1-yl)acetyl]-4-fluoro-N-[(S)-[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide	529.2	530.2

596		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl]-1-[2-(1-methyl-1H-indazol-3-yl)acetyl]pyrrolidine-2-carboxamide	543.2	544.2
597		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl]-1-[2-(1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl)acetyl]pyrrolidine-2-carboxamide	558.2	559.2
598		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl]-1-[2-(1H-indol-2-yl)acetyl]pyrrolidine-2-carboxamide	528.2	529.2
599		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl]-1-[2-(2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)acetyl]pyrrolidine-2-carboxamide	545.2	546.2

600		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl]-1-[2-(3-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-1-yl)acetyl]pyrrolidine-2-carboxamide	559.2	560.2
601		tert-butyl 2-{2-[(2S,4R)-4-fluoro-2-{[(S)-[6-fluoro-5-(1-methylcyclopropyl)pyridin-2-yl](phenyl)methyl]carbamoyl}pyrrolidin-1-yl]-2-oxoethyl}-1H-indole-1-carboxylate	628.3	629.3

Example S-13: Synthesis of (2*S*,4*R*)-1-(2-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)acetyl)-4-fluoro-*N*-((*S*)-(5-isopropyl-4-methylpyridin-2-yl)(phenyl)methyl)pyrrolidine-2-carboxamide

(Compound 602)



[0718] Step a: To a mixture of 5-isopropyl-4-methylpicolinaldehyde (3 g, 18.4 mmol, 1 eq) and (*R*)-2-methylpropane-2-sulfinamide (2.90 g, 23.9 mmol, 1.3 eq) in THF (5 mL) at 25 ºC under N_2 was added Ti(O*i*-Pr)$_4$ (10.4 g, 36.7 mmol, 2 eq). The resulting mixture was warmed to 80 ºC and stirred for 1 h. The reaction mixture was then quenched with H_2O (30 mL) and extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give (*R*,*E*)-*N*-((5-isopropyl-4-methylpyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{14}H_{22}N_2OS$: 267.1; found: 267.1.

[0719] Step b: To a mixture of (*R*,*E*)-*N*-((5-isopropyl-4-methylpyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide (850 mg, 3.19 mmol, 1 eq) in DCM (5 mL) at 0 ºC under N_2 was added PhLi (1 M in Et_2O, 8.0 mL, 2.5 eq). The resulting mixture was warmed to 25 ºC and stirred for 16 h. The reaction mixture was then quenched with aq. NH_4Cl solution

(10 mL), and the resulting biphasic mixture was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by prep-HPLC to give (*R*)-*N*-((*S*)-(5-isopropyl-4-methylpyridin-2-yl)(phenyl)methyl)-2-methylpropane-2-sulfinamide. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{20}H_{28}N_2OS$: 345.2; found: 345.1.

[0720] Step c: To a solution of (*R*)-*N*-((*S*)-(5-isopropyl-4-methylpyridin-2-yl)(phenyl)methyl)-2-methylpropane-2-sulfinamide (75 mg, 217 μmol, 1 eq) in EtOAc (2 mL) at 0 °C was added HCl/EtOAc (4 M, 5 mL), and the resulting mixture was warmed to 25 °C and stirred for 1 h. The reaction mixture was then concentrated under reduced pressure to give (*S*)-(5-isopropyl-4-methylpyridin-2-yl)(phenyl)methanaminium chloride. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{16}H_{20}N_2$: 241.2; found: 241.1.

[0721] Step d: To a mixture of (*S*)-(5-isopropyl-4-methylpyridin-2-yl)(phenyl)methanaminium chloride (65 mg, 234 μmol, 1 eq) and (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (71.2 mg, 305 μmol, 1.3 eq) in MeCN (3 mL) at –20 °C under N_2 was added *N*-methylimidazole (57.8 mg, 704 μmol, 56.1 μL, 3 eq) and chloro-*N*,*N*,*N*′,*N*′-tetramethylformamidinium hexafluorophosphate (TCFH, 85.7 mg, 305 μmol, 1.3 eq), and the resulting mixture was warmed to 0 °C and stirred for 1 h. The reaction mixture was then quenched with H_2O (10 mL), and the resulting biphasic mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by prep-TLC to give *tert*-butyl (2*S*,4*R*)-4-fluoro-2-(((*S*)-(5-isopropyl-4-methylpyridin-2-yl)(phenyl)methyl)carbamoyl)pyrrolidine-1-carboxylate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{26}H_{34}FN_3O_3$: 456.3; found: 456.1.

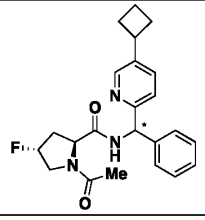
[0722] Step e: To a solution of *tert*-butyl (2*S*,4*R*)-4-fluoro-2-(((*S*)-(5-isopropyl-4-methylpyridin-2-yl)(phenyl)methyl)carbamoyl)pyrrolidine-1-carboxylate (35 mg, 76.8 μmol, 1 eq) in EtOAc (2 mL) at 25 °C under N_2 was added HCl/EtOAc (4 M, 2 mL). The resulting mixture was stirred at 25 °C for 1 h. The reaction mixture was then concentrated under reduced pressure to give (2*S*,4*R*)-4-fluoro-2-(((*S*)-(5-isopropyl-4-methylpyridin-2-

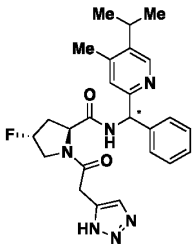
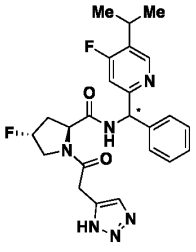
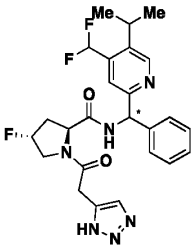
yl)(phenyl)methyl)carbamoyl)pyrrolidin-1-ium chloride. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{21}H_{26}FN_3O$: 356.2; found: 356.1.

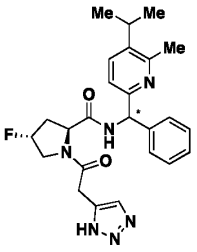
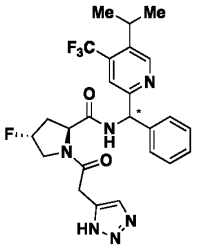
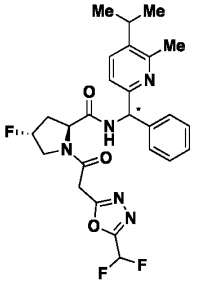
[0723] Step f: To a mixture of (2*S*,4*R*)-4-fluoro-2-(((*S*)-(5-isopropyl-4-methylpyridin-2-yl)(phenyl)methyl)carbamoyl)pyrrolidin-1-ium chloride (45.3 mg, 127 μmol, 1 eq) and 2-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)acetic acid (34.1 mg, 191 μmol, 1.5 eq) in MeCN (3 mL) at –20 ºC under N_2 was added chloro-*N,N,N′,N′*-tetramethylformamidinium hexafluorophosphate (TCFH, 53.7 mg, 191 μmol, 1.5 eq) and *N*-methylimidazole (31.4 mg, 382 μmol, 3 eq). The resulting mixture was warmed to 0 ºC and stirred for 1 h. The reaction mixture was then diluted with H_2O (10 mL), and the resulting biphasic mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by prep-HPLC to give (2*S*,4*R*)-1-(2-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)acetyl)-4-fluoro-*N*-((*S*)-(5-isopropyl-4-methylpyridin-2-yl)(phenyl)methyl)pyrrolidine-2-carboxamide. ^{1}H NMR (4.7:1 rotamer ratio, asterisk denotes distinct minor rotamer peaks, obscured peaks not reported, 400 MHz, methanol-d_4) δ 8.39* (s, 1H), 8.32 (s, 1H), 7.38 – 7.19 (m, 5H), 7.16 – 7.12 (m, 1H), 7.09* (s, 1H), 7.01* (s, 1H), 6.15* (s, 1H), 6.11 (s, 1H), 5.48 – 5.20 (m, 1H), 4.74 – 4.67 (m, 1H), 4.23* (s, 1H), 4.16 – 4.03 (m, 1H), 3.99 – 3.81 (m, 1H), 3.24 – 3.13 (m, 1H), 2.70 – 2.56 (m, 1H), 2.37 – 2.32 (m, 3H), 2.28 – 2.07 (m, 1H), 1.32 – 1.25 (m, 6H). LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{26}H_{28}F_3N_5O_3$: 516.2; found 516.2.

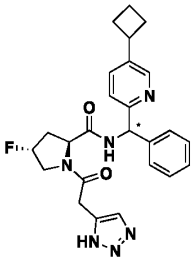
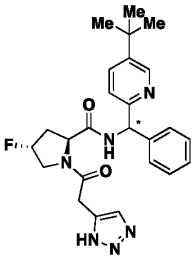
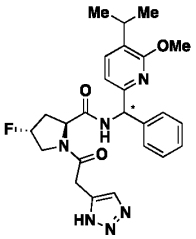
[0724] The following compounds in Table T-13 were synthesized using procedures similar to Compound 602 using the appropriate starting materials.

Table T-13

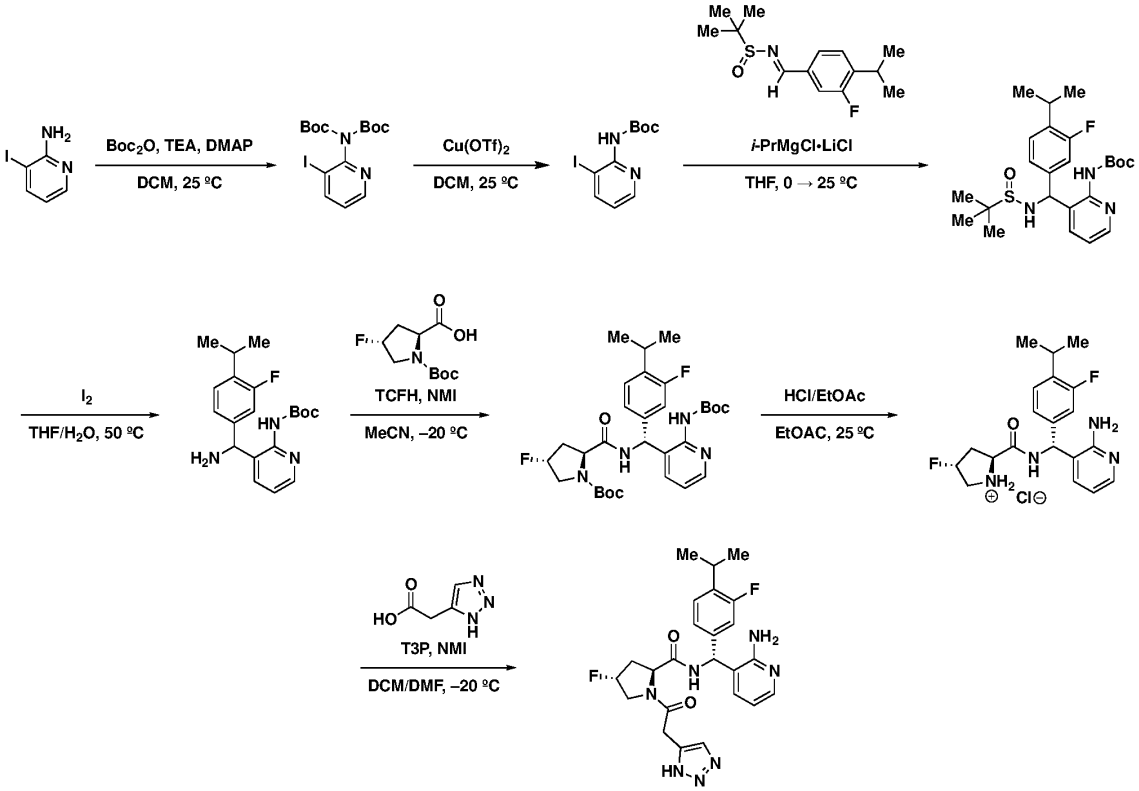
Compound No.	Structure	IUPAC	Exact mass (g/mol)	LCMS, Found $[M + H]^+$
603		(2S,4R)-1-acetyl-N-[(S) or (R)-(5-cyclobutylpyridin-2-yl)(phenyl)methyl]-4-	395.2	396.2

		fluoropyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, first-eluting isomer)		
604		(2S,4R)-4-fluoro-N-[(S) or (R)-[4-methyl-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, first-eluting isomer)	464.2	465.2
605		(2S,4R)-4-fluoro-N-[(S) or (R)-[4-fluoro-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, first-eluting isomer)	468.2	469.1
606		(2S,4R)-N-[(S) or (R)-[4-(difluoromethyl)-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1,	500.2	501.2

		first-eluting isomer)		
607		(2S,4R)-4-fluoro-N-[(S) or (R)-[6-methyl-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, first-eluting isomer)	464.2	465.2
608		(2S,4R)-4-fluoro-N-[(S) or (R)-phenyl[5-(propan-2-yl)-4-(trifluoromethyl)pyridin-2-yl]methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, first-eluting isomer)	518.2	519.2
609		(2S,4R)-1-{2-[5-(difluoromethyl)-1,3,4-oxadiazol-2-yl]acetyl}-4-fluoro-N-[(S) or (R)-[6-methyl-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, first-eluting isomer)	515.2	516.2

610		(2S,4R)-N-[(S) or (R)-(5-cyclobutylpyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, first-eluting isomer)	462.2	463.2
611		(2S,4R)-N-[(S) or (R)-(5-tert-butylpyridin-2-yl)(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, first-eluting isomer)	464.2	465.1
612		(2S,4R)-4-fluoro-N-[(S) or (R)-[6-methoxy-5-(propan-2-yl)pyridin-2-yl](phenyl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, first-eluting isomer)	480.2	481.1

Example S-14: Synthesis of (2*S*,4*R*)-1-(2-(1*H*-1,2,3-triazol-5-yl)acetyl)-*N*-((*R*)-(2-aminopyridin-3-yl)(3-fluoro-4-isopropylphenyl)methyl)-4-fluoropyrrolidine-2-carboxamide (Compound 613)



[0725] Step a: To a solution of 3-iodopyridin-2-amine (9.00 g, 40.9 mmol, 1 eq) in DCM (200 mL) was added TEA (102 mmol, 14.2 mL, 2.5 eq) and Boc_2O (49.1 mmol, 11.3 mL, 1.2 eq), DMAP (500 mg, 4.09 mmol, 0.1 eq). The resulting mixture was stirred at 25 °C for 15 h. The reaction mixture was then cooled to 0 °C and quenched by addition of water (100 mL), and the resulting biphasic mixture was adjusted to pH = 6 using aq. HCl solution (4 N). The resulting mixture was extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was triturated with petroleum ether to give *tert*-butyl (*tert*-butoxycarbonyl)(3-iodopyridin-2-yl)carbamate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{15}H_{21}IN_2O_4$: 421.0; found 421.1.

[0726] Step b: To a solution of *tert*-butyl (*tert*-butoxycarbonyl)(3-iodopyridin-2-yl)carbamate (15.0 g, 35.7 mmol, 1 eq) in DCM (100 mL) was added bis(trifluoromethylsulfonyloxy)copper (12.9 g, 35.7 mmol, 1 eq). The resulting mixture was stirred at 25 °C for 20 min. The reaction mixture was then cooled to 0 °C and quenched by addition of water (100 mL). The resulting biphasic mixture was then extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give *tert*-butyl (3-iodopyridin-2-yl)carbamate, which was carried forward to the next step without further purification or characterization.

[0727] Step c: To a solution of *tert*-butyl (3-iodopyridin-2-yl)carbamate (7.13 g, 22.3 mmol, 3 eq) in THF (45 mL) at 0 °C was added *i*-PrMgCl·LiCl (1.3 M in THF, 28.6 mL, 5 eq), and the resulting mixture was stirred at 0 °C for 2 h. Then, (*E*)-*N*-(3-fluoro-4-isopropylbenzylidene)-2-methylpropane-2-sulfinamide (2 g, 7.42 mmol, 1 eq) in THF (0.5 mL) was added dropwise. The resulting mixture was allowed to warm to 25 °C and stirred for 2 h. The reaction mixture was then cooled to 0 °C and quenched by addition of saturated aq. NH_4Cl solution (50 mL). The resulting biphasic mixture was then extracted with EtOAc (2 x 30 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give *tert*-butyl (3-(((*tert*-butylsulfinyl)amino)(3-fluoro-4-isopropylphenyl)methyl)pyridin-2-yl)carbamate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{24}H_{34}FN_3O_3S$: 464.2; found 464.1.

[0728] Step d: To a solution of *tert*-butyl (3-(((*tert*-butylsulfinyl)amino)(3-fluoro-4-isopropylphenyl)methyl)pyridin-2-yl)carbamate (3.3 g, 7.12 mmol, 1 eq) in THF (25 mL) and H_2O (5 mL) was added I_2 (4.52 g, 17.8 mmol, 2.5 eq). The resulting mixture was warmed to 50 °C and stirred for 1 h. The reaction mixture was then cooled to 0 °C and quenched by addition of saturated aq. $Na_2S_2O_3$ solution (30 mL), and the resulting biphasic mixture was extracted with EtOAc (2 x 30 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give *tert*-butyl (3-(amino(3-fluoro-4-isopropylphenyl)methyl)pyridin-2-yl)carbamate, which was carried forward

to the next step without further purification. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{20}H_{26}FN_3O_2$: 360.2; found 360.1.

[0729] Step e: To a solution of *tert*-butyl (3-(amino(3-fluoro-4-isopropylphenyl)methyl)pyridin-2-yl)carbamate (2.4 g, 6.68 mmol, 1 eq) and (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (1.87 g, 8.01 mmol, 1.2 eq) in MeCN (25 mL) at –20 °C was added *N*-methylimidazole (NMI, 2.74 g, 33.4 mmol, 2.6 mL, 5 eq) and chloro-*N*,*N*,*N*′,*N*′-tetramethylformamidinium hexafluorophosphate (TCFH, 2.06 g, 7.34 mmol, 1.1 eq). The resulting mixture was stirred at –20 °C for 0.5 h. The reaction mixture was then warmed to 0 °C and quenched by addition of water (20 mL), and the resulting biphasic mixture was extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give *tert*-butyl (2*S*,4*R*)-2-(((*R*)-(2-((*tert*-butoxycarbonyl)amino)pyridin-3-yl)(3-fluoro-4-isopropylphenyl)methyl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate (first-eluting isomer) and *tert*-butyl (2*S*,4*R*)-2-(((*S*)-(2-((*tert*-butoxycarbonyl)amino)pyridin-3-yl)(3-fluoro-4-isopropylphenyl)methyl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate (second-eluting isomer) as separate diastereomers that were carried forward individually. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{30}H_{40}F_2N_4O_5$: 575.3; found 575.2.

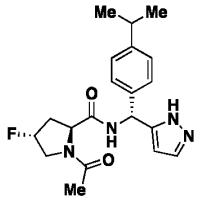
[0730] Step f: To a solution of *tert*-butyl (2*S*,4*R*)-2-(((*R*)-(2-((*tert*-butoxycarbonyl)amino)pyridin-3-yl)(3-fluoro-4-isopropylphenyl)methyl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate (700 mg, 1.22 mmol, 1 eq) in EtOAc (10 mL) was added HCl/EtOAc (4 M, 20 mL). The resulting mixture was stirred at 25 °C for 15 h. The reaction mixture was then concentrated under reduced pressure to give (2*S*,4*R*)-2-(((*R*)-(2-aminopyridin-3-yl)(3-fluoro-4-isopropylphenyl)methyl)carbamoyl)-4-fluoropyrrolidin-1-ium chloride, which was carried forward to the next step without additional purification. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{20}H_{24}F_2N_4O$: 375.2; found 375.1.

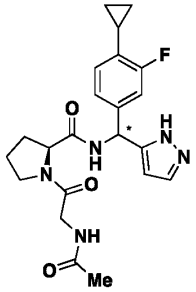
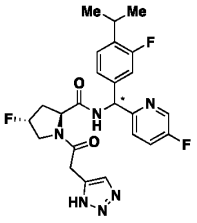
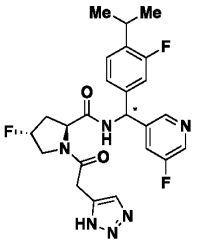
[0731] Step g: To a solution of (2*S*,4*R*)-2-(((*R*)-(2-aminopyridin-3-yl)(3-fluoro-4-isopropylphenyl)methyl)carbamoyl)-4-fluoropyrrolidin-1-ium chloride (200 mg, 487 µmol, 1 eq) and 2-(1*H*-1,2,3-triazol-5-yl)acetic acid (61.9 mg, 487 µmol, 1 eq) in DCM (5 mL) and DMF (0.5 mL) at –20 °C was added *N*-methylimidazole (NMI, 400 mg, 4.87 mmol, 10 eq) and T3P

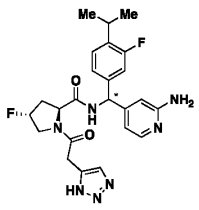
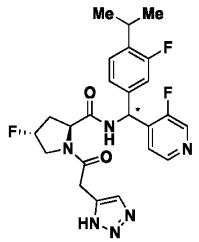
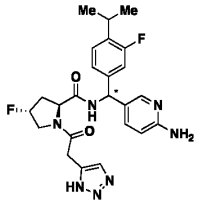
(633 µmol, 370 µL, 50% purity, 1.3 eq). The resulting mixture was stirred at –20 ºC for 1 h. The reaction mixture was then warmed to 0 ºC and quenched by addition of water (10 mL), and the resulting biphasic mixture was extracted with EtOAc (2 x 15 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by prep-HPLC to give (2*S*,4*R*)-1-(2-(1*H*-1,2,3-triazol-5-yl)acetyl)-*N*-((*R*)-(2-aminopyridin-3-yl)(3-fluoro-4-isopropylphenyl)methyl)-4-fluoropyrrolidine-2-carboxamide. ^{1}H NMR (4.3:1 rotamer ratio, asterisk denotes distinct minor rotamer peaks, obscured peaks not reported, 400 MHz, DMSO-d_6) δ 14.69 (br s, 1H), 9.16* (d, *J* = 8.1 Hz, 1H), 8.87 (d, *J* = 8.1 Hz, 1H), 7.90 – 7.83 (m, 1H), 7.65 (br s, 1H), 7.37 – 7.24 (m, 1H), 7.18 – 6.93 (m, 3H), 6.55 – 6.44 (m, 1H), 6.12* (d, *J* = 8.1 Hz, 1H), 5.94 (d, *J* = 7.9 Hz, 1H), 5.77* (s, 2H), 5.62 (s, 2H), 5.49 – 5.19 (m, 1H), 4.83 – 4.73* (m, 1H), 4.48 (t, *J* = 8.5 Hz, 1H), 4.09 – 3.96 (m, 1H), 3.88 – 3.67 (m, 2H), 3.19 – 3.09 (m, 1H), 2.09 – 1.86 (m, 1H), 1.20 (d, *J* = 6.9 Hz, 6H). LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{24}H_{27}F_2N_7O_2$: 484.2; found 484.1.

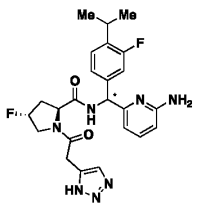
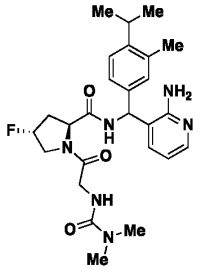
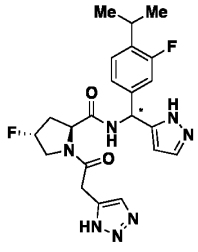
[0732] The following compounds in Table T-14 were synthesized using procedures similar to Compound 613 using the appropriate starting materials.

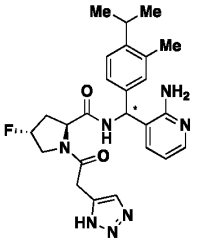
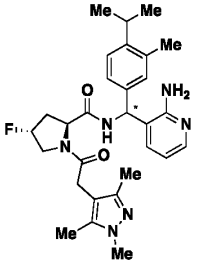
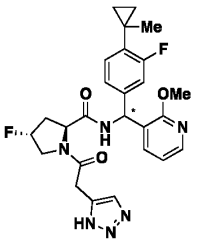
Table T-14

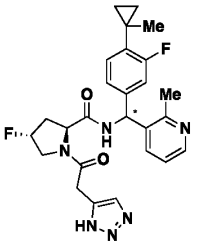
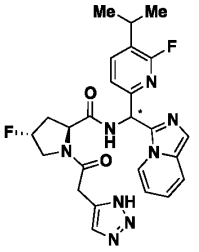
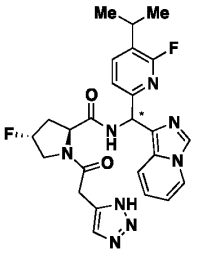
Compound No.	Structure	IUPAC	Exact mass (g/mol)	LCMS, Found $[M + H]^+$
614		(2S,4R)-1-acetyl-4-fluoro-N-[(S)-[4-(propan-2-yl)phenyl](1H-pyrazol-5-yl)methyl]pyrrolidine-2-carboxamide	372.2	373.2

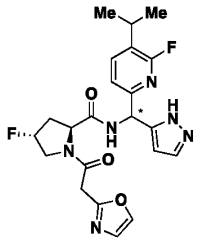
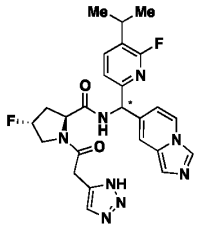
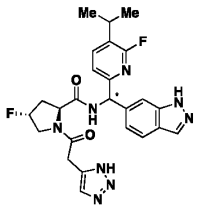
615		(2S)-N-[(R) or (S)-(4-cyclopropyl-3-fluorophenyl)(1H-pyrazol-5-yl)methyl]-1-(2-acetamidoacetyl)pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, second-eluting isomer)	427.2	428.1
616		(2S,4R)-4-fluoro-N-[(R) or (S)-[3-fluoro-4-(propan-2-yl)phenyl](5-fluoropyridin-2-yl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, first-eluting isomer)	486.2	487.1
617		(2S,4R)-4-fluoro-N-[(R) or (S)-[3-fluoro-4-(propan-2-yl)phenyl](5-fluoropyridin-3-yl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, first-eluting isomer)	486.2	487.1

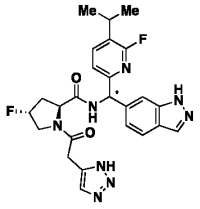
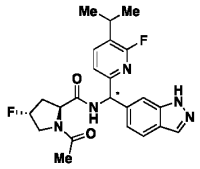
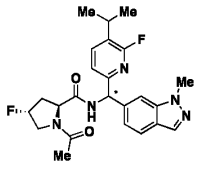
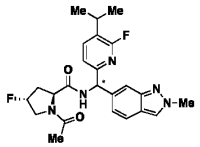
618		(2S,4R)-N-[(S) or (R)-(2-aminopyridin-4-yl)[3-fluoro-4-(propan-2-yl)phenyl]methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, first-eluting isomer)	483.2	484.1
619		(2S,4R)-4-fluoro-N-[(R) or (S)-[3-fluoro-4-(propan-2-yl)phenyl](3-fluoropyridin-4-yl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, first-eluting isomer)	486.2	487.1
620		(2S,4R)-N-[(R) or (S)-(6-aminopyridin-3-yl)[3-fluoro-4-(propan-2-yl)phenyl]methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide (column: DAICEL CHIRALPAK IG-3, first-eluting isomer)	483.2	484.1

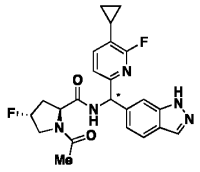
621		(2S,4R)-N-[(R) or (S)-(6-aminopyridin-2-yl)[3-fluoro-4-(propan-2-yl)phenyl]methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, second-eluting isomer)	483.2	484.1
622		(2S,4R)-N-[(R) or (S)-(2-aminopyridin-3-yl)[3-methyl-4-(propan-2-yl)phenyl]methyl]-1-{2-[(dimethylcarbamoyl)amino]acetyl}-4-fluoropyrrolidine-2-carboxamide (column: Waters Xbridge BEH C18, second-eluting isomer)	498.3	499.2
623		(2S,4R)-4-fluoro-N-[(R) or (S)-[3-fluoro-4-(propan-2-yl)phenyl](1H-pyrazol-5-yl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, second-eluting isomer)	457.2	458.1

624		(2S,4R)-N-[(R) or (S)-(2-aminopyridin-3-yl)[3-methyl-4-(propan-2-yl)phenyl]methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide (column: Lux Cellulose-2, second-eluting isomer)	479.2	480.1
625		(2S,4R)-N-[(R) or (S)-(2-aminopyridin-3-yl)[3-methyl-4-(propan-2-yl)phenyl]methyl]-4-fluoro-1-[2-(1,3,5-trimethyl-1H-pyrazol-4-yl)acetyl]pyrrolidine-2-carboxamide (column: DAICEL CHIRALPAK AD-3, first-eluting isomer)	520.3	521.2
626		(2S,4R)-4-fluoro-N-[(R) or (S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](2-methoxypyridin-3-yl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide (column: DAICEL CHIRALPAK AD-3, second-eluting isomer)	510.2	511.3

627		(2S,4R)-4-fluoro-N-[(R) or (S)-[3-fluoro-4-(1-methylcyclopropyl)phenyl](2-methylpyridin-3-yl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, first-eluting isomer)	494.2	495.2
628		(2S,4R)-4-fluoro-N-[(R) or (S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl]({imidazo[1,5-a]pyridin-3-yl})methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide (column: DAICEL CHIRALPAK AD-3, first-eluting isomer)	508.2	509.2
629		(2S,4R)-4-fluoro-N-[(S) or (R)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl]({imidazo[1,5-a]pyridin-1-yl})methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide (column: DAICEL CHIRALPAK AD-3, first-eluting isomer)	508.2	509.1

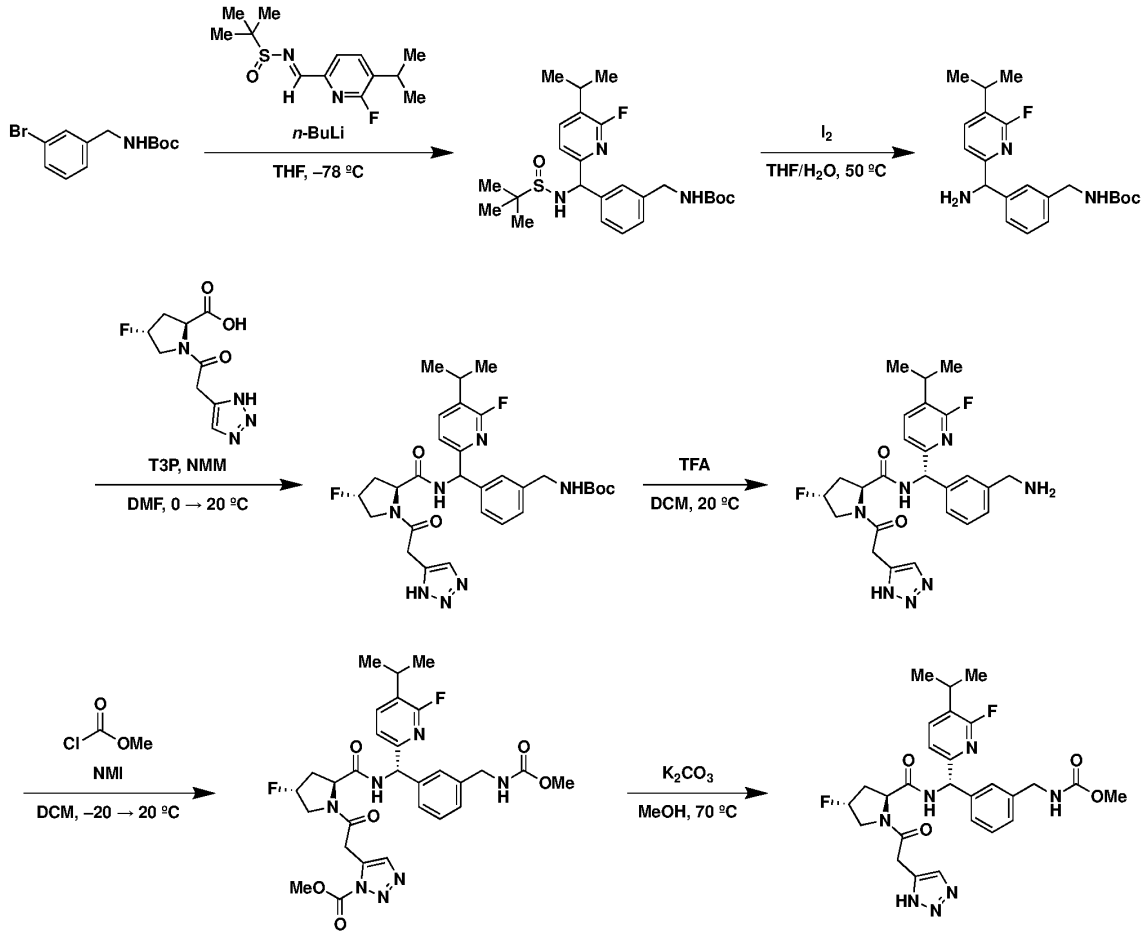
630		(2S,4R)-4-fluoro-N-[(S) or (R)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](1H-pyrazol-5-yl)methyl]-1-[2-(1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide (column: DAICEL CHIRALPAK AD-3, second-eluting isomer)	458.2	459.1
631		(2S,4R)-4-fluoro-N-[(S) or (R)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl]({imidazo[1,5-a]pyridin-7-yl})methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, first-eluting isomer)	508.2	509.2
632		(2S,4R)-4-fluoro-N-[(S) or (R)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](1H-indazol-6-yl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, first-eluting isomer)	508.2	509.1

633		(2S,4R)-4-fluoro-N-[(R) or (S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](1H-indazol-6-yl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, second-eluting isomer)	508.2	509.3
634		(2S,4R)-1-acetyl-4-fluoro-N-[(S) or (R)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](1H-indazol-6-yl)methyl]pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, first-eluting isomer)	441.2	442.1
635		(2S,4R)-1-acetyl-4-fluoro-N-[(S) or (R)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](1-methyl-1H-indazol-6-yl)methyl]pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, first-eluting isomer)	455.2	456.2
636		(2S,4R)-1-acetyl-4-fluoro-N-[(S) or (R)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](2-	455.2	456.1

		methyl-2H-indazol-6-yl)methyl]pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, first-eluting isomer)		
637		(2S,4R)-1-acetyl-N-[(S) or (R)-(5-cyclopropyl-6-fluoropyridin-2-yl)(1H-indazol-6-yl)methyl]-4-fluoropyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, second-eluting isomer)	439.1	440.1

Example S-15: Synthesis of methyl (3-((*S*)-((2*S*,4*R*)-1-(2-(1*H*-1,2,3-triazol-5-yl)acetyl)-4-fluoropyrrolidine-2-carboxamido)(6-fluoro-5-isopropylpyridin-2-yl)methyl)benzyl)carbamate

(Compound 638)



[0733] Step a: To a solution of *tert*-butyl (3-bromobenzyl)carbamate (7.94 g, 27.7 mmol, 1.5 eq) in THF (30 mL) at –78 ºC under N_2 was added *n*-BuLi (2.5 M in hexane, 18.5 mL, 2.5 eq), and the resulting mixture was stirred at –78 ºC for 0.5 h. (*E*)-*N*-((6-fluoro-5-isopropylpyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide (5 g, 18.5 mmol, 1 eq) in THF (20 mL) was then added at –78 ºC. The resulting mixture was stirred at –78 ºC for 1.5 h. The reaction was then quenched by addition of saturated aq. NH_4Cl solution (20 mL), and the resulting biphasic mixture was extracted with ethyl acetate (3 x 30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give *tert*-butyl (3-(((*tert*-butylsulfinyl)amino)(6-fluoro-5-isopropylpyridin-2-yl)methyl)benzyl)carbamate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{25}H_{36}FN_3O_3S$: 478.3; found 478.3.

[0734] Step b: To a solution of *tert*-butyl (3-(((*tert*-butylsulfinyl)amino)(6-fluoro-5-isopropylpyridin-2-yl)methyl)benzyl)carbamate (6 g, 12.5 mmol, 1 eq) in THF: H_2O (5:1, 60 mL) was added I_2 (2.55 g, 10.1 mmol, 0.8 eq). The resulting mixture was warmed to 50 ºC and stirred for 1 h. The reaction was then quenched with saturated aq. $Na_2S_2O_3$ solution (100 mL), and the resulting biphasic mixture was extracted with ethyl acetate (3 x 50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give *tert*-butyl (3-(amino(6-fluoro-5-isopropylpyridin-2-yl)methyl)benzyl)carbamate, which was carried forward to the next step without additional purification. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{21}H_{28}FN_3O_2$: 374.2; found 374.2.

[0735] Step c: To a solution of *tert*-butyl (3-(amino(6-fluoro-5-isopropylpyridin-2-yl)methyl)benzyl)carbamate (2 g, 5.36 mmol, 1 eq) in DMF (20 mL) at 0 ºC was added (2*S*,4*R*)-1-(2-(1*H*-1,2,3-triazol-5-yl)acetyl)-4-fluoropyrrolidine-2-carboxylic acid (2.94 g, 8.04 mmol, 80% purity, 1.3 eq), *N*-methylmorpholine (NMM, 16.1 mmol, 1.7 mL, 3 eq), and T3P (10.7 mmol, 6.3 mL, 50% purity, 2 *eq*), sequentially. The resulting mixture was warmed to 20 ºC and stirred for 16 h. The reaction mixture was then quenched with H_2O (50 mL), and the resulting biphasic mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give *tert*-butyl (3-(((2*S*,4*R*)-1-(2-(1*H*-1,2,3-triazol-5-yl)acetyl)-4-fluoropyrrolidine-2-carboxamido)(6-fluoro-5-isopropylpyridin-2-yl)methyl)benzyl)carbamate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{30}H_{37}F_2N_7O_4$: 598.3; found 598.4.

[0736] Step d: To a solution of *tert*-butyl (3-(((2*S*,4*R*)-1-(2-(1*H*-1,2,3-triazol-5-yl)acetyl)-4-fluoropyrrolidine-2-carboxamido)(6-fluoro-5-isopropylpyridin-2-yl)methyl)benzyl)carbamate (1.2 g, 2.00 mmol, 1 eq) in DCM (12 mL) was added TFA (6.75 mmol, 3 mL, 40 eq). The resulting mixture was stirred at 20 ºC for 1 h. The reaction mixture was then adjusted to pH to 5–6 using saturated aq. $NaHCO_3$ solution, and the resulting biphasic mixture was extracted with ethyl acetate (3 x 50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by prep-HPLC (column: Phenomenex Luna C18) to give (2*S*,4*R*)-1-(2-(1*H*-1,2,3-triazol-5-yl)acetyl)-*N*-((*R*)-(3-(aminomethyl)phenyl)(6-fluoro-5-isopropylpyridin-2-yl)methyl)-4-fluoropyrrolidine-2-

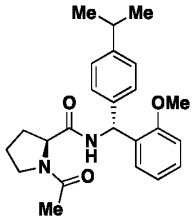
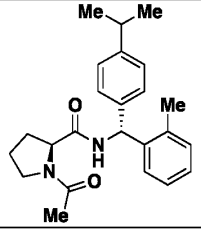
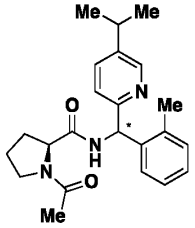
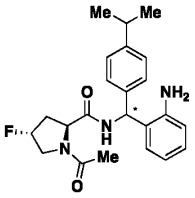
carboxamide (first-eluting isomer) and (2*S*,4*R*)-1-(2-(1*H*-1,2,3-triazol-5-yl)acetyl)-*N*-((*S*)-(3-(aminomethyl)phenyl)(6-fluoro-5-isopropylpyridin-2-yl)methyl)-4-fluoropyrrolidine-2-carboxamide (second-eluting isomer) as separated diastereomers that were carried forward individually. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{25}H_{29}F_2N_7O_2$: 498.2; found 498.2.

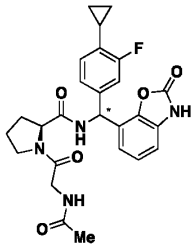
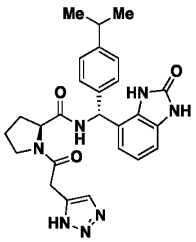
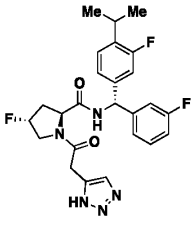
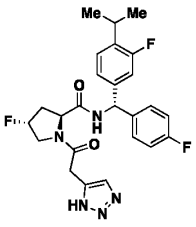
[0737] Step e: To a solution of (2*S*,4*R*)-1-(2-(1*H*-1,2,3-triazol-5-yl)acetyl)-*N*-((*S*)-(3-(aminomethyl)phenyl)(6-fluoro-5-isopropylpyridin-2-yl)methyl)-4-fluoropyrrolidine-2-carboxamide (35 mg, 65.5 µmol, 1 eq) in DCM (1 mL) at –20 ºC was added *N*-methylimidazole (NMI, 262 µmol, 20.9 µL, 4 eq), methyl chloroformate (190 mg, 2.01 mmol, 30.7 eq). The resulting mixture was warmed to 25 ºC and stirred for 3 h. The reaction was then quenched with H_2O (10 mL), and the resulting biphasic mixture was extracted with ethyl acetate (3 x 15 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give methyl 5-(2-((2*S*,4*R*)-4-fluoro-2-(((*S*)-(6-fluoro-5-isopropylpyridin-2-yl)(3-(((methoxycarbonyl)amino)methyl)phenyl)methyl)carbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-1*H*-1,2,3-triazole-1-carboxylate, which was carried forward to the next step without further purification. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{29}H_{33}F_2N_7O_6$: 614.3 found 614.3.

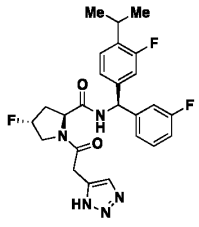
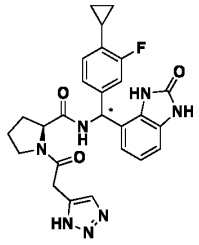
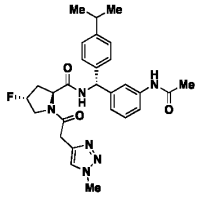
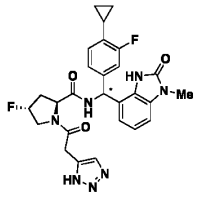
[0738] Step f: To a solution of methyl 5-(2-((2*S*,4*R*)-4-fluoro-2-(((*S*)-(6-fluoro-5-isopropylpyridin-2-yl)(3-(((methoxycarbonyl)amino)methyl)phenyl)methyl)carbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-1*H*-1,2,3-triazole-1-carboxylate (36 mg, 58.7 µmol, 1 eq) in MeOH (0.5 mL) was added K_2CO_3 (16.2 mg, 117 µmol, 2 eq). The resulting mixture was warmed to 70 ºC and stirred at for 1 h. The reaction mixture was then filtered, and the filtrate was concentrated under reduced pressure. The crude residue obtained was purified by prep-HPLC to give methyl (3-((*S*)-((2*S*,4*R*)-1-(2-(1*H*-1,2,3-triazol-5-yl)acetyl)-4-fluoropyrrolidine-2-carboxamido)(6-fluoro-5-isopropylpyridin-2-yl)methyl)benzyl)carbamate. ^{1}H NMR (2.9:1 rotamer ratio, asterisk denotes distinct minor rotamer peaks, obscured peaks not reported, 400 MHz, DMSO-d_6) δ 14.75 (br s, 1H), 9.28* (d, *J* = 7.9 Hz, 1H), 8.90 (d, *J* = 8.1 Hz, 1H), 7.92 – 7.80 (m, 1H), 7.62 (s, 1H), 7.41 – 7.05 (m, 5H), 6.07* (d, *J* = 7.6 Hz, 1H), 5.95 (d, *J* = 7.8 Hz, 1H), 5.49 – 5.19 (m, 1H), 4.90* (t, *J* = 8.0 Hz, 1H), 4.62 (t, *J* = 8.3 Hz, 1H), 4.22 – 3.62 (m, 5H), 3.54 – 3.49 (m, 3H), 3.09 – 2.99 (m, 1H), 2.16 – 1.91 (m, 1H), 1.24 – 1.12 (m, 6H). LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{27}H_{31}F_2N_7O_4$: 556.2; found 556.3.

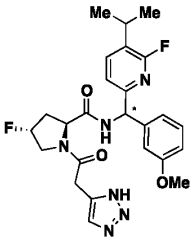
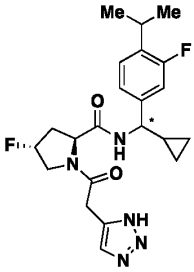
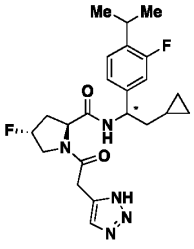
[0739] The following compounds in Table T-15 were synthesized using procedures similar to Compound 638 using the appropriate starting materials.

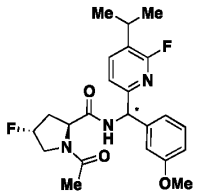
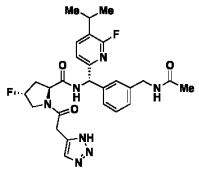
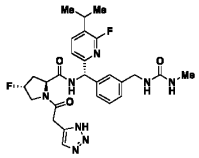
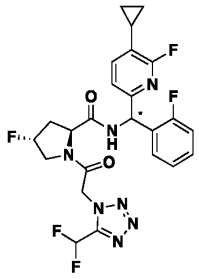
Table T-15

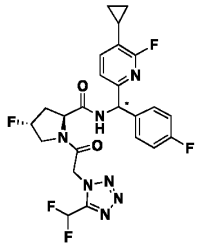
Compound No.	Structure	IUPAC	Exact mass (g/mol)	LCMS, Found [M + H]+
639		(2S)-1-acetyl-N-[(R)-(2-methoxyphenyl)[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	394.2	395.3
640		(2S)-1-acetyl-N-[(R)-(2-methylphenyl)[4-(propan-2-yl)phenyl]methyl]pyrrolidine-2-carboxamide	378.2	379.3
641		(2S)-1-acetyl-N-[(S) or (R)-(2-methylphenyl)[5-(propan-2-yl)pyridin-2-yl]methyl]pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, first-eluting isomer)	379.2	380.2
642		(2S,4R)-1-acetyl-N-[(R) or (S)-(2-aminophenyl)[4-(propan-2-yl)phenyl]methyl]-4-fluoropyrrolidine-2-carboxamide (column: DAICEL CHIRALPAK	397.2	398.1

		AD-3, first-eluting isomer)		
643		(2S)-N-[(R) or (S)-(4-cyclopropyl-3-fluorophenyl)(2-oxo-2,3-dihydro-1,3-benzoxazol-7-yl)methyl]-1-(2-acetamidoacetyl)pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, second-eluting isomer)	494.2	495.2
644		(2S)-N-[(R)-(2-oxo-2,3-dihydro-1H-1,3-benzodiazol-4-yl)[4-(propan-2-yl)phenyl]methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide	487.2	488.1
645		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](3-fluorophenyl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide	485.2	486.1
646		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(propan-2-yl)phenyl](4-fluorophenyl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide	485.2	486.1

647		(2S,4R)-4-fluoro-N-[(R)-[3-fluoro-4-(propan-2-yl)phenyl](3-fluorophenyl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide	485.2	486.1
648		(2S)-N-[(S)-(4-cyclopropyl-3-fluorophenyl)(2-oxo-2,3-dihydro-1H-1,3-benzodiazol-4-yl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, second-eluting isomer)	503.2	504.1
649		(2S,4R)-N-[(R)-(3-acetamidophenyl)[4-(propan-2-yl)phenyl]methyl]-4-fluoro-1-[2-(1-methyl-1H-1,2,3-triazol-4-yl)acetyl]pyrrolidine-2-carboxamide	520.3	521.2
650		(2S,4R)-N-[(R) or (S)-(4-cyclopropyl-3-fluorophenyl)(1-methyl-2-oxo-2,3-dihydro-1H-1,3-benzodiazol-4-yl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide	535.2	536.1

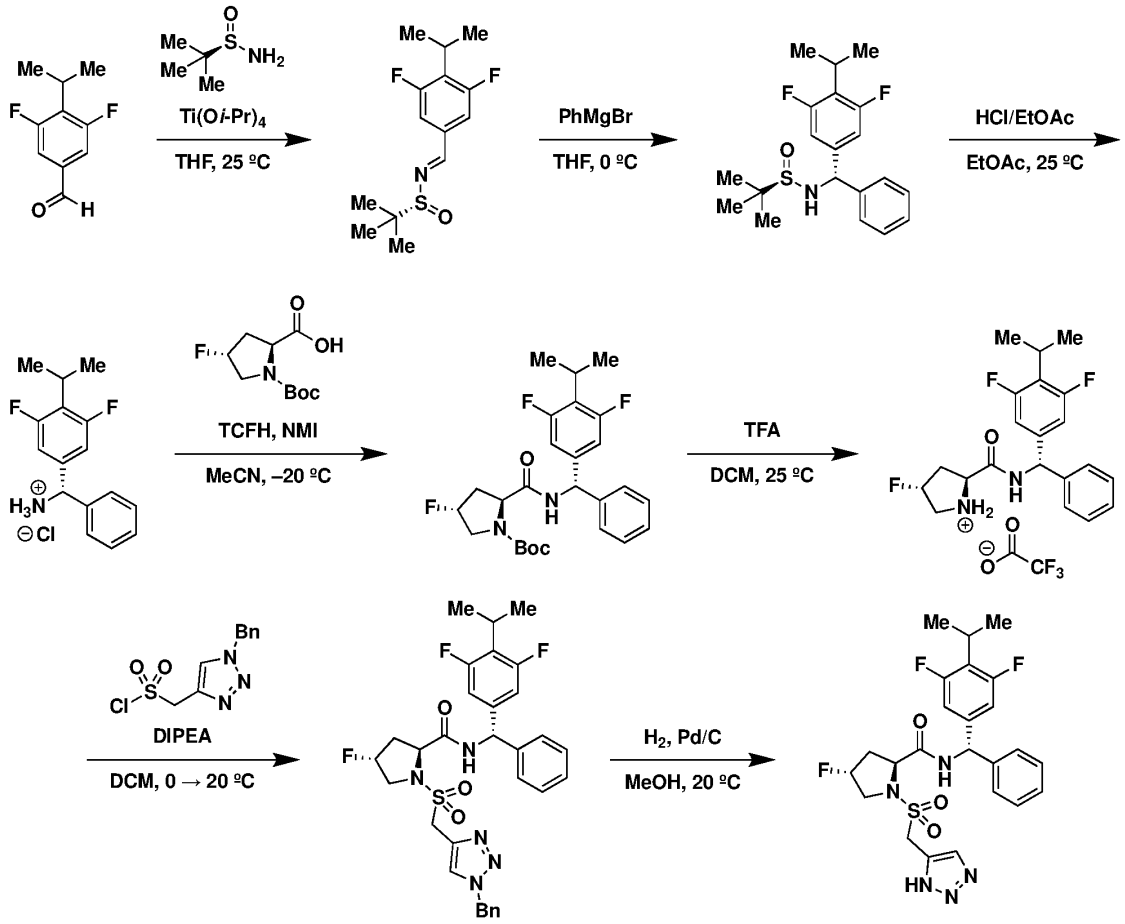
		(column: REGIS (s,s) WHELK-O1, second-eluting isomer)		
651		(2S,4R)-4-fluoro-N-[(S) or (R)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](3-methoxyphenyl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, first-eluting isomer)	498.2	499.1
652		(2S,4R)-N-[(S) or (R)-cyclopropyl[3-fluoro-4-(propan-2-yl)phenyl]methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide (column: DAICEL CHIRALPAK IC-3, second-eluting isomer)	431.2	432.3
653		(2S,4R)-N-[(1S) or (1R)-2-cyclopropyl-1-[3-fluoro-4-(propan-2-yl)phenyl]ethyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1,	445.2	446.1

		second-eluting isomer)		
654		(2S,4R)-1-acetyl-4-fluoro-N-[(S) or (R)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](3-methoxyphenyl)methyl]pyrrolidine-2-carboxamide (column: DAICEL CHIRALPAK IC-3, first-eluting isomer)	431.2	432.1
655		(2S,4R)-N-[(S)-[3-(acetamidomethyl)phenyl][6-fluoro-5-(propan-2-yl)pyridin-2-yl]methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide	539.2	540.3
656		(2S,4R)-4-fluoro-N-[(S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl](3-{[(methylcarbamoyl)amino]methyl}phenyl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide	554.3	555.2
657		(2S,4R)-N-[(S) or (R)-(5-cyclopropyl-6-fluoropyridin-2-yl)(2-fluorophenyl)methyl]-1-{2-[5-(difluoromethyl)-1H-1,2,3,4-tetrazol-1-	535.2	536.3

		yl]acetyl}-4-fluoropyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, first-eluting isomer)		
658		(2S,4R)-N-[(S) or (R)-(5-cyclopropyl-6-fluoropyridin-2-yl)(4-fluorophenyl)methyl]-1-{2-[5-(difluoromethyl)-1H-1,2,3,4-tetrazol-1-yl]acetyl}-4-fluoropyrrolidine-2-carboxamide (column: DAICEL CHIRALPAK AD-3, second-eluting isomer)	535.2	536.2

Example S-16: Synthesis of (2*S*,4*R*)-1-(((1*H*-1,2,3-triazol-5-yl)methyl)sulfonyl)-*N*-((*S*)-(3,5-difluoro-4-isopropylphenyl)(phenyl)methyl)-4-fluoropyrrolidine-2-carboxamide

(Compound 659)



[0740] Step a: To a solution of 3,5-difluoro-4-isopropylbenzaldehyde (1.05 g, 5.70 mmol, 1 eq) and (*R*)-2-methylpropane-2-sulfinamide (1.04 g, 8.55 mmol, 1.5 eq) in THF (20 mL) was added Ti(O*i*-Pr)$_4$ (3.24 g, 11.4 mmol, 3.37 mL, 2 eq). The resulting mixture was stirred at 25 ºC for 15 h. The reaction mixture was then quenched with water (20 mL). The resulting biphasic mixture was filtered, and the filtrate was extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with brine (2 x 30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give (*R*,*E*)-*N*-(3,5-difluoro-4-isopropylbenzylidene)-2-methylpropane-2-sulfinamide, which was carried forward to the next step without further purification or characterization.

[0741] Step b: To a solution of (*R*,*E*)-*N*-(3,5-difluoro-4-isopropylbenzylidene)-2-methylpropane-2-sulfinamide (1.4 g, 4.87 mmol, 1 eq) in THF (15 mL) at 0 °C was added phenylmagnesium bromide (3 M in diethyl ether, 2.44 mL, 1.5 eq). The resulting mixture was stirred at 0 °C for 1 h. The reaction mixture was then quenched by addition of saturated aq. NH_4Cl solution (15 mL), and the resulting biphasic mixture was extracted with EtOAc (2 x 30 mL). The combined organic extracts were washed with brine (2 x 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give (*R*)-*N*-((*S*)-(3,5-difluoro-4-isopropylphenyl)(phenyl)methyl)-2-methylpropane-2-sulfinamide. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{20}H_{25}F_2NOS$: 366.2; found 366.1.

[0742] Step c: To a solution of (*R*)-*N*-((*S*)-(3,5-difluoro-4-isopropylphenyl)(phenyl)methyl)-2-methylpropane-2-sulfinamide (540 mg, 1.48 mmol, 1 eq) in EtOAc (10 mL) was added HCl/EtOAc (4 M, 10 mL). The resulting mixture was stirred at 25 °C for 0.5 h. The reaction mixture was then filtered, and the solid was washed with petroleum ether to give (*S*)-(3,5-difluoro-4-isopropylphenyl)(phenyl)methanaminium chloride, which was carried forward to the next step without further purification or characterization.

[0743] Step d: To a solution of (*S*)-(3,5-difluoro-4-isopropylphenyl)(phenyl)methanaminium chloride (0.22 g, 739 µmol, 1 eq) and (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (190 mg, 813 µmol, 1.1 eq) in MeCN (10 mL) at –20 °C was added *N*-methylimidazole (NMI, 303 mg, 3.69 mmol, 294 µL, 5 eq) and chloro-*N*,*N*,*N*′,*N*′-tetramethylformamidinium hexafluorophosphate (TCFH, 228 mg, 813 µmol, 1.1 eq). The resulting mixture was stirred at –20 °C for 1 h. The reaction mixture was then quenched by addition of ice-water (5 mL) at –20 °C, and the resulting biphasic mixture was adjusted to pH = 5 with aqueous HCl (4 N). The resulting biphasic mixture was then extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give *tert*-butyl (2*S*,4*R*)-2-(((*S*)-(3,5-difluoro-4-isopropylphenyl)(phenyl)methyl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{26}H_{31}F_3N_2O_3$: 477.2; found 477.3.

[0744] Step e: To a solution of *tert*-butyl (2*S*,4*R*)-2-(((*S*)-(3,5-difluoro-4-isopropylphenyl)(phenyl)methyl)carbamoyl)-4-fluoropyrrolidine-1-carboxylate (0.35 g, 734 µmol, 1 eq) in DCM (10 mL) was added TFA (3.08 g, 27.0 mmol, 2 mL, 36.8 eq). The mixture was stirred at 25 ºC for 1 h. The mixture was then concentrated under reduced pressure to give (2*S*,4*R*)-2-(((*S*)-(3,5-difluoro-4-isopropylphenyl)(phenyl)methyl)carbamoyl)-4-fluoropyrrolidin-1-ium 2,2,2-trifluoroacetate. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{21}H_{23}F_3N_2O$: 377.2; found 377.1.

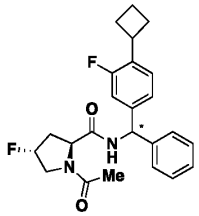
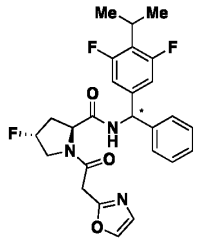
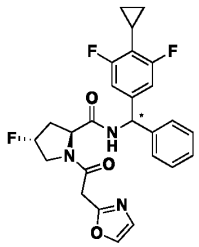
[0745] Step f: To a mixture of (2*S*,4*R*)-2-(((*S*)-(3,5-difluoro-4-isopropylphenyl)(phenyl)methyl)carbamoyl)-4-fluoropyrrolidin-1-ium 2,2,2-trifluoroacetate (100 mg, 265 µmol, 1 eq) and DIPEA (343 mg, 2.66 mmol, 10 eq) in DCM (5 mL) at 0 ºC was added (1-benzyl-1*H*-1,2,3-triazol-4-yl)methanesulfonyl chloride (216 mg, 797 µmol, 3 eq) in portions. The resulting mixture was warmed to 20 ºC and stirred for 3 h. The reaction mixture was then poured into ice-water (30 mL) and stirred for 10 min. The resulting biphasic mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by prep-HPLC to give (2*S*,4*R*)-1-(((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)sulfonyl)-*N*-((*S*)-(3,5-difluoro-4-isopropylphenyl)(phenyl)methyl)-4-fluoropyrrolidine-2-carboxamide. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{31}H_{32}F_3N_5O_3S$: 612.2; found 612.3.

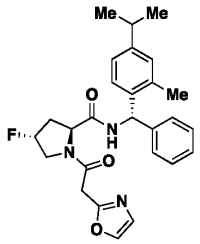
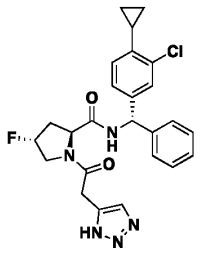
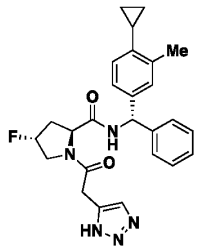
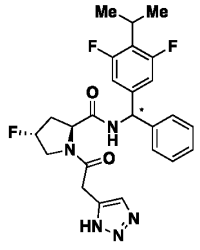
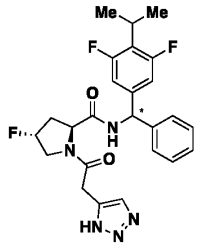
[0746] Step g: To a solution of (2*S*,4*R*)-1-(((1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl)sulfonyl)-*N*-((*S*)-(3,5-difluoro-4-isopropylphenyl)(phenyl)methyl)-4-fluoropyrrolidine-2-carboxamide (20 mg, 32.7 µmol, 1 eq) in MeOH (50 mL) was added Pd/C (100 mg, 10% purity). The resulting suspension was degassed under vacuum and purged with H_2. The resulting mixture was stirred under H_2 (50 psi) at 20 ºC for 16 h. The reaction mixture was then filtered, and the filtrate was concentrated under reduced pressure. The crude residue obtained was purified by prep-HPLC to give (2*S*,4*R*)-1-(((1*H*-1,2,3-triazol-5-yl)methyl)sulfonyl)-*N*-((*S*)-(3,5-difluoro-4-isopropylphenyl)(phenyl)methyl)-4-fluoropyrrolidine-2-carboxamide. ^{1}H NMR (400 MHz, DMSO-d_6) δ 15.04 (br s, 1H), 9.05 (d, *J* = 8.1 Hz, 1H), 7.79 (br s, 1H), 7.40 – 7.23 (m, 5H), 6.96 (d, *J* = 9.4 Hz, 2H), 6.11 (d, *J* = 8.0 Hz, 1H), 5.32 (d, *J* = 52.6 Hz, 1H), 4.68 – 4.48 (m, 3H), 3.79 – 3.66 (m, 1H), 3.51 (dd, *J* = 39.0, 12.6

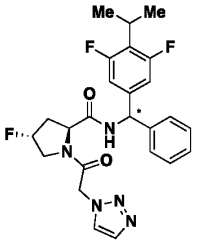
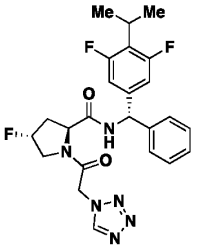
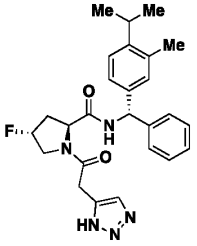
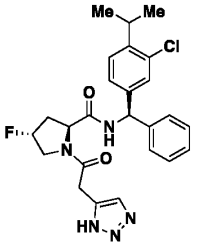
Hz, 1H), 3.29 – 3.19 (m, 1H), 2.75 – 2.54 (m, 1H), 2.18 – 1.97 (m, 1H), 1.25 (d, J = 7.1 Hz, 6H). LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{24}H_{26}F_3N_5O_3S$: 522.2; found 522.1.

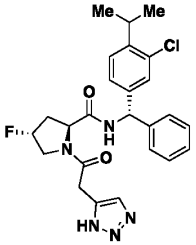
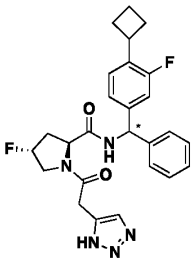
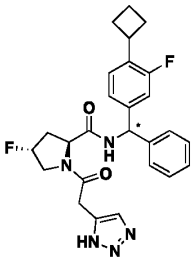
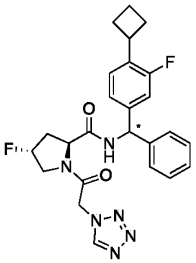
[0747] The following compounds in Table T-16 were synthesized using procedures similar to Compound 659 using the appropriate starting materials.

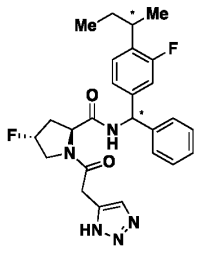
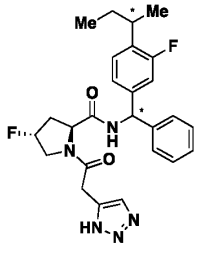
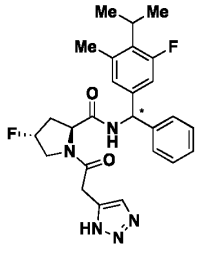
Table T-16

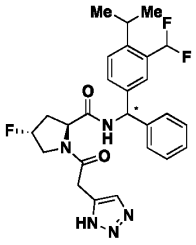
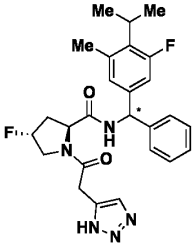
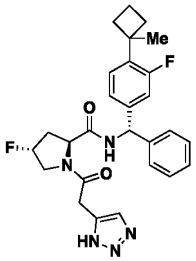
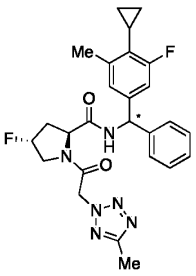
Compound No.	Structure	IUPAC	Exact mass (g/mol)	LCMS, Found $[M + H]^+$
660		(2S,4R)-1-acetyl-N-[(S) or (R)-(4-cyclobutyl-3-fluorophenyl)(phenyl)methyl]-4-fluoropyrrolidine-2-carboxamide (column: DAICEL CHIRALPAK AS-3, first-eluting isomer)	412.2	413.2
661		(2S,4R)-N-[(S) or (R)-[3,5-difluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-4-fluoro-1-[2-(1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide (column: CHIRALCEL OD-3, first-eluting isomer)	485.2	486.1
662		(2S,4R)-N-[(S)-(4-cyclopropyl-3,5-difluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide	483.2	484.1

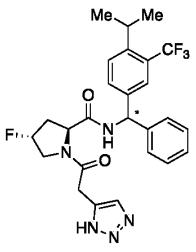
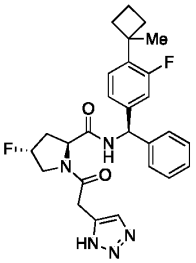
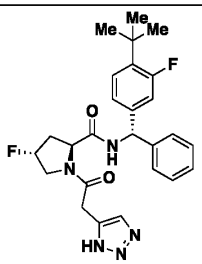
		(column: CHIRALCEL OD-3, first-eluting isomer)		
663		(2S,4R)-4-fluoro-N-[(S)-[2-methyl-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(1,3-oxazol-2-yl)acetyl]pyrrolidine-2-carboxamide	463.2	486.1 (M + Na)
664		(2S,4R)-N-[(S)-(3-chloro-4-cyclopropylphenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide	481.2	482.2
665		(2S,4R)-N-[(S)-(4-cyclopropyl-3-methylphenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide	461.2	462.3
666		(2S,4R)-N-[(R) or (S)-[3,5-difluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide	485.2	486.1
667		(2S,4R)-N-[(S) or (R)-[3,5-difluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide	485.2	486.1

668		(2S,4R)-N-[(S) or (R)-[3,5-difluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-1-yl)acetyl]pyrrolidine-2-carboxamide (column: CHIRALCEL OD-3, first-eluting isomer)	485.2	486.1
669		(2S,4R)-N-[(S)-[3,5-difluoro-4-(propan-2-yl)phenyl](phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3,4-tetrazol-1-yl)acetyl]pyrrolidine-2-carboxamide	486.2	487.1
670		(2S,4R)-4-fluoro-N-[(S)-[3-methyl-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide	463.2	464.1
671		(2S,4R)-N-[(R)-[3-chloro-4-(propan-2-yl)phenyl](phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide	483.2	484.2

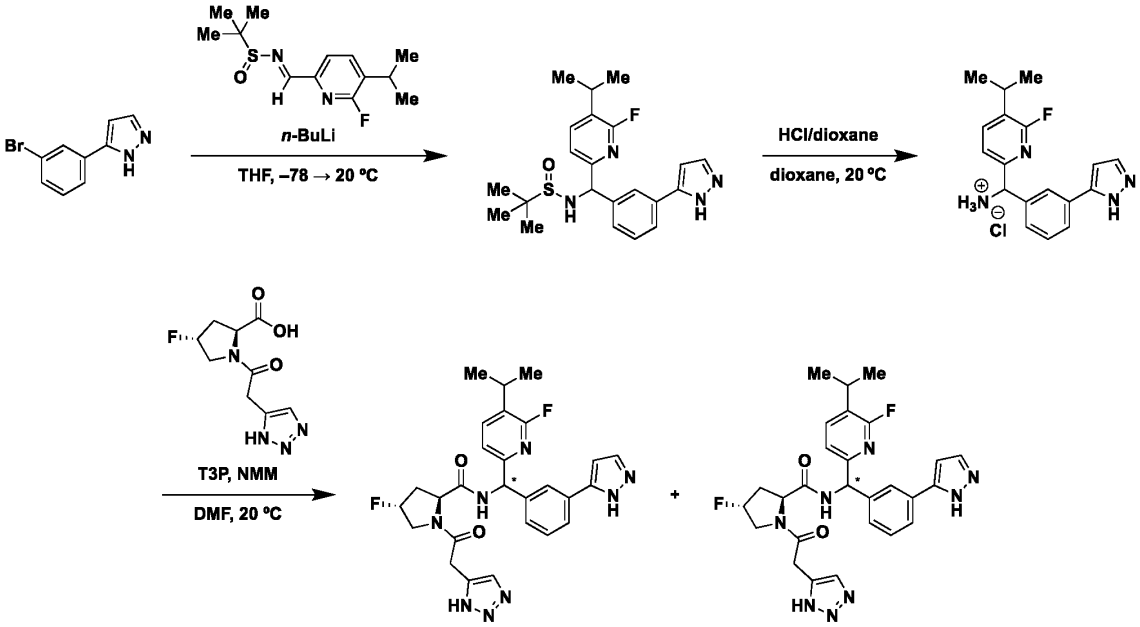
672		(2S,4R)-N-[(S)-[3-chloro-4-(propan-2-yl)phenyl](phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide	483.2	484.2
673		(2S,4R)-N-[(R) or (S)-(4-cyclobutyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide (column: CHIRALCEL OD-3, second-eluting isomer)	479.2	480.2
674		(2S,4R)-N-[(S) or (R)-(4-cyclobutyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide (column: CHIRALCEL OD-3, first-eluting isomer)	479.2	480.2
675		(2S,4R)-N-[(S) or (R)-(4-cyclobutyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3,4-tetrazol-1-yl)acetyl]pyrrolidine-2-carboxamide (column: CHIRALCEL	480.2	481.2

		AD-3, first-eluting isomer)		
676		(2S,4R)-N-[(R) or (S)-{4-[(2R) or (2S)-butan-2-yl]-3-fluorophenyl}(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, second-eluting isomer)	481.2	482.1
677		(2S,4R)-N-[(S) or (R)-{4-[(2R) or (2S)-butan-2-yl]-3-fluorophenyl}(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, first-eluting isomer)	481.2	482.1
678		(2S,4R)-4-fluoro-N-[(R) or (S)-[3-fluoro-5-methyl-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide (column: CHIRALCEL IC-3, second-eluting isomer)	481.2	482.3

679		(2S,4R)-N-[(S)-[3-(difluoromethyl)-4-(propan-2-yl)phenyl](phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide	499.2	500.2
680		(2S,4R)-4-fluoro-N-[(S) or (R)-[3-fluoro-5-methyl-4-(propan-2-yl)phenyl](phenyl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide (column: CHIRALCEL IC-3, first-eluting isomer)	481.2	482.3
681		(2S,4R)-4-fluoro-N-[(S)-[3-fluoro-4-(1-methylcyclobutyl)phenyl](phenyl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide	493.2	494.3
682		(2S,4R)-N-[(S) or (R)-(4-cyclopropyl-3-fluoro-5-methylphenyl)(phenyl)methyl]-4-fluoro-1-[2-(5-methyl-2H-1,2,3,4-tetrazol-2-yl)acetyl]pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1,	494.2	512.2

		second-eluting isomer)		
683		(2S,4R)-4-fluoro-N-[(S) or (R)-phenyl[4-(propan-2-yl)-3-(trifluoromethyl)phenyl]methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide (column: CHIRALCEL IC-3, first-eluting isomer)	517.2	518.1
684		(2S,4R)-4-fluoro-N-[(R)-[3-fluoro-4-(1-methylcyclobutyl)phenyl](phenyl)methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide	493.2	494.3
685		(2S,4R)-N-[(S)-(4-tert-butyl-3-fluorophenyl)(phenyl)methyl]-4-fluoro-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide	481.2	482.3

Example S-17: Synthesis of (2*S*,4*R*)-1-(2-(1*H*-1,2,3-triazol-5-yl)acetyl)-*N*-((*S*) or (*R*)-(3-(1*H*-pyrazol-5-yl)phenyl)(6-fluoro-5-isopropylpyridin-2-yl)methyl)-4-fluoropyrrolidine-2-carboxamide and (2*S*,4*R*)-1-(2-(1*H*-1,2,3-triazol-5-yl)acetyl)-*N*-((*R*) or (*S*)-(3-(1*H*-pyrazol-5-yl)phenyl)(6-fluoro-5-isopropylpyridin-2-yl)methyl)-4-fluoropyrrolidine-2-carboxamide (Compounds 686 and 687)



[0748] Step a: To a solution of 5-(3-bromophenyl)-1*H*-pyrazole (619 mg, 2.77 mmol, 1.5 eq) in THF (5 mL) at –78 °C under N_2 was added *n*-BuLi (2.5 M in hexane, 1.85 mL, 2.5 eq), and the resulting mixture was stirred at –78 °C for 0.5 h. (*E*)-*N*-((6-fluoro-5-isopropylpyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide (0.5 g, 1.85 mmol, 1 eq) in THF (1 mL) was then added dropwise at –78 °C. The resulting mixture was allowed to warm to 20 °C and stirred for 2 h. The reaction was then quenched with saturated aq. NH_4Cl (10 mL), and the resulting biphasic mixture was extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give *N*-((3-(1*H*-pyrazol-5-yl)phenyl)(6-fluoro-5-isopropylpyridin-2-yl)methyl)-2-methylpropane-2-sulfinamide. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{22}H_{27}FN_4OS$: 415.2; found 415.2.

[0749] Step b: To a solution of *N*-((3-(1*H*-pyrazol-5-yl)phenyl)(6-fluoro-5-isopropylpyridin-2-yl)methyl)-2-methylpropane-2-sulfinamide (0.5 g, 1.21 mmol, 1 eq) in dioxane (5 mL) was added HCl/dioxane (4 M, 5 mL). The resulting mixture was stirred at 20 °C for 2 h. The mixture was then concentrated under reduced pressure. The crude residue obtained was triturated with MTBE (5 mL) to give (3-(1*H*-pyrazol-5-yl)phenyl)(6-fluoro-5-

isopropylpyridin-2-yl)methanaminium chloride. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{18}H_{19}FN_4$: 311.2; found 311.2.

[0750] Step c: To a solution of (3-(1*H*-pyrazol-5-yl)phenyl)(6-fluoro-5-isopropylpyridin-2-yl)methanaminium chloride (0.15 g, 432 µmol, 1 eq) and (2*S*,4*R*)-1-(2-(1*H*-1,2,3-triazol-5-yl)acetyl)-4-fluoropyrrolidine-2-carboxylic acid (136 mg, 562 µmol, 1.3 eq) in DMF (2 mL) at 0 ºC was added *N*-methylmorpholine (NMM, 175 mg, 1.73 mmol, 190 µL, 4 eq) and T3P (550 mg, 865 µmol, 50% purity, 2 eq). The resulting mixture was warmed to 20 ºC and stirred for 16 h. The reaction mixture was then diluted with water and extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by prep-HPLC (column: Phenomenex C18) to give (2*S*,4*R*)-1-(2-(1*H*-1,2,3-triazol-5-yl)acetyl)-*N*-((*R*)-(3-(1*H*-pyrazol-5-yl)phenyl)(6-fluoro-5-isopropylpyridin-2-yl)methyl)-4-fluoropyrrolidine-2-carboxamide (Compound 687; first-eluting isomer) and (2*S*,4*R*)-1-(2-(1*H*-1,2,3-triazol-5-yl)acetyl)-*N*-((*S*)-(3-(1*H*-pyrazol-5-yl)phenyl)(6-fluoro-5-isopropylpyridin-2-yl)methyl)-4-fluoropyrrolidine-2-carboxamide (Compound 686; second-eluting isomer).

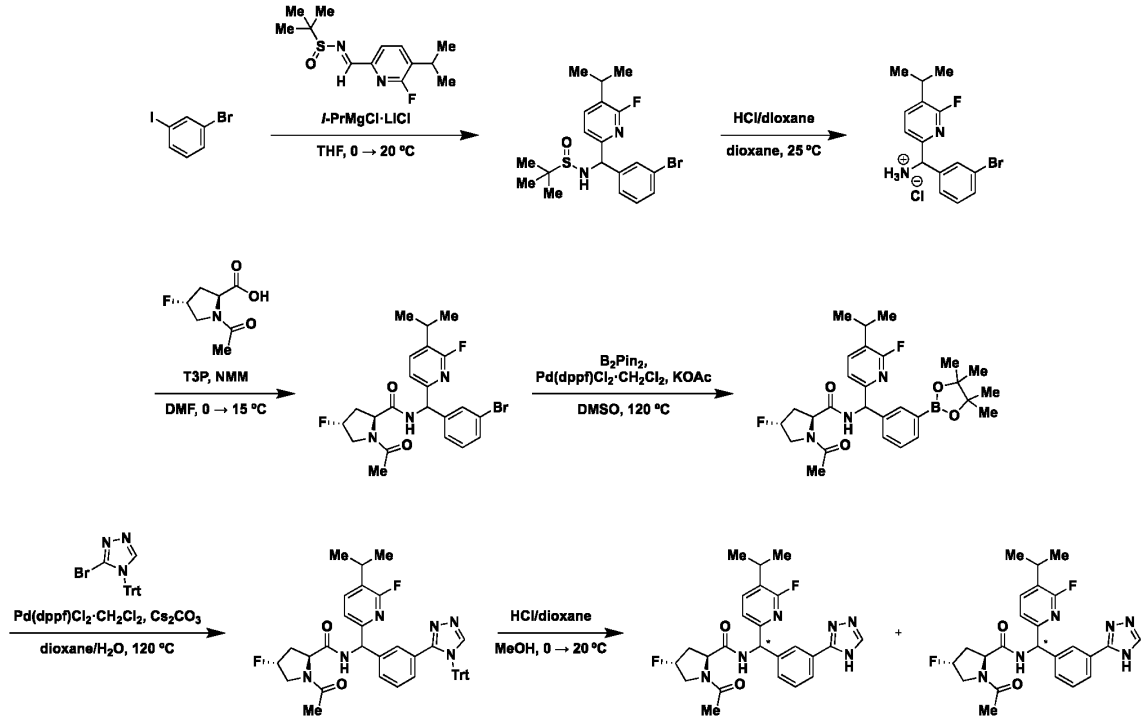
[0751] First-eluting isomer (Compound 687): ^{1}H NMR (2.9:1 rotamer ratio, asterisk denotes minor rotamer peaks, obscured peaks not reported, 400 MHz, DMSO-d_6) δ 12.89 (s, 1H), 9.41* (d, J = 7.8 Hz, 1H), 9.06 (d, J = 8.3 Hz, 1H), 7.86 (t, J = 8.9 Hz, 1H), 7.82 – 7.59 (m, 3H), 7.54 (d, J = 7.6 Hz, 1H), 7.44 – 7.26 (m, 2H), 7.26 – 7.14 (m, 1H), 6.67 (s, 1H), 6.15* (d, J = 7.9 Hz, 1H), 6.03 (d, J = 8.1 Hz, 1H), 5.48 – 5.19 (m, 1H), 4.96 – 4.85* (m, 1H), 4.65 (t, J = 8.3 Hz, 1H), 4.14 – 3.62 (m, 3H), 3.11 – 2.92 (m, 1H), 2.10 – 1.89 (m, 1H), 1.23 – 1.17 (m, 6H), 1.17 – 1.12* (m, 6H). LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{27}H_{28}F_2N_8O_2$: 535.2; found 535.2.

[0752] Second-eluting isomer (Compound 686): ^{1}H NMR (3.3:1 rotamer ratio, asterisk denotes minor rotamer peaks, obscured peaks not reported, 400 MHz, DMSO-d_6) δ 14.77 (br s, 1H), 13.24* (br s, 1H), 12.85 (br s, 1H), 9.35* (d, J = 7.8 Hz, 1H), 9.01 (d, J = 8.1 Hz, 1H), 7.93 – 7.77 (m, 2H), 7.77 – 7.56 (m, 3H), 7.41 – 7.25 (m, 2H), 7.16 (d, J = 7.7 Hz, 1H), 6.75 – 6.70 (m, 1H), 6.61* (s, 1H), 6.13* (d, J = 7.8 Hz, 1H), 6.03 (d, J = 8.0 Hz, 1H), 5.50 – 5.21 (m, 1H), 4.92* (t, J = 8.0 Hz, 1H), 4.66 (t, J = 8.3 Hz, 1H), 4.13 – 3.65 (m, 4H), 3.05 (hept,

J = 6.9 Hz, 1H), 2.14 – 1.93 (m, 1H), 1.24 – 1.17 (m, 6H). LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{27}H_{28}F_2N_8O_2$: 535.2; found 535.2.

Example S-18: Synthesis of (2*S*,4*R*)-*N*-((*S*) or (*R*)-(3-(4*H*-1,2,4-triazol-3-yl)phenyl)(6-fluoro-5-isopropylpyridin-2-yl)methyl)-1-acetyl-4-fluoropyrrolidine-2-carboxamide and (2*S*,4*R*)-*N*-((*R*) or (*S*)-(3-(4*H*-1,2,4-triazol-3-yl)phenyl)(6-fluoro-5-isopropylpyridin-2-yl)methyl)-1-acetyl-4-fluoropyrrolidine-2-carboxamide

(Compounds 688 and 689)



[0753] Step a: To a solution of 1-bromo-3-iodobenzene (8.06 g, 28.4 mmol, 1.1 eq) in THF (40 mL) at 0 °C under N_2 was added *i*-PrMgCl·LiCl (1.3 M in THF, 21.9 mL, 1.1 eq) in a dropwise manner. The resulting mixture was stirred at 0 °C for 2 h before (*E*)-*N*-((6-fluoro-5-isopropylpyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide (7 g, 25.8 mmol, 1 eq) in THF (20 mL) was added in a dropwise manner at 0 °C. The resulting mixture was allowed to warm to 20 °C and stirred for 1h. The reaction was then quenched with saturated aq. NH_4Cl solution (20

mL), and the resulting biphasic mixture was extracted with ethyl acetate (3 x 40 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give *N*-((3-bromophenyl)(6-fluoro-5-isopropylpyridin-2-yl)methyl)-2-methylpropane-2-sulfinamide. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{19}H_{24}BrFN_2OS$: 427.1; found 427.1.

[0754] Step b: To a solution of *N*-((3-bromophenyl)(6-fluoro-5-isopropylpyridin-2-yl)methyl)-2-methylpropane-2-sulfinamide (6 g, 14.0 mmol, 1 eq) in dioxane (20 mL) at 25 ºC was added HCl/dioxane (50 mL). The resulting mixture was stirred at 25 ºC for 1 h. The reaction mixture was then filtered to give (3-bromophenyl)(6-fluoro-5-isopropylpyridin-2-yl)methanaminium chloride. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{15}H_{16}BrFN_2$: 323.0; found 323.0.

[0755] Step c: To a solution of (3-bromophenyl)(6-fluoro-5-isopropylpyridin-2-yl)methanaminium chloride (5.8 g, 16.1 mmol, 1 eq) in DMF (30 mL) at 0 ºC was added NMM (64.5 mmol, 7 mL, 4 eq), (2*S*,4*R*)-1-acetyl-4-fluoropyrrolidine-2-carboxylic acid (4.24 g, 24.2 mmol, 1.5 eq), and T3P (32.3 mmol, 19 mL, 50% purity, 2 eq), sequentially. The resulting mixture was warmed to 15 ºC and stirred for 1 h. The reaction mixture was then poured into ice-water (50 mL) and stirred for 5 min. The resulting biphasic mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give (2*S*,4*R*)-1-acetyl-*N*-((3-bromophenyl)(6-fluoro-5-isopropylpyridin-2-yl)methyl)-4-fluoropyrrolidine-2-carboxamide. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{22}H_{24}BrF_2N_3O_2$: 480.1; found 480.0.

[0756] Step d: To a mixture of (2*S*,4*R*)-1-acetyl-*N*-((3-bromophenyl)(6-fluoro-5-isopropylpyridin-2-yl)methyl)-4-fluoropyrrolidine-2-carboxamide (2 g, 4.16 mmol, 1 eq) and bis(pinacolato)diboron (1.16 g, 4.58 mmol, 1.1 eq) in DMSO (20 mL) was added potassium acetate (1.02 g, 10.4 mmol, 2.5 eq). The resulting mixture was then degassed and purged with N_2. To this mixture added $Pd(dppf)Cl_2.CH_2Cl_2$ (340 mg, 416 µmol, 0.1 eq), and the resulting mixture was degassed and purged with N_2. The reaction mixture was then warmed to 120 ºC and stirred for 2 h under N_2 atmosphere. The reaction mixture was then filtered, and the filtrate was

concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give (2*S*,4*R*)-1-acetyl-4-fluoro-*N*-((6-fluoro-5-isopropylpyridin-2-yl)(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl)pyrrolidine-2-carboxamide. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{28}H_{36}BF_2N_3O_4$: 528.3; found 528.4.

[0757] Step e: To a mixture of (2*S*,4*R*)-1-acetyl-4-fluoro-*N*-((6-fluoro-5-isopropylpyridin-2-yl)(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl)pyrrolidine-2-carboxamide (1 g, 1.90 mmol, 1 eq) and 3-bromo-4-trityl-4*H*-1,2,4-triazole (888 mg, 2.28 mmol, 1.2 eq) in dioxane (7 mL) and H_2O (0.5 mL) was added Cs_2CO_3 (1.24 g, 3.79 mmol, 2 eq). The resulting mixture was degassed and purged with N_2, and then $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (310 mg, 379 μmol, 0.2 eq) was added in one portion. The resulting mixture was degassed and purged with N_2. The reaction mixture was then warmed to 120 °C and stirred for 1 h under N_2 atmosphere. The reaction solution was then filtered, and the filtrate was concentrated under reduced pressure. The crude residue obtained was purified by column chromatography to give (2*S*,4*R*)-1-acetyl-4-fluoro-*N*-((6-fluoro-5-isopropylpyridin-2-yl)(3-(4-trityl-4*H*-1,2,4-triazol-3-yl)phenyl)methyl)pyrrolidine-2-carboxamide. LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{43}H_{40}F_2N_6O_2$: 711.3; found 711.3.

[0758] Step f: To a solution of (2*S*,4*R*)-1-acetyl-4-fluoro-*N*-((6-fluoro-5-isopropylpyridin-2-yl)(3-(4-trityl-4*H*-1,2,4-triazol-3-yl)phenyl)methyl)pyrrolidine-2-carboxamide (0.7 g, 984 μmol, 1 eq) in MeOH (5 mL) at 0 °C was added HCl/dioxane (4M, 10 mL). The resulting mixture was allowed to warm to 20 °C and stirred for 2 h. The reaction mixture was then concentrated under reduced pressure. The crude residue obtained was purified by prep-TLC to give (2*S*,4*R*)-*N*-((*S*)-(3-(4*H*-1,2,4-triazol-3-yl)phenyl)(6-fluoro-5-isopropylpyridin-2-yl)methyl)-1-acetyl-4-fluoropyrrolidine-2-carboxamide. This mixture of diastereomers was then purified by prep-HPLC (column: Phenomenex Luna C18) to give (2*S*,4*R*)-*N*-((*R*) or (*S*)-(3-(4*H*-1,2,4-triazol-3-yl)phenyl)(6-fluoro-5-isopropylpyridin-2-yl)methyl)-1-acetyl-4-fluoropyrrolidine-2-carboxamide (Compound 689, first-eluting isomer) and (2*S*,4*R*)-*N*-((*S*) or (*R*)-(3-(4*H*-1,2,4-triazol-3-yl)phenyl)(6-fluoro-5-isopropylpyridin-2-yl)methyl)-1-acetyl-4-fluoropyrrolidine-2-carboxamide (Compound 688, second-eluting isomer).

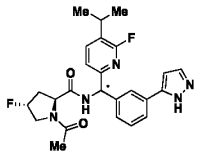
[0759] First-eluting isomer (Compound 689): ^1H NMR (2:1 rotamer ratio, asterisk denotes minor rotamer peaks, obscured peaks not reported, 400 MHz, DMSO-d_6) δ 9.34* (d, *J* =

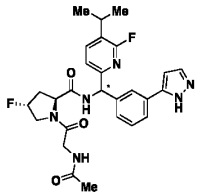
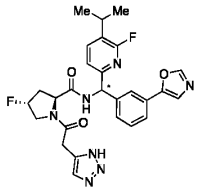
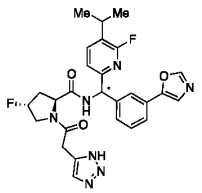
7.9 Hz, 1H), 9.09 (d, *J* = 8.1 Hz, 1H), 8.52 – 8.39 (m, 1H), 8.04 – 7.99* (m, 1H), 7.97 – 7.85 (m, 3H), 7.64 – 7.58 (m, 1H), 7.50 – 7.31 (m, 2H), 6.15* (d, *J* = 7.8 Hz, 1H), 6.03 (d, *J* = 8.0 Hz, 1H), 5.46 – 5.17 (m, 1H), 4.73* (t, *J* = 8.0 Hz, 1H), 4.60 (t, *J* = 8.3 Hz, 1H), 3.96 – 3.60 (m, 2H), 3.12 – 2.98 (m, 1H), 2.47 – 2.37 (m, 1H), 2.12 – 1.89 (m, 4H), 1.81* (s, 3H), 1.25 – 1.16 (m, 6H). LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{24}H_{26}F_2N_6O_2$: 469.2; found 469.2.

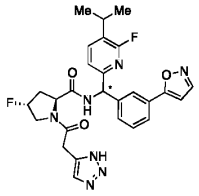
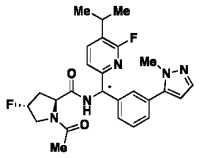
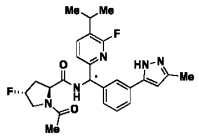
[0760] Second-eluting isomer (Compound 688): ^{1}H NMR (2:1 rotamer ratio, asterisk denotes minor rotamer peaks, obscured peaks not reported, 400 MHz, DMSO-d_6) δ 14.20 (br s, 1H), 9.32* (d, *J* = 8.0 Hz, 1H), 9.02 (d, *J* = 8.1 Hz, 1H), 8.47 (br s, 1H), 8.07 – 7.82 (m, 3H), 7.49 – 7.35 (m, 3H), 6.15* (d, *J* = 8.0 Hz, 1H), 6.06 (d, *J* = 8.0 Hz, 1H), 5.48 – 5.17 (m, 1H), 4.75* (t, *J* = 8.1 Hz, 1H), 4.62 (t, *J* = 8.4 Hz, 1H), 3.96 – 3.62 (m, 2H), 3.12 – 3.00 (m, 1H), 2.24 – 1.92 (m, 4H), 1.77* (s, 3H), 1.24 – 1.17 (m, 6H). LC-MS (ESI): m/z: $[M + H]^+$ calculated for $C_{24}H_{26}F_2N_6O_2$: 469.2; found 469.2.

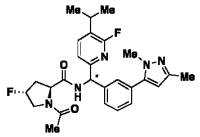
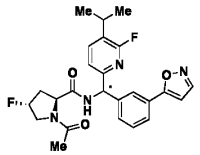
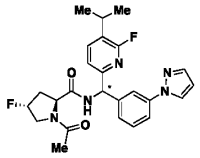
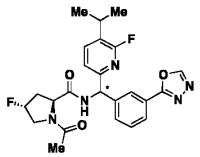
[0761] The following compounds in Table T-17 were synthesized using procedures similar to Compound 686, 687, 688 and 689 using the appropriate starting materials.

Table T-17

Compound No.	Structure	IUPAC	Exact mass (g/mol)	LCMS, Found [M + H]$^+$
690		(2S,4R)-1-acetyl-4-fluoro-N-[(S) or (R)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl][3-(1H-pyrazol-5-yl)phenyl]methyl] pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, first-eluting isomer)	467.2	468.2

691		(2S,4R)-1-(2-acetamidoacetyl)-4-fluoro-N-[(S) or (R)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl][3-(1H-pyrazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, first-eluting isomer)	524.2	525.1
692		(2S,4R)-4-fluoro-N-[(R) or (S)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl][3-(1,3-oxazol-5-yl)phenyl]methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, second-eluting isomer)	535.2	536.1
693		(2S,4R)-4-fluoro-N-[(S) or (R)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl][3-(1,3-oxazol-5-yl)phenyl]methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, first-eluting isomer)	535.2	536.1

694		(2S,4R)-4-fluoro-N-[(S) or (R)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl][3-(1,2-oxazol-5-yl)phenyl]methyl]-1-[2-(1H-1,2,3-triazol-5-yl)acetyl]pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, first-eluting isomer)	535.2	536.2
695		(2S,4R)-1-acetyl-4-fluoro-N-[(S) or (R)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl][3-(1-methyl-1H-pyrazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, first-eluting isomer)	481.2	482.1
696		(2S,4R)-1-acetyl-4-fluoro-N-[(S) or (R)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl][3-(3-methyl-1H-pyrazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, first-eluting isomer)	481.2	482.2

697		(2S,4R)-1-acetyl-N-[(S) or (R)-[3-(1,3-dimethyl-1H-pyrazol-5-yl)phenyl][6-fluoro-5-(propan-2-yl)pyridin-2-yl]methyl]-4-fluoropyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, first-eluting isomer)	495.2	496.2
698		(2S,4R)-1-acetyl-4-fluoro-N-[(S) or (R)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl][3-(1,2-oxazol-5-yl)phenyl]methyl] pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, first-eluting isomer)	468.2	469.1
699		(2S,4R)-1-acetyl-4-fluoro-N-[(S) or (R)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl][3-(1H-pyrazol-1-yl)phenyl]methyl] pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, first-eluting isomer)	467.2	468.1
700		(2S,4R)-1-acetyl-4-fluoro-N-[(S) or (R)-[6-fluoro-5-(propan-2-yl)pyridin-2-yl][3-(1,3,4-oxadiazol-	469.1	470.2

		2-yl)phenyl]methyl] pyrrolidine-2-carboxamide (column: REGIS (s,s) WHELK-O1, first-eluting isomer)		

Biological Examples

Example B-1

[0762] The GYS1 coupled enzyme assay is a kinetic biochemical assay that indirectly quantifies the rate of glycogen synthesis by coupling the conversion of GYS1 substrate UDP-glucose into UDP with downstream enzymatic reactions. UDP is released from UDP-glucose as glucose monomers are linked into the growing glycogen strand by GYS1. The coupled assay then proceeds with pyruvate kinase utilizing UDP and phospho(enol)pyruvate (PEP) to form pyruvate. Lactate dehydrogenase then converts pyruvate and NADH into lactate and NAD+. Oxidation of NADH to NAD+ can be measured continuously with a plate reader by quantifying the decrease in NADH absorbance at 340 nm over time.

[0763] Compounds that inhibit the hGYS1 enzyme and, subsequently, the downstream conversion of NADH to NAD+, were tested using assay ready plates (black, clear bottom 384 well plates) in a final DMSO reaction volume of 2.5% DMSO. The Assay Buffer contained 50 mM Tris pH 7.5, 2 mM $MgCl_2$, and 100 mM KCl. Fresh stocks of BSA at a final concentration of 0.02% and TCEP at 1 mM were added before splitting buffer into hGYS1 buffer and substrate buffer. To the hGYS1 buffer, rabbit liver glycogen was added at a final concentration of 0.2% glycogen. Glucose-6-Phosphate was added at 1 mM, recombinant hGYS1/GN1 protein was added at 50 nM to the substrate buffer, phosphoenolpyruvate (PEP) was added at 2 mM, UDP-Glucose was added at 0.8 mM, NADH) was added at 0.6 mM, and Pyruvate Kinase/ Lactate Dehydrogenase was added at 20 units/mL. The reaction was initiated by mixing hGYS1 buffer and substrate buffer at a 1:1 ratio. Both buffers were plated using a liquid dispensing device with hGYS1 buffer plated first followed by the substrate buffer. Plates were spun briefly to eliminate air bubbles and are immediately read in continuous mode at an

absorbance of 340 nm, for 10 time points in one-minute increments, for a total of 10 minutes. The slope from these 10 time points was normalized to the positive and negative control wells. The duplicate % inhibition values are then averaged and fit to a Hill equation for dose response according to the Levenberg-Marquardt algorithm with the Hill equation maximum set to 100 and the minimum set to 0.

[0764] The results are shown in Table 2 below, which reports the IC_{50} of each compound. Unless otherwise specified, IC_{50} values are reported as the geometric mean of at least 2 assay runs on separate days. Each run represents the average of a technical replicate, where each compound was assayed twice in the same plate. As shown in the table below, the compounds of the present invention are potent inhibitors of human GYS1. A superscript "# " symbol in Table 2 indicates results from a single assay run.

[0765] Note that, in Table 2, the compounds are referred to by the corresponding Compound No. in Table 1, which is also referred to in the synthetic examples. When one or more of the numbered compounds are identified by stereochemistry (for example, (*R*)- or (*S*)-), the specific stereoisomer for which data is provided in Table 2 may be identified by the elution order of such compound as described in the synthetic examples. To illustrate, Compound 497 is the first-eluting isomer in step g of Example S-7 and Compound 498 is the second-eluting isomer in step g of Example S-7.

Table 2

Compound No.	PK/LDH IC_{50} (μM)
1	0.033
2	0.059
3	0.168
4	0.998
5	0.353
6	0.211
7	0.113
8	0.042
9	0.059
10	0.050
11	0.091
12	0.415
13	0.147
14	0.129
15	0.048
16	0.033
17	0.034
18	0.045
19	0.047
20	0.046
21	0.027
22	0.043
23	0.070
24	0.050
25	0.235
26	0.036
27	0.023

Compound No.	PK/LDH IC_{50} (μM)
28	0.060
29	0.070
30	0.947
31	0.048
32	0.023
33	0.106
34	0.075
35	0.185
36	0.073
37	0.045
38	0.051
39	0.050
40	0.026
41	0.031
42	0.495
43	0.091
44	0.106
45	0.058
46	0.136
47	0.138
48	0.044
49	0.039
50	0.017
51	0.019
52	0.037
53	0.789
54	0.047

Compound No.	PK/LDH IC_{50} (μM)
55	0.043
56	0.041
57	0.231
58	0.145
59	0.085
60	0.188
61	0.243
62	0.064
63	0.015
64	0.081
65	0.076
66	0.082
67	0.010
68	0.034
69	0.036
70	0.050
71	0.375
72	0.472
73	0.105
74	0.705
75	0.224
76	0.106
77	0.008
78	0.953
79	0.313
80	0.318
81	0.025

Compound No.	PK/LDH IC_{50} (μM)
82	0.504
83	0.015
84	0.010
85	0.154
86	0.012
87	0.028
88	0.049
89	0.060
90	0.032
91	0.047
92	0.439
93	0.108
94	0.188
95	0.130
96	0.021
97	0.712
98	0.244
99	0.065
100	0.073
101	0.054
102	0.058
103	0.162
104	0.061
105	0.249
106	0.186
107	0.019
108	0.077

Compound No.	PK/LDH IC_{50} (μM)
109	0.041
110	0.033
111	1.085
112	0.854
113	1.042
114	0.208
115	0.493
116	0.121
117	0.049
118	0.020
119	0.109
120	0.343
121	0.015
122	0.989
123	1.001
124	0.078
125	0.023
126	0.011
127	0.318
128	0.056
129	0.217
130	0.007
131	0.563
132	0.099
133	0.010
134	0.041
135	0.044

Compound No.	PK/LDH IC_{50} (μM)
136	0.009
137	0.017
138	0.012
139	0.357
140	0.067
141	0.181
142	0.077
143	0.323
144	0.168
145	0.915
146	0.206
147	0.127
148	0.344
149	0.332
150	0.554
151	0.241
152	0.132
153	0.412
154	0.285
155	0.206
156	0.304
157	0.392
158	0.070
159	0.740
160	0.069
161	0.374
162	0.136

Compound No.	PK/LDH IC_{50} (μM)
163	0.135
164	0.467
165	0.361
166	0.056
167	0.116
168	0.439
169	0.091
170	0.306
171	0.097
172	0.255
173	0.844
174	0.179
175	0.582
176	0.410
177	0.349
178	0.038
179	0.031
180	0.235
181	0.449
182	0.748
183	0.041
184	0.075
185	0.026
186	0.097
187	0.073
188	0.237
189	0.095

Compound No.	PK/LDH IC_{50} (μM)
190	0.220
191	0.131
192	0.076
193	0.303
194	0.027
195	0.044
196	0.143
197	0.128
198	0.031
199	1.190
200	4.419
201	0.461
202	0.071
203	0.862
204	3.527
205	3.737
206	2.484
207	0.387
208	0.113
209	0.091
210	0.107
211	0.469
212	0.095
213	0.282
214	0.853
215	3.772
216	0.247

Compound No.	PK/LDH IC_{50} (μM)
217	0.096
218	0.293
219	0.101
220	0.038
221	0.043
222	0.040
223	0.062
224	0.070
225	0.044
226	0.083
227	0.076
228	0.077
229	0.025
230	0.117
231	0.105
232	0.025
233	0.252
234	0.695
235	0.342
236	0.058
237	0.054
238	0.046
239	0.067
240	0.060
241	0.082
242	0.079
243	0.086

Compound No.	PK/LDH IC_{50} (μM)
244	0.077
245	1.312
246	0.033
247	0.010
248	0.012
249	0.021
250	0.043
251	0.053
252	0.186
253	0.067
254	0.075
255	0.088
256	0.039
257	0.007
258	0.026
259	0.015
260	0.035
261	0.059
262	0.062
263	0.080
264	0.130
265	0.041
266	0.089
267	0.464
268	0.018
269	0.014
270	0.096

Compound No.	PK/LDH IC_{50} (μM)
271	0.036
272	0.054
273	0.149
274	0.264
275	0.076
276	0.020
277	0.031
278	0.011
279	0.234
280	0.149
281	0.059
282	0.049
283	0.058
284	0.090
285	0.149
286	0.147
287	0.124
288	0.109
289	0.056
290	0.056
291	0.053
292	0.1109
293	0.038
294	0.006
295	0.013
296	0.087
297	0.015

Compound No.	PK/LDH IC_{50} (μM)
298	0.012
299	0.022
300	0.028
301	0.046
302	0.067
303	0.036
304	0.073
305	0.024
306	0.078
307	0.010
308	0.011
309	0.055
310	0.075
311	0.127
312	0.097
313	0.039
314	0.063
315	0.023
316	0.037
317	0.017
318	0.020
319	0.007
320	0.197
321	0.124
322	0.013
323	0.074
324	0.142

Compound No.	PK/LDH IC_{50} (μM)
325	0.075
326	0.020
327	0.121
328	0.016
329	0.336
330	0.021
331	0.023
332	0.025
333	0.165
334	0.145
335	0.037
336	0.015
337	0.027
338	0.034
339	0.018
340	0.018
341	0.780
342	0.034
343	0.027
344	0.013
345	0.032
346	0.024
347	0.030
348	0.024
349	0.025
350	0.020
351	0.008

Compound No.	PK/LDH IC_{50} (μM)
352	0.005
353	0.007
354	0.005
355	0.018
356	0.013
357	0.021
358	0.011
359	0.063
360	0.019
361	0.010
362	0.090
363	0.019
364	0.080
365	0.007
366	0.020
367	0.016
368	0.005
369	0.537
370	0.569
371	0.343
372	0.036
373	0.014
374	0.022
375	0.006
376	0.008
377	0.012
378	0.006

Compound No.	PK/LDH IC_{50} (μM)
379	0.008
380	0.047
381	0.058
382	0.034
383	0.027
384	0.033
385	0.017
386	0.005
387	0.005
388	0.005
389	0.004
390	0.027
391	0.006
392	0.005
393	0.008
394	0.007
395	0.008
396	0.013
397	0.009
398	0.009
399	0.008
400	0.012
401	0.010
402	0.059
403	0.004
404	0.006
405	0.020

Compound No.	PK/LDH IC_{50} (μM)
406	0.041
407	0.015
408	0.008
409	0.010
410	0.008
411	0.010
412	0.007
413	0.006
414	0.003
415	0.048
416	0.025
417	0.023
418	0.697
419	2.190
420	3.563
421	0.294
422	0.166
423	0.350
424	0.287
425	0.224
426	0.363
427	0.165
428	0.374
429	0.114
430	0.191
431	0.221
432	0.185

Compound No.	PK/LDH IC_{50} (μM)
433	0.091
434	0.109
435	0.149
436	0.173
437	0.157
438	0.303
439	0.185
440	0.447
441	0.051
442	0.023
443	0.028
444	0.044
445	0.075
446	0.098
447	0.096
448	0.071
449	0.039
450	0.094
451	0.095
452	0.040
453	0.077
454	0.072
455	0.291
456	0.055
457	0.032
458	0.071
459	0.028

Compound No.	PK/LDH IC_{50} (μM)
460	0.187
461	0.026
462	0.024
463	0.025
464	0.023
465	0.547
466	0.238
467	0.324
468	0.091
469	0.061
470	0.082
471	0.029
472	0.022
473	0.100
474	0.043
475	0.077
476	0.039
477	0.020
478	0.069
479	0.055
480	0.079
481	0.247
482	0.068
483	0.049
484	0.066
485	0.210
486	0.041

Compound No.	PK/LDH IC_{50} (μM)
487	0.068
488	0.031
489	0.353
490	0.052
491	0.093
492	0.138
493	0.103
494	0.661
495	0.066
496	0.086
497	0.369
498	>10
499	2.258
500	>100
501	0.003
502	0.01
503	0.008
504	0.003
505	0.02
506	0.004
507	0.022
508	0.021
509	0.008
510	0.009
511	0.012
512	0.015
513	0.014

Compound No.	PK/LDH IC_{50} (μM)
514	0.007
515	0.004
516	0.008
517	0.008
518	1.498
519	0.008
520	0.557
521	2.606
522	0.005
523	0.005
524	0.006
525	0.004
526	0.011
527	0.007
528	0.015
529	0.016
530	0.012
531	0.008
532	0.065
533	0.043
534	0.057
535	0.012
536	0.024
537	0.011
538	0.048
539	0.068
540	0.047

Compound No.	PK/LDH IC_{50} (μM)
541	0.055
542	0.011
543	0.049
544	0.011
545	1.68
546	0.027
547	0.016
548	0.328
549	0.006
550	0.042
551	0.007
552	0.082
553	0.008
554	0.034
555	0.097
556	0.027
557	0.424
558	0.136
559	1.58
560	0.144
561	0.036
562	0.685
563	0.063
564	0.056
565	0.048
566	0.046
567	0.642

Compound No.	PK/LDH IC_{50} (μM)
568	0.089
569	0.066
570	0.082
571	0.075
572	0.205
573	0.178
574	0.022
575	0.119
576	0.085
577	0.478
578	0.613
579	0.059
580	0.249
581	0.269
582	0.319
583	0.105
584	0.104
585	0.202
586	0.010
587	0.109
588	0.036
589	0.101
590	2.553
591	0.032
592	0.01
593	0.019
594	0.05

Compound No.	PK/LDH IC_{50} (μM)
595	0.025
596	0.02
597	0.064
598	0.153
599	0.04
600	0.036
601	0.034
602	0.092
603	0.602
604	0.176
605	0.168
606	1.125
607	0.333
608	2.856
609	0.225
610	0.107
611	0.547
612	2.182
613	0.130
614	1.149
615	1.578
616	1.324
617	1.644
618	1.515
619	1.157
620	0.142
621	0.555

Compound No.	PK/LDH IC_{50} (μM)
622	0.443
623	0.111
624	0.408
625	0.139
626	0.805
627	1.618
628	2.778
629	1.483
630	0.092
631	0.176
632	0.013
633	1.598
634	0.043
635	0.082
636	0.071
637	0.453
638	0.399
639	0.921
640	1.445
641	2.95
642	1.333
643	2.185
644	0.273
645	0.1
646	0.048
647	1.643
648	0.616

Compound No.	PK/LDH IC_{50} (μM)
649	0.483
650	1.436
651	0.077
652	1.203
653	0.262
654	0.252
655	1.008
656	1.301
657	0.127
658	0.099
659	0.331
660	0.309
661	0.043
662	0.227
663	2.022
664	0.115
665	0.099
666	2.273
667	0.023
668	0.025
669	0.04
670	0.071
671	0.849
672	0.082
673	1.74
674	0.096
675	0.101

Compound No.	PK/LDH IC_{50} (μM)
676	0.554
677	0.051
678	1.065
679	0.577
680	0.015
681	0.03
682	0.116
683	2.362
684	1.332
685	0.204
686	0.013
687	3.82
688	0.106
689	>10.0
690	0.047
691	0.015
692	2.48
693	0.056
694	0.034
695	0.929
696	0.103
697	1.777
698	0.151
699	0.051
700	0.321
701	0.446
702	1.256

Compound No.	PK/LDH IC_{50} (μM)
703	2.159
704	2.218
705	1.722
707	1.992
708	2.508
709	1.144
710	0.146
711	0.03
712	0.015
713	0.074
714	0.045
715	0.105
716	2.161
717	1.481
718	2.618
719	0.254
720	2.45
721	0.079
722	0.085
723	0.046
724	0.034
725	0.015
726	0.03
727	0.017
728	0.036
729	0.039
730	0.037

Compound No.	PK/LDH IC_{50} (μM)
731	0.066
732	0.027
733	0.005
734	0.026
735	0.005
736	0.02
737	0.037
738	0.105
739	0.017
740	0.009
741	0.016
742	0.024
743	0.028
744	0.046
745	0.024
746	0.07
747	0.016
748	0.015
749	0.006
750	0.011
751	0.013
752	0.021
753	0.021
754	0.027
755	0.102
756	0.023
757	0.029

Compound No.	PK/LDH IC_{50} (μM)
758	0.032
759	0.018
760	0.017
761	0.055
762	0.027
763	0.466
764	0.155
765	0.047
766	0.038
767	0.106
768	0.121
769	0.022
770	0.062
771	0.033
772	0.356
773	0.124
774	0.022
775	1.08
776	1.151
777	0.042
778	0.381
779	0.016
780	0.009
781	0.011
782	0.011
783	0.005
784	0.005

Compound No.	PK/LDH IC_{50} (μM)
785	0.006
786	0.003
787	0.007
788	0.02
789	0.01
790	0.008
791	0.007
792	0.006
793	0.012
794	0.002
795	0.011
796	0.005
797	0.016
798	0.012
799	0.004
800	0.009
801	0.024
802	0.009
803	0.004
804	0.017
805	0.012
806	0.006
807	0.019
808	0.012
809	0.007
810	0.357

Example B-2

[0766] The GYS1 cell based assay is a bioluminescent assay that quantifies the glucose resulting from glycogen digestion; the quantified glucose is an indirect measure of GYS1 glycogen synthesis. Newly synthesized glycogen is digested using Glucoamylase; the resulting glucose is quantified by using the Glucose-glo assay kit from Promega. Glucose-glo works by coupling glucose oxidation and NADH production with a bioluminescent system that is activated with NADH. Glucose is oxidized by Glucose dehydrogenase and the reaction reduces NAD+ to NADH; NADH activates Reductase which reduces a pro-luciferin Reductase Substrate to luciferin. Luciferin is detected in a luciferase reaction using Ultra-Glo rLuciferase and ATP, and the luminesce produced is proportional to the glucose in the sample. The luminescence is measured as a single point read in a plate reader.

[0767] Compounds that inhibit the hGYS1 enzyme and, subsequently, the glycogen synthesis in cells, were tested using assay ready plates (white, clear bottom 384 well plates) in a final DMSO reaction volume of 1% DMSO. Compounds in the assay ready plates were mixed with media with no additives, except for 20 mM glucose prior to cell addition. HeLa cells were starved in media with no additives, except for 1X Glutamax for 24 h. Starved HeLa cells were plated, in a 1:1 ratio to the media in the assay ready plate and incubated for 24h at 37°C and 5% CO_2. Cells were washed in 1X PBS buffer and lysed in lysis buffer containing 50% 1X PBS and 25% 0.3 N HCl of the final volume in the well or reaction volume; cells were incubated with lysis buffer for 10 minutes and quenched with the remaining 25% of the reaction volume that consisted of 450 mM Tris pH 8.0. Lysates were mixed in a 1:1 ratio with Glucoamylase in 100 mM Sodium Acetate buffer, pH 5.3; the mixture was incubated for 1h at 37 °C. The digested lysate was mixed in a 1:1 ratio with Glucose-glo detection mixture as per vendor recommendations (Luciferase detection buffer, Reductase, Reductase substrate, Glucose dehydrogenase, and NAD) in read-out plates (solid white 384-well plates) and incubated for 1 h at RT. The plates were read using a plate reader with luminescence capabilities. Each compound concentration Relative Luminescence Unit (RLU) was averaged and normalized to the average RLU of the positive and negative controls to obtain a percentage inhibition. The normalized data

vs. concentration was plotted; to determine the half-maximal concentration (IC_{50}), the Levenberg-Marquardt algorithm was used to fit a Hill equation to the dose response data.

[0768] The results are shown in Table 3 below, which reports the IC_{50} of each compound. Unless otherwise specified, IC_{50} values are reported as the geometric mean of at least 2 assay runs on separate days. As shown in the table below, the compounds of the present invention are potent inhibitors of human GYS1. Unless otherwise specified, IC_{50} values are reported as the geometric mean of at least two assay runs on separate days. Each run represents the average of a technical replicate, where each compound was assayed twice in the same plate. A superscript "#" symbol in Table 3 indicates results from a single assay run.

Table 3

Compound No.	Avg IC_{50} (μM)
1	0.42
2	1.09
17	0.33
21	0.47
49	0.36
77	0.12
126	0.17
136	0.17
138	0.27
145	> 10.00
149	> 10.00
166	0.78
177	2.09
178	0.41
179	0.4
183	0.93
184	3.03
198	0.39
201	3.7
202	1.86
219	1.41
227	1.31
236	0.81
239	1.56
240	2.09
241	1.14
242	1.14
243	2.25
244	1.8
246	0.62
247	0.18
248	0.2
249	1.15
250	1.27
252	2.48
253	1.09

Compound No.	Avg IC_{50} (μM)
254	1.23
255	1.01
256	0.99
257	0.24
258	0.74
259	0.28
260	0.53
261	1.8
262	3.63
263	1.95
264	4.29
265	0.83
266	1.22
267	4.3
268	0.83
269	0.24
270	1.4
271	0.87
272	0.71
273	1.79
274	3.23
275	1.05
276	0.4
277	0.65
278	0.23
279	2.31
280	1.53
281	1.56
282	4.18
283	2.4
284	5.19
285	> 18.64
286	> 30.00
287	11.81
293	0.66
294	0.16

Compound No.	Avg IC_{50} (μM)
295	0.59
296	4.44
297	0.7
298	0.26
299	0.42
300	0.57
301	0.9
302	1.23
303	1.52
304	2.33
305	0.63
306	0.81
307	0.5
308	0.33
309	0.97
310	1.29
311	2.1
312	0.83
313	0.86
314	1.01
315	0.73
316	0.93
317	0.39
318	0.58
319	0.24
320	1.59
321	1.24
322	0.29
323	0.9
326	0.34
330	0.56
332	0.27
335	0.45
336	0.28
338	0.39
339	0.31

Compound No.	Avg IC_{50} (μM)
340	0.25
342	0.37
343	0.46
347	0.4
348	0.27
349	0.4
351	0.13
352	0.11
353	0.09
354	0.06
355	0.16
356	0.19
357	0.22
358	0.19
359	0.96
360	0.31
361	0.21
362	1.15
363	0.32
364	0.48
365	1.19
367	0.47
368	0.15
369	> 30.00
371	3.88
372	1.1
373	0.21
374	0.36
375	0.57
377	0.14
378	0.17
379	0.19
380	0.45
381	0.44
382	0.52
383	0.41

Compound No.	Avg IC_{50} (μM)
384	0.7
385	0.39
386	0.08
387	0.03
388	0.12
389	0.05
390	1.03
391	0.15
392	0.1
393	0.12
394	0.15
395	0.24
396	0.33
397	0.4
398	0.28
399	0.15
400	0.17
401	0.29
402	0.85
403	0.14
404	0.07
405	0.49
406	0.76
407	0.42
408	0.35
409	0.29
410	0.13
411	0.22
412	0.12
413	0.16
414	0.06
415	0.71
416	0.47
417	0.45
423	> 9.26
425	3.59

Compound No.	Avg IC_{50} (μM)
427	1.96
431	3.35
433	1.48
442	0.86
445	1.66
446	2.19
447	5.32
448	1.35
449	0.7
450	1.73
451	1.57
452	0.98
453	1.84
454	1.6
455	3.62
456	1.08
457	0.72
458	1.33
459	0.75
460	2.42
461	0.57
462	0.64
463	0.67
464	0.65
465	6.04
466	2.32
467	4.81
468	1.43
469	1.18
470	0.96
471	0.7
472	0.54
473	1.77
474	0.88
475	1.29
476	0.9

Compound No.	Avg IC_{50} (μM)
477	0.63
478	1.19
479	1.43
480	1.12
481	7.77
482	1.41
483	0.72
484	0.82
485	3.72
486	1.02
487	2.09
488	0.88
490	2.87
491	5.55
492	> 30.00
493	15.77
494	12.41
495	1.5
496	1.82
497	> 5.67
498	> 10.00
501	0.05
502	0.17
503	0.24
504	0.06
505	0.35
506	0.37
507	0.26
508	0.31
509	0.18
510	0.23
511	0.26
512	0.29
513	0.22
514	0.77
515	0.1

Compound No.	Avg IC_{50} (μM)
516	0.71
517	0.54
518	10.68
519	0.22
520	> 30.00
521	> 30.00
522	0.45
523	0.08
524	0.19
525	0.05
526	0.13
527	0.25
528	0.33
529	1.04
530	0.91
531	0.06
532	1.18
533	1.21
534	1.28
535	1.22
536	0.35
537	0.16
538	1.22
539	0.96
540	0.59
541	0.65
542	1.48
543	0.61
544	0.26
545	> 30.00
546	0.51
547	0.36
548	5.76
549	0.12
550	0.65
551	0.21

Compound No.	Avg IC_{50} (μM)
552	1.12
553	0.4
554	0.38
555	0.66
556	0.76
557	5.78
558	2.46
559	> 22.13
560	1.8
561	0.87
562	7.07
563	0.78
564	0.79
565	1.21
566	0.77
567	11.54
568	0.96
569	0.96
570	1.22
571	0.93
572	3.6
573	1.66
574	0.2
575	2.09
576	1.8
577	3.98
578	6.66
579	1.83
580	4.27
581	3.92
582	8.08
583	1.64
584	4.07
585	3.21
586	0.15
587	2.39

Compound No.	Avg IC_{50} (μM)
588	0.48
589	1.42
590	23.43
591	0.31
592	0.33
593	0.28
594	0.72
595	0.46
596	0.28
597	1.32
598	2.18
599	0.72
600	0.62
601	0.71
602	0.76
604	1.59
605	2.13
607	3.29
608	> 10.00
609	1.65
610	1.01
611	5.32
612	> 28.95
622	> 10.00
623	4.07
624	5.79
625	1.14
626	> 30.00
627	29.51
628	> 30.00
629	> 23.95
630	2.13
631	13.62
632	0.66
633	> 30.00
638	> 23.41

Compound No.	Avg IC_{50} (μM)
650	> 10.00
651	1.57
652	21.64
653	3.75
654	3.29
655	> 30.00
656	10.85
657	1.5
658	1.66
659	4.35
667	0.29
668	0.32
669	0.47
670	0.66
672	1.22
674	0.71
675	1.13
676	13.99
677	0.99
678	> 10.00
679	8.49
680	0.27
681	0.43
682	2.09
683	> 30.00
684	13.81
685	2.71
686	0.64
687	>30
690	0.9
691	0.39
692	> 30.00
693	1.15
694	1.21
695	> 26.28
696	2.71

Compound No.	Avg IC_{50} (μM)
697	9.2
710	2.34
711	0.63
712	0.33
713	0.86
714	1.39
716	22.26
717	> 25.76
718	> 30.00
719	2.22
720	> 30.00
721	1.09
722	1.45
723	0.72
724	0.63
725	0.31
726	0.54
727	0.91
728	0.79
729	0.71
730	0.76
731	1.62
732	1.37
733	0.15
734	1.73
735	0.27
736	0.78
737	0.55
738	1.21
739	0.34
740	0.32
741	0.71
742	0.63
743	0.48
744	1.52
745	0.51

Compound No.	Avg IC_{50} (μM)
746	1.62
747	0.42
748	0.53
749	0.25
750	0.26
751	0.47
752	0.64
753	0.32
754	0.42
755	1.06
756	1.7
757	0.4
758	1.16
759	0.59
760	0.37
766	0.35
768	1.23
769	0.29
771	0.54
772	4.53
773	1.2
774	0.19
775	> 17.54
776	> 9.01
777	0.93
778	7.01
779	0.33
780	0.28
781	0.27
782	0.22
783	0.08
784	0.31
785	0.13
786	0.05
787	0.13
788	0.34

Compound No.	Avg IC_{50} (μM)
789	0.28
790	0.25
791	0.39
792	0.21
793	0.58
794	0.04
795	0.24
796	0.11
797	0.29
798	0.22
799	0.1
800	0.18
801	0.38
802	0.37
803	0.08
804	0.14
805	0.28
806	0.09
807	0.45
809	0.19
810	5.28

Example B-3

[0769] The GYS2 coupled enzyme assay is a kinetic biochemical assay that indirectly quantifies the rate of glycogen synthesis by coupling the conversion of GYS2 substrate UDP-glucose into UDP with downstream enzymatic reactions. UDP is released from UDP-glucose as glucose monomers are linked into the growing glycogen strand by GYS2. The coupled assay then proceeds with pyruvate kinase utilizing UDP and phospho(enol)pyruvate (PEP) to form pyruvate. Lactate dehydrogenase then converts pyruvate and NADH into lactate and NAD+. Oxidation of NADH to NAD+ can be measured continuously with a plate reader by quantifying the decrease in NADH absorbance at 340 nm over time.

[0770] Compounds that inhibit the hGYS2 enzyme and, subsequently, the downstream conversion of NADH to NAD+, were tested using assay ready plates (black, clear bottom 384 well plates) in a final DMSO reaction volume of 2.5% DMSO. The Assay Buffer contained 50 mM Tris pH 7.5, 2 mM $MgCl_2$, and 100 mM KCl. Fresh stocks of BSA at a final concentration of 0.02% and TCEP 1 mM were added before splitting buffer into hGYS2 buffer and substrate buffer. To the hGYS2 buffer, rabbit liver glycogen was added at a final concentration of 0.2% glycogen. Glucose-6-Phosphate was added at 2 mM, recombinant hGYS2/GN1 protein was added at 200 nM to the substrate buffer, phosphoenolpyruvate (PEP) was added at 2 mM, UDP-Glucose was added at 2 mM, NADH was added at 0.6 mM, and Pyruvate Kinase/Lactate Dehydrogenase was added at 20 units/mL. The reaction was initiated by mixing hGYS2 buffer and substrate buffer at a 1:1 ratio. Both buffers were plated using a liquid dispensing device with hGYS2 buffer plated first followed by the substrate buffer. Plates were spun briefly to eliminate air bubbles and are immediately read in continuous mode at an absorbance of 340 nm, for 10 time points in one-minute increments, for a total of 10 minutes. The slope from these 10 time points was normalized to the positive and negative control wells. The duplicate % inhibition values are then averaged and fit to a Hill equation for dose response according to the Levenberg-Marquardt algorithm with the Hill equation maximum set to 100 and the minimum set to 0.

[0771] The results are shown in Table 4 below, which reports the IC_{50} of each compound. Unless otherwise specified, IC_{50} values are reported as the geometric mean of at least 2 assay runs on separate days. As shown in the table below, the compounds of the present

invention are not potent inhibitors of human GYS2. Unless otherwise specified, IC_{50} values are reported as the geometric mean of at least two assay runs on separate days. Each run represents the average of a technical replicate, where each compound was assayed twice in the same plate. A superscript "#" symbol in Table 4 indicates results from a single assay run.

Table 4

Compound No.	Avg_IC50 (μM)
1	> 100.0
2	> 100.0
3	> 100.0
6	> 100.0
7	> 100.0
8	> 100.0
9	> 100.0
10	> 100.0
11	> 100.0
13	> 100.0
14	> 100.0
15	> 100.0
16	> 100.0
17	> 100.0
18	> 100.0
21	> 100.0
22	> 100.0
23	> 100.0
24	> 100.0
25	> 100.0
26	> 100.0
27	> 100.0
28	> 100.0
29	> 100.0
31	> 100.0
32	> 100.0
33	> 100.0
34	> 100.0
35	> 100.0
36	> 100.0
37	> 100.0
38	> 100.0
40	> 100.0
41	> 100.0
44	> 100.0
46	> 100.0

Compound No.	Avg_IC50 (μM)
48	> 100.0
49	> 100.0
50	> 100.0
51	> 100.0
52	> 100.0
55	> 100.0
56	> 100.0
57	> 100.0
58	> 100.0
59	> 100.0
60	> 100.0
61	> 100.0
62	> 100.0
63	> 100.0
64	> 100.0
65	> 100.0
67	> 100.0
68	> 100.0
69	> 100.0
70	> 100.0
73	> 100.0
75	> 100.0
76	> 100.0
77	> 100.0
81	> 100.0
83	> 100.0
84	> 100.0
85	> 100.0
86	> 100.0
87	> 100.0
88	> 100.0
89	> 100.0
90	> 100.0
91	> 100.0
93	> 100.0
94	> 100.0

Compound No.	Avg_IC50 (μM)
95	> 100.0
96	> 100.0
98	> 100.0
99	> 100.0
100	> 100.0
101	> 100.0
102	> 100.0
103	> 100.0
104	> 100.0
105	> 100.0
106	> 100.0
107	> 100.0
108	> 100.0
109	> 100.0
110	> 100.0
114	> 100.0
117	> 100.0
118	> 100.0
119	> 100.0
121	> 100.0
125	> 100.0
126	> 100.0
128	> 100.0
129	> 100.0
130	> 100.0
133	> 100.0
134	> 100.0
135	> 100.0
136	> 100.0
137	> 100.0
138	> 100.0
140	> 100.0
141	> 100.0
142	> 100.0
144	> 100.0
146	> 100.0

Compound No.	Avg_IC50 (μM)
147	> 100.0
151	> 100.0
154	> 100.0
155	> 100.0
158	> 100.0
160	> 100.0
162	> 100.0
163	> 100.0
166	> 100.0
167	> 100.0
169	> 100.0
171	> 100.0
172	> 100.0
174	> 100.0
178	> 100.0
179	> 100.0
180	> 100.0
183	> 100.0
184	> 100.0
185	> 100.0
187	> 100.0
188	> 100.0
189	> 100.0
190	> 100.0
191	> 100.0
192	> 100.0
193	> 100.0
194	> 100.0
195	> 100.0
196	> 100.0
197	> 100.0
198	> 100.0
202	> 100.0
203	> 100.0
204	> 100.0
205	> 100.0

Compound No.	Avg_IC50 (μM)
206	> 100.0
207	> 100.0
208	> 100.0
209	> 100.0
210	> 100.0
213	> 100.0
214	> 100.0
216	> 100.0
217	> 100.0
218	> 100.0
219	> 100.0
220	> 100.0
221	> 100.0
222	> 100.0
223	> 100.0
224	> 100.0
226	> 100.0
227	> 100.0
228	> 100.0
229	> 100.0
231	> 100.0
232	> 100.0
233	> 100.0
236	> 100.0
237	> 100.0
238	> 100.0
239	> 100.0
240	> 100.0
241	> 100.0
242	> 100.0
243	> 100.0
244	> 100.0
245	> 100.0
246	> 100.0
247	> 100.0
248	> 100.0

Compound No.	Avg_IC50 (μM)
249	> 100.0
250	> 100.0
251	> 100.0
252	> 100.0
253	> 100.0
254	> 100.0
255	> 100.0
256	> 100.0
257	> 100.0
258	> 100.0
259	> 100.0
260	> 100.0
261	> 100.0
262	> 100.0
263	> 100.0
264	> 100.0
265	> 100.0
266	> 100.0
268	> 100.0
269	> 100.0
270	> 100.0
271	> 100.0
272	> 100.0
273	> 100.0
274	> 100.0
275	> 100.0
276	> 100.0
277	> 100.0
278	> 100.0
279	> 100.0
280	> 100.0
281	> 100.0
282	> 100.0
283	> 100.0
284	> 100.0
287	> 100.0

Compound No.	Avg_IC50 (μM)
288	> 100.0
289	> 100.0
290	> 100.0
291	> 100.0
292	> 100.0
293	>100.0
294	> 100.0
295	> 100.0
296	> 100.0
298	> 100.0
299	> 100.0
300	> 100.0
301	> 100.0
302	> 100.0
303	> 100.0
304	> 100.0
306	> 100.0
307	> 100.0
308	> 100.0
309	> 100.0
310	> 100.0
311	> 100.0
312	> 100.0
313	> 100.0
314	> 100.0
315	> 100.0
316	> 100.0
317	> 100.0
318	> 100.0
319	> 100.0
320	> 100.0
321	> 100.0
322	> 100.0
323	> 100.0
324	> 100.0
325	> 100.0

Compound No.	Avg_IC50 (μM)
326	> 100.0
328	> 100.0
330	> 100.0
331	> 100.0
332	> 100.0
333	> 100.0
334	> 100.0
335	> 100.0
336	> 100.0
337	> 100.0
338	> 100.0
339	> 100.0
340	> 100.0
342	> 100.0
343	> 100.0
344	> 100.0
345	> 100.0
346	> 100.0
347	> 100.0
348	> 100.0
349	> 100.0
350	> 100.0
351	> 100.0
352	> 100.0
353	> 100.0
354	> 100.0
355	> 100.0
356	> 100.0
357	> 100.0
358	> 100.0
359	> 100.0
360	> 100.0
361	> 100.0
362	> 100.0
363	> 100.0
364	> 100.0

Compound No.	Avg_IC50 (μM)
365	> 100.0
366	> 100.0
367	> 100.0
368	> 82.29
369	> 100.0
371	> 100.0
372	> 100.0
373	> 100.0
374	> 100.0
375	> 77.43
376	> 100.0
377	> 100.0
378	> 100.0
379	> 100.0
380	> 100.0
381	> 100.0
382	> 100.0
383	> 100.0
384	> 100.0
385	> 100.0
386	> 100.0
387	36.22
388	> 100.0
389	> 90.29
390	> 100.0
391	89.32
392	> 100.0
393	> 100.0
394	> 100.0
395	> 100.0
396	> 100.0
398	> 100.0
399	> 100.0
400	> 100.0
401	> 100.0
402	> 100.0

Compound No.	Avg_IC50 (μM)
403	> 100.0
404	> 100.0
405	> 100.0
406	> 100.0
407	> 100.0
408	> 100.0
409	> 100.0
410	> 100.0
411	> 100.0
412	> 100.0
413	> 100.0
414	78.66
415	> 100.0
416	> 100.0
417	> 100.0
418	> 100.0
421	> 100.0
422	> 100.0
424	> 100.0
425	> 100.0
426	> 100.0
427	> 100.0
428	> 100.0
430	> 100.0
431	> 100.0
432	> 100.0
433	> 100.0
434	> 100.0
435	> 100.0
436	> 100.0
437	> 100.0
439	> 100.0
441	> 100.0
442	> 100.0
443	> 100.0
444	> 100.0

Compound No.	Avg_IC50 (μM)
445	> 100.0
446	> 100.0
447	> 100.0
448	> 100.0
449	> 100.0
450	> 100.0
451	> 100.0
452	> 100.0
453	> 100.0
454	> 100.0
455	> 100.0
456	> 100.0
457	> 100.0
458	> 100.0
459	> 100.0
462	> 100.0
463	> 100.0
464	> 100.0
465	> 100.0
466	> 100.0
467	> 100.0
468	> 100.0
469	> 100.0
470	> 100.0
471	> 100.0
472	> 100.0
474	> 100.0
475	> 100.0
476	> 100.0
477	> 100.0
478	68.22
479	> 100.0
480	> 100.0
481	> 100.0
482	> 100.0
483	> 100.0

Compound No.	Avg_IC50 (μM)
484	> 100.0
485	> 100.0
486	> 100.0
487	> 100.0
488	> 100.0
490	> 100.0
491	> 100.0
492	> 100.0
495	> 100.0
496	> 100.0
497	> 100.0
501	> 100.0
502	> 100.0
503	> 100.0
504	> 100.0
505	> 100.0
506	> 100.0
507	> 100.0
508	> 100.0
509	> 100.0
510	> 100.0
511	> 100.0
512	> 100.0
513	> 100.0
514	> 100.0
515	> 100.0
516	> 100.0
517	> 100.0
518	> 100.0
519	> 100.0
520	> 100.0
522	> 100.0
532	> 100.0
533	> 100.0
534	> 100.0
535	> 100.0

Compound No.	Avg_IC50 (μM)
536	> 100.0
537	> 100.0
538	> 100.0
539	> 100.0
540	> 100.0
541	> 100.0
542	> 100.0
544	> 100.0
546	> 100.0
547	> 100.0
548	> 100.0
549	> 100.0
550	> 100.0
551	> 100.0
552	> 100.0
553	> 100.0
554	> 100.0
556	> 100.0
558	> 100.0
560	> 100.0
561	> 100.0
562	> 100.0
563	> 100.0
564	> 100.0
565	> 100.0
566	> 100.0
567	> 100.0
568	94.24
569	> 100.0
570	> 100.0
571	> 100.0
572	> 100.0
573	> 100.0
574	> 100.0
575	> 100.0
576	> 100.0

Compound No.	Avg_IC50 (μM)
577	41.18
578	79.27
579	> 100.0
580	> 100.0
581	> 100.0
582	> 100.0
583	> 100.0
584	> 91.76
585	> 100.0
586	> 100.0
587	> 100.0
588	> 100.0
589	> 100.0
590	> 100.0
591	> 100.0
592	> 100.0
593	> 100.0
594	> 100.0
595	> 100.0
596	> 96.68
597	> 100.0
599	> 100.0
600	> 100.0
602	> 100.0
603	> 100.0
604	> 100.0
605	> 100.0
607	> 100.0
609	> 100.0
611	> 100.0
613	> 100.0
620	> 100.0
623	> 100.0
625	> 100.0
630	> 100.0
631	> 100.0

Compound No.	Avg_IC50 (μM)
632	> 100.0
639	> 100.0
640	> 100.0
642	> 100.0
644	> 100.0
645	> 100.0
646	> 100.0
651	> 100.0
653	> 100.0
659	17.53
660	> 100.0
661	> 100.0
662	> 100.0
664	> 100.0
665	> 100.0
667	> 100.0
668	> 100.0
669	> 100.0
670	> 100.0
671	> 100.0
672	> 100.0
674	> 100.0
675	> 100.0
676	> 100.0
677	> 100.0
679	>100
680	93.0
681	> 100.0
682	> 100.0
685	> 100.0
686	> 100.0
690	> 100.0
710	> 100.0
711	> 100.0
719	> 100.0
722	> 100.0

Compound No.	Avg_IC50 (μM)
723	> 100.0
724	> 100.0
725	> 100.0
726	> 100.0
727	> 100.0
728	> 100.0
729	> 100.0
731	> 100.0
732	> 100.0
733	> 100.0
734	> 100.0
735	> 100.0
736	> 100.0
765	> 100.0
766	> 100.0
767	> 100.0
768	> 100.0
769	> 100.0
770	> 100.0
771	> 100.0
772	> 100.0
773	> 100.0
774	> 100.0
777	> 100.0
779	> 100.0
780	> 100.0
781	> 100.0
782	> 100.0
783	> 100.0
784	> 100.0
785	> 100.0
786	> 100.0
787	> 100.0
788	> 100.0
789	> 100.0
790	> 100.0

Compound No.	Avg_IC50 (μM)
791	> 100.0
792	> 100.0
793	> 100.0
794	> 100.0
795	> 100.0
809	> 100.0
810	> 100.0

Example B-4

[0772] Pompe disease is a glycogen storage disease caused by mutations in the enzyme acid alpha-glucosidase resulting in pathological accumulation of glycogen. Glycogen can accumulate in virtually all tissues, but the primary pathology affects skeletal and cardiac muscle. Inhibiting the synthesis of muscle glycogen could reduce the pathologic build-up of glycogen by acting as a substrate reduction therapy. Savage et. al. identified a predicted protein truncating variant (PTV) in the PPP1R3A gene (a regulator of glycogen metabolism) in ~0.5% of Europeans, which results in ~65% reduction in muscle glycogen (Savage et. al., A Prevalent Variant in PPP1R3A Impairs Glycogen Synthesis and Reduces Muscle Glycogen Content in Humans and Mice. *PLoS Medicine.* 2008; herein incorporated by reference in its entirety). PPP1R3A functions as a key activator of muscle glycogen synthase 1 (GYS1) by dephosphorylating the enzyme and maximizing activity. FIG. **1** demonstrates the pathway in which PPP1R3A (loss of function) LoF leads to reduction in muscle glycogen.

[0773] Large biobanks enable investigation of the consequences of genetic variation on many health-related phenotypes. To assess the consequences of a predicted 65% loss of muscle glycogen, association study was performed in the UK Biobank comparing phenotypes between PPP1R3A PTV carriers and non-carriers. Genetic association studies were performed using REGENIE (Mbatchou, J., Barnard, L., Backman, J. et al. Computationally efficient whole-genome regression for quantitative and binary traits. Nat Genet 53, 1097–1103, 2021), adjusted for age, sex, and the first 10 principal components of ancestry. Quantitative traits were normalized using an inverse rank normal transformation.

[0774] With regards to FIGS. **2A-2H,** the association between PPP1R3A PTV and the quantitative phenotypes of left ventricular ejection (LVEF) (%) (FIG. **2A**), left ventricle wall thickness (mm) (FIG. **2B**), exercise output (watts) (FIG. **2C**), max heart rate (HR) exercise (bpm) (FIG. **2D**), PQ interval (ms) (FIG. **2E**), QRS duration (ms) (FIG. **2F**), QT interval (ms) (FIG. **2G**), and serum glucose (mmol/L) (FIG. **2H**), are depicted. Phenotype values are plotted by PPP1R3A dosage for UK Biobank participants. No association between PPP1R3A PTV and the quantitative phenotypes in the UK Biobank was identified.

[0775] Table 5 below lists the P-value and number of participants (N) for the results depicted in FIGS. **2A-H**. No associations between *PPP1R3A* PTV and cardiac parameters, including left ventricular ejection fraction (p=0.871) and wall thickness (p=0.168) were identified. There was no evidence of changes in EKG cardiac conduction intervals nor in any muscle performance measurements (n=49,616), including maximum heart rate (p=0.444) and maximum workload during an exercise test (p=0.100). Further, no changes in serum glucose (p=0.71) or any other members of a panel of ~170 serum metabolites were observed.

Table 5

Phenotype	P-value	N
LVEF	0.871	27,716
LV Wall Thickness	0.168	27,579
Exercise Output	0.100	49,616
Max HR Exercise	0.444	49,603
QRS Duration	0.527	29,507
PQ Interval	0.366	16,694
QT Interval	0.222	17,574
Serum Glucose	0.477	294,042

[0776] As shown in Table 6 below, no association between PPP1R3A PTV and key health outcomes was also observed. In addition to the phenotypes in Table 6, no phenome-wide significant associations between PPP1R3A PTV and rates of any ICD10 code with over 100 occurrences in UK Biobank was observed.

Table 6

Disease	Effect (SE)	P-value	N Cases
Type 2 Diabetes	-0.094 (0.073)	0.200	18,868
Liver Cirrhosis	-0.041 (0.273)	0.880	1,325
Heart Failure	-0.061 (0.127)	0.630	6,117

[0777] After performing an extensive Phenome-wide association study in UK Biobank, no significant associations between any key outcomes or phenotypes and loss of function of *PPP1R3A* were found. The results provided herein demonstrate that loss of function variants in the *PPP1R3A* gene are not associated with adverse health outcomes in a large biobank population. This suggests that partial reduction in muscle glycogen (~65%) from

birth is well tolerated and supports the potential safety of pharmacologic reduction of muscle glycogen.

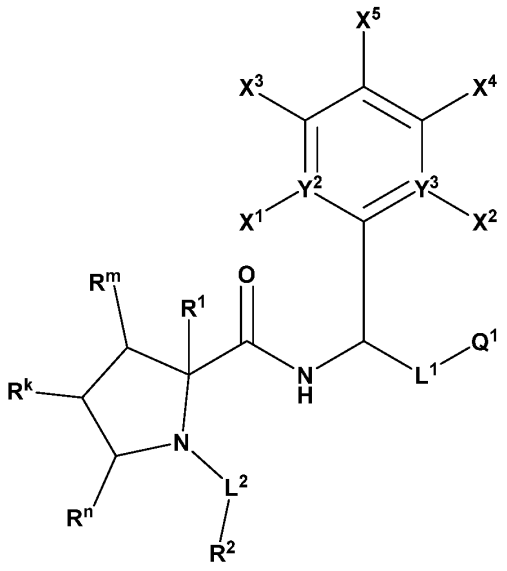
[0778] All publications, patent applications, patents, and other references mentioned herein are expressly incorporated by reference in their entireties, to the same extent as if each were incorporated by reference individually.

[0779] It is to be understood that, while the disclosure has been described in conjunction with the above embodiments, the foregoing description and examples are intended to illustrate and not limit the scope of the disclosure. Other aspects, advantages and modifications within the scope of the disclosure will be apparent to those skilled in the art to which the disclosure pertains.

CLAIMS

What is claimed is:

1. A compound of formula (I'):



(I'),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein:

Y^2 and Y^3 are each C, or

one of Y^2 and Y^3 is N and the other of Y^2 and Y^3 is C;

X^1 and X^2 are each independently H, C_{1-6}alkyl, or C_{1-6}alkoxy;

X^3 and X^4 are each independently H, halo, C_{1-6}alkyl, C_{1-6}alkoxy, or 5-20 membered heteroaryl, wherein the C_{1-6}alkyl of X^3 and X^4 is optionally substituted with one of more halo;

X^5 is H, C_{1-6}alkyl, C_{1-6}alkoxy, or C_{3-10}cycloalkyl;

either

(1) L^1 is absent; and

Q^1 is selected from (i) to (iv):

(i) phenyl, wherein the phenyl of Q^1 is substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, $-NH_2$, -NH-C(O)-(C_{1-6}alkyl), -NH-C(O)-(3-15 membered heterocyclyl), C_{3-10}cycloalkyl, or 5-20 membered heteroaryl, wherein

the C_{1-6}alkyl is optionally substituted with one or more halo, -NH-C(O)-NH(C_{1-6}alkyl), -NH-C(O)-C_{1-6}alkyl, or -NH-C(O)-C_{1-6}alkoxy,

the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl, and

the 5-20 membered heteroaryl is optionally substituted with one or more C_{1-6}alkyl,

(ii) 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of Q^1 is optionally substituted with one or more oxo, or C_{1-6}alkyl,

(iii) 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of Q^1 is optionally substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, $-NH_2$, or C_{3-10}cycloalkyl, wherein,

the C_{1-6}alkyl is optionally substituted with one or more halo, and

the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl, and

(iv) C_{3-10}cycloalkyl;

or

(2) L^1 is $-CH_2-$; and

Q^1 is C_{3-10}cycloalkyl;

L^2 is -C(O)- or $-S(O)_2-$

R^1 is H or C_{1-6}alkyl;

R^k is H, halo, -OH, $-NH_2$, or -NH-C(O)C_{1-6}alkyl;

R^m is H, -OH, or C_{1-6}alkyl;

R^n is H, C_{1-6}alkyl, or C_{3-10}cycloalkyl or R^n taken together with the carbon atom to which it is attached forms C_{3-5} cycloalkyl;

or R^k is taken together with either R^m or R^n, and the atoms to which they are attached, to form cyclopropyl; and

R^2 is selected from (i) to (vii):

(i) C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is optionally substituted with one or more R^a, wherein R^a is:

(a) -OH,

(b) cyano,

(c) C_{2-6}alkynyl,

(d) C_{6-20}aryl, wherein the C_{6-20}aryl of R^a is optionally substituted with one or more halo, cyano, C_{1-6}alkoxy, or -NH-C(O)-C_{1-6}alkyl,

(e) 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^a is optionally substituted with one or more R^c, wherein

R^c is halo, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, or -C(O)-C_{1-6}alkoxy, wherein

the C_{1-6}alkyl of R^c is optionally substituted with one or more halo or C_{2-6}alkynyl, and

the -C(O)-C_{1-6}alkoxy of R^c is optionally substituted with one or more halo,

(f) -N(R^c)(R^d), wherein R^c and R^d of -N(R^c)(R^d) are, independently of each other, H, C_{1-6}alkyl,
-C(O)-C_{1-6}alkyl, -C(O)-C_{1-6}alkoxy, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -C(O)-(3-15 membered heterocyclyl), -CH_2-C(O)-NH_2, 3-15 membered heterocyclyl, or 5-20 membered heteroaryl, wherein

the C_{1-6}alkyl of R^c or R^d is optionally substituted with one or more -C(O)-NH_2,

the -C(O)-C_{1-6}alkyl of R^c or R^d is optionally substituted with one or more halo,

the 3-15 membered heterocyclyl and the 5-20 membered heteroaryl of R^c or R^d are independently optionally substituted with one or more C_{1-6}alkyl,

the -C(O)-(3-15 membered heterocyclyl) of R^c or R^d is optionally substituted with one or more halo, -C(O)-C_{1-6}alkoxy, or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, C_{1-6}alkoxy, or C_{3-10}cycloalkyl, and

the C_{1-6}alkyl of the -C(O)-N(C_{1-6}alkyl)$_2$ of R^c or R^d are, independently of each other, optionally substituted with one or more halo or C_{6-20}aryl,

(g) -O-R^e, wherein R^e is C_{1-6}alkyl, C_{6-20}aryl, -C(O)-(3-15 membered heterocyclyl), -C(O)-N-(C_{1-6}alkyl)$_2$, or 5-20 membered heteroaryl, wherein

the C_{1-6}alkyl of R^e is optionally substituted with one or more C_{1-6}alkoxy, wherein the C_{1-6}alkoxy is optionally substituted with one or more C_{2-6}alkynyl,

the C_{6-20}aryl of R^e is optionally substituted with one or more C_{1-6}alkyl, and

the -C(O)-(3-15 membered heterocyclyl) of R^e is optionally substituted with one or more C_{1-6}alkyl, C_{1-6}alkoxy, or -C(O)-C_{1-6}alkoxy, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, C_{1-6}alkoxy, or C_{3-10}cycloalkyl,

(h) -C(O)-R^e, wherein R^e is -NH_2, -OH, or 3-15 membered heterocyclyl, or

(i) -$S(O)_2$-R^f, wherein R^f is C_{1-6}alkyl or 3-15 membered heterocyclyl,

provided that, when R^2 is unsubstituted methyl, then either

(1) Q^1 is 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of Q^1 is optionally substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, -NH_2, C_{3-10}cycloalkyl, or -OH, and wherein Q^1 is not unsubstituted pyridyl, or

(2) Q^1 is phenyl, wherein the phenyl of Q^1 is substituted with

(i) at least one C_{3-6}alkyl, wherein the at least one C_{3-6}alkyl is optionally substituted with one or more halo, or

(ii) at least one C_{3-10}cycloalkyl, wherein the at least one C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl, or

(iii) at least one 5-20 membered heteroaryl, wherein the at least one 5-20 membered heteroaryl is optionally substituted with one or more C_{1-6}alkyl,

(ii) C_{3-10}cycloalkyl, wherein the C_{3-10}cycloalkyl of R^2 is optionally substituted with one or more R^q, wherein R^q is 5-20 membered heteroaryl or C_{6-20}aryl, wherein the C_{6-20}aryl of R^q is optionally substituted with one or more C_{1-6}alkoxy,

(iii) 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^2 is optionally substituted with one or more halo, oxo, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, or 5-20 membered heteroaryl,

(iv) 5-20 membered heteroaryl or -(C_{1-4}alkyl)(5-20 membered heteroaryl), wherein the C_{1-4} alkyl is optionally substituted with one or more or more –OH, halo, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, and wherein the 5-20 membered heteroaryl is optionally substituted with one or more R^s, wherein

R^s is halo, C_{1-6}alkyl, C_{1-6}alkoxy, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, -NH-C(O)-C_{1-6}alkyl, C_{6-20}aryl, C_{3-10}cycloalkyl, 3-15 membered heterocyclyl, 5-20 membered heteroaryl, or -C(O)-C_{1-6}alkoxy, wherein

the C_{1-6}alkyl of R^s is optionally substituted with one or more halo, C_{1-6}alkoxy, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, -NH-C(O)C_{1-6}alkyl, or -NH-C(O)-C_{1-6}alkoxy, and

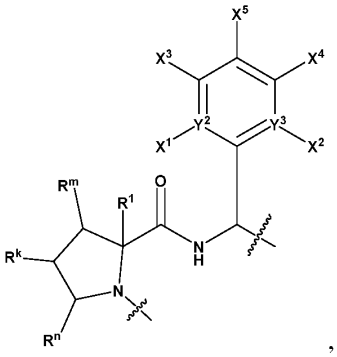
the 3-15-membered heterocyclyl of R^s is optionally substituted with one or more halo or -C(O)-C_{1-6}alkoxy,

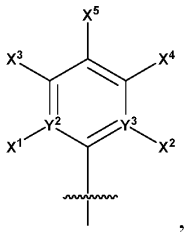
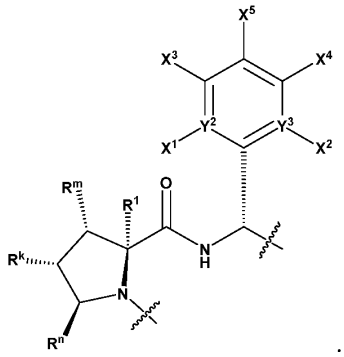
(v) -N(R^g)(R^h), wherein R^g and R^h are independently H or C_{1-6}alkyl,

(vi) -C(O)-R^j, wherein R^j is C_{3-10}cycloalkyl, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, or -NH(5-20 membered heteroaryl), and

(vii) C_{6-20}aryl, wherein the C_{6-20}aryl of R^2 is optionally substituted with one or more 5-20 membered heteroaryl or -O-R^p, wherein R^p is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^p is optionally substituted with one or more -C(O)-C_{1-6}alkyl.

2. The compound of claim 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the moiety represented by



, with carbon atoms bearing moieties  , R^k, R^m, R^n, and R^1, has a stereochemical configuration of the formula:  .

3. The compound of claim 1 or claim 2, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Q^1 is 5-20 membered heteroaryl, wherein the 5-20 membered heteroaryl of Q^1 is optionally substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, -NH_2, or C_{3-10}cycloalkyl, wherein

the C_{1-6}alkyl is optionally substituted with one or more halo, and

the C_{3-10}cycloalkyl is optionally substituted with one or more C_{1-6}alkyl or halo.

4. The compound of any one of claims 1-3, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Q^1 is pyridinyl, wherein the pyridinyl of Q^1 is optionally substituted with one or more halo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, $-NH_2$, or C_{3-10}cycloalkyl, wherein

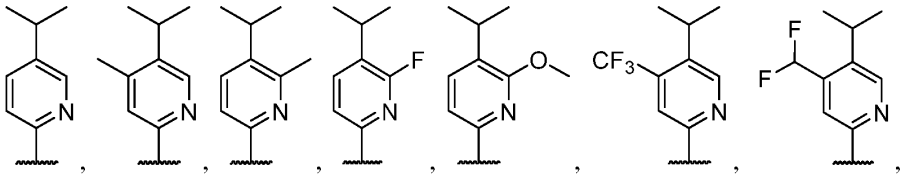
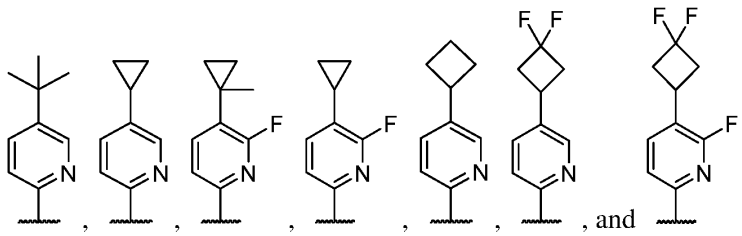
the C_{1-6}alkyl is optionally substituted with one or more halo, and

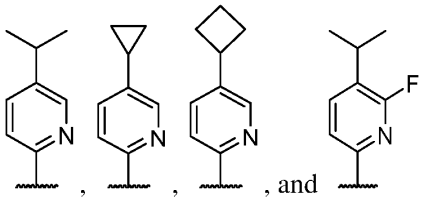
the C_{3-10}cycloalkyl is optionally substituted with one or more C_{1-6}alkyl or halo.

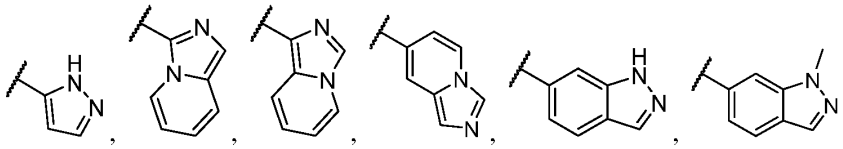
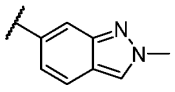
5. The compound of any one of claims 1-4, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Q^1 is 2-pyridinyl, wherein the 2-pyridinyl of Q^1 is optionally substituted with one or more halo, C_{1-6}alkyl, C_{1-6}alkoxy, or C_{3-10}cycloalkyl, wherein

the C_{1-6}alkyl is optionally substituted with one or more halo, and

the C_{3-10}cycloalkyl is optionally substituted with one or more C_{1-6}alkyl or halo.

6. The compound of any one of claims 1-5, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Q^1 is selected from the group consisting of  ,  , and .

7. The compound of any one of claims 1-6, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Q^1 is selected from the group consisting of  .

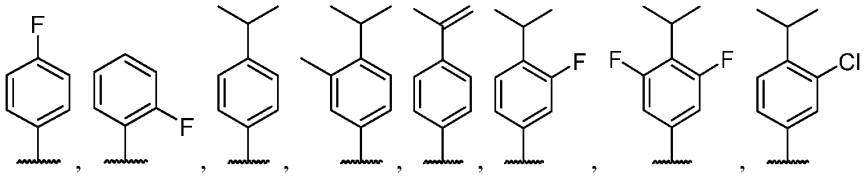
8. The compound of any one of claims 1-3, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Q^1 is selected from the group consisting of  , and  .

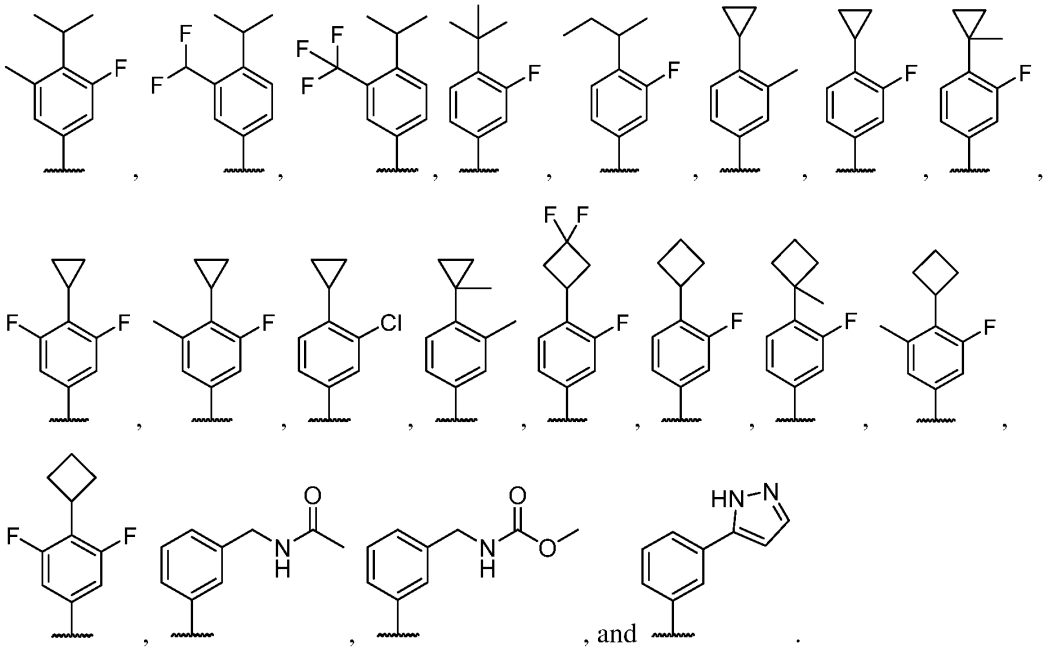
9. The compound of claim 1 or claim 2, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Q^1 is phenyl, wherein the phenyl of Q^1 is substituted with one or more halo, C_{1-6}alkyl, C_{2-6} alkenyl, $-NH_2$, -NH-C(O)-(C_{1-6}alkyl), -NH-C(O)-(3-15 membered heterocyclyl), C_{3-10}cycloalkyl, or 5-20 membered heteroaryl, wherein

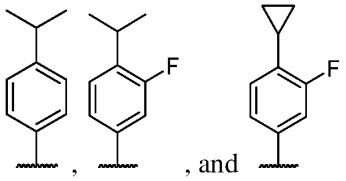
the C_{1-6}alkyl is optionally substituted with one or more halo, -NH-C(O)-NH(C_{1-6}alkyl), -NH-C(O)-C_{1-6}alkyl, or -NH-C(O)-C_{1-6}alkoxy,

the C_{3-10}cycloalkyl is optionally substituted with one or more halo or C_{1-6}alkyl, and

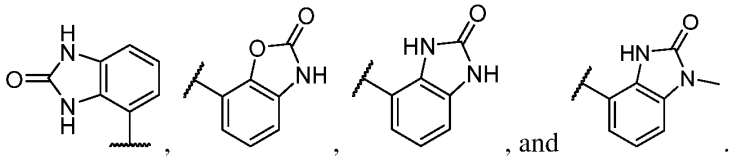
the 5-20 membered heteroaryl is optionally substituted with one or more C_{1-6}alkyl.

10. The compound of any one of claims 1, 2 and 9, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Q^1 is selected from the group consisting of  .



11. The compound of any one of claims 1, 2, 9 and 10, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Q^1 is selected from the group consisting of  .

12. The compound of claim 1 or claim 2, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Q^1 is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of Q^1 is optionally substituted with one or more oxo, or $C_{1\text{-}6}$alkyl.

13. The compound of any one of claims 1, 2 or 12, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein Q^1 is selected from the group consisting of  .

14. The compound of any one of claims 1-13, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein X^1, X^2, X^3, X^4, and X^5 are each H.

15. The compound of any one of claims 1-14, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^m is H, R^n is H, and R^k is H, halo, -OH, $-NH_2$, or -NH-C(O)$C_{1\text{-}6}$alkyl.

16. The compound of any one of claims 1-15, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^m is H, R^n is H, and R^k is halo, -OH, or $-NH_2$.

17. The compound of any one of claims 1-16, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^m is H, R^n is H, and R^k is halo.

18. The compound of any one of claims 1-17, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^m is H, R^n is H, and R^k is fluoro.

19. The compound of any one of claims 1-14, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^k is taken together with either R^m or R^n, and the atoms to which they are attached, to form cyclopropyl.

20. The compound of any one of claims 1-14, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^n taken together with the carbon atom to which it is attached forms cyclopropyl.

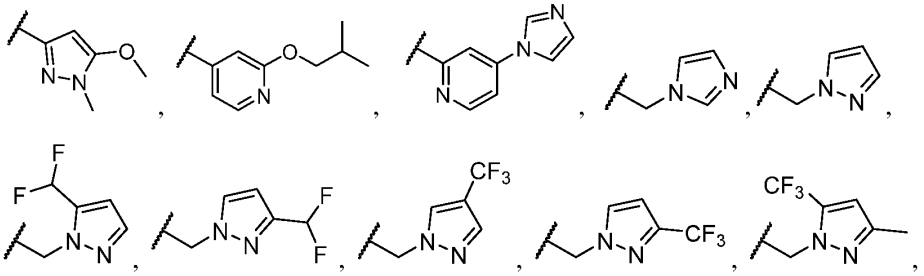
21. The compound of any one of claims 1-20, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^1 is H.

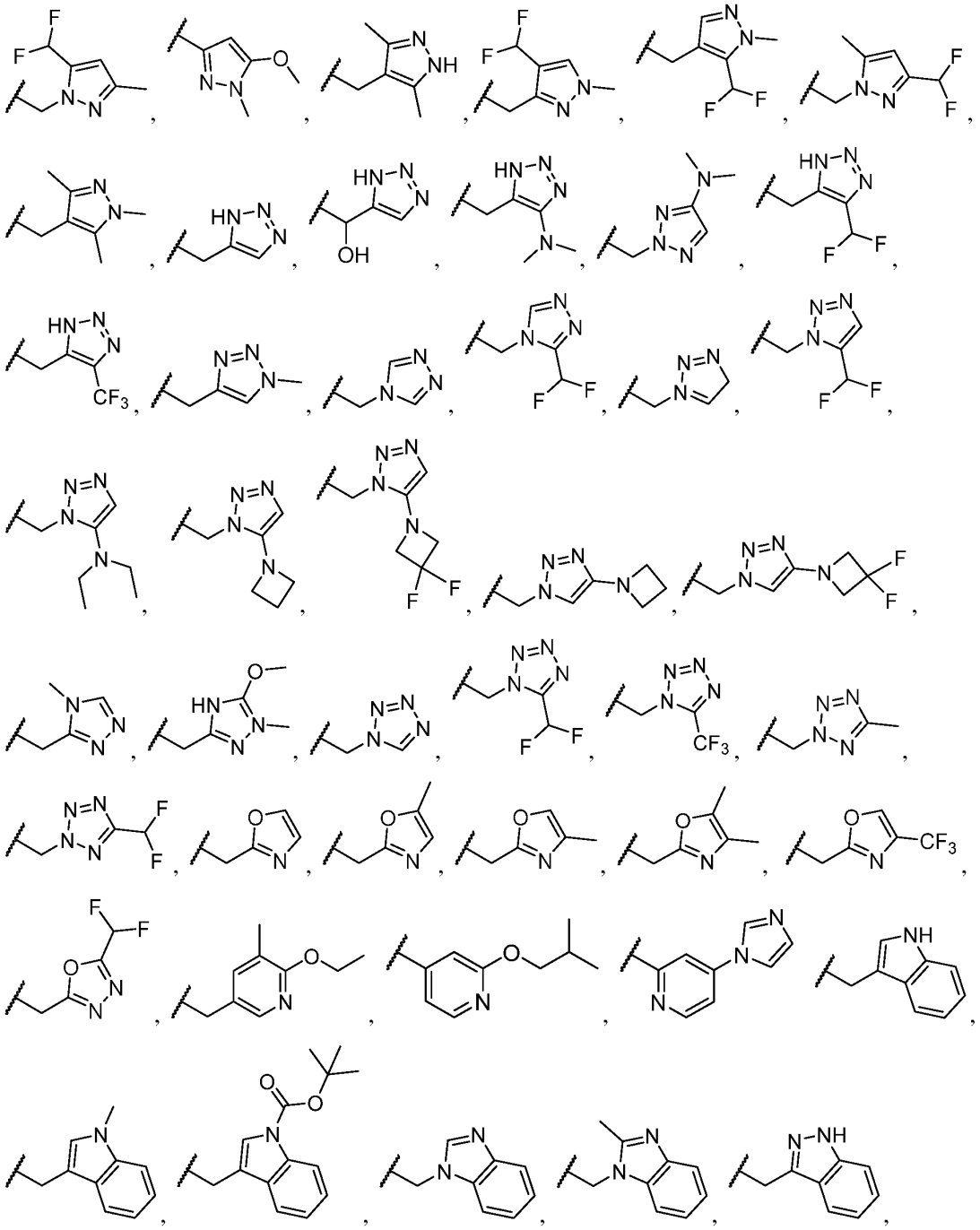
22. The compound of any one of claims 1-21, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is 5-20 membered heteroaryl or -(C_{1-4}alkyl)(5-20 membered heteroaryl), wherein the C_{1-4} alkyl is optionally substituted with one or more or more –OH, halo, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, and wherein the 5-20 membered heteroaryl is optionally substituted with one or more R^s.

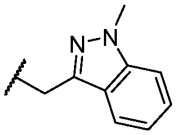
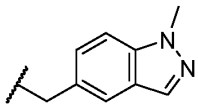
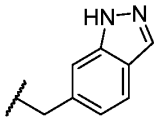
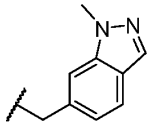
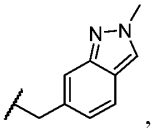
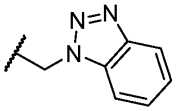
23. The compound of any one of claims 1-22, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is 5-10 membered heteroaryl or -(methyl)(5-10 membered heteroaryl), wherein the methyl is optionally substituted with one or more or more –OH, and wherein the 5-10 membered heteroaryl is optionally substituted with one or more R^s, wherein R^s is halo, C_{1-6}alkyl, C_{1-6}alkoxy, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, -NH-C(O)-C_{1-6}alkyl, C_{6-20}aryl, C_{3-10}cycloalkyl, 3-15 membered heterocyclyl, 5-20 membered heteroaryl, or -C(O)-C_{1-6}alkoxy, wherein

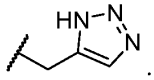
the C_{1-6}alkyl of R^s is optionally substituted with one or more fluoro, and

the 3-15-membered heterocyclyl of R^s is optionally substituted with one or more fluoro.

24. The compound of any one of claims 1-23, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is selected from the group consisting of 



 ,  ,  ,  ,  , and  .

25. The compound of any one of claims 1-24, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is  .

26. The compound of any one of claims 1-21, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is optionally substituted with one or more R^a.

27. The compound of any one of claims 1-21 and 26, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^a is optionally substituted with one or more R^c.

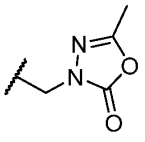
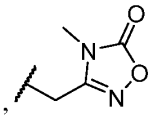
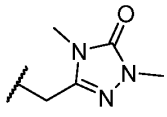
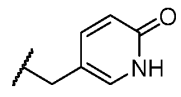
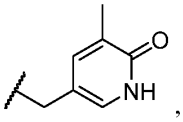
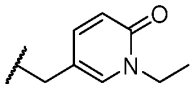
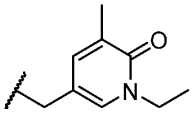
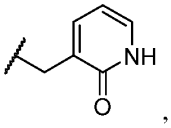
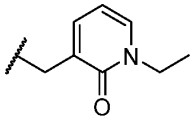
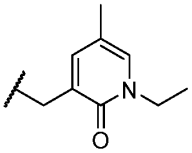
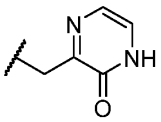
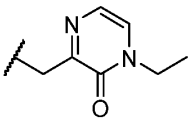
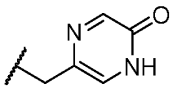
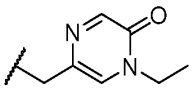
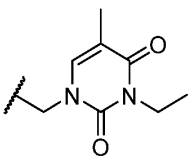
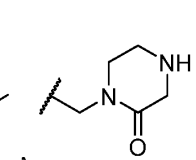
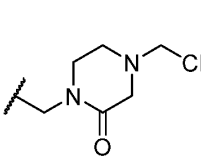
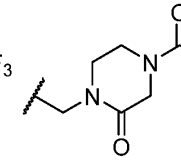
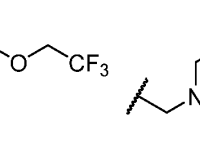
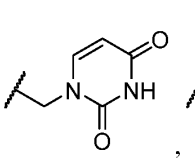
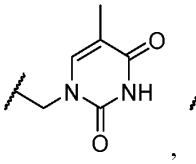
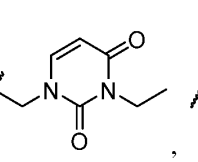
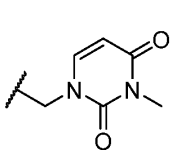
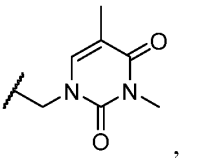
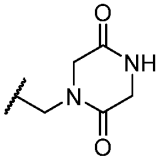
28. The compound of any one of claims 1-21, 26, and 27, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^a is optionally substituted with one or more R^c.

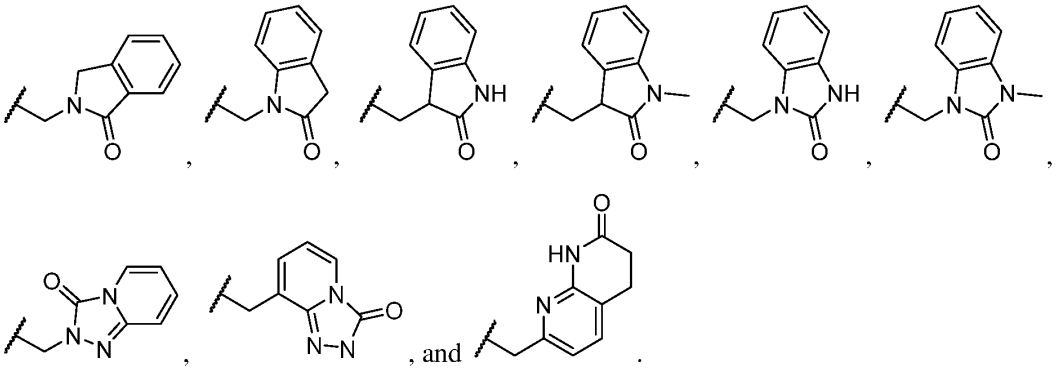
29. The compound of any one of claims 1-21 and 26-28, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-8 membered

heterocyclyl, wherein the 3-8 membered heterocyclyl of R^a is optionally substituted with one or more halo, oxo, C_{1-6}alkyl, C_{1-6}alkoxy, -C(O)-C_{1-6}alkyl, or -C(O)-C_{1-6}alkoxy, wherein

the C_{1-6}alkyl of R^c is optionally substituted with one or more halo or C_{2-6}alkynyl, and

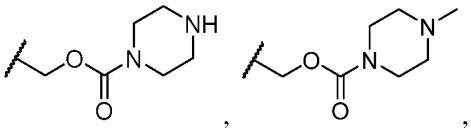
the -C(O)-C_{1-6}alkoxy of R^c is optionally substituted with one or more halo.

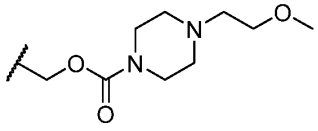
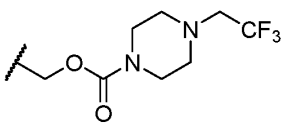
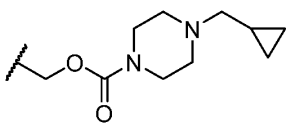
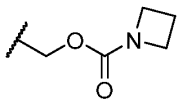
30. The compound of any one of claims 1-21 and 26-29, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is selected from the group consisting of  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , , , , ,  .



31. The compound of any one of claims 1-21, and 26 or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e wherein R^e is -C(O)-(3-15 membered heterocyclyl), wherein the -C(O)-(3-15 membered heterocyclyl) of R^e is optionally substituted with one or more C_{1-6}alkyl, C_{1-6}alkoxy, or -C(O)-C_{1-6}alkoxy, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, C_{1-6}alkoxy, or C_{3-10}cycloalkyl.

32. The compound of any one of claims 1-21, 26, and 31, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e, wherein R^e is -C(O)-(3-15 membered heterocyclyl), wherein the -C(O)-(3-15 membered heterocyclyl) of R^e is optionally substituted with one or more C_{1-6}alkyl, C_{1-6}alkoxy, or -C(O)-C_{1-6}alkoxy, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, C_{1-6}alkoxy, or C_{3-10}cycloalkyl.

33. The compound of any one of claims 1-21, 26, 31 and 32, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is selected from the group consisting of 


, 
, 
, and 
.

34. The compound of any one of claims 1-21, and 26, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is -N(R^c)(R^d), and wherein R^c and R^d of -N(R^c)(R^d) are, independently of each other, H, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-C_{1-6}alkoxy, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -C(O)-(3-15 membered heterocyclyl), -CH_2-C(O)-NH_2, 3-15 membered heterocyclyl, or 5-20 membered heteroaryl, wherein

the C_{1-6}alkyl of R^c or R^d is optionally substituted with one or more -C(O)-NH_2,

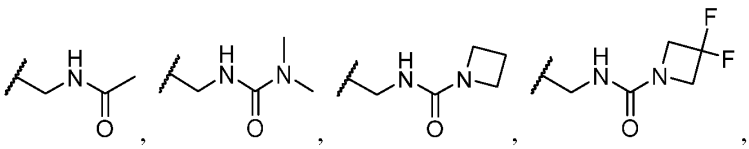
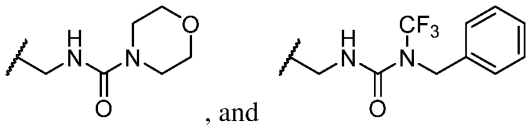
the -C(O)-C_{1-6}alkyl of R^c or R^d is optionally substituted with one or more halo,

the 3-15 membered heterocyclyl and the 5-20 membered heteroaryl of R^c or R^d are independently optionally substituted with one or more C_{1-6}alkyl,

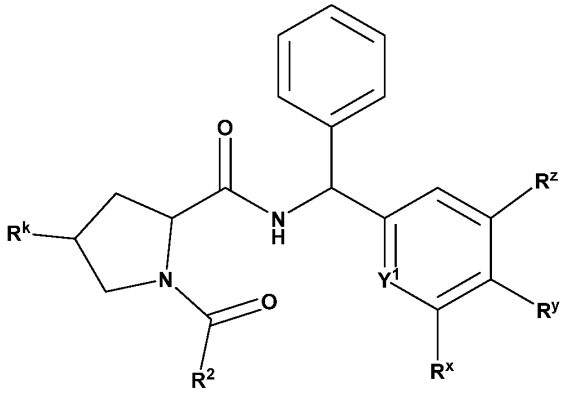
the -C(O)-(3-15 membered heterocyclyl) of R^c or R^d is optionally substituted with one or more halo, -C(O)-C_{1-6}alkoxy, or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, C_{1-6}alkoxy, or C_{3-10}cycloalkyl, and

the C_{1-6}alkyl of the -C(O)-N(C_{1-6}alkyl)$_2$ of R^c or R^d are, independently of each other, optionally substituted with one or more halo or C_{6-20}aryl.

35. The compound of any one of claims 1-21, 26, and 34, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is selected

from the group consisting of  ,  , and .

36. The compound of claim 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound is of formula (I-A):


(I-A),

or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein

Y^1 is CH or N;

R^x and R^z are independently H, halo, $C_{1\text{-}6}$alkyl, or -NH_2, wherein, when Y^1 is CH, the $C_{1\text{-}6}$alkyl of R^x or R^z may be optionally substituted with one or more halo; and

R^y is (i) $C_{1\text{-}6}$alkyl, or (ii) $C_{3\text{-}10}$cycloalkyl, wherein the $C_{3\text{-}10}$cycloalkyl is optionally substituted with one or more halo or $C_{1\text{-}6}$alkyl.

37. The compound of claim 1 or claim 36, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^x is H, fluoro, or methyl, and R^y is (i) isopropyl, or (ii) C_{3-4}cycloalkyl, wherein the C_{3-4}cycloalkyl is optionally substituted with one or more fluoro or methyl.

38. The compound of any one of claims 1, 36, and 37 or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^k is H or halo.

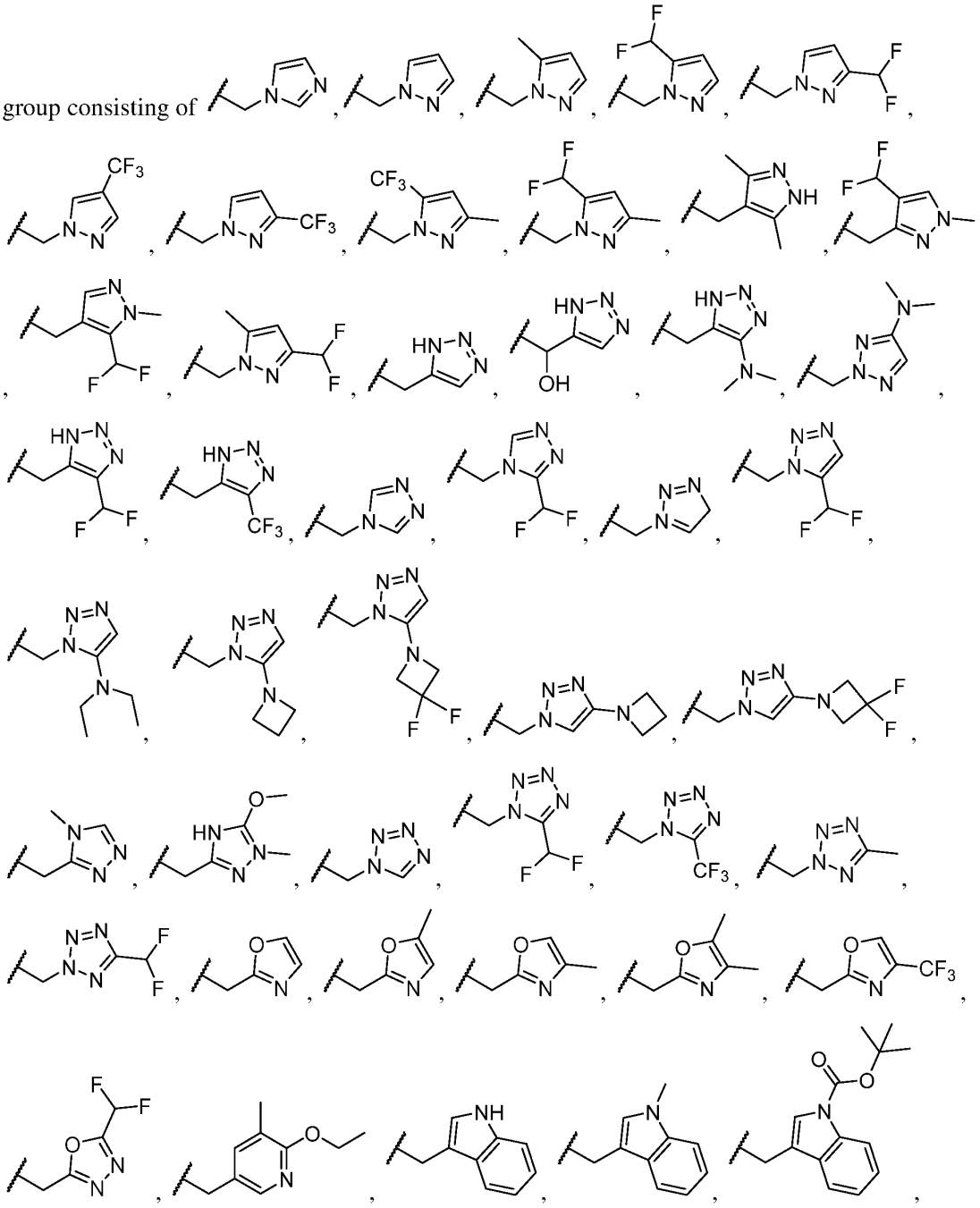
39. The compound of any one of claims 1 and 36-38, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is 5-20 membered heteroaryl or -(C_{1-4}alkyl)(5-20 membered heteroaryl), wherein the C_{1-4} alkyl is optionally substituted with one or more or more –OH, halo, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, and wherein the 5-20 membered heteroaryl is optionally substituted with one or more R^s.

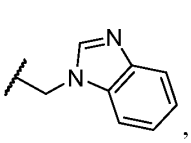
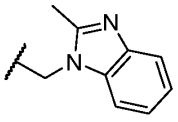
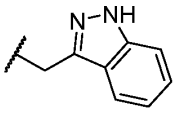
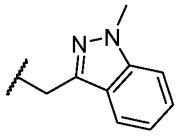
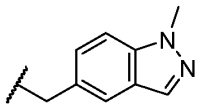
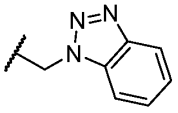
40. The compound of any one of claims 1 and 36-39, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is 5-20 membered heteroaryl or -(C_{1-4}alkyl)(5-20 membered heteroaryl), wherein the C_{1-4} alkyl is optionally substituted with one or more or more –OH, and wherein the 5-20 membered heteroaryl is optionally substituted with one or more R^s.

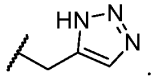
41. The compound of any one of claims 1 and 36-40, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is 5-10 membered heteroaryl or -(methyl)(5-10 membered heteroaryl), wherein the methyl is optionally substituted with one or more or more –OH, and wherein the 5-10 membered heteroaryl is optionally substituted with one or more R^s, wherein R^s is halo, C_{1-6}alkyl, C_{1-6}alkoxy, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, -NH-C(O)-C_{1-6}alkyl, C_{6-20}aryl, C_{3-10}cycloalkyl, 3-15 membered heterocyclyl, 5-20 membered heteroaryl, or -C(O)-C_{1-6}alkoxy, wherein

the C_{1-6}alkyl of R^s is optionally substituted with one or more halo, C_{1-6}alkoxy, -NH_2, -NH(C_{1-6}alkyl), -N(C_{1-6}alkyl)$_2$, -NH-C(O)C_{1-6}alkyl, or -NH-C(O)-C_{1-6}alkoxy, and

the 3-15-membered heterocyclyl of R^s is optionally substituted with one or more halo or -C(O)-C_{1-6}alkoxy.

42. The compound of any one of claims 1 and 36-41, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is selected from the group consisting of 

 ,  ,  ,  ,  , and  .

43. The compound of any one of claims 1 and or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is  .

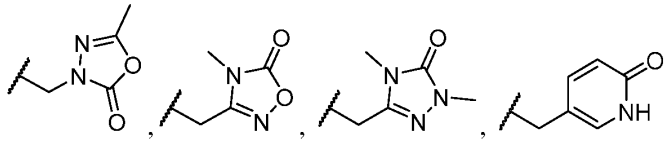
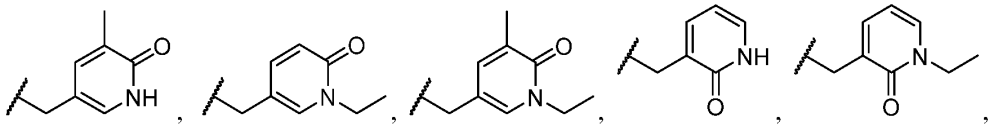
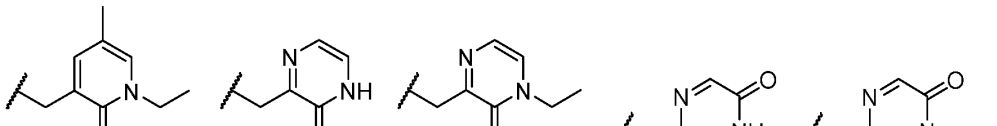
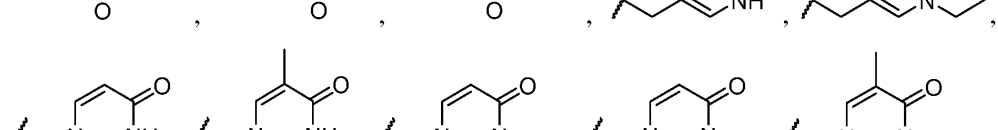
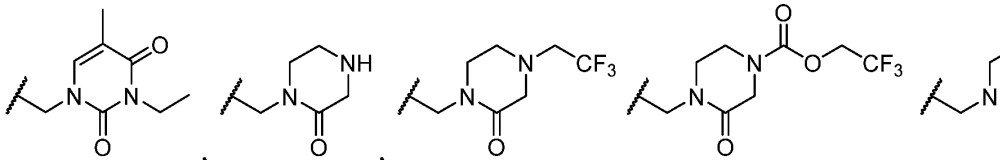
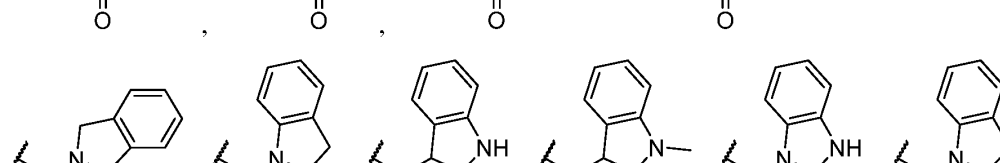
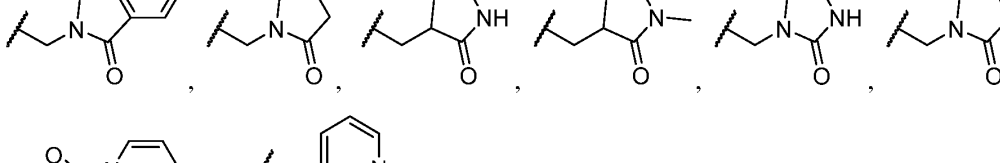
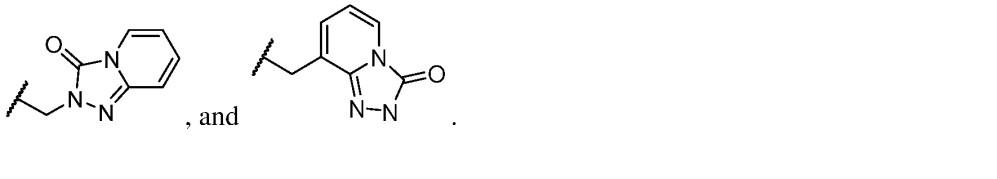
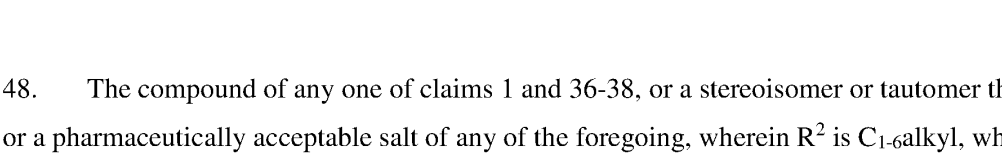
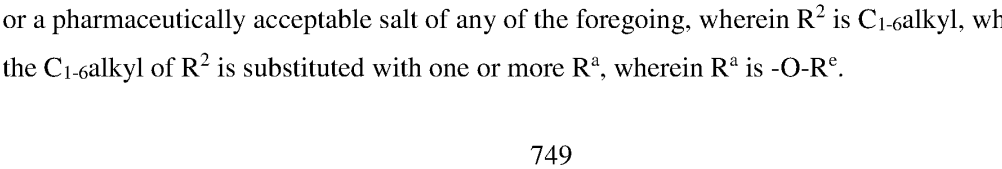
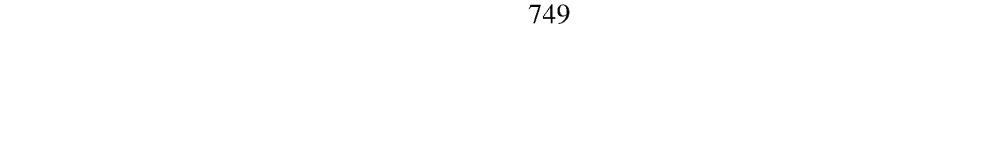
44. The compound of any one of claims 1 and 36-38, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is $C_{1\text{-}6}$alkyl, wherein the $C_{1\text{-}6}$alkyl of R^2 is optionally substituted with one or more R^a.

45. The compound of any one of claims 1, 36-38, and 44, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is $C_{1\text{-}6}$alkyl, wherein the $C_{1\text{-}6}$alkyl of R^2 is substituted with one or more R^a, wherein R^a is 3-15 membered heterocyclyl, wherein the 3-15 membered heterocyclyl of R^a is optionally substituted with one or more R^c.

46. The compound of any one of claims 1, 36-38, 44, and 45, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is 3-8 membered heterocyclyl, wherein the 3-8 membered heterocyclyl of R^a is optionally substituted with one or more halo, oxo, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, -C(O)-$C_{1\text{-}6}$alkyl, or -C(O)-$C_{1\text{-}6}$alkoxy, wherein

the $C_{1\text{-}6}$alkyl of R^c is optionally substituted with one or more halo or $C_{2\text{-}6}$alkynyl, and

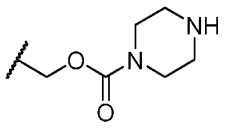
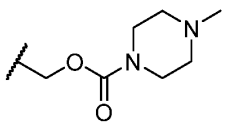
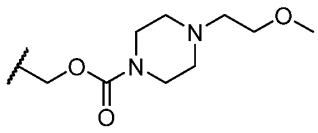
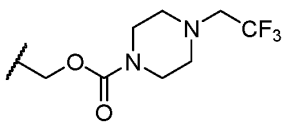
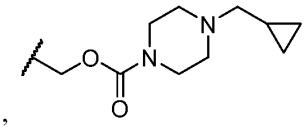
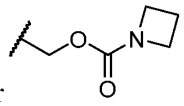
the -C(O)-$C_{1\text{-}6}$alkoxy of R^c is optionally substituted with one or more halo.

47. The compound of any one of claims 1, 36-38, and 44-46, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is selected from the group consisting of  ,  ,  ,  , ,  ,  ,  ,  ,  ,  ,  , , and .

48. The compound of any one of claims 1 and 36-38, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is $C_{1\text{-}6}$alkyl, wherein the $C_{1\text{-}6}$alkyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e.

49. The compound of any one of claims 1, 36-38, and 48, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -O-R^e, wherein R^e is -C(O)-(3-15 membered heterocyclyl) wherein the -C(O)-(3-15 membered heterocyclyl) of R^e is optionally substituted with one or more C_{1-6}alkyl, C_{1-6}alkoxy, or -C(O)-C_{1-6}alkoxy, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, C_{1-6}alkoxy, or C_{3-10}cycloalkyl.

50. The compound of any one of claims 1, 36-38, 48 and 49, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is


,

,

,

,

, or

.

51. The compound of any one of claims 1, and 36-38, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is C_{1-6}alkyl, wherein the C_{1-6}alkyl of R^2 is substituted with one or more R^a, wherein R^a is -N(R^c)(R^d), and wherein R^c and R^d of -N(R^c)(R^d) are, independently of each other, H, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-C_{1-6}alkoxy, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -C(O)-(3-15 membered heterocyclyl), -CH_2-C(O)-NH_2, 3-15 membered heterocyclyl, or 5-20 membered heteroaryl, wherein

the C_{1-6}alkyl of R^c or R^d is optionally substituted with one or more -C(O)-NH_2, and

the -C(O)-C_{1-6}alkyl of R^c or R^d is optionally substituted with one or more halo,

the 3-15 membered heterocyclyl and the 5-20 membered heteroaryl of R^c or R^d are independently optionally substituted with one or more C_{1-6}alkyl,

the -C(O)-(3-15 membered heterocyclyl) of R^c or R^d is optionally substituted with one or more halo, -C(O)-C_{1-6}alkoxy, or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, C_{1-6}alkoxy, or C_{3-10}cycloalkyl, and

the C_{1-6}alkyl of the -C(O)-N(C_{1-6}alkyl)$_2$ of R^c or R^d are, independently of each other, optionally substituted with one or more halo or C_{6-20}aryl.

52. The compound of any one of claims 1, 36-38, and 51, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is methyl, wherein the methyl of R^2 is substituted with one or more R^a, wherein R^a is -N(R^c)(R^d) and wherein R^c and R^d of -N(R^c)(R^d) are, independently of each other, H, C_{1-6}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-C_{1-6}alkoxy, -C(O)-NH_2, -C(O)-NH(C_{1-6}alkyl), -C(O)-N(C_{1-6}alkyl)$_2$, -C(O)-(3-15 membered heterocyclyl), -CH_2-C(O)-NH_2, 3-15 membered heterocyclyl, or 5-20 membered heteroaryl, wherein

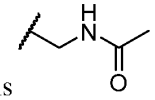
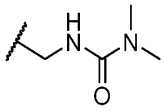
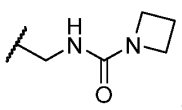
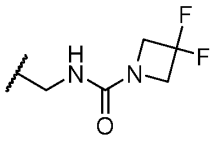
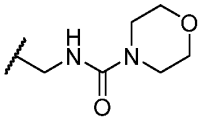
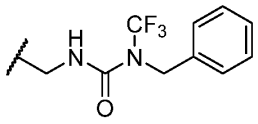
the C_{1-6}alkyl of R^c or R^d is optionally substituted with one or more -C(O)-NH_2,

the -C(O)-C_{1-6}alkyl of R^c or R^d is optionally substituted with one or more halo,

the 3-15 membered heterocyclyl and the 5-20 membered heteroaryl of R^c or R^d are independently optionally substituted with one or more C_{1-6}alkyl,

the -C(O)-(3-15 membered heterocyclyl) of R^c or R^d is optionally substituted with one or more halo, -C(O)-C_{1-6}alkoxy, or C_{1-6}alkyl, wherein the C_{1-6}alkyl is optionally substituted with one or more halo, C_{1-6}alkoxy, or C_{3-10}cycloalkyl, and

the C_{1-6}alkyl of the -C(O)-N(C_{1-6}alkyl)$_2$ of R^c or R^d are, independently of each other, optionally substituted with one or more halo or C_{6-20}aryl.

53. The compound of any one of claims 1, 36-38, 51, and 52 or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein R^2 is  ,  ,  ,  ,  , or  .

54. The compound of claim 1, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, is selected from Compounds 1-810 of Table 1.

55. The compound of claim 1, or claim 54 or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein the compound, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, is selected from Compounds 1-500 of Table 1.

56. A pharmaceutical composition comprising (i) a compound of any one of claims 1-55, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, and (ii) one or more pharmaceutically acceptable excipients.

57. A method of treating a GYS1-mediated disease, disorder, or condition in an individual in need thereof, comprising administering to the individual an effective amount of a compound of any one of claims 1-55, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition of claim 56.

58. The method of claim 57, wherein the disease, disorder, or condition is a glycogen storage disorder (GSD).

59. The method of claim 57 or claim 58, wherein the disease, disorder, or condition is selected from the group consisting of Pompe disease, Cori disease (GSD III), adult polyglucosan body disease (APBD), and Lafora disease.

60. The method of any one of claims 57-59, wherein the disease, disorder, or condition is Pompe disease.

61. The method of claim 57, wherein the disease, disorder, or condition is cancer.

62. The method of claim 57 or claim 61, wherein the disease, disorder, or condition is selected from the group consisting of Ewing sarcoma (ES), clear cell renal cell carcinoma (ccRCC), glycogen rich clear cell carcinoma (GRCC) breast cancer, non-small-cell lung carcinoma (NSCLC), and acute myeloid leukemia (AML).

63. The method of claim 57, wherein the individual has a GAA mutation.

64. The method of claim 63, wherein the GAA mutation is a loss-of-function mutation.

65. A kit, comprising (i) a compound of any one of claims 1-55, or a stereoisomer or tautomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, or a pharmaceutical composition of claim 56, and (ii) instructions for use in treating an GYS1-mediated disease, disorder, or condition in an individual in need thereof.

66. The kit of claim 65, wherein the disease, disorder, or condition is a glycogen storage disorder (GSD).

67. The kit of claim 65 or claim 66, wherein the disease, disorder, or condition is selected from the group consisting of Pompe disease, Cori disease (GSD III), adult polyglucosan body disease (APBD), and Lafora disease.

68. The kit of any one of claims 65-67, wherein the disease, disorder, or condition is Pompe disease.

69. The kit of claim 68, wherein the disease, disorder, or condition is cancer.

70. The kit of claim 65 or claim 69, wherein the disease, disorder, or condition is selected from the group consisting of Ewing sarcoma (ES), clear cell renal cell carcinoma (ccRCC), glycogen rich clear cell carcinoma (GRCC) breast cancer, non-small-cell lung carcinoma (NSCLC), and acute myeloid leukemia (AML).

71. The kit of claim 65, wherein the individual has a GAA mutation.

72. The kit of claim 71, wherein the GAA mutation is a loss-of-function mutation.

73. A method of modulating GYS1 in a cell, comprising exposing the cell to a composition comprising an effective amount of a GYS1 modulator, or a pharmaceutical composition comprising a GYS1 modulator.

74. A method of inhibiting GYS1 in a cell, comprising exposing the cell to a composition comprising an effective amount of a GYS1 inhibitor, or a pharmaceutical composition comprising a GYS1 inhibitor.

75. A method of reducing tissue glycogen stores in an individual in need thereof, comprising administering to the individual an effective amount of a GYS1 inhibitor, or a pharmaceutical composition comprising a GYS1 inhibitor.

76. A method of treating a GYS1-mediated disease, disorder, or condition in an individual in need thereof, comprising subjecting the individual to glycogen substrate reduction therapy.

77. The method of claim 76, wherein the disease, disorder, or condition is a glycogen storage disorder (GSD).

78. The method of claim 76 or claim 77, wherein the disease, disorder, or condition is selected from the group consisting of Pompe disease, Cori disease (GSD III), adult polyglucosan body disease (APBD), and Lafora disease.

79. The method of any one of claims 76-78, wherein the disease, disorder, or condition is Pompe disease.

80. The method of claim 76, wherein the disease, disorder, or condition is cancer.

81. The method of claim 76 or claim 80, wherein the disease, disorder, or condition is selected from the group consisting of Ewing sarcoma (ES), clear cell renal cell carcinoma (ccRCC), glycogen rich clear cell carcinoma (GRCC) breast cancer, non-small-cell lung carcinoma (NSCLC), and acute myeloid leukemia (AML).

82. The method of claim 76, wherein the individual has a GAA mutation.

83. The method of claim 82, wherein the GAA mutation is a loss-of-function mutation.

84. The method of any one of claims 73-75 wherein the GYS1 inhibitor is selective for GYS1 over GYS2.

85. The method of claim 84, wherein the GYS1 inhibitor is greater than 500 or 1,000 or 1,500 or 1,700-fold selective for GYS1 over GYS2.

86. The method of any one of claims 76-83 wherein the glycogen substrate reduction therapy comprises administering to the individual a GYS1 inhibitor.

87. The method of claim 86, wherein the GYS1 inhibitor is a small molecule.

88. The method of claim 87, wherein the GYS1 inhibitor is selective for GYS1 over GYS2.

89. The method of claim 88, wherein the GYS1 inhibitor is greater than 500 or 1,000 or 1,500 or 1,700-fold selective for GYS1 over GYS2.

90. The method of any one of claims 57-64, or 74-89, comprising reducing the level of glycogen in skeletal muscle.