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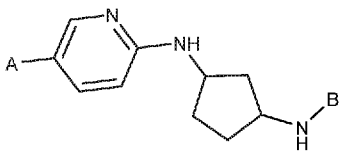
(54) Title: DIAMINOCYCLOPENTYLPYRIDINE DERIVATIVES FOR THE TREATMENT OF A DISEASE OR DISORDER



(I)

(57) Abstract: The disclosure relates to a compound of Formula (I) or a pharmaceutically acceptable salt thereof wherein A and B are as described herein, as well as compositions and methods of using such compounds.

DIAMINOCYCLOPENTYLPYRIDINE DERIVATIVES FOR THE TREATMENT OF A DISEASE OR DISORDER

RELATED APPLICATIONS

[001] This application claims the benefit of and priority to U.S. Provisional Application Nos. 63/278,754, filed November 12, 2021, 63/325,988 filed March 31, 2022, and 63/379,562 filed October 14, 2022, the entire contents of each of which are hereby incorporated by reference in their entireties.

TECHNICAL FIELD

[002] The present disclosure is directed to modulators of proprotein convertase subtilisin/ kexin type 9 (PCSK9) useful in the treatment of diseases or disorders. Specifically, the disclosure is concerned with compounds, compositions, and methods of treating diseases or disorders associated with PCSK9.

BACKGROUND

[003] Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a member of the secretory subtilase, subtilisin serine protease family, and is expressed in many tissues and cell types. The PCSK9 protein contains a signal sequence, a prodomain, a catalytic domain containing a conserved triad of residues (D186, H226 and S386), and a C-terminal domain and is synthesized as a soluble 74-kDa precursor that undergoes autocatalytic cleavage in the endoplasmic reticulum. The autocatalytic activity has been shown to be required for secretion.

[004] PCSK9 has pronounced effects on plasma low density lipoprotein cholesterol (LDL-C) levels via its modulation of hepatic low density lipoprotein receptors (LDLR), the main route by which cholesterol is removed from the circulation. PCSK9 binds the LDLR and directs it to lysosomal degradation, thereby increasing plasma LDL-C levels and, in turn, coronary heart disease (CHD) risk. (Maxwell K. N., Proc. Natl. Acad. Sci., 101, 2004, 7100-7105; Park, S. W., J. Biol. Chem. 279, 2004, 50630-50638; Lagace T.A., et. al. J. Clin. Invest. 2006, 116(11):2995-3005). Overexpression of mouse or human PCSK9 in mice has been shown to elevate total and LDL-C levels and dramatically reduce hepatic LDLR protein, without an observed effect on the levels of mRNA, SREBP, or SREBP protein nuclear to cytoplasmic ratio. (Maxwell K. N., Proc. Natl. Acad. Sci. 101, 2004, 7100-7105). Moreover, mutations in PCSK9 that cause loss of PCSK9 function in mouse models have also been shown to lower total and LDL-C levels. (Cohen, J. C., et al., N. Engl. J. Med., 354, 2006, 1264-1272). Thus, the results indicate that modulation of PCSK9 results in a reduction of LDLR protein levels.

[005] Gene deletion of PCSK9 has also been conducted in mice. PCSK9 knockout mice show an approximate 50% reduction in plasma cholesterol levels and enhanced sensitivity to statins in reducing

plasma cholesterol (Rashid, S., et al., Proc. Natl. Acad. Sci., 2005, 102:5374-5379). Human genetic data strongly support the role of PCSK9 in LDL homeostasis. The link between PCSK9 and plasma LDL-C levels was first established by the discovery of PCSK9 missense mutations in patients with an autosomal dominant form of familial hypercholesterolemia (Abifadel, M., et al., Nature, 2003, 34:154-6). Patients carrying PCSK9 gain-of-function alleles have increased plasma LDL-C levels and premature CHD, whereas those with PCSK9 loss-of-function alleles have markedly reduced plasma LDL-C and are protected from CHD.

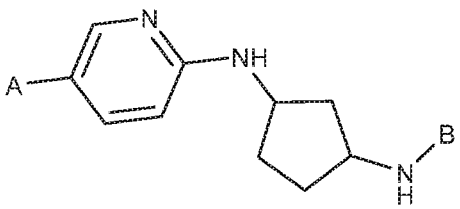
[006] PCSK9 also plays a role in Lipoprotein (a) (Lp(a)) metabolism. Lp(a) is a proatherogenic lipoprotein comprised of an LDL particle covalently linked to apoLp(a). Human genetic studies indicate that Lp(a) is causally associated with CHD risk. PCSK9 therapeutic antibodies have been shown to significantly reduce Lp(a) levels in patients with hypercholesterolemia. (Desai, N.R., et. al., Circulation. 2013, 128(9):962-969; Lambert, G., et. al., Clin. Sci., 2017, 131, 261-268). Patients receiving statin therapy treated with a monoclonal antibody against PCSK9 have shown up to 32% reduction in Lp(a) levels compared to placebo. (Desai N.R., et. al., Circulation. 2013, 128(9):962-969).

[007] In addition to having cardiovascular effects, PCSK9 plays an important role in sepsis, a life-threatening condition caused by a body's response to infection. Overexpression of PSCK9 in septic mice has been shown to aggravate sepsis by increasing inflammation, while inhibition of PCSK9 has been shown to reduce mortality. (Dwivedi, D. J., et al., Shock, 2016, 46(6), 672–680). Moreover, flow cytometry studies in human HepG2 cells have shown that PCSK9 negatively regulates gram-negative lipopolysaccharide (LPS) uptake by hepatocytes through the regulation of the LDLR-mediated bacterial lipid uptake of lipoteichoic acid (LTA) and LPS through an LDL-dependent mechanism. (Grin, P.M., et al., Nature, 2018, 8(1):10496) Thus, inhibition of PCSK9 has the potential to treat sepsis by reducing the body's immune response to an infection.

[008] Inhibition of PCSK9 with a small molecule inhibitor has the potential to be a treatment for a range of diseases. For these reasons, there remains a need for small molecule inhibitors of PCSK9.

SUMMARY

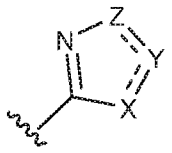
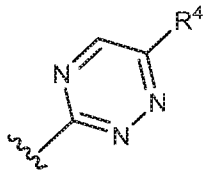
[009] In a first aspect, the disclosure relates to a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof wherein:

A is a 5 or 6 membered heterocycle or heteroaryl containing at least one N and at least one oxo at a ring carbon and is optionally substituted with (C_1-C_6)alkyl;

B is  or  ;

X is N, O, or S;

Y is CR^1 or N;

Z is CR^2, NR^3, O, or S;

R^1 and R^2 are each, independently selected from H, halogen, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_6-C_{10})aryl, a 4 to 6 membered heterocyclyl comprising 1, 2 or 3 heteroatoms selected from O and N, or a 5 or 6 membered heteroaryl comprising 1, 2 or 3 heteroatoms selected from O and N, wherein the (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_6-C_{10})aryl, heterocyclyl, or heteroaryl are each independently optionally substituted with one or more substituents selected from halogen, -OH, –CN, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_3-C_6)cycloalkyl, -SO_2(C_1-C_6)alkyl, -COOH, and -COO(C_1-C_6)alkyl;

R^3 is absent, H or (C_1-C_6)alkyl; and

R^4 is H, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy or (C_3-C_6)cycloalkyl, wherein the (C_1-C_6)alkoxy is optionally substituted with halogen.

[010] In another aspect, the present disclosure relates to a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers.

[011] In another aspect, the present disclosure relates to a combination comprising a compound of Formula I or a pharmaceutically acceptable salt thereof and one or more pharmaceutical agents.

[012] In another aspect, the present disclosure relates to a method for treating a disease or disorder comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof.

[013] In some embodiments, the disease or disorder is selected from hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, sitosterolemia, atherosclerosis, arteriosclerosis, coronary heart disease, peripheral vascular disease, vascular inflammation, xanthoma, peripheral arterial disease, elevated Lp(a), elevated LDL, elevated TRL, and elevated triglycerides. In some embodiments, the disease or disorder is selected from sepsis, psoriasis and cancer.

[014] In yet another aspect, the present disclosure relates to a method of modulating PCSK9 comprising administering to a patient in need thereof a compound of Formula I or a pharmaceutically acceptable salt thereof. In still another aspect, the present disclosure relates to a method of inhibiting PCSK9 comprising administering to a patient in need thereof a compound of Formula I or a pharmaceutically acceptable salt thereof.

[015] In another aspect, the present disclosure relates to a compound of Formula I or a pharmaceutically acceptable salt thereof for use as a medicament.

[016] In another aspect, the present disclosure relates to a compound of Formula I or a pharmaceutically acceptable salt thereof for use in the treatment of a disease or disorder.

[017] In yet another aspect, the present disclosure relates to a compound of Formula I for use in the manufacture of a medicament for treating a disease or disorder.

[018] In still another aspect, the present disclosure relates to use of a compound of Formula I or a pharmaceutically acceptable salt thereof in the treatment of a disease or disorder.

[019] Other features and advantages of the disclosure will be apparent from the following detailed description and claims.

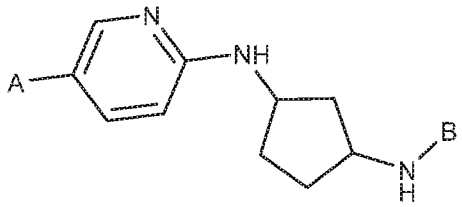
DETAILED DESCRIPTION

[020] In certain aspects, the disclosure provides substituted diaminocyclopentylpyridine compounds, and pharmaceutical compositions thereof. In particular, such substituted compounds are useful as PCSK9 inhibitors, and thus can be used to treat or prevent a disease or condition.

[021] The details of the disclosure are set forth in the accompanying description below. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, illustrative methods and materials are now described. Other features, objects, and advantages of the disclosure will be apparent from the description and from the claims. In the specification and the appended claims, the singular forms also include the plural unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. All patents and publications cited in this specification are incorporated herein by reference in their entireties.

Compounds

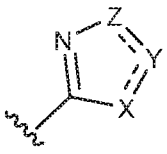
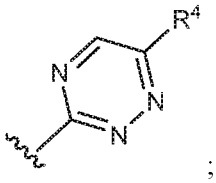
[022] In one aspect, the disclosure therefore provides a compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof wherein:

A is a 5 or 6 membered heterocycle or heteroaryl containing at least one N and at least one oxo at a ring carbon and is optionally substituted with (C_1-C_6)alkyl;

B is  or  ;

X is N, O, or S;

Y is CR^1 or N;

Z is CR^2, NR^3, O, or S;

R^1 and R^2 are each, independently selected from H, halogen, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_6-C_{10})aryl, a 4 to 6 membered heterocyclyl comprising 1, 2 or 3 heteroatoms selected from O and N, or a 5 or 6 membered heteroaryl comprising 1, 2 or 3 heteroatoms selected from O and N, wherein the (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_6-C_{10})aryl, heterocyclyl, or heteroaryl are each independently optionally substituted with one or more substituents selected from halogen, -OH, –CN, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_3-C_6)cycloalkyl, -SO_2(C_1-C_6)alkyl, -COOH, and -COO(C_1-C_6)alkyl;

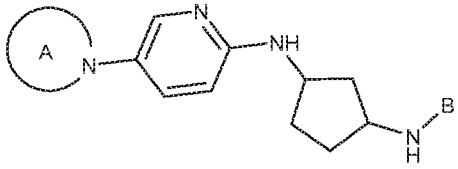
R^3 is absent, H or (C_1-C_6)alkyl; and

R^4 is H, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy or (C_3-C_6)cycloalkyl, wherein the (C_1-C_6)alkoxy is optionally substituted with halogen.

[023] Unless specified otherwise, the term “compounds of the present disclosure” or “compound of the present disclosure” refers to compounds of formula (I) thereof, and exemplified compounds, and salts thereof, as well as all stereoisomers (including diastereoisomers and enantiomers), rotamers, tautomers and isotopically labeled compounds (including deuterium substitutions), as well as inherently formed moieties.

[024] Various embodiments of the disclosure are described herein. It will be recognized that features specified in each embodiment may be combined with other specified features of other embodiments to provide further embodiments.

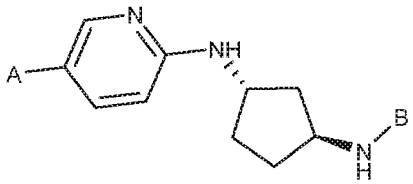
[025] In some embodiments, the compound is a compound of formula II



II

or a pharmaceutically acceptable salt thereof.

[026] In some embodiments, the compound is a compound of formula III

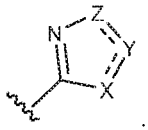
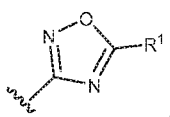
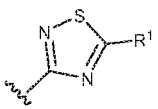
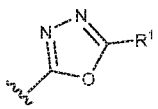
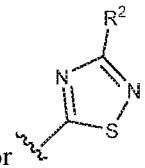
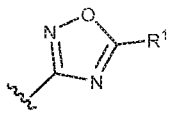
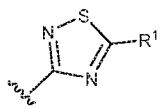
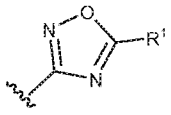


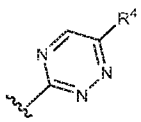
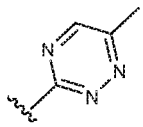
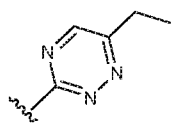
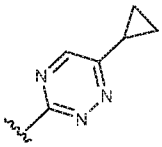
III

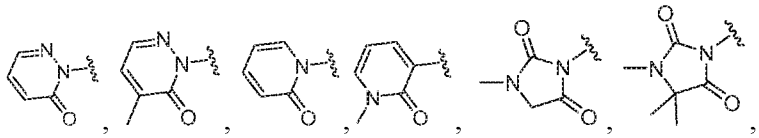
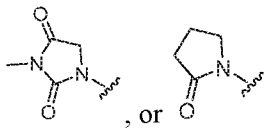
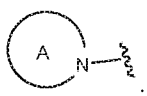
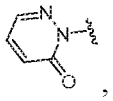
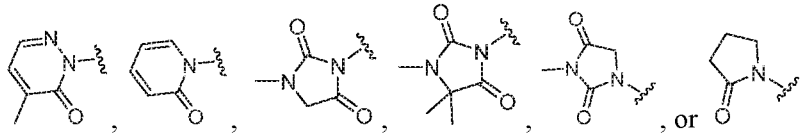
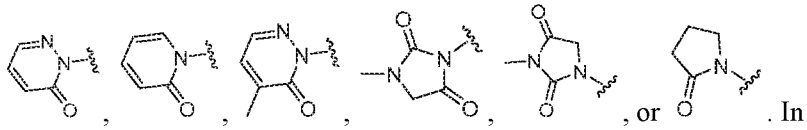
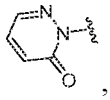
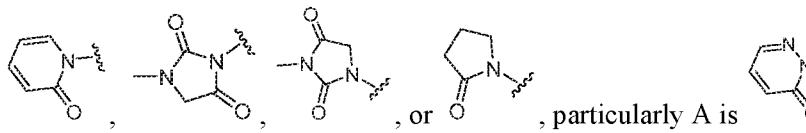
or a pharmaceutically acceptable salt thereof.

[027] In some embodiments, at least one of X, Y and Z is N. In some embodiments, when X is O or S, Z is CR^2 or N. In some embodiments, when Z is O or S, X is N.

[028] In some embodiments, X is N. In some embodiments, X is N, Y is CR^1, and Z is O or S

[029] In some embodiments, B is  . In some embodiments, B is  ,  ,  , or  , particularly B is  or  , more particularly B is  .

[030] In some embodiments, B is  . In some embodiments, B is  ,  ,  , or .

[031] In some embodiments, A is  ,  , or . In some embodiments, A is  . In some embodiments, A is  ,  , or . In some embodiments, A is  , or . In some embodiments, A is  ,  , or , particularly A is .

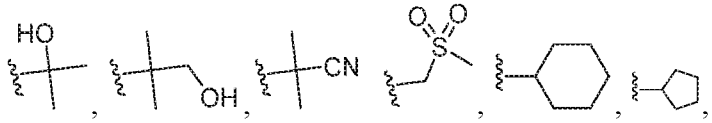
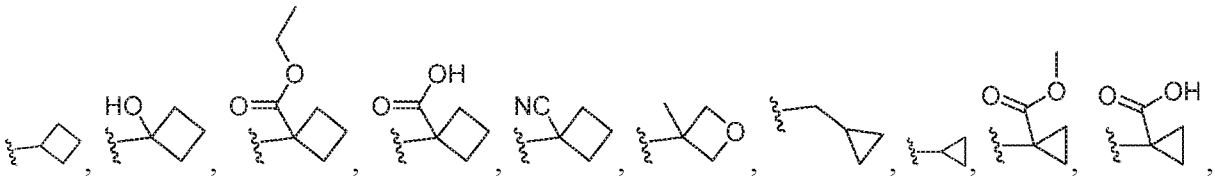
[032] In some embodiments, R^1 is H, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_6-C_{10})aryl, a 4 to 6 membered heterocyclyl comprising 1, 2 or 3 heteroatoms selected from O and N, or a 5 or 6 membered heteroaryl comprising 1, 2 or 3 heteroatoms selected from O and N, wherein the (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_6-C_{10})aryl, heterocyclyl, or heteroaryl are each independently optionally substituted with one or more substituents selected from halogen, -OH, –CN, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_3-C_6)cycloalkyl, -SO_2(C_1-C_6)alkyl, -COOH, and -COO(C_1-C_6)alkyl. In some embodiments, R^1 is H, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_6-C_{10})aryl, a 4 to 6 membered heterocyclyl comprising 1 heteroatom selected from O and N, or a 5 or 6 membered heteroaryl comprising 1 or 3 heteroatoms selected from N, wherein the (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_6-C_{10})aryl, heterocyclyl, or heteroaryl are each independently optionally substituted with one or more substituents selected from halogen, -OH, –CN, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_3-C_6)cycloalkyl, -SO_2(C_1-C_6)alkyl, -COOH, and -COO(C_1-C_6)alkyl.

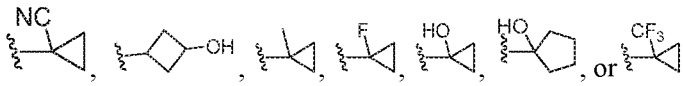
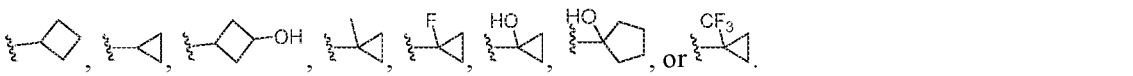
[033] In some embodiments, R^1 is H, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, or (C_6-C_{10})aryl, wherein the (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, or (C_6-C_{10})aryl are each independently optionally substituted with one or more substituents selected from halogen, -OH, –CN, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, and (C_1-C_6)alkoxy. In some embodiments, R^1 is H, (C_1-C_6)alkyl optionally substituted with one or more halogen, -CN, (C_3-C_6)cycloalkyl optionally substituted with one or more substituents selected from halogen, -OH, (C_1-C_6)alkyl and (C_1-C_6)haloalkyl, or (C_6-C_{10})aryl optionally substituted one or more with halogen or CN. In some embodiments, R^1 is (C_1-C_6)alkyl optionally substituted with one or more halogen or -CN, (C_3-

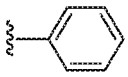
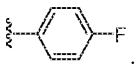
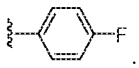
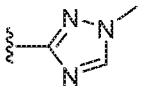
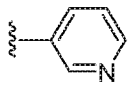
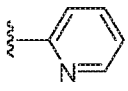
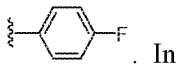
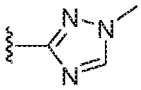
C_6)cycloalkyl optionally substituted with one or more substituents selected from halogen, -OH, (C_1-C_6)alkyl and (C_1-C_6)haloalkyl, or (C_6-C_{10})aryl optionally substituted with one or more halogen or -CN. In some embodiments, R^1 is H, (C_1-C_6)alkyl optionally substituted with one or more halogen, (C_3-C_6)cycloalkyl optionally substituted with one or more substituents selected from halogen, -OH, (C_1-C_6)alkyl and (C_1-C_6)haloalkyl, or (C_6-C_{10})aryl optionally substituted one or more with halogen. In some embodiments, R^1 is (C_1-C_6)alkyl optionally substituted with one or more halogen, (C_3-C_6)cycloalkyl optionally substituted with one or more substituents selected from halogen, -OH, (C_1-C_6)alkyl and (C_1-C_6)haloalkyl, or (C_6-C_{10})aryl optionally substituted with one or more halogen. In some embodiments, R^1 is H, (C_1-C_6)alkyl optionally substituted with one or more fluoro, (C_3-C_6)cycloalkyl optionally substituted with one or more substituents selected from fluoro, -OH, (C_1-C_6)alkyl and (C_1-C_6)fluoroalkyl, or (C_6-C_{10})aryl optionally substituted one or more with fluorine. In some embodiments, R^1 is (C_1-C_6)alkyl optionally substituted with fluoro, (C_3-C_6)cycloalkyl optionally substituted with one or more substituents selected from fluoro, -OH, (C_1-C_6)alkyl and (C_1-C_6)haloalkyl, or (C_6-C_{10})aryl optionally substituted with one or more fluoro. In some embodiments, R^1 is (C_1-C_6)alkyl optionally substituted with one or more fluoro or -CN. In some embodiments, R^1 is (C_1-C_6)alkyl optionally substituted with one or more fluoro. In some embodiments, R^1 is unsubstituted (C_1-C_6)alkyl. In some embodiments, R^1 is (C_3-C_6)cycloalkyl optionally substituted with one or more substituents selected from fluoro, -OH, (C_1-C_6)alkyl and (C_1-C_6)fluoroalkyl. In certain embodiments, R^1 is (C_3-C_6)cycloalkyl.

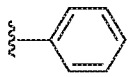
[034] In some embodiments, R^1 is phenyl optionally substituted with one or more fluoro.

[035] In some embodiments, R^1 is -CH_3, -CH_2CH_3, -CHF_2, -CF_3, -CF_2CH_3, -CH_2CF_3, -CH_2CN,  , or  . In certain embodiments, R^1 is -CH_3, -CH_2CH_3, -CHF_2, -CF_3, -CF_2CH_3,  , or  . In certain embodiments, R^1 is -CH_3, -CH_2CH_3, -CHF_2, -CF_3, or -CF_2CH_3. In certain preferred embodiments, R^1 is -CH_3, -CHF_2, or -CF_3.

[036] In some embodiments, R^1 is 


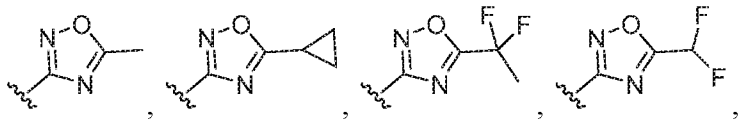



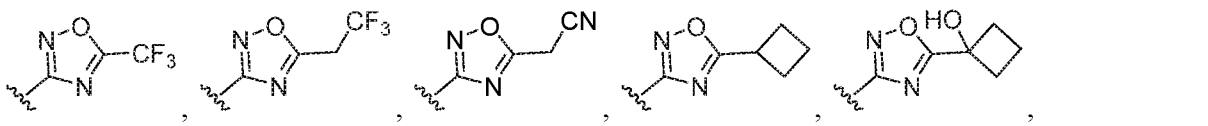
[037] In some embodiments, R^1 is  or  . In some embodiments, R^1 is  . In some embodiments, R^1 is  ,  , or  .  . In some embodiments, R^1 is  .

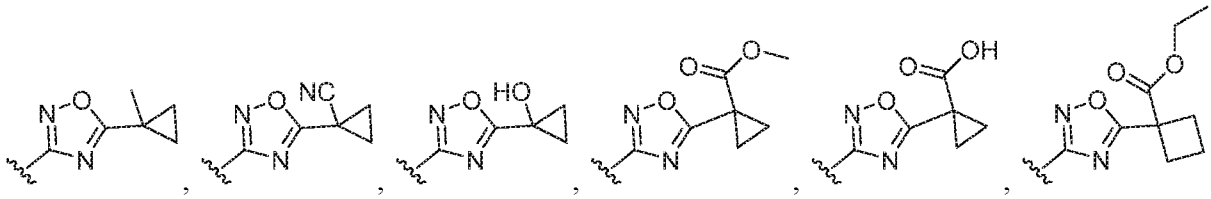
[038] In some embodiments, R^2 is H, halogen, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, or $(C_6\text{-}C_{10})$aryl. In some embodiments, R^2 is H, fluoro, chloro, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, or $(C_6\text{-}C_{10})$aryl. In some embodiments, R^2 is halogen, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, or phenyl. In some embodiments, R^2 is fluoro, chloro, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, or phenyl. In some embodiments, R^2 is -Cl, $-CH_3$,  , or  .

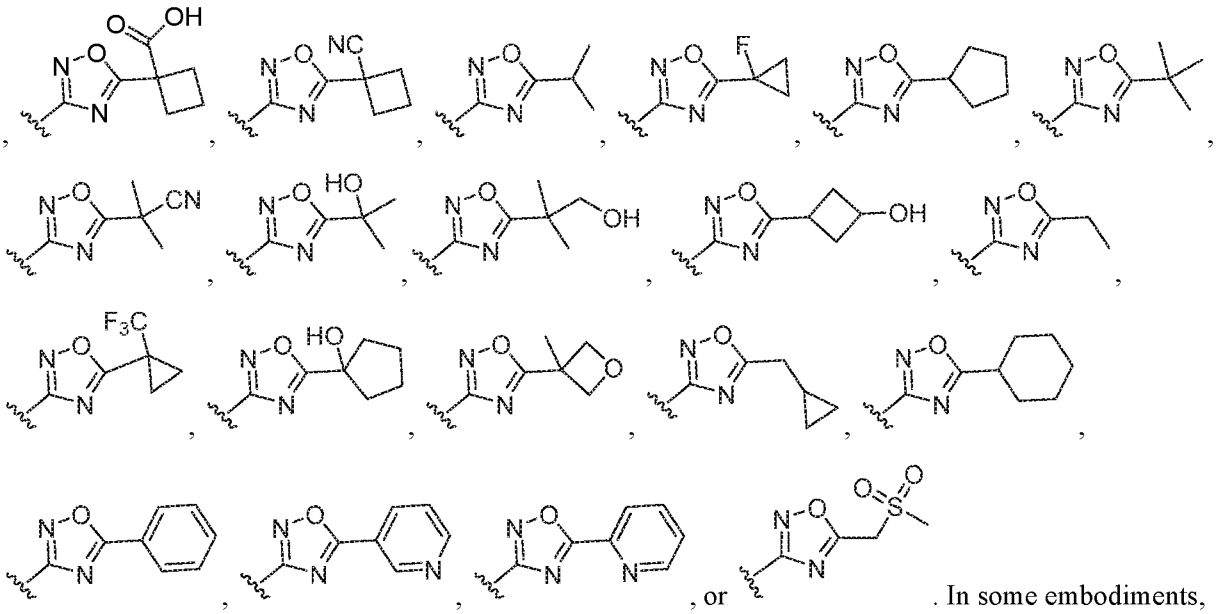
[039] In some preferred embodiments, R^3 is H.

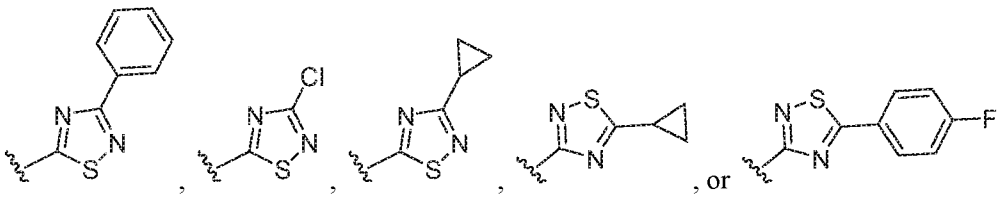
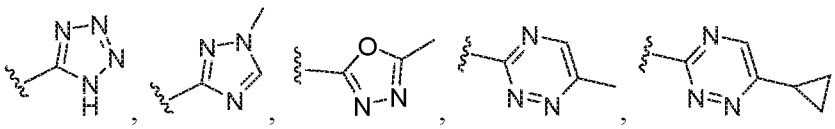
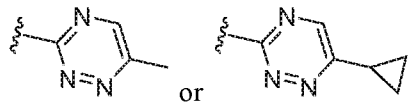
In some embodiments, R^4 is $(C_1\text{-}C_6)$alkyl or $(C_3\text{-}C_6)$cycloalkyl. In some embodiments, R^4 is $(C_1\text{-}C_6)$alkyl. In some embodiments, R^4 is methyl, ethyl, or cyclopropyl. In some embodiments, R^4 is methyl or ethyl. In some embodiments, R^4 is $(C_1\text{-}C_6)$alkoxy optionally substituted with halogen. In some embodiments, R^4 is $–OCF^3$.

[040] In some embodiments, B is 







. In some embodiments, B is  . In some embodiments, B is  . In certain embodiments, B is  or .

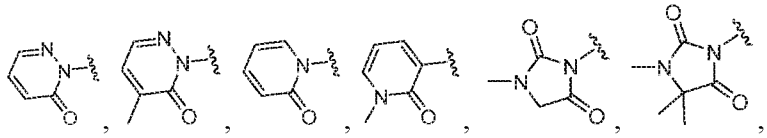
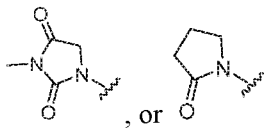
[041] Embodiment 1. A compound of formula (I), or a pharmaceutically acceptable salt thereof, as described above.

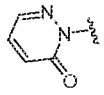
[042] Embodiment 2. A compound according to embodiment 1 or a pharmaceutically acceptable salt thereof, wherein at least one of X, Y and Z is N.

[043] Embodiment 3. A compound according to embodiment 1 or embodiment 2 or a pharmaceutically acceptable salt thereof, wherein when X is O or S, Z is CR^2 or N.

[044] Embodiment 4. A compound according to any one of embodiments 1 to 3 or a pharmaceutically acceptable salt thereof, wherein when Z is O or S, X is N.

[045] Embodiment 5. A compound according to embodiment 1 or a pharmaceutically acceptable salt thereof, wherein R^4 is methyl, ethyl, or cyclopropyl.

[046] Embodiment 6. A compound according to any one of embodiments 1 to 5 or a pharmaceutically acceptable salt thereof, wherein A is  ,  , or .

[047] Embodiment 7. A compound according to any one of embodiments 1 to 6 or a pharmaceutically acceptable salt thereof, wherein A is  .

[048] Embodiment 8. A compound according to any one of embodiments 1 to 7 or a pharmaceutically acceptable salt thereof, wherein X is N.

[049] Embodiment 9. A compound according to any one of embodiments 1 to 8 or a pharmaceutically acceptable salt thereof, wherein X is N, Y is CR^1, and Z is O or S.

[050] Embodiment 10. A compound according to any one of embodiments 1 to 9 or a pharmaceutically acceptable salt thereof, wherein X is N, Y is CR^1, and Z is O.

[051] Embodiment 11. A compound according to any one of embodiments 1 to 10 or a pharmaceutically acceptable salt thereof, wherein R^1 is H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_6\text{-}C_{10})$aryl, a 4 to 6 membered heterocyclyl comprising 1, 2 or 3 heteroatoms selected from O and N, or a 5 or 6 membered heteroaryl comprising 1, 2 or 3 heteroatoms selected from O and N, wherein the $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_6\text{-}C_{10})$aryl, heterocyclyl, or heteroaryl are each independently optionally substituted with one or more substituents selected from halogen, -OH, –CN, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_3\text{-}C_6)$cycloalkyl, $-SO_2(C_1\text{-}C_6)$alkyl, -COOH, and $-COO(C_1\text{-}C_6)$alkyl.

[052] Embodiment 12. A compound according to any one of embodiments 1 to 11 or a pharmaceutically acceptable salt thereof, wherein R^1 is H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_6\text{-}C_{10})$aryl, a 4 to 6 membered heterocyclyl comprising 1 heteroatom selected from O and N, or a 5 or 6 membered heteroaryl comprising 1 or 3 heteroatoms selected from N, wherein the $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_6\text{-}C_{10})$aryl, heterocyclyl, or heteroaryl are each independently optionally substituted with one or more substituents selected from halogen, -OH, –CN, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_3\text{-}C_6)$cycloalkyl, $-SO_2(C_1\text{-}C_6)$alkyl, -COOH, and $-COO(C_1\text{-}C_6)$alkyl.

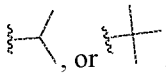
[053] Embodiment 13. A compound according to any one of embodiments 1 to 12 or a pharmaceutically acceptable salt thereof, wherein R^1 is H, $(C_1\text{-}C_6)$alkyl optionally substituted with one or more halogen, -CN, $(C_3\text{-}C_6)$cycloalkyl optionally substituted with one or more substituents selected from

halogen, -OH, (C_1-C_6)alkyl and (C_1-C_6)haloalkyl, or (C_6-C_{10})aryl optionally substituted one or more with halogen or -CN.

[054] Embodiment 14. A compound according to any one of embodiments 1 to 13 or a pharmaceutically acceptable salt thereof, wherein R^1 is (C_1-C_6)alkyl optionally substituted with one or more halogen or -CN, (C_3-C_6)cycloalkyl optionally substituted with one or more substituents selected from halogen, -OH, (C_1-C_6)alkyl and (C_1-C_6)haloalkyl, or (C_6-C_{10})aryl optionally substituted with one or more halogen or -CN.

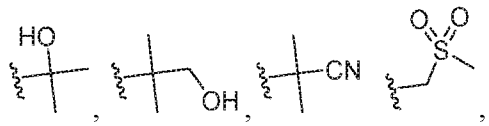
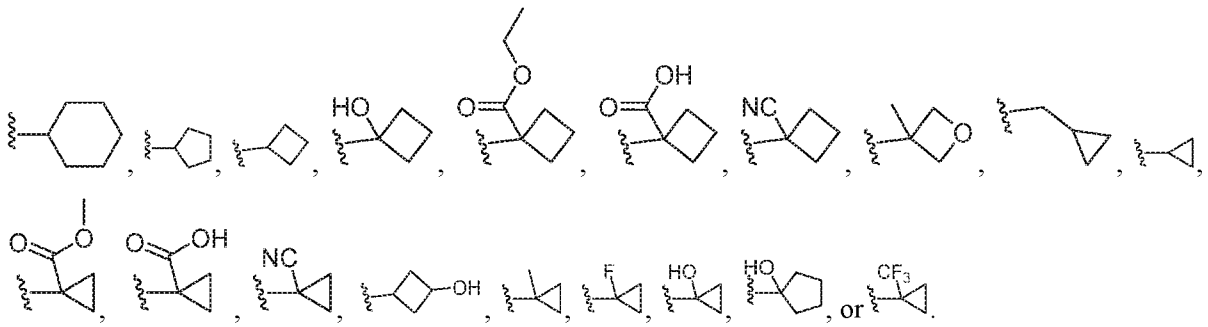
[055] Embodiment 15. A compound according to embodiment 13 or a pharmaceutically acceptable salt thereof, wherein each halogen is fluoro.

[056] Embodiment 16. A compound according to any one of embodiments 1 to 15 or a pharmaceutically acceptable salt thereof, wherein R^1 is (C_1-C_6)alkyl optionally substituted with one or more fluoro or -CN.

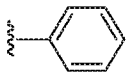
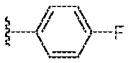
[057] Embodiment 17. A compound according to any one of embodiments 1 to 16, wherein R^1 is $-CH_3$, $-CH_2CH_3$, $-CHF_2$, $-CF_3$, $-CF_2CH_3$, $-CH_2CF_3$, $-CH_2CN$,  , or .

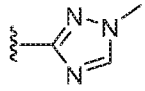
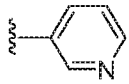
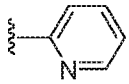
[058] Embodiment 18. A compound according to any one of embodiments 1 to 17, wherein R^1 is $-CH_3$, $-CHF_2$, or $-CF_3$.

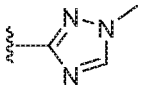
[059] Embodiment 19. A compound according to any one of embodiments 1 to 14 or a pharmaceutically acceptable salt thereof, wherein R^1 is (C_3-C_6)cycloalkyl optionally substituted with one or more substituents selected from fluoro, -OH, (C_1-C_6)alkyl and (C_1-C_6)fluoroalkyl.

[060] Embodiment 20. A compound according to any one of embodiments 1 to 13 or a pharmaceutically acceptable salt thereof, wherein R^1 is  ,  .

[061] Embodiment 21. A compound according to any one of embodiments 1 to 13 or a pharmaceutically acceptable salt thereof, wherein R^1 is phenyl optionally substituted with one or more fluoro.

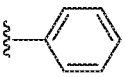
[062] Embodiment 22. A compound according to embodiments 21 or a pharmaceutically acceptable salt thereof, wherein R^1 is  or  .

[063] Embodiment 23. A compound according to any one of embodiments 1 to 13 or a pharmaceutically acceptable salt thereof, wherein R^1 is  ,  , or  .

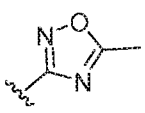
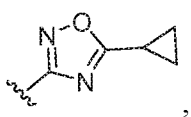
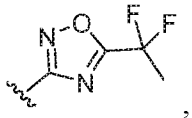
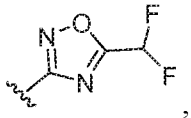
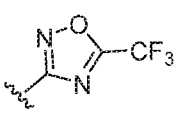
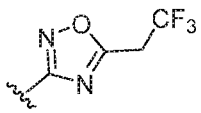
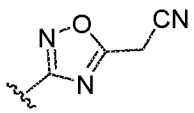
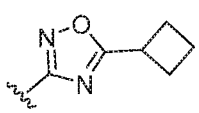
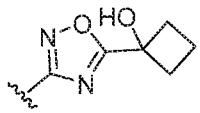
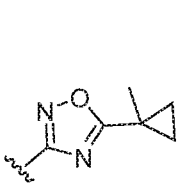
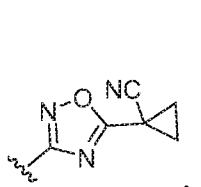
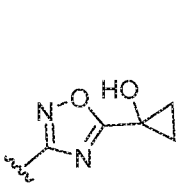
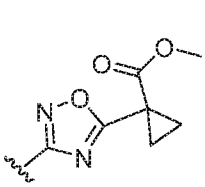
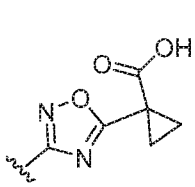
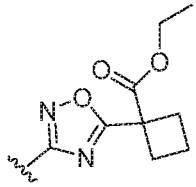
Embodiment 24. A compound according to any one of embodiments 1 to 13 or a pharmaceutically acceptable salt thereof, wherein R^1 is ,  .

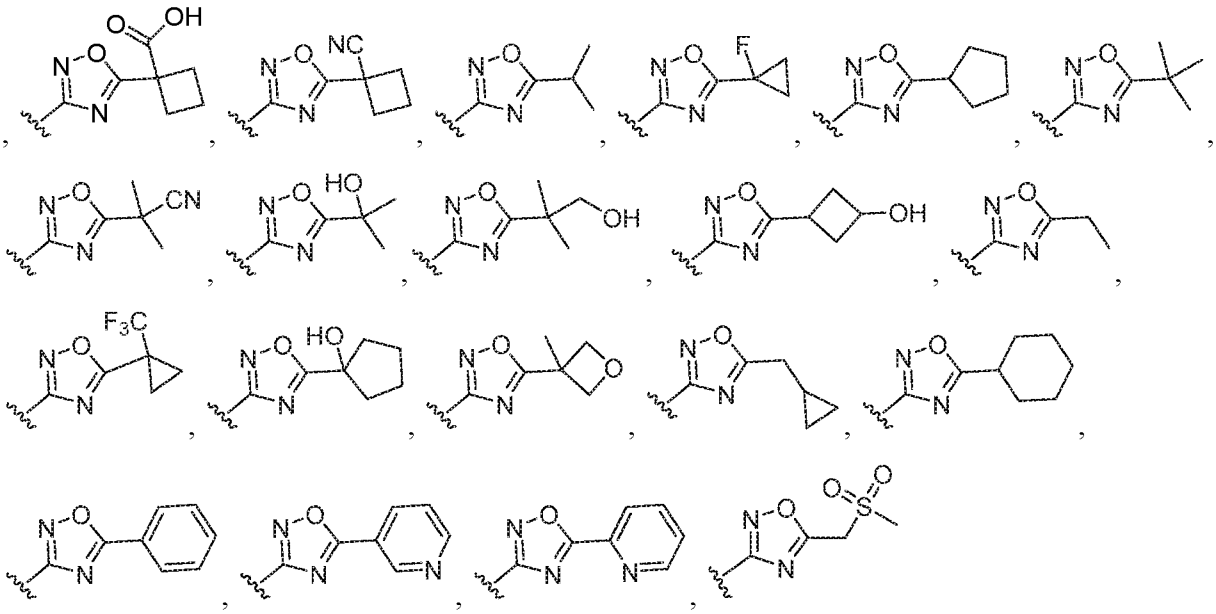
[064] Embodiment 25. A compound according to any one of embodiments 1 to 3, 5 to 8, and 11 to 24 or a pharmaceutically acceptable salt thereof, wherein R^2 is H, halogen, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, or $(C_6\text{-}C_{10})$aryl.

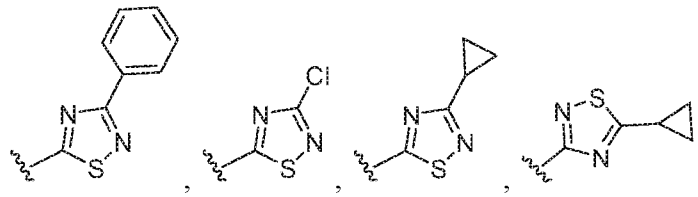
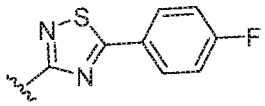
[065] Embodiment 26. A compound according to any one of embodiments 1to 3, 5 to 8, and 11 to 22 or a pharmaceutically acceptable salt thereof, wherein R^2 is halogen, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, or phenyl

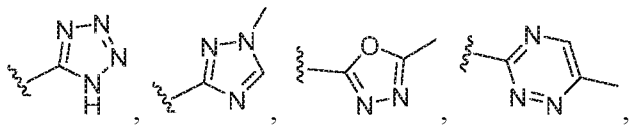
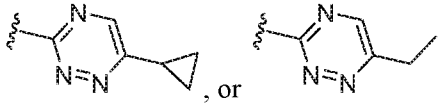
[066] Embodiment 27. A compound according to any one of embodiments 1 to 3, 5 to 8, and 11 to 26 or a pharmaceutically acceptable salt thereof, wherein R^2 is -Cl, $-CH_3$,  , or  .

[067] Embodiment 28. A compound according to any one of embodiments 1 to 3, 5 to 8, and 11 to 27 or a pharmaceutically acceptable salt thereof, wherein R^3 is H.

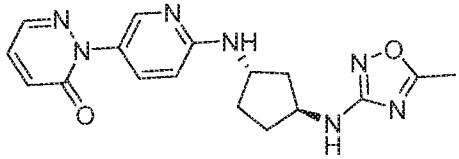
[068] Embodiment 29. A compound according to any one of embodiments 1 to 4 or a pharmaceutically acceptable salt thereof, wherein B is  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  .

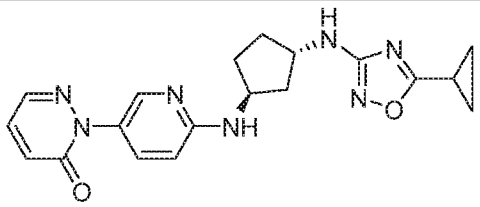
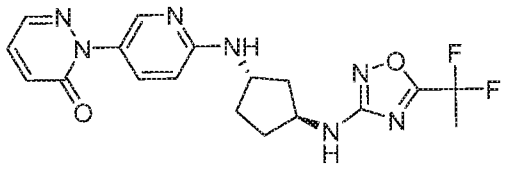
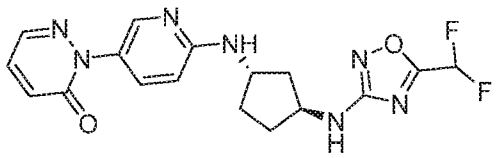
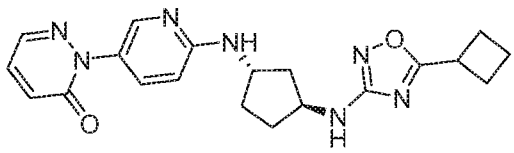
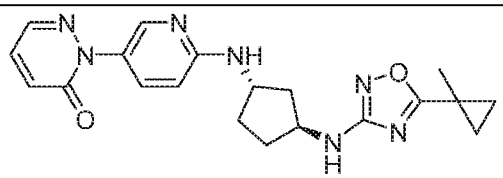
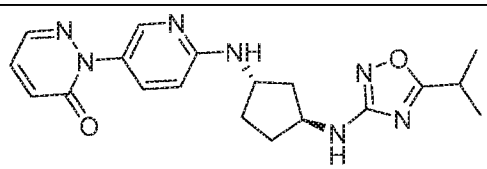
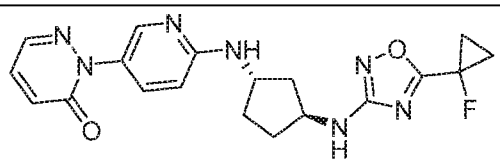
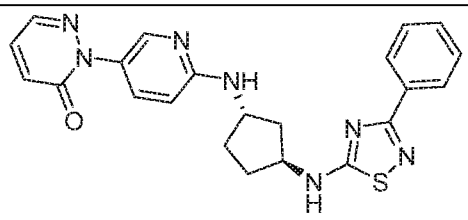


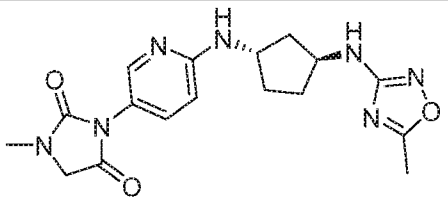
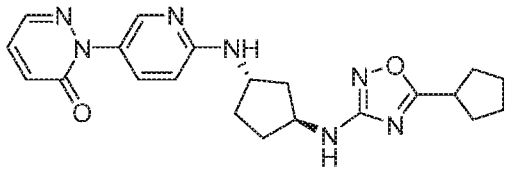
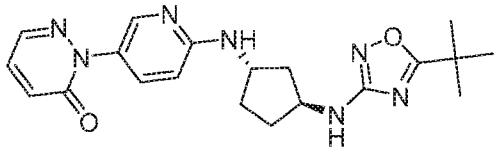
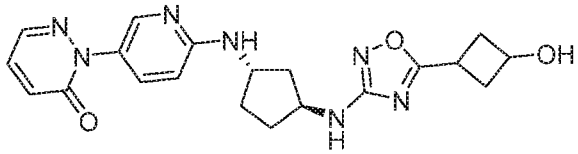
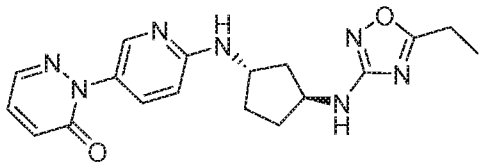
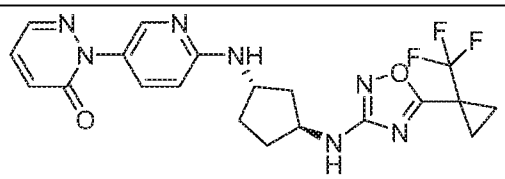
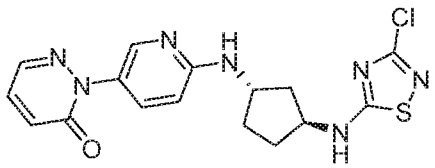
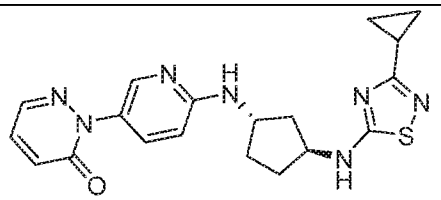
[069] Embodiment 30. A compound according to any one of embodiments 1 to 4 or a pharmaceutically acceptable salt thereof,, wherein B is  , or  .

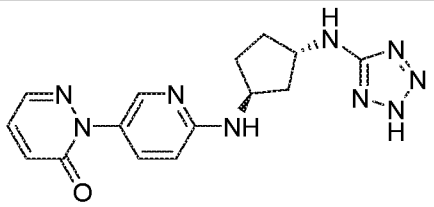
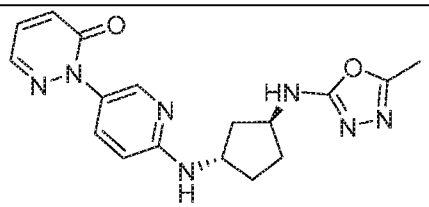
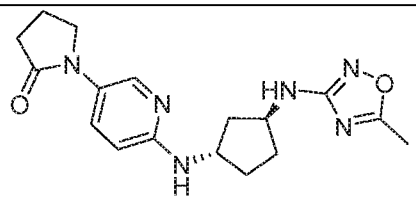
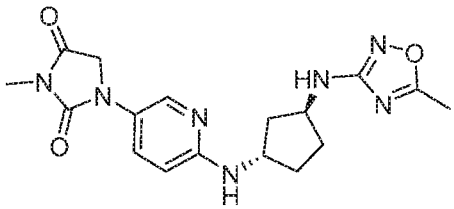
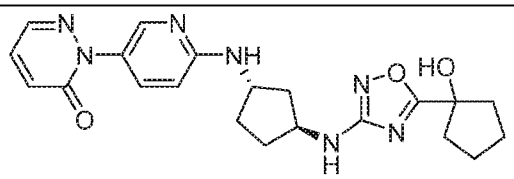
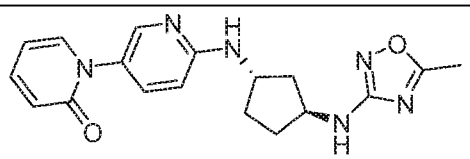
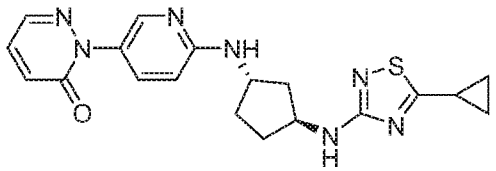
[070] Embodiment 31. A compound according to any one of embodiments 1 to 4 or a pharmaceutically acceptable salt thereof, wherein B is  , or  .

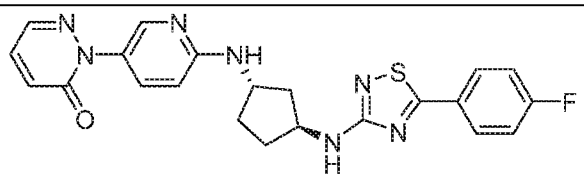
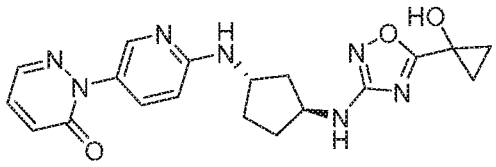
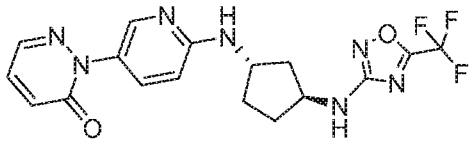
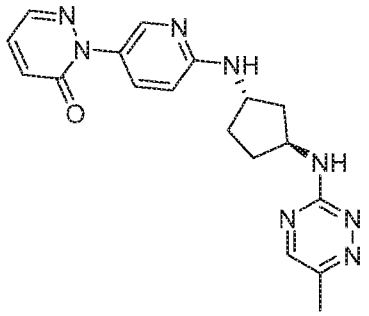
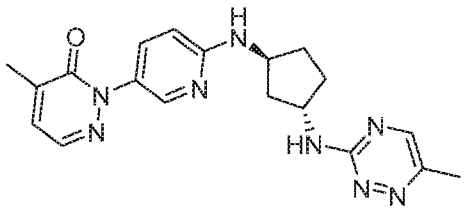
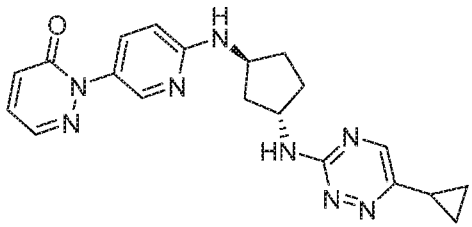
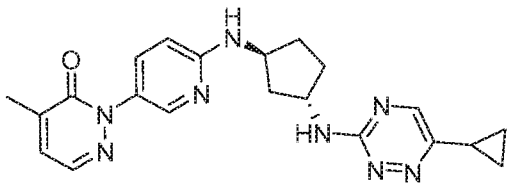
[071] Embodiments 32 and 33. A compound according to embodiment 1 or a pharmaceutically acceptable salt thereof selected from:

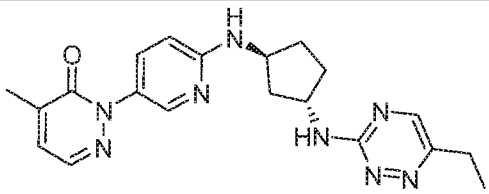
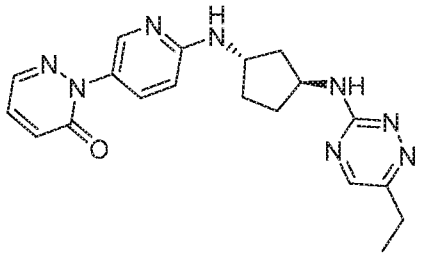
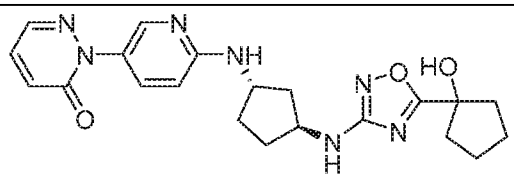
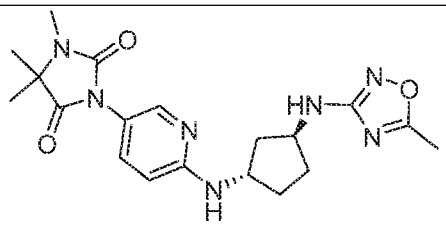
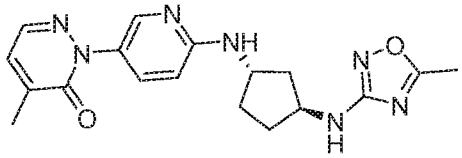
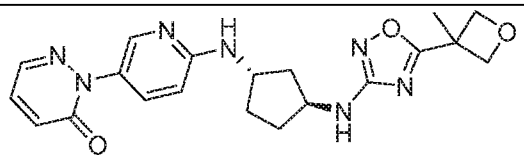
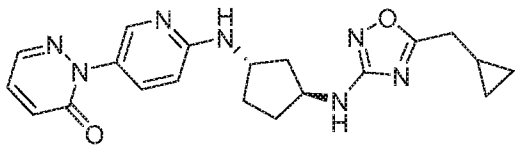
Example	Structure	Name
1		2-(6-(((1S,3S)-3-((5-methyl-1,2,4-oxadiazol-3-yl)amino) cyclopentyl) amino) pyridin-3-yl) pyridazin-3(2H)-one

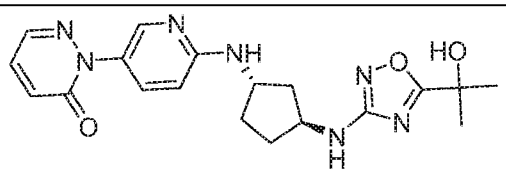
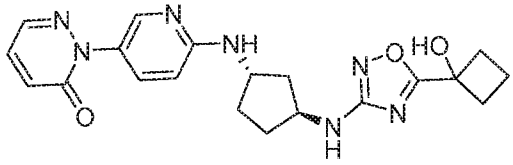
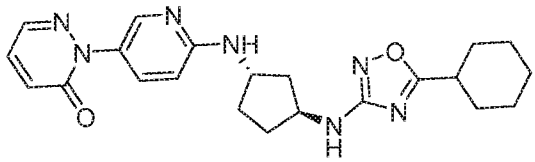
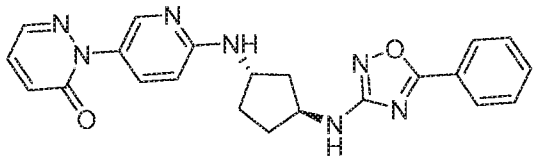
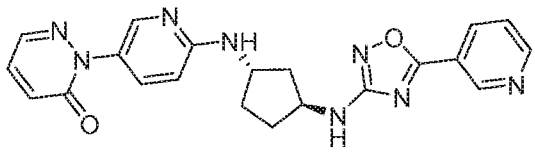
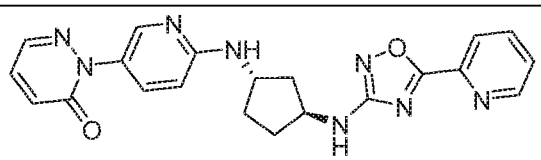
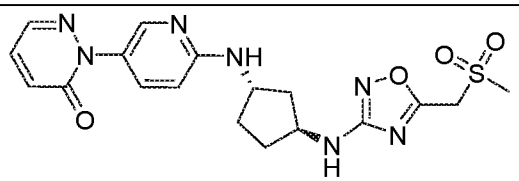
2		2-(6-(((1S,3S)-3-((5-cyclopropyl-1,2,4-oxadiazol-3-yl)amino) cyclopentyl) amino)pyridin-3-yl) pyridazin-3(2H)-one
3		2-(6-(((1S,3S)-3-((5-(1,1-difluoroethyl)-1,2,4-oxadiazol-3-yl) amino) cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one
4		2-(6-(((1S,3S)-3-((5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one
5		2-(6-(((1S,3S)-3-((5-cyclobutyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one
6		2-(6-(((1S,3S)-3-((5-(1-methylcyclopropyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one
7		2-(6-(((1S,3S)-3-((5-isopropyl-1,2,4-oxadiazol-3-yl)amino) cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one
8		2-(6-(((1S,3S)-3-((5-(1-fluorocyclopropyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one
9		2-(6-(((1S,3S)-3-((3-phenyl-1,2,4-thiadiazol-5-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one

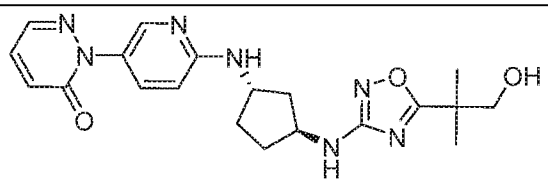
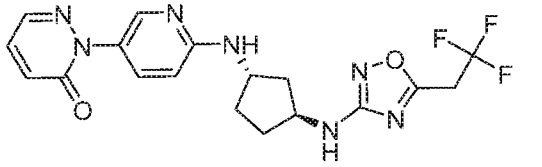
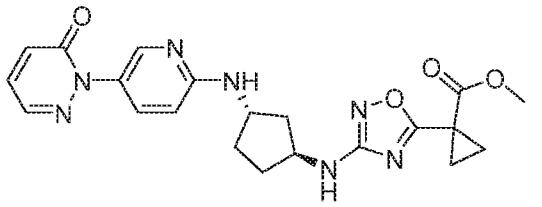
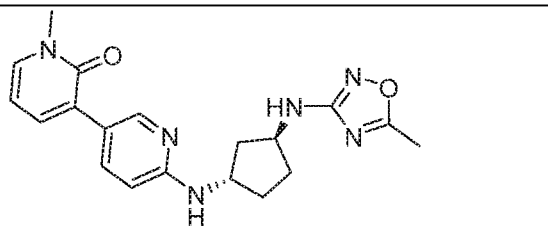
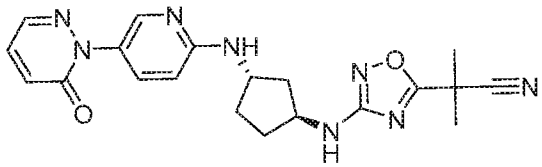
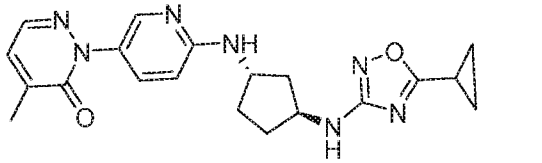
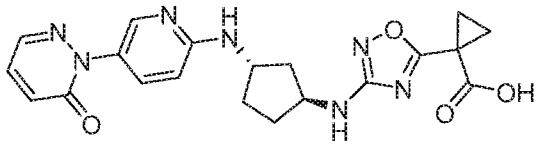
10		1-methyl-3-(6-(((1S,3S)-3-((5-methyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)imidazolidine-2,4-dione
11		2-(6-(((1S,3S)-3-((5-cyclopentyl-1,2,4-oxadiazol-3-yl)amino) cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one
12		2-(6-(((1S,3S)-3-((5-(tert-butyl)-1,2,4-oxadiazol-3-yl)amino) cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one
13		2-(6-(((1S,3S)-3-((5-(3-hydroxycyclobutyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one
14		2-(6-(((1S,3S)-3-((5-ethyl-1,2,4-oxadiazol-3-yl)amino) cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one
15		2-(6-(((1S,3S)-3-((5-(1-(trifluoromethyl)cyclopropyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one
16		2-(6-(((1S,3S)-3-((3-chloro-1,2,4-thiadiazol-5-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one
17		2-(6-(((1S,3S)-3-((3-cyclopropyl-1,2,4-thiadiazol-5-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one

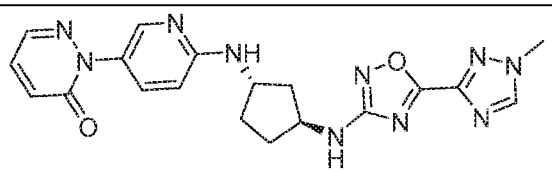
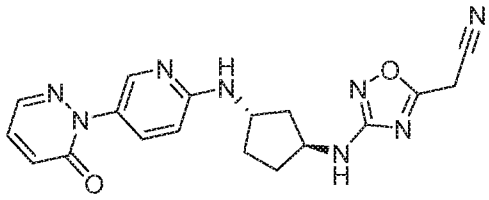
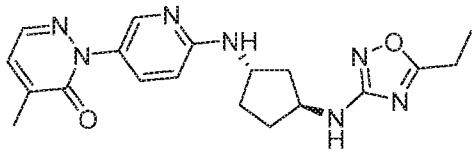
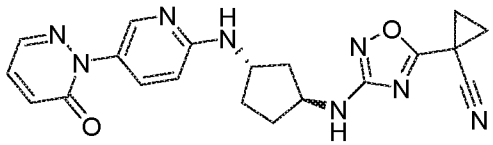
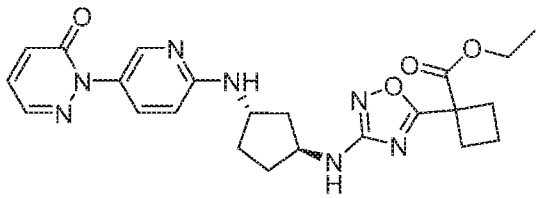
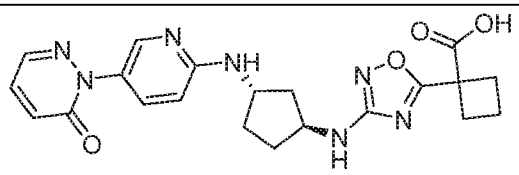
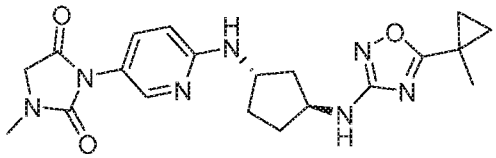
18		2-(6-(((1S,3S)-3-((2H-tetrazol-5-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one
19		2-(6-(((1S,3S)-3-((5-methyl-1,3,4-oxadiazol-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one
20		1-(6-(((1S,3S)-3-((5-methyl-1,2,4-oxadiazol-3-yl)amino) cyclopentyl)amino)pyridin-3-yl)pyrrolidin-2-one
21		3-methyl-1-(6-(((1S,3S)-3-((5-methyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)imidazolidine-2,4-dione
22		2-(6-(((1S,3S)-3-((5-(1-hydroxycyclopentyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one
23		6'-(((1S,3S)-3-((5-methyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one
24		2-(6-(((1S,3S)-3-((5-cyclopropyl-1,2,4-thiadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one

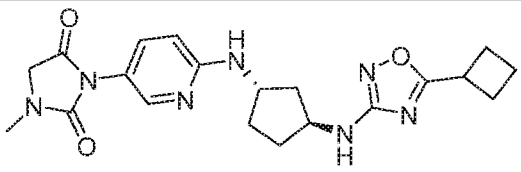
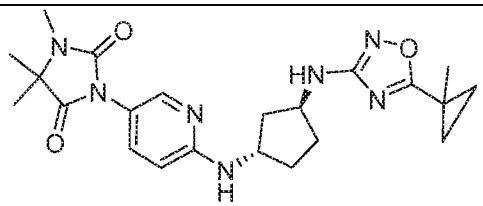
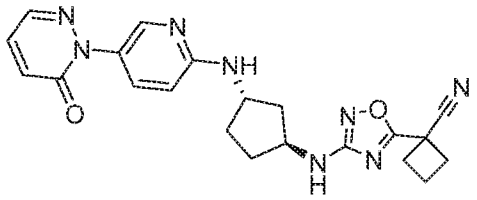
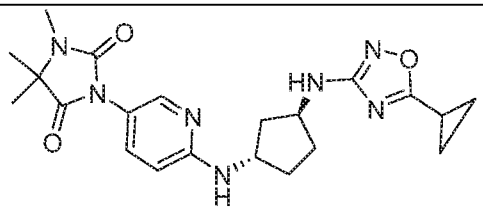
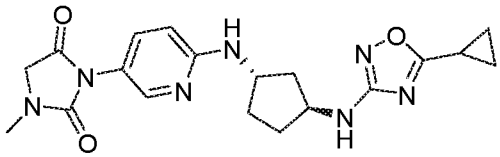
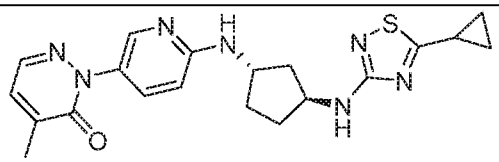
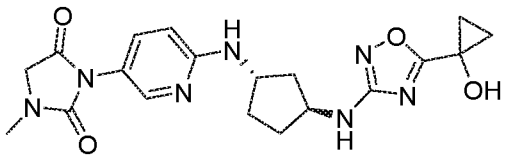
25		2-(6-(((1S,3S)-3-((5-(4-fluorophenyl)-1,2,4-thiadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one
26		2-(6-(((1S,3S)-3-((5-(1-hydroxycyclopropyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one
27		2-(6-(((1S,3S)-3-((5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one
29		2-(6-(((1S,3S)-3-((6-methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one
30		4-methyl-2-(6-(((1S,3S)-3-((6-methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one
31		2-(6-(((1S,3S)-3-((6-cyclopropyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one
32		2-(6-(((1S,3S)-3-((6-cyclopropyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-4-methylpyridazin-3(2H)-one

33		2-(6-(((1S,3S)-3-((6-ethyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-4-methylpyridazin-3(2H)-one
34		2-(6-(((1S,3S)-3-((6-ethyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one
35		2-(6-(((1S,3S)-3-((5-(1-hydroxycyclopentyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one
36		1,5,5-trimethyl-3-(6-(((1S,3S)-3-((5-methyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)imidazolidine-2,4-dione
37		4-methyl-2-(6-(((1S,3S)-3-((5-methyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one
38		2-(6-(((1S,3S)-3-((5-(3-methyloxetan-3-yl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one
39		2-(6-(((1S,3S)-3-((5-(cyclopropylmethyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one

40		2-(6-(((1S,3S)-3-((5-(2-hydroxypropan-2-yl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one
41		2-(6-(((1S,3S)-3-((5-(1-hydroxycyclobutyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one
42		2-(6-(((1S,3S)-3-((5-cyclohexyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one
43		2-(6-(((1S,3S)-3-((5-phenyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one
44		2-(6-(((1S,3S)-3-((5-(pyridin-3-yl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one
45		2-(6-(((1S,3S)-3-((5-(pyridin-2-yl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one
46		2-(6-(((1S,3S)-3-((5-((methylsulfonyl)methyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one

47		2-(6-(((1S,3S)-3-((5-(1-hydroxy-2-methylpropan-2-yl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one
48		2-(6-(((1S,3S)-3-((5-(2,2,2-trifluoroethyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one
49		methyl 1-(3-(((1S,3S)-3-((5-(6-oxopyridazin-1(6H)-yl)pyridin-2-yl)amino)cyclopentyl)amino)-1,2,4-oxadiazol-5-yl)cyclopropane-1-carboxylate
50		1-methyl-6'-(((1S,3S)-3-((5-methyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)-[3,3'-bipyridin]-2(1H)-one
51		2-methyl-2-(3-(((1S,3S)-3-((5-(6-oxopyridazin-1(6H)-yl)pyridin-2-yl)amino)cyclopentyl)amino)-1,2,4-oxadiazol-5-yl)propanenitrile
52		2-(6-(((1S,3S)-3-((5-cyclopropyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-4-methylpyridazin-3(2H)-one
53		1-(3-(((1S,3S)-3-((5-(6-oxopyridazin-1(6H)-yl)pyridin-2-yl)amino)cyclopentyl)amino)-1,2,4-oxadiazol-5-yl)cyclopropane-1-carboxylic acid

54		2-(6-(((1S,3S)-3-((5-(1-methyl-1H-1,2,4-triazol-3-yl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one
55		2-(3-(((1S,3S)-3-((5-(6-oxopyridazin-1(6H)-yl)pyridin-2-yl)amino)cyclopentyl)amino)-1,2,4-oxadiazol-5-yl)acetonitrile
56		2-(6-(((1S,3S)-3-((5-ethyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-4-methylpyridazin-3(2H)-one
57		1-(3-(((1S,3S)-3-((5-(6-oxopyridazin-1(6H)-yl)pyridin-2-yl)amino)cyclopentyl)amino)-1,2,4-oxadiazol-5-yl)cyclopropane-1-carbonitrile
58		ethyl 1-(3-(((1S,3S)-3-((5-(6-oxopyridazin-1(6H)-yl)pyridin-2-yl)amino)cyclopentyl)amino)-1,2,4-oxadiazol-5-yl)cyclobutane-1-carboxylate
59		1-(3-(((1S,3S)-3-((5-(6-oxopyridazin-1(6H)-yl)pyridin-2-yl)amino)cyclopentyl)amino)-1,2,4-oxadiazol-5-yl)cyclobutane-1-carboxylic acid
60		1-methyl-3-(6-(((1S,3S)-3-((5-(1-methylcyclopropyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)imidazolidine-2,4-dione

61		3-(6-(((1S,3S)-3-((5-cyclobutyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-methylimidazolidine-2,4-dione
62		1,5,5-trimethyl-3-(6-(((1S,3S)-3-((5-(1-methylcyclopropyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)imidazolidine-2,4-dione
63		1-(3-(((1S,3S)-3-((5-(6-oxopyridazin-1(6H)-yl)pyridin-2-yl)amino)cyclopentyl)amino)-1,2,4-oxadiazol-5-yl)cyclobutane-1-carbonitrile
64		3-(6-(((1S,3S)-3-((5-cyclopropyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1,5,5-trimethylimidazolidine-2,4-dione
65		3-(6-(((1S,3S)-3-((5-cyclopropyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-methylimidazolidine-2,4-dione
66		2-(6-(((1S,3S)-3-((5-cyclopropyl-1,2,4-thiadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-4-methylpyridazin-3(2H)-one
67		3-(6-(((1S,3S)-3-((5-(1-hydroxycyclopropyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-methylimidazolidine-2,4-dione

[072] Additionally, Applicants have surprisingly and unexpectedly found that compounds of Formula (I) exhibit low or no inhibition of the human Ether-a-go-go-Related Gene (hERG). As discussed herein, some aspects of cardiovascular toxicity of a compound can be measured using a hERG assay. The hERG gene encodes the inward rectifying voltage gated potassium channel in the heart known as $K_v11.1$, which is involved in cardiac repolarization. Inhibition of the hERG current causes QT interval prolongation resulting in potentially fatal ventricular tachyarrhythmia. hERG inhibition an important antitarget that must be avoided. In some embodiments, compounds of Formula I exhibited no measurable hERG inhibition. This lack of cardiovascular toxicity by the compounds of Formula I is surprising and unexpected, especially considering the inhibition of hERG by 2-(6-(((1S,3S)-3-((5-cyclopropylpyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one and 3-(6-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-methylimidazolidine-2,4-dione.

[073] As used herein, the terms "salt" or "salts" refers to an acid addition or base addition salt of a compound of the present disclosure. "Salts" include in particular "pharmaceutical acceptable salts". The term "pharmaceutically acceptable salts" refers to salts that retain the biological effectiveness and properties of the compounds of this disclosure and, which typically are not biologically or otherwise undesirable. In many cases, the compounds of the present disclosure are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto. When both a basic group and an acid group are present in the same molecule, the compounds of the present disclosure may also form internal salts, e.g., zwitterionic molecules.

[074] Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids.

[075] Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like.

[076] Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, sulfosalicylic acid, and the like.

[077] Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases.

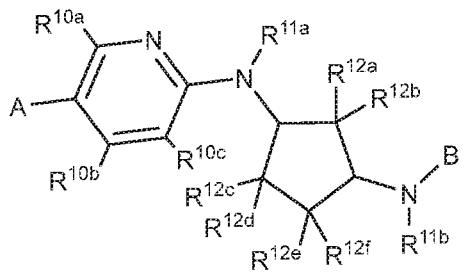
[078] Inorganic bases from which salts can be derived include, for example, ammonium salts and metals from columns I to XII of the periodic table. In certain embodiments, the salts are derived from sodium, potassium, ammonium, calcium, magnesium, iron, silver, zinc, and copper; particularly suitable salts include ammonium, potassium, sodium, calcium and magnesium salts.

[079] Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like. Certain organic amines include isopropylamine, benzathine, cholinate, diethanolamine, diethylamine, lysine, meglumine, piperazine and tromethamine.

[080] In another aspect, the present disclosure provides compounds of the present disclosure in acetate, ascorbate, adipate, aspartate, benzoate, besylate, bromide/hydrobromide, bicarbonate/carbonate, bisulfate/sulfate, camphorsulfonate, caprate, chloride/hydrochloride, chlortheophyllonate, citrate, ethandisulfonate, fumarate, gluceptate, gluconate, glucuronate, glutamate, glutarate, glycolate, hippurate, hydroiodide/iodide, isethionate, lactate, lactobionate, laurylsulfate, malate, maleate, malonate, mandelate, mesylate, methylsulphate, mucate, naphthoate, napsylate, nicotinate, nitrate, octadecanoate, oleate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, polygalacturonate, propionate, sebacate, stearate, succinate, sulfosalicylate, sulfate, tartrate, tosylate trifenatate, trifluoroacetate or xinafoate salt form.

[081] Any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulae given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Isotopes that can be incorporated into compounds of the disclosure include, for example, isotopes of hydrogen.

[082] In another aspect, the disclosure provides a compound of formula (Ia)



(Ia)

or a pharmaceutically acceptable salt thereof, wherein

each R^{10a}, R^{10b}, R^{10c}, R^{11a}, R^{11b}, R^{12a}, R^{12b}, R^{12c}, R^{12d}, R^{12e} and R^{12} is independently selected from H or deuterium; and A and B are as defined herein.

[083] Further, incorporation of certain isotopes, particularly deuterium (i.e., ^{2}H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements or an improvement in therapeutic index or tolerability. It is understood that deuterium in this context is regarded as a substituent of a compound of the present disclosure. The

concentration of deuterium, may be defined by the isotopic enrichment factor. The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope. If a substituent in a compound of this disclosure is denoted as being deuterium, such compound has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation). It should be understood that the term “isotopic enrichment factor” can be applied to any isotope in the same manner as described for deuterium.

[084] Other examples of isotopes that can be incorporated into compounds of the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F ^{31}P, ^{32}P, ^{35}S, ^{36}Cl, ^{123}I, ^{124}I, ^{125}I respectively. Accordingly it should be understood that the disclosure includes compounds that incorporate one or more of any of the aforementioned isotopes, including for example, radioactive isotopes, such as ^{3}H and ^{14}C, or those into which non-radioactive isotopes, such as ^{2}H and ^{13}C are present. Such isotopically labelled compounds are useful in metabolic studies (with ^{14}C), reaction kinetic studies (with, for example ^{2}H or ^{3}H), detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F or labeled compound may be particularly desirable for PET or SPECT studies. Isotopically-labeled compounds of the present disclosure can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.

[085] Any asymmetric atom (e.g., carbon or the like) of the compound(s) of the present disclosure can be present in racemic or enantiomerically enriched, for example the (*R*)-, (*S*)- or (*R,S*)- configuration. In certain embodiments, each asymmetric atom has at least 50 % enantiomeric excess, at least 60 % enantiomeric excess, at least 70 % enantiomeric excess, at least 80 % enantiomeric excess, at least 90 % enantiomeric excess, at least 95 % enantiomeric excess, or at least 99 % enantiomeric excess in the (*R*)- or (*S*)- configuration. Substituents at atoms with unsaturated double bonds may, if possible, be present in *cis*- (*Z*)- or *trans*- (*E*)- form.

[086] Accordingly, as used herein a compound of the present disclosure can be in the form of one of the possible stereoisomers, rotamers, atropisomers, tautomers or mixtures thereof, for example, as

substantially pure geometric (*cis* or *trans*) stereoisomers, diastereomers, optical isomers (antipodes), racemates or mixtures thereof.

[087] Any resulting mixtures of stereoisomers can be separated on the basis of the physicochemical differences of the constituents, into the pure or substantially pure geometric or optical isomers, diastereomers, racemates, for example, by chromatography and/or fractional crystallization.

[088] Any resulting racemates of compounds of the present disclosure or of intermediates can be resolved into the optical antipodes by known methods, *e.g.*, by separation of the diastereomeric salts thereof, obtained with an optically active acid or base, and liberating the optically active acidic or basic compound. In particular, a basic moiety may thus be employed to resolve the compounds of the present disclosure into their optical antipodes, *e.g.*, by fractional crystallization of a salt formed with an optically active acid, *e.g.*, tartaric acid, dibenzoyl tartaric acid, diacetyl tartaric acid, di-*O,O'*-*p*-toluoyl tartaric acid, mandelic acid, malic acid or camphor-10-sulfonic acid. Racemic compounds of the present disclosure or racemic intermediates can also be resolved by chiral chromatography, *e.g.*, high pressure liquid chromatography (HPLC) using a chiral adsorbent.

Pharmaceutical Compositions

[089] In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound of the present disclosure, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers. In a further embodiment, the composition comprises at least two pharmaceutically acceptable carriers, such as those described herein.

[090] In some embodiments, pharmaceutical composition further comprises at least one additional pharmaceutically active agent. In some embodiments, the additional pharmaceutically active agent is selected from hypolipidemic agents, niacin and analogs thereof, bile acid sequestrants, a thyroid hormone mimetic, thyroid hormone receptor (THR) β-selective agonist, a microsomal triglyceride transfer protein (MTP) inhibitor, an acyl CoA:diacylglycerol acyltransferase 1 (DGAT1) inhibitor, a Niemann Pick C1-like 1 (NPC1-L 1) inhibitor, an agonist of ATP Binding Cassette (ABC) proteins G5 or G8, an inhibitory nucleic acid targeting PCSK9, an inhibitory nucleic acid targeting Lp(a), an inhibitory nucleic acid targeting apoB 100, apoA-I up-regulator/inducer, ABCA 1 stabilizer or inducer, phospholipid transfer protein (PL TP) inhibitor, fish oil, anti-diabetic agent, anti-obesity agent, agonists of peroxisome proliferator-activator receptors, ATP citrate lyase (ACL) inhibitor, and anti-hypertensive agents, an antibody targeting PCSK9, an immune checkpoint inhibitor and combinations thereof. In certain preferred embodiments, the additional pharmaceutically active agent is selected from bempedoic acid, statins, ezetimibe, inclisiran, pelacarsen, evolocumab, PD-1, PD-L1, PD-L2 and combinations thereof

[091] The pharmaceutical composition can be formulated for particular routes of administration such as oral administration, parenteral administration (e.g. by injection, infusion, transdermal or topical administration), and rectal administration. Topical administration may also pertain to inhalation or intranasal application. The pharmaceutical compositions of the present disclosure can be made up in a solid form (including, without limitation, capsules, tablets, pills, granules, powders or suppositories), or in a liquid form (including, without limitation, solutions, suspensions or emulsions). Tablets may be either film coated or enteric coated according to methods known in the art. Typically, the pharmaceutical compositions are tablets or gelatin capsules comprising the active ingredient together with one or more of:

a) diluents, *e.g.*, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine;

b) lubricants, *e.g.*, silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also

c) binders, *e.g.*, magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone; if desired

d) disintegrants, *e.g.*, starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and

e) absorbents, colorants, flavors and sweeteners.

[092] Liquid, particularly injectable, compositions can, for example, be prepared by dissolution, dispersion, etc. For example, the disclosed compound is dissolved in or mixed with a pharmaceutically acceptable solvent such as, for example, water, saline, aqueous dextrose, glycerol, ethanol, and the like, to thereby form an injectable isotonic solution or suspension. Proteins such as albumin, chylomicron particles, or serum proteins can be used to solubilize the disclosed compounds.

[093] The disclosed compounds can be also formulated as a suppository that can be prepared from fatty emulsions or suspensions; using polyalkylene glycols such as propylene glycol, as the carrier.

[094] Parental injectable administration is generally used for subcutaneous, intramuscular or intravenous injections and infusions. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions or solid forms suitable for dissolving in liquid prior to injection.

[095] Compositions can be prepared according to conventional mixing, granulating or coating methods, respectively, and the present pharmaceutical compositions can contain from about 0.1% to about 99%, from about 5% to about 90%, or from about 1% to about 20% of the disclosed compound by weight or volume.

[096] The dosage regimen utilizing the disclosed compound is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal or hepatic function of the patient; and the particular disclosed compound employed. A physician or veterinarian of ordinary skill in the art can

readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

[097] The pharmaceutical composition or combination of the present disclosure may, for example, be in unit dosage of about 1-1000 mg of active ingredient(s) for a subject of about 50-70 kg. In one embodiment, the compositions are in the form of a tablet that can be scored. The therapeutically effective dosage of a compound, the pharmaceutical composition, or the combinations thereof, is dependent on the species of the subject, the body weight, age and individual condition, the disorder or disease or the severity thereof being treated.

[098] Embodiment 34. A pharmaceutical composition comprising a compound according to any one of embodiments 1 to 33 or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers.

[099] Embodiment 35. The pharmaceutical composition of embodiment 34, further comprising at least one additional pharmaceutically active agent.

[100] Embodiment 36. The pharmaceutical composition of embodiment 35, wherein the additional pharmaceutically active agent is selected from hypolipidemic agents, niacin and analogs thereof, bile acid sequestrants, a thyroid hormone mimetic, thyroid hormone receptor (THR) β-selective agonist, a microsomal triglyceride transfer protein (MTP) inhibitor, an acyl CoA:diacylglycerol acyltransferase 1 (DGAT1) inhibitor, a Niemann Pick C1-like 1 (NPC1-L 1) inhibitor, an agonist of ATP Binding Cassette (ABC) proteins G5 or G8, an inhibitory nucleic acid targeting PCSK9 protein expression, an inhibitory nucleic acid targeting Lp(a) protein expression, an inhibitory nucleic acid targeting apoB 100, apoA-I up-regulator/inducer, ABCA 1 stabilizer or inducer, phospholipid transfer protein (PL TP) inhibitor, fish oil, anti-diabetic agent, anti-obesity agent, agonists of peroxisome proliferator-activator receptors, ATP citrate lyase (ACL) inhibitor, and anti-hypertensive agents, an antibody targeting PCSK9, an immune checkpoint inhibitor and combinations thereof.

Activity of the Compounds

[101] The activity of compounds according to the present disclosure as PCSK9 inhibitors can be assessed using a time resolved fluorescence resonance energy transfer (TR-FRET) assay. This TR-FRET assay measures the ability of a compounds of the present disclosure to compete for binding with Alexa Fluor 647 labeled probe in a known region of human PCSK9. The assay provides measures of both potency (IC50) and efficacy (Amax).

[102] Solutions of varying concentrations are prepared by diluting a compound of the disclosure in dimethylsulfoxide (DMSO) and the resulting solutions are pipetted into a plate. DMSO is used as a no displacement inactive control. An intermediate plate is prepared in by transferring a known amount of

each compound solution and of the control from the compound plate into a corresponding well containing assay buffer and mixing thoroughly. A third plate is then prepared to be used for the assay by adding Terbium labeled human PCSK9, followed by a known amount of each solution from the intermediate plate. Unlabeled human PCSK9 in assay buffer containing DMSO is used as a control for the assay. Following incubation, Alexa Fluor 647 labeled probe is added to each well of the assay plate and the resulting mixture is incubated for an additional period of time. The TR-FRET signal is measured and the FRET ratio (FRET/Terbium) is used to calculate the IC_{50} and Amax of the compounds.

Method of Synthesizing the Compounds

[103] The compounds of the present disclosure may be made by a variety of methods, including standard chemistry. Suitable synthetic routes are depicted in the Schemes given below.

[104] The compounds of Formula (I) may be prepared by methods known in the art of organic synthesis as set forth in part by the following synthetic schemes. In the schemes described below, it is well understood that protecting groups for sensitive or reactive groups are employed where necessary in accordance with general principles or chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York 1999). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art. The selection processes, as well as the reaction conditions and order of their execution, shall be consistent with the preparation of compounds of Formula (I).

[105] Those skilled in the art will recognize if a stereocenter exists in the compounds of Formula (I). Accordingly, the present disclosure includes both possible stereoisomers (unless specified in the synthesis) and includes not only racemic compounds but the individual enantiomers and/or diastereomers as well. When a compound is desired as a single enantiomer or diastereomer, it may be obtained by stereospecific synthesis or by resolution of the final product or any convenient intermediate. Resolution of the final product, an intermediate, or a starting material may be affected by any suitable method known in the art. See, for example, "Stereochemistry of Organic Compounds" by E. L. Eliel, S. H. Wilen, and L. N. Mander (Wiley-Interscience, 1994).

[106] The compounds described herein may be made from commercially available starting materials or synthesized using known organic, inorganic, and/or enzymatic processes.

Methods of Use

[107] In yet another aspect, the present disclosure is directed to a method of treating or preventing a disease or disorder comprising administering to a patient in need thereof an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof or a pharmaceutical composition

comprising a compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier.

[108] In another aspect, the disclosure is directed to a method of modulating PCSK9 comprising administering to a patient in need thereof a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[109] In another aspect, the disclosure is directed to a method of inhibiting PCSK9. The method involves administering to a patient in need thereof an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[110] Another aspect of the disclosure relates to a method of treating, preventing, inhibiting, or eliminating a disease or disorder in which PCSK9 plays a role. The method comprises administering to a patient in need of a treatment for diseases or disorders in which PCSK9 plays a role an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[111] Another aspect of the present disclosure relates to a method of treating, preventing, inhibiting, or eliminating a disease or disorder in a patient associated with the inhibition of PCSK9, the method comprising administering to a patient in need thereof an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[112] In another aspect, the present disclosure relates to a method of treating, preventing, inhibiting, or eliminating a PCSK9-mediated disease or disorder. The method comprises administering to a patient in need of a treatment for a PCSK9-mediated disease or disorder an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, or tautomer thereof, or a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier.

[113] In another aspect, the present disclosure relates to a method of reducing Lp(a), reducing Lp(a) plasma levels, reducing Lp(a) serum levels, reducing serum TRL or LDL levels, reducing serum triglyceride levels, reducing LDL-C, reducing total plasma apoB concentrations, reducing LDL apoB, reducing TRL apoB, or reducing non HDL-C. The method comprises administering to a patient in need thereof an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[114] In another aspect, the present disclosure relates to a compound of Formula (I), or a pharmaceutically acceptable salt thereof for use a medicament.

[115] Another aspect of the present disclosure relates to a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier for use in the treatment, prevention, inhibition, or elimination of a PCSK9-mediated disease or disorder.

[116] In another aspect, the present disclosure relates to a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt, thereof, and a pharmaceutically acceptable carrier for use in the treatment, prevention, inhibition, or elimination of a disease or disorder in which PCSK9 plays a role.

[117] In another aspect, the present disclosure relates to a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt, thereof, and a pharmaceutically acceptable carrier for use in the treatment, prevention, inhibition, or elimination of a disease or disorder , wherein the disease or disorder is selected from hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, sitosterolemia, atherosclerosis, arteriosclerosis, coronary heart disease, peripheral vascular disease, vascular inflammation, xanthoma, peripheral arterial disease, , elevated Lp(a), elevated LDL, elevated TRL, and elevated triglycerides. In another aspect, the present disclosure relates to a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt, thereof, and a pharmaceutically acceptable carrier for use in the treatment, prevention, inhibition, or elimination of a disease or disorder , the disease or disorder is selected from sepsis, psoriasis, psoriasis and cancer.

[118] Another aspect of the present disclosure relates to the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier in the manufacture of a medicament for treating of a PCSK9-mediated disease or disorder.

[119] Another aspect of the present disclosure relates to a compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, or tautomer thereof, or a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable thereof, and a pharmaceutically acceptable carrier for use in the treatment, prevention, inhibition, or elimination of hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, sitosterolemia, atherosclerosis, arteriosclerosis, coronary heart disease, peripheral vascular disease, vascular inflammation, xanthoma, peripheral arterial disease, elevated Lp(a), elevated LDL, elevated TRL, and elevated triglycerides.

Another aspect of the present disclosure relates to a compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, or tautomer thereof, or a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable thereof, and a pharmaceutically acceptable carrier for use in the treatment, prevention, inhibition, or elimination of sepsis, psoriasis, and cancer.

[120] Another aspect of the present disclosure relates to a compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, or tautomer thereof, or a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier for use in the manufacture of a medicament for treating a disease in which PCSK9 plays a role.

[121] In another aspect, the present disclosure relates to the use of a compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, or tautomer thereof, or a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier in the manufacture of a medicament treating a PCSK9-mediated disease or disorder.

[122] In another aspect, the present disclosure relates to the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier in the manufacture of a medicament for treating, preventing, inhibiting, or eliminating hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, sitosterolemia, atherosclerosis, arteriosclerosis, coronary heart disease, peripheral vascular disease, vascular inflammation, xanthoma, peripheral arterial disease, elevated Lp(a), elevated LDL, elevated TRL, and elevated triglycerides. In another aspect, the present disclosure relates to the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier in the manufacture of a medicament for treating, preventing, inhibiting, or eliminating sepsis, psoriasis, and cancer.

[123] In certain embodiments, the disease or disorder is a PCSK9-mediated disease or disorder. In some embodiments, the PCSK9-mediated disease or disorder is selected from hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, sitosterolemia, atherosclerosis, arteriosclerosis, coronary heart disease, peripheral vascular disease, vascular inflammation, xanthoma, peripheral arterial disease, elevated Lp(a), elevated LDL, elevated TRL, and elevated triglycerides. In some embodiments, the PCSK9-mediated disease or disorder is selected from sepsis, psoriasis, and cancer.

[124] In some embodiments, the disease or disorder is selected from hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, sitosterolemia, atherosclerosis, arteriosclerosis, coronary heart

disease, peripheral vascular disease, vascular inflammation, xanthoma, peripheral arterial disease, elevated Lp(a), elevated LDL, elevated TRL, and elevated triglycerides. In some embodiments, the disease or disorder is selected from sepsis, psoriasis, and cancer.

[125] The disclosed compounds of the disclosure can be administered in effective amounts to treat or prevent a disorder and/or prevent the development thereof in subjects.

[126] Embodiment 37. The pharmaceutical composition of any one of embodiments 34 to 36 for use in the treatment of a PCSK9-mediated disease or disorder.

[127] Embodiment 38. The pharmaceutical composition of any one of embodiments 34 to 36 for use in the treatment of a disease or disorder, wherein the disease or disorder is selected from hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, sitosterolemia, atherosclerosis, arteriosclerosis, coronary heart disease, peripheral vascular disease, vascular inflammation, xanthoma, peripheral arterial disease, elevated Lp(a), elevated LDL, elevated TRL, and elevated triglycerides.

[128] Embodiment 41. A method for treating or preventing a disease or disorder comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to any one of the embodiments 1 to 33, or a pharmaceutically acceptable salt thereof.

[129] Embodiment 42. The method of embodiment 41, wherein the disease or disorder is a PCSK9-mediated disease or disorder.

[130] Embodiment 43. The method of embodiments 42, wherein the PCSK9-mediated disease or disorder is selected from hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, sitosterolemia, atherosclerosis, arteriosclerosis, coronary heart disease, peripheral vascular disease, vascular inflammation, xanthoma, peripheral arterial disease, elevated Lp(a), elevated LDL, elevated TRL, and elevated triglycerides.

[131] Embodiment 44. A method for treating a disease or disorder comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to any one of the embodiments 1-33, or a pharmaceutically acceptable salt thereof, wherein the disease or disorder is selected from selected from hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, sitosterolemia, atherosclerosis, arteriosclerosis, coronary heart disease, peripheral vascular disease, vascular inflammation, xanthoma, peripheral arterial disease, elevated Lp(a), elevated LDL, elevated TRL, and elevated triglycerides.

[132] Embodiment 45. A method of modulating PCSK9 comprising administering to a patient in need thereof a compound of any one of embodiments 1 to 33 or a pharmaceutically acceptable salt thereof.

[133] Embodiment 46. A method of inhibiting PCSK9 comprising administering to a patient in need thereof a compound of any one of embodiments 1 to 33 or a pharmaceutically acceptable salt thereof.

[134] Embodiment 47. The method of any one of embodiments 41 to 46, wherein administering the compound is oral, parental, subcutaneous, by injection, or by infusion.

[135] Embodiment 48. A compound according to any one of embodiments 1 to 33 or a pharmaceutically acceptable salt thereof, for use as a medicament.

[136] Embodiment 49. A compound according to any one of embodiments 1 to 33 or a pharmaceutically acceptable salt thereof, for use in the treatment of a PCSK9-mediated disease or disorder.

[137] Embodiment 50. The compound of embodiment 49, wherein the PCSK9-mediated disease or disorder selected from hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, sitosterolemia, atherosclerosis, arteriosclerosis, coronary heart disease, peripheral vascular disease, vascular inflammation, xanthoma, peripheral arterial disease, elevated Lp(a), elevated LDL, elevated TRL, and elevated triglycerides.

[138] Embodiment 51. A compound according to any one of embodiments 1 to 33 or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease or disorder, wherein the disease or disorder is selected from hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, sitosterolemia, atherosclerosis, arteriosclerosis, coronary heart disease, peripheral vascular disease, vascular inflammation, xanthoma, peripheral arterial disease, elevated Lp(a), elevated LDL, elevated TRL, and elevated triglycerides.

[139] Embodiment 52. A compound according to any one of the embodiments 1 to 33, or a pharmaceutically acceptable salt thereof, for use in the manufacture of a medicament for treating of a PCSK9-mediated disease or disorder.

[140] Embodiment 53. The compound for use in the manufacture of a medicament of embodiment 52, wherein the disease or disorder is selected from hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, sitosterolemia, atherosclerosis, arteriosclerosis, coronary heart disease, peripheral vascular disease, vascular inflammation, xanthoma, peripheral arterial disease, elevated Lp(a), elevated LDL, elevated TRL, and elevated triglycerides.

[141] Embodiment 54. Use of a compound according to any one of embodiments 1 to 33, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a PCSK9-mediated disease or disorder.

[142] Embodiment 55. The use of embodiment 54, wherein said PCSK9-mediated disease or disorder selected from hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, sitosterolemia, atherosclerosis, arteriosclerosis, coronary heart disease, peripheral vascular disease, vascular inflammation, xanthoma, peripheral arterial disease, elevated Lp(a), elevated LDL, elevated TRL, and elevated triglycerides.

[143] Embodiment 56. Use of a compound according to any one of embodiments 1 to 33, or a pharmaceutically acceptable salt thereof, in the treatment of a disease or disorder, wherein the disease or disorder is selected from hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, sitosterolemia, atherosclerosis, arteriosclerosis, coronary heart disease, peripheral vascular disease, vascular inflammation, xanthoma, peripheral arterial disease, elevated Lp(a), elevated LDL, elevated TRL, and elevated triglycerides.

Combination Therapy

[144] The compounds of the disclosure can be administered in therapeutically effective amounts in a combinational therapy with one or more therapeutic agents (pharmaceutical combinations) or modalities, e.g., non-drug therapies. For example, synergistic effects can occur with other cardiovascular agents, antihypertensive agents, coronary vasodilators, and diuretic substances. Where the compounds of the application are administered in conjunction with other therapies, dosages of the co-administered compounds will of course vary depending on the type of co-drug employed, on the specific drug employed, on the condition being treated and so forth.

[145] The compounds of the present disclosure may be administered either simultaneously with, or before or after, one or more other therapeutic agent. The compound of the present disclosure may be administered separately, by the same or different route of administration, or together in the same pharmaceutical composition as the other agents. A therapeutic agent is, for example, a chemical compound, peptide, antibody, antibody fragment or nucleic acid, which is therapeutically active or enhances the therapeutic activity when administered to a patient in combination with a compound of the present disclosure.

[146] In one embodiment, the disclosure provides a product comprising a compound of the present disclosure and at least one other therapeutic agent as a combined preparation for simultaneous, separate or sequential use in therapy. In one embodiment, the therapy is the treatment of a disease or condition mediated by PCSK9. Products provided as a combined preparation include a composition comprising the compound of the present disclosure and the other therapeutic agent(s) together in the same pharmaceutical composition, or the compound of the present disclosure and the other therapeutic agent(s) in separate form, e.g. in the form of a kit.

[147] In another aspect, the disclosure includes a compound of Formula (I) or a pharmaceutically acceptable salt thereof, for use in a combination therapy. A compound, composition, medicament and compounds for use of Formula according to any one of embodiments 1 to 33 or embodiments 41 to 44, or any embodiment of Formula (I) or a pharmaceutically acceptable salt thereof, may also be used to advantage in combination with one or more other therapeutic agents.

[148] Another aspect of the disclosure is directed to pharmaceutical compositions comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable carrier, and one or more therapeutic agents. The pharmaceutical acceptable carrier may further include an excipient, diluent, or surfactant.

[149] Combination therapy includes the administration of the subject compounds in further combination with other biologically active ingredients (such as, but not limited to, a second agent such as, but not limited to, a cardiovascular agent, an adrenergic blocker, an antihypertensive agent, an angiotensin system inhibitor, an angiotensin-converting enzyme (ACE) inhibitor, a coronary vasodilator, a diuretic, or an adrenergic stimulant or a second agent that targets PCSK9) and non-drug therapies (such as, but not limited to, surgery or radiation treatment). For instance, the compounds of the application can be used in combination with other pharmaceutically active compounds, preferably compounds that are able to enhance the effect of the compounds of the application. The compounds of the application can be administered simultaneously (as a single preparation or separate preparation) or sequentially to the other drug therapy or treatment modality. In general, a combination therapy envisions administration of two or more drugs during a single cycle or course of therapy.

[150] In some embodiments, compounds of the application can be used in combination with agents known to be beneficial for reducing cholesterol, including LDL-C, non-HDL-C, triglyceride-lowering agents, and total cholesterol and/or raising HDL-C.

[151] Exemplary therapeutic agents that may be used in combination with the compounds of the disclosure, include, but are not limited to, hypolipidemic agents, niacin and analogs thereof, bile acid sequestrants, a thyroid hormone mimetic, thyroid hormone receptor (THR) β-selective agonist, a microsomal triglyceride transfer protein (MTP) inhibitor, an acyl CoA:diacylglycerol acyltransferase 1 (DGAT1) inhibitor, a Niemann Pick C1-like 1 (NPC1-L 1) inhibitor, an agonist of ATP Binding Cassette (ABC) proteins G5 or G8, an inhibitory nucleic acid targeting PCSK9 protein expression (e.g., inclisiran), an inhibitory nucleic acid targeting Lp(a) protein expression (e.g., pelacarsen, an inhibitory nucleic acid targeting apoB 100, apoA-I up-regulator/inducer, ABCA 1 stabilizer or inducer, phospholipid transfer protein (PL TP) inhibitor, fish oil, anti-diabetic agent, anti-obesity agent, agonists of peroxisome proliferator-activator receptors, ATP citrate lyase (ACL) inhibitor, and anti-hypertensive agents, an antibody targeting PCSK9 (e.g., evolocumab), an immune checkpoint inhibitor (e.g., PD-1, PD-L1, PD-L2) and combinations thereof.

[152] Examples of hypolipidemic agents that may be used in combination with the compounds of the disclosure include, but are not limited to, an HMG-CoA reductase inhibitor, squalene synthase inhibitors, LXR agonist, FXR agonist, fibrates, cholesterol absorption inhibitors, nicotinic acid bile acid binding resins, bempedoic acid, nicotinic acid and other GPR109 agonists, and aspirin.

[153] HMG-CoA reductase inhibitors (i.e., statins) are a class of drugs used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase, which plays a central role in the production of cholesterol in the liver. Increased cholesterol levels have been associated with cardiovascular diseases and statins are therefore used in the prevention of these diseases. Exemplary statins include, but are not limited to, atorvastatin, cerivastatin, compactin, dalvastatin, dihydrocompactin, fluindostatin, fluvastatin, lovastatin, pitavastatin, mevastatin, pravastatin, rivastatin, simvastatin, and velostatin, or pharmaceutically acceptable salts thereof.

[154] Fibrates or fibric acid derivatives lower triglycerides and raise HDL cholesterol. They may have little effect on LDL cholesterol. For example, Gemfibrozil or fenofibrate is prescribed for people who have very high triglycerides or who have low HDL and high triglycerides. Gemfibrozil may be used to reduce the risk of heart attack in people with coronary artery disease (CAD) who have low HDL and high triglycerides. Examples of fibrates include, but are not limited to, clofibrate, gemfibrozil, fenofibrate, ciprofibrate, and bezafibrate.

[155] Cholesterol absorption inhibitors are a class of compounds that prevents the uptake of cholesterol from the small intestine into the circulatory system, and, in turn, reduce plasma LDL-C concentrations. Increased cholesterol levels are associated with increased CVD risk; thus, cholesterol absorption inhibitors are used with the goal of reducing CVD risk. A non-limiting example of a cholesterol absorption inhibitor is Ezetimibe.

[156] Examples of bile acid sequestrants that may be used in combination with the compounds of the disclosure include, but are not limited to, cholestyramine, colestipol, and colesvelam.

[157] A non-limiting example of a thyroid hormone mimetic that may be used in combination with the compounds of the disclosure is compound KB2115.

[158] A non-limiting example of a thyroid hormone receptor (THR) β-selective agonist that may be used in combination with the compounds of the disclosure is MGL-3196.

[159] DGAT is an enzyme that catalyzes the last step in triacylglycerol biosynthesis. DGAT catalyzes the coupling of a 1,2-diacylglycerol with a fatty acyl-CoA resulting in Coenzyme A and triacylglycerol. Two enzymes that display DGAT activity have been identified: DGAT1 (acyl coA-diacylglycerol acyl transferase 1, see Cases et al, Proc. Natl. Acad. Sci. 95:13018-13023, 1998) and DGAT2 (acyl coA-diacylglycerol acyl transferase 2, see Cases et al, J. Biol. Chem. 276:38870-38876, 2001). DGAT1 and DGAT2 do not share significant protein sequence homology. Importantly, DGAT1 knockout mice are protected from high fat diet-induced weight gain and insulin resistance (Smith et al, Nature Genetics 25:87-90, 2000). The phenotype of the DGAT1 knockout mice suggests that a DGAT1 inhibitor has utility for the treatment of obesity and obesity-associated complications. DGAT1 inhibitors useful in said combination are compounds and analogs generically and specifically disclosed e.g. in WO2007/126957

and WO2009/040410, in particular in the compound claims and the final products of the working examples, the subject-matter of the final products, the pharmaceutical preparations and the claims.

[160] Examples of DGAT1 inhibitors suitable for use in combination with compounds of the present disclosure, include but are not limited to, {4-[4-(3-Methoxy-5-phenylamino-pyridin-2-yl)-phenyl]-cyclohexyl}-acetic acid, (4-{4-[5-(1-Methyl-1H-pyrazol-3-ylamino)-pyridin-2-yl]-phenyl}-cyclohexyl)-acetic acid, (4-{4-[5-(5-Fluoro-6-methoxy-pyridin-3-ylamino)-pyridin-2-yl]-phenyl}-cyclohexyl)-acetic acid, (4-{5-[5-(6-Trifluoromethyl-pyridin-3-ylamino)-pyridin-2-yl]-spirocyclohexylidenyl-1,1'-indanyl}-acetic acid, (4-{4-[5-(Benzooxazol-2-ylamino)-pyridin-2-yl]-phenyl}-cyclohexyl)-acetic acid, 4-(4-{4-[2-(3-Chlorophenylamino)-oxazol-5-yl]-phenyl}-cyclohexyl)-butyric acid, (4-{4-[5-(6-Trifluoromethyl-pyridin-3-ylamino)-pyridin-2-yl]-phenyl}-cyclohexyl)-acetic acid, (6-{4-[4-(2H-Tetrazol-5-ylmethyl)-cyclohexyl]-phenyl}-pyridazin-3-yl)-(6-trifluoromethyl-pyridin-3-yl)-amine, 3-(4-{4-[6-(6-Trifluoromethyl-pyridin-3-ylamino)-pyridazin-3-yl]-phenyl}-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one, (1-{4-[6-(3-Trifluoromethyl-phenylamino)-pyridazin-3-yl]-phenyl}-piperidin-4-yl)-acetic acid, (4-{4-[4-Methyl-6-(6-trifluoromethyl-pyridin-3-ylamino)-pyridazin-3-yl]-phenyl}-cyclohexyl)-acetic acid, (4-{4-[5-(6-Trifluoromethyl-pyridin-3-ylamino)-pyrazin-2-yl]-phenyl}-cyclohexyl)-acetic acid, 6-[5-(4-Chloro-phenyl)-[1,3,4]oxadiazol-2-yl]-2-(2,6-dichloro-phenyl)-1H-benzoimidazole, 6-(5-Cyclohexyl-[1,3,4]oxadiazol-2-yl)-2-(2,6-dichloro-phenyl)-1H-benzoimidazole, 6-(5-Butyl-[1,3,4]oxadiazol-2-yl)-2-(2,6-dichloro-phenyl)-1H-benzoimidazole, 2-(2,6-Dichloro-phenyl)-6-[5-(5-methyl-pyridin-3-yl)-[1,3,4]oxadiazol-2-yl]-1H-benzoimidazole, 6-[5-(4-Chloro-phenyl)-[1,3,4]oxadiazol-2-yl]-2-(2,6-dimethyl-4-morpholin-4-yl-phenyl)-1H-benzoimidazole, 6-[5-(4-Chloro-phenyl)-[1,3,4]oxadiazol-2-yl]-2-(3,5-dichloro-pyridin-4-yl)-1H-benzoimidazole, 3-(4-{5-[5-(4-Methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-1H-benzoimidazol-2-yl}-3,5-dimethyl-phenyl)-2,2-dimethyl-propionic acid, 3-(4-{6-[5-(4-Methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-1H-benzoimidazol-2-yl}-3,5-dimethyl-phenyl)-propionic acid, 3-(4-{6-[5-(4-methoxyphenylamino)-[1,3,4]oxadiazol-2-yl]-1H-benzimidazol-2-yl}-3,5-dimethylphenyl)-propionic acid, [3-(4-{6-[5-(4-Chloro-phenyl)-[1,3,4]oxadiazol-2-yl]-1H-benzoimidazol-2-yl}-3,5-dimethyl-phenyl)-propyl]-phosphonic acid, 2-(2,6-Dichloro-phenyl)-6-(4,5-diphenyl-oxazol-2-yl)-1H-benzoimidazole, (4-{6-[5-(4-Chloro-phenyl)-[1,3,4]oxadiazol-2-yl]-1H-benzoimidazol-2-yl}-3,5-dimethyl-phenoxy)-acetic acid, 2-(2,6-Dichloro-phenyl)-6-(5-pyrrolidin-1-yl-[1,3,4]oxadiazol-2-yl)-1H-benzoimidazole, and 3,5-Dimethyl-4-{6-[5-(4-trifluoromethyl-phenylamino)-[1,3,4]oxadiazol-2-yl]-1H-benzoimidazol-2-yl}-phenol.

[161] A non-limiting example of a Niemann Pick C1-like 1 (NPC1-L1) inhibitor that may be used in combination with the compounds of the disclosure is ezetimibe.

[162] Apolipoprotein A-I is a protein that in humans is encoded by the APOA1 gene. It has a specific role in lipid metabolism. Apolipoprotein A-I is the major protein component of high density lipoprotein

(HDL) in plasma. Chylomicrons secreted from enterocytes also contain ApoA-I but it is quickly transferred to HDL in the bloodstream. The protein promotes cholesterol efflux from tissues to the liver for excretion. It is a cofactor for lecithin cholesterolacyltransferase (LCAT) which is responsible for the formation of most plasma cholesteryl esters. Infusion of a variant of apoA-I in humans has been shown to regress atherosclerotic plaque, as assessed by intravascular ultrasound; thus, apoA-I reduces CVD risk and has the ability to both slow progression and induce regression of atherosclerosis. A non-limiting example of an apoA-I up-regulator/inducer is RVX208.

[163] ATP-binding cassette transporter, ABCA1 (member 1 of human transporter sub-family ABCA), also known as the cholesterol efflux regulatory protein (CERP) is a protein which in humans is encoded by the ABCA1 gene. This transporter is a major regulator of cellular cholesterol and phospholipid homeostasis. A non-limiting example of an ABCA1 regulator is Probucol. Probucol lowers the level of cholesterol in the bloodstream by increasing the rate of LDL catabolism. Additionally, probucol may inhibit cholesterol synthesis and delay cholesterol absorption. Probucol is a powerful antioxidant, which inhibits the oxidation of cholesterol in LDLs; this slows the formation of foam cells, which contribute to atherosclerotic plaques.

[164] The liver X receptor (LXR) is a member of the nuclear receptor family of transcription factors and is closely related to nuclear receptors such as PPAR, FXR and RXR. Liver X receptors (LXRs) are important regulators of cholesterol, fatty acids and glucose homeostasis. LXR agonists are effective for treatment of murine models of atherosclerosis, diabetes, anti-inflammation and Alzheimer's disease. Treatment with LXR agonists (including but not limited to, hypocholamide, T0901317, GW3965, or N,N-dimethyl-3-beta-hydroxy-cholenamide (DMHCA)) lowers the cholesterol level in serum and liver and inhibits the development of atherosclerosis in murine disease models. Examples of LXR agonists include, but are not limited to, GW3965 (a synthetic nonsteroidal liver X receptor (LXR) agonist/activator) and T0901317 (a dual LXR, FXR agonist).

[165] The farnesoid X receptor (FXR), also known as NR1H4 (nuclear receptor subfamily 1, group H, member 4) is a nuclear hormone receptor with activity similar to that seen in other steroid receptors such as estrogen or progesterone but more similar in form to PPAR, LXR and RXR. Activation of the nuclear receptor FXR is known to improve hyperglycemia and hyperlipidemia. A non-limiting example of a FXR agonist is GW4064 (3-(2,6-Dichlorophenyl)-4-(3'-carboxy-2-chlorostilben-4-yl)oxymethyl-5-isopropylisoxazole).

[166] Phospholipid transfer protein (PLTP) is a protein that in humans is encoded by the PLTP gene. The protein encoded by this gene is one of at least two lipid transfer proteins found in human plasma, with CETP being the other. The encoded protein transfers phospholipids from triglyceride-rich lipoproteins to HDL. In addition to regulating the size of HDL particles, this protein may be involved in

cholesterol metabolism. At least two transcript variants encoding different isoforms have been found for this gene. Because PLTP influences the metabolism of both triglyceride-rich lipoproteins and HDL, modulation of this transfer protein has the potential to alter cardiovascular disease risk.

[167] Fish oil is derived from the tissues of oily fish. Fish oils contain the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), precursors of eicosanoids that are known to have many health benefits. Fish oil and other omega-3 sources are most highly recommended for the following conditions: hypertriglyceridemia, secondary cardiovascular disease and prevention of high blood pressure. For example, Lovaza ® is used along with a low-fat and low-cholesterol diet to lower very high triglycerides (fats) in your blood. Examples of omega-3 fatty acids that may be used in combination with the compounds of the disclosure include, but are not limited to Lovaza ® and Vascepa ® (icosapent ethyl).

[168] Examples of anti-diabetic agents that may be used in combination with the compounds of the disclosure include, but are not limited to, insulin, insulin derivatives and mimetics; insulin secretagogues such as the sulfonylureas; insulinotropic sulfonylurea receptor ligands such as meglitinides, e.g., nateglinide and repaglinide; protein tyrosine phosphatase-1B (PTP-1B) inhibitors including, but not limited to, PTP-112; GSK3 (glycogen synthase kinase-3) inhibitors including, but not limited to, SB-517955, SB-4195052, SB-216763, NN-57-05441 and NN-57-05445; RXR ligands including, but not limited to, GW-0791 and AGN-194204; sodium-dependent glucose cotransporter inhibitors including, but not limited to, T-1095; glycogen phosphorylase A inhibitors including, but not limited to, BAY R3401; biguanides including, but not limited to, metformin; alpha-glucosidase inhibitors including, but not limited to, acarbose; GLP-1 (glucagon like peptide-1), GLP-1 analogs including, but not limited to, Exendin-4 and GLP-1 mimetics; and DPPIV (dipeptidyl peptidase IV) inhibitors including, but not limited to, vildagliptin; GLP-1 receptor agonists inhibitors including, but not limited to semaglutide.

[169] Examples of sulfonylureas include, but are not limited to, tolbutamide, chlorpropamide, tolazamide, acetohexamide, 4-chloro-*N*-[(1-pyrolidinylamino)carbonyl]-benzenesulfonamide (glycopyramide), glibenclamide (glyburide), gliclazide, 1-butyl-3-metanilylurea, carbutamide, glibonuride, glipizide, gliquidone, glisoxepid, glybuthiazole, glibuzole, glyhexamide, glymidine, glypinamide, phenbutamide, amaryl, and tolylcyclamide, or pharmaceutically acceptable salts thereof.

[170] DPP-IV (dipeptidyl peptidase IV) is responsible for inactivating GLP-1. More particularly, DPP-IV generates a GLP-1 receptor antagonist and thereby shortens the physiological response to GLP-1. GLP-1 is a major stimulator of pancreatic insulin secretion and has direct beneficial effects on glucose disposal.

[171] The DPP-IV inhibitor can be peptidic or, preferably, non-peptidic. Examples of DPP-IV inhibitors also include, but are not limited to, generically and specifically DPP-IV inhibitors disclosed in

WO 98/19998, DE 196 16 486 A1, WO 00/34241 and WO 95/15309, in each case in particular in the compound claims and the final products of the working examples, the subject-matter of the final products, the pharmaceutical preparations and the claims are hereby incorporated into the present application by reference to these publications.

[172] GLP-1 (glucagon like peptide-1) is an insulinotropic protein which is described, *e.g.*, by W.E. Schmidt et al. in *Diabetologia*, 28, 1985, 704-707 and in US 5,705,483. The term "GLP-1 agonists" includes variants and analogs of GLP-1(7-36)NH_2 which are disclosed in particular in U.S. 5,120,712, U.S. 5,118666, U.S. 5,512,549, WO 91/11457 and by C. Orskov, et al, in *J. Biol. Chem.*, 264 (1989) 12826. Further examples include GLP-1(7-37), in which compound the carboxy-terminal amide functionality of Arg^{36} is displaced with Gly at the 37^{th} position of the GLP-1(7-36)NH_2 molecule and variants and analogs thereof including GLN^9-GLP-1(7-37), D-GLN^9-GLP-1(7-37), acetyl LYS^9-GLP-1(7-37), LYS^{18}-GLP-1(7-37) and, in particular, GLP-1(7-37)OH, VAL^8-GLP-1(7-37), GLY^8-GLP-1(7-37), THR^8-GLP-1(7-37), MET^8-GLP-1(7-37) and 4-imidazopropionyl-GLP-1. Special preference is also given to the GLP agonist analog exendin-4, described by Greig, *et al.*, in *Diabetologia,* 1999, 42, 45-50.

[173] Also included in the definition "anti-diabetic agent" are insulin sensitivity enhancers which restore impaired insulin receptor function to reduce insulin resistance and consequently enhance the insulin sensitivity. Examples include hypoglycemic thiazolidinedione derivatives (*e.g.*, glitazone, (*S*)-((3,4-dihydro-2-(phenyl-methyl)-2*H*-1-benzopyran-6-yl)methyl-thiazolidine-2,4-dione (englitazone), 5-{[4-(3-(5-methyl-2-phenyl-4-oxazolyl)-1-oxopropyl)-phenyl]-methyl}-thiazolidine-2,4-dione (darglitazone), 5-{[4-(1-methyl-cyclohexyl)methoxy)-phenyl]methyl}-thiazolidine-2,4-dione (ciglitazone), 5-{[4-(2-(1-indolyl)ethoxy)phenyl]methyl}-thiazolidine-2,4-dione (DRF2189), 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)-ethoxy)]benzyl}-thiazolidine-2,4-dione (BM-13.1246), 5-(2-naphthylsulfonyl)-thiazolidine-2,4-dione (AY-31637), bis{4-[(2,4-dioxo-5-thiazolidinyl)methyl]phenyl}methane (YM268), 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)-2-hydroxyethoxy]benzyl}-thiazolidine-2,4-dione (AD-5075), 5-[4-(1-phenyl-1-cyclopropanecarbonylamino)-benzyl]-thiazolidine-2,4-dione (DN-108) 5-{[4-(2-(2,3-dihydroindol-1-yl)ethoxy)phenyl]methyl}-thiazolidine-2,4-dione, 5-[3-(4-chloro-phenyl])-2-propynyl]-5-phenylsulfonyl)thiazolidine-2,4-dione, 5-[3-(4-chlorophenyl])-2-propynyl]-5-(4-fluorophenyl-sulfonyl)thiazolidine-2,4-dione, 5-{[4-(2-(methyl-2-pyridinyl-amino)-ethoxy)phenyl]methyl}-thiazolidine-2,4-dione (rosiglitazone), 5-{[4-(2-(5-ethyl-2-pyridyl)ethoxy)phenyl]-methyl}thiazolidine-2,4-dione (pioglitazone), 5-{[4-((3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-yl)methoxy)-phenyl]-methyl}-thiazolidine-2,4-dione (troglitazone), 5-[6-(2-fluoro-benzyloxy)naphthalen-2-ylmethyl]-thiazolidine-2,4-dione (MCC555), 5-{[2-(2-naphthyl)-benzoxazol-5-yl]-methyl}thiazolidine-

2,4-dione (T-174) and 5-(2,4-dioxothiazolidin-5-ylmethyl)-2-methoxy-N-(4-trifluoromethyl-benzyl)benzamide (KRP297)).

[174] Examples of anti-obesity agents that may be used in combination with the compounds of the disclosure include, but are not limited to, semaglutide, GDF15, orlistat, sibutramine, phentermine and Cannabinoid Receptor 1 (CB1) antagonists e.g., rimonabant.

[175] Examples of agonists of peroxisome proliferator-activator receptors that may be used in combination with the compounds of the disclosure include, but are not limited to, fenofibrate, pioglitazone, rosiglitazone, tesaglitazar, BMS-298585, L-796449, the compounds specifically described in the patent application WO 2004/103995 i.e. compounds of examples 1 to 35 or compounds specifically listed in claim 21, or the compounds specifically described in the patent application WO 03/043985 i.e. compounds of examples 1 to 7 or compounds specifically listed in claim 19 and especially (R)-1-{4-[5-methyl-2-(4-trifluoromethyl-phenyl)-oxazol-4-ylmethoxy]-benzenesulfonyl}-2,3-dihydro-1H-indole-2-carboxylic or a salt thereof.

[176] Examples of anti-hypertensive agents that may be used in combination with the compounds of the disclosure include, but are not limited to, loop diuretics; angiotensin converting enzyme (ACE); inhibitors of the Na-K-ATPase membrane pump; neutralendopeptidase (NEP) inhibitors; ACE/NEP inhibitors; angiotensin II antagonists; renin inhibitors; β-adrenergic receptor blockers; inotropic agents; calcium channel; aldosterone receptor antagonists; and aldosterone synthase inhibitors.

[177] Examples of loop diuretics that may be used in combination with the compounds of the disclosure include, but are not limited to, ethacrynic acid, furosemide and torsemide.

[178] The term "ACE-inhibitor" (also called angiotensin converting enzyme inhibitors) includes molecules that interrupt the enzymatic degradation of angiotensin I to angiotensin II. Such compounds may be used for the regulation of blood pressure and for the treatment of congestive heart failure. Examples include, but are not limited to, alacepril, benazepril, benazeprilat, captopril, ceronapril, cilazapril, delapril, enalapril, enaprilat, fosinopril, imidapril, lisinopril, moexipril, moveltopril, perindopril, quinapril, ramipril, spirapril, temocapril, and trandolapril, or a pharmaceutically acceptable salt thereof.

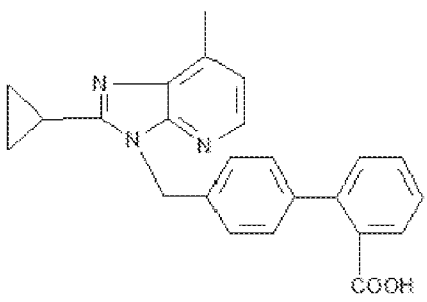
[179] A non-limiting example of an inhibitor of the Na-K-ATPase membrane pump is digoxin.

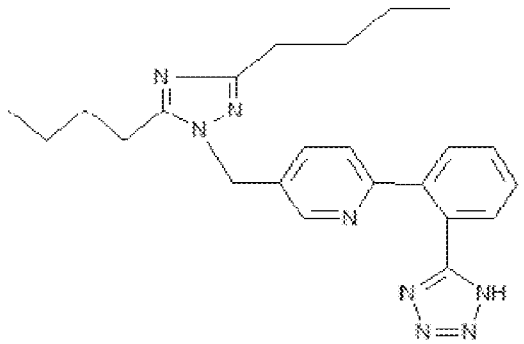
[180] The term "NEP inhibitor" refers to a compound that inhibits neutral endopeptidase (NEP). Examples include, but are not limited to, Candoxatril, Candoxatrilat, Dexecadotril, Ecadotril, Racecadotril, Sampatrilat, Fasidotril, Omapatrilat, Gemopatrilat, Daglutril, SCH-42495, SCH-32615, UK-447841, AVE-0848, PL-37, and (2R,4s)-5-Biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester, or a pharmaceutically acceptable salt thereof. NEP inhibitors also include Phosphono/biaryl substituted dipeptide derivatives, as disclosed in U.S. Patent 5,155,100. NEP inhibitors

also include N-mercaptoacyl phenylalanine derivative as disclosed in PCT application WO 2003/104200. NEP inhibitors also include dual-acting antihypertensive agents as disclosed in PCT applications WO 2008/133896, WO 2009/035543, or WO 2009/134741. Other examples include compounds disclosed in U.S. applications12/788,794; 12/788,766, and 12/947,029. NEP inhibitors also include compounds disclosed in WO 2010/136474, WO 2010/136493, WO 2011/061271, WO 2012/065953, WO 2012/065956, WO 2014/126979, and WO 2014/015965. Other examples of NEP inhibitors are compounds disclosed in WO2015116786, WO2015116760, WO2014138053, WO2014025891, WO2013184934, WO2013067163, WO2012166389, WO2012166387, WO2012112742, and WO2012082853.

[181] The term "ACE/NEP inhibitors" refers to a compound that inhibits both angiotensin converting enzyme(ACE) and neutral endopeptidase (NEP). Examples of ACE/NEP inhibitors that may be used in combination with the compounds of the disclosure include, but are not limited to, omapatrilat, sampatrilat, and fasidotril.

[182] The class of angiotensin II antagonists or AT_1 receptor antagonists comprises compounds having differing structural features, essentially preferred are the non-peptidic ones. Examples of angiotensin II antagonists that may be used in combination with the compounds of the disclosure include, but are not limited to, valsartan, losartan, candesartan, eprosartan, irbesartan, saprisartan, tasosartan, telmisartan, the compounds with the designation E-1477 and ZD-8731 of the following formulae



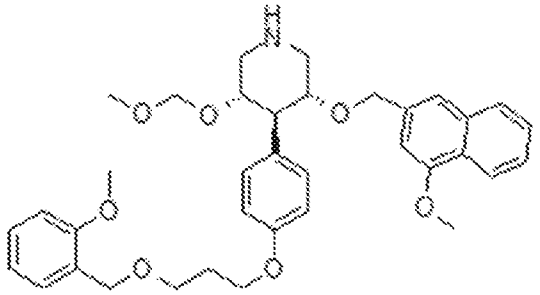


SC-52458 ZD-8731

or, in each case, a pharmaceutically acceptable salt thereof.

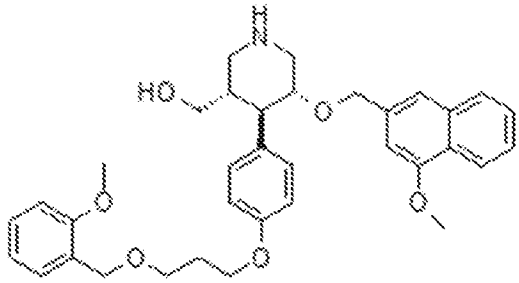
[183] The term "renin inhibitor" includes ditekiren (chemical name: [1S-[1R,2R,4R(1R,2R)]]-1-[(1,1-dimethylethoxy)carbonyl]-L-proly l-L-phenylalanyl-N-[2-hydroxy-5-methyl-1-(2-methylpropyl)-4-[[[2-methyl-1-[[(2 pyridinylmrthyl)amino]carbonyl]butyl]amino]carbonyl]hexyl]-N-alfa-methyl-L-histidinamide); terlakiren (chemical name: [R-(R,S)]-N-(4-morpholinylcarbonyl)-L-phenylalanyl-N-[1-(cyclohexylmethyl)-2-hydroxy-3-(1-methylethoxy)-3-oxopropyl]-S-methyl-L-cysteineamide); Aliskiren (chemical name: (2S,4s,5S,7S)-5-amino-N-(2-carbamoyl-2,2-dimethylethyl)-4-hydroxy-7-{[4-methoxy-

3-(3-methoxypropoxy)phenyl]methyl}-8-methyl-2-(propan-2-yl)nonanamide) and zankiren (chemical name: [1S-[1R[R(R)],2S,3r]]-N-[1-(cyclohexylmethyl)-2,3-dihydroxy-5-m ethylhexyl]-alfa-[[2-[[(4-methyl-1-piperazinyl)sulfonyl]methyl]-1-oxo-3-phenylpropyl]-amino]-4-thiazolepropanamide), or, hydrochloride salts thereof, or, SPP630, SPP635 and SPP800 as developed by Speedel, or RO 66-1132 and RO 66-1168 of Formula (A) and (B):



(A)

and



(B)

,

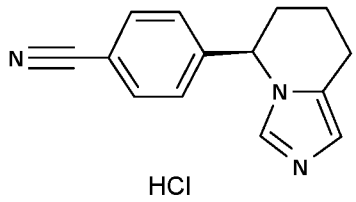
or pharmaceutically acceptable salts thereof. The term "aliskiren", if not defined specifically, is to be understood both as the free base and as a salt thereof, especially a pharmaceutically acceptable salt thereof, most preferably a hemi-fumarate salt thereof.

[184] Examples of β-adrenergic receptor blockers that may be used in combination with the compounds of the disclosure include, but are not limited to, acebutolol, atenolol, betaxolol, bisoprolol, metoprolol, nadolol, propranolol, sotalol, and timolol.

[185] Examples of inotropic agents that may be used in combination with the compounds of the disclosure include, but are not limited to, digoxin, dobutamine, and milrinone; Inotropes as used herein include, for example, dobutamine, isoproterenol, milrinone, amirinone, levosimendan, epinephrine, norepinephrine, isoproterenol, and digoxin.

[186] Examples of calcium channel blockers that may be used in combination with the compounds of the disclosure include, but are not limited to, amlodipine, bepridil, diltiazem, felodipine, nicardipine, nimodipine, nifedipine, nisoldipine and verapamil.

[187] The class of aldosterone synthase inhibitors comprises both steroidal and non-steroidal aldosterone synthase inhibitors, the latter being most preferred. The class of aldosterone synthase inhibitors comprises compounds having differing structural features. Examples of aldosterone synthase inhibitor that can be used in combination with the compounds of the present disclosure include, but are not limited to, the (+)-enantiomer of the hydrochloride of fadrozole (U.S. patents 4,617,307 and 4,889,861) of formula



or, if appropriable, a pharmaceutically acceptable salt thereof; and compounds and analogs generically and specifically disclosed e.g. in US2007/0049616, in particular in the compound claims and the final products of the working examples, the subject-matter of the final products, the pharmaceutical preparations and the claims are hereby incorporated into the present application by reference to this publication. Examples of aldosterone synthase inhibitors that can be used in combination with the compounds of the present disclosure include, but are not limited to, without limitation 4-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-5-yl)-3-methylbenzonitrile; 5-(2-chloro-4-cyanophenyl)-6,7-dihydro-5H-pyrrolo[1,2-c]imidazole-5-carboxylic acid (4-methoxybenzyl)methylamide; 4'-fluoro-6-(6,7,8,9-tetrahydro-5H-imidazo[1,5-a]azepin-5-yl)biphenyl-3-carbonitrile; 5-(4-Cyano-2-methoxyphenyl)-6,7-dihydro-5H-pyrrolo[1,2-c]imidazole-5-carboxylic acid butyl ester; 4-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-5-yl)-2-methoxybenzonitrile; 5-(2-Chloro-4-cyanophenyl)-6,7-dihydro-5H-pyrrolo[1,2-c]imidazole-5-carboxylic acid 4-fluorobenzyl ester; 5-(4-Cyano-2-trifluoromethoxyphenyl)-6,7-dihydro-5H-pyrrolo[1,2-c]imidazole-5-carboxylic acid methyl ester; 5-(4-Cyano-2-methoxyphenyl)-6,7-dihydro-5H-pyrrolo[1,2-c]imidazole-5-carboxylic acid 2-isopropoxyethyl ester; 4-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-5-yl)-2-methylbenzonitrile; 4-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-5-yl)-3-fluorobenzonitrile; 4-(6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-5-yl)-2-methoxybenzonitrile; 3-Fluoro-4-(7-methylene-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-5-yl)benzonitrile; cis-3-Fluoro-4-[7-(4-fluoro-benzyl)-5,6,7,8-tetrahydro-imidazo[1,5-a]pyridin-5-yl]benzonitrile; 4'-Fluoro-6-(9-methyl-6,7,8,9-tetrahydro-5H-imidazo[1,5-a]azepin-5-yl)biphenyl-3-carbonitrile; 4'-Fluoro-6-(9-methyl-6,7,8,9-tetrahydro-5H-imidazo[1,5-a]azepin-5-yl)biphenyl-3-carbonitrile or in each case, the (R) or (S) enantiomer thereof; or if appropriable, a pharmaceutically acceptable salt thereof.

[188] The term aldosterone synthase inhibitors also include, but are not limited to, compounds and analogs disclosed in WO2008/076860, WO2008/076336, WO2008/076862, WO2008/027284, WO2004/046145, WO2004/014914, and WO2001/076574.

[189] Furthermore, Aldosterone synthase inhibitors also include, but are not limited to, compounds and analogs disclosed in U.S. patent applications US2007/0225232, US2007/0208035, US2008/0318978, US2008/0076794, US2009/0012068, US20090048241 and in PCT applications WO2006/005726, WO2006/128853, WO2006128851, WO2006/128852, WO2007065942, WO2007/116099, WO2007/116908, WO2008/119744 and in European patent application EP 1886695.

Preferred aldosterone synthase inhibitors suitable for use in the present disclosure include, without limitation 8-(4-Fluorophenyl)-5,6-dihydro-8H-imidazo[5,1-c1[1 ,41oxazine; 4-(5,6-Dihydro-8H-imidazo[5,1-c][1 ,4]oxazin-8-yl)-2-fluorobenzonitrile; 4-(5,6-Dihydro-8H-imidazo[5,1-c][1 ,4]oxazin-8-yl)-2,6-difluorobenzonitrile; 4-(5,6-Dihydro-8H-imidazo[5,1-c][1 ,4]oxazin-8-yl)-2-methoxybenzonitrile; 3-(5,6-Dihydro-8H-imidazo[5,1-c][1 ,4]oxazin-8-yl)benzonitrile; 4-(5,6-Dihydro-8H-imidazo[5,1-c][1 ,4]oxazin-8-yl)phthalonitrile; 4-(8-(4-Cyanophenyl)-5,6-dihydro-8H-imidazo[5,1-c][1 ,4]oxazin-8-yl)benzonitrile; 4-(5,6-Dihydro-8H-imidazo[5,1-c][1 ,4]oxazin-8-yl)benzonitrile; 4-(5,6-Dihydro-8H-imidazo[5,1-c][1 ,4]oxazin-8-yl)naphthalene-1-carbonitrile; 8-[4-(1 H-Tetrazol-5-yl)phenyl1-5,6-dihvdro-8H-imidazo[5,1-c][1 ,4]oxazine as developed by Speedel or in each case, the (R) or (S) enantiomer thereof; or if appropriable, a pharmaceutically acceptable salt thereof.

[190] Aldosterone synthase inhibitors useful in said combination include, but are not limited to, compounds and analogs generically and specifically disclosed e.g. in WO 2009/156462 and WO 2010/130796, in particular in the compound claims and the final products of the working examples, the subject-matter of the final products, the pharmaceutical preparations and the claims. Preferred Aldosterone Synthase inhibitors suitable for combination in the present disclosure include, 3-(6-Fluoro-3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzonitrile hydrochloride, 1-(4-Methanesulfonyl-benzyl)-3-methyl-2-pyridin-3-yl-1H-indole, 2-(5-Benzyloxy-pyridin-3-yl)-6-chloro-1-methyl-1H-indole, 5-(3-Cyano-1-methyl-1H-indol-2-yl)-nicotinic acid ethyl ester, N-[5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-ethanesulfonamide, Pyrrolidine-1-sulfonic acid 5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-yl ester, N-Methyl-N-[5-(1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-methanesulfonamide, 6-Chloro-1-methyl-2-{5-[(2-pyrrolidin-1-yl-ethylamino)-methyl]-pyridin-3-yl}-1H-indole-3-carbonitrile, 6-Chloro-2-[5-(4-methanesulfonyl-piperazin-1-ylmethyl)-pyridin-3-yl]-1-methyl-1H-indole-3-carbonitrile, 6-Chloro-1-methyl-2-{5-[(1-methyl-piperidin-4-ylamino)-methyl]-pyridin-3-yl}-1H-indole-3-carbonitrile, Morpholine-4-carboxylic acid [5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-amide, N-[5-(6-Chloro-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-ethanesulfonamide, C,C,C-Trifluoro-N-[5-(1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-methanesulfonamide, N-[5-(3-Chloro-4-cyano-phenyl)-pyridin-3-yl]-4-trifluoromethyl-benzenesulfonamide, N-[5-(3-Chloro-4-cyano-phenyl)-pyridin-3-yl]-1-phenyl-methanesulfonamide, N-(5-(3-chloro-4-cyanophenyl)pyridin-3-yl)butane-1-sulfonamide, N-(1-(5-(4-cyano-3-methoxyphenyl)pyridin-3-yl)ethyl)ethanesulfonamide, N-((5-(3-chloro-4-cyanophenyl)pyridin-3-yl)(cyclopropyl)methyl)ethanesulfonamide, N-(cyclopropyl(5-(1H-indol-5-yl)pyridin-3-yl)methyl)ethanesulfonamide, N-(cyclopropyl(5-naphtalen-1-yl-pyridin-3-yl)methyl)ethanesulfonamide, Ethanesulfonic acid [5-(6-chloro-1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)-pyridin-3-ylmethyl]-amide and Ethanesulfonic acid {[5-(3-chloro-4-cyano-phenyl)-pyridin-3-yl]-cyclopropyl-methyl}-ethyl-amide.

[191] Lipid-lowering agents are known in the art, and described, *e.g.*, in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 11th Ed., Brunton, Lazo and Parker, Eds., McGraw-Hill (2006); *2009 Physicians' Desk Reference (PDR)*, for example, in the 63rd (2008) Eds., Thomson PDR.

[192] "Combination therapy" is intended to embrace administration of these therapeutic agents in a sequential manner, wherein each therapeutic agent is administered at a different time and in any order, or in alternation and in any order, as well as administration of these therapeutic agents, or at least two of the therapeutic agents, in a substantially simultaneous manner. Substantially simultaneous administration can be accomplished, for example, by administering to the subject a single capsule having a fixed ratio of each therapeutic agent or in multiple, single capsules for each of the therapeutic agents. Sequential or substantially simultaneous administration of each therapeutic agent can be effected by any appropriate route including, but not limited to, oral routes, intravenous routes, intramuscular routes, and direct absorption through mucous membrane tissues. The therapeutic agents can be administered by the same route or by different routes. For example, a first therapeutic agent of the combination selected may be administered by intravenous injection while the other therapeutic agents of the combination may be administered orally. Alternatively, for example, all therapeutic agents may be administered orally or all therapeutic agents may be administered by intravenous injection. The sequence in which the therapeutic agents are administered is not narrowly critical.

[193] Embodiment 39. A combination comprising of a compound according to any one of embodiments 1 to 33 or a pharmaceutically acceptable salt thereof and one or more additional pharmaceutical agents.

[194] Embodiment 40. The combination of embodiment 39, where the one or more agents additional pharmaceutically active agent is selected from hypolipidemic agents, niacin and analogs thereof, bile acid sequestrants, a thyroid hormone mimetic, thyroid hormone receptor (THR) β-selective agonist, a microsomal triglyceride transfer protein (MTP) inhibitor, an acyl CoA:diacylglycerol acyltransferase 1 (DGAT1) inhibitor, a Niemann Pick C1-like 1 (NPC1-L 1) inhibitor, an agonist of ATP Binding Cassette (ABC) proteins G5 or G8, an inhibitory nucleic acid targeting PCSK9 protein expression, an inhibitory nucleic acid targeting Lp(a) protein expression, an inhibitory nucleic acid targeting apoB 100, apoA-I up-regulator/inducer, ABCA 1 stabilizer or inducer, phospholipid transfer protein (PL TP) inhibitor, fish oil, anti-diabetic agent, anti-obesity agent, agonists of peroxisome proliferator-activator receptors, ATP citrate lyase (ACL) inhibitor, and anti-hypertensive agents, an antibody targeting PCSK9, an immune checkpoint inhibitor and combinations thereof

[195] In accordance with the foregoing, the present disclosure also provides a therapeutic combination, e.g., a kit, kit of parts, e.g., for use in any method as defined herein, comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, to be used concomitantly or in sequence with at least

one pharmaceutical composition comprising at least another therapeutic agent, selected from hypolipidemic agents, niacin and analogs thereof, bile acid sequestrants, a thyroid hormone mimetic, thyroid hormone receptor (THR) β-selective agonist, a microsomal triglyceride transfer protein (MTP) inhibitor, an acyl CoA:diacylglycerol acyltransferase 1 (DGAT1) inhibitor, a Niemann Pick C1-like 1 (NPC1-L 1) inhibitor, an agonist of ATP Binding Cassette (ABC) proteins G5 or G8, an inhibitory nucleic acid targeting PCSK9 protein expression (e.g., inclisiran), an inhibitory nucleic acid targeting Lp(a) protein expression (e.g., pelacarsen, an inhibitory nucleic acid targeting apoB 100, apoA-I up-regulator/inducer, ABCA 1 stabilizer or inducer, phospholipid transfer protein (PL TP) inhibitor, fish oil, anti-diabetic agent, anti-obesity agent, agonists of peroxisome proliferator-activator receptors, ATP citrate lyase (ACL) inhibitor, and anti-hypertensive agents, an antibody targeting PCSK9 (e.g., evolocumab), an immune checkpoint inhibitor (e.g., PD-1, PD-L1, PD-L2) and combinations thereof. The kit may comprise instructions for its administration. The combination can be a fixed combination (e.g. in the same pharmaceutical composition) or a free combination (e.g. in separate pharmaceutical compositions).

[196] Similarly, the present disclosure provides a kit of parts comprising: (i) a pharmaceutical composition of the disclosure; and (ii) a pharmaceutical composition comprising a compound selected from a hypolipidemic agents, niacin and analogs thereof, bile acid sequestrants, a thyroid hormone mimetic, thyroid hormone receptor (THR) β-selective agonist, a microsomal triglyceride transfer protein (MTP) inhibitor, an acyl CoA:diacylglycerol acyltransferase 1 (DGAT1) inhibitor, a Niemann Pick C1-like 1 (NPC1-L 1) inhibitor, an agonist of ATP Binding Cassette (ABC) proteins G5 or G8, an inhibitory nucleic acid targeting PCSK9 protein expression (e.g., inclisiran), an inhibitory nucleic acid targeting Lp(a) protein expression (e.g., pelacarsen, an inhibitory nucleic acid targeting apoB 100, apoA-I up-regulator/inducer, ABCA 1 stabilizer or inducer, phospholipid transfer protein (PL TP) inhibitor, fish oil, anti-diabetic agent, anti-obesity agent, agonists of peroxisome proliferator-activator receptors, ATP citrate lyase (ACL) inhibitor, and anti-hypertensive agents, an antibody targeting PCSK9 (e.g., evolocumab), an immune checkpoint inhibitor (e.g., PD-1, PD-L1, PD-L2) and combinations thereof, in the form of two separate units of the components (i) to (ii).

[197] Likewise, the present disclosure provides a method as defined above comprising co-administration, e.g., concomitantly or in sequence, of a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a second drug substance, said second drug substance being hypolipidemic agents, niacin and analogs thereof, bile acid sequestrants, a thyroid hormone mimetic, thyroid hormone receptor (THR) β-selective agonist, a microsomal triglyceride transfer protein (MTP) inhibitor, an acyl CoA:diacylglycerol acyltransferase 1 (DGAT1) inhibitor, a Niemann Pick C1-like 1 (NPC1-L 1) inhibitor, an agonist of ATP Binding Cassette (ABC) proteins G5 or G8, an inhibitory nucleic acid targeting PCSK9 protein expression (e.g., inclisiran), an inhibitory nucleic acid

targeting Lp(a) protein expression (e.g., pelacarsen, an inhibitory nucleic acid targeting apoB 100, apoA-I up-regulator/inducer, ABCA 1 stabilizer or inducer, phospholipid transfer protein (PL TP) inhibitor, fish oil, anti-diabetic agent, anti-obesity agent, agonists of peroxisome proliferator-activator receptors, ATP citrate lyase (ACL) inhibitor, and anti-hypertensive agents, an antibody targeting PCSK9 (e.g., evolocumab), an immune checkpoint inhibitor (e.g., PD-1, PD-L1, PD-L2) and combinations thereof, e.g., as indicated above.

Definitions

[198] Terms not specifically defined herein should be given the meanings that would be given to them by one of skill in the art in light of the disclosure and the context. For purposes of interpreting this specification, the following definitions will apply unless specified otherwise and whenever appropriate, terms used in the singular will also include the plural and vice versa.

[199] It must be noted that as used herein and in the appended claims, the singular forms "a", "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "the pharmaceutical formulation" includes reference to one or more pharmaceutical formulations; and so forth.

[200] The term "acyl", as used herein, refers to a group represented by the general formula hydrocarbylC(O)—, preferably alkylC(O)—.

[201] The term "acyloxy", as used herein, refers to a group represented by the general formula hydrocarbylC(O)O—, preferably alkylC(O)O—.

[202] The term "alkenyl", as used herein, refers to an aliphatic group containing at least one double bond and is intended to include both "unsubstituted alkenyls" and "substituted alkenyls", the latter of which refers to alkenyl moieties having substituents replacing a hydrogen on one or more carbons of the alkenyl group. Such substituents may occur on one or more carbons that are included or not included in one or more double bonds. Moreover, such substituents include all those contemplated for alkyl groups, as discussed below, except where stability is prohibitive. For example, substitution of alkenyl groups by one or more alkyl, carbocyclyl, aryl, heterocyclyl, or heteroaryl groups is contemplated. Examples of alkenyl groups include ethenyl, propenyl, *n*-butenyl, iso-butenyl, pentenyl, or hexenyl.

[203] The term "alkoxy", as used herein, refers to an alkyl group, preferably a lower alkyl group, having an oxygen attached thereto, e.g., -O(alkyl). Representative alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy, tert-butoxy and the like. Representative substituted alkoxy groups include, but are not limited to, —OCF_3 and the like.

[204] An "alkyl" group or "alkane" is a straight chained or branched non-aromatic hydrocarbon which is completely saturated. Typically, a straight chained or branched alkyl group has from 1 to about 20

carbon atoms, preferably from 1 to about 10 unless otherwise defined. Examples of straight chained and branched alkyl groups include methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, tert-butyl, pentyl, hexyl, pentyl and octyl. A C_1-C_6 straight chained or branched alkyl group is also referred to as a "lower alkyl" group. Moreover, the term "alkyl" (or "lower alkyl") as used throughout the specification, examples, and claims is intended to include both "unsubstituted alkyls" and "substituted alkyls", the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents, if not otherwise specified, can include, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxyl, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain can themselves be substituted, if appropriate. For instance, the substituents of a substituted alkyl may include substituted and unsubstituted forms of amino, azido, imino, amido, phosphoryl (including phosphonate and phosphinate), sulfonyl (including sulfate, sulfonamido, sulfamoyl and sulfonate), and silyl groups, as well as ethers, alkylthios, carbonyls (including ketones, aldehydes, carboxylates, and esters), ----CF_3, ----CN and the like. Exemplary substituted alkyls are described below. Cycloalkyls can be further substituted with alkyls, alkenyls, alkoxys, alkylthios, aminoalkyls, carbonyl-substituted alkyls, ----CF_3, ----CN, and the like.

[205] The term "alkynyl", as used herein, refers to an aliphatic group containing at least one triple bond and is intended to include both "unsubstituted alkynyls" and "substituted alkynyls", the latter of which refers to alkynyl moieties having substituents replacing a hydrogen on one or more carbons of the alkynyl group. Such substituents may occur on one or more carbons that are included or not included in one or more triple bonds. Moreover, such substituents include all those contemplated for alkyl groups, as discussed above, except where stability is prohibitive. For example, substitution of alkynyl groups by one or more alkyl, carbocyclyl, aryl, heterocyclyl, or heteroaryl groups is contemplated. Examples of alkenyl groups include ethynyl, propargyl, n-butynyl, iso-butynyl, pentynyl, or hexynyl.

[206] The term "aryl", as used herein, include substituted or unsubstituted single-ring aromatic groups in which each atom of the ring is carbon. Preferably the ring is a 5- to 7-membered ring, more preferably a 6-membered ring. The term "aryl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is aromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Aryl groups include, but are not limited to, phenyl, biphenyl, naphthyl, anthracenyl,

phenalenyl, phenanthrenyl, indanyl, indenyl, tetrahydronaphthalenyl, tetrahydrobenzoannulenyl, and the like.

[207] The term "C_{x-y}" when used in conjunction with a chemical moiety, such as, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy is meant to include groups that contain from x to y carbons in the chain. For example, the term "C_{x-y}alkyl" refers to substituted or unsubstituted saturated hydrocarbon groups, including straight-chain alkyl and branched-chain alkyl groups that contain from x to y carbons in the chain, including haloalkyl groups such as trifluoromethyl and 2,2,2-trifluoroethyl, etc. C_0 alkyl indicates a hydrogen where the group is in a terminal position, a bond if internal. The terms "C_{2-y}alkenyl" and "C_{2-y}alkynyl" refer to substituted or unsubstituted unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond respectively.

[208] The terms "carbocycle", and "carbocyclic", as used herein, refers to a saturated or unsaturated ring in which each atom of the ring is carbon. The term carbocycle includes both aromatic carbocycles and non-aromatic carbocycles. Non-aromatic carbocycles include both cycloalkane rings, in which all carbon atoms are saturated, and cycloalkene rings, which contain at least one double bond. "Carbocycle" includes 5-7 membered monocyclic and 8-12 membered bicyclic rings. Each ring of a bicyclic carbocycle may be selected from saturated, unsaturated and aromatic rings. Carbocycle includes bicyclic molecules in which one, two or three or more atoms are shared between the two rings. The term "fused carbocycle" refers to a bicyclic carbocycle in which each of the rings shares two adjacent atoms with the other ring. Each ring of a fused carbocycle may be selected from saturated, unsaturated and aromatic rings. In an exemplary embodiment, an aromatic ring, e.g., phenyl, may be fused to a saturated or unsaturated ring, e.g., cyclohexane, cyclopentane, or cyclohexene. Any combination of saturated, unsaturated and aromatic bicyclic rings, as valence permits, is included in the definition of carbocyclic. Exemplary "carbocycles" include cyclopentane, cyclohexane, bicyclo[2.2.1]heptane, 1,5-cyclooctadiene, 1,2,3,4-tetrahydronaphthalene, bicyclo[4.2.0]oct-3-ene, naphthalene and adamantane. Exemplary fused carbocycles include decalin, naphthalene, 1,2,3,4-tetrahydronaphthalene, bicyclo[4.2.0]octane, 4,5,6,7-tetrahydro-1H-indene and bicyclo[4.1.0]hept-3-ene. "Carbocycles" may be susbstituted at any one or more positions capable of bearing a hydrogen atom.

[209] A "cycloalkyl" group is a cyclic hydrocarbon which is completely saturated. "Cycloalkyl" includes monocyclic and bicyclic rings. Typically, a monocyclic cycloalkyl group has from 3 to about 10 carbon atoms, more typically 3 to 8 carbon atoms unless otherwise defined. The second ring of a bicyclic cycloalkyl may be selected from saturated, unsaturated and aromatic rings. Cycloalkyl includes bicyclic molecules in which one, two or three or more atoms are shared between the two rings. The term "fused cycloalkyl" refers to a bicyclic cycloalkyl in which each of the rings shares two adjacent atoms with the

other ring. The second ring of a fused bicyclic cycloalkyl may be selected from saturated, unsaturated and aromatic rings.

[210] The terms “halo” and “halogen”, as used herein, means halogen and includes chloro, fluoro, bromo, and iodo.

[211] The term "haloalkyl", as used herein, refers to an alkyl group substituted by one or more halo. Examples of (C_{1-6})haloalkyl include, but are not limited to, trifluoromethyl, difluoromethyl, fluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,3-dibromopropan-2-yl, 3-bromo-2-fluoropropyl and 1,4,4-trifluorobutan-2-yl.

[212] The terms “hetaralkyl” and “heteroaralkyl”, as used herein, refers to an alkyl group substituted with a hetaryl group.

[213] The term “heteroalkyl”, as used herein, refers to a saturated or unsaturated chain of carbon atoms and at least one heteroatom, wherein no two heteroatoms are adjacent.

[214] The terms “heteroaryl” and “hetaryl” include substituted or unsubstituted aromatic single ring structures, preferably 5- to 7-membered rings, more preferably 5- to 6-membered rings, whose ring structures include at least one heteroatom, preferably one to four heteroatoms, more preferably one or two heteroatoms. The terms “heteroaryl” and “hetaryl” also include polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is heteroaromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Heteroaryl groups include, but are not limited to, furyl, thienyl, pyrrolyl, pyridyl, pyridyl N-oxide, pyrazolyl, pyrimidinyl, imidazolyl, isoxazolyl, oxazolyl, oxadiazolyl, pyrazinyl, indolyl, thiophen-2-yl, quinolyl, benzopyranyl, isothiazolyl, thiazolyl, thiadiazole, indazole, benzimidazolyl, thieno[3,2-b]thiophene, triazolyl, triazinyl, imidazo[1,2-b]pyrazolyl, furo[2,3-c]pyridinyl, imidazo[1,2-a]pyridinyl, indazolyl, pyrrolo[2,3-c]pyridinyl, pyrrolo[3,2-c]pyridinyl, pyrazolo[3,4-c]pyridinyl, thieno[3,2-c]pyridinyl, thieno[2,3-c]pyridinyl, thieno[2,3-b]pyridinyl, benzothiazolyl, indolyl, indolinyl, indolinonyl, dihydrobenzothiophenyl, dihydrobenzofuranyl, benzofuran, chromanyl, thiochromanyl, tetrahydroquinolinyl, dihydrobenzothiazine, dihydrobenzoxanyl, quinolinyl, isoquinolinyl, 1,6-naphthyridinyl, benzo[de]isoquinolinyl, pyrido[4,3-b][1,6]naphthyridinyl, thieno[2,3-b]pyrazinyl, quinazolinyl, tetrazolo[1,5-a]pyridinyl, [1,2,4]triazolo[4,3-a]pyridinyl, isoindolyl, pyrrolo[2,3-b]pyridinyl, pyrrolo[3,4-b]pyridinyl, pyrrolo[3,2-b]pyridinyl, imidazo[5,4-b]pyridinyl, pyrrolo[1,2-a]pyrimidinyl, tetrahydropyrrolo[1,2-a]pyrimidinyl, 3,4-dihydro-2H-1Δ2-pyrrolo[2,1-b]pyrimidine, dibenzo[b,d]thiophene, pyridin-2-one, furo[3,2-c]pyridinyl, furo[2,3-c]pyridinyl, 1H-pyrido[3,4-b][1,4]thiazinyl, benzooxazolyl, benzoisoxazolyl, furo[2,3-b]pyridinyl, benzothiophenyl, 1,5-naphthyridinyl, furo[3,2-b]pyridine, [1,2,4]triazolo[l,5-a]pyridinyl, benzo[1,2,3]triazolyl, imidazo[1,2-a]pyrimidinyl, [1,2,4]triazolo[4,3-b]pyridazinyl, benzo[c][1,2,5]thiadiazolyl, benzo[c][1,2,5]oxadiazole,

1,3-dihydro-2H-benzo[d]imidazol-2-one, 3,4-dihydro-2H-pyrazolo[1,5-b][1,2]oxazinyl, 4,5,6,7-tetrahydropyrazolo[1,5-a]pyridinyl, thiazolo[5,4 d]thiazolyl, imidazo[2,1-b][1,3,4]thiadiazolyl, thieno[2,3-b]pyrrolyl, 3H-indolyl, indolinyl, indolinonyl, dihydrobenzothiophenyl, dihydrobenzofuran, chromanyl, thiochromanyl, tetrahydroquinolinyl, dihydrobenzothiazine,3,4-dihydro-lH-isoquinolinyl, 2,3-dihydrobenzofuran, indolinyl, indolyl, and dihydrobenzoxanyl.

[215] The term "heteroatom" as used herein means an atom of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, and sulfur.

[216] The terms "heterocyclyl", "heterocycle", and "heterocyclic" refer to substituted or unsubstituted non-aromatic ring structures, preferably 3- to 10-membered rings, more preferably 3- to 7-membered rings, whose ring structures include at least one heteroatom, preferably one to four heteroatoms, more preferably one or two heteroatoms. The terms "heterocyclyl" and "heterocyclic" also include polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is heterocyclic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Heterocyclyl groups include, for example, piperidine, piperazine, pyrrolidine, morpholine, lactones, lactams, and the like. Heterocyclyl groups can also be substituted by oxo groups. For example, "heterocyclyl" encompasses both pyrrolidine and pyrrolidinone.

[217] The term "hydroxyalkyl", as used herein, refers to an alkyl group substituted with a hydroxy group.

[218] "Haloalkyl", as used herein, refers to an alkyl group substituted with one or more halogens. Examples of haloalkyl groups include, but are not limited to, trifluoromethyl, difluoromethyl, pentafluoroethyl, trichloromethyl, etc.

[219] As used herein, the term "oxo" refers to a carbonyl group. When an oxo substituent occurs on an otherwise saturated group, such as with an oxo-substituted cycloalkyl group (e.g., 3-oxo-cyclobutyl), the substituted group is still intended to be a saturated group. When a group is referred to as being substituted by an "oxo" group, this can mean that a carbonyl moiety (i.e., —C(=O)—) replaces a methylene unit (i.e., —CH_2—).

[220] The term "optionally substituted" means that a given chemical moiety (e.g., an alky l group) can (but is not required to) be bonded other substituents (e.g., heteroatoms). For instance, an alkyl group that is optionally substituted can be a fully saturated alkyl chain (e.g., a pure hydrocarbon). Alternatively, the same optionally substituted alkyl group can have substituents different from hydrogen. For instance, it can, at any point along the chain be bounded to a halogen atom, a hydroxyl group, or any other substituent described herein. Thus, the term "optionally substituted" means that a given chemical moiety has the potential to contain other functional groups, but does not necessarily have any further

functional groups. Suitable substituents used in the optional substitution of the described groups include, without limitation, halogen, oxo, -OH, -CN, -COOH, $-CH_2CN$, $-O-(C_1-C_6)$alkyl, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkyl, (C_1-C_6)haloalkoxy, $-O-(C_2-C_6)$alkenyl, $-O-(C_2-C_6)$alkynyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, -OH, $-OP(O)(OH)_2$, $-OC(O)(C_1-C_6)$alkyl, $-C(O)(C_1-C_6)$alkyl, $-OC(O)O(C_1-C_6)$alkyl, $-NH_2$, $-NH((C_1-C_6)alkyl)$, $-N((C_1-C_6)alkyl)_2$, $-NHC(O)(C_1-C_6)$alkyl, $-C(O)NH(C_1-C_6)$alkyl, $-S(O)_2(C_1-C_6)$alkyl, $-S(O)NH(C_1-C_6)$alkyl, and $S(O)N((C_1-C_6)alkyl)_2$. The substituents can themselves be optionally substituted. "Optionally substituted" as used herein also refers to substituted or unsubstituted whose meaning is described below.

[221] The term "substituted" means that the specified group or moiety bears one or more suitable substituents wherein the substituents may connect to the specified group or moiety at one or more positions. For example, an aryl substituted with a cycloalkyl may indicate that the cycloalkyl connects to one atom of the aryl with a bond or by fusing with the aryl and sharing two or more common atoms.

[222] The term "unsubstituted" means that the specified group bears no substituents.

[223] "Pharmaceutically-acceptable acid addition salt" means those salts which retain the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulfamic acid, nitric acid, phosphoric acid, and the like, and organic acids such as acetic acid, trichloroacetic acid, trifluoroacetic acid, adipic acid, alginic acid, ascorbic acid, aspartic acid, benzenesulfonic acid, benzoic acid, 2-acetoxybenzoic acid, butyric acid, camphoric acid, camphorsulfonic acid, cinnamic acid, citric acid, digluconic acid, ethanesulfonic acid, glutamic acid, glycolic acid, glycerophosphoric acid, hemisulfic acid, heptanoic acid, hexanoic acid, formic acid, fumaric acid, 2-hydroxyethanesulfonic acid (isethionic acid), lactic acid, maleic acid, hydroxymaleic acid, malic acid, malonic acid, mandelic acid, mesitylenesulfonic acid, methanesulfonic acid, naphthalenesulfonic acid, nicotinic acid, 2-naphthalenesulfonic acid, oxalic acid, pamoic acid, pectinic acid, phenylacetic acid, 3-phenylpropionic acid, picric acid, pivalic acid, propionic acid, pyruvic acid, pyruvic acid, salicylic acid, stearic acid, succinic acid, sulfanilic acid, tartaric acid, p-toluenesulfonic acid, undecanoic acid, and the like.

[224] "Pharmaceutically-acceptable base addition salt" means those salts which retain the biological effectiveness and properties of the free acids and which are not biologically or otherwise undesirable, formed with inorganic bases such as ammonia or hydroxide, carbonate, or bicarbonate of ammonium or a metal cation such as sodium, potassium, lithium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like. Particularly preferred are the ammonium, potassium, sodium, calcium, and magnesium salts. Salts derived from pharmaceutically-acceptable organic nontoxic bases include salts of primary, secondary, and tertiary amines, quaternary amine compounds, substituted amines including

naturally occurring substituted amines, cyclic amines and basic ion-exchange resins, such as methylamine, dimethylamine, trimethylamine, ethylamine, diethylamine, triethylamine, isopropylamine, tripropylamine, tributylamine, ethanolamine, diethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, *N*-ethylpiperidine, tetramethylammonium compounds, tetraethylammonium compounds, pyridine, *N,N*-dimethylaniline, *N*-methylpiperidine, *N*-methylmorpholine, dicyclohexylamine, dibenzylamine, *N,N*-dibenzylphenethylamine, 1-ephenamine, *N,N'*-dibenzylethylenediamine, polyamine resins, and the like. Particularly preferred organic nontoxic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline, and caffeine.

[225] A "patient" or "subject" is a mammal, e.g., a human, mouse, rat, guinea pig, dog, cat, horse, cow, pig, or nonhuman primate, such as a monkey, chimpanzee, baboon or, rhesus. In certain embodiments, the subject is a primate. In yet other embodiments, the subject is a human.

[226] The terms "pharmaceutically effective amount" or "therapeutically effective amount" or "effective amount" means an amount of a compound according to the disclosure which, when administered to a patient in need thereof, is sufficient to effect treatment for disease-states, conditions, or disorders for which the compounds have utility. Such an amount would be sufficient to elicit the biological or medical response of a tissue, system, or patient that is sought by a researcher or clinician. The amount of a compound according to the disclosure which constitutes a therapeutically effective amount will vary depending on such factors as the compound and its biological activity, the composition used for administration, the time of administration, the route of administration, the rate of excretion of the compound, the duration of treatment, the type of disease-state or disorder being treated and its severity, drugs used in combination with or coincidentally with the compounds of the disclosure, and the age, body weight, general health, sex, and diet of the patient. Such a therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to their own knowledge, the prior art, and this disclosure.

[227] As used herein, the term "pharmaceutical composition" refers to a compound of the disclosure, or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, or tautomer thereof, together with at least one pharmaceutically acceptable carrier, in a form suitable for oral or parenteral administration.

[228] "Carrier" encompasses carriers, excipients, and diluents and means a material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting a pharmaceutical agent from one organ, or portion of the body, to another organ, or portion of the body of a subject.

[229] "Combination" refers to either a fixed combination in one dosage unit form, or a combined administration where a compound of the present disclosure and at least one combination partner (e.g. another drug as explained below, also referred to as "therapeutic agent" or "co-agent") may be administered independently at the same time or separately within time intervals, especially where these time intervals allow that the combination partners show a beneficial effect from the co-action of these therapeutic agents. The beneficial effect of the combination includes, but is not limited to, a cooperative, e.g., synergistic, effect and/or a pharmacokinetic or pharmacodynamic co-action, or any combination thereof, resulting from the combination of therapeutic agents. In one embodiment, administration of these therapeutic agents in combination is carried out over a defined time period (e.g., minutes, hours, days or weeks depending upon the combination selected). "

[230] The single components may be packaged in a kit or separately. One or both of the components (e.g., powders or liquids) may be reconstituted or diluted to a desired dose prior to administration. The terms "co-administration" or "combined administration" or the like as utilized herein are meant to encompass administration of the selected combination partner to a single subject in need thereof (e.g. a patient), and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time.

[231] The term "pharmaceutical combination" as used herein means a product that results from the mixing or combining of more than one therapeutic agent and includes both fixed and non-fixed combinations of the therapeutic agents. The term "fixed combination" means that the therapeutic agents, e.g., a compound of the present disclosure and a combination partner, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the therapeutic agents, e.g., a compound of the present disclosure and a combination partner, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the two compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of three or more therapeutic agents.

[232] A subject is "in need of" a treatment if such subject would benefit biologically, medically, or in quality of life from such treatment (preferably, a human).

[233] The term "PCSK9" or "proprotein convertase subtilisin/kexin type 9" interchangeably refer to a naturally-occurring human proprotein convertase belonging to the proteinase K subfamily of the secretory subtilase family. PCSK9 is synthesized as a soluble zymogen that undergoes autocatalytic intramolecular processing in the endoplasmic reticulum, and is thought to function as a proprotein convertase. PCSK9 plays a role in cholesterol homeostasis and may have a role in the differentiation of cortical neurons.

Mutations in the PCSK9 gene are a cause of autosomal dominant familial hypercholesterolemia. (Burnett and Hooper, Clin. Biochem. Rev. (2008) 29(1):11-26)

[234] As used herein, the term “inhibit”, “inhibition”, or “inhibiting” refers to the reduction or suppression of a given condition, symptom, or disorder, or disease, or a significant decrease in the baseline activity of a biological activity or process.

[235] As used herein, the term “treat”, “treating", or "treatment" of any disease or disorder refers to alleviating or ameliorating the disease or disorder (i.e., slowing or arresting the development of the disease or at least one of the clinical symptoms thereof); or alleviating or ameliorating at least one physical parameter or biomarker associated with the disease or disorder, including those which may not be discernible to the patient.

[236] As used herein, the term “prevent”, “preventing", or “prevention” of any disease or disorder refers to the prophylactic treatment of the disease or disorder; or delaying the onset or progression of the disease or disorder.

[237] “Pharmaceutically acceptable” means that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

[238] “Disorder” means, and is used interchangeably with, the terms disease, condition, or illness, unless otherwise indicated.

[239] “Administer”, “administering”, or “administration” means to either directly administering a disclosed compound or pharmaceutically acceptable salt of the disclosed compound or a composition to a subject, or administering a prodrug derivative or analog of the compound or pharmaceutically acceptable salt of the compound or composition to the subject, which can form an equivalent amount of active compound within the subject’s body.

[240] “Compounds of the present disclosure”, “Compounds of Formula (I)”, “compounds of the disclosure”, and equivalent expressions (unless specifically identified otherwise) refer to compounds of Formulae (I) and (Ia) as herein described including the salts particularly the pharmaceutically acceptable salts thereof, where the context so permits thereof, as well as all stereoisomers (including diastereoisomers and enantiomers), rotamers, tautomers, and isotopically labelled compounds (including deuterium (“D”) substitutions).

[241] In a specific embodiment, the term “about” or “approximately” means within 20%, preferably within 10%, and more preferably within 5% of a given value or range.

[242] As used herein, a "modulator of PCSK9" refers to a compound or molecule that is able to modulate PCSK9 biological activity or function, and/or downstream pathway(s) mediated by PCSK9 activity.

[243] As used herein, an "inhibitor of PCSK9" refers to a compound or molecule that is able to inhibit PCSK9 biological activity or function, and/or downstream pathway(s) mediated by PCSK9 signaling. An inhibitor of PCSK9 activity encompasses compounds that block, antagonize, suppress or reduce (to any degree including significantly) PCSK9 biological activity, including downstream pathways mediated by PCSK9 activity.

[244] As used herein, "disorders or diseases responsive to the inhibition of PCSK9," "disorders and conditions responsive to the inhibition of PCSK9," "disorders and conditions responsive to the inhibition of PCSK9 activity," "disorders responsive to the inhibition of PCSK9," "disorders responsive to the inhibition of PCSK9 activity," "disorders in which PCSK9 plays a role," "PCSK9-mediated disease or disorder" and like terms include, but are not limited to, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, sitosterolemia, atherosclerosis, arteriosclerosis, coronary heart disease, peripheral vascular disease, vascular inflammation, xanthoma, peripheral arterial disease, sepsis, cancer, psoriasis, elevated Lp(a), elevated LDL, elevated TRL, and elevated triglycerides.

[245] As used herein, "Inhibition of PCSK9 activity," or "inhibition of PCSK9," refers to a decrease in the PCSK9 activity, e.g., by administration of the compound of the disclosure.

[246] The term "hypercholesterolemia" or "dyslipidemia" includes, e.g., familial and non-familial hypercholesterolemia. Familial hypercholesterolemia (FH) is an autosomal dominant disorder characterized by elevation of serum cholesterol bound to low density lipoprotein (LDL). Familial hypercholesterolemia includes both heterozygous FH and homozygous FH. Hypercholesterolemia (or dyslipidemia) is the presence of high levels of cholesterol in the blood. It is a form of hyperlipidemia (elevated levels of lipids in the blood) and hyperlipoproteinemia (elevated levels of lipoproteins in the blood).

[247] Hyperlipidemia is an elevation of lipids in the bloodstream. These lipids include cholesterol, cholesterol esters, phospholipids and triglycerides. Hyperlipidemia includes for example, type I, IIa, IIb, III, IV and V.

[248] Hypertriglyceridemia denotes high blood levels of triglycerides. Elevated levels of triglycerides are associated with atherosclerosis, even in the absence of hypercholesterolemia, and predispose to cardiovascular disease.

[249] "Sitosterolemia" or "phytosterolemia" is a rare autosomal recessively inherited lipid metabolic disorder characterized by hyperabsorption of sitosterol from the gastrointestinal tract and decreased biliary excretion of dietary sterols (i.e., leading to hypercholesterolemia, tendon and tuberous xanthomas, premature development of atherosclerosis) and altered cholesterol synthesis.

[250] “Atherosclerosis” includes hardening of arteries associated with deposition of fatty substances, cholesterol, cellular waste products, calcium and fibrin in the inner lining of an artery. The buildup that results is called plaque.

[251] “Atherosclerosis” or “arteriosclerotic vascular disease (ASVD)” is a specific form of arteriosclerosis involving thickening, hardening and loss of elasticity of the walls of arteries as a result of invasion and accumulation of white blood cells, containing both living, active white blood cells (producing inflammation) and remnants of dead cells, including cholesterol and triglycerides. Atherosclerosis is therefore a syndrome affecting arterial blood vessels due to a chronic inflammatory response of white blood cells in the walls of arteries.

[252] “Coronary heart disease,” also known as atherosclerotic artery disease, atherosclerotic cardiovascular disease, coronary heart disease or ischemic heart disease is the most common type of heart disease and cause of heart attacks. The disease is caused by plaque building up along the inner walls of the arteries of the heart, which narrows the lumen of arteries and reduces blood flow to the heart.

[253] “Xanthoma” is a cutaneous manifestation of lipidosis in which lipids accumulate in large foam cells within the skin. Xanthomas are associated with hyperlipidemias.

[254] The term "elevated Lp(a) concentration", as used herein, refers to a serum Lp(a) concentration above 30 mg/dl (75 nmol/L). "Elevated serum Lp(a)" means a serum Lp(a) level greater than about 14 mg/dL. In certain embodiments, a patient is considered to exhibit elevated serum Lp(a) if the level of serum Lp{a) measured in the patient is greater than about 15 mg/dL, about 20 mg/dL, about 25 mg/dL, about 30 mg/dL, about 35 mg/dL, about 40 mg/dL, about 45 mg/dL, about 50 mg/dL, about 60 mg/dL, about 70 mg/dL, about 80 mg/dL, about 90 mg/dL, about 100 mg/dL, about 20 mg/dL, about 140 mg/dL, about 150 mg dL, about 180 mg/dL, or about 200 mg/dL The serum Lp(a) level can be measured in a patient post-prandial. In some embodiments, the Lp(a) level is measured after a period of time of fasting (e.g., after fasting for 8 hrs, 8 hrs, 10 hrs, 12 hrs or more). Exemplary methods for measuring serum Lp(a) in a patient include, but are not limited to, rate immunonephelometry, ELISA, nephelometry, immunoturbidimetry, and dissociation-enhanced lanthanide fluorescent immunoassay, although any clinically acceptable diagnostic method can be used in the context of the present disclosure.

[255] By “elevated triglyceride levels” or “ETL” is meant any degree of triglyceride levels that is determined to be undesirable or is targeted for modulation.

[256] “Sepsis” is a systemic reaction characterized by arterial hypotension, metabolic acidosis, decreased systemic vascular resistance, tachypnea, and organ dysfunction. Sepsis can result from septicemia (i.e., organisms, their metabolic end-products or toxins in the blood stream), including bacteremia (i.e., bacteria in the blood), as well as toxemia (i.e., toxins in the blood), including endotoxemia (i.e., endotoxin in the blood). The term "sepsis" also encompasses systemic reactions

resulting from fungemia (i.e., fungi in the blood), viremia (i.e., viruses or virus particles in the blood), and parasitemia (i.e., helminthic or protozoan parasites in the blood). Thus, septicemia and septic shock (acute circulatory failure resulting from septicemia often associated with multiple organ failure and a high mortality rate) may be caused by a number of organisms.

Examples

[257] The disclosure is further illustrated by the following examples and synthesis schemes, which are not to be construed as limiting this disclosure in scope or spirit to the specific procedures herein described. It is to be understood that the examples are provided to illustrate certain embodiments and that no limitation to the scope of the disclosure is intended thereby. It is to be further understood that resort may be had to various other embodiments, modifications, and equivalents thereof which may suggest themselves to those skilled in the art without departing from the spirit of the present disclosure and/or scope of the appended claims.

[258] Compounds of the present disclosure may be prepared by methods known in the art of organic synthesis. In all of the methods it is understood that protecting groups for sensitive or reactive groups may be employed where necessary in accordance with general principles of chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T. W. Green and P. G. M. Wuts (1999) Protective Groups in Organic Synthesis, 3rd edition, John Wiley & Sons). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art.

[259] Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Proton nuclear magnetic resonance (NMR) spectra were obtained on either Bruker Avance spectrometer or Varian Oxford 400 MHz spectrometer unless otherwise noted. NMR spectra are given in ppm (δ) and coupling constants, *J*, are reported in Hertz. Tetramethylsilane (TMS) was used as an internal standard. Chemical shifts are reported in ppm relative to dimethyl sulfoxide (δ 2.50), methanol (δ 3.31), chloroform (δ 7.26) or other solvent as indicated in NMR spectral data. A small amount of dry sample (2-5 mg) is dissolved in an appropriate deuterated solvent (1 mL). Mass spectra (ESI-MS) were collected using a Waters System (Acquity UPLC and a Micromass ZQ mass spectrometer) or Agilent-1260 Infinity (6120 Quadrupole); all masses reported are the m/z of the protonated parent ions unless recorded otherwise. The chemical names were generated using ChemBioDraw Ultra v14 from CambridgeSoft.

[260] Temperatures are given in degrees Celsius. As used herein, unless specified otherwise, the term "room temperature" or "ambient temperature" means a temperature of from 15 degrees centigrade to 30 degrees centigrade, such as of from 20 degrees centigrade to 30 degrees centigrade, such as of from 20 degrees centigrade to 25 degrees centigrade. If not mentioned otherwise, all evaporations are performed under reduced pressure, typically between about 15 mm Hg and 100 mm Hg (= 20-133 mbar). The

structure of final products, intermediates and starting materials is confirmed by standard analytical methods, *e.g.*, microanalysis and spectroscopic characteristics, *e.g.*, MS, IR, NMR. Abbreviations used are those conventional in the art.

[261] All starting materials, building blocks, reagents, acids, bases, dehydrating agents, solvents, and catalysts utilized to synthesis the compounds of the present disclosure are either commercially available or can be produced by organic synthesis methods known to one of ordinary skill in the art.

Table 1. Abbreviations used in the following examples and elsewhere herein are:

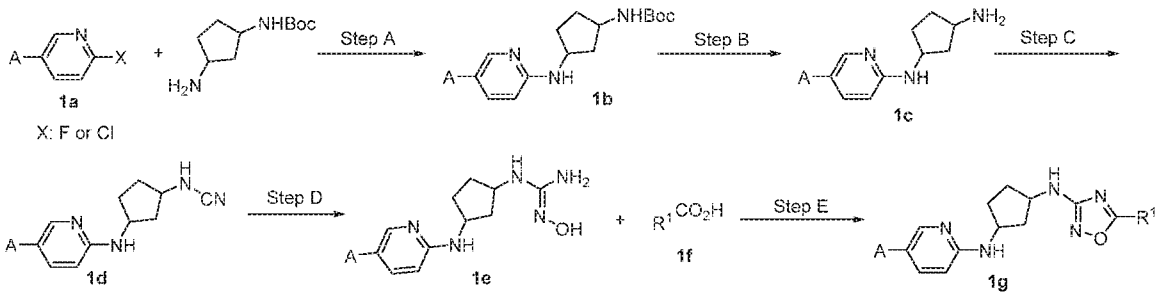
Ac: Acetyl	m: multiplet
ACN, MeCN: acetonitrile	Me and MeOH: methyl and methanol
aq.: aqueous	min: minute(s)
Ar: aromatic	MS: mass
Boc: *tert*-butyloxycarbonyl	m/z: mass to charge ratio
BSA: bovine serum albumin	M and mM: molar and millimolar
br: broad	mg: milligram
d: doublet; dd: doublet of doublets	µL, mL and L: microliter, milliliter and liter
DCE: dichloroethane	NMP: *N*-methyl-2-pyrrolidone
DCM: dichloromethane	NMR: nuclear magnetic resonance
DMA: dimethylacetamide	PCSK9: proprotein convertase subtilisin/kexin type 9 serine protease
DMF: *N*,*N*-dimethylformamide	ppm: parts per million
DMSO: dimethylsulfoxide	Ph: phenyl
DIPEA: *N*,*N*-diisopropylethylamine	PyBroP: benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate
dppf: 1,1'-bis(diphenylphosphino)ferrocene	q: quartet
EDC: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide	rt: room temperature
ESI-MS: electrospray ionization mass spectrometry	s: singlet

Et and EtOAc: ethyl and ethyl acetate	sat.: saturated
HATU: *O*-(7-azobenzotriazol-1-yl)-1,1,3,3-tetramethyluroniumhexafluorophosphate	t: triplet
HEPES: 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid	TEA: triethylamine
hERG: the human ether-à-go-go-related gene	tert: tertiary
HPLC: high pressure liquid chromatography	THF: tetrahydrofuran
h, hr: hour(s)	TFA and TFAA: trifluoroacetic acid and trifluoroacetic anhydride
IPA: isopropanol	TR-FRET: time resolved fluorescence resonance energy transfer
LC and LCMS: liquid chromatography and liquid chromatography-mass spectrometry	wt and wt%: weight and percentage by weight

General synthetic routes

[262] Typically, the compounds of formula (I) can be prepared according to the Schemes provided *infra.*

[263] **Scheme 1** represents the general synthesis of a compound of formula (I).



wherein R^1, A are as defined in herein.

Step A: *tert*-butyl (3-aminocyclopentyl)carbamate is reacted with **1a** in the presence of a suitable base such as diisopropylethylamine at a suitable temperature such as 120 °C to form **1b**.

Step B: Deprotection of the protecting group to form **1c** in the presence of a strong acid such as hydrochloric acid or trifluoroacetic acid.

Step C: Cyanamide **1d** can be formed through a nucleophilic substitution reaction of **1c** with cyanogen bromide and a suitable base such as sodium acetate.

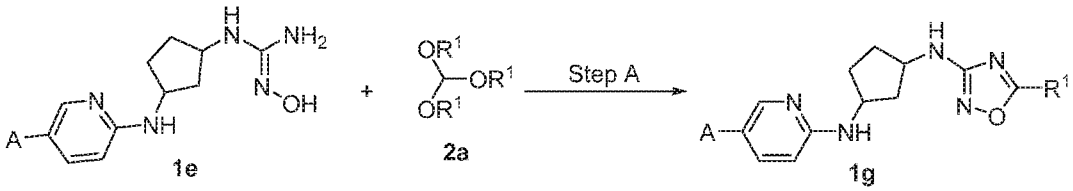
Step D: Cyanamide **1d** is reacted with hydroxyamine to form *N*-hydroxyguanidine **1e**.

Step E: *N*-hydroxyguanidine **1e** can be converted to the target compound 1,2,4-oxadiazole **1g** by the following two conditions.

Condition E-1: Acylation with various acid **1f** using coupling reagents such as HATU in presence of a suitable base such as *N,N*-diisopropylethylamine.

Condition E-2: Cyclization at a suitable temperature such as 100 °C to form **1g**.

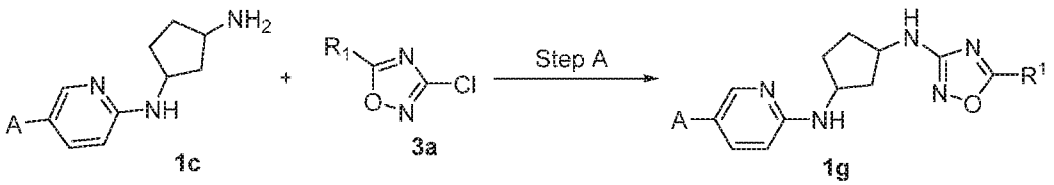
[264] **Scheme 2** represents the alternative synthesis of a compound of formula (I) in Scheme 1.



wherein R^1, A are as defined in herein.

Step A: *N*-hydroxyguanidine **1e** can be converted to the target compound 1,2,4-oxadiazole **1g** by reacting with an orthoester **2a**.

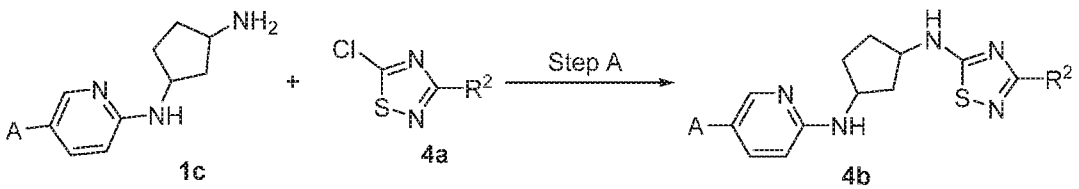
[265] **Scheme 3** represents the alternative synthesis of a compound of formula (I) in Scheme 1.



wherein R^1, A are as defined in herein.

Step A: Amine **1c** is reacted with 3-chloro-1,2,4-thiadiazole **3a** to form the target compound **1g** in the presence of a suitable base such as *N,N*-diisopropylethylamine at a suitable temperature such as 100 °C.

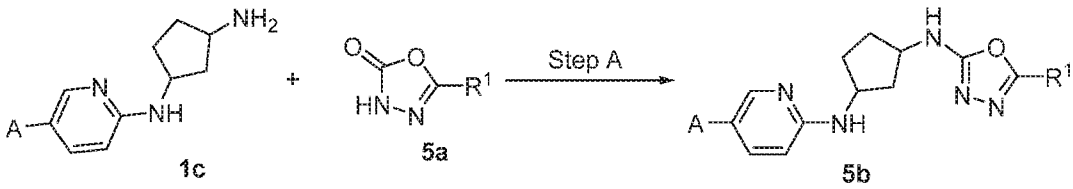
[266] **Scheme 4** represents the general synthesis of a compound of formula (I).



wherein R^2, A are as defined in herein.

Step A: Amine **1c** is reacted with 5-chloro-1,2,4-thiadiazole 4a to form the target compound **4b** in the presence of a suitable base such as *N,N*-diisopropylethylamine at a suitable temperature such as 110 °C.

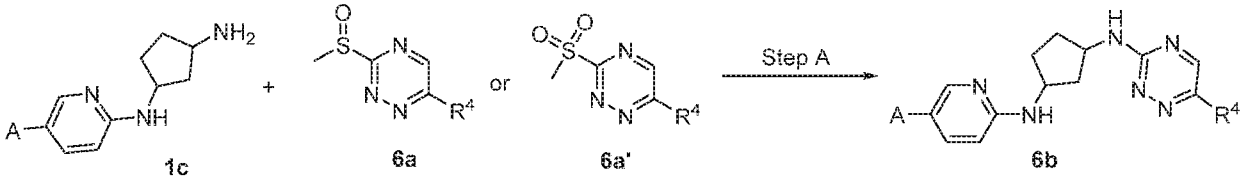
[267] **Scheme 5** represents the general synthesis of a compound of Formula (I).



wherein R^1, A are as defined in herein.

Step A: Amine **1c** is reacted with 1,3,4-oxadiazol-2(3*H*)-one **5a** to form the target compound **5b** with a coupling reagent such as PyBroP in the presence of a suitable base such as *N,N*-diisopropylethylamine.

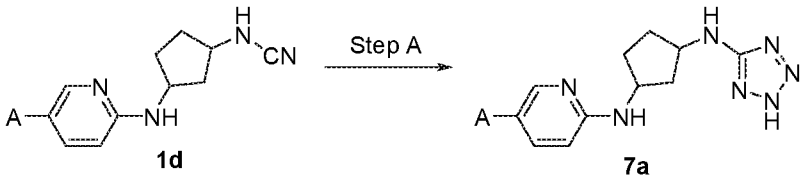
[268] **Scheme 6** represents the general synthesis of a compound of Formula (I).



wherein R^4, A are as defined in herein.

Step A: Amine **1c** is reacted with 3-(methylsulfinyl)-1,2,4-triazine **6a** or 3-(methylsulfonyl)-1,2,4-triazine **6a'** to form the target compound **6b** in the presence of a suitable base such as sodium carbonate.

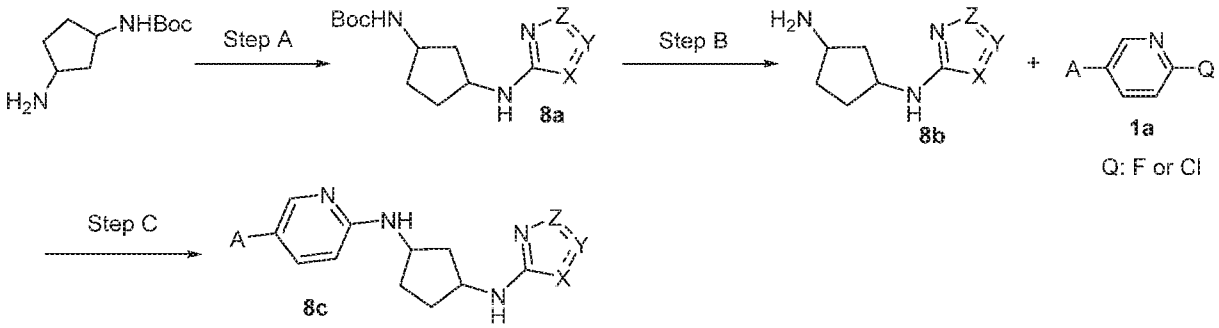
[269] **Scheme 7** represents the general synthesis of a compound of formula (I).



wherein A is as defined herein.

Step A: Cyanamide **1d** reacted with sodium azide to form the target compound **7a**.

[270] **Scheme 8** represents the general synthesis of a compound of formula (I).



wherein X, Y, Z, and A are as defined in herein.

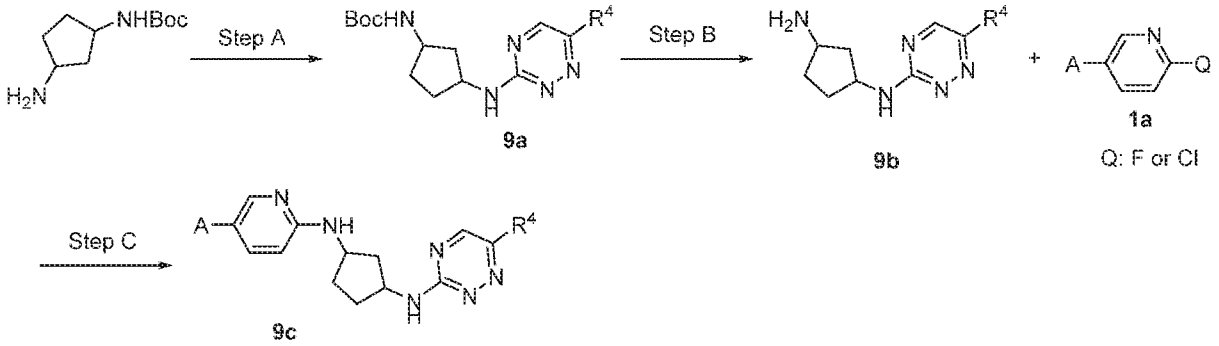
Step A: Intermediate **8a** can be formed by either of the following conditions

- Scheme 1 Step C, D, and E
- Scheme 2 Step A
- Scheme 3 Step A
- Scheme 4 Step A
- Scheme 5 Step A
- Scheme 6 Step A

Step B: Deprotection of the protecting group to form amine **8b** in the presence of a strong acid such as hydrochloric acid or trifluoroacetic acid.

Step C: Amine **8b** is reacted with **1a** to form the target compound **8c** following Scheme 1 Step A.

[271] **Scheme 9** represents the general synthesis of a compound of formula (I).



wherein R^4, and A are as defined in in herein.

Step A: Intermediate **9a** is formed following Scheme 6 Step A.

Step B: Deprotection of the protecting group to form **9b** in the presence of a strong acid such as hydrochloric acid or trifluoroacetic acid.

Step C: Amine **9b** is reacted with **1a** to form the target compound **9c** following Scheme 1 Step A.

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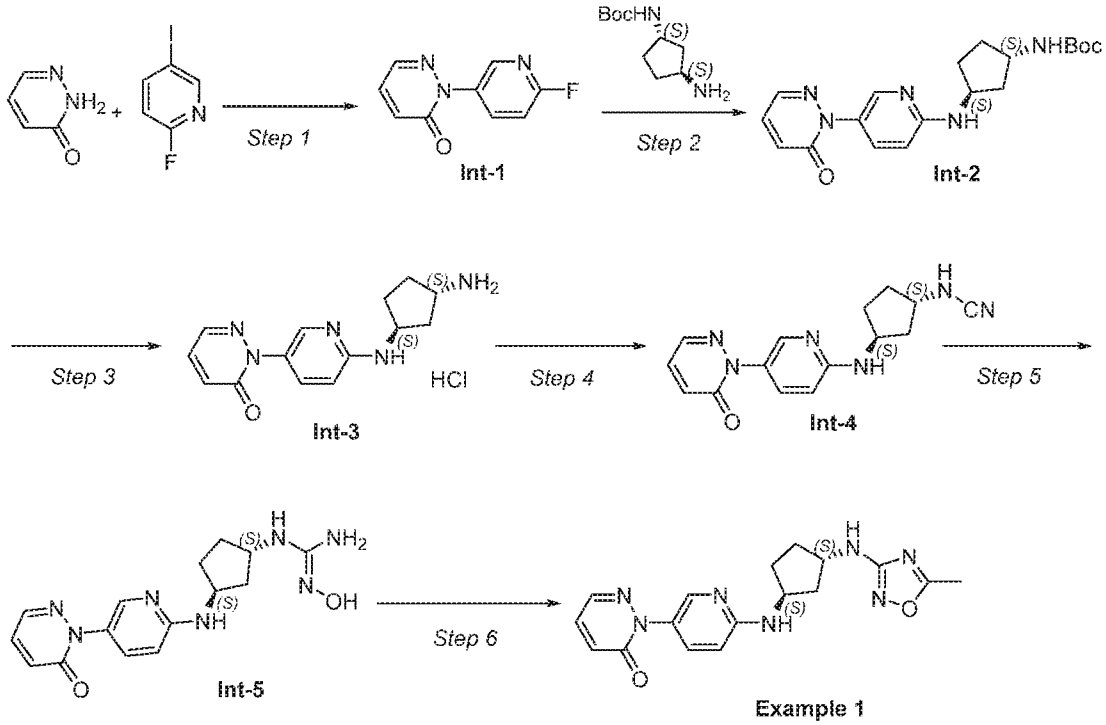
Example 1: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-methyl-1,2,4-oxadiazol-3-yl) amino)cyclopentyl)amino) pyridin-3-yl)pyridazin-3(2*H*)-one



***Step-1*: Synthesis of 2-(6-fluoropyridin-3-yl)pyridazin-3(2*H*)-one (Int-1)**

[272] To a solution of 2-fluoro-5-iodopyridine (10 g, 44.84 mmol) in DMSO (150 mL), potassium carbonate (12.4 g, 89.69 mmol), pyridazin-3(2*H*)-one (4.52 g, 47.09 mmol) were added and the reaction mixture was purged with argon for 15 min at room temperature, then CuI (0.85 g, 4.48 mmol) and *N,N*-dimethylcyclohexane-1,2-diamine (0.95 g, 6.72 mmol) were added and purged with argon for another 10 min. After stirring at 130 °C for 16 h, the reaction was quenched with water and the product was extracted with EtOAc. The organic phases were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 0-70% EtOAc in hexane) to afford the title compound as a yellow solid (5.5 g, 64%). ESI-MS *m/z*: 191.7 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.50 – 8.49 (m,1H), 8.24 – 8.19 (m,1H), 8.05 (dd, *J* = 4.0, 1.6 Hz, 1H), 7.48 (dd, *J* = 9.6, 3.6 Hz, 1H), 7.21 – 7.18 (m, 1H), 7.09 (dd, *J* = 9.6, 1.6 Hz, 1H).

***Step-2*: Synthesis of *tert*-butyl ((1*S*,3*S*)-3-((5-(6-oxopyridazin-1(6*H*)-yl)pyridin-2-yl)amino)cyclopentyl)carbamate (Int-2)**

[273] To a solution of *tert*-butyl ((1*S*,3*S*)-3-aminocyclopentyl)carbamate (2.5 g, 12.48 mmol) in DMSO (30 mL), DIPEA (6.5 mL, 37.44 mmol) and **Int-1** (2.86 g, 14.97 mmol) were added. After stirring at 120

°C for 16 h, the reaction mixture was quenched with water and the product was extracted with EtOAc. The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 0-70% EtOAc in hexane) to afford the title compound as an off-white solid (2.5 g, 54%), ESI-MS *m/z*: 372.05 $[M+H]^+$.

***Step-3*: Synthesis of 2-(6-(((1*S*,3*S*)-3-aminocyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one hydrochloride (Int-3)**

[274] A mixture of **Int-2** (1.2 g, 3.23 mmol) in 4 M HCl in 1,4-dioxane (15 mL) was stirred for 2 h at room temperature. The mixture was concentrated under reduced pressure. The residue was triturated three times with *n*-pentane (10 mL) to afford the title compound as a brown solid (1.2 g), which was used in the next step without further purification. ESI-MS m/z: 271.8 $[M+H]^+$.

***Step-4*: Synthesis of *N*-((1*S*,3*S*)-3-((5-(6-oxopyridazin-1(6*H*)-yl)pyridin-2-yl)amino)cyclopentyl)cyanamide (Int-4)**

[275] To a solution of **Int-3** (1.5 g, 4.87 mmol) in THF (50 mL) were added NaOAc (1.2 g, 14.62 mmol) and cyanogen bromide (1.55 g, 14.62 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 16 h, then filtered through a Celite® pad, the filtrate was concentrated under reduced pressure to afford the crude title compound as a yellow sticky solid (1.8 g), which was used in the next step without further purification. ESI-MS m/z: 296.85 $[M+H]^+$.

***Step-5*: Synthesis of 2-hydroxy-1-((1*S*,3*S*)-3-((5-(6-oxopyridazin-1(6*H*)-yl)pyridin-2-yl)amino) cyclopentyl)guanidine (Int-5)**

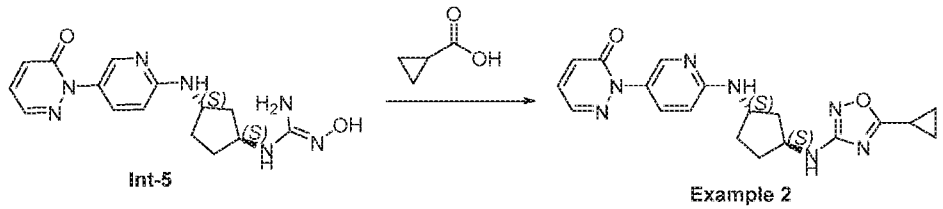
[276] A mixture of **Int-4** (1.11 g, 3 mmol), hydroxylamine hydrochloride (1.67 g, 24 mmol) and TEA (3.35 mL, 24 mmol) in EtOH (20 mL) was stirred at 50 °C overnight. The reaction mixture was concentrated under reduced pressure, and the residue was purified by reverse phase flash column chromatography on C18 (eluent: 10-80% 0.1% NH_4OH in ACN/water) to afford the title compound as a yellow solid (680 mg, 69%), ESI-MS m/z: 330.1 $[M+H]^+$.

***Step-6*: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-methyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino) pyridin-3-yl)pyridazin-3(2*H*)-one (Example 1)**

[277] To a mixture of **Int-5** (150 mg, 90 wt%, 0.41 mmol) in 1,1,1-trimethoxyethane (12 mL, 94 mmol) was added acetic acid (24 µM, 0.41 mmol). After stirring at 60 °C for 3 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography on C18 (eluent: 10-80% ACN/water with 0.1% NH_4OH) to provide the title compound as a yellow solid (120 mg, 81%). ESI-MS m/z: 354.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.15 (d, *J* = 2.4 Hz, 1H), 8.02 (dd, *J* = 3.6, 1.6 Hz, 1H), 7.61 (dd, *J* = 9.3, 2.8 Hz, 1H), 7.46 (dd, *J* = 9.3, 3.6 Hz,

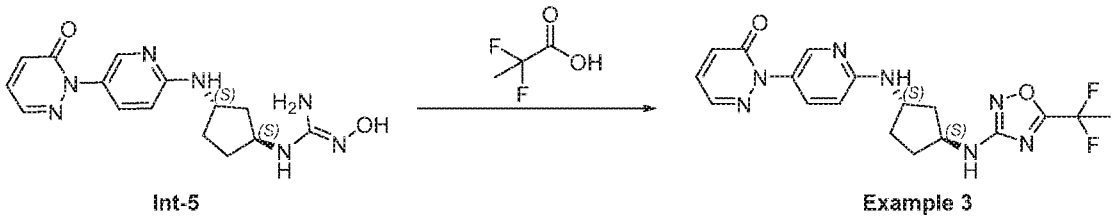
1H), 7.06 (dd, *J* = 9.6, 1.6 Hz, 1H), 6.59 (d, *J* = 9.6 Hz, 1H), 4.37 – 4.30 (m, 1H), 4.01 – 3.95 (m, 1H), 2.41 (s, 3H), 2.29 – 2.19 (m, 2H), 2.10 – 2.02 (m, 1H), 1.99 – 1.90 (m, 1H), 1.66 – 1.55 (m, 2H).

Example 2: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-cyclopropyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl) amino)pyridin-3-yl) pyridazin-3(2*H*)-one



[278] To a solution of cyclopropanecarboxylic acid (30 mg, 0.34 mmol) in DCM (4 mL), was added HATU (0.132 g, 0.34 mmol) followed by DIPEA (70 µL, 0.41 mmol). After stirring at room temperature for 30 min, the reaction mixture was added dropwise to a solution of **Int-5** (0.138 g, 0.41 mmol) in DCM (6 mL) and NMP (0.2 mL). After stirring at room temperature for 1 h, the mixture was concentrated under reduced pressure, the residue was dissolved in DCE (5 mL). The mixture was heated under stirring at 100 °C for 2 h, then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 0-10% MeOH in DCM). The crude product was purified by preparative HPLC (20-40% acetonitrile/0.02% NH_4OH in water; WATERS XBRIDGE (150 mm x 20 mm), 5.0 µm column, flow rate 15 mL/min) to afford the title compound as a yellow solid (35 mg, 27%), ESI-MS m/z: 380.15 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.15 – 8.14 (m, 1H), 8.02 (dd, *J* = 3.6, 1.6 Hz, 1H), 7.60 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.45 (dd, *J* = 9.2, 3.6 Hz, 1H), 7.06 (dd, *J* = 9.2, 1.6 Hz, 1H), 6.58 (d, *J* = 8.8 Hz, 1H), 4.28 – 4.19 (m, 1H), 3.90 – 3.82 (m, 1H), 2.10 – 2.05 (m, 2H), 2.01 – 1.91 (m, 2H), 1.78 – 1.70 (m, 1H), 1.58 – 1.43 (m, 2H), 1.18 – 1.14 (m, 2H), 1.11 – 1.08 (m, 2H).

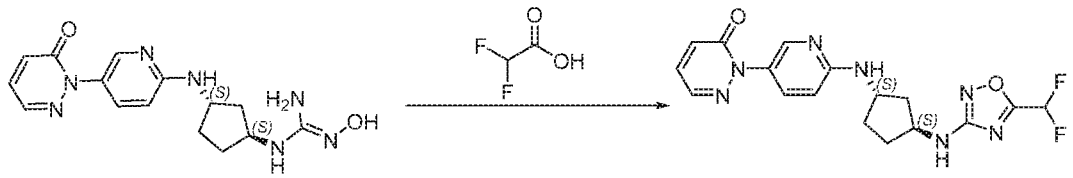
Example 3: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-(1,1-difluoroethyl)-1,2,4-oxadiazol-3-yl) amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one



[279] To a solution of 1-fluorocyclopropane-1-carboxylic acid (40 mg, 0.36 mmol) in DCM (4 mL), was added HATU (0.138 g, 0.36 mmol) followed by DIPEA (70 µL, 0.43 mmol) at room temperature. After stirring at room temperature for 30 min, the reaction mixture was added dropwise to a solution of **Int-5** (0.144 g, 0.43 mmol) in DCM (6 mL) and NMP (0.2 mL). After stirring at room temperature for 1

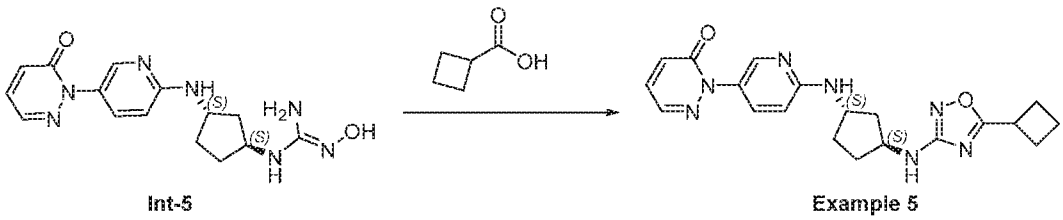
h, the mixture was concentrated under reduced pressure, the residue was dissolved in DCE (5 mL) and heated at 100 °C for 2 h. The mixture was concentrated under reduced pressure and purified by flash column chromatography on silica gel (eluent: 0-10% MeOH in DCM). The obtained crude product was purified by preparative HPLC (20-40% acetonitrile/0.02% NH_4OH in water; WATERS XBRIDGE (150 mm x 20 mm), 5.0 µm column, flow rate 15 mL/min) to afford the title compound as a yellow solid (40 mg, 27%), ESI-MS m/z: 404.05 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.14 (dd, *J* = 2.8, 0.8 Hz, 1H), 8.02 (dd, *J* = 4.0, 2.0 Hz, 1H), 7.59 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.45 (dd, *J* = 9.2, 4.0 Hz, 1H), 7.05 (dd, *J* = 9.2, 1.6 Hz, 1H), 6.59 (d, J = 8.8 Hz, 1H), 4.36 – 4.32 (m, 1H), 4.04 – 4.00 (m, 1H), 2.27 – 2.22 (m, 2H), 2.11 – 2.07 (m, 1H), 2.04 (t, *J* = 18.8 Hz, 3H), 1.98 – 1.94 (m, 1H), 1.67 – 1.58 (m, 2H).

Example 4: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one



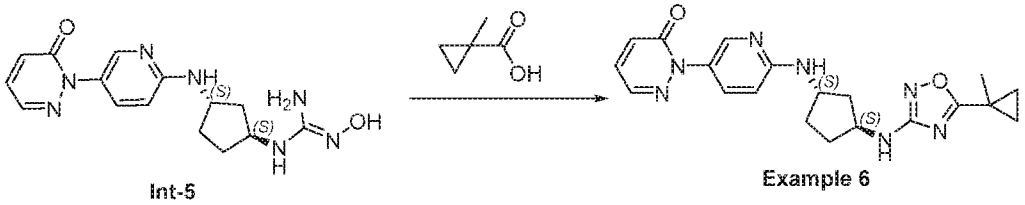
[280] To a solution of 2,2-difluoroacetic acid (25 mg, 0.26 mmol) in DCM (4 mL) was added HATU (100 mg, 0.26 mmol) followed by DIPEA (50 µL, 0.31 mmol). After stirring at room temperature for 30 min, the reaction mixture was added dropwise to a solution of **Int-5** (103 mg, 0.31 mmol) in DCM (6 mL) and NMP (0.2 mL). After stirring at room temperature for 1 h, the mixture was concentrated under reduced pressure, the residue was dissolved in DCE (5 mL). After stirring at 100 °C for 2 h, the mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 0-10% MeOH in DCM). The crude product was purified by preparative HPLC (20-60% acetonitrile/0.02% NH_4OH in water; Gemini NX, 250 mm x 20 mm, 5.0 µm column, flow rate 20 mL/min) to afford the title compound as a yellow oil (27 mg, 33%), ESI-MS m/z: 390.15 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.15 (dd, *J* = 2.4, 0.4 Hz, 1H), 8.02 (dd, *J* = 4.0, 1.6 Hz, 1H), 7.60 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.45 (dd, *J* = 9.2, 4.0 Hz, 1H), 7.05 (dd, *J* = 9.2, 1.6 Hz, 1H), 6.91 (t, *J* = 52.0 Hz, 1H), 6.59 (d, *J* = 8.8 Hz, 1H), 4.37 – 4.32 (m, 1H), 4.04 – 4.00 (m, 1H), 2.29 – 2.22 (m, 2H), 2.11 – 2.06 (m, 1H), 1.99 – 1.93 (m, 1H), 1.69 – 1.57 (m, 2H).

Example 5: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-cyclobutyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one



[281] To a solution of cyclobutanoic acid (20 mg, 0.19 mmol) in DCM (4 mL), was added HATU (75 mg, 0.19 mmol) followed by DIPEA (0.1 mL, 0.23 mmol). After stirring at room temperature for 30 min, the reaction mixture was added dropwise to a solution of **Int-5** (78 mg, 0.19 mmol) in DCM (6 mL) and NMP (0.2 mL). After stirring at room temperature for 1 h, the mixture was concentrated under reduced pressure, and the residue was dissolved in DCE (5 mL). After stirring at 100 °C for 2 h, the mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 0-10% MeOH in DCM). The obtained crude product was purified by preparative HPLC (20-50% acetonitrile/0.02% NH_4OH in water; WATERS XBRIDGE (150 mm x 20 mm), 5.0 µm column, flow rate 15 mL/min) to afford the title compound as a yellow solid (20 mg, 21%), ESI-MS m/z: 394.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.15 (d, J = 2.8 Hz, 1H), 8.03 (dd, J = 4.0, 1.6 Hz, 1H), 7.60 (dd, J = 9.2, 2.8 Hz, 1H), 7.46 (dd, J = 9.2, 3.6 Hz, 1H), 7.06 (dd, J = 9.2, 1.6 Hz, 1H), 6.59 (d, J = 9.2 Hz, 1H), 4.37 – 4.32 (m, 1H), 4.02 – 3.97 (m, 1H), 3.67 – 3.60 (m, 1H), 2.43 – 2.37 (m, 4H), 2.27 – 2.21 (m, 2H), 2.14 – 1.94 (m, 4H), 1.69 – 1.56 (m, 2H).

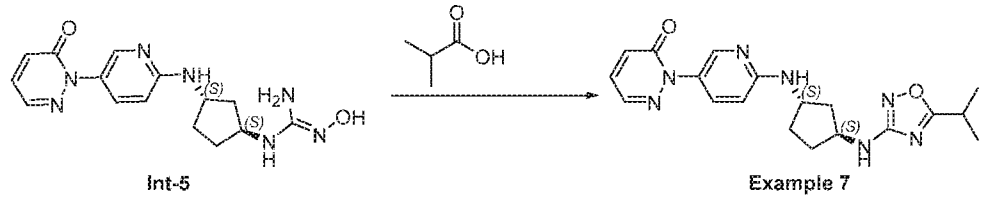
Example 6: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-(1-methylcyclopropyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one



[282] To a solution 1-methylcyclopropane-1-carboxylic acid (36 mg, 0.35 mmol) in DCM (2 mL), was added HATU (0.137 g, 0.35 mmol) followed by DIPEA (0.1 mL, 0.43 mmol). After stirring at room temperature for 30 min, the reaction mixture was added dropwise to a solution of **Int-5** (0.15 g, 0.43 mmol) in DCM (6 mL) and NMP (0.2 mL). After stirring at room temperature for 1 h, the mixture was concentrated under reduced pressure, and the residue was dissolved in DCE (5 mL). After stirring at 100 °C for 2 h, the mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 0-10% MeOH in DCM). The obtained crude product was purified by preparative HPLC (20-50% acetonitrile/0.02% NH_4OH in water; WATERS XBRIDGE (150 mm x 20 mm), 5.0 µm column, flow rate 15 mL/min) to provide the title compound as a yellow solid (50

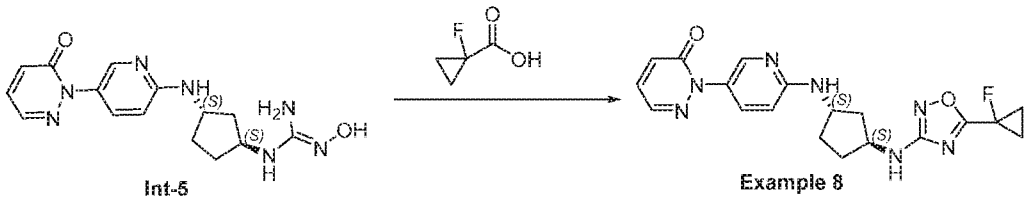
mg, 28%). ESI-MS m/z: 394.15 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.14 (dd, *J* = 2.4, 0.4 Hz, 1H), 8.02 (dd, *J* = 4.0, 1.6 Hz, 1H), 7.59 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.45 (dd, *J* = 9.6, 4.0 Hz, 1H), 7.05 (dd, *J* = 9.6, 1.6 Hz, 1H), 6.58 (d, *J* = 8.8 Hz, 1H), 4.35 – 4.28 (m, 1H), 3.98 – 3.92 (m, 1H), 2.26 – 2.21 (m, 2H), 2.05 – 2.01 (m, 1H), 1.96 – 1,91 (m, 1H), 1.64 – 1.54 (m, 2H), 1.46 (s, 3H), 1.29 (dd, *J* = 7.2, 3.6 Hz, 2H), 0.97 (dd, *J* = 6.8, 4.0 Hz, 2H).

Example 7: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-isopropyl-1,2,4-oxadiazol-3-yl)amino) cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one



[283] To a solution of isobutyric acid (40 mg, 0.45 mmol) in DCM (5 mL), were added HATU (0.172 g, 0.45 mmol) followed by DIPEA (0.1 mL, 0.54 mmol). After stirring at room temperature for 30 min, the reaction mixture was added dropwise to a solution of **Int-5** (0.179 g, 0.45 mmol) in DCM (6 mL) and NMP (0.2 mL). After stirring at room temperature for 1 h, the mixture was concentrated under reduced pressure, and the residue was dissolved in DCE (5 mL). The mixture was heated under stirring at 100 °C for 2 h, then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 0-10% MeOH in DCM). The obtained crude product was purified by preparative HPLC (20-60% acetonitrile/0.02% NH_4OH in water; Gemini NX, 250 mm x 20 mm, 5.0 µm column, flow rate 20 mL/min) to afford the title compound as a yellow solid (59 mg, 28%), ESI-MS m/z: 381.95 $[M+H]+$. ^1H NMR (400 MHz, CD_3OD) δ 8.15 (dd, *J* = 2.8, 0.8 Hz, 1H), 8.02 (dd, *J* = 4.0, 1.6 Hz, 1H), 7.60 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.45 (dd, *J* = 9.2, 3.6 Hz, 1H), 7.06 (dd, *J* = 5.6, 1.6 Hz, 1H), 6.59 (d, *J* = 8.8 Hz, 1H), 4.37 – 4.31 (m, 1H), 4.01 – 3.95 (m, 1H), 3.11 – 3.01 (m, 1H), 2.28 – 2.26 (m, 2H), 2.08 – 2.03 (m, 1H), 1.98 – 1.92 (m, 1H), 1.67 – 1.57 (m, 2H), 1.32 (d, *J* = 7.2 Hz, 6H).

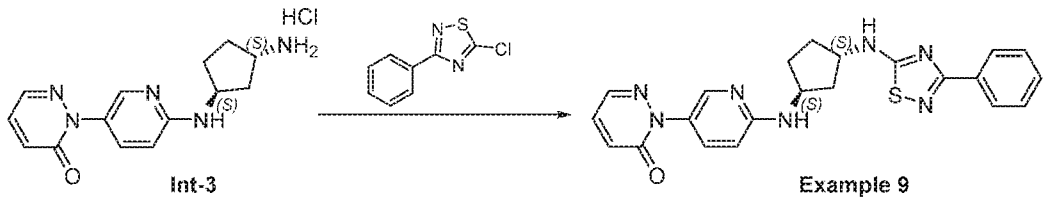
Example 8: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-(1-fluorocyclopropyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one



[284] To a solution of 1-fluorocyclopropane-1-carboxylic acid (29 mg, 0.27 mmol) in DCM (4 mL), was added HATU (106 mg, 0.27 mmol) followed by DIPEA (60 µL, 0.33 mmol) at room temperature.

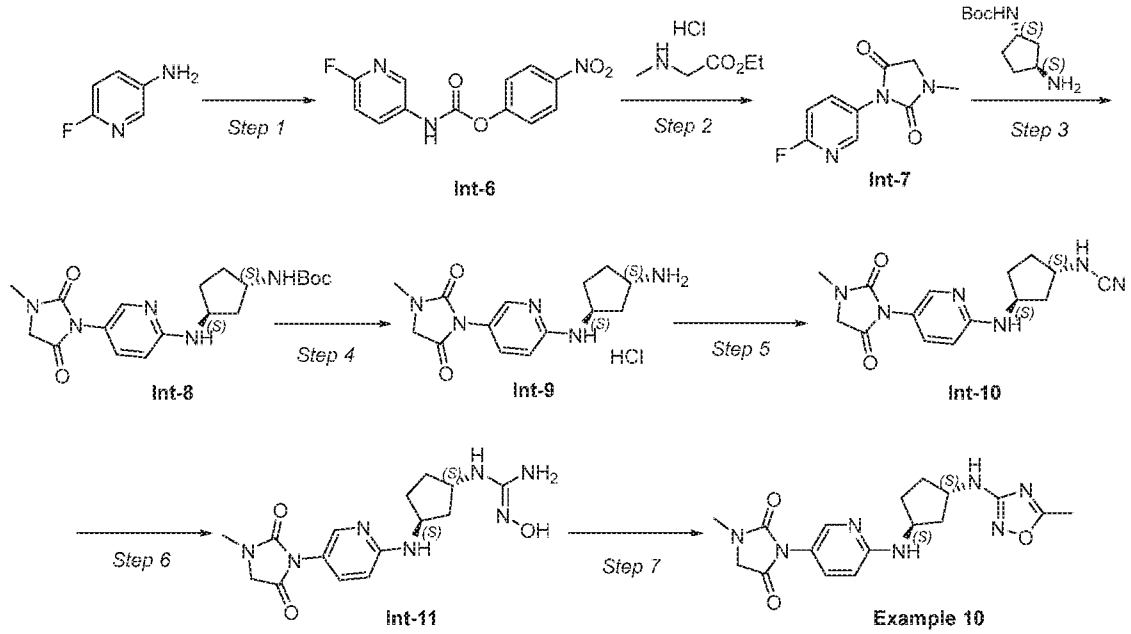
After stirring at room temperature for 30 min, the reaction mixture was added dropwise to a solution of **Int-5** (0.11 g, 0.33 mmol) in DCM (6 mL) and NMP (0.2 mL). After stirring at room temperature for 1 h, the mixture was concentrated under reduced pressure, and the residue was dissolved in DCE (5 mL). After stirring at 100 °C for 2 h, the mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 0-10% MeOH in DCM). The crude product was purified by preparative HPLC (20-70% acetonitrile/0.05% NH_4OH in water; WATERS XBRIDGE (150 mm x 20 mm), 5.0 µm column, flow rate 15 mL/min) to provide the title compound as a yellow solid (30 mg, 27%). ESI-MS m/z: 398.10 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.15 (dd, *J* = 2.4, 0.4 Hz, 1H), 8.03 (dd, *J* = 4.0, 1.6 Hz, 1H), 7.60 (dd, *J* = 5.2, 2.8 Hz, 1H), 7.46 (dd, *J* = 9.2, 3.6 Hz, 1H), 7.06 (dd, *J* = 9.6, 2.0 Hz, 1H), 6.59 (d, *J* = 8.8 Hz, 1H), 4.36 – 4.31 (m, 1H), 4.02 – 3.96 (m, 1H), 2.28 – 2.21 (m, 2H), 2.08 – 2.02 (m, 1H), 1.98 – 1.93 (m, 1H), 1.69 – 1.59 (m, 4H), 1.47 – 1.42 (m, 2H).

Example 9: Synthesis of 2-(6-(((1*S*,3*S*)-3-((3-phenyl-1,2,4-thiadiazol-5-yl)amino) cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one



[285] To a solution of **Int-3** (60 mg, 0.19 mmol) in DMA (1 mL), DIPEA (0.1 mL, 0.58 mmol) was added followed by 5-chloro-3-phenyl-1,2,4-thiadiazole (57 mg, 0.29 mmol).The resulting reaction mixture was stirred at 80 °C for 16 h. After quenching with water, the product was extracted with EtOAc. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 0-10% MeOH in DCM) to provide the title compound as a yellow solid (30 mg, 36%). ESI-MS m/z: 432.25 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.18 – 8.17 (m, 1H), 8.14 – 8.10 (m, 2H), 8.03 (dd, *J* = 4.0, 1.6 Hz, 1H), 7.61 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.48 – 7.40 (m, 4H), 7.06 (dd, *J* = 9.6, 2.0 Hz, 1H), 6.61 (d, *J* = 8.8 Hz, 1H), 4.43 – 4.38 (m, 1H), 4.30 – 4.23 (m, 1H), 2.38 – 2.28 (m, 2H), 2.21 – 2.05 (m, 2H), 1.79 – 1.61 (m, 2H).

Example 10: Synthesis of 1-methyl-3-(6-(((1*S*,3*S*)-3-((5-methyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)imidazolidine-2,4-dione



***Step-1*: Synthesis of 4-nitrophenyl(6-fluoropyridin-3-yl)carbamate (Int-6)**

[286] To a solution of 6-fluoropyridin-3-amine (5 g, 44.64 mmol) in acetonitrile (100 mL), was added 4-nitrophenyl chloroformate (9.89 g, 49.1 mmol) in acetonitrile (10 mL) dropwise. After stirring at room temperature for 30 min, the precipitation was collected by filtration and washed with acetonitrile to afford the title compound as a brown solid (7 g, 56%), ESI-MS m/z: 278.1 $[M+H]^+$.

***Step-2*: Synthesis of 3-(6-fluoropyridin-3-yl)-1-methylimidazolidine-2,4-dione (Int-7)**

[287] To a mixture of ethyl methylglycinate hydrochloride (2.95 g, 25.27 mmol) in acetonitrile (120 mL) was added DIPEA (13.2 mL, 75.81 mmol). After stirring for 15 min, the mixture was added **Int-6** (7 g, 25.27 mmol) portion wise. After stirring at room temperature for 20 min, the reaction mixture was concentrated under reduced pressure, the residue was purified by flash column chromatography on silica gel (eluent: 0-60% EtOAc in hexane) to afford the title compound as a brown oil (4 g, 75%). ESI-MS m/z: 210.05 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.31-8.30 (m, 1H), 8.05-8.00 (m, 1H), 7.21-7.18 (m, 1H), 4.13 (s, 3H), 3.04 (s, 3H).

***Step-3*: Synthesis of *tert*-butyl ((1*S*,3*S*)-3-((5-(3-methyl-2,5-dioxoimidazolidin-1-yl)pyridin-2-yl)amino)cyclopentyl)carbamate (Int-8)**

[288] To a solution of *tert*-butyl ((1*S*,3*S*)-3-aminocyclopentyl)carbamate (0.8 g, 3.99 mmol) in DMSO (10 mL), were added DIPEA (2.1 mL, 11.98 mmol) and **Int-7** (1 g, 4.79 mmol) at room temperature. After stirring at 120 °C for 16 h, the mixture was quenched with water and extracted with EtOAc. The combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 0-60%

EtOAc in hexane) to afford the title compound as an off white solid (0.2 g, 13%). ESI-MS m/z: 390.2 $[M+H]^+$.

***Step-4*: Synthesis of 3-(6-(((1*S*,3*S*)-3-aminocyclopentyl)amino)pyridin-3-yl)-1-methylimidazolidine-2,4-dione hydrochloride (Int-9)**

[289] A mixture of **Int-8** (0.2 g, 0.51 mmol) in 4M HCl in 1,4-dioxane (2 mL) was stirred for 2 h at room temperature. The reaction mixture was concentrated under reduced pressure. The residue was triturated three times with *n*-pentane to provide the crude title compound as a brown solid (0.2 g), which was used in next step without purification. ESI-MS m/z: 290.15 $[M+H]^+$.

***Step-5*: Synthesis of *N*-((1*S*,3*S*)-3-((5-(3-methyl-2,5-dioxoimidazolidin-1-yl)pyridin-2-yl)amino)cyclopentyl)cyanamide (Int-10)**

[290] To a solution of **Int-9** (200 mg, 0.65 mmol) in THF (15 mL), were added NaOAc (160 mg, 1.95 mmol) and cyanogen bromide (205 mg, 1.95 mmol) at 0 °C. After stirring at room temperature for 16h, the reaction mixture was filtered through a Celite® pad and the filtrate was concentrated under reduced pressure to afford the crude title compound as a yellow sticky solid (0.24 g, 80%), which was used in next step without purification. ESI-MS m/z: 315.2 $[M+H]^+$.

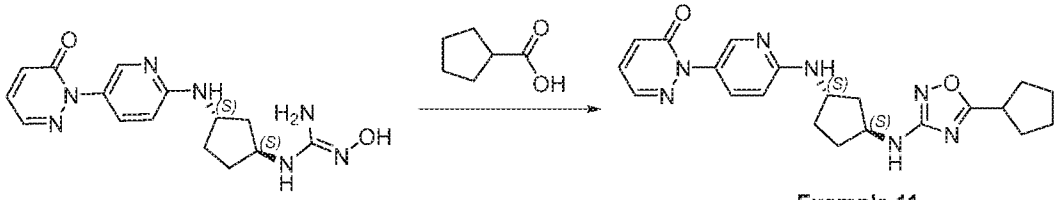
***Step-6*: Synthesis of 2-hydroxy-1-((1*S*,3*S*)-3-((5-(3-methyl-2,5-dioxoimidazolidin-1-yl)pyridin-2-yl)amino)cyclopentyl)guanidine (Int-11)**

[291] To a solution of **Int-10** (0.2 g, 0.64 mmol) in EtOH (10 mL), was added TEA (0.18 mL, 1.27 mmol) followed by hydroxylamine hydrochloride (49 mg, 0.7 mmol). The mixture was heated at 50 °C for 1 h, then concentrated under reduced pressure to afford the crude title compound as a yellow gum. (0.3 g), which was used in the next step without further purification. ESI-MS m/z: 348.25 $[M+H]^+$.

***Step-7:* Synthesis of 1-methyl-3-(6-(((1*S*,3*S*)-3-((5-methyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)imidazolidine-2,4-dione (Example 10)**

[292] A mixture of **Int-11** (0.3 g, 0.86 mmol) in trimethyl orthoacetate (3 mL), DCE (3 mL) and NMP (0.2 mL), was added acetic acid (20 µL). The resulting mixture was stirred at 80 °C for 2 h. After concentration under reduced pressure, the residue was purified by flash column chromatography on silica gel (eluent: 0-10% MeOH in DCM). The crude product was purified by preparative HPLC (10-50% acetonitrile/0.02% NH_4OH in water; Gemini NX, 250 mm x 20 mm, 5.0 µm column, flow rate 20 mL/min) to afford the title compound as a colorless solid (10 mg, 3%) ESI-MS m/z: 371.95 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.81 (d, J = 2.0 Hz, 1H), 7.27 (dd, J = 9.2, 2.8 Hz, 1H), 6.47 (dd, J = 9.2, 0.4 Hz, 1H), 4.23 – 4.18 (m, 1H), 3.98 (s, 2H), 3.91 – 3.83 (m, 1H), 2.96 (s, 3H), 2.31 (s, 3H), 2.19 – 2.07 (m, 2H), 2.00 – 1.91 (m, 1H), 1.85 – 1.78 (m, 1H), 1.59 – 1.41 (m, 2H).

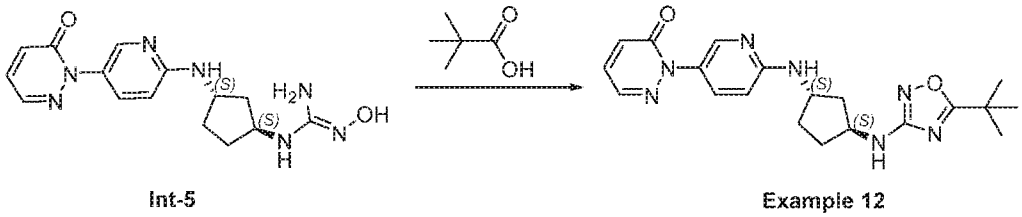
Example 11: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-cyclopentyl-1,2,4-oxadiazol-3-yl)amino) cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one



Int-5 Example 11

[293] To a solution of cyclopentanecarboxylic acid (60 mg, 0.53 mmol) in DCM (3 mL), was added HATU (0.2 g, 0.53 mmol) followed by DIPEA (0.11 mL, 0.63 mmol) at room temperature. After stirring at room temperature for 30 min, the reaction mixture was added dropwise to a solution of **Int-5** (0.21 g, 0.631 mmol) in DCM (7 mL) and NMP (0.5 mL). After stirring at room temperature for 1 h, the mixture was concentrated under reduced pressure, the residue was dissolved in DCE (5 mL). After stirring at 100 °C for 2 h, the mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 0-10% MeOH in DCM). The crude product was purified by preparative HPLC (20-60% acetonitrile/0.02% NH_4OH in water; Gemini NX, 250 mm x 20 mm, 5.0 µm column, flow rate 20 mL/min) to afford the title compound as a yellow solid (65 mg, 25%). ESI-MS m/z: 408.15 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.15 (dd, *J* = 2.8, 0.4 Hz, 1H), 8.02 (dd, *J* = 4.0, 1.6 Hz, 1H), 7.60 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.45 (dd, *J* = 9.2, 3.6 Hz, 1H), 7.06 (dd, *J* = 9.6, 1.6 Hz, 1H), 6.59 (d, *J* = 9.2 Hz, 1H), 4.38 – 4.30 (m, 1H), 4.02 – 3.95 (m, 1H), 3.18 – 3.17 (m, 1H), 2.30 – 2.19 (m, 2H), 2.12 – 2.03 (m, 3H), 1.98 – 1.75 (m, 5H), 1.73 – 1.54 (m, 4H).

Example 12: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-(*tert*-butyl)-1,2,4-oxadiazol-3-yl)amino) cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one

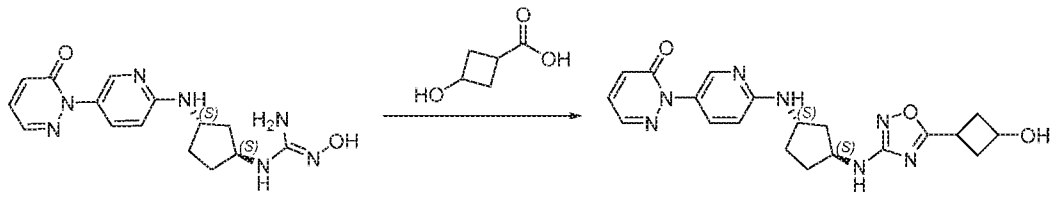


Int-5 Example 12

[294] To a solution of pivalic acid (50 mg, 0.49 mmol) in DCM (3 mL), was added HATU (186 mg, 0.49 mmol) followed by DIPEA (0.1 mL, 0.59 mmol). After stirring at room temperature for 30 min, the reaction mixture was added dropwise to a solution of **Int-5** (192 mg, 0.587 mmol) in DCM (5 mL) and NMP (0.5 mL). After stirring at room temperature for 1 h, the mixture was concentrated under reduced pressure, the residue was dissolved in DCE (5 mL). After stirring at 100°C for 2 h, the mixture was concentrated under reduced pressure. was purified by flash column chromatography on silica gel (eluent:

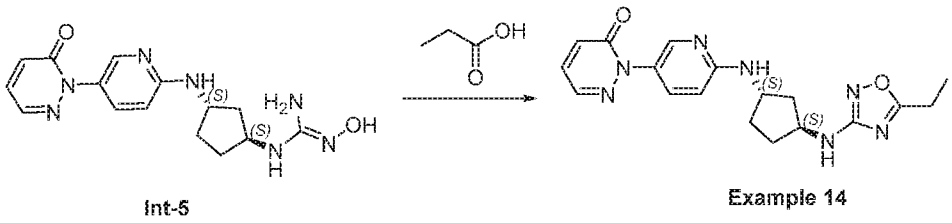
0-10% MeOH in DCM). The crude product was purified by preparative HPLC (20-60% acetonitrile/0.02% NH_4OH in water; WATERS XBRIDGE (150 mm x 20 mm), 5.0 µm column, flow rate 15 mL/min) to afford the title compound as a yellow solid (70 mg, 30%) ESI-MS m/z: 396.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.15 (dd, J = 2.8, 0.8 Hz, 1H), 8.02 (dd, J = 3.6, 1.6 Hz, 1H), 7.60 (dd, J = 9.2, 2.8 Hz, 1H), 7.46 (dd, J = 9.2, 4.0 Hz, 1H), 7.06 (dd, J = 9.6, 1.6 Hz, 1H), 6.60 – 6.58 (m, 1H), 4.38 – 4.29 (m, 1H), 4.01 – 3.94 (m, 1H), 2.30 – 2.18 (m, 2H), 2.11 – 2.03 (m, 1H), 1.98 – 1.89 (m, 1H), 1.70 – 1.52 (m, 2H), 1.37 (s, 9H).

Example 13: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-(3-hydroxycyclobutyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one



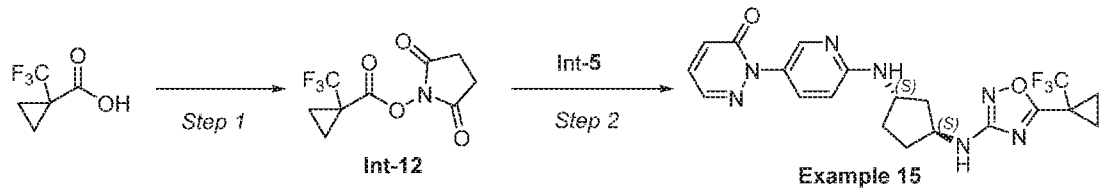
[295] To a solution of 3-hydroxycyclobutane-1-carboxylic acid (50 mg, 0.43 mmol) in DCM (4 mL), was added HATU (0.133 g, 0.43 mmol) followed by DIPEA (90 µL, 0.52 mmol). After stirring at room temperature for 30 min, the reaction mixture was added dropwise to a solution of **Int-5** (0.17 g, 0.52 mmol) in DCM (6 mL) and NMP (0.5 mL). After stirring at room temperature for 1 h, the mixture was concentrated under reduced pressure, the residue was dissolved in DCE (5 mL). After stirring at 100 °C for 2 h, the mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 0-10% MeOH in DCM) The crude product was purified by preparative HPLC (10-50% acetonitrile/0.02% NH_4OH in water; WATERS XBRIDGE (150 mm x 20 mm), 5.0 µm column, flow rate 15 mL/min) to afford the title compound as a yellow solid (60 mg, 28%), ESI-MS m/z: 410.05 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.05 (dd, J = 2.8, 0.8 Hz, 1H), 7.92 (dd, J = 3.6, 1.6 Hz, 1H), 7.50 (dd, J = 9.2, 2.8 Hz, 1H), 7.35 (dd, J = 9.6, 4.0 Hz, 1H), 6.96 (dd, J = 9.6, 1.6 Hz, 1H), 6.48 (d, J = 9.2 Hz, 1H), 4.28 – 4.20 (m, 1H), 4.17 – 4.08 (m, 1H), 3.92 – 3.85 (m, 1H), 3.02 – 2.92 (m, 1H), 2.63 – 2.55 (m, 2H), 2.20 – 2.09 (m, 4H), 2.01 – 1.92 (m, 1H), 1.78 – 1.70 (m, 1H), 1.60 – 1.42 (m, 2H).

Example 14: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-ethyl-1,2,4-oxadiazol-3-yl)amino) cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one



[296] To a solution of propionic acid (35 mg, 0.47 mmol) in DCM (2 mL), was added HATU (180 mg, 0.47 mmol) followed by DIPEA (90 µL, 0.56 mmol). After stirring at room temperature for 30 min, the reaction mixture was added dropwise to a solution of **Int-5** (154 mg, 0.467 mmol) in DCM (5 mL) and NMP (0.5 mL). After stirring at room temperature for 1 h, the mixture was concentrated under reduced pressure, the residue was dissolved in DCE (5 mL). The mixture was heated at 100 °C for 2 h, then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 0-10% MeOH in DCM). The crude product was purified by preparative HPLC (10-75% acetonitrile/0.05% NH_4OH in water; Gemini NX, 250 mm x 20 mm, 5.0 µm column, flow rate 18 mL/min) to afford the title compound as a yellow solid (45 mg, 22%), ESI-MS m/z: 368.15 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.15 (dd, *J* = 2.8, 0.8 Hz, 1H), 8.02 (dd, *J* = 4.0, 1.6 Hz, 1H), 7.60 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.46 (dd, *J* = 9.6, 4.0 Hz, 1H), 7.06 (dd, *J* = 9.6, 1.6 Hz, 1H), 6.58 (d, *J* = 9.2 Hz, 1H), 4.38 – 4.29 (m, 1H), 4.02 – 3.95 (m, 1H), 2.77 (q, *J* = 7.6 Hz, 2H), 2.28 – 2.18 (m, 2H), 2.11 – 2.03 (m, 1H), 1.98 – 1.90 (m, 1H), 1.60 – 1.52 (m, 2H), 1.30 (t, *J* = 7.6 Hz, 3H).

Example 15: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-(1-(trifluoromethyl)cyclopropyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one



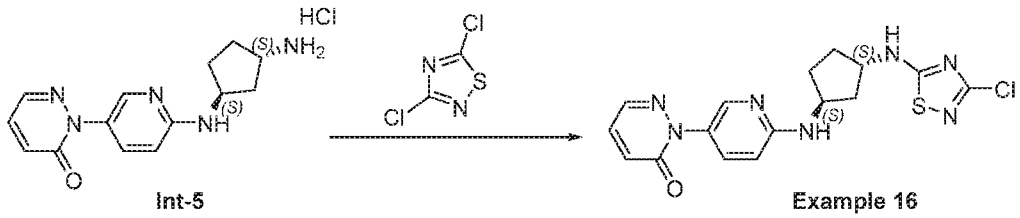
***Step-1*: Synthesis of 2,5-dioxopyrrolidin-1-yl 1-(trifluoromethyl)cyclopropane-1-carboxylate (Int-12)**

[297] To a solution of 1-hydroxypyrrolidine-2,5-dione (1 g, 8.69 mmol) in DCM (10 mL), were added 1-(trifluoromethyl)cyclopropane-1-carboxylic acid (1.3 g, 8.69 mmol), DMAP (106 mg, 0.87 mmol) and DIC (1.3 mL, 8.69 mmol) dropwise at room temperature. After stirring for 12 h, the reaction mixture was filtered through a Celite® pad, washed with DCM. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 0-60% EtOAc in hexane) to provide the title compound as an off-white solid (1.5 g, 66%). ^1H NMR (300 MHz, CDCl3) δ 2.84 (s, 4H), 1.79-1.72 (m, 2H), 1.64-1.58 (m, 2H).

***Step-2*: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-(1-(trifluoromethyl)cyclopropyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one (Example 15)**

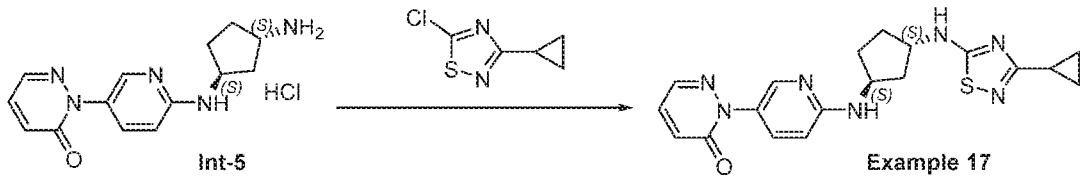
[298] To a solution of 2,5-dioxopyrrolidin-1-yl 1-(trifluoromethyl)cyclopropane-1-carboxylate (114 mg, 0.45 mmol) in NMP (3 mL), was added **Int-5** (150 mg, 0.453 mmol). After stirring at room temperature for 4 h, then the mixture was heated to 70 °C and stirred for 16 h. The reaction mixture was quenched with water and extracted with EtOAc. The combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC (10-75% acetonitrile/0.05% NH_4OH in water; Gemini NX, 250 mm x 20 mm, 5.0 µm column, flow rate 18 mL/min) to provide the title compound as a yellow solid (50 mg, 25%). ESI-MS m/z: 448.15 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.14 (dd, J = 2.8, 0.8 Hz, 1H), 8.01 (dd, J = 4.0, 1.6 Hz, 1H), 7.59 (dd, J = 9.2, 2.8 Hz, 1H), 7.45 (dd, J = 9.6, 4.0 Hz, 1H), 7.05 (dd, J = 9.2, 1.6 Hz, 1H), 6.57 (d, J = 9.2 Hz, 1H), 4.35 – 4.28 (m, 1H), 4.01 – 3.92 (m, 1H), 2.30 – 2.18 (m, 2H), 2.11 – 2.03 (m, 1H), 2.97 – 2.87 (m, 1H), 1.60 – 1.52 (m, 6H).

Example 16: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-chloro-1,2,4-thiadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one



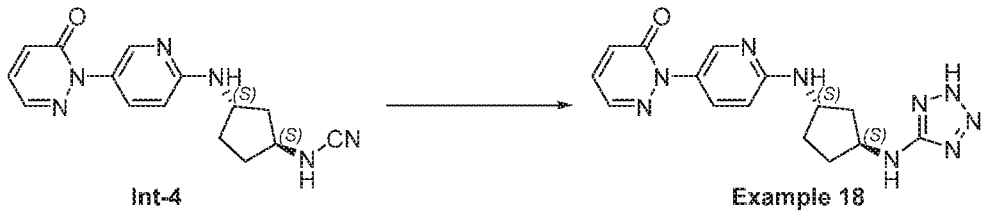
[299] To a solution 2-(6-(((1*S*,3*S*)-3-aminocyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one hydrochloride (60 mg, 0.19 mmol) in DMA (2 mL), DIPEA (0.1 mL, 0.58 mmol) and 3,5-dichloro-1,2,4-thiadiazole (60 mg, 0.38 mmol) were added at room temperature. After stirring at 80 °C for 16 h, the reaction mixture was quenched with water and extracted with EtOAc. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 0-10% MeOH in DCM) to provide the title compound as a pale yellow solid (30 mg, 39%), ESI-MS m/z: 390.10 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.14 (d, J = 2.4 Hz, 1H), 8.01 (dd, J = 4.0, 1.6 Hz, 1H), 7.58 (dd, J = 8.8, 2.4 Hz, 1H), 7.44 (dd, J = 9.2, 4.0 Hz, 1H), 7.04 (dd, J = 9.2, 1.6 Hz, 1H), 6.57 (d, J = 8.8 Hz, 1H), 4.37 – 4.31 (m, 1H), 4.16 – 4.12 (m, 1H), 2.30 – 2.22 (m, 2H), 2.10 – 1.98 (m, 2H), 1.68 – 1.59 (m, 2H).

Example 17: Synthesis of 2-(6-(((1*S*,3*S*)-3-((3-cyclopropyl-1,2,4-thiadiazol-5-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one



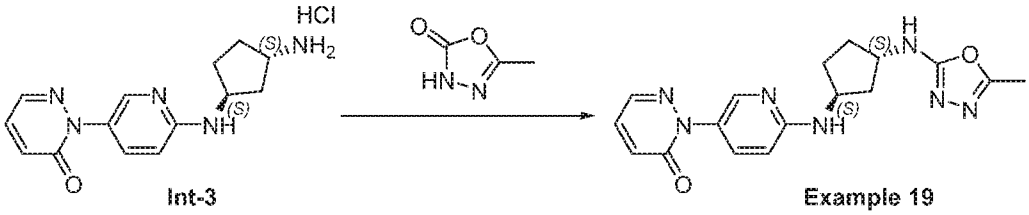
[300] To a solution of **Int-5** (0.1 g, 0.32 mmol) in DMSO (5 mL), was added DIPEA (0.17 mL, 0.97 mmol) followed by 5-chloro-3-cyclopropyl-1,2,4-thiadiazole (78 mg, 0.48 mmol). After stirring at 110 °C for 16 h, the reaction mixture was quenched with water and extracted with EtOAc. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 0-10% MeOH in DCM). The crude product was purified by preparative HPLC (20-40% acetonitrile/0.02% NH_4OH in water; WATERS XBRIDGE (150 mm x 19 mm), 5.0 µm column, flow rate 15 mL/min) to provide the title compound as a yellow solid (40 mg, 31%), ESI-MS m/z: 396.25 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.16 (dd, *J* = 2.8, 0.8 Hz, 1H), 8.02 (dd, *J* = 4.0, 2.0 Hz, 1H), 7.60 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.45 (dd, *J* = 8.8, 4.0 Hz, 1H), 7.06 (dd, *J* = 9.6, 1.6 Hz, 1H), 6.60 – 6.58 (m, 1H), 4.38 – 4.31 (m, 1H), 4.15 – 4.08 (m, 1H), 2.31 – 2.21 (m, 2H), 2.12 – 2.04 (m, 1H), 2.04 – 1.95 (m, 2H), 1.71 – 1.58 (m, 2H), 1.00 – 0.96 (m, 2H), 0.94 – 0.90 (m, 2H).

Example 18: Synthesis of 2-(6-(((1*S*,3*S*)-3-((2*H*-tetrazol-5-yl)amino) cyclopentyl) amino)pyridin-3-yl)pyridazin-3(2*H*)-one



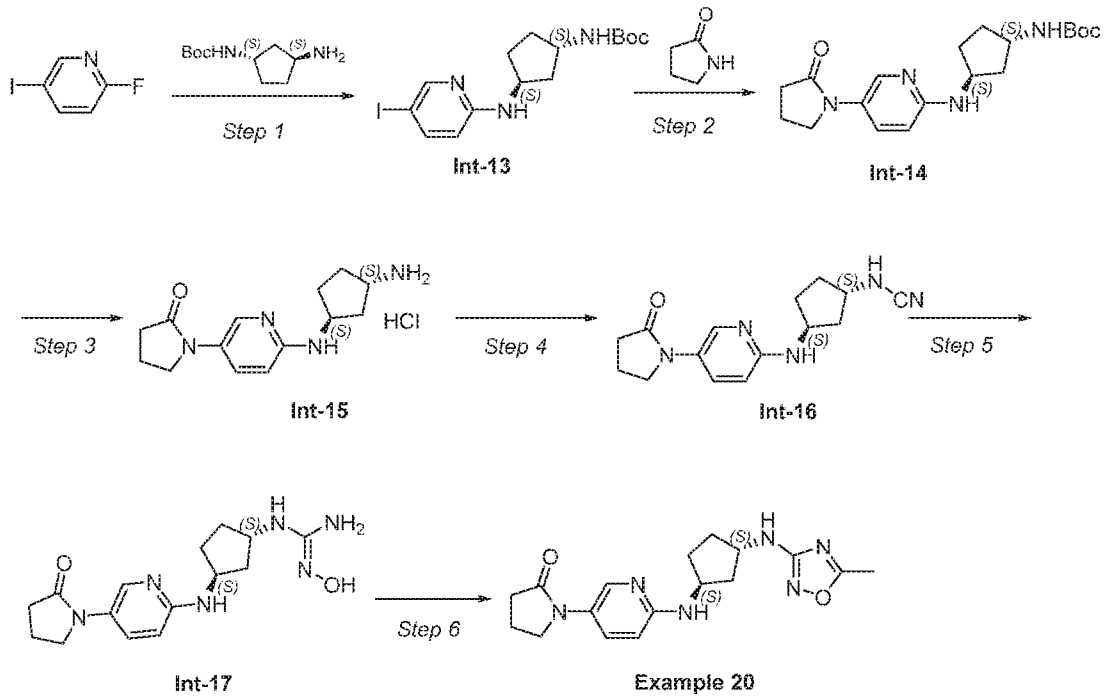
[301] To a solution of **Int-4** (0.2 g, 0.67 mmol) in DMF (5 mL), were added sodium azide (0.44 g, 6.74 mmol) and ammonium chloride (0.36 g, 6.74 mmol). After stirring at 90 °C for 16 h, the reaction mixture was quenched with water and extracted with DCM. The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (10-40% acetonitrile/0.05% NH_4OH in water; YMC (150 mm x 21.2 mm), 5.0 µm column, flow rate 18 mL/min) to afford the title compound as a yellow solid (40 mg, 17%). ESI-MS m/z: 340.15 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.17 (dd, *J* = 2.8, 0.8 Hz, 1H), 8.02 (dd, *J* = 4.0, 1.6 Hz, 1H), 7.62 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.46 (dd, *J* = 9.6, 4.0 Hz, 1H), 7.06 (dd, *J* = 9.6, 1.6 Hz, 1H), 6.61 (d, *J* = 9.2 Hz, 1H), 4.88 – 4.80 (m, 1H), 4.59 – 4.50 (m, 1H), 2.58 – 2.50 (m, 1H), 2.48 – 2.39 (m, 2H), 2.22 – 2.08 (m, 2H), 1.82 – 1.71 (m, 1H).

Example 19: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-methyl-1,3,4-oxadiazol-2-yl)amino) cyclopentyl) amino)pyridin-3-yl)pyridazin-3(2*H*)-one



[302] To a solution of **Int-3** (80 mg, 0.25 mmol) in DMF (1 mL), DIPEA (80 µL, 0.518 mmol), 5-methyl-1,3,4-oxadiazol-2(3*H*)-one (13 mg, 0.12 mmol) and PyBrop (13 mg, 0.31 mmol) were added sequentially. After stirring at room temperature for 16 h, the reaction mixture was quenched with water and extracted with DCM. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (10-60% acetonitrile/0.02% NH_4OH in water; WATERS XBRIDGE (150 mm x 19 mm), 5.0 µm column, flow rate 15 mL/min) to afford the title compound as a yellow solid (4 mg, 4%). ESI-MS m/z: 353.90 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.15 (dd, J = 2.4, 0.4 Hz, 1H), 8.02 (dd, J = 4.0, 1.6 Hz, 1H), 7.59 (dd, J = 8.8, 2.8 Hz, 1H), 7.45 (dd, J = 9.6, 4.0 Hz, 1H), 7.06 (dd, J = 9.6, 1.6 Hz, 1H), 6.58 (d, J = 9.2 Hz, 1H), 4.39 – 4.32 (m, 1H), 4.12 – 4.06 (m, 1H), 2.36 (s, 3H), 2.29 – 2.21 (m, 2H), 2.12 – 1.93 (m, 2H), 1.69 – 1.57 (m, 2H).

Example 20: Synthesis of 1-(6-(((1*S*,3*S*)-3-((5-methyl-1,2,4-oxadiazol-3-yl)amino) cyclopentyl)amino)pyridin-3-yl)pyrrolidin-2-one



***Step-1*: Synthesis of *tert*-butyl ((1*S*,3*S*)-3-((5-iodopyridin-2-yl)amino)cyclopentyl)carbamate (Int-13)**

[303] To a solution of *tert*-butyl ((1*S*,3*S*)-3-aminocyclopentyl)carbamate (1.5 g, 7.48 mmol) in DMSO (20 mL), was added DIPEA (3.9 mL, 22.46 mmol) and 2-fluoro-5-iodopyridine (2 g, 8.98 mmol). After stirring at 120 °C for 16 h, the reaction mixture was quenched with water and extracted with EtOAc. The combined organic phases were washed with water dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 0-25% EtOAc in hexane) to afford the title compound as a colorless solid (2 g, 66%). ESI-MS m/z: 403.95 $[M+H]^+$.

***Step-2*: Synthesis of *tert*-butyl ((1*S*,3*S*)-3-((5-(2-oxopyrrolidin-1-yl)pyridin-2-yl)amino)cyclopentyl)carbamate (Int-14)**

[304] To a solution of **Int-13** (0.5 g, 1.23 mmol) in IPA (5 mL), K_3PO_4 (0.79 g, 3.71 mmol) and pyrrolidin-2-one (0.21 g, 0.47 mmol) were added. The reaction mixture was purged with argon for 15 min at room temperature. Then CuI (0.12 g, 0.61 mmol) and *N,N*-dimethylcyclohexane-1,2-diamine (88 mg, 0.61 mmol) were added and purged with argon for another 10 min. After stirring at 110 °C for 16 h, the mixture was quenched with water and extracted with EtOAc. The combined organic phases were washed with water, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 20-70% EtOAc in hexane) to afford the title compound as an off white solid (0.4 g, 89%). ESI-MS m/z: 361.15 $[M+H]^+$.

***Step-3*: Synthesis of 1-(6-(((1S,3S)-3-aminocyclopentyl) amino) pyridin-3-yl) pyrrolidine-2-one hydrochloride (Int-15)**

[305] A mixture of **Int-14** (0.4 g, 1.1 mmol) in 4 M HCl in 1,4-dioxane (5 mL) was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure. The residue was triturated three times with *n*-pentane to provide the crude title compound as a brown solid (0.4 g), which was carried to the next step without further purification. ESI-MS m/z: 260.8 $[M+H]^+$.

***Step-4*: Synthesis of *N*-((1*S*,3*S*)-3-((5-(2-oxopyrrolidin-1-yl)pyridin-2-yl)amino)cyclopentyl)cyanamide (Int-16)**

[306] To a solution of **Int-15** (0.4 g, 1.34 mmol) in THF (20 mL), was added NaOAc (0.33 g, 4.04 mmol) and cyanogen bromide (0.43 g, 4.04 mmol) at 0 °C. After stirring at RT for 16 h, the reaction mixture was filtered through a Celite® pad, washed with EtOAc. The filtrate was concentrated under reduced pressure to compound as a yellow gum(0.5 g), which was used in the next step without further purification. ESI-MS m/z: 286.15 $[M+H]^+$.

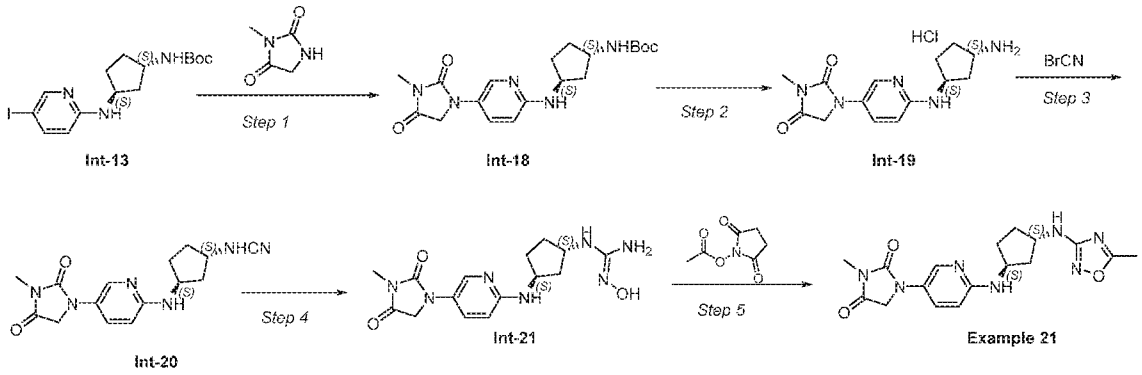
***Step-5*: Synthesis of 2-hydroxy-1-((1*S*,3*S*)-3-((5-(2-oxopyrrolidin-1-yl)pyridin-2-yl)amino)cyclopentyl) guanidine (Int-17)**

[307] To a solution of **Int-16** (0.5 g, 1.75 mmol) in EtOH (10 mL), was added hydroxylamine hydrochloride (0.13 g, 1.92 mmol) and TEA (0.5 mL, 3.5 mmol). After stirring at 50 °C for 1 h, the reaction mixture was concentrated under reduced pressure. The residue was purified with reverse phase flash column chromatography on C18 (eluent: 2-30% MeCN in water) to afford the title compound as a colorless solid (0.18 g, 33%). ESI-MS m/z: 318.9 $[M+H]^+$.

***Step-6*: Synthesis of 1-(6-(((1*S*,3*S*)-3-((5-methyl-1,2,4-oxadiazol-3-yl)amino) cyclopentyl)amino)pyridin-3-yl)pyrrolidin-2-one (Example 20)**

[308] To a solution of **Int-17** (90 mg, 0.28 mmol) in trimethyl orthoacetate (10 mL), was added acetic acid (50 µL). After stirring at 60 °C for 30 min. the reaction mixture was concentrated under reduced pressure. The residue was purified by preparative HPLC (10-40% acetonitrile/0.05% NH_4OH in water; WATERS XSelect (250 mm x 19 mm), 5.0 µm column, flow rate 18 mL/min) to afford the title compound as a colorless solid (2 mg, 2%). ESI-MS m/z: 343.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.07 (dd, *J* = 2.8, 0.8 Hz, 1H), 7.62 (dd, *J* = 9.2, 2.8 Hz, 1H), 6.54 (d, *J* = 9.2 Hz, 1H), 4.30 – 4.21 (m, 1H), 3.99 – 3.92 (m, 1H), 3.83 (t, *J* = 7.0 Hz, 2H), 2.55 (t, *J* = 8.0 Hz, 2H), 2.41 (s, 3H), 2.27 – 2.12 (m, 4H), 2.08 – 1.99 (m, 1H), 1.93 – 1.86 (m, 1H), 1.68 – 1.50 (m, 2H).

Example 21: Synthesis of 3-methyl-1-(6-(((1*S*,3*S*)-3-((5-methyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)imidazolidine-2,4-dione



***Step-1*: Synthesis of *tert*-butyl ((1*S*,3*S*)-3-((5-(3-methyl-2,4-dioxoimidazolidin-1-yl)pyridin-2-yl)amino)cyclopentyl)carbamate (Int-18)**

[309] To a solution of **Int-13** (500 mg, 1.24 mmol) in IPA (6 mL), K_3PO_4 (790 mg, 3.72 mmol) and 3-methylimidazolidine-2,4-dione (283 mg, 2.48 mmol) were added. The resulting reaction mixture was purged with argon for 15 min. CuI (118 mg, 0.62 mmol) and *N,N*-dimethylcyclohexane-1,2-diamine (88 mg, 0.62 mmol) were added and purged with argon for another 10 min. After stirring at 110 °C for 16 h, the reaction mixture was quenched with water and extracted with EtOAc. The combined organic phases were washed with water, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 20-70% EtOAc in hexane) to afford the title compound as an off white solid (0.4 g, 83%). ESI-MS m/z: 390.2 $[M+H]^+$.

***Step-2*: Synthesis of 1-(6-(((1*S*,3*S*)-3-aminocyclopentyl)amino)pyridin-3-yl)-3-methylimidazolidine-2,4-dione hydrochloride (Int-19)**

[310] A mixture of **Int-18** (400 mg, 1.03 mmol) in 4M HCl in 1,4-dioxane (5 mL) was stirred for 2 h at room temperature. The reaction mixture was concentrated under reduced pressure. The residue was triturated three times with *n*-pentane to provide the crude title compound as a brown solid (0.43 g), which was used in the next step without further purification. ESI-MS m/z: 289.85 $[M+H]^+$.

***Step-3*: Synthesis of *N*-((1*S*,3*S*)-3-((5-(3-methyl-2,4-dioxoimidazolidin-1-yl)pyridin-2-yl)amino)cyclopentyl)cyanamide**

[311] To a solution of **Int-19** (430 mg, 1.32 mmol) in THF (15 mL), was added NaOAc (325 mg, 3.96 mmol) and cyanogen bromide (420 mg, 3.96 mmol). After stirring at room temperature for 16 h, the reaction mixture was filtered through a Celite® pad, washed with EtOAc. The filtrate was concentrated under reduced pressure to afford the crude title compound as a brown sticky solid (0.395 g), which was used in the next step without further purification. ESI-MS m/z: 314.85 $[M+H]^+$.

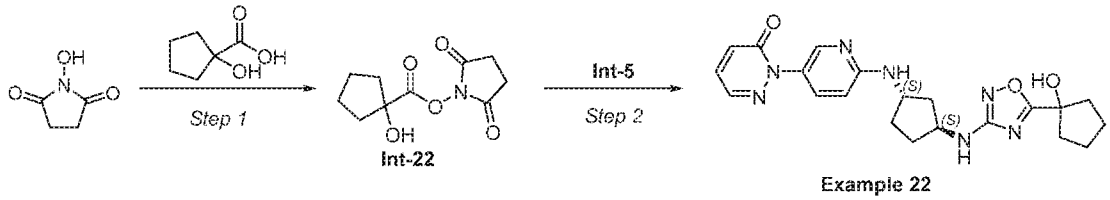
***Step-4*: Synthesis of 2-hydroxy-1-((1*S*,3*S*)-3-((5-(3-methyl-2,4-dioxoimidazolidine-1-yl)pyridin-2-yl)amino)cyclopentyl)guanidine (Int-21)**

[312] To a solution of **Int-20** (395 mg, 1.26 mmol) in EtOH (10 mL), was added hydroxylamine hydrochloride (96 mg, 1.38 mmol) and TEA (0.35 mL, 2.51 mmol). The mixture was heated under stirring at 50 °C for 1 h, then concentrated under reduced pressure. The residue was purified by reverse phase flash column chromatography on C18 (eluent: 2-30% MeCN in water) to afford the title compound as an off-white solid (76 mg, 17%). ESI-MS m/z: 348.15 $[M+H]^+$.

***Step-5*: Synthesis of 3-methyl-1-(6-(((1*S*,3*S*)-3-((5-methyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)imidazolidine-2,4-dione (Example 21)**

[313] To a solution of **Int-21** (70 mg, 0.2 mmol) in NMP (1 mL), was added 2,5-dioxopyrrolidin-1-yl acetate (24.4 mg, 0.18 mmol). After stirring at room temperature for 3 h, the reaction mixture was heated at 70 °C for 16 h. The reaction mixture was quenched with water and the product was extracted with EtOAc. The combined organic phases were washed with water, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC (10-40% acetonitrile/0.05% NH_4OH in water; WATERS XSelect (250 mm x 19 mm), 5.0 µm column, flow rate 18 mL/min) to afford the title compound as a colorless solid (7 mg, 9%). ESI-MS m/z: 372.15 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.10 (dd, *J* = 2.8, 0.4 Hz, 1H), 7.64 (dd, *J* = 9.2, 2.8 Hz, 1H), 6.54 (d, *J* = 9.2 Hz, 1H), 4.33 (s, 2H), 4.30 – 4.21 (m, 1H), 3.99 – 3.91 (m, 1H), 3.03 (s, 3H), 2.40 (s, 3H), 2.28 – 2.15 (m, 2H), 2.07 – 1.99 (m, 1H), 1.92 – 1.83 (m, 1H), 1.68 – 1.49 (m, 2H).

Example 22: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-(1-hydroxycyclopentyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one



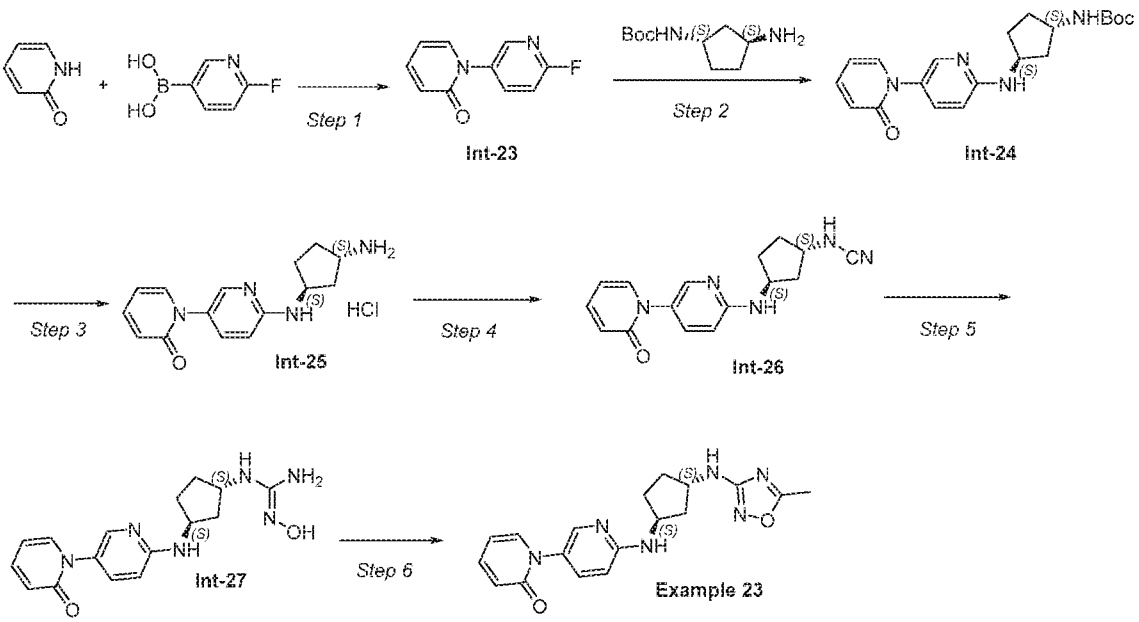
***Step-1*: Synthesis of 2,5-dioxopyrrolidin-1-yl 1-hydroxycyclopentane-1-carboxylate**

[314] To a solution of 1-hydroxycyclopentane-1-carboxylic acid (100 mg, 0.768 mmol) and 1-hydroxypyrrolidine-2,5-dione (124 mg, 1.08 mmol) in THF (5 mL) was added a solution of EDC hydrochloride (177 mg, 0.92 mmol) in DCM (2 mL) dropwise at 0 °C. The mixture was allowed to warm to room temperature and was stirred for 16 h. The reaction mixture was concentrated under reduced pressure. The residue was partitioned between water and EtOAc. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide crude title compound as off-white solid (0.2 g), which was used in the next step without further purification. ^1H NMR (300 MHz, $CDCl_3$) δ 2.82 (s, 4H), 2.41-2.31 (m, 2H), 2.05-1.82 (m, 6H).

***Step-2*: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-(1-hydroxycyclopentyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one (Example 22)**

[315] To a solution of **Int-22** (124 mg, 0.55 mmol) in NMP (3 mL) was added **Int-5** (180 mg, 0.55 mmol). After stirring at room temperature for 4 h, the reaction mixture was heated under stirring to 70 °C for 16 h. After quenching with water, the product was extracted with EtOAc. The combined organic phases were washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by preparative HPLC (10-40% acetonitrile/0.05% NH_4OH in water; WATERS XSelect (250 mm x 19 mm), 5.0 µm column, flow rate 18 mL/min) to afford the title compound as yellow solid (9 mg, 4%). ESI-MS m/z: 424.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.14 (dd, *J* = 2.8, 0.4 Hz,1H), 8.02 (dd, *J* = 4.0, 1.6 Hz, 1H), 7.59 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.45 (dd, *J* = 9.6, 4.0 Hz, 1H), 7.05 (dd, *J* = 9.6, 2.0 Hz, 1H), 6.58 (d, *J* = 9.2 Hz, 1H), 4.38 – 4.30 (m, 1H), 4.03 – 3.96 (m, 1H), 2.30 – 2.19 (m, 2H), 2.18 – 1.88 (m, 8H), 1.86 – 1.78 (m, 2H), 1.70 – 1.52 (m, 2H).

Example 23: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-(1-hydroxycyclopentyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one



***Step-1*: Synthesis of 6'-fluoro-2*H*-[1,3'-bipyridin]-2-one (Int-23)**

[316] To a solution of pyridin-2(1*H*)-one (5 g, 24.4 mmol) in DCM (150 mL), was added pyridine (2.65 g, 33.6 mmol), (6-fluoropyridin-3-yl)boronic acid (3.79 g, 26.9 mmol). After stirring at room temperature for 10 min, $Cu(OAc)_2$ (4.068 g, 22.4 mmol) was added to the mixture. The resulting mixture was stirred at room temperature with oxygen balloon for 16 h. After quenching with water, the product was extracted with DCM. The combined organic phases were dried over sodium sulfate, filtered, and concentrated

under reduced pressure. The residue was purified with flash column chromatography on silica gel (eluent: 0-70% EtOAc in hexane) to afford the title compound as a yellow solid (0.68 g, 16%). ESI-MS m/z: 190.5 $[M+H]^+$.

***Step-2*: Synthesis of *tert*-butyl ((1*S*,3*S*)-3-((2-oxo-2*H*-[1,3'-bipyridin]-6'-yl)amino) cyclopentyl)carbamate**

[317] To a solution of *tert*-butyl ((1*S*,3*S*)-3-aminocyclopentyl)carbamate (500 mg, 2.5 mmol) in NMP (20 mL) was added DIPEA (1.3 mL, 7.5 mmol) and **Int-23** (573 mg, 3 mmol). The mixture was heating under stirring in a microwave reactor at 140 °C for 3 h, then quenched with water and extracted with EtOAc. The combined organic phases were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified with flash column chromatography on silica gel (eluent: 0-70% EtOAc in hexane) to afford the title compound as an off white solid (0.28 g, 30%). ESI-MS m/z: 371.2 $[M+H]^+$.

***Step-3*: Synthesis of 6'-(((1*S*,3*S*)-3-aminocyclopentyl)amino)-2*H*-[1,3'-bipyridin]-2-one hydrochloride (Int-25)**

[318] To a mixture of **Int-24** (0.28 g, 0.756 mmol) in DCM (10 mL) was added 4M HCl in 1,4-dioxane (2.3 mL). After stirring for 2 h at room temperature, the reaction mixture was concentrated under reduced pressure. The residue was triturated three times with *n*-pentane to provide crude title compound as a brown solid (0.3 g), which was used in the next step without further purification. ESI-MS m/z: 271.05 $[M+H]^+$.

***Step-4:* Synthesis of *N*-((1*S*,3*S*)-3-((2-oxo-2*H*-[1,3'-bipyridin]-6'-yl)amino)cyclopentyl)cyanamide (Int-26)**

[319] To a solution of **Int-25** (0.3 g, 0.98 mmol) in THF (10 mL) was added NaOAc (241 mg, 2.94 mmol) and cyanogen bromide (308 mg, 2.94 mmol) at 0 °C. After stirring at room temperature for 16 h, the reaction mixture was filtered through a Celite® pad, and the reside was washed with EtOAc. The filtrate was wash fractions were combined and concentrated under reduced pressure to afford the crude title compound as a brown gum(0.4 g), which was used in next step without further purification. ESI-MS m/z: 296.1 $[M+H]^+$.

***Step-5*: Synthesis of 2-hydroxy-1-((1*S*,3*S*)-3-((2-oxo-2*H*-[1,3'-bipyridin]-6'-yl)amino)cyclopentyl)guanidine (Int-27)**

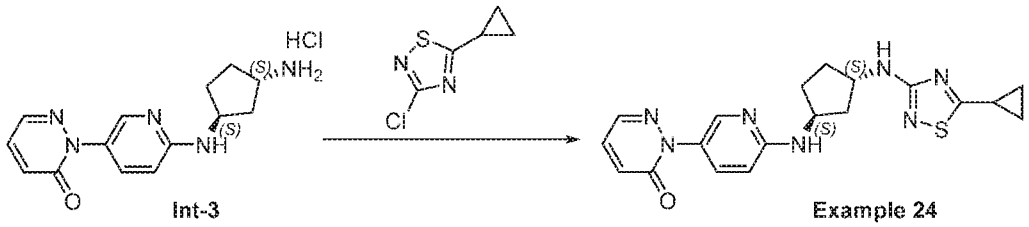
[320] To a solution of **Int-26** (400 mg, 1.36 mmol) in EtOH (10 mL), were added hydroxylamine hydrochloride (102 mg, 1.49 mmol) and TEA (0.3 mL, 2.71 mmol). The mixture was heated under stirring at 50 °C for 1 h, then concentrated under reduced pressure. The residue was purified by reverse

phase flash column chromatography on C18 (eluent: 2-30% acetonitrile in water) to afford the title compound as a yellow gum (0.18 g, 41%). ESI-MS m/z: 329.1 $[M+H]^+$.

***Step-6*: Synthesis of 6'-(((1*S*,3*S*)-3-((5-methyl-1,2,4-oxadiazol-3-yl)amino) cyclopentyl)amino)-2*H*-[1,3'-bipyridin]-2-one (Example 23)**

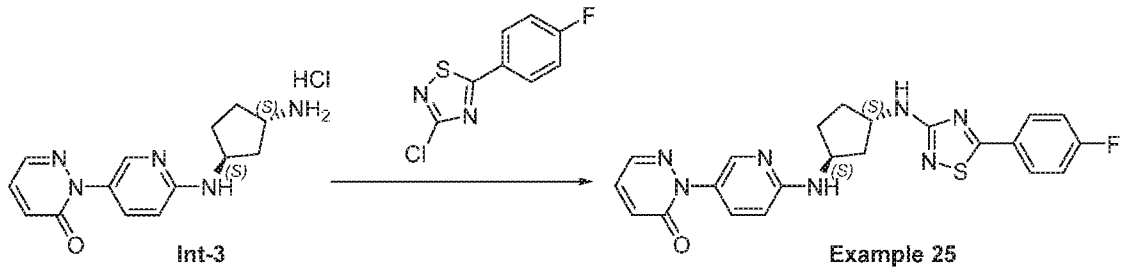
[321] To a solution of acetic acid (8 mg, 0.25 mmol) in DCM (4 mL), was added HATU (95 mg, 0.25 mmol) followed by DIPEA (39 mg, 0.3 mmol). After stirring for 30 min, the reaction mixture was added dropwise to a solution of **Int-27** (99 mg, 0.3 mmol) in DCM (5 mL) and NMP (0.5 mL). After stirring at room temperature for 1 h, the reaction mixture was concentrated under reduced pressure and the residue was dissolved in DCE (5 mL). The mixture was heated under stirring at 100 °C for 2 h, then concentrated under reduced pressure. The residue was purified with flash column chromatography on silica gel (eluent: 0-10% MeOH in DCM). The crude product was purified by preparative HPLC (15-55% acetonitrile/0.05% NH_4OH in water; Kinetex® EVO (250 mm x 19 mm), 5.0 µm column, flow rate 15 mL/min) to afford the title compound as a colorless solid (7 mg, 7%). ESI-MS m/z: 353.05 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.93 (dd, J = 2.8, 0.8 Hz 1H), 7.62 – 7.56 (m, 2H), 7.42 (dd, J = 9.2, 2.8 Hz, 1H), 6.62 – 6.58 (m, 2H), 6.47 – 6.43 (m, 1H), 4.37 – 4.30 (m, 1H), 4.01 – 3.93 (m, 1H), 2.40 (s, 3H), 2.38 – 2.16 (m, 2H), 2.10 – 2.01 (m, 1H), 1.96 – 1.88 (m 1H), 1.68 – 1.51 (m, 2H).

Example 24: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-cyclopropyl-1,2,4-thiadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one



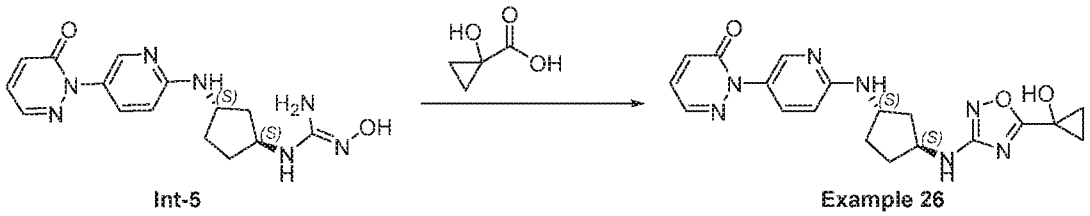
[322] To a solution of **Int-3** (10 mg, 0.029 mmol) and 3-chloro-5-cyclopropyl-1,2,4-thiadiazole (14 mg, 0.087 mmol) in NMP (0.5 mL) was added DIPEA (0.5 mL, 2.96 mmol). The mixture was heated under stirring at 160 °C for 6 h, then purified by reverse phase flash column chromatography on C18 (eluent: 10-80% ACN/water with 0.1% NH_4OH) to provide the title compound as a yellow solid (4.4 mg, 28%). ESI-MS m/z: 396.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.27 (d, 1H, J = 2.4 Hz), 8.11 (dd, 1H, J = 2.4, 9.8 Hz), 7.98 (dd, 1H, J = 1.5, 3.9 Hz), 7.39 (dd, 1H, J = 3.9, 9.3 Hz), 7.15-7.10 (m, 1H), 6.61 (d, J = 9.2 Hz, 1H) 4.28-4.19 (m, 2H), 2.42-2.19 (m, 3H), 2.15-2.08 (m, 2H), 1.75-1.69 (m, 2H), 1.27-1.16 (m, 2H), 1.07-0.92 (m, 2H).

Example 25: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-(4-fluorophenyl)-1,2,4-thiadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one



[323] To a solution of **Int-3** (22.94 mg, 0.075 mmol) and 3-chloro-5-(4-fluorophenyl)-1,2,4-thiadiazole (8 mg, 0.037 mmol) in NMP (0.5 mL) was added DIPEA (0.5 mL, 2.96 mmol). The mixture was heated under stirring at 180 °C for 1.5 h, then purified by reverse phase flash column chromatography on C18 (eluent: 10-80% ACN/water with 0.1% NH_4OH) to provide the title compound as a yellow solid (1.2 mg, 7%). ESI-MS m/z: 450.7 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.25 (d, 1H, J = 2.4 Hz), 8.04 (dd, 1H, J = 2.4, 9.8 Hz), 7.97 (dd, 1H, J = 1.5, 3.9 Hz), 7.92-7.88 (m, 2H), 7.39 (dd, 1H, J = 3.9, 9.8 Hz), 7.19-7.13 (m, 2H), 7.05-6.98 (m, 2H), 4.31-4.29 (m, 1H), 4.21-4.16 (m, 1H), 2.32-2.22 (m, 2H), 2.11-2.08 (m, 2H) 1.71-1.64 (m, 2H)

Example 26: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-(1-hydroxycyclopropyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one



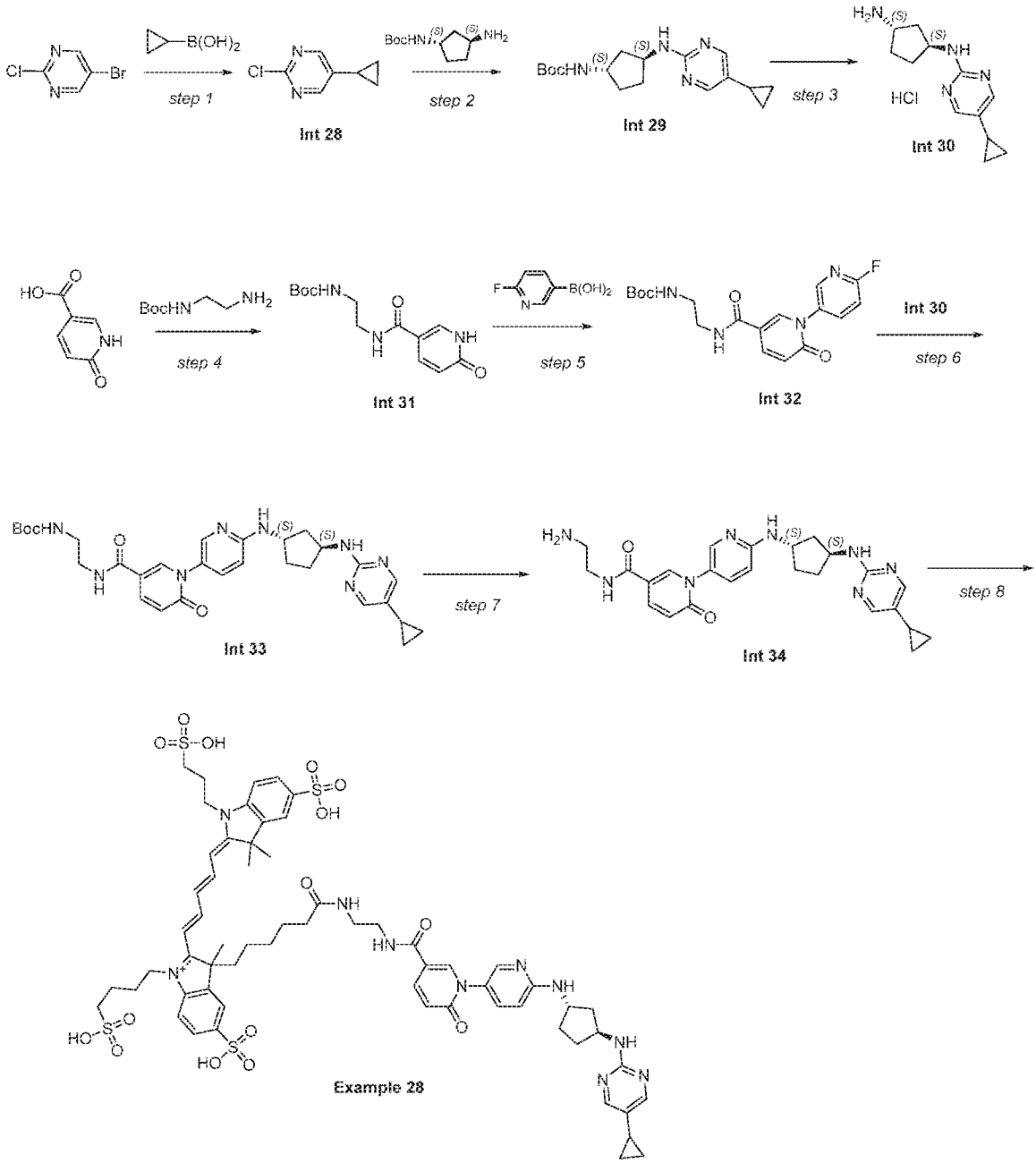
[324] A mixture of 1-hydroxycyclopropane-1-carboxylic acid (2.48 mg, 0.024 mmol), HATU (9.24 mg, 0.024 mmol) and DIPEA (12.73 µL, 0.073 mmol) in DMF (0.5 mL) was stirred at room temperature for 20 min, then **Int-5** (10 mg, 0.024 mmol) was added to the mixture. After stirring at room temperature for another 30 min., the reaction mixture was heated under stirring at 100 °C for 1 h. After cooling to room temperature, the mixture was purified by reverse phase flash column chromatography on C18 (eluent: 10-80% ACN/water with 0.1% NH_4OH) to provide the title compound as a yellow solid (0.3 mg, 3%). ESI-MS m/z: 396.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.70-8.69 (m, 1H), 8.09 (d, 1H, J = 9.0 Hz), 7.92 (d, 1H, J = 4.3 Hz), 7.47 (d, 1H, J = 9.6 Hz), 7.09 (dd, 1H, J = 4.3, 9.6 Hz), 6.86 (d, 1H, J = 9.0 Hz), 4.14-4.08 (m, 2H), 2.29-2.25 (m, 1H,), 2.17-2.10 (m, 3H), 1.65-1.53 (m, 2H), 1.17-1.12 (m, 2H), 0.96-0.90 (m, 2H).

Example 27: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one

Int-5 Example 27

[325] To a mixture of **Int-5** (11 mg, 0.033 mmol) in pyridine (0.5 mL) was added TFAA (7.08 µL, 0.05 mmol) at 0 °C. After stirring at room temperature for 1 h, the mixture was heated at 60 °C for 2 h. After cooling to rt, the mixture was purified by reverse phase flash column chromatography on C18 (eluent: 10-80% ACN/water with 0.1% NH_4OH) to provide the title compound as a yellow solid (0.4 mg, 3%). ESI-MS m/z: 408.2 $[M+H]^+$.^{1}H NMR (400 MHz, CD_3OD) δ 8.69-8.67 (m, 1H), 8.09 (d, 1H, J = 9.0 Hz), 7.92 (d, 1H, J = 4.3 Hz), 7.47 (d, 1H, J = 9.6 Hz), 7.09 (dd, 1H, J = 4.3, 9.6 Hz), 6.86 (d, 1H, J = 9.0 Hz), 4.31-4.10 (m, 2H), 2.27-2.05 (m, 4H), 1.65-1.53 (m, 2H).

Example 28: Synthesis of 3-(6-((2-(6'-(((1*S*,3*S*)-3-((5-cyclopropylpyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2*H*-[1,3'-bipyridine]-5-carboxamido)ethyl)amino)-6-oxohexyl)-2-((1*E*,3*E*)-5-((*E*)-3,3-dimethyl-5-sulfo-1-(3-sulfopropyl)indolin-2-ylidene)penta-1,3-dien-1-yl)-3-methyl-5-sulfo-1-(4-sulfobutyl)-3*H*-indol-1-ium



***Step-1*: Synthesis of 2-chloro-5-cyclopropylpyrimidine (Int-28)**

[326] To a solution of 5-bromo-2-chloropyrimidine (3 g, 15.5 mmol) in 1,4-dioxane (50 mL) was added cyclopropyl boronic acid (1.6 g, 18.61 mmol) followed by Cs_2CO_3 (7.6 g, 23.26 mmol) at room temperature. After degassing with argon for 15 min, Pd(dppf)Cl_2.DCM (0.38 g, 0.46 mmol) was added to the mixture and the mixture was further purged with argon for 10 min at room temperature. The mixture was heated under stirring at 90 °C for 16 h, then filtered through a Celite® pad and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica

gel (eluent: 0-20% EtOAc in hexane) to afford the title compound as a yellow solid (1.8 g, 75%). ESI-MS m/z: 155.10 $[M+H]^+$.

***Step-2*: Synthesis of *tert*-butyl ((1*S*,3*S*)-3-((5-cyclopropylpyrimidin-2-yl)amino)cyclopentyl)carbamate (Int-29)**

[327] To a solution of **Int-28** (0.8 g, 5.17 mmol) in DMSO (20 mL), were added DIPEA (2.7 mL, 15.52 mmol) and *tert*-butyl ((1*S*,3*S*)-3aminocyclopentyl) carbamate (1.09 g, 5.43 mmol) at room temperature. The mixture was heated under stirring at 110 °C for 16 h, then cooled to rt and quenched with water. The product was extracted with EtOAc. The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 0-40% EtOAc in hexane) to afford the title compound as a colorless solid (0.8 g, 49%). ESI-MS m/z: 318.85 $[M+H]^+$.

***Step-3*: Synthesis of (1*S*,3*S*)-N^1-(5-cyclopropylpyrimidin-2-yl)cyclopentane-1,3-diamine hydrochloride (Int-30)**

[328] A mixture of **Int-29** (0.8 g, 2.51 mmol) in 4 M HCl in 1,4-dioxane (8 mL) was stirred for 2 h. The mixture was concentrated under reduced pressure. The residue was triturated three times with *n*-pentane (10 mL) to afford the title compound as a colorless solid (0.8 g), which was used in the next step without further purification. ESI-MS m/z: 218.75 $[M+H]^+$.

***Step-4*: Synthesis of *tert*-butyl (2-(6-oxo-1,6-dihydropyridine-3-carboxamido)ethyl)carbamate (Int-31)**

[329] To a solution of 6-oxo-1,6-dihydropyridine-3-carboxylic acid (1 g, 7.18 mmol) in DMF (10 mL) were added HATU (3.5 g, 9.35 mmol) and DIPEA (4.9 mL, 28.77 mmol) followed by *tert*-butyl (2-aminoethyl) carbamate (1.3 g, 7.9 mmol) at 0 °C. The mixture was allowed to warm to room temperature and was stirred for 16 h. The mixture was quenched with water. The product was extracted with EtOAc. The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 0-20% EtOAc in hexane) to afford the title compound as a yellow solid (1.4 g, 69%). ESI-MS m/z: 281.75 $[M+H]^+$.

***Step-5*: Synthesis of *tert*-butyl (2-(6'-fluoro-2-oxo-2*H*-[1,3'-bipyridine]-5-carboxamido)ethyl)carbamate (Int-32)**

[330] To a stirred solution of **Int-31** (1 g, 3.55 mmol) in DCM (20 mL) was added (6-fluoropyridin-3-yl)boronic acid (601 mg, 4.26 mmol) at room temperature. The mixture was purged with oxygen for 10 min., then TEA (1.5 mL, 10.66 mmol) and copper acetate (1.9 g, 10.66 mmol) were added at room temperature. After stirring under O_2 balloon for 48 h at room temperature, the reaction mixture was

diluted with cold water. The product was extracted with DCM. The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 0-20% EtOAc in hexane) to afford the title compound as yellow sticky solid (0.4 g, 30%). ESI-MS m/z: 376.85 $[M+H]^+$.

***Step-6*: Synthesis of *tert*-butyl (2-(6'-(((1*S*,3*S*)-3-((5-cyclopropylpyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2*H*-[1,3'-bipyridine]-5-carboxamido)ethyl)carbamate (Int-33)**

[331] To a stirred solution of **Int-32** (0.23 g, 0.61 mmol) in DMSO (5 mL), was added DIPEA (0.31 mL, 1.83 mmol), followed by **Int-30** (0.156 g, 0.61 mmol). The reaction mixture was heated under stirring at 120 °C for 16 h, then cooled to rt. The mixture was quenched with water and extracted with EtOAc. The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 0-10% MeOH in DCM) to afford the title compound as a brown solid (80 mg, 23%). ESI-MS m/z: 575.35 $[M+H]^+$.

***Step-7*: Synthesis of *N*-(2-aminoethyl)-6'-(((1*S*,3*S*)-3-((5-cyclopropylpyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2*H*-[1,3'-bipyridine]-5-carboxamide (Int-34)**

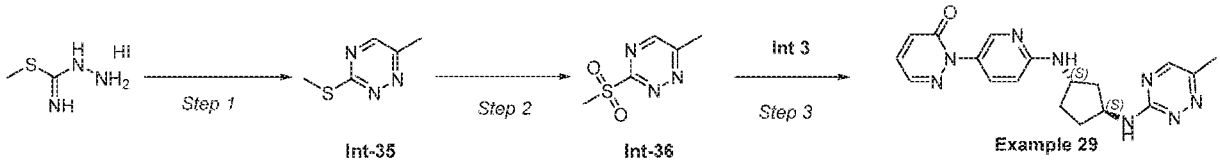
[332] 4 M HCl in 1,4-dioxane (2 mL) was added to a mixture of **Int-33** (0.8 g, 2.51 mmol) in MeOH (2 mL) at room temperature. After stirring at room temperature for 2 h, the mixture was concentrated under reduced pressure. The residue was purified by preparative HPLC (10-50% acetonitrile/0.02% NH_4OH in water; WATERS XBRIDGE (19 mm x150 mm), 5.0 µm column, flow rate 20 mL/min) to afford the title compound as an off-white solid (20 mg, 30%). ESI-MS m/z: 475.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.24 (d, J = 2.4 Hz, 1H), 8.07 (s, 2H), 8.01 – 7.97 (m, 2H), 7.47 (dd, J = 8.8, 2.4 Hz, 1H), 6.62 (dd, J = 10.0, 2.4 Hz, 2H), 4.41 – 4.31 (m, 2H), 3.47 (t, J = 6.0 Hz, 2H), 2.91 (t, J = 6.4 Hz, 2H), 2.32 – 2.19 (m, 2H), 1.99 (t, J = 6.8 Hz, 2H), 1.79 – 1.72 (m, 1H), 1.65 – 1.53 (m, 2H), 0.94 – 0.87 (m, 2H), 0.63 – 0.58 (m, 2H).

***Step-8*: Synthesis of 3-(6-((2-(6'-(((1*S*,3*S*)-3-((5-cyclopropylpyrimidin-2-yl)amino)cyclopentyl)amino)-2-oxo-2*H*-[1,3'-bipyridine]-5-carboxamido)ethyl)amino)-6-oxohexyl)-2-((1*E*,3*E*)-5-((*E*)-3,3-dimethyl-5-sulfo-1-(3-sulfopropyl)indolin-2-ylidene)penta-1,3-dien-1-yl)-3-methyl-5-sulfo-1-(4-sulfobutyl)-3*H*-indol-1-ium**

[333] A solution of Alexa Fluor® 647 NHS ester (21 mg, 0.016 mmol) in acetonitrile (1 mL) was added to **Int-33** (7.82 mg, 0.016 mmol), followed by DIPEA (57.6 µL, 0.33 mmol) at room temperature. The reaction vial was wrapped in aluminum foil. After stirring at room temperature for 4 h, the mixture was purified by reverse phase flash column chromatography on C18 (eluent: 10-80% ACN/water with 0.1%

NH_4OH) to provide the ammonium salt of the title compound as a blue solid (15.6 mg, 67%). ESI-MS m/z: 665.22 $[M+2H]^{2+}$.

Example 29: Synthesis of 2-(6-(((1*S*,3*S*)-3-((6-methyl-1,2,4-triazin-3-yl)amino) cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one



***Step-1*: Synthesis of 6-methyl-3-(methylthio)-1,2,4-triazine (Int-35)**

[334] To a stirred solution of methyl hydrazinecarbimidothioate hydrogen iodide (5 g, 21.45 mmol) in EtOH (100 mL), was added 1,1-dimethoxypropan-2-one (2.5 g, 21.45 mmol) at room temperature. After stirring at 70 °C for 4 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 0-20% EtOAc in hexane) to provide the title compound as a brown oil (2.3 g, 76%). ESI-MS *m/z*: 141.95 $[M+H]^+$.

***Step-2*: Synthesis of 6-methyl-3-(methylsulfonyl)-1,2,4-triazine (Int-36)**

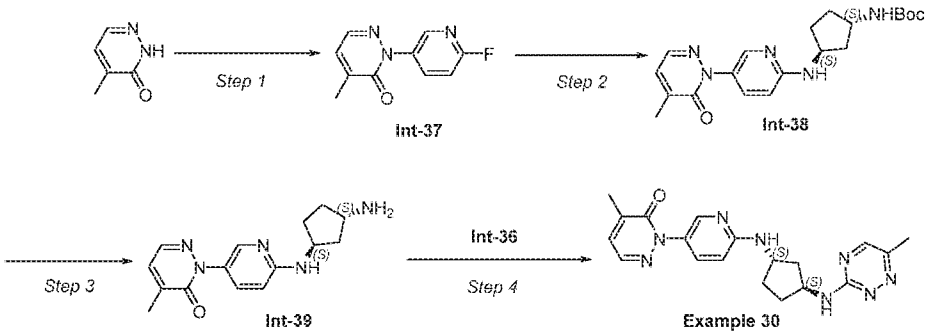
[335] To a solution of **Int-35** (2.3 g, 16.29 mmol) in DCM (50 mL), was added mCPBA (8.4 g, 48.87 mmol) portion wise at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 2 h. The reaction mixture was concentrated under reduced pressure, and then the residue was purified by flash column chromatography on silica gel (eluent: 20-80% EtOAc in hexane) to provide the title compound as an off white solid (1.3 g, 61%). ESI-MS *m/z*: 173.95 $[M+H]^+$.

***Step-3*: Synthesis of 2-(6-(((1*S*,3*S*)-3-((6-methyl-1,2,4-triazin-3-yl)amino) cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one (Example 29)**

[336] To a solution of **Int-3** (1 g, 3.69 mmol) in NMP (10 mL), was added Na_2CO_3 (0.78 g, 7.37 mmol) followed by **Int-36** (0.96 g, 5.53 mmol). After stirring at room temperature for 16 h, the reaction mixture was quenched with water and the product was extracted with EtOAc. The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 0-10% DCM in MeOH). The obtained crude product was purified by preparative HPLC (10-45% acetonitrile/0.02% NH_4OH in water; WATERS XSELECT (250 mm x 20 mm), 5.0 µm column, flow rate 18 mL/min) to afford the title compound as a yellow solid (60 mg, 4.4%). ESI-MS *m/z*: 364.9 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.18 (s, 1H), 8.14 (d, *J* = 2.8 Hz, 1H), 8.01 (dd, *J* = 4.0, 1.6 Hz, 1H), 7.59 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.45 (dd, *J* = 9.6,

4.0 Hz, 1H), 7.05 (dd, *J* = 9.6, 1.6 Hz, 1H), 6.59 (d, *J* = 9.2 Hz, 1H), 4.49 – 4.32 (m, 2H), 2.43 (s, 3H), 2.32 – 2.22 (m, 2H), 2.10 – 1.99 (m, 2H), 1.71 – 1.55 (m, 2H).

Example 30: Synthesis of 2-(6-(((1*S*,3*S*)-3-aminocyclopentyl) amino)pyridin-3-yl)-4-methylpyridazin-3(2*H*)-one



***Step-1*: Synthesis of 2-(6-fluoropyridin-3-yl)-4-methylpyridazin-3(2*H*)-one (Int-37)**

[337] To a solution of 2-fluoro-5-iodopyridine (5 g, 22.42 mmol) in DMSO (100 mL), was added potassium carbonate (6.1 g, 44.84 mmol) followed by 4-methylpyridazin-3(2*H*)-one (2.5 g, 23.54 mmol). The reaction mixture was purged with argon for 15 min at room temperature, then CuI (0.42 g, 2.24 mmol) and *trans-N, N*-dimethylcyclohexane-1,2-diamine (0.31 g, 2.24 mmol) were added and purged with argon for another 10 min. After stirring at 130 °C for 16 h, the reaction mixture was quenched with water and the product was extracted with EtOAc. The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 0-60% EtOAc in hexane) to afford the title compound as an off white solid (1.5 g, 32%). ESI-MS *m/z*: 205.9 $[M+H]^+$.

***Step-2*: Synthesis of tert-butyl ((1*S*,3*S*)-3-((5-(5-methyl-6-oxopyridazin-1(6*H*)-yl) pyridine-2-yl) amino) cyclopentyl) carbamate (Int-38)**

[338] To a solution of *tert*-butyl ((1*S*,3*S*)-3-aminocyclopentyl)carbamate (1 g, 4.99 mmol) in DMSO (20 mL), were added DIPEA (2.56 mL, 14.98 mmol) and **Int-37**(1.1 g, 5.49 mmol). After stirring at 120 °C for 16 h, the reaction mixture was quenched with water and the product was extracted with EtOAc. The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 0-70% EtOAc in hexane) to afford the title compound as an off-white solid (1.5 g, 78%), ESI-MS *m/z*: 386.0 $[M+H]^+$.

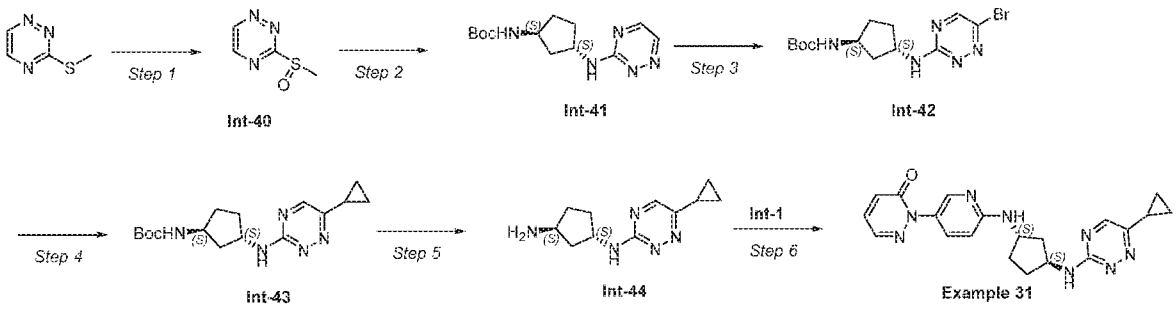
***Step3:* Synthesis of 2-(6-(((1*S*,3*S*)-3-aminocyclopentyl)amino)pyridin-3-yl)-4-methylpyridazin-3(2*H*)-one (Int-39)**

[339] To a mixture of **Int-38** (1.5 g, 3.89 mmol) in MeOH (10 ml) was added 4 M HCl in 1,4-dioxane (6 mL). After stirring for 2 h at room temperature, the mixture was concentrated under reduced pressure. The crude product was treated with Amberlyst® A21 ion exchange resin (3 g) in MeOH (20 mL) and stirred for 15 min. Then the mixture was filtered to remove the resin and the resin was washed with methanol. The filtrate was concentrated under reduced pressure to afford the title compound as a brown solid (1.3 g, crude), which was used in the next step without further purification. ESI-MS m/z: 285.95 $[M+H]^+$.

Step-4: **Synthesis of 4-methyl-2-(6-(((1*S*,3*S*)-3-((6-methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one (Example 30)**

[340] To a solution of **Int-39** (0.3 g, 1.05 mmol) in NMP (5 mL), was added Na_2CO_3 (0.22 g, 2.1 mmol) followed by **Int-36** (0.18 g, 1.05 mmol). After stirring at rt for 16 h, the reaction mixture was quenched with water and the product was extracted with EtOAc. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 0-10% MeOH in DCM). The crude product was purified by preparative HPLC (20-40% acetonitrile/0.02% NH_4OH in water; WATERS XSELECT (250 mm x 20 mm), 5.0 µm column, flow rate 18 mL/min) to provide the title compound as a yellow solid (23 mg, 5.7%), ESI-MS m/z: 379.05 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.19 (s, 1H), 8.13 (dd, *J* = 2.8, 0.4 Hz, 1H), 7.89 (d, *J* = 4.0, Hz, 1H), 7.58 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.33 – 7.32 (m, 1H), 6.60 (dd, *J* = 8.8, 0.4 Hz, 1H), 4.49 – 4.33 (m, 2H), 2.44 (s, 3H), 2.32 – 2.24 (m, 2H), 2.22 (s, 3H), 2.12 – 1.98 (m, 2H), 1.69 – 1.60 (m, 2H).

<u>Example 31: Synthesis of 2-(6-(((1*S*,3*S*)-3-((6-cyclopropyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one</u>



***Step-1*: Synthesis of 3-(methylsulfinyl)-1,2,4-triazine (Int-40)**

[341] To a solution of 3-(methylthio)-1,2,4-triazine (3 g, 23.59 mmol) in DCM (300 mL) was added mCPBA (12.21 g, 70.77 mmol) portion wise at -50°C. After stirring at -50°C for 4 h, the reaction mixture was filtered through a Celite® pad, the filtrate was concentrated under reduced pressure. The residue was

purified by flash column chromatography on silica gel (eluent: 20-80% EtOAc in Hexane) to provide title compound as a yellow sticky solid (2.5 g, 74%). ESI-MS m/z: 143.9 $[M+H]^+$.

***Step-2*: Synthesis of tert-butyl ((1*S*,3*S*)-3-((1,2,4-triazin-3-yl)amino)cyclopentyl) carbamate (Int-41)**

[342] To a solution of *tert*-butyl ((1*S*,3*S*)-3-aminocyclopentyl)carbamate (2 g, 9.98 mmol) in NMP (20 mL) were added Na_2CO_3 (3.17 g, 29.96 mmol) and **Int-40** (2.14 g, 14.98 mmol). After stirring for 16 h, the reaction mixture was quenched with cold water and the product was extracted with EtOAc. The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 0-10% MeOH in DCM) to afford the title compound as an off-white solid (2.3 g, 82%), ESI-MS *m/z*: 280.0 $[M+H]^+$.

***Step-3*: Synthesis of tert-butyl ((1*S*,3*S*)-3-((6-bromo-1,2,4-triazin-3-yl)amino)cyclopentyl)carbamate (Int-42)**

[343] To a stirred solution of **Int-41** (3.5 g, 12.52 mmol) in acetonitrile (80 mL) and water (120 mL) was added NBS (2.3 g, 13.14 mmol) portion wise. After stirring for 8 h, the reaction mixture was quenched with water and the product was extracted with EtOAc. The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 0-10% MeOH in DCM) to afford the title compound as a yellow solid (2.9 g, 65%), ESI-MS *m/z*: 359.75 $[M+H]^+$.

***Step-4*: Synthesis of tert-butyl ((1*S*,3*S*)-3-((6-cyclopropyl-1,2,4-triazin-3-yl)amino) cyclopentyl)carbamate (Int-43)**

[344] To a solution of **Int-42** (1 g, 2.79 mmol) in a mixture of 1,4-dioxane and water (30 mL, 3:1), were added cyclopropyl boronic acid (1.2 g, 13.95 mmol) and Cs_2CO_3 (2.72 g, 8.37 mmol) and the reaction mixture was purged with argon for 15 min, then $Pd(OAc)_2$ (63 mg, 0.27 mmol) and tricyclohexyl phosphine (0.16 g 0.55 mmol) were added and purged with argon for another 10 min. After stirring at 100 °C for 16 h, the reaction mixture was filtered through a Celite® pad, the filtrate was quenched with water and the product was extracted with EtOAc. The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 0-10% MeOH in DCM) to afford the title compound as a brown solid (0.65 g, 72.8%). ESI-MS *m/z*: 319.95 $[M+H]^+$.

***Step-5*: Synthesis of (1*S*,3*S*)-*N1*-(6-cyclopropyl-1,2,4-triazin-3-yl)cyclopentane-1,3-diamine (Int-44)**

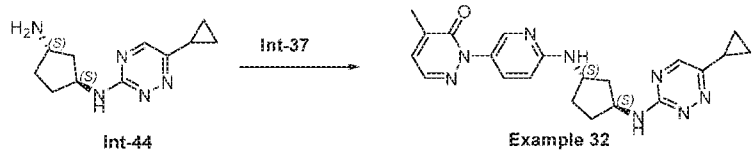
[345] A mixture of **Int-43** (0.65 g, 2.03 mmol) in 4 M HCl in 1,4-dioxane (7 mL) was stirred for 2 h at room temperature. The mixture was concentrated under reduced pressure. The crude was treated with Amberlyst® A21 ion exchange resin (1.3 g) in MeOH (20 mL) and stirred for 15 min. The mixture was

filtered to remove the resin and the resin was washed with methanol. The filtrate was concentrated under reduced pressure to afford the title compound as a brown solid (0.6 g, crude), which was used in the next step without further purification. ESI-MS m/z: 220.0 $[M+H]^+$.

***Step-6*: Synthesis of 2-(6-(((1*S*,3*S*)-3-((6-cyclopropyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one (Example 31)**

[346] To a solution of **Int-44** (450 mg, 2.05 mmol) in NMP (3 mL), were added DIPEA (0.58 mL, 6.15 mmol) and **Int-1** (470 mg, 2.46 mmol). After stirring at 140 °C for 3 h under microwave irradiation, the reaction mixture was quenched with water and the product was extracted with EtOAc. The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 0-10% MeOH in DCM). The crude product was purified by preparative HPLC (20-60% acetonitrile/0.02% NH_4OH in water; YMC (150 mm x 21.2 mm), 5.0 µm column, flow rate 15 mL/min) to provide the title compound as a yellow solid (35 mg, 4.3%), ESI-MS m/z: 391.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.16 (s, 1H), 8.15 (dd, *J* = 2.8, 0.8 Hz, 1H), 8.03 (dd, *J* = 3.6, 1.6 Hz, 1H), 7.60 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.46 (dd, *J* = 9.2, 3.6 Hz, 1H), 7.06 (dd, *J* = 9.2, 1.6 Hz, 1H), 6.60 (dd, *J* = 8.8, 0.4 Hz, 1H), 4.45 – 4.32 (m, 2H), 2.31 – 2.25 (m, 2H), 2.09 – 2.00 (m, 3H), 1.68 – 1.62 (m, 2H), 1.05 – 0.95 (m, 4H).

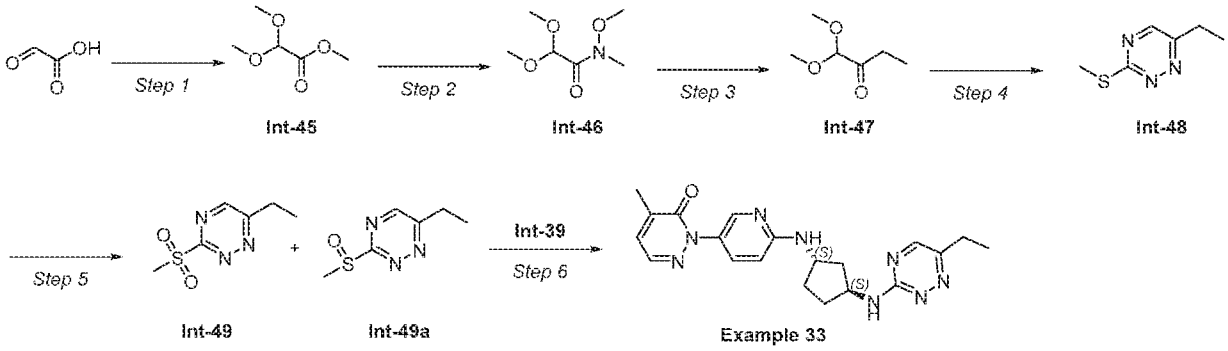
Example 32: Synthesis of 2-(6-(((1*S*,3*S*)-3-((6-cyclopropyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-4-methylpyridazin-3(2*H*)-one



Int-44 Example 32

[347] To a solution of **Int-44** (200 mg, 0.91 mmol) in NMP (2 mL), DIPEA (0.4 mL, 2.73 mmol) was added followed by **Int-37** (220 mg, 1.09 mmol). After stirring at 140 °C for 3 h under microwave irradiation, the reaction mixture was quenched with water and the product was extracted with EtOAc. The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 0-10% MeOH in DCM) to provide the title compound as a brown solid (30 mg, 8.1%), ESI-MS m/z: 405.05 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.16 (s, 1H), 8.13 (d, *J* = 2.4 Hz, 1H), 7.89 (d, *J* = 4.0 Hz, 1H), 7.58 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.33 – 7.32 (m, 1H), 6.59 (d, *J* = 9.2 Hz, 1H), 4.47 – 4.32 (m, 2H), 2.32 – 2.26 (m, 2H), 2.22 (s, 3H), 2.10 – 2.01 (m, 3H), 1.68 – 1.59 (m, 2H), 1.06 – 0.95 (m, 4H).

Example 33: Synthesis of 2-(6-(((1*S*,3*S*)-3-((6-ethyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-4-methylpyridazin-3(2*H*)-one



***Step-1*: Synthesis of methyl 2,2-dimethoxyacetate (Int-45)**

[348] To a solution of 2-oxoacetic acid (20 g, 270.1 mmol) in trimethoxy methane (150 mL) was added conc. H_2SO_4 (2 mL). After stirring at 100 °C for 4 h, the reaction mixture was quenched with cold water and the product was extracted with EtOAc. The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to provide the crude title compound as a pale yellow liquid (15 g, 41%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.82 (s, 1H), 3.80 (s, 3H), 3.42 (s, 6H).

***Step-2*: Synthesis of *N,2,2*-trimethoxy-*N*-methylacetamide (Int-46)**

[349] To a solution of *N,O*-dimethyl hydroxylamine hydrochloride (15.2 g, 156.7 mmol) in THF (200 mL) was added 0.5 M isopropyl magnesium chloride in THF (156 mL, 313.4 mmol) at -78 °C. After stirring at -78 °C for 30 min, **Int-45** (15 g, 111.9 mmol) was added dropwise at -78 °C to the reaction mixture. After stirring at -78 °C for 1.5 h, the reaction mixture was quenched with saturated ammonium chloride solution and the product was extracted with EtOAc. The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 0-25% EtOAc in hexane) to provide the title compound as a pale yellow liquid (6 g, 33%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.07 (s, 1H), 3.66 (s, 3H), 3.32 (s, 6H), 3.11 (s, 3H).

***Step-3*: Synthesis of 1,1-dimethoxybutan-2-one (Int-47)**

[350] To a solution of **Int-46** (6 g, 3.68 mmol) in THF (250 mL) was added 3 M ethyl magnesium bromide in ether (2.4 mL, 7.36 mmol) at -78 °C. After stirring at -78 °C for 1 h, the reaction mixture was quenched with saturated ammonium chloride solution and the product was extracted with EtOAc. The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 0-30% EtOAc in hexane) to provide the title compound as a pale yellow liquid (2.6 g, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.48 (s, 1H), 3.40 (s, 6H), 2.57 (q, J = 7.2 Hz, 2H), 1.05 (t, J = 7.2 Hz, 3H).

***Step-4*: Synthesis of 6-ethyl-3-(methylthio)-1,2,4-triazine (Int-48)**

[351] A mixture of methyl hydrazinecarbimidothioate hydroiodide (5 g, 21.4 mmol) and **Int-47** (2.5 g, 21.4 mmol) in EtOH (100 mL) was heated at 70 °C for 4 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 0-25% EtOAc in hexane) to provide the title compound as a pale brown solid (1 g, 30%), ESI-MS m/z: 155.95 $[M+H]^+$.

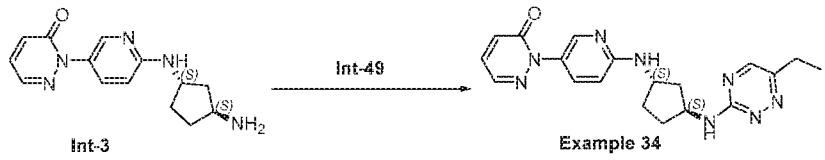
***Step-5*: Synthesis of 6-ethyl-3-(methylsulfonyl)-1,2,4-triazine and 6-ethyl-3-(methylsulfinyl)-1,2,4-triazine (Int-49 / Int-49a)**

[352] To a solution of **Int-48** (1 g, 7.09 mmol) in DCM (15 mL) was added mCPBA (6 g, 35.4 mmol) portion wise at 0°C. After stirring at rt for 2 h, the reaction mixture was filtered through a Celite® pad, the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 0-20% EtOAc in hexane and 0-5% MeOH in DCM) to provide both 6-ethyl-3-(methylsulfonyl)-1,2,4-triazine as pale-brown solid (0.48 g, 40%), ESI-MS m/z: 187.85 [M+H], and 6-ethyl-3-(methylsulfinyl)-1,2,4-triazine as pale-brown solid (0.2 g, 18%), ESI-MS m/z: 171.90 $[M+H]^+$.

***Step-6*: Synthesis of 2-(6-(((1S,3S)-3-((6-ethyl-1,2,4-triazin-3-yl)amino)cyclopentyl) amino)pyridin-3-yl)-4-methylpyridazin-3(2*H*)-one (Example 33)**

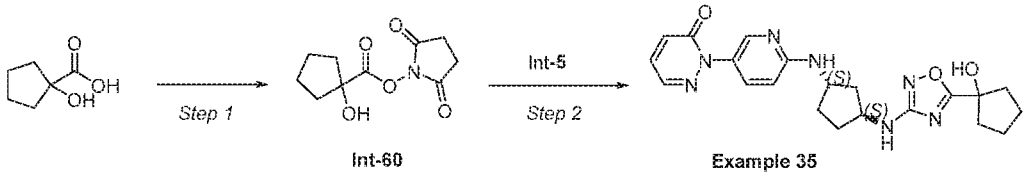
[353] ***Batch-1:*** To a solution of **Int-39** (330 mg, 1.16 mmol) in NMP (5 mL), was added Na_2CO_3 (243 mg, 2.32 mmol) followed by **Int-49a** (200 mg, 1.16 mmol). The reaction mixture was stirred at rt for 16 h. ***Batch-2*:** To the stirred solution of **Int-39** (732 mg, 2.56 mmol) in NMP (5 mL), was added Na_2CO_3 (537 mg, 5.12 mmol) followed by **Int-49** (480 mg, 2.56 mmol). The reaction mixture was stirred at rt for 16 h. The combined reaction mixtures were quenched with water and the product was extracted with EtOAc. The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 0-10% DCM in MeOH). The obtained crude product was purified by preparative HPLC (10-50% acetonitrile/0.02% NH_4OH in water; WATERS XBRIDGE (150 mm x 19 mm), 5.0 µm column, flow rate 10 mL/min) to afford the title compound as a yellow solid (90 mg, 6.5%). ESI-MS *m/z*: 393.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.22 (s, 1H), 8.13 (d, J = 2.0 Hz, 1H), 7.88 (d, J = 4.4 Hz, 1H), 7.59 (dd, J = 9.2, 2.8 Hz, 1H), 7.33 – 7.32 (m, 1H), 6.60 (d, J = 8.8 Hz, 1H), 4.49 – 4.34 (m, 2H), 2.77 (q, J = 7.6 Hz, 2H), 2.33 – 2.28 (m, 2H), 2.22 (s, 3H), 2.10 – 2.01 (m, 2H), 1.69 – 1.60 (m, 2H), 1.28 (t, J = 7.6 Hz, 3H).

Example 34: Synthesis of 2-(6-(((1S,3S)-3-((6-ethyl-1,2,4-triazin-3-yl)amino)cyclopentyl) amino)pyridin-3-yl)pyridazin-3(2*H*)-one



[354] To a solution of **Int-3** (0.4 g, 1.474 mmol) in NMP (5 mL), was added Na_2CO_3 (0.31 g, 2.95 mmol) followed by **Int-49** (0.27 g, 1.47 mmol). After stirring at rt for 16 h, the reaction mixture was quenched with water and the product was extracted with EtOAc. The combined organic phases were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 0-10% DCM in MeOH). The obtained crude product was purified by preparative HPLC (50% EtOH: MeOH (1:1) / hexane, Chiralpak IH (250 mm x 21.2 mm), 5.0 µm column, flow rate 15 mL/min) to afford the title compound as a brown solid (6 mg, 1.0%). ESI-MS *m/z*: 378.9 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.21 (s, 1H), 8.15 (dd, *J* = 2.8, 0.4 Hz, 1H), 8.03 (dd, *J* = 4.0, 2.0 Hz, 1H), 7.59 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.46 (dd, *J* = 9.2, 3.6 Hz, 1H), 7.06 (dd, *J* = 9.6, 1.6 Hz, 1H), 6.60 (dd, *J* = 9.2, 0.8 Hz, 1H), 4.49 – 4.43 (m,1H), 4.39 – 4.35 (m, 1H), 2.77 (q, *J* = 7.6 Hz, 2H), 2.32 – 2.25 (m, 2H), 2.09 – 2.01 (m, 2H), 1.68 – 1.61 (m, 2H), 1.28 (t, *J* = 7.6 Hz, 3H).

Example 35: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-(1-hydroxycyclopentyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one



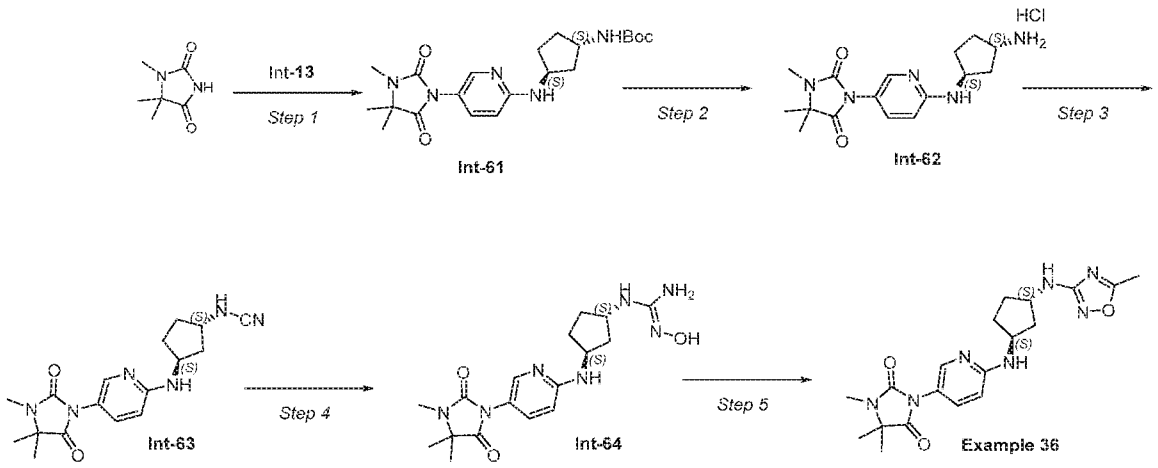
***Step-1*: Synthesis of 2,5-dioxopyrrolidin-1-yl 1-hydroxycyclopentane-1-carboxylate (Int-35)**

Int-60 was synthesized following the **Int-12** starting from commercially available 1-hydroxycyclopentane-1-carboxylic acid. ^1H NMR (300 MHz, $CDCl_3$) δ 2.86 (s, 4H), 2.61 (s, 1H), 2.38 – 2.33 (m, 2H), 2.04 – 1.84 (m, 6H).

***Step-2*: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-(1-hydroxycyclopentyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one (Example 35)**

Example 35 was synthesized following the **Example 15** starting from **Int-5**. ESI-MS m/z: 424.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.14 (d, *J* = 2.8 Hz, 1H), 8.02 (dd, *J* = 4.0, 1.6 Hz, 1H), 7.59 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.45 (dd, *J* = 9.6, 4.0 Hz, 1H), 7.05 (dd, *J* = 9.6, 2.0 Hz, 1H), 6.58 (d, *J* = 9.2 Hz, 1H), 4.38 – 4.30 (m, 1H), 4.01 – 3.93 (m, 1H), 2.30 – 2.21 (m, 2H), 2.16 – 1.86 (m, 8H), 1.83 – 1.74 (m, 2H), 1.66 – 1.52 (m, 2H).

Example 36: Synthesis of 1,5,5-trimethyl-3-(6-(((1*S*,3*S*)-3-((5-methyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)imidazolidine-2,4-dione



***Step-1*: Synthesis of tert-butyl ((1*S*,3*S*)-3-((5-(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)pyridin-2-yl)amino)cyclopentyl)carbamate (Int-61)**

Int-61 was synthesized following the **Int-14** starting from commercially available 1,5,5-trimethylimidazolidine-2,4-dione, ESI-MS m/z: 418.25 $[M+H]^+$.

***Step-2*: Synthesis of 3-(6-(((1*S*,3*S*)-3-aminocyclopentyl) amino) pyridin-3-yl)-1,5,5-trimethylimidazolidine-2,4-dione hydrochloride (Int-62)**

Int-62 was synthesized following the **Int-3** starting from **Int-61**, ESI-MS m/z: 318.15 $[M+H]^+$.

***Step-3*: Synthesis of N-((1*S*,3*S*)-3-((5-(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)pyridin-2-yl)amino)cyclopentyl)cyanamide (Int-63)**

Int-63 was synthesized following the **Int-4** starting from **Int-62**, ESI-MS m/z: 343.15 $[M+H]^+$.

***Step-4*: Synthesis of 2-hydroxy-1-((1*S*,3*S*)-3-((5-(3,4,4-trimethyl-2,5-dioxoimidazolidin-1-yl)pyridin-2-yl)amino)cyclopentyl)guanidine (Int-64)**

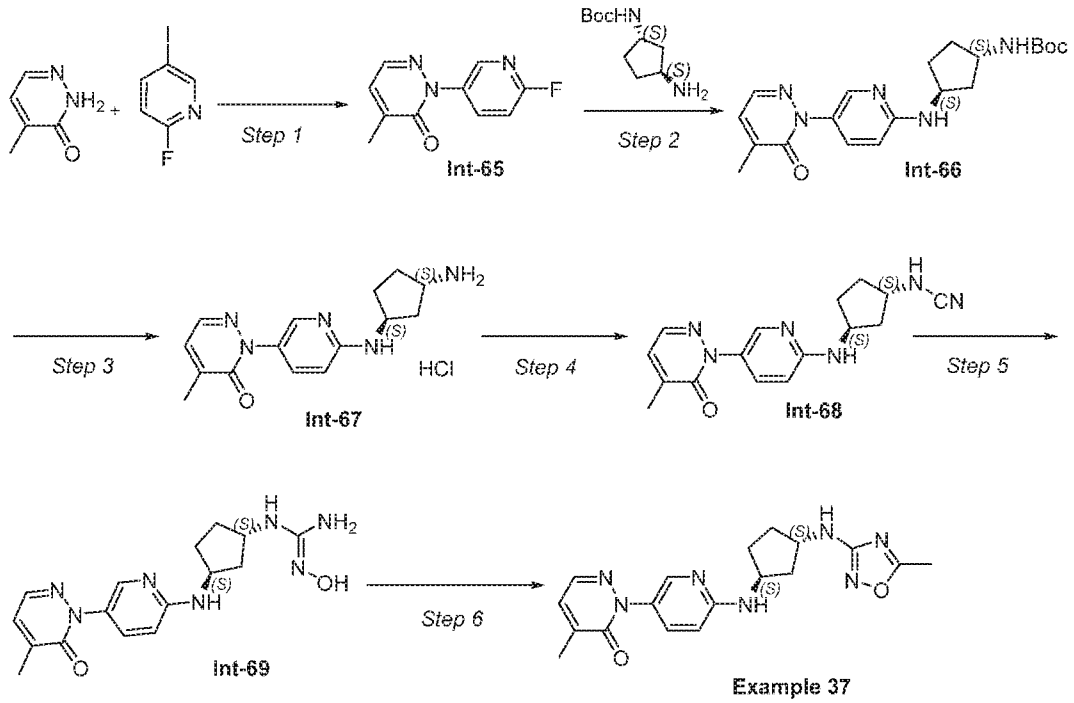
Int-64 was synthesized following the **Int-5** starting from **Int-63**, ESI-MS m/z: 375.95 $[M+H]^+$.

***Step-5*: Synthesis of 1,5,5-trimethyl-3-(6-(((1*S*,3*S*)-3-((5-methyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)imidazolidine-2,4-dione (Example 36)**

Example 36 was synthesized following the **Example 1** starting from **Int-64**. ESI-MS m/z: 400.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.10 (d, J = 2.0 Hz, 1H), 6.56 (dd, J = 9.2, 2.8 Hz, 1H), 5.76 (d, J = 9.2 Hz,

1H), 3.51 – 3.48 (m, 1H), 3.17 – 3.14 (m, 1H), 2.15 (s, 3H), 1.60 (s, 3H), 1.44 – 1.38 (m, 2H), 1.26 – 1.21 (m, 1H), 1.14 – 1.02 (m, 1H), 0.85 – 0.73 (m, 2H), 0.67 (s, 6H).

Example 37: Synthesis of 4-methyl-2-(6-(((1*S*,3*S*)-3-((5-methyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one



***Step-1*: Synthesis of 2-(6-fluoropyridin-3-yl)-4-methylpyridazin-3(2*H*)-one (Int-65)**

Int-65 was synthesized following the **Int-1** starting from commercially available 4-methylpyridazin-3(2H)-one, ESI-MS m/z: 205.70 $[M+H]^+$.

***Step-2*: Synthesis of tert-butyl ((1*S*,3*S*)-3-((5-(5-methyl-6-oxopyridazin-1(6*H*)-yl)pyridin-2-yl)amino)cyclopentyl)carbamate (Int-66)**

Int-66 was synthesized following the **Int-2** starting from **Int-65**, ESI-MS m/z: 385.75 $[M+H]^+$.

***Step-3*: Synthesis of 2-(6-(((1*S*,3*S*)-3-aminocyclopentyl) amino) pyridin-3-yl)-4-methylpyridazin-3(2H)-one hydrochloride (Int-67)**

Int-67 was synthesized following the **Int-3** starting from **Int-66**, ESI-MS m/z: 286.10 $[M+H]^+$.

***Step-4*: Synthesis of *N*-((1*S*,3*S*)-3-((5-(5-methyl-6-oxopyridazin-1(6*H*)-yl) pyridin-2-yl)amino)cyclopentyl)cyanamide (Int-68)**

Int-68 was synthesized following the **Int-4** starting from **Int-67**, ESI-MS m/z: 310.95 $[M+H]^+$.

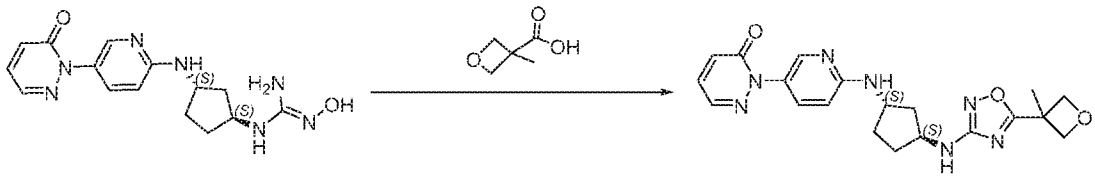
***Step-5*: Synthesis of 2-hydroxy-1-((1*S*,3*S*)-3-((5-(5-methyl-6-oxopyridazin-1(6*H*)-yl)pyridin-2-yl)amino)cyclopentyl)guanidine (Int-69)**

Int-69 was synthesized following the **Int-5** starting from **Int-68**, ESI-MS m/z: 344.20 $[M+H]^+$.

***Step-6*: Synthesis of 4-methyl-2-(6-(((1*S*,3*S*)-3-((5-methyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one (Example 37)**

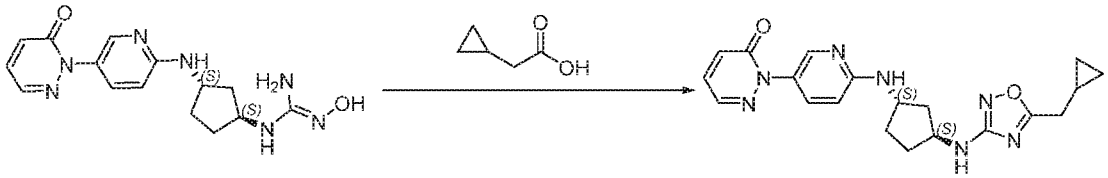
Example 37 was synthesized following the **Example 1** starting from **Int-69**. ESI-MS m/z: 368.15 $[M+H]^+$. ^1H NMR (400 MHz, CD3OD) δ 8.13 (d, *J* = 2.4 Hz, 1H), 7.89 (d, *J* = 4.0 Hz, 1H), 7.59 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.33 – 7.32 (m, 1H), 6.59 (d, *J* = 9.2 Hz, 1H), 4.35 – 4.32 (m, 1H), 3.99 - 3.96 (m, 1H), 2.41 (s, 3H), 2.27 – 2.19 (m, 2H), 2.21 (s, 3H), 2.10 – 2.03 (m, 1H), 1.97 – 1.90 (m, 1H), 1.67 – 1.56 (m, 2H).

Example 38: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-(3-methyloxetan-3-yl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one



Example 38 was synthesized following the **Example 2** starting from **Int-5** with commercially available 3-methyloxetane-3-carboxylic acid. ESI-MS m/z: 410.10 $[M+H]^+$. ^1H NMR (400 MHz, CD3OD) δ 8.15 (d, *J* = 2.4 Hz, 1H), 8.03 (dd, *J* = 3.6, 1.6 Hz, 1H), 7.60 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.46 (dd, *J* = 9.6, 4.0 Hz, 1H), 7.06 (dd, *J* = 9.6, 1.6 Hz, 1H), 6.59 (d, *J* = 9.2 Hz, 1H), 5.00 (d, *J* = 8.0 Hz, 2H), 4.57 (d, *J* = 6.0 Hz, 2H), 4.37 – 4.33 (m, 1H), 4.03 - 3.99 (m, 1H), 2.28 – 2.22 (m, 2H), 2.12 – 2.03 (m, 1H), 1.99 – 1.93 (m, 1H), 1.69 (s, 3H), 1.67 – 1.58 (m, 2H).

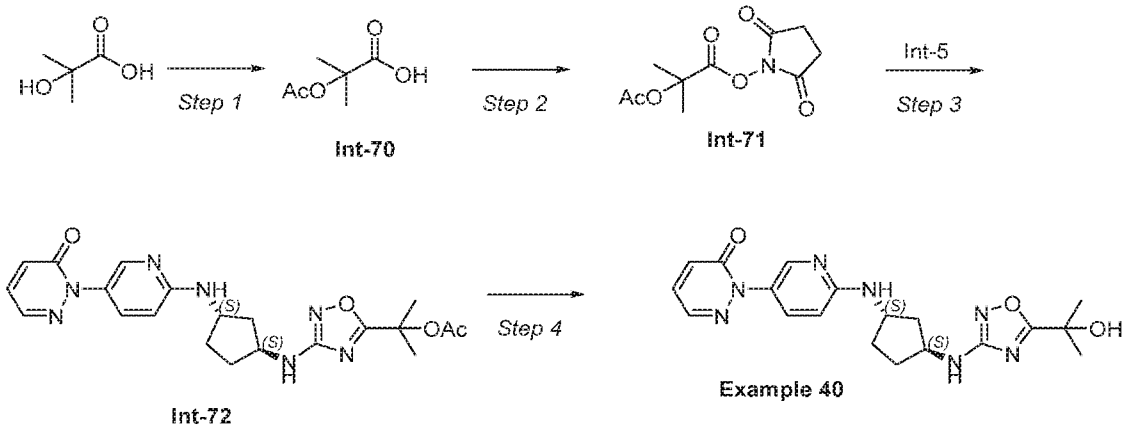
Example 39: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-(cyclopropylmethyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one



Example 39 was synthesized following the **Example 2** starting from **Int-5** with commercially available 2-cyclopropylacetic acid. ESI-MS m/z: 394.15 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.15 (d, *J* = 2.4 Hz, 1H), 8.03 (dd, *J* = 4.0, 1.6 Hz, 1H), 7.60 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.46 (dd, *J* = 9.2, 4.0 Hz, 1H), 7.06 (dd,

J = 9.6, 1.6 Hz, 1H), 6.59 (d, *J* = 9.2 Hz, 1H), 4.36 - 4.33 (m, 1H), 4.01 – 3.96 (m, 1H), δ 2.66 (d, *J* = 7.2 Hz, 2H), 2.28 – 2.22 (m, 2H), 2.12 – 2.03 (m, 1H), 1.98 – 1.95 (m, 1H), 1.67 – 1.52 (m, 2H), 1.17 – 1.08 (m, 1H), 0.61 - 0.57 (m, 2H), 0.30 – 0.26 (m, 2H).

Example 40: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-(2-hydroxypropan-2-yl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one



***Step-1*: Synthesis of Synthesis of 2-acetoxy-2-methylpropanoic acid (Int-70)**

The mixture of 2-hydroxy-2-methylpropanoic acid (1.0 g, 9.60 mmol) in acetyl chloride (1.5 g, 19.21 mmol) was stirred at rt for 16 h. The reaction mixture was concentrated under reduced pressure to dryness. The residue was purified by flash column chromatography on silica gel (eluent: 0-10% EtOAc in hexane) to afford the title compound as a colorless liquid (1.3 g, 93%). ^{1}H NMR: (DMSO- d_6,400 MHz): δ 12.54 (br s, 1H), 1.99 (s, 3H), 1.45 (s, 6H).

***Step-2*: Synthesis of 2,5-dioxopyrrolidin-1-yl 2-acetoxy-2-methylpropanoate (Int-71)**

Int-71 was synthesized following the **Int-12** starting from **Int-71**. ^{1}H NMR: (CD_3OD, 400 MHz): δ 2.82 (s, 4H), 2.08 (s, 3H), 1.69 (s, 6H).

***Step-3*: Synthesis of 2-(3-(((1*S*,3*S*)-3-((5-(6-oxopyridazin-1(6*H*)-yl)pyridin-2-yl)amino)cyclopentyl)amino)-1,2,4-oxadiazol-5-yl)propan-2-yl acetate (Int-72)**

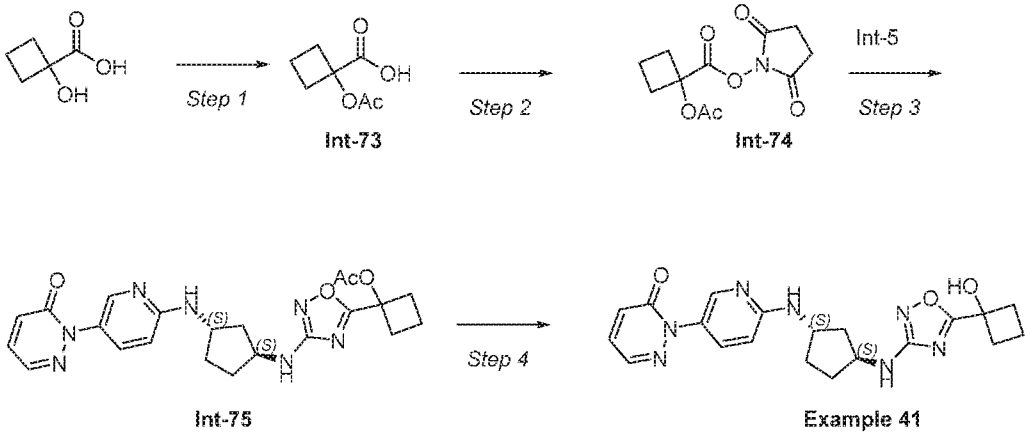
Int-72 was synthesized following the **Example 15** starting from **Int-5 and Int-71**. ESI-MS m/z: 439.95 $[M+H]^+$.

***Step-4*: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-(2-hydroxypropan-2-yl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one (Example 40)**

To a stirred solution of **Int-72** (180 mg, 0.40 mmol) in MeOH (3.0 mL) was added potassium carbonate (113 mg, 0.81 mmol) at 0°C. After stirring at rt for 3 h, the reaction was quenched with water and the product was extracted with EtOAc. The organic phases were combined, dried over anhydrous sodium

sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (10-40% acetonitrile/0.02% NH_4OH in water; WATER X BRIDGE, 150 mm x 20 mm, 5.0 µm column, flow rate 15 mL/min) to afford the title compound as a yellow solid (30 mg, 18%), ESI-MS m/z: 398.10 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.15 (d, J = 2.4 Hz, 1H), 8.03 (dd, J = 3.6, 1.6 Hz, 1H), 7.60 (dd, J = 8.8, 2.4 Hz, 1H), 7.46 (dd, J = 9.2, 3.6 Hz, 1H), 7.06 (dd, J = 9.6, 1.6 Hz, 1H), 6.59 (d, J = 9.2 Hz, 1H), 4.36 - 4.33 (m, 1H), 4.00 – 3.98 (m, 1H), 2.29 – 2.19 (m, 2H), 2.12 – 2.03 (m, 1H), 1.98 – 1.95 (m, 1H), 1.68 – 1.52 (m, 2H), 1.56 (s, 6H).

Example 41: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-(1-hydroxycyclobutyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one



***Step-1*: Synthesis of 2-acetoxy-2-methylpropanoic acid (Int-73)**

Int-73 was synthesized following the **Int-70** starting from commercially available 1-hydroxycyclobutane-1-carboxylic acid. ^1H NMR: ($CDCl_3$, 300MHz): δ 2.82 – 2.68 (m, 2H), 2.44 – 2.30 (m, 2H), 2.11 (s, 3H), 2.08 – 1.89 (m, 2H).

***Step-2*: Synthesis of 2,5-dioxopyrrolidin-1-yl 1-acetoxycyclobutane-1-carboxylate (Int-74)**

Int-74 was synthesized following the **Int-12** starting from **Int-73**. ^1H NMR: ($CDCl_3$, 300MHz): δ 2.95 – 2.92 (m, 2H), 2.82 (s, 4H), 2.53 – 2.42 (m, 2H), 2.14 (s, 3H), 2.12 – 1.92 (m, 2H).

***Step-3*: Synthesis of 1-(3-(((1*S*,3*S*)-3-((5-(6-oxopyridazin-1(6H)-yl)pyridin-2-yl)amino)cyclopentyl)amino)-1,2,4-oxadiazol-5-yl)cyclobutyl acetate (Int-75)**

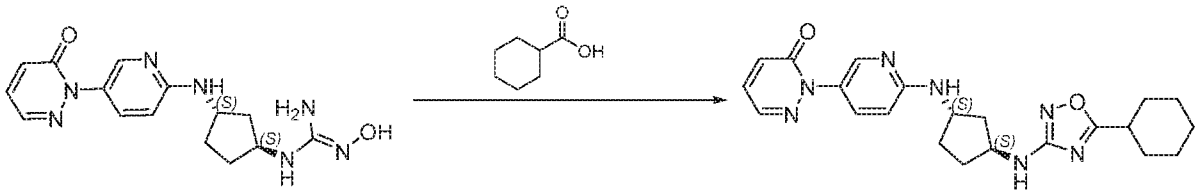
Int-75 was synthesized following the **Example 15** starting from **Int-5 and Int-74**. ESI-MS m/z: 452.10 $[M+H]^+$.

***Step-4*: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-(1-hydroxycyclobutyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one (Example 41)**

Example 41 was synthesized following the **Example 41** starting from **Int-75**. ESI-MS m/z: 410.15 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d6) δ 7.34 (d, J = 2.4 Hz, 1H), 7.22 (dd, J = 3.6, 1.2 Hz, 1H), 6.79

(dd, *J* = 9.2, 2.8 Hz, 1H), 6.65 (dd, *J* = 9.6, 4.0 Hz, 1H), 6.25 (dd, *J* = 9.6, 1.6 Hz, 1H), 5.78 (d, *J* = 8.8 Hz, 1H), 3.55 – 3.52 (m, 1H), 3.22 – 3.18 (m, 1H), 1.84 – 1.78 (m, 2H), 1.59 – 1.41 (m, 4H), 1.30 – 1.21 (m, 1H), 1.20 – 1.06 (m, 3H), 0.86 – 0.77 (m, 2H).

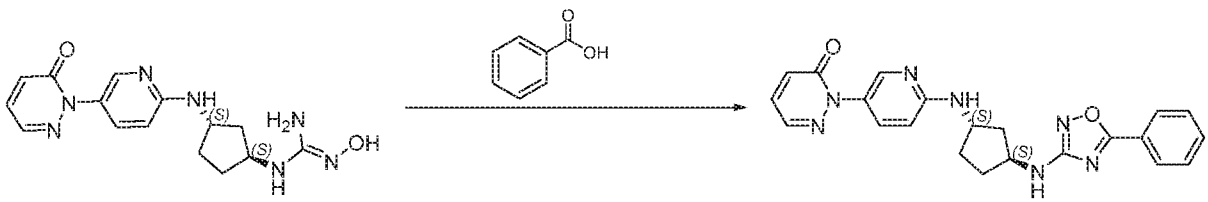
Example 42: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-cyclohexyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one



Int-5 Example 42

Example 42 was synthesized following the **Example 2** starting from **Int-5** with commercially available cyclohexanecarboxylic acid. ESI-MS m/z: 422.40 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.15 (d, *J* = 2.4 Hz, 1H), 8.03 (dd, *J* = 4.0, 1.6 Hz, 1H), 7.60 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.46 (dd, *J* = 9.2, 3.6 Hz, 1H), 7.06 (dd, *J* = 9.6, 1.6 Hz, 1H), 6.59 (d, *J* = 8.8 Hz, 1H), 4.39 – 4.31 (m, 1H), 4.01 – 3.97 (m, 1H), 2.86 – 2.69 (m, 1H), 2.30 – 2.19 (m, 2H), 2.11 – 1.90 (m, 4H), 1.85 – 1.78 (m, 2H), 1.73 – 1.52 (m, 5H), 1.49 – 1.28 (m, 3H),

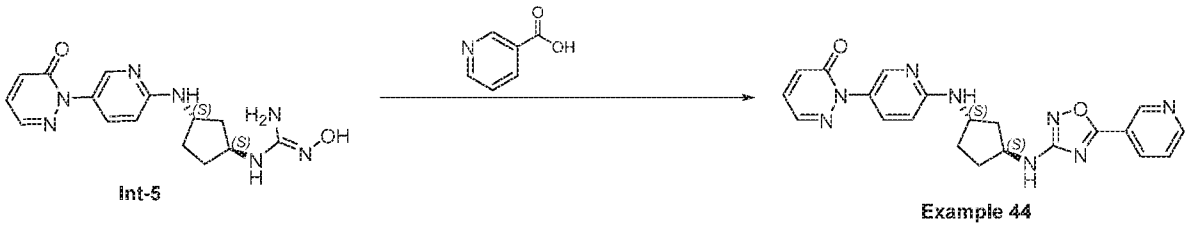
Example 43: 2-(6-(((1*S*,3*S*)-3-((5-phenyl-1,2,4-oxadiazol-3-yl)amino) cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one



Int-5 Example 43

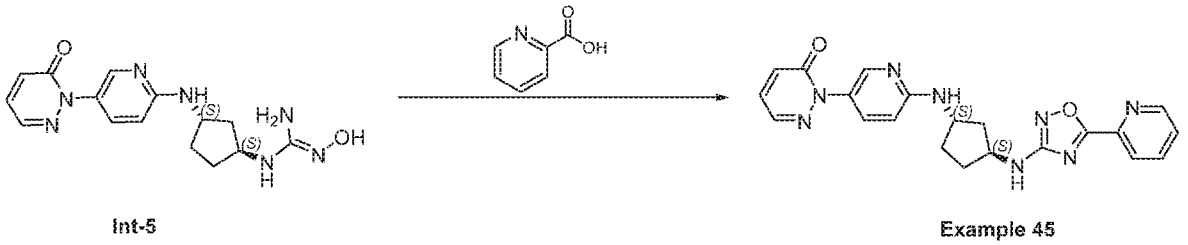
Example 43 was synthesized following the **Example 2** starting from **Int-5** with commercially available benzoic acid. ESI-MS m/z: 416.0 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.15 (d, *J* = 2.4 Hz, 1H), 8.08 – 8.02 (m, 3H), 7.65 – 7.59 (m, 2H), 7.57 – 7.53 (m, 2H), 7.46 (dd, *J* = 9.6, 4.0 Hz, 1H), 7.06 (dd, *J* = 9.6, 1.6 Hz, 1H), 6.61 (d, *J* = 9.2 Hz, 1H), 4.41 – 4.37 (m, 1H), 4.11 – 4.07 (m, 1H), 2.32 – 2.25 (m, 2H), 2.15 – 2.10 (m, 1H), 2.03 – 1.98 (m, 1H), 1.72 – 1.61 (m, 2H).

Example 44: 2-(6-(((1*S*,3*S*)-3-((5-(pyridin-3-yl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one



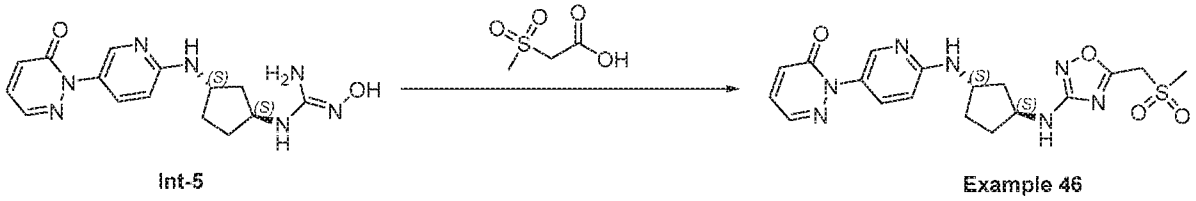
Example 44 was synthesized following the **Example 2** starting from **Int-5 with** commercially available nicotinic acid. ESI-MS m/z: 416.95 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 9.19 (d, J = 1.6 Hz, 1H), 8.77 – 8.75 (m, 1H), 8.46 – 8.43 (m, 1H), δ 8.20 (d, J = 2.0 Hz, 1H), δ 8.03 (dd, J = 4.0, 1.6 Hz, 1H), 7.74 – 7.72 (m, 1H), 7.64 – 7.61 (m, 1H), 7.46 (dd, J = 9.2, 3.6 Hz, 1H), 7.06 (dd, J = 9.6, 1.6 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 4.41 – 4.33 (m, 1H), 4.14 – 4.08 (m, 1H), 2.35 – 2.26 (m, 2H), 2.18 – 2.11 (m, 1H), 2.06 – 2.01 (m, 1H), 1.75 – 1.62 (m, 2H).

Example 45: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-(pyridin-2-yl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one



Example 45 was synthesized following the **Example 2** starting from **Int-5** with commercially available picolinic acid. ESI-MS m/z: 417.10 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.73 – 8.72 (m, 1H), 8.21 – 8.16 (m, 2H), 8.07 – 8.02 (m, 2H), 7.66 – 7.60 (m, 2H), 7.45 (dd, J = 9.6, 4.0 Hz, 1H), 7.05 (dd, J = 9.6, 4.0 Hz, 1H), 6.61 (d, J = 9.2 Hz, 1H), 4.41 – 4.35 (m, 1H), 4.15 – 4.08 (m, 1H), 2.32 – 2.25 (m, 2H), 2.18 – 2.11 (m, 1H), 2.05 – 1.98 (m, 1H), 1.75 – 1.60 (m, 2H).

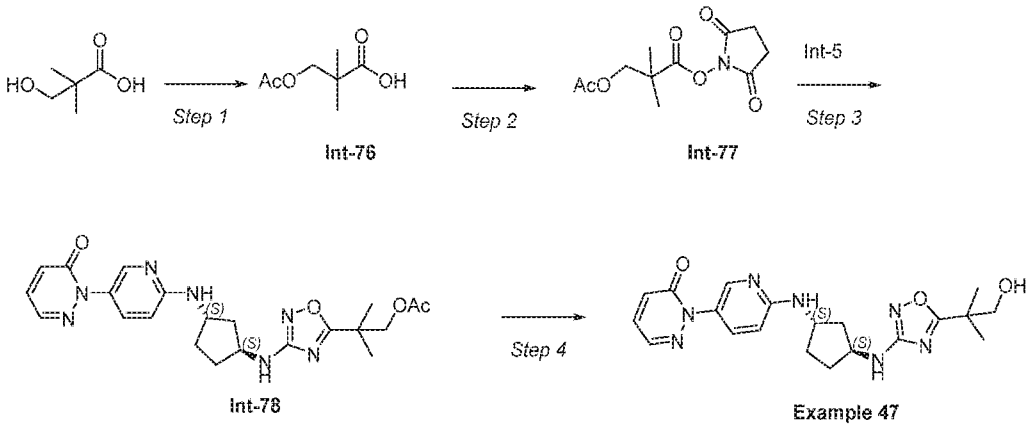
Example 46: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-((methylsulfonyl)methyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one



Example 46 was synthesized following the **Example 2** starting from **Int-5** with commercially available 2-(methylsulfonyl)acetic acid. ESI-MS m/z: 432.05 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.15 (d, J = 2.8 Hz, 1H), 8.03 (dd, J = 4.0, 1.6 Hz, 1H), δ 7.60 (dd, J = 9.2, 2.8 Hz, 1H), 7.46 (dd, J = 9.2, 3.6 Hz, 1H), 7.06

(dd, *J* = 9.2, 1.6 Hz, 1H), 6.59 (d, *J* = 8.8 Hz, 1H), 4.89 (s, 2 H), 4.37 – 4.32 (m, 1H), 4.04 – 4.00 (m, 1H), 3.19 (s, 3 H), 2.28 – 2.17 (m, 2H), 2.11 – 2.02 (m, 1H), 1.99 – 1.94 (m, 1H), 1.70 – 1.53 (m, 2H).

Example 47: 2-(6-(((1*S*,3*S*)-3-((5-(1-hydroxy-2-methylpropan-2-yl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one



***Step-1*: Synthesis of 3-acetoxy-2,2-dimethylpropanoic acid (Int-76)**

Int-76 was synthesized following the **Int-70** starting from commercially available 3-hydroxy-2,2-dimethylpropanoic acid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.18 (s, 2H), 2.08 (s, 3 H), 1.35 (s, 6 H).

***Step-2*: Synthesis of 2,5-dioxopyrrolidin-1-yl 3-acetoxy-2,2-dimethylpropanoate (Int-77)**

Int-77 was synthesized following the **Int-12** starting from **Int-76**. ^{1}H NMR: (400MHz, DMSO-d_6) δ 4.15 (s, 2H), 3.32 (s, 4 H), 2.03 (s, 3 H), 1.33 (s, 6H)

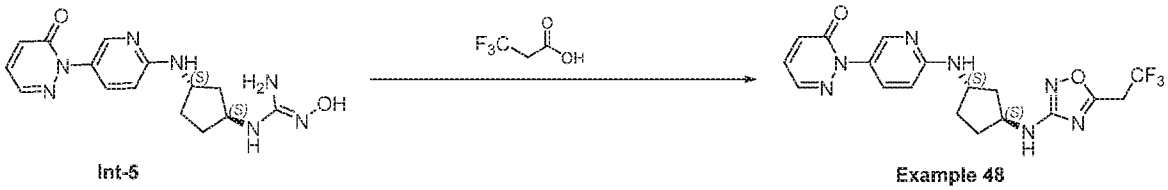
***Step-3*: Synthesis of 2-methyl-2-(3-(((1*S*,3*S*)-3-((5-(6-oxopyridazin-1(6H)-yl)pyridin-2-yl)amino)cyclopentyl)amino)-1,2,4-oxadiazol-5-yl)propyl acetate (Int-78)**

Int-78 was synthesized following the **Example 15** starting from **Int-5** and **Int-77**. ESI-MS m/z: 454.10 $[M+H]^+$.

***Step-4*: Synthesis of Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-(1-hydroxy-2-methylpropan-2-yl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one (Example 47)**

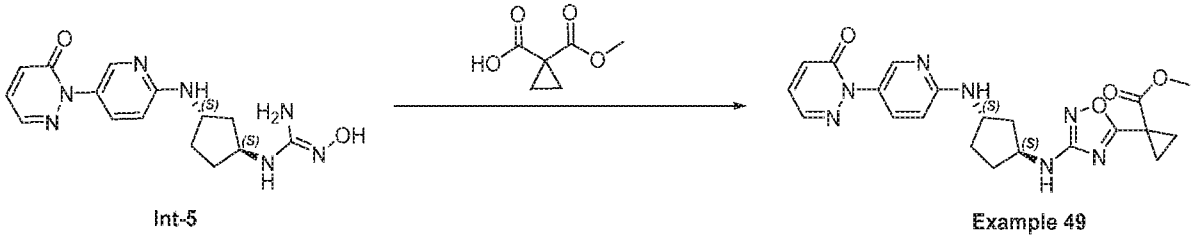
Example 47 was synthesized following the **Example 40** starting from **Int-78**. ESI-MS m/z: 412.15 $[M+H]^+$. ^{1}H NMR (400 MHz, CD_3OD) δ 8.15 (d, *J* = 2.8 Hz, 1H), 8.03 (dd, *J* = 3.6, 1.6 Hz, 1H), δ 7.60 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.46 (dd, *J* = 9.6, 4.0 Hz, 1H), 7.06 (dd, *J* = 9.2, 1.6 Hz, 1H), 6.59 (d, *J* = 9.2 Hz, 1H), 4.38 – 4.31 (m, 1H), 4.02 – 3.97 (m, 1H), 3.66 (s, 2 H), 2.30 – 2.19 (m, 2H), 2.11 – 2.04 (m, 1H), 1.98 – 1.92 (m, 1H), 1.68 – 1.53 (m, 2H), 1.33 (s, 6 H).

Example 48: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-(2,2,2-trifluoroethyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one



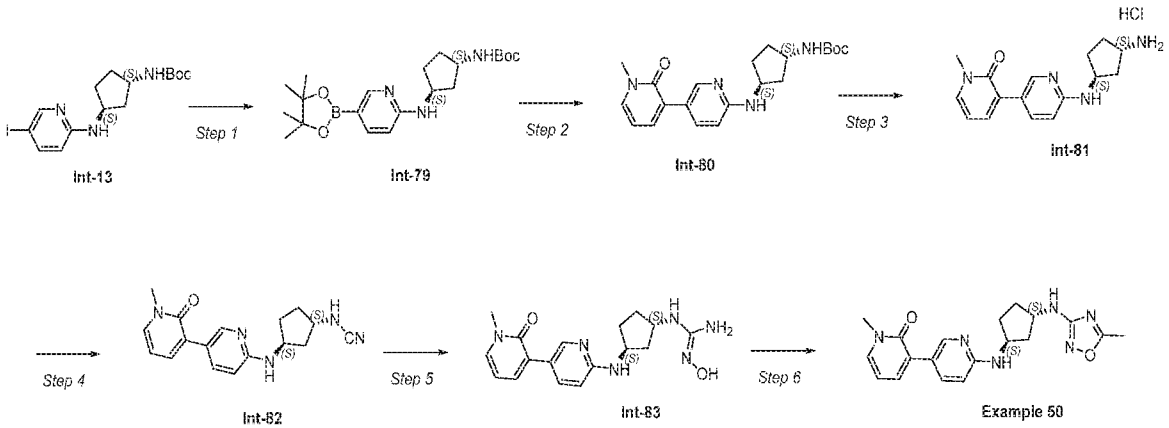
Example 48 was synthesized following the **Example 2** starting from **Int-5 with** commercially available 3,3,3-trifluoropropanoic acid. ESI-MS m/z: 422.15 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.18 (d, J = 2.8 Hz, 1H), 8.03 (dd, J = 4.0, 1.6 Hz, 1H), δ 7.68 (dd, J = 9.2, 2.4 Hz, 1H), 7.47 (dd, J = 9.6, 4.0 Hz, 1H), 7.07 (dd, J = 9.2, 1.6 Hz, 1H), 6.65 (d, J = 9.2 Hz, 1H), 4.38 – 4.31 (m, 1H), 4.03 – 3.98 (m, 1H), 3.92-3.86 (m, 2 H), 2.34 – 2.21 (m, 2H), 2.18 – 2.07 (m, 1H), 2.01 – 1.97 (m, 1H), 1.70 – 1.58 (m, 2H).

Example 49: methyl 1-(3-(((1*S*,3*S*)-3-((5-(6-oxopyridazin-1(6H)-yl)pyridin-2-yl)amino)cyclopentyl)amino)-1,2,4-oxadiazol-5-yl)cyclopropane-1-carboxylate



Example 49 was synthesized following the **Example 2** starting from **Int-5** with commercially available 1-(methoxycarbonyl)cyclopropane-1-carboxylic acid. ESI-MS m/z: 438.15 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.15 (d, J = 2.8 Hz, 1H), 8.03 (dd, J = 4.0, 1.6 Hz, 1H), δ 7.60 (dd, J = 8.8, 2.4 Hz, 1H), 7.46 (dd, J = 9.2, 3.6 Hz, 1H), 7.06 (dd, J = 9.2, 1.6 Hz, 1H), 6.59 (d, J = 9.2 Hz, 1H), 4.39 – 4.31 (m, 1H), 4.03 – 3.98 (m, 1H), 3.74 (s, 3 H), 2.29 – 2.20 (m, 2H), 2.11 – 2.03 (m, 1H), 1.98 – 1.89 (m, 1H), 1.72 – 1.55 (m, 6H).

Example 50: Synthesis of 1-methyl-6'-(((1*S*,3*S*)-3-((5-methyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)-[3,3'-bipyridin]-2(1*H*)-one



***Step-1*: Synthesis of Synthesis of *tert*-butyl ((1*S*,3*S*)-3-((5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) pyridin-2-yl) amino) cyclopentyl) carbamate (Int-79)**

To a solution of **Int-13** (0.4 g, 0.992 mmol) in DMSO (10 mL) were added bispinacolatodiborane (0.5 g, 1.984 mmol), KOAc (0.49 g, 4.959 mmol) and $Pd(dppf)Cl_2$.DCM (81 mg, 0.099 mmol). After stirred at 80°C for 16 h, the reaction mixture was quenched with water and extracted with EtOAc. The combined organic phases were washed with water dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to provide crude product (0.7 g, crude) as a brown liquid. ESI-MS m/z: 322.15 $[M+H]^+$, boronic acid mass.

***Step-2*: Synthesis of *tert*-butyl ((1S,3*S*)-3-((1'-methyl-2'-oxo-1',2'-dihydro-[3,3'-bipyridin]-6-yl) amino) cyclopentyl) carbamate (Int-80)**

To a solution of 3-bromo-1-methylpyridin-2(1H)-one (0.1 g, 0.532 mmol) in dioxane (4 mL) and water (1 ml) were added **Int-79** (0.32 g, 0.798 mmol), Na_2CO_3 (0.11 g, 1.064 mmol) and $Pd(dppf)Cl_2$.DCM (43 mg, 0.053 mmol). After stirred at 100°C for 16 h, the reaction mixture was quenched with water and extracted with EtOAc. The combined organic phases were washed with water dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: 0-3% MeOH in DCM) to afford the title compound as a brown sticky solid (0.1 g, 49%). ESI-MS m/z: 385.15 $[M+H]^+$.

***Step-3*: Synthesis of 6'-(((1*S*,3*S*)-3-aminocyclopentyl) amino)-1-methyl-[3,3'-bipyridin]-2(1*H*)-one hydrochloride (Int-81)**

Int-81 was synthesized following the **Int-3** starting from **Int-80**, ESI-MS m/z: 285.10 $[M+H]^+$.

***Step-4*: Synthesis of N-((1*S*,3*S*)-3-((1'-methyl-2'-oxo-1',2'-dihydro-[3,3'-bipyridin]-6-yl) amino) cyclopentyl) cyanamide (Int-82)**

Int-82 was synthesized following the **Int-4** starting from **Int-81**, ESI-MS m/z: 310.05 $[M+H]^+$.

***Step-5*: Synthesis of 2-hydroxy-1-((1*S*,3*S*)-3-((1'-methyl-2'-oxo-1',2'-dihydro-[3,3'-bipyridin]-6-yl)amino)cyclopentyl)guanidine (Int-83)**

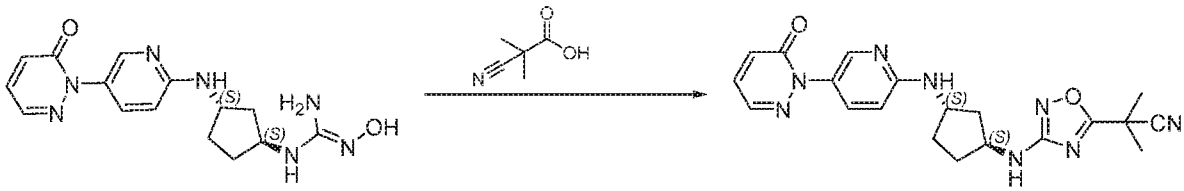
Int-83 was synthesized following the **Int-5** starting from **Int-82**, ESI-MS m/z: 343.15 $[M+H]^+$.

***Step-6*: Synthesis of 1-methyl-6'-(((1*S*,3*S*)-3-((5-methyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)-[3,3'-bipyridin]-2(1*H*)-one (Example 50)**

Example 50 was synthesized following the **Example 1** starting from **Int-83**. ESI-MS m/z: 367.15 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.27 (d, *J* = 2.4 Hz, 1H), 7.78 (dd, *J* = 9.2, 2.4 Hz, 1H), δ 7.59 (d, *J* = 6.8

Hz, 2H), 6.57 (d, *J* = 9.2 Hz, 1H), 6.43 (t, *J* = 6.8 Hz, 1H), 4.35 – 4.27 (m, 1H), 4.03 – 3.96 (m, 1H), 3.61 (s, 3H), 2.41 (s, 3H), 2.29 – 2.18 (m, 2H), 2.11 – 2.03 (m, 1H), 1.98 – 1.89 (m, 1H), 1.69 – 1.52 (m, 2H).

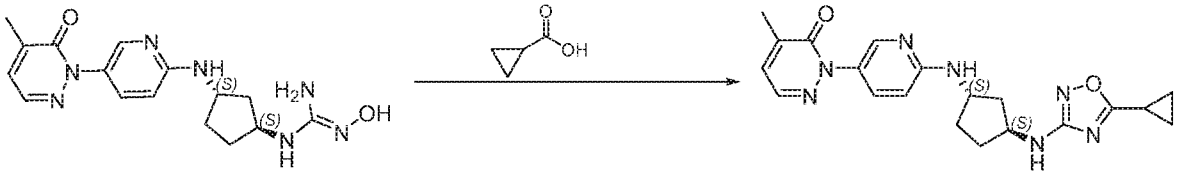
Example 51: Synthesis of 2-methyl-2-(3-(((1*S*,3*S*)-3-((5-(6-oxopyridazin-1(6*H*)-yl) pyridin-2-yl)amino)cyclopentyl)amino)-1,2,4-oxadiazol-5-yl)propanenitrile



Int-5 Example 51

Example 51 was synthesized following the **Example 2** starting from **Int-5** with commercially available 2-cyano-2-methylpropanoic acid. ESI-MS m/z: 407.0 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.15 (d, *J* = 2.4 Hz, 1H), 8.03 (dd, *J* = 4.0, 1.6 Hz, 1H), δ 7.60 (dd, *J* = 9.2, 2.8, Hz, 1H), 7.46 (dd, *J* = 9.6, 4.0 1H), 7.06 (dd, *J* = 9.2, 1.6 Hz, 1H), δ 6.59 (d, *J* = 9.2 Hz, 1H), 4.38 – 4.32 (m, 1H), 4.03 – 3.96 (m, 1H), 2.30 – 2.20 (m, 2H), 2.12 – 2.06 (m, 1H), 2.0 – 1.91 (m, 1H), 1.80 (s, 6H), 1.70 – 1.57 (m, 2H).

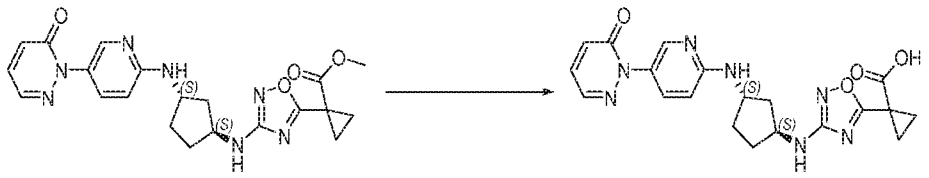
Example 52: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-cyclopropyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-4-methylpyridazin-3(2*H*)-one



Int-44 Example 52

Example 52 was synthesized following the **Example 2** starting from **Int-69** with commercially available cyclopropane carboxylic acid. ESI-MS m/z: 394.15 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.13 (d, *J* = 2.4 Hz, 1H), 7.89 (d, *J* = 4.0 Hz, 1H), δ 7.58 (dd, *J* = 9.2, 2.8, Hz, 1H), 7.33 - 7.32 (m, 1H), 6.58 (d, *J* = 9.2 Hz, 1H), 4.38 – 4.30 (m, 1H), 4.01 – 3.94 (m, 1H), 2.30 – 2.19 (m, 5H), 2.11 – 2.03 (m, 2H), 1.98 – 1.90 (m, 1H), 1.67 – 1.54 (m, 2H), 1.20 – 1.15 (m, 2H), 1.12 – 1.05 (m, 2H).

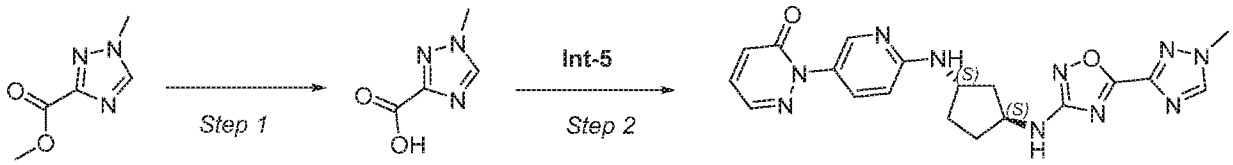
Example 53: Synthesis of 1-(3-(((1*S*,3*S*)-3-((5-(6-oxopyridazin-1(6*H*)-yl)pyridin-2-yl)amino)cyclopentyl)amino)-1,2,4-oxadiazol-5-yl)cyclopropane-1-carboxylic acid



Example 49 Example 53

To a solution of **Example 49** (200 mg, 0.45 mmol) in MeOH (3.0 mL) and THF(7.0 mL) was added LiOH.H2O (56 mg, 1.37 mmol) in H_2O (1.0 mL). After stirred for 2 h, the reaction was quenched with water and the product was extracted with EtOAc. The organic phases were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. . The residue was purified by preparative HPLC (20-75% acetonitrile/0.1% formic acid in water; Gemini NX, 250 mm x 20 mm,5.0 µm column, flow rate 15 mL/min) to afford the title compound as a yellow solid (30 mg, 16%), ESI-MS m/z: 424.10 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.15 (d, *J* = 2.8 Hz, 1H), 8.03 (dd, *J* = 4.0, 1.6 Hz, 1H), 7.61 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.46 (dd, *J* = 9.6, 4.0 Hz, 1H), 7.06 (dd, *J* = 9.2, 1.2 Hz, 1H), 6.60 (d, *J* = 9.2 Hz, 1H), 4.39 – 4.31 (m, 1H), 4.03 – 3.98 (m, 1H), 2.29 – 2.20 (m, 2H), 2.12 – 2.03 (m, 1H), 1.99 – 1.89 (m, 1H), 1.71 – 1.55 (m, 4H), 1.53 – 1.49 (m, 2H).

Example 54: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-(1-methyl-1H-1,2,4-triazol-3-yl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one



Int-84 Example 54

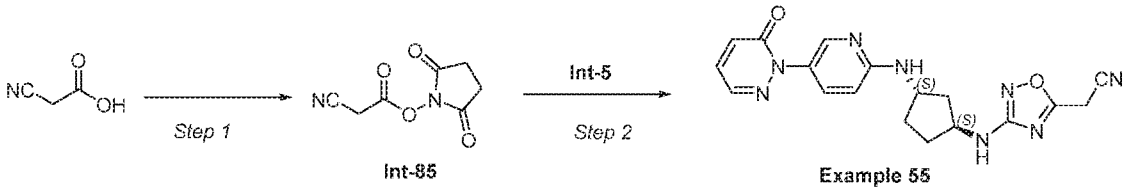
***Step-1*: Synthesis of 1-methyl-1H-1,2,4-triazole-3-carboxylic acid (Int-84)**

To a solution of methyl 1-methyl-1H-1,2,4-triazole-3-carboxylate (0.3 g, 2.126 mmol) in MeOH (1 mL) and water (1 mL) was added KOH (0.13 g, 2.338 mmol).). After stirred for 2 h, the reaction was quenched with 1N HCl to pH=3-4 and concentrated under reduced pressure. . The residue was purified by preparative HPLC (0-15% acetonitrile/0.1% formic acid in water, Kinetex EVO, 250 mm x 21.2 mm,5.0 µm column, flow rate 18 mL/min) to afford the title compound as an off-white solid (150 mg, 55%), ^1H NMR (300 MHz, DMSO-d_6) δ 8.55 (s, 1H), 3.91 (s, 3H).

***Step-2*: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-(1-methyl-1H-1,2,4-triazol-3-yl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2*H*)-one (Example 54)**

Example 54 was synthesized following the **Example 2** starting from **Int-5** and **Int-84**. ESI-MS m/z: 421.10 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.59 (s, 1H), 8.16 (d, *J* = 2.4 Hz, 1H), 8.03 (dd, *J* = 3.6, 1.6 Hz, 1H), δ 7.61 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.46 (dd, *J* = 9.2, 3.6 Hz, 1H), 7.06 (dd, *J* = 9.6, 1.6 Hz, 1H), 6.60 (d, *J* = 8.8 Hz, 1H), 4.41 – 4.33 (m, 1H), 4.13 – 4.07 (m, 1H), 4.05 (s, 3H), 2.34 – 2.23 (m, 2H), 2.20 – 2.10 (m, 1H), 2.08 – 1.96 (m, 1H), 1.72 – 1.59 (m, 2H).

Example 55: Synthesis of 2-(3-(((1*S*,3*S*)-3-((5-(6-oxopyridazin-1(6*H*)-yl)pyridin-2-yl)amino)cyclopentyl)amino)-1,2,4-oxadiazol-5-yl)acetonitrile



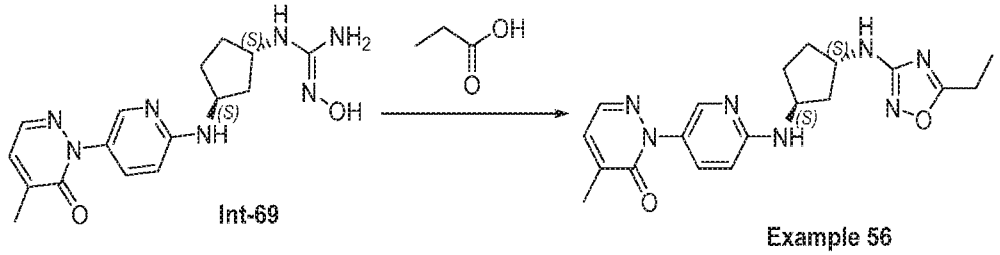
***Step-1*: Synthesis of 2,5-dioxopyrrolidin-1-yl 2-cyanoacetate (Int-85)**

Int-85 was synthesized following the **Int-12** starting from commercially available 2-cyanoacetic acid. ^1H NMR (300 MHz, CD_3OD) δ 3.68 (s, 2H), 2.67 (s, 4H).

***Step-2*: Synthesis of 2-(3-(((1*S*,3*S*)-3-((5-(6-oxopyridazin-1(6*H*)-yl)pyridin-2-yl)amino)cyclopentyl)amino)-1,2,4-oxadiazol-5-yl)acetonitrile (Example 55)**

Example 55 was synthesized following the **Example 15** starting from **Int-5** and **Int-85**. ESI-MS m/z: 378.90 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 2.4 Hz, 1H), 8.18 (dd, *J* = 3.6, 1.6 Hz, 1H), δ 7.70 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.24 (dd, *J* = 9.6, 4.0 Hz, 1H), 7.04 (dd, *J* = 9.6, 1.6 Hz, 1H), 6.43 (d, *J* = 8.8 Hz, 1H), 4.89 – 4.80 (m, 1H), 4.64 – 4.60 (m, 1H), 4.33 – 4.26 (m, 1H), 4.13 – 4.05 (m, 1H), 3.91 (s, 2H), 2.35 – 2.28 (m, 2H), 2.15 – 2.08 (m, 1H), 2.04 – 1.98 (m, 1H), 1.68 – 1.52 (m, 2H).

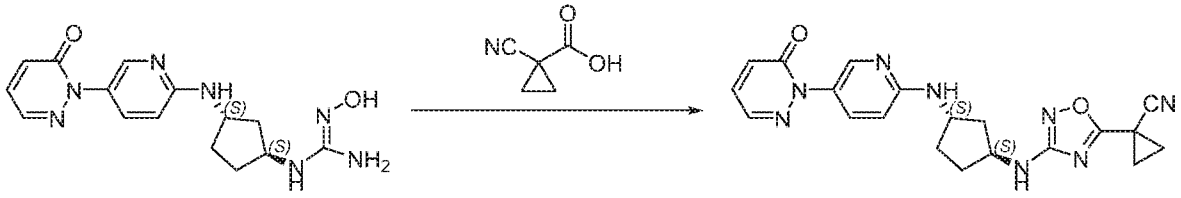
Example 56: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-ethyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-4-methylpyridazin-3(2*H*)-one



Example 56 was synthesized following the **Example 2** starting from **Int-69** with commercially available propionic acid. ESI-MS m/z: 382.20 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.12 (d, *J* = 2.4 Hz, 1H), 7.88 (d, *J* = 4.0 Hz, 1H), 7.57 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.33 – 7.31 (m, 1H), 6.58 (d, *J* = 9.2 Hz, 1H), 4.37 –

4.31 (m, 1H), 4.02 – 3.96 (m, 1H), 2.75 (q, *J* = 7.6 Hz, 2H), 2.29 – 2.21 (m, 2H), 2.20 (s, 3H), 2.09 – 2.03 (m, 1H), 1.99 – 1.90 (m, 1H), 1.66 – 1.56 (m, 2H), 1.30 (t, *J* = 7.6 Hz, 3H).

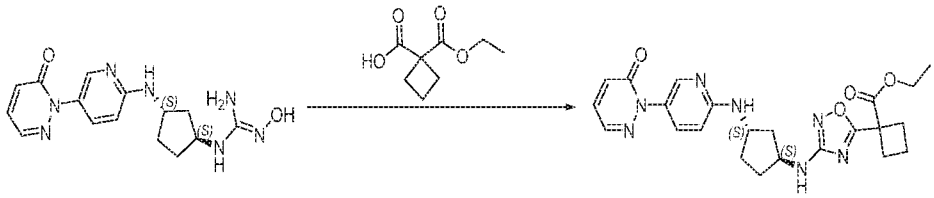
Example 57: Synthesis of 1-(3-(((1*S*,3*S*)-3-((5-(6-oxopyridazin-1(6*H*)-yl)pyridin-2-yl)amino)cyclopentyl)amino)-1,2,4-oxadiazol-5-yl)cyclopropane-1-carbonitrile



Int-5 Example 57

Example 57 was synthesized following the **Example 2** starting from **Int-5** with commercially available 1-cyanocyclopropane-1-carboxylic acid. ESI-MS m/z: 405.02 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.14 (d, *J* = 2.8 Hz, 1H), 8.02 (dd, *J* = 4.0, 1.6 Hz, 1H), 7.59 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.45 (dd, *J* = 9.6, 4.0 Hz, 1H), 7.05 (dd, *J* = 9.6, 1.6 Hz, 1H), 6.58 (d, *J* = 9.2 Hz, 1H), 4.37 – 4.31 (m, 1H), 3.98 – 3.95 (m, 1H), 2.29 – 2.19 (m, 2H), 2.09 – 2.03 (m, 1H), 1.96 – 1.89 (m, 3H), 1.85 – 1.82 (m, 2H), 1.66 – 1.52 (m, 2H).

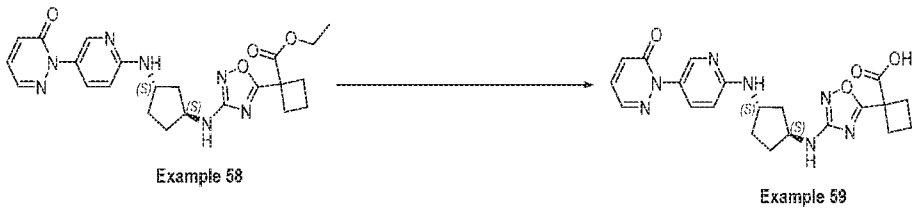
Example 58: Synthesis of ethyl 1-(3-(((1*S*,3*S*)-3-((5-(6-oxopyridazin-1(6*H*)-yl)pyridin-2-yl)amino)cyclopentyl)amino)-1,2,4-oxadiazol-5-yl)cyclobutane-1-carboxylate



Int-5 Example 58

Example 58 was synthesized following the **Example 2** starting from **Int-5** with commercially available 1-(ethoxycarbonyl)cyclobutane-1-carboxylic acid. ESI-MS m/z: 466.0 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.15 (dd, *J* = 2.4, 0.4 Hz, 1H), 8.03 (dd, *J* = 4.0, 1.6 Hz, 1H), 7.60 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.47 (dd, *J* = 9.2, 4.0 Hz, 1H), 7.06 (dd, *J* = 9.2, 1.6 Hz, 1H), 6.59 (dd, *J* = 8.8, 0.4 Hz, 1H), 4.38 – 4.32 (m, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 4.04 – 3.98 (m, 1H), 2.82 – 2.72 (m, 2H), 2.70 – 2.62 (m, 2H), 2.31 – 2.20 (m, 2H), 2.12 – 2.04 (m, 3H), 1.99 – 1.91 (m, 1H), 1.69 – 1.55 (m, 2H), 1.24 (t, *J* = 7.2 Hz, 3H).

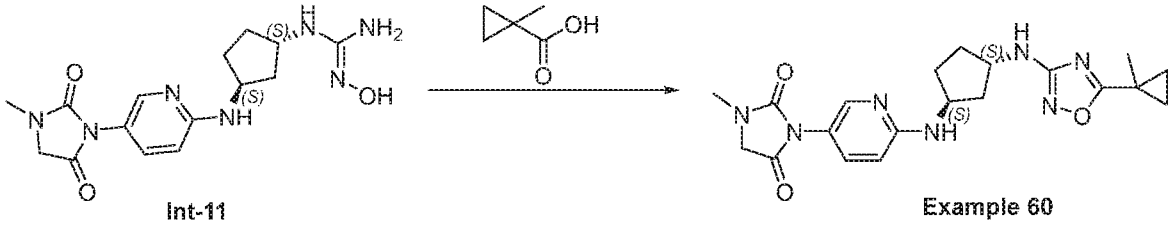
Example 59: Synthesis of 1-(3-(((1*S*,3*S*)-3-((5-(6-oxopyridazin-1(6*H*)-yl)pyridin-2-yl)amino)cyclopentyl)amino)-1,2,4-oxadiazol-5-yl)cyclobutane-1-carboxylic acid



Example 58 Example 59

Example 59 was synthesized following the **Example 53** starting from **Example 58**. ESI-MS m/z: 437.95 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.16 (d, J = 2.4 Hz, 1H), 8.03 (dd, J = 3.6, 1.6 Hz, 1H), 7.62 (dd, J = 9.2, 2.8 Hz, 1H), 7.46 (dd, J = 9.6, 4.0 Hz, 1H), 7.06 (dd, J = 9.6, 1.6 Hz, 1H), 6.61 (d, J = 9.2 Hz, 1H), 4.38 – 4.31 (m, 1H), 4.05 – 3.98 (m, 1H), 2.81 – 2.71 (m, 2H), 2.69 – 2,61 (m, 2H), 2.30 – 2.19 (m, 2H), 2.14 – 2.02 (m, 3H), 2.01 – 1.93 (m, 1H), 1.69 – 1.55 (m, 2H).

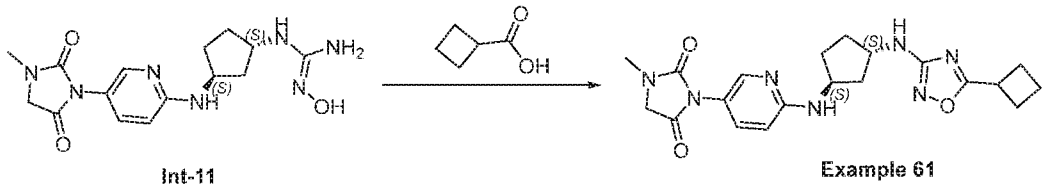
Example 60: Synthesis of 1-methyl-3-(6-(((1*S*,3*S*)-3-((5-(1-methylcyclopropyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)imidazolidine-2,4-dione



Int-11 Example 60

Example 60 was synthesized following the **Example 2** starting from **Int-11** with commercially available 1-methylcyclopropane-1-carboxylic acid. ESI-MS m/z: 412.25 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.90 (dd, J = 2.4, 0.4 Hz, 1H), 7.35 (dd, J = 9.2, 2.8 Hz, 1H), 6.56 (dd, J = 9.2, 0.8 Hz, 1H), 4.31 – 4.25 (m, 1H), 4.07 (s, 2H), 3.98 – 3.91 (m, 1H), 3.01 (s, 3H), 2.28 – 2.13 (m, 2H), 2.08 – 2.00 (m, 1H), 1.93 – 1.86 (m, 1H), 1.65 – 1.51 (m, 2H), 1.45 (s, 3H), 1.32 – 1.27 (m, 2H), 0.98 – 0.92 (m, 2H).

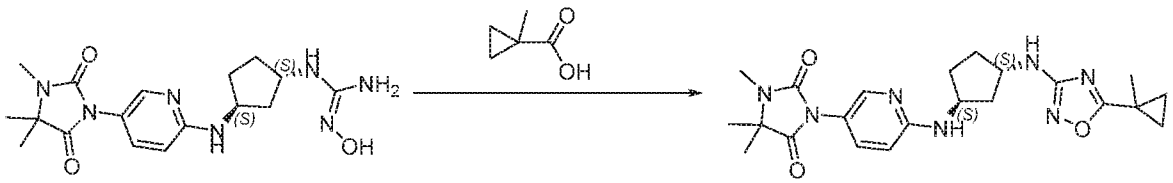
Example 61: Synthesis of 3-(6-(((1*S*,3*S*)-3-((5-cyclobutyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-methylimidazolidine-2,4-dione



Int-11 Example 61

Example 61 was synthesized following the **Example 2** starting from **Int-11** with commercially available cyclobutanecarboxylic acid. ESI-MS m/z: 412.25 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.90 (d, J = 2.8 Hz, 1H), 7.35 (dd, J = 8.8, 2.4 Hz, 1H), 6.56 (dd, J = 9.2, 0.8 Hz, 1H), 4.32 – 4.27 (m, 1H), 4.07 (s, 2H), 4.01 – 3.93 (m, 1H), 3.65 – 3.59 (m, 1H), 3.01 (s, 3H), 2.42 – 2.34 (m, 4H), 2.25 – 2.18 (m, 2H), 2.15 – 2.08 (m, 1H), 2.07 – 1.98 (m, 2H), 1.95 – 1.89 (m, 1H), 1.65 – 1.52 (m, 2H).

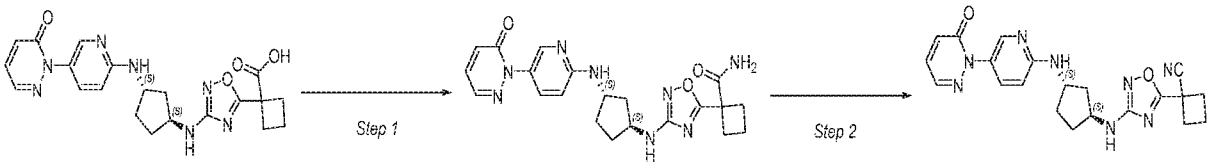
Example 62: Synthesis of 1,5,5-trimethyl-3-(6-(((1*S*,3*S*)-3-((5-(1-methylcyclopropyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)imidazolidine-2,4-dione



Int-39 Example 62

Example 62 was synthesized following the **Example 2** starting from **Int-64** with commercially available 1-methylcyclopropane-1-carboxylic acid. ESI-MS m/z: 440.0 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.91 – 7.90 (m, 1H), 7.37 (dd, *J* = 9.2, 2.8 Hz, 1H), 6.57 (dd, *J* = 9.2, 0.8 Hz, 1H), 4.32 – 4.26 (m, 1H), 3.99 – 3.92 (m, 1H), 2.95 (s, 3H), 2.28 – 2.17 (m, 2H), 2.08 – 2.01 (m, 1H), 1.93 – 1.88 (m, 1H), 1.65 – 1.52 (m, 2H), 1.48 (s, 6H), 1.47 (s, 3H), 1.31 – 1.28 (m, 2H), 0.98 – 0.96 (m, 2H).

Example 63: Synthesis of 1-(3-(((1*S*,3*S*)-3-((5-(6-oxopyridazin-1(6H)-yl)pyridin-2-yl)amino)cyclopentyl)amino)-1,2,4-oxadiazol-5-yl)cyclobutane-1-carbonitrile



Example 59 Int-61 Example 63

***Step-1*: Synthesis of Synthesis of 1-(3-(((1*S*,3*S*)-3-((5-(6-oxopyridazin-1(6*H*)-yl)pyridin-2-yl)amino)cyclopentyl)amino)-1,2,4-oxadiazol-5-yl)cyclobutane-1-carboxamide (Int-86)**

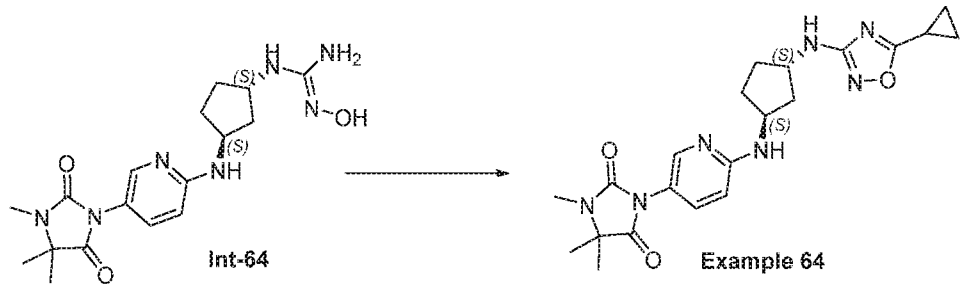
[355] To a solution of **Example 59** (35 mg, 0.08 mmol) in DMF (1.0 mL) were added ammonium chloride (21 mg, 0.40 mmol), HATU (45 mg, 0.12 mmol) and DIPEA (0.06 mL, 0.40 mmol). After stirring for 48 h, the reaction was quenched with water and the product was extracted with EtOAc. The organic phases were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to provide crude product as a pale brown sticky solid (50 mg, Crude) . ESI-MS *m/z*: 436.95 $[M+H]^+$.

***Step-2*: Synthesis of 1-(3-(((1*S*,3*S*)-3-((5-(6-oxopyridazin-1(6H)-yl)pyridin-2-yl)amino)cyclopentyl)amino)-1,2,4-oxadiazol-5-yl)cyclobutane-1-carbonitrile (Example 63)**

To a solution of **Int-86** (40 mg, 0.09 mmol) in DCM (1.0 mL) was added triethylamine (0.05 mL,0.36 mmol) and trifluoracetic anhydride (0.01 mL,0.11 mmol) at 0°C. The mixture was allowed to warm up to rt, and stirred for 1 h. After methanol (0.5 mL) and K_2CO_3 (86 mg, 0.63 mmol) were added, the reaction mixture was stirred for 48 h. After quenched with water, the product was extracted with EtOAc. The organic phases were combined, dried over anhydrous sodium sulfate, filtered and concentrated under

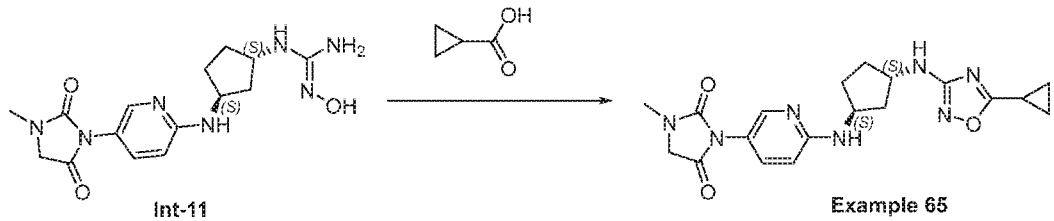
reduced pressure. The residue was purified by preparative HPLC (30-75% acetonitrile/0.02% NH4OH in water; WATERS X BRIDGE, 250 mm x 20 mm,5.0 µm column, flow rate 15 mL/min) to afford the title compound as a yellow solid (7 mg, 18%), ESI-MS m/z: 419.05 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.15 (d, *J* = 2.8 Hz, 1H), 8.03 (dd, *J* = 4.0, 2.0 Hz, 1H), 7.60 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.46 (dd, *J* = 9.6, 4.0 Hz, 1H), 7.06 (dd, *J* = 9.6, 1.6 Hz, 1H), 6.59 (d, *J* = 9.2 Hz, 1H), 4.39 – 4.31 (m, 1H), 4.05 – 3.97 (m, 1H), 2.88 – 2.81 (m, 4H), 2.40 – 2.20 (m, 4H), 2.16 – 2.06 (m, 1H), 1.99 – 1.90 (m, 1H), 1.68 – 1.58 (m, 2H).

Example 64: Synthesis of 3-(6-(((1*S*,3*S*)-3-((5-cyclopropyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1,5,5-trimethylimidazolidine-2,4-dione



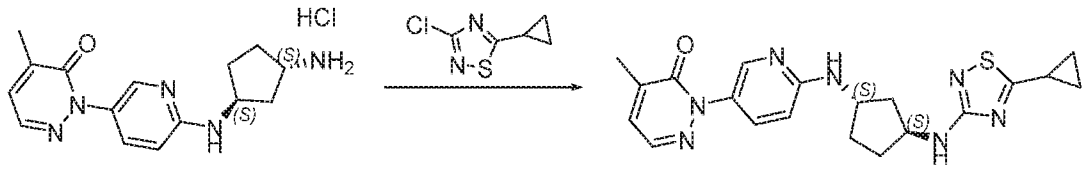
Example 64 was synthesized following the **Example 2** starting from **Int-64** with commercially available cyclopropanecarboxylic acid. ESI-MS m/z: 426.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.91 (d, *J* = 2.8 Hz, 1H), 7.37 (dd, *J* = 9.2, 2.8 Hz, 1H), 6.57 (dd, *J* = 8.8, 0.4 Hz, 1H), 4.32 – 4.25 (m, 1H), 3.99 – 3.91 (m, 1H), 2.95 (s, 3H), 2.28 – 2.18 (m, 2H), 2.10 – 2.00 (m, 2H), 1.95 – 1.87 (m, 1H), 1.65 – 1.52 (m, 2H), 1.48 (s, 6H), 1.19 – 1.12 (m, 2H), 1.11 – 1.08 (m, 2H).

Example 65: Synthesis of 3-(6-(((1*S*,3*S*)-3-((5-cyclopropyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-methylimidazolidine-2,4-dione



Example 65 was synthesized following the **Example 2** starting from **Int-11** with commercially available 1-methylcyclopropane-1-carboxylic acid. ESI-MS m/z: 398.25 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.91 (d, *J* = 2.8 Hz, 1H), 7.36 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.56 (dd, *J* = 9.2, 0.8 Hz, 1H), 4.31 – 4.26 (m, 1H), 4.08 (s, 2H), 3.99 – 3.92 (m, 1H), 3.02 (s, 3H), 2.27 – 2.18 (m, 2H), 2.10 – 2.01 (m, 2H), 1.97 – 1.88 (m, 1H), 1.65 – 1.52 (m, 2H), 1.19 – 1.12 (m, 2H), 1.11 – 1.07 (m, 2H).

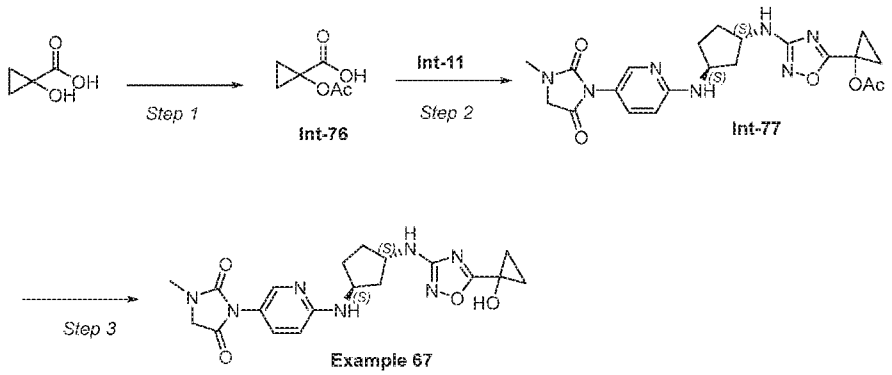
Example 66: Synthesis of 2-(6-(((1*S*,3*S*)-3-((5-cyclopropyl-1,2,4-thiadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-4-methylpyridazin-3(2*H*)-one



Int-67 Example 66

Example 66 was synthesized following the **Example 24** starting from **Int-67.** ESI-MS m/z: 410.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.12 (d, *J* = 2.4 Hz, 1H), 7.87 (d, *J* = 4.0 Hz, 1H), 7.57 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.32 – 7.31 (m, 1H), 6.58 (d, *J* = 8.8 Hz, 1H), 4.35 – 4.29 (m, 1H), 4.28 – 4.21 (m, 1H), 2.37 – 2.30 (m, 1H), 2.29 – 2.21 (m, 5H), 2.05 – 1.91 (m, 2H), 1.63 – 1.52 (m, 2H), 1.22 – 1.18 (m, 2H), 1.10 – 1.07 (m, 2H).

Example 67: Synthesis of 3-(6-(((1*S*,3*S*)-3-((5-(1-hydroxycyclopropyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-methylimidazolidine-2,4-dione



Int-76 Int-77 Example 67

***Step-1*: Synthesis of 1-acetoxycyclopropane-1-carboxylic acid (Int-76)**

Int-76 was synthesized following the **Int-70** starting from commercially available 1-hydroxycyclopropane-1-carboxylic acid. ^1H NMR (400 MHz, DMSO-d_6) δ 12.86 (s, 1H), 2.01 (s, 3H), 1.36 – 1.33 (m, 2H), 1.17 – 1.13 (m, 2H).

***Step-2*: Synthesis of 1-(3-(((1*S*,3*S*)-3-((5-(3-methyl-2,5-dioxoimidazolidin-1-yl)pyridin-2-yl)amino)cyclopentyl)amino)-1,2,4-oxadiazol-5-yl)cyclopropyl acetate (Int-77)**

Int-77 was synthesized following the **Example 2** starting from **Int-76** and **Int-11**. ESI-MS m/z: 456.10 $[M+H]^+$.

***Step-3*: Synthesis of 3-(6-(((1*S*,3*S*)-3-((5-(1-hydroxycyclopropyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-methylimidazolidine-2,4-dione (Example 67)**

To a solution of **Int-77** (60 mg, 0.13 mmol) in THF (1.0 mL) was added 6N HCl (1.0 mL) at 0°C. The mixture was allowed to warm up to rt and stirred for 48 h. After quenched with saturated sodium

bicarbonate solution until pH=7-8, the product was extracted with EtOAc. The organic phases were combined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (10-40% acetonitrile/0.1% formic acid in water; ZODIAC, C18, 250 mm x 19 mm,5.0 µm column, flow rate 15 mL/min) to afford the title compound as a yellow solid (3 mg, 6%), ESI-MS m/z: 413.95 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.91 (d, J = 2.8 Hz, 1H), 7.43 (dd, J = 8.8, 2.4 Hz, 1H), 6.62 (d, J = 8.8 Hz, 1H), 4.31 – 4.25 (m, 1H), 4.09 (s, 2H), 4.01 – 3.94 (m, 1H), 3.02 (s, 3H), 2.28 – 2.18 (m, 2H), 2.09 – 2.02 (m, 1H), 1.98 – 1.91 (m, 1H), 1.65 – 1.56 (m, 2H), 1.34 – 1.25 (m, 4H).

Example 68: PCSK9 Ligand Binding Assay

[356] The PCSK9 binding of the compounds of the disclosure was measured using a time resolved fluorescence resonance energy transfer (TR-FRET) assay. This TR-FRET assay measures the ability of a compounds of the present disclosure to compete for binding with Alexa Fluor 647 labeled probe in a known region of human PCSK9. The assay provides measures of both potency (IC50) and efficacy (Amax).

[357] Materials

- Human PCSK9
- Human PCSK9 Terbium
- Alexa Fluor 647 labeled probe, prepared as described in Example 28.
- Proxi plate-low volume assay plate (PerkinElmer #6008280)
- Greiner V-bottom (Greiner BioOne #781280)
- Assay Buffer
    - 20 mM HEPES, pH 7.5
    - 150 mM NaCl
    - 1 mM $CaCl_2$
    - 0.01% v/v Tween20
    - 0.01% w/v BSA

[358] A master compound plate was prepared in a Greiner V bottom plate by diluting compounds of the disclosure in dimethylsulfoxide to the correct concentration for the desired top concentration based on the desired final concentration: for a 30 µM final concentration the master plate concentration is 1.5 mM (68 µL DMSO + 12 µL 10 mM of a compound of the disclosure), for a 10 µM final concentration the master plate concentration is 0.5 mM (76 µL DMSO + 4 µL 10 mM of a compound of the disclosure), for a 3 µM final concentration the master plate concentration is 150 µM (69 µL DMSO + 1 µL 10 mM of a compound of the disclosure). These solutions were pipetted into columns 1 and 11 of the compound plate.

Threefold serial dilutions were generated in columns 2-10 and 12-20 of the compound plate by transferring 10 µL into 20 µL of DMSO. Columns 21 and 22 of the compound plate were negative controls containing DMSO alone.

[359] An intermediate plate was generated in a Greiner V bottom plate by transferring 8 µL from each well of the master plate into a corresponding well containing 92 µL of assay buffer and mixing thoroughly.

[360] A Proxi plate-low volume assay plate was used for the assay. To all wells of the plate was added 10 µL of 7 nM Human PCSK9 Terbium, followed by 5 µL from the intermediate plate. For the competition displacement control wells in columns 23 and 24 of the plate, 5 µL of unlabeled human PCSK9 was added at 4 µM in assay buffer containing 8% DMSO. Following a 30 minute incubation, 5 µL of 120 µM Alexa Fluor 647 labeled probe was added and the mixture was incubated for an additional 2 hours.

[361] The TR-FRET signal was measured on an EnVision instrument with a 60 ms delay, 330 nm excitation and 665 nm emission (FRET), and 330 nM excitation and 615 nm (Terbium). The FRET ratio (FRET/ Terbium) was used for calculations.

DATA ANALYSIS

[362] No inhibition (0%) was observed from the wells containing DMSO (Control) in columns 21 and 22 of the compound plate. Full inhibition (100%) was observed from the wells containing 1 µM human PCSK9 (Control) in columns 23 and 24 of the plate. Data is expressed as percent inhibition: (value - 0%)/(100% - 0%) – Table 2.

Table 2: PCSK9 Ligand Binding Assay

Example	Inhibition Rank
1	1
2	1
3	1
4	1
5	1
6	1
7	1
8	1
9	3
10	1
11	1
12	1
13	1
14	1
15	1
16	3
17	2
18	3
19	3
20	2
21	1
22	1
23	1
24	1
25	2
26	1
27	2
29	1
30	1
31	1

32	1
33	1
34	1
35	1
36	2
37	1
38	1
39	1
40	1
41	1
42	1
43	1
44	1
45	2
46	1
47	1
48	1
49	1
50	1
51	1
52	1
53	3
54	2
55	1
56	1
57	1
58	2
59	1
60	1
61	1
62	1
63	1
64	1

65	1
66	1
67	1
Ranking: 1 IC_{50} <0.05µM 2 0.05 µM < IC_{50} <0.5µM 3 0.5µM < IC_{50} <20µM	

Example 69: hERG Qpatch Assay

[363] The cardiovascular toxicity of certain compounds was measured using a hERG Qpatch assay. Briefly, hERG expressing cell lines were produced using CHO-K1 T-Rex inducible plasmid system (Invitrogen) as described previously (Cao *et al*, Assay Drug Dev. Technol. 2010, 8, 766-780). Cell lines were maintained in Ham's F12 nutrient mixture containing 10% FBS, blasticidin (10 mg/mL; InvivoGen), hygromycin B (200 mg/mL;InvivoGen), Zeocin (200 mg/mL, Invitrogen), and neomycin (200 mg/mL, Invitrogen) using SelecT automated cell culture system (TAP Biosystems, Cambridge, U.K.). hERG and hCav1.2 channels expression was induced with tetracycline (0.25−1 µg/mL, Invitrogen) at least 24 h prior to the experiment. hERG currents were recorded using the Qpatch automated patch clamp systems (Sophion Bioscience Inc., North Brunswick, NJ) in the whole (single) cell configuration. hERG expressing CHO-K1 cells were harvested with Detachin (Genlantis) and stored in the modified serum-free SFM-2 media (Life Technologies) at room temperature. The extracellular solution contained (in mM) NaCl (145), KCl (4), MgCl2 (1), CaCl2 (2), and HEPES (10), pH 7.4, with NaOH. The intracellular solution contained KCl (135), MgCl2 (1.75), CaCl2 (5.4), EGTA (10), K2-ATP (4), and HEPES (10), pH 7.2, with KOH.

[364] After whole cell configuration was achieved, the cell was held at −90 mV, and a 0.1 s pulse to −50 mV was delivered to measure the leaking current, which was subtracted from the tail current online. Then the cell was depolarized to +20 mV for 4 s (prepulse), followed by a 4 s test pulse to −50 mV to reveal the hERG tail current. To monitor changes in the current amplitude, this voltage protocol was repeatedly applied every 20 s. Test compounds were first diluted in DMSO for six dose−response experiments and then dissolved in the extracellular solution using Freedom EVO liquid handling robotic system (Tecan, Männedorf, Switzerland). The final DMSO concentration in samples was 0.3% v/v. Amitriptyline (Sigma) was tested as a positive control. Data were analyzed using a MatLab-based program and using Sophion QPatch Assay software. The data, shown in Table 3, represent the results of a single experiment.

Table 3: hERG Qpatch Assay

Example	hERG Qpatch IC50 [μM]
Reference compound 1	19.3
Reference compound 2	12.5
1	>30
2	>30
5	>30
6	>30
10	>30
24	>30
29	>30
31	>30
37	>30
39	>30

Reference Compound 1 is 2-(6-(((1S,3S)-3-((5-cyclopropylpyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one. The compound was prepared following the procedure reported in WO2020150473. Reference Compound 2 is 3-(6-(((1S,3S)-3-((5-(difluoromethoxy)pyrimidin-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-methylimidazolidine-2,4-dione The compound was prepared following the procedure reported in WO2020150473.

[365] As show in Table 3, Examples 1, 2, 5, 6, 10, 24, 29 and 31 showed unexpectedly reduced inhibition of the hERG channel, compared to the reference compounds (Reference compounds 1 and 2). Reduced inhibition of the hERG channel may translate into an improved safety profile for the compounds as compared to reference compounds.

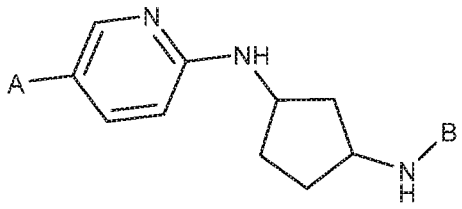
Equivalents

[366] Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, numerous equivalents to the specific embodiments described specifically herein. Such equivalents are intended to be encompassed in the scope of the following claims.

CLAIMS

What is claimed is:

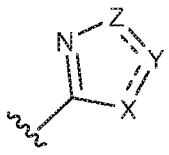
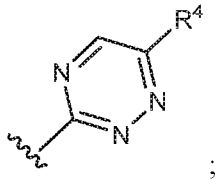
1. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof wherein:

A is a 5 or 6 membered heterocycle or heteroaryl containing at least one N and at least one oxo at a ring carbon and is optionally substituted with (C_1-C_6)alkyl;

B is  or  ;

X is N, O, or S;

Y is CR^1 or N;

Z is CR^2, NR^3, O, or S;

R^1 and R^2 are each, independently selected from H, halogen, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_6-C_{10})aryl, a 4 to 6 membered heterocyclyl comprising 1, 2 or 3 heteroatoms selected from O and N, or a 5 or 6 membered heteroaryl comprising 1, 2 or 3 heteroatoms selected from O and N, wherein the (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_6-C_{10})aryl, heterocyclyl, or heteroaryl are each independently optionally substituted with one or more substituents selected from halogen, -OH, –CN, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_3-C_6)cycloalkyl, -SO_2(C_1-C_6)alkyl, -COOH, and -COO(C_1-C_6)alkyl;

R^3 is absent, H or (C_1-C_6)alkyl; and

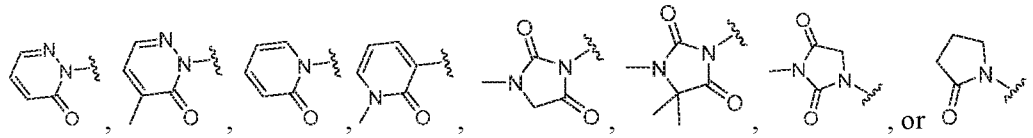
R^4 is H, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy or (C_3-C_6)cycloalkyl, wherein the (C_1-C_6)alkoxy is optionally substituted with halogen.

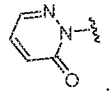
2. A compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein at least one of X, Y and Z is N.

3. A compound according to claim 1 or claim 2 or a pharmaceutically acceptable salt thereof, wherein when X is O or S, Z is CR^2 or N.

4. A compound according to any one of claims 1 to 3 or a pharmaceutically acceptable salt thereof, wherein when Z is O or S, X is N.

5. A compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein R^4 is methyl, ethyl, or cyclopropyl.

6. A compound according to any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof, wherein A is  , or .

7. A compound according to any one of claims 1 to 6 or a pharmaceutically acceptable salt thereof, wherein A is  .

8. A compound according to any one of claims 1 to 7 or a pharmaceutically acceptable salt thereof, wherein X is N.

9. A compound according to any one of claims 1 to 8 or a pharmaceutically acceptable salt thereof, wherein X is N, Y is CR^1, and Z is O or S.

10. A compound according to any one of claims 1 to 9 or a pharmaceutically acceptable salt thereof, wherein X is N, Y is CR^1, and Z is O.

11. A compound according to any one of claims 1 to 10 or a pharmaceutically acceptable salt thereof, wherein R^1 is H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_6\text{-}C_{10})$aryl, a 4 to 6 membered heterocyclyl comprising 1, 2 or 3 heteroatoms selected from O and N, or a 5 or 6 membered heteroaryl comprising 1, 2 or 3 heteroatoms selected from O and N, wherein the $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_6\text{-}C_{10})$aryl, heterocyclyl, or heteroaryl are each independently optionally substituted with one or more substituents selected from halogen, -OH, –CN, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, $(C_1\text{-}C_6)$alkoxy, $(C_3\text{-}C_6)$cycloalkyl, -$SO_2(C_1\text{-}C_6)$alkyl, -COOH, and -$COO(C_1\text{-}C_6)$alkyl.

12. A compound according to any one of claims 1 to 11 or a pharmaceutically acceptable salt thereof, wherein R^1 is H, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_6\text{-}C_{10})$aryl, a 4 to 6 membered heterocyclyl

comprising 1 heteroatom selected from O and N, or a 5 or 6 membered heteroaryl comprising 1 or 3 heteroatoms selected from N, wherein the (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_6-C_{10})aryl, heterocyclyl, or heteroaryl are each independently optionally substituted with one or more substituents selected from halogen, -OH, –CN, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)alkoxy, (C_3-C_6)cycloalkyl, -SO_2(C_1-C_6)alkyl, -COOH, and -COO(C_1-C_6)alkyl.

13. A compound according to any one of claims 1 to 12 or a pharmaceutically acceptable salt thereof, wherein R^1 is H, (C_1-C_6)alkyl optionally substituted with one or more halogen, -CN, (C_3-C_6)cycloalkyl optionally substituted with one or more substituents selected from halogen, -OH, (C_1-C_6)alkyl and (C_1-C_6)haloalkyl, or (C_6-C_{10})aryl optionally substituted one or more with halogen.

14. A compound according to any one of claims 1 to 13 or a pharmaceutically acceptable salt thereof, wherein R^1 is (C_1-C_6)alkyl optionally substituted with one or more halogen or -CN, (C_3-C_6)cycloalkyl optionally substituted with one or more substituents selected from halogen, -OH, (C_1-C_6)alkyl and (C_1-C_6)haloalkyl, or (C_6-C_{10})aryl optionally substituted with one or more halogen or -CN.

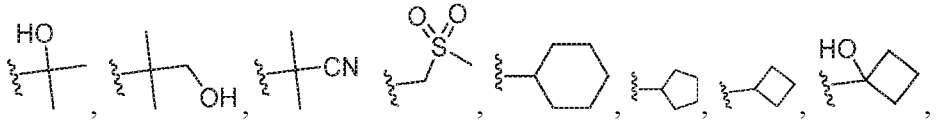
15. A compound according to claim 13 or a pharmaceutically acceptable salt thereof, wherein each halogen is fluoro.

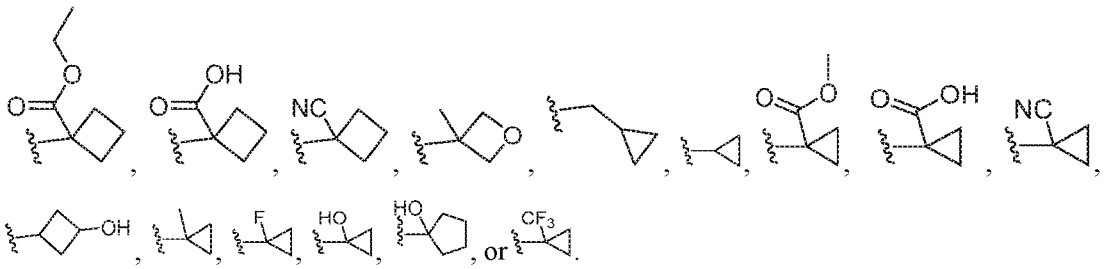
16. A compound according to any one of claims 1 to 15 or a pharmaceutically acceptable salt thereof, wherein R^1 is (C_1-C_6)alkyl optionally substituted with one or more fluoro or -CN.

17. A compound according to any one of claims 1 to 16, wherein R^1 is -CH_3, -CH_2CH_3, -CHF_2, -CF_3, -CF_2CH_3, -CH_2CF_3, -CH_2CN,  , or  .

18. A compound according to any one of claims 1 to 17, wherein R^1 is -CH_3, -CHF_2, or -CF_3.

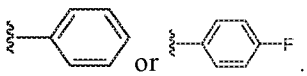
19. A compound according to any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof, wherein R^1 is (C_3-C_6)cycloalkyl optionally substituted with one or more substituents selected from fluoro, -OH, (C_1-C_6)alkyl and (C_1-C_6)fluoroalkyl.

20. A compound according to any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof, wherein R^1 is  .



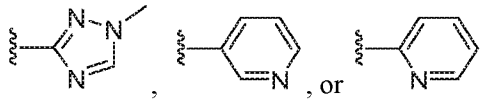
21. A compound according to any one of claims 1 to 13 or a pharmaceutically acceptable salt thereof, wherein R^1 is phenyl optionally substituted with one or more fluoro.

22. A compound according to claim 21 or a pharmaceutically acceptable salt thereof, wherein R^1 is



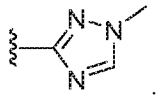
.

23. A compound according to any one of claims 1 to 13 or a pharmaceutically acceptable salt thereof, wherein R^1 is



.

24. A compound according to any one of claims 1 to 13 or a pharmaceutically acceptable salt thereof, wherein R^1 is

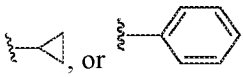


.

25. A compound according to any one of claims 1 to 3, 5 to 8, and 11 to 24 or a pharmaceutically acceptable salt thereof, wherein R^2 is H, halogen, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, or $(C_6\text{-}C_{10})$aryl.

26. A compound according to any one of claims 1to 3, 5 to 8, and 11 to 25 or a pharmaceutically acceptable salt thereof, wherein R^2 is halogen, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, or phenyl

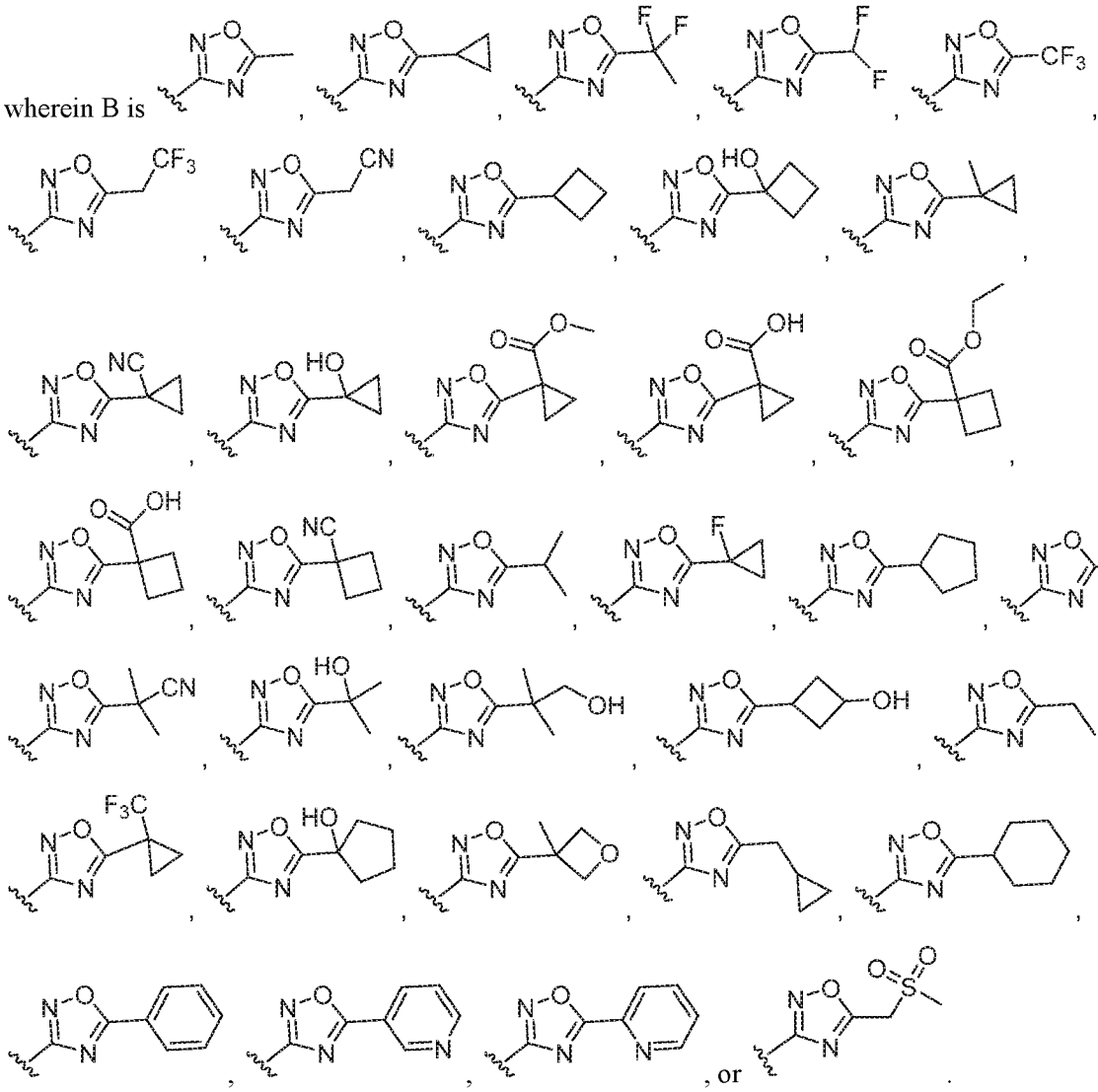
27. A compound according to any one of claims 1 to 3, 5 to 8, and 11 to 26 or a pharmaceutically acceptable salt thereof, wherein R^2 is -Cl, $-CH_3$,



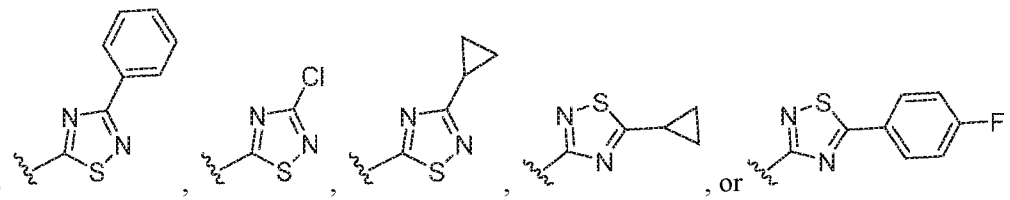
.

28. A compound according to any one of claims 1 to 3, 5 to 7, and 11 to 27 or a pharmaceutically acceptable salt thereof, wherein R^3 is H.

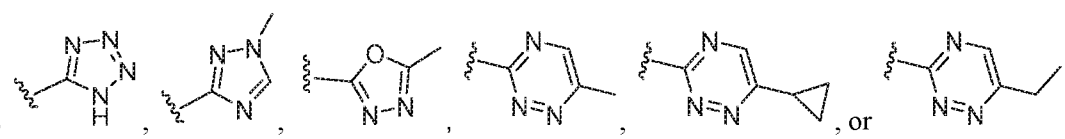
29. A compound according to any one of claims 1 to 4 or a pharmaceutically acceptable salt thereof,

wherein B is 

30. A compound according to any one of claims 1 to 4 or a pharmaceutically acceptable salt thereof,,

wherein B is 

31. A compound according to any one of claims 1 to 4 or a pharmaceutically acceptable salt thereof,

wherein B is 

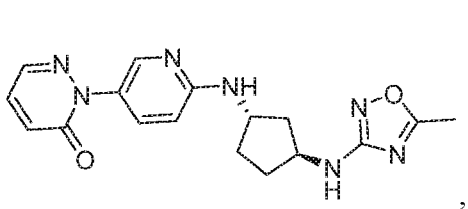
32. A compound according to claim 1 or a pharmaceutically acceptable salt thereof selected from:
2-(6-(((1S,3S)-3-((5-cyclobutyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one;
2-(6-(((1S,3S)-3-((5-cyclopropyl-1,2,4-thiadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one;
2-(6-(((1S,3S)-3-((5-(3-hydroxycyclobutyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one;
2-(6-(((1S,3S)-3-((3-chloro-1,2,4-thiadiazol-5-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one;
2-(6-(((1S,3S)-3-((5-(1-methylcyclopropyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one;
3-methyl-1-(6-(((1S,3S)-3-((5-methyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)imidazolidine-2,4-dione;
2-(6-(((1S,3S)-3-((5-(1,1-difluoroethyl)-1,2,4-oxadiazol-3-yl) amino) cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one;
2-(6-(((1S,3S)-3-((5-(1-fluorocyclopropyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one;
2-(6-(((1S,3S)-3-((5-ethyl-1,2,4-oxadiazol-3-yl)amino) cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one;
2-(6-(((1S,3S)-3-((3-cyclopropyl-1,2,4-thiadiazol-5-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one;
2-(6-(((1S,3S)-3-((5-methyl-1,2,4-oxadiazol-3-yl)amino) cyclopentyl) amino) pyridin-3-yl) pyridazin-3(2H)-one;
2-(6-(((1S,3S)-3-((5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one;
2-(6-(((1S,3S)-3-((5-(1-hydroxycyclopropyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one;
2-(6-(((1S,3S)-3-((5-(difluoromethyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one;
2-(6-(((1S,3S)-3-((5-cyclopentyl-1,2,4-oxadiazol-3-yl)amino) cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one;

2-(6-(((1S,3S)-3-((5-cyclopropyl-1,2,4-oxadiazol-3-yl)amino) cyclopentyl) amino)pyridin-3-yl) pyridazin-3(2H)-one;
2-(6-(((1S,3S)-3-((3-phenyl-1,2,4-thiadiazol-5-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one;
2-(6-(((1S,3S)-3-((5-isopropyl-1,2,4-oxadiazol-3-yl)amino) cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one;
2-(6-(((1S,3S)-3-((5-(tert-butyl)-1,2,4-oxadiazol-3-yl)amino) cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one;
2-(6-(((1S,3S)-3-((5-(4-fluorophenyl)-1,2,4-thiadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one;
2-(6-(((1S,3S)-3-((2H-tetrazol-5-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-;
2-(6-(((1S,3S)-3-((5-methyl-1,3,4-oxadiazol-2-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one;
1-methyl-3-(6-(((1S,3S)-3-((5-methyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)imidazolidine-2,4-dione;
2-(6-(((1S,3S)-3-((5-(1-(trifluoromethyl)cyclopropyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one;
1-(6-(((1S,3S)-3-((5-methyl-1,2,4-oxadiazol-3-yl)amino) cyclopentyl)amino)pyridin-3-yl)pyrrolidin-2-one;
2-(6-(((1S,3S)-3-((5-(1-hydroxycyclopentyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one;
6'-(((1S,3S)-3-((5-methyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)-2H-[1,3'-bipyridin]-2-one;
2-(6-(((1S,3S)-3-((6-methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one;
4-methyl-2-(6-(((1S,3S)-3-((6-methyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one;
2-(6-(((1S,3S)-3-((6-cyclopropyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one;
2-(6-(((1S,3S)-3-((6-cyclopropyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-4-methylpyridazin-3(2H)-one;
2-(6-(((1S,3S)-3-((6-ethyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-4-methylpyridazin-3(2H)-one;
2-(6-(((1S,3S)-3-((6-ethyl-1,2,4-triazin-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one:

2-(6-(((1S,3S)-3-((5-(1-hydroxycyclopentyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one;
1,5,5-trimethyl-3-(6-(((1S,3S)-3-((5-methyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)imidazolidine-2,4-dione;
4-methyl-2-(6-(((1S,3S)-3-((5-methyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one;
2-(6-(((1S,3S)-3-((5-(3-methyloxetan-3-yl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one;
2-(6-(((1S,3S)-3-((5-(cyclopropylmethyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one;
2-(6-(((1S,3S)-3-((5-(2-hydroxypropan-2-yl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one;
2-(6-(((1S,3S)-3-((5-(1-hydroxycyclobutyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one;
2-(6-(((1S,3S)-3-((5-cyclohexyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one;
2-(6-(((1S,3S)-3-((5-phenyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one;
2-(6-(((1S,3S)-3-((5-(pyridin-3-yl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one;
2-(6-(((1S,3S)-3-((5-(pyridin-2-yl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one;
2-(6-(((1S,3S)-3-((5-((methylsulfonyl)methyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one;
2-(6-(((1S,3S)-3-((5-(1-hydroxy-2-methylpropan-2-yl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one;
2-(6-(((1S,3S)-3-((5-(2,2,2-trifluoroethyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one;
methyl 1-(3-(((1S,3S)-3-((5-(6-oxopyridazin-1(6H)-yl)pyridin-2-yl)amino)cyclopentyl)amino)-1,2,4-oxadiazol-5-yl)cyclopropane-1-carboxylate;
1-methyl-6'-(((1S,3S)-3-((5-methyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)-[3,3'-bipyridin]-2(1H)-one;
2-methyl-2-(3-(((1S,3S)-3-((5-(6-oxopyridazin-1(6H)-yl)pyridin-2-yl)amino)cyclopentyl)amino)-1,2,4-oxadiazol-5-yl)propanenitrile;

2-(6-(((1S,3S)-3-((5-cyclopropyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-4-methylpyridazin-3(2H)-one;
1-(3-(((1S,3S)-3-((5-(6-oxopyridazin-1(6H)-yl)pyridin-2-yl)amino)cyclopentyl)amino)-1,2,4-oxadiazol-5-yl)cyclopropane-1-carboxylic acid;
2-(6-(((1S,3S)-3-((5-(1-methyl-1H-1,2,4-triazol-3-yl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)pyridazin-3(2H)-one;
2-(3-(((1S,3S)-3-((5-(6-oxopyridazin-1(6H)-yl)pyridin-2-yl)amino)cyclopentyl)amino)-1,2,4-oxadiazol-5-yl)acetonitrile;
2-(6-(((1S,3S)-3-((5-ethyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-4-methylpyridazin-3(2H)-one;
1-(3-(((1S,3S)-3-((5-(6-oxopyridazin-1(6H)-yl)pyridin-2-yl)amino)cyclopentyl)amino)-1,2,4-oxadiazol-5-yl)cyclopropane-1-carbonitrile;
ethyl 1-(3-(((1S,3S)-3-((5-(6-oxopyridazin-1(6H)-yl)pyridin-2-yl)amino)cyclopentyl)amino)-1,2,4-oxadiazol-5-yl)cyclobutane-1-carboxylate;
1-(3-(((1S,3S)-3-((5-(6-oxopyridazin-1(6H)-yl)pyridin-2-yl)amino)cyclopentyl)amino)-1,2,4-oxadiazol-5-yl)cyclobutane-1-carboxylic acid;
1-methyl-3-(6-(((1S,3S)-3-((5-(1-methylcyclopropyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)imidazolidine-2,4-dione;
3-(6-(((1S,3S)-3-((5-cyclobutyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-methylimidazolidine-2,4-dione;
1,5,5-trimethyl-3-(6-(((1S,3S)-3-((5-(1-methylcyclopropyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)imidazolidine-2,4-dione;
1-(3-(((1S,3S)-3-((5-(6-oxopyridazin-1(6H)-yl)pyridin-2-yl)amino)cyclopentyl)amino)-1,2,4-oxadiazol-5-yl)cyclobutane-1-carbonitrile;
3-(6-(((1S,3S)-3-((5-cyclopropyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1,5,5-trimethylimidazolidine-2,4-dione;
3-(6-(((1S,3S)-3-((5-cyclopropyl-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-methylimidazolidine-2,4-dione;
2-(6-(((1S,3S)-3-((5-cyclopropyl-1,2,4-thiadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-4-methylpyridazin-3(2H)-one; and
3-(6-(((1S,3S)-3-((5-(1-hydroxycyclopropyl)-1,2,4-oxadiazol-3-yl)amino)cyclopentyl)amino)pyridin-3-yl)-1-methylimidazolidine-2,4-dione.

33. A compound according to claim 1 or a pharmaceutically acceptable salt thereof selected from: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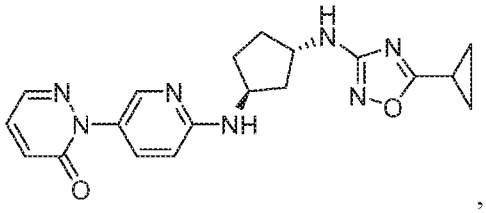
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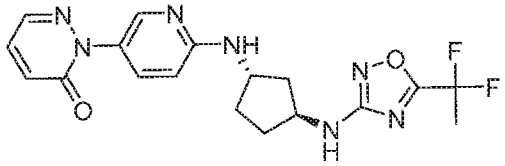
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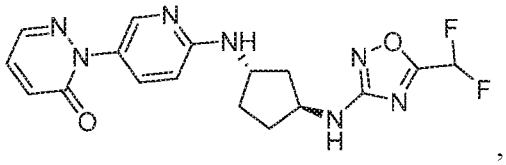
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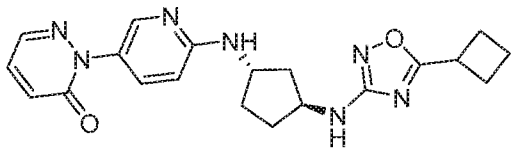
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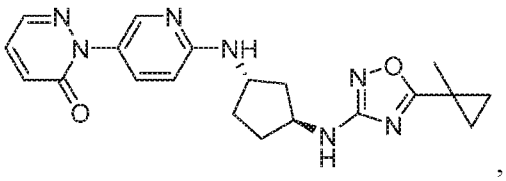
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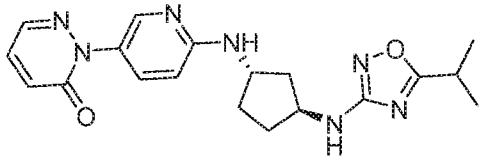
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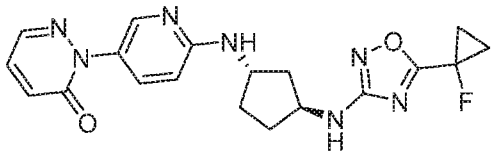
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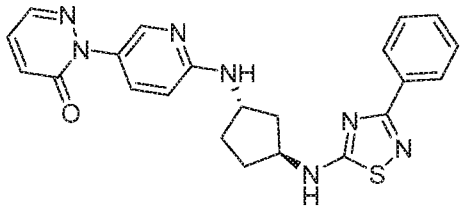
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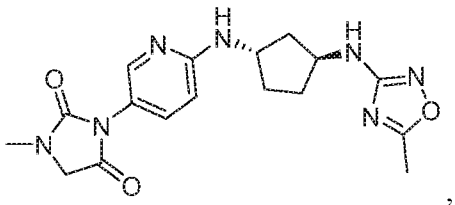
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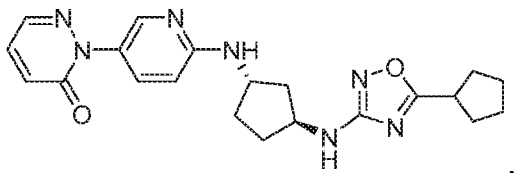
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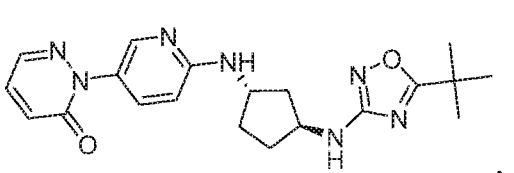
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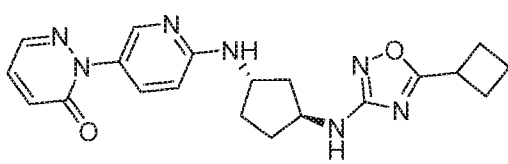
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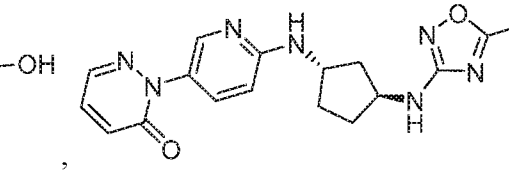
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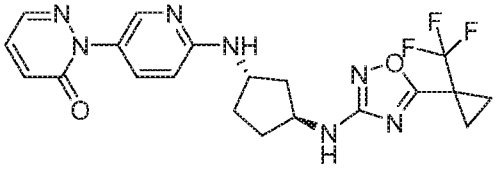
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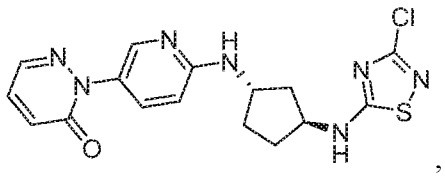
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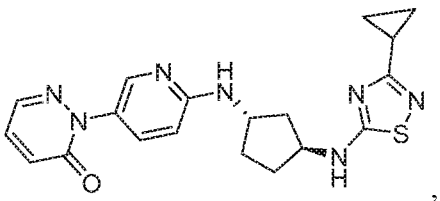
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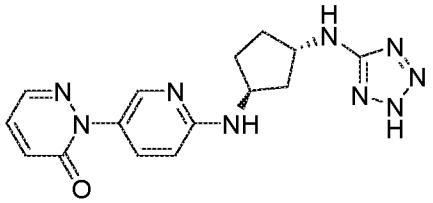
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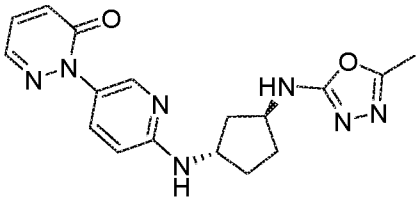
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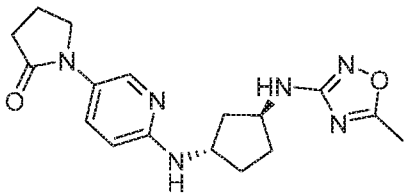
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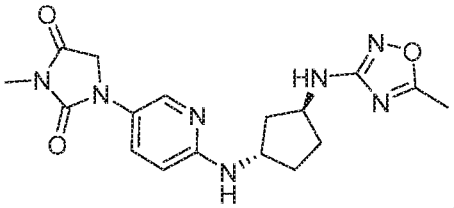
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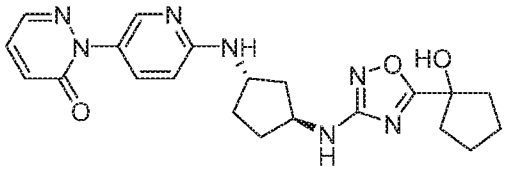
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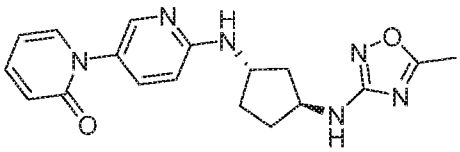
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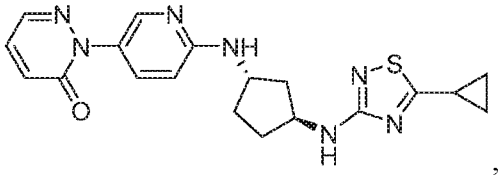
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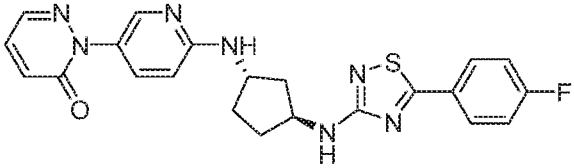
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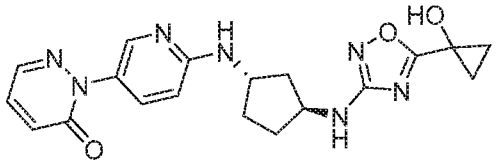
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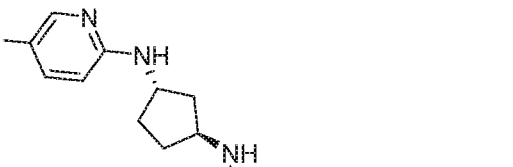
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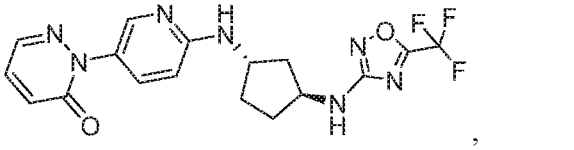
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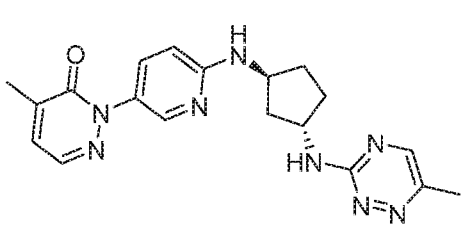
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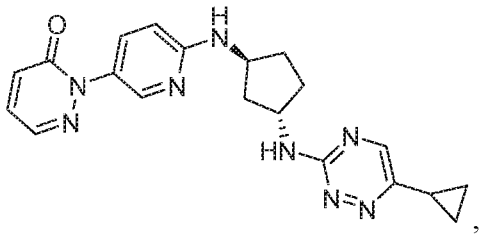
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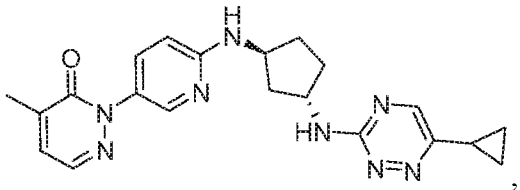
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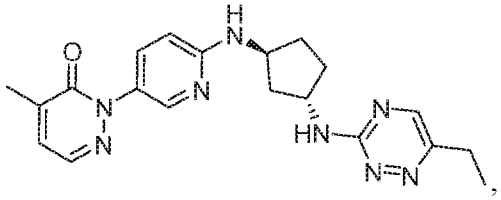
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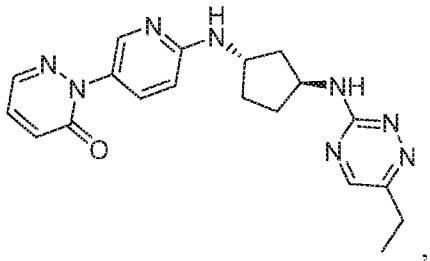
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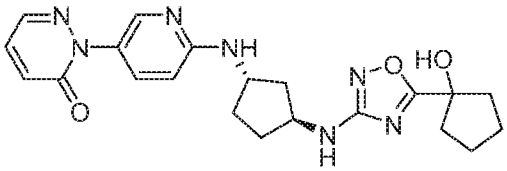
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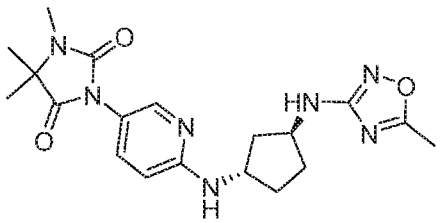
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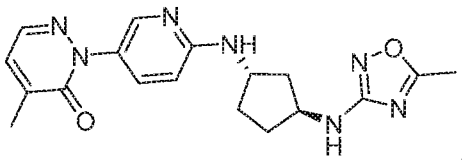
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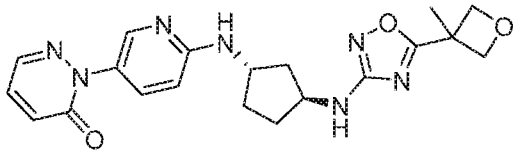
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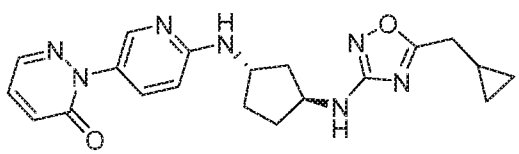
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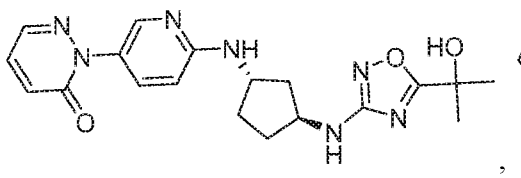
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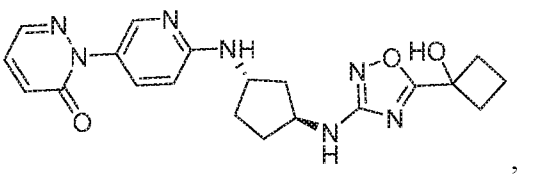
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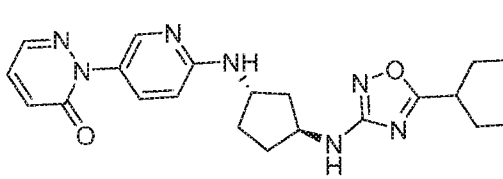
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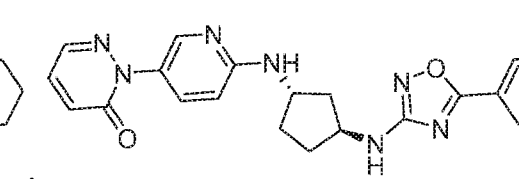
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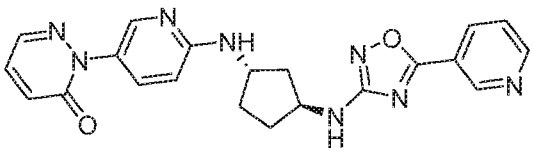
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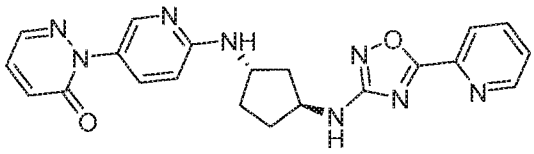
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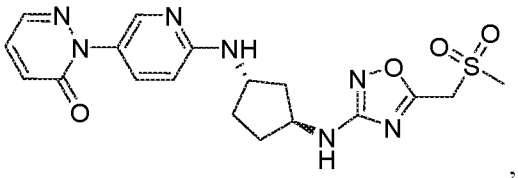
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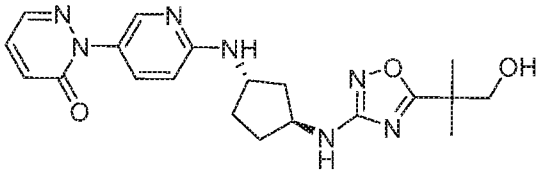
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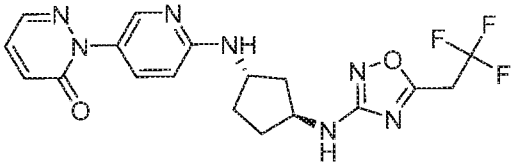
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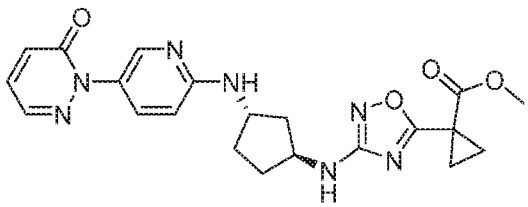
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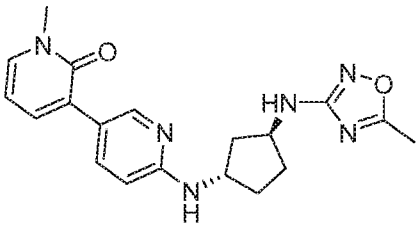
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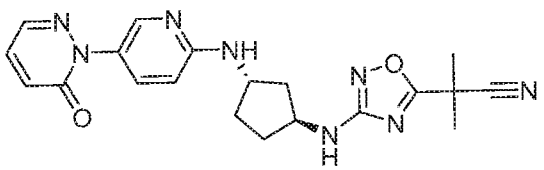
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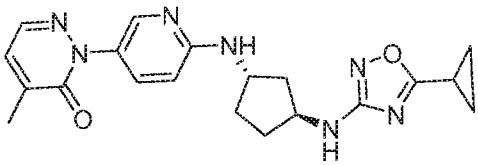
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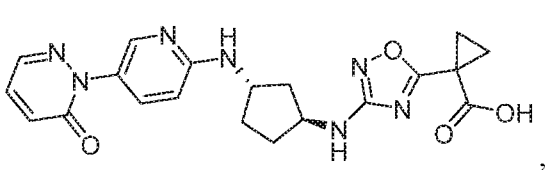
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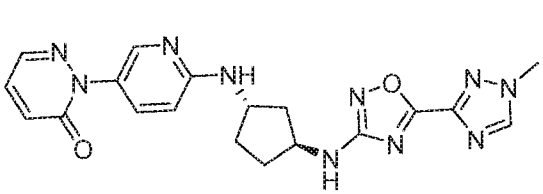
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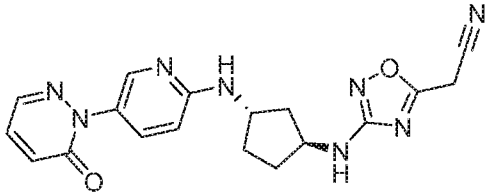
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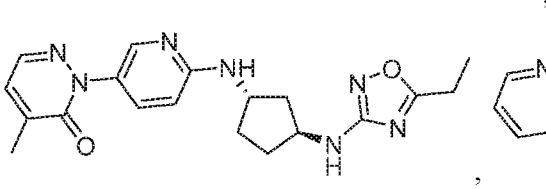
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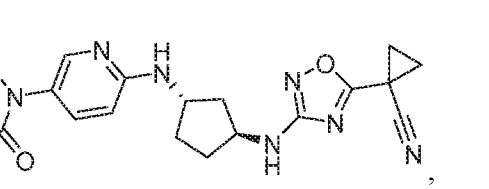
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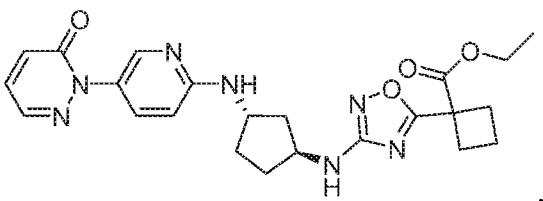
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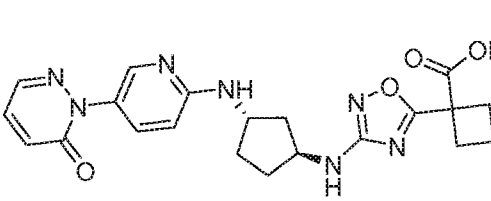
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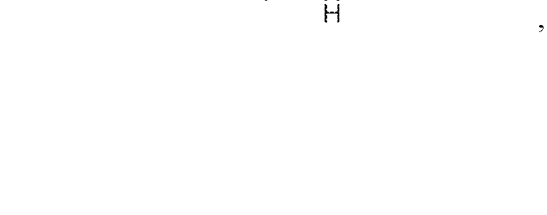
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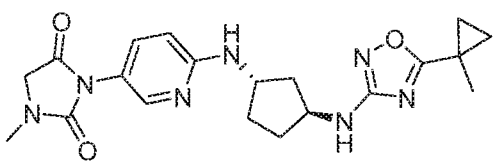
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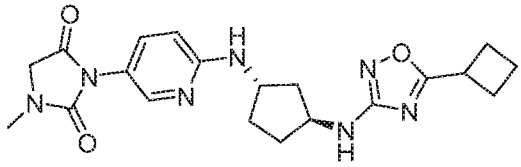
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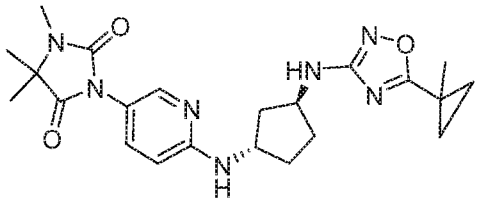
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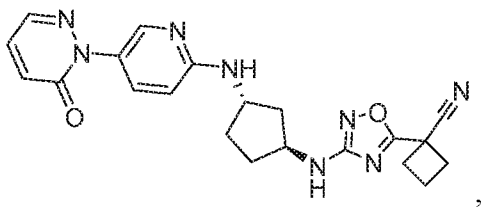
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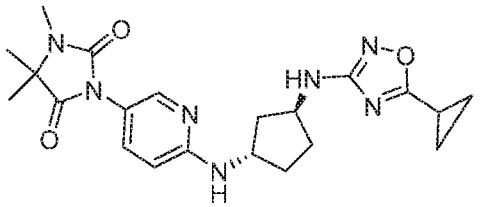
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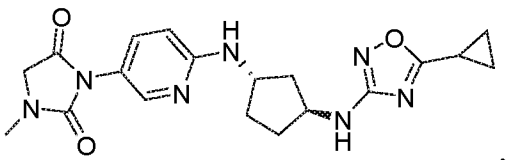
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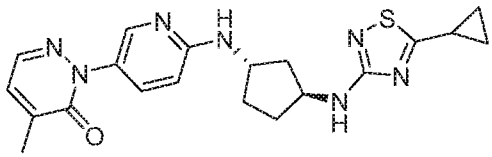
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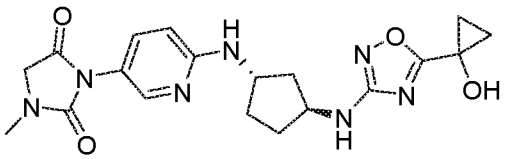
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34. A pharmaceutical composition comprising a compound according to any one of claims 1 to 33 or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers.

35. The pharmaceutical composition of claim 34, further comprising at least one additional pharmaceutically active agent.

36. The pharmaceutical composition of claim 35, wherein the additional pharmaceutically active agent is selected from hypolipidemic agents, niacin and analogs thereof, bile acid sequestrants, a thyroid hormone mimetic, thyroid hormone receptor (THR) β-selective agonist, a microsomal triglyceride transfer protein (MTP) inhibitor, an acyl CoA:diacylglycerol acyltransferase 1 (DGAT1) inhibitor, a Niemann Pick C1-like 1 (NPC1-L 1) inhibitor, an agonist of ATP Binding Cassette (ABC) proteins G5 or G8, an inhibitory nucleic acid targeting PCSK9 protein expression, an inhibitory nucleic acid targeting Lp(a) protein expression, an inhibitory nucleic acid targeting apoB 100, apoA-I up-regulator/inducer, ABCA 1

stabilizer or inducer, phospholipid transfer protein (PL TP) inhibitor, fish oil, anti-diabetic agent, anti-obesity agent, agonists of peroxisome proliferator-activator receptors, ATP citrate lyase (ACL) inhibitor, and anti-hypertensive agents, an antibody targeting PCSK9, an immune checkpoint inhibitor and combinations thereof.

37. The pharmaceutical composition of any one of claims 34 to 36 for use in the treatment of a PCSK9-mediated disease or disorder.

38. The pharmaceutical composition of any one of claims 34 to 36 for use in the treatment of a disease or disorder, wherein the disease or disorder is selected from hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, sitosterolemia, atherosclerosis, arteriosclerosis, coronary heart disease, peripheral vascular disease, vascular inflammation, xanthoma, peripheral arterial disease, elevated Lp(a), elevated LDL, elevated TRL, and elevated triglycerides.

39. A combination comprising of a compound according to any one of claims 1 to 33 or a pharmaceutically acceptable salt thereof and one or more additional pharmaceutical agents.

40. The combination of claim 39, where the one or more agents additional pharmaceutically active agent is selected from hypolipidemic agents, niacin and analogs thereof, bile acid sequestrants, a thyroid hormone mimetic, thyroid hormone receptor (THR) β-selective agonist, a microsomal triglyceride transfer protein (MTP) inhibitor, an acyl CoA:diacylglycerol acyltransferase 1 (DGAT1) inhibitor, a Niemann Pick C1-like 1 (NPC1-L 1) inhibitor, an agonist of ATP Binding Cassette (ABC) proteins G5 or G8, an inhibitory nucleic acid targeting PCSK9 protein expression, an inhibitory nucleic acid targeting Lp(a) protein expression, an inhibitory nucleic acid targeting apoB 100, apoA-I up-regulator/inducer, ABCA 1 stabilizer or inducer, phospholipid transfer protein (PL TP) inhibitor, fish oil, anti-diabetic agent, anti-obesity agent, agonists of peroxisome proliferator-activator receptors, ATP citrate lyase (ACL) inhibitor, and anti-hypertensive agents, an antibody targeting PCSK9, an immune checkpoint inhibitor and combinations thereof

41. A method for treating or preventing a disease or disorder comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to any one of the claims 1 to 33, or a pharmaceutically acceptable salt thereof.

42. The method of claim 41, wherein the disease or disorder is a PCSK9-mediated disease or disorder.

43. The method of claim 42, wherein the PCSK9-mediated disease or disorder is selected from hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, sitosterolemia, atherosclerosis, arteriosclerosis, coronary heart disease, peripheral vascular disease, vascular inflammation, xanthoma, peripheral arterial disease, elevated Lp(a), elevated LDL, elevated TRL, and elevated triglycerides.

44. A method for treating a disease or disorder comprising administering to a patient in need thereof a therapeutically effective amount of a compound according to any one of the claims 1 to 33, or a pharmaceutically acceptable salt thereof, wherein the disease or disorder is selected from selected from hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, sitosterolemia, atherosclerosis, arteriosclerosis, coronary heart disease, peripheral vascular disease, vascular inflammation, xanthoma, peripheral arterial disease, elevated Lp(a), elevated LDL, elevated TRL, and elevated triglycerides.

45. A method of modulating PCSK9 comprising administering to a patient in need thereof a compound of any one of claims 1 to 33 or a pharmaceutically acceptable salt thereof.

46. A method of inhibiting PCSK9 comprising administering to a patient in need thereof a compound of any one of claims 1 to 33 or a pharmaceutically acceptable salt thereof.

47. The method of any one of claims 41 to 46, wherein administering the compound is oral, parental, subcutaneous, by injection, or by infusion.

48. A compound according to any one of claims 1 to 33 or a pharmaceutically acceptable salt thereof, for use as a medicament.

49. A compound according to any one of claims 1 to 33 or a pharmaceutically acceptable salt thereof, for use in the treatment of a PCSK9-mediated disease or disorder.

50. The compound of claim 48, wherein the PCSK9-mediated disease or disorder selected from hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, sitosterolemia, atherosclerosis, arteriosclerosis, coronary heart disease, peripheral vascular disease, vascular inflammation, xanthoma, peripheral arterial disease, elevated Lp(a), elevated LDL, elevated TRL, and elevated triglycerides.

51. A compound according to any one of claims 1 to 33 or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease or disorder, wherein the disease or disorder is selected from hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, sitosterolemia, atherosclerosis, arteriosclerosis, coronary heart disease, peripheral vascular disease, vascular inflammation, xanthoma, peripheral arterial disease, elevated Lp(a), elevated LDL, elevated TRL, and elevated triglycerides.

52. A compound according to any one of the claims 1 to 33, or a pharmaceutically acceptable salt thereof, for use in the manufacture of a medicament for treating of a PCSK9-mediated disease or disorder.

53. The compound for use in the manufacture of a medicament of claim 52, wherein the disease or disorder is selected from hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, sitosterolemia, atherosclerosis, arteriosclerosis, coronary heart disease, peripheral vascular disease, vascular inflammation, xanthoma, peripheral arterial disease, elevated Lp(a), elevated LDL, elevated TRL, and elevated triglycerides.

54. Use of a compound according to any one of claims 1 to 33, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a PCSK9-mediated disease or disorder.

55. The use of claim 54, wherein said PCSK9-mediated disease or disorder selected from hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, sitosterolemia, atherosclerosis, arteriosclerosis, coronary heart disease, peripheral vascular disease, vascular inflammation, xanthoma, peripheral arterial disease, elevated Lp(a), elevated LDL, elevated TRL, and elevated triglycerides.

56. Use of a compound according to any one of claims 1 to 33, or a pharmaceutically acceptable salt thereof, in the treatment of a disease or disorder, wherein the disease or disorder is selected from hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, sitosterolemia, atherosclerosis, arteriosclerosis, coronary heart disease, peripheral vascular disease, vascular inflammation, xanthoma, peripheral arterial disease, elevated Lp(a), elevated LDL, elevated TRL, and elevated triglycerides.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2022/060845

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/14 C07D413/14 C07D417/14 A61K31/501 A61K31/4439
A61P3/06
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2020/150474 A1 (DOGMA THERAPEUTICS INC [US]) 23 July 2020 (2020-07-23) claims; examples	1-56
A	WO 2020/150473 A2 (DOGMA THERAPEUTICS INC [US]) 23 July 2020 (2020-07-23) cited in the application claims; examples	1-56

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

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 February 2023	24/02/2023

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

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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