

COMPOUNDS WHICH BIND TO PNPLA3I148M AND THEIR USE TO TREAT LIVER DISEASES

FIELD OF THE INVENTION

5 The present invention relates to compounds, and pharmaceutically acceptable salts and isomers of such compounds, which bind to patatin-like phospholipase domain-containing protein 3 (PNPLA3) mutation PNPLA3I148M. In addition, the invention relates to pharmaceutical compositions and combinations comprising such compounds and to their use in methods for the treatment of diseases associated with PNPLA3I148M.

BACKGROUND OF THE INVENTION

10 Patatin-like phospholipase-domain-containing 2 (PNPLA2; also known as adipose triglyceride lipase, ATGL) and PNPLA3 (also known as adiponutrin) are encoded by close paralogues and appear to have opposite functions on triglycerides (TAGs) mobilization and storage. The human PNPLA3 gene is expressed in the liver and highly induced during the fed state and is likely important in lipid partitioning in times of nutrient surplus, which is in contrast to PNPLA2, the primary triglyceride (TAG) lipase activated in times of energetic need (e.g. fasting) (Wilson et al., 2006).

15 Nonalcoholic fatty liver disease (NAFLD) is a spectrum of conditions that begins as the benign state of hepatic steatosis and progresses in a subset of patients to severe states including nonalcoholic steatohepatitis (NASH), cirrhosis with liver fibrosis and hepatocellular carcinoma (HCC). Recently, non-alcoholic fatty liver disease (NAFLD) was renamed to metabolic dysfunction-associated steatotic liver disease (MASLD), and subsequently nonalcoholic steatohepatitis (NASH) was renamed to metabolic dysfunction-associated steatohepatitis (MASH) (Rinella et al., 2023).

20 Global prevalence of NAFLD is estimated to be about 25% and constantly increasing (Younossi et al., 2018; Younossi and Henry, 2021). In Western markets, there are currently no approved medicines to treat NAFLD. Gastric bypass surgery and/or weight loss of greater than 10% are the therapies with the most clinical benefit (Lassailly et al., 2015; Lassailly et al., 2020).

25 Predicting who will progress from steatosis to NASH, cirrhosis, and HCC is challenging. In 2008, a genome wide association studies (GWAS) identified a nonsynonymous variant in a gene encoding PNPLA3 that is causal for developing steatosis and increasing the risk for NASH progression (Romeo et al., 2008). The identified variant (rs738409) results in a change of the amino acid sequence at position 148 replacing an isoleucine with a methionine (I148M).

30 Subsequent GWAS studies identified additional genes and at the same time corroborated the dominant effect of the PNPLA3I148M variant (reviewed by (Trepo and Valenti, 2020)). Prevalence for PNPLA3I148M variant varies around the globe with the highest allele frequency in Mexico and Hispanic Americans with more than 50% (Younossi et al., 2018). PNPLA3I148M

is also strongly associated with progression to severe liver disease in alcoholic steatohepatitis, viral hepatitis, Wilson's disease, hereditary hemochromatosis, autoimmune hepatitis, and primary sclerosing cholangitis (Dongiovanni et al., 2013; Mederacke et al., 2020). NASH caused by PNPLA3I148M is inherited in an autosomal dominant pattern with penetrance influenced by obesity and diabetes.

Neither overexpression of the wild type allele nor gene deletion causes a disease phenotype in mice. In contrast, over expression of the human PNPLA3I148M in the mouse liver under the control of an albumin promoter coupled with a high sucrose diet results in elevated hepatic triglyceride levels and NAFLD-related phenotypes (Li et al., 2012; Smagris et al., 2015). A reduced proteasomal degradation of PNPLA3 on the lipid droplets has been suggested as a possible pathophysiological mechanism causing this phenotype (BasuRay et al., 2017; BasuRay et al., 2019).

α/β -hydrolase-domain-containing 5 (ABHD5; also known as CGI-58) is an essential co-activator of PNPLA2. Accumulation of PNPLA3I148M on lipid droplets interferes with TAG hydrolysis by sequestering ABHD5 (CGI-58) on lipid droplets, and as a result limits cofactor availability for activation of ATGL (PNPLA2), which results in an increase in hepatic TG levels. (Yang, W. et. al., 2019).

Linden et al. were the first to demonstrate that liver targeted silencing using an antisense oligonucleotide (ASO) of a human PNPLA3I148M mutation expressed in a mouse knock-in model reduced liver steatosis and several other NASH relevant features such as hepatic inflammation and fibrosis (Linden et al., 2019). However, to date the use of small molecule binders to PNPLA3I148M to treat liver disease have yet to be described.

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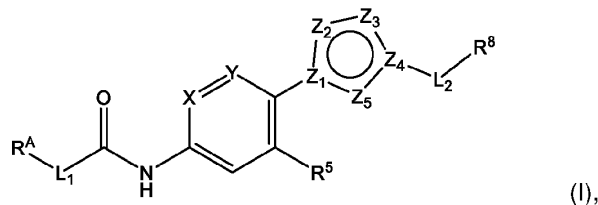
SUMMARY OF THE INVENTION

There remains the need for low molecular weight compounds which bind to PNPLA3I148M, thereby normalizing lipolysis and can therefore be used to treat a wide range of liver diseases related to the pathophysiology of PNPLA3I148M.

5 Provided herein are compounds which bind to PNPLA3I148M, thereby normalizing lipolysis, and therefore such compounds can be used to treat a PNPLA3I148M associated disease. In an embodiment of this aspect the PNPLA3I148M associated disease is a liver disease. In another embodiment of this aspect, the PNPLA3I148M associated disease is a metabolic dysfunction-associated steatotic liver disease (MASLD). In another embodiment of this aspect, the PNPLA3I148M associated disease is a nonalcoholic fatty liver disease
10 (NAFLD). In another embodiment of this aspect, the PNPLA3I148M associated disease is an alcoholic liver disease (ALD). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction-associated steatohepatitis (MASH), nonalcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH), cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC). In an embodiment of this aspect the PNPLA3I148M
15 associated disease is metabolic dysfunction-associated steatohepatitis (MASH). In an embodiment of this aspect the PNPLA3I148M associated disease is nonalcoholic steatohepatitis (NASH). In an embodiment of this aspect the PNPLA3I148M associated disease is alcoholic steatohepatitis (ASH). In an embodiment of this aspect the PNPLA3I148M associated disease cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC).

20 Furthermore, provided herein are compounds which bind to PNPLA3I148M, thereby disrupting the complex of ABHD5 and PNPLA3I148M (i.e. PNPLA3I148M-ABHD5), which results in normalizing lipolysis, and therefore, such compounds can be used to treat a PNPLA3I148M associated disease. In an embodiment of this aspect the PNPLA3I148M associated disease is a liver disease. In another embodiment of this aspect, the PNPLA3I148M
25 associated disease is a metabolic dysfunction-associated steatotic liver disease (MASLD). In another embodiment of this aspect, the PNPLA3I148M associated disease is a nonalcoholic fatty liver disease (NAFLD). In another embodiment of this aspect, the PNPLA3I148M associated disease is an alcoholic liver disease (ALD). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction-associated steatohepatitis (MASH),
30 nonalcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH), cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction-associated steatohepatitis (MASH). In an embodiment of this aspect the PNPLA3I148M associated disease is nonalcoholic steatohepatitis (NASH). In an embodiment of this aspect the PNPLA3I148M associated disease
35 is alcoholic steatohepatitis (ASH). In an embodiment of this aspect the PNPLA3I148M associated disease cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC).

In one aspect, the compounds provided herein which bind to PNPLA3I148M are compounds having the structure of Formula (I), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof:



wherein R^A , L_1 , X , Y , R^5 , Z_1 , Z_2 , Z_3 , Z_4 , Z_5 , L_2 and R^8 are as defined herein.

In another aspect disclosed herein is a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, and one or more pharmaceutically acceptable carriers.

In another aspect disclosed herein is a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, and one or more pharmaceutically acceptable carriers.

In another aspect disclosed herein is a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, and one or more therapeutically active agents.

In another aspect disclosed herein is a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, and one or more therapeutically active agents.

In another aspect disclosed herein is a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable acid addition salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable acid addition salt of a stereoisomer thereof, and one or more pharmaceutically acceptable carriers.

In another aspect disclosed herein is a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable acid addition salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable acid addition salt of a stereoisomer thereof, and one or more pharmaceutically acceptable carriers.

In another aspect disclosed herein is a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable acid addition salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable acid addition salt of a stereoisomer thereof, and one or more therapeutically active agents.

In another aspect disclosed herein is a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable acid addition salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable acid addition salt of a stereoisomer thereof, and one or more therapeutically active agents.

5 In another aspect disclosed herein is a pharmaceutical combination comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, and one or more therapeutically active agents.

10 In another aspect disclosed herein is a pharmaceutical combination comprising a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, and one or more therapeutically active agents.

In another aspect disclosed herein is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof for use as a medicament.

15 In another aspect disclosed herein is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof for use in treating a PNPLA3I148M associated disease. In an embodiment of this aspect the PNPLA3I148M associated disease is a liver disease. In another embodiment of this aspect, the PNPLA3I148M associated disease is a metabolic dysfunction-associated steatotic liver disease (MASLD). In another embodiment of this aspect, the PNPLA3I148M associated disease is a nonalcoholic fatty liver disease (NAFLD). In another embodiment of this aspect, the PNPLA3I148M associated disease is an alcoholic liver disease (ALD). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction-associated steatohepatitis (MASH), nonalcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH), cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction-associated steatohepatitis (MASH). In an embodiment of this aspect the PNPLA3I148M associated disease is nonalcoholic steatohepatitis (NASH). In an embodiment of this aspect the PNPLA3I148M associated disease is alcoholic steatohepatitis (ASH). In an embodiment of this aspect the PNPLA3I148M associated disease is cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC).

25 In another aspect disclosed herein is the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof for the treatment of a PNPLA3I148M associated disease. In an embodiment of this aspect the PNPLA3I148M associated disease is a liver disease. In another embodiment of this aspect, the PNPLA3I148M associated disease is a metabolic dysfunction-associated steatotic liver disease (MASLD). In another embodiment of

this aspect, the PNPLA3I148M associated disease is a nonalcoholic fatty liver disease (NAFLD). In another embodiment of this aspect, the PNPLA3I148M associated disease is an alcoholic liver disease (ALD). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction–associated steatohepatitis (MASH), nonalcoholic
5 steatohepatitis (NASH), alcoholic steatohepatitis (ASH), cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction–associated steatohepatitis (MASH). In an embodiment of this aspect the PNPLA3I148M associated disease is nonalcoholic steatohepatitis (NASH). In an embodiment of this aspect the PNPLA3I148M associated disease
10 is alcoholic steatohepatitis (ASH). In an embodiment of this aspect the PNPLA3I148M associated disease cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC).

In another aspect disclosed herein is the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof in the manufacture of a medicament for the treatment
15 of a PNPLA3I148M associated disease. In an embodiment of this aspect the PNPLA3I148M associated disease is a liver disease. In another embodiment of this aspect, the PNPLA3I148M associated disease is a metabolic dysfunction-associated steatotic liver disease (MASLD). In another embodiment of this aspect, the PNPLA3I148M associated disease is a nonalcoholic fatty liver disease (NAFLD). In an embodiment of this aspect the PNPLA3I148M associated
20 disease is metabolic dysfunction–associated steatohepatitis (MASH), nonalcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH), cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction–associated steatohepatitis (MASH). In an embodiment of this aspect the PNPLA3I148M associated disease is nonalcoholic
25 steatohepatitis (NASH). In an embodiment of this aspect the PNPLA3I148M associated disease is alcoholic steatohepatitis (ASH). In an embodiment of this aspect the PNPLA3I148M associated disease cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC).

In another aspect disclosed herein is a method for treating a PNPLA3I148M associated disease comprising administering to a subject in need thereof a compound of Formula (I), or a
30 pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof. In an embodiment of this aspect the PNPLA3I148M associated disease is a liver disease. In another embodiment of this aspect, the PNPLA3I148M associated disease is a metabolic dysfunction-associated steatotic liver disease (MASLD). In another embodiment of this aspect, the PNPLA3I148M associated disease is a nonalcoholic
35 fatty liver disease (NAFLD). In another embodiment of this aspect, the PNPLA3I148M associated disease is an alcoholic liver disease (ALD). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction–associated steatohepatitis (MASH), nonalcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH), cirrhosis with liver fibrosis

or hepatocellular carcinoma (HCC). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction–associated steatohepatitis (MASH). In an embodiment of this aspect the PNPLA3I148M associated disease is nonalcoholic steatohepatitis (NASH). In an embodiment of this aspect the PNPLA3I148M associated disease is alcoholic steatohepatitis (ASH). In an embodiment of this aspect the PNPLA3I148M associated disease cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC).

In another aspect disclosed herein is a method for treating a PNPLA3I148M associated disease comprising administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof. In an embodiment of this aspect the PNPLA3I148M associated disease is a liver disease. In another embodiment of this aspect, the PNPLA3I148M associated disease is a metabolic dysfunction-associated steatotic liver disease (MASLD). In another embodiment of this aspect, the PNPLA3I148M associated disease is a nonalcoholic fatty liver disease (NAFLD). In another embodiment of this aspect, the PNPLA3I148M associated disease is an alcoholic liver disease (ALD). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction–associated steatohepatitis (MASH), nonalcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH), cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction–associated steatohepatitis (MASH). In an embodiment of this aspect the PNPLA3I148M associated disease is nonalcoholic steatohepatitis (NASH). In an embodiment of this aspect the PNPLA3I148M associated disease is alcoholic steatohepatitis (ASH). In an embodiment of this aspect the PNPLA3I148M associated disease cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC).

In another aspect disclosed herein is a method for normalizing lipolysis by administering to a subject in need thereof of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof.

In another aspect disclosed herein is a method for normalizing lipolysis by administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof.

In another aspect disclosed herein is a method for normalizing lipolysis by disrupting a PNPLA3I148M-ABHD5 complex, wherein the method comprises administering to a subject in need thereof a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof.

In another aspect disclosed herein is a method for normalizing lipolysis by disrupting a PNPLA3I148M-ABHD5 complex, wherein the method comprises administering to a subject in

need thereof a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof.

In another aspect disclosed herein is a method for treating a PNPLA3I148M associated disease by normalizing lipolysis, wherein the method comprises administering to a subject in need thereof of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof. In an embodiment of this aspect the PNPLA3I148M associated disease is a liver disease. In another embodiment of this aspect, the PNPLA3I148M associated disease is a metabolic dysfunction-associated steatotic liver disease (MASLD). In another embodiment of this aspect, the PNPLA3I148M associated disease is a nonalcoholic fatty liver disease (NAFLD). In another embodiment of this aspect, the PNPLA3I148M associated disease is an alcoholic liver disease (ALD). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction-associated steatohepatitis (MASH), nonalcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH), cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction-associated steatohepatitis (MASH). In an embodiment of this aspect the PNPLA3I148M associated disease is nonalcoholic steatohepatitis (NASH). In an embodiment of this aspect the PNPLA3I148M associated disease is alcoholic steatohepatitis (ASH). In an embodiment of this aspect the PNPLA3I148M associated disease cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC).

In another aspect disclosed herein is a method for treating a PNPLA3I148M associated disease by normalizing lipolysis, wherein the method comprises administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof. In an embodiment of this aspect the PNPLA3I148M associated disease is a liver disease. In another embodiment of this aspect, the PNPLA3I148M associated disease is a metabolic dysfunction-associated steatotic liver disease (MASLD). In another embodiment of this aspect, the PNPLA3I148M associated disease is a nonalcoholic fatty liver disease (NAFLD). In another embodiment of this aspect, the PNPLA3I148M associated disease is an alcoholic liver disease (ALD). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction-associated steatohepatitis (MASH), nonalcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH), cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction-associated steatohepatitis (MASH). In an embodiment of this aspect the PNPLA3I148M associated disease is nonalcoholic steatohepatitis (NASH). In an embodiment of this aspect the PNPLA3I148M associated disease

is alcoholic steatohepatitis (ASH). In an embodiment of this aspect the PNPLA3I148M associated disease cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC).

In another aspect, provided herein are intermediate compounds useful for making the compounds of Formula (I) as defined herein, or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof.

In certain embodiments, the compounds of Formula (I) may bind to patatin-like phospholipase domain-containing protein 3 (PNPLA3).

BRIEF DESCRIPTION OF THE FIGURES

Figure 1: illustrates a representative powder X-ray diffractogram (XRPD) curve of (S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide monohydrate.

Figure 2: illustrates a representative differential scanning calorimetry (DSC) curve of (S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide monohydrate.

Figure 3: illustrates a representative thermogravimetric analysis (TGA) curve of (S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide monohydrate.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The term "alkyl," as used herein, refers to a saturated branched or straight chain hydrocarbon. In certain embodiments an alkyl group is a "C₁-C₂alkyl", "C₁-C₃alkyl" or "C₁-C₄alkyl" group, wherein the terms "C₁-C₂alkyl", "C₁-C₃alkyl" and "C₁-C₄alkyl", as used herein, refer to the alkyl group containing at least 1, and at most 2, 3 or 4 carbon atoms, respectively. "C₁-C₂alkyl" groups are methyl and ethyl. Non-limiting examples of "C₁-C₃alkyl" groups include methyl, ethyl, n-propyl, and isopropyl. Non-limiting examples of "C₁-C₄alkyl" groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

The term "alkenyl," as used herein, refers to a partially saturated branched or straight hydrocarbon chain having one more double bonds. In certain embodiments an alkenyl group is a "C₂-C₃alkenyl", "C₂-C₄alkenyl", "C₂-C₅alkenyl", "C₂-C₆alkenyl", "C₂-C₇alkenyl", "C₂-C₈alkenyl", "C₂-C₉alkenyl" or "C₂-C₁₀alkenyl", wherein the terms "C₂-C₃alkenyl", "C₂-C₄alkenyl", "C₂-C₅alkenyl", "C₂-C₆alkenyl", "C₂-C₇alkenyl", "C₂-C₈alkenyl", "C₂-C₉alkenyl" and "C₂-C₁₀alkenyl", as used herein, refer to an alkenyl group containing at least 2, and at most 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms, respectively. Non-limiting examples of alkenyl groups include ethenyl, n-propenyl, isopropenyl, n-butenyl, isobutenyl, sec-butenyl, tert-butenyl, n-pentenyl, isopentenyl, n-hexenyl, n-heptenyl, n-octenyl, n-nonenyl and n-decenyl.

The term "alkynyl," as used herein, refers to a partially saturated branched or straight hydrocarbon chain having one more triple bonds. In certain embodiments an alkynyl group is a

"C₂-C₃alkynyl", "C₂-C₄alkynyl", "C₂-C₅alkynyl", "C₂-C₆alkynyl", "C₂-C₇alkynyl", "C₂-C₈alkynyl", "C₂-C₉alkynyl" or "C₂-C₁₀alkynyl", wherein the terms "C₂-C₃alkynyl", "C₂-C₄alkynyl", "C₂-C₅alkynyl", "C₂-C₆alkynyl", "C₂-C₇alkynyl", "C₂-C₈alkynyl", "C₂-C₉alkynyl" and "C₂-C₁₀alkynyl", as used herein, refer to an alkynyl group containing at least 2, and at most 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms, respectively. Non-limiting examples of alkynyl groups include ethynyl, propynyl, butynyl, sec-butynyl, *n*-pentynyl, isopentynyl, *n*-hexynyl, *n*-heptynyl, *n*-octynyl, *n*-nonynyl and *n*-decynyl.

The term "alkoxy", as used herein, refers to -O-alkyl, wherein the "alkyl" group is as defined herein. In certain embodiments an alkoxy group is a "C₁-C₂alkoxy", "C₁-C₃alkoxy" or "C₁-C₄alkoxy", wherein the terms "C₁-C₂alkoxy", "C₁-C₃alkoxy" and "C₁-C₄alkoxy", as used herein, refer to -O-C₁-C₂alkyl, -O-C₁-C₃alkyl or -O-C₁-C₄alkyl, respectively. "C₁-C₂alkoxy" groups are methoxy and ethoxy. Non-limiting examples of "C₁-C₃alkoxy" groups include methoxy, ethoxy, *n*-propoxy and isopropoxy. Non-limiting examples of "C₁-C₄alkoxy" groups include methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, isobutoxy, sec-butoxy and tert-butoxy.

The term "diC₁-C₄alkylamino", as used herein, refers to a -NR₂ group, where each R is a C₁-C₄alkyl.

The term "C₃-C₄cycloalkyl" as used herein, refers to a saturated, monocyclic hydrocarbon ring system having 3 to 4 carbon atoms as ring members. Non-limiting examples of such "C₃-C₄cycloalkyl" groups include cyclopropyl and cyclobutyl.

The term "C₃-C₆cycloalkyl" as used herein, refers to a saturated, monocyclic hydrocarbon ring system having 3 to 6 carbon atoms as ring members. Non-limiting examples of such "C₃-C₆cycloalkyl" groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term "C₃-C₈cycloalkyl" as used herein, refers to a saturated, monocyclic hydrocarbon ring system having 3 to 8 carbon atoms as ring members. Non-limiting examples of such "C₃-C₈cycloalkyl" groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

The term "C₁-C₄fluoroalkyl" as used herein, refer to the respective "C₁-C₄alkyl", as defined herein, wherein at least one of the hydrogen atoms of the "C₁-C₄alkyl" is replaced by a fluoro atom. The C₁-C₄fluoroalkyl groups can be monoC₁-C₄fluoroalkyl, wherein such C₁-C₄fluoroalkyl groups have one fluoro atom. Additionally, the C₁-C₄fluoroalkyl groups can be diC₁-C₄fluoroalkyl wherein such C₁-C₄fluoroalkyl groups can have two fluoro atoms. Furthermore, the C₁-C₄fluoroalkyl groups can be polyC₁-C₄fluoroalkyl wherein such C₁-C₄fluoroalkyl groups can have two or more fluoro atoms. Such polyC₁-C₄fluoroalkyl can be perfluoroC₁-C₄fluoroalkyl where all the hydrogen atoms of the respective C₁-C₄alkyl have been replaced with fluoro atoms. Non-limiting examples of "C₁-C₄fluoroalkyl" groups include fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, difluoroethyl, trifluoroethyl, pentafluoroethyl, difluoropropyl and heptafluoropropyl.

The term "C₁-C₄fluoroalkoxy" as used herein, refer to the respective "C₁-C₄alkoxy", as

defined herein, wherein at least one of the hydrogen atoms of the "C₁-C₄alkyl" of the "C₁-C₄alkoxy" is replaced by a fluoro atom. The C₁-C₄fluoroalkoxy groups can be monoC₁-C₄fluoroalkoxy, wherein such C₁-C₄fluoroalkoxy groups have one fluoro atom. Additionally, the C₁-C₄fluoroalkoxy groups can be diC₁-C₄fluoroalkoxy wherein such C₁-C₄fluoroalkoxy groups can have two fluoro atoms. Furthermore, the C₁-C₄fluoroalkoxy groups can be polyC₁-C₄fluoroalkoxy wherein such C₁-C₄fluoroalkoxy groups can have two or more fluoro atoms. Such polyC₁-C₄fluoroalkoxy can be perfluoroC₁-C₄fluoroalkoxy where all the hydrogen atoms of the respective C₁-C₄alkyl have been replaced with fluoro atoms. Non-limiting examples of "C₁-C₄fluoroalkoxy" groups include fluoromethoxy, difluoromethoxy, trifluoromethoxy, fluoroethoxy, difluoroethoxy, trifluoroethoxy, pentafluoroethoxy, difluoropropoxy and heptafluoropropoxy.

The term "C₁-C₄hydroxyalkyl", as used herein, refers to C₁-C₄alkyl, as defined herein, wherein one or more hydrogen atoms of the "C₁-C₄alkyl" is replaced by one or more hydroxy groups.

The term "carbonyl" as used herein, refers to a -C(=O)- group.

The term "cyano" as used herein, refers to a -CN group.

The term "halogen", as used herein, refer to fluoro (F), chloro (Cl), bromo (Br) and iodo (I).

The term "5- to 6- membered monocyclic heteroaryl," as used herein, refers to an aromatic, 5- or 6- membered monocyclic ring system wherein 1, 2, 3 or 4 ring members are each independently selected from N, NR⁴, NR⁹, O and S, where R⁴ and NR⁹ are as defined herein. Non-limiting examples of 5- to 6- membered monocyclic heteroaryl groups, include furazanyl, furyl, imidazolyl, isoxazolyl, isothiazolyl, oxazolyl, oxadiazolyl, pyrazolyl, pyrrolyl, pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, thiazolyl, thiadiazolyl, thienyl, triazinyl, triazolyl and tetrazolyl.

The term "partially saturated 9-, 10-, 11- or 12-membered bicyclic carbocyclyl", as used herein, refers to a fused bicyclic hydrocarbon ring structure having 9-, 10-, 11- or 12 ring members which comprises one or more double bonds and is not aromatic.

The term "partially saturated 5- or 6-membered heterocyclyl", as used herein, refers to a monocyclic ring structure having 5- or 6 ring members wherein 1 or 2 ring members are each independently selected from N, NR⁹, O and S, (where R⁹ is as defined herein), and monocyclic ring structure comprises one or more double bonds and is not aromatic.

In certain embodiments, the term "partially saturated 5- or 6-membered heterocyclyl", as used herein, may also refer to a monocyclic ring structure having 5- or 6 ring members wherein one ring member is S(=O)₂ and 1, 2 or 3 other ring members are each independently selected from N, NR⁹, O and S, (where R⁹ is as defined herein), and monocyclic ring structure comprises one or more double bonds and is not aromatic.

The term "partially saturated 8-, 9-, 10-, 11- or 12-membered fused bicyclic heterocyclyl", as used herein, refers to a fused bicyclic ring structure having 8-, 9-, 10-, 11- or 12 ring members wherein 1, 2, 3 or 4 ring members are each independently selected from N, NR⁴, NR⁹, O and S, (where R⁴ and R⁹ are as defined herein), and the fused bicyclic ring structure comprises one or

more double bonds. In particular, the partially saturated heterocyclyl is a 10 membered fused bicyclic heterocyclyl containing 1, 2 or 3 ring members independently selected from N, NR⁴, R⁹, O and S, where R⁴ and R⁹ are as defined herein. Non-limiting examples of partially saturated 8-, 9-, 10-, 11- or 12-membered fused bicyclic heterocyclyl groups, as used herein, include

5 chromanyl, 3,4-dihydro-2H-benzo[b][1,4]oxazinyl, 6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazinyl, 3,4-dihydro-2H-pyrano[2,3-b]pyridinyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzo[b][1,4]dioxinyl, 1,4,5,6-tetrahydrocyclopenta[c]pyrazolyl, and 4,5,6,7-tetrahydro-1H-indazolyl. Other, non-limiting examples of heterocycloalkyl groups include

10 dihydrobenzofuranyl, dihydrobenzo[c]thiophenyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrobenzthiazolyl, dihydrobenzimidazolyl, dihydrocinnolyl, dihydrofurazanyl, dihydrofuryl, dihydroimidazolyl, dihydroindolyl, dihydroindoliziny, dihydroindazolyl, dihydroisoindolyl, dihydroisoquinolyl, dihydroisoxazolyl, dihydroisothiazolyl, dihydrooxazolyl, dihydrooxaindolyl, dihydrooxadiazolyl, dihydropyrazolyl, dihydropyrrolyl, dihydrophthalazinyl, dihydropyridyl, dihydropyridazinyl, dihydropyrazinyl, dihydropyrimidinyl, dihydroquinoxalyl, dihydroquinolyl,

15 dihydroquinazolyl, dihydrotetrazolyl, dihydrothiazolyl, dihydrothiadiazolyl, dihydrothienyl, dihydrotriazinyl, dihydrotriazolyl, tetrahydrobenzofuranyl, tetrahydrobenzo[c]thiophenyl, tetrahydrobenzothiophenyl, tetrahydrobenzoxazolyl, tetrahydrobenzthiazolyl, tetrahydrobenzimidazolyl, tetrahydrocinnolyl, tetrahydroindolyl, tetrahydroindoliziny, tetrahydroindazolyl, tetrahydroisoindolyl, tetrahydroisoquinolyl, tetrahydrooxaindolyl, tetrahydrophthalazinyl, tetrahydropyridyl, tetrahydropyridazinyl, tetrahydropyrazinyl, tetrahydropyrimidinyl, tetrahydroquinoxalyl, tetrahydroquinolyl, tetrahydroquinazolyl,

20 tetrahydrotriazinyl, hexahydrobenzofuranyl, hexahydrobenzo[c]thiophenyl, hexahydrobenzothiophenyl, hexahydrobenzoxazolyl, hexahydrobenzthiazolyl, hexahydrobenzimidazolyl, hexahydrocinnolyl, hexahydroindolyl, hexahydroindoliziny, hexahydroindazolyl, hexahydroisoindolyl, hexahydroisoquinolyl, hexahydrooxaindolyl, hexahydrophthalazinyl, hexahydroquinoxalyl, hexahydroquinolyl, hexahydroquinazolyl, octahydrocinnolyl, octahydroisoquinolyl, octahydrophthalazinyl, octahydroquinoxalyl, octahydroquinolyl and octahydroquinazolyl.

The term 6- or 7- membered fused bicyclic heterocyclyl, as used herein, refers to a fused

30 bicyclic ring structure having 6- or 7- ring members wherein 1 or 2 ring members are each independently selected from N, NR⁹, O and S, (where R⁹ is as defined herein), and the fused bicyclic ring structure comprises one or more double bonds and is not aromatic.

The term "4-, 5- or 6 membered heterocycloalkyl" as used herein, refers to a 4, 5 or 6 membered, saturated ring wherein 1, 2 or 3 ring members are each independently selected from

35 N, NR⁹, O and S, where R⁹ is as defined herein. Non-limiting examples of 4-, 5- or 6 membered heterocycloalkyl groups, as used herein, include azetidyl (which includes azetidin-1-yl, azetidin-2-yl and azetidin-3-yl), pyrrolidinyl (which includes pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, pyrrolidin-4-yl and pyrrolidin-5-yl), piperidinyl (which includes piperidin-1-yl,

piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperidin-5-yl and piperidin-6-yl), piperazinyl (which includes piperazin-1-yl, piperazin-2-yl, piperazin-3-yl, piperazin-4-yl, piperazin-5-yl and piperazin-6-yl) and pyrazolidinyl (which includes pyrazolidin-1-yl, pyrazolidin-2-yl, pyrazolidin-3-yl, pyrazolidin-4-yl and pyrazolidin-5-yl).

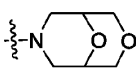
- 5 The term "5 or 6 membered heterocycloalkyl" as used herein, refers to a 5 or 6 membered, saturated ring wherein 1 or 2 ring members are each independently selected from N, NR⁹, O and S, where R⁹ is as defined herein. The heterocycloalkyl group can be attached to another group at a nitrogen or a carbon atom. Non-limiting examples of 5 or 6 membered heterocycloalkyl groups, as used herein, include pyrrolidinyl (which includes pyrrolidin-1-yl, 10 pyrrolidin-2-yl, pyrrolidin-3-yl, pyrrolidin-4-yl and pyrrolidin-5-yl), tetrahydrofuranyl (which includes tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrofuran-4-yl and tetrahydrofuran-5-yl), tetrahydrothienyl (which includes tetrahydrothien-2-yl, tetrahydrothien-3-yl, tetrahydrothien-4-yl and tetrahydrothien-5-yl), piperidinyl (which includes piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperidin-5-yl and piperidin-6-yl), tetrahydropyranyl (which includes 15 tetrahydropyran-2-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, tetrahydropyran-5-yl and tetrahydropyran-6-yl), tetrahydrothiopyranyl (which includes tetrahydrothiopyran-2-yl, tetrahydrothiopyran-3-yl, tetrahydrothiopyran-4-yl, tetrahydrothiopyran-5-yl and tetrahydrothiopyran-6-yl), piperazinyl (which includes piperazin-1-yl, piperazin-2-yl, piperazin-3-yl, piperazin-4-yl, piperazin-5-yl and piperazin-6-yl), morpholinyl (which includes morpholin-2-yl, 20 morpholin-3-yl, morpholin-4-yl, morpholin-5-yl and morpholin-6-yl), thiomorpholinyl (which includes thiomorpholin-2-yl, thiomorpholin-3-yl, thiomorpholin-4-yl, thiomorpholin-5-yl and thiomorpholin-6-yl), dithianyl (which includes dithian-2-yl, dithian-3-yl, dithian-5-yl and dithian-6-yl), dioxolanyl (which includes dioxolan-2-yl, dioxolan-4-yl and dioxolan-5-yl), and pyrazolidinyl (which includes pyrazolidin-1-yl, pyrazolidin-2-yl, pyrazolidin-3-yl, pyrazolidin-4-yl and 25 pyrazolidin-5-yl).

In certain embodiments, the term "4-, 5- or 6 membered heterocycloalkyl" as used herein, may also refer to a 4, 5 or 6 membered, saturated ring wherein one ring member is S(=O)₂, and 1, 2 or 3 other ring members are each independently selected from N, NR⁹ and O, where R⁹ is as defined herein.

- 30 In certain embodiments, the term "4-, 5- or 6 membered heterocycloalkyl" as used herein, may also refer to a 4, 5 or 6 membered, saturated ring wherein one ring member is S(=O)₂, S(=O) or S(=O)(=NH).

- 35 The term "6 membered heterocycloalkyl" as used herein, refers to a 6 membered, saturated ring wherein 1 or 2 ring members are each independently selected from N, NR⁹, O and S, where R⁹ is as defined herein.

The phrase "a 6- membered heterocycloalkyl having 1 to 2 ring members independently selected from N, NR⁹, O and S, wherein the heterocycloalkyl has a C₁-C₃alkyl bridge or a -CH₂OCH₂- bridge", as used herein refers to a 6 membered heterocycloalkyl which has a C₁-

C₃alkyl bridge or a -CH₂OCH₂- bridge. By way of example,  and .

The term "hydroxy" as used herein, refers to an -OH group.

The term "oxo" as used herein, refers to a -C(=O)- group.

The term "6-, 7-, 8-, 9- or 10- membered spiro bicyclic heterocycloalkyl", as used herein
 5 refers to a bicyclic ring system having "6-, 7-, 8-, 9- or 10- ring members wherein the bicyclic
 ring system comprises two ring systems spiro attached to each other and wherein 1,2 or 3 ring
 members of the bicyclic ring system are each independently selected from N, NR⁹, O and S,
 where R⁹ is as defined herein.

The term "spiro attached", as used herein, refers to the attachment of one ring system to
 10 another ring system via one carbon atom common to both rings.

The term "isomers", as used herein, refers to different compounds that have the same
 molecular formula but differ in arrangement and configuration of the atoms. Also as used herein,
 the term "an optical isomer" or "a stereoisomer" refers to any of the various stereo isomeric
 configurations which may exist for a given compound of Formula (I) and includes geometric
 15 isomers. It is understood that a substituent may be attached at a chiral center of a carbon atom.
 The term "chiral" refers to molecules which have the property of non-superimposability on their
 mirror image partner, while the term "achiral" refers to molecules which are superimposable on
 their mirror image partner. Therefore, the invention includes enantiomers, diastereomers or
 racemates of the compound. "Enantiomers" are a pair of stereoisomers that are non-
 20 superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a
 "racemic" mixture. The term is used to designate a racemic mixture where appropriate.

"Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are
 not mirror-images of each other. The absolute stereochemistry is specified according to the
 Cahn- Ingold- Prelog R-S system. When a compound is a pure enantiomer the stereochemistry
 25 at each chiral carbon may be specified by either *R* or *S*. Resolved compounds whose absolute
 configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or
 levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line.
 Certain compounds described herein contain one or more asymmetric centers or axes and may
 thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be
 30 defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)-.

The terms "combination" or "pharmaceutical combination," as used herein, refers to either a
 fixed combination in one dosage unit form, or a combined administration where a compound of
 Formula (I) and a 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
 35 separately within time intervals, especially where these time intervals allow that the combination
 partners show a cooperative, e.g. synergistic effect. 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. 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 Formula (I) 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 Formula (I) 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 agent.

The term "combination therapy" or "in combination with" or "pharmaceutical combination" refers to the administration of two or more therapeutic agents to treat a therapeutic condition or disorder described in the present disclosure. Such administration encompasses co-administration of these therapeutic agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients. Alternatively, such administration encompasses co-administration in multiple, or in separate containers (e.g., capsules, powders, and liquids) for each active ingredient. Powders and/or liquids may be reconstituted or diluted to a desired dose prior to administration. In addition, such administration also encompasses use of each type of therapeutic agent being administered prior to, concurrent with, or sequentially to each other with no specific time limits. In each case, the treatment regimen will provide beneficial effects of the drug combination in treating the conditions or disorders described herein.

As used herein the term "co-administer" refers to the presence of two active agents in the blood of an individual. Active agents that are co-administered can be concurrently or sequentially delivered.

The terms "composition" or "pharmaceutical composition," as used herein, refers to a compound of Formula (I), or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, in a form suitable for oral or parenteral administration.

As used herein, the term "contacting" refers to the bringing together of the indicated moieties in an in vitro system or an in vivo system.

A "patient," "subject" or "individual" are used interchangeably and refer to either a human or non-human animal. The term includes mammals such as humans. Typically, the animal is a

mammal. A "patient," "subject" or "individual" also refers to for example, primates (e.g., humans, male or female), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, fish, birds and the like. In certain embodiments, the subject is a primate. Preferably, the "patient," "subject" or "individual" is a human.

5 As used herein, the term "pharmaceutically acceptable carrier" refers to a substance useful in the preparation or use of a pharmaceutical composition and includes, for example, suitable diluents, solvents, dispersion media, surfactants, antioxidants, preservatives, isotonic agents, buffering agents, emulsifiers, absorption delaying agents, salts, drug stabilizers, binders, excipients, disintegration agents, lubricants, wetting agents, sweetening agents, flavoring
10 agents, dyes, and combinations thereof, as would be known to those skilled in the art (see, for example, Remington The Science and Practice of Pharmacy, 22nd Ed. Pharmaceutical Press, 2013, pp. 1049-1070).

The phrase "pharmaceutically acceptable" indicates that the substance, composition or dosage form must be compatible chemically and/or toxicologically, with the other ingredients
15 comprising a formulation, and/or the mammal being treated therewith.

The term "a subject in need of such treatment", refers to a subject which would benefit biologically, medically or in quality of life from such treatment.

The term "therapeutically effective amount," as used herein, refers to an amount of a compound of Formula (I) that will ameliorate symptoms, alleviate conditions, slow or delay
20 disease progression, or elicit the biological or medical response of a subject.

As used herein, the term "treat", "treating" or "treatment" of any disease or disorder, refers to the management and care of a patient for the purpose of combating the disease, condition, or disorder, or eliminating the disease, condition or disorder.

In addition, the terms "treatment," "treating," as used herein, refers to alleviating or
25 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.

As used herein, a subject is "in need of" a treatment if such subject would benefit
30 biologically, medically or in quality of life from such treatment.

Unless specified otherwise, the terms "compound of the invention", "compounds of the invention", "compound of the present invention" or "compounds of the present invention" refers to a compound or compounds of Formula (I), or subformulae thereof, such as Formula (I-a), Formula (I-b), Formula (I-c), Formula (I-d), Formula (I-e), and Formula (I-f) and exemplified
35 compounds, and salts thereof, as well as all stereoisomers (including diastereoisomers and enantiomers) thereof.

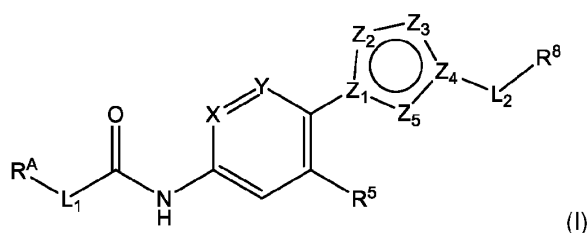
Unless specified otherwise, the phrase "compounds of Formula (I), or a subformula thereof," as used herein refers to compounds having the structure of Formula (I) or the structure of a

subformula selected from Formula (I-a), Formula (I-b), Formula (I-c), Formula (I-d), Formula (I-e), and Formula (I-f), and salts thereof, as well as all stereoisomers (including diastereoisomers and enantiomers) thereof.

As used herein, wavy line, as depicted here “ $R-\overset{\textcircled{\text{X}}}{-}$ ”, is a symbol denoting the point of attachment of R, to other part of the molecule.

Compounds of the Invention

Provided herein are compounds which bind to PNPLA3I148M and have the structure of Formula (I), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof:



wherein:

-X=Y- is -CR^x=CR^y-, -CR^x=N- or -N=CR^y-;

R^x is H, D, halogen or C₁-C₄alkyl;

R^y is H, D, halogen, -CN, C₁-C₄alkyl, C₁-C₄fluoroalkyl or C₁-C₄alkoxy;

R⁵ is H, halogen, -CN, C₁-C₄alkyl, C₁-C₄fluoroalkyl or C₁-C₄alkoxy;

R^A is:

- (i) phenyl which is unsubstituted or is substituted with 1, 2, 3 or 4 R¹ groups;
 - (ii) a partially saturated 9-, 10-, 11- or 12-membered bicyclic carbocyclyl which is unsubstituted or is substituted with 1 to 4 R¹ groups;
 - (iii) a 5- or 6- membered monocyclic heteroaryl having 1, 2, 3 or 4 ring members independently selected from N, NR⁴, O and S, wherein the monocyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 R¹ groups;
- or
- (iv) a partially saturated 8-, 9-, 10-, 11- or 12-membered fused bicyclic heterocyclyl having 1, 2, 3 or 4 ring members independently selected from N, NR⁴, O and S, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 R¹ groups;

each R¹ is independently selected from the group consisting of halogen, C₁-C₄alkyl, C₂-C₄alkenyl, C₂-C₄alkynyl, C₁-C₄alkoxy, C₁-C₄alkoxycarbonyl, C₃-C₆cycloalkyl, C₁-C₄fluoroalkyl, C₁-C₄fluoroalkoxy, pentafluorosulfanyl, C₁-C₄hydroxyalkyl, C₁-C₄thioalkyl, azido, diC₁-C₄alkylamino, diC₁-C₄alkylaminocarbonyl, D, CD₃, cyano, formyl, phenyl and a 5- to 6-membered heterocycloalkyl comprising 1 or 2 ring members independently selected from N, NR⁴, O and S;

- L₁ is a bond, $-(\text{CR}^2\text{R}^3)_p-$, $-(\text{CR}^2\text{R}^3)_p\text{-NR}^4-$, $-(\text{CR}^2\text{R}^3)_p\text{-O-}$, $-\text{NR}^4(\text{CR}^2\text{R}^3)_q-$, $-(\text{CR}^2\text{R}^3)_q\text{NR}^4-$, $-\text{O-}(\text{CR}^2\text{R}^3)_p-$ or $-\text{S-}(\text{CR}^2\text{R}^3)_p-$;
- R² is H, D, halogen or C₁-C₄alkyl;
- R³ is H, D, halogen, C₁-C₄alkyl, C₁-C₄alkoxy, OH, amino or *t*-Boc-amino;
- 5 or R² and R³, together with the C atom to which they are attached, are linked to form C₃-C₄cycloalkyl which is unsubstituted or is substituted with a single substituent selected from C₁-C₄alkyl and oxo;
- each R⁴ is independently selected from the group consisting of H and C₁-C₄alkyl;
- p is 1, 2 or 3;
- 10 q is 0, 1 or 2;
- Z₁ is N or C; Z₂ is N or CR^z; Z₃ is N or CR^z; Z₄ is N or C; Z₅ is N or CR^z;
- wherein each R^z is independently selected from the group consisting of H, halogen, C₁-C₄alkyl and C₁-C₄fluoroalkyl; and provided that at least two, and not more than four, of Z₁, Z₂, Z₃, Z₄ and Z₅ are N;
- 15 L₂ is a bond, $-(\text{CR}^6\text{R}^7)_n-$ or $-(\text{CR}^6\text{R}^7)_n\text{O}^*$, where the * indicates the point of attachment to R⁸;
- each R⁶ is independently selected from the group consisting of H, C₁-C₄alkyl, C₁-C₄fluoroalkyl and C₁-C₄hydroxyalkyl;
- each R⁷ is independently selected from the group consisting of H, C₁-C₄alkyl, C₁-C₄fluoroalkyl and C₁-C₄hydroxyalkyl;
- 20 or R⁶ and R⁷, together with the C atom to which they are attached, are linked to form C₃-C₆cycloalkyl, oxetanyl, tetrahydrofuranlyl or tetrahydropyranyl;
- n is 1, 2 or 3;
- R⁸ is:
- (i) 4-, 5- or 6-membered heterocycloalkyl having 1, 2 or 3 ring members independently selected from N, NR⁹, O and S, wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents each independently selected from -OH, -CN, -N(R¹⁰)₂, halogen, C₁-C₄fluoroalkyl, C₁-C₄alkyl, C₁-C₄alkoxy, oxo and a 5- or 6- membered monocyclic heteroaryl having 1, 2, 3 or 4 ring members independently selected from N, NR⁹, O and S, wherein the monocyclic heteroaryl is unsubstituted;
- 25 (ii) 4-, 5- or 6-membered heterocycloalkyl wherein one ring member is S(=O)₂, S(=O) or S(=O)(=NH), and wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from -OH, C₁-C₄alkyl and oxo;
- 30 (iii) 4-, 5- or 6-membered heterocycloalkyl wherein one ring member is S(=O)₂ or S(=O), and 1, 2 or 3 other ring members are independently selected from N, NR⁹ and O, and wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents each independently selected from C₁-C₄alkyl and oxo;
- 35 (iv) a partially saturated 5- or 6-membered heterocyclyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the partially saturated

- heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents independently selected from -OH, C₁-C₄alkyl, and oxo;
- (v) a partially saturated 5- or 6-membered heterocyclyl wherein one ring member is S(=O)₂ and 1, 2 or 3 other ring members are independently selected from N, NR⁹, O and S, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents independently selected from -OH, C₁-C₄alkyl, and oxo;
- (vi) a 5- or 6- membered monocyclic heteroaryl having 1, 2, 3 or 4 ring members independently selected from N, NR⁹, O and S, wherein the monocyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents each independently selected from -OH, C₁-C₄alkoxy and C₁-C₄alkyl;
- (vii) a 6- or 7-membered fused bicyclic heterocyclyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from -OH, -N(R¹⁰)₂, C₁-C₄alkyl-NH₂, halogen, C₁-C₄alkyl, and oxo;
- (viii) a partially saturated 8-, 9-, 10-, 11- or 12-membered fused bicyclic heterocyclyl having 1, 2, 3 or 4 ring members independently selected from N, NR⁹, O and S, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from -OH, -N(R¹⁰)₂, C₁-C₄alkyl-NH₂, halogen, C₁-C₄alkyl, and oxo;
- (ix) a 6-, 7-, 8-, 9- or 10- membered spiro bicyclic heterocycloalkyl having 1, 2 or 3 ring members independently selected from N, NR⁹, O and S, wherein the spiro bicyclic heterocycloalkyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from -OH, -N(R¹⁰)₂, C₁-C₄alkyl-NH₂, halogen, C₁-C₄alkyl, and oxo;
- (x) a 6- membered heterocycloalkyl having 1 to 2 ring members independently selected from N, NR⁹, O and S, wherein the heterocycloalkyl has a C₁-C₃alkyl bridge or a -CH₂OCH₂- bridge;
- (xi) phenyl which is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from -S(=O)₂N(R¹⁰)₂, -OH, -N(R¹⁰)₂, C₁-C₄alkyl-NH₂, halogen and C₁-C₄alkyl;
- or
- (xii) C₄-C₈cycloalkyl which is unsubstituted or is substituted with 1, 2, 3 or 4 substituents independently selected from -OH, -N(R¹⁰)₂, -S(=O)₂R¹⁰, C₁-C₄alkyl-NH₂, halogen, C₁-C₄alkoxy, C₁-C₄alkyl, and oxo;
- R⁹ is H, C₁-C₄alkyl, benzyl, C₁-C₄alkyl-OR¹⁰, -C(=O)OR¹⁰ or -C(=O)R¹⁰, and
 R¹⁰ is H or C₁-C₄alkyl.

Further aspects and examples of the compounds of Formula (I) are provided in the following

embodiments. It will be recognized that features specified in each embodiment may be combined with other specified features to provide further embodiments.

In an embodiment of compounds of Formula (I), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a

5 stereoisomer thereof:

-X=Y- is -CR^x=CR^y-, -CR^x=N- or -N=CR^y-;

R^x is H, D, halogen or C₁-C₄alkyl;

R^y is H, D, halogen, -CN, C₁-C₄alkyl, C₁-C₄fluoroalkyl or C₁-C₄alkoxy;

R⁵ is H, halogen, -CN, C₁-C₄alkyl, C₁-C₄fluoroalkyl or C₁-C₄alkoxy;

10 R^A is:

(i) phenyl which is unsubstituted or is substituted with 1, 2, 3 or 4 R¹ groups;

(ii) a partially saturated 9-, 10-, 11- or 12-membered bicyclic carbocyclyl which is unsubstituted or is substituted with 1 to 4 R¹ groups;

(iii) a 5- or 6- membered monocyclic heteroaryl having 1, 2, 3 or 4 ring members
15 independently selected from N, NR⁴, O and S, wherein the monocyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 R¹ groups;

or

(iv) a partially saturated 8-, 9-, 10-, 11- or 12-membered fused bicyclic heterocyclyl having
20 1, 2, 3 or 4 ring members independently selected from N, NR⁴, O and S, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 R¹ groups;

each R¹ is independently selected from the group consisting of halogen, C₁-C₄alkyl, C₂-
C₄alkenyl, C₂-C₄alkynyl, C₁-C₄alkoxy, C₁-C₄alkoxycarbonyl, C₃-C₆cycloalkyl, C₁-
C₄fluoroalkyl, C₁-C₄fluoroalkoxy, pentafluorosulfanyl, C₁-C₄hydroxyalkyl, C₁-C₄thioalkyl,
25 azido, diC₁-C₄alkylamino, diC₁-C₄alkylaminocarbonyl, D, CD₃, cyano, formyl, phenyl and a 5-
to 6-membered heterocycloalkyl comprising 1 or 2 ring members independently selected
from N, NR⁴, O and S;

L₁ is a bond, -(CR²R³)_p-, -(CR²R³)_p-NR⁴-, -(CR²R³)_p-O-, -NR⁴(CR²R³)_q-, -(CR²R³)_qNR⁴-, -O-
(CR²R³)_p- or -S-(CR²R³)_p-;

R² is H, D, halogen or C₁-C₄alkyl;

30 R³ is H, D, halogen, C₁-C₄alkyl, C₁-C₄alkoxy, OH, amino or *t*-Boc-amino;

or R² and R³, together with the C atom to which they are attached, are linked to form C₃-

C₄cycloalkyl which is unsubstituted or is substituted with a single substituent selected from
C₁-C₄alkyl and oxo;

each R⁴ is independently selected from the group consisting of H and C₁-C₄alkyl;

35 p is 1, 2 or 3;

q is 0, 1 or 2;

Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is N;

or Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is CR^z;

or Z_1 is C, Z_2 is CR^z , Z_3 is N, Z_4 is N and Z_5 is CR^z ;

or Z_1 is C, Z_2 is N, Z_3 is N, Z_4 is N and Z_5 is CR^z ;

or Z_1 is N, Z_2 is CR^z , Z_3 is CR^z , Z_4 is C and Z_5 is N;

each R^z is independently selected from the group consisting of H, halogen, C_1 - C_4 alkyl and C_1 -

5 C_4 fluoroalkyl;

L_2 is a bond, $-(CR^6R^7)_n-$ or $-(CR^6R^7)_nO^*$, where the * indicates the point of attachment to R^6 ;

each R^6 is independently selected from the group consisting of H, C_1 - C_4 alkyl, C_1 - C_4 fluoroalkyl and C_1 - C_4 hydroxyalkyl;

each R^7 is independently selected from the group consisting of H, C_1 - C_4 alkyl, C_1 - C_4 fluoroalkyl

10 and C_1 - C_4 hydroxyalkyl;

or R^6 and R^7 , together with the C atom to which they are attached, are linked to form C_3 -

C_6 cycloalkyl, oxetanyl, tetrahydrofuranlyl or tetrahydropyranylyl;

n is 1, 2 or 3;

R^6 is:

- 15 (i) 4-, 5- or 6-membered heterocycloalkyl having 1, 2 or 3 ring members independently selected from N, NR^9 , O and S, wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents each independently selected from -OH, -CN, - $N(R^{10})_2$, halogen, C_1 - C_4 fluoroalkyl, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, oxo and a 5- or 6- membered monocyclic heteroaryl having 1, 2, 3 or 4 ring members independently selected from N, NR^9 , O and S, wherein the monocyclic heteroaryl is unsubstituted;
- 20 (ii) 4-, 5- or 6-membered heterocycloalkyl wherein one ring member is $S(=O)_2$, $S(=O)$ or $S(=O)(=NH)$, and wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from -OH, C_1 - C_4 alkyl and oxo;
- 25 (iii) 4-, 5- or 6-membered heterocycloalkyl wherein one ring member is $S(=O)_2$ or $S(=O)$, and 1, 2 or 3 other ring members are independently selected from N, NR^9 and O, and wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents each independently selected from C_1 - C_4 alkyl and oxo;
- 30 (iv) a partially saturated 5- or 6-membered heterocyclyl having 1 or 2 ring members independently selected from N, NR^9 , O and S, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents independently selected from -OH, C_1 - C_4 alkyl, and oxo;
- 35 (v) a partially saturated 5- or 6-membered heterocyclyl wherein one ring member is $S(=O)_2$ and 1, 2 or 3 other ring members are independently selected from N, NR^9 , O and S, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents independently selected from -OH, C_1 - C_4 alkyl, and oxo;
- (vi) a 5- or 6- membered monocyclic heteroaryl having 1, 2, 3 or 4 ring members independently selected from N, NR^9 , O and S, wherein the monocyclic heteroaryl is

unsubstituted or is substituted with 1, 2, 3 or 4 substituents each independently selected from -OH, C₁-C₄alkoxy and C₁-C₄alkyl;

- (vii) a 6- or 7-membered fused bicyclic heterocyclyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from -OH, -N(R¹⁰)₂, C₁-C₄alkyl-NH₂, halogen, C₁-C₄alkyl, and oxo;
- (viii) a partially saturated 8-, 9-, 10-, 11- or 12-membered fused bicyclic heterocyclyl having 1, 2, 3 or 4 ring members independently selected from N, NR⁹, O and S, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from -OH, -N(R¹⁰)₂, C₁-C₄alkyl-NH₂, halogen, C₁-C₄alkyl, and oxo;
- (ix) a 6-, 7-, 8-, 9- or 10- membered spiro bicyclic heterocycloalkyl having 1, 2 or 3 ring members independently selected from N, NR⁹, O and S, wherein the spiro bicyclic heterocycloalkyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from -OH, -N(R¹⁰)₂, C₁-C₄alkyl-NH₂, halogen, C₁-C₄alkyl, and oxo;
- (x) a 6- membered heterocycloalkyl having 1 to 2 ring members independently selected from N, NR⁹, O and S, wherein the heterocycloalkyl has a C₁-C₃alkyl bridge or a -CH₂OCH₂- bridge;
- (xi) phenyl which is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from -S(=O)₂N(R¹⁰)₂, -OH, -N(R¹⁰)₂, C₁-C₄alkyl-NH₂, halogen and C₁-C₄alkyl;
- or
- (xii) C₄-C₈cycloalkyl which is unsubstituted or is substituted with 1, 2, 3 or 4 substituents independently selected from -OH, -N(R¹⁰)₂, -S(=O)₂R¹⁰, C₁-C₄alkyl-NH₂, halogen, C₁-C₄alkoxy, C₁-C₄alkyl, and oxo;

R⁹ is H, C₁-C₄alkyl, benzyl, C₁-C₄alkyl-OR¹⁰, -C(=O)OR¹⁰ or -C(=O)R¹⁰,

and

R¹⁰ is H or C₁-C₄alkyl.

- 30 In an embodiment of compounds of Formula (I), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof:

-X=Y- is -CR^x=CR^y-, -CR^x=N- or -N=CR^y-;

R^x is H, D or halogen;

- 35 R^y is H, D, halogen or -CN;

R⁵ is halogen or -CN;

R^A is:

- (i) phenyl which is substituted with 1 or 2 R¹ groups;

- (ii) a 5- or 6- membered monocyclic heteroaryl having 1 or 2 ring members independently selected from N and NR⁴, wherein the monocyclic heteroaryl is substituted with 1 or 2 R¹ groups;
- or
- 5 (iii) a partially saturated 8-, 9- or 10-membered fused bicyclic heterocyclyl having 1, 2 or 3 ring member independently selected from N, NR⁴ and O, wherein the fused bicyclic heterocyclyl is substituted with 1, 2 or 3 R¹ groups;
- each R¹ is independently selected from the group consisting of halogen, D, CD₃, C₁-C₄alkyl, C₁-C₄fluoroalkyl, C₁-C₄fluoroalkoxy, C₃-C₆cycloalkyl and pentafluorosulfanyl;
- 10 L₁ is a bond, -(CR²R³)_p-, -NR⁴(CR²R³)_q- or -O-(CR²R³)_p-;
- R² is H, D or halogen;
- R³ is H, D, halogen, OH or C₁-C₄alkyl;
- or R² and R³, together with the C atom to which they are attached, are linked to form C₃-C₄cycloalkyl which is unsubstituted
- 15 R⁴ is H or C₁-C₄alkyl;
- p is 1;
- q is 0;
- Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is N;
- or Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is CR^z;
- 20 or Z₁ is C, Z₂ is CR^z, Z₃ is N, Z₄ is N and Z₅ is CR^z;
- or Z₁ is C, Z₂ is N, Z₃ is N, Z₄ is N and Z₅ is CR^z;
- each R^z is H;
- L₂ is a bond, -(CR⁶R⁷)_n- or -(CR⁶R⁷)_nO-*, where the * indicates the point of attachment to R⁸;
- each R⁶ is independently selected from the group consisting of H, C₁-C₄alkyl, C₁-C₄fluoroalkyl
- 25 and C₁-C₄hydroxyalkyl;
- each R⁷ is independently selected from the group consisting of H, C₁-C₄alkyl, C₁-C₄fluoroalkyl and C₁-C₄hydroxyalkyl;
- or R⁶ and R⁷, together with the C atom to which they are attached, are linked to form tetrahydropyranyl;
- 30 n is 1 or 2;
- R⁸ is:
- (i) 4-, 5- or 6-membered heterocycloalkyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2 or 3 substituents each independently selected from -OH, -CN, -
- 35 N(R¹⁰)₂, halogen, C₁-C₄fluoroalkyl, C₁-C₄alkyl, C₁-C₄alkoxy, oxo and a 5- or 6-membered monocyclic heteroaryl having 1 or 2 ring members independently selected from N and NR⁹, wherein the monocyclic heteroaryl is unsubstituted;

- (ii) 5- membered heterocycloalkyl wherein one ring member is $S(=O)_2$, $S(=O)$ or $S(=O)(=NH)$, and wherein the heterocycloalkyl is unsubstituted or is substituted with a substituent selected from -OH and C_1 - C_4 alkyl;
- (iii) 6-membered heterocycloalkyl wherein one ring member is $S(=O)_2$ or $S(=O)$, and one
5 other ring member is selected from N, NR^9 and O, and wherein the heterocycloalkyl is unsubstituted or is substituted with a substituent selected from C_1 - C_4 alkyl;
- (iv) a partially saturated 6-membered heterocyclyl having 1 or 2 ring members independently selected from N, NR^9 , O and S, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with an oxo;
- (v) a partially saturated 6-membered heterocyclyl wherein one ring member is $S(=O)_2$ and
10 one other ring member is selected from N, NR^4 , and O, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with an oxo;
- (vi) a 5- or 6- membered monocyclic heteroaryl having 1, 2, 3 or 4 ring members independently selected from N, NR^9 and O, wherein the monocyclic heteroaryl is
15 unsubstituted or is substituted with a substituent selected from -OH, C_1 - C_4 alkoxy and C_1 - C_4 alkyl;
- (vii) a 6- membered fused bicyclic heterocyclyl having 1 ring member selected from N and NR^9 , wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with an oxo;
- (viii) a partially saturated 10- membered fused bicyclic heterocyclyl having 1, 2, or 3 ring
20 members independently selected from N, NR^9 , and O, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with an oxo;
- (ix) a 7- membered spiro bicyclic heterocycloalkyl having 1 ring member selected from N, NR^9 , and O, wherein the spiro bicyclic heterocycloalkyl is unsubstituted;
- (x) a 6- membered heterocycloalkyl having 1 to 2 ring members independently selected
25 from N, NR^9 and O, wherein the heterocycloalkyl has a C_1 - C_3 alkyl bridge or a -
 CH_2OCH_2 - bridge;
- (xi) phenyl which is substituted with $-S(=O)_2N(R^{10})_2$;
or
- (xii) C_4 - C_8 cycloalkyl which is substituted with 1, 2 or 3 substituents independently selected
30 from -OH, $-N(R^{10})_2$, $-S(=O)_2R^{10}$, C_1 - C_4 alkyl- NH_2 , halogen and C_1 - C_4 alkoxy;
 R^9 is H, C_1 - C_4 alkyl, benzyl, C_1 - C_4 alkyl- OR^{10} , $-C(=O)OR^{10}$ or $-C(=O)R^{10}$,
and
 R^{10} is H or C_1 - C_4 alkyl.

35 In an embodiment of compounds of Formula (I), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof:

-X=Y- is $-CR^x=CR^y-$, $-CR^x=N-$ or $-N=CR^y-$;

R^x is H or F;

R^y is H, F or CN;

R⁵ is F, Cl or CN;

R^A is:

- 5 (i) phenyl which is substituted with 1 to 2 R¹ groups;
 - (ii) pyrazolyl or pyridinyl, which are substituted with 1 or 2 R¹ groups;
 - or
 - (iii) chromanyl, 3,4-dihydro-2H-pyrano[2,3-b]pyridinyl, 3,4-dihydro-2H-benzo[b][1,4]oxazinyl, 6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazinyl, 5,6-dihydrocyclopenta[c]pyrazol-1(4H)-yl, 2,3-dihydrobenzo[b][1,4]dioxinyl, 4,5,6,7-tetrahydro-1H-indazolyl, 1H-benzo[d]imidazolyl, or 2,3-dihydrobenzofuranyl, each of which is unsubstituted or are substituted with 1 or 2 R¹ group;
- each R¹ is independently selected from the group consisting of F, Cl, Br, methyl, isopropyl, t-butyl, cyclopropyl, -CF₃, CHF₂, CF₂CF₃, OCF₃, and SF₅;
- 15 L₁ is a bond, -(CR²R³)_p-, -NR⁴(CR²R³)_q- or -O-(CR²R³)_p-;
- R² is H or F;
- R³ is H, OH, F or methyl;
- or R² and R³, together with the C atom to which they are attached, are linked to form cyclopropyl which is unsubstituted;
- 20 R⁴ is H, methyl or ethyl;
- p is 1;
- q is 0;
- Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is N;
- or Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is CR^z;
- 25 or Z₁ is C, Z₂ is CR^z, Z₃ is N, Z₄ is N and Z₅ is CR^z;
- or Z₁ is C, Z₂ is N, Z₃ is N, Z₄ is N and Z₅ is CR^z;
- each R^z is H;
- L₂ is a bond, -(CR⁶R⁷)_n- or -(CR⁶R⁷)_nO-*, where the * indicates the point of attachment to R⁸;
- each R⁶ is independently selected from the group consisting of H, methyl, isopropyl, -CH₂OH
- 30 and CH₂CF₃;
- each R⁷ is independently selected from the group consisting of H, methyl, isopropyl, -CH₂OH and CH₂CF₃;
- or R⁶ and R⁷, together with the C atom to which they are attached, are linked to form tetrahydropyranyl;
- 35 n is 1 or 2;
- R⁸ is:
- (i) 4-, 5- or 6-membered heterocycloalkyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the heterocycloalkyl is unsubstituted or is

substituted with 1, 2 or 3 substituents each independently selected from -OH, -CN, NH₂, F, CF₃, methyl, methoxy, oxo and a 5- or 6- membered monocyclic heteroaryl having 1 or 2 ring members independently selected from N and NR⁹, wherein the monocyclic heteroaryl is unsubstituted;

- 5 (ii) 5- membered heterocycloalkyl wherein one ring member is S(=O)₂, S(=O) or S(=O)(=NH), and wherein the heterocycloalkyl is unsubstituted or is substituted with a substituent selected from OH and methyl;
- (iii) 6-membered heterocycloalkyl wherein one ring member is S(=O)₂ or S(=O), and one other ring member is selected from N, NR⁹ and O, and wherein the heterocycloalkyl is
10 unsubstituted or is substituted with a methyl,
- (iv) a partially saturated 6-membered heterocyclyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with an oxo;
- (v) a partially saturated 6-membered heterocyclyl wherein one ring member is S(=O)₂ and
15 one other ring member is selected from N, NR⁴, and O, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with an oxo;
- (vi) a 5- or 6- membered monocyclic heteroaryl having 1, 2, 3 or 4 ring members independently selected from N, NR⁹ and O, wherein the monocyclic heteroaryl is unsubstituted or is substituted with a substituent selected from -OH methoxy and
20 methyl;
- (vii) a 6- membered fused bicyclic heterocyclyl having 1 ring member selected from N and NR⁹, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with an oxo;
- (viii) a partially saturated 10- membered fused bicyclic heterocyclyl having 1, 2, or 3 ring
25 members independently selected from N, NR⁹, and O, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with an oxo;
- (ix) a 7- membered spiro bicyclic heterocycloalkyl having 1 ring member selected from N, NR⁹, and O, wherein the spiro bicyclic heterocycloalkyl is unsubstituted;
- (x) a 6- membered heterocycloalkyl having 1 to 2 ring members independently selected
30 from N, NR⁹ and O, wherein the heterocycloalkyl has a C₁-C₃alkyl bridge or a -CH₂OCH₂- bridge;
- (xi) phenyl which is substituted with -S(=O)₂NH₂;
or
- (xii) cyclobutyl, cyclopentyl, or cyclohexyl which is substituted with 1, 2 or 3 substituents
35 independently selected from -OH, -NH₂, -S(=O)₂CH₃, -CH₂NH₂, F, and methoxy;

and

R⁹ is H, methyl, benzyl, -C(=O)CH₃, -C(=O)O(CH₃)₃, CH₂CH₂OH or CH₂CH₂OCH₃.

In an embodiment of compounds of Formula (I), or a stereoisomer thereof, or a

pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof:

-X=Y- is -CR^x=CR^y-, or -CR^x=N-;

R^x is H;

5 R^y is H, F or CN;

R⁵ is F or CN;

R^A is:

(i) phenyl which is substituted with 1 to 2 R¹ groups;

(ii) pyrazolyl or pyridinyl, which is substituted with 1 or 2 R¹ groups;

10 or

(iii) chromanyl or 3,4-dihydro-2H-pyrano[2,3-b]pyridinyl, which are unsubstituted or are substituted with an R¹ group;

each R¹ is independently selected from the group consisting of F, Cl, methyl, -CF₃ and SF₅;

L₁ is a bond, -(CR²R³)_p-, -NR⁴(CR²R³)_q- or -O-(CR²R³)_p-;

15 R² is H;

R³ is H, OH or methyl;

R⁴ is H, methyl or ethyl;

p is 1;

q is 0;

20 Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is N;

or Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is CR^z;

or Z₁ is C, Z₂ is CR^z, Z₃ is N, Z₄ is N and Z₅ is CR^z;

or Z₁ is C, Z₂ is N, Z₃ is N, Z₄ is N and Z₅ is CR^z;

each R^z is H;

25 L₂ is a bond, -(CR⁶R⁷)_n- or -(CR⁶R⁷)_nO-*, where the * indicates the point of attachment to R⁶;

each R⁶ is independently selected from the group consisting of H, methyl and -CH₂OH;

each R⁷ is independently selected from the group consisting of H, methyl and -CH₂OH;

n is 1 or 2;

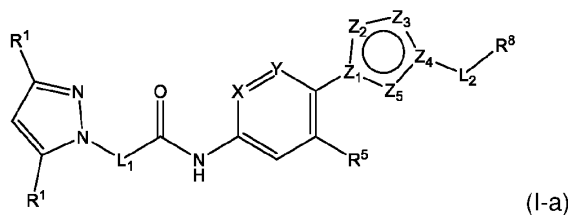
R⁸ is:

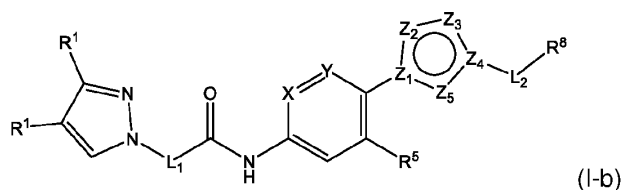
30 (i) 4-, 5- or 6-membered heterocycloalkyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2 or 3 substituents each independently selected from -OH, -CN, NH₂, F, CF₃, methyl, methoxy, oxo and a 5- or 6- membered monocyclic heteroaryl having 1 or 2 ring members independently selected from N and NR⁹, wherein the monocyclic
35 heteroaryl is unsubstituted;

(ii) 5- membered heterocycloalkyl wherein one ring member is S(=O)₂, S(=O) or S(=O)(=NH), and wherein the heterocycloalkyl is unsubstituted or is substituted with a substituent selected from OH and methyl;

- (iii) 6-membered heterocycloalkyl wherein one ring member is $S(=O)_2$ or $S(=O)$, and one other ring member is selected from N, NR^9 and O, and wherein the heterocycloalkyl is unsubstituted or is substituted with a methyl,
- (iv) a partially saturated 6-membered heterocyclyl having 1 or 2 ring members independently selected from N, NR^9 , O and S, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with an oxo;
- (v) a partially saturated 6-membered heterocyclyl wherein one ring member is $S(=O)_2$ and one other ring member is selected from N, NR^4 , and O, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with an oxo;
- (vi) a 5- or 6- membered monocyclic heteroaryl having 1, 2, 3 or 4 ring members independently selected from N, NR^9 and O, wherein the monocyclic heteroaryl is unsubstituted or is substituted with a substituent selected from -OH methoxy and methyl;
- (vii) a 6- membered fused bicyclic heterocyclyl having 1 ring member selected from N and NR^9 , wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with an oxo;
- (viii) a partially saturated 10- membered fused bicyclic heterocyclyl having 1, 2, or 3 ring members independently selected from N, NR^9 , and O, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with an oxo;
- (ix) a 7- membered spiro bicyclic heterocycloalkyl having 1 ring member selected from N, NR^9 , and O, wherein the spiro bicyclic heterocycloalkyl is unsubstituted;
- (x) a 6- membered heterocycloalkyl having 1 to 2 ring members independently selected from N, NR^9 and O, wherein the heterocycloalkyl has a C_1 - C_3 alkyl bridge or a $-CH_2OCH_2-$ bridge;
- (xi) phenyl which is substituted with $-S(=O)_2NH_2$;
- or
- (xii) cyclobutyl, cyclopentyl, or cyclohexyl which is substituted with 1, 2 or 3 substituents independently selected from -OH, $-NH_2$, $-S(=O)_2CH_3$, $-CH_2NH_2$, F, and methoxy;
- and
- R^9 is H, methyl, benzyl, $-C(=O)CH_3$, $-C(=O)O(CH_3)_3$, CH_2CH_2OH or $CH_2CH_2OCH_3$.

In an embodiment of compounds of Formula (I), the compounds provided herein are compounds of Formula (I-a) or Formula (I-b), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof:





wherein:

-X=Y- is -CR^x=CR^y-, -CR^x=N- or -N=CR^y-;

R^x is H, D, halogen or C₁-C₄alkyl;

5 R^y is H, D, halogen, -CN, C₁-C₄alkyl, C₁-C₄fluoroalkyl or C₁-C₄alkoxy;

R⁵ is H, halogen, -CN, C₁-C₄alkyl, C₁-C₄fluoroalkyl or C₁-C₄alkoxy;

each R¹ is independently selected from the group consisting of halogen, C₁-C₄alkyl, C₂-

C₄alkenyl, C₂-C₄alkynyl, C₁-C₄alkoxy, C₁-C₄alkoxycarbonyl, C₃-C₆cycloalkyl, C₁-

C₄fluoroalkyl, C₁-C₄fluoroalkoxy, pentafluorosulfanyl, C₁-C₄hydroxyalkyl, C₁-C₄thioalkyl,

10 azido, diC₁-C₄alkylamino, diC₁-C₄alkylaminocarbonyl, D, CD₃, cyano, formyl, phenyl and a 5-
to 6-membered heterocycloalkyl comprising 1 or 2 ring members independently selected
from N, NR⁴, O and S;

L₁ is -(CR²R³)_p-, -(CR²R³)_p-NR⁴-, -(CR²R³)_p-O-, -NR⁴(CR²R³)_q-, -(CR²R³)_qNR⁴-, -O-(CR²R³)_p- or -
S-(CR²R³)_p-;

15 R² is H, D, halogen or C₁-C₄alkyl;

R³ is H, D, halogen, C₁-C₄alkyl, C₁-C₄alkoxy, OH, amino or *t*-Boc-amino;

or R² and R³, together with the C atom to which they are attached, are linked to form C₃-

C₄cycloalkyl which is unsubstituted or is substituted with a single substituent selected from
C₁-C₄alkyl and oxo;

20 each R⁴ is independently selected from the group consisting of H and C₁-C₄alkyl;

p is 1, 2 or 3;

q is 0, 1 or 2;

Z₁ is N or C; Z₂ is N or CR^z; Z₃ is N or CR^z; Z₄ is N or C; Z₅ is N or CR^z;

wherein each R^z is independently selected from the group consisting of H, halogen, C₁-

25 C₄alkyl and C₁-C₄fluoroalkyl; and provided that at least two, and not more than four, of
Z₁, Z₂, Z₃, Z₄ and Z₅ are N;

L₂ is a bond, -(CR⁶R⁷)_n- or -(CR⁶R⁷)_nO-*, where the * indicates the point of attachment to R⁸;

each R⁶ is independently selected from the group consisting of H, C₁-C₄alkyl, C₁-C₄fluoroalkyl
and C₁-C₄hydroxyalkyl;

30 each R⁷ is independently selected from the group consisting of H, C₁-C₄alkyl, C₁-C₄fluoroalkyl
and C₁-C₄hydroxyalkyl;

or R⁶ and R⁷, together with the C atom to which they are attached, are linked to form C₃-

C₆cycloalkyl, oxetanyl, tetrahydrofuranlyl or tetrahydropyranyl;

n is 1, 2 or 3;

35 R⁸ is:

- (i) 4-, 5- or 6-membered heterocycloalkyl having 1, 2 or 3 ring members independently selected from N, NR⁹, O and S, wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents each independently selected from -OH, -CN, -N(R¹⁰)₂, halogen, C₁-C₄fluoroalkyl, C₁-C₄alkyl, C₁-C₄alkoxy, oxo and a 5- or 6- membered monocyclic heteroaryl having 1, 2, 3 or 4 ring members independently selected from N, NR⁹, O and S, wherein the monocyclic heteroaryl is unsubstituted;
- (ii) 4-, 5- or 6-membered heterocycloalkyl wherein one ring member is S(=O)₂, S(=O) or S(=O)(=NH), and wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from -OH, C₁-C₄alkyl and oxo;
- (iii) 4-, 5- or 6-membered heterocycloalkyl wherein one ring member is S(=O)₂ or S(=O), and 1, 2 or 3 other ring members are independently selected from N, NR⁹ and O, and wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents each independently selected from C₁-C₄alkyl and oxo;
- (iv) a partially saturated 5- or 6-membered heterocyclyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents independently selected from -OH, C₁-C₄alkyl, and oxo;
- (v) a partially saturated 5- or 6-membered heterocyclyl wherein one ring member is S(=O)₂ and 1, 2 or 3 other ring members are independently selected from N, NR⁹, O and S, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents independently selected from -OH, C₁-C₄alkyl, and oxo;
- (vi) a 5- or 6- membered monocyclic heteroaryl having 1, 2, 3 or 4 ring members independently selected from N, NR⁹, O and S, wherein the monocyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents each independently selected from -OH, C₁-C₄alkoxy and C₁-C₄alkyl;
- (vii) a 6- or 7-membered fused bicyclic heterocyclyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from -OH, -N(R¹⁰)₂, C₁-C₄alkyl-NH₂, halogen, C₁-C₄alkyl, and oxo;
- (viii) a partially saturated 8-, 9-, 10-, 11- or 12-membered fused bicyclic heterocyclyl having 1, 2, 3 or 4 ring members independently selected from N, NR⁹, O and S, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from -OH, -N(R¹⁰)₂, C₁-C₄alkyl-NH₂, halogen, C₁-C₄alkyl, and oxo;
- (ix) a 6-, 7-, 8-, 9- or 10- membered spiro bicyclic heterocycloalkyl having 1, 2 or 3 ring members independently selected from N, NR⁹, O and S, wherein the spiro bicyclic heterocycloalkyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each

independently selected from -OH, -N(R¹⁰)₂, C₁-C₄alkyl-NH₂, halogen, C₁-C₄alkyl, and oxo;

(x) a 6-membered heterocycloalkyl having 1 to 2 ring members independently selected from N, NR⁹, O and S, wherein the heterocycloalkyl has a C₁-C₃alkyl bridge or a -CH₂OCH₂- bridge;

(xi) phenyl which is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from -S(=O)₂N(R¹⁰)₂, -OH, -N(R¹⁰)₂, C₁-C₄alkyl-NH₂, halogen and C₁-C₄alkyl;

or

(xii) C₄-C₈cycloalkyl which is unsubstituted or is substituted with 1, 2, 3 or 4 substituents independently selected from -OH, -N(R¹⁰)₂, -S(=O)₂R¹⁰, C₁-C₄alkyl-NH₂, halogen, C₁-C₄alkoxy, C₁-C₄alkyl, and oxo;

R⁹ is H, C₁-C₄alkyl, benzyl, C₁-C₄alkyl-OR¹⁰, -C(=O)OR¹⁰ or -C(=O)R¹⁰, and

R¹⁰ is H or C₁-C₄alkyl.

In an embodiment of compounds of Formula (I-a) and Formula (I-b), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof:

-X=Y- is -CR^x=CR^y-, -CR^x=N- or -N=CR^y-;

R^x is H, D, halogen or C₁-C₄alkyl;

R^y is H, D, halogen, -CN, C₁-C₄alkyl, C₁-C₄fluoroalkyl or C₁-C₄alkoxy;

R⁵ is H, halogen, -CN, C₁-C₄alkyl, C₁-C₄fluoroalkyl or C₁-C₄alkoxy;

each R¹ is independently selected from the group consisting of halogen, C₁-C₄alkyl, C₂-

C₄alkenyl, C₂-C₄alkynyl, C₁-C₄alkoxy, C₁-C₄alkoxycarbonyl, C₃-C₆cycloalkyl, C₁-

C₄fluoroalkyl, C₁-C₄fluoroalkoxy, pentafluorosulfanyl, C₁-C₄hydroxyalkyl, C₁-C₄thioalkyl, azido, diC₁-C₄alkylamino, diC₁-C₄alkylaminocarbonyl, D, CD₃, cyano, formyl, phenyl and a 5- to 6-membered heterocycloalkyl comprising 1 or 2 ring members independently selected from N, NR⁴, O and S;

L₁ is -(CR²R³)_p-, -(CR²R³)_p-NR⁴-, -(CR²R³)_p-O-, -NR⁴(CR²R³)_q-, -(CR²R³)_qNR⁴-, -O-(CR²R³)_p- or -S-(CR²R³)_p-;

R² is H, D, halogen or C₁-C₄alkyl;

R³ is H, D, halogen, C₁-C₄alkyl, C₁-C₄alkoxy, OH, amino or *t*-Boc-amino;

or R² and R³, together with the C atom to which they are attached, are linked to form C₃-

C₄cycloalkyl which is unsubstituted or is substituted with a single substituent selected from

C₁-C₄alkyl and oxo;

each R⁴ is independently selected from the group consisting of H and C₁-C₄alkyl;

p is 1, 2 or 3;

q is 0, 1 or 2;

- Z_1 is N, Z_2 is CR^z , Z_3 is N, Z_4 is C and Z_5 is N;
 or Z_1 is N, Z_2 is CR^z , Z_3 is N, Z_4 is C and Z_5 is CR^z ;
 or Z_1 is C, Z_2 is CR^z , Z_3 is N, Z_4 is N and Z_5 is CR^z ;
 or Z_1 is C, Z_2 is N, Z_3 is N, Z_4 is N and Z_5 is CR^z ;
 5 or Z_1 is N, Z_2 is CR^z , Z_3 is CR^z , Z_4 is C and Z_5 is N;
 each R^z is independently selected from the group consisting of H, halogen, C_1 - C_4 alkyl and C_1 - C_4 fluoroalkyl;
 L_2 is a bond, $-(CR^6R^7)_n-$ or $-(CR^6R^7)_nO^*$, where the * indicates the point of attachment to R^8 ;
 each R^6 is independently selected from the group consisting of H, C_1 - C_4 alkyl, C_1 - C_4 fluoroalkyl
 10 and C_1 - C_4 hydroxyalkyl;
 each R^7 is independently selected from the group consisting of H, C_1 - C_4 alkyl, C_1 - C_4 fluoroalkyl
 and C_1 - C_4 hydroxyalkyl;
 or R^6 and R^7 , together with the C atom to which they are attached, are linked to form C_3 -
 C_6 cycloalkyl, oxetanyl, tetrahydrofuranlyl or tetrahydropyranyl;
 15 n is 1, 2 or 3;
 R^8 is:
- (i) 4-, 5- or 6-membered heterocycloalkyl having 1, 2 or 3 ring members independently
 selected from N, NR^9 , O and S, wherein the heterocycloalkyl is unsubstituted or is
 substituted with 1, 2, 3 or 4 substituents each independently selected from -OH, -CN, -
 20 $N(R^{10})_2$, halogen, C_1 - C_4 fluoroalkyl, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, oxo and a 5- or 6-
 membered monocyclic heteroaryl having 1, 2, 3 or 4 ring members independently
 selected from N, NR^9 , O and S, wherein the monocyclic heteroaryl is unsubstituted;
 - (ii) 4-, 5- or 6-membered heterocycloalkyl wherein one ring member is $S(=O)_2$, $S(=O)$ or
 $S(=O)(=NH)$, and wherein the heterocycloalkyl is unsubstituted or is substituted with 1,
 25 2, 3 or 4 substituents, each independently selected from -OH, C_1 - C_4 alkyl and oxo;
 - (iii) 4-, 5- or 6-membered heterocycloalkyl wherein one ring member is $S(=O)_2$ or $S(=O)$,
 and 1, 2 or 3 other ring members are independently selected from N, NR^9 and O, and
 wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2, 3 or 4
 substituents each independently selected from C_1 - C_4 alkyl and oxo;
 - (iv) a partially saturated 5- or 6-membered heterocyclyl having 1 or 2 ring members
 independently selected from N, NR^9 , O and S, wherein the partially saturated
 heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents
 independently selected from -OH, C_1 - C_4 alkyl, and oxo;
 - (v) a partially saturated 5- or 6-membered heterocyclyl wherein one ring member is
 35 $S(=O)_2$ and 1, 2 or 3 other ring members are independently selected from N, NR^9 , O
 and S, wherein the partially saturated heterocyclyl is unsubstituted or is substituted
 with 1, 2, 3 or 4 substituents independently selected from -OH, C_1 - C_4 alkyl, and oxo;

- (vi) a 5- or 6- membered monocyclic heteroaryl having 1, 2, 3 or 4 ring members independently selected from N, NR⁹, O and S, wherein the monocyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents each independently selected from -OH, C₁-C₄alkoxy and C₁-C₄alkyl;
- 5 (vii) a 6- or 7-membered fused bicyclic heterocyclyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from -OH, -N(R¹⁰)₂, C₁-C₄alkyl-NH₂, halogen, C₁-C₄alkyl, and oxo;
- (viii) a partially saturated 8-, 9-, 10-, 11- or 12-membered fused bicyclic heterocyclyl having 1, 2, 3 or 4 ring members independently selected from N, NR⁹, O and S, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from -OH, -N(R¹⁰)₂, C₁-C₄alkyl-NH₂, halogen, C₁-C₄alkyl, and oxo;
- 10 (ix) a 6-, 7-, 8-, 9- or 10- membered spiro bicyclic heterocycloalkyl having 1, 2 or 3 ring members independently selected from N, NR⁹, O and S, wherein the spiro bicyclic heterocycloalkyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from -OH, -N(R¹⁰)₂, C₁-C₄alkyl-NH₂, halogen, C₁-C₄alkyl, and oxo;
- 15 (x) a 6- membered heterocycloalkyl having 1 to 2 ring members independently selected from N, NR⁹, O and S, wherein the heterocycloalkyl has a C₁-C₃alkyl bridge or a -CH₂OCH₂- bridge;
- 20 (xi) phenyl which is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from -S(=O)₂N(R¹⁰)₂, -OH, -N(R¹⁰)₂, C₁-C₄alkyl-NH₂, halogen and C₁-C₄alkyl;
- 25 or
- (xii) C₄-C₈cycloalkyl which is unsubstituted or is substituted with 1, 2, 3 or 4 substituents independently selected from -OH, -N(R¹⁰)₂, -S(=O)₂R¹⁰, C₁-C₄alkyl-NH₂, halogen, C₁-C₄alkoxy, C₁-C₄alkyl, and oxo;
- R⁹ is H, C₁-C₄alkyl, benzyl, C₁-C₄alkyl-OR¹⁰, -C(=O)OR¹⁰ or -C(=O)R¹⁰,
- 30 and
- R¹⁰ is H or C₁-C₄alkyl.

In an embodiment of compounds of Formula (I-a) and Formula (I-b), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof:

- 35 -X=Y- is -CR^x=CR^y-, -CR^x=N- or -N=CR^y-;
- R^x is H, D or halogen;
- R^y is H, D, halogen or -CN;
- R⁵ is halogen or -CN;

- each R^1 is independently selected from the group consisting of halogen, D, CD_3 , C_1 - C_4 alkyl, C_1 - C_4 fluoroalkyl, C_1 - C_4 fluoroalkoxy, C_3 - C_6 cycloalkyl and pentafluorosulfanyl;
- L_1 is $-(CR^2R^3)_p-$, $-NR^4(CR^2R^3)_q-$ or $-O-(CR^2R^3)_p-$;
- R^2 is H, D or halogen;
- 5 R^3 is H, D, halogen, OH or C_1 - C_4 alkyl;
- or R^2 and R^3 , together with the C atom to which they are attached, are linked to form C_3 - C_4 cycloalkyl which is unsubstituted
- R^4 is H or C_1 - C_4 alkyl;
- p is 1;
- 10 q is 0;
- Z_1 is N, Z_2 is CR^z , Z_3 is N, Z_4 is C and Z_5 is N;
- or Z_1 is N, Z_2 is CR^z , Z_3 is N, Z_4 is C and Z_5 is CR^z ;
- or Z_1 is C, Z_2 is CR^z , Z_3 is N, Z_4 is N and Z_5 is CR^z ;
- or Z_1 is C, Z_2 is N, Z_3 is N, Z_4 is N and Z_5 is CR^z ;
- 15 each R^z is H;
- L_2 is a bond, $-(CR^6R^7)_n-$ or $-(CR^6R^7)_nO^*$, where the * indicates the point of attachment to R^8 ;
- each R^6 is independently selected from the group consisting of H, C_1 - C_4 alkyl, C_1 - C_4 fluoroalkyl and C_1 - C_4 hydroxyalkyl;
- each R^7 is independently selected from the group consisting of H, C_1 - C_4 alkyl, C_1 - C_4 fluoroalkyl and C_1 - C_4 hydroxyalkyl;
- 20 or R^6 and R^7 , together with the C atom to which they are attached, are linked to form tetrahydropyranyl;
- n is 1 or 2;
- R^8 is:
- 25 (i) 4-, 5- or 6-membered heterocycloalkyl having 1 or 2 ring members independently selected from N, NR^9 , O and S, wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2 or 3 substituents each independently selected from -OH, -CN, - $N(R^{10})_2$, halogen, C_1 - C_4 fluoroalkyl, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, oxo and a 5- or 6-membered monocyclic heteroaryl having 1 or 2 ring members independently selected
- 30 from N and NR^9 , wherein the monocyclic heteroaryl is unsubstituted;
- (ii) 5- membered heterocycloalkyl wherein one ring member is $S(=O)_2$, $S(=O)$ or $S(=O)(=NH)$, and wherein the heterocycloalkyl is unsubstituted or is substituted with a substituent selected from -OH and C_1 - C_4 alkyl;
- (iii) 6-membered heterocycloalkyl wherein one ring member is $S(=O)_2$ or $S(=O)$, and one
- 35 other ring member is selected from N, NR^9 and O, and wherein the heterocycloalkyl is unsubstituted or is substituted with a substituent selected from C_1 - C_4 alkyl;

- (iv) a partially saturated 6-membered heterocyclyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with an oxo;
- (v) a partially saturated 6-membered heterocyclyl wherein one ring member is S(=O)₂ and one other ring member is selected from N, NR⁴, and O, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with an oxo;
- (vi) a 5- or 6- membered monocyclic heteroaryl having 1, 2, 3 or 4 ring members independently selected from N, NR⁹ and O, wherein the monocyclic heteroaryl is unsubstituted or is substituted with a substituent selected from -OH, C₁-C₄alkoxy and C₁-C₄alkyl;
- (vii) a 6- membered fused bicyclic heterocyclyl having 1 ring member selected from N and NR⁹, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with an oxo;
- (viii) a partially saturated 10- membered fused bicyclic heterocyclyl having 1, 2, or 3 ring members independently selected from N, NR⁹, and O, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with an oxo;
- (ix) a 7- membered spiro bicyclic heterocycloalkyl having 1 ring member selected from N, NR⁹, and O, wherein the spiro bicyclic heterocycloalkyl is unsubstituted;
- (x) a 6- membered heterocycloalkyl having 1 to 2 ring members independently selected from N, NR⁹ and O, wherein the heterocycloalkyl has a C₁-C₃alkyl bridge or a -CH₂OCH₂- bridge;
- (xi) phenyl which is substituted with -S(=O)₂N(R¹⁰)₂;
- or
- (xii) C₄-C₈cycloalkyl which is substituted with 1, 2 or 3 substituents independently selected from -OH, -N(R¹⁰)₂, -S(=O)₂R¹⁰, C₁-C₄alkyl-NH₂, halogen and C₁-C₄alkoxy;
- R⁹ is H, C₁-C₄alkyl, benzyl, C₁-C₄alkyl-OR¹⁰, -C(=O)OR¹⁰ or -C(=O)R¹⁰, and
- R¹⁰ is H or C₁-C₄alkyl.

In an embodiment of compounds of Formula (I-a) and Formula (I-b), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof:

-X=Y- is -CR^x=CR^y-, -CR^x=N- or -N=CR^y-;

R^x is H or F;

R^y is H, F or CN;

R⁵ is F, Cl or CN;

each R¹ is independently selected from the group consisting of F, Cl, Br, methyl, isopropyl, t-butyl, cyclopropyl, -CF₃, CHF₂, CF₂CF₃, OCF₃, and SF₅;

L₁ is -(CR²R³)_p-, -NR⁴(CR²R³)_q- or -O-(CR²R³)_p-;

R² is H or F;

R³ is H, OH, F or methyl;

or R² and R³, together with the C atom to which they are attached, are linked to form cyclopropyl which is unsubstituted;

5 R⁴ is H, methyl or ethyl;

p is 1;

q is 0;

Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is N;

or Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is CR^z;

10 or Z₁ is C, Z₂ is CR^z, Z₃ is N, Z₄ is N and Z₅ is CR^z;

or Z₁ is C, Z₂ is N, Z₃ is N, Z₄ is N and Z₅ is CR^z;

each R^z is H;

L₂ is a bond, -(CR⁶R⁷)_n- or -(CR⁶R⁷)_nO-*, where the * indicates the point of attachment to R⁸;

each R⁶ is independently selected from the group consisting of H, methyl, isopropyl, -CH₂OH

15 and CH₂CF₃;

each R⁷ is independently selected from the group consisting of H, methyl, isopropyl, -CH₂OH and CH₂CF₃;

or R⁶ and R⁷, together with the C atom to which they are attached, are linked to form tetrahydropyranyl;

20 n is 1 or 2;

R⁸ is:

- (i) 4-, 5- or 6-membered heterocycloalkyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2 or 3 substituents each independently selected from -OH, -CN, 25 NH₂, F, CF₃, methyl, methoxy, oxo and a 5- or 6- membered monocyclic heteroaryl having 1 or 2 ring members independently selected from N and NR⁹, wherein the monocyclic heteroaryl is unsubstituted;
- (ii) 5- membered heterocycloalkyl wherein one ring member is S(=O)₂, S(=O) or S(=O)(=NH), and wherein the heterocycloalkyl is unsubstituted or is substituted with a substituent selected from OH and methyl;
- 30 (iii) 6-membered heterocycloalkyl wherein one ring member is S(=O)₂ or S(=O), and one other ring member is selected from N, NR⁹ and O, and wherein the heterocycloalkyl is unsubstituted or is substituted with a methyl,
- (iv) a partially saturated 6-membered heterocyclyl having 1 or 2 ring members 35 independently selected from N, NR⁹, O and S, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with an oxo;

- (v) a partially saturated 6-membered heterocyclyl wherein one ring member is $S(=O)_2$ and one other ring member is selected from N, NR^9 , and O, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with an oxo;
- (vi) a 5- or 6- membered monocyclic heteroaryl having 1, 2, 3 or 4 ring members independently selected from N, NR^9 and O, wherein the monocyclic heteroaryl is unsubstituted or is substituted with a substituent selected from -OH methoxy and methyl;
- (vii) a 6- membered fused bicyclic heterocyclyl having 1 ring member selected from N and NR^9 , wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with an oxo;
- (viii) a partially saturated 10- membered fused bicyclic heterocyclyl having 1, 2, or 3 ring members independently selected from N, NR^9 , and O, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with an oxo;
- (ix) a 7- membered spiro bicyclic heterocycloalkyl having 1 ring member selected from N, NR^9 , and O, wherein the spiro bicyclic heterocycloalkyl is unsubstituted;
- (x) a 6- membered heterocycloalkyl having 1 to 2 ring members independently selected from N, NR^9 and O, wherein the heterocycloalkyl has a C_1 - C_3 alkyl bridge or a $-CH_2OCH_2-$ bridge;
- (xi) phenyl which is substituted with $-S(=O)_2NH_2$;
- or
- (xii) cyclobutyl, cyclopentyl, or cyclohexyl which is substituted with 1, 2 or 3 substituents independently selected from -OH, $-NH_2$, $-S(=O)_2CH_3$, $-CH_2NH_2$, F, and methoxy;

and

R^9 is H, methyl, benzyl, $-C(=O)CH_3$, $-C(=O)O(CH_3)_3$, CH_2CH_2OH or $CH_2CH_2OCH_3$.

- In an embodiment of compounds of Formula (I-a) and Formula (I-b), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof:

$-X=Y-$ is $-CR^x=CR^y-$ or $-CR^x=N-$;

R^x is H;

- R^y is H, D, halogen or $-CN$;

R^5 is halogen or $-CN$;

each R^1 is independently selected from the group consisting of halogen, C_1 - C_4 alkyl, C_1 -

C_4 fluoroalkyl and pentafluorosulfanyl;

L_1 is $-(CR^2R^3)_p-$, $-NR^4(CR^2R^3)_q-$ or $-O-(CR^2R^3)_p-$;

- R^2 is H;

R^3 is H, OH or C_1 - C_4 alkyl;

R^4 is H or C_1 - C_4 alkyl;

p is 1;

- q is 0;
- Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is N;
- or Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is CR^z;
- or Z₁ is C, Z₂ is CR^z, Z₃ is N, Z₄ is N and Z₅ is CR^z;
- 5 or Z₁ is C, Z₂ is N, Z₃ is N, Z₄ is N and Z₅ is CR^z;
- each R^z is H;
- L₂ is a bond, -(CR⁶R⁷)_n- or -(CR⁶R⁷)_nO-*, where the * indicates the point of attachment to R⁶;
- each R⁶ is independently selected from the group consisting of H, C₁-C₄alkyl, and C₁-C₄hydroxyalkyl;
- 10 each R⁷ is independently selected from the group consisting of H, C₁-C₄alkyl, and C₁-C₄hydroxyalkyl;
- n is 1 or 2;
- R⁸ is:
- (i) 4-, 5- or 6-membered heterocycloalkyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2 or 3 substituents each independently selected from -OH, -CN, -N(R¹⁰)₂, halogen, C₁-C₄fluoroalkyl, C₁-C₄alkyl, C₁-C₄alkoxy, oxo and a 5- or 6-membered monocyclic heteroaryl having 1 or 2 ring members independently selected from N and NR⁹, wherein the monocyclic heteroaryl is unsubstituted;
 - 15 (ii) 5- membered heterocycloalkyl wherein one ring member is S(=O)₂, S(=O) or S(=O)(=NH), and wherein the heterocycloalkyl is unsubstituted or is substituted with a substituent selected from -OH and C₁-C₄alkyl;
 - (iii) 6-membered heterocycloalkyl wherein one ring member is S(=O)₂ or S(=O), and one other ring member is selected from N, NR⁹ and O, and wherein the heterocycloalkyl is unsubstituted or is substituted with a substituent selected from C₁-C₄alkyl;
 - 20 (iv) a partially saturated 6-membered heterocyclyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with an oxo;
 - (v) a partially saturated 6-membered heterocyclyl wherein one ring member is S(=O)₂ and one other ring member is selected from N, NR⁹, and O, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with an oxo;
 - 25 (vi) a 5- or 6- membered monocyclic heteroaryl having 1, 2, 3 or 4 ring members independently selected from N, NR⁹ and O, wherein the monocyclic heteroaryl is unsubstituted or is substituted with a substituent selected from -OH, C₁-C₄alkoxy and C₁-C₄alkyl;
 - 30 (vii) a 6- membered fused bicyclic heterocyclyl having 1 ring member selected from N and NR⁹, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with an oxo;
 - 35

- (viii) a partially saturated 10- membered fused bicyclic heterocyclyl having 1, 2, or 3 ring members independently selected from N, NR⁹, and O, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with an oxo;
- (ix) a 7- membered spiro bicyclic heterocycloalkyl having 1 ring member selected from N, NR⁹, and O, wherein the spiro bicyclic heterocycloalkyl is unsubstituted;
- (x) a 6- membered heterocycloalkyl having 1 to 2 ring members independently selected from N, NR⁹ and O, wherein the heterocycloalkyl has a C₁-C₃alkyl bridge or a -CH₂OCH₂- bridge;
- (xi) phenyl which is substituted with -S(=O)₂N(R¹⁰)₂;
- or
- (xii) C₄-C₈cycloalkyl which is substituted with 1, 2 or 3 substituents independently selected from -OH, -N(R¹⁰)₂, -S(=O)₂R¹⁰, C₁-C₄alkyl-NH₂, halogen and C₁-C₄alkoxy;
- R⁹ is H, C₁-C₄alkyl, benzyl, C₁-C₄alkyl-OR¹⁰, -C(=O)OR¹⁰ or -C(=O)R¹⁰, and
- R¹⁰ is H or C₁-C₄alkyl.

In an embodiment of compounds of Formula (I-a) and Formula (I-b), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof:

-X=Y- is -CR^x=CR^y- or -CR^x=N-;

R^x is H;

R^y is H, F or CN;

R⁵ is F or CN;

each R¹ is independently selected from the group consisting of F, Cl, methyl, -CF₃, and SF₅;

L₁ is -(CR²R³)_p-, -NR⁴(CR²R³)_q- or -O-(CR²R³)_p-;

R² is H;

R³ is H, OH or methyl;

R⁴ is H, methyl or ethyl;

p is 1;

q is 0;

Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is N;

or Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is CR^z;

or Z₁ is C, Z₂ is CR^z, Z₃ is N, Z₄ is N and Z₅ is CR^z;

or Z₁ is C, Z₂ is N, Z₃ is N, Z₄ is N and Z₅ is CR^z;

each R^z is H;

L₂ is a bond, -(CR⁶R⁷)_n- or -(CR⁶R⁷)_nO-*, where the * indicates the point of attachment to R⁶;

each R⁶ is independently selected from the group consisting of H, methyl and -CH₂OH;

each R⁷ is independently selected from the group consisting of H, methyl and -CH₂OH;

n is 1 or 2;

R⁸ is:

- (i) 4-, 5- or 6-membered heterocycloalkyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2 or 3 substituents each independently selected from -OH, -CN, NH₂, F, CF₃, methyl, methoxy, oxo and a 5- or 6- membered monocyclic heteroaryl having 1 or 2 ring members independently selected from N and NR⁹, wherein the monocyclic heteroaryl is unsubstituted;
- (ii) 5- membered heterocycloalkyl wherein one ring member is S(=O)₂, S(=O) or S(=O)(=NH), and wherein the heterocycloalkyl is unsubstituted or is substituted with a substituent selected from OH and methyl;
- (iii) 6-membered heterocycloalkyl wherein one ring member is S(=O)₂ or S(=O), and one other ring member is selected from N, NR⁹ and O, and wherein the heterocycloalkyl is unsubstituted or is substituted with a methyl,
- (iv) a partially saturated 6-membered heterocyclyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with an oxo;
- (v) a partially saturated 6-membered heterocyclyl wherein one ring member is S(=O)₂ and one other ring member is selected from N, NR⁹, and O, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with an oxo;
- (vi) a 5- or 6- membered monocyclic heteroaryl having 1, 2, 3 or 4 ring members independently selected from N, NR⁹ and O, wherein the monocyclic heteroaryl is unsubstituted or is substituted with a substituent selected from -OH methoxy and methyl;
- (vii) a 6- membered fused bicyclic heterocyclyl having 1 ring member selected from N and NR⁹, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with an oxo;
- (viii) a partially saturated 10- membered fused bicyclic heterocyclyl having 1, 2, or 3 ring members independently selected from N, NR⁹, and O, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with an oxo;
- (ix) a 7- membered spiro bicyclic heterocycloalkyl having 1 ring member selected from N, NR⁹, and O, wherein the spiro bicyclic heterocycloalkyl is unsubstituted;
- (x) a 6- membered heterocycloalkyl having 1 to 2 ring members independently selected from N, NR⁹ and O, wherein the heterocycloalkyl has a C₁-C₃alkyl bridge or a -CH₂OCH₂- bridge;
- (xi) phenyl which is substituted with -S(=O)₂NH₂;
or
- (xii) cyclobutyl, cyclopentyl, or cyclohexyl which is substituted with 1, 2 or 3 substituents independently selected from -OH, -NH₂, -S(=O)₂CH₃, -CH₂NH₂, F, and methoxy;

and

R⁹ is H, methyl, benzyl, -C(=O)CH₃, -C(=O)O(CH₃)₃, CH₂CH₂OH or CH₂CH₂OCH₃.

In an embodiment of compounds of Formula (I-a) and Formula (I-b), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof:

-X=Y- is -CR^x=N-;

R^x is H;

R⁵ is halogen;

each R¹ is independently selected from the group consisting of halogen, C₁-C₄alkyl and C₁-

10 C₄fluoroalkyl

L₁ is -(CR²R³)_p-;

R² is H;

R³ is H, or C₁-C₄alkyl;

p is 1;

15 Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is N;

or Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is CR^z;

or Z₁ is C, Z₂ is CR^z, Z₃ is N, Z₄ is N and Z₅ is CR^z;

or Z₁ is C, Z₂ is N, Z₃ is N, Z₄ is N and Z₅ is CR^z;

each R^z is H;

20 L₂ is a bond or -(CR⁶R⁷)_n-;

each R⁶ is independently selected from the group consisting of H and C₁-C₄alkyl;

each R⁷ is independently selected from the group consisting of H and C₁-C₄alkyl;

n is 1 or 2;

R⁸ is:

- 25 (i) 4-, 5- or 6-membered heterocycloalkyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2 or 3 substituents each independently selected from -OH, halogen, C₁-C₄fluoroalkyl, C₁-C₄alkyl, and oxo;
- 30 (ii) 5- membered heterocycloalkyl wherein one ring member is S(=O)₂, or S(=O)(=NH), and wherein the heterocycloalkyl is unsubstituted or is substituted with a substituent selected from C₁-C₄alkyl;
- (iii) 6-membered heterocycloalkyl wherein one ring member is S(=O)₂ or S(=O), and one other ring member is selected from N, NR⁹ and O, and wherein the heterocycloalkyl is unsubstituted or is substituted with a substituent selected from C₁-C₄alkyl;
- 35 (iv) a partially saturated 6-membered heterocyclyl having 1 or 2 ring members independently selected from O and S, wherein the partially saturated heterocyclyl is unsubstituted;

- (v) a partially saturated 6-membered heterocyclyl wherein one ring member is $S(=O)_2$ and one other ring member is O, wherein the partially saturated heterocyclyl is unsubstituted;
- (vi) a 5- membered monocyclic heteroaryl having 3 ring members independently selected from N, and O, wherein the monocyclic heteroaryl is unsubstituted;
- (vii) a 6- membered fused bicyclic heterocyclyl having 1 ring member selected from NR^9 , wherein the fused bicyclic heterocyclyl is unsubstituted;
- (viii) a 7- membered spiro bicyclic heterocycloalkyl having 1 ring member selected from N, NR^9 , and O, wherein the spiro bicyclic heterocycloalkyl is unsubstituted;
- (ix) a 6- membered heterocycloalkyl having 1 ring members selected from NR^9 , wherein the heterocycloalkyl has a C_1 - C_3 alkyl bridge;
- or
- (x) C_4 - C_8 cycloalkyl which is substituted with 1, 2 or 3 substituents independently selected from -OH, $-N(R^{10})_2$, C_1 - C_4 alkyl- NH_2 and halogen;
- R^9 is H, C_1 - C_4 alkyl, or $-C(=O)R^{10}$,
and
 R^{10} is H or C_1 - C_4 alkyl.

- In an embodiment of compounds of Formula (I-a) and Formula (I-b), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof:
- X=Y- is $-CR^x=N-$;
 R^x is H;
 R^5 is F;
each R^1 is independently selected from the group consisting of F, Cl, methyl and $-CF_3$;
- L_1 is $-(CR^2R^3)_p-$,
 R^2 is H;
 R^3 is H or methyl;
 p is 1;
 Z_1 is N, Z_2 is CR^z , Z_3 is N, Z_4 is C and Z_5 is N;
or Z_1 is N, Z_2 is CR^z , Z_3 is N, Z_4 is C and Z_5 is CR^z ;
or Z_1 is C, Z_2 is CR^z , Z_3 is N, Z_4 is N and Z_5 is CR^z ;
or Z_1 is C, Z_2 is N, Z_3 is N, Z_4 is N and Z_5 is CR^z ;
each R^z is H;
 L_2 is a bond or $-(CR^6R^7)_n-$;
each R^6 is independently selected from the group consisting of H and methyl;
each R^7 is independently selected from the group consisting of H and methyl;
 n is 1 or 2;
 R^8 is:

- (i) 4-, 5- or 6-membered heterocycloalkyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2 or 3 substituents each independently selected from -OH, F, CF₃, methyl and oxo;
- 5 (ii) 5- membered heterocycloalkyl wherein one ring member is S(=O)₂ or S(=O)(=NH), and wherein the heterocycloalkyl is unsubstituted or is substituted with a methyl;
- (iii) 6-membered heterocycloalkyl wherein one ring member is S(=O)₂ or S(=O), and one other ring member is selected from N, NR⁹ and O, and wherein the heterocycloalkyl is unsubstituted or is substituted with a methyl,
- 10 (iv) a partially saturated 6-membered heterocyclyl having 1 or 2 ring members independently selected from O and S, wherein the partially saturated heterocyclyl is unsubstituted;
- (v) a partially saturated 6-membered heterocyclyl wherein one ring member is S(=O)₂ and one other ring member is and O, wherein the partially saturated heterocyclyl is
- 15 unsubstituted;
- (vi) a 5- membered monocyclic heteroaryl having 3 ring members independently selected from N and O, wherein the monocyclic heteroaryl is unsubstituted;
- (vii) a 6- membered fused bicyclic heterocyclyl having 1 ring member selected from NR⁹, wherein the fused bicyclic heterocyclyl is unsubstituted;
- 20 (viii) a 7- membered spiro bicyclic heterocycloalkyl having 1 ring member selected from NR⁹, and O, wherein the spiro bicyclic heterocycloalkyl is unsubstituted;
- (ix) a 6- membered heterocycloalkyl having 1 ring members selected from NR⁹, wherein the heterocycloalkyl has a C₁-C₃alkyl bridge;
- or
- 25 (x) cyclobutyl, cyclopentyl, or cyclohexyl which is substituted with 1, 2 or 3 substituents independently selected from -OH, -NH₂, -CH₂NH₂, and F;

and

R⁹ is H, methyl or -C(=O)CH₃.

30 In an embodiment of compounds of Formula (I-a) and Formula (I-b), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof:

-X=Y- is -CR^x=N-;

R^x is H;

R⁵ is halogen;

35 each R¹ is independently selected from the group consisting of halogen, C₁-C₄alkyl and C₁-C₄fluoroalkyl

L₁ is -(CR²R³)_p-;

R² is H;

- R³ is H, or C₁-C₄alkyl;
 p is 1;
 Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is N;
 or Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is CR^z;
- 5 each R^z is H;
 L₂ is a bond or -(CR⁶R⁷)_n;
 each R⁶ is independently selected from the group consisting of H and C₁-C₄alkyl;
 each R⁷ is independently selected from the group consisting of H and C₁-C₄alkyl;
 n is 1 or 2;
- 10 R⁸ is:
- (i) 4-, 5- or 6-membered heterocycloalkyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2 or 3 substituents each independently selected from -OH, halogen, C₁-C₄fluoroalkyl, C₁-C₄alkyl, and oxo;
 - 15 (ii) 5- membered heterocycloalkyl wherein one ring member is S(=O)₂, or S(=O)(=NH), and wherein the heterocycloalkyl is unsubstituted or is substituted with a substituent selected from C₁-C₄alkyl;
 - (iii) 6-membered heterocycloalkyl wherein one ring member is S(=O)₂ or S(=O), and one other ring member is selected from N, NR⁹ and O, and wherein the heterocycloalkyl is unsubstituted or is substituted with a substituent selected from C₁-C₄alkyl;
 - 20 (iv) a partially saturated 6-membered heterocyclyl having 1 or 2 ring members independently selected from O and S, wherein the partially saturated heterocyclyl is unsubstituted;
 - (v) a partially saturated 6-membered heterocyclyl wherein one ring member is S(=O)₂ and one other ring member is O, wherein the partially saturated heterocyclyl is unsubstituted;
 - 25 (vi) a 5- membered monocyclic heteroaryl having 3 ring members independently selected from N, and O, wherein the monocyclic heteroaryl is unsubstituted;
 - (vii) a 6- membered fused bicyclic heterocyclyl having 1 ring member selected from NR⁹, wherein the fused bicyclic heterocyclyl is unsubstituted;
 - 30 (viii) a 7- membered spiro bicyclic heterocycloalkyl having 1 ring member selected from N, NR⁹, and O, wherein the spiro bicyclic heterocycloalkyl is unsubstituted;
 - (ix) a 6- membered heterocycloalkyl having 1 ring members selected from NR⁹, wherein the heterocycloalkyl has a C₁-C₃alkyl bridge;
 - 35 or
 - (x) C₄-C₈cycloalkyl which is substituted with 1, 2 or 3 substituents independently selected from -OH, -N(R¹⁰)₂, C₁-C₄alkyl-NH₂ and halogen;
- R⁹ is H, C₁-C₄alkyl, or -C(=O)R¹⁰,

and

R¹⁰ is H or C₁-C₄alkyl.

In an embodiment of compounds of Formula (I-a) and Formula (I-b), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof:

-X=Y- is -CR^x=N-;

R^x is H;

R⁵ is F;

each R¹ is independently selected from the group consisting of F, Cl, methyl and -CF₃;

10 L₁ is -(CR²R³)_p-;

R² is H;

R³ is H or methyl;

p is 1;

Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is N;

15 or Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is CR^z;

each R^z is H;

L₂ is a bond or -(CR⁶R⁷)_n-;

each R⁶ is independently selected from the group consisting of H and methyl;

each R⁷ is independently selected from the group consisting of H and methyl;

20 n is 1 or 2;

R⁸ is:

- (i) 4-, 5- or 6-membered heterocycloalkyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2 or 3 substituents each independently selected from -OH, F, CF₃, methyl and oxo;
- 25 (ii) 5- membered heterocycloalkyl wherein one ring member is S(=O)₂ or S(=O)(=NH), and wherein the heterocycloalkyl is unsubstituted or is substituted with a methyl;
- (iii) 6-membered heterocycloalkyl wherein one ring member is S(=O)₂ or S(=O), and one other ring member is selected from N, NR⁹ and O, and wherein the heterocycloalkyl is unsubstituted or is substituted with a methyl,
- 30 (iv) a partially saturated 6-membered heterocyclyl having 1 or 2 ring members independently selected from O and S, wherein the partially saturated heterocyclyl is unsubstituted;
- (v) a partially saturated 6-membered heterocyclyl wherein one ring member is S(=O)₂ and one other ring member is and O, wherein the partially saturated heterocyclyl is unsubstituted;
- 35 (vi) a 5- membered monocyclic heteroaryl having 3 ring members independently selected from N and O, wherein the monocyclic heteroaryl is unsubstituted;

- (vii) a 6- membered fused bicyclic heterocyclyl having 1 ring member selected from NR^9 , wherein the fused bicyclic heterocyclyl is unsubstituted;
- (viii) a 7- membered spiro bicyclic heterocycloalkyl having 1 ring member selected from NR^9 , and O, wherein the spiro bicyclic heterocycloalkyl is unsubstituted;
- 5 (ix) a 6- membered heterocycloalkyl having 1 ring members selected from NR^9 , wherein the heterocycloalkyl has a $\text{C}_1\text{-C}_3$ alkyl bridge;
- or
- (x) cyclobutyl, cyclopentyl, or cyclohexyl which is substituted with 1, 2 or 3 substituents independently selected from -OH, - NH_2 , - CH_2NH_2 , and F;

10 and

R^9 is H, methyl or $-\text{C}(=\text{O})\text{CH}_3$.

In an embodiment of compounds of Formula (I-a) and Formula (I-b), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof:

15 $-\text{X}=\text{Y}-$ is $-\text{CR}^x=\text{N}-$;

R^x is H;

R^5 is halogen;

each R^1 is independently selected from the group consisting of halogen, $\text{C}_1\text{-C}_4$ alkyl and $\text{C}_1\text{-C}_4$ fluoroalkyl;

20 L_1 is $-(\text{CR}^2\text{R}^3)_p-$;

R^2 is H;

R^3 is H;

p is 1;

Z_1 is N, Z_2 is CR^z , Z_3 is N, Z_4 is C and Z_5 is N;

25 each R^z is H;

L_2 is a bond;

R^8 is pyrrolidinyl which is substituted with 1 or 2 each independently selected from halogen and $\text{C}_1\text{-C}_4$ fluoroalkyl.

30 In an embodiment of compounds of Formula (I-a) and Formula (I-b), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof:

$-\text{X}=\text{Y}-$ is $-\text{CR}^x=\text{N}-$;

R^x is H;

R^5 is F;

35 each R^1 is independently selected from the group consisting of F, Cl, methyl, and CF_3 ;

L_1 is $-(\text{CR}^2\text{R}^3)_p-$;

R^2 is H;

R^3 is H;

p is 1;

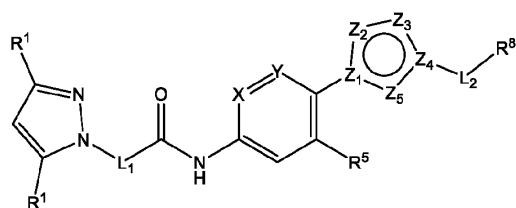
Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is N;

each R^z is H;

L₂ is a bond;

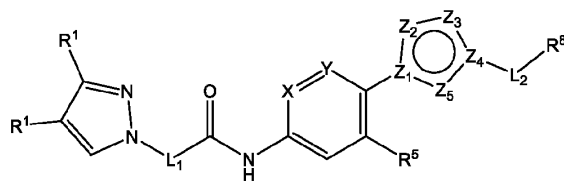
- 5 R⁸ is pyrrolidinyl which is substituted with 1 or 2 each independently selected from F and CF₃.

In any one of the aforementioned embodiments the compound of Formula (I) is a compound of Formula (I-a), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof:



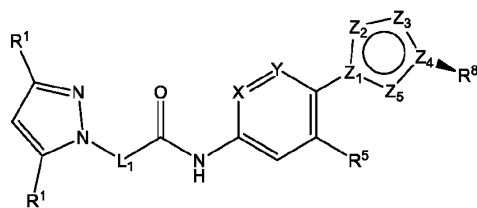
(I-a).

- 10 In any one of the aforementioned embodiments the compound of Formula (I) is a compound of Formula (I-b), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof:

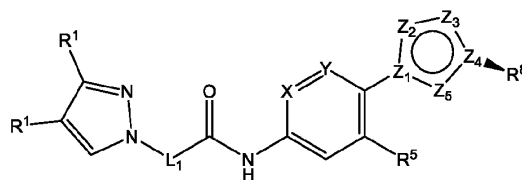


(I-b).

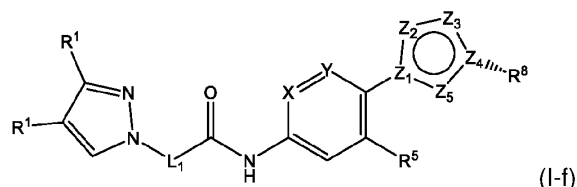
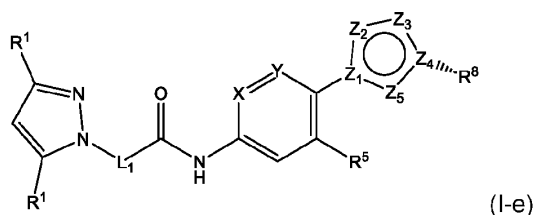
- 15 In an embodiment of compounds of Formula (I), the compounds provided herein are compounds of Formula (I-c), Formula (I-d), Formula (I-e) or Formula (I-f), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof:



(I-c)



(I-d)



wherein:

-X=Y- is -CR^x=CR^y-, -CR^x=N- or -N=CR^y-;

5 R^x is H, D, halogen or C₁-C₄alkyl;

R^y is H, D, halogen, -CN, C₁-C₄alkyl, C₁-C₄fluoroalkyl or C₁-C₄alkoxy;

R⁵ is H, halogen, -CN, C₁-C₄alkyl, C₁-C₄fluoroalkyl or C₁-C₄alkoxy;

each R¹ is independently selected from the group consisting of halogen, C₁-C₄alkyl, C₂-

10 C₄alkenyl, C₂-C₄alkynyl, C₁-C₄alkoxy, C₁-C₄alkoxycarbonyl, C₃-C₆cycloalkyl, C₁-C₄fluoroalkyl, C₁-C₄fluoroalkoxy, pentafluorosulfanyl, C₁-C₄hydroxyalkyl, C₁-C₄thioalkyl, azido, diC₁-C₄alkylamino, diC₁-C₄alkylaminocarbonyl, D, CD₃, cyano, formyl, phenyl and a 5- to 6-membered heterocycloalkyl comprising 1 or 2 ring members independently selected from N, NR⁴, O and S;

15 L₁ is -(CR²R³)_p-, -(CR²R³)_p-NR⁴-, -(CR²R³)_p-O-, -NR⁴(CR²R³)_q-, -(CR²R³)_qNR⁴-, -O-(CR²R³)_p- or -S-(CR²R³)_p-;

R² is H, D, halogen or C₁-C₄alkyl;

R³ is H, D, halogen, C₁-C₄alkyl, C₁-C₄alkoxy, OH, amino or *t*-Boc-amino;

or R² and R³, together with the C atom to which they are attached, are linked to form C₃-

20 C₄cycloalkyl which is unsubstituted or is substituted with a single substituent selected from C₁-C₄alkyl and oxo;

each R⁴ is independently selected from the group consisting of H and C₁-C₄alkyl;

p is 1, 2 or 3;

q is 0, 1 or 2;

Z₁ is N or C; Z₂ is N or CR^z; Z₃ is N or CR^z; Z₄ is N or C; Z₅ is N or CR^z;

25 wherein each R^z is independently selected from the group consisting of H, halogen, C₁-C₄alkyl and C₁-C₄fluoroalkyl; and provided that at least two, and not more than four, of Z₁, Z₂, Z₃, Z₄ and Z₅ are N;

each R⁶ is independently selected from the group consisting of H, C₁-C₄alkyl, C₁-C₄fluoroalkyl and C₁-C₄hydroxyalkyl;

each R⁷ is independently selected from the group consisting of H, C₁-C₄alkyl, C₁-C₄fluoroalkyl and C₁-C₄hydroxyalkyl;

or R⁶ and R⁷, together with the C atom to which they are attached, are linked to form C₃-

C₆cycloalkyl, oxetanyl, tetrahydrofuranlyl or tetrahydropyranyl;

5 n is 1, 2 or 3;

R⁸ is:

- (i) 4-, 5- or 6-membered heterocycloalkyl having 1, 2 or 3 ring members independently selected from N, NR⁹, O and S, wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents each independently selected from -OH, -CN, -N(R¹⁰)₂, halogen, C₁-C₄fluoroalkyl, C₁-C₄alkyl, C₁-C₄alkoxy, oxo and a 5- or 6- membered monocyclic heteroaryl having 1, 2, 3 or 4 ring members independently selected from N, NR⁹, O and S, wherein the monocyclic heteroaryl is unsubstituted;
- 10 (ii) 4-, 5- or 6-membered heterocycloalkyl wherein one ring member is S(=O)₂, S(=O) or S(=O)(=NH), and wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from -OH, C₁-C₄alkyl and oxo;
- 15 (iii) 4-, 5- or 6-membered heterocycloalkyl wherein one ring member is S(=O)₂ or S(=O), and 1, 2 or 3 other ring members are independently selected from N, NR⁹ and O, and wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents each independently selected from C₁-C₄alkyl and oxo;
- 20 (iv) a partially saturated 5- or 6-membered heterocyclyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents independently selected from -OH, C₁-C₄alkyl, and oxo;
- 25 (v) a partially saturated 5- or 6-membered heterocyclyl wherein one ring member is S(=O)₂ and 1, 2 or 3 other ring members are independently selected from N, NR⁹, O and S, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents independently selected from -OH, C₁-C₄alkyl, and oxo;
- 30 (vi) a 5- or 6- membered monocyclic heteroaryl having 1, 2, 3 or 4 ring members independently selected from N, NR⁹, O and S, wherein the monocyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents each independently selected from -OH, C₁-C₄alkoxy and C₁-C₄alkyl;
- 35 (vii) a 6- or 7-membered fused bicyclic heterocyclyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from -OH, -N(R¹⁰)₂, C₁-C₄alkyl-NH₂, halogen, C₁-C₄alkyl, and oxo;
- (viii) a partially saturated 8-, 9-, 10-, 11- or 12-membered fused bicyclic heterocyclyl having 1, 2, 3 or 4 ring members independently selected from N, NR⁹, O and S, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4

- substituents, each independently selected from -OH, -N(R¹⁰)₂, C₁-C₄alkyl-NH₂, halogen, C₁-C₄alkyl, and oxo;
- (ix) a 6-, 7-, 8-, 9- or 10- membered spiro bicyclic heterocycloalkyl having 1, 2 or 3 ring members independently selected from N, NR⁹, O and S, wherein the spiro bicyclic heterocycloalkyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from -OH, -N(R¹⁰)₂, C₁-C₄alkyl-NH₂, halogen, C₁-C₄alkyl, and oxo;
- (x) a 6- membered heterocycloalkyl having 1 to 2 ring members independently selected from N, NR⁹, O and S, wherein the heterocycloalkyl has a C₁-C₃alkyl bridge or a -CH₂OCH₂- bridge;
- (xi) phenyl which is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from -S(=O)₂N(R¹⁰)₂, -OH, -N(R¹⁰)₂, C₁-C₄alkyl-NH₂, halogen and C₁-C₄alkyl;
- or
- (xii) C₄-C₈cycloalkyl which is unsubstituted or is substituted with 1, 2, 3 or 4 substituents independently selected from -OH, -N(R¹⁰)₂, -S(=O)₂R¹⁰, C₁-C₄alkyl-NH₂, halogen, C₁-C₄alkoxy, C₁-C₄alkyl, and oxo;
- R⁹ is H, C₁-C₄alkyl, benzyl, C₁-C₄alkyl-OR¹⁰, -C(=O)OR¹⁰ or -C(=O)R¹⁰, and
- R¹⁰ is H or C₁-C₄alkyl.

In an embodiment of compounds of Formula (I-c), Formula (I-d), Formula (I-e) or Formula (I-f), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof:

-X=Y- is -CR^x=CR^y-, -CR^x=N- or -N=CR^y-;

- R^x is H, D, halogen or C₁-C₄alkyl;
- R^y is H, D, halogen, -CN, C₁-C₄alkyl, C₁-C₄fluoroalkyl or C₁-C₄alkoxy;
- R⁵ is H, halogen, -CN, C₁-C₄alkyl, C₁-C₄fluoroalkyl or C₁-C₄alkoxy;
- each R¹ is independently selected from the group consisting of halogen, C₁-C₄alkyl, C₂-C₄alkenyl, C₂-C₄alkynyl, C₁-C₄alkoxy, C₁-C₄alkoxycarbonyl, C₃-C₆cycloalkyl, C₁-C₄fluoroalkyl, C₁-C₄fluoroalkoxy, pentafluorosulfanyl, C₁-C₄hydroxyalkyl, C₁-C₄thioalkyl, azido, diC₁-C₄alkylamino, diC₁-C₄alkylaminocarbonyl, D, CD₃, cyano, formyl, phenyl and a 5- to 6-membered heterocycloalkyl comprising 1 or 2 ring members independently selected from N, NR⁴, O and S;
- L₁ is -(CR²R³)_p-, -(CR²R³)_p-NR⁴-, -(CR²R³)_p-O-, -NR⁴(CR²R³)_q-, -(CR²R³)_qNR⁴-, -O-(CR²R³)_p- or -S-(CR²R³)_p-;
- R² is H, D, halogen or C₁-C₄alkyl;
- R³ is H, D, halogen, C₁-C₄alkyl, C₁-C₄alkoxy, OH, amino or *t*-Boc-amino;

- or R² and R³, together with the C atom to which they are attached, are linked to form C₃-C₄cycloalkyl which is unsubstituted or is substituted with a single substituent selected from C₁-C₄alkyl and oxo;
- each R⁴ is independently selected from the group consisting of H and C₁-C₄alkyl;
- 5 p is 1, 2 or 3;
- q is 0, 1 or 2;
- Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is N;
- or Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is CR^z;
- or Z₁ is C, Z₂ is CR^z, Z₃ is N, Z₄ is N and Z₅ is CR^z;
- 10 or Z₁ is C, Z₂ is N, Z₃ is N, Z₄ is N and Z₅ is CR^z;
- or Z₁ is N, Z₂ is CR^z, Z₃ is CR^z, Z₄ is C and Z₅ is N;
- each R^z is independently selected from the group consisting of H, halogen, C₁-C₄alkyl and C₁-C₄fluoroalkyl;
- each R⁶ is independently selected from the group consisting of H, C₁-C₄alkyl, C₁-C₄fluoroalkyl
- 15 and C₁-C₄hydroxyalkyl;
- each R⁷ is independently selected from the group consisting of H, C₁-C₄alkyl, C₁-C₄fluoroalkyl and C₁-C₄hydroxyalkyl;
- or R⁶ and R⁷, together with the C atom to which they are attached, are linked to form C₃-C₆cycloalkyl, oxetanyl, tetrahydrofuranyl or tetrahydropyranyl;
- 20 n is 1, 2 or 3;
- R⁸ is:
- (i) 4-, 5- or 6-membered heterocycloalkyl having 1, 2 or 3 ring members independently selected from N, NR⁹, O and S, wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents each independently selected from -OH, -CN, -N(R¹⁰)₂, halogen, C₁-C₄fluoroalkyl, C₁-C₄alkyl, C₁-C₄alkoxy, oxo and a 5- or 6- membered monocyclic heteroaryl having 1, 2, 3 or 4 ring members independently selected from N, NR⁹, O and S, wherein the monocyclic heteroaryl is unsubstituted;
- 25
- (ii) 4-, 5- or 6-membered heterocycloalkyl wherein one ring member is S(=O)₂, S(=O) or S(=O)(=NH), and wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from -OH, C₁-C₄alkyl and oxo;
- 30
- (iii) 4-, 5- or 6-membered heterocycloalkyl wherein one ring member is S(=O)₂ or S(=O), and 1, 2 or 3 other ring members are independently selected from N, NR⁹ and O, and wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents each independently selected from C₁-C₄alkyl and oxo;
- 35
- (iv) a partially saturated 5- or 6-membered heterocyclyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents independently selected from -OH, C₁-C₄alkyl, and oxo;

- (v) a partially saturated 5- or 6-membered heterocyclyl wherein one ring member is $S(=O)_2$ and 1, 2 or 3 other ring members are independently selected from N, NR^9 , O and S, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents independently selected from -OH, C_1 - C_4 alkyl, and oxo;
- 5 (vi) a 5- or 6- membered monocyclic heteroaryl having 1, 2, 3 or 4 ring members independently selected from N, NR^9 , O and S, wherein the monocyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents each independently selected from -OH, C_1 - C_4 alkoxy and C_1 - C_4 alkyl;
- 10 (vii) a 6- or 7-membered fused bicyclic heterocyclyl having 1 or 2 ring members independently selected from N, NR^9 , O and S, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from -OH, $-N(R^{10})_2$, C_1 - C_4 alkyl- NH_2 , halogen, C_1 - C_4 alkyl, and oxo;
- 15 (viii) a partially saturated 8-, 9-, 10-, 11- or 12-membered fused bicyclic heterocyclyl having 1, 2, 3 or 4 ring members independently selected from N, NR^9 , O and S, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from -OH, $-N(R^{10})_2$, C_1 - C_4 alkyl- NH_2 , halogen, C_1 - C_4 alkyl, and oxo;
- 20 (ix) a 6-, 7-, 8-, 9- or 10- membered spiro bicyclic heterocycloalkyl having 1, 2 or 3 ring members independently selected from N, NR^9 , O and S, wherein the spiro bicyclic heterocycloalkyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from -OH, $-N(R^{10})_2$, C_1 - C_4 alkyl- NH_2 , halogen, C_1 - C_4 alkyl, and oxo;
- 25 (x) a 6- membered heterocycloalkyl having 1 to 2 ring members independently selected from N, NR^9 , O and S, wherein the heterocycloalkyl has a C_1 - C_3 alkyl bridge or a $-CH_2OCH_2-$ bridge;
- (xi) phenyl which is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from $-S(=O)_2N(R^{10})_2$, -OH, $-N(R^{10})_2$, C_1 - C_4 alkyl- NH_2 , halogen and C_1 - C_4 alkyl;
- or
- 30 (xii) C_4 - C_8 cycloalkyl which is unsubstituted or is substituted with 1, 2, 3 or 4 substituents independently selected from -OH, $-N(R^{10})_2$, $-S(=O)_2R^{10}$, C_1 - C_4 alkyl- NH_2 , halogen, C_1 - C_4 alkoxy, C_1 - C_4 alkyl, and oxo;
- R^9 is H, C_1 - C_4 alkyl, benzyl, C_1 - C_4 alkyl- OR^{10} , $-C(=O)OR^{10}$ or $-C(=O)R^{10}$,
and
- 35 R^{10} is H or C_1 - C_4 alkyl.

In an embodiment of compounds of Formula (I-c), Formula (I-d), Formula (I-e) or Formula (I-f), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof:

- X=Y- is -CR^x=CR^y-, -CR^x=N- or -N=CR^y-;
 R^x is H, D or halogen;
 R^y is H, D, halogen or -CN;
 R⁵ is halogen or -CN;
- 5 each R¹ is independently selected from the group consisting of halogen, D, CD₃, C₁-C₄alkyl, C₁-C₄fluoroalkyl, C₁-C₄fluoroalkoxy, C₃-C₆cycloalkyl and pentafluorosulfanyl;
 L₁ is -(CR²R³)_p-, -NR⁴(CR²R³)_q- or -O-(CR²R³)_p-;
 R² is H, D or halogen;
 R³ is H, D, halogen, OH or C₁-C₄alkyl;
- 10 or R² and R³, together with the C atom to which they are attached, are linked to form C₃-C₄cycloalkyl which is unsubstituted
 R⁴ is H or C₁-C₄alkyl;
 p is 1;
 q is 0;
- 15 Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is N;
 or Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is CR^z;
 or Z₁ is C, Z₂ is CR^z, Z₃ is N, Z₄ is N and Z₅ is CR^z;
 or Z₁ is C, Z₂ is N, Z₃ is N, Z₄ is N and Z₅ is CR^z;
 each R^z is H;
- 20 each R⁶ is independently selected from the group consisting of H, C₁-C₄alkyl, C₁-C₄fluoroalkyl and C₁-C₄hydroxyalkyl;
 each R⁷ is independently selected from the group consisting of H, C₁-C₄alkyl, C₁-C₄fluoroalkyl and C₁-C₄hydroxyalkyl;
 or R⁶ and R⁷, together with the C atom to which they are attached, are linked to form
- 25 tetrahydropyranyl;
 n is 1 or 2;
 R⁸ is:
- (i) 4-, 5- or 6-membered heterocycloalkyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2 or 3 substituents each independently selected from -OH, -CN, -N(R¹⁰)₂, halogen, C₁-C₄fluoroalkyl, C₁-C₄alkyl, C₁-C₄alkoxy, oxo and a 5- or 6- membered monocyclic heteroaryl having 1 or 2 ring members independently selected from N and NR⁹, wherein the monocyclic heteroaryl is unsubstituted;
- 30 (ii) 5- membered heterocycloalkyl wherein one ring member is S(=O)₂, S(=O) or S(=O)(=NH), and wherein the heterocycloalkyl is unsubstituted or is substituted with a substituent selected from -OH and C₁-C₄alkyl;
- 35

- (iii) 6-membered heterocycloalkyl wherein one ring member is $S(=O)_2$ or $S(=O)$, and one other ring member is selected from N, NR^9 and O, and wherein the heterocycloalkyl is unsubstituted or is substituted with a substituent selected from C_1 - C_4 alkyl;
 - (iv) a partially saturated 6-membered heterocyclyl having 1 or 2 ring members independently selected from N, NR^9 , O and S, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with an oxo;
 - (v) a partially saturated 6-membered heterocyclyl wherein one ring member is $S(=O)_2$ and one other ring member is selected from N, NR^4 , and O, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with an oxo;
 - (vi) a 5- or 6- membered monocyclic heteroaryl having 1, 2, 3 or 4 ring members independently selected from N, NR^9 and O, wherein the monocyclic heteroaryl is unsubstituted or is substituted with a substituent selected from -OH, C_1 - C_4 alkoxy and C_1 - C_4 alkyl;
 - (vii) a 6- membered fused bicyclic heterocyclyl having 1 ring member selected from N and NR^9 , wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with an oxo;
 - (viii) a partially saturated 10- membered fused bicyclic heterocyclyl having 1, 2, or 3 ring members independently selected from N, NR^9 , and O, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with an oxo;
 - (ix) a 7- membered spiro bicyclic heterocycloalkyl having 1 ring member selected from N, NR^9 , and O, wherein the spiro bicyclic heterocycloalkyl is unsubstituted;
 - (x) a 6- membered heterocycloalkyl having 1 to 2 ring members independently selected from N, NR^9 and O, wherein the heterocycloalkyl has a C_1 - C_3 alkyl bridge or a - CH_2OCH_2 - bridge;
 - (xi) phenyl which is substituted with $-S(=O)_2N(R^{10})_2$;
or
 - (xii) C_4 - C_8 cycloalkyl which is substituted with 1, 2 or 3 substituents independently selected from -OH, $-N(R^{10})_2$, $-S(=O)_2R^{10}$, C_1 - C_4 alkyl- NH_2 , halogen and C_1 - C_4 alkoxy;
- R^9 is H, C_1 - C_4 alkyl, benzyl, C_1 - C_4 alkyl- OR^{10} , $-C(=O)OR^{10}$ or $-C(=O)R^{10}$,
- and
- R^{10} is H or C_1 - C_4 alkyl.

In an embodiment of compounds of Formula (I-c), Formula (I-d), Formula (I-e) or Formula (I-f), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof:

- X=Y- is $-CR^x=CR^y-$, $-CR^x=N-$ or $-N=CR^y-$;
- R^x is H or F;
- R^y is H, F or CN;
- R^5 is F, Cl or CN;

- each R^1 is independently selected from the group consisting of F, Cl, Br, methyl, isopropyl, t-butyl, cyclopropyl, $-CF_3$, CHF_2 , CF_2CF_3 , OCF_3 , and SF_5 ;
- L_1 is $-(CR^2R^3)_p-$, $-NR^4(CR^2R^3)_q-$ or $-O-(CR^2R^3)_p-$;
- R^2 is H or F;
- 5 R^3 is H, OH, F or methyl;
- or R^2 and R^3 , together with the C atom to which they are attached, are linked to form cyclopropyl which is unsubstituted;
- R^4 is H, methyl or ethyl;
- p is 1;
- 10 q is 0;
- Z_1 is N, Z_2 is CR^z , Z_3 is N, Z_4 is C and Z_5 is N;
- or Z_1 is N, Z_2 is CR^z , Z_3 is N, Z_4 is C and Z_5 is CR^z ;
- or Z_1 is C, Z_2 is CR^z , Z_3 is N, Z_4 is N and Z_5 is CR^z ;
- or Z_1 is C, Z_2 is N, Z_3 is N, Z_4 is N and Z_5 is CR^z ;
- 15 each R^z is H;
- each R^6 is independently selected from the group consisting of H, methyl, isopropyl, $-CH_2OH$ and CH_2CF_3 ;
- each R^7 is independently selected from the group consisting of H, methyl, isopropyl, $-CH_2OH$ and CH_2CF_3 ;
- 20 or R^6 and R^7 , together with the C atom to which they are attached, are linked to form tetrahydropyranyl;
- n is 1 or 2;
- R^8 is:
- (i) 4-, 5- or 6-membered heterocycloalkyl having 1 or 2 ring members independently
- 25 selected from N, NR^9 , O and S, wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2 or 3 substituents each independently selected from $-OH$, $-CN$, NH_2 , F, CF_3 , methyl, methoxy, oxo and a 5- or 6- membered monocyclic heteroaryl having 1 or 2 ring members independently selected from N and NR^9 , wherein the monocyclic heteroaryl is unsubstituted;
- (ii) 5- membered heterocycloalkyl wherein one ring member is $S(=O)_2$, $S(=O)$ or $S(=O)(=NH)$, and wherein the heterocycloalkyl is unsubstituted or is substituted with a
- 30 substituent selected from OH and methyl;
- (iii) 6-membered heterocycloalkyl wherein one ring member is $S(=O)_2$ or $S(=O)$, and one other ring member is selected from N, NR^9 and O, and wherein the heterocycloalkyl is
- 35 unsubstituted or is substituted with a methyl,
- (iv) a partially saturated 6-membered heterocyclyl having 1 or 2 ring members independently selected from N, NR^9 , O and S, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with an oxo;

- (v) a partially saturated 6-membered heterocyclyl wherein one ring member is $S(=O)_2$ and one other ring member is selected from N, NR^9 , and O, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with an oxo;
- (vi) a 5- or 6- membered monocyclic heteroaryl having 1, 2, 3 or 4 ring members independently selected from N, NR^9 and O, wherein the monocyclic heteroaryl is unsubstituted or is substituted with a substituent selected from -OH methoxy and methyl;
- (vii) a 6- membered fused bicyclic heterocyclyl having 1 ring member selected from N and NR^9 , wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with an oxo;
- (viii) a partially saturated 10- membered fused bicyclic heterocyclyl having 1, 2, or 3 ring members independently selected from N, NR^9 , and O, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with an oxo;
- (ix) a 7- membered spiro bicyclic heterocycloalkyl having 1 ring member selected from N, NR^9 , and O, wherein the spiro bicyclic heterocycloalkyl is unsubstituted;
- (x) a 6- membered heterocycloalkyl having 1 to 2 ring members independently selected from N, NR^9 and O, wherein the heterocycloalkyl has a C_1 - C_3 alkyl bridge or a $-CH_2OCH_2-$ bridge;
- (xi) phenyl which is substituted with $-S(=O)_2NH_2$;
- or
- (xii) cyclobutyl, cyclopentyl, or cyclohexyl which is substituted with 1, 2 or 3 substituents independently selected from -OH, $-NH_2$, $-S(=O)_2CH_3$, $-CH_2NH_2$, F, and methoxy;

and

R^9 is H, methyl, benzyl, $-C(=O)CH_3$, $-C(=O)O(CH_3)_3$, CH_2CH_2OH or $CH_2CH_2OCH_3$.

- In an embodiment of compounds of Formula (I-c), Formula (I-d), Formula (I-e) or Formula (I-f), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof:

$-X=Y-$ is $-CR^x=CR^y-$ or $-CR^x=N-$;

R^x is H;

- R^y is H, D, halogen or $-CN$;

R^5 is halogen or $-CN$;

each R^1 is independently selected from the group consisting of halogen, C_1 - C_4 alkyl, C_1 -

C_4 fluoroalkyl and pentafluorosulfanyl;

L_1 is $-(CR^2R^3)_p-$, $-NR^4(CR^2R^3)_q-$ or $-O-(CR^2R^3)_p-$;

- R^2 is H;

R^3 is H, OH or C_1 - C_4 alkyl;

R^4 is H or C_1 - C_4 alkyl;

p is 1;

q is 0;

Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is N;

or Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is CR^z;

or Z₁ is C, Z₂ is CR^z, Z₃ is N, Z₄ is N and Z₅ is CR^z;

5 or Z₁ is C, Z₂ is N, Z₃ is N, Z₄ is N and Z₅ is CR^z;

each R^z is H;

each R⁶ is independently selected from the group consisting of H, C₁-C₄alkyl, and C₁-

C₄hydroxyalkyl;

each R⁷ is independently selected from the group consisting of H, C₁-C₄alkyl, and C₁-

10 C₄hydroxyalkyl;

n is 1 or 2;

R⁸ is:

- (i) 4-, 5- or 6-membered heterocycloalkyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2 or 3 substituents each independently selected from -OH, -CN, -N(R¹⁰)₂, halogen, C₁-C₄fluoroalkyl, C₁-C₄alkyl, C₁-C₄alkoxy, oxo and a 5- or 6- membered monocyclic heteroaryl having 1 or 2 ring members independently selected from N and NR⁹, wherein the monocyclic heteroaryl is unsubstituted;
- 15 (ii) 5- membered heterocycloalkyl wherein one ring member is S(=O)₂, S(=O) or S(=O)(=NH), and wherein the heterocycloalkyl is unsubstituted or is substituted with a substituent selected from -OH and C₁-C₄alkyl;
- (iii) 6-membered heterocycloalkyl wherein one ring member is S(=O)₂ or S(=O), and one other ring member is selected from N, NR⁹ and O, and wherein the heterocycloalkyl is unsubstituted or is substituted with a substituent selected from C₁-C₄alkyl;
- 25 (iv) a partially saturated 6-membered heterocyclyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with an oxo;
- (v) a partially saturated 6-membered heterocyclyl wherein one ring member is S(=O)₂ and one other ring member is selected from N, NR⁴, and O, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with an oxo;
- 30 (vi) a 5- or 6- membered monocyclic heteroaryl having 1, 2, 3 or 4 ring members independently selected from N, NR⁹ and O, wherein the monocyclic heteroaryl is unsubstituted or is substituted with a substituent selected from -OH, C₁-C₄alkoxy and C₁-C₄alkyl;
- 35 (vii) a 6- membered fused bicyclic heterocyclyl having 1 ring member selected from N and NR⁹, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with an oxo;

- (viii) a partially saturated 10- membered fused bicyclic heterocyclyl having 1, 2, or 3 ring members independently selected from N, NR⁹, and O, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with an oxo;
- (ix) a 7- membered spiro bicyclic heterocycloalkyl having 1 ring member selected from N, NR⁹, and O, wherein the spiro bicyclic heterocycloalkyl is unsubstituted;
- (x) a 6- membered heterocycloalkyl having 1 to 2 ring members independently selected from N, NR⁹ and O, wherein the heterocycloalkyl has a C₁-C₃alkyl bridge or a -CH₂OCH₂- bridge;
- (xi) phenyl which is substituted with -S(=O)₂N(R¹⁰)₂;
- or
- (xii) C₄-C₈cycloalkyl which is substituted with 1, 2 or 3 substituents independently selected from -OH, -N(R¹⁰)₂, -S(=O)₂R¹⁰, C₁-C₄alkyl-NH₂, halogen and C₁-C₄alkoxy;
- R⁹ is H, C₁-C₄alkyl, benzyl, C₁-C₄alkyl-OR¹⁰, -C(=O)OR¹⁰ or -C(=O)R¹⁰, and
- R¹⁰ is H or C₁-C₄alkyl.

In an embodiment of compounds of Formula (I-c), Formula (I-d), Formula (I-e) or Formula (I-f), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof:

-X=Y- is -CR^x=CR^y- or -CR^x=N-;

R^x is H;

R^y is H, F or CN;

R⁵ is F or CN;

each R¹ is independently selected from the group consisting of F, Cl, methyl, -CF₃, and SF₅;

L₁ is -(CR²R³)_p-, -NR⁴(CR²R³)_q- or -O-(CR²R³)_p-;

R² is H;

R³ is H, OH or methyl;

R⁴ is H, methyl or ethyl;

p is 1;

q is 0;

Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is N;

or Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is CR^z;

or Z₁ is C, Z₂ is CR^z, Z₃ is N, Z₄ is N and Z₅ is CR^z;

or Z₁ is C, Z₂ is N, Z₃ is N, Z₄ is N and Z₅ is CR^z;

each R^z is H;

each R⁶ is independently selected from the group consisting of H, methyl and -CH₂OH;

each R⁷ is independently selected from the group consisting of H, methyl and -CH₂OH;

n is 1 or 2;

R⁸ is:

- (i) 4-, 5- or 6-membered heterocycloalkyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2 or 3 substituents each independently selected from -OH, -CN, NH₂, F, CF₃, methyl, methoxy, oxo and a 5- or 6- membered monocyclic heteroaryl having 1 or 2 ring members independently selected from N and NR⁹, wherein the monocyclic heteroaryl is unsubstituted;
- (ii) 5- membered heterocycloalkyl wherein one ring member is S(=O)₂, S(=O) or S(=O)(=NH), and wherein the heterocycloalkyl is unsubstituted or is substituted with a substituent selected from OH and methyl;
- (iii) 6-membered heterocycloalkyl wherein one ring member is S(=O)₂ or S(=O), and one other ring member is selected from N, NR⁹ and O, and wherein the heterocycloalkyl is unsubstituted or is substituted with a methyl,
- (iv) a partially saturated 6-membered heterocyclyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with an oxo;
- (v) a partially saturated 6-membered heterocyclyl wherein one ring member is S(=O)₂ and one other ring member is selected from N, NR⁹, and O, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with an oxo;
- (vi) a 5- or 6- membered monocyclic heteroaryl having 1, 2, 3 or 4 ring members independently selected from N, NR⁹ and O, wherein the monocyclic heteroaryl is unsubstituted or is substituted with a substituent selected from -OH methoxy and methyl;
- (vii) a 6- membered fused bicyclic heterocyclyl having 1 ring member selected from N and NR⁹, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with an oxo;
- (viii) a partially saturated 10- membered fused bicyclic heterocyclyl having 1, 2, or 3 ring members independently selected from N, NR⁹, and O, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with an oxo;
- (ix) a 7- membered spiro bicyclic heterocycloalkyl having 1 ring member selected from N, NR⁹, and O, wherein the spiro bicyclic heterocycloalkyl is unsubstituted;
- (x) a 6- membered heterocycloalkyl having 1 to 2 ring members independently selected from N, NR⁹ and O, wherein the heterocycloalkyl has a C₁-C₃alkyl bridge or a -CH₂OCH₂- bridge;
- (xi) phenyl which is substituted with -S(=O)₂NH₂;
- or
- (xii) cyclobutyl, cyclopentyl, or cyclohexyl which is substituted with 1, 2 or 3 substituents independently selected from -OH, -NH₂, -S(=O)₂CH₃, -CH₂NH₂, F, and methoxy;

and

R⁹ is H, methyl, benzyl, -C(=O)CH₃, -C(=O)O(CH₃)₃, CH₂CH₂OH or CH₂CH₂OCH₃.

In an embodiment of compounds of Formula (I-c), Formula (I-d), Formula (I-e) or Formula (I-f), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof:

- 5 -X=Y- is -CR^x=N-;
R^x is H;
R⁵ is halogen;
each R¹ is independently selected from the group consisting of halogen, C₁-C₄alkyl and C₁-C₄fluoroalkyl
- 10 L₁ is -(CR²R³)_p-;
R² is H;
R³ is H, or C₁-C₄alkyl;
p is 1;
Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is N;
15 or Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is CR^z;
or Z₁ is C, Z₂ is CR^z, Z₃ is N, Z₄ is N and Z₅ is CR^z;
or Z₁ is C, Z₂ is N, Z₃ is N, Z₄ is N and Z₅ is CR^z;
each R^z is H;
each R⁶ is independently selected from the group consisting of H and C₁-C₄alkyl;
20 each R⁷ is independently selected from the group consisting of H and C₁-C₄alkyl;
n is 1 or 2;
R⁸ is:
(i) 4-, 5- or 6-membered heterocycloalkyl having 1 or 2 ring members independently
selected from N, NR⁹, O and S, wherein the heterocycloalkyl is unsubstituted or is
25 substituted with 1, 2 or 3 substituents each independently selected from -OH, halogen,
C₁-C₄fluoroalkyl, C₁-C₄alkyl, and oxo;
(ii) 5- membered heterocycloalkyl wherein one ring member is S(=O)₂, or S(=O)(=NH),
and wherein the heterocycloalkyl is unsubstituted or is substituted with a substituent
selected from C₁-C₄alkyl;
30 (iii) 6-membered heterocycloalkyl wherein one ring member is S(=O)₂ or S(=O), and one
other ring member is selected from N, NR⁹ and O, and wherein the heterocycloalkyl is
unsubstituted or is substituted with a substituent selected from C₁-C₄alkyl;
(iv) a partially saturated 6-membered heterocyclyl having 1 or 2 ring members
independently selected from O and S, wherein the partially saturated heterocyclyl is
35 unsubstituted;
(v) a partially saturated 6-membered heterocyclyl wherein one ring member is S(=O)₂ and
one other ring member is O, wherein the partially saturated heterocyclyl is
unsubstituted;

- (vi) a 5- membered monocyclic heteroaryl having 3 ring members independently selected from N, and O, wherein the monocyclic heteroaryl is unsubstituted;
- (vii) a 6- membered fused bicyclic heterocyclyl having 1 ring member selected from NR^9 , wherein the fused bicyclic heterocyclyl is unsubstituted;
- 5 (viii) a 7- membered spiro bicyclic heterocycloalkyl having 1 ring member selected from N, NR^9 , and O, wherein the spiro bicyclic heterocycloalkyl is unsubstituted;
- (ix) a 6- membered heterocycloalkyl having 1 ring members selected from NR^9 , wherein the heterocycloalkyl has a $\text{C}_1\text{-C}_3$ alkyl bridge;
- or
- 10 (x) $\text{C}_4\text{-C}_8$ cycloalkyl which is substituted with 1, 2 or 3 substituents independently selected from $-\text{OH}$, $-\text{N}(\text{R}^{10})_2$, $\text{C}_1\text{-C}_4$ alkyl- NH_2 and halogen;
- R^9 is H, $\text{C}_1\text{-C}_4$ alkyl, or $-\text{C}(=\text{O})\text{R}^{10}$,
and
 R^{10} is H or $\text{C}_1\text{-C}_4$ alkyl.
- 15 In an embodiment of compounds of Formula (I-c), Formula (I-d), Formula (I-e) or Formula (I-f), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof:
- $-\text{X}=\text{Y}-$ is $-\text{CR}^x=\text{N}-$;
- R^x is H;
- 20 R^5 is F;
- each R^1 is independently selected from the group consisting of F, Cl, methyl and $-\text{CF}_3$;
- L_1 is $-(\text{CR}^2\text{R}^3)_p-$,
- R^2 is H;
- R^3 is H or methyl;
- 25 p is 1;
- Z_1 is N, Z_2 is CR^z , Z_3 is N, Z_4 is C and Z_5 is N;
- or Z_1 is N, Z_2 is CR^z , Z_3 is N, Z_4 is C and Z_5 is CR^z ;
- or Z_1 is C, Z_2 is CR^z , Z_3 is N, Z_4 is N and Z_5 is CR^z ;
- or Z_1 is C, Z_2 is N, Z_3 is N, Z_4 is N and Z_5 is CR^z ;
- 30 each R^z is H;
- each R^6 is independently selected from the group consisting of H and methyl;
- each R^7 is independently selected from the group consisting of H and methyl;
- n is 1 or 2;
- R^8 is:
- 35 (i) 4-, 5- or 6-membered heterocycloalkyl having 1 or 2 ring members independently selected from N, NR^9 , O and S, wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2 or 3 substituents each independently selected from $-\text{OH}$, F, CF_3 , methyl and oxo;

- (ii) 5- membered heterocycloalkyl wherein one ring member is $S(=O)_2$ or $S(=O)(=NH)$, and wherein the heterocycloalkyl is unsubstituted or is substituted with a methyl;
- (iii) 6-membered heterocycloalkyl wherein one ring member is $S(=O)_2$ or $S(=O)$, and one other ring member is selected from N, NR^9 and O, and wherein the heterocycloalkyl is unsubstituted or is substituted with a methyl,
- (iv) a partially saturated 6-membered heterocyclyl having 1 or 2 ring members independently selected from O and S, wherein the partially saturated heterocyclyl is unsubstituted;
- (v) a partially saturated 6-membered heterocyclyl wherein one ring member is $S(=O)_2$ and one other ring member is and O, wherein the partially saturated heterocyclyl is unsubstituted;
- (vi) a 5- membered monocyclic heteroaryl having 3 ring members independently selected from N and O, wherein the monocyclic heteroaryl is unsubstituted;
- (vii) a 6- membered fused bicyclic heterocyclyl having 1 ring member selected from NR^9 , wherein the fused bicyclic heterocyclyl is unsubstituted;
- (viii) a 7- membered spiro bicyclic heterocycloalkyl having 1 ring member selected from NR^9 , and O, wherein the spiro bicyclic heterocycloalkyl is unsubstituted;
- (ix) a 6- membered heterocycloalkyl having 1 ring members selected from NR^9 , wherein the heterocycloalkyl has a C_1 - C_3 alkyl bridge;
- or
- (x) cyclobutyl, cyclopentyl, or cyclohexyl which is substituted with 1, 2 or 3 substituents independently selected from -OH, - NH_2 , - CH_2NH_2 , and F;

and

R^9 is H, methyl or $-C(=O)CH_3$.

- In an embodiment of compounds of Formula (I-c), Formula (I-d), Formula (I-e) or Formula (I-f), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof:

$-X=Y-$ is $-CR^x=N-$;

R^x is H;

- R^5 is halogen;

each R^1 is independently selected from the group consisting of halogen, C_1 - C_4 alkyl and C_1 - C_4 fluoroalkyl

L_1 is $-(CR^2R^3)_p-$;

R^2 is H;

- R^3 is H, or C_1 - C_4 alkyl;

p is 1;

Z_1 is N, Z_2 is CR^z , Z_3 is N, Z_4 is C and Z_5 is N;

or Z_1 is N, Z_2 is CR^z , Z_3 is N, Z_4 is C and Z_5 is CR^z ;

each R^z is H;

each R^6 is independently selected from the group consisting of H and C_1 - C_4 alkyl;

each R^7 is independently selected from the group consisting of H and C_1 - C_4 alkyl;

n is 1 or 2;

5 R^8 is:

- (i) 4-, 5- or 6-membered heterocycloalkyl having 1 or 2 ring members independently selected from N, NR^9 , O and S, wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2 or 3 substituents each independently selected from -OH, halogen, C_1 - C_4 fluoroalkyl, C_1 - C_4 alkyl, and oxo;
- 10 (ii) 5- membered heterocycloalkyl wherein one ring member is $S(=O)_2$, or $S(=O)(=NH)$, and wherein the heterocycloalkyl is unsubstituted or is substituted with a substituent selected from C_1 - C_4 alkyl;
- (iii) 6-membered heterocycloalkyl wherein one ring member is $S(=O)_2$ or $S(=O)$, and one other ring member is selected from N, NR^9 and O, and wherein the heterocycloalkyl is
15 unsubstituted or is substituted with a substituent selected from C_1 - C_4 alkyl;
- (iv) a partially saturated 6-membered heterocyclyl having 1 or 2 ring members independently selected from O and S, wherein the partially saturated heterocyclyl is unsubstituted;
- (v) a partially saturated 6-membered heterocyclyl wherein one ring member is $S(=O)_2$ and
20 one other ring member is O, wherein the partially saturated heterocyclyl is unsubstituted;
- (vi) a 5- membered monocyclic heteroaryl having 3 ring members independently selected from N, and O, wherein the monocyclic heteroaryl is unsubstituted;
- (vii) a 6- membered fused bicyclic heterocyclyl having 1 ring member selected from NR^9 ,
25 wherein the fused bicyclic heterocyclyl is unsubstituted;
- (viii) a 7- membered spiro bicyclic heterocycloalkyl having 1 ring member selected from N, NR^9 , and O, wherein the spiro bicyclic heterocycloalkyl is unsubstituted;
- (ix) a 6- membered heterocycloalkyl having 1 ring members selected from NR^9 , wherein the heterocycloalkyl has a C_1 - C_3 alkyl bridge;
- 30 or
- (x) C_4 - C_8 cycloalkyl which is substituted with 1, 2 or 3 substituents independently selected from -OH, $-N(R^{10})_2$, C_1 - C_4 alkyl- NH_2 and halogen;

R^9 is H, C_1 - C_4 alkyl, or $-C(=O)R^{10}$,

and

35 R^{10} is H or C_1 - C_4 alkyl.

In an embodiment of compounds of Formula (I-c), Formula (I-d), Formula (I-e) or Formula (I-f), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof:

-X=Y- is -CR^x=N-;

R^x is H;

R⁵ is F;

each R¹ is independently selected from the group consisting of F, Cl, methyl and -CF₃;

5 L₁ is -(CR²R³)_p-;

R² is H;

R³ is H or methyl;

p is 1;

Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is N;

10 or Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is CR^z;

each R^z is H;

each R⁶ is independently selected from the group consisting of H and methyl;

each R⁷ is independently selected from the group consisting of H and methyl;

n is 1 or 2;

15 R⁸ is:

(i) 4-, 5- or 6-membered heterocycloalkyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2 or 3 substituents each independently selected from -OH, F, CF₃, methyl and oxo;

20 (ii) 5- membered heterocycloalkyl wherein one ring member is S(=O)₂ or S(=O)(=NH), and wherein the heterocycloalkyl is unsubstituted or is substituted with a methyl;

(iii) 6-membered heterocycloalkyl wherein one ring member is S(=O)₂ or S(=O), and one other ring member is selected from N, NR⁹ and O, and wherein the heterocycloalkyl is unsubstituted or is substituted with a methyl,

25 (iv) a partially saturated 6-membered heterocyclyl having 1 or 2 ring members independently selected from O and S, wherein the partially saturated heterocyclyl is unsubstituted;

(v) a partially saturated 6-membered heterocyclyl wherein one ring member is S(=O)₂ and one other ring member is and O, wherein the partially saturated heterocyclyl is unsubstituted;

30 (vi) a 5- membered monocyclic heteroaryl having 3 ring members independently selected from N and O, wherein the monocyclic heteroaryl is unsubstituted;

(vii) a 6- membered fused bicyclic heterocyclyl having 1 ring member selected from NR⁹, wherein the fused bicyclic heterocyclyl is unsubstituted;

35 (viii) a 7- membered spiro bicyclic heterocycloalkyl having 1 ring member selected from NR⁹, and O, wherein the spiro bicyclic heterocycloalkyl is unsubstituted;

(ix) a 6- membered heterocycloalkyl having 1 ring members selected from NR⁹, wherein the heterocycloalkyl has a C₁-C₃alkyl bridge;

or

(x) cyclobutyl, cyclopentyl, or cyclohexyl which is substituted with 1, 2 or 3 substituents independently selected from -OH, -NH₂, -CH₂NH₂, and F;

and

5 R⁹ is H, methyl or -C(=O)CH₃.

In an embodiment of compounds of Formula (I-c), Formula (I-d), Formula (I-e) or Formula (I-f), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof:

-X=Y- is -CR^x=N-;

10 R^x is H;

R⁵ is halogen;

each R¹ is independently selected from the group consisting of halogen, C₁-C₄alkyl and C₁-C₄fluoroalkyl;

L₁ is -(CR²R³)_p-;

15 R² is H;

R³ is H;

p is 1;

Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is N;

each R^z is H;

20 R⁸ is pyrrolidinyl which is substituted with 1 or 2 each independently selected from halogen and C₁-C₄fluoroalkyl.

In an embodiment of compounds of Formula (I-c) and Formula (I-d), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof:

25 -X=Y- is -CR^x=N-;

R^x is H;

R⁵ is F;

each R¹ is independently selected from the group consisting of F, Cl, methyl, and CF₃;

L₁ is -(CR²R³)_p-;

30 R² is H;

R³ is H;

p is 1;

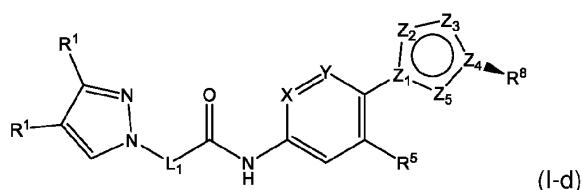
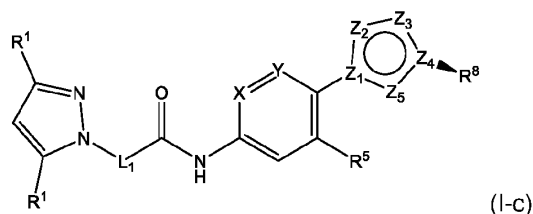
Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is N;

each R^z is H;

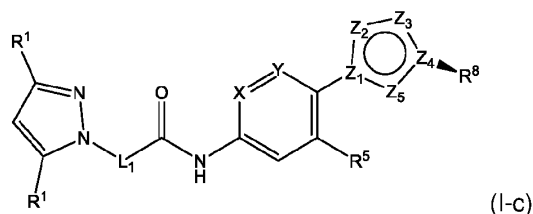
35 R⁸ is pyrrolidinyl which is substituted with 1 or 2 each independently selected from F and CF₃.

In any one of the aforementioned embodiments the compound of Formula (I) is a compound of Formula (I-c) or Formula (I-d), or a stereoisomer thereof, or a pharmaceutically acceptable

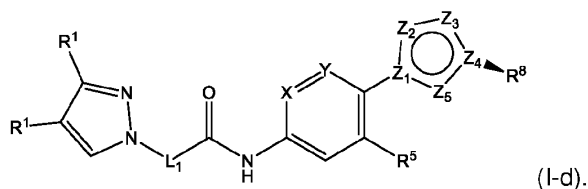
salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof:



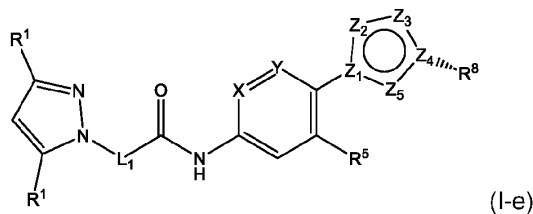
In any one of the aforementioned embodiments the compound of Formula (I) is a compound of Formula (I-c), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof:



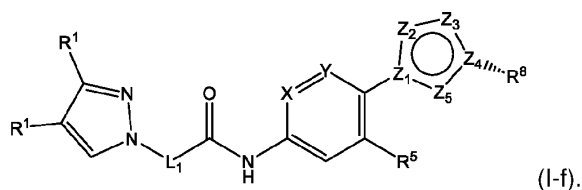
In any one of the aforementioned embodiments the compound of Formula (I) is a compound of Formula (I-d), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof:



In any one of the aforementioned embodiments the compound of Formula (I) is a compound of Formula (I-e), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof:



In any one of the aforementioned embodiments the compound of Formula (I) is a compound of Formula (I-f), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof:



In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, -X=Y- is -CR^x=CR^y-, -CR^x=N- or -N=CR^y-.

- 5 In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, -X=Y- is -CR^x=N- or -N=CR^y-.

- In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, -X=Y- is -CR^x=N-.
- 10

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, -X=Y- is -N=CR^y-.

- In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, -X=Y- is -N=CR^y-;
- 15

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^x is H, D, halogen or C₁-C₄alkyl.

- 20 In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^x is H.

- In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^x is D.
- 25

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^x is halogen. In certain embodiments, R^x is F.

- 30 In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^x is C₁-C₄alkyl. In certain embodiments, R^x is methyl or ethyl.

- In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^x is H, D, F or methyl.
- 35

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^x is H or F.

5 In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^x is H, D or F.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^y is H, D, halogen, CN, C₁-C₄alkyl, C₁-C₄fluoroalkyl
10 or C₁-C₄alkoxy.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^y is H, D, halogen or CN.

15 In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^y is H, halogen or CN.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^y is H, F or CN.

20 In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^y is H.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^y is D.
25

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^y is halogen. In certain embodiments, R^y is F.

30 In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^y is C₁-C₄alkyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^y is C₁-C₄fluoroalkyl.

35 In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^y is C₁-C₄alkoxy.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a

stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁵ is H, halogen, C₁-C₄alkyl, C₁-C₄fluoroalkyl or C₁-C₄alkoxy.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁵ is H, halogen or CN.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁵ is H, F, Cl or CN.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁵ is H.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁵ is halogen. In certain embodiments, R⁵ is F or Cl. In other embodiments, R⁵ is F.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁵ is C₁-C₄alkyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁵ is C₁-C₄fluoroalkyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁵ is C₁-C₄alkoxy.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, each R¹ is independently selected from the group consisting of halogen, C₁-C₄alkyl, C₂-C₄alkenyl, C₂-C₄alkynyl, C₁-C₄alkoxy, C₁-C₄alkoxycarbonyl, C₃-C₆cycloalkyl, C₁-C₄fluoroalkyl, C₁-C₄fluoroalkoxy, pentafluorosulfanyl, C₁-C₄hydroxyalkyl, C₁-C₄thioalkyl, azido, diC₁-C₄alkylamino, diC₁-C₄alkylaminocarbonyl, D, CD₃, cyano, formyl, phenyl and a 5- to 6-membered heterocycloalkyl comprising 1 or 2 ring members independently selected from N, NR⁴, O and S.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, each R¹ is independently selected from the group consisting of halogen, D, CD₃, C₁-C₄alkyl, C₃-C₆cycloalkyl, C₁-C₄fluoroalkyl, C₁-C₄fluoroalkoxy and pentafluorosulfanyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, each R¹ is independently selected from the group consisting of halogen, C₁-C₄alkyl, C₃-C₆cycloalkyl, C₁-C₄fluoroalkyl, C₁-C₄fluoroalkoxy and pentafluorosulfanyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, each R¹ is independently selected from the group consisting of halogen, C₁-C₄alkyl, C₁-C₄fluoroalkyl and pentafluorosulfanyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, each R¹ is independently selected from halogen. In certain embodiments, each R¹ is independently selected from F, Cl or Br. In other embodiments, R¹ is F or Cl. In other embodiments, R¹ is F. In other embodiments, R¹ is Cl. In other

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, each R¹ is independently selected from C₁-C₄alkyl. In certain embodiments, each R¹ is independently selected from methyl, ethyl, isopropyl, and t-butyl. In other embodiments, each R¹ is independently selected from methyl, isopropyl, and t-butyl. In other embodiments, each R¹ is methyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, each R¹ is independently selected from C₃-C₆cycloalkyl. In certain embodiments, R¹ is cyclopropyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R¹ is -CD₃.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R¹ is D.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, each R¹ is independently selected from C₁-C₄fluoroalkyl. In certain embodiments, each R¹ is independently selected from -CF₃, -CHF₂, and -CF₂CF₃. In certain embodiments, each R¹ is -CF₃.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, each R¹ is independently selected from C₁-C₄fluoroalkyl.

acceptable salt of a stereoisomer thereof, each R^1 is independently selected from C_1 - C_4 fluoroalkoxy. In certain embodiments, each R^1 is independently selected from $-OCF_3$, $-OCHF_2$, and $-OCF_2CF_3$. In other embodiments, R^1 is $-OCF_3$.

In an embodiment of compounds of Formula (I) or Formula (I-a), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^1 is pentafluorosulfanyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, each R^1 is independently selected from the group consisting of C_1 - C_4 alkyl, C_2 - C_4 alkenyl, C_2 - C_4 alkynyl, C_1 - C_4 hydroxyalkyl and C_1 - C_4 thioalkyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, each R^1 is independently selected from the group consisting of C_1 - C_4 alkoxy and C_1 - C_4 alkoxycarbonyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, each R^1 is independently selected from the group consisting of azido, diC_1 - C_4 alkylamino, diC_1 - C_4 alkylaminocarbonyl, cyano and formyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, each R^1 is independently selected from the group consisting of phenyl and a 5- to 6-membered heterocycloalkyl comprising 1 or 2 ring members independently selected from N, NR^4 , O and S.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, L_1 is a bond, $-(CR^2R^3)_p-$, $-(CR^2R^3)_p-NR^4-$, $-(CR^2R^3)_p-O-$, $-NR^4(CR^2R^3)_q-$, $-(CR^2R^3)_qNR^4-$, $-O-(CR^2R^3)_p-$ or $-S-(CR^2R^3)_p-$.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, L_1 is a bond, $-(CR^2R^3)_p-$, $-NR^4(CR^2R^3)_q-$ or $-O-(CR^2R^3)_p-$.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, L_1 is a bond.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, L_1 is $-(CR^2R^3)_p-$. In certain embodiments L_1 is $-CH_2-$, $-$

CH(OH), -CH(CH₃)-, -CF₂- or . In other embodiments L₁ is -CH₂-. In other embodiments

L₁ is -CH(CH₃)-. In other embodiments L₁ is -CH(OH)-. In other embodiments L₁ is . In other embodiments L₁ is -CF₂-.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, L₁ is -NR⁴-(CR²R³)_q- or -(CR²R³)_pNR⁴-. 5

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, L_1 is $-NR^4-(CR^3R^3)_q-$. In certain embodiments, L_1 is $-NR^4-$. In other embodiments L_1 is $-NH-$, $-N(CH_3)-$ or $-N(CH_2CH_3)-$. In other embodiments L_1 is $-NH-$. In other embodiments L_1 is $-N(CH_3)-$. In other embodiments L_1 is $-N(CH_2CH_3)-$.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, L₁ is -O-(CR²R³)_p-. In certain embodiments L₁ is-O-(CR²R³)_p-. In certain embodiments L₁ is -O-CH₂-.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, L_1 is $-(CR^2R^3)_p-O-$. In other embodiments L_1 is $-(CR^2R^3)-O-$. In other embodiments L_1 is $-CH_2-O-$.

20 In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, L₁ is a -(CR²R³)_p-NR⁴-. In other embodiments L₁ is -(CR²R³)-NR⁴-. In other embodiments L₁ is -CH₂-NR⁴-.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, L_1 is $-S-(CR^2R^3)_p-$. In certain embodiments L_1 is $-S-(CR^2R^3)-$. In certain embodiments L_1 is $-S-CH_2-$.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R² is H, D, halogen or C₁-C₄alkyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R² is H, halogen or C₁-C₄alkyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R² is H.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R² is D.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R² is halogen. In certain embodiments R² is F.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R³ is H, D, halogen, C₁-C₄alkyl C₁-C₄alkoxy, OH, amino or *t*-Boc-amino.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R³ is H, halogen, C₁-C₄alkyl C₁-C₄alkoxy, OH, amino or *t*-Boc-amino.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R³ is H, C₁-C₄alkyl or OH.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R³ is H.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R³ is D.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R³ is halogen. In certain embodiments R³ is F.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R³ is C₁-C₄alkyl. In certain embodiments R³ is methyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R³ is C₁-C₄alkoxy.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R³ is hydroxy.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R³ is amino.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R³ is *t*-Boc-amino.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R² is C₁-C₄alkyl. In certain embodiments R² is methyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R² and R³, together with the C atom to which they are attached, are linked to form C₃-C₄cycloalkyl which is unsubstituted or is substituted with a single substituent selected from C₁-C₄alkyl and oxo. In other embodiments R² and R³, together with the C atom to which they are attached, are linked to form C₃-C₄cycloalkyl which is unsubstituted.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, each R⁴ is independently selected from the group consisting of H and C₁-C₄alkyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁴ is H.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁴ is C₁-C₄alkyl. In other embodiments R⁴ is methyl or ethyl. In other embodiments R⁴ is methyl. In other embodiments R⁴ is ethyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, L₂ is a bond, -(CR⁶R⁷)_n- or -(CR⁶R⁷)_nO^{*}, where the * indicates the point of attachment to R⁸.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, L₂ is a bond.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, L₂ is -(CR⁶R⁷)_n- or -(CR⁶R⁷)_nO⁻.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, L₂ is -(CR⁶R⁷)_n-. In certain embodiments L₂ is -(CR⁶R⁷)-. In other embodiments L₂ is -CH₂- or -CH₂CH₂-. In other embodiments L₂ is -CH₂-. In other embodiments L₂ is -CH₂CH₂-. In other embodiments L₂ is -C(CH₃)₂-. In other embodiments

L₂ is -CH(CH₂OH)-.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, L₂ is -(CR⁶R⁷)_nO-*, where the * indicates the point of attachment to R⁸. In certain embodiments L₂ is -(CR⁶R⁷)O-. In other embodiments L₂ is -CH₂O- or -(CR⁶R⁷)O-*, where the * indicates the point of attachment to R⁸. In other embodiments L₂ is -CH₂O-. In other embodiments L₂ is -CH₂CH₂O-. In other embodiments L₂ is -C(CH₃)₂O-.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, each R⁶ is independently selected from the group consisting of H, C₁-C₄alkyl, C₁-C₄fluoroalkyl and C₁-C₄hydroxyalkyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁶ is H.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁶ is C₁-C₄alkyl. In other embodiments, R⁶ is methyl, ethyl or isopropyl. In other embodiments, R⁶ is methyl or isopropyl. In other embodiments, R⁶ is methyl. In other embodiments, R⁶ is isopropyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁶ is C₁-C₄fluoroalkyl. In other embodiments, R⁶ is -CF₃ or -CH₂CF₃. In other embodiments, R⁶ is -CH₂CF₃. In other embodiments, R⁶ is -CF₃.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁶ is C₁-C₄hydroxyalkyl. In certain embodiments R⁶ is -CH₂OH.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, each R⁷ is independently selected from the group consisting of H, C₁-C₄alkyl, C₁-C₄fluoroalkyl and C₁-C₄hydroxyalkyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁷ is H.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁷ is C₁-C₄alkyl. In other embodiments, R⁷ is methyl, ethyl or isopropyl. In other embodiments, R⁷ is methyl or isopropyl. In other embodiments, R⁷ is

methyl. In other embodiments, R⁷ is isopropyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁷ is C₁-C₄fluoroalkyl. In other embodiments, R⁷ is -

5 CF₃ or -CH₂CF₃. In other embodiments, R⁷ is -CH₂CF₃. In other embodiments, R⁷ is -CF₃.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁷ is C₁-C₄hydroxyalkyl. In certain embodiments R⁷ is -CH₂OH.

10 In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁶ and R⁷, together with the C atom to which they are attached, are linked to form C₃-C₆cycloalkyl, oxetanyl, tetrahydrofuranyl or tetrahydropyranyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁶ and R⁷, together with the C atom to which they are attached, are linked to form tetrahydropyranyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁶ and R⁷, together with the C atom to which they are attached, are linked to form C₃-C₆cycloalkyl. In certain embodiments R⁶ and R⁷, together with the C atom to which they are attached, are linked to form cyclopropyl. In certain embodiments R⁶ and R⁷, together with the C atom to which they are attached, are linked to form cyclobutyl. In certain embodiments R⁶ and R⁷, together with the C atom to which they are attached, are linked to form cyclopentyl. In certain embodiments R⁶ and R⁷, together with the C atom to which they are attached, are linked to form cyclohexyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁶ and R⁷, together with the C atom to which they are attached, are linked to form oxetanyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁶ and R⁷, together with the C atom to which they are attached, are linked to form tetrahydrofuranyl.

35 In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁸ is

- (i) 4-, 5- or 6-membered heterocycloalkyl having 1, 2 or 3 ring members independently selected from N, NR⁹, O and S, wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents each independently selected from -OH, -CN, -N(R¹⁰)₂, halogen, C₁-C₄fluoroalkyl, C₁-C₄alkyl, C₁-C₄alkoxy, oxo and a 5- or 6- membered monocyclic heteroaryl having 1, 2, 3 or 4 ring members independently selected from N, NR⁹, O and S, wherein the monocyclic heteroaryl is unsubstituted;
- (ii) 4-, 5- or 6-membered heterocycloalkyl wherein one ring member is S(=O)₂, S(=O) or S(=O)(=NH), and wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from -OH, C₁-C₄alkyl and oxo;
- (iii) 4-, 5- or 6-membered heterocycloalkyl wherein one ring member is S(=O)₂ or S(=O), and 1, 2 or 3 other ring members are independently selected from N, NR⁹ and O, and wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents each independently selected from C₁-C₄alkyl and oxo;
- (iv) a partially saturated 5- or 6-membered heterocyclyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents independently selected from -OH, C₁-C₄alkyl, and oxo;
- (v) a partially saturated 5- or 6-membered heterocyclyl wherein one ring member is S(=O)₂ and 1, 2 or 3 other ring members are independently selected from N, NR⁹, O and S, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents independently selected from -OH, C₁-C₄alkyl, and oxo;
- (vi) a 5- or 6- membered monocyclic heteroaryl having 1, 2, 3 or 4 ring members independently selected from N, NR⁹, O and S, wherein the monocyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents each independently selected from -OH, C₁-C₄alkoxy and C₁-C₄alkyl;
- (vii) a 6- or 7-membered fused bicyclic heterocyclyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from -OH, -N(R¹⁰)₂, C₁-C₄alkyl-NH₂, halogen, C₁-C₄alkyl, and oxo;
- (viii) a partially saturated 8-, 9-, 10-, 11- or 12-membered fused bicyclic heterocyclyl having 1, 2, 3 or 4 ring members independently selected from N, NR⁹, O and S, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with 1,

2, 3 or 4 substituents, each independently selected from -OH, -N(R¹⁰)₂, C₁-C₄alkyl-NH₂, halogen, C₁-C₄alkyl, and oxo;

(ix) a 6-, 7-, 8-, 9- or 10- membered spiro bicyclic heterocycloalkyl having 1, 2 or 3 ring members independently selected from N, NR⁹, O and S, wherein the spiro bicyclic heterocycloalkyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from -OH, -N(R¹⁰)₂, C₁-C₄alkyl-NH₂, halogen, C₁-C₄alkyl, and oxo;

(x) a 6- membered heterocycloalkyl having 1 to 2 ring members independently selected from N, NR⁹, O and S, wherein the heterocycloalkyl has a C₁-C₃alkyl bridge or a -CH₂OCH₂- bridge;

(xi) phenyl which is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from -S(=O)₂N(R¹⁰)₂, -OH, -N(R¹⁰)₂, C₁-C₄alkyl-NH₂, halogen and C₁-C₄alkyl;

or

(xii) C₄-C₈cycloalkyl which is unsubstituted or is substituted with 1, 2, 3 or 4 substituents independently selected from -OH, -N(R¹⁰)₂, -S(=O)₂R¹⁰, C₁-C₄alkyl-NH₂, halogen, C₁-C₄alkoxy, C₁-C₄alkyl, and oxo.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁸ is 4-, 5- or 6-membered heterocycloalkyl having 1, 2 or 3 ring members independently selected from N, NR⁹, O and S, wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents each independently selected from -OH, -CN, -N(R¹⁰)₂, halogen, C₁-C₄fluoroalkyl, C₁-C₄alkyl, C₁-C₄alkoxy, oxo and a 5- or 6-membered monocyclic heteroaryl having 1, 2, 3 or 4 ring members independently selected from N, NR⁹, O and S, wherein the monocyclic heteroaryl is unsubstituted.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁸ is 4-, 5- or 6-membered heterocycloalkyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2 or 3 substituents each independently selected from -OH, -CN, -N(R¹⁰)₂, halogen, C₁-C₄fluoroalkyl, C₁-C₄alkyl, C₁-C₄alkoxy, oxo and a 5- or 6-membered monocyclic heteroaryl having 1 or 2 ring members independently selected from N and NR⁹, wherein the monocyclic heteroaryl is unsubstituted.

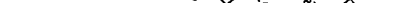
In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁸ is 4-, 5- or 6-membered heterocycloalkyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2 or 3 substituents each independently selected from -

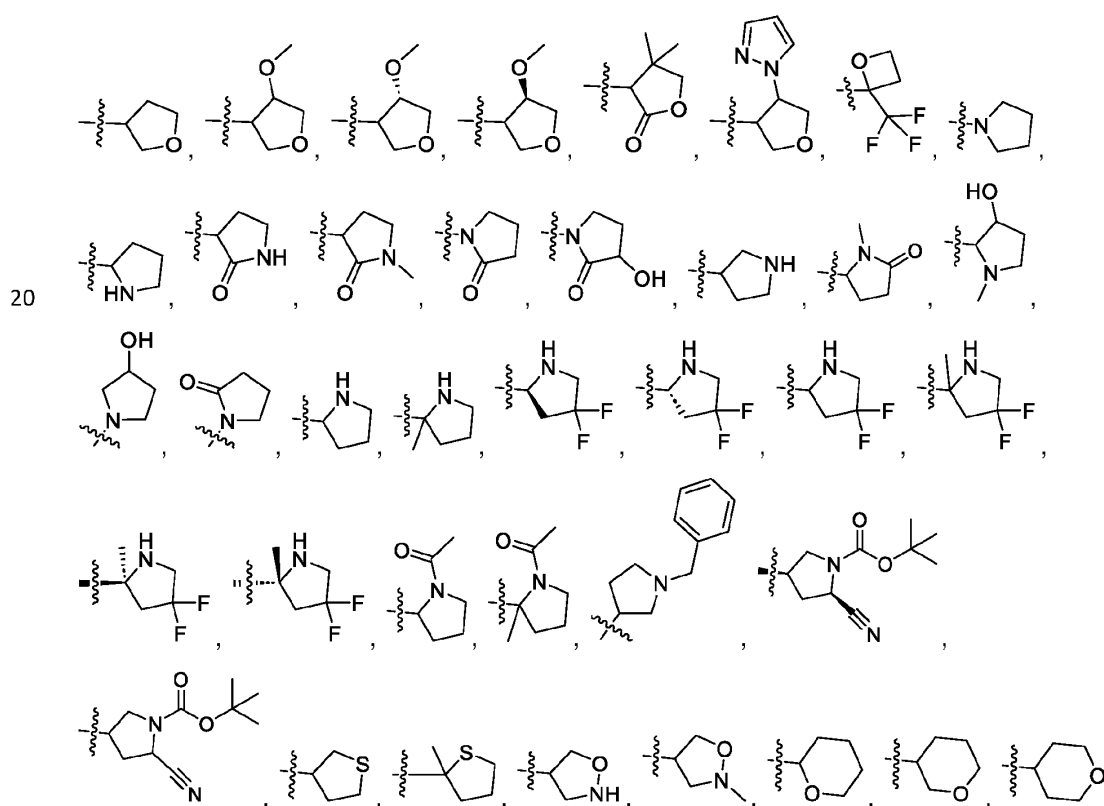
OH, -CN, NH₂, F, CF₃, methyl, methoxy, oxo and a 5- or 6- membered monocyclic heteroaryl having 1 or 2 ring members independently selected from N and NR⁹, wherein the monocyclic heteroaryl is unsubstituted.

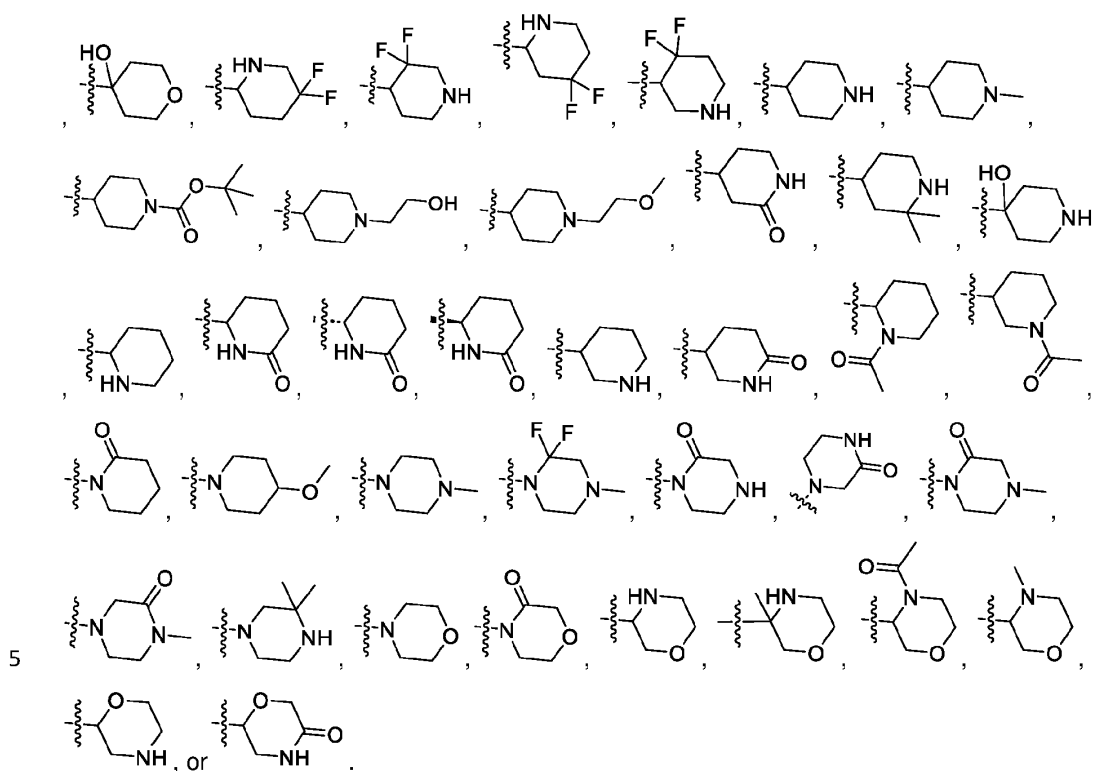
In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁸ is 4-, 5- or 6-membered heterocycloalkyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2 or 3 substituents each independently selected from -OH, halogen, C₁-C₄fluoroalkyl, C₁-C₄alkyl, and, oxo.

10 In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁸ is 4-, 5- or 6-membered heterocycloalkyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2 or 3 substituents each independently selected from -
15 OH, - F, CF₃, methyl and oxo.

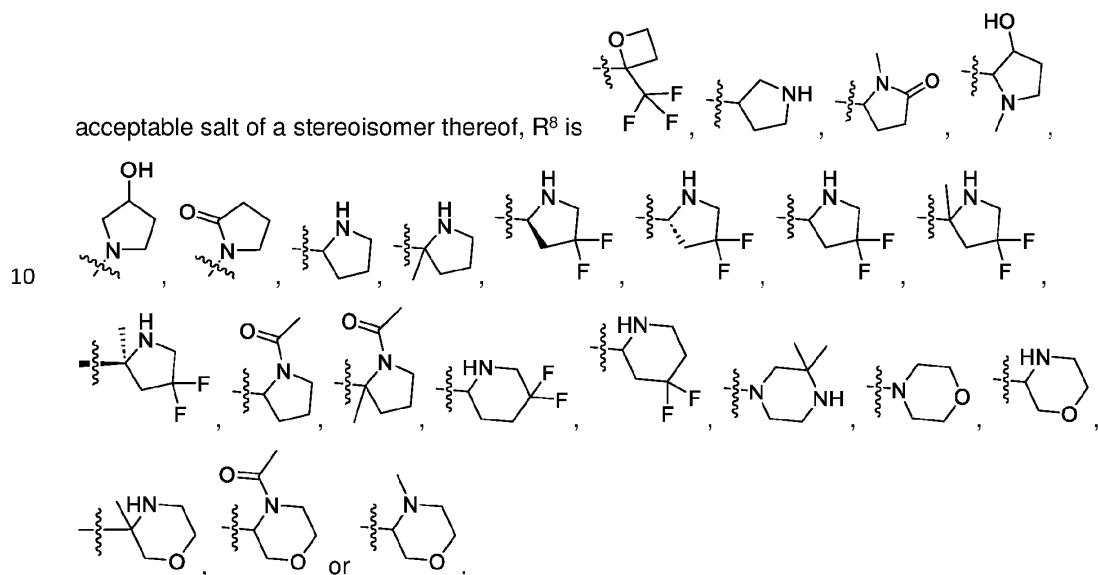
In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically

acceptable salt of a stereoisomer thereof, R^8 is 





In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically



In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁸ is 4-, 5- or 6-membered heterocycloalkyl wherein one ring member is S(=O)₂, S(=O) or S(=O)(=NH), and wherein the heterocycloalkyl is

unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from -OH, C₁-C₄alkyl and oxo.

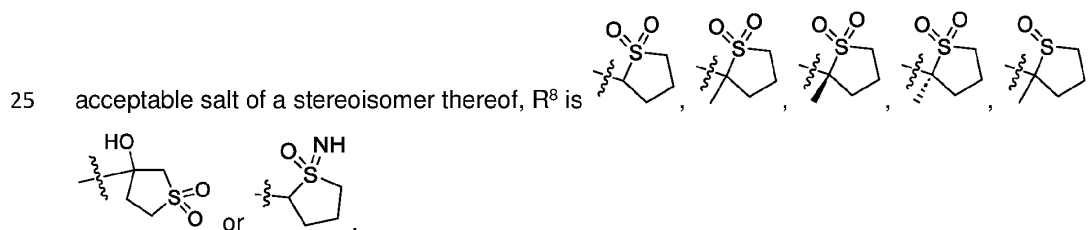
In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁸ is a 5- membered heterocycloalkyl wherein one ring member is S(=O)₂, S(=O) or S(=O)(=NH), and wherein the heterocycloalkyl is unsubstituted or is substituted with a substituent selected from -OH and C₁-C₄alkyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁸ is a 5- membered heterocycloalkyl wherein one ring member is S(=O)₂, S(=O) or S(=O)(=NH), and wherein the heterocycloalkyl is unsubstituted or is substituted with a substituent selected from OH and methyl.

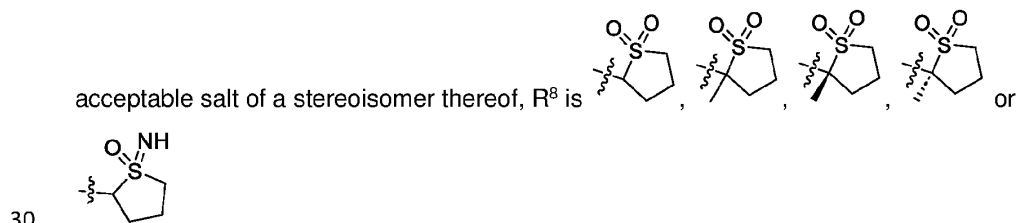
In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁸ is a 5- membered heterocycloalkyl wherein one ring member is S(=O)₂, or S(=O)(=NH), and wherein the heterocycloalkyl is unsubstituted or is substituted with a substituent selected from C₁-C₄alkyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁸ is a 5- membered heterocycloalkyl wherein one ring member is S(=O)₂ or S(=O)(=NH), and wherein the heterocycloalkyl is unsubstituted or is substituted with a methyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁸ is



In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁸ is



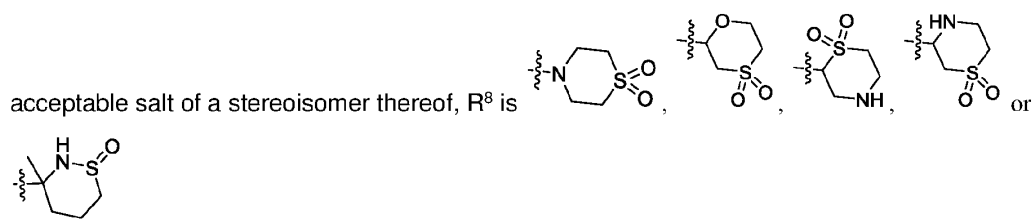
In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁸ is

stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^8 is 4-, 5- or 6-membered heterocycloalkyl wherein one ring member is $S(=O)_2$ or $S(=O)$, and 1, 2 or 3 other ring members are independently selected from N, NR^9 and O, and wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents each independently selected from C_1 - C_4 alkyl and oxo.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^8 is a 6-membered heterocycloalkyl wherein one ring member is $S(=O)_2$ or $S(=O)$, and one other ring member is selected from N, NR^9 and O, and wherein the heterocycloalkyl is unsubstituted or is substituted with a a substituent selected from C_1 - C_4 alkyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^8 is a 6-membered heterocycloalkyl wherein one ring member is $S(=O)_2$ or $S(=O)$, and one other ring member is selected from N, NR^9 and O, and wherein the heterocycloalkyl is unsubstituted or is substituted with a methyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^8 is



In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^8 is a partially saturated 5- or 6-membered heterocyclyl having 1 or 2 ring members independently selected from N, NR^9 , O and S, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents independently selected from -OH, C_1 - C_4 alkyl, and oxo.

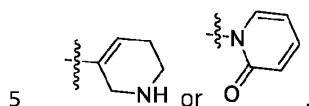
In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^8 is a partially saturated 6-membered heterocyclyl having 1 or 2 ring members independently selected from N, NR^9 , O and S, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with an oxo.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^8 is a partially saturated 6-membered heterocyclyl having 1 or 2 ring members independently selected from O and S, wherein the partially

saturated heterocyclyl is unsubstituted.

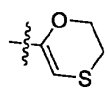
In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically

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In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically

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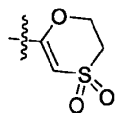
10 In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^8 is a partially saturated 5- or 6-membered heterocyclyl wherein one ring member is $S(=O)_2$ and 1, 2 or 3 other ring members are independently selected from N, NR^9 , O and S, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents independently selected from -OH, 15 C_1 - C_4 alkyl, and oxo.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^8 is a partially saturated 6-membered heterocyclyl wherein one ring member is $S(=O)_2$ and one other ring member is selected from N, NR^9 , and O, 20 wherein the partially saturated heterocyclyl is unsubstituted or is substituted with an oxo.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^8 is a partially saturated 6-membered heterocyclyl wherein one ring member is $S(=O)_2$ and one other ring member is and O, wherein the partially 25 saturated heterocyclyl is unsubstituted.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically

acceptable salt of a stereoisomer thereof, R^8 is



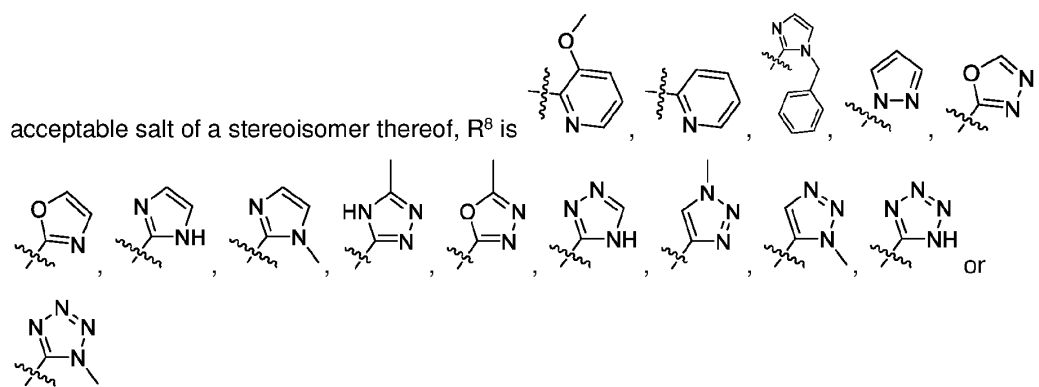
30 In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^8 is a 5- or 6- membered monocyclic heteroaryl

having 1, 2, 3 or 4 ring members independently selected from N, NR⁹, O and S, wherein the monocyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents each independently selected from -OH, C₁-C₄alkoxy and C₁-C₄alkyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁸ is a 5- or 6- membered monocyclic heteroaryl having 1, 2, 3 or 4 ring members independently selected from N, NR⁹ and O, wherein the monocyclic heteroaryl is unsubstituted or is substituted with a substituent selected from -OH methoxy and methyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁸ is a 5- membered monocyclic heteroaryl having 3 ring members independently selected from N and O, wherein the monocyclic heteroaryl is unsubstituted.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically



In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically



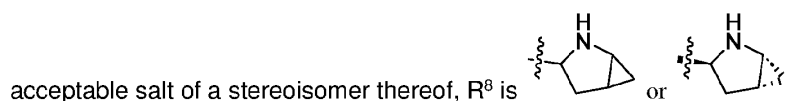
In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁸ is a 6- or 7-membered fused bicyclic heterocyclyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from -OH, -N(R¹⁰)₂, C₁-C₄alkyl-NH₂, halogen, C₁-C₄alkyl, and oxo.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically

acceptable salt of a stereoisomer thereof, R^8 is a 6- membered fused bicyclic heterocyclyl having 1 ring member selected from N and NR^9 , wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with an oxo.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^8 is a 6- membered fused bicyclic heterocyclyl having 1 ring member selected from NR^9 , wherein the fused bicyclic heterocyclyl is unsubstituted.

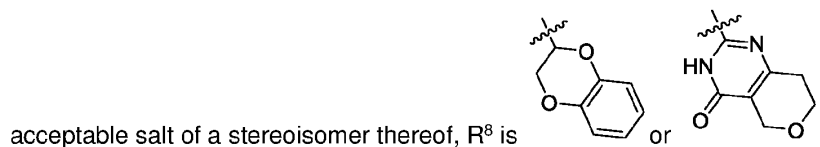
In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically



In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^8 is a partially saturated 8-, 9-, 10-, 11- or 12- membered fused bicyclic heterocyclyl having 1, 2, 3 or 4 ring members independently selected from N, NR^9 , O and S, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from -OH, $-N(R^{10})_2$, C_1 - C_4 alkyl- NH_2 , halogen, C_1 - C_4 alkyl, and oxo.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^8 is a partially saturated 10- membered fused bicyclic heterocyclyl having 1, 2, or 3 ring members independently selected from N, NR^9 , and O, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with an oxo.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically

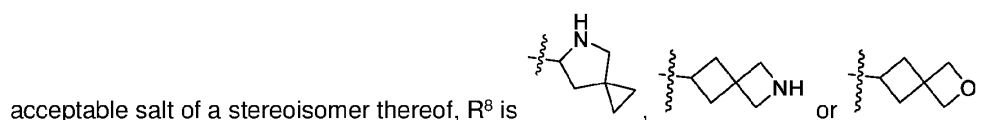


In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^8 is a 6-, 7-, 8-, 9- or 10- membered spiro bicyclic heterocycloakyl having 1, 2 or 3 ring members independently selected from N, NR^9 , O and S, wherein the spiro bicyclic heterocycloakyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from -OH, $-N(R^{10})_2$, C_1 - C_4 alkyl- NH_2 , halogen, C_1 - C_4 alkyl, and oxo.

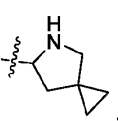
In certain embodiments of compounds of Formula (I), or a subformula thereof, or a

stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^8 is a 7-membered spiro bicyclic heterocycloalkyl having 1 ring member selected from NR^9 , and O, wherein the spiro bicyclic heterocycloalkyl is unsubstituted.

- 5 In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically



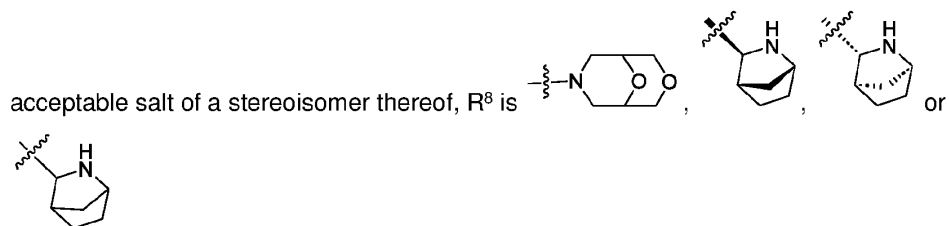
In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically

- 10 acceptable salt of a stereoisomer thereof, R^8 is
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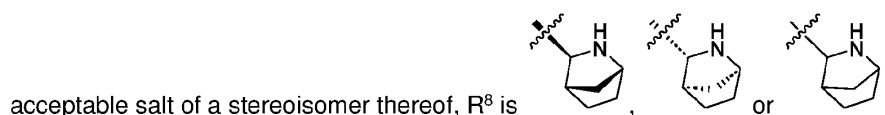
In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^8 is a 6-membered heterocycloalkyl having 1 to 2 ring members independently selected from N, NR^9 , O and S, wherein the heterocycloalkyl has a C_1 - C_3 alkyl bridge or a $-CH_2OCH_2-$ bridge

- 15 In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^8 is a 6-membered heterocycloalkyl having 1 ring members selected from NR^9 , wherein the heterocycloalkyl has a C_1 - C_3 alkyl bridge.

- 20 In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically



- 25 In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically

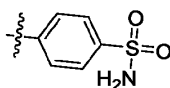


In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically

acceptable salt of a stereoisomer thereof, R^8 is phenyl which is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from $-S(=O)_2N(R^{10})_2$, $-OH$, $-N(R^{10})_2$, C_1 - C_4 alkyl- NH_2 , halogen and C_1 - C_4 alkyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^8 is phenyl which is substituted with $-S(=O)_2NH_2$.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically



acceptable salt of a stereoisomer thereof, R^8 is

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^8 is C_4 - C_8 cycloalkyl which is unsubstituted or is substituted with 1, 2, 3 or 4 substituents independently selected from $-OH$, $-N(R^{10})_2$, $-S(=O)_2R^{10}$, C_1 - C_4 alkyl- NH_2 , halogen, C_1 - C_4 alkoxy, C_1 - C_4 alkyl, and oxo.

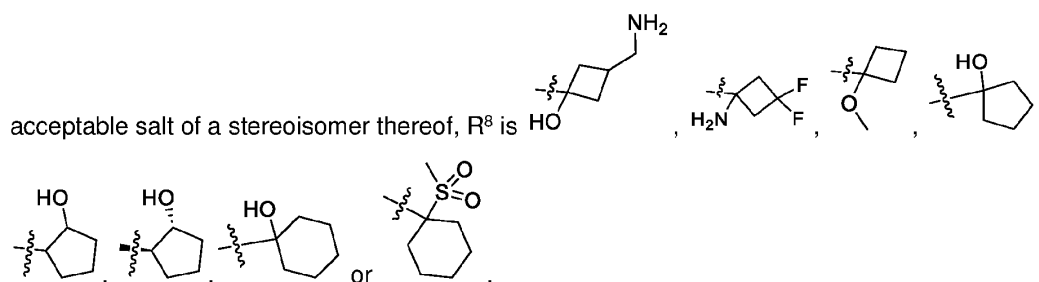
In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^8 is C_4 - C_8 cycloalkyl which is substituted with 1, 2 or 3 substituents independently selected from $-OH$, $-N(R^{10})_2$, $-S(=O)_2R^{10}$, C_1 - C_4 alkyl- NH_2 , halogen and C_1 - C_4 alkoxy.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^8 is cyclobutyl, cyclopentyl, or cyclohexyl which is substituted with 1, 2 or 3 substituents independently selected from $-OH$, $-NH_2$, $-S(=O)_2CH_3$, $-CH_2NH_2$, F, and methoxy.

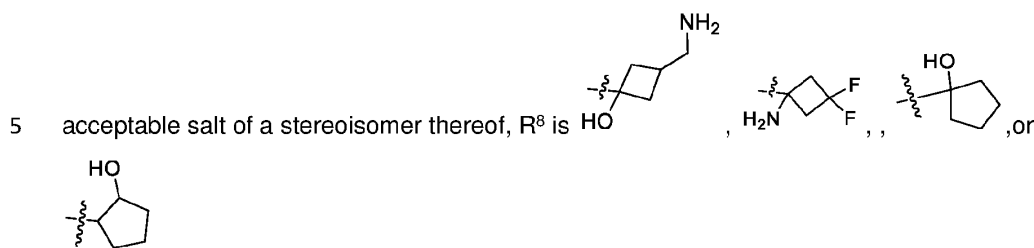
In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^8 is C_4 - C_8 cycloalkyl which is substituted with 1, 2 or 3 substituents independently selected from $-OH$, $-N(R^{10})_2$, C_1 - C_4 alkyl- NH_2 and halogen.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^8 is cyclobutyl, cyclopentyl, or cyclohexyl which is substituted with 1, 2 or 3 substituents independently selected from $-OH$, $-NH_2$, $-CH_2NH_2$, and F.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically



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In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^9 is H, C_1 - C_4 alkyl, benzyl, C_1 - C_4 alkyl- OR^{10} , -
 10 $C(=O)OR^{10}$ or $-C(=O)R^{10}$. In certain embodiments, R^9 is H, methyl, benzyl, $-C(=O)CH_3$, -
 $C(=O)O(CH_3)_3$, CH_2CH_2OH or $CH_2CH_2OCH_3$.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^9 is H, C_1 - C_4 alkyl or $-C(=O)R^{10}$. In certain
 15 embodiments, R^9 is H, methyl or $-C(=O)CH_3$.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^9 is H.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^9 is C_1 - C_4 alkyl. In other embodiments, R^9 is methyl.
 20

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^9 is $-C(=O)R^{10}$. In certain embodiments, R^9 is -
 25 $C(=O)CH_3$.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^9 is $-C(=O)OR^{10}$. In certain embodiments, R^9 is -
 $C(=O)O(CH_3)_3$.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁹ is benzyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R⁹ is C₁-C₄alkyl-OR¹⁰. In other embodiments, R⁹ is -CH₂OH. In other embodiments, R⁹ is -CH₂CH₂OH. In other embodiments, R⁹ is -CH₂CH₂OCH₃.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R¹⁰ is H or C₁-C₄alkyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R¹⁰ is H.

15 In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R¹⁰ is C₁-C₄alkyl. In other embodiments, R¹⁰ is methyl, ethyl or t-butyl. In other embodiments, R¹⁰ is methyl or t-butyl. In other embodiments, R¹⁰ is methyl. In other embodiments, R¹⁰ is ethyl. In other embodiments, R¹⁰ is t-butyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, n is 1, 2 or 3. In other embodiments, n is 1 or 2. In other embodiments, n is 1.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, p is 1, 2 or 3. In other embodiments, p is 1 or 2. In other embodiments, p is 1.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, q is 0, 1 or 2. In other embodiments, q is 0 or 1. In 30 other embodiments, q is 0.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, Z₁ is N or C; Z₂ is N or CR^z; Z₃ is N or CR^z; Z₄ is N or C; Z₅ is N or CR^z; wherein each R^z is independently selected from the group consisting of H, halogen, C₁-C₄alkyl and C₁-C₄fluoroalkyl; and provided that at least two, and not more than four, of Z₁, Z₂, Z₃, Z₄ and Z₅ are N.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically

acceptable salt of a stereoisomer thereof,

Z_1 is N, Z_2 is CR^z , Z_3 is N, Z_4 is C and Z_5 is N;

or Z_1 is N, Z_2 is CR^z , Z_3 is N, Z_4 is C and Z_5 is CR^z ;

or Z_1 is C, Z_2 is CR^z , Z_3 is N, Z_4 is N and Z_5 is CR^z ;

5 or Z_1 is C, Z_2 is N, Z_3 is N, Z_4 is N and Z_5 is CR^z ;

or Z_1 is N, Z_2 is CR^z , Z_3 is CR^z , Z_4 is C and Z_5 is N;

where each R^z is independently selected from the group consisting of H, halogen, C_1 -

C_4 alkyl and C_1 - C_4 fluoroalkyl.

10 In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof,

Z_1 is N, Z_2 is CR^z , Z_3 is N, Z_4 is C and Z_5 is N;

or Z_1 is N, Z_2 is CR^z , Z_3 is N, Z_4 is C and Z_5 is CR^z ;

or Z_1 is C, Z_2 is CR^z , Z_3 is N, Z_4 is N and Z_5 is CR^z ;

15 or Z_1 is C, Z_2 is N, Z_3 is N, Z_4 is N and Z_5 is CR^z ;

where each R_z is H.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof,

20 Z_1 is N, Z_2 is CR^z , Z_3 is N, Z_4 is C and Z_5 is N;

or Z_1 is N, Z_2 is CR^z , Z_3 is N, Z_4 is C and Z_5 is CR^z ;

where each R_z is H.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, Z_1 is N, Z_2 is CR^z , Z_3 is N, Z_4 is C and Z_5 is N, where each R^z is independently selected from the group consisting of H, halogen, C_1 - C_4 alkyl and C_1 - C_4 fluoroalkyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, Z_1 is N, Z_2 is CR^z , Z_3 is N, Z_4 is C and Z_5 is CR^z , where each R^z is independently selected from the group consisting of H, halogen, C_1 - C_4 alkyl and C_1 - C_4 fluoroalkyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, Z_1 is C, Z_2 is CR^z , Z_3 is N, Z_4 is N and Z_5 is CR^z , where each R^z is independently selected from the group consisting of H, halogen, C_1 - C_4 alkyl and C_1 - C_4 fluoroalkyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a

stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, Z_1 is C, Z_2 is N, Z_3 is N, Z_4 is N and Z_5 is CR^z , where each R^z is independently selected from the group consisting of H, halogen, C_1 - C_4 alkyl and C_1 - C_4 fluoroalkyl.

5 In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, Z_1 is N, Z_2 is CR^z , Z_3 is CR^z , Z_4 is C and Z_5 is N, where each R^z is independently selected from the group consisting of H, halogen, C_1 - C_4 alkyl and C_1 - C_4 fluoroalkyl.

10 In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, each R^z is independently selected from the group consisting of H, halogen, C_1 - C_4 alkyl or C_1 - C_4 fluoroalkyl.

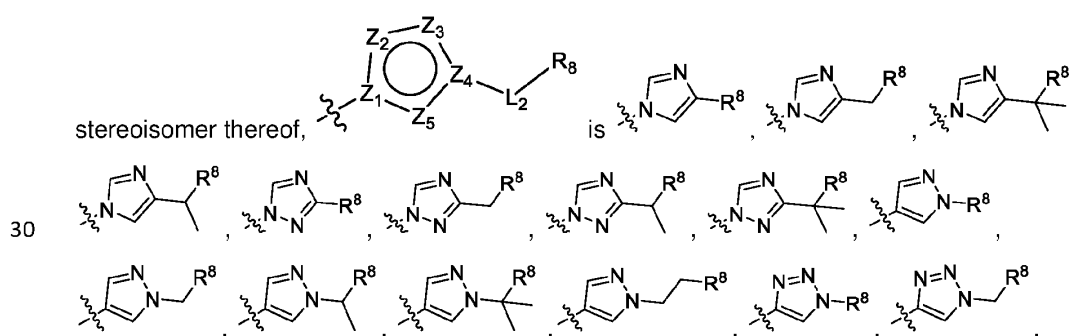
In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, each R^z is independently selected from the group consisting of H or halogen.

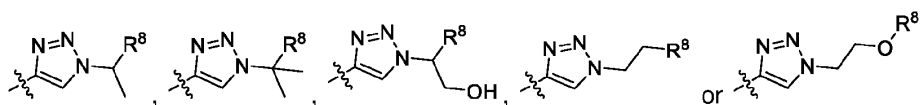
15 In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, each R^z is independently selected from the group consisting of H or F.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^z is H.

25 In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^z is halogen. In other embodiments, R^z is F.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a





In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof,

R^A is:

- (i) phenyl which is unsubstituted or is substituted with 1, 2, 3 or 4 R^1 groups;
 - (ii) a partially saturated 9-, 10-, 11- or 12-membered bicyclic carbocyclyl which is unsubstituted or is substituted with 1 to 4 R^1 groups;
 - (iii) a 5- or 6- membered monocyclic heteroaryl having 1, 2, 3 or 4 ring members independently selected from N, NR^4 , O and S, wherein the monocyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 R^1 groups;
- or
- (iv) a partially saturated 8-, 9-, 10-, 11- or 12-membered fused bicyclic heterocyclyl having 1, 2, 3 or 4 ring members independently selected from N, NR^4 , O and S, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 R^1 groups.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^A is phenyl which is unsubstituted or is substituted with 1, 2, 3 or 4 R^1 groups.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^A is phenyl which is unsubstituted

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^A is phenyl which substituted with 1 or 2 R^1 groups.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^A is phenyl which substituted with 1 or 2 substituents independently selected from halogen, C_1 - C_4 alkyl, C_1 - C_4 fluoroalkyl, and pentafluorosulfanyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^A is phenyl which substituted with 1 or 2 substituents independently selected from F, CF_3 , CF_2CF_3 and SF_5 .

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a

stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^A is a partially saturated 9-, 10-, 11- or 12-membered bicyclic carbocyclyl which is unsubstituted or is substituted with 1 to 4 R¹ groups.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^A is a 5- or 6- membered monocyclic heteroaryl having 1, 2, 3 or 4 ring members independently selected from N, NR⁴, O and S, wherein the monocyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 R¹ groups.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^A is a 5- or 6- membered monocyclic heteroaryl having 1 or 2 ring members independently selected from N and NR⁴, wherein the monocyclic heteroaryl is substituted with 1 or 2 R¹ groups.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^A is a 5- or 6- membered monocyclic heteroaryl having 1 or 2 ring members independently selected from N and NR⁴, wherein the monocyclic heteroaryl is substituted with 1 or 2 substituents independently selected from halogen, C₁-C₄alkyl and C₁-C₄fluoroalkyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^A is a 5- or 6- membered monocyclic heteroaryl having 1 or 2 ring members independently selected from N and NR⁴, wherein the monocyclic heteroaryl is substituted with 1 or 2 substituents independently selected from F, Cl, CF₃, and methyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^A is pyrazolyl or pyridinyl which are substituted with 1 or 2 R¹ groups.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^A is pyrazolyl or pyridinyl which are substituted with 1 or 2 substituents independently selected from halogen, C₁-C₄alkyl and C₁-C₄fluoroalkyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^A is pyrazolyl or pyridinyl which are substituted with 1 or 2 substituents independently selected from F, Cl, CF₃, and methyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a

stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^A is a partially saturated 8-, 9-, 10-, 11- or 12-membered fused bicyclic heterocyclyl having 1, 2, 3 or 4 ring members independently selected from N, NR^4 , O and S, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 R^1 groups.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^A is a partially saturated 8-, 9- or 10-membered fused bicyclic heterocyclyl having 1, 2 or 3 ring member independently selected from N, NR^4 and O, wherein the fused bicyclic heterocyclyl is substituted with 1, 2 or 3 R^1 groups.

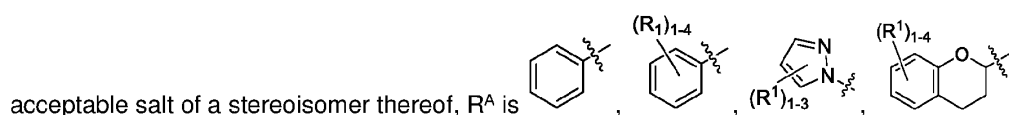
In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^A is a partially saturated 8-, 9- or 10-membered fused bicyclic heterocyclyl having 1, 2 or 3 ring member independently selected from N, NR^4 and O, wherein the fused bicyclic heterocyclyl is substituted with 1, 2 or 3 substituents independently selected from halogen, C_1 - C_4 alkyl and C_1 - C_4 fluoroalkyl.

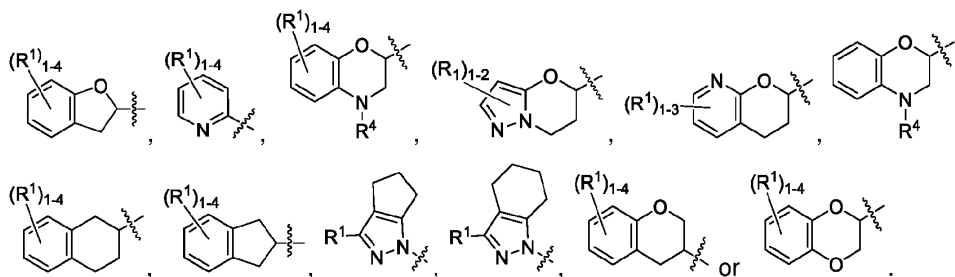
In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^A is chromanyl, 3,4-dihydro-2H-pyrano[2,3-b]pyridinyl, 3,4-dihydro-2H-benzo[b][1,4]oxazinyl, 6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazinyl, 5,6-dihydrocyclopenta[c]pyrazol-1(4H)-yl, 2,3-dihydrobenzo[b][1,4]dioxinyl, 4,5,6,7-tetrahydro-1H-indazolyl, 1H-benzo[d]imidazolyl, or 2,3-dihydrobenzofuranyl, each of which is unsubstituted or substituted with 1 or 2 R^1 groups.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^A is a partially saturated 10-membered fused bicyclic heterocyclyl having 1 or 2 ring members independently selected from N and O, wherein the fused bicyclic heterocyclyl is substituted with 1 substituent selected from halogen, C_1 - C_4 alkyl and C_1 - C_4 fluoroalkyl.

In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^A is chromanyl or 3,4-dihydro-2H-pyrano[2,3-b]pyridinyl substituted with CF_3 .

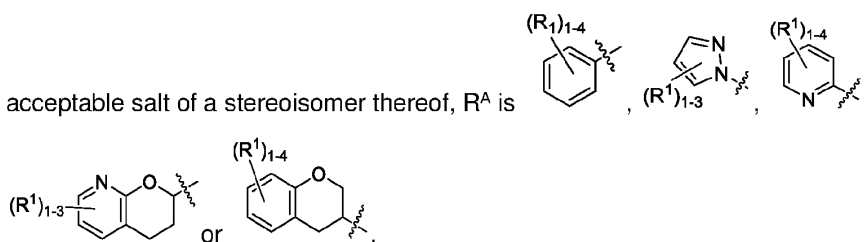
In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, R^A is





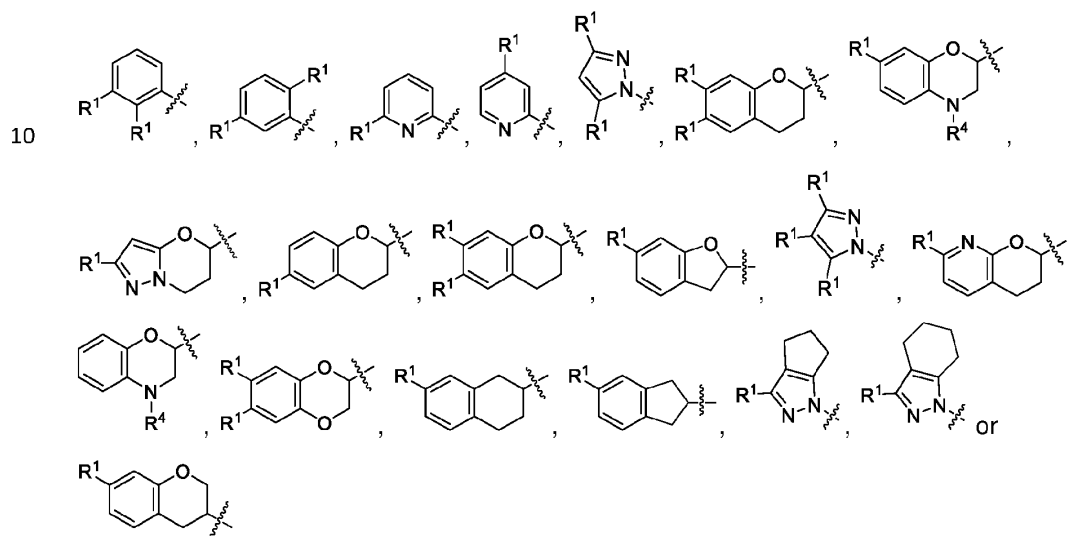
In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically

5 acceptable salt of a stereoisomer thereof, R^A is

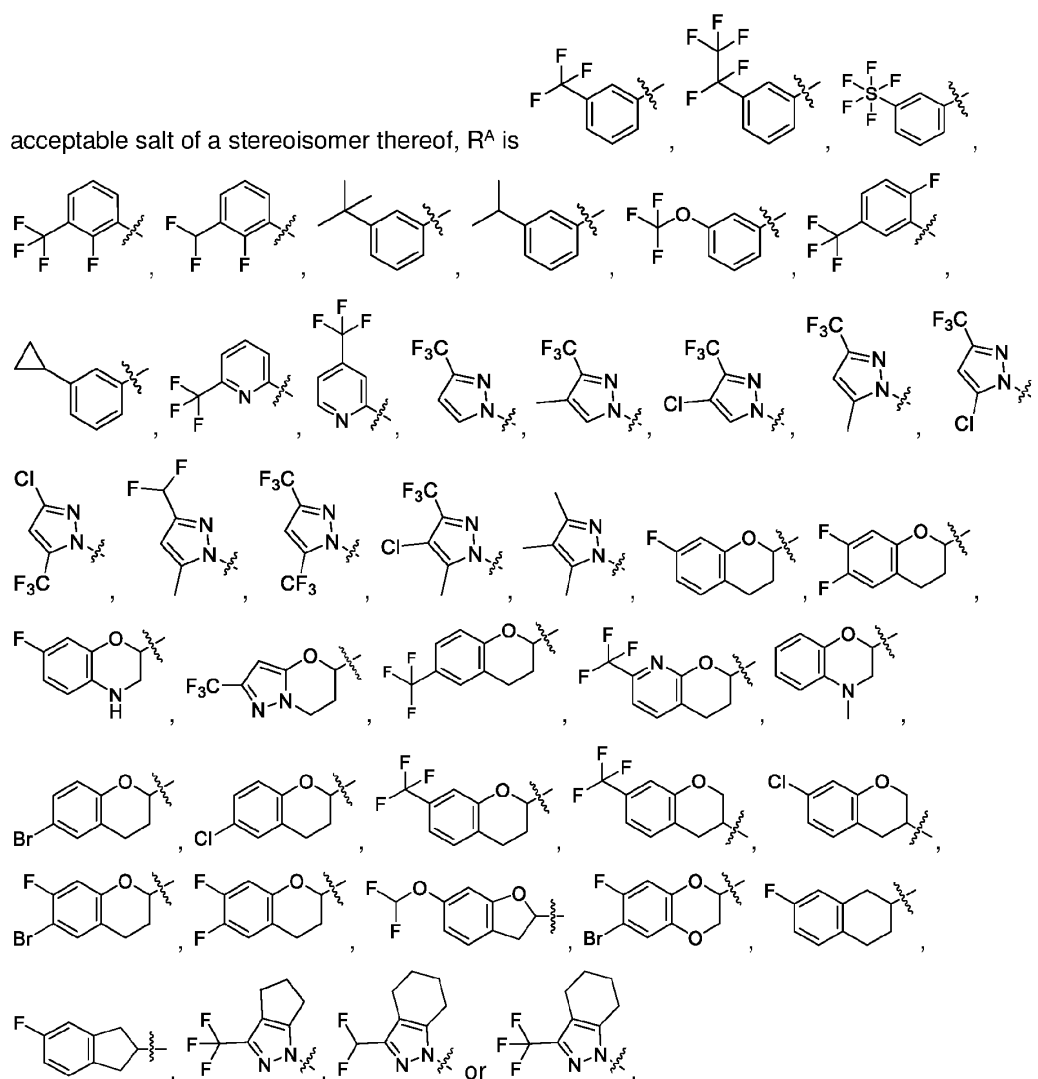


In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically

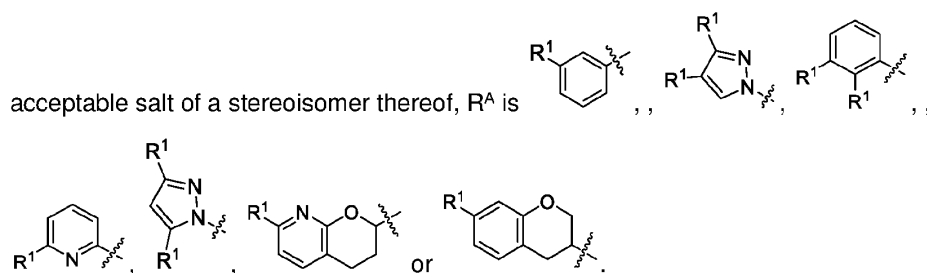
acceptable salt of a stereoisomer thereof, R^A is



15 In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically



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In certain embodiments of compounds of Formula (I), or a subformula thereof, or a
5 stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically

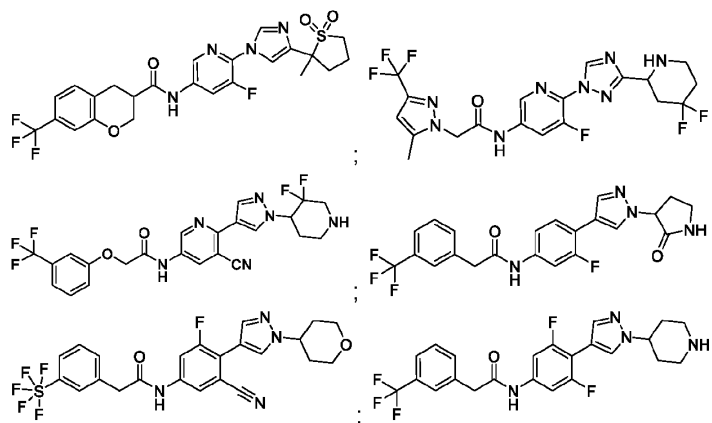
acceptable salt of a stereoisomer thereof, R^A is

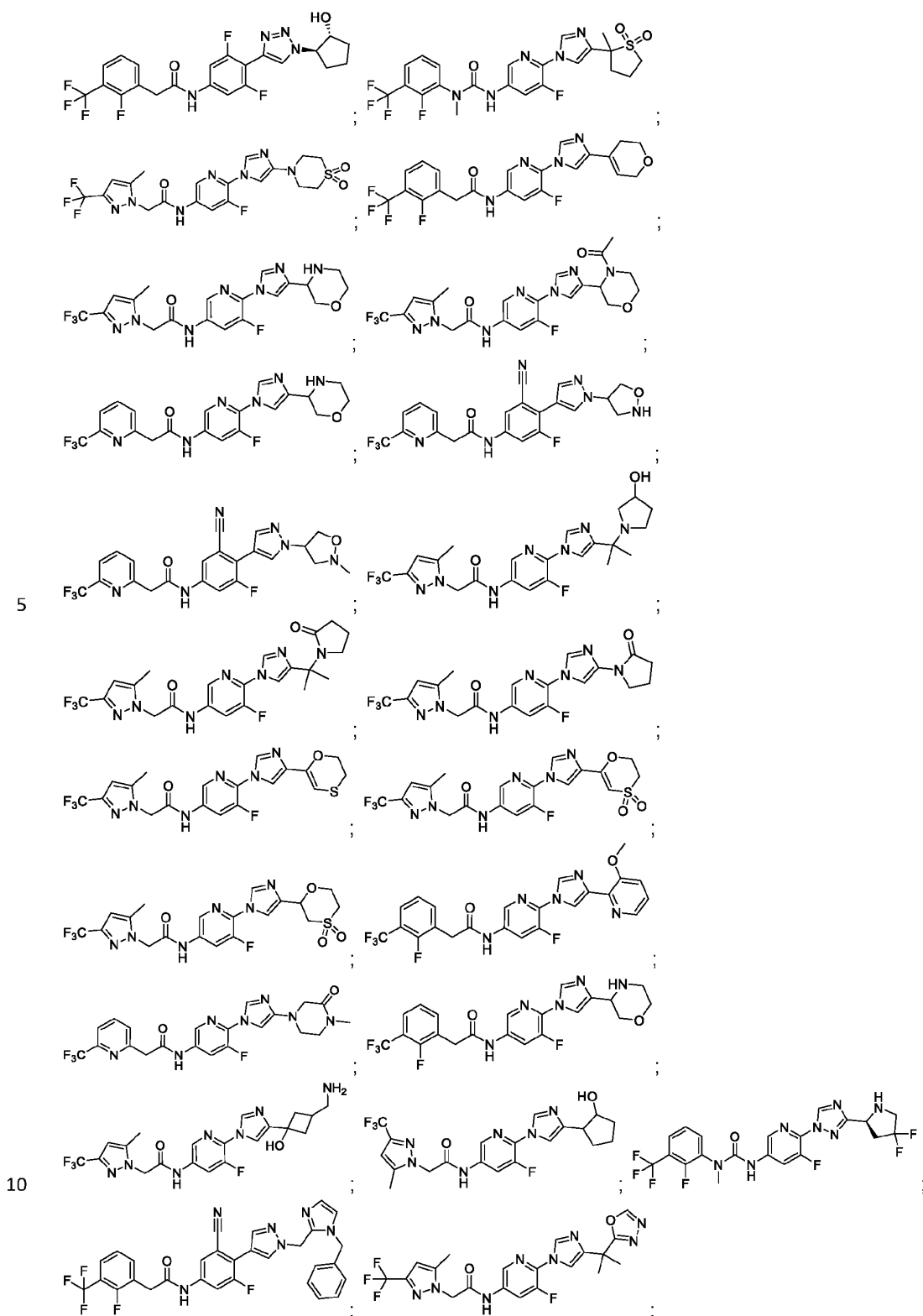
The image displays various chemical structures representing potential R^A substituents. These include:

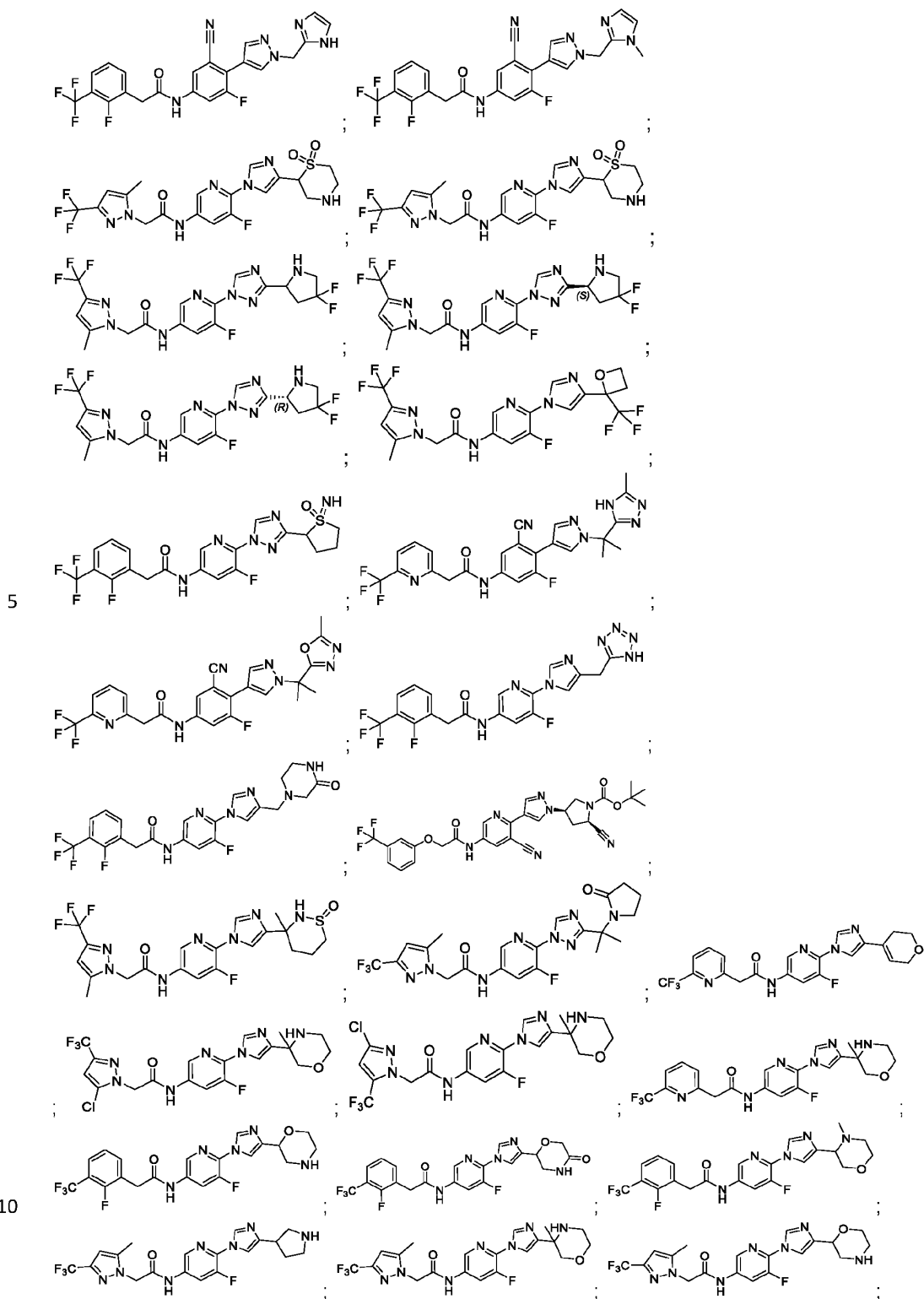
- A phenyl ring.
- A pyridine ring.
- A benzodioxane derivative.
- A benzofuran derivative.
- A pyridine ring with a substituent at the 3-position.
- A benzodioxane derivative with an N-R⁴ group.
- A benzimidazole derivative.
- A quinoline derivative.
- A tetralin derivative.
- A fluorene derivative.
- A bicyclic system with a nitrogen atom.
- A bicyclic system with a nitrogen atom and a substituent.

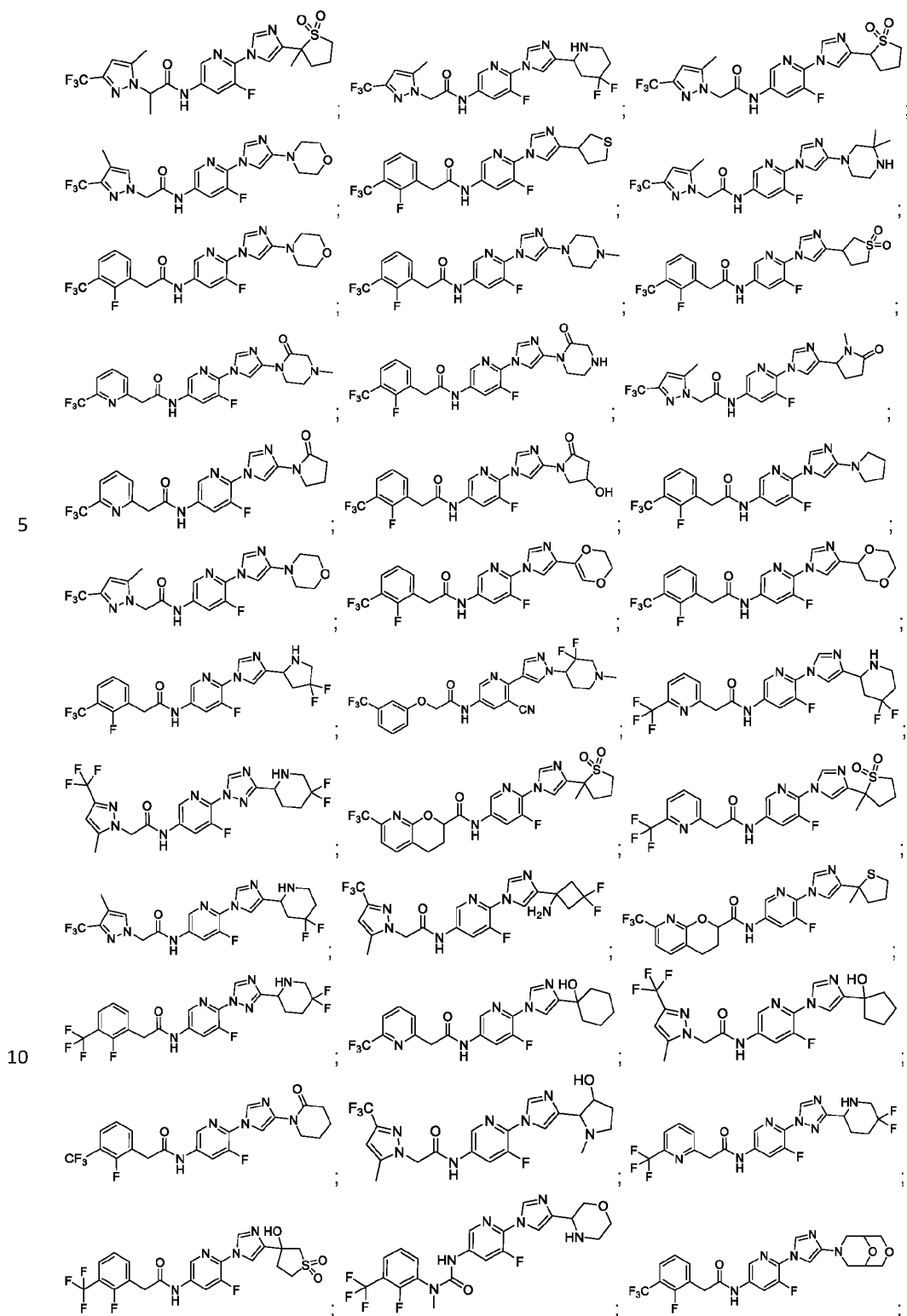
10 In certain embodiments of compounds of Formula (I), or a subformula thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof,

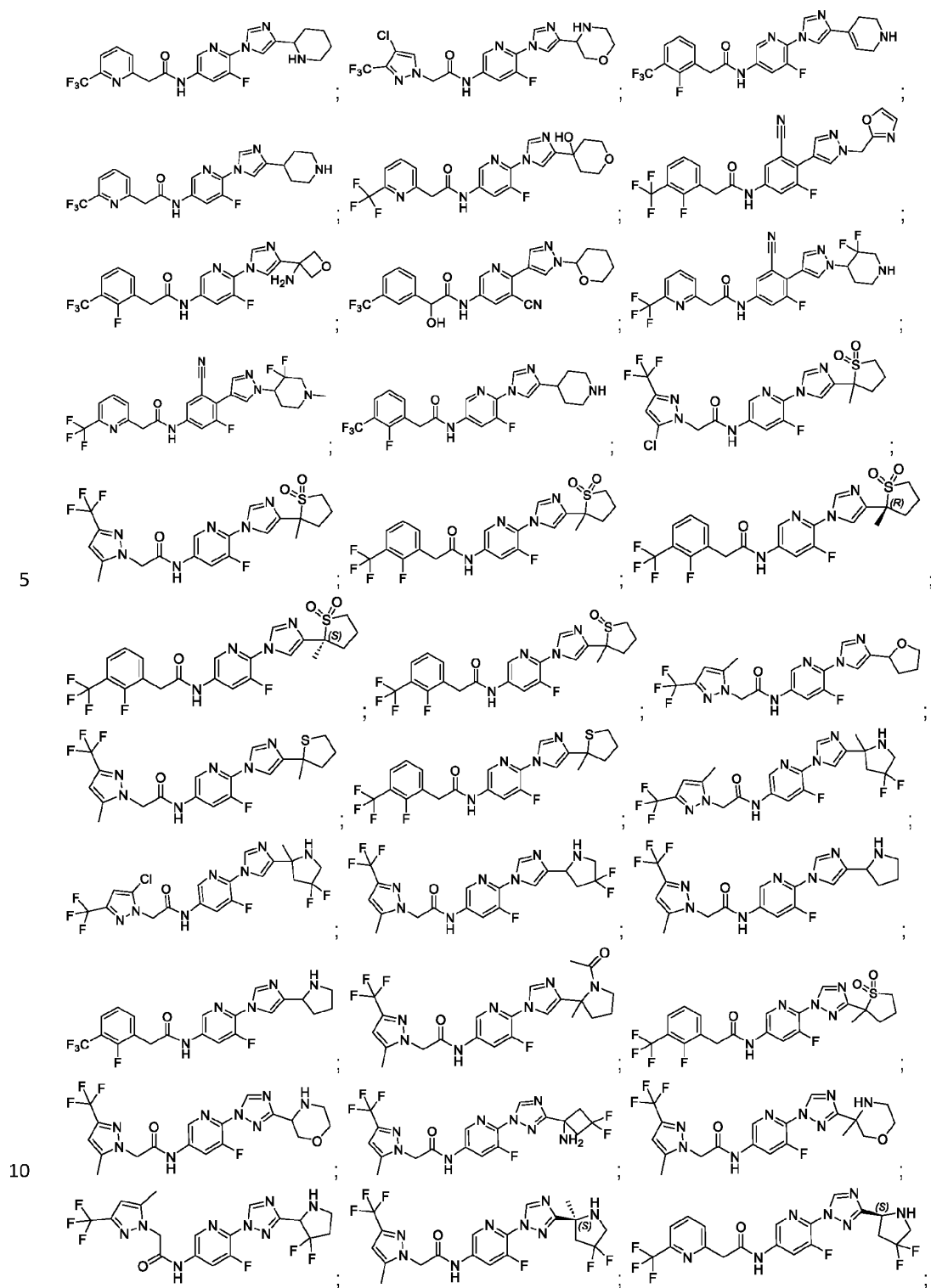
In an embodiment of compounds of Formula (I), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, compounds of Formula (I) are selected from:

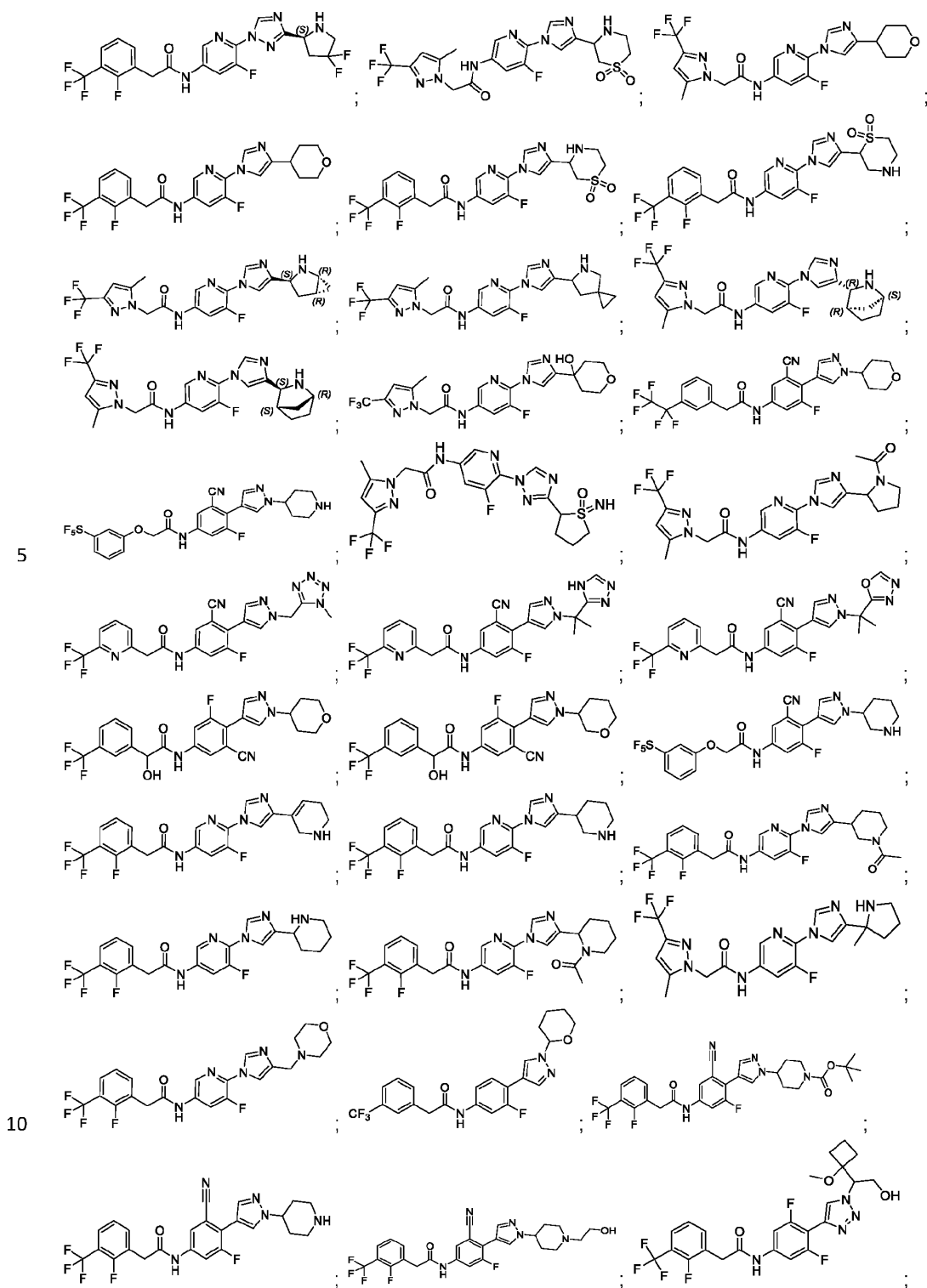


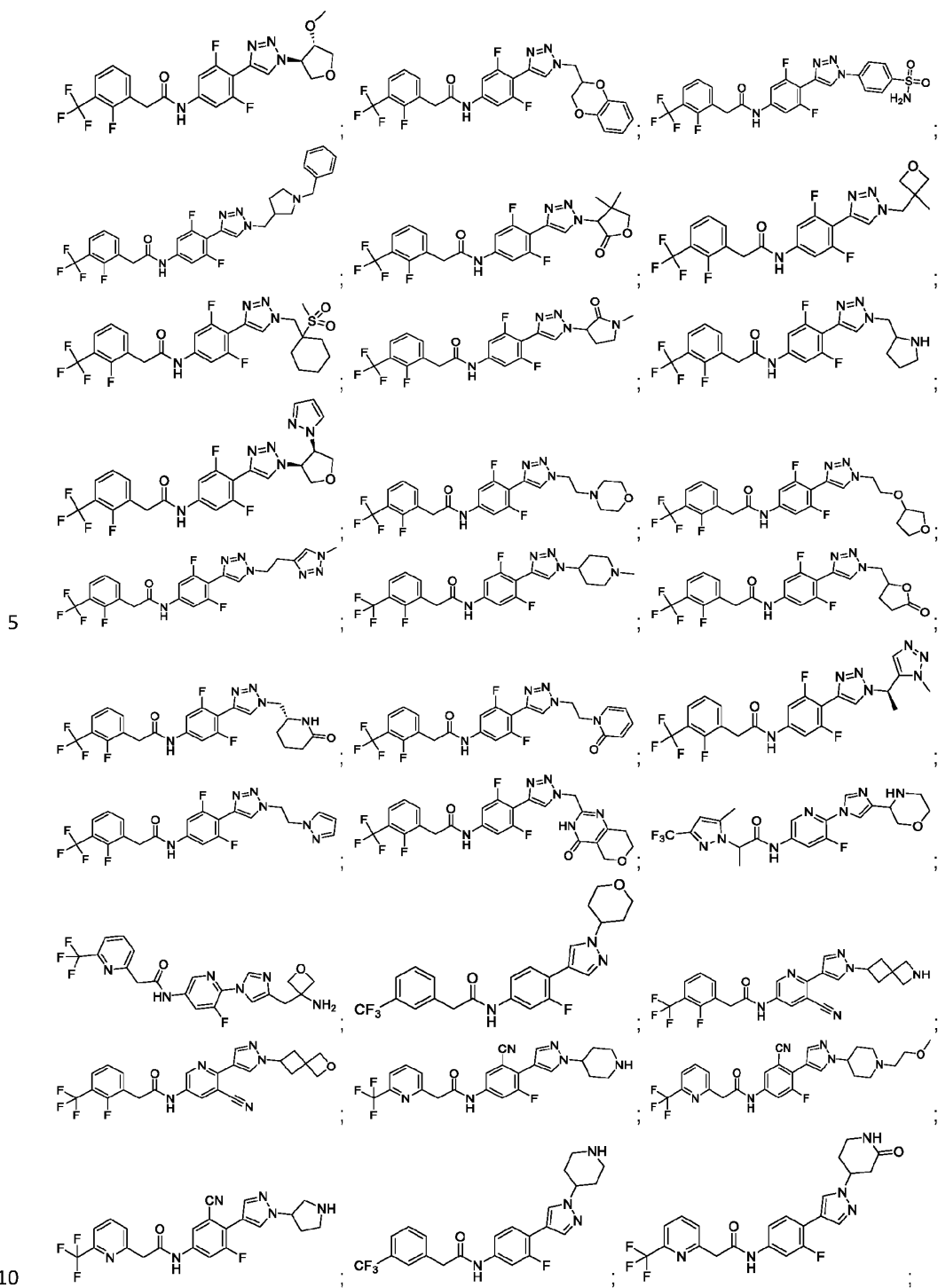


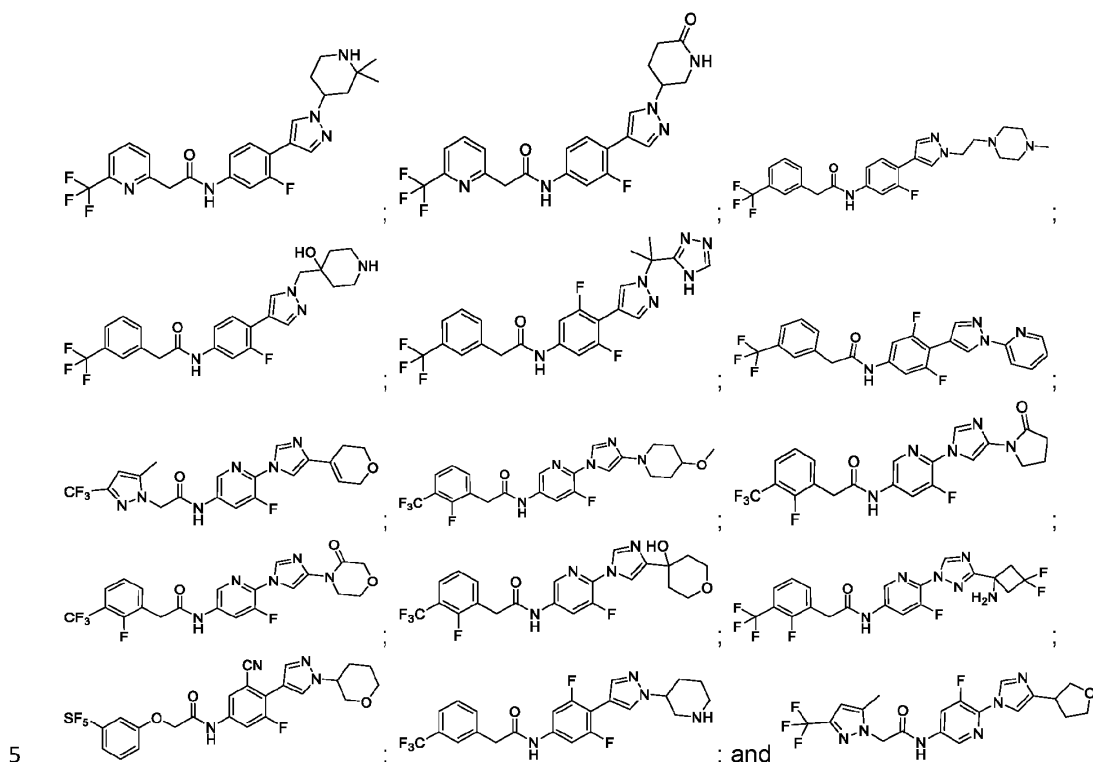












In an embodiment of compounds of Formula (I), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, compounds of Formula (I) are selected from:

- 10 N-(5-fluoro-6-(4-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-7-(trifluoromethyl)chromane-3-carboxamide;
- (R or S)-N-(5-fluoro-6-(4-((R or S)-2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-7-(trifluoromethyl)chromane-3-carboxamide;
- (R)-N-(5-fluoro-6-(4-((R or S)-2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-7-(trifluoromethyl)chromane-3-carboxamide;
- 15 (S)-N-(5-fluoro-6-(4-((R or S)-2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-7-(trifluoromethyl)chromane-3-carboxamide;
- N-(6-(3-(4,4-difluoropiperidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
- 20 (R or S)-N-(6-(3-(4,4-difluoropiperidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
- (R)-N-(6-(3-(4,4-difluoropiperidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
- (S)-N-(6-(3-(4,4-difluoropiperidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
- 25 N-(5-cyano-6-(1-(3,3-difluoropiperidin-4-yl)-1H-pyrazol-4-yl)pyridin-3-yl)-2-(3-(trifluoromethyl)phenoxy)acetamide;
- N-(3-fluoro-4-(1-(2-oxopyrrolidin-3-yl)-1H-pyrazol-4-yl)phenyl)-2-(3-(trifluoromethyl)phenyl)acetamide;
- 30 (R or S)-N-(3-fluoro-4-(1-(2-oxopyrrolidin-3-yl)-1H-pyrazol-4-yl)phenyl)-2-(3-(trifluoromethyl)phenyl)acetamide;
- (R)-N-(3-fluoro-4-(1-(2-oxopyrrolidin-3-yl)-1H-pyrazol-4-yl)phenyl)-2-(3-(trifluoromethyl)phenyl)acetamide;

- (S)-N-(3-fluoro-4-(1-(2-oxopyrrolidin-3-yl)-1H-pyrazol-4-yl)phenyl)-2-(3-(trifluoromethyl)phenyl)acetamide;
N-(3-cyano-5-fluoro-4-(1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)phenyl)-2-(3-(pentafluoro- λ 6-sulfaneyl)phenyl)acetamide;
5 N-(3,5-difluoro-4-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)phenyl)-2-(3-(trifluoromethyl)phenyl)acetamide;
N-(3,5-difluoro-4-(1-((1R,2R)-2-hydroxycyclopentyl)-1H-1,2,3-triazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
10 1-(2-fluoro-3-(trifluoromethyl)phenyl)-3-(5-fluoro-6-(4-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-1-methylurea;
(R or S)-1-(2-fluoro-3-(trifluoromethyl)phenyl)-3-(5-fluoro-6-(4-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-1-methylurea;
N-(6-(4-(1,1-dioxidothiomorpholino)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
15 N-(6-(4-(3,6-dihydro-2H-pyran-4-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
N-(5-fluoro-6-(4-(morpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
N-(6-(4-(4-acetylmorpholin-3-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
20 (R or S)-N-(6-(4-(4-acetylmorpholin-3-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
(R)-N-(6-(4-(4-acetylmorpholin-3-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
25 (S)-N-(6-(4-(4-acetylmorpholin-3-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
N-(5-fluoro-6-(4-(morpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
(R or S)-N-(5-fluoro-6-(4-(morpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
30 (R)-N-(5-fluoro-6-(4-(morpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
(S)-N-(5-fluoro-6-(4-(morpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
35 N-(3-cyano-5-fluoro-4-(1-(isoxazolidin-4-yl)-1H-pyrazol-4-yl)phenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
N-(3-cyano-5-fluoro-4-(1-(2-methylisoxazolidin-4-yl)-1H-pyrazol-4-yl)phenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
N-(5-fluoro-6-(4-(2-(3-hydroxypyrrolidin-1-yl)propan-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
40 N-(5-fluoro-6-(4-(2-(2-oxopyrrolidin-1-yl)propan-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
N-(5-fluoro-6-(4-(2-oxopyrrolidin-1-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
45 N-(6-(4-(5,6-dihydro-1,4-oxathiin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
N-(6-(4-(4,4-dioxido-5,6-dihydro-1,4-oxathiin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
N-(6-(4-(4,4-dioxido-1,4-oxathian-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
50 2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(3-methoxypyridin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
N-(5-fluoro-6-(4-(4-methyl-3-oxopiperazin-1-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
55 2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(morpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;

- N-(6-(4-(3-(aminomethyl)-1-hydroxycyclobutyl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
- N-(6-(4-((1r or 1s,3r or 3s)-3-(Aminomethyl)-1-hydroxycyclobutyl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
- 5 N-(5-fluoro-6-(4-(2-hydroxycyclopentyl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
- N-(5-fluoro-6-(4-(((1R or 1S),(2R or 2S))-2-hydroxycyclopentyl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
- 10 N-(5-fluoro-6-(4-(((1R),(2R))-2-hydroxycyclopentyl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
- N-(5-fluoro-6-(4-(((1R),(2S))-2-hydroxycyclopentyl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
- N-(5-fluoro-6-(4-(((1S),(2R))-2-hydroxycyclopentyl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
- 15 N-(5-fluoro-6-(4-(((1S),(2S))-2-hydroxycyclopentyl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
- (S)-3-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-1-(2-fluoro-3-(trifluoromethyl)phenyl)-1-methylurea;
- N-(4-(1-((1-benzyl-1H-imidazol-2-yl)methyl)-1H-pyrazol-4-yl)-3-cyano-5-fluorophenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
- 20 N-(6-(4-(2-(1,3,4-oxadiazol-2-yl)propan-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
- N-(4-(1-((1H-imidazol-2-yl)methyl)-1H-pyrazol-4-yl)-3-cyano-5-fluorophenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
- 25 N-(3-cyano-5-fluoro-4-(1-((1-methyl-1H-imidazol-2-yl)methyl)-1H-pyrazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
- N-(6-(4-(1,1-Dioxidothiomorpholin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
- (R or S)-N-(6-(4-(1,1-Dioxidothiomorpholin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
- 30 (R)-N-(6-(4-(1,1-Dioxidothiomorpholin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
- (S)-N-(6-(4-(1,1-Dioxidothiomorpholin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
- 35 N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
- (S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
- (R)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
- 40 N-(5-fluoro-6-(4-(2-(trifluoromethyl)oxetan-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
- 2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(3-(1-imino-1-oxidotetrahydro-1H-1λ6-thiophen-2-yl)-1H-1,2,4-triazol-1-yl)pyridin-3-yl)acetamide;
- 45 N-(3-cyano-5-fluoro-4-(1-(2-(5-methyl-4H-1,2,4-triazol-3-yl)propan-2-yl)-1H-pyrazol-4-yl)phenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
- N-(3-cyano-5-fluoro-4-(1-(2-(5-methyl-1,3,4-oxadiazol-2-yl)propan-2-yl)-1H-pyrazol-4-yl)phenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
- N-(6-(4-(1H-tetrazol-5-yl)methyl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
- 50 2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(3-oxopiperazin-1-yl)methyl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
- tert-butyl (2R,4R)-2-cyano-4-(4-(3-cyano-5-(2-(3-(trifluoromethyl)phenoxy)acetamido)pyridin-2-yl)-1H-pyrazol-1-yl)pyrrolidine-1-carboxylate;
- 55 N-(5-fluoro-6-(4-(3-methyl-1-oxido-1,2-thiazinan-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;

- (R or S)-N-(5-fluoro-6-(4-(3-methyl-1-oxido-1,2-thiazinan-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
- (R)-N-(5-fluoro-6-(4-(3-methyl-1-oxido-1,2-thiazinan-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
- 5 (S)-N-(5-fluoro-6-(4-(3-methyl-1-oxido-1,2-thiazinan-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
- N-(5-fluoro-6-(3-(2-(2-oxopyrrolidin-1-yl)propan-2-yl)-1H-1,2,4-triazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
- 10 N-(6-(4-(3,6-dihydro-2H-pyran-4-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
- 2-(5-chloro-3-(trifluoromethyl)-1H-pyrazol-1-yl)-N-(5-fluoro-6-(4-(3-methylmorpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
- (R or S)-2-(5-chloro-3-(trifluoromethyl)-1H-pyrazol-1-yl)-N-(5-fluoro-6-(4-(3-methylmorpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
- 15 (R)-2-(5-chloro-3-(trifluoromethyl)-1H-pyrazol-1-yl)-N-(5-fluoro-6-(4-(3-methylmorpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
- (S)-2-(5-chloro-3-(trifluoromethyl)-1H-pyrazol-1-yl)-N-(5-fluoro-6-(4-(3-methylmorpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
- 20 2-(3-chloro-5-(trifluoromethyl)-1H-pyrazol-1-yl)-N-(5-fluoro-6-(4-(3-methylmorpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
- N-(5-fluoro-6-(4-(3-methylmorpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
- (R or S)-N-(5-fluoro-6-(4-(3-methylmorpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
- 25 (R)-N-(5-fluoro-6-(4-(3-methylmorpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
- (S)-N-(5-fluoro-6-(4-(3-methylmorpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
- 30 2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(morpholin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
- (R or S)-2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(morpholin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
- (R)-2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(morpholin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
- 35 (S)-2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(morpholin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
- 2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(5-oxomorpholin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
- 2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(4-methylmorpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
- 40 N-(5-fluoro-6-(4-(pyrrolidin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
- (R or S)-2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(morpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
- 45 (R)-2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(morpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
- (S)-2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(morpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
- N-(5-fluoro-6-(4-(3-methylmorpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
- 50 (R or S)-N-(5-fluoro-6-(4-(3-methylmorpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
- (R)-N-(5-fluoro-6-(4-(morpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
- 55 (S)-N-(5-fluoro-6-(4-(morpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;

- N-(5-fluoro-6-(4-(morpholin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
(R or S)-N-(5-fluoro-6-(4-(morpholin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
5 (R)-N-(5-fluoro-6-(4-(morpholin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
(S)-N-(5-fluoro-6-(4-(morpholin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
10 N-(5-fluoro-6-(4-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)propanamide;
(R or S)-N-(5-fluoro-6-(4-((R or S)-2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)propanamide;
(R)-N-(5-fluoro-6-(4-((R)-2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)propanamide;
15 (S)-N-(5-fluoro-6-(4-((S)-2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)propanamide;
(R)-N-(5-fluoro-6-(4-((S)-2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)propanamide;
(S)-N-(5-fluoro-6-(4-((S)-2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)propanamide;
20 N-(6-(4-(4,4-difluoropiperidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
(R or S)-N-(6-(4-(4,4-difluoropiperidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
25 (R)-N-(6-(4-(4,4-difluoropiperidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
(S)-N-(6-(4-(4,4-difluoropiperidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
30 N-(6-(4-(1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
(R or S)-N-(6-(4-(1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
(R)-N-(6-(4-(1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
35 (S)-N-(6-(4-(1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
N-(5-fluoro-6-(4-morpholino-1H-imidazol-1-yl)pyridin-3-yl)-2-(4-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(tetrahydrothiophen-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
40 N-(6-(4-(3,3-dimethylpiperazin-1-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-morpholino-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
45 2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(4-methylpiperazin-1-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
N-(6-(4-(1,1-dioxidotetrahydrothiophen-3-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
50 (R or S)-N-(6-(4-(1,1-dioxidotetrahydrothiophen-3-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
(R)-N-(6-(4-(1,1-dioxidotetrahydrothiophen-3-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
(S)-N-(6-(4-(1,1-dioxidotetrahydrothiophen-3-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
55 N-(5-fluoro-6-(4-(4-methyl-2-oxopiperazin-1-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;

- 2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(2-oxopiperazin-1-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
N-(5-fluoro-6-(4-(1-methyl-5-oxopyrrolidin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
5 (R or S)-N-(5-fluoro-6-(4-(1-methyl-5-oxopyrrolidin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
(R)-N-(5-fluoro-6-(4-(1-methyl-5-oxopyrrolidin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
(S)-N-(5-fluoro-6-(4-(1-methyl-5-oxopyrrolidin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
10 N-(5-fluoro-6-(4-(2-oxopyrrolidin-1-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(4-hydroxy-2-oxopyrrolidin-1-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
15 2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(pyrrolidin-1-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
N-(5-fluoro-6-(4-morpholino-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
N-(6-(4-(5,6-dihydro-1,4-dioxin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
20 N-(6-(4-(1,4-dioxan-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
(R or S)-N-(6-(4-(1,4-dioxan-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
(R)-N-(6-(4-(1,4-dioxan-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
(S)-N-(6-(4-(1,4-dioxan-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
25 N-(6-(4-(4,4-difluoropyrrolidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
(R or S)-N-(6-(4-(4,4-difluoropyrrolidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
(R)-N-(6-(4-(4,4-difluoropyrrolidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
(S)-N-(6-(4-(4,4-difluoropyrrolidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
30 N-(6-(4-(4,4-difluoropyrrolidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
(R or S)-N-(6-(4-(4,4-difluoropyrrolidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
(R)-N-(6-(4-(4,4-difluoropyrrolidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
(S)-N-(6-(4-(4,4-difluoropyrrolidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
35 N-(5-cyano-6-(1-(3,3-difluoro-1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)pyridin-3-yl)-2-(3-(trifluoromethyl)phenoxy)acetamide;
N-(6-(4-(4,4-difluoropiperidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
40 (R or S)-N-(6-(4-(4,4-difluoropiperidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
(R)-N-(6-(4-(4,4-difluoropiperidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
(S)-N-(6-(4-(4,4-difluoropiperidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
45 N-(6-(3-(5,5-difluoropiperidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
(R or S)-N-(6-(3-(5,5-difluoropiperidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
(R)-N-(6-(3-(5,5-difluoropiperidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
(S)-N-(6-(3-(5,5-difluoropiperidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
50 N-(5-fluoro-6-(4-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-7-(trifluoromethyl)-3,4-dihydro-2H-pyrano[2,3-b]pyridine-2-carboxamide;

- N-(5-fluoro-6-(4-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
(R or S)-N-(5-fluoro-6-(4-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
5 (R)-N-(5-fluoro-6-(4-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
(S)-N-(5-fluoro-6-(4-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
10 N-(6-(4-(4,4-difluoropiperidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(4-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
N-(6-(4-(1-amino-3,3-difluorocyclobutyl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
N-(5-fluoro-6-(4-(2-methyltetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-7-(trifluoromethyl)-3,4-dihydro-2H-pyrano[2,3-b]pyridine-2-carboxamide;
15 N-(6-(3-(5,5-difluoropiperidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
(R or S)-N-(6-(3-(5,5-difluoropiperidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
(R)-N-(6-(3-(5,5-difluoropiperidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
20 (S)-N-(6-(3-(5,5-difluoropiperidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
N-(5-fluoro-6-(4-(1-hydroxycyclohexyl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
25 N-(5-fluoro-6-(4-(1-hydroxycyclopentyl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(2-oxopiperidin-1-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
N-(5-fluoro-6-(4-(3-hydroxy-1-methylpyrrolidin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
30 N-(6-(3-(5,5-difluoropiperidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
(R or S)-N-(6-(3-(5,5-difluoropiperidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
35 (R)-N-(6-(3-(5,5-difluoropiperidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
(S)-N-(6-(3-(5,5-difluoropiperidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(3-hydroxy-1,1-dioxidotetrahydrothiophen-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
40 (R or S)-2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(3-hydroxy-1,1-dioxidotetrahydrothiophen-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
(R)-2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(3-hydroxy-1,1-dioxidotetrahydrothiophen-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
45 (S)-2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(3-hydroxy-1,1-dioxidotetrahydrothiophen-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
1-(2-fluoro-3-(trifluoromethyl)phenyl)-3-(5-fluoro-6-(4-(morpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-1-methylurea;
(R or S)-1-(2-fluoro-3-(trifluoromethyl)phenyl)-3-(5-fluoro-6-(4-(morpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-1-methylurea;
50 (R)-1-(2-fluoro-3-(trifluoromethyl)phenyl)-3-(5-fluoro-6-(4-(morpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-1-methylurea;
(S)-1-(2-fluoro-3-(trifluoromethyl)phenyl)-3-(5-fluoro-6-(4-(morpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-1-methylurea;
55 N-(6-(4-(3,9-dioxo-7-azabicyclo[3.3.1]nonan-7-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;

- N-(5-fluoro-6-(4-(piperidin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
(R or S)-N-(5-fluoro-6-(4-(piperidin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
5 (R)-N-(5-fluoro-6-(4-(piperidin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
(S)-N-(5-fluoro-6-(4-(piperidin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
10 (2-(4-chloro-3-(trifluoromethyl)-1H-pyrazol-1-yl)-N-(5-fluoro-6-(4-(morpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
(R or S)-2-(4-chloro-3-(trifluoromethyl)-1H-pyrazol-1-yl)-N-(5-fluoro-6-(4-(morpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
(R)-2-(4-chloro-3-(trifluoromethyl)-1H-pyrazol-1-yl)-N-(5-fluoro-6-(4-(morpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
15 (S)-2-(4-chloro-3-(trifluoromethyl)-1H-pyrazol-1-yl)-N-(5-fluoro-6-(4-(morpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(1,2,3,6-tetrahydropyridin-4-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
N-(5-fluoro-6-(4-(piperidin-4-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
20 N-(5-fluoro-6-(4-(4-hydroxytetrahydro-2H-pyran-4-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
N-(3-cyano-5-fluoro-4-(1-(oxazol-2-ylmethyl)-1H-pyrazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
25 N-(6-(4-(3-aminooxetan-3-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
N-(5-cyano-6-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)pyridin-3-yl)-2-hydroxy-2-(3-(trifluoromethyl)phenyl)acetamide;
N-(3-cyano-4-(1-(3,3-difluoropiperidin-4-yl)-1H-pyrazol-4-yl)-5-fluorophenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
30 N-(3-cyano-4-(1-(3,3-difluoro-1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)-5-fluorophenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(piperidin-4-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
35 2-(5-chloro-3-(trifluoromethyl)-1H-pyrazol-1-yl)-N-(5-fluoro-6-(4-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
(R or S)-2-(5-chloro-3-(trifluoromethyl)-1H-pyrazol-1-yl)-N-(5-fluoro-6-(4-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
(R)-2-(5-chloro-3-(trifluoromethyl)-1H-pyrazol-1-yl)-N-(5-fluoro-6-(4-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
40 (S)-2-(5-chloro-3-(trifluoromethyl)-1H-pyrazol-1-yl)-N-(5-fluoro-6-(4-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
N-(5-fluoro-6-(4-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
45 (R or S)-N-(5-fluoro-6-(4-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
(R)-N-(5-fluoro-6-(4-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
(S)-N-(5-fluoro-6-(4-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
50 2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
(R)-2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
55 (S)-2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;

- 2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(2-methyl-1-oxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
N-(5-fluoro-6-(4-(tetrahydrofuran-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
5 (R or S)-N-(5-fluoro-6-(4-(tetrahydrofuran-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
(R)-N-(5-fluoro-6-(4-(tetrahydrofuran-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
(S)-N-(5-fluoro-6-(4-(tetrahydrofuran-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
10 N-(5-fluoro-6-(4-(2-methyltetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(2-methyltetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
15 N-(6-(4-(4,4-difluoro-2-methylpyrrolidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
(R or S)-N-(6-(4-(4,4-difluoro-2-methylpyrrolidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
(R)-N-(6-(4-(4,4-difluoro-2-methylpyrrolidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
20 (S)-N-(6-(4-(4,4-difluoro-2-methylpyrrolidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
2-(5-chloro-3-(trifluoromethyl)-1H-pyrazol-1-yl)-N-(6-(4-(4,4-difluoro-2-methylpyrrolidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)acetamide;
25 N-(6-(4-(4,4-difluoropyrrolidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
(R or S)-N-(6-(4-(4,4-difluoropyrrolidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
(R)-N-(6-(4-(4,4-difluoropyrrolidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
30 (S)-N-(6-(4-(4,4-difluoropyrrolidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
N-(5-fluoro-6-(4-(pyrrolidin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
35 (R or S)-N-(5-fluoro-6-(4-(pyrrolidin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
(R)-N-(5-fluoro-6-(4-(pyrrolidin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
(S)-N-(5-fluoro-6-(4-(pyrrolidin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
40 (R)-N-(5-fluoro-6-(4-(pyrrolidin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(pyrrolidin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
(R or S)-2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(pyrrolidin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
45 (R)-2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(pyrrolidin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
(S)-2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(pyrrolidin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
N-(6-(4-(1-acetyl-2-methylpyrrolidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
50 2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(3-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-1,2,4-triazol-1-yl)pyridin-3-yl)acetamide;
(R or S)-2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(3-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-1,2,4-triazol-1-yl)pyridin-3-yl)acetamide;
55 (R)-2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(3-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-1,2,4-triazol-1-yl)pyridin-3-yl)acetamide;

- (S)-2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(3-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-1,2,4-triazol-1-yl)pyridin-3-yl)acetamide;
N-(5-fluoro-6-(3-(morpholin-3-yl)-1H-1,2,4-triazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
5 (R or S)-N-(5-fluoro-6-(3-(morpholin-3-yl)-1H-1,2,4-triazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
(R)-N-(5-fluoro-6-(3-(morpholin-3-yl)-1H-1,2,4-triazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
(S)-N-(5-fluoro-6-(3-(morpholin-3-yl)-1H-1,2,4-triazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
10 N-(6-(3-(1-amino-3,3-difluorocyclobutyl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
N-(5-fluoro-6-(3-(3-methylmorpholin-3-yl)-1H-1,2,4-triazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
15 (R or S)-N-(5-fluoro-6-(3-(3-methylmorpholin-3-yl)-1H-1,2,4-triazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
(R)-N-(5-fluoro-6-(3-(3-methylmorpholin-3-yl)-1H-1,2,4-triazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
(S)-N-(5-fluoro-6-(3-(3-methylmorpholin-3-yl)-1H-1,2,4-triazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
20 N-(6-(3-(3,3-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
(R or S)-N-(6-(3-(3,3-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
25 (R)-N-(6-(3-(3,3-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
(S)-N-(6-(3-(3,3-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
(S)-N-(6-(3-(4,4-difluoro-2-methylpyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
30 (S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
(S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
35 N-(6-(4-(1,1-dioxidothiomorpholin-3-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
(R or S)-N-(6-(4-(1,1-dioxidothiomorpholin-3-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
(R)-N-(6-(4-(1,1-dioxidothiomorpholin-3-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
40 (S)-N-(6-(4-(1,1-dioxidothiomorpholin-3-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
N-(5-fluoro-6-(4-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
45 2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
N-(6-(4-(1,1-dioxidothiomorpholin-3-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
(R or S)-N-(6-(4-(1,1-dioxidothiomorpholin-3-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
50 (R)-N-(6-(4-(1,1-dioxidothiomorpholin-3-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
(S)-N-(6-(4-(1,1-dioxidothiomorpholin-3-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
55 N-(6-(4-(1,1-dioxidothiomorpholin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;

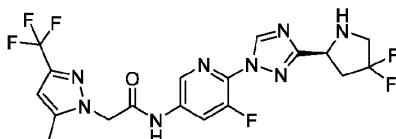
- (R or S)-N-(6-(4-(1,1-dioxidothiomorpholin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
(R)-N-(6-(4-(1,1-dioxidothiomorpholin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
5 (S)-N-(6-(4-(1,1-dioxidothiomorpholin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
N-(6-(4-((1R,3S,5R)-2-azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
N-(6-(4-(5-azaspiro[2.4]heptan-6-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
10 (R or S)-N-(6-(4-(5-azaspiro[2.4]heptan-6-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
(R)-N-(6-(4-(5-azaspiro[2.4]heptan-6-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
15 (S)-N-(6-(4-(5-azaspiro[2.4]heptan-6-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
N-(6-(4-((1S,3R,4R)-2-azabicyclo[2.2.1]heptan-3-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
N-(6-(4-((1R,3S,4S)-2-azabicyclo[2.2.1]heptan-3-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
20 N-(5-fluoro-6-(4-(4-hydroxytetrahydro-2H-pyran-4-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
N-(3-cyano-5-fluoro-4-(1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)phenyl)-2-(3-(perfluoroethyl)phenyl)acetamide;
25 N-(3-cyano-5-fluoro-4-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)phenyl)-2-(3-(pentafluoro-l6-sulfaneyl)phenoxy)acetamide;
N-(5-Fluoro-6-(3-(1-imino-1-oxidotetrahydro-1H-1l6-thiophen-2-yl)-1H-1,2,4-triazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
N-(6-(4-(1-acetylpyrrolidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
30 (R or S)-N-(6-(4-(1-acetylpyrrolidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
N-(3-cyano-5-fluoro-4-(1-(1-methyl-1H-tetrazol-5-yl)methyl)-1H-pyrazol-4-yl)phenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
35 N-(4-(1-(2-(4H-1,2,4-triazol-3-yl)propan-2-yl)-1H-pyrazol-4-yl)-3-cyano-5-fluorophenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
N-(4-(1-(2-(1,3,4-oxadiazol-2-yl)propan-2-yl)-1H-pyrazol-4-yl)-3-cyano-5-fluorophenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
N-(3-cyano-5-fluoro-4-(1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)phenyl)-2-hydroxy-2-(3-(trifluoromethyl)phenyl)acetamide;
40 N-(3-cyano-5-fluoro-4-(1-(tetrahydro-2H-pyran-3-yl)-1H-pyrazol-4-yl)phenyl)-2-hydroxy-2-(3-(trifluoromethyl)phenyl)acetamide;
N-(3-cyano-5-fluoro-4-(1-(piperidin-3-yl)-1H-pyrazol-4-yl)phenyl)-2-(3-(pentafluoro-l6-sulfaneyl)phenoxy)acetamide;
45 2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(1,2,5,6-tetrahydropyridin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(piperidin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
N-(6-(4-(1-acetylpyrrolidin-3-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
50 (R or S)-N-(6-(4-(1-acetylpyrrolidin-3-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(piperidin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
55 (R or S)-2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(piperidin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;

- (R)-2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(piperidin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
(S)-2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(piperidin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
5 N-(6-(4-(1-acetylpiperidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
N-(5-fluoro-6-(4-(2-methylpyrrolidin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
(R or S)-N-(5-fluoro-6-(4-(2-methylpyrrolidin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
10 (R)-N-(5-fluoro-6-(4-(2-methylpyrrolidin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
(S)-N-(5-fluoro-6-(4-(2-methylpyrrolidin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
15 2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(morpholinomethyl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
N-(3-fluoro-4-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)phenyl)-2-(3-(trifluoromethyl)phenyl)acetamide;
tert-butyl 4-(4-(2-cyano-6-fluoro-4-(2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamido)phenyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate;
20 N-(3-cyano-5-fluoro-4-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
N-(3-cyano-5-fluoro-4-(1-(1-(2-hydroxyethyl)piperidin-4-yl)-1H-pyrazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
25 N-(3,5-difluoro-4-(1-(2-hydroxy-1-(1-methoxycyclobutyl)ethyl)-1H-1,2,3-triazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
N-(3,5-difluoro-4-(1-((3R,4S)-4-methoxytetrahydrofuran-3-yl)-1H-1,2,3-triazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
N-(4-(1-((2,3-dihydrobenzo[b][1,4]dioxin-2-yl)methyl)-1H-1,2,3-triazol-4-yl)-3,5-difluorophenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
30 N-(3,5-difluoro-4-(1-(4-sulfamoylphenyl)-1H-1,2,3-triazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
N-(4-(1-((1-benzylpyrrolidin-3-yl)methyl)-1H-1,2,3-triazol-4-yl)-3,5-difluorophenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
35 N-(4-(1-(4,4-dimethyl-2-oxotetrahydrofuran-3-yl)-1H-1,2,3-triazol-4-yl)-3,5-difluorophenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
N-(3,5-difluoro-4-(1-((3-methyloxetan-3-yl)methyl)-1H-1,2,3-triazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
N-(3,5-difluoro-4-(1-((1-(methylsulfonyl)cyclohexyl)methyl)-1H-1,2,3-triazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
40 N-(3,5-difluoro-4-(1-(1-methyl-2-oxopyrrolidin-3-yl)-1H-1,2,3-triazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
N-(3,5-difluoro-4-(1-(pyrrolidin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
45 N-(4-(1-((3S,4R)-4-(1H-pyrazol-1-yl)tetrahydrofuran-3-yl)-1H-1,2,3-triazol-4-yl)-3,5-difluorophenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
N-(3,5-difluoro-4-(1-(2-morpholinoethyl)-1H-1,2,3-triazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
N-(3,5-difluoro-4-(1-(2-((tetrahydrofuran-3-yl)oxy)ethyl)-1H-1,2,3-triazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
50 N-(3,5-difluoro-4-(1-(2-(1-methyl-1H-1,2,3-triazol-4-yl)ethyl)-1H-1,2,3-triazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
N-(3,5-difluoro-4-(1-(1-methylpiperidin-4-yl)-1H-1,2,3-triazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
55 N-(3,5-difluoro-4-(1-((5-oxotetrahydrofuran-2-yl)methyl)-1H-1,2,3-triazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;

- (R)-N-(3,5-difluoro-4-(1-((6-oxopiperidin-2-yl)methyl)-1H-1,2,3-triazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
N-(3,5-difluoro-4-(1-(2-(2-oxopyridin-1(2H)-yl)ethyl)-1H-1,2,3-triazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
5 (R)-N-(3,5-difluoro-4-(1-(1-(1-methyl-1H-1,2,3-triazol-5-yl)ethyl)-1H-1,2,3-triazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
N-(4-(1-(2-(1H-pyrazol-1-yl)ethyl)-1H-1,2,3-triazol-4-yl)-3,5-difluorophenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
N-(3,5-difluoro-4-(1-((4-oxo-3,5,7,8-tetrahydro-4H-pyrano[4,3-d]pyrimidin-2-yl)methyl)-1H-1,2,3-triazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
10 N-(5-fluoro-6-(4-(morpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)propanamide;
N-(6-(4-(3-aminooxetan-3-yl)methyl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
15 N-(3-fluoro-4-(1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)phenyl)-2-(3-(trifluoromethyl)phenyl)acetamide;
N-(6-(1-(2-azaspiro[3.3]heptan-6-yl)-1H-pyrazol-4-yl)-5-cyanopyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
N-(6-(1-(2-oxaspiro[3.3]heptan-6-yl)-1H-pyrazol-4-yl)-5-cyanopyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
20 N-(3-cyano-5-fluoro-4-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)phenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
N-(3-cyano-5-fluoro-4-(1-(1-(2-methoxyethyl)piperidin-4-yl)-1H-pyrazol-4-yl)phenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
25 N-(3-cyano-5-fluoro-4-(1-(pyrrolidin-3-yl)-1H-pyrazol-4-yl)phenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
N-(3-fluoro-4-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)phenyl)-2-(3-(trifluoromethyl)phenyl)acetamide;
N-(3-fluoro-4-(1-(2-oxopiperidin-4-yl)-1H-pyrazol-4-yl)phenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
30 N-(4-(1-(2,2-dimethylpiperidin-4-yl)-1H-pyrazol-4-yl)-3-fluorophenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
N-(3-fluoro-4-(1-(6-oxopiperidin-3-yl)-1H-pyrazol-4-yl)phenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide;
N-(3-fluoro-4-(1-(2-(4-methylpiperazin-1-yl)ethyl)-1H-pyrazol-4-yl)phenyl)-2-(3-(trifluoromethyl)phenyl)acetamide;
35 N-(3-fluoro-4-(1-((4-hydroxypiperidin-4-yl)methyl)-1H-pyrazol-4-yl)phenyl)-2-(3-(trifluoromethyl)phenyl)acetamide;
N-(4-(1-(2-(4H-1,2,4-triazol-3-yl)propan-2-yl)-1H-pyrazol-4-yl)-3,5-difluorophenyl)-2-(3-(trifluoromethyl)phenyl)acetamide;
40 N-(3,5-difluoro-4-(1-(pyridin-2-yl)-1H-pyrazol-4-yl)phenyl)-2-(3-(trifluoromethyl)phenyl)acetamide;
N-(6-(4-(3,6-dihydro-2H-pyran-4-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide;
2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(4-methoxypiperidin-1-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
45 2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(2-oxopyrrolidin-1-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(3-oxomorpholino)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
50 2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(4-hydroxytetrahydro-2H-pyran-4-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide;
N-(6-(3-(1-amino-3,3-difluorocyclobutyl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide;
N-(3-cyano-5-fluoro-4-(1-(tetrahydro-2H-pyran-3-yl)-1H-pyrazol-4-yl)phenyl)-2-(3-(pentafluoro-
55 l6-sulfaneyl)phenoxy)acetamide;
N-(3,5-difluoro-4-(1-(piperidin-3-yl)-1H-pyrazol-4-yl)phenyl)-2-(3-(trifluoromethyl)phenyl)acetamide; and

N-(5-fluoro-6-(4-(tetrahydrofuran-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide.

In an embodiment of compounds of Formula (I), Formula (I-a) and Formula (I-c), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, the compound is (S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide and has the structure



In an embodiment of compounds of Formula (I), Formula (I-a) and Formula (I-c), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, the compound of is crystalline (S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide.

In an embodiment of compounds of Formula (I), Formula (I-a) and Formula (I-c), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, wherein the crystalline (S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide is characterized by having a powder X-ray diffractogram comprising at least four reflections at 2-Theta angles selected from the group consisting of $(12.36 \pm 0.2)^\circ$, $(16.90 \pm 0.2)^\circ$, $(17.49 \pm 0.2)^\circ$, $(19.21 \pm 0.2)^\circ$, $(20.15 \pm 0.2)^\circ$, $(21.77 \pm 0.2)^\circ$, $(23.01 \pm 0.2)^\circ$, $(23.47 \pm 0.2)^\circ$, $(25.91 \pm 0.2)^\circ$ and $(29.88 \pm 0.2)^\circ$, when measured at a temperature in the range of from 20 to 40 °C with Cu-Kalpha radiation having a wavelength of 0.15406 nm.

In an embodiment of compounds of Formula (I), Formula (I-a) and Formula (I-c), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, wherein the crystalline (S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide is characterized by having a powder X-ray diffractogram comprising reflections at 2-Theta angles of $(16.90 \pm 0.2)^\circ$, $(17.49 \pm 0.2)^\circ$, $(23.01 \pm 0.2)^\circ$, $(25.91 \pm 0.2)^\circ$ and $(29.88 \pm 0.2)^\circ$, when measured at a temperature in the range of from 20 to 40 °C with Cu-Kalpha radiation having a wavelength of 0.15406 nm.

In an embodiment of compounds of Formula (I), Formula (I-a) and Formula (I-c), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, wherein the crystalline (S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide is characterized by having a powder X-ray diffractogram shown in

Figure 1.

In an embodiment of compounds of Formula (I), Formula (I-a) and Formula (I-c), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, wherein the crystalline (S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide is characterized by having a differential scanning calorimetry curve comprising an endothermic peak having a peak temperature of $(176.8 \pm 0.5)^\circ\text{C}$, when measured at a heating rate of $10^\circ\text{C}/\text{min}$.

In an embodiment of compounds of Formula (I), Formula (I-a) and Formula (I-c), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, wherein the crystalline (S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide is characterized by having a differential scanning calorimetry curve as shown in Figure 2.

In an embodiment of compounds of Formula (I), Formula (I-a) and Formula (I-c), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, wherein the crystalline (S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide is characterized by having a thermogravimetric analysis curve showing a mass loss of not more than 3.56 weight%, based on the weight of the crystalline (S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide, when heated from 20°C to 350°C at a rate of $10^\circ\text{C}/\text{min}$.

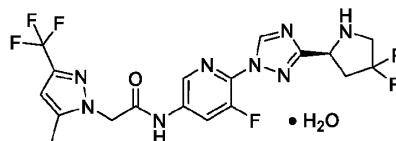
In an embodiment of compounds of Formula (I), Formula (I-a) and Formula (I-c), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, wherein the crystalline (S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide is characterized by having a thermogravimetric analysis curve as shown in Figure 3.

In an embodiment of compounds of Formula (I), Formula (I-a) and Formula (I-c), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, wherein the crystalline (S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide is (S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide monohydrate.

In an embodiment of compounds of Formula (I), Formula (I-a) and Formula (I-c), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, the compound is (S)-N-(6-(3-(4,4-difluoropyrrolidin-2-

yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-

yl)acetamide monohydrate and has the structure



In an embodiment of compounds of Formula (I), Formula (I-a) and Formula (I-c), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, the compound is amorphous (S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide.

Depending on the choice of the starting materials and procedures, the compounds can be present in the form of one of the possible isomers or as mixtures thereof, for example as pure optical isomers, or as isomer mixtures, such as racemates and diastereoisomer mixtures, depending on the number of asymmetric carbon atoms. The present invention is meant to include all such possible isomers, including racemic mixtures, diastereomeric mixtures and optically pure forms. Optically active (*R*)- and (*S*)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. If the compound contains a double bond, the substituent may be *E* or *Z* configuration. If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a *cis*- or *trans*-configuration. All tautomeric forms are also intended to be included.

As used herein, the terms “salt” or “salts” refers to an acid addition or base addition salt of a compound of the invention. “Salts” include in particular “pharmaceutical acceptable salts”. The terms “pharmaceutically acceptable salt” or “pharmaceutically acceptable salts”, as used herein, refers to a salt or salts that retain the biological effectiveness and properties of the compounds of this invention and, which typically are not biologically or otherwise undesirable. In many cases, the compounds of the present invention are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. The organic acid or inorganic acids used to form pharmaceutically acceptable acid addition salts of compounds of the present invention include, but are not limited to, acetic acid, adipic acid, ascorbic acid, aspartic acid, benzoic acid, benzenesulfonic acid, carbonic acid, camphor sulfonic acid, capric acid, chlorotheophyllinate, citric acid, ethanedisulfonic acid, fumaric acid, D-glycero-D-gulo-Heptonicacid, galactaric acid, galactaric acid/mucic acid, gluceptic acid, glucoheptonic acid, gluconic acid, glucuronic acid, glutamic acid, glutaric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, hydroiodic acid, isethionic acid, lactic acid, lactobionic acid, lauryl sulfuric acid, malic acid, maleic acid, malonic acid, mandelic acid, mesylic acid, methanesulfonic acid, mucic acid, naphthoic acid, 1-hydroxy-2-naphthoic acid, naphthalenesulfonic acid, 2-naphthalenesulfonic acid, nicotinic acid, nitric acid, octadecanoic

acid, oleic acid, oxalic acid, palmitic acid, pamoic acid, phosphoric acid, polygalacturonic acid, propionic acid, sebacic acid, stearic acid, succinic acid, sulfosalicylic acid, sulfuric acid, tartaric acid, p-toluenesulfonic acid, trifluoroacetic acid and triphenylacetic acid.

Salt forms of the compounds of the present invention can be converted into the free
5 compounds by treatment with a suitable basic agent.

Pharmaceutically acceptable acid addition salts of compounds of the present invention include, but are not limited to, acetate, adipate, ascorbate, aspartate, benzoate, besylate, benzenesulfonate, bicarbonate/carbonate, bisulfate/sulfate, bromide/hydrobromide, camphor sulfonate, camsylate, caprate, chloride/hydrochloride, chlorotheophyllinate, citrate, edisylate,
10 ethanedisulfonate, fumarate, gluceptate, glucoheptonate, gluconate, glucuronate, glutamate, glutarate, glycolate, hippurate, hydroiodide/iodide, isethionate, lactate, lactobionate, laurylsulphate, malate, maleate, malonate, mandelate, mesylate, methanesulfonate, methylsulfate, mucate, naphthoate, napsylate, 2-napsylate, naphthalenesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, octadecanoate, oleate, oxalate, palmitate, pamoate,
15 phosphate/hydrogen phosphate/dihydrogen phosphate, polygalacturonate, propionate, sebacate, stearate, succinate, sulfosalicylate, sulfate, tartrate, tosylate, p-toluenesulfonate, trifluoroacetate, trifenate, triphenylacetate and xinafoate salt forms.

The pharmaceutically acceptable salts of the present invention can be synthesized from a basic or acidic moiety, by conventional chemical methods. Generally, such salts can be
20 prepared by reacting free acid forms of these compounds with a stoichiometric amount of the appropriate base (such as Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate or the like), or by reacting free base forms of these compounds with a stoichiometric amount of the appropriate acid. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two. Generally, use of non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or
25 acetonitrile is desirable, where practicable.

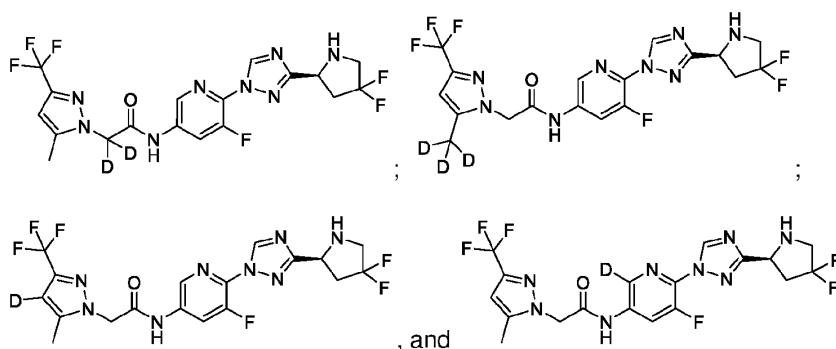
Any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulae given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass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

Further, incorporation of certain isotopes, particularly deuterium (i.e., ^2H 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
35 compound of the present invention. 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 invention 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.

Other examples of isotopes that can be incorporated into compounds of the present invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as ^3H , ^{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 invention includes compounds that incorporate one or more of any of the aforementioned isotopes, including for example, radioactive isotopes, such as ^3H and ^{14}C , or those into which non-radioactive isotopes, such as ^2H and ^{13}C are present. Such isotopically labelled compounds are useful in metabolic studies (with ^{14}C), reaction kinetic studies (with, for example ^2H or ^3H), 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 invention 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.).

Compounds of the present invention can exist in a deuterated form, by way of example as shown below:



Any asymmetric atom (e.g., carbon or the like) of the compound(s) of the present invention 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.

Accordingly, as used herein a compound of the present invention can be in the form of one
5 of the possible isomers, rotamers, atropisomers, tautomers or mixtures thereof, for example, as substantially pure geometric (*cis* or *trans*) isomers, diastereomers, optical isomers (antipodes), racemates or mixtures thereof.

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

Any resulting racemates of final products or 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
15 invention 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 products can also be resolved by chiral chromatography, *e.g.*, high pressure liquid chromatography (HPLC) using a chiral adsorbent.

20

Processes for Making Compounds of Invention

General procedures for preparing compounds of the present invention are described herein. In the reactions described, reactive functional groups, for example hydroxy, amino, imino or carboxy groups, where these are desired in the final product, may be protected to avoid their
25 unwanted participation in the reactions. Within the scope of this text, only a readily removable group that is not a constituent of the particular desired end product of the compounds of the present invention is designated a "protecting group", unless the context indicates otherwise. The protection of functional groups by such protecting groups, the protecting groups themselves, and their cleavage reactions are described for example in standard reference works, such as J.
30 F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York 1999.

All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples,
35 or exemplary language (*e.g.* "such as") provided herein is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention otherwise claimed.

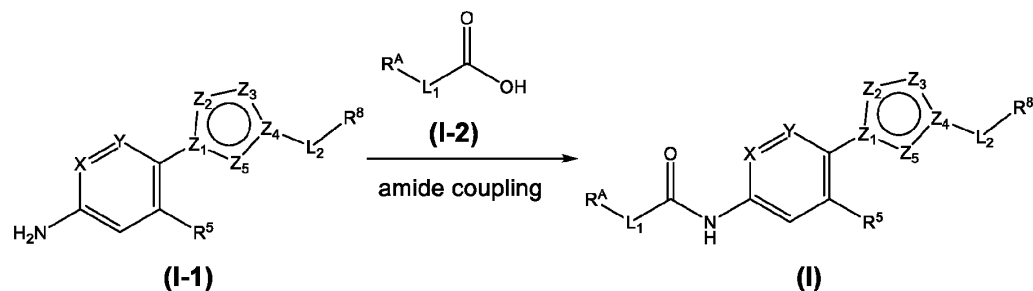
Methods of synthesizing compounds of the invention

Compounds of the present invention were made by processes described herein and as illustrated in the Examples. The combination of various building blocks and intermediates described herein can be applied to yield compounds of the invention. Non-limiting examples of synthetic schemes used to make compounds of the present invention are illustrated below in Schemes 1 to 8. Further guidance can be found in the examples section.

General Synthetic Routes

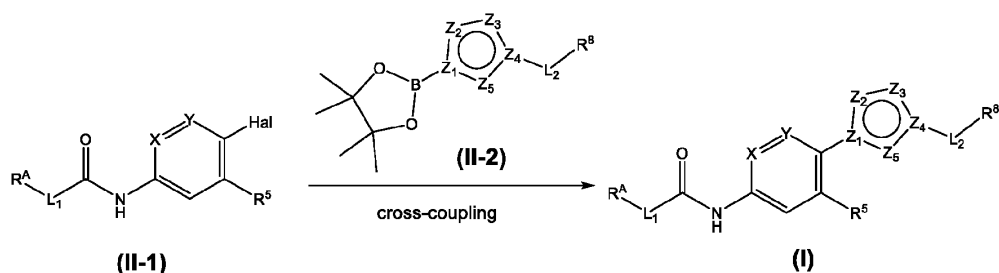
Several methods for preparing the compounds of this disclosure are described in the following schemes. Starting materials and intermediates are purchased, made from known procedures, or prepared as otherwise illustrated. In some cases, the order of carrying out the steps of reaction schemes may be varied to facilitate the reaction or to avoid unwanted reactions. The R groups and other variables in the Schemes correspond to those defined in Formula (I).

Scheme 1:



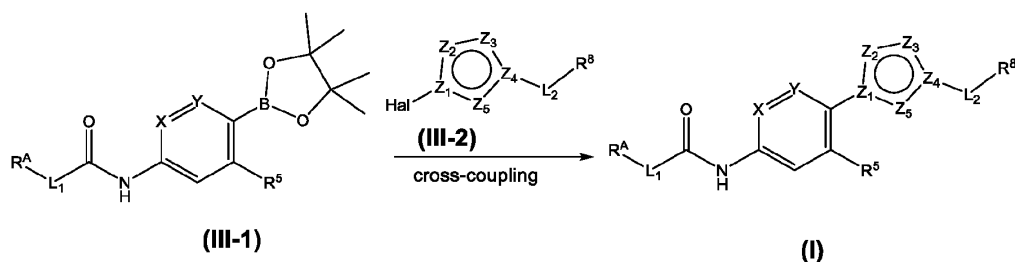
Compounds of Formula (I) as disclosed herein can be synthesized as outlined in Scheme I. An aromatic amine **I-1** is reacted with a carboxylic acid **I-2** under standard amide bond-forming conditions, for example in the presence of an amide coupling reagent such as HATU, T3P, EDCI or 1-chloro-N,N,2-trimethylpropenylamine and a base such as DIPEA, Et₃N or pyridine in a solvent such as DCM, THF or DMF. For certain compounds of Formula (I), the R⁸ group may possess an atom or atoms that is/are either (a) initially protected, for example N-Boc, N-Bn, N-Cbz or O-trialkylsilyl, and are subsequently deprotected, (b) oxidized, for example S → SO₂ or (c) reduced, for example C=C → HC-CH. The groups R^A, L₁, X, Y, R⁵, Z₁, Z₂, Z₃, Z₄, Z₅, L₂ and R⁸ are as defined herein, e.g. according to any one of claims 1 to 11.

Scheme II:



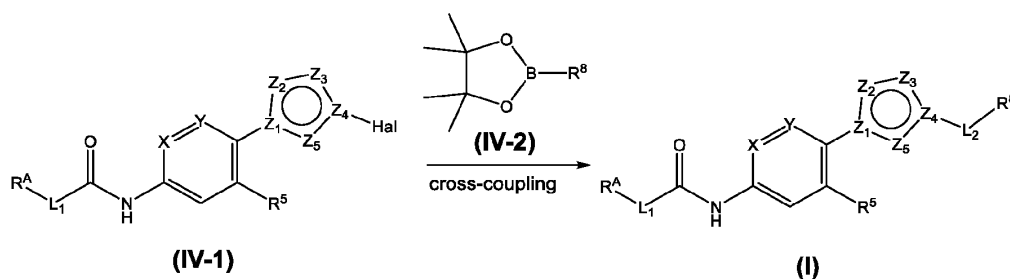
Compounds of Formula (I) as disclosed herein can be synthesized as outlined in Scheme II. A halogenated aromatic **II-1** can be reacted with a heteroaryl **II-2** containing a coupling partner such as a boronic acid/ester (or stannane) in a Suzuki (or Stille) cross-coupling reaction in the presence of a palladium catalyst such as Pd(dppf)Cl₂, Pd(dtbpf)Cl₂, XPhos-Pd-G3 or (Ph₃P)₄Pd with a base such as K₂CO₃, Na₂CO₃, Cs₂CO₃, NaHCO₃ or K₃PO₄ in a solvent such as dioxane, DME, DMF or toluene. For certain compounds of Formula (I), the R⁸ group may possess an atom or atoms that is/are either (a) initially protected, for example N-Boc, N-Bn, N-Cbz or O-trialkylsilyl, and are subsequently deprotected, (b) oxidized, for example S → SO₂ or (c) reduced, for example C=C → HC-CH. The groups R^A, L₁, X, Y, R⁵, Z₁, Z₂, Z₃, Z₄, Z₅, L₂ and R⁸ are as defined herein, e.g. according to any one of claims 1 to 11.

Scheme III:



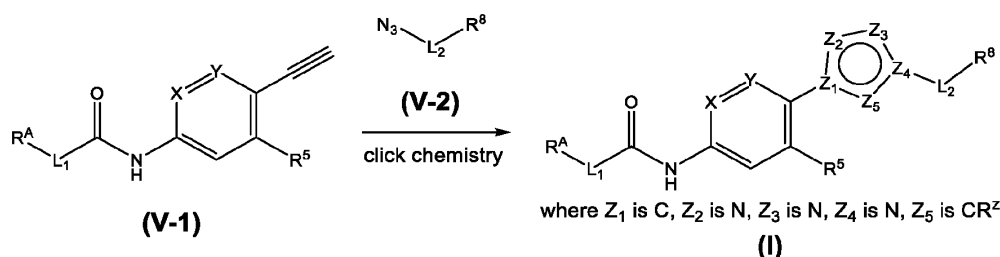
Compounds of Formula (I) as disclosed herein can be synthesized as outlined in Scheme III. An aromatic **III-1** coupling partner, such as a boronic acid/ester (or stannane), can be reacted with a halogenated heteroaryl **III-2** in a Suzuki (or Stille) cross-coupling reaction in the presence of a palladium catalyst such as Pd(dppf)Cl₂, Pd(dtbpf)Cl₂, XPhos-Pd-G3 or (Ph₃P)₄Pd with a base such as K₂CO₃, Na₂CO₃, Cs₂CO₃, NaHCO₃ or K₃PO₄ in a solvent such as dioxane, DME, DMF or toluene. For certain compounds of Formula (I), the R⁸ group may possess an atom or atoms that is/are either (a) initially protected, for example N-Boc, N-Bn, N-Cbz or O-trialkylsilyl, and are subsequently deprotected, (b) oxidized, for example S → SO₂ or (c) reduced, for example C=C → HC-CH. The groups R^A, L₁, X, Y, R⁵, Z₁, Z₂, Z₃, Z₄, Z₅, L₂ and R⁸ are as defined herein, e.g. according to any one of claims 1 to 11.

Scheme IV:



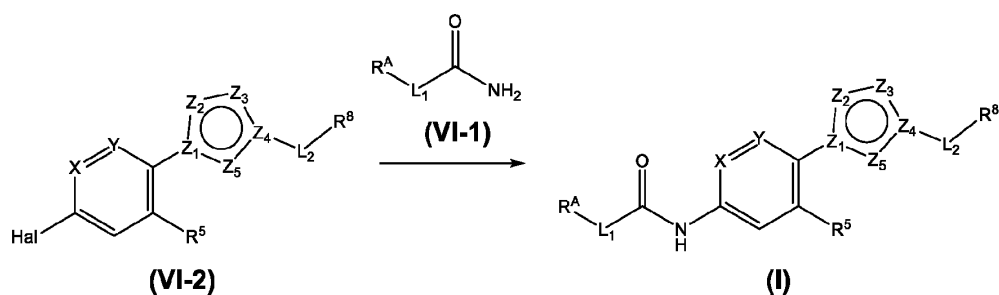
Compounds of Formula (I) as disclosed herein can be synthesized as outlined in Scheme IV. A halogenated heteroaryl **IV-1** can be reacted with a **IV-2** coupling partner, such as a boronic acid/ester (or stannane), in a Suzuki (or Stille) cross-coupling reaction in the presence of a palladium catalyst such as $Pd(dppf)Cl_2$, $Pd(dtbpf)Cl_2$, $XPhos-Pd-G3$ or $(Ph_3P)_4Pd$ with a base such as K_2CO_3 , Na_2CO_3 , Cs_2CO_3 , $NaHCO_3$ or K_3PO_4 in a solvent such as dioxane, DME, DMF or toluene. For certain compounds of Formula (I), the R^8 group may possess an atom or atoms that is/are either (a) initially protected, for example N-Boc, N-Bn, N-Cbz or O-trialkylsilyl, and are subsequently deprotected, (b) oxidized, for example $S \rightarrow SO_2$ or (c) reduced, for example $C=C \rightarrow HC-CH$. The groups R^A , L_1 , X , Y , R^5 , Z_1 , Z_2 , Z_3 , Z_4 , Z_5 , L_2 and R^8 are as defined herein, e.g. according to any one of claims 1 to 11.

Scheme V:



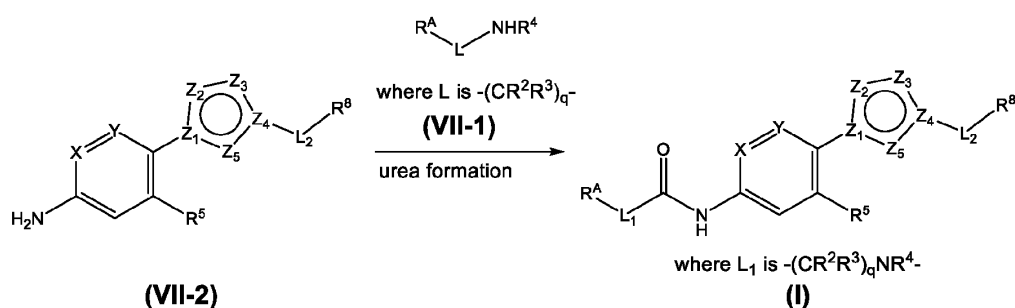
Compounds of Formula (I) as disclosed herein can be synthesized as outlined in Scheme V. An alkyne-substituted aromatic **V-1** can be reacted with an azide **V-2** in the presence of a metal catalyst such as $CuSO_4 \cdot 5H_2O$, $Cu(OAc)_2 \cdot H_2O$, CuI , $[CuBr(PPh_3)_3]$ or $Cp^*RuCl(PPh_3)_2$ with or without an additive such as sodium ascorbate, DBU, DABCO/HOAc or L-proline in a solvent such as DMSO, DMF, $H_2O/tBuOH$, dioxane or DCM. For certain compounds of Formula (I), the R^8 group may possess an atom or atoms that is/are either (a) initially protected, for example N-Boc, N-Bn, N-Cbz or O-trialkylsilyl, and are subsequently deprotected, (b) oxidized, for example $S \rightarrow SO_2$ or (c) reduced, for example $C=C \rightarrow HC-CH$. The groups R^A , L_1 , X , Y , R^5 , Z_1 , Z_2 , Z_3 , Z_4 , Z_5 , L_2 and R^8 are as defined herein, e.g. according to any one of claims 1 to 11.

Scheme VI:



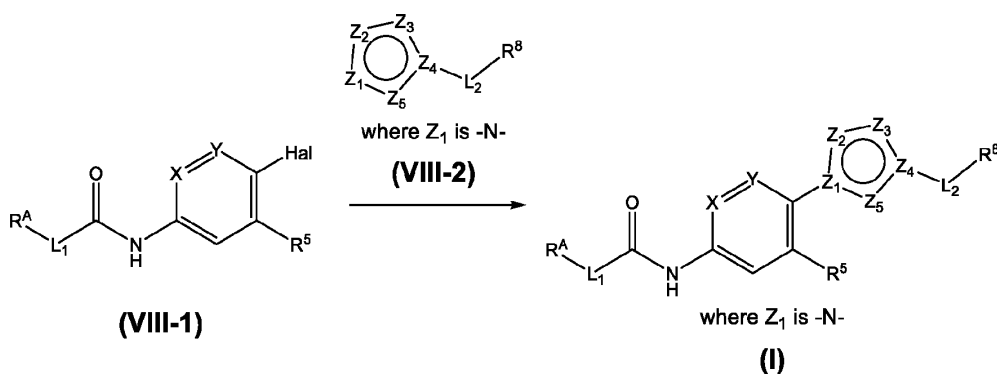
Compounds of Formula (I) as disclosed herein can be synthesized as outlined in Scheme VI. An amide **VI-1** can be arylated with a halogenated heteroaryl **VI-2** in the presence of either a palladium catalyst system such as Pd(dppf)Cl₂, Pd(OAc)₂, Brettphos-Pd-G3 or Pd₂(dba)₃ with a ligand such as dppp, BINAP, Xantphos or t-BuBrettphos and a base such as K₂CO₃, Na₂CO₃, Cs₂CO₃ or K₃PO₄ in a solvent such as dioxane, DME, DMF, t-BuOH or toluene. Alternatively, a copper catalyst system such as CuI with a ligand such as 1,2-diaminocyclohexane or N,N'-dimethylethylenediamine and a base such as K₂CO₃, Na₂CO₃, Cs₂CO₃ or K₃PO₄ in a solvent such as dioxane, DME, DMF, t-BuOH or toluene may be used. For certain compounds of Formula (I), the R⁸ group may possess an atom or atoms that is/are either (a) initially protected, for example N-Boc, N-Bn, N-Cbz or O-trialkylsilyl, and are subsequently deprotected, (b) oxidized, for example S → SO₂ or (c) reduced, for example C=C → HC-CH. The groups R^A, L₁, X, Y, R⁵, Z₁, Z₂, Z₃, Z₄, Z₅, L₂ and R⁸ are as defined herein, e.g. according to any one of claims 1 to 11.

15 Scheme VII:



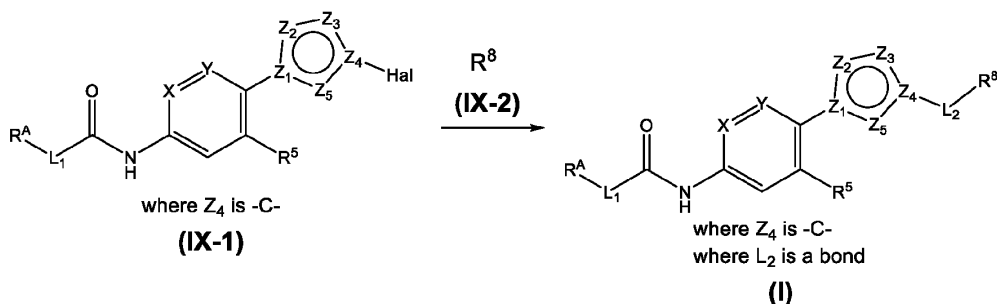
Compounds of Formula (I) as disclosed herein can be synthesized as outlined in Scheme VII. An amine **VII-1** can be reacted with an aromatic amine **VII-2** in the presence of a coupling agent such as CDI, phosgene or triphosgene in the presence of a base such as DIPEA or Et₃N in a solvent such as DMSO, DMF, NMP or DCM. For certain compounds of Formula (I), the R⁸ group may possess an atom or atoms that is/are either (a) initially protected, for example N-Boc, N-Bn, N-Cbz or O-trialkylsilyl, and are subsequently deprotected, (b) oxidized, for example S → SO₂ or (c) reduced, for example C=C → HC-CH. The groups R^A, L₁, X, Y, R⁵, Z₁, Z₂, Z₃, Z₄, Z₅, L₂ and R⁸ are as defined herein, e.g. according to any one of claims 1 to 11.

25 Scheme VIII:



Compounds of Formula (I) as disclosed herein can be synthesized as outlined in Scheme VIII. A halogenated heteroaryl **VIII-1** can be reacted with a nitrogen-containing heterocycle **VIII-2** in a Buchwald/Hartwig coupling reaction in the presence of a palladium catalyst such as tBuXPhos-Pd-G3 or Pd₂(dba)₃ with or without a ligand such as t-BuXphos, Me₄-di-t-BuXPhos or t-BuBrettphos in the presence of a base such as K₂CO₃, Na₂CO₃, Cs₂CO₃ or K₃PO₄ in a solvent such as dioxane, DME, DMF or toluene. Alternatively, a copper catalyst system such as CuI, CuBr or Cu₂O with or without a ligand such as 1,2-diaminocyclohexane or N,N'-dimethylethylenediamine in the presence of a base such as K₂CO₃, Na₂CO₃, Cs₂CO₃ or KOH in a solvent such as DME, DMF, DMSO or ACN may be used. For certain compounds of Formula (I), the R⁸ group may possess an atom or atoms that is/are either (a) initially protected, for example N-Boc, N-Bn, N-Cbz or O-trialkylsilyl, and are subsequently deprotected, (b) oxidized, for example S → SO₂ or (c) reduced, for example C=C → HC-CH. The groups R^A, L₁, X, Y, R⁵, Z₁, Z₂, Z₃, Z₄, Z₅, L₂ and R⁸ are as defined herein, e.g. according to any one of claims 1 to 11. Z₂, Z₃, Z₄, Z₅, L₂ and R⁸ are as defined herein, e.g. according to any one of claims 1 to 11.

Scheme IX:



Compounds of Formula (I) as disclosed herein can be synthesized as outlined in Scheme IX. A halogenated heteroaryl **IX-1** can be reacted with a nitrogen-containing heterocycle **IX-2** in a Buchwald/Hartwig coupling reaction in the presence of a palladium catalyst such as tBuXPhos-Pd-G3, Pd-PEPPSI-Ipent or Pd₂(dba)₃ with or without a ligand such as BINAP, t-BuXphos, Me₄-di-t-BuXPhos or t-BuBrettphos in the presence of a base such as NaOt-Bu,

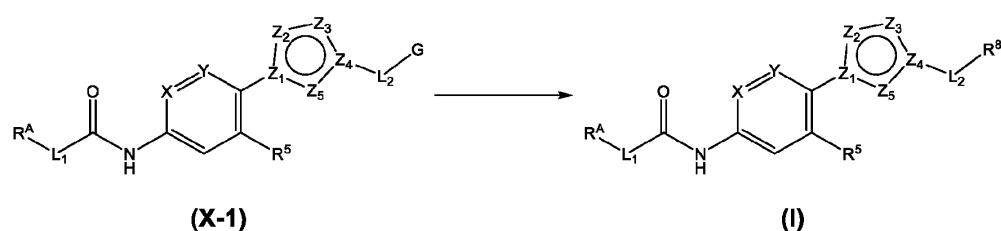
Cs₂CO₃ or K₃PO₄ in a solvent such as dioxane, DME, DMF or DMA. Alternatively, a copper catalyst system such as CuI with a ligand such as 1,2-diaminocyclohexane, N,N'-

dimethylethylenediamine or trans-(1*r*,2*r*)-N,N'-bismethyl-1,2-cyclohexanediamine in the

presence of a base such as K₂CO₃, Na₂CO₃, Cs₂CO₃ or KOH in a solvent such as dioxane,

- 5 DME, DMF, DMSO or ACN may be used. For certain compounds of Formula (I), the R⁸ group may possess an atom or atoms that is/are either (a) initially protected, for example N-Boc, N-Bn, N-Cbz or O-trialkylsilyl, and are subsequently deprotected, (b) oxidized, for example S → SO₂ or (c) reduced, for example C=C → HC-CH. The groups R^A, L₁, X, Y, R⁵, Z₁, Z₂, Z₃, Z₄, Z₅, L₂ and R⁸ are as defined herein, e.g. according to any one of claims 1 to 11.

10 Scheme X:



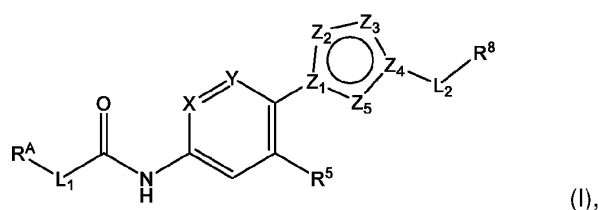
Compounds of Formula (I) as disclosed herein can be synthesized as outlined in Scheme X.

A heteroaryl **X-I** contains a functional group G which can be converted to a R⁸ group, for

example (i) an amine which can be alkylated and/or acylated or (ii) an acid which can be

- 15 converted to an acyl hydrazide and then cyclized with either trimethyl orthoformate or ethyl acetimidate to give either an oxadiazole or a triazole or (iii) a ketone which can be reacted with trimethylsulfoxonium ylide to give an oxetane or (iv) an aldehyde which can undergo reductive amination with an amine or (v) a nitrile which can be reacted with NaN₃ to give a tetrazole or (vi) a tetrahydrothiophene which can be reacted with NH₄OAc and (diacetoxyiodo)benzene to give a
- 20 1,2-thiazinane 1-oxide. For certain compounds of Formula (I), the R⁸ group may possess an atom or atoms that is/are either (a) initially protected, for example N-Boc, N-Bn, N-Cbz or O-trialkylsilyl, and are subsequently deprotected, (b) oxidized, for example S → SO₂ or (c) reduced, for example C=C → HC-CH. The groups R^A, L₁, X, Y, R⁵, Z₁, Z₂, Z₃, Z₄, Z₅, L₂ and R⁸ are as defined herein, e.g. according to any one of claims 1 to 11.

- 25 In another aspect provided herein is a process for making a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein an intermediate is prepared, and wherein the compound of Formula (I) is



wherein the groups R^A, L₁, X, Y, R⁵, Z₁, Z₂, Z₃, Z₄, Z₅, L₂ and R⁸ are as defined herein, e.g. according to any one of claims 1 to 11.

Routes of Administration and Pharmaceutical Compositions

For the therapeutic uses of compounds of Formula (I) and subformulae thereof, such compounds can be administered either alone or as part of a pharmaceutical composition. Accordingly, in another aspect provided herein, are a pharmaceutical compositions, which
5 comprise a compound of Formula (I), or pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers. In certain embodiments the pharmaceutical compositions comprises a compound of Formula (I-a) or Formula (I-b), or pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers. The pharmaceutical composition can be formulated for particular routes of administration such as
10 oral administration and parenteral administration (e.g. by injection or infusion administration). In certain embodiments, the pharmaceutical composition comprising a compound of Formula (I), Formula (I-a) or Formula (I-b) can be formulated for intramuscularly, intravenously, subcutaneously or oral administration.

The pharmaceutical compositions of the present invention can be made up in a solid form
15 (including without limitation capsules, tablets, pills, granules or powders) 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
20 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
25 desired
d) disintegrants, e.g., starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or
e) absorbents, colorants, flavors and sweeteners.

Suitable compositions for oral administration include pharmaceutical composition,
30 comprising a compound of Formula (I) in the form of tablets, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use are prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions can contain one or more agents selected from the group consisting of sweetening agents, flavoring agents,
35 coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets may contain the active ingredient in admixture with nontoxic

pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients are, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example, starch, gelatin or acacia; and
5 lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets are uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed. Formulations for oral use can be presented as hard gelatin capsules wherein the active
10 ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil.

Certain injectable compositions are aqueous isotonic solutions or suspensions. Said compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting
15 or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances. Said compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and contain about 0.1-75%, or contain about 1-50%, of the active ingredient.

A compound of Formula (I), or pharmaceutical composition comprising a compound of
20 Formula (I), for use in a subject (e.g., human) is typically administered orally or parenterally at a therapeutic dose. In general, 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. In certain embodiments, a compound of Formula (I-a), or pharmaceutical
25 composition comprising a compound of Formula (I-a), for use in a subject (e.g., human) is typically administered orally or parenterally at a therapeutic dose. In general, 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.

Accordingly, provided herein are pharmaceutical compositions comprising a compound of
30 Formula (I), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, and one or more pharmaceutically acceptable carriers. In certain embodiments, the pharmaceutical compositions comprise a compound of Formula (I-a), or a pharmaceutically acceptable salt thereof, or a stereoisomer
35 thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, and one or more pharmaceutically acceptable carriers.

Also provided herein are pharmaceutical compositions comprising a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a

stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, and one or more pharmaceutically acceptable carriers. In certain embodiments, the pharmaceutical composition comprises a therapeutically effective amount of a compound of Formula (I-a), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, and one or more pharmaceutically acceptable carriers.

In another aspect provided herein are pharmaceutical compositions comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, and one or more therapeutically active agents. In certain embodiments, the pharmaceutical compositions comprise a compound of Formula (I-a), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, and one or more therapeutically active agents.

In another aspect provided herein are pharmaceutical compositions comprising a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, and one or more therapeutically active agents. In certain embodiments, the pharmaceutical compositions comprise a compound of Formula (I-a), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, and one or more therapeutically active agents.

Pharmacology and Utility

The compounds of Formula (I) and subformulae thereof (i.e. Formula (I-a) and Formula (I-b)), provided herein, in free form or in pharmaceutically acceptable salt form, exhibit valuable pharmacological properties. In particular compounds of Formula (I) and subformulae thereof (i.e. Formula (I-a) and Formula (I-b)) bind to PNPLA3I148M, which thereby normalizes lipolysis; therefore such compounds may be used to treat a PNPLA3I148M associated disease. The PNPLA3I148M associated disease can be a liver disease, in particular a metabolic dysfunction-associated steatotic liver disease (MASLD). The PNPLA3I148M associated disease can be a liver disease, in particular a nonalcoholic fatty liver disease (NAFLD). In another embodiment of this aspect, the PNPLA3I148M associated disease is an alcoholic liver disease (ALD). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction-associated steatohepatitis (MASH), nonalcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH), cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction-associated steatohepatitis (MASH). In an embodiment of this aspect the PNPLA3I148M associated disease is nonalcoholic steatohepatitis (NASH). In an embodiment of this aspect the PNPLA3I148M associated disease is alcoholic steatohepatitis (ASH). In an embodiment of this

aspect the PNPLA3I148M associated disease cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC).

Furthermore, the compounds of Formula (I) and subformulae thereof (i.e. Formula (I-a) and Formula (I-b)), provided herein are compounds which bind to PNPLA3I148M, thereby disrupting the complex of ABHD5 and PNPLA3I148M (i.e. PNPLA3I148M-ABHD5), which results in normalizing lipolysis, and therefore, such compounds may be used to treat a PNPLA3I148M associated disease. The PNPLA3I148M associated disease can be a liver disease, in particular a metabolic dysfunction-associated steatotic liver disease (MASLD). The PNPLA3I148M associated disease can be a liver disease, in particular a nonalcoholic fatty liver disease (NAFLD). In another embodiment of this aspect, the PNPLA3I148M associated disease is an alcoholic liver disease (ALD). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction-associated steatohepatitis (MASH), nonalcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH), cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction-associated steatohepatitis (MASH). In an embodiment of this aspect the PNPLA3I148M associated disease is nonalcoholic steatohepatitis (NASH). In an embodiment of this aspect the PNPLA3I148M associated disease is alcoholic steatohepatitis (ASH). In an embodiment of this aspect the PNPLA3I148M associated disease cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC).

The compounds of Formula (I) and subformulae thereof (i.e. Formula (I-a) and Formula (I-b)), provided herein bind to PNPLA3I148M, which normalizes lipolysis as indicated by the *in vitro* tests provided herein.

Accordingly, the compounds of Formula (I), and subformulae thereof (i.e. Formula (I-a) and Formula (I-b)), provided herein, may be useful in therapy, such as in the treatment of a PNPLA3I148M associated disease. The PNPLA3I148M associated disease can be a liver disease, in particular a metabolic dysfunction-associated steatotic liver disease (MASLD). The PNPLA3I148M associated disease can be a liver disease, in particular a nonalcoholic fatty liver disease (NAFLD). In another embodiment of this aspect, the PNPLA3I148M associated disease is an alcoholic liver disease (ALD). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction-associated steatohepatitis (MASH), nonalcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH), cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction-associated steatohepatitis (MASH). In an embodiment of this aspect the PNPLA3I148M associated disease is nonalcoholic steatohepatitis (NASH). In an embodiment of this aspect the PNPLA3I148M associated disease is alcoholic steatohepatitis (ASH). In an embodiment of this aspect the PNPLA3I148M associated disease cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC).

In addition, the compounds of Formula (I) and subformulae thereof (i.e. Formula (I-a) and Formula (I-b)), provided herein, may be useful for use as research chemicals, e.g. as tool compounds.

In another aspect disclosed herein is a method for treating a PNPLA3I148M associated disease comprising administering to a subject in need thereof a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof. In an embodiment of this aspect the PNPLA3I148M associated disease is a liver disease. In another embodiment of this aspect, the PNPLA3I148M associated disease is a metabolic dysfunction-associated steatotic liver disease (MASLD). In another embodiment of this aspect, the PNPLA3I148M associated disease is a nonalcoholic fatty liver disease (NAFLD). In another embodiment of this aspect, the PNPLA3I148M associated disease is an alcoholic liver disease (ALD). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction-associated steatohepatitis (MASH), nonalcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH), cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction-associated steatohepatitis (MASH). In an embodiment of this aspect the PNPLA3I148M associated disease is nonalcoholic steatohepatitis (NASH). In an embodiment of this aspect the PNPLA3I148M associated disease is alcoholic steatohepatitis (ASH). In an embodiment of this aspect the PNPLA3I148M associated disease cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC).

In another aspect disclosed herein is a method for treating a PNPLA3I148M associated disease comprising administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof. In an embodiment of this aspect the PNPLA3I148M associated disease is a liver disease. In another embodiment of this aspect, the PNPLA3I148M associated disease is a metabolic dysfunction-associated steatotic liver disease (MASLD). In another embodiment of this aspect, the PNPLA3I148M associated disease is a nonalcoholic fatty liver disease (NAFLD). In another embodiment of this aspect, the PNPLA3I148M associated disease is an alcoholic liver disease (ALD). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction-associated steatohepatitis (MASH), nonalcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH), cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction-associated steatohepatitis (MASH). In an embodiment of this aspect the PNPLA3I148M associated disease is nonalcoholic steatohepatitis (NASH). In an embodiment of this aspect the PNPLA3I148M associated disease is alcoholic steatohepatitis (ASH). In an embodiment of this aspect the PNPLA3I148M associated disease cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC).

In another aspect disclosed herein is a method for treating a PNPLA3I148M associated disease by normalizing lipolysis, wherein the method comprises administering to a subject in need thereof of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof. In an embodiment of this aspect the PNPLA3I148M associated disease is a liver disease. In another embodiment of this aspect, the PNPLA3I148M associated disease is a metabolic dysfunction-associated steatotic liver disease (MASLD). In another embodiment of this aspect, the PNPLA3I148M associated disease is a nonalcoholic fatty liver disease (NAFLD). In another embodiment of this aspect, the PNPLA3I148M associated disease is an alcoholic liver disease (ALD). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction-associated steatohepatitis (MASH), nonalcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH), cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction-associated steatohepatitis (MASH). In an embodiment of this aspect the PNPLA3I148M associated disease is nonalcoholic steatohepatitis (NASH). In an embodiment of this aspect the PNPLA3I148M associated disease is alcoholic steatohepatitis (ASH). In an embodiment of this aspect the PNPLA3I148M associated disease cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC).

In another aspect disclosed herein is a method for treating a PNPLA3I148M associated disease by normalizing lipolysis, wherein the method comprises administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof. In an embodiment of this aspect the PNPLA3I148M associated disease is a liver disease. In another embodiment of this aspect, the PNPLA3I148M associated disease is a metabolic dysfunction-associated steatotic liver disease (MASLD). In another embodiment of this aspect, the PNPLA3I148M associated disease is a nonalcoholic fatty liver disease (NAFLD). In another embodiment of this aspect, the PNPLA3I148M associated disease is an alcoholic liver disease (ALD). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction-associated steatohepatitis (MASH), nonalcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH), cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction-associated steatohepatitis (MASH). In an embodiment of this aspect the PNPLA3I148M associated disease is nonalcoholic steatohepatitis (NASH). In an embodiment of this aspect the PNPLA3I148M associated disease is alcoholic steatohepatitis (ASH). In an embodiment of this aspect the PNPLA3I148M associated disease cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC).

In another aspect disclosed herein is a method for normalizing lipolysis by administering to a subject in need thereof of a compound of Formula (I), or a pharmaceutically acceptable salt

thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof.

In another aspect disclosed herein is a method for normalizing lipolysis by administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof.

In another aspect disclosed herein is a method for normalizing lipolysis by disrupting a PNPLA3I148M-ABHD5 complex, wherein the method comprises administering to a subject in need thereof a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof.

In another aspect disclosed herein is a method for normalizing lipolysis by disrupting a PNPLA3I148M-ABHD5 complex, wherein the method comprises administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof.

In another aspect disclosed herein is a compound of Formula (I), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof for use as a medicament.

Also provided herein is the use of a compound of Formula (I) or Formula (I-a), or a pharmaceutically acceptable salt thereof, in therapy.

In another aspect disclosed herein is a compound of Formula (I), and subformulae thereof (i.e. Formula (I-a) and Formula (I-b)), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof for use in treating a PNPLA3I148M associated disease. In an embodiment of this aspect the PNPLA3I148M associated disease is a liver disease. In another embodiment of this aspect, the PNPLA3I148M associated disease is a metabolic dysfunction-associated steatotic liver disease (MASLD). In another embodiment of this aspect, the PNPLA3I148M associated disease is a nonalcoholic fatty liver disease (NAFLD). In another embodiment of this aspect, the PNPLA3I148M associated disease is an alcoholic liver disease (ALD). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction-associated steatohepatitis (MASH), nonalcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH), cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction-associated steatohepatitis (MASH). In an embodiment of this aspect the PNPLA3I148M associated disease is nonalcoholic steatohepatitis (NASH). In an embodiment of this aspect the PNPLA3I148M associated disease is alcoholic steatohepatitis (ASH). In an embodiment of this aspect the PNPLA3I148M associated disease cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC).

In another aspect disclosed herein is the use of a compound of Formula (I), and subformulae thereof (i.e. Formula (I-a) and Formula (I-b)), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof for the treatment of a PNPLA3I148M associated disease. In an embodiment of this aspect the PNPLA3I148M associated disease is a liver disease. In another embodiment of this aspect, the PNPLA3I148M associated disease is a metabolic dysfunction-associated steatotic liver disease (MASLD). In another embodiment of this aspect, the PNPLA3I148M associated disease is a nonalcoholic fatty liver disease (NAFLD). In another embodiment of this aspect, the PNPLA3I148M associated disease is an alcoholic liver disease (ALD). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction-associated steatohepatitis (MASH), nonalcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH), cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction-associated steatohepatitis (MASH). In an embodiment of this aspect the PNPLA3I148M associated disease is nonalcoholic steatohepatitis (NASH). In an embodiment of this aspect the PNPLA3I148M associated disease is alcoholic steatohepatitis (ASH). In an embodiment of this aspect the PNPLA3I148M associated disease cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC).

In another aspect disclosed herein is the use of a compound of Formula (I), and subformulae thereof (i.e. Formula (I-a) and Formula (I-b)), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof in the manufacture of a medicament for the treatment of a PNPLA3I148M associated disease. In an embodiment of this aspect the PNPLA3I148M associated disease is a liver disease. In another embodiment of this aspect, the PNPLA3I148M associated disease is a metabolic dysfunction-associated steatotic liver disease (MASLD). In another embodiment of this aspect, the PNPLA3I148M associated disease is a nonalcoholic fatty liver disease (NAFLD). In another embodiment of this aspect, the PNPLA3I148M associated disease is an alcoholic liver disease (ALD). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction-associated steatohepatitis (MASH), nonalcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH), cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction-associated steatohepatitis (MASH). In an embodiment of this aspect the PNPLA3I148M associated disease is nonalcoholic steatohepatitis (NASH). In an embodiment of this aspect the PNPLA3I148M associated disease is alcoholic steatohepatitis (ASH). In an embodiment of this aspect the PNPLA3I148M associated disease cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC).

Another aspect provided herein is a method for treating a PNPLA3I148M associated disease in a patient in need thereof, the method comprising (a) determining the presence of the missense variant (I148M) in patatin-like phospholipase domain-containing protein 3 (PNPLA3)

and (b) administering to the patient a therapeutically effective amount of a compound of Formula (I), or subformulae thereof (i.e. Formula (I-a) and Formula (I-b)), or a pharmaceutically acceptable salt thereof. In an embodiment of this aspect, the PNPLA3I148M associated disease is a liver disease. In another embodiment of this aspect, the PNPLA3I148M associated disease is a metabolic dysfunction-associated steatotic liver disease (MASLD). In another embodiment of this aspect, the PNPLA3I148M associated disease is a nonalcoholic fatty liver disease (NAFLD). In another embodiment of this aspect, the PNPLA3I148M associated disease is an alcoholic liver disease (ALD). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction-associated steatohepatitis (MASH), nonalcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH), cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction-associated steatohepatitis (MASH). In an embodiment of this aspect the PNPLA3I148M associated disease is nonalcoholic steatohepatitis (NASH). In an embodiment of this aspect the PNPLA3I148M associated disease is alcoholic steatohepatitis (ASH). In an embodiment of this aspect the PNPLA3I148M associated disease is cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC).

In another aspect provided herein are methods for disrupting a PNPLA3I148M-ABHD5 complex in a cell, comprising contacting the cell with an effective amount of a compound of Formula (I) or subformulae thereof (i.e. Formula (I-a) and Formula (I-b)), or pharmaceutically acceptable salt thereof. In an embodiment of this aspect, the contacting is *in vitro*, while in another embodiment, the contacting is *in vivo*.

Administration and Combination Therapy

In certain instances, it may be advantageous to administer a compound of Formula (I), or subformulae thereof (i.e. Formula (I-a) and Formula (I-b)), or pharmaceutically acceptable salt thereof, in combination with one or more additional therapeutic agents. The compound of Formula (I), or subformulae thereof (i.e. Formula (I-a) and Formula (I-b)), or pharmaceutically acceptable salt thereof, may be administered separately, by the same or different route of administration, or together in the same pharmaceutical composition as the other therapeutic agent(s). 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 Formula (I), or subformulae thereof (i.e. Formula (I-a) and Formula (I-b)), or pharmaceutically acceptable salt thereof.

In another aspect disclosed herein is a pharmaceutical combination comprising a compound of Formula (I), or subformulae thereof (i.e. Formula (I-a) and Formula (I-b)), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, and one or more therapeutically active agents.

In another aspect disclosed herein is a pharmaceutical combination comprising a therapeutically effective amount of a compound of Formula (I), or subformulae thereof (i.e.

Formula (I-a) and Formula (I-b)), or a pharmaceutically acceptable salt thereof, or a stereoisomer thereof, or a pharmaceutically acceptable salt of a stereoisomer thereof, and one or more therapeutically active agents.

Accordingly, another aspect provided herein are combinations for use in the treatment, of a
 5 PNPLA3I148M associated disease, wherein a compound of Formula (I), or subformulae thereof (i.e. Formula (I-a) and Formula (I-b)), or pharmaceutically acceptable salt thereof, is used in combination with one or more additional active agents. In certain embodiments of this aspect the active agent(s) is selected from:

- 10 a) Anti-fibrotic-anti-inflammatory agents: for example Galectin 3 inhibitors such as Belapectin:
- b) Glucose transport modulators: for example SGLT-2 inhibitors such as dapagliflozin
- c) Immune modulators: for example CCR5 antagonist such as Leronlimab
- d) Insulins: for example Prandial Insulin
- e) Lipid modulators: for example THRbeta agonists such as Resmetirom: and Omega-3
 15 Fatty Acids such as Icosabuturate:
- f) Metabolism modulators: for example GLP-1 agonist such as semaglutide:
- g) PPAR modulators: for example pan-PPAR agonist Lanifibranor:
- h) an HSD17B13 inhibitor

In an embodiment of this aspect, the PNPLA3I148M associated disease is a liver disease. In
 20 another embodiment of this aspect, the PNPLA3I148M associated disease is a metabolic dysfunction-associated steatotic liver disease (MASLD). In another embodiment of this aspect, the PNPLA3I148M associated disease is a nonalcoholic fatty liver disease (NAFLD). In another embodiment of this aspect, the PNPLA3I148M associated disease is an alcoholic liver disease (ALD). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic
 25 dysfunction-associated steatohepatitis (MASH), nonalcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH), cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction-associated steatohepatitis (MASH). In an embodiment of this aspect the PNPLA3I148M associated disease is nonalcoholic steatohepatitis (NASH). In an embodiment of this aspect the
 30 PNPLA3I148M associated disease is alcoholic steatohepatitis (ASH). In an embodiment of this aspect the PNPLA3I148M associated disease cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC).

In another aspect provided herein is a product comprising a compound of Formula (I), or subformulae thereof (i.e. Formula (I-a) and Formula (I-b)), or pharmaceutically acceptable salt
 35 thereof, 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 PNPLA3I148M associated disease. Such products provided as a combined preparation include a composition comprising the compound of Formula (I), or subformulae thereof (i.e. Formula (I-

a) and Formula (I-b)), or pharmaceutically acceptable salt thereof, and the other therapeutic agent(s) together in the same pharmaceutical composition (fixed combination), or the compound of Formula (I), or subformulae thereof (i.e. Formula (I-a) and Formula (I-b)), or pharmaceutically acceptable salt thereof, and the other therapeutic agent(s) in separate form (non-fixed combination), e.g. in the form of a kit. In an embodiment of this aspect, the PNPLA3I148M associated disease is a liver disease. In another embodiment of this aspect, the PNPLA3I148M associated disease is a metabolic dysfunction-associated steatotic liver disease (MASLD). In another embodiment of this aspect, the PNPLA3I148M associated disease is a nonalcoholic fatty liver disease (NAFLD). In another embodiment of this aspect, the PNPLA3I148M associated disease is an alcoholic liver disease (ALD). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction-associated steatohepatitis (MASH), nonalcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH), cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC). In an embodiment of this aspect the PNPLA3I148M associated disease is metabolic dysfunction-associated steatohepatitis (MASH). In an embodiment of this aspect the PNPLA3I148M associated disease is nonalcoholic steatohepatitis (NASH). In an embodiment of this aspect the PNPLA3I148M associated disease is alcoholic steatohepatitis (ASH). In an embodiment of this aspect the PNPLA3I148M associated disease cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC). In one embodiment, the kit comprises means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is a blister pack, as typically used for the packaging of tablets, capsules and the like. In certain embodiments, the kit may be used for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit typically comprises directions for administration.

EXPERIMENTAL

Preparation of Compounds

Compounds of the present invention can be prepared as described in the following Examples, which are intended to illustrate the invention and are not to be construed as being limitations thereof. All starting materials, building blocks, reagents, acids, bases, dehydrating agents, solvents, and catalysts utilized to prepare the compounds of the present invention are either commercially available or can be produced by organic synthesis methods known to one of ordinary skill in the art. Furthermore, the compounds of the present invention can be produced by organic synthesis methods known to one of ordinary skill in the art as shown in the following examples.

The structures of all final products, intermediates and starting materials are confirmed by standard analytical spectroscopic characteristics, *e.g.*, MS, IR, NMR. The absolute

stereochemistry of representative examples 33a and 106b were determined by analyses of X-ray crystal structures. In all other cases where X-ray structures are not available, the stereochemistry has been assigned as a result of the use of chiral building blocks of known absolute configuration. Where the absolute stereochemistry of the compounds in the Examples is specified, the Cahn-Ingold-Prelog system is used for assigning stereochemical descriptors to the examples.

General Conditions

Temperatures are given in degrees Celsius. If not mentioned otherwise, all evaporations are performed under reduced pressure, typically between about 4 mm Hg and 75 mm Hg (= 5-100 mbar).

Celite Hyflo: Celite® (the Celite corporation) - filtering aid based on diatomaceous earth

Phase separator: Biotage – Isolute phase separator – (Part number: 120-1908-F for 70 ml and part number: 120-1909-J for 150 ml)

SiliaMetS®Thiol: SiliCYCLE thiol metal scavenger – (R51030B, Particle Size: 40-63 µm)

Si-TMT: TCI – 2,4,6-trimercaptotriazine Silica Gel – (S0865) [CAS No. 1226494-16-1]

Instrumentation

NMR:

Measurements were performed on a Bruker Ultrashield™400 (400 MHz), Bruker Ultrashield™Plus 600 (600 MHz), a Bruker Ascend™400 (400 MHz), a Bruker Avance™ DRX 500 (500 MHz), a Varian Agilent (400 MHz) or a Varian Unityplus 400 (400 MHz) spectrometer, both with and without tetramethylsilane as an internal standard.

Chemical shifts (δ-values) are reported in ppm downfield from tetramethylsilane, spectra splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), multiplet, unresolved or more overlapping signals (m), broad signal (br). Only signals of protons that are observed and not overlapping with solvent peaks are reported. Solvents are given in parentheses. Spectra were measured at 298K, unless indicated otherwise, and were referenced relative to the solvent resonance.

UPLC-MS and MS

UPLC-MS-1: XBridge BEH C18; particle size: 2.5 µm; column size: 2.1 x 50 mm; eluent A: H₂O + 5 mM NH₄OH; eluent B: ACN + 5 mM NH₄OH; gradient: 2 to 98% B in 1.40 min then 98% B for 0.60 min; flow rate: 1 ml/min; column temperature: 80°C.

UPLC-MS-2: CORTECS C18+; particle size: 2.7 µm; column size: 2.1 x 50 mm; eluent A: H₂O + 4.76% IPA + 0.05% HCOOH + 3.75 mM ammonium acetate; eluent B: IPA+ 0.05% HCOOH; gradient: 1 to 50% B in 1.40 min, 50 to 98% B in 0.30 min, then 98% for 0.10 min; flow rate: 1 ml/min; column temperature: 80°C.

- UPLC-MS-3: Acquity BEH C18; particle size: 1.7 μm ; column size: 2.1 x 100 mm; eluent A: H_2O + 4.76% IPA + 0.05% HCOOH + 3.75 mM ammonium acetate; eluent B: IPA + 0.05% HCOOH ; gradient: 1 to 60% B in 8.40 min then 60 to 98% B in 1 min; flow rate: 0.4 ml/min; column temperature: 80°C.
- 5 UPLC-MS-4: Acquity HSS T3; particle size: 1.8 μm ; column size: 2.1 x 50 mm; eluent A: H_2O + 0.05% HCOOH + 3.75 mM ammonium acetate; eluent B: ACN + 0.04% HCOOH ; gradient: 5 to 98% B in 1.40 min then 98% B for 0.40 min; flow rate: 1 ml/min; column temperature: 60°C.
- UPLC-MS-5: Waters CSH-C18; particle size: 1.7 μm ; column size: 2.1 x 50 mm; eluent A: H_2O + 0.2% HCOOH ; eluent B: ACN; gradient: 5 to 98% B in 1.40 min, then to 100% B in 0.5 min; flow rate: 1 ml/min; column temperature: 40°C.
- 10 UPLC-MS-6: Waters HSS-CN; particle size: 1.7 μm ; column size: 2.1 x 50 mm; eluent A: H_2O + 0.2% HCOOH ; eluent B: ACN; gradient: 5 to 98% B in 1.40 min, then to 100% B in 0.5 min; flow rate: 1 ml/min; column temperature: 40°C.
- UPLC-MS-7: CORTECS C18+; particle size: 2.7 μm ; column size: 2.1 x 50 mm; eluent A: H_2O + 4.76% IPA + 0.05% HCOOH + 3.75 mM ammonium acetate; eluent B: IPA + 0.05% HCOOH ; gradient: curved from 1 to 98% B in 1.70 min; flow rate: 1 ml/min; column temperature: 80°C.
- 15 UPLC-MS-8: CORTECS C18+; particle size: 2.7 μm ; column size: 2.1 x 50 mm; eluent A: H_2O + 0.05% HCOOH + 3.75 mM ammonium acetate; eluent B: IPA + 0.05% HCOOH ; gradient: 5 to 50% B in 1.40 min, 50 to 98% B in 0.30 min, then 98% for 0.10 min; flow rate: 1 ml/min; column temperature: 80°C.
- 20 UPLC-MS-9: Acquity BEH C18; particle size: 1.7 μm ; column size: 2.1 x 100 mm; eluent A: H_2O + 0.05% HCOOH + 3.75 mM ammonium acetate; eluent B: IPA + 0.05% HCOOH ; gradient: 5 to 60% B in 8.40 min, 60 to 98% B in 1 min then 98% for 0.4 min; flow rate: 0.4 ml/min; column temperature: 80°C.
- 25 **HPLC-MS**
- HPLC-MS-1: Synergi 2.5 μm MAX-RP 100 A Mercury; eluents :0.1% HCOOH in H_2O (A)/ ACN(B); gradient: 0.1/5, 0.5/5, 1.0/95, 1.5/95, 2.0/5, 3.0/5; flow rate: 2.0 ml/min; column temp: 40°C
- HPLC-MS-2: Kinetex EVO 2.6 μm ; 50 x 4.6mm; mobile phase: 0.1% HCOOH in H_2O (A)/ ACN(B); gradient (time/%B): 0/30, 0.5/30, 1.0/95, 2.4/95, 2.5/30, 3.0/30; flow rate: 2.0 ml/min)
- 30 HPLC-MS-3: Evo ESI 3200 2.6 μm ; 50 x 4.6 mm; mobile phase: 0.1% HCOOH in H_2O (A)/ 0.1% HCOOH in ACN(B); gradient (time/%B): 0/30, 0.2/30, 0.7/95, 2.0/95, 2.5/30, 3.5/30;
- HPLC-MS-4: Kinetex EVO C18 5 μm ; 30 x 2.1 mm; eluent A: H_2O + 0.0375% TFA ; eluent B: ACN + 0.01875% TFA; gradient: 5 to 95% B in 0.8 min, 95% B for 0.4 min, 95 to 5% B in 0.01 min, then 5% B for 0.29 min; flow rate: 1.5 ml/min; column temperature: 50°C.
- 35 HPLC-MS-5: Kinetex 2.6 μm , 100 A 30 x 3 mm; mobile phase: 0.1% HCOOH in H_2O (A)/ 0.1% HCOOH in ACN(B); gradient (time/%B): 0.1/20, 0.25/20, 0.75/95, 1.75/95, 2.0/20, 2.5/20; flow rate: 1.0 ml/min, Temp.: 40°C

HPLC-MS-6: CORTECS C18+; particle size: 2.7 µm; column size: 4.6 x 30 mm; eluent A: H₂O + 0.05% HCOOH; eluent B: ACN + 0.05% HCOOH; gradient: 5 to 95% B in 1 min, then 95% for 1 min; flow rate: 1.8 ml/min; column temperature: 45°C.

- HPLC-MS-7: Synergi 2.5 µ MAX-RP 100 A Mercury; eluent A: H₂O + 0.1% HCOOH; eluent B: ACN; Gradient (time/%B) : 0.1/5, 0.5/5, 1.0/95, 1.5/95, 2.0/5, 3.0/5; flow rate : 2.0 ml/min; column temperature: 40°C.

HPLC-MS-8: Agilent Poroshell 120 SB-C18 2.7 µm, 30 x 4.6 mm; eluent A: H₂O + 0.1% TFA; eluent B: ACN + 0.1% TFA; Gradient (time/%B) : 0.00/1, 0.01/1, 1.50/100, 1.73/100, 1.74/1; flow rate : 3.0 ml/min; column temperature: 60°C.

- HPLC-MS-9: Acquity BEH C18; particle size: 1.7 µm; column size: 2.1 x 50 mm; eluent A: H₂O + 0.1% HCOOH + 2mM ammonium acetate; eluent B: ACN + 0.1% HCOOH; gradient (time/%B/flow rate): 0.01/5/0.55, 0.6/70/0.60, 0.80/90/0.65, 1.10/100/0.65 (hold for 0.6 min), 1.71/5/0.55 (hold for 0.29 min); column temperature: RT.

Normal Phase (NP) Chromatography:

- 15 Normal phase chromatography was run on silica gel using prepacked columns, as detailed below, or using glass columns following standard flash chromatography methodology, unless otherwise stated.

System 1 Teledyne ISCO, CombiFlash Rf

System 2 Biotage Isolera

- 20 Column pre-packed RediSep Rf cartridges, or SNAP cartridges

Sample adsorption onto Isolute, or on silica gel, or applied as solutions

Chiral NP- methods (C-NP):

Reversed Phase non-chiral (RP-HPLC) and chiral HPLC (C-HPLC):

RP-HPLC-1: column: YMC Triart C18 5 µm; 150 x 20 mm; mobile phase; flow rate: 19 ml/min.

- 25 RP-HPLC-2: column: Waters X-Bridge C18 OBD 5 µm; 100 x 30 mm; mobile phase; flow rate: 40 ml/min.

RP-HPLC-3: column: Waters X-Bridge C18 OBD 5 µm; 100 x 30 mm; mobile phase; flow rate: 50 ml/min.

- 30 RP-HPLC-4: column: Waters X-Bridge C18 OBD 5 µm; 100 x 50 mm; mobile phase; flow rate: 140 ml/min.

RP-HPLC-5: column: LUNA C18 OBD 5 µm; 250 x 21.2 mm; mobile phase; flow rate: 18 ml/min.

- C-HPLC-1: column: Chiralpak IG 5 µm; 250 x 4.6 mm; mobile phase; flow rate: 1 ml/min; column temperature: 25°C.

C-HPLC-2: column: Chiralpak IG 5 µm; 250 x 30 mm; mobile phase; flow rate: 25 ml/min; column temperature: 25°C.

C-HPLC-3: column: Chiralcel OJ-H 5 μ m; 240 x 30 mm; mobile phase; flow rate: 40 ml/min; column temperature: 30°C.

C-HPLC-4: column: Chiralcel OJ-3 3 μ m; 100 x 3 mm; mobile phase; flow rate: 0.42 ml/min; column temperature: 25°C.

- 5 C-HPLC-5: column: Chiralpak AD-3 3 μ m; 100 x 3 mm; mobile phase; flow rate: 0.42 ml/min; column temperature: 25°C.

C-HPLC-6: column: Chiralpak IG 5 μ m; 250 x 30 mm; mobile phase; flow rate: 16 ml/min; column temperature: 25°C.

- 10 C-HPLC-7: column: Chiralcel OD-3 3 μ m; 100 x 3 mm; mobile phase; flow rate: 0.42 ml/min; column temperature: 25°C.

C-HPLC-8: column: Lux Cellulose-4 5 μ m; 250 x 21.2 mm; mobile phase; flow rate: 15 ml/min.

C-HPLC-9: column: Lux Cellulose-4 5 μ m; 150 x 4.6 mm; mobile phase; flow rate: 1.0 ml/min; column temperature: 25°C.

- 15 C-HPLC-10: column: Regis(S,S) Whelk-01 5 μ m; 250 x 4.6 mm; mobile phase; flow rate: 1.0 ml/min; column temperature: 25°C.

C-HPLC-11: column: ChiralPak ID 10 μ m; 250 x 30 mm; mobile phase; flow rate: 80 ml/min; column temperature: 25°C.

C-HPLC-12: column: ChiralPak ID 5 μ m; 250 x 4.6 mm; mobile phase; flow rate: 1.0 ml/min; column temperature: 25°C.

20

Chiral SFC methods (C-SFC):

C-SFC-1: column: Chiralpak AS-H 10 μ m; 250 x 50 mm; mobile phase; flow rate: 100 ml/min; column temperature: 40°C; back pressure: 110 bar.

- 25 C-SFC-2: column: Chiralpak AS 5 μ m; 150 x 4.6 mm; mobile phase; flow rate: 3 ml/min; column temperature: 40°C; back pressure: 1800 psi.

C-SFC-3: column: Chiralpak IN 5 μ m; 250 x 30 mm; mobile phase; flow rate: 95 ml/min; column temperature: 40°C; back pressure: 110 bar.

C-SFC-4: column: Chiralpak IG 5 μ m; 250 x 50 mm; mobile phase; flow rate: 100 ml/min; column temperature: 40°C; back pressure: 110 bar.

- 30 C-SFC-5: column: Chiralpak IG 5 μ m; 100 x 4.6 mm; mobile phase; flow rate: 3 ml/min; column temperature: 40°C; back pressure: 1800 psi.

C-SFC-6: column: Chiralpak IC 5 μ m; 250 x 30 mm; mobile phase; flow rate: 80 ml/min; column temperature: 40°C; back pressure: 120 bar.

- 35 C-SFC-7: column: Chiralpak AD 5 μ m; 100 x 4.6 mm; mobile phase; flow rate: 3 ml/min; column temperature: 40°C; back pressure: 1800 psi.

C-SFC-8: column: Lux cellulose 2 (OZ-like) 5 μ m; 250 x 30 mm; mobile phase; flow rate: 80 ml/min; column temperature: 40°C; back pressure: 140 bar.

- C-SFC-9: column: Chiralpak AD 5 μm ; 250 x 30 mm; mobile phase; flow rate: 100 ml/min; column temperature: 40°C; back pressure: 120 bar.
- C-SFC-10: column: Chiralpak IG 5 μm ; 250 x 30 mm; mobile phase; flow rate: 80 ml/min; column temperature: 40°C; back pressure: 130 bar.
- 5 C-SFC-11: column: Chiralpak IG 5 μm ; 250 x 30 mm; mobile phase; flow rate: 80 ml/min; column temperature: 40°C; back pressure: 110 bar.
- C-SFC-12: column: Chiralpak IC 5 μm ; 250 x 30 mm; mobile phase; flow rate: 90 ml/min; column temperature: 36°C; back pressure: 130 bar.
- C-SFC-13: column: Chiralpak IG 5 μm ; 250 x 30 mm; mobile phase; flow rate: 110 ml/min; column temperature: 40°C; back pressure: 130 bar.
- 10 C-SFC-14: column: Chiralpak IC 5 μm ; 100 x 4.6 mm; mobile phase; flow rate: 3 ml/min; column temperature: 40°C; back pressure: 1800 psi.
- C-SFC-15: column: Chiralcel OZ 5 μm ; 100 x 4.6 mm; mobile phase; flow rate: 3 ml/min; column temperature: 40°C; back pressure: 1800 psi.
- 15 C-SFC-16: column: Lux Cel-2 5 μm ; 250 x 30 mm; mobile phase; flow rate: 80 ml/min; column temperature: 36°C; back pressure: 120 bar.
- C-SFC-17: column: Chiralpak OZ 5 μm ; 233 x 30 mm; mobile phase; flow rate: 80 ml/min; column temperature: 40°C; back pressure: 120 bar.
- C-SFC-18: column: Chiralpak IG 5 μm ; 250 x 50 mm; mobile phase; flow rate: 110 ml/min; column temperature: 40°C; back pressure: 110 bar.
- 20 C-SFC-19: column: Lux Cel-2 5 μm ; 250 x 30 mm; mobile phase; flow rate: 80 ml/min; column temperature: 36°C; back pressure: 130 bar.
- C-SFC-20: column: Chiralpak IG 5 μm ; 250 x 30 mm; mobile phase; flow rate: 80 ml/min; column temperature: 40°C; back pressure: 120 bar.
- 25 C-SFC-21: column: Chiralpak IG 5 μm ; 250 x 30 mm; mobile phase; flow rate: 110 ml/min; column temperature: 40°C; back pressure: 120 bar.
- C-SFC-22: column: Chiralpak IC 5 μm ; 250 x 30 mm; mobile phase; flow rate: 80 ml/min; column temperature: 40°C; back pressure: 130 bar.
- C-SFC-23: column: Chiralpak IC 5 μm ; 100 x 4.6 mm; mobile phase; flow rate: 3 ml/min; column temperature: 40°C; back pressure: 1800 psi.
- 30 C-SFC-24: column: Chiralpak AD 3 μm ; 50 x 4.6 mm; mobile phase; flow rate: 3 ml/min; column temperature: 35°C; back pressure: 100 bar.
- C-SFC-25: column: Chiralpak IG 5 μm ; 250 x 30 mm; mobile phase; flow rate: 95 ml/min; column temperature: 40°C; back pressure: 120 bar.
- 35 C-SFC-26: column: Chiralpak IG 5 μm ; 250 x 30 mm; mobile phase; flow rate: 80 ml/min; column temperature: 40°C; back pressure: 100 bar.
- C-SFC-27: column: Chiralpak IG 5 μm ; 250 x 30 mm; mobile phase; flow rate: 95 ml/min; column temperature: 40°C; back pressure: 110 bar.

- C-SFC-28: column: Lux Cel-2 5 μm ; 250 x 30 mm; mobile phase; flow rate: 80 ml/min; column temperature: 40°C; back pressure: 120 bar.
- C-SFC-29: column: Chiralpak IC 5 μm ; 250 x 30 mm; mobile phase; flow rate: 80 ml/min; column temperature: 36°C; back pressure: 130 bar.
- 5 C-SFC-30: column: Chiralpak IG 5 μm ; 250 x 30 mm; mobile phase; flow rate: 80 ml/min; column temperature: 36°C; back pressure: 130 bar.
- C-SFC-31: column: Chiralpak AD 5 μm ; 250 x 30 mm; mobile phase; flow rate: 80 ml/min; column temperature: 40°C; back pressure: 120 bar.
- C-SFC-32: column: Lux cellulose 2 (OZ-like) 5 μm ; 250 x 30 mm; mobile phase; flow rate: 80 ml/min; column temperature: 40°C; back pressure: 110 bar.
- 10 C-SFC-33: column: Chiralpak AD 5 μm ; 250 x 30 mm; mobile phase; flow rate: 80 ml/min; column temperature: 40°C; back pressure: 130 bar.
- C-SFC-34: column: Chiralpak IG 10 μm ; 250 x 30 mm; mobile phase; flow rate: 80 ml/min; column temperature: 38°C; back pressure: 100 bar.
- 15 C-SFC-35: column: Lux cellulose 2 (OZ-like) 5 μm ; 250 x 30 mm; mobile phase; flow rate: 75 ml/min; column temperature: 40°C; back pressure: 110 bar.
- C-SFC-36: column: Chiralpak OZ 5 μm ; 250 x 30 mm; mobile phase; flow rate: 80 ml/min; column temperature: 40°C; back pressure: 120 bar.
- C-SFC-37: column: Chiralpak AD 5 μm ; 250 x 30 mm; mobile phase; flow rate: 75 ml/min; column temperature: 40°C; back pressure: 140 bar.
- 20 C-SFC-38: column: Chiralpak IC 5 μm ; 250 x 30 mm; mobile phase; flow rate: 80 ml/min; column temperature: 40°C; back pressure: 100 bar.
- C-SFC-39: column: Chiralpak IG 5 μm ; 250 x 30 mm; mobile phase; flow rate: 80 ml/min; column temperature: 40°C; back pressure: 120 bar.
- 25 C-SFC-40: column: Chiralpak IC 5 μm ; 250 x 30 mm; mobile phase; flow rate: 75 ml/min; column temperature: 40°C; back pressure: 110 bar.
- C-SFC-41: column: Chiralpak IB-N 5 μm ; 250 x 30 mm; mobile phase; flow rate: 80 ml/min; column temperature: 40°C; back pressure: 130 bar.
- C-SFC-42: column: Chiralpak IC 5 μm ; 250 x 30 mm; mobile phase; flow rate: 80 ml/min; column temperature: 40°C; back pressure: 90 bar.
- 30

XRPD method

- X-ray powder diffraction (XRPD) patterns were obtained using a Bruker AXS D8 Advance instrument in Bragg-Brentano configuration. Powders were analyzed using a Si-zero background sample holder. The radiation was Cu K α ($\lambda = 1.5406 \text{ \AA}$). Patterns were measured between 4° and 45° 2theta.
- 35

Sample amount: 5-10mg

Sample holder: Si-zero background sample holder

XRPD parameter

Instrument	Bruker AXS D8 Advance
Detector	LYNXEYE with a receiving slit 3° detector opening
Radiation	CuK α (0.15406 nm)
Monochromator	Kb-filter (0.5% Ni)
X-ray generator power	40 kV, 40 mA
Step size	0.005° / step
Time per step	1 s / step
Scan range	4° to 45° (2-theta value)
Scan time	2.5 h
Slits	Primary axial Soller slit 2.5° a fixed divergence slit 0.6 mm (=0.34°), an 8.0 mm detector slit and a secondary axial Soller slit 2.5°

Abbreviations

	ACN	acetonitrile
	Ar	argon
5	B2Pin2	bis(pinacolato)diboron
	BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
	Boc ₂ O	di-tert-butyl dicarbonate
	BrettPhos-Pd-G3	[(2-di-cyclohexylphosphino-3,6-dimethoxy-2',4',6'- triisopropyl-1,1'-biphenyl)-2-(2'-amino-1,1' -biphenyl)]palladium(II) methanesulfonate
10	CDI	1,1'-carbonyldiimidazole
	d	day(s)
	DAST	diethylaminosulfur trifluoride
	DCE	1,2-dichloroethane
	DCM	dichloromethane
15	DIPEA	diisopropylethylamine
	DIAD	diisopropyl azodicarboxylate
	DMAP	4-dimethylaminopyridine
	DME	1,4-dimethoxyethane
	DMF	N,N-dimethylformamide
20	DMP	Dess-Martin periodinane
	DMSO	dimethylsulfoxide
	EDCI.HCl	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride salt
	eq.	equivalent(s)
	Et ₃ N	triethylamine
25	EtOAc	EtOAc
	EtOH	ethanol
	h	hour(s)

	HATU	1-bis(dimethylamino)methylene-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
	HBTU	1-[bis(dimethylamino)methylene]-1H-benzotriazoliumhexafluorophosphate(1-) 3-oxide
5	HCl	hydrochloride or hydrochloric acid
	HFIP	hexafluoro-2-propanol
	HOAc	acetic acid
	HOBt	1-hydroxy-7-azabenzotriazole
	HOTs.H ₂ O	<i>p</i> -toluenesulfonic acid monohydrate
10	IPA	isopropanol
	LAH	lithium aluminium hydride
	LCMS	liquid chromatography and mass spectrometry
	LDA	lithium diisopropylamide
	LED	light emitting diodes
15	LiHMDS	lithium bis(trimethylsilyl)amide
	mCPBA	3-chlorobenzoperoxoic acid
	MeI	methyl iodide
	MeOH	methanol
	MS	mass spectrometry
20	MsCl	methanesulfonyl chloride
	mg	milligram
	min	minute(s)
	ml	milliliter
	mmol	millimole
25	m/z	mass to charge ratio
	NBS	N-bromosuccinimide
	PdCl ₂ (dppf).CH ₂ Cl ₂	1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex
	PdCl ₂ (dtbpf)	1,1'-bis-(di-tert.-butylphosphino-)ferrocene-palladiumdichloride
30	Pd ₂ (dba) ₃	Tris-(dibenzylidenacetone)-dipalladium(0)
	Pd-PEPPSI-I _p ent	[1,3-bis(2,6-di-3-pentylphenyl)imidazol-2-ylidene](3-chloropyridyl)dichloropalladium(II)
	PPTS	pyridinium 4-toluenesulfonate
	rac	racemic
35	Rt	retention time
	RT	room temperature
	SFC	supercritical fluid chromatography
	TBAF	tetra- <i>n</i> -butylammonium fluoride
	TBME	methyl <i>tert</i> -butyl ether

TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TosMIC	tosylmethyl isocyanide
5 T3P	propylphosphonic anhydride
wt.	weight
Xphos	2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
XPhos-Pd-G3	(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) methanesulfonate

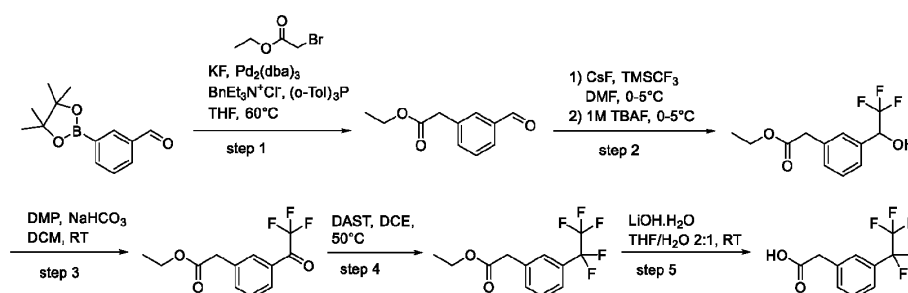
10 The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees Celsius. If not mentioned otherwise, all evaporations are performed under reduced pressure, typically between about 15 mm Hg and 100 mm Hg (= 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.

All starting materials, building blocks, reagents, acids, bases, dehydrating agents, solvents, and catalysts utilized to synthesis the compounds of the present invention are either commercially available or can be produced by organic synthesis methods known to one of ordinary skill in the art. Further, the compounds of the present invention can be produced by organic synthesis methods known to one of ordinary skill in the art as shown in the following examples.

Synthesis of Intermediates

A Intermediates

25 **Intermediate A-M1**: 2-(3-(Perfluoroethyl)phenyl)acetic acid



Step 1: 3-Formylphenylboronic acid pinacol ester [CAS No. 380151-86-0] (5.80 g, 25 mmol), KF (4.36 g, 75 mmol), tri-*o*-tolylphosphine (0.761 g, 2.500 mmol), benzyltriethylammonium chloride (0.569 g, 2.500 mmol) and Pd₂(dba)₃ (0.687 g, 0.750 mmol) were suspended in 30 ml THF and put under argon. The mixture was degassed with argon for 5 min, then ethyl 2-bromoacetate (4.16 ml, 37.5 mmol) was added. The resulting suspension was stirred at 60°C under argon for

2 d. Then the reaction mixture was cooled to RT and quenched with H₂O and extracted with EtOAc (3x). The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by NP chromatography on silica gel to give ethyl 2-(3-formylphenyl)acetate. UPLC-MS-2: Rt = 0.68 min; MS m/z [M+H]⁺ 193.2.

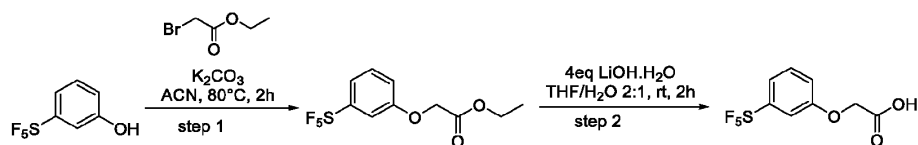
- 5 Step 2: Ethyl 2-(3-formylphenyl)acetate (step 1, 1 g, 5.20 mmol) was dissolved in 5 ml DMF, CsF (0.079 g, 0.520 mmol) was added and the reaction mixture was cooled to 0°C. Trimethyl(trifluoromethyl)silane (1.002 ml, 6.76 mmol) was added dropwise at 0°C. The resulting solution was stirred for 2 h at 0-5°C. After that TBAF, 1M in THF (5.20 ml, 5.20 mmol) was added dropwise at 0°C and stirring was continued at 0-5°C for 30 min. H₂O was added to the
- 10 reaction mixture follow by extraction with TBME (3x). The combined org. layers were washed with brine, dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by chromatography on silica gel to give ethyl 2-(3-(2,2,2-trifluoro-1-hydroxyethyl)phenyl)acetate. UPLC-MS-2: Rt = 0.83 min; MS m/z [M+H]⁺ 263.1.

- Step 3: Ethyl 2-(3-(2,2,2-trifluoro-1-hydroxyethyl)phenyl)acetate (step 2, 900 mg, 2.78 mmol)
- 15 was dissolved in 20 ml DCM, NaHCO₃ (934 mg, 11.12 mmol) and DMP (4127 mg, 9.73 mmol) were added. The reaction mixture was stirred at RT for 2 h. After that, H₂O was added and the resulting mixture was stirred for 1 h at RT, followed by extraction with DCM (3x). The combined org. phases were washed with H₂O and brine, dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by chromatography on silica gel to give ethyl 2-(3-(2,2,2-
- 20 trifluoroacetyl)phenyl)acetate. UPLC-MS-2: Rt = 0.84 min (broad peak); MS m/z [M+H₂O+NH₄]⁺ 296.2.

- Step 4: Ethyl 2-(3-(2,2,2-trifluoroacetyl)phenyl)acetate (step 3, 700 mg, 2.56 mmol) was dissolved in 25 ml DCE, DAST (2.026 ml, 15.33 mmol) was added at RT and the resulting mixture was heated for 18 h at 50°C in a sealed vial. Then the reaction mixture was slowly
- 25 added to 100 ml MeOH under stirring, followed by concentration in vacuo. The residue was purified by chromatography on silica gel to give ethyl 2-(3-(perfluoroethyl)phenyl)acetate. ¹H NMR (600 MHz, DMSO-d₆) δ 7.66 - 7.56 (m, 4H), 4.09 (q, 2H), 3.84 (s, 2H), 1.18 (t, 3H).

- Step 5: Ethyl 2-(3-(perfluoroethyl)phenyl)acetate (step 4, 455 mg, 1.612 mmol) was dissolved in 24 ml THF, 12 ml H₂O was added followed by addition of LiOH.H₂O (1000 mg, 23.83 mmol).
- 30 The resulting suspension was stirred vigorously for 18 h at RT. Then more H₂O was added and the mixture was extracted with Et₂O. The Et₂O phase was removed and the aqueous layer was acidified by the addition of 4N aq. HCl, (5.97 ml, 23.86 mmol). The mixture was extracted with EtOAc (3x), and the combined org. phases were washed with brine, dried (Na₂SO₄) and the solvents were evaporated This was followed adding with toluene and concentration in vacuo
- 35 (this procedure was repeated 2 additional times) to give 2-(3-(perfluoroethyl)phenyl)acetic acid which was used without further purification. UPLC-MS-2: Rt = 1.02 min; MS m/z [M-H]⁻ 253.1.

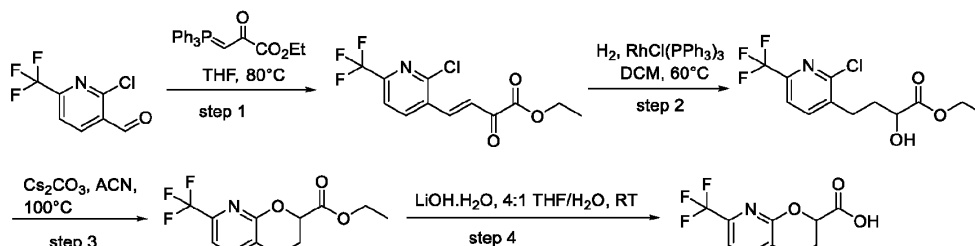
Intermediate A-M2: 2-(3-(Pentafluoro-λ⁶-sulfaneyl)phenoxy)acetic acid



Step 1: A mixture of 3-(pentafluoro- λ^6 -sulfaneyl)phenol (2 g, 9.08 mmol), K_2CO_3 (2.51 g, 18.17 mmol) and ethyl 2-bromoacetate (1.209 ml, 10.90 mmol) in ACN (20 ml) was stirred at 80°C for 1 h. The reaction mixture was cooled to RT, diluted with EtOAc and washed with H_2O (3x) and brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by NP chromatography (eluent: EtOAc/cyclohexane 0:100 to 30:70 in 20 min) to give ethyl 2-(3-(pentafluoro- λ^6 -sulfaneyl)phenoxy)acetate. UPLC-MS-2: Rt = 1.18 min; MS m/z $[M+NH_4]^+$ 324.2.

Step 2: A mixture of ethyl 2-(3-(pentafluoro- λ^6 -sulfaneyl)phenoxy)acetate (step 1, 2.56 g, 8.36 mmol) and $LiOH \cdot H_2O$ (1.503 g, 35.8 mmol) in THF (24 ml) and H_2O (12 ml) was stirred at RT for 3 h. After diluting with EtOAc, the reaction mixture was neutralized with 1N aq. HCl and then extracted with EtOAc (3x). The combined organic phases were washed with H_2O and brine, dried (Na_2SO_4) and concentrated under reduced pressure to give 2-(3-(pentafluoro- λ^6 -sulfaneyl)phenoxy)acetic acid. UPLC-MS-2: Rt = 0.86 min; MS m/z $[M-H]^-$ 277.1.

Intermediate A-M3: 7-(Trifluoromethyl)-3,4-dihydro-2H-pyrano[2,3-b]pyridine-2-carboxylic acid



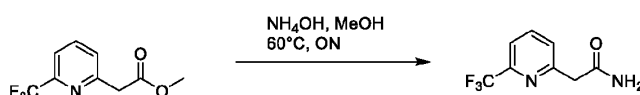
Step 1: 2-Chloro-6-(trifluoromethyl)nicotinaldehyde (5.5 g, 26.2 mmol) was dissolved in 200 ml THF under an argon atmosphere. Ethyl 2-oxo-3-(triphenyl- λ^5 -phosphaneylidene)propanoate (10.37 g, 27.6 mmol) was added to the solution and the mixture was stirred at reflux temperature for 18 h. After that the reaction mixture was cooled to RT and concentrated in vacuo. The residue was purified by chromatography on silica gel to give ethyl (E)-4-(2-chloro-6-(trifluoromethyl)pyridin-3-yl)-2-oxobut-3-enoate. UPLC-MS-2: Rt = 1.06 min; MS m/z $[M+H]^+$ 308.

Step 2: A mixture of ethyl (E)-4-(2-chloro-6-(trifluoromethyl)pyridin-3-yl)-2-oxobut-3-enoate (step 1, 430 mg, 1.398 mmol) and $RhCl(PPh_3)_3$ (129mg, 0.14 mmol) in 28 ml DCM, was hydrogenated in an autoclave (20 bar H_2 , 60°C) overnight. The reaction mixture was then concentrated in vacuo and the resulting residue was stirred in Et_2O and sonicated. The suspension was filtered and the filter cake was washed with n-hexane. The combined filtrate was concentrated in vacuo to give ethyl 4-(2-chloro-6-(trifluoromethyl)pyridin-3-yl)-2-hydroxybutanoate. UPLC-MS-3: Rt = 4.64 min; MS m/z $[M+H]^+$ 312.

Step 3: Ethyl 4-(2-chloro-6-(trifluoromethyl)pyridin-3-yl)-2-hydroxybutanoate (step 2, 5.33 g, 17.1 mmol) was dissolved in 150 ml ACN and Cs_2CO_3 (11.1 mg, 34.2 mmol) was added. The mixture heated to ca. 100°C (reflux) and stirred for a total of ca. 6 h (with a second addition of 1 equivalent of Cs_2CO_3 after 2 h) at this temperature. The reaction mixture was then cooled to RT, H₂O was added and the resulting mixture was extracted with EtOAc (3x). The combined organic phases were washed with brine, dried and concentrated in vacuo to give ethyl 7-(trifluoromethyl)-3,4-dihydro-2H-pyrano[2,3-b]pyridine-2-carboxylate which was purified by column chromatography on silica gel. UPLC-MS-2: Rt = 0.83 min; MS m/z $[\text{M}+\text{H}]^+$ 276.

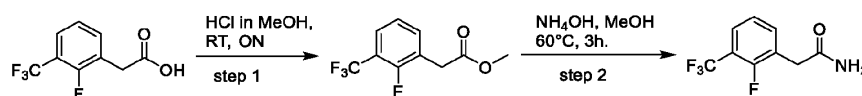
Step 4: Ethyl 7-(trifluoromethyl)-3,4-dihydro-2H-pyrano[2,3-b]pyridine-2-carboxylate (step 3, 230 mg, 0.501 mmol) was dissolved in 8 ml THF and a solution of $\text{LiOH}\cdot\text{H}_2\text{O}$ (42.1 mg, 1.003 mmol) in 2 ml H₂O was added. This mixture was stirred at RT for 1 h. After that the reaction mixture was diluted with H₂O and extracted with TBME (2x) The aq. layer was freeze dried to give 7-(trifluoromethyl)-3,4-dihydro-2H-pyrano[2,3-b]pyridine-2-carboxylic acid as the lithium salt (containing LiOH). UPLC-MS-2: Rt = 0.47 min; MS m/z $[\text{M}+\text{H}]^+$ 248.

Intermediate A-M4: 2-(6-(Trifluoromethyl)pyridin-2-yl)acetamide



To a solution of methyl 2-(6-(trifluoromethyl)pyridin-2-yl)acetate (200 mg, 0.913 mmol) in MeOH (2 ml) was added NH_4OH (28-30% in H_2O) (2 ml, 0.913 mmol) and the reaction mixture was stirred at 60°C overnight. The reaction mixture was evaporated to dryness and purified by silica gel column chromatography eluting with a gradient of MeOH (0-10%) in DCM . Fractions containing the desired product were combined and evaporated to give 2-(6-(trifluoromethyl)pyridin-2-yl)acetamide. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ 8.03 (t, 1H), 7.77 (d, 1H), 7.66 (d, 1H), 7.63 (s, 1H), 7.07 (s, 1H), 3.70 (s, 2H). UPLC-MS-2: Rt = 0.36 min; MS m/z $[\text{M}+\text{H}]^+$ 205.1.

Intermediate A-M5: 2-(2-Fluoro-3-(trifluoromethyl)phenyl)acetamide

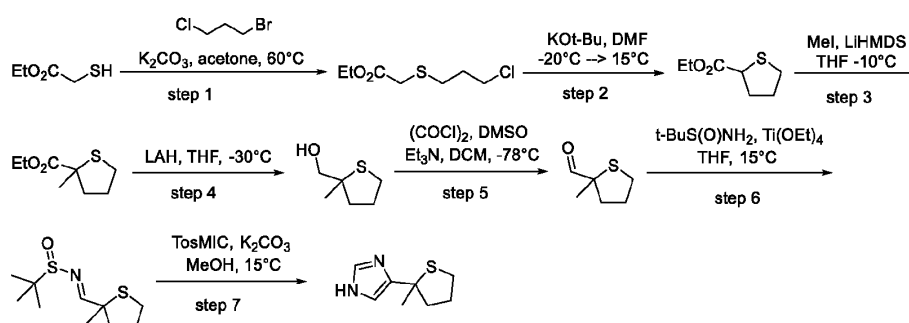


Step 1: A solution of 2-fluoro-3-(trifluoromethyl)phenylacetic acid (500 mg, 2.251 mmol) in 1.25 M HCl in MeOH (4 ml, 5.00 mmol) was stirred at RT overnight. The reaction mixture was evaporated, the residue was taken up with DCM and washed with an aqueous saturated solution of NaHCO_3 . The organic layer was dried using a phase separator and evaporated to give methyl 2-(2-fluoro-3-(trifluoromethyl)phenyl)acetate which was used in the next step without further purification. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ 7.74 - 7.69 (m, 2H), 7.39 (t, 1H), 3.88 (s, 2H), 3.65 (s, 3H). 8.03 (t, 1H), 7.77 (d, 1H), 7.66 (d, 1H), 7.63 (s, 1H), 7.07 (s, 1H), 3.70 (s, 2H). UPLC-MS-2: Rt = 1.05 min; MS m/z $[\text{M}+\text{NH}_4]^+$ 254.2.

Step 2: To a solution of methyl 2-(2-fluoro-3-(trifluoromethyl)phenyl)acetate (step 1, 488 mg, 2.066 mmol) in MeOH (5 ml) was added NH₄OH (28-30% in H₂O) (5 ml, 2.066 mmol). The reaction mixture was stirred at 60°C for 3 h. The reaction mixture was evaporated to dryness and purified by silica gel column chromatography eluting with a gradient of EtOAc (0-100%) in cyclohexane. Fractions containing the desired product were combined and evaporated to give 2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide. ¹H NMR (600 MHz, DMSO-d₆) δ 7.66 (tt, 2H), 7.60 (s, 1H), 7.35 (t, 1H), 7.06 (s, 1H), 3.56 (d, 2H). UPLC-MS-2: Rt = 0.67 min; MS m/z [M+H]⁺ 222.2.

10 B Intermediates

Intermediate B-M1: 4-(2-Methyltetrahydrothiophen-2-yl)-1H-imidazole



Step 1: 1-Bromo-3-chloropropane (787.2 g, 5.0 mol) was added dropwise to a mixture of ethyl 2-mercaptoacetate (500 g, 4.2 mol) and K₂CO₃ (580.5 g, 4.2 mol) in acetone (2.5 l) at 15°C and then the mixture was warmed to 60°C. After 16 h, the mixture was cooled to 15°C and filtered. The filter cake was washed with acetone and the filtrate was concentrated to give ethyl 2-((3-chloropropyl)thio)acetate which was used directly in the next step without purification. ¹H NMR (400 MHz, CDCl₃) δ 4.17 (q, 2H), 3.66 (dt, 2H), 3.20 (m, 2H), 2.79 (m, 2H), 2.01 (m, 2H), 1.30 (m, 3H).

Step 2: KOt-Bu (460.1 g, 4.1 mol) was added in 5 portions to a solution of ethyl 2-((3-chloropropyl)thio)acetate (step 1, 856.1 g, 3.4 mol) in DMF (5.1 l) at -20°C. After stirring for 30 min, the mixture was warmed to 15°C. After 16 h, the reaction mixture was acidified (pH 5~6) with 1N aq. HCl and extracted with 1:1 EtOAc/heptane. The organic phase was washed with brine, dried (Na₂SO₄) and concentrated under reduced pressure to give ethyl tetrahydrothiophene-2-carboxylate which was used directly in the next step without purification. ¹H NMR (300 MHz, CDCl₃) δ 4.16 (m, 2H), 3.90 (dd, 1H), 2.91 (m, 2H), 2.26 (m, 2H), 1.99 (m, 2H), 1.26 (t, 3H).

Step 3: LiHMDS (1M, 3.5 l, 3.5 mol) and then MeI (496.8 g, 3.5 mol) were added to a solution of ethyl tetrahydrothiophene-2-carboxylate (step 2, 400 g, 2.3 mol) in THF (2 l) at 0°C. After 1 h, the reaction mixture was quenched with sat. aq. NH₄Cl solution, diluted with TBME and H₂O, stirred for 10 min and then the phases were separated. The aqueous phase was extracted with

TBME. The combined organic phases were washed with 10% aq. brine solution, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by normal phase chromatography (eluent : EtOAc/heptane 1:10) to give ethyl 2-methyltetrahydrothiophene-2-carboxylate. ^1H NMR (300 MHz, CDCl_3) δ 4.13 (m, 2H), 3.22 (m, 2H), 2.50 (m, 1H), 2.16 (m, 2H), 1.68 (m, 1H), 1.60 (s, 3H), 1.26 (t, 3H).

Step 4: LAH (2M/THF) (1 l, 2 mol) was added dropwise to a solution of ethyl 2-methyltetrahydrothiophene-2-carboxylate (step 3, 310 g, 1.7 mol) in THF (2.2 l) at -30°C . After 1 h, the reaction mixture was quenched with H_2O (93 g), 15% aq. NaOH (93 g) and H_2O (279 g) and then Na_2SO_4 (3.7 kg) was added. After stirring for 30 min, the mixture was filtered and the filtrate was concentrated under reduced pressure to give (2-methyltetrahydrothiophen-2-yl)methanol which was used directly in the next step without purification. ^1H NMR (300 MHz, DMSO-d_6) δ 4.82 (t, 1H), 3.32 (dd, 1H), 3.15 (dd, 1H), 2.73 (m, 2H), 1.75-2.01 (m, 3H), 1.43 (m, 1H), 1.24 (s, 3H).

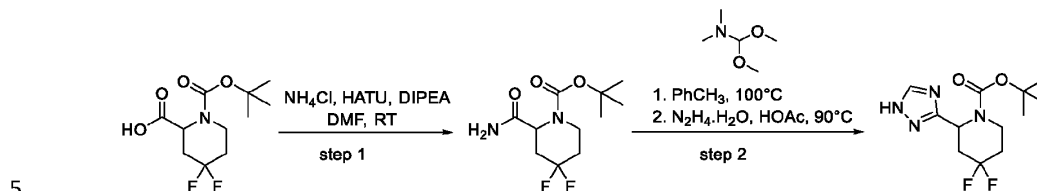
Step 5: $(\text{COCl})_2$ (330 g, 2.6 mol) was added dropwise to a solution of DMSO (507.8 g, 6.5 mol) in DCM (2.8 l) at -78°C . After stirring for 30 min, a solution of (2-methyltetrahydrothiophen-2-yl)methanol (step 4, 186.7 g, 1.3 mol) in DCM (934 ml) was added dropwise. After 1 h, the reaction mixture was quenched with Et_3N (708.3 g, 7 mol) and then warmed to RT. After stirring for 1 h, H_2O was added and the phases were separated. The organic phase was washed with 10% aq. brine solution, dried (Na_2SO_4) and concentrated under reduced pressure to give 2-methyltetrahydrothiophene-2-carbaldehyde which was used directly in the next step without purification. ^1H NMR (300 MHz, DMSO-d_6) δ 9.19 (d, 1H), 3.00 (dt, 1H), 2.85 (dt, 1H), 1.99-2.27 (m, 3H), 1.76 (m, 1H), 1.37 (s, 3H).

Step 6: $\text{Ti}(\text{OEt})_4$ (361.1 g, 1583.2 mmol) was added to a solution of 2-methyltetrahydrothiophene-2-carbaldehyde (step 5, 110 g, 791.6 mmol) and 2-methylpropane-2-sulfinamide (115.1 g, 949.9 mmol) in THF (1.1 l) at 15°C . After 16 h, the reaction mixture was diluted with EtOAc and brine, stirred for 30 min and then filtered. The filtrate was separated, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by normal phase chromatography (eluent : EtOAc/heptane 1:30) to give (E)-2-methyl-N-((2-methyltetrahydrothiophen-2-yl)methylene)propane-2-sulfinamide. ^1H NMR (300 MHz, DMSO-d_6) δ 7.78 (d, 1H), 2.88-3.13 (m, 2H), 2.03-2.30 (m, 3H), 1.86 (m, 1H), 1.55 (s, 3H), 1.12 (d, 9H).

Step 7: K_2CO_3 (86.8 g, 628.3 mmol) and TosMIC (73.6 g, 377 mmol) were added to a solution of (E)-2-methyl-N-((2-methyltetrahydrothiophen-2-yl)methylene)propane-2-sulfinamide (Step 6, 70 g, 251.3 mmol) in MeOH (700 ml) at 15°C . After stirring for 16 h, the reaction mixture was concentrated under reduced pressure. The residue was diluted with DCM and H_2O , stirred for 30 min and then the phases were separated. The organic phase was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by normal phase

chromatography (eluent : DCM/MeOH 10:1) to give 4-(2-methyltetrahydrothiophen-2-yl)-1H-imidazole. ¹H NMR (300 MHz, DMSO-d₆) δ 7.52 (d, 1H), 6.87 (d, 1H), 2.94 (t, 2H), 2.30 (m, 1H), 2.06 (m, 2H), 1.85 (dt, 1H), 1.65 (s, 3H).

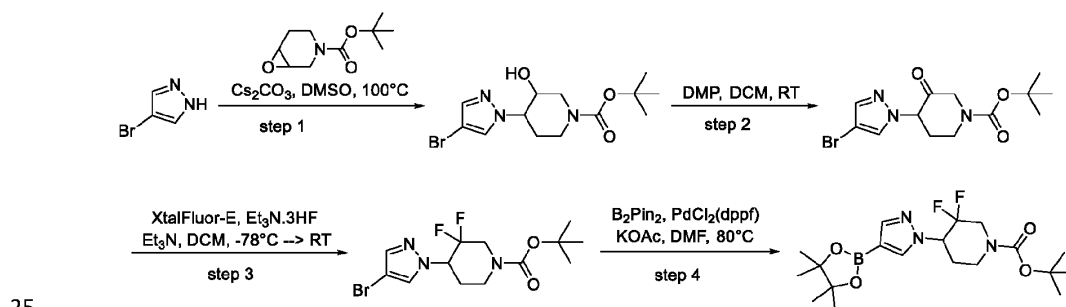
Intermediate B-M2: tert-Butyl 4,4-difluoro-2-(1H-1,2,4-triazol-3-yl)piperidine-1-carboxylate



Step 1: NH₄Cl (4.033 g, 75.4 mmol), HATU (2.15 g, 5.655 mmol) and DIPEA (1.31 ml, 7.54 mmol) were added to a solution of 1-(tert-butoxycarbonyl)-4,4-difluoropiperidine-2-carboxylic acid [CAS No. 661458-34-0] (1 g, 3.77 mmol) in DMF (15 ml) at RT. After 60 h, the reaction mixture was diluted with EtOAc and washed with sat. aq. NH₄Cl and sat. aq. NaHCO₃. The organic layer was dried (phase separator) and concentrated under reduced pressure to give tert-butyl 2-carbamoyl-4,4-difluoropiperidine-1-carboxylate which was used in the next step without further purification. UPLC-MS-2: Rt = 0.57 min; MS m/z [M-Boc]⁺ 165.2.

Step 2: 1,1-Dimethoxy-N,N-dimethylmethanamine (901.8 mg, 7.568 mmol) was added to a solution of tert-butyl 2-carbamoyl-4,4-difluoropiperidine-1-carboxylate (step 1, 1 g, 3.784 mmol) in toluene (20 ml). After stirring at 100°C for 18 h, the reaction mixture was evaporated to dryness under reduced pressure. The residue was dissolved in HOAc (20 ml). Hydrazine monohydrate (50%, 485.1 mg, 7.568 mmol) was added and the mixture was stirred at 90°C. After 2 h, the reaction mixture was poured onto ice and extracted with EtOAc (3x). The combined organic layers were washed with sat. aq. NaHCO₃ and brine, dried (Na₂SO₄) and concentrated under reduced pressure to give tert-butyl 4,4-difluoro-2-(1H-1,2,4-triazol-3-yl)piperidine-1-carboxylate which was used in the next step without further purification. UPLC-MS-2: Rt = 0.71 min; MS m/z [M+H]⁺ 289.1.

Intermediate B-M3: tert-Butyl 3,3-difluoro-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate



Step 1: A mixture of tert-butyl 7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate [CAS No. 161157-50-2] (111 mg, 0.557 mmol) and 4-bromo-1H-pyrazole (90 mg, 0.613 mmol), Cs₂CO₃

(272 mg, 0.836 mmol) in DMSO (4.1 ml) was heated in a sealed tube at 100°C. After 2.5 h, the reaction mixture was diluted with H₂O and extracted with EtOAc (2x). The combined organic layers were washed with brine, dried (phase separator) and concentrated under reduced pressure. The residue was purified by normal phase chromatography (eluent :

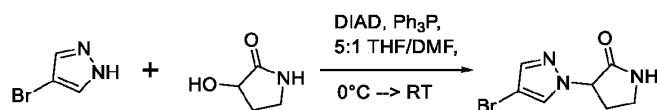
- 5 EtOAc/cyclohexane 0:1 to 40:60) to give tert-butyl 4-(4-bromo-1H-pyrazol-1-yl)-3-hydroxypiperidine-1-carboxylate. ¹H NMR (400 MHz, DMSO-d₆) δ 7.98 (d, 1H), 7.53 (s, 1H), 5.26 (d, 1H), 3.85-4.16 (m, 3H), 3.63 (m, 1H), 2.81 (m, 1H), 2.59 (m, 1H), 1.76-1.94 (m, 2H), 1.41 (s, 9H). UPLC-MS-2: Rt = 0.92 min; MS m/z [M-Boc]⁺ 246.2/248.1.

- Step 2: DMP (31.9 mg, 0.075 mmol) was added to a solution of tert-butyl 4-(4-bromo-1H-pyrazol-1-yl)-3-hydroxypiperidine-1-carboxylate (step 1, 20 mg, 0.058 mmol) in DCM (0.58 ml) under Ar at RT. After 2 h, the reaction mixture was filtered. The filtrate was diluted with H₂O and extracted with DCM (3x). The combined organic layers were dried (phase separator) and concentrated under reduced pressure. The residue was purified by normal phase chromatography (eluent : EtOAc/cyclohexane 0:1 to 50:50) to give tert-butyl 4-(4-bromo-1H-pyrazol-1-yl)-3-oxopiperidine-1-carboxylate. UPLC-MS-2: Rt = 0.89 min; MS m/z [M+H]⁺ 344.3/346.3 and 362.3/364.3 (mixture of ketone and hydrate).
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- Step 3: XtalFluor-E (1.018 g, 4.44 mmol), Et₃N.3HF (0.483 ml, 2.96 mmol) and then Et₃N (0.205 ml, 1.48 mmol) were slowly added consecutively to a solution of tert-butyl 4-(4-bromo-1H-pyrazol-1-yl)-3-oxopiperidine-1-carboxylate (step 2, 510 mg, 1.48 mmol) in DCM (25 ml) under Ar at -78°C. After 1 h, the mixture was warmed to RT. After 2 h, the reaction mixture was cooled to 0°C and quenched with sat. aq. NaHCO₃, stirred for 30 min and then extracted with DCM (3x). The combined organic layers were dried (phase separator) and concentrated under reduced pressure. The residue was purified by normal phase chromatography (eluent : EtOAc/cyclohexane 0:1 to 40:60) to give tert-butyl 4-(4-bromo-1H-pyrazol-1-yl)-3,3-difluoropiperidine-1-carboxylate. ¹H NMR (400 MHz, DMSO-d₆) δ 8.11 (s, 1H), 7.63 (s, 1H), 5.00 (m, 1H), 4.23 (m, 1H), 4.09 (m, 1H), 3.42 (m, 1H), 3.09 (m, 1H), 2.29 (m, 1H), 2.06 (m, 1H), 1.42 (s, 9H). UPLC-MS-3: Rt = 5.61 min; MS m/z [M-Boc]⁺ 266.0/268.0.
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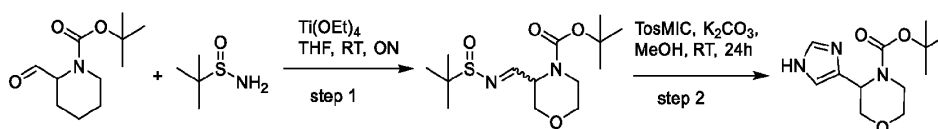
- Step 4: A mixture of tert-butyl 4-(4-bromo-1H-pyrazol-1-yl)-3,3-difluoropiperidine-1-carboxylate (Step 3, 358 mg, 0.978 mmol), KOAc (480 mg, 4.89 mmol), B₂Pin₂ [CAS No. 73183-34-3] (745 mg, 2.93 mmol) in DMF (3.3 ml) was degassed by bubbling Ar through for 5 min. PdCl₂(dppf) (71.5 mg, 0.098 mmol) was added, the vial sealed and the mixture was heated to 80°C. After 16 h, the reaction mixture was diluted with H₂O and extracted with DCM (3x). The combined organic layers were dried (phase separator) and concentrated under reduced pressure. The residue was purified by normal phase chromatography (eluent : EtOAc/cyclohexane 0:1 to 30:70) to give tert-butyl 3,3-difluoro-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate. UPLC-MS-2: Rt = 1.20 min; MS m/z [M+H]⁺ 414.5.
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Intermediate B-M4: 3-(4-Bromo-1H-pyrazol-1-yl)pyrrolidin-2-one



DIAD (0.794 ml, 4.08 mmol) was added to a solution of 4-bromo-1H-pyrazole (300 mg, 2.04 mmol), 3-hydroxypyrrolidin-2-one (227 mg, 2.24 mmol) and Ph_3P (803 mg, 3.06 mmol) in THF (5 ml) and DMF (1 ml) at 0°C and then the mixture was warmed to RT. After stirring overnight, the reaction mixture was diluted with H_2O and extracted with EtOAc (3x). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by normal phase chromatography (eluent : EtOAc/hexane) to give 3-(4-bromo-1H-pyrazol-1-yl)pyrrolidin-2-one. HPLC-MS: Rt 1.54 min; MS m/z $[\text{M}+\text{H}]^+$ 230.1/232.1.

Intermediate B-M5: tert-Butyl 3-(1H-imidazol-4-yl)morpholine-4-carboxylate

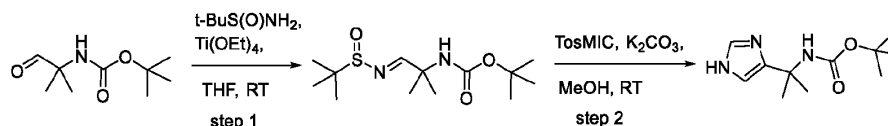


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Step 1: Titaniummethoxide (1.36 g, 1.24 ml, 5.97 mmol) was added dropwise to a solution of tert-butyl 3-formylmorpholine-4-carboxylate (642 mg, 2.98 mmol) and 2-methylpropane-2-sulfonamide (559 mg, 4.47 mmol) in THF (12 ml) and the reaction mixture was stirred at RT overnight. The reaction mixture was diluted with EtOAc (10 ml) and brine (10 ml) and stirred at RT for 30 min. The precipitate was removed by filtration over a Celite® pad and the biphasic filtrate was separated. The aqueous layer was extracted with EtOAc. The combined organic layers were dried using a phase separator and evaporated. The crude product was purified using silica gel column chromatography eluting with a gradient of EtOAc (0-50%) in cyclohexane. Fractions containing the product were combined and evaporated to give tert-butyl 3-(((tert-butylsulfinyl)imino)methyl)morpholine-4-carboxylate. UPLC-MS-2: Rt = 0.94 min; MS m/z $[\text{M}+\text{H}+\text{Na}]^+$ 341.1.

Step 2: To a solution of tert-butyl 3-(((tert-butylsulfinyl)imino)methyl)morpholine-4-carboxylate (step 1, 875 mg, 2.75 mmol) in MeOH (20 ml) were added K_2CO_3 (949 mg, 2.5 eq, 6.87 mmol) and TosMIC (1.07 g, 5.50 mmol) and the reaction mixture was stirred at RT for 24 h. The reaction mixture was filtered over a Celite® pad, washed with DCM/MeOH and the filtrate was evaporated to dryness to give tert-butyl 3-(1H-imidazol-4-yl)morpholine-4-carboxylate which was used without further purification. UPLC-MS-2: Rt = 0.36 min; MS m/z $[\text{M}+\text{H}]^+$ 254.1.

Intermediate B-M6: tert-Butyl (2-(1H-imidazol-4-yl)propan-2-yl)carbamate

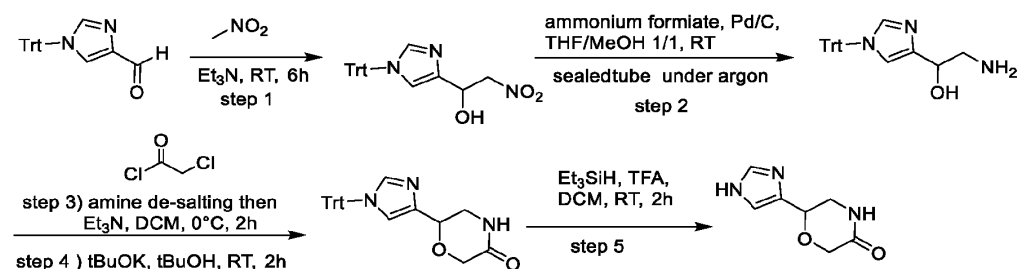


Step 1: Titaniummethoxide (2.2 ml, 11 mmol) was added to a mixture of tert-butyl (2-methyl-1-oxopropan-2-yl)carbamate (1 g, 5.3 mmol) and 2-methylpropane-2-sulfonamide (0.78 g, 6.4

mmol) in THF (35 ml) at RT. After 3 d, the reaction mixture was quenched with H₂O and extracted with EtOAc (2x). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure to give tert-butyl (E)-1-((tert-butylsulfinyl)imino)-2-methylpropan-2-yl)carbamate which was used in the next step without further purification. UPLC-MS-2: Rt = 1.07 min; MS m/z [M+Na]⁺ 313.2.

Step 2: K₂CO₃ (1.88 g, 13.6 mmol) and TosMIC (1.17 g, 6 mmol) were added to a solution of tert-butyl (E)-1-((tert-butylsulfinyl)imino)-2-methylpropan-2-yl)carbamate (step 1, 1.76 g, 5.45 mmol) in MeOH (25 ml) at RT. After stirring for 24 h, the reaction mixture was concentrated under reduced pressure. The residue was diluted with DCM, filtered through a phase separator cartridge and the filtrate was concentrated under reduced pressure to give tert-butyl (2-(1H-imidazol-4-yl)propan-2-yl)carbamate which was used without further purification. UPLC-MS-2: Rt = 0.31 min; MS m/z [M+H]⁺ 226.1.

Intermediate B-M7: 6-(1H-Imidazol-4-yl)morpholin-3-one



Step 1: To a solution of 1-trityl-1H-imidazole-4-carbaldehyde [CAS No. 33016-47-6] (3 g, 8.86 mmol) in nitromethane (50 ml, 927 mmol) was added Et₃N (2.458 ml, 17.73 mmol) and the resulting solution was stirred at RT for 4 h. Further nitromethane (20 ml, 8.86 mmol) was added stirring was continued for 2 h at RT. The reaction mixture was evaporated to dryness and the solid was triturated with Et₂O (30 ml), filtered and washed with Et₂O (2x20 ml) and dried to give 2-nitro-1-(1-trityl-1H-imidazol-4-yl)ethan-1-ol. UPLC-MS-2: Rt = 1.11 min; MS m/z [M+Na]⁺ 422.1.

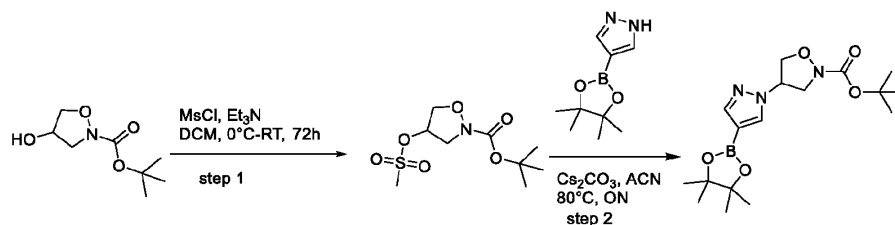
Step 2: A microwave vial was charged with 2-nitro-1-(1-trityl-1H-imidazol-4-yl)ethan-1-ol (step 1, 1 g, 2.378 mmol), ammonium formate (0.750 g, 11.89 mmol) and Pd/C 10% (0.253 g, 0.238 mmol) under an atmosphere of argon. THF (10 ml) and MeOH (10 ml) were added and the reaction mixture was stirred at RT for 72 h. The reaction mixture was filtered through a Celite® pad, washed with MeOH and evaporated. The crude product was purified using reverse phase column chromatography eluting with a gradient of ACN in H₂O+0.1% HCOOH (10% to 100%). Fractions containing the desired product were combined, frozen and lyophilized to give 2-amino-1-(1-trityl-1H-imidazol-4-yl)ethan-1-ol. ¹H NMR (600 MHz, DMSO-d₆) δ 7.42 - 7.38 (m, 9H), 7.32 (d, 1H), 7.09 (dd, 6H), 6.78 (s, 1H), 4.56 (dd, 1H), 2.97 (dd, 1H), 2.80 (dd, 1H). UPLC-MS-2: Rt = 0.82 min; MS m/z [M+Na]⁺ 392.4.

Step 3: To a solution of 2-amino-1-(1-trityl-1H-imidazol-4-yl)ethan-1-ol (step 2, 1.731 g, 4.17 mmol) and Et₃N (1.155 ml, 8.33 mmol) in DCM (25 ml) was added 2-chloroacetyl chloride (0.365 ml, 4.58 mmol) dropwise. The reaction mixture was stirred at 0°C for 2 h. The reaction mixture was diluted with DCM and washed with H₂O. Phases were separated and the aqueous layer was extracted with DCM. The combined organic layers were dried using a phase separator and evaporated to give 2-chloro-N-(2-hydroxy-2-(1-trityl-1H-imidazol-4-yl)ethyl)acetamide which was used in the next step without further purification. UPLC-MS-2: Rt = 1.18 min; MS m/z [M+Na]⁺ 544.3.

Step 4: To a solution of crude 2-chloro-N-(2-hydroxy-2-(1-trityl-1H-imidazol-4-yl)ethyl)acetamide (step 3, 1.739 g, 1.092 mmol) in t-BuOH (25 ml) was added tBuOK (935 mg, 8.33 mmol) and the reaction mixture was stirred at RT for 1 h. The reaction mixture was diluted with H₂O and DCM. An aqueous saturated solution of NH₄Cl was added and the phases were separated. The aqueous layer was extracted with DCM (2x). The combined organic layers were dried using a phase separator and evaporated. The crude product was purified using silica gel column chromatography eluting with a gradient of MeOH in DCM (0-40%). Fractions containing the desired product were combined and evaporated to give 6-(1-trityl-1H-imidazol-4-yl)morpholin-3-one. ¹H NMR (600 MHz, DMSO-d₆) δ 8.04 (d, 1H), 7.44 - 7.37 (m, 9H), 7.36 (d, 1H), 7.09 - 7.05 (m, 6H), 6.87 (d, 1H), 4.69 (dd, 1H), 4.08 (d, 1H), 4.02 (d, 1H), 3.47 (dd, 1H), 3.38 - 3.34 (m, 1H). UPLC-MS-2: Rt = 1.02 min; MS m/z [M+Na]⁺ 432.4.

Step 5: A solution of 6-(1-trityl-1H-imidazol-4-yl)morpholin-3-one (step 4, 614 mg, 1.469 mmol), TFA (1.132 ml, 14.69 mmol) and triethylsilane (0.258 ml, 1.616 mmol) in DCM (12 ml) was stirred at RT for 2 h. The reaction mixture was evaporated to dryness and the residue was taken up in DCM/H₂O. HCl 1M aq solution was added and the phases were separated. The aqueous layer was washed with DCM (2x), frozen and lyophilized to give 6-(1H-imidazol-4-yl)morpholin-3-one. ¹H NMR (600 MHz, DMSO-d₆) δ 14.70 (m, 2H), 9.14 (d, 1H), 8.29 (d, 1H), 7.76 (t, 1H), 5.01 (dd, 1H), 4.22 (d, 1H), 4.16 (d, 1H), 3.57 - 3.50 (m, 2H). UPLC-MS-2: MS m/z [M+H]⁺ 168.0.

Intermediate B-M8: tert-Butyl 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)isoxazolidine-2-carboxylate

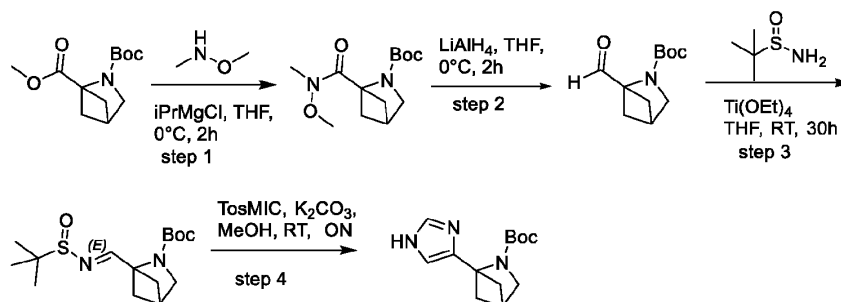


Step 1: To a solution of tert-butyl 4-hydroxyisoxazolidine-2-carboxylate (400 mg, 2.114 mmol) in DCM (20 ml) was added Et₃N (0.589 ml, 4.23 mmol), the reaction mixture was cooled to 0°C using an ice bath and methanesulfonyl chloride (0.329 ml, 4.23 mmol) was added dropwise. The

reaction mixture was allowed to warm up to RT and stirred 72 h. The reaction mixture was diluted with DCM, the organic layer was washed with an aqueous saturated solution of NaHCO₃ and dried using a phase separator. The resulting solution was evaporated to give tert-butyl 4-((methylsulfonyl)oxy)isoxazolidine-2-carboxylate which was directly used in the next step without further purification. ¹H NMR (600 MHz, DMSO-d₆) δ 5.62 - 5.59 (m, 1H), 4.06 (dd, 1H), 4.00 (dd, 1H), 3.82 (d, 1H), 3.81 (s, 1H), 3.26 (s, 3H), 1.42 (s, 9H). UPLC-MS-2: MS [M-Boc+H]⁺ 168.1.

Step 2: To a solution of 4-pyrazoleboronic acid pinacol ester (200 mg, 1.010 mmol) in ACN (10 ml) were added tert-butyl 4-((methylsulfonyl)oxy)isoxazolidine-2-carboxylate (step 1, 600 mg, 2.110 mmol) and Cs₂CO₃ (2073 mg, 6.36 mmol) and the reaction was stirred at 80°C overnight. The reaction mixture was diluted with H₂O and DCM. The aqueous layer was extracted with DCM (2x), the combined organic layers were washed with brine, dried using a phase separator and evaporated to give tert-butyl 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)isoxazolidine-2-carboxylate which was used without further purification. ¹H NMR (600 MHz, DMSO-d₆) δ 7.97 (s, 1H), 7.62 (s, 1H), 5.48 - 5.43 (m, 1H), 4.20 - 4.15 (m, 2H), 3.95 (dd, 1H), 3.86 (dd, 1H), 1.41 (s, 9H), 1.24 (s, 12H). UPLC-MS-2: MS [M-Boc+H]⁺ 266.4.

Intermediate B-M9: tert-Butyl 1-(1H-imidazol-4-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate



Step 1: To a solution of 2-(tert-butyl) 1-methyl 2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate (1.00 g, 4.14 mmol) and N,O-dimethylhydroxylamine hydrochloride (606 mg, 6.22 mmol) in THF (5 ml) at 0°C was added isopropylmagnesium chloride (2M/THF) (852 mg, 4.14 ml, 8.29 mmol) dropwise. The reaction mixture was stirred at 0°C for 2 h. The reaction mixture was diluted with EtOAc and washed with a saturated solution of NH₄Cl. Phases were separated and the aqueous layer was extracted with EtOAc (2x). The combined organic layers were washed with brine, dried using a phase separator and evaporated. The crude product was purified using reverse phase column chromatography eluting with a gradient of ACN (10-100%) in H₂O+0.1% HCOOH. Fractions containing the desired product were combined, an aqueous saturated solution of NaHCO₃ was added and the aqueous solution was extracted with DCM (3x). The combined organic layers were dried using a phase separator cartridge and evaporated to give tert-butyl 1-(methoxy(methyl)carbamoyl)-2-azabicyclo[2.1.1]hexane-2-carboxylate which was used in the next step without further purification. ¹H NMR (600 MHz, DMSO-d₆) δ 3.61 (s, 3H),

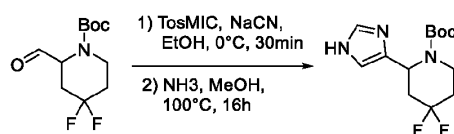
3.32 - 3.30 (m, 2H), 3.10 (s, 3H), 2.67 (t, 1H), 2.19 - 2.03 (m, 1H), 2.02 - 1.88 (m, 1H), 1.82 - 1.67 (m, 1H), 1.50 - 1.41 (m, 1H), 1.35 (s, 9H). UPLC-MS-2: Rt = 0.67 min; MS m/z [M+H]⁺ 271.2.

Step 2: A solution of tert-butyl 1-(methoxy(methyl)carbamoyl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (step 1, 454.0 mg, 1.579 mmol) in THF (15 ml) at 0 °C under argon was treated with a solution of LiAlH₄ (1M/THF) (89.87 mg, 2.368 ml, 2.368 mmol). The reaction mixture was stirred at 0°C for 2 h. The reaction mixture was carefully quenched with H₂O at 0°C, an aqueous saturated solution of NaHCO₃ was added and the mixture stirred for 10 min at RT and extracted with EtOAc (2x). The combined organic layers were concentrated to give tert-butyl 1-formyl-2-azabicyclo[2.1.1]hexane-2-carboxylate which was used in the next step without further purification. ¹H NMR (600 MHz, DMSO-d₆) δ 9.66 (d, 1H), 3.37 (s, 2H), 2.76 (d, 1H), 2.00 (ddd, 2H), 1.51 (dd, 2H), 1.42 - 1.36 (m, 9H). UPLC-MS-2: Rt = 0.81 min; MS m/z [M+H-Boc]⁺ 112.0.

Step 3: To a solution of tert-butyl 1-formyl-2-azabicyclo[2.1.1]hexane-2-carboxylate (step 2, 329.5 mg, 1.154 mmol) and 2-methylpropane-2-sulfinamide (216.3 mg, 97% wt, 1.731 mmol) in THF (8.0 ml) was added titaniummethoxide (526.6 mg, 480.4 μL, 2.308 mmol) and the reaction mixture was stirred for 36 h at RT. The reaction mixture was diluted with EtOAc and brine and stirred at RT for 30 min. The precipitate was removed by filtration over a Celite® pad, the filtrate phases were separated and the aqueous layer was extracted with EtOAc (2x). The combined organic layers were dried using a phase separator and evaporated. The crude product was purified using silica gel column chromatography eluting with a gradient of EtOAc (0-60%) in cyclohexane. Fractions containing the desired product were combined and evaporated to give tert-butyl (E)-1-(((tert-butylsulfinyl)imino)methyl)-2-azabicyclo[2.1.1]hexane-2-carboxylate. ¹H NMR (600 MHz, DMSO-d₆) δ 8.19 (s, 1H), 3.39 (s, 2H), 2.80 (t, 1H), 2.19 - 2.11 (m, 1H), 1.95 - 1.88 (m, 1H), 1.83 - 1.68 (m, 1H), 1.55 - 1.48 (m, 1H), 1.36 (s, 9H), 1.13 (s, 9H). UPLC-MS-2: Rt = 1.11 min; MS m/z [M+H-Boc]⁺ 215.1.

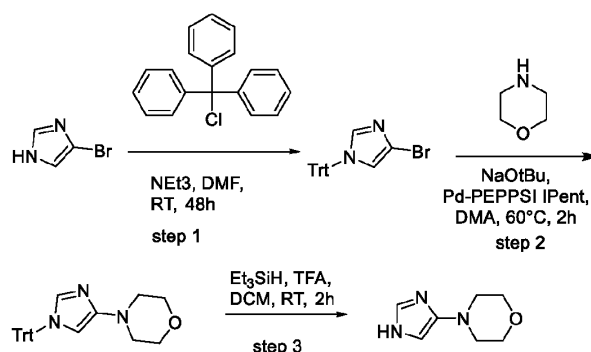
Step 4: To a solution of tert-butyl (E)-1-(((tert-butylsulfinyl)imino)methyl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (step 3, 298.7 mg,) in MeOH (3.0 ml) were added K₂CO₃ (328.2 mg, 2.5 eq, 2.375 mmol) and TosMIC (370.9 mg, 1.900 mmol). The reaction mixture was stirred at RT for 18 h. The reaction mixture was filtered over a Celite® pad, washed with DCM/MeOH and the filtrate was evaporated to dryness to give tert-butyl 1-(1H-imidazol-4-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate which was used without further purification. ¹H NMR (600 MHz, DMSO-d₆) δ 8.19 (s, 1H), 3.39 (s, 2H), 2.80 (t, 1H), 2.19 - 2.11 (m, 1H), 1.95 - 1.88 (m, 1H), 1.83 - 1.68 (m, 1H), 1.55 - 1.48 (m, 1H), 1.36 (s, 9H), 1.13 (s, 9H). UPLC-MS-2: Rt = 0.67 min; MS m/z [M+H]⁺ 250.1.

Intermediate B-M10: Tert-butyl 4,4-difluoro-2-(1H-imidazol-4-yl)piperidine-1-carboxylate



To a solution of tert-butyl 4,4-difluoro-2-formylpiperidine-1-carboxylate (218 mg, 875 μ mol) in ethanol (4.00 ml) was added TosMIC (188 mg, 962 μ mol). The suspension was cooled to 0°C under argon and NaCN (6.43 mg, 0.15 eq, 131 μ mol) was added, the resulting mixture was allowed to stir at RT for 1 h. The reaction mixture was concentrated to dryness. The intermediate was dissolved in ammonia (7M/MeOH) (700 mg, 5.87 ml, 4 mmol), transferred to a microwave vial, closed and stirred at 100°C for 20 h. The reaction mixture was cooled to RT and concentrated. The residue was triturated with DCM, the precipitate was filtered and rinsed with DCM. The filtrate was concentrated to give tert-butyl 4,4-difluoro-2-(1H-imidazol-4-yl)piperidine-1-carboxylate. ^1H NMR (600 MHz, DMSO- d_6) δ 9.22 (d, 1H), 8.98 (dd, 1H), 8.46 (t, 1H), 7.60 (d, 1H), 5.49 (d, 1H), 4.11 (d, 1H), 3.09 (s, 1H), 2.79 (t, 1H), 2.39 – 2.26 (m, 2H), 2.02 – 1.99 (m, 1H), 1.43 (s, 9H). UPLC-MS-2: Rt = 1.05 min; MS m/z [M+H] $^+$ 428.2.

Intermediate B-M11 4-(1H-Imidazol-4-yl)morpholine



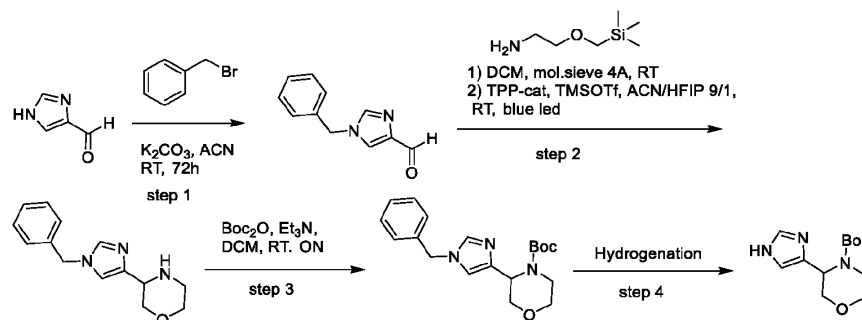
Step1: To a solution of 4-bromo-1H-imidazole (700 mg, 4.76 mmol) in DMF (8 ml) was added Et₃N (1.333 ml, 9.53 mmol) and the reaction mixture was stirred 15 min before (chloromethanetriyl)tribenzene (1461 mg, 5.24 mmol) was added. The suspension was stirred for 48 h at RT. Further DMF (8 ml) and (chloromethanetriyl)tribenzene (1461 mg, 5.24 mmol) were added and the reaction mixture sonicated for 2 h at 65°C. The reaction mixture was diluted with EtOAc and the suspension was filtered to give 4-bromo-1-trityl-1H-imidazole which was used in the following step without further purification. ^1H NMR (400 MHz, DMSO- d_6) δ 7.04 (s, 1H) 7.11 (d, 6 H) 7.37 - 7.46 (m, 10 H). UPLC-MS-2: Rt = 1.34 min.

Step 2: 4-Bromo-1-trityl-1H-imidazole (step 1, 200 mg, 0.514 mmol), NaOtBu (148 mg, 1.541 mmol) and Pd-PEPPSI IPent (40.7 mg, 0.051 mmol) were mixed under an atmosphere of argon. DMA anhydrous (4 ml) and morpholine (0.135 ml, 1.541 mmol) were added and the reaction mixture was stirred at 60°C for 2 h. The reaction mixture was diluted with EtOAc and washed twice with an aqueous saturated solution of NaHCO₃. The organic phase was dried (Na₂SO₄)

and concentrated. The crude material was purified by silica gel column chromatography eluting with a gradient of EtOAc in cyclohexane. Fractions containing the desired product were collected and concentrated to give 4-(1-trityl-1H-imidazol-4-yl)morpholine. ¹H NMR (600 MHz, DMSO-d₆) δ 7.42 - 7.33 (m, 9H), 7.13 - 7.09 (m, 6H), 7.08 (d, 1H), 6.05 (d, 1H), 3.66 - 3.59 (m, 4H), 2.91 - 2.83 (m, 4H). UPLC-MS-2: Rt = 1.20 min; MS m/z [M+H]⁺ 396.2.

Step 3: To a mixture of 4-(1-trityl-1H-imidazol-4-yl)morpholine (step 2, 150 mg, 379 μmol) in DCM (3 ml) at 25°C were added triethylsilane (48.5 mg, 66.6 μl, 417 μmol) and TFA (432 mg, 292 μl, 3.79 mmol). The resulting mixture was stirred at RT for 2 h. The reaction mixture was concentrated and purified via reversed phase column chromatography eluting with a gradient of ACN (0-10%) in H₂O+0.1%NH₄OH. Fractions containing the desired compound were collected and lyophilized to give 4-(1H-imidazol-4-yl)morpholine. ¹H NMR (600 MHz, DMSO-d₆) δ 11.62 (s, 1H), 7.35 (d, 1H), 6.31 (d, 1H), 3.70 - 3.65 (m, 4H), 2.94 - 2.87 (m, 4H). UPLC-MS-2: Rt = 0.13 min; MS m/z [M+H]⁺ 154.0.

Intermediate B-M12: tert-Butyl 3-(1H-imidazol-4-yl)morpholine-4-carboxylate



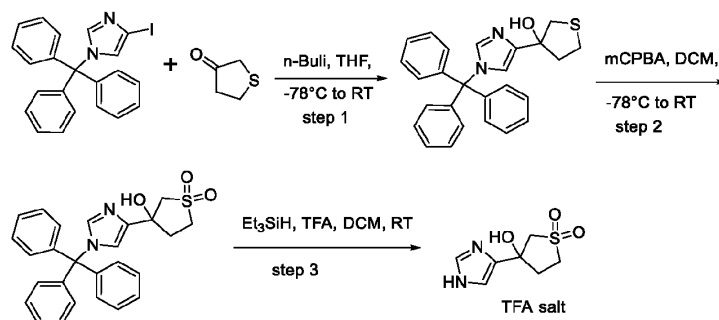
Step1: To a solution of 1H-imidazole-4-carbaldehyde (2 g, 20.81 mmol) in ACN (200 ml) were added K₂CO₃ (5.75 g, 41.6 mmol) and benzyl bromide (2.72 ml, 22.90 mmol). The reaction mixture was stirred for 72 h at RT, concentrated, the residue was dissolved in EtOAc and washed with H₂O and brine. The organic layers were dried using a phase separator and evaporated to give crude mixture of regioisomers. The crude mixture was purified by silica gel column chromatography eluting with a gradient of MeOH (0-10%) in DCM. Fractions containing the desired product were combined, evaporated and re-purified using silica gel column chromatography eluting with a gradient of MeOH (0-10%) in DCM. Fractions containing the desired product were combined and evaporated to give the 1-benzyl-1H-imidazole-4-carbaldehyde. ¹H NMR (600 MHz, DMSO-d₆) δ 9.70 (s, 1H), 8.12 (d, 1H), 8.00 (d, 1H), 7.39 - 7.36 (m, 2H), 7.33 (d, 3H), 5.29 (s, 2H). UPLC-MS-2: Rt = 0.42 min; MS m/z [M+H]⁺ 187.2.

Step 2: To an oven dried flask containing molecular sieves 4A (1 g) was added 1-benzyl-1H-imidazole-4-carbaldehyde (step 1, 521 mg, 2.52 mmol), followed by a solution of 2-((trimethylsilyl)methoxy)ethan-1-amine (SLAP M) reagent (Aldrich) (445 mg, 3.02 mmol) in dry DCM (10 ml). The reaction mixture was stirred at RT under an inert atmosphere overnight. The

reaction mixture was filtered through a pad of Celite® and the filtrate was concentrated to give the crude uncyclized imine as product. The imine was dissolved in ACN (18 ml) and HFIP (2 ml) and transferred to the respective reaction vessel. 2,4,6-triphenylpyrilium tetrafluoroborate (200 mg, 0.504 mmol) and TMSOTf (0.546 ml, 3.02 mmol) were added and the reaction mixture was then stirred and irradiated with a blue LED at RT for 72 h. Further 2,4,6-triphenylpyrilium tetrafluoroborate (200 mg, 0.504 mmol) and TMSOTf (0.546 ml, 3.02 mmol) were added and the reaction mixture was stirred and irradiated with a blue LED at RT for 24 h. The reaction mixture was concentrated, adsorbed on isolate and purified by reverse phase column chromatography eluting with a gradient of ACN (10-100%) in H₂O+0.1% HCOOH. Fractions containing the desired product were combined and re-purified by reverse phase column chromatography eluting with a gradient of ACN (5-100%) in H₂O+7.3mM NH₄OH. Fractions containing the desired product were combined, frozen and lyophilized to give 3-(1-benzyl-1H-imidazol-4-yl)morpholine. ¹H NMR (600 MHz, DMSO-d₆) δ 7.65 (d, 1H), 7.35 (tt, 2H), 7.31 - 7.27 (m, 1H), 7.27 - 7.25 (m, 2H), 6.97 (t, 1H), 5.12 (s, 2H), 3.79 (dd, 1H), 3.66 (dd, 2H), 3.36 (dd, 1H), 3.20 - 3.14 (m, 1H), 2.81 - 2.73 (m, 2H). UPLC-MS-1: Rt = 0.54 min; MS m/z [M+H]⁺ 244.2.

Step 3: To a solution of 3-(1-benzyl-1H-imidazol-4-yl)morpholine (step 2, 200 mg, 0.532 mmol) in DCM (5 ml) were added Boc₂O (0.185 ml, 0.798 mmol) and Et₃N (0.221 ml, 1.597 mmol) and the reaction mixture was stirred at RT overnight. The reaction mixture was diluted with an aqueous saturated solution of NaHCO₃ and extracted with DCM (2x). The combined organic layers were dried using a phase separator and evaporated. The crude product was purified by silica gel column chromatography eluting with a gradient of MeOH (0-10%) in DCM. Fractions containing the desired product were combined, evaporated and re-purified by reverse phase column chromatography eluting with a gradient (0-100%) of ACN in H₂O+7.3mM NH₄OH. Fractions containing the desired product were combined, evaporated and re-purified using reverse phase column chromatography eluting with a gradient of ACN (5-100%) in H₂O+7.3mM NH₄OH. Fractions containing the desired product were combined, frozen and lyophilized to give tert-butyl 3-(1-benzyl-1H-imidazol-4-yl)morpholine-4-carboxylate. ¹H NMR (600 MHz, DMSO-d₆) δ 7.69 (d, 1H), 7.35 (tt, 2H), 7.31 - 7.28 (m, 1H), 7.27 - 7.24 (m, 2H), 6.90 (t, 1H), 5.15 (d, 2H), 4.80 (s, 1H), 4.16 (d, 1H), 3.76 - 3.66 (m, 1H), 3.61 - 3.54 (m, 2H), 3.36 (dd, 1H), 3.04 (s, 1H), 1.34 (s, 9H). UPLC-MS-2: Rt = 0.66 min; MS m/z [M+H]⁺ 344.4.

Step 4: A vial was charged with a solution of tert-butyl 3-(1-benzyl-1H-imidazol-4-yl)morpholine-4-carboxylate (step 3, 60 mg, 0.157 mmol) in MeOH (1.57 ml), then Pd(OH)₂ (11.04 mg, 0.016 mmol) was added and the resulting reaction mixture was placed in an autoclave and stirred at RT under H₂ (10 bar) overnight. The reaction mixture was filtered over a pad of Celite® and the filtrate was evaporated to give tert-butyl 3-(1H-imidazol-4-yl)morpholine-4-carboxylate. ¹H NMR (600 MHz, DMSO-d₆) δ 7.72 (d, 1H), 7.00 (t, 1H), 5.10 - 5.05 (m, 1H), 4.26 (d, 1H), 3.88 (dd, 1H), 3.78 (td, 2H), 3.54 (ddd, 1H), 3.20 (ddd, 1H), 1.48 (s, 9H). UPLC-MS-2: Rt = 0.35 min; MS m/z [M+H]⁺ 254.3.

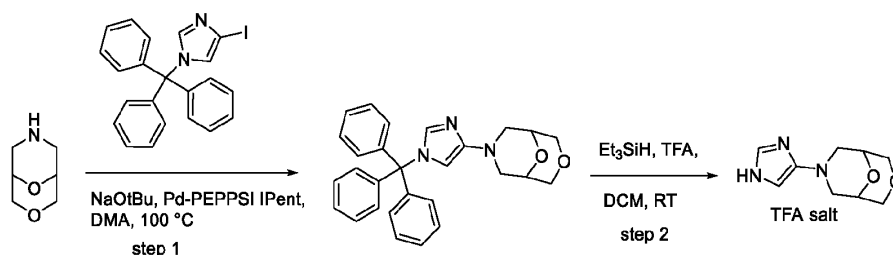
Intermediate B-M13: 3-Hydroxy-3-(1H-imidazol-4-yl)tetrahydrothiophene 1,1-dioxide

Step 1: To a solution of 4-iodo-1-trityl-1H-imidazole [CAS No. 96797-15-8] (1800 mg, 4.126 mmol) in THF (42 ml) at -78°C was dropwise added n-butyllithium (1.6 M in hexane) (5.673 ml, 9.076 mmol). The reaction mixture was stirred at -78°C for 10 min, then dihydrothiophen-3(2H)-one [CAS No. 1003-04-9] (506 mg, 4.951 mmol) in THF (42 ml) was added dropwise. The reaction was then allowed to warm to RT for 1.5 h. The reaction mixture was treated with sat. aq. NaHCO₃ solution and extracted with EtOAc (2x) and washed with brine. The organic phase was dried (phase separator) and concentrated under vacuum. The residue was purified by normal phase chromatography (eluent: cyclohexane/EtOAc 95:5 to 20:80 in 23 min). A second purification was done using RP-HPLC (eluent: H₂O/ACN 90:10 to 0:100 in 20 min) to give 3-(1-trityl-1H-imidazol-4-yl)tetrahydrothiophen-3-ol. UPLC-MS-2: Rt = 1.18 min; MS m/z [M-H]⁻ 411.3.

Step 2: mCPBA (383 mg, 2.219 mmol) was added to a -78°C solution of 3-(1-trityl-1H-imidazol-4-yl)tetrahydrothiophen-3-ol (step 1, 1089 mg, 41% wt, 1.082 mmol) in DCM (4.2 ml). The reaction was stirred at -78°C for 2 h and was then allowed to warm to RT. After 2 h, the reaction mixture was diluted with DCM and washed with 0.1M aq. Na₂S₂O₃ and sat. aq. NaHCO₃ solution. The organic layer was dried (phase separator) and concentrated under reduced pressure and the residue was purified by normal phase chromatography (eluent : cyclohexane/EtOAc 100:0 to 30:70) to give 3-hydroxy-3-(1-trityl-1H-imidazol-4-yl)tetrahydrothiophene 1,1-dioxide. UPLC-MS-2: Rt = 1.03 min; MS m/z [M+H]⁺ 445.2.

Step 3: At RT 3-hydroxy-3-(1-trityl-1H-imidazol-4-yl)tetrahydrothiophene 1,1-dioxide (step 2, 547 mg, 1.23 mmol) was dissolved in DCM (15.4 ml). To this solution TFA (0.948 ml, 12.3 mmol) followed by triethylsilane (0.216 ml, 1.354 mmol) was added. After 2 h at RT H₂O and DCM were added and the layers were separated. The organic layer was washed with H₂O again and the combined aqueous layer was extracted once again with DCM. The aqueous layer was lyophilized to give 3-hydroxy-3-(1H-imidazol-4-yl)tetrahydrothiophene 1,1-dioxide as a TFA salt. UPLC-MS-2: Rt = 0.12 min; MS m/z [M+H]⁺ 203.1.

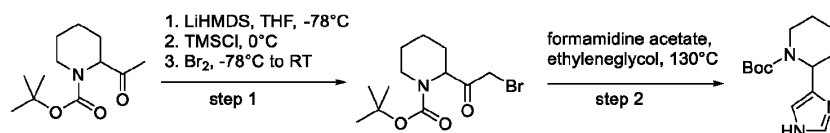
Intermediate B-M14: 7-(1H-imidazol-4-yl)-3,9-dioxo-7-azabicyclo[3.3.1]nonane



Step 1: 3,9-Dioxabicyclo[3.3.1]nonane hydrochloride [CAS No. 1803587-96-3] (207 mg, 58% wt, 0.725 mmol) was added to a mixture of 4-iodo-1-trityl-1H-imidazole [CAS No. 96797-15-8] (316 mg, 0.725 mmol), NaOtBu (2M/THF) (1.45 ml, 2.90 mmol) and Pd-PEPPSI-Ipent (57.4 mg, 0.072 mmol) in DMA (3.2 ml) under Ar at RT. After flushing with Ar, the reaction vial was sealed and warmed to 100°C. After 1 h, the reaction mixture was diluted with EtOAc and washed with sat. aq. NaHCO₃. The organic layer was dried (phase separator) and concentrated under reduced pressure and the residue was purified by normal phase chromatography (eluent: cyclohexane/EtOAc 100:0 to 0:100 in 16 min) to give 7-(1-trityl-1H-imidazol-4-yl)-3,9-dioxabicyclo[3.3.1]nonane. UPLC-MS-2: Rt = 1.12 min; MS m/z [M+H]⁺ 438.3.

Step 2: At RT 7-(1-trityl-1H-imidazol-4-yl)-3,9-dioxabicyclo[3.3.1]nonane (step 1, 171 mg, 0.328 mmol) was dissolved in DCM (4 ml). To this solution TFA (0.253 ml, 3.28 mmol) followed by triethylsilane (0.058 ml, 0.361 mmol) was added. After 2 h at RT H₂O and DCM was added and the layers were separated. The organic layer was washed with H₂O again and the combined aqueous layer was extracted once again with DCM. The aqueous layer was lyophilized to give 7-(1H-imidazol-4-yl)-3,9-dioxabicyclo[3.3.1]nonane as a TFA salt. UPLC-MS-2: Rt = 0.13 min; MS m/z [M+H]⁺ 196.1.

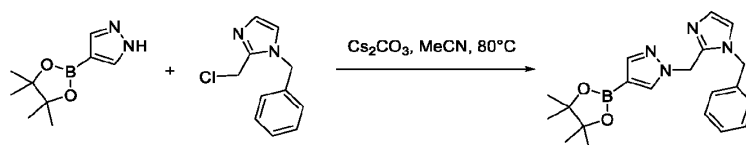
Intermediate B-M15: tert-Butyl 2-(1H-imidazol-4-yl)piperidine-1-carboxylate



Step 1: At RT and under Ar tert-butyl 2-acetylpiperidine-1-carboxylate (837 mg, 3.68 mmol) was dissolved in THF (8 ml) and then cooled to -78°C. LiHMDS (1 M/THF) (5.15 ml, 5.16 mmol) was added dropwise and the mixture was stirred at -78°C for 1 h. TMSCl (0.941 ml, 7.36 mmol) was added dropwise and the reaction mixture was allowed to warm to 0°C for 0.5 h. Then the mixture was cooled to -78°C, bromine (0.247 ml, 4.79 mmol) was added and the mixture was allowed to warm to RT and stirred for 35 min. The reaction mixture was quenched with 10 ml of 10% aq. Na₂S₂O₃ solution and 30 ml sat. aq. NH₄Cl and extracted with EtOAc (2x). The combined organic phase was dried by elution through a separating phase cartridge and evaporated to give a residue which was purified by normal phase chromatography (eluent: cyclohexane/EtOAc 100:0 to 60:40 in 16 min) to give tert-butyl 2-(2-bromoacetyl)piperidine-1-carboxylate. UPLC-MS-2: Rt = 1.07 min; MS m/z [M+H]⁺ 206.1/208.1 (-Boc).

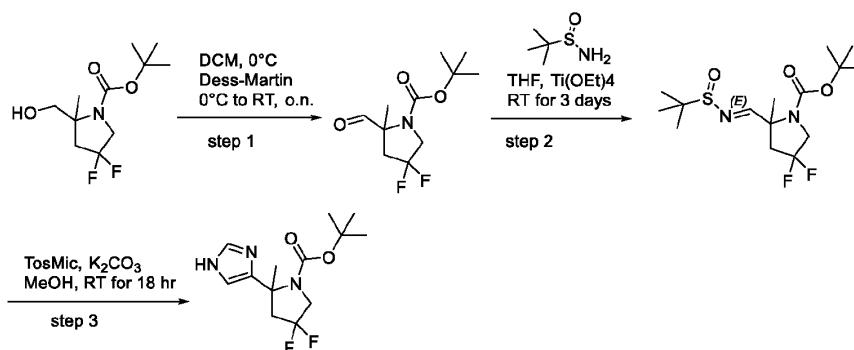
Step 2: tert-Butyl 2-(2-bromoacetyl)piperidine-1-carboxylate (step 1, 721 mg, 2.355 mmol) and formamidine acetate (1226 mg, 11.77 mmol) were dissolved in ethylene glycol (4.7 ml) and then the mixture was heated to 130°C for 1 h. To the reaction mixture H₂O was added and the mixture was extracted with EtOAc (2x). The combined organic phases were dried by elution
 5 through a separating phase cartridge and then evaporated to give tert-butyl 2-(1H-imidazol-4-yl)piperidine-1-carboxylate. UPLC-MS-2: Rt = 0.53 min; MS m/z [M+H]⁺ 252.2.

Intermediate B-M16: 1-((1-Benzyl-1H-imidazol-2-yl)methyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole



- 10 To a solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole [CAS No. 269410-08-4] (1 g, 5.15 mmol) in ACN (20 ml) was added Cs₂CO₃ (5.04 g, 15.46 mmol) and 1-benzyl-2-(chloromethyl)-1H-imidazole [CAS No. 19276-03-0] (1.879 g, 7.73 mmol). The reaction mixture was stirred at 80°C for 18 h. The reaction mixture was diluted with DCM and then washed with 20 ml of H₂O. The organic phase was dried (phase separator) and concentrated under vacuum.
 15 The residue was purified by normal phase chromatography (eluent: cyclohexane/EtOAc 100:0 to 60:40 in 35 min) to give 1-((1-benzyl-1H-imidazol-2-yl)methyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole. UPLC-MS-2: Rt = 0.79 min; MS m/z [M+H]⁺ 365.3.

Intermediate B-M17: tert-Butyl 4,4-difluoro-2-(1H-imidazol-4-yl)-2-methylpyrrolidine-1-carboxylate



- 20 Step 1: tert-Butyl 4,4-difluoro-2-(hydroxymethyl)-2-methylpyrrolidine-1-carboxylate [CAS No. 1823389-65-6] (900.0 mg, 1 eq, 3.582 mmol) was dissolved in 30 ml DCM under argon and cooled to 0°C. Dess-Martin periodinane (1.823 g, 1.2 eq, 4.298 mmol) was added to the mixture. The ice bath was removed, and the mixture was stirred overnight at RT. Then the
 25 reaction mixture was diluted with DCM and washed with sat. aq. NaHCO₃ solution (2x). The aqueous layer was extracted with DCM. The combined organic layers were filtered, dried, and concentrated in vacuo to give a greyish solid containing tert-butyl 4,4-difluoro-2-formyl-2-

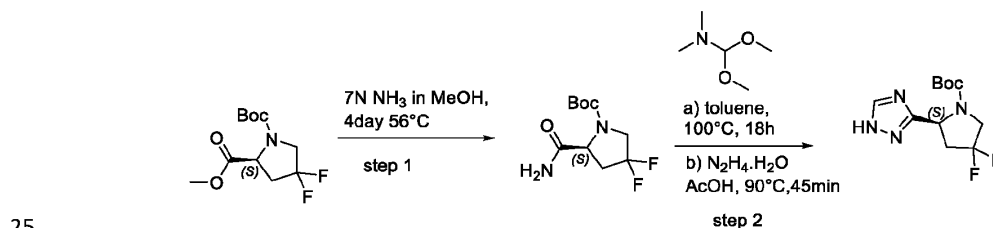
methylpyrrolidine-1-carboxylate. ¹H NMR (600 MHz, DMSO) δ 9.42 (s, 1H), 8.13 – 8.05 (m, 1H), 8.05 – 7.98 (m, 1H), 7.87 (dd, J = 8.3, 0.9 Hz, 1H), 7.81 – 7.75 (m, 1H), 3.97 – 3.80 (m, 2H), 2.68 (ddt, J = 44.2, 22.3, 13.1 Hz, 1H), 2.41 – 2.28 (m, 1H), 2.26 (s, 3H), 1.50 – 1.36 (m, 9H), 1.34 (s, 5H). Desired product in 5:6 mixture with byproduct of Dess-Martin reagent.

- 5 Estimated purity 45%. The provisionally interpreted UPLC-MS and ¹H.NMR data support the proposed structural assignment for tert-butyl 4,4-difluoro-2-formyl-2-methylpyrrolidine-1-carboxylate (2.000 g, 3.6 mmol, 100 %, 45% Purity)

- Step 2: tert-Butyl 4,4-difluoro-2-formyl-2-methylpyrrolidine-1-carboxylate (step 1, ca. 2 g, 45%, 1 eq, 3.791 mmol) was dissolved in THF (35 ml) at RT under argon. 2-Methylpropane-2-sulfinamide (643.3 mg, 1.4 eq, 5.308 mmol) and titaniummethoxide (2.594 g, 2.367 ml, 3.0 eq, 11.37 mmol) were added to the mixture, which was stirred for 3 d at RT. Then the reaction mixture was quenched with H₂O and diluted with EtOAc to give a slurry. After stirring for 30 min at RT, the mixture was extracted EtOAc (2x). The combined organic phases were washed with brine, filter dried and concentrated in vacuo to give tert-butyl (E)-2-(((tert-butylsulfinyl)imino)methyl)-4,4-difluoro-2-methylpyrrolidine-1-carboxylate. UPLC-MS-8: Rt = 1.24/1.26 min; MS m/z [M-Boc+H]⁺ = 253.2 (double peak accounting for diastereoisomers).

- Step 3: To a solution of tert-butyl (E)-2-(((tert-butylsulfinyl)imino)methyl)-4,4-difluoro-2-methylpyrrolidine-1-carboxylate (step 2, 1.500 g, 1 eq, 4.256 mmol) in MeOH (30.00 mL) K₂CO₃ (1.470 g, 2.5 eq, 10.64 mmol) and TosMIC (830.9 mg, 1 eq, 4.256 mmol) were added. The mixture was stirred for 18 hr at RT. Then the mixture was concentrated in vacuo and the residue containing tert-butyl 4,4-difluoro-2-(1H-imidazol-4-yl)-2-methylpyrrolidine-1-carboxylate, 4-methylbenzenesulfinic acid was used directly in the following step without further purification. UPLC-MS-8: Rt = 0.49 - 0.58 min (broad peak); MS m/z [M+H]⁺ = 288.2.

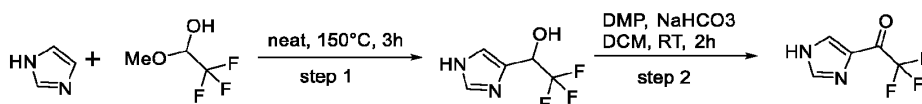
Intermediate B-M18: tert-Butyl (S)-4,4-difluoro-2-(1H-1,2,4-triazol-3-yl)pyrrolidine-1-carboxylate



- Step 1: 1-(tert-Butyl) 2-methyl (S)-4,4-difluoropyrrolidine-1,2-dicarboxylate [CAS No. 21149-99-5] (5.100 g, 1 eq, 19.23 mmol) was dissolved in ammonia (7N/MeOH) (39.4 g, 50 ml). The solution was stirred at 56°C for 18 h (gentle reflux). More ammonia (7N/MeOH) (39.4 g, 50 ml) was added and stirring was continued at 56°C for 3 d. Then the reaction mixture was concentrated in vacuo to give tert-butyl (S)-2-carbamoyl-4,4-difluoropyrrolidine-1-carboxylate. UPLC-MS-8: Rt = 0.55 min; MS m/z [M-Boc+H]⁺ = 151.1.
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Step 2: To a stirred suspension of tert-butyl (S)-2-carbamoyl-4,4-difluoropyrrolidine-1-carboxylate (step 1, 4.820 g, 1 eq, 19.26 mmol) in 75 ml toluene 1,1-dimethoxy-N,N-dimethylmethanamine (4.590 g, 5.12 ml, 2 eq, 38.52 mmol) was added at RT, and the reaction mixture was heated to 100°C. The suspension was stirred at 100°C for 18 h. After that the reaction mixture was concentrated in vacuo and dried under HV. The residue was dissolved in HOAc (75 ml) followed by slow addition of hydrazine monohydrate (2.469 g, 2.418 ml, 50% wt, 2 eq, 38.52 mmol) at RT (exothermic reaction). This mixture was stirred at 90°C for 45 min and kept for 16 h at RT. Then the reaction mixture was poured onto ice/H₂O and extracted with EtOAc (3x). The combined organic layers were washed with sat. NaHCO₃ (3x) and brine, dried (Na₂SO₄) and concentrated in vacuo. Co-evaporation with toluene (3x) was carried out to completely remove the HOAc. From this, tert-butyl (S)-4,4-difluoro-2-(1H-1,2,4-triazol-3-yl)pyrrolidine-1-carboxylate was obtained. UPLC-MS-8: Rt 0.63 min; MS m/z [M-H]⁻ = 273.1.

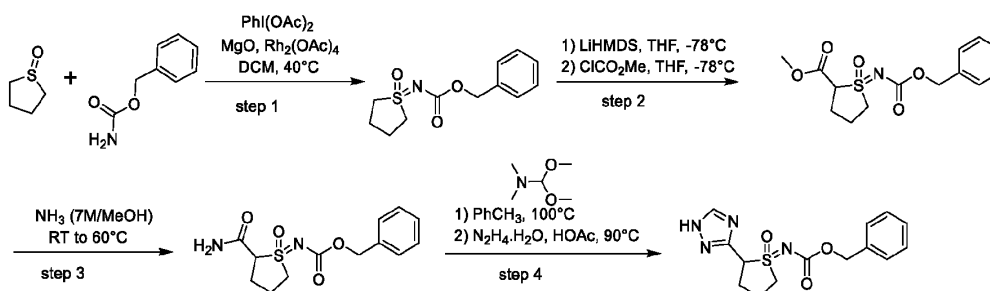
Intermediate B-M19: 2,2,2-Trifluoro-1-(1H-imidazol-4-yl)ethan-1-one



Step 1: 1H-Imidazole (2.094 g, 4 eq, 30.75 mmol) was suspended in 2,2,2-trifluoro-1-methoxyethan-1-ol (1000 mg, 1 eq, 7.688 mmol) in a 12 ml microwave vial and capped. The reaction mixture was stirred in a heating block at 150°C for 3 h and then cooled to RT. The reaction mixture was transferred to a flask, washed with MeOH, then concentrated in vacuo give crude product which was purified on silica gel (TBME/EtOH) to give 2,2,2-trifluoro-1-(1H-imidazol-4-yl)ethan-1-ol in a ca. 1:2 mixture with imidazole which was used in the next step.

Step 2: 2,2,2-Trifluoro-1-(1H-imidazol-4-yl)ethan-1-ol (step 1, 2.3 g, 33% wt, 1 eq, 4.6 mmol) was dissolved in 50 ml DCM. NaHCO₃ (1.5 g, 4 eq, 18 mmol) and DMP (6.8 g, 3.5 eq, 16 mmol) were added. The reaction mixture was stirred at RT for 1 h. Then H₂O was added and the resulting mixture was stirred for 30 min to give a precipitate. Sat. NaHCO₃ solution was added to adjust the pH of the mixture to 8. This mixture was extracted with DCM (3x). The combined organic phases were washed with H₂O and brine, dried (Na₂SO₄) and concentrated in vacuo to give crude product which was purified on silica gel (TBME/EtOH) to give 2,2,2-trifluoro-1-(1H-imidazol-4-yl)ethan-1-one. UPLC-MS: Rt = 0.38 min; MS m/z [M+H]⁺ = 165.0.

Intermediate B-M20: Benzyl (1-oxido-2-(1H-1,2,4-triazol-3-yl)tetrahydro-1λ⁶-thiophen-1-ylidene)carbamate



Step 1: To a slurry of tetrahydrothiophene 1-oxide (2608 mg, 1 eq, 25.04 mmol), benzyl carbamate (5.677 g, 1.5 eq, 37.55 mmol), magnesium oxide (4.04 g, 4.0 eq, 100.1 mmol) and rhodium(II)acetate dimer (553.3 mg, 0.05 eq, 1.252 mmol) in 200 ml DCM at RT and put under argon, phenyl- λ^3 -iodanediyl diacetate (12.10 g, 1.5 eq, 37.55 mmol) was added to form a slurry. Stirring was continued overnight at 40°C. Then the reaction mixture was cooled to RT and diluted with DCM. H₂O and sat. aq. NaHCO₃ were added, and the mixture was extracted with DCM (3x). The combined organic phases were dried over a phase separator SPE cartridge and concentrated in vacuo. The residue was purified on silica gel (cyclohexane/TBME/EtOH) to give benzyl (1-oxidotetrahydro-1 λ^6 -thiophen-1-ylidene)carbamate. ¹H NMR (600 MHz, DMSO-*d*₆) δ 7.30 - 7.39 (m, 5H), 5.03 (s, 2H), 3.50 - 3.56 (m, 2H), 3.33 - 3.37 (m, 1H), 2.16 - 2.22 (m, 2H), 2.05 - 2.12 (m, 2H). UPLC-MS-8: Rt = 0.63 min; MS m/z [M+H]⁺ = 254.

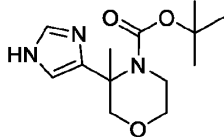
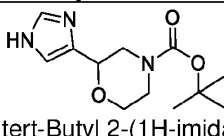
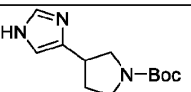
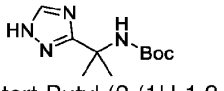
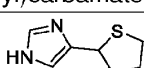
Step 2: Benzyl (1-oxidotetrahydro-1 λ^6 -thiophen-1-ylidene)carbamate (step 1, 3.000 g, 1 eq, 11.84 mmol) was dissolved in dry abs. 100.0 ml THF at RT, put under argon and cooled to -78°C. Lithium bis(trimethylsilyl)amide (3.765 g, 22.50 ml, 1.000 molar, 1.9 eq, 22.50 mmol) in 5 ml THF was slowly added at -78 °C and stirring was continued for 40 min at -78°C. Then methyl carbonochloridate (1.790 g, 1.6 eq, 18.95 mmol, dissolved in THF) was added dropwise over 5 min to the reaction mixture with maintaining the temperature below -70°C. The resulting solution was stirred for 30 min at -78°C. After that, the mixture was warmed to RT, followed by the addition of H₂O and EtOAc. Phases were separated and the aqueous phase was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over a phase separator and concentrated in vacuo. The residue was purified on silica gel (cyclohexane/TBME/EtOH) to give methyl 1-(((benzyloxy)carbonyl)imino)tetrahydro-1H-1 λ^6 -thiophene-2-carboxylate 1-oxide. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.43 - 7.28 (m, 5H), 5.06 (s, 1H), 5.05 - 4.95 (m, 1H), 4.67 - 4.41 (m, 1H), 3.82 - 3.64 (m, 4H), 3.64 - 3.36 (m, 1H), 2.47 - 2.13 (m, 3H), 2.12 - 2.00 (m, 1H). UPLC-MS-8: Rt = 0.63 min; MS m/z [M+H]⁺ = 312.

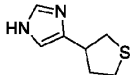
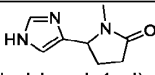
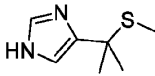
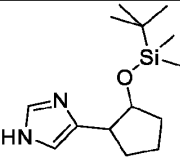
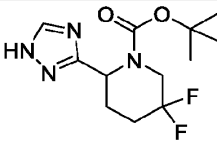
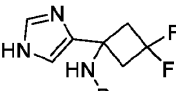
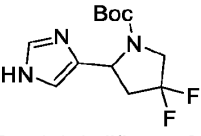
Step 3: Methyl 1-(((benzyloxy)carbonyl)imino)tetrahydro-1H-1 λ^6 -thiophene-2-carboxylate 1-oxide (step 2, 1.86 g, 90% wt, 1 eq, 5.3850 mmol) was taken in ca. 22 ml ammonia (7M/MeOH) and transferred into a 20 ml microwave vial and stirred overnight at 60°C. Then the reaction mixture was concentrated in vacuo to give benzyl (2-carbamoyl-1-oxidotetrahydro-1 λ^6 -thiophen-

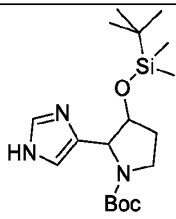
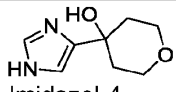
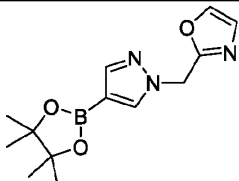
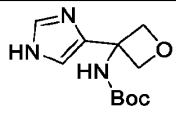
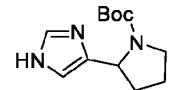
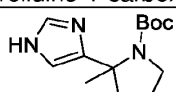
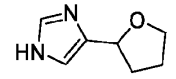
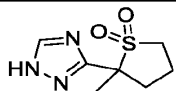
1-ylidene)carbamate. UPLC-MS-8: Rt = 0.41/0.48 min (2 peaks due to diastereomeric mixture); MS m/z [M+H]⁺ = 297.

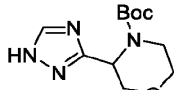
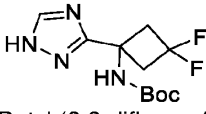
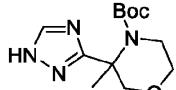
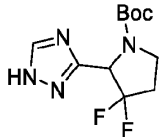
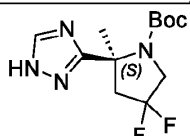
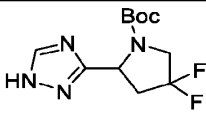
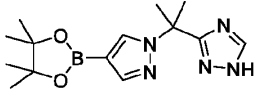
Step 4: Benzyl (2-carbamoyl-1-oxidotetrahydro-1λ⁶-thiophen-1-ylidene)carbamate (step 3, 1.5462 g, 1 eq, 5.2177 mmol) was dissolved in 25 mL toluene and 1,1-dimethoxy-N,N-dimethylmethanamine (1.2435 g, 1.39 ml, 2 eq, 10.435 mmol) was added to the mixture which was then stirred at 100°C for 2 h. Then the mixture was concentrated in vacuo and the residue was diluted with 25 ml HOAc and treated with hydrazine hydrate (522.4 mg, 508.2 µl, 2 eq, 10.435 mmol). This mixture was heated to 90°C and stirred for 1 h. Then ice/H₂O was added to the reaction mixture at RT, followed by extraction with EtOAc (3x). The combined organic layers were dried over a phase separator and concentrated in vacuo to give benzyl (1-oxido-2-(1H-1,2,4-triazol-3-yl)tetrahydro-1λ⁶-thiophen-1-ylidene)carbamate. UPLC-MS-8: Rt = 0.42/0.48min (2 peaks due to diastereomeric mixture); MS m/z [M+H]⁺ = 321.0.

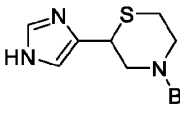
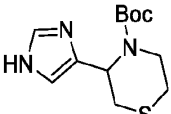
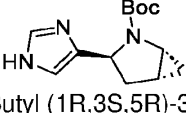
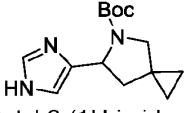
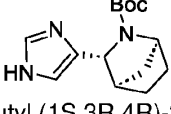
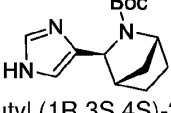
The following intermediates were prepared using methods similar to those used in the synthesis of Intermediates B-M1 to B-M20 from intermediates which were either commercially available or were obtained by methods described herein.

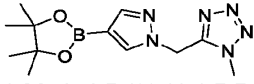
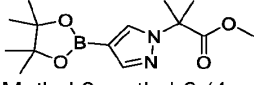
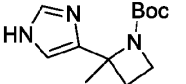
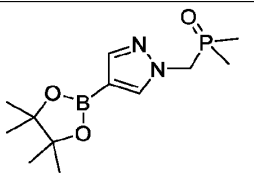
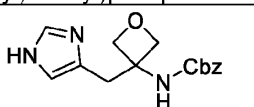
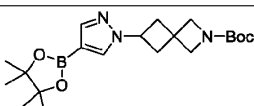
Intermediate	Structure	Method	Characterizing Data
B-T1	 tert-Butyl 3-(1H-imidazol-4-yl)-3-methylmorpholine-4-carboxylate	Analogous to Intermediate B-M5 using tert-butyl 3-formyl-3-methylmorpholine-4-carboxylate and 2-methylpropane-2-sulfonamide in step 1 and TosMIC, NaH in MeOH/DME (1/1), 60°C in step 2	UPLC-MS-8: Rt 0.35 min; MS m/z [M+H] ⁺ 268.1.
B-T2	 tert-Butyl 2-(1H-imidazol-4-yl)morpholine-4-carboxylate	Analogous to Intermediate B-M7 using tert-butyl 3-formyl-3-methylmorpholine-4-carboxylate and 2-methylpropane-2-sulfonamide in step 1 and TosMIC, NaH in MeOH/DME (1/1), 60°C in step 2	UPLC-MS-2: Rt 0.37 min; MS m/z [M+H] ⁺ 254.1.
B-T3	 tert-Butyl 3-(1H-imidazol-4-yl)pyrrolidine-1-carboxylate	Analogous to Intermediate B-M6 using 1-Boc-3-pyrrolidinecarbaldehyde and 2-methylpropane-2-sulfonamide in step 1	UPLC-MS-2: Rt 0.42 min; MS m/z [M+H] ⁺ 238.2.
B-T4	 tert-Butyl (2-(1H-1,2,4-triazol-3-yl)propan-2-yl)carbamate	Analogous to Intermediate B-M2 using 2-((tert-butoxycarbonyl)amino)-2-methylpropanoic acid	UPLC-MS-8: Rt 0.48 min; MS m/z [M+H] ⁺ 227.1.
B-T5	 2-(1H-1,2,4-triazol-3-yl)tetrahydrothiophene	Analogous to Intermediate B-M5 using tetrahydrothiophene-	UPLC-MS-2: Rt 0.17 min;

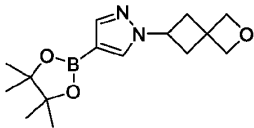
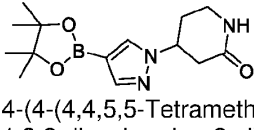
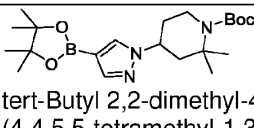
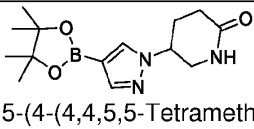
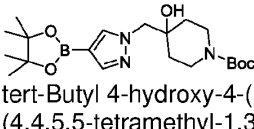
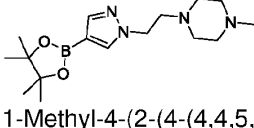
Intermediate	Structure	Method	Characterizing Data
	4-(Tetrahydrothiophen-2-yl)-1H-imidazole	2-carbaldehyde and 2-methylpropane-2-sulfinamide in step 1	MS m/z [M+H] ⁺ 155.0.
B-T6	 4-(Tetrahydrothiophen-3-yl)-1H-imidazole	Analogous to Intermediate B-M5 using tetrahydrothiophene-3-carbaldehyde and 2-methylpropane-2-sulfinamide step 1	UPLC-MS-2: Rt 0.17 min; MS m/z [M+H] ⁺ 155.0.
B-T7	 5-(1H-imidazol-4-yl)-1-methylpyrrolidin-2-one	Analogous to Intermediate B-M5 using 1-methyl-5-oxopyrrolidine-2-carbaldehyde	UPLC-MS-2: Rt 0.12 min; MS m/z [M+H] ⁺ 166.0.
B-T8	 4-(2-(Methylthio)propan-2-yl)-1H-imidazole	Analogous to Intermediate B-M5 using 1-2-methyl-2-(methylthio)propanal	UPLC-MS-2: Rt 0.33 min; MS m/z [M+H] ⁺ 157.0.
B-T9	 4-(2-((tert-butyl)dimethylsilyloxy)cyclopentyl)-1H-imidazole	Analogous to Intermediate B-M5 using 2-((tert-butyl)dimethylsilyloxy)cyclopentane-1-carbaldehyde (cis/trans mixture) [CAS No. 1243165-08-3] / [CAS No. 2170216-54-1]	UPLC-MS-8: Rt 0.97 min; MS m/z [M+H] ⁺ 267.1.
B-T10	 tert-Butyl (S)-5,5-difluoro-2-(1H-1,2,4-triazol-3-yl)piperidine-1-carboxylate	Analogous to Intermediate B-M2 using 1-(tert-butoxycarbonyl)-5,5-difluoropiperidine-2-carboxylic acid [CAS No. 1255663-95-6]	UPLC-MS-8: Rt 0.87 min; MS m/z [M-H] ⁻ 287.2.
B-T11	 tert-Butyl (3,3-difluoro-1-(1H-imidazol-4-yl)cyclobutyl)carbamate	Analogous to Intermediate B-M5 using tert-butyl (3,3-difluoro-1-formylcyclobutyl)carbamate [CAS No. 1232365-43-3]	UPLC-MS-2: Rt 0.36 min; MS m/z [M+H] ⁺ 274.0.
B-T12	 tert-Butyl 4,4-difluoro-2-(1H-imidazol-4-yl)pyrrolidine-1-carboxylate	Analogous to Intermediate B-M5 using tert-butyl (S)-4,4-difluoro-2-formylpyrrolidine-1-carboxylate [CAS No. 1194032-45-5]	UPLC-MS-8: Rt 0.44 min; MS m/z [M+H] ⁺ 274.0.

Intermediate	Structure	Method	Characterizing Data
B-T13	 tert-Butyl 3-((tert-butyldimethylsilyl)oxy)-2-(1H-imidazol-4-yl)pyrrolidine-1-carboxylate	Analogous to Intermediate B-M5 using tert-butyl (2S,3R)-3-((tert-butyldimethylsilyl)oxy)-2-formylpyrrolidine-1-carboxylate [CAS No. 627531-58-2].	UPLC-MS-8: Rt 1.00 min; MS m/z [M+H] ⁺ 368.2.
B-T14	 4-(1H-imidazol-4-yl)tetrahydro-2H-pyran-4-ol	Analogous to step 1 & 3 of Intermediate B-M13 using 4-iodo-1-trityl-1H-imidazole [CAS No. 96797-15-8] and tetrahydro-4H-pyran-4-one [CAS No. 29943-42-8].	UPLC-MS-2: Rt 0.13 min; MS m/z [M+H] ⁺ 169.2.as TFA salt
B-T15	 2-((4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)methyl)oxazole	Analogous to Intermediate B-M16 using 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole [CAS No. 269410-08-4] and 2-(chloromethyl)oxazole [CAS No. 185246-17-7].	UPLC-MS-8: Rt 0.70 min; MS m/z [M+H] ⁺ 276.3.
B-T16	 tert-Butyl (3-(1H-imidazol-4-yl)oxetan-3-yl)carbamate	Analogous to Intermediate B-M5 using tert-butyl (3-formyloxetan-3-yl)carbamate [CAS No. 885669-84-1]	UPLC-MS-8: Rt 0.23 min; MS m/z [M+H] ⁺ 240.2.
B-T17	 tert-Butyl 2-(1H-imidazol-4-yl)pyrrolidine-1-carboxylate	Analogous to Intermediate B-M10 using tert-butyl 2-formylpyrrolidine-1-carboxylate	UPLC-MS-2: Rt 0.71 min; MS m/z [M+H] ⁺ 238.3.
B-T18	 tert-Butyl 2-(1H-imidazol-4-yl)-2-methylpyrrolidine-1-carboxylate	Analogous to Intermediate B-M5 using tert-butyl 2-formyl-2-methylpyrrolidine-1-carboxylate [CAS No. 946484-82-8]	UPLC-MS-8: Rt 0.38 min; MS m/z [M+H] ⁺ 252.2
B-T19	 4-(Tetrahydrofuran-2-yl)-1H-imidazole	Analogous to Intermediate B-M10 using tetrahydrofuran-2-carbaldehyde	UPLC-MS-2: Rt 0.28 min; MS m/z [M+H] ⁺ 139.1
B-T20	 2-methyltetrahydrothiophene-2-sulfone	Analogous to Intermediate B-M2 using 2-methyltetrahydrothiophene-2-	UPLC-MS-2: Rt 0.13-0.17 min; MS m/z [M+H] ⁺ 202.2

Intermediate	Structure	Method	Characterizing Data
	2-Methyl-2-(1H-1,2,4-triazol-3-yl)tetrahydrothiophene 1,1-dioxide	carboxylic acid 1,1-dioxide [CAS No. 18458-95-2]	
B-T21	 tert-Butyl 3-(1H-1,2,4-triazol-3-yl)morpholine-4-carboxylate	Analogous to Intermediate B-M2 using 4-(tert-butoxycarbonyl)morpholine-3-carboxylic acid [CAS No. 212650-43-6]	UPLC-MS-8: Rt 0.54 min; MS m/z [M+H] ⁺ 255.2
B-T22	 tert-Butyl (3,3-difluoro-1-(1H-1,2,4-triazol-3-yl)cyclobutyl)carbamate	Analogous to Intermediate B-M2 using 1-((tert-butoxycarbonyl)amino)-3,3-difluorocyclobutane-1-carboxylic acid [CAS No. 1363380-83-9]	UPLC-MS-8: Rt 0.63 min; MS m/z [M+H] ⁺ 275.1
B-T23	 tert-Butyl 3-methyl-3-(1H-1,2,4-triazol-3-yl)morpholine-4-carboxylate	Analogous to Intermediate B-M2 using N-Boc-3-methylmorpholine-3-carboxylic acid [CAS No. 1052680-53-1]	UPLC-MS-8: Rt 0.50 min; MS m/z [M+H] ⁺ 269.3
B-T24	 tert-Butyl 3,3-difluoro-2-(1H-1,2,4-triazol-3-yl)pyrrolidine-1-carboxylate	Analogous to Intermediate B-M2 using 1-(tert-butoxycarbonyl)-3,3-difluoropyrrolidine-2-carboxylic acid [CAS No. 1822567-84-9]	UPLC-MS-8: Rt 0.62 min; MS m/z [M+H] ⁺ 275.1
B-T25	 tert-Butyl (S)-4,4-difluoro-2-methyl-2-(1H-1,2,4-triazol-3-yl)pyrrolidine-1-carboxylate	Analogous to Intermediate B-M2 using (S)-1-(tert-butoxycarbonyl)-4,4-difluoro-2-methylpyrrolidine-2-carboxylic acid [CAS No. 1194032-23-9]	UPLC-MS-8: Rt 0.73 min; MS m/z [M-H] ⁻ 287.1
B-T26	 tert-Butyl 4,4-difluoro-2-(1H-1,2,4-triazol-3-yl)pyrrolidine-1-carboxylate	Analogous to Intermediate B-M2 using 4,4-difluoro-1-Boc-2-pyrrolidinecarboxylic acid [CAS No. 1000313-01-8]	UPLC-MS-8: Rt 0.63 min; MS m/z [M+H] ⁺ 275.1
B-T27	 3-(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)propanamide [CAS No. 1282518-81-3]	Analogous to Intermediate B-M2/Step 2 using 2-methyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)propanamide [CAS No. 1282518-81-3]	HPLC-MS: Rt 1.99 min; MS m/z [M+H] ⁺ 304.3

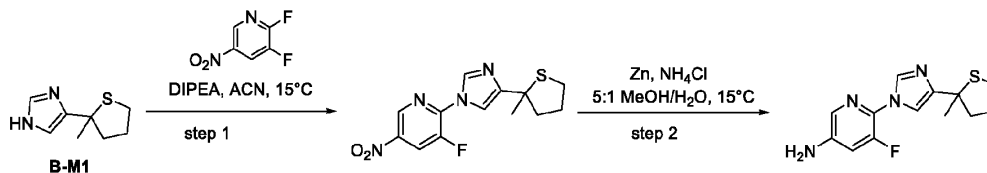
Intermediate	Structure	Method	Characterizing Data
	dioxaborolan-2-yl)-1H-pyrazol-1-yl)propan-2-yl)-1H-1,2,4-triazole		
B-T28	 tert-Butyl 2-(1H-imidazol-4-yl)thiomorpholine-4-carboxylate	Analogous to Intermediate B-M9 using 4-(tert-butoxycarbonyl)thiomorpholine-2-carboxylic acid [CAS No. 134676-67-8] following first the procedure described in WO 2014/23258 to prepare the corresponding N-methoxy-N-methyl-carboxamide	UPLC-MS-8: Rt 0.39 min; MS m/z [M+H] ⁺ 270
B-T29	 tert-Butyl 3-(1H-imidazol-4-yl)thiomorpholine-4-carboxylate	Analogous to Intermediate B-M9 using 4-(tert-butoxycarbonyl)thiomorpholine-3-carboxylic acid [CAS No. 128453-98-5] following first the procedure described in WO 2014/23258 to prepare the corresponding N-methoxy-N-methyl-carboxamide	UPLC-MS-2: Rt 0.37 min; MS m/z [M+H] ⁺ 270.1
B-T30	 tert-Butyl (1R,3S,5R)-3-(1H-imidazol-4-yl)-2-azabicyclo[3.1.0]hexane-2-carboxylate	Analogous to Intermediate B-M9 using (1R,3S,5R)-2-(tert-butoxycarbonyl)-2-azabicyclo[3.1.0]hexane-3-carboxylic acid [CAS No. 197142-34-0] following first the procedure described in WO 2014/23258 to prepare the corresponding N-methoxy-N-methyl-carboxamide	UPLC-MS-2: Rt 0.37 min; MS m/z [M+H] ⁺ 250.3
B-T31	 tert-Butyl 6-(1H-imidazol-4-yl)-5-azaspiro[2.4]heptane-5-carboxylate	Analogous to Intermediate B-M5 using (S)-tert-butyl 6-formyl-5-azaspiro[2.4]heptane-5-carboxylate [CAS No. 1262397-14-7]	UPLC-MS-2: Rt 0.47 min; MS m/z [M+H] ⁺ 264.2
B-T32	 tert-Butyl (1S,3R,4R)-3-(1H-imidazol-4-yl)-2-azabicyclo[2.2.1]heptane-2-carboxylate	Analogous to Intermediate B-M9 using (1S,3R,4R)-2-[(tert-butoxy)carbonyl]-2-azabicyclo[2.2.1]heptane-3-carboxylic acid [CAS No. 291775-53-6] following first the procedure described in WO 2014/23258 to prepare the corresponding N-methoxy-N-methyl-carboxamide	UPLC-MS-2: Rt 0.45 min; MS m/z [M+H] ⁺ 264.3
B-T33	 tert-Butyl (1R,3S,4S)-3-(1H-imidazol-4-yl)-2-azabicyclo[2.2.1]heptane-2-carboxylate	Analogous to Intermediate B-M9 using (1R,3S,4S)-2-[(tert-butoxy)carbonyl]-2-azabicyclo[2.2.1]heptane-3-carboxylic acid [CAS No. 291775-59-2] following first the	UPLC-MS-2: Rt 0.49 min; MS m/z [M+H] ⁺ 264.3

Intermediate	Structure	Method	Characterizing Data
	azabicyclo[2.2.1]heptane-2-carboxylate	procedure described in WO 2014/23258 to prepare the corresponding N-methoxy-N-methyl-carboxamide	
B-T34	 1-Methyl-5-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)methyl)-1H-tetrazole	Analogous to Intermediate B-M16 using 5-(chloromethyl)-1-methyl-1H-tetrazole [CAS No. 57235-84-4]	UPLC-MS-2: Rt 0.59 min; MS m/z [M+H] ⁺ 291.1
B-T35	 Methyl 2-methyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)propanoate	Analogous to Intermediate B-M16 using methyl 2-bromo-2-methylpropanoate [CAS No. 23426-63-3]	HPLC-MS-9: Rt 1.42 min; MS m/z [M+H] ⁺ 295.4
B-T36	 tert-Butyl 2-(1H-imidazol-4-yl)-2-methylazetidine-1-carboxylate	Analogous to Intermediate B-M9 using 1-(tert-butoxycarbonyl)-2-methylazetidine-2-carboxylic acid [CAS No. 449758-77-4] following first the procedure described in WO 2014/23258 to prepare the corresponding N-methoxy-N-methyl-carboxamide	UPLC-MS-8: Rt 0.38 min; MS m/z [M+H] ⁺ 238.2
B-T37	 Dimethyl((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)methyl)phosphine oxide	Analogous to Intermediate B-M16 using (chloromethyl)dimethylphosphine oxide [CAS No. 1638-75-1] and K ₂ CO ₃ in DMF	UPLC-MS-2: Rt 0.57 min; MS m/z [M+H] ⁺ 285.2
B-T38	 Benzyl (3-((1H-imidazol-4-yl)methyl)oxetan-3-yl)carbamate	Analogous to Intermediate B-M10 using ethyl 2-(3-(((benzyloxy)carbonyl)amino)oxetan-3-yl)acetate [CAS No. 1207175-05-0] using first DIBAL-H/DCM/-78°C to prepare the corresponding aldehyde	UPLC-MS-2: Rt 0.25 min; MS m/z [M+H] ⁺ 288.2
B-T39	 tert-Butyl 6-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)-2-azaspiro[3.3]heptane-2-carboxylate	Analogous to Intermediate B-M8 using tert-butyl 6-hydroxy-2-azaspiro[3.3]heptane-2-carboxylate [CAS No. 1147557-97-8]	HPLC-MS-7: Rt 1.58 min; MS m/z [M+H] ⁺ 390.1

Intermediate	Structure	Method	Characterizing Data
	pyrazol-1-yl)-2-azaspiro[3.3]heptane-2-carboxylate		
B-T40	 1-(2-Oxaspiro[3.3]heptan-6-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole	Analogous to Intermediate B-M8 using 2-oxaspiro[3.3]heptan-6-ol [CAS No. 1363381-08-1] and TsCl	HPLC-MS-7: Rt 1.46 min; MS m/z [M+H] ⁺ 290.8
B-T41	 4-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)piperidin-2-one	Analogous to Intermediate B-M4 using 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole [CAS No. 269410-08-4] and 4-hydroxypiperidin-2-one [CAS No. 476014-76-3]	HPLC-MS-4: Rt 0.80 min; MS m/z [M+H] ⁺ 292.3
B-T42	 tert-Butyl 2,2-dimethyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate	Analogous to Intermediate B-M4 using 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole [CAS No. 269410-08-4] and tert-butyl 4-hydroxy-2,2-dimethylpiperidine-1-carboxylate [CAS No. 1502162-73-3]	HPLC-MS-4: Rt 1.06 min; MS m/z [M+H] ⁺ 406.4
B-T43	 5-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)piperidin-2-one	Analogous to Intermediate B-M4 using 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole [CAS No. 269410-08-4] and 5-hydroxypiperidin-2-one [CAS No. 19365-07-2]	HPLC-MS-4: Rt 0.79 min; MS m/z [M+H] ⁺ 292.3
B-T44	 tert-Butyl 4-hydroxy-4-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)methyl)piperidine-1-carboxylate	Analogous to Intermediate B-M3/Step 1 using 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole [CAS No. 269410-08-4] and tert-butyl 1-oxa-6-azaspiro[2.5]octane-6-carboxylate [CAS No. 147804-30-6] with NaH/DMF	HPLC-MS-4: Rt 0.95 min; MS m/z [M+H] ⁺ 408.3
B-T45	 1-Methyl-4-(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)ethyl)piperazine	Analogous to Intermediate B-M16 using 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole [CAS No. 269410-08-4] and 1-(2-chloroethyl)-4-methylpiperazine [CAS No. 39123-20-1]	HPLC-MS: Rt 1.84 min; MS m/z [M+H] ⁺ 321.2

C Intermediates

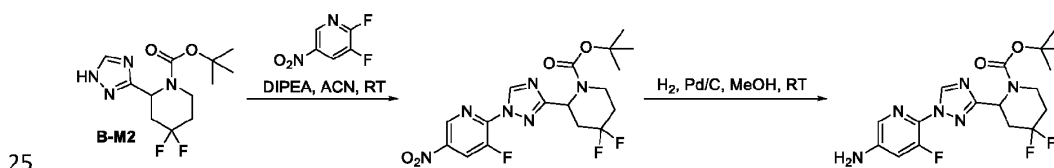
Intermediate C-M1: 5-Fluoro-6-(4-(2-methyltetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-amine



- 5 **Step 1:** 2,3-Difluoro-5-nitropyridine [CAS No. 954219-68-2] (31 g, 193.9 mmol) and DIPEA (75.1 g, 581.7 mmol) were added to a solution of Intermediate B-M1 (34.2 g, 193.9 mmol) in ACN (684 ml) at 15°C. After stirring for 1 h, the reaction mixture was diluted with EtOAc and washed with brine. The organic phase was dried (Na₂SO₄) and concentrated under reduced pressure. The residue was triturated with 1:5 TBME/heptane to give 3-fluoro-2-(4-(2-
- 10 methyltetrahydrothiophen-2-yl)-1H-imidazol-1-yl)-5-nitropyridine. ¹H NMR (300 MHz, DMSO-d₆) δ 9.20 (d, 1H), 8.96 (dd, 1H), 8.42 (m, 1H), 7.73 (t, 1H), 3.00 (dd, 2H), 2.40 (dt, 1H), 2.09 (td, 2H), 1.92 (m, 1H), 1.72 (s, 3H).

- Step 2:** Zinc powder (54.2 g, 829.5 mmol) and NH₄Cl (44.4 g, 829.5 mmol) were added to a solution of 3-fluoro-2-(4-(2-methyltetrahydrothiophen-2-yl)-1H-imidazol-1-yl)-5-nitropyridine (step
- 15 1, 53 g, 165.9 mmol) in 5:1 MeOH/H₂O (318 ml) at 15°C. After stirring for 16 h, the reaction mixture was diluted with MeOH and filtered. The filter cake was washed with MeOH and the filtrate was concentrated under reduced pressure. The residue was diluted with EtOAc and the mixture was washed with H₂O and brine, dried (Na₂SO₄) and concentrated under reduced pressure. The residue was triturated with 1:5 TBME/heptane to give 5-fluoro-6-(4-(2-
- 20 methyltetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-amine. ¹H NMR (300 MHz, DMSO-d₆) δ 7.94 (t, 1H), 7.67 (dd, 1H), 7.37 (t, 1H), 6.98 (dd, 1H), 5.87 (s, 2H), 2.96 (t, 2H), 2.38 (m, 1H), 2.08 (m, 2H), 1.84 (m, 1H), 1.69 (s, 3H).

Intermediate C-M2: tert-Butyl 2-(1-(5-amino-3-fluoropyridin-2-yl)-1H-1,2,4-triazol-3-yl)-4,4-difluoropiperidine-1-carboxylate

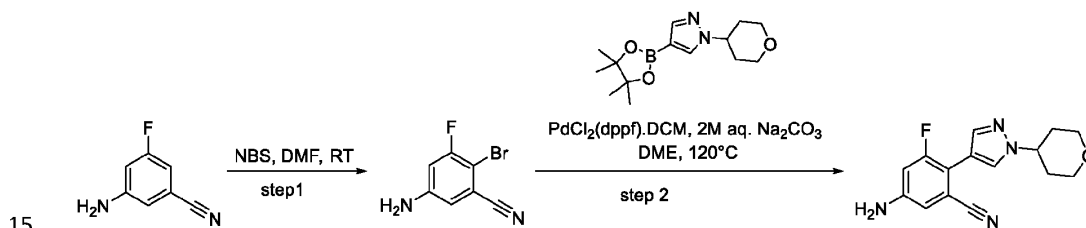


- 25 **Step 1:** A solution of 2,3-difluoro-5-nitropyridine [CAS No. 954219-68-2] (610.8 mg, 3.815 mmol) in ACN (5 ml) was added to a solution of Intermediate B-M2 (1.1 g, 3.815 mmol) and DIPEA (1.99 ml, 11.45 mmol) in ACN (30 ml) at RT. After stirring for 1 week, the reaction mixture was diluted with EtOAc and washed with H₂O, sat. aq. NH₄Cl and sat. aq. NaHCO₃. The organic
- 30 layer was dried (phase separator) and concentrated under reduced pressure and the residue was purified by normal phase chromatography (eluent : EtOAc/cyclohexane 0:1 to 53:47) to give

tert-butyl 4,4-difluoro-2-(1-(3-fluoro-5-nitropyridin-2-yl)-1H-1,2,4-triazol-3-yl)piperidine-1-carboxylate. ¹H NMR (600 MHz, DMSO-d₆) δ 9.33 (s, 1H), 9.25 (d, 1H), 9.01 (dd, 1H), 5.62 (br s, 1H), 4.14 (m, 1H), 2.73 (m, 1H), 2.51 (m, 1H), 1.96-2.09 (m, 2H), 1.39 (br s, 9H). UPLC-MS-8: Rt = 1.06 min; MS m/z [M+Na]⁺ 451.2.

- 5 **Step 2:** A mixture of tert-butyl 4,4-difluoro-2-(1-(3-fluoro-5-nitropyridin-2-yl)-1H-1,2,4-triazol-3-yl)piperidine-1-carboxylate (step 1, 280 mg, 0.654 mmol) and Pd/C (34.8 mg) in MeOH (15 ml) was stirred under 1 atm of hydrogen at RT. After 2 h, the reaction mixture was filtered over Celite® and the filtrate was concentrated under reduced pressure to give tert-butyl 2-(1-(5-amino-3-fluoropyridin-2-yl)-1H-1,2,4-triazol-3-yl)-4,4-difluoropiperidine-1-carboxylate which was
10 used without further purification. ¹H NMR (600 MHz, DMSO-d₆) δ 8.80 (s, 1H), 7.70 (d, 1H), 6.98 (dd, 1H), 6.13 (s, 2H), 5.54 (br s, 1H), 4.06-4.13 (m, 2H), 2.69 (m, 1H), 2.42 (m, 1H), 1.91-2.05 (m, 2H), 1.37 (br s, 9H). UPLC-MS-8: Rt = 0.85 min; MS m/z [M+H]⁺ 399.1.

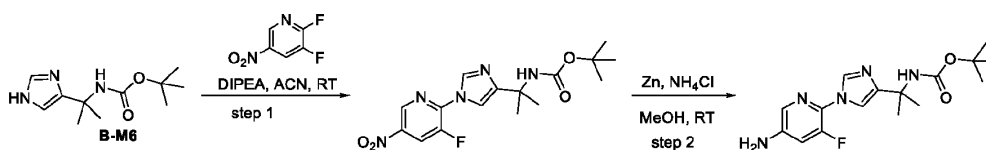
Intermediate C-M3: 5-Amino-3-fluoro-2-(1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)benzonitrile



- Step 1:** NBS (13.07 g, 73.5 mmol) was added to a solution of 3-amino-5-fluorobenzonitrile [CAS No. 210992-28-2] (10 g, 73.5 mmol) in DMF (100 ml) under nitrogen at RT. After 1 h, the reaction mixture was poured onto ice/H₂O and the resulting solid filtered and dried under vacuum to give 5-amino-2-bromo-3-fluorobenzonitrile. HPLC-MS-9: Rt 1.27 min; MS m/z [M-H]⁻
20 213.2/215.2.

- Step 2:** 2M aq. Na₂CO₃ (0.581 ml, 1.163 mmol) was added to a suspension of 1-(tetrahydro-2H-pyran-4-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole [CAS No. 1040377-03-4] (380 mg, 1.366 mmol), 5-amino-2-bromo-3-fluorobenzonitrile (step 1, 250 mg, 1.163 mmol) and PdCl₂(dppf)·DCM (95 mg, 0.116 mmol) in DME (6 ml). After degassing with Ar for 5 min, the
25 reaction vial was sealed and warmed to 120°C. After 15 min, the reaction mixture was cooled to RT, diluted with EtOAc and washed with H₂O and brine. The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure and the residue was purified by normal phase chromatography (eluent : DCM/(MeOH + 2% v/v 7M NH₃/MeOH) 99:1 to 90:10) to give 5-amino-3-fluoro-2-(1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)benzonitrile. UPLC-MS-2: Rt = 0.55
30 min; MS m/z [M+H]⁺ 287.2.

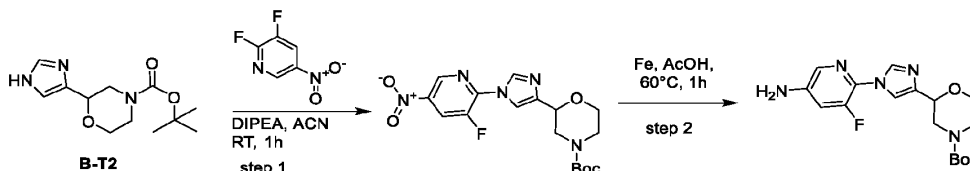
Intermediate C-M4: tert-Butyl (2-(1-(5-amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)propan-2-yl)carbamate



Step 1: 2,3-Difluoro-5-nitropyridine [CAS No. 954219-68-2] (882.9 mg, 5.516 mmol) and DIPEA (2.88 ml, 16.55 mmol) were added to a solution of Intermediate B-M6 (2.18 g, 5.516 mmol) in ACN (20 ml) at RT. After stirring for 6 h, the reaction mixture was diluted with EtOAc and washed with sat. aq. NaHCO₃. The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure and the residue was purified by normal phase chromatography (eluent : EtOAc/cyclohexane 0:1 to 1:0) to give tert-butyl (2-(1-(3-fluoro-5-nitropyridin-2-yl)-1H-imidazol-4-yl)propan-2-yl)carbamate. UPLC-MS-2: Rt = 0.99 min; MS m/z [M+H]⁺ 366.2.

Step 2: Zinc (5.712 g, 87.36 mmol) and NH₄Cl (4.673 g, 87.36 mmol) were added to a mixture of tert-butyl (2-(1-(3-fluoro-5-nitropyridin-2-yl)-1H-imidazol-4-yl)propan-2-yl)carbamate (step 1, 798 mg, 2.184 mmol) in MeOH (24 ml) and H₂O (8 ml) at RT. After 30 min, the reaction mixture was diluted with 1:1 DCM/MeOH and filtered through Hyflo[®]. The filtrate was concentrated under reduced pressure. The residue was diluted with DCM and washed with H₂O (2x). The organic layer was dried (Na₂SO₄) and concentrated under reduce pressure to give tert-butyl (2-(1-(5-amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)propan-2-yl)carbamate which was used directly without purification. ¹H NMR (600 MHz, DMSO-d₃) δ 7.93 (s, 1H), 7.68 (m, 1H), 7.25 (s, 1H), 7.00 (dd, 1H), 6.72 (br s, 1H), 5.88 (s, 2H), 1.51 (s, 6H), 1.29-1.39 (m, 9H). UPLC-MS-2: = 0.63 min; MS m/z [M+H]⁺ 336.2.

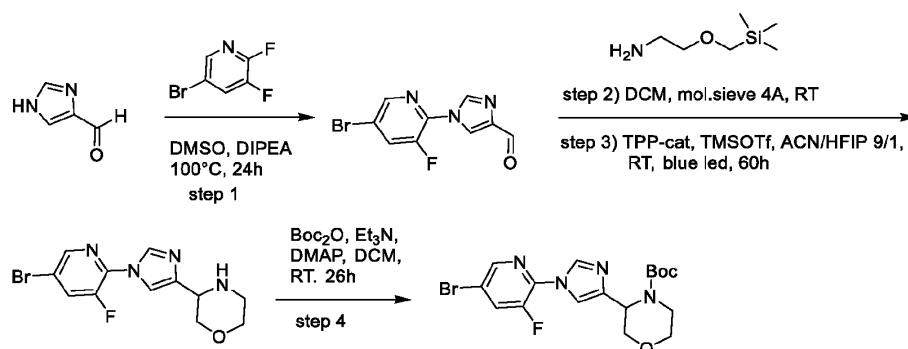
Intermediate C-M5: tert-Butyl 2-(1-(5-amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)morpholine-4-carboxylate



Step 1: To a solution of crude Intermediate B-T2 (235 mg, 0.929 mmol) in ACN (8 ml) were added 2,3-difluoro-5-nitropyridine [CAS No. 954219-68-2] (0.095 ml, 0.929 mmol) and DIPEA (0.487 ml, 2.79 mmol) and the reaction mixture was stirred at RT for 1 h. The reaction mixture was diluted with EtOAc, quenched with H₂O and a saturated aqueous solution of NaHCO₃. Phases were separated and the aqueous layer was extracted with EtOAc (2x). The combined organic layers were washed with brine, dried (Na₂SO₄) and evaporated. The crude product was purified by silica gel column chromatography eluting with a gradient of EtOAc (0-100%) in cyclohexane. Fractions containing the desired product were combined and evaporated to give tert-butyl 2-(1-(3-fluoro-5-nitropyridin-2-yl)-1H-imidazol-4-yl)morpholine-4-carboxylate. UPLC-MS-2: Rt = 0.90 min; MS m/z [M+H]⁺ 394.1.

Step 2: To a suspension of tert-butyl 2-(1-(3-fluoro-5-nitropyridin-2-yl)-1H-imidazol-4-yl)morpholine-4-carboxylate (step 1, 101 mg, 0.246 mmol) in HOAc (2 ml) was added iron (68.8 mg, 1.232 mmol) and the resulting suspension was stirred at 60°C for 1 h. The reaction mixture was diluted with DCM/MeOH (9/1, 20 ml), filtered through a pad of Celite®, washed with DCM/MeOH (9/1) and the filtrate was evaporated. The crude product was purified by silica gel column chromatography eluting with a gradient of MeOH (0-20%) in DCM. Fractions containing the desired product were combined and evaporated to give tert-butyl 2-(1-(5-amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)morpholine-4-carboxylate. ¹H NMR (600 MHz, DMSO-d₆) δ 7.99 (d, 1H), 7.69 - 7.66 (m, 1H), 7.47 (s, 1H), 7.00 (dd, 1H), 5.93 (s, 2H), 4.37 (dd, 1H), 4.00 (d, 1H), 3.87 (d, 1H), 3.76 (s, 1H), 3.53 (t, 1H), 2.97 (s, 1H), 1.42 (s, 9H). UPLC-MS-2: Rt = 0.71 min; MS m/z [M+H]⁺ 342.2.

Intermediate C-M6: tert-Butyl 3-(1-(5-bromo-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)morpholine-4-carboxylate



Step 1: To a solution of 1H-imidazole-4-carbaldehyde (1 g, 10.41 mmol) in DMSO (40 ml) were added 5-bromo-2,3-difluoropyridine (1.117 ml, 10.41 mmol) and DIPEA (7.27 ml, 41.6 mmol). The reaction mixture was stirred at 100°C for 24 h, diluted with EtOAc, quenched with H₂O and a saturated aqueous solution of NaHCO₃. Phases were separated and the aqueous layer was extracted with EtOAc (2x). The combined organic layers were washed with brine, dried using a phase separator and evaporated. The crude product was purified via RP-HPLC eluting with a gradient of ACN (10% to 100%) in H₂O+0.1% HCOOH. Fractions containing the desired product were combined, a saturated aqueous solution of NaHCO₃ was added and the aqueous solution was extracted with DCM (3x). The combined organic layers were dried using a phase separator and evaporated to give 1-(5-bromo-3-fluoropyridin-2-yl)-1H-imidazole-4-carbaldehyde. ¹H NMR (600 MHz, DMSO-d₆) δ 9.87 (d, 1H), 8.62 (m, 3H), 8.49 (d, 1H). UPLC-MS-2: Rt = 0.47 min; MS m/z [M+H]⁺ 270.0, 272.0.

Step 2: To an oven dried flask containing molecular sieves 4A (1 g) was added 1-(5-bromo-3-fluoropyridin-2-yl)-1H-imidazole-4-carbaldehyde (step 1, 1.1 g, 3.83 mmol) followed by a solution of 2-((trimethylsilyl)methoxy)ethan-1-amine (SLAP M) (0.677 g, 4.59 mmol) in dry DCM (20 ml) under inert atmosphere and the reaction mixture was stirred at RT for 3 h. The reaction

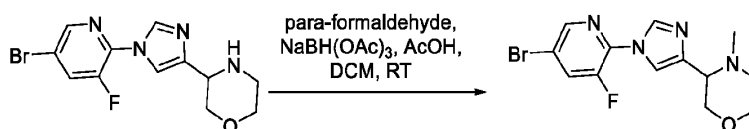
mixture was filtered through a Celite® pad and the filtrate was concentrated to give (E)-1-(1-(5-bromo-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)-N-(2-((trimethylsilyl)methoxy)ethyl)methanimine.

¹H NMR (600 MHz, DMSO-d₆) δ 8.59 - 8.58 (m, 1H), 8.56 (dd, 1H), 8.36 (t, 1H), 8.23 (d, 1H), 8.09 (t, 1H), 3.68 - 3.63 (m, 2H), 3.58 (t, 2H), 3.11 (s, 2H), -0.02 (s, 9H).

- 5 **Step 3:** A vial charged with molecular sieves and magnetic bar was charged with (E)-1-(1-(5-bromo-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)-N-(2-((trimethylsilyl)methoxy)ethyl)methanimine (step 2, 1.672 g, 3.35 mmol) dissolved in ACN (18 ml) and HFIP (2 ml). 2,4,6-triphenylpyrilium tetrafluoroborate (0.303 g, 0.766 mmol) and TMSOTf (0.830 ml, 4.59 mmol) were added and the reaction mixture was stirred and irradiated with a blue LED lamp at RT for 60 h under argon.
- 10 The reaction mixture was concentrated and purified by RP-HPLC eluting with a gradient of ACN (0% to 100%) in H₂O+0.1% HCOOH. Fractions containing the product were combined, frozen and lyophilized to give 3-(1-(5-bromo-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)morpholine, which was re-purified via RP-HPLC eluting with a gradient of ACN (0% to 100%) in H₂O + 7.3 mM NH₄OH. Fractions containing the desired product were combined, frozen and lyophilized to give
- 15 3-(1-(5-bromo-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)morpholine. ¹H NMR (600 MHz, DMSO-d₆) δ 8.55 (d, 1H), 8.52 (dd, 1H), 8.25 (t, 1H), 7.61 (q, 1H), 7.46 - 7.32 (m, 1H), 3.89 (dd, 1H), 3.80 (dd, 1H), 3.70 (dt, 1H), 3.44 - 3.39 (m, 1H), 3.28 (d, 1H), 2.85 - 2.80 (m, 2H). UPLC-MS-2: Rt = 0.25 min; MS m/z [M+H]⁺ 327.1, 329.1.

- Step 4:** To a solution of 3-(1-(5-bromo-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)morpholine (step 3, 163 mg, 0.478 mmol) in DCM (4 ml) were added Boc₂O (0.222 ml, 0.957 mmol), Et₃N (0.199 ml, 1.435 mmol) and DMAP (5.84 mg, 0.048 mmol). The reaction mixture was stirred at RT for 24 h. The reaction mixture was diluted with an aqueous saturated solution of NaHCO₃ and extracted with DCM (2x). The combined organic layers were dried using a phase separator and evaporated. The crude product was purified by silica gel column chromatography eluting with a
- 25 gradient of EtOAc (0-100%) in cyclohexane. Fractions containing the desired product were combined and evaporated to give tert-butyl 3-(1-(5-bromo-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)morpholine-4-carboxylate. ¹H NMR (600 MHz, DMSO-d₆) δ 8.55 (d, 1H), 8.52 (dd, 1H), 8.28 (t, 1H), 7.52 (s, 1H), 4.94 (s, 1H), 4.27 (d, 1H), 3.77 (d, 1H), 3.68 (dd, 1H), 3.64 (dd, 1H), 3.41 (td, 1H), 3.10 (s, 1H), 1.41 (s, 9H). UPLC-MS-2: Rt = 1.03 min; MS m/z [M+H]⁺ 427.1, 429.1.

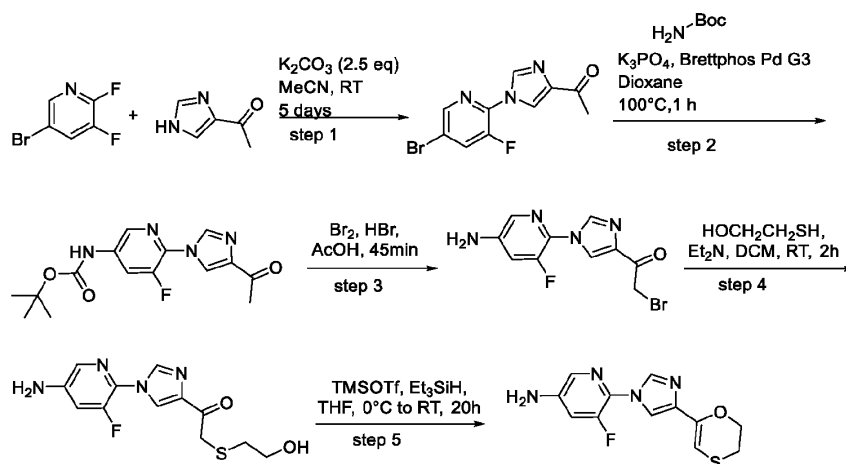
- 30 **Intermediate C-M7:** 3-(1-(5-Bromo-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)-4-methylmorpholine



- To a solution of 3-(1-(5-bromo-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)morpholine (see Intermediate C-M6/Step 3, 100 mg, 0.293 mmol) in DCM (3 ml) were added paraformaldehyde (55.6 mg, 1.761 mmol) and HOAc (0.034 ml, 0.587 mmol), followed by portion wise addition of
- 35 NaBH(OAc)₃ (385 mg, 1.761 mmol). The resulting suspension was stirred at RT overnight.

Further paraformaldehyde (55.6 mg, 1.761 mmol) and $\text{NaBH}(\text{OAc})_3$ (385 mg, 1.761 mmol) were added and the reaction mixture stirred at RT for an additional 24 h. The reaction mixture was diluted with DCM and an aqueous saturated solution of NaHCO_3 , phases were separated and the aqueous phase was extracted with DCM (2x). The combined organic layers were washed
 5 with brine, dried using a phase separator and evaporated. The crude product was purified by RP-HPLC eluting with a gradient of ACN (10-100%) in $\text{H}_2\text{O}+7.3\text{mM NH}_4\text{OH}$. Fractions containing the desired product were combined, an aqueous saturated solution of NaHCO_3 was added and the aqueous phase was extracted with DCM (3x). The combined organic layers were dried using a phase separator and evaporated to give 3-(1-(5-bromo-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)-4-methylmorpholine. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ 8.56 - 8.54 (m, 1H), 8.52 (dd, 1H), 8.25 (t, 1H), 7.65 (t, 1H), 3.78 (d, 1H), 3.70 - 3.66 (m, 1H), 3.60 (td, 1H), 3.46 (dd, 1H), 3.13 (dd, 1H), 2.77 - 2.73 (m, 1H), 2.23 (td, 1H), 2.07 (s, 3H). UPLC-MS-1: R_t = 0.71 min; MS m/z $[\text{M}+\text{H}]^+$ 341.0, 344.0.

Intermediate C-M8: 6-(4-(5,6-Dihydro-1,4-oxathiin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-amine
 15 amine



Step 1: To a solution of 5-bromo-2,3-difluoropyridine (6 g, 30.9 mmol) and 1-(1H-imidazol-4-yl)ethan-1-one (4.8 g, 43.6 mmol) in ACN (150 ml) was added K_2CO_3 (15.06 g, 109 mmol) and the resulting suspension was stirred at RT for 5 d. Solvent was removed and the crude product was purified by silica gel column chromatography eluting with a gradient of EtOAc (80-100%) in cyclohexane. Fractions containing the desired product were concentrated to give 1-(1-(5-bromo-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)ethan-1-one. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ 8.65 - 8.59 (m, 2H), 8.40 (dt, 2H), 2.50 (s, 3H). UPLC-MS-1: R_t = 0.57 min; MS m/z $[\text{M}+\text{H}]^+$ 284.0, 286.0.
 20

Step 2: 1-(1-(5-Bromo-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)ethan-1-one (step 1, 2.9 g, 10.21 mmol) was dissolved in dioxane (100 ml) under argon at RT. tert-Butyl carbamate (2.392 g, 20.42 mmol), K_3PO_4 (5.42 g, 25.5 mmol) and BrettPhos Pd G3 (0.463 g, 0.510 mmol) were added and the reaction mixture was stirred at 100°C for 3 h. The reaction mixture was diluted
 25

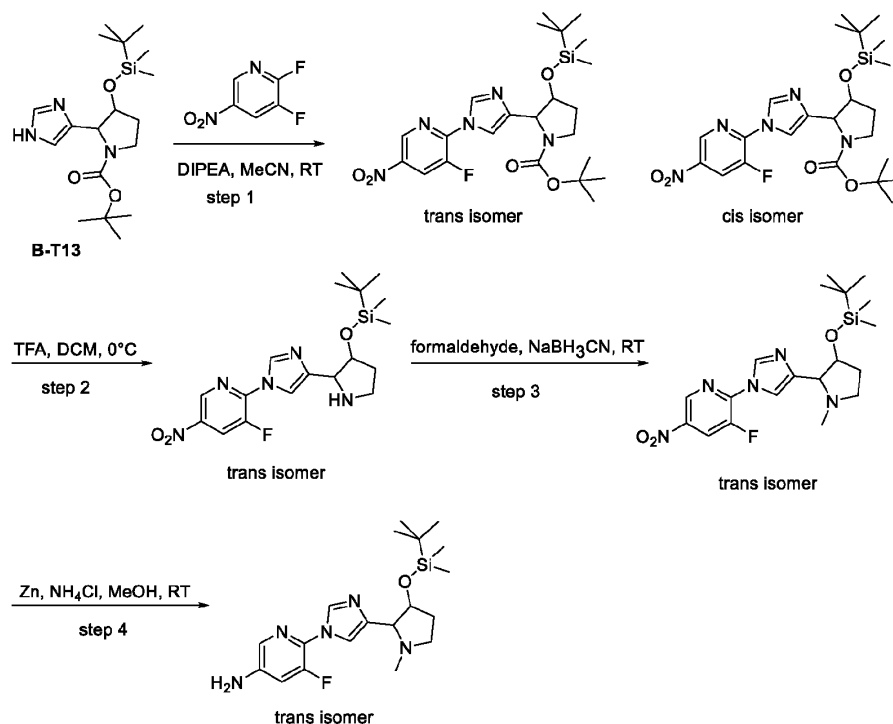
with H₂O and extracted with DCM (2x). Organic phases were combined, dried and concentrated. The crude product was purified using silica gel column chromatography eluting with a gradient of EtOAc (0-100%) in cyclohexane. Fractions containing the desired product were concentrated to give tert-butyl (6-(4-acetyl-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)carbamate, 1-(1-(3-fluoropyridin-2-yl)-1H-imidazol-4-yl)ethan-1-one. UPLC-MS-1: Rt = 0.87 min; MS m/z [M+H]⁺ 321.3, 286.0.

Step 3: To a mixture of tert-butyl (6-(4-acetyl-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)carbamate (step 2, 50 mg, 0.156 mmol) in HBr in HOAc (200 µl, 1.215 mmol) was added Br₂ (8.04 µl, 0.156 mmol). The resulting mixture was stirred at RT for 45 min. The suspension was diluted with Et₂O, centrifuged and the liquid phase was removed. The same procedure was repeated twice. The remaining powder was dried to give 1-(1-(5-amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)-2-bromoethan-1-one. ¹H NMR (600 MHz, DMSO-d₆) δ 8.50 - 8.48 (m, 1H), 8.44 - 8.41 (m, 1H), 7.74 (dd, 1H), 7.06 (dd, 1H), 4.73 (s, 2H). UPLC-MS-1: Rt = 0.44 min; MS m/z [M+H]⁺ 299.1, 301.1.

Step 4: To a solution of 2-mercaptoethanol (0.169 ml, 2.397 mmol) and Et₃N (0.554 ml, 4.00 mmol) in DCM (8 ml) was added 1-(1-(5-amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)-2-bromoethan-1-one (step 3, 335 mg, 0.799 mmol). The resulting mixture was stirred at RT for 2 h. The reaction mixture was diluted with DCM and washed with an aqueous saturated solution of NaHCO₃. The aqueous phase was extracted with DCM. The combined organic phases were dried (Na₂SO₄) and concentrated to give 1-(1-(5-amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)-2-((2-hydroxyethyl)thio)ethan-1-one. ¹H NMR (600 MHz, DMSO-d₆) δ 8.30 - 8.28 (m, 1H), 8.19 - 8.17 (m, 1H), 7.73 - 7.71 (m, 1H), 7.04 - 7.00 (m, 1H), 6.07 (s, 2H), 4.81 (t, 1H), 3.83 (s, 2H), 3.56 - 3.51 (m, 2H), 2.64 (t, 2H). UPLC-MS-1: Rt = 0.24 min; MS m/z [M+H]⁺ 279.0.

Step 5: To a suspension of 1-(1-(5-amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)-2-((2-hydroxyethyl)thio)ethan-1-one (step 4, 200 mg, 0.675 mmol) in THF (5 ml), cooled to 0°C, TMSOTf (0.183 ml, 1.012 mmol) and triethylsilane (0.162 ml, 1.012 mmol) were added and the resulting solution was allowed to stir at RT for 20 h. The reaction mixture was quenched with MeOH and Et₃N (0.281 ml, 2.025 mmol) was added. The solution was adsorbed on Isolute and the crude product was purified by silica gel column chromatography eluting with a gradient of MeOH (NH₃.7N) (0-90%) in DCM. Fractions containing the desired compound were combined and concentrated to give 6-(4-(5,6-dihydro-1,4-oxathiin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-amine. ¹H NMR (600 MHz, DMSO-d₆) δ 8.00 (t, 1H), 7.68 (dd, 1H), 7.35 (t, 1H), 6.99 (dd, 1H), 5.92 (s, 2H), 5.89 (s, 1H), 4.37 - 4.32 (m, 2H), 3.09 - 3.03 (m, 2H). UPLC-MS-1: Rt = 0.55 min; MS m/z [M+H]⁺ 279.0.

Intermediate C-M9: 6-(4-(3-((tert-Butyldimethylsilyl)oxy)-1-methylpyrrolidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-amine



- Step 1:** At RT a vial was charged with Intermediate B-T13 (1.400 g, 70% wt, 2.666 mmol), 2,3-difluoro-5-nitropyridine [CAS No. 954219-68-2] (469.5 mg, 2.933 mmol), ACN (17.70 ml) and DIPEA (1.034 g, 1.39 ml, 7.999 mmol). The mixture was stirred at RT for 3 h. The reaction mixture was basified with sat. aq. NaHCO₃ solution and extracted with EtOAc (2x). The combined organic phases were washed with brine and dried via a phase separator. The solvent was removed under reduced pressure to give a residue which was purified by normal phase chromatography (eluent: cyclohexane/EtOAc 100:0 to 70:30 in 45 min) to give the 1st eluting trans isomer and the 2nd eluting cis isomer of tert-butyl 3-((tert-butyldimethylsilyl)oxy)-2-(1-(3-fluoro-5-nitropyridin-2-yl)-1H-imidazol-4-yl)pyrrolidine-1-carboxylate.

trans isomer: ¹H NMR (700 MHz, DMSO-d₆) δ 9.21 (t, 1H), 8.98 (dd, 1H), 8.44 (d, 1H), 7.63 (d, 1H), 4.61 (d, 1H), 4.40 – 4.37 (m, 1H), 3.49 (dt, 2H), 2.14 (q, 1H), 1.81 – 1.69 (m, 1H), 1.41 (s, 4H), 1.28 (s, 5H), 0.88 (s, 9H), 0.18 – 0.03 (m, 6H). UPLC-MS-8: Rt = 1.61 min; MS m/z [M+H]⁺ 508.3.

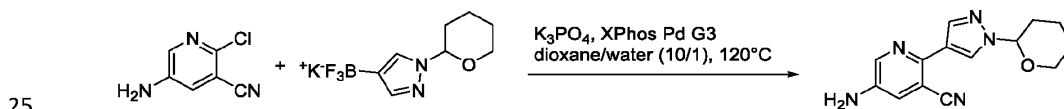
- Step 2:** At RT a vial was charged with tert-butyl 3-((tert-butyldimethylsilyl)oxy)-2-(1-(3-fluoro-5-nitropyridin-2-yl)-1H-imidazol-4-yl)pyrrolidine-1-carboxylate (step 1, 309.0 mg, 608.7 μmol) and DCM (6 ml) and the mixture was cooled to 0°C. Then TFA (1.388 g, 937.9 μl, 12.17 mmol) was added dropwise. After 2.5 h additional TFA (500 μl) and after further 2.5 h additional TFA (300 μl) was added. After 6 h, the reaction mixture was basified with sat. aq. NaHCO₃ and extracted with DCM (3x). The combined organic phases were dried by elution through a separating phase cartridge and evaporated to give the trans isomer of 2-(4-(3-((tert-

butyldimethylsilyl)oxy)pyrrolidin-2-yl)-1H-imidazol-1-yl)-3-fluoro-5-nitropyridine. UPLC-MS-8: Rt = 0.99 min; MS m/z [M+H]⁺ 408.2.

Step 3: At RT a vial was charged with 2-(4-(3-((tert-butyldimethylsilyl)oxy)pyrrolidin-2-yl)-1H-imidazol-1-yl)-3-fluoro-5-nitropyridine (step 2, 224.0 mg, 85% wt, 467.2 μmol), ACN (3.5 ml) and formaldehyde (192.2 mg, 176.3 μl, 36.5% wt, 2.336 mmol). Then sodium cyanoborohydride (61.81 mg, 95% wt, 934.4 μmol) was added at RT. After 1.5 h at RT additional formaldehyde (192.2 mg, 176.3 μl, 36.5% wt, 2.336 mmol) and sodium cyanoborohydride (61.81 mg, 95% wt, 934.4 μmol) were added. After 19 h at RT additional formaldehyde (192.2 mg, 176.3 μl, 36.5% wt, 2.336 mmol) and sodium cyanoborohydride (61.81 mg, 95% wt, 934.4 μmol) were added. After 21 h, the reaction mixture was extracted with H₂O and EtOAc (3x) and 2-Me-THF (4x). The combined organic phases were dried by elution through a separating phase cartridge and evaporated to give a residue which was purified by normal phase chromatography (eluent: cyclohexane/EtOAc 80:20 to 0:100 in 11 min) to give the trans isomer of 2-(4-(3-((tert-butyldimethylsilyl)oxy)-1-methylpyrrolidin-2-yl)-1H-imidazol-1-yl)-3-fluoro-5-nitropyridine. UPLC-MS-2: Rt = 0.94 min; MS m/z [M+H]⁺ 422.2.

Step 4: At RT 2-(4-(3-((tert-butyldimethylsilyl)oxy)-1-methylpyrrolidin-2-yl)-1H-imidazol-1-yl)-3-fluoro-5-nitropyridine (step 3, 119.0 mg, 98% wt, 276.6 μmol) was dissolved in MeOH (5.840 ml) and zinc (180.9 mg, 2.766 mmol) and NH₄Cl (148.0 mg, 2.766 mmol) were added. The mixture was stirred at RT for 1.5 h. Then, the reaction mixture was extracted with H₂O and EtOAc (3x) and 2-Me-THF (4x). The combined organic phases were dried by elution through a separating phase cartridge and evaporated to give the trans isomer of 6-(4-(3-((tert-butyldimethylsilyl)oxy)-1-methylpyrrolidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-amine. UPLC-MS-2: Rt = 0.82 min; MS m/z [M+H]⁺ 392.4.

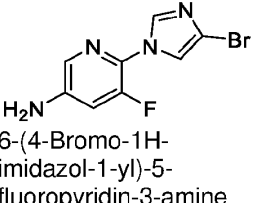
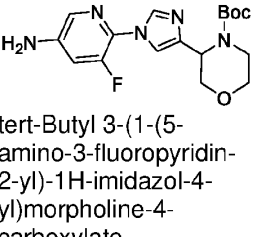
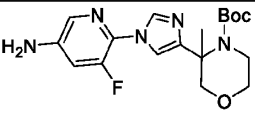
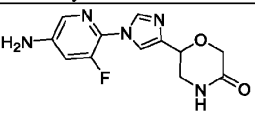
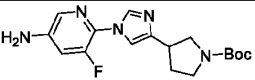
Intermediate C-M10: 5-Amino-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)nicotinonitrile

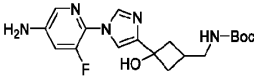
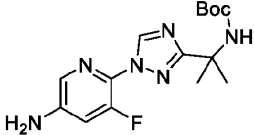
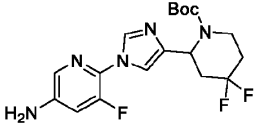
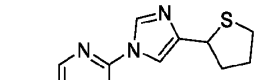
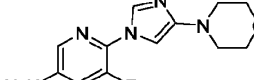


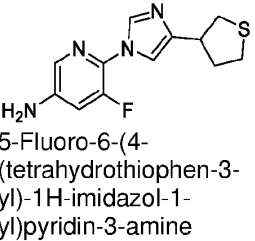
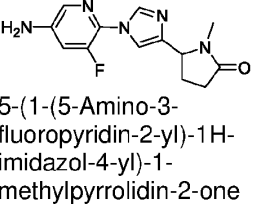
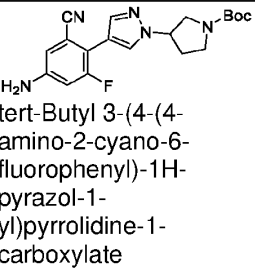
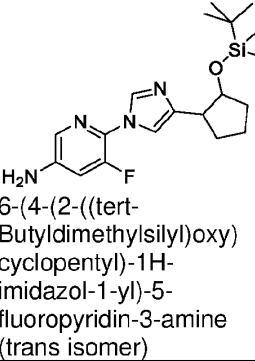
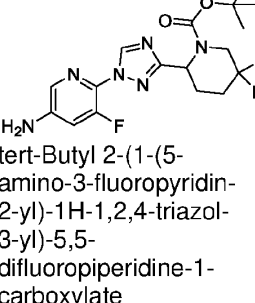
To a mixture of 5-amino-2-chloronicotinonitrile [CAS No. 13600-46-9] (50 mg, 0.326 mmol) in dioxane/ H₂O (v/v 10/1) (5 ml) were added K₃PO₄ (276 mg, 1.302 mmol), potassium trifluoro[1-(oxan-2-yl)-1H-pyrazol-4-yl]borate [CAS No. 1423013-22-2] (168 mg, 0.651 mmol) and XPhos Pd G3 (28 mg, 33 μmol). The reaction mixture was degassed and stirred at 120°C for 1 h. H₂O was added and the mixture was extracted with DCM. The combined organic phases were evaporated under reduced pressure. The residue was purified by normal phase chromatography (eluent: cyclohexane/EtOAc 94:6 to 0:100 in 18 min) to give 5-amino-2-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)nicotinonitrile. UPLC-MS-2: Rt = 0.54 min; MS m/z [M+H]⁺ 270.2.

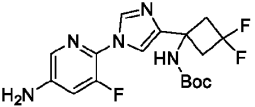
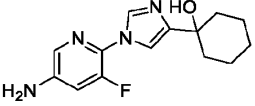
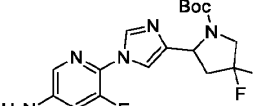
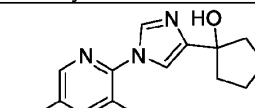
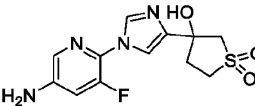
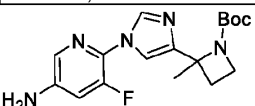
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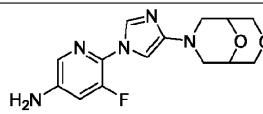
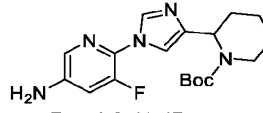
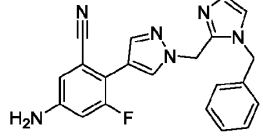
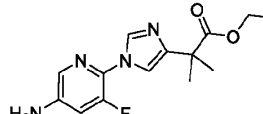
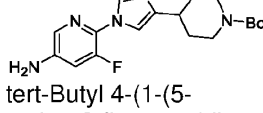
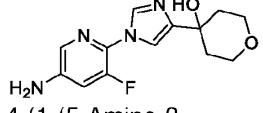
The following intermediates were prepared using methods similar to Intermediates C-M1 to C-M10 from intermediates which are either commercially available or were obtained by methods described herein.

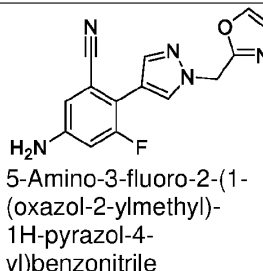
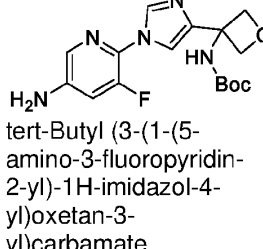
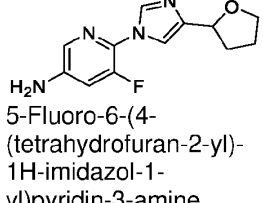
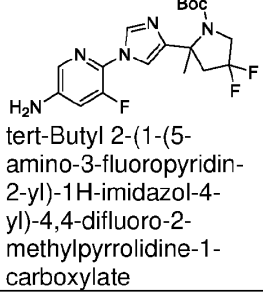
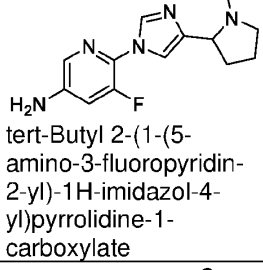
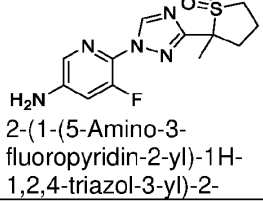
Intermediate	Structure	Method	Characterizing Data
C-T1	 6-(4-Bromo-1H-imidazol-1-yl)-5-fluoropyridin-3-amine	Analogous to Intermediate C-M1 using 4-bromo-1H-imidazole [CAS No. 2302-25-2] in Step 1 and Fe/HOAc/60°C in Step 2	UPLC-MS-2: Rt 0.66 min; MS m/z [M+H] ⁺ 287.1/289.1.
C-T2 (rac) C-T2 (Peak 1) C-T2 (Peak 2)	 tert-Butyl 3-(1-(5-amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)morpholine-4-carboxylate	Analogous to Intermediate C-M1 using Intermediate B-M5 followed by C-SFC (Daicel Chiralpak AD 10 µm, 250 x 50 mm) 1 st eluting enantiomer and 2 nd eluting enantiomer	¹ H NMR (600 MHz, DMSO-d ₆) δ 8.00 (t, 1H), 7.69 (dd, 1H), 7.28 (d, 1H), 7.00 (dd, 1H), 5.91 (s, 2H), 4.92 (d, 1H), 4.25 (d, 1H), 3.76 (dd, 1H), 3.67 - 3.64 (m, 1H), 3.64 - 3.59 (m, 1H), 3.41 - 3.36 (m, 1H), 3.11 (s, 1H), 1.40 (s, 9H). UPLC-MS-2: Rt 0.68 min; MS m/z [M+H] ⁺ 364.2. Peak 1: C-SFC-24 (mobile phase: CO ₂ /EtOH +0.05%NH ₃ (60:40)): Rt = 0.56 min. Peak 2: C-SFC-24 (mobile phase: CO ₂ /EtOH +0.05%NH ₃ (60:40)): Rt = 1.39 min.
C-T3	 tert-Butyl 3-(1-(5-amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)-3-methylmorpholine-4-carboxylate	Analogous to Intermediate C-M1 using Intermediate B-T1	¹ H NMR (600 MHz, DMSO-d ₆) δ 7.95 (d, 1H), 7.68 (d, 1H), 7.26 (d, 1H), 7.00 (dd, 1H), 5.89 (s, 2H), 3.79 (d, 1H), 3.76 (q, 1H), 3.69 (ddd, 1H), 3.55 - 3.48 (m, 1H), 3.40 - 3.35 (m, 2H), 1.61 (s, 3H), 1.20 (s, 9H). UPLC-MS-8: Rt 0.67 min; MS m/z [M+H] ⁺ 378.1.
C-T4	 6-(1-(5-Amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)morpholin-3-one	Analogous to Intermediate C-M5 using Intermediate B-M7	¹ H NMR (600 MHz, DMSO-d ₆) δ 8.10 (d, 1H), 8.01 (d, 1H), 7.68 (d, 1H), 7.55 (s, 1H), 7.00 (dd, 1H), 5.94 (s, 2H), 4.77 (dd, 1H), 4.15 (d, 1H), 4.08 (d, 1H), 3.58 (dd, 1H), 3.42 - 3.39 (m, 1H). UPLC-MS-1: Rt 0.31 min; MS m/z [M+H] ⁺ 276.0.
C-T5	 6-(1-(5-Amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)pyrrolidine-1-carboxylate	Analogous to Intermediate C-M5	¹ H NMR (600 MHz, DMSO-d ₆) δ 7.97 (d, 1H), 7.68 (dd, 1H), 7.37 (s, 1H), 6.99 (dd,

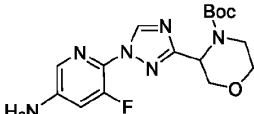
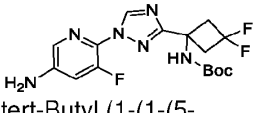
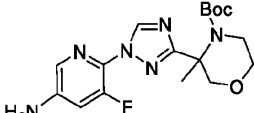
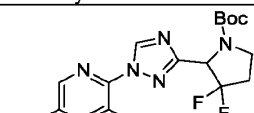
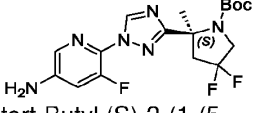
Intermediate	Structure	Method	Characterizing Data
	tert-Butyl 3-(1-(5-amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)pyrrolidine-1-carboxylate	using Intermediate B-T3	¹ H), 5.90 (s, 2H), 3.59 (td, 1H), 3.43 – 3.37 (m, 1H), 3.37 – 3.34 (m, 1H), 3.31 – 3.22 (m, 2H), 2.19 – 2.10 (m, 1H), 2.05 – 1.96 (m, 1H), 1.40 (s, 9H). UPLC-MS-1: Rt 0.75 min; MS m/z [M+H] ⁺ 348.2.
C-T6	 tert-Butyl ((3-(1-(5-amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)-3-hydroxycyclobutyl)methyl)carbamate	Analogous to Intermediate C-M1 using Intermediate B-M9	UPLC-MS-2: Rt 0.95 min; MS m/z [M+H] ⁺ 390.2.
C-T7	 tert-Butyl (2-(1-(5-amino-3-fluoropyridin-2-yl)-1H-1,2,4-triazol-3-yl)propan-2-yl)carbamate	Analogous to Intermediate C-M4 using Intermediate B-T4	¹ H NMR (600 MHz, DMSO-d ₆) δ 8.69 (s, 1H), 7.75 – 7.67 (m, 1H), 6.98 (dd, 2H), 6.07 (s, 2H), 1.60 – 1.57 (m, 1H), 1.54 (s, 7H), 1.32 (s, 11H). UPLC-MS-8: Rt 0.67 min; MS m/z [M+H] ⁺ 337.3.
C-T8	 tert-Butyl 2-(1-(5-amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)-4,4-difluoropiperidine-1-carboxylate	Analogous to Intermediate C-M5 using Intermediate B-M10	¹ H NMR (600 MHz, DMSO-d ₆) δ 7.99 (t, 1H), 7.68 (dd, 1H), 7.23 (d, 1H), 6.99 (dd, 1H), 5.91 (s, 2H), 5.44 (d, 1H), 4.07 (d, 1H), 3.08 (t, 1H), 2.79 – 2.70 (m, 1H), 2.28 (ddt, 1H), 2.01 – 1.93 (m, 2H), 1.41 (d, 9H). UPLC-MS-2: Rt 0.85 min; MS m/z [M+H] ⁺ 398.2.
C-T9	 5-Fluoro-6-(4-(tetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-amine	Analogous to Intermediate C-M1 using Intermediate B-T5	¹ H NMR (600 MHz, DMSO-d ₆) δ 7.80 (t, 1H), 7.66 (dd, 1H), 6.98 (dd, 1H), 6.80 – 6.76 (m, 1H), 5.84 (s, 2H), 3.75 – 3.64 (m, 4H), 3.02 – 2.96 (m, 4H). UPLC-MS-2: Rt 0.85 min; MS m/z [M+H] ⁺ 398.2.
C-T10	 5-Fluoro-6-(4-morpholino-1H-imidazol-1-yl)pyridin-3-amine	Analogous to Intermediate C-M5 using Intermediate B-M11	¹ H NMR (600 MHz, DMSO-d ₆) δ 7.80 (t, 1H), 7.66 (dd, 1H), 6.98 (dd, 1H), 6.80 – 6.76 (m, 1H), 5.84 (s, 2H), 3.75 – 3.64 (m, 4H), 3.02 – 2.96 (m, 4H). UPLC-MS-2: Rt 0.32 min; MS m/z [M+H] ⁺ 264.1.

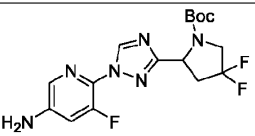
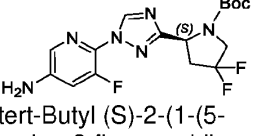
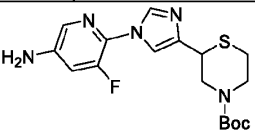
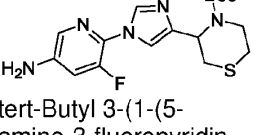
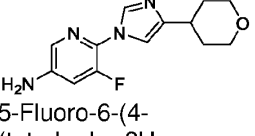
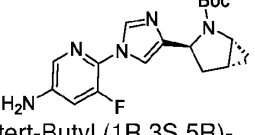
Intermediate	Structure	Method	Characterizing Data
C-T11	 5-Fluoro-6-(4-(tetrahydrothiophen-3-yl)-1H-imidazol-1-yl)pyridin-3-amine	Analogous to Intermediate C-M5 using Intermediate B-T6	¹ H NMR (600 MHz, DMSO-d ₆) δ 7.95 (t, 1H), 7.68 (dd, 1H), 7.40 (d, 1H), 6.99 (dd, 1H), 5.89 (s, 2H), 3.33 - 3.28 (m, 1H), 3.07 (dd, 1H), 2.91 (dd, 1H), 2.88 - 2.85 (m, 2H), 2.32 - 2.23 (m, 1H), 2.10 - 2.02 (m, 1H). UPLC-MS-2: Rt 0.38 min; MS m/z [M+H] ⁺ 265.3.
C-T12	 5-(1-(5-Amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)-1-methylpyrrolidin-2-one	Analogous to Intermediate C-M5 using Intermediate B-T7	¹ H NMR (600 MHz, DMSO-d ₆) δ 8.03 (t, 1H), 7.69 (dd, 1H), 7.57 - 7.53 (m, 1H), 7.00 (dd, 1H), 5.93 (s, 2H), 4.58 (dd, 1H), 2.54 (s, 3H), 2.45 - 2.40 (m, 1H), 2.32 - 2.23 (m, 2H), 2.09 - 2.03 (m, 1H). UPLC-MS-2: Rt 0.25 min; MS m/z [M+H] ⁺ 276.1.
C-T13	 tert-Butyl 3-(4-(4-amino-2-cyano-6-fluorophenyl)-1H-pyrazol-1-yl)pyrrolidine-1-carboxylate	Analogous to Intermediate C-M3/Step 2 using tert-butyl 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)pyrrolidine-1-carboxylate [CAS No. 1359974-18-7] with Cs ₂ CO ₃	HPLC-MS-2: Rt 1.53 min; MS m/z [M+H] ⁺ 372.3.
C-T14 (trans)	 6-(4-(2-((tert-Butyldimethylsilyl)oxy)cyclopentyl)-1H-imidazol-1-yl)-5-fluoropyridin-3-amine (trans isomer)	Analogous to Intermediate C-M4 using Intermediate B-T9	UPLC-MS-8: Rt 1.29 min; MS m/z [M+H] ⁺ 377.3.
C-T15 (rac)	 tert-Butyl 2-(1-(5-amino-3-fluoropyridin-2-yl)-1H-1,2,4-triazol-3-yl)-5,5-difluoropiperidine-1-carboxylate	Analogous to Intermediate C-M2 using Intermediate B-T10	UPLC-MS-8: Rt 0.96 min; MS m/z [M+H] ⁺ 399.3.

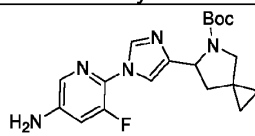
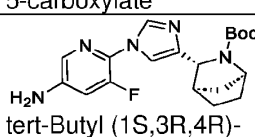
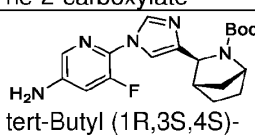
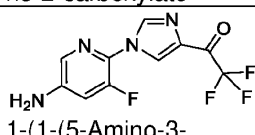
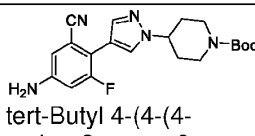
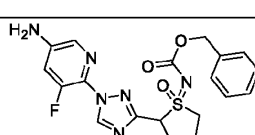
Intermediate	Structure	Method	Characterizing Data
C-T16	 tert-Butyl (1-(1-(5-amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)-3,3-difluorocyclobutyl)carbamate	Analogous to Intermediate C-M4 using Intermediate B-T11	UPLC-MS-8: Rt 0.86 min; MS m/z [M+H] ⁺ 384.2.
C-T17	 1-(1-(5-Amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)cyclohexan-1-ol	Analogous to Intermediate C-M4 using 1-(1H-imidazol-4-yl)cyclohexan-1-ol [CAS No. 123914-25-0]	UPLC-MS-2: Rt 0.17 min; MS m/z [M+H] ⁺ 277.3.
C-T18 (rac)	 tert-Butyl 2-(1-(5-amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)-4,4-difluoropyrrolidine-1-carboxylate	Analogous to Intermediate C-M4 using Intermediate B-T12	UPLC-MS-8: Rt 0.89 min; MS m/z [M-H] ⁻ 382.1.
C-T19	 1-(1-(5-Amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)cyclopentan-1-ol	Analogous to Intermediate C-M2 using 1-(1H-imidazol-4-yl)cyclopentan-1-ol [CAS No. 123914-22-7]	UPLC-MS-8: Rt 0.32 min; MS m/z [M+H] ⁺ 263.3.
C-T20 (rac)	 3-(1-(5-Amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)-3-hydroxytetrahydrothiophene 1,1-dioxide	Analogous to Intermediate C-M2 using Intermediate B-M13	UPLC-MS-2: Rt 0.14 min; MS m/z [M+H] ⁺ 313.2.
C-T21 (rac)	 tert-Butyl 2-(1-(5-amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)-2-methylazetidine-1-carboxylate	Analogous to Intermediate C-M1 using Intermediate B-T36	UPLC-MS-8: Rt 0.73 min; MS m/z [M+H] ⁺ 348.3.

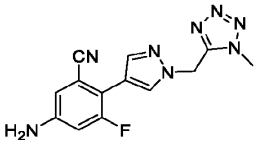
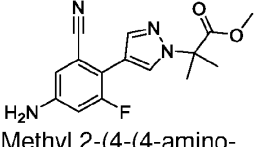
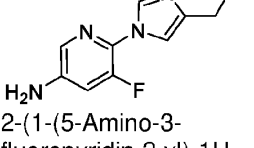
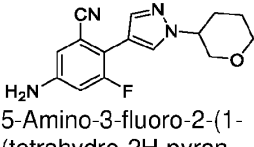
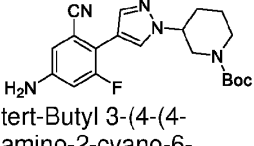
Intermediate	Structure	Method	Characterizing Data
C-T22	 6-(4-(3,9-Dioxo-7-azabicyclo[3.3.1]nona-7-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-amine	Analogous to Intermediate C-M2 using Intermediate B-M14	UPLC-MS-2: Rt 0.25 min; MS m/z [M+H] ⁺ 306.2.
C-T23 (rac)	 tert-Butyl 2-(1-(5-amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)piperidine-1-carboxylate	Analogous to Intermediate C-M2 using Intermediate B-M15	UPLC-MS-2: Rt 0.87 min; MS m/z [M+H] ⁺ 362.1.
C-T24	 5-Amino-2-(1-((1-benzyl-1H-imidazol-2-yl)methyl)-1H-pyrazol-4-yl)-3-fluorobenzonitrile	Analogous to Intermediate C-M3/Step 2 using Intermediate B-M16	UPLC-MS-2: Rt 0.54 min; MS m/z [M+H] ⁺ 373.3.
C-T25	 Ethyl 2-(1-(5-amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)-2-methylpropanoate	Analogous to Intermediate C-M2 using ethyl 2-(1H-imidazol-4-yl)-2-methylpropanoate [CAS No. 21149-99-5]	UPLC-MS-2: Rt 0.55 min; MS m/z [M+H] ⁺ 293.2.
C-T26	 tert-Butyl 4-(1-(5-amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)piperidine-1-carboxylate	Analogous to Intermediate C-M2 using tert-butyl 4-(1H-imidazol-4-yl)piperidine-1-carboxylate [CAS No. 152241-38-8]	UPLC-MS-2: Rt 0.74 min; MS m/z [M+H] ⁺ 362.3.
C-T27	 4-(1-(5-Amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)tetrahydro-2H-pyran-4-ol	Analogous to Intermediate C-M4 using Intermediate B-T14	UPLC-MS-2: Rt 0.20 min; MS m/z [M+H] ⁺ 279.1.

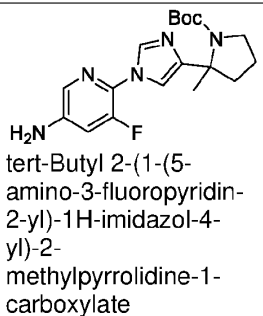
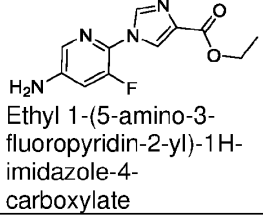
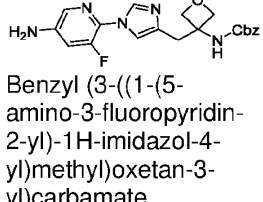
Intermediate	Structure	Method	Characterizing Data
C-T28	 5-Amino-3-fluoro-2-(1-(oxazol-2-ylmethyl)-1H-pyrazol-4-yl)benzonitrile	Analogous to Intermediate C-M3/Step 2 using Intermediate B-T15	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ 8.16 – 8.09 (m, 2H), 7.74 (s, 1H), 7.23 (s, 1H), 6.81 (d, 1H), 6.73 (dd, 1H), 5.94 (s, 2H), 5.60 (s, 2H). UPLC-MS-2: Rt 0.45 min; MS m/z [M+H] ⁺ 284.1.
C-T29	 tert-Butyl (3-(1-(5-amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)oxetan-3-yl)carbamate	Analogous to Intermediate C-M4 using Intermediate B-T16	UPLC-MS-8: Rt 0.65 min; MS m/z [M+H] ⁺ 350.1.
C-T30	 5-Fluoro-6-(4-(tetrahydrofuran-2-yl)-1H-imidazol-1-yl)pyridin-3-amine	Analogous to Intermediate C-M1 using Intermediate B-T19	UPLC-MS-2: Rt 0.31 min; MS m/z [M+H] ⁺ 249.3.
C-T31	 tert-Butyl 2-(1-(5-amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)-4,4-difluoro-2-methylpyrrolidine-1-carboxylate	Analogous to Intermediate C-M1 using Intermediate B-M17	UPLC-MS-8: Rt 0.96 min; MS m/z [M+H] ⁺ 398.3.
C-T32	 tert-Butyl 2-(1-(5-amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)pyrrolidine-1-carboxylate	Analogous to Intermediate C-M1 using Intermediate B-T17	UPLC-MS-2: Rt 0.71 min; MS m/z [M+H] ⁺ 348.3.
C-T33	 2-(1-(5-Amino-3-fluoropyridin-2-yl)-1H-1,2,4-triazol-3-yl)-2-oxo-1,3-dioxolane	Analogous to Intermediate C-M1 using Intermediate B-T20	UPLC-MS-2: Rt 0.27 min; MS m/z [M+H] ⁺ 312.2.

Intermediate	Structure	Method	Characterizing Data
	methyltetrahydrothiophene 1,1-dioxide		
C-T34	 tert-Butyl 3-(1-(5-amino-3-fluoropyridin-2-yl)-1H-1,2,4-triazol-3-yl)morpholine-4-carboxylate	Analogous to Intermediate C-M1 using Intermediate B-T21	UPLC-MS-8: Rt 0.67 min; MS m/z [M+H] ⁺ 365.3.
C-T35	 tert-Butyl (1-(1-(5-amino-3-fluoropyridin-2-yl)-1H-1,2,4-triazol-3-yl)-3,3-difluorocyclobutyl)carbamate	Analogous to Intermediate C-M1 using Intermediate B-T22	UPLC-MS-8: Rt 0.78 min; MS m/z [M+H] ⁺ 385.3.
C-T36	 tert-Butyl 3-(1-(5-amino-3-fluoropyridin-2-yl)-1H-1,2,4-triazol-3-yl)-3-methylmorpholine-4-carboxylate	Analogous to Intermediate C-M1 using Intermediate B-T23	UPLC-MS-8: Rt 0.66 min; MS m/z [M+H] ⁺ 379.3.
C-T37	 tert-Butyl 2-(1-(5-amino-3-fluoropyridin-2-yl)-1H-1,2,4-triazol-3-yl)-3,3-difluoropyrrolidine-1-carboxylate	Analogous to Intermediate C-M1 using Intermediate B-T24	UPLC-MS-8: Rt 0.78 min; MS m/z [M+H] ⁺ 385.1
C-T38	 tert-Butyl (S)-2-(1-(5-amino-3-fluoropyridin-2-yl)-1H-1,2,4-triazol-3-yl)-4,4-difluoro-2-methylpyrrolidine-1-carboxylate	Analogous to Intermediate C-M1 using Intermediate B-T25	UPLC-MS-8: Rt 0.89 min; MS m/z [M+H] ⁺ 399.1

Intermediate	Structure	Method	Characterizing Data
C-T39	 tert-Butyl 2-(1-(5-amino-3-fluoropyridin-2-yl)-1H-1,2,4-triazol-3-yl)-4,4-difluoropyrrolidine-1-carboxylate	Analogous to Intermediate C-M1 using Intermediate B-T26	UPLC-MS-8: Rt 0.81 min; MS m/z [M+H] ⁺ 385.3.
C-T40	 tert-Butyl (S)-2-(1-(5-amino-3-fluoropyridin-2-yl)-1H-1,2,4-triazol-3-yl)-4,4-difluoropyrrolidine-1-carboxylate	Analogous to Intermediate C-M1 using Intermediate B-M18	¹ H NMR (600 MHz, DMSO-d ₆) δ 8.83 (s, 1H), 7.70 (dd, 1H), 6.98 (dd, 1H), 6.14 (s, 2H), 5.16 (d, 1H), 3.91 (s, 1H), 3.86 - 3.77 (m, 1H), 3.03 (td, 1H), 2.57 - 2.51 (m, 1H), 1.29 (d, 9H). UPLC-MS-8: Rt 0.80 min; MS m/z [M+H] ⁺ 385.3.
C-T41	 tert-Butyl 2-(1-(5-amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)thiomorpholine-4-carboxylate	Analogous to Intermediate C-M1 using Intermediate B-T28	UPLC-MS-8: Rt 0.85 min; MS m/z [M+H] ⁺ 380.
C-T42	 tert-Butyl 3-(1-(5-amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)thiomorpholine-4-carboxylate	Analogous to Intermediate C-M1 using Intermediate B-T29	UPLC-MS-2: Rt 0.79 min; MS m/z [M+H] ⁺ 380.3.
C-T43	 5-Fluoro-6-(4-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-1-yl)pyridin-3-amine	Analogous to Intermediate C-M1 using 4-(tetrahydro-2H-pyran-4-yl)-1H-imidazole [CAS No. 1935037-79-8]	UPLC-MS-2: Rt 0.21 min; MS m/z [M+H] ⁺ 263.3.
C-T44	 tert-Butyl (1R,3S,5R)-3-(1-(5-amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)-2-oxo-1,2,3,4-tetrahydropyridine-5-carboxylate	Analogous to Intermediate C-M1 using Intermediate B-T30	UPLC-MS-2: Rt 0.74 min; MS m/z [M+H] ⁺ 360.3.

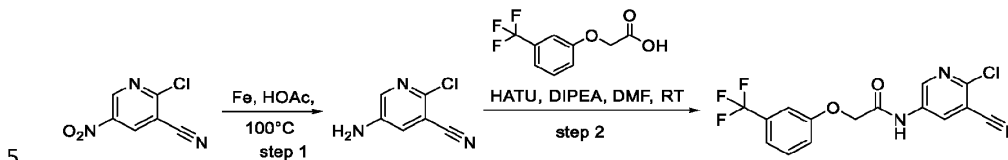
Intermediate	Structure	Method	Characterizing Data
	azabicyclo[3.1.0]hexane-2-carboxylate		
C-T45	 tert-Butyl 6-(1-(5-amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)-5-azaspiro[2.4]heptane-5-carboxylate	Analogous to Intermediate C-M1 using Intermediate B-T31	UPLC-MS-2: Rt 0.82 min; MS m/z [M+H] ⁺ 374.4.
C-T46	 tert-Butyl (1S,3R,4R)-3-(1-(5-amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)-2-azabicyclo[2.2.1]heptane-2-carboxylate	Analogous to Intermediate C-M1 using Intermediate B-T32	UPLC-MS-2: Rt 0.81 min; MS m/z [M+H] ⁺ 374.3.
C-T47	 tert-Butyl (1R,3S,4S)-3-(1-(5-amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)-2-azabicyclo[2.2.1]heptane-2-carboxylate	Analogous to Intermediate C-M1 using Intermediate B-T33	UPLC-MS-2: Rt 0.82 min; MS m/z [M+H] ⁺ 374.3.
C-T48	 1-(1-(5-Amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)-2,2,2-trifluoroethan-1-one	Analogous to Intermediate C-M1 using Intermediate B-M19	UPLC-MS-2: Rt 0.46 min; MS m/z [M+H] ⁺ 275.2.
C-T49	 tert-Butyl 4-(4-(4-amino-2-cyano-6-fluorophenyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate	Analogous to Intermediate C-M3/Step 2 using tert-butyl 4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate [CAS No. 877399-74-1]	UPLC-MS-2: Rt 0.95 min; MS m/z [M-Boc+H] ⁺ 286.4
C-T50	 Benzyl (2-(1-(5-amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)-2-oxo-1,2,3,4-tetrahydrothiazole-5-yl)carbamate	Analogous to Intermediate C-M1 using Intermediate B-M20	UPLC-MS-8: Rt 0.54/0.60 min (2 peaks due to diastereomeric mixture); MS m/z [M+H] ⁺ 431.

Intermediate	Structure	Method	Characterizing Data
	1H-1,2,4-triazol-3-yl)-1-oxidotetrahydro-1λ ⁶ -thiophen-1-ylidene)carbamate		
C-T51	 5-Amino-3-fluoro-2-((1-methyl-1H-tetrazol-5-yl)methyl)-1H-pyrazol-4-yl)benzonitrile	Analogous to Intermediate C-M3/Step 2 using Intermediate B-T34	UPLC-MS-2: Rt 0.33 min; MS m/z [M+H] ⁺ 299.2.
C-T52	 Methyl 2-(4-(4-amino-2-cyano-6-fluorophenyl)-1H-pyrazol-1-yl)-2-methylpropanoate	Analogous to Intermediate C-M3/Step 2 using Intermediate B-T35	UPLC-MS-2: Rt 0.68 min; MS m/z [M+H] ⁺ 303.
C-T53	 2-(1-(5-Amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)acetonitrile	Analogous to C-M1 using 2-(1H-imidazol-4-yl)acetonitrile [CAS No. 18502-05-1]	UPLC-MS-2: Rt 0.28 min; MS m/z [M+H] ⁺ 218.2.
C-T54	 5-Amino-3-fluoro-2-(1-(tetrahydro-2H-pyran-3-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-4-yl)benzonitrile	Analogous to Intermediate C-M3/Step 2 using 1-(tetrahydro-2H-pyran-3-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole [CAS No. 2223009-52-5]	UPLC-MS-2: Rt 0.62 min; MS m/z [M+H] ⁺ 287.2.
C-T55	 tert-Butyl 3-(4-(4-amino-2-cyano-6-fluorophenyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate	Analogous to Intermediate C-M3/Step 2 using tert-butyl 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate [CAS No. 1092563-74-0]	UPLC-MS-2: Rt 0.94 min; MS m/z [M-Boc+H] ⁺ 287.2.

Intermediate	Structure	Method	Characterizing Data
C-T56	 tert-Butyl 2-(1-(5-amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)-2-methylpyrrolidine-1-carboxylate	Analogous to Intermediate C-M1 using Intermediate B-T18	UPLC-MS-2: Rt 0.77 min; MS m/z [M+H] ⁺ 362.4.
C-T57	 Ethyl 1-(5-amino-3-fluoropyridin-2-yl)-1H-imidazole-4-carboxylate	Analogous to Intermediate C-M2 using ethyl 1H-imidazole-4-carboxylate [CAS No. 23785-21-9]	HPLC-MS-3: Rt 0.47 min; MS m/z [M+H] ⁺ 251.4.
C-T58	 Benzyl (3-((1-(5-amino-3-fluoropyridin-2-yl)-1H-imidazol-4-yl)methyl)oxetan-3-yl)carbamate	Analogous to Intermediate C-M1 using Intermediate B-T38	UPLC-MS-2: Rt 0.53 min; MS m/z [M+H] ⁺ 398.8.

D Intermediates

Intermediate D-M1: N-(6-Chloro-5-cyanopyridin-3-yl)-2-(3-(trifluoromethyl)phenoxy)acetamide

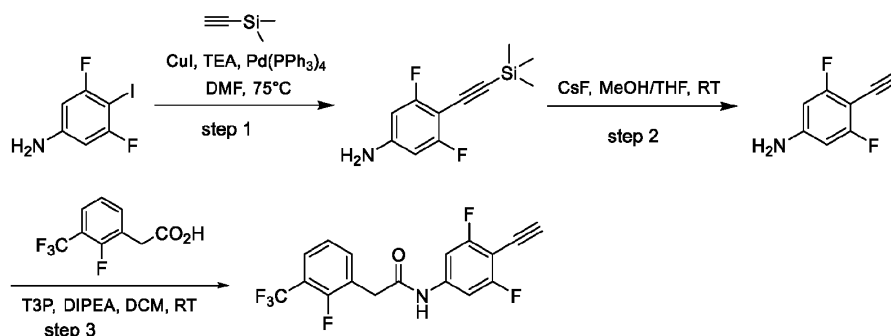


Step 1: A mixture of 2-chloro-5-nitronicotinonitrile [CAS No. 31309-08-7] (400 mg, 1.114 mmol) and Fe (1.18 g, 21.14 mmol) in HOAc (6 ml) was stirred at 100°C. After 2.5 h, the reaction mixture was filtered over Hyflo®. The filtrate was basified with sat. aq. NaHCO₃ and extracted with DCM (2x). The combined organic layers were dried (phase separator) and concentrated under reduced pressure to give 5-amino-2-chloronicotinonitrile. UPLC-MS-1: Rt = 0.49 min; MS m/z [M+H]⁺ 154.1/156.2.

Step 2: A solution of 5-amino-2-chloronicotinonitrile (step 1, 214 mg, 1.003 mmol), 2-(3-(trifluoromethyl)phenoxy)acetic acid [CAS No. 349-82-6] (265 mg, 1.204 mmol), DIPEA (0.35 ml, 2.007 mmol) and HATU (763 mg, 2.007 mmol) in DMF (10 ml) was stirred at RT. After 5 h, the reaction mixture was basified with sat. aq. NaHCO₃ and extracted with EtOAc (2x). The combined organic layers were washed with brine, dried (phase separator), concentrated under

reduced pressure and the residue was purified by normal phase chromatography (eluent : EtOAc/cyclohexane 0:1 to 30:70) to give N-(6-chloro-5-cyanopyridin-3-yl)-2-(3-(trifluoromethyl)phenoxy)acetamide. ¹H NMR (400 MHz, DMSO-d₆) δ 10.74 (br s, 1H), 8.89 (d, 1H), 8.64 (d, 1H), 7.57 (m, 1H), 7.32-7.39 (m, 3H), 4.90 (s, 2H). UPLC-MS-2: Rt = 1.09 min; MS m/z [M+H]⁺ 356.2/358.1.

Intermediate D-M2: N-(4-Ethynyl-3,5-difluorophenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide

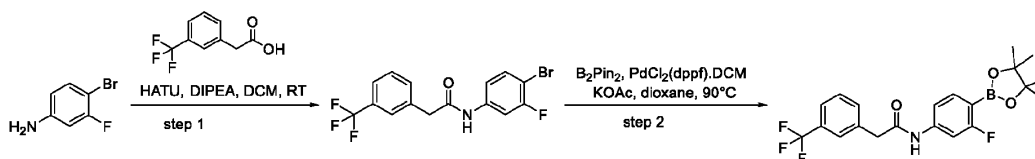


Step 1: CuI (67 mg, 0.352 mmol), Pd(PPh₃)₄ (271 mg, 0.235 mmol) and then Et₃N (7.1 g, 70.584 mmol) were added to a solution of 3,5-difluoro-4-iodoaniline [CAS No. 1542-34-3] (3 g, 11.764 mmol) in DMF (30 ml) under N₂ at RT. The reaction mixture was warmed to 75°C and then treated with ethynyltrimethylsilane (1.7 g, 17.647 mmol). After 12 h, the mixture was diluted with H₂O and extracted with EtOAc (2x). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure to give 3,5-difluoro-4-((trimethylsilyl)ethynyl)aniline which was used without further purification.

Step 2: K₂CO₃ (737 mg, 5.333 mmol) was added to a solution of 3,5-difluoro-4-((trimethylsilyl)ethynyl)aniline (step 1, 1 g, 4.444 mmol) in MeOH (10 ml) at RT. After stirring for 12 h, the reaction mixture was diluted with H₂O and extracted with EtOAc (2x). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by normal phase chromatography (eluent : EtOAc/hexane 20:80 to 30:70) to give 4-ethynyl-3,5-difluoroaniline. ¹H NMR (400 MHz, CDCl₃) δ 6.15-6.18 (m, 2H), 4.05 (br s, 2H), 3.36 (s, 1H).

Step 3: DIPEA (0.7 ml, 3.921 mmol) and T3P (831 mg, 2.614 mmol) were added to a solution of 4-ethynyl-3,5-difluoroaniline (step 2, 200 mg, 1.307 mmol) and 2-(2-fluoro-3-(trifluoromethyl)phenyl)acetic acid [CAS No. 194943-83-4] (377 mg, 1.699 mmol) at RT. After stirring for 12 h, the reaction mixture was diluted with H₂O and extracted with EtOAc (2x). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure to give N-(4-ethynyl-3,5-difluorophenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide which was without further purification.

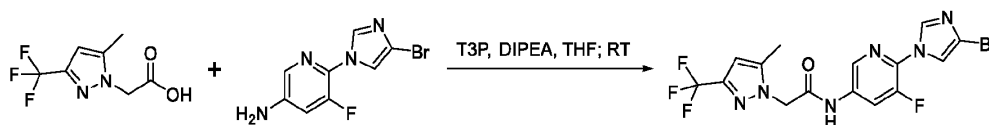
Intermediate D-M3: N-(3-Fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2-(3-(trifluoromethyl)phenyl)acetamide



Step 1: DIPEA (10.69 ml, 61.2 mmol) and then HATU (13.97 g, 36.7 mmol) were added to a mixture of 2-(3-(trifluoromethyl)phenyl)acetic acid [CAS No. 351-35-9] (5.0 g, 24.49 mmol) and 4-bromo-3-fluoroaniline [CAS No. 656-65-5] (5.58 g, 29.4 mmol) in DCM (50 ml). After stirring overnight, the reaction mixture was diluted with H₂O and extracted with EtOAc. The organic layer was washed with brine, dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by normal phase chromatography (eluent: 20% EtOAc/hexane) to give N-(4-bromo-3-fluorophenyl)-2-(3-(trifluoromethyl)phenyl)acetamide. HPLC-MS: Rt 2.58 min; MS m/z [M+H]⁺ 375.9/377.9.

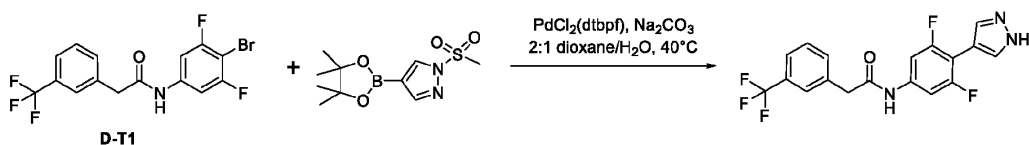
Step 2: B₂Pin₂ [CAS No. 73183-34-3] (149 mg, 0.585 mmol), PdCl₂(dppf).DCM adduct (19.91 mg, 0.024 mmol) and KOAc (115 mg, 1.170 mmol) were added to a solution of N-(4-bromo-3-fluorophenyl)-2-(3-(trifluoromethyl)phenyl)acetamide (step 1, 73 mg, 0.194 mmol) in dioxane (3 ml). The reaction mixture was stirred at 90°C for 18 h under argon. The reaction mixture was diluted with EtOAc and then extracted with 25 ml of H₂O. The organic phase was dried (Na₂SO₄) and concentrated under vacuum to give N-(3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-2-(3-(trifluoromethyl)phenyl)acetamide which was used without further purification. HPLC-MS: Rt 2.57 min; MS m/z [M+H]⁺ 424.2.

Intermediate D-M4: N-(6-(4-Bromo-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide



DIPEA (2.03 ml, 11.67 mmol) and then T3P (50% in EtOAc) (6.9 ml, 11.67 mmol) were added to a solution of 2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid [CAS No. 345637-71-0] and Intermediate C-T1 (1 g, 3.89 mmol) in THF (30 ml) at RT. After 1.5 h, the reaction mixture was quenched with H₂O and extracted with DCM (2x). The combined organic layers were washed with sat. aq. NaHCO₃ and brine, dried (phase separator) and concentrated under reduced pressure. The residue was purified by normal phase chromatography (eluent : DCM/(9:1 DCM/MeOH) 100:0 to 30:70) to give N-(6-(4-bromo-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide. UPLC-MS-2: Rt = 1.02 min; MS m/z [M+H]⁺ 447.1/449.2.

Intermediate D-M5: N-(3,5-Difluoro-4-(1H-pyrazol-4-yl)phenyl)-2-(3-(trifluoromethyl)phenyl)acetamide

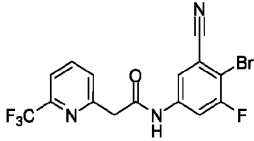
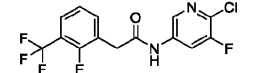
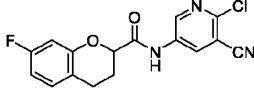
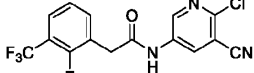
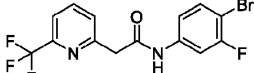
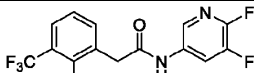


PdCl₂(dtbpf) (6.48 mg, 9.95 μmol) was added to a mixture of Intermediate D-T1 (20 mg, 0.050 mmol), 1-(methylsulfonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole [CAS No. 944994-03-0] (16.24 mg, 0.060 mmol) and Na₂CO₃ (10.54 mg, 0.099 mmol) in 2:1 dioxane/H₂O (3 ml). The mixture was degassed and stirred at 40°C. After 1 h, the reaction mixture was diluted with MeOH and purified by RP-HPLC to N-(3,5-difluoro-4-(1H-pyrazol-4-yl)phenyl)-2-(3-(trifluoromethyl)phenyl)acetamide. HPLC-MS: Rt 2.46 min; MS m/z [M+H]⁺ 382.0

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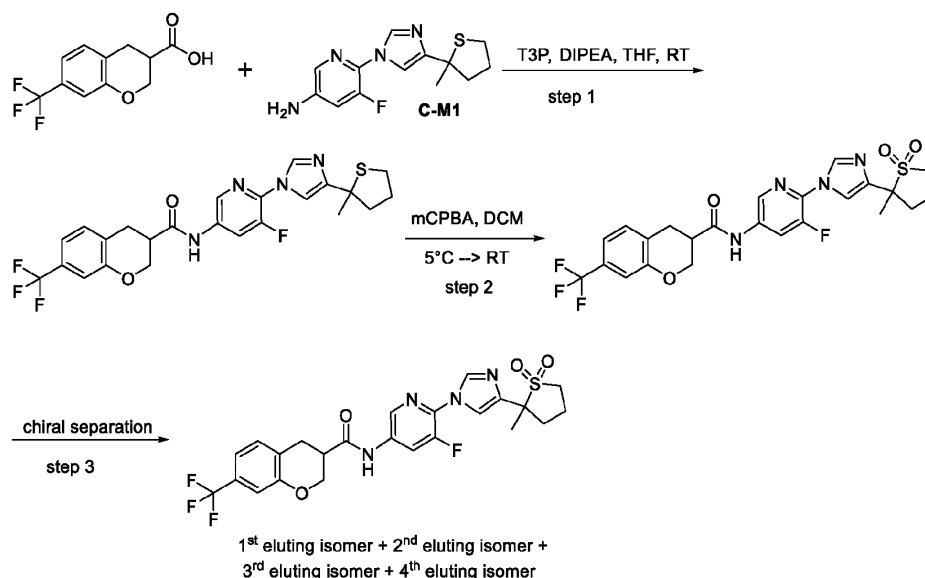
The following intermediates were prepared using methods similar to Intermediates D-M1 to D-M5 from intermediates which are either commercially available or were obtained by methods described herein.

Intermediate	Structure	Method	Characterizing Data
D-T1	 N-(4-Bromo-3,5-difluorophenyl)-2-(3-(trifluoromethyl)phenyl)acetamide	Analogous to D-M3/Step 1 from 4-bromo-3,5-difluoroaniline [CAS No. 203302-95-8]	ES/MS m/z [M+H] ⁺ 394.0/396.0
D-T2	 N-(6-(4-Bromo-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	Analogous to D-M4 from 2-(2-fluoro-3-(trifluoromethyl)phenyl)acetic acid [CAS No. 194943-83-4]	UPLC-MS-2: Rt 1.18 min; MS m/z [M+H] ⁺ 461.2/463.2
D-T3	 N-(6-(4-Bromo-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide	Analogous to D-M4 using 2-(6-(trifluoromethyl)pyridin-2-yl)acetic acid [CAS No. 1000565-32-1]	UPLC-MS-2: Rt 1.03 min; MS m/z [M+H] ⁺ 444.3/446.3

Intermediate	Structure	Method	Characterizing Data
D-T4	 N-(4-Bromo-3-cyano-5-fluorophenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide	Analogous to D-M4 using 2-(6-(trifluoromethyl)pyridin-2-yl)acetic acid [CAS No. 1000565-32-1] and 5-amino-2-bromo-3-fluorobenzonitrile	UPLC-MS-2: Rt 1.13 min; MS m/z [M+H] ⁺ 402.4/404.2
D-T5	 N-(6-Chloro-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	Analogous to D-M4 using 6-chloro-5-fluoropyridin-3-amine and 2-(2-fluoro-3-(trifluoromethyl)phenyl)acetic acid [CAS No. 194943-83-4]	UPLC-MS-2: Rt 1.18 min; MS m/z [M+H] ⁺ 351.2
D-T6	 N-(6-Chloro-5-cyanopyridin-3-yl)-7-fluorochromane-2-carboxamide	Analogous to D-M1 using 7-fluorochromane-2-carboxylic acid [CAS No. 944904-25-0] and T3P and THF in Step 2	UPLC-MS-2: Rt 1.02 min; MS m/z [M-H] ⁻ 330.1/332.1
D-T7	 N-(6-Chloro-5-cyanopyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	Analogous to D-M1 using 2-(2-fluoro-3-(trifluoromethyl)phenyl)acetic acid [CAS No. 194943-83-4] and T3P and EtOAc in Step 2	HPLC-MS-6: Rt 1.60 min; MS m/z [M+H] ⁺ 358.1/360.1
D-T8	 N-(4-Bromo-3-fluorophenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide	Analogous to Intermediate D-M3/Step 1 using 2-(6-(trifluoromethyl)pyridin-2-yl)acetic acid [CAS No. 1000565-32-1]	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.66 (s, 1H), 8.09 (m, 1H), 7.82 (d, 1H), 7.72-7.78 (m, 2H), 7.64 (t, 1H), 7.30 (m, 1H), 4.01 (s, 2H). HPLC-MS: Rt 2.49 min; MS m/z [M+H] ⁺ 378.9
D-T9	 N-(5,6-Difluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	Analog Intermediate D-M3/Step 1 using 2-(2-fluoro-3-(trifluoromethyl)phenyl)acetic acid [CAS No. 194943-83-4] and 5,6-difluoropyridin-3-amine [1214344-65-6] with T3P (50% in EtOAc)	UPLC-MS-2: Rt 1.12 min; MS m/z [M-H] ⁻ 333.1

Preparation of Final Compounds

Example 1: N-(5-Fluoro-6-(4-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-7-(trifluoromethyl)chromane-3-carboxamide and (R or S)-N-(5-fluoro-6-(4-((R or S)-2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-7-(trifluoromethyl)chromane-3-carboxamide



Step 1: 7-(Trifluoromethyl)chromane-3-carboxylic acid [CAS No. 1956332-20-9] (132.7 mg, 0.539 mmol), T3P (50% in EtOAc) (0.481 ml, 0.808 mmol) and DIPEA (0.282 ml, 1.617 mmol) were added to a solution of Intermediate C-M1 (150 mg, 0.539 mmol) in THF (3 ml) at RT. After 30 min, the reaction mixture was diluted with EtOAc and washed with sat. aq. NaHCO₃ and sat. aq. NH₄Cl. The organic layer was dried (phase separator) and concentrated under reduced pressure and the residue was purified by normal phase chromatography (eluent : EtOAc/cyclohexane 0:100 to 100:0) to give N-(5-fluoro-6-(4-(2-methyltetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-7-(trifluoromethyl)chromane-3-carboxamide. UPLC-MS-8: Rt = 0.74-0.81 min (multiple peaks); MS m/z [M+H]⁺ 507.3.

Step 2: mCPBA (156.7 mg, 0.908 mmol) was added to an ice-cooled solution of N-(5-fluoro-6-(4-(2-methyltetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-7-(trifluoromethyl)chromane-3-carboxamide (step 1, 200 mg, 0.395 mmol) in DCM (5 ml). The reaction was allowed to warm to RT. After 18 h, the reaction mixture was diluted with DCM and washed with 0.5M aq. Na₂S₂O₃. The organic layer was dried (phase separator) and concentrated under reduced pressure and the residue was purified by normal phase chromatography (eluent : EtOAc/cyclohexane 0:100 to 100:0) to give N-(5-fluoro-6-(4-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-7-(trifluoromethyl)chromane-3-carboxamide (diastereomeric mixture). UPLC-MS-8: Rt = 1.13 min; MS m/z [M+H]⁺ 539.3.

Step 3: The diastereomers of N-(5-fluoro-6-(4-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-7-(trifluoromethyl)chromane-3-carboxamide (diastereomeric mixture) (step 2, 140 mg, 0.26 mmol) were separated first by C-SFC-1 (mobile phase: CO₂/(MeOH+0.05%NH₃) 70/30) (to give the 3rd and 4th eluting isomers) and then (for the mixture of the 1st and 2nd eluting isomers) by C-SFC-3 ((mobile phase: CO₂/(MeOH+0.05%NH₃) 70/30) to give the individual isomers of N-(5-fluoro-6-(4-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-7-(trifluoromethyl)chromane-3-carboxamide.

Example 1a: (R or S)-N-(5-fluoro-6-(4-((R or S)-2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-7-(trifluoromethyl)chromane-3-carboxamide: 1st eluting isomer: C-SFC-2 (mobile phase: CO₂/(MeOH+0.05%NH₃) 75/25): Rt = 1.5 min.

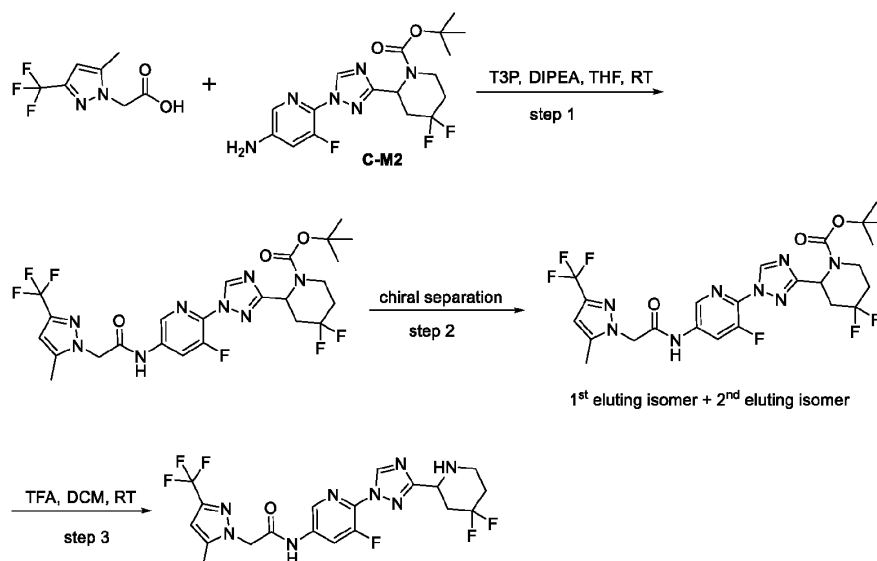
Example 1b: (R or S)-N-(5-fluoro-6-(4-((R or S)-2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-7-(trifluoromethyl)chromane-3-carboxamide: 2nd eluting isomer: C-SFC-2 (mobile phase: CO₂/(MeOH+0.05%NH₃) 75/25): Rt = 1.6 min.

Example 1c: (R or S)-N-(5-fluoro-6-(4-((R or S)-2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-7-(trifluoromethyl)chromane-3-carboxamide: 3rd eluting isomer: ¹H NMR (600 MHz, DMSO-*d*₆) δ 10.91 (s, 1H), 8.51 (d, 1H), 8.33 (dd, 1H), 8.26 (s, 1H), 7.82 (s, 1H), 7.41 (d, 1H), 7.22 (d, 1H), 7.12 (s, 1H), 4.53 (m, 1H), 4.20 (m, 1H), 3.21-3.27 (m, 1H), 3.13-3.21 (m, 2H), 3.06-3.13 (m, 2H), 2.72 (m, 1H), 2.23 (m, 1H), 2.08-2.17 (m, 2H), 1.65 (s, 3H). UPLC-MS-8: Rt = 1.11 min; MS m/z [M+H]⁺ 539.2. C-SFC-2 (mobile phase:

CO₂/(MeOH+0.05%NH₃) 75/25): Rt = 2.3 min.

Example 1d: (R or S)-N-(5-fluoro-6-(4-((R or S)-2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-7-(trifluoromethyl)chromane-3-carboxamide: 4th eluting isomer: C-SFC-2 (mobile phase: CO₂/(MeOH+0.05%NH₃) 75/25): Rt = 3.4 min.

Example 2: N-(6-(3-(4,4-Difluoropiperidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide and (R or S)-N-(6-(3-(4,4-difluoropiperidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide



Step 1: 2-(5-Methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid [CAS No. 345637-71-0] (41.8 mg, 0.201 mmol), DIPEA (0.105 ml, 0.602 mmol) and T3P (50% in EtOAc) (0.179 ml, 0.301 mmol) were added to a solution of Intermediate C-M2 (80 mg, 0.201 mmol) in THF (3 ml) at RT.

- 5 After 18 h, additional 2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid [CAS No. 345637-71-0] (41.8 mg, 0.201 mmol), DIPEA (0.105 ml, 0.602 mmol) and T3P (50% in EtOAc) (0.179 ml, 0.301 mmol) were added. After another 1 h, the reaction mixture was diluted with EtOAc and washed with sat. aq. NH_4Cl and sat. aq. NaHCO_3 . The organic layer was dried (phase separator) and concentrated under reduced pressure and the residue was purified by
- 10 normal phase chromatography (eluent : EtOAc/cyclohexane 0:100 to 100:0) to give tert-butyl 4,4-difluoro-2-(1-(3-fluoro-5-(2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)pyridin-2-yl)-1H-1,2,4-triazol-3-yl)piperidine-1-carboxylate (racemic mixture). UPLC-MS-8: Rt = 1.22 min; MS m/z $[\text{M}+\text{H}]^+$ 589.4.

Step 2: The enantiomers of tert-butyl 4,4-difluoro-2-(1-(3-fluoro-5-(2-(5-methyl-3-

- 15 (trifluoromethyl)-1H-pyrazol-1-yl)acetamido)pyridin-2-yl)-1H-1,2,4-triazol-3-yl)piperidine-1-carboxylate (racemic mixture) (step 1, 110 mg, 0.187 mmol) were separated by C-SFC-4 ((mobile phase: $\text{CO}_2/(\text{IPA}+0.05\%\text{NH}_3)$ 65/35).

1st eluting isomer: UPLC-MS-8: Rt = 1.25 min; MS m/z $[\text{M}+\text{H}]^+$ 589.1. C-SFC-5 (mobile phase: $\text{CO}_2/(\text{IPA}+0.05\%\text{NH}_3)$ 75/25): Rt = 0.96 min.

- 20 2nd eluting isomer: C-SFC-5 (mobile phase: $\text{CO}_2/(\text{IPA}+0.05\%\text{NH}_3)$ 75/25): Rt = 1.56 min.

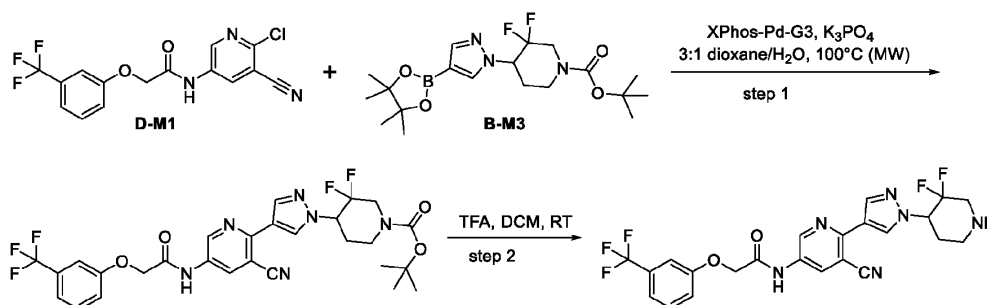
Step 3: TFA (0.065 ml, 0.850 mmol) was added to a solution of tert-butyl 4,4-difluoro-2-(1-(3-fluoro-5-(2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)pyridin-2-yl)-1H-1,2,4-triazol-3-yl)piperidine-1-carboxylate (2nd eluting isomer) (step 2, 50 mg, 0.085 mmol) in DCM (0.4 ml) at RT. After 2.5 h, the reaction mixture was loaded onto a Pora Pack cartridge and TFA was

25 removed by eluting with MeOH. The cartridge was then eluted with 7M NH_3/MeOH . H_2O was

added to the eluent and the solution was lyophilized to give **Example 2**: (R or S)-N-(6-(3-(4,4-difluoropiperidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide. ¹H NMR (600 MHz, DMSO-*d*₆) δ 11.13 (br s, 1H), 9.07 (s, 1H), 8.53 (d, 1H), 8.30 (dd, 1H), 6.56 (s, 1H), 5.19 (s, 2H), 3.94 (m, 1H), 3.13 (m, 1H), 2.74 (m, 1H), 2.60 (m, 1H), 2.34 (m, 1H), 2.32 (s, 3H), 1.96-2.12 (m, 2H), 1.88 (m, 1H). UPLC-MS-8: Rt = 0.69 min; MS m/z [M+H]⁺ 489.2.

tert-Butyl 4,4-difluoro-2-(1-(3-fluoro-5-(2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)pyridin-2-yl)-1H-1,2,4-triazol-3-yl)piperidine-1-carboxylate (1st eluting isomer) (step 2, 47 mg, 0.080 mmol) was treated analogously to give **Example 2b**: (R or S)-N-(6-(3-(4,4-difluoropiperidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide. ¹H NMR (600 MHz, DMSO-*d*₆) δ 11.18 (s, 1H), 9.07 (s, 1H), 8.53 (d, 1H), 8.30 (dd, 1H), 6.56 (s, 1H), 5.20 (s, 2H), 3.97 (m, 1H), 3.14 (m, 1H), 2.76 (m, 1H), 2.34 (m, 1H), 2.32 (s, 3H), 1.97-2.14 (m, 2H), 1.89 (m, 1H). UPLC-MS-8: Rt = 0.75 min; MS m/z [M+H]⁺ 489.1.

Example 3: N-(5-Cyano-6-(1-(3,3-difluoropiperidin-4-yl)-1H-pyrazol-4-yl)pyridin-3-yl)-2-(3-(trifluoromethyl)phenoxy)acetamide

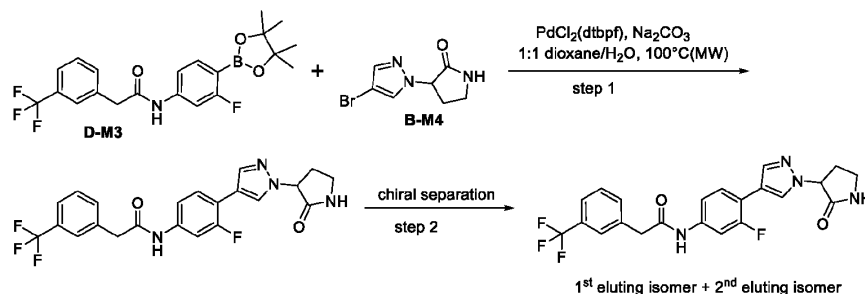


Step 1: Ar was bubbled through a mixture of Intermediate B-M3 (130 mg, 0.315 mmol), Intermediate D-M1 (112 mg, 0.315 mmol) and K₃PO₄ (200 mg, 0.944 mmol) in dioxane (5.1 ml) and H₂O (1.7 ml) at RT. XPhos-Pd-G3 (40.0 mg, 0.0047 mmol) was added, the vial was sealed and the mixture was heated at 100°C in a microwave. After 1 h, the reaction mixture was diluted with H₂O and extracted with EtOAc (2x). The combined organic layers were washed with brine, dried (phase separator) and concentrated under reduced pressure. The residue was dissolved in EtOAc and the solution was treated with Si-Thiol resin (200 mg). After stirring for 1 h, the mixture was filtered and concentrated under reduced pressure and the residue was purified by normal phase chromatography (eluent : EtOAc/cyclohexane 0:100 to 50:50) to give tert-butyl 4-(4-(3-cyano-5-(2-(3-(trifluoromethyl)phenoxy)acetamido)pyridin-2-yl)-1H-pyrazol-1-yl)-3,3-difluoropiperidine-1-carboxylate. UPLC-MS-2: Rt = 1.27 min; MS m/z [M-H]⁻ 605.3.

Step 2: TFA (0.145 ml, 1.879 mmol) was added to a solution of tert-butyl 4-(4-(3-cyano-5-(2-(3-(trifluoromethyl)phenoxy)acetamido)pyridin-2-yl)-1H-pyrazol-1-yl)-3,3-difluoropiperidine-1-

carboxylate (step 1, 114 mg, 0.188 mmol) in DCM (0.47 ml) at RT. After 1.5 h, the reaction mixture was basified with sat. aq. NaHCO₃, stirred for 15 min and then extracted with DCM (3x). The combined organic layers were dried (phase separator) and concentrated under reduced pressure and the residue was purified by RP-HPLC-1 (mobile phase: H₂O/ACN 90:10 to 50:50) to give N-(5-cyano-6-(1-(3,3-difluoropiperidin-4-yl)-1H-pyrazol-4-yl)pyridin-3-yl)-2-(3-(trifluoromethyl)phenoxy)acetamide. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.64 (s, 1H), 8.99 (d, 1H), 8.53 (d, 1H), 8.43 (s, 1H), 8.19 (s, 1H), 7.58 (m, 1H), 7.36-7.40 (m, 2H), 7.35 (m, 1H), 5.02 (m, 1H), 4.90 (s, 2H), 3.19 (m, 1H), 3.06 (m, 1H), 2.92 (m, 1H), 2.57-2.75 (m, 2H), 2.29 (m, 1H), 2.08 (m, 1H). UPLC-MS-2: Rt = 0.79 min; MS m/z [M+H]⁺ 507.3.

- 10 **Example 4:** N-(3-Fluoro-4-(1-(2-oxopyrrolidin-3-yl)-1H-pyrazol-4-yl)phenyl)-2-(3-(trifluoromethyl)phenyl)acetamide and (R or S)-N-(3-fluoro-4-(1-(2-oxopyrrolidin-3-yl)-1H-pyrazol-4-yl)phenyl)-2-(3-(trifluoromethyl)phenyl)acetamide



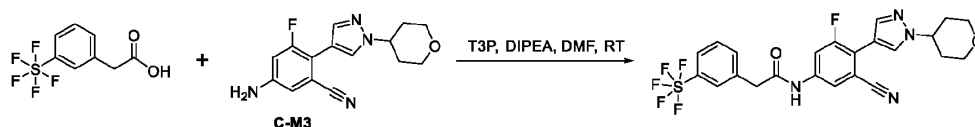
- Step 1: A mixture of Intermediate D-M3 (170 mg, 0.197 mmol), Intermediate B-M4 (54.3 mg, 0.236 mmol), Na₂CO₃ (41.7 mg, 0.394 mmol) and PdCl₂(dtbpf) (12.8 mg, 0.020 mmol) in dioxane (1.5 ml) and H₂O (1.5 ml) was degassed and then heated at 100°C in a microwave. After 1 h, the reaction mixture was diluted with EtOAc and washed with H₂O. The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure and the residue was purified by basic RP prep-HPLC to give N-(3-fluoro-4-(1-(2-oxopyrrolidin-3-yl)-1H-pyrazol-4-yl)phenyl)-2-(3-(trifluoromethyl)phenyl)acetamide (racemic mixture). HPLC-MS: Rt 2.32 min; MS m/z [M+H]⁺ 447.0.

- Step 2: The enantiomers of N-(3-fluoro-4-(1-(2-oxopyrrolidin-3-yl)-1H-pyrazol-4-yl)phenyl)-2-(3-(trifluoromethyl)phenyl)acetamide (racemic mixture) (step 1, 37 mg, 0.083 mmol) were separated by SFC to give the individual enantiomers (R or S)-N-(3-fluoro-4-(1-(2-oxopyrrolidin-3-yl)-1H-pyrazol-4-yl)phenyl)-2-(3-(trifluoromethyl)phenyl)acetamide.

Example 4a: 1st eluting isomer: ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.45 (s, 1H), 8.14 (m, 2H), 7.90 (d, 1H), 7.55-7.71 (m, 6H), 7.32 (dd, 1H), 5.10 (t, 1H), 3.81 (s, 2H), 3.39 (m, 1H), 3.29 (m, 1H), 2.42-2.58 (m, 2H). HPLC-MS: Rt 2.32 min; MS m/z [M+H]⁺ 447.0.

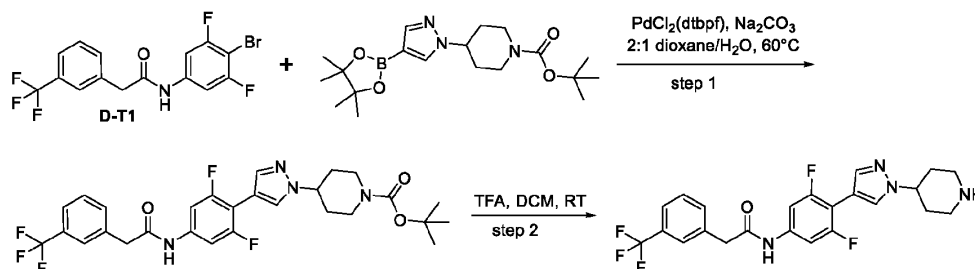
Example 4b: 2nd eluting isomer: HPLC-MS: Rt 2.32 min; MS m/z [M+H]⁺ 447.0.

Example 5: N-(3-Cyano-5-fluoro-4-(1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)phenyl)-2-(3-(pentafluoro- λ^6 -sulfaneyl)phenyl)acetamide



DIPEA (0.052 ml, 0.299 mmol) and T3P (50% in EtOAc) (0.089 ml, 0.149 mmol) were added to a suspension of 2-(3-(pentafluoro- λ^6 -sulfaneyl)phenyl)acetic acid [CAS No. 1211578-68-5] (39.1 mg, 0.149 mmol) and Intermediate C-M3 (50 mg, 0.100 mmol) at RT. After 30 min, the reaction mixture was diluted with EtOAc and washed with H₂O (3x) and brine, dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by RP-HPLC-2 (mobile phase: (H₂O+7.3 mM NH₄OH)/(ACN+7.3 mM NH₄OH) 70:30 to 30:70) to give N-(3-cyano-5-fluoro-4-(1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)phenyl)-2-(3-(pentafluoro- λ^6 -sulfaneyl)phenyl)acetamide. ¹H NMR (600 MHz, DMSO-*d*₆) δ 10.75 (s, 1H), 8.24 (s, 1H), 7.84-7.90 (m, 4H), 7.82 (m, 1H), 7.57-7.64 (m, 2H), 4.53 (m, 1H), 3.93-4.02 (m, 2H), 3.88 (s, 2H), 3.45-3.51 (m, 2H), 1.94-2.03 (m, 4H). UPLC-MS-2: Rt = 1.13 min; MS m/z [M+H]⁺ 531.2.

Example 6: N-(3,5-Difluoro-4-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)phenyl)-2-(3-(trifluoromethyl)phenyl)acetamide

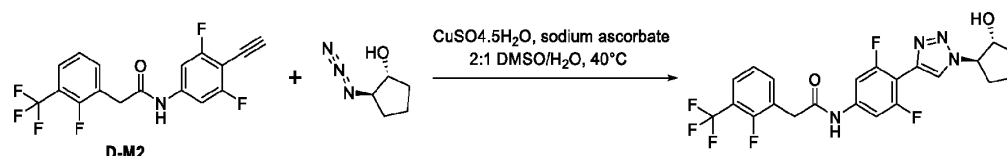


Step 1: PdCl₂(dtbpf) (6.8 mg, 0.0105 mmol) was added to a mixture of Intermediate D-T1 (140 mg, 0.210 mmol), tert-butyl 4-(4-(2,6-difluoro-4-(2-(3-(trifluoromethyl)phenyl)acetamido)phenyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate [CAS No. 877399-74-1] (119 mg, 0.314 mmol) and Na₂CO₃ (67 mg, 0.629 mmol) in dioxane (2 ml) and H₂O (1 ml) at RT. After degassing, the mixture was stirred at 60°C overnight. The reaction mixture was cooled to RT, diluted with H₂O and extracted with EtOAc (3x). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure to give tert-butyl 4-(4-(2,6-difluoro-4-(2-(3-(trifluoromethyl)phenyl)acetamido)phenyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate which was used directly in the next step without purification. HPLC-MS: Rt 2.67 min; MS m/z [M+H]⁺ 565.1.

Step 2: TFA (1 ml) was added to a solution of tert-butyl 4-(4-(2,6-difluoro-4-(2-(3-(trifluoromethyl)phenyl)acetamido)phenyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (step 1, 118 mg, 0.180 mmol) in DCM (1 ml) at RT. After stirring for 1 h, the reaction mixture was concentrated under reduced pressure. The residue was diluted with MeOH and filtered. The

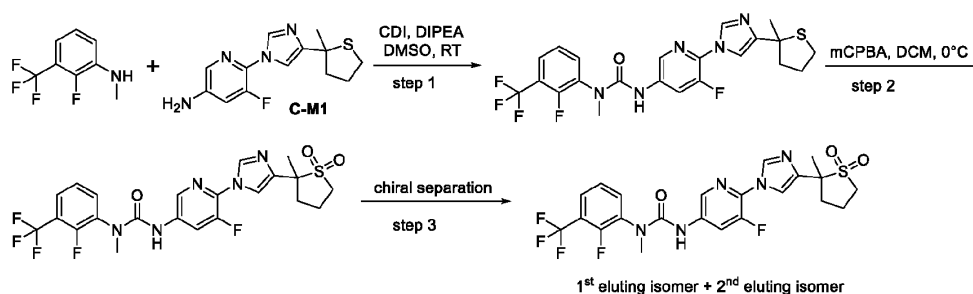
filtrate was purified by basic RP prep-HPLC to give N-(3,5-difluoro-4-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)phenyl)-2-(3-(trifluoromethyl)phenyl)acetamide. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.61 (s, 1H), 8.07 (d, 1H), 7.78 (t, 1H), 7.70 (d, 1H), 7.62-7.66 (m, 2H), 7.58 (m, 1H), 7.37-7.45 (m, 2H), 4.28 (m, 1H), 3.82 (s, 2H), 3.04 (m, 2H), 2.58 (m, 2H), 1.89-1.97 (m, 2H), 1.75-1.86 (m, 2H). HPLC-MS: Rt 2.19 min; MS *m/z* [M+H]⁺ 465.1.

Example 7: N-(3,5-Difluoro-4-(1-((1R,2R)-2-hydroxycyclopentyl)-1H-1,2,3-triazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide (racemic mixture)



Intermediate D-M2 (50 mg, 0.140 mmol), CuSO₄·5H₂O (70 mg, 0.280 mmol) and sodium ascorbate (83 mg, 0.419 mmol) were added to a solution of rac-(1R,2R)-2-azidocyclopentanol (39.4 mg, 0.280 mmol) in DMSO (2 ml) and H₂O (1 ml) at RT. After stirring at 40°C overnight, the reaction mixture was diluted with EtOAc and washed with H₂O. The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure and the residue was purified by RP prep-HPLC to give N-(3,5-difluoro-4-(1-((1R,2R)-2-hydroxycyclopentyl)-1H-1,2,3-triazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide. ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.75 (s, 1H), 8.41 (s, 1H), 7.68-7.79 (m, 2H), 7.37-7.48 (m, 3H), 5.26 (d, 1H), 4.69 (m, 1H), 4.32 (m, 1H), 3.89 (s, 2H), 2.26 (m, 1H), 1.96-2.07 (m, 2H), 1.76-1.85 (m, 2H), 1.60 (m, 1H). HPLC-MS-8: Rt 1.29 min; MS *m/z* [M+H]⁺ 485.1.

Example 8: 1-(2-Fluoro-3-(trifluoromethyl)phenyl)-3-(5-fluoro-6-(4-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-1-methylurea and (R or S)-1-(2-fluoro-3-(trifluoromethyl)phenyl)-3-(5-fluoro-6-(4-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-1-methylurea



Step 1: CDI (233 mg, 1.437 mmol) was added to a mixture of Intermediate C-M1 (100 mg, 0.359 mmol), 2-fluoro-N-methyl-3-(trifluoromethyl)aniline [CAS No. 1261808-48-3] (260 mg, 0.539 mmol) and DIPEA (0.188 ml, 1.078 mmol) in DMSO (4 ml) at RT. After 18 h, the reaction mixture was diluted with H₂O and extracted with DCM. The organic layer was dried (phase separator) and concentrated under reduced pressure and the residue was purified by normal

phase chromatography (eluent : EtOAc/cyclohexane 0:100 to 100:0) to give 1-(2-fluoro-3-(trifluoromethyl)phenyl)-3-(5-fluoro-6-(4-(2-methyltetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-1-methylurea. UPLC-MS-8: Rt = 1.22 min; MS m/z [M+H]⁺ 498.0.

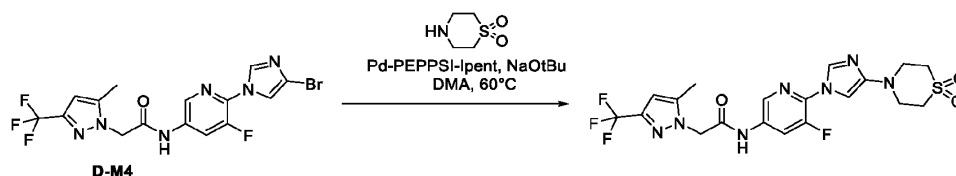
- Step 2:** A solution of mCPBA (66 mg, 0.295 mmol) in DCM (5 ml) was added dropwise to a solution of 1-(2-fluoro-3-(trifluoromethyl)phenyl)-3-(5-fluoro-6-(4-(2-methyltetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-1-methylurea (step 1, 79 mg, 0.134 mmol) in DCM (10 ml) at 0°C. After 30 min, the reaction mixture was diluted with DCM and washed with sat. aq. NaHCO₃ and brine. The organic layer was dried (phase separator) and concentrated under reduced pressure and the residue was purified by normal phase chromatography (eluent : EtOAc/cyclohexane 0:100 to 60:40) to give 1-(2-fluoro-3-(trifluoromethyl)phenyl)-3-(5-fluoro-6-(4-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-1-methylurea (racemic mixture). UPLC-MS-8: Rt = 0.93 min; MS m/z [M+H]⁺ 530.2.

- Step 3:** The enantiomers of 1-(2-fluoro-3-(trifluoromethyl)phenyl)-3-(5-fluoro-6-(4-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-1-methylurea (racemic mixture) (Step 2, 60 mg, 0.114 mmol) were separated by C-SFC-6 (mobile phase: CO₂/(MeOH+0.05%NH₃) 60/40) to give (R or S)-1-(2-fluoro-3-(trifluoromethyl)phenyl)-3-(5-fluoro-6-(4-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-1-methylurea.

- Example 8a:** 1st eluting isomer: C-SFC-5 (mobile phase: CO₂/(IPA+0.05%NH₃) 60/40): Rt = 1.27 min.

Example 8b: 2nd eluting isomer: ¹H NMR (600 MHz, DMSO-*d*₆) δ 9.16 (s, 1H), 8.43 (d, 1H), 8.22 (s, 1H), 8.16 (dd, 1H), 7.88 (m, 1H), 7.75-7.80 (m, 2H), 7.50 (m, 1H), 3.31 (s, 3H), 3.14-3.27 (m, 2H), 2.71 (m, 1H), 2.23 (m, 1H), 2.07-2.17 (m, 2H), 1.64 (s, 3H). UPLC-MS-8: Rt = 0.93 min; MS m/z [M+H]⁺ 530.3. C-SFC-5 (mobile phase: CO₂/(IPA+0.05%NH₃) 60/40): Rt = 1.76 min.

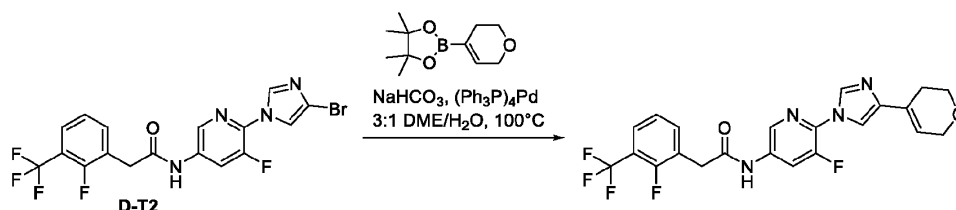
- Example 9:** N-(6-(4-(1,1-Dioxidothiomorpholino)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide



- Thiomorpholine 1,1-dioxide [CAS No. 39093-93-1] (136 mg, 1.01 mmol) was added to a mixture of Intermediate D-M4 (150 mg, 0.335 mmol), NaOtBu (97 mg, 1.01 mmol) and Pd-PEPPSI-Ipent (27 mg, 0.034 mmol) in DMA (3 ml) under Ar at RT. After flushing with Ar, the reaction vial was sealed and warmed to 60°C. After 18 h, the reaction mixture was diluted with EtOAc and washed with sat. aq. NaHCO₃. The organic layer was dried (phase separator) and concentrated under reduced pressure and the residue was purified by RP-HPLC-2 (mobile phase: (H₂O+7.3 mM NH₄OH)/ACN 95:5 to 30:70) to give N-(6-(4-(1,1-dioxidothiomorpholino)-1H-imidazol-1-yl)-

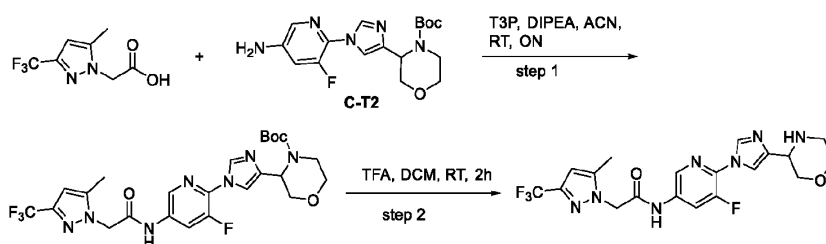
5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide. ¹H NMR (600 MHz, DMSO-*d*₆) δ 11.14 (br, 1H), 8.45 (s, 1H), 8.25 (d, 1H), 8.08 (s, 1H), 7.19 (s, 1H), 6.56 (s, 1H), 5.16 (s, 2H), 3.66-3.74 (m, 4H), 3.10-3.17 (m, 4H), 2.31 (s, 3H). UPLC-MS-2: Rt = 0.78 min; MS m/z [M+H]⁺ 502.3.

- 5 **Example 10:** N-(6-(4-(3,6-Dihydro-2H-pyran-4-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide



- A solution of Intermediate D-T2 (50 mg, 0.108 mmol), 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [CAS No. 287944-16-5] (25 mg, 0.119 mmol), NaHCO₃ (27 mg, 0.325 mmol) and (Ph₃P)₄Pd (6 mg, 0.0054 mmol) in DME (2.3 ml) and H₂O (0.78 ml) at RT under Ar was stirred at 100°C overnight. After 18 h, the reaction mixture was diluted with EtOAc and sat. aq. NaHCO₃. The separated organic layer was washed with brine, dried (MgSO₄) and concentrated under reduced pressure and the residue was purified by RP-HPLC-21 (mobile phase: (H₂O+0.1% TFA)/(ACN+0.1% TFA) 80:20 to 0:100) to give N-(6-(4-(3,6-dihydro-2H-pyran-4-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.94 (br s, 1H), 8.48 (d, 1H), 8.29 (dd, 1H), 8.23 (m, 1H), 7.69-7.80 (m, 2H), 7.69 (s, 1H), 7.41 (m, 1H), 6.40 (s, 1H), 4.19-4.26 (m, 2H), 3.95 (s, 2H), 3.76-3.84 (m, 2H), 2.35-2.42 (m, 2H). UPLC-MS-2: Rt = 1.07 min; MS m/z [M+H]⁺ 465.1.

- 20 **Example 11:** N-(5-fluoro-6-(4-(morpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide

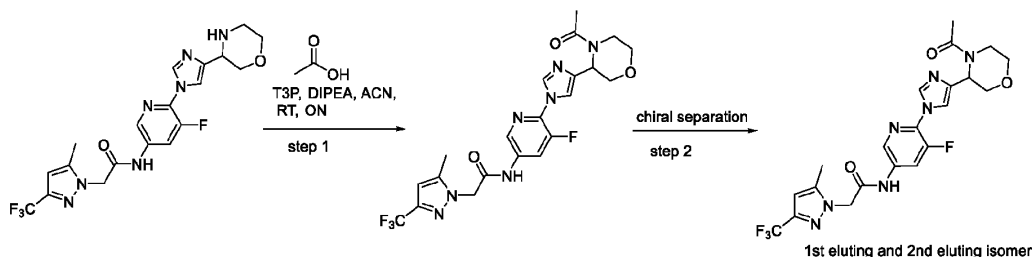


- Step 1:** To a solution of Intermediate C-T2 (200.0 mg, 1 eq, 550.4 μmol) in ACN (5 ml) were added 2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid [CAS No. 345637-71-0] (126.0 mg, 605.4 μmol), DIPEA (213.4 mg, 288 μl, 1.651 mmol) and T3P (50% in EtOAc) (700.5 mg, 651.0 μl, 1.101 mmol) and the reaction mixture was stirred overnight at RT. Further T3P (50% in EtOAc) (700.5 mg, 651.0 μl, 1.101 mmol) and DIPEA (213.4 mg, 288 μl, 1.651 mmol) were added and the reaction mixture was continued to stir at RT for 2 h to complete conversion. The

reaction mixture was diluted with DCM, washed with an aqueous saturated solution of NaHCO_3 . Phases were separated and aqueous layer was extracted with DCM (2x). The combined organic layers were washed with brine, dried using a phase separator and evaporated. The crude product was purified using silica gel column chromatography eluting with a gradient of MeOH (0-20%) in DCM. Fractions containing the product were combined and evaporated to give tert-butyl 3-(1-(3-fluoro-5-(2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)pyridin-2-yl)-1H-imidazol-4-yl)morpholine-4-carboxylate. ^1H NMR (600 MHz, DMSO-d_6) δ 11.09 (s, 1H), 8.47 (d, 1H), 8.27 (dd, 1H), 8.23 (d, 1H), 7.49 (s, 1H), 6.57 (s, 1H), 5.18 (s, 2H), 4.94 (s, 1H), 4.26 (d, 1H), 3.79 - 3.74 (m, 1H), 3.67 (dd, 1H), 3.66 - 3.62 (m, 1H), 3.40 (td, 1H), 3.11 (s, 1H), 2.31 (s, 3H), 1.41 (s, 9H). UPLC-MS-2: R_t = 1.16 min; MS m/z $[\text{M}+\text{H}]^+$ 554.2.

Step 2: To a solution of tert-butyl 3-(1-(3-fluoro-5-(2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)pyridin-2-yl)-1H-imidazol-4-yl)morpholine-4-carboxylate (step 1, 309.0 mg, 547.1 μmol) in DCM (3 ml) was added TFA (1.248 g, 10.94 mmol) and the reaction mixture was stirred at RT for 2 h. The reaction mixture was co-evaporated with DCM (3x), dissolved in DCM (10 ml), neutralized with ammonia/MeOH to pH 8 and concentrated. The crude product was purified by reverse phase column chromatography (RediSep Rf 50 g GOLD C18 column) eluting with a gradient of ACN (0% to 100%) in H_2O (containing 7.3mM NH_4OH). Fractions containing the desired product were combined, frozen and lyophilized to give N-(5-fluoro-6-(4-(morpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide. ^1H NMR (600 MHz, DMSO-d_6) δ 11.08 (s, 1H), 8.47 (d, 1H), 8.26 (dd, 1H), 8.19 (t, 1H), 7.58 (s, 1H), 6.57 (s, 1H), 5.18 (s, 2H), 3.89 (dd, 1H), 3.80 (dd, 1H), 3.71 (dt, 1H), 3.44 - 3.41 (m, 1H), 3.30 - 3.27 (m, 1H), 2.86 - 2.80 (m, 2H), 2.31 (s, 3H). UPLC-MS-8: R_t = 0.62 min; MS m/z $[\text{M}+\text{H}]^+$ 454.2.

Example 12: N-(6-(4-(4-Acetylmorpholin-3-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide and (R or S)-N-(6-(4-(4-acetylmorpholin-3-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide



Step 1: To a solution of N-(5-fluoro-6-(4-(morpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (Example 11, 219.6 mg, 484.3 μmol) in ACN (2 ml) were added acetic acid (58.17 mg, 968.7 μmol), DIPEA (250.4 mg, 1.937 mmol) and T3P (50% in EtOAc) (616.4 mg, 968.7 μmol) and the reaction mixture was stirred at RT

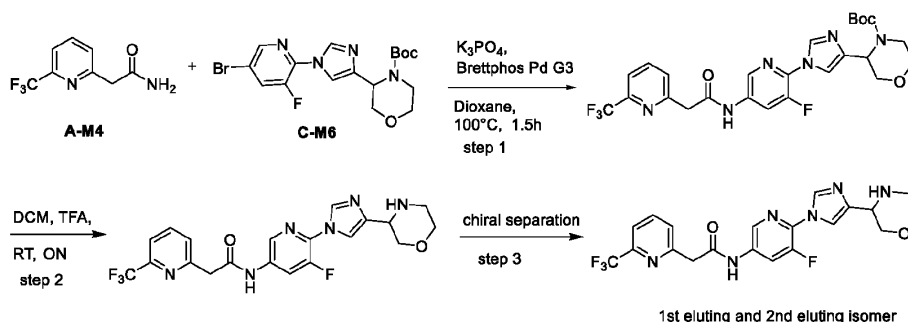
overnight. The reaction mixture was diluted with EtOAc, washed with a saturated solution of aq. NaHCO₃, phases were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried using a phase separator and evaporated. The crude product was purified by silica gel column chromatography eluting with a gradient of MeOH (0-20%) in DCM. Fractions containing the product were combined and evaporated to give N-(6-(4-(4-acetylmorpholin-3-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide. ¹H NMR (600 MHz, DMSO-d₆) δ 8.00 - 7.83 (m, 1H), 4.40 - 4.23 (m, 1H), 3.83 - 3.75 (m, 1H), 3.69 (t, 1H), 3.66 - 3.56 (m, 1H), 3.49 (ddd, 1H), 3.32 - 3.28 (m, 1H), 3.19 - 2.97 (m, 1H), 2.94 (ddd, 1H), 2.87 - 2.78 (m, 1H), 1.38 (d, 9H), 1.10 (d, 9H). UPLC-MS-8: Rt = 0.80 min; MS m/z [M+H]⁺ 496.1.

Step 2: The enantiomers of N-(6-(4-(4-acetylmorpholin-3-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (racemic mixture) (step 1, 233 mg, 0.47 mmol) were separated by C-SFC-10 (mobile phase: CO₂/(MeOH+0.05%NH₃) 63/37) to give (R or S)-N-(6-(4-(4-acetylmorpholin-3-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide: 1st (Example 12a) and 2nd (Example 12b).

Example 12a: 1st eluting isomer: ¹H NMR (600 MHz, DMSO-d₆) δ 11.10 (s, 1H), 8.47 (d, 1H), 8.31 - 8.18 (m, 2H), 7.59 (d, 1H), 6.57 (s, 1H), 5.18 (s, 2H), 4.95+5.37 (d, 1H), 4.31 (dd, 1H), 4.05 (d, 1H), 3.85 - 3.77 (m, 1H), 3.77 - 3.69 (m, 1H), 3.64 - 3.57 (m, 1H), 3.46 - 3.35 (m, 2H), 2.75 (td, 1H), 2.31 (s, 3H), 2.16 (d, 3H). UPLC-MS-8: Rt = 0.78 min; MS m/z [M+H]⁺ 496.2. C-SFC-8 (mobile phase: CO₂/(MeOH+0.05%NH₃) 70/30): Rt = 3.01 min.

Example 12b: 2nd eluting isomer: ¹H NMR (600 MHz, DMSO-d₆) δ 11.10 (s, 1H), 8.47 (d, 1H), 8.31 - 8.18 (m, 2H), 7.59 (d, 1H), 6.57 (s, 1H), 5.18 (s, 2H), 5.4+4.95 (s, 1H), 4.31 (dd, 1H), 4.05 (d, 1H), 3.86 - 3.77 (m, 1H), 3.74 (dd, 1H), 3.61 (t, 1H), 3.46 - 3.37 (m, 2H), 2.78 - 2.71 (m, 1H), 2.31 (s, 3H), 2.17 (d, 3H). UPLC-MS-8: Rt = 0.78 min; MS m/z [M+H]⁺ 496.2. C-SFC-8 (mobile phase: CO₂/(MeOH+0.05%NH₃) 70/30): Rt = 3.62 min.

Example 13: N-(5-Fluoro-6-(4-(morpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide



Step 1: A microwave vial was charged with Intermediate C-M6 (127 mg, 0.297 mmol), Intermediate A-M4 (91 mg, 0.446 mmol), K₃PO₄ (158 mg, 0.743 mmol), BrettPhos Pd G3 (53.9 mg, 0.059 mmol) and dry dioxane (2 ml). The reaction mixture was stirred at 10°C for 1.5 h. The

mixture was cooled to RT, diluted with EtOAc and washed with H₂O and brine. The organic layers were dried using a phase separator and evaporated. The crude product was purified using silica gel column chromatography eluting with a gradient of MeOH (0-20%) in DCM. Fractions containing the desired product were combined and evaporated to give tert-butyl 3-(1-(3-fluoro-5-(2-(6-(trifluoromethyl)pyridin-2-yl)acetamido)pyridin-2-yl)-1H-imidazol-4-yl)morpholine-4-carboxylate. UPLC-MS-2: Rt = 1.05 min; MS m/z [M+H]⁺ 551.3.

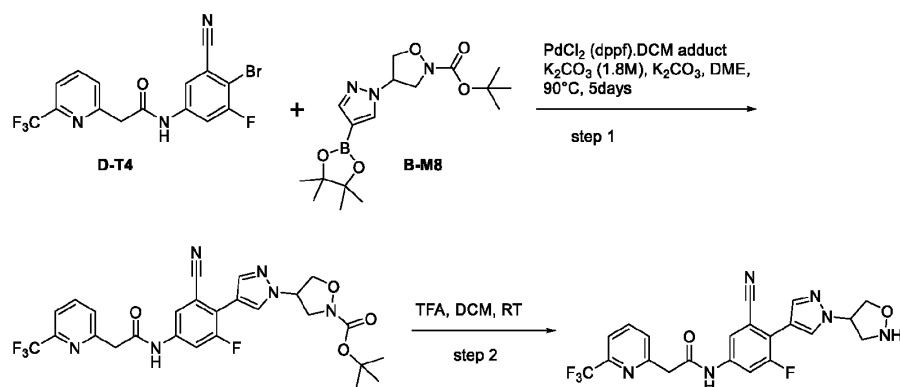
Step 2: To a solution of tert-butyl 3-(1-(3-fluoro-5-(2-(6-(trifluoromethyl)pyridin-2-yl)acetamido)pyridin-2-yl)-1H-imidazol-4-yl)morpholine-4-carboxylate (step 1, 157.5 mg, 0.206 mmol) in DCM (1 ml) was added TFA (0.317 ml, 4.12 mmol) and the reaction mixture was stirred at RT overnight. The reaction mixture was co-evaporated with DCM (3x) to give a crude product which was purified via RP-HPLC-2 (mobile phase: H₂O + 7.3mM NH₄OH/ACN, 5% to 100% in 20 min). Fractions containing the desired product were combined, frozen and lyophilized to give N-(5-fluoro-6-(4-(morpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide (racemic mixture). ¹H NMR (600 MHz, DMSO-d₆) δ 10.97 (s, 1H), 8.48 (d, 1H), 8.28 (dd, 1H), 8.18 (t, 1H), 8.10 (t, 1H), 7.83 (dd, 1H), 7.77 (d, 1H), 7.56 (q, 1H), 4.06 (d, 2H), 3.89 (dd, 1H), 3.79 (dd, 1H), 3.70 (dt, 1H), 3.41 (ddd, 1H), 3.30 - 3.26 (m, 1H), 2.83 (p, 2H). UPLC-MS-2: Rt = 0.50 min; MS m/z [M+H]⁺ 451.1.

Step 3: The racemic mixture of N-(5-fluoro-6-(4-(morpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide (step 2, 35.4 mg, 0.078 mmol) was separated by chiral prep. HPLC using C-HPLC-3 (mobile phase: n-heptane/EtOH/MeOH+0.05%DEA (84:8:8) to give the 1st (Example 13a) and 2nd (Example 13b) eluting isomers. Received enantiomers were re-purified via prep. HPLC using RP-HPLC-2 (mobile phase: (H₂O+7.3 mM NH₄OH/ACN 95:5 to 0:100).

Example 13a: (R or S)-N-(5-Fluoro-6-(4-(morpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide: 1st eluting isomer: ¹H NMR (600 MHz, DMSO-d₆) δ 10.98 (s, 1H), 8.48 (d, 1H), 8.29 (dd, 1H), 8.18 (t, 1H), 8.10 (t, 1H), 7.83 (d, 1H), 7.77 (d, 1H), 7.56 (q, 1H), 4.07 (s, 2H), 3.89 (dd, 1H), 3.81 - 3.76 (m, 1H), 3.72 - 3.68 (m, 1H), 3.41 (ddd, 1H), 3.28 (m, 1H), 2.83 (m, 2H), 2.67 (s, 1H). UPLC-MS-2: Rt = 0.50 min; MS m/z [M+H]⁺ 451.1. C-HPLC-4 (mobile phase: heptane+DEA:EtOH/MeOH (50:50)+DEA 84/16): Rt = 8.20 min.

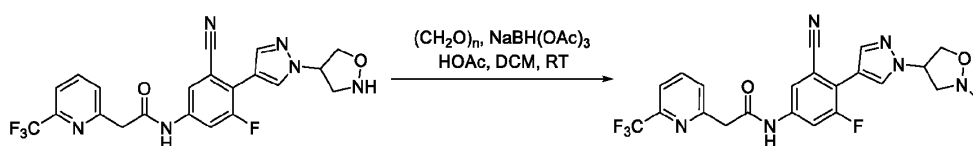
Example 13b: (R or S)-N-(5-Fluoro-6-(4-(morpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide: 2nd eluting isomer: ¹H NMR (600 MHz, DMSO-d₆) δ 10.97 (s, 1H), 8.48 (d, 1H), 8.28 (dd, 1H), 8.18 (t, 1H), 8.10 (t, 1H), 7.83 (d, 1H), 7.77 (d, 1H), 7.58 - 7.55 (m, 1H), 4.07 (s, 2H), 3.89 (dd, 1H), 3.79 (dd, 1H), 3.70 (dt, 1H), 3.41 (ddd, 1H), 3.31 - 3.25 (m, 1H), 2.85 - 2.80 (m, 2H), 2.72 - 2.63 (s, 1H). UPLC-MS-2: Rt = 0.50 min; MS m/z [M+H]⁺ 451.1. HPLC-4 (mobile phase: heptane+DEA:EtOH/MeOH (50:50)+DEA 84/16): Rt = 10.99 min.

Example 14: N-(3-Cyano-5-fluoro-4-(1-(isoxazolidin-4-yl)-1H-pyrazol-4-yl)phenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide



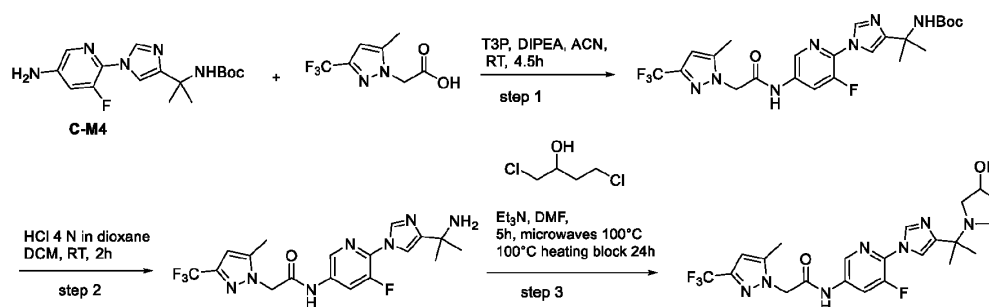
- Step 1: To a solution of Intermediate D-T4 (80 mg, 0.191 mmol) in DME (2 ml) was added
- 5 Intermediate B-M8 (102 mg, 0.210 mmol), 1.8M aq. K_2CO_3 (0.318 ml, 0.573 mmol) and $PdCl_2(dppf).DCM$ (7.8 mg, 0.010 mmol) and the reaction mixture was stirred at 90°C. Additional Intermediate B-M8 (102 mg, 0.210 mmol), $PdCl_2(dppf).DCM$ (7.8 mg, 0.010 mmol) and K_2CO_3 (79 mg, 0.573 mmol) were added after 3 d. Additional $PdCl_2(dppf).DCM$ (31.2 mg, 0.038 mmol) was added after 4 d. The reaction mixture was partitioned between DCM and H_2O . The organic
- 10 layer was dried using a phase separator and evaporated. The crude product was purified using silica gel column chromatography (eluent : EtOAc/cyclohexane 0:100 to 100:0 and then changing to MeOH (0-20%) in DCM) to give tert-butyl 4-(4-(2-cyano-6-fluoro-4-(2-(6-(trifluoromethyl)pyridin-2-yl)acetamido)phenyl)-1H-pyrazol-1-yl)isoxazolidine-2-carboxylate. UPLC-MS-2: Rt = 1.08 min; MS m/z $[M+Na]^+$ 583.4.
- 15 Step 2: To a solution of tert-butyl 4-(4-(2-cyano-6-fluoro-4-(2-(6-(trifluoromethyl)pyridin-2-yl)acetamido)phenyl)-1H-pyrazol-1-yl)isoxazolidine-2-carboxylate (step 1, 84 mg, 0.105 mmol) in DCM (1 ml) was added TFA (0.162 ml, 2.098 mmol). The reaction mixture was stirred overnight at RT. The mixture was evaporated to dryness, filtered using a syringe filter and the crude product was purified by RP-HPLC-2 (mobile phase: H_2O +7.3mM NH_4OH /ACN 95:5 to
- 20 0:100). Fractions containing the desired product were combined, frozen and lyophilized to give N-(3-cyano-5-fluoro-4-(1-(isoxazolidin-4-yl)-1H-pyrazol-4-yl)phenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide. 1H NMR (600 MHz, $DMSO-d_6$) δ 10.89 (s, 1H), 8.38 (s, 1H), 8.08 (t, 1H), 8.01 (s, 1H), 7.92 - 7.86 (m, 2H), 7.80 (d, 1H), 7.74 (d, 1H), 5.81 (ddt, 1H), 4.54 (dd, 1H), 4.43 (dd, 1H), 4.10-4.01 (m, 2H), 4.04 (s, 2H). UPLC-MS-2: Rt = 0.81 min; MS m/z $[M+H]^+$ 461.3.

- 25 **Example 15:** N-(3-Cyano-5-fluoro-4-(1-(2-methylisoxazolidin-4-yl)-1H-pyrazol-4-yl)phenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide



To a solution of N-(3-cyano-5-fluoro-4-(1-(isoxazolidin-4-yl)-1H-pyrazol-4-yl)phenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide (Example 14, 33 mg, 0.042 mmol) in DCM (500 μ l) were added paraformaldehyde (7.91 mg, 0.250 mmol) and HOAc (4.77 μ l, 0.083 mmol) followed by portionwise addition of NaBH(OAc)₃ (54.7 mg, 0.250 mmol). The resulting suspension was stirred at RT for 5 h. Further paraformaldehyde (7.91 mg, 0.250 mmol) and NaBH(OAc)₃ (54.7 mg, 0.250 mmol) were added and the reaction mixture was stirred at RT overnight. More paraformaldehyde (7.91 mg, 0.250 mmol), HOAc (4.77 μ l, 0.083 mmol) and NaBH(OAc)₃ (54.7 mg, 0.250 mmol) were added and the reaction was stirred at RT for 72 h. Additional paraformaldehyde (7.91 mg, 0.250 mmol), HOAc (4.77 μ l, 0.083 mmol) and NaBH(OAc)₃ (54.7 mg, 0.250 mmol) were added and the mixture was stirred at RT for 4 h to complete the reaction. The reaction mixture was diluted with DCM and an aqueous saturated solution of NaHCO₃ was added. Phases were separated and the aqueous phase was extracted with DCM. The combined organic layers were washed with brine, dried using a phase separator and evaporated. The crude product was purified by RP-HPLC-2 (mobile phase: H₂O+7.3mM NH₄OH/ACN 95:5 to 0:100). Fractions containing the desired product were combined, frozen and lyophilized to give N-(3-cyano-5-fluoro-4-(1-(2-methylisoxazolidin-4-yl)-1H-pyrazol-4-yl)phenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide. ¹H NMR (600 MHz, DMSO-d₆) δ 10.86 (s, 1H), 8.30 - 8.24 (m, 1H), 8.09 (t, 1H), 7.94 - 7.89 (m, 1H), 7.89 - 7.85 (m, 2H), 7.83 (d, 1H), 7.76 (d, 1H), 5.57 - 5.47 (m, 1H), 4.15 - 4.06 (m, 1H), 4.04 (s, 2H), 3.94 - 3.75 (m, 1H), 3.49 (d, 1H), 3.03 - 2.77 (m, 1H), 2.73 - 2.62 (m, 3H). UPLC-MS-2: Rt = 0.88 min; MS m/z [M+H]⁺ 475.4.

Example 16: N-(5-Fluoro-6-(4-(2-(3-hydroxypyrrolidin-1-yl)propan-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide



Step 1: To a solution of Intermediate C-M4 (150.0 mg, 384.6 μ mol) in ACN (2.5 ml) were added 2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid [CAS No. 345637-71-0] (120.1 mg, 577.0 μ mol), DIPEA (149.1 mg, 201 μ l, 1.154 mmol) and T3P (50% in EtOAc) (489.5 mg, 455.0 μ l, 769.3 μ mol) and the reaction mixture was stirred at RT for 2 h. Further 2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid (120.1 mg, 577.0 μ mol), DIPEA (149.1 mg, 201 μ l, 1.154 mmol) and T3P (50% in EtOAc) (489.5 mg, 455.0 μ l, 769.3 μ mol) were added and stirring was continued at RT for 2.5 h. The reaction mixture was diluted with EtOAc, washed with an aqueous saturated solution of NaHCO₃. Phases were separated and the aqueous layer was

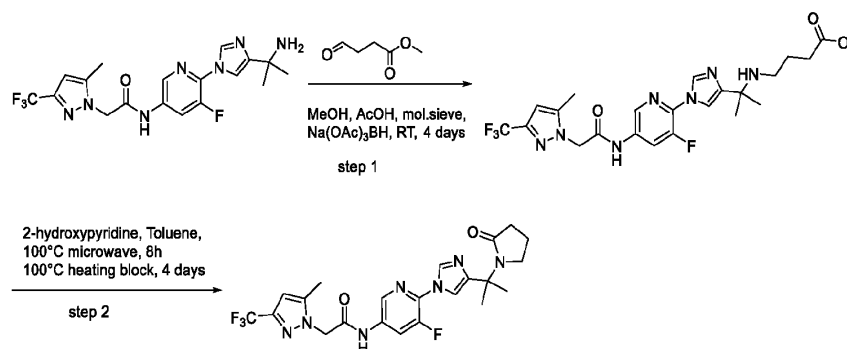
extracted with EtOAc (2x). The combined organic layers were washed with brine, dried using a phase separator and evaporated. The crude product was purified using silica gel column chromatography eluting with a gradient of EtOAc (0-100%) in cyclohexane. Fractions containing the desired product were combined and evaporated to give tert-butyl (2-(1-(3-fluoro-5-(2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)pyridin-2-yl)-1H-imidazol-4-yl)propan-2-yl)carbamate. ¹H NMR (600 MHz, DMSO-d₆) δ 11.07 (bs, 1H), 8.47 (d, 1H), 8.26 (dd, 1H), 8.15 (d, 1H), 7.44 (s, 1H), 6.75 (s, 1H), 6.56 (s, 1H), 5.16 (s, 2H), 2.31 (s, 3H), 1.52 (d, 6H), 1.34 (s, 9H). UPLC-MS-8: Rt = 1.19 min; MS m/z [M+H]⁺ 526.2.

Step 2: A solution of tert-butyl (2-(1-(3-fluoro-5-(2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)pyridin-2-yl)-1H-imidazol-4-yl)propan-2-yl)carbamate (step 1, 171.0 mg, 90% wt, 292.9 μmol) and 4M HCl/dioxane (213.6 mg, 1.464 ml, 5.857 mmol) in DCM (1 ml) was stirred at RT for 2 h. The reaction mixture was evaporated to dryness. The residue was dissolved in H₂O and the aqueous layer was basified with an aqueous saturated solution of NaHCO₃ then extracted with DCM (2x). The combined organic layers were dried using a phase separator and evaporated to give N-(6-(4-(2-aminopropan-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide. ¹H NMR (600 MHz, DMSO-d₆) δ 8.46 (d, 1H), 8.25 (dd, 1H), 8.16 (s, 1H), 7.51 (s, 1H), 6.56 (s, 1H), 5.17 (s, 2H), 2.31 (s, 3H), 1.35 (s, 6H). UPLC-MS-8: Rt = 0.65 min; MS m/z [M+H]⁺ 426.2.

Step 3: To a solution of N-(6-(4-(2-aminopropan-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (step 2, 50.00 mg, 110.5 μmol) and Et₃N (55.90 mg, 77.0 μl, 5 eq, 552.4 μmol) in DMF (0.500 ml) was added 1,4-dichlorobutan-2-ol (17.38 mg, 13.5 μl, 121.5 μmol) and the reaction mixture was stirred at 100°C for 1 h using microwave irradiation. Further Et₃N (55.90 mg, 77.0 μl, 552.4 μmol) and 1,4-dichlorobutan-2-ol (17.38 mg, 13.5 μl, 121.5 μmol) were added and the reaction mixture was continued to stir at 100°C for 4 h using microwave irradiation. More Et₃N (55.90 mg, 77.0 μl, 552.4 μmol) and 1,4-dichlorobutan-2-ol (17.38 mg, 13.5 μl, 121.5 μmol) were added and stirring was continued overnight at 100°C using a heating block. The reaction mixture was diluted with EtOAc and washed with H₂O and brine. The combined organic layers were dried using a phase separator and evaporated. The crude product was purified using silica gel column chromatography eluting with a gradient of MeOH (0-90%) in DCM+0.2% 7N NH₃. Fractions containing the desired product were combined, evaporated and re-purified using prep RP-HPLC-3 (mobile phase: H₂O+0.1%TFA/ACN 95:5 to 0:100). Fractions containing the desired compound were combined and the aqueous solution was extracted with DCM (3x). The combined organic layers were dried using a phase separator and concentrated to give N-(5-fluoro-6-(4-(2-(3-hydroxypyrrolidin-1-yl)propan-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide. ¹H NMR (600 MHz, DMSO-d₆) δ 11.07 (s, 1H), 8.47 (dd, 1H), 8.27 (dd, 1H), 8.18 (s, 1H), 7.56 (s, 1H), 6.57 (s, 1H), 5.18 (s, 2H), 4.55 (s, 1H), 4.10 - 4.01 (m, 1H), 2.91 - 2.78 (m,

1H), 2.76 - 2.67 (m, 1H), 2.64 - 2.56 (m, 1H), 2.44 - 2.37 (m, 1H), 2.32 (s, 3H), 1.87 - 1.74 (m, 1H), 1.44 (m, 1H), 1.41 (s, 6H). UPLC-MS-8: Rt = 0.69 min; MS m/z [M+H]⁺ 496.2.

Example 17: N-(5-Fluoro-6-(4-(2-(2-oxopyrrolidin-1-yl)propan-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide



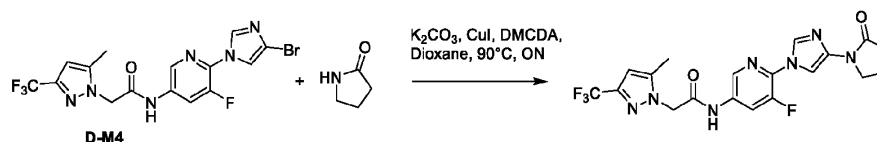
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Step 1: A solution of N-(6-(4-(2-aminopropan-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (Example 16/step 2, 150.0 mg, 292.0 μ mol), methyl 4-oxobutanoate (67.81 mg, 61.15 μ l, 584.0 μ mol) and HOAc (17.53 mg, 16.71 μ l, 292.0 μ mol) in MeOH (3.0 ml) was stirred at RT for 20 min. NaBH(OAc)₃ (123.8 mg, 584.0 μ mol) was added and the reaction mixture was stirred at RT for 72 h. Methyl 4-oxobutanoate (67.81 mg, 61.15 μ l, 584.0 μ mol) and HOAc (17.53 mg, 16.71 μ l, 292.0 μ mol) were added to reaction mixture followed by NaBH(OAc)₃ (123.8 mg, 584.0 μ mol). The reaction mixture was diluted with DCM and carefully quenched with H₂O and washed with an aqueous saturated solution of NaHCO₃. Phases were separated and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried (Na₂SO₄) and evaporated. The crude product was purified using silica gel column chromatography eluting with a gradient of MeOH (0-20%) in DCM. Fractions containing the product were combined and evaporated to give methyl 4-((2-(1-(3-fluoro-5-(2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)pyridin-2-yl)-1H-imidazol-4-yl)propan-2-yl)amino)butanoate. ¹H NMR (600 MHz, DMSO-d₆) δ 11.09 (s, 1H), 8.47 (d, 1H), 8.26 (dd, 1H), 8.18 (s, 1H), 7.49 (s, 1H), 6.56 (s, 1H), 5.17 (s, 2H), 3.54 (s, 3H), 2.34 - 2.29 (m, 7H), 1.58 (p, 2H), 1.33 (s, 6H). UPLC-MS-8: Rt = 0.66 min; MS m/z [M+H]⁺ 526.2.

Step 2: A solution of methyl 4-((2-(1-(3-fluoro-5-(2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)pyridin-2-yl)-1H-imidazol-4-yl)propan-2-yl)amino)butanoate (step 1, 37.80 mg, 68.33 μ mol) and 2-hydroxypyridine (13.00 mg, 136.7 μ mol) in toluene (0.60 ml) was stirred at 120°C for 7 h under microwave irradiation. The reaction mixture was allowed to cool to RT, diluted with DCM and washed with an aqueous saturated solution of NaHCO₃ and brine. The organic layer was dried using a phase separator and evaporated. The crude product was purified by silica gel column chromatography eluting with a gradient of MeOH (0-20%) in DCM. Fractions containing the desired product were combined, evaporated and re-purified using RP-

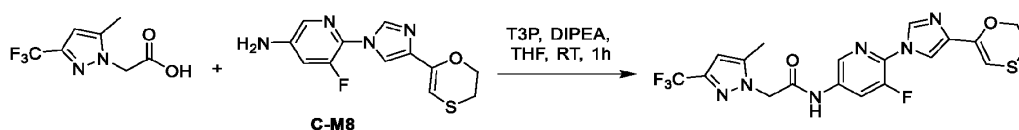
HPLC eluting with a gradient of ACN (5-100%) in H₂O+ 0.1%NH₄OH. Fractions containing the desired product were combined, an aqueous saturated solution of NaHCO₃ was added and the aqueous solution was extracted with DCM (3x). The combined organic layers were dried using a phase separator and evaporated and re-purified using RP-HPLC eluting with a gradient of ACN (5-100%) in H₂O+ 0.1% HCOOH. Fractions containing the desired product were combined and the aqueous solution was extracted with DCM (3x). The combined organic layers were dried using a phase separator and concentrated. The residue was triturated in ACN/H₂O (1/2), frozen and lyophilized to give N-(5-fluoro-6-(4-(2-(2-oxopyrrolidin-1-yl)propan-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide. ¹H NMR (600 MHz, DMSO-d₆) δ 11.08 (s, 1H), 8.45 (d, 1H), 8.28 (dd, 1H), 8.17 (dd, 1H), 7.52 (t, 1H), 6.59 - 6.53 (m, 1H), 5.16 (s, 2H), 3.38 (t, 2H), 2.31 (d, 3H), 2.18 (dd, 2H), 1.89 - 1.78 (m, 2H), 1.69 (s, 6H). UPLC-MS-8: Rt = 0.93 min; MS m/z [M+H]⁺ 494.1.

Example 18: N-(5-Fluoro-6-(4-(2-(2-oxopyrrolidin-1-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide



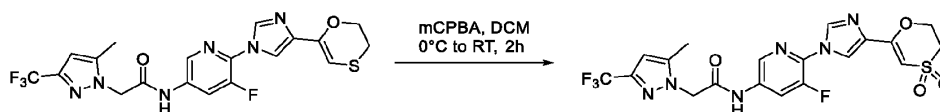
A sealed tube was charged with Intermediate D-M4 (150.0 mg, 332.1 μmol), CuI (94.87 mg, 1.5 eq, 498.1 μmol) and K₂CO₃ (137.7 mg, 3 eq, 996.2 μmol) followed by addition of ACN (5 ml), pyrrolidin-2-one (56.53 mg, 50.5 μl, 664.1 μmol) and trans-(1*r*,2*r*)-N,N'-bismethyl-1,2-cyclohexanediamine (141.7 mg, 157 μl, 498.1 μmol) under argon. The reaction mixture was stirred at 90°C overnight. The reaction mixture was diluted with EtOAc and washed with H₂O. Phases were separated and the aqueous layer was extracted with EtOAc and DCM. The combined organic layers were washed with brine, dried using a phase separator and evaporated. The crude product was purified using RP-HPLC eluting with a gradient of ACN (10%-100%) in H₂O+0.1% HCOOH. Fractions containing the desired product were combined, an aqueous saturated solution of NaHCO₃ was added and the aqueous solution was extracted with DCM (3x). The combined organic layers were dried using a phase separator and evaporated. The residue was triturated in ACN (1.5 ml), centrifuged and the supernatant was removed. The remaining solid was dried using high vacuum to give N-(5-fluoro-6-(4-(2-oxopyrrolidin-1-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide. ¹H NMR (600 MHz, DMSO-d₆) δ 11.08 (s, 1H), 8.48 (d, 1H), 8.29 (dd, 1H), 8.18 (t, 1H), 7.98 (d, 1H), 6.57 (s, 1H), 5.18 (s, 2H), 3.91 (t, 2H), 2.47 (d, 2H), 2.31 (s, 3H), 2.11 (p, 2H). UPLC-MS-2: Rt = 0.87 min; MS m/z [M+H]⁺ 452.2.

Example 19: N-(6-(4-(5,6-Dihydro-1,4-oxathiin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide



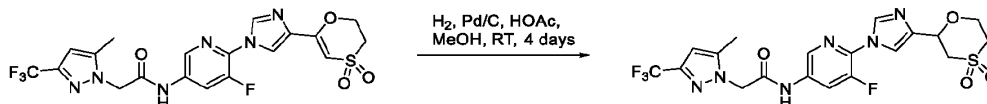
To a solution of 2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid [CAS No. 345637-71-0] (71.8 mg, 0.345 mmol), Intermediate C-M8 (80 mg, 0.287 mmol) and DIPEA (0.151 ml, 0.862 mmol) in THF (2 ml) was added T₃P (50% in EtOAc) (0.257 ml, 0.431 mmol) and the resulting solution was stirred at RT for 1 h. The reaction mixture was diluted with EtOAc and washed with an aqueous saturated solution of NaHCO₃ (2x). The organic phase was dried (Na₂SO₄) and concentrated. The crude product was purified by RP-HPLC eluting with a gradient of ACN (0-70%) in H₂O+0.1%NH₄OH. Fractions containing the desired product were combined and lyophilized to give N-(6-(4-(5,6-dihydro-1,4-oxathiin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide. ¹H NMR (600 MHz, DMSO-d₆) δ 11.10 (s, 1H), 8.46 (d, 1H), 8.26 (dd, 1H), 8.24 (t, 1H), 7.53 (t, 1H), 6.57 (s, 1H), 5.96 (d, 1H), 5.18 (s, 2H), 4.40 - 4.33 (m, 2H), 3.11 - 3.05 (m, 2H), 2.31 (d, 3H). UPLC-MS-2: Rt = 1.06 min; MS m/z [M+H]⁺ 469.1.

Example 20: N-(6-(4-(4,4-Dioxido-5,6-dihydro-1,4-oxathiin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide



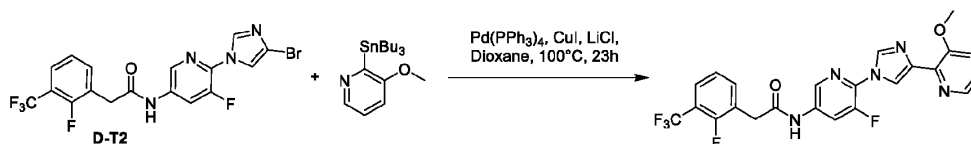
To a mixture of N-(6-(4-(5,6-dihydro-1,4-oxathiin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (Example 19, 90 mg, 0.19 mmol) in DCM (4 ml) at 0°C was added mCPBA (99 mg, 0.58 mmol) and the resulting mixture was allowed to stir at RT for 2 h. The reaction mixture was quenched with 10 ml of Na₂S₂O₃ 5%, stirred at RT for 30 min, diluted with H₂O and extracted with DCM (3x). The combined organic phases were washed with an aqueous saturated solution of NaHCO₃, dried (Na₂SO₄) and concentrated to give N-(6-(4-(4,4-dioxido-5,6-dihydro-1,4-oxathiin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide. ¹H NMR (600 MHz, DMSO-d₆) δ 11.17 (s, 1H), 8.50 (d, 1H), 8.38 (t, 1H), 8.29 (dd, 1H), 8.06 (t, 1H), 6.57 (s, 1H), 6.43 - 6.39 (m, 1H), 5.20 (s, 2H), 4.84 - 4.77 (m, 2H), 3.66 - 3.59 (m, 2H), 2.33 - 2.28 (m, 3H). UPLC-MS-2: Rt = 0.76 min; MS m/z [M+H]⁺ 501.3.

Example 21: N-(6-(4-(4,4-Dioxido-1,4-oxathian-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide



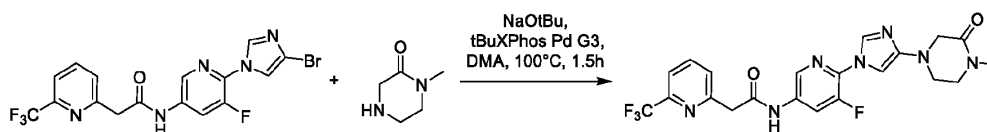
To a solution of Example 20 (72 mg, 0.14 mmol) and HOAc (43 mg, 41 μ l, 0.72 mmol) in MeOH (5 ml) and THF (3 ml) filled with argon was added Pd/C (77 mg, 10% wt, 72 μ mol). The resulting suspension was stirred under an atmosphere of hydrogen for 24 h at RT. Further Pd/C (77 mg, 10% wt, 72 μ mol) was added and the suspension was continued to stir under an atmosphere of hydrogen for 48 h. More Pd/C (77 mg, 10% wt, 72 μ mol) was added and stirring was continued under an atmosphere of hydrogen for 24 h. The reaction mixture was filtered through a pad of Hyflo[®] and rinsed with MeOH and DCM. The filtrate was concentrated and purified by RP-HPLC eluting with a gradient of ACN (0-60%) in H₂O+0.1%NH₄OH. Fractions containing the desired product were combined and lyophilized to give : N-(6-(4-(4,4-dioxido-1,4-oxathian-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide. ¹H NMR (600 MHz, DMSO-d₆) δ 8.42 (d, 1H), 8.28 (dd, 1H), 8.23 (s, 1H), 7.78 (s, 1H), 6.55 (s, 1H), 5.12 (s, 2H), 4.88 (dd, 1H), 4.32 (ddd, 1H), 3.96 (td, 1H), 3.56 - 3.51 (m, 1H), 3.44 (ddd, 1H), 3.36 - 3.29 (m, 1H), 3.26 - 3.21 (m, 1H), 2.30 (s, 3H). UPLC-MS-2: Rt = 0.71 min; MS m/z [M+H]⁺ 503.1.

Example 22: 2-(2-Fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(3-methoxypyridin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide



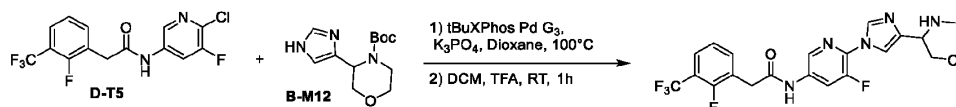
Intermediate D-T2 (50 mg, 0.108 mmol), Pd(PPh₃)₄ (12.53 mg, 10.84 μ mol), CuI (10.32 mg, 0.054 mmol) and LiCl (9.19 mg, 0.217 mmol) were mixed in a sealed flask under an atmosphere of argon. A solution of 3-methoxy-2-(tributylstannyl)pyridine (216 mg, 0.542 mmol) in anhydrous dioxane (2 ml) was added and the reaction mixture was stirred at 100°C for 23 h. The reaction mixture was cooled to RT and diluted with EtOAc, washed with an aqueous saturated solution of NaHCO₃, dried (Na₂SO₄) and concentrated. The crude product was purified by RP-HPLC eluting with a gradient of ACN in H₂O+0.1% HCOOH (10-70%). Fractions containing the desired product were collected and lyophilized and repurified by silica gel column chromatography eluting with a gradient elution of MeOH 7N NH₃ (0-100%) in DCM. Fractions containing the desired product were collected and concentrated to give 2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(3-methoxypyridin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide. ¹H NMR (600 MHz, DMSO-d₆) δ 11.00 (s, 1H), 8.52 (d, 1H), 8.36 - 8.30 (m, 2H), 8.27 (t, 1H), 8.23 (dd, 1H), 7.78 (t, 1H), 7.75 - 7.71 (m, 1H), 7.53 (dd, 1H), 7.42 (t, 1H), 7.29 (dd, 1H), 3.97 (s, 2H), 3.95 (s, 3H). UPLC-MS-2: Rt = 0.86 min; MS m/z [M+H]⁺ 490.4.

Example 23: N-(5-Fluoro-6-(4-(4-methyl-3-oxopiperazin-1-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide



Intermediate D-T3 (30 mg, 0.068 mmol), 1-methylpiperazin-2-one (12.21 mg, 0.081 mmol), NaOtBu (19.47 mg, 0.203 mmol) and tBuXPhos Pd G3 (5.37 mg, 6.75 μ mol) were mixed in a sealed vial under an atmosphere of argon. DMA anhydrous (0.5 ml) was added and the reaction mixture was stirred at 100°C for 1.5 h. The reaction mixture was diluted with EtOAc and washed with an aqueous saturated solution of NaHCO₃. The organic phase was dried (Na₂SO₄) and concentrated. The crude material was purified by RP-HPLC eluting with a gradient of ACN in H₂O+0.1% HCOOH. Fractions containing the desired product were collected, basified with NaHCO₃ and extracted with EtOAc (2x). The organic phase was dried (Na₂SO₄), concentrated and re-purified by silica gel column chromatography eluting with a gradient of EtOAc/EtOH (3/1: 0-100%) in cyclohexane. Fractions containing the desired product were combined and concentrated to give N-(5-fluoro-6-(4-(4-methyl-3-oxopiperazin-1-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide. ¹H NMR (600 MHz, DMSO-d₆) δ 8.45 (d, 1H), 8.33 (dd, 1H), 8.16 (d, 1H), 8.05 (t, 1H), 7.74 (dd, 2H), 7.17 (t, 1H), 4.08 (s, 2H), 3.76 (s, 2H), 3.58 - 3.47 (m, 4H), 3.03 (s, 3H). UPLC-MS-2: Rt = 0.77 min; MS m/z [M+H]⁺ 478.5.

Example 24: 2-(2-Fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(morpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide

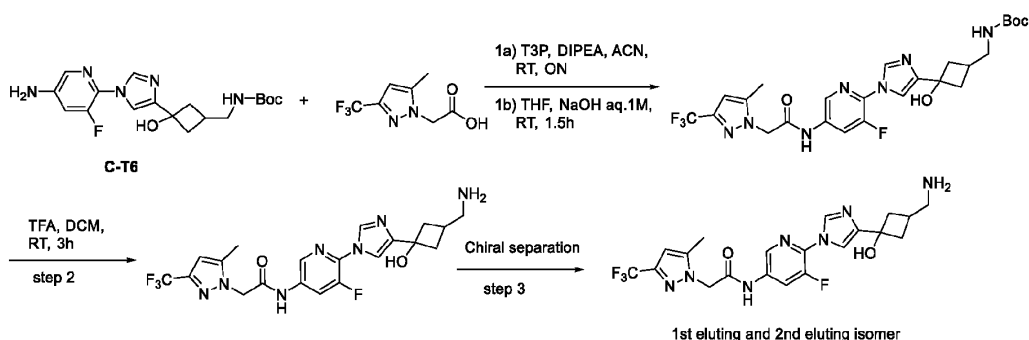


Step 1: A microwave vial was charged with Intermediate D-T5 (40 mg, 0.114 mmol), tBuXPhos Pd G3 (18.12 mg, 0.023 mmol), K₃PO₄ (72.6 mg, 0.342 mmol) and a solution of Intermediate B-M12 (30 mg, 0.116 mmol) in dry dioxane (1 ml) was added. The reaction mixture was degassed with argon and stirred at 100°C under inert atmosphere overnight. Further tBuXPhos Pd G3 (18.12 mg, 0.023 mmol) and K₃PO₄ (72.6 mg, 0.342 mmol) were added and stirring was continued at 100°C for 1 h. The reaction mixture was diluted with H₂O and DCM. Phases were separated and the aqueous layer was extracted with DCM (2x). The combined organic layers were dried using a phase separator and evaporated to give tert-butyl 3-(1-(3-fluoro-5-(2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamido)pyridin-2-yl)-1H-imidazol-4-yl)morpholine-4-carboxylate which was used in the following step without further purification. UPLC-MS-2: Rt = 1.20 min; MS m/z [M+H]⁺ 568.5.

Step 2: tert-Butyl 3-(1-(3-fluoro-5-(2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamido)pyridin-2-yl)-1H-imidazol-4-yl)morpholine-4-carboxylate (step 1, 124.6 mg, 0.068 mmol) was dissolved in DCM and TFA (0.264 ml, 3.42 mmol) was added. The reaction mixture was stirred at RT for 1 h. The reaction mixture was evaporated and the product was purified via RP-HPLC eluting with a

gradient of ACN (1-100%) in H₂O+7.3mM NH₄OH. Fractions containing the desired product were combined, frozen and lyophilized to give 2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(morpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide. ¹H NMR (600 MHz, DMSO-d₆) δ 10.95 (s, 1H), 8.48 (d, 1H), 8.28 (dd, 1H), 8.20 (d, 1H), 7.77 (t, 1H), 7.74 - 7.70 (m, 1H), 7.60 (s, 1H), 7.41 (t, 1H), 3.95 (s, 2H), 3.91 (dd, 1H), 3.86 (s, 1H), 3.73 (dt, 1H), 3.45 (ddd, 1H), 3.31 (s, 1H), 2.90 - 2.83 (m, 2H). UPLC-MS-2: Rt = 1.20 min; MS m/z [M+H]⁺ 468.3.

Example 25: N-(6-(4-(3-(Aminomethyl)-1-hydroxycyclobutyl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide, N-(6-(4-((1r,3r)-3-(Aminomethyl)-1-hydroxycyclobutyl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide and N-(6-(4-((1s,3s)-3-(Aminomethyl)-1-hydroxycyclobutyl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide



Step 1: To a solution of Intermediate C-T6 (121 mg, 317 μmol) in ACN (2.0 ml) were added 2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid [CAS No. 345637-71-0] (99.1 mg, 1.5 eq, 476 μmol), DIPEA (123 mg, 166 μl, 3 eq, 952 μmol) and T3P (50% in EtOAc) (404 mg, 375 μl, 2 eq, 635 μmol) and the reaction mixture was stirred at RT for 2 h. Further DIPEA (123 mg, 166 μl, 952 μmol) and T3P (50% in EtOAc) (404 mg, 375 μl, 635 μmol) were added and the reaction mixture was stirred overnight at RT. The reaction mixture was diluted with EtOAc, washed with an aqueous saturated solution of NaHCO₃. Phases were separated and the aqueous layer was extracted with EtOAc (2x). The combined organic layers were washed with brine, dried using a phase separator and evaporated. The crude material was dissolved in THF (2 ml) and NaOH 1M aqueous solution (0.04 g, 1 ml, 1 mmol) was added. The clear orange solution was stirred at RT for 1.5 h. The reaction mixture was diluted with EtOAc and an aqueous saturated solution of NH₄Cl. Phases were separated and the aqueous layer was extracted EtOAc (2x). The combined organic layers were washed with brine, dried using a phase separator and evaporated. The crude product was purified using silica gel column chromatography eluting with a gradient of MeOH (0-20%) in DCM. Fractions containing the desired product were combined and evaporated to give tert-butyl ((3-(1-(3-fluoro-5-(2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)pyridin-2-yl)-1H-imidazol-4-yl)-3-hydroxycyclobutyl)methyl)carbamate and mixture of isomers. ¹H NMR (600 MHz, DMSO-d₆) δ 11.07 (s, 1H), 8.47 (t, 1H), 8.26 (dt, 1H), 8.20 (q, 1H), 7.50 (dt, 1H), 6.85 (q, 1H), 6.57 (s, 1H),

5.39 (d, 1H), 5.18 (s, 2H), 3.04 - 2.97 (m, 2H), 2.45 - 2.40 (m, 1H), 2.31 (s, 3H), 2.26 - 2.06 (m, 2H), 1.94 - 1.88 (m, 1H), 1.37 (d, 9H). UPLC-MS-2: Rt = 1.04-1.05 min; MS m/z [M+H]⁺ 568.2.

Step 2: To a solution of tert-butyl ((3-(1-(3-fluoro-5-(2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)pyridin-2-yl)-1H-imidazol-4-yl)-3-hydroxycyclobutyl)methyl)carbamate (step 1,
5 156.9 mg, 276.5 μ mol) in DCM (1.50 ml) was added TFA (630.4 mg, 426.0 μ l, 5.529 mmol). The reaction mixture was stirred at RT for 3 h. The reaction mixture was co-evaporated with DCM (3x), dissolved in DCM (10 ml), neutralized with ammonia/MeOH to pH 8 and concentrated. The crude product was purified via reversed phase RP-HPLC-3: (mobile phase:

H₂O+0.1%NH₄OH/ACN 05:95 to 0:100). Fractions containing the desired product were

10 combined, frozen and lyophilized to give N-(6-(4-(3-(aminomethyl)-1-hydroxycyclobutyl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (racemic mixture). ¹H NMR (600 MHz, DMSO-d₆) δ 11.12 (Bs, 1H), 8.46 (d, 1H), 8.26 (dt, 1H), 8.22 - 8.17 (m, 1H), 7.55 - 7.44 (m, 1H), 6.73 (s, 0H), 6.57 (s, 1H), 5.42 - 5.36 (m, 1H), 5.18 (s, 2H), 3.03 (q, 1H), 2.63 (d, 1H), 2.57 - 2.53 (m, 1H), 2.46 - 2.41 (m, 1H), 2.31 (s, 3H), 2.24 - 2.09
15 (m, 2H), 1.96 - 1.86 (m, 1H). UPLC-MS-8: Rt = 0.53 min; MS m/z [M+H]⁺ 468.1.

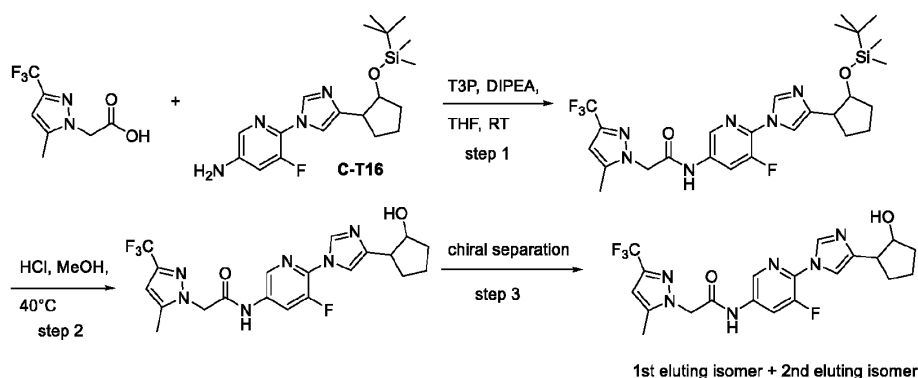
Step 3: N-(6-(4-((1r,3r)-3-(Aminomethyl)-1-hydroxycyclobutyl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide and N-(6-(4-((1s,3s)-3-(Aminomethyl)-1-hydroxycyclobutyl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide

20 The mixture of N-(6-(4-(3-(aminomethyl)-1-hydroxycyclobutyl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (step 2, 99.30 mg, 212 μ mol) was separated by chiral C-SFC-13 (mobile phase: CO₂/(MeOH+0.05%NH₃) 50/50) to give the 1st (Example 25a) and 2nd (Example 25b) eluting isomers.

Example 25a: 1st eluting isomer: ¹H NMR (600 MHz, DMSO-d₆) δ 8.46 (d, 1H), 8.26 (dd, 1H),
25 8.21 - 8.17 (m, 1H), 7.48 - 7.44 (m, 1H), 6.56 (s, 1H), 5.35 (d, 1H), 5.17 (s, 2H), 3.04 (t, 1H), 2.62 (d, 2H), 2.41 - 2.37 (m, 1H), 2.31 (s, 3H), 2.24 - 2.12 (m, 4H). UPLC-MS-8: Rt = 0.51 min; MS m/z [M+H]⁺ 468.4. C-SFC-5 CO₂/(MeOH+0.05%NH₃) 50/50): Rt = 1.05 min.

Example 25b: 2nd eluting isomer: ¹H NMR (600 MHz, DMSO-d₆) δ 8.47 (d, 1H), 8.26 (dd, 1H),
8.19 (t, 1H), 7.54 - 7.51 (m, 1H), 6.56 (s, 1H), 5.37 (s, 0H), 5.17 (s, 2H), 3.03 (t, 1H), 2.63 - 2.60
30 (m, 2H), 2.44 (d, 1H), 2.31 (s, 3H), 2.13 - 2.06 (m, 1H), 1.91 (dt, 2H). UPLC-MS-8: Rt = 0.51 min; MS m/z [M+H]⁺ 468.4. C-SFC-5 (mobile phase: CO₂/(MeOH+0.05%NH₃) 50/50): Rt = 2.90 min.

Example 26: N-(5-Fluoro-6-(4-(2-hydroxycyclopentyl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide and N-(5-fluoro-6-(4-((1S,(2R or 2S))-2-hydroxycyclopentyl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide
35



Step 1: 2-(5-Methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid [CAS No. 345637-71-0]

(121.6 mg, 0.584 mmol), T3P (50% in EtOAc) (0.474 ml, 0.797 mmol) and DIPEA (0.278 ml, 1.593 mmol) were added to a solution of Intermediate C-T14 (200 mg, 0.531 mmol) in THF (6.8 ml) at RT. After 2.5 h, the reaction mixture was diluted with EtOAc and washed with sat. aq. NaHCO₃ and sat. aq. NH₄Cl. The organic layer was dried (phase separator) and concentrated under reduced pressure and the residue was purified by normal phase chromatography (eluent : DCM:MeOH 9:1 / DCM from 0:100 to 45:55) to give N-(6-(4-(2-((tert-butyl)dimethylsilyl)oxy)cyclopentyl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide. UPLC-MS-8: Rt = 1.64 min; MS m/z [M+H]⁺ 567.4.

Step 2: A solution of N-(6-(4-(2-((tert-butyl)dimethylsilyl)oxy)cyclopentyl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (step 1, 196 mg, 345.9 μmol) and HCl (1.25M/MeOH) (30.3 mg, 0.664 ml, 830.1 μmol) in MeOH (3.3 ml) was stirred at 40°C for 7 h. An aqueous saturated solution of NaHCO₃ was added to the reaction mixture, extracted with EtOAc (2x) and washed with brine. The combined organic layers were dried using a phase separator and evaporated under reduced pressure. The residue was purified by normal phase chromatography (eluent : DCM:MeOH 9:1 / DCM from 0:100 to 90:10) to give N-(5-fluoro-6-(4-(2-hydroxycyclopentyl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.05 (s, 1H), 8.49 – 8.44 (m, 1H), 8.25 (dd, 1H), 8.19 – 8.13 (m, 1H), 7.47 (s, 1H), 6.56 (s, 1H), 5.17 (s, 2H), 4.64 (d, 1H), 4.11 (q, 1H), 2.90 – 2.81 (m, 1H), 2.31 (s, 3H), 2.07 – 1.96 (m, 1H), 1.92 – 1.80 (m, 1H), 1.79 – 1.59 (m, 3H), 1.57 – 1.45 (m, 1H). UPLC-MS-8: Rt = 0.86 min; MS m/z [M+H]⁺ 453.0.

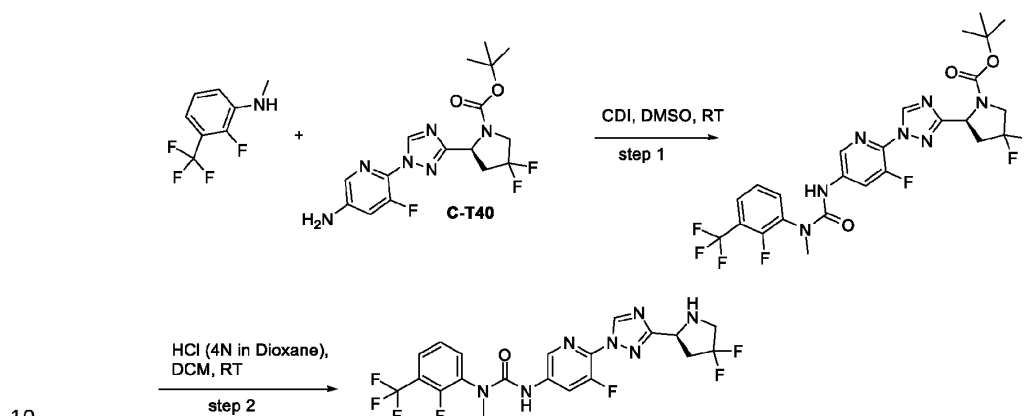
Step 3: The enantiomers of N-(5-fluoro-6-(4-(2-hydroxycyclopentyl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (trans according to NMR) (step 2, 140 mg) were separated by C-SFC-28 (mobile phase: CO₂/(MeOH+0.05%NH₃) 65/35).

Example 26a: 1st eluting isomer: ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.08 (s, 1H), 8.48 – 8.43 (m, 1H), 8.25 (dd, 1H), 8.18 – 8.13 (m, 1H), 7.47 (s, 1H), 6.56 (s, 1H), 5.17 (s, 2H), 4.63 (d, 1H), 4.10 (q, 1H), 2.90 – 2.81 (m, 1H), 2.31 (s, 3H), 2.09 – 1.94 (m, 1H), 1.93 – 1.80 (m, 1H), 1.80 –

1.58 (m, 3H), 1.58 – 1.45 (m, 1H). UPLC-MS-8: Rt = 0.87 min; MS m/z [M+H]⁺ 453.3. C-SFC-15 (mobile phase: CO₂/(MeOH+0.05%NH₃) 75/25): Rt = 2.96 min.

Example 26b: 2nd eluting isomer: ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.07 (s, 1H), 8.48 – 8.43 (m, 1H), 8.25 (dd, 1H), 8.18 – 8.13 (m, 1H), 7.47 (s, 1H), 6.56 (s, 1H), 5.17 (s, 2H), 4.64 (d, 1H), 4.10 (q, 1H), 2.89 – 2.83 (m, 1H), 2.31 (s, 3H), 2.09 – 1.96 (m, 1H), 1.93 – 1.80 (m, 1H), 1.80 – 1.58 (m, 3H), 1.58 – 1.43 (m, 1H). UPLC-MS-8: Rt = 0.87 min; MS m/z [M+H]⁺ 453.3. C-SFC-15 (mobile phase: CO₂/(MeOH+0.05%NH₃) 75/25): Rt = 4.05 min.

Example 27: (S)-3-(6-(3-(4,4-Difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-1-(2-fluoro-3-(trifluoromethyl)phenyl)-1-methylurea

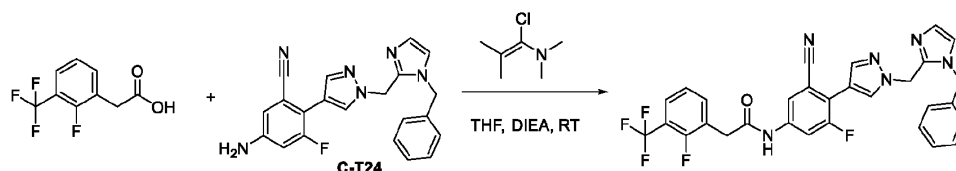


Step 1: To a solution of 2-fluoro-N-methyl-3-(trifluoromethyl)aniline [CAS No. 1261808-48-3] (226 mg, 40% wt, 0.468 mmol) and CDI (253 mg, 1.561 mmol) in DMSO (5 ml) was added Intermediate C-T40 (150 mg, 0.390 mmol) at RT. After 5 d, the reaction mixture was diluted with H₂O and extracted with TBME. The organic layer was dried (phase separator) and concentrated under reduced pressure and the residue was purified by normal phase chromatography (eluent : EtOAc/cyclohexane 15:85 to 100:0) to give tert-butyl (S)-4,4-difluoro-2-(1-(3-fluoro-5-(3-(2-fluoro-3-(trifluoromethyl)phenyl)-3-methylureido)pyridin-2-yl)-1H-1,2,4-triazol-3-yl)pyrrolidine-1-carboxylate. UPLC-MS-8: Rt = 1.23 min; MS m/z [M+H]⁺ 604.2.

Step 2: A solution of tert-butyl (S)-4,4-difluoro-2-(1-(3-fluoro-5-(3-(2-fluoro-3-(trifluoromethyl)phenyl)-3-methylureido)pyridin-2-yl)-1H-1,2,4-triazol-3-yl)pyrrolidine-1-carboxylate (step 1, 102 mg, 169 μmol) and HCl (4M/dioxane) (61.6 mg, 0.422 ml, 1.69 mmol) in DCM (5 ml) was stirred at RT for 5 h. The reaction mixture was evaporated to dryness. The residue was dissolved in H₂O and the aqueous layer was basified with an aqueous saturated solution of NaHCO₃ then extracted with DCM (2x). The combined organic layers were dried using a phase separator and evaporated. The residue was purified by normal phase chromatography (eluent : DCM/MeOH 95:5 to 70:30) to give (S)-3-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-1-(2-fluoro-3-(trifluoromethyl)phenyl)-1-methylurea. ¹H NMR (600 MHz, DMSO-*d*₆) δ ppm 1.40 (br s, 1 H) 2.53 – 2.59 (m, 1 H) 2.61 – 2.71 (m, 1 H)

3.12 – 3.20 (m, 1 H) 3.40 – 3.52 (m, 1 H) 4.51 (br t, 1 H) 7.50 (br t, 1 H) 7.78 (br s, 1 H) 7.88 (br s, 1 H) 8.18 (br d, 1 H) 8.47 (br s, 1 H) 9.03 (br s, 1 H) 9.23 (br s, 1 H). UPLC-MS-8: Rt = 0.92 min; MS m/z [M+H]⁺ 504.0.

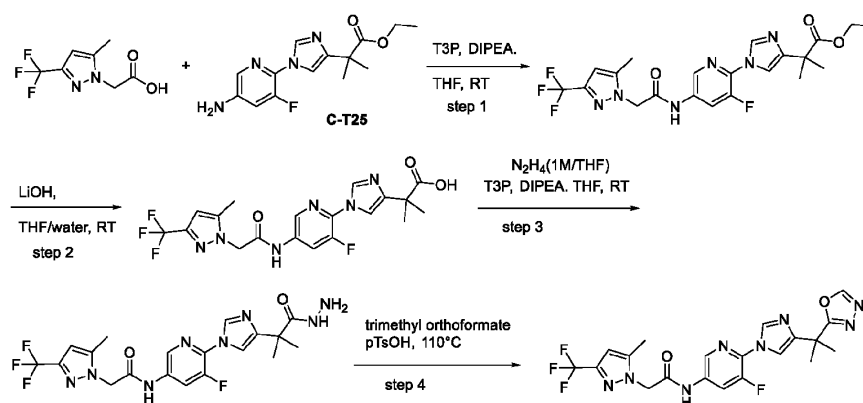
Example 28: N-(4-(1-((1-Benzyl-1H-imidazol-2-yl)methyl)-1H-pyrazol-4-yl)-3-cyano-5-fluorophenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide



To a solution of 2-(2-fluoro-3-(trifluoromethyl)phenyl)acetic acid [CAS No. 194943-83-4] (184 mg, 0.829 mmol) in THF (1.5 ml) was added 1-chloro-N,N,2-trimethylprop-1-en-1-amine [CAS No. 26189-59-3] (0.219 ml, 1.658 mmol) and the reaction mixture was stirred for 30 min at RT under argon. The mixture was then added to a suspension of Intermediate C-T24 (190 mg, 0.332 mmol) and DIPEA (0.174 ml, 0.995 mmol) in THF (1.5 ml) and continued to stir for 45 min at RT under argon. The reaction was quenched with H₂O and extracted with EtOAc (2x) and the combined organic layers were washed with brine, dried using a SPE phase separator cartridge and evaporated. The crude product was purified by RP-HPLC-2 (mobile phase:

ACN/(H₂O+0.1%NH₄OH) 5/95 to 100/0) to give N-(4-(1-((1-benzyl-1H-imidazol-2-yl)methyl)-1H-pyrazol-4-yl)-3-cyano-5-fluorophenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide. ¹H NMR (600 MHz, DMSO-*d*₆) δ 10.83 (s, 1H), 8.12 (s, 1H), 7.87 – 7.82 (m, 3H), 7.78 – 7.69 (m, 2H), 7.40 (t, 1H), 7.32 – 7.26 (m, 2H), 7.26 – 7.21 (m, 1H), 7.19 (d, 1H), 7.11 – 7.06 (m, 2H), 6.92 (d, 1H), 5.52 (s, 2H), 5.33 (s, 2H), 3.92 (s, 2H). UPLC-MS-2: Rt = 1.08 min; MS m/z [M+H]⁺ 577.3.

Example 29: N-(6-(4-(2-(1,3,4-Oxadiazol-2-yl)propan-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide



Step 1: To a solution of Intermediate C-T25 (120 mg, 411 μmol) in THF (1.5 ml) was added 2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid [CAS No. 345637-71-0] (94.0 mg, 452 μmol), T3P (196 mg, 182 μl, 616 μmol) and DIPEA (159 mg, 215 μl, 1.23 mmol). The reaction

mixture was stirred at RT for 84 h. The reaction mixture was diluted with 20 ml of DCM and then washed with 10 ml of a saturated aqueous NaHCO₃ and NH₄Cl solution. The organic phase was dried (phase separator) and concentrated under vacuum. The residue was purified by normal phase chromatography (eluent: cyclohexane/EtOAc 100:0 to 0:100 in 7 min, then 100% EtOAc for 10 min) to give ethyl 2-(1-(3-fluoro-5-(2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)pyridin-2-yl)-1H-imidazol-4-yl)-2-methylpropanoate. UPLC-MS-2: Rt = 1.12 min; MS m/z [M+H]⁺ 483.3.

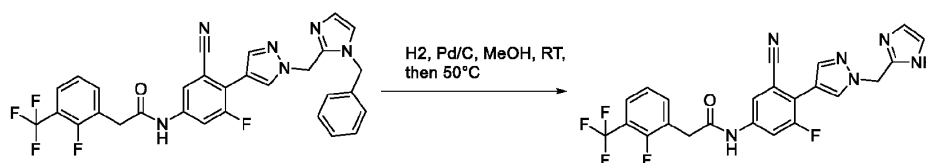
Step 2: To a solution of ethyl 2-(1-(3-fluoro-5-(2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)pyridin-2-yl)-1H-imidazol-4-yl)-2-methylpropanoate (step 1, 180 mg, 373 μmol) in THF (1 ml) and H₂O (0.2 ml) was added LiOH.H₂O (78.3 mg, 1.87 mmol). The reaction mixture was stirred at RT for 18 h. The reaction mixture was diluted with H₂O and carefully neutralized through dropwise addition of 4M aq. HCl to adjust the mixture to pH 5-6. The crude reaction mixture was extracted twice with a DCM/MeOH (v/v 9:1) mixture. The combined organic phases were dried (phase separator) and concentrated under vacuum to give crude 2-(1-(3-fluoro-5-(2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)pyridin-2-yl)-1H-imidazol-4-yl)-2-methylpropanoic acid which was used without further purification in the next step. UPLC-MS-2: Rt = 0.88 min; MS m/z [M+H]⁺ 455.3.

Step 3: To a solution of 2-(1-(3-fluoro-5-(2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)pyridin-2-yl)-1H-imidazol-4-yl)-2-methylpropanoic acid (step 2, 115 mg, 253 μmol) in THF (1 ml) was added hydrazine (1M/THF) (24.3 mg, 759 μl, 759 μmol), T3P (242 mg, 225 μl, 759 μmol) and DIPEA (164 mg, 220 μl, 1.27 mmol). The reaction mixture was stirred at RT for 18 h. Additional hydrazine (24.3 mg, 759 μl, 1 molar, 759 μmol), DIEA (164 mg, 220 μl, 1.27 mmol) and T3P (242 mg, 225 μl, 759 μmol) was added and the stirring at RT was continued for additional 60 h. The last reagent addition was repeated once and the stirring at RT was continued for additional 18 h to complete the reaction. The reaction mixture was diluted with 10 ml of DCM and then washed with 5 ml of H₂O. The organic phase was dried (phase separator) and concentrated under vacuum. The residue was purified by normal phase chromatography (eluent: DCM/MeOH 100:0 to 90:10 in 12 min, then isocratic 90:10 for 10 min) to give N-(5-fluoro-6-(4-(1-hydrazineyl-2-methyl-1-oxopropan-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide. UPLC-MS-2: Rt = 0.78 min; MS m/z [M+H]⁺ 469.3.

Step 4: To a solution of N-(5-fluoro-6-(4-(1-hydrazineyl-2-methyl-1-oxopropan-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (step 3, 15 mg, 32 μmol) in trimethyl orthoformate (0.34 g, 0.35 ml, 3.2 mmol) was added p-TsOH (0.91 mg, 4.8 μmol). The reaction mixture was stirred at 110°C for 6 h. The crude mixture was directly purified by RP-HPLC-2 (mobile phase: ACN/(H₂O+0.1%NH₄OH) 5/95 to 100/0). The pure fractions were combined and volatiles were removed under reduced pressure, followed by freeze-drying

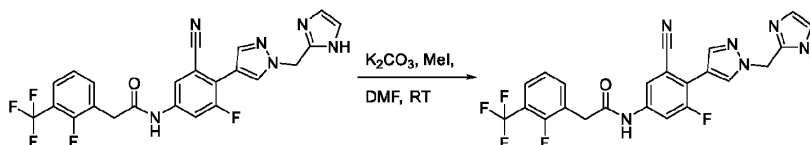
overnight to give N-(6-(4-(2-(1,3,4-oxadiazol-2-yl)propan-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide. ¹H NMR (600 MHz, DMSO-*d*₆) δ 11.08 (s, 1H), 9.12 (s, 1H), 8.47 (d, 1H), 8.27 (dd, 1H), 8.18 (s, 1H), 7.66 (s, 1H), 6.57 (s, 1H), 5.18 (s, 2H), 2.31 (s, 3H), 1.75 (s, 6H). UPLC-MS-2: Rt = 0.89 min; MS m/z [M+H]⁺ 479.3.

- 5 **Example 30:** N-(4-(1-((1H-imidazol-2-yl)methyl)-1H-pyrazol-4-yl)-3-cyano-5-fluorophenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide



- To a solution of N-(4-(1-((1-benzyl-1H-imidazol-2-yl)methyl)-1H-pyrazol-4-yl)-3-cyano-5-fluorophenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide (Example 28, 170 mg, 0.295 mmol) in MeOH (2.5 ml) and DCM (2.5 ml) was added Pd-C (10%) (31.4 mg, 0.295 mmol). The reaction mixture was heated at 50°C for 18 h. The reaction mixture was filtered through Celite® and rinsed with MeOH. The solvent was removed under reduced pressure and the crude mixture was purified by RP-HPLC-2 (mobile phase: ACN/(H₂O+0.1%NH₄OH) 5/95 to 100/0). The pure fractions were combined and volatiles were removed under reduced pressure, followed by freeze-drying overnight to give N-(4-(1-((1H-imidazol-2-yl)methyl)-1H-pyrazol-4-yl)-3-cyano-5-fluorophenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide. ¹H NMR (600 MHz, DMSO-*d*₆) δ 12.24 (s, 1H), 10.83 (s, 1H), 8.21 (s, 1H), 7.89 - 7.83 (m, 3H), 7.78 - 7.70 (m, 2H), 7.40 (t, 1H), 7.11 (s, 1H), 6.87 (s, 1H), 5.41 (s, 2H), 3.92 (s, 2H). UPLC-MS-2: Rt = 0.85 min; MS m/z [M+H]⁺ 487.2.

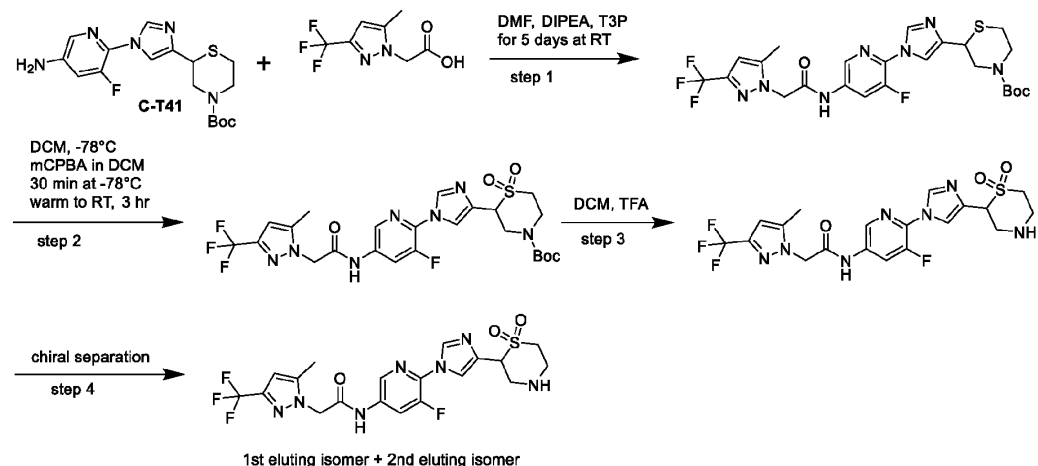
- 20 **Example 31:** N-(3-Cyano-5-fluoro-4-(1-((1-methyl-1H-imidazol-2-yl)methyl)-1H-pyrazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide



- To a solution of N-(4-(1-((1H-imidazol-2-yl)methyl)-1H-pyrazol-4-yl)-3-cyano-5-fluorophenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide (Example 30, 70 mg, 0.130 mmol) in DMF (1 ml) was added K₂CO₃ (35.8 mg, 0.259 mmol) and MeI (0.016 ml, 0.259 mmol). The reaction mixture was stirred at RT for 18 h. The reaction mixture was diluted with EtOAc and then washed with 3ml of H₂O. The organic phase was dried (phase separator) and concentrated under vacuum. The residue was purified by normal phase chromatography (eluent: DCM/MeOH 100:0 to 95:5 in 15 min, then isocratic 95:5 for 5 min) and then RP-HPLC-4 (mobile phase: (H₂O+0.1%TFA)/(ACN+0.1%TFA) 73/27 to 53/47). The pure fractions were combined and volatiles were removed under reduced pressure, followed by freeze-drying overnight to give N-(3-cyano-5-fluoro-4-(1-((1-methyl-1H-imidazol-2-yl)methyl)-1H-pyrazol-4-yl)phenyl)-2-(2-fluoro-

3-(trifluoromethyl)phenyl)acetamide. ¹H NMR (600 MHz, DMSO-d₆) δ 10.90 (s, 1H), 8.44 (s, 1H), 7.95 (s, 1H), 7.91 - 7.86 (m, 2H), 7.78 - 7.70 (m, 2H), 7.63 (s, 1H), 7.55 (s, 1H), 7.41 (t, 1H), 5.82 (s, 2H), 3.93 (s, 2H), 3.84 (s, 3H). UPLC-MS-2: Rt = 0.85 min; MS m/z [M+H]⁺ 501.4.

Example 32: N-(6-(4-(1,1-Dioxidothiomorpholin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide



Step 1: Intermediate C-T41 (320.0 mg, 90% wt, 1 eq, 759.0 μmol) was dissolved in 6 ml THF and 2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid [CAS No. 345637-71-0] (189.6 mg, 1.2 eq, 910.8 μmol), DIPEA (588.6 mg, 793 μl, 6.0 eq, 4.554 mmol) and T3P (50% in EtOAc) (1.207 g, 1.123 ml, 2.5 eq, 1.897 mmol) were added to the mixture, which was stirred overnight at RT. Then T3P (50% in EtOAc) (241.5 mg, 224.6 μl, 0.5 eq, 379.5 μmol) was added to the mixture and stirring was continued for another 5 d. After that the reaction mixture was quenched with sat. aq. NaHCO₃ and extracted with EtOAc (2X). The combined organic phases were washed with brine and concentrated in vacuo. The residue was purified by chromatography on silica gel (cyclohexane/EtOAc) followed by RP-HPLC eluting with a gradient of ACN (5-100%) in H₂O+0.2% HCOOH to give tert-butyl 2-(1-(3-fluoro-5-(2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)pyridin-2-yl)-1H-imidazol-4-yl)thiomorpholine-4-carboxylate. ¹H NMR (600 MHz, DMSO-d₆) δ 11.10 (s, 1H), 8.47 (d, 1H), 8.27 (dd, 2H), 7.68 (s, 1H), 6.57 (s, 1H), 5.18 (s, 2H), 4.20 (d, 1H), 3.96 (dd, 2H), 3.59 (s, 1H), 3.27 (s, 2H), 2.78 - 2.63 (m, 2H), 2.31 (s, 3H), 1.39 (s, 9H). UPLC-MS-8: Rt = 1.25 min; MS m/z [M+H]⁺ = 570.3.

Step 2: A solution of mCPBA (289.1 mg, 70% wt, 3.5 eq., 1.173 mmol) in 5 ml of DCM was slowly added to a cooled (to -78°C) solution of tert-butyl 2-(1-(3-fluoro-5-(2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)pyridin-2-yl)-1H-imidazol-4-yl)thiomorpholine-4-carboxylate (step 1, 200.9 mg, 95% wt, 1 eq, 335.1 μmol) in 10 ml DCM. The reaction mixture was stirred for 30 min at -78°C, then warmed to 24°C and stirred for 3 h. After that, the reaction mixture was quenched by addition of Na₂S₂O₃·5H₂O (aq) and sat. aq. NaHCO₃, then extracted with EtOAc (2x). The combined organic phases were washed with brine, filter dried and

concentrated in vacuo. The residue was purified by chromatography on silica gel (cyclohexane/EtOAc) to give tert-butyl 2-(1-(3-fluoro-5-(2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)pyridin-2-yl)-1H-imidazol-4-yl)thiomorpholine-4-carboxylate 1,1-dioxide. ¹H NMR (600 MHz, DMSO-d₆) δ 11.12 (s, 1H), 8.49 (d, 1H), 8.29 (d, 2H), 7.81 (s, 1H), 6.57 (s, 1H), 5.19 (s, 2H), 4.56 (s, 1H), 4.20 (d, 2H), 3.73 (d, 4H), 2.31 (s, 3H), 1.39 (d, 9H). UPLC-MS-8: Rt = 1.04 min; MS m/z [M+H]⁺ = 602.

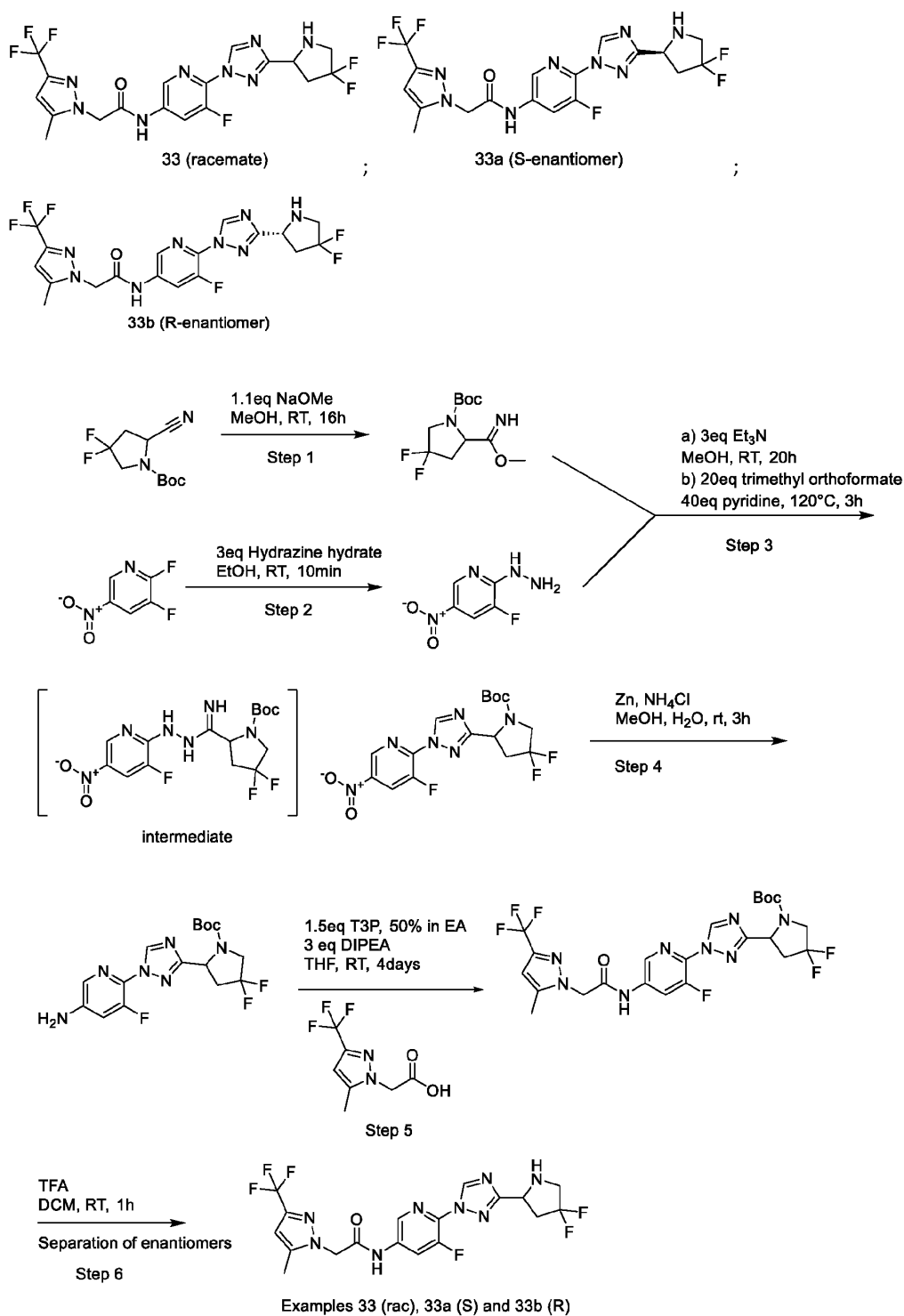
Step 3: tert-Butyl 2-(1-(3-fluoro-5-(2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)pyridin-2-yl)-1H-imidazol-4-yl)thiomorpholine-4-carboxylate 1,1-dioxide (step 2, 150.2 mg, 99% wt, 1 eq., 247.2 μmol) was dissolved in 5 ml DCM and put under argon, then treated with TFA (704.6 mg, 476.1 μl, 25 eq, 6.179 mmol). The reaction mixture was stirred overnight at RT. Then DCM was added, followed by the addition of sat. aq. NaHCO₃. The mixture was extracted with DCM (2x). The combined organic layers were filter dried and concentrated in vacuo to give N-(6-(4-(1,1-dioxidothiomorpholin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide as a racemic mixture. UPLC-MS-8: Rt = 0.60 min; MS m/z [M+H]⁺ = 502.

Step 4: The enantiomers of N-(6-(4-(1,1-dioxidothiomorpholin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (racemic mixture) (step 3, 124 mg, 0.247 mmol) were separated by C-SFC-22 (mobile phase: CO₂/(MeOH+0.05%NH₃) (65:35)). (R or S)-N-(6-(4-(1,1-dioxidothiomorpholin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide.

Example 32a: (R or S)-N-(6-(4-(1,1-Dioxidothiomorpholin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide 1st eluting isomer: C-SFC-14 (mobile phase: CO₂/(MeOH+0.05%NH₃) 65:35): Rt = 2.29 min.

Example 32b: (R or S)-N-(6-(4-(1,1-Dioxidothiomorpholin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide 2nd eluting isomer: ¹H-NMR (600 MHz, DMSO-d₆) δ 11.16 (s, 1H), 8.49 (d, 1H), 8.32 – 8.18 (m, 2H), 7.78 (s, 1H), 6.57 (s, 1H), 5.18 (s, 2H), 4.30 (dd, 1H), 3.43 (d, 1H), 3.31 – 3.26 (m, 1H), 3.24 – 3.13 (m, 2H), 3.12 – 3.03 (m, 2H), 2.31 (s, 3H). UPLC-MS-8: Rt = 0.59 min; MS m/z [M+H]⁺ = 502. C-SFC-14 (mobile phase: CO₂/(MeOH+0.05%NH₃) 65:35): Rt = 3.12 min.

Example 33: N-(6-(3-(4,4-Difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide, (S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide and (R)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide



5 Step 1: Sodium methoxide (25% in MeOH) (863.4 mg, 914 μ l, 1.11 Eq, 3.996 mmol)

was diluted with MeOH (5 ml) under Ar. A solution of tert-butyl 2-cyano-4,4-difluoropyrrolidine-1-carboxylate (880.0 mg, 95% Wt, 1 Eq, 3.600 mmol) in MeOH (5 ml) was added under stirring to give a brown solution which was stirred for 16 h at RT. Then 0.5 ml sat. NH_4Cl solution and DCM were added. The aqueous layer was brought to pH 6 by addition of 1N HCl and extracted with DCM (3x). The combined org. layers were washed with brine, dried (Na_2SO_4) and concentrated in vacuo to give tert-butyl 4,4-difluoro-2-(imino(methoxy)methyl)pyrrolidine-1-carboxylate which was used in the next step without further purification.

Step 2: A solution of 2,3-difluoro-5-nitropyridine (1000 mg, 1 Eq, 6.247 mmol) in EtOH (5 ml) was added to a solution of hydrazine hydrate (1.201 g, 1.167 ml, 50% Wt, 3 Eq, 18.74 mmol) in EtOH (15 ml), under Ar to turn immediately into a brown solution. After 30 min of stirring at RT, the reaction mixture was diluted with DCM, dried (Na_2SO_4) and concentrated in vacuo to give a brown solid to which 3 ml of IPA were added. This mixture was sonicated until a fine black-brown precipitate had formed that was filtered and washed with minimal amounts of IPA. The precipitate was dried under high vacuum to give 3-fluoro-2-hydrazineyl-5-nitropyridine. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ 9.60 (s, 1H), 8.84 (d, 1H), 8.12 - 8.03 (m, 1H), 4.81 (s, 2H). UPLC-MS-2: $[\text{M}+\text{H}]^+ = 173.2$, $\text{Rt} = 0.25$ min.

Step 3: To a solution of tert-butyl 4,4-difluoro-2-(imino(methoxy)methyl)pyrrolidine-1-carboxylate (step 1) (1.001 g, 95% Wt, 1 Eq, 3.600 mmol) in MeOH (30 ml) was added Et_3N (1.093 g, 1.51 ml, 3 Eq, 10.80 mmol) and then 3-fluoro-2-hydrazineyl-5-nitropyridine (step 2) (657.2 mg, 99% Wt, 1.05 Eq, 3.780 mmol). The resulting mixture was stirred for 4 d. LCMS showed the presence of the likely intermediate (tert-butyl 4,4-difluoro-2-((2-(3-fluoro-5-nitropyridin-2-yl)hydrazineyl)(imino)methyl)pyrrolidine-1-carboxylate) at $\text{Rt} = 0.55$ min. The mixture was concentrated to dryness, then dissolved in pyridine (11.4 g, 11.6 ml, 40 Eq, 144.0 mmol) and trimethyl orthoformate (7.641 g, 7.88 ml, 20 Eq, 72.00 mmol) was added. This mixture was heated to 120°C and stirred for 3 h, then for another 16 h at 80°C . The reaction mixture was concentrated in vacuo to afford an oily residue which was dissolved in DCM. The DCM solution was washed with H_2O (3x) and brine. The org. phase was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (cyclohexane/EtOAc) to give tert-butyl 4,4-difluoro-2-(1-(3-fluoro-5-nitropyridin-2-yl)-1H-1,2,4-triazol-3-yl)pyrrolidine-1-carboxylate. UPLC-MS-2: $[\text{M}+\text{Na}]^+ = 437$, $\text{Rt} = 0.92$ min.

Step 4: To a solution of tert-butyl 4,4-difluoro-2-(1-(3-fluoro-5-nitropyridin-2-yl)-1H-1,2,4-triazol-3-yl)pyrrolidine-1-carboxylate (step 3, 230.0 mg, 1 Eq, 555.1 μmol) in MeOH (25 ml) and H_2O (5 ml) was added zinc powder (181.5 mg, 5 Eq, 2.775 mmol) and ammonium chloride (148.5 mg, 5 Eq, 2.775 mmol). The mixture was sonicated at RT for 5 min, then stirred at RT for 3 h. After that, the reaction mixture was diluted with MeOH and filtered. The filtrate was concentrated in vacuo. The residue was dissolved in 95:5 DCM/MeOH and washed with brine. The org. layer was filtered through phase separator SPE cartridge and concentrated in vacuo to give tert-butyl

2-(1-(5-amino-3-fluoropyridin-2-yl)-1H-1,2,4-triazol-3-yl)-4,4-difluoropyrrolidine-1-carboxylate which was used in the next step without further purification. UPLC-MS-2: $[M-H]^- = 383.4$, $R_t = 0.75$ min.

Step 5: 2-(5-Methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid (123.5 mg, 95% Wt, 1.2 Eq, 563.5 μmol) and tert-butyl 2-(1-(5-amino-3-fluoropyridin-2-yl)-1H-1,2,4-triazol-3-yl)-4,4-difluoropyrrolidine-1-carboxylate (step 4, 190.0 mg, 95% Wt, 1 Eq, 469.6 μmol) were dissolved in THF (20 ml). DIPEA (182.1 mg, 245 μl , 3 Eq, 1.409 mmol) and T3P (50% in EtOAc) (448.3 mg, 419.3 μl , 1.5 Eq, 704.4 μmol) were added to give a brown solution which was stirred at RT for 4 d. The reaction was quenched by addition of H_2O , diluted with EtOAc, washed with sat. NaHCO_3 , H_2O (3x) and brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified on silica gel [cyclohexane/(TBME/EtOH(3:1))] to afford tert-butyl 4,4-difluoro-2-(1-(3-fluoro-5-(2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)pyridin-2-yl)-1H-1,2,4-triazol-3-yl)pyrrolidine-1-carboxylate. UPLC-MS-2: $[M+H]^+ = 575.4$, $R_t = 1.14$ min.

Step 6: tert-Butyl 4,4-difluoro-2-(1-(3-fluoro-5-(2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)pyridin-2-yl)-1H-1,2,4-triazol-3-yl)pyrrolidine-1-carboxylate (step 5, 92.00 mg, 95% Wt, 1 Eq, 152.1 μmol) was dissolved in DCM (2 ml). TFA (1.480 g, 1 ml, 85.32 Eq, 12.98 mmol) was added and the mixture was stirred for 2 h at RT. Then the reaction mixture was concentrated dried in vacuo. The residue was dissolved in DCM, and the solution was washed with sat. NaHCO_3 solution. The org. layer was filtered over a phase separator SPE cartridge and concentrated in vacuo to give N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (racemic mixture).

The enantiomers of N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (racemic mixture) (72 mg, 0.15 mmol) were separated by C-SFC-36 (mobile phase: $\text{CO}_2/\text{MeOH}+0.05\%\text{NH}_3$ (70:30)).

Example 33a: (S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide 1st eluting isomer: ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ 11.18 (s, 1H), 9.08 (s, 1H), 8.52 (d, 1H), 8.30 (dd, 1H), 6.57 (s, 1H), 5.20 (s, 2H), 4.51 (t, 1H), 3.33 (s, 1H), 3.16 (q, 1H), 2.66 (ddt, 1H), 2.58 - 2.53 (m, 1H), 2.32 (s, 3H). UPLC-MS-2: $[M+H]^+ = 475.2$, $R_t = 0.69$ min. C-SFC-15 (mobile phase: $\text{CO}_2/(\text{MeOH}+0.05\%\text{NH}_3)$ 70:30): $R_t = 1.89$ min. (99.5% ee).

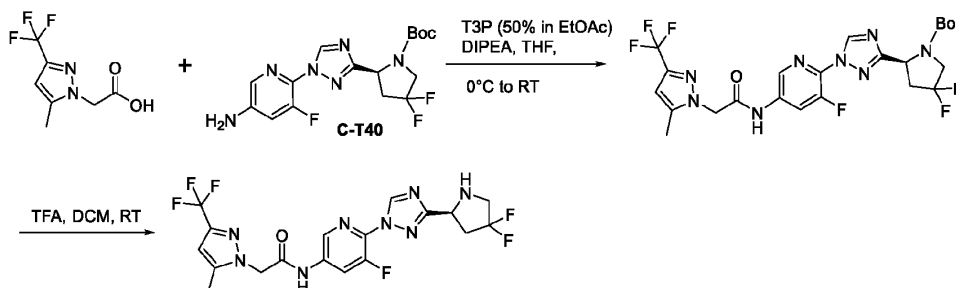
Single-compound crystal X-ray analysis confirmed S-configuration at the chiral center, i.e.

Example 33a = (S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide.

Example 33b: (R)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide 2nd eluting isomer: ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ 11.18 (s, 1H), 9.08 (s, 1H), 8.52 (d, 1H), 8.31 (dd, 1H), 6.57 (s, 1H), 5.20 (s, 2H),

4.51 (q, 1H), 3.33 (s, 1H), 3.23 - 3.09 (m, 1H), 2.75 - 2.57 (m, 2H), 2.32 (s, 3H). UPLC-MS-2: $[M+H]^+ = 475.2$, $R_t = 0.70$ min. C-SFC-15 (mobile phase: $CO_2/(MeOH+0.05\%NH_3)$ 70:30): $R_t = 2.80$ min.

- 5 Alternatively, (S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (Example 33a) was prepared from chiral starting material, Intermediate C-T40, as described below:

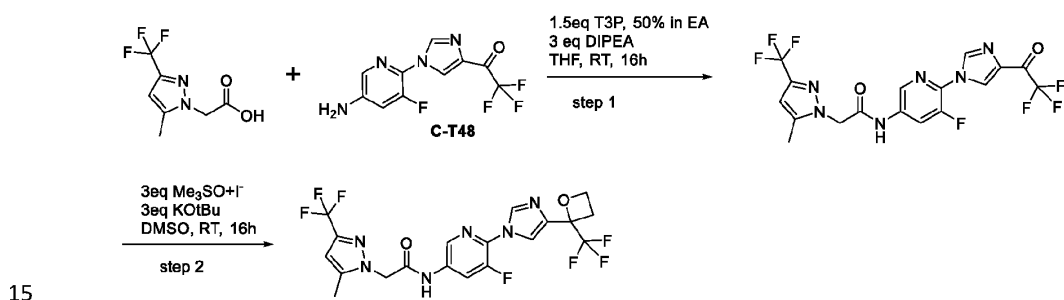


- Step 1:** 2-(5-Methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid [CAS No. 345637-71-0] (2.111 g, 95% wt, 1.10 eq, 9.633 mmol) and tert-butyl (S)-2-(1-(5-amino-3-fluoropyridin-2-yl)-1H-1,2,4-triazol-3-yl)-4,4-difluoropyrrolidine-1-carboxylate (Intermediate C-T40, 3.400 g, 99% wt, 1 eq, 8.757 mmol) were dissolved in 100 ml THF. The solution was cooled in an ice bath and DIPEA (3.396 g, 4.58 ml, 3 eq, 26.27 mmol) was added, followed by slow addition of T3P (50% in EtOAc) (8.359 g, 7.820 ml, 1.5 eq, 13.14 mmol). The cooling bath was removed, and the reaction mixture was stirred at RT for 1 h. After that, the reaction mixture was diluted with EtOAc (400 ml) and H_2O (50 ml) was added under stirring. The phases were separated, and the organic phase was washed with 10% citric acid (2x), H_2O , sat. $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated in vacuo to give a foam. This material was dissolved in TBME (15 ml), and this solution was added dropwise to heptane (200 ml) while treating with ultrasound.
- 20 The precipitate that formed during this procedure was filtered off, washed with heptane, and dried under HV to give tert-butyl (S)-4,4-difluoro-2-(1-(3-fluoro-5-(2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)pyridin-2-yl)-1H-1,2,4-triazol-3-yl)pyrrolidine-1-carboxylate. 1H NMR (600 MHz, $DMSO-d_6$) δ 11.20 (s, 1H), 9.08 (s, 1H), 8.53 (d, 1H), 8.30 (dd, 1H), 6.57 (s, 1H), 5.20 (s, 2H), 5.17 (s, 1H), 3.92 (s, 1H), 3.90 - 3.79 (m, 1H), 3.09 - 2.98 (m, 1H), 2.53 (s, 1H),
- 25 2.32 (d, 3H), 1.44 - 1.14 (m, 9H). UPLC-MS-8: $R_t = 1.19$ min; MS m/z $[M+H]^+ = 575.3$.

- Step 2:** tert-Butyl (S)-4,4-difluoro-2-(1-(3-fluoro-5-(2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)pyridin-2-yl)-1H-1,2,4-triazol-3-yl)pyrrolidine-1-carboxylate (step 1, 4.890 g, 95% wt, 1 eq, 8.086 mmol) was dissolved in 20 ml DCM and under stirring TFA (8.880 g, 6.0 ml, 9.631 eq, 77.88 mmol) was added and the solution was stirred for 3 h at RT, after which more
- 30 TFA (4.440 g, 3.0 ml, 4.816 eq, 38.94 mmol) was added with stirring continued for another 1 h at RT. Then the reaction mixture was concentrated in vacuo, toluene was added, followed by concentration in vacuo, then EtOAc/toluene 3:1 was added followed by concentration in vacuo.

The residue was dissolved in EtOAc (400 ml) and sat. NaHCO₃ solution (100 ml) was added under stirring. Phases were separated and the organic phase was washed with sat. NaHCO₃ solution and brine, dried (Na₂SO₄), filtered over a phase separator SPE cartridge and concentrated in vacuo and the solid obtained was dissolved in EtOAc (20 ml) at 40°C and treated with ultrasound until precipitation started to occur. At this point, 1:2 TBME/heptane (150 ml) was added and the ultrasound treatment continued. The precipitate was filtered off and washed with heptane (2x), then dried under HV at 35°C for 18 h to give (S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide. ¹H NMR (600 MHz, DMSO-d₆) δ 11.19 (s, 1H), 9.08 (s, 1H), 8.53 (d, 1H), 8.31 (dd, 1H), 6.57 (s, 1H), 5.20 (s, 2H), 4.52 (t, 1H), 3.33 (d, 2H), 3.16 (q, 1H), 2.66 (ddt, 1H), 2.55 (d, 1H), 2.32 (s, 3H). UPLC-MS-8: Rt = 0.73 min; MS m/z [M+H]⁺ = 475.1.

Example 34: N-(5-Fluoro-6-(4-(2-(trifluoromethyl)oxetan-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide

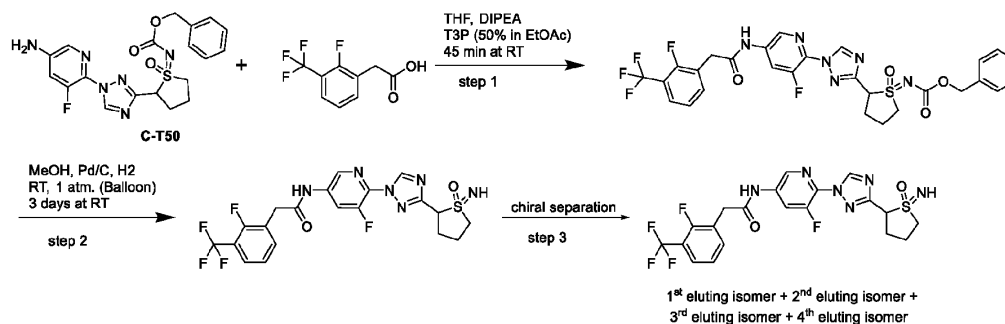


Step 1: 2-(5-Methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid [CAS No. 345637-71-0] (62 mg, 1.3 eq, 0.30 mmol) and Intermediate C-T48 (70 mg, 90% wt, 1 eq, 0.23 mmol) were dissolved in 1 ml THF, DIPEA (89 mg, 0.12 ml, 3 eq, 0.69 mmol) and T3P (50% in EtOAc) (0.22 g, 0.21 ml, 1.5 eq, 0.34 mmol) were added and the solution was stirred at RT for 16 h. Then the reaction mixture was diluted with EtOAc, washed with water (3x) and with brine, dried (Na₂SO₄) and concentrated in vacuo to give N-(5-fluoro-6-(4-(2,2,2-trifluoroacetyl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide. UPLC-MS-2: Rt = 0.96 min (very broad peak); MS m/z [M+H]⁺ = 465.3 and [M+H₃O]⁺ = 483.3.

Step 2: KOtBu (56 mg, 2.4 eq, 0.50 mmol) was dissolved in 1 ml DMSO, trimethylsulfoxonium iodide (110 mg, 2.4 eq, 500 μmol) was added and the reaction mixture was stirred for 30 min at RT. A solution of N-(5-fluoro-6-(4-(2,2,2-trifluoroacetyl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (step 1, 95 mg, 1 eq, 0.20 mmol) in 1 ml DMSO was added dropwise and stirred for 16 h. The reaction mixture was then diluted with EtOAc, washed with brine, (Na₂SO₄) and concentrated in vacuo to give crude product which was purified on silica gel (hexane/TBME/EtOH) to give N-(5-fluoro-6-(4-(2-(trifluoromethyl)oxetan-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide. ¹H NMR (600 MHz, DMSO-d₆) δ 11.13 (s, 1H), 8.49 (d, 1H), 8.36 (d,

1H), 8.30 (dd, 1H), 7.83 (s, 1H), 6.57 (s, 1H), 5.19 (s, 2H), 4.70 - 4.55 (m, 2H), 3.30 - 3.27 (m, 1H), 3.04 (ddd, 1H), 2.31 (s, 3H). UPLC-MS-2: Rt = 1.08 min; MS m/z [M+H]⁺ = 493.3.

Example 35: 2-(2-Fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(3-(1-imino-1-oxidotetrahydro-1H-1λ⁶-thiophen-2-yl)-1H-1,2,4-triazol-1-yl)pyridin-3-yl)acetamide (mixture of isomers)



5

Step 1: To a solution of Intermediate C-T50 (495.0 mg, 1.150 mmol) in 10.00 ml THF, DIPEA (668.8 mg, 901 μl, 4.5 eq, 5.175 mmol), 2-(2-fluoro-3-(trifluoromethyl)phenyl)acetic acid [CAS No. 194943-83-4] (332.1 mg, 1.3 eq, 1.495 mmol) and T3P (50% in EtOAc) (2.195 g, 2.042 ml, 3.0 eq, 3.450 mmol) were added. The resulting mixture was stirred for 45 min at RT. After that

10 H₂O and EtOAc were added to the reaction mixture and the phases were separated. The aqueous phase was extracted with EtOAc (2x). The combined organic phases were washed with brine and concentrated in vacuo. The residue was purified on silica gel

(cyclohexane/EtOAc) to give benzyl (2-(1-(3-fluoro-5-(2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamido)pyridin-2-yl)-1H-1,2,4-triazol-3-yl)-1-oxidotetrahydro-1λ⁶-

15 thiophen-1-ylidene)carbamate. ¹H NMR (400 MHz, DMSO-d₆) δ 11.06 (s, 1H), 9.26 - 9.08 (m, 1H), 8.63 - 8.46 (m, 1H), 8.45 - 8.25 (m, 1H), 7.84 - 7.64 (m, 2H), 7.53 - 7.06 (m, 7H), 5.28 - 4.72 (m, 3H), 3.97 (s, 2H), 3.95 - 3.81 (m, 1H), 3.75 - 3.59 (m, 1H), 3.47 - 3.39 (m, 3H), 2.75 - 2.57 (m, 2H), 2.49 - 2.45 (m, 2H), 2.49 - 2.36 (m, 1H), 2.26 - 2.06 (m, 1H). UPLC-MS-8: Rt = 1.08/1.12 min (2 peaks due diastereomeric mixture); MS m/z [M+H]⁺ = 634.

20 **Step 2:** Benzyl (2-(1-(3-fluoro-5-(2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamido)pyridin-2-yl)-1H-1,2,4-triazol-3-yl)-1-oxidotetrahydro-1λ⁶-thiophen-1-ylidene)carbamate (step 1, 800.0 mg, 1 eq, 1.261 mmol) was dissolved in 15.00 ml MeOH and Pd/C (134.2 mg, 10% wt, 0.1 eq, 126.1 μmol) was added and the mixture was put under hydrogen (balloon) and stirred overnight. The balloon was replaced by a freshly filled hydrogen-balloon and stirring continued for another 24

25 h. Then the reaction mixture was diluted with MeOH/DCM (1:1) and filtered over a pad of Celite®. The pad was washed several times with MeOH/DCM. The filtrate was concentrated to a lower volume and a precipitate formed. After standing for some time, the precipitate was filtered off to give 2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(3-(1-imino-1-oxidotetrahydro-1H-1λ⁶-thiophen-2-yl)-1H-1,2,4-triazol-1-yl)pyridin-3-yl)acetamide (diastereomeric mixture). The

30 filtrate was purified on silica gel (DCM/MeOH) to give additional product. ¹H NMR (400 MHz,

DMSO- d_6) δ 11.04 (s, 1H), 9.19 - 9.04 (m, 1H), 8.53 (d, 1H), 8.33 (dd, 1H), 7.77 (t, 1H), 7.72 (t, 1H), 7.41 (t, 1H), 4.45 (dt, 1H), 4.17 (s, 1H), 3.97 (s, 2H), 3.41 (s, 1H), 3.27 - 2.96 (m, 2H), 2.68 - 2.52 (m, 2H), 2.35 (dd, 1H), 2.19 - 2.05 (m, 1H). UPLC-MS-8: Rt = 0.86 min; MS m/z $[M+H]^+$ = 501.2.

- 5 **Step 3:** The diastereomers of 2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(3-(1-imino-1-oxidotetrahydro-1H-1 λ^6 -thiophen-2-yl)-1H-1,2,4-triazol-1-yl)pyridin-3-yl)acetamide (diastereomeric mixture) (Step 2, 251 mg, 0.476 mmol) were separated first by C-SFC-40 (mobile phase: CO₂/IPA+0.05%NH₃ (50:50)) (to give the 1st and 3rd eluting isomers) and then (for the mixture of the 2nd and 4th eluting isomers) by C-SFC-41 (mobile phase: CO₂/MeOH+0.05%NH₃ (60:40)) to give the title compounds as solids.

Example 35a: 1st eluting isomer: C-HPLC-7 (mobile phase: (heptane+Et₂NH)/((1:1 EtOH/MeOH)+Et₂NH) 65:35): Rt = 5.43 min.

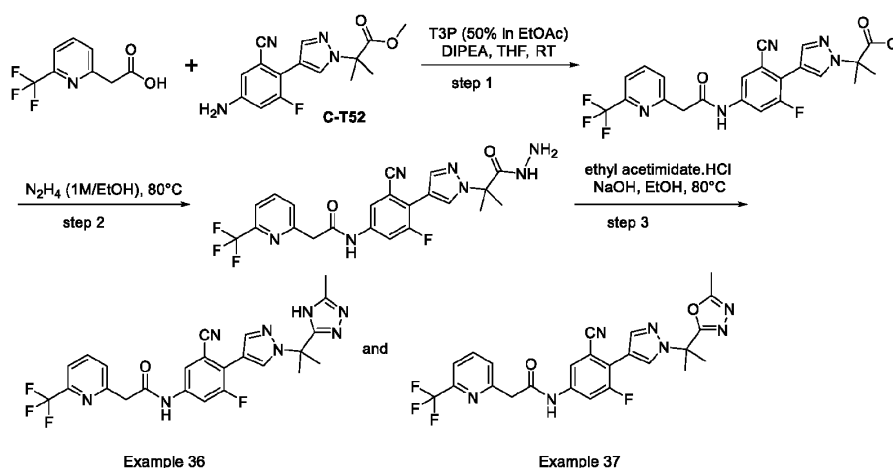
Example 35b: 2nd eluting isomer: C-HPLC-7 (mobile phase: (heptane+Et₂NH)/((1:1 EtOH/MeOH)+Et₂NH) 65:35): Rt = 6.12 min.

- 15 **Example 35c:** 3rd eluting isomer: C-HPLC-7 (mobile phase: (heptane+Et₂NH)/((1:1 EtOH/MeOH)+Et₂NH) 65:35): Rt = 7.48 min.

Example 35d: 4th eluting isomer: ¹H NMR (400 MHz, DMSO- d_6) δ 10.95 (d, 1H), 9.10 (s, 1H), 8.50 (d, 1H), 8.34 (dd, 1H), 7.83 - 7.64 (m, 2H), 7.40 (t, 1H), 4.43 (t, 1H), 4.16 (s, 1H), 3.95 (s, 2H), 3.23 - 3.15 (m, 1H), 3.11 - 2.99 (m, 1H), 2.68 - 2.54 (m, 2H), 2.41 - 2.27 (m, 1H), 2.19 - 2.03 (m, 1H). UPLC-MS-8: Rt = 0.83 min; MS m/z $[M+H]^+$ 501.2. C-HPLC-7 (mobile phase: (heptane+Et₂NH)/((1:1 EtOH/MeOH)+Et₂NH) 65:35): Rt = 14.64 min.

Example 36/37: N-(3-Cyano-5-fluoro-4-(1-(2-(5-methyl-4H-1,2,4-triazol-3-yl)propan-2-yl)-1H-pyrazol-4-yl)phenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide and N-(3-Cyano-5-fluoro-4-(1-(2-(5-methyl-1,3,4-oxadiazol-2-yl)propan-2-yl)-1H-pyrazol-4-yl)phenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide

- 25



Step 1: 2-(6-(Trifluoromethyl)pyridin-2-yl)acetic acid [CAS No.1000565-32-1] (180 mg, 0.877 mmol) and Intermediate C-T52 (190 mg, 0.628 mmol) were dissolved in 5 ml THF, DIPEA (0.329 ml, 1.885 mmol) and T3P (50% in EtOAc) (0.561 ml, 0.943 mmol) were added and the solution was stirred at RT for 1 h. After that, the reaction mixture was diluted with EtOAc,

5 washed with H₂O (3x) and brine, dried (Na₂SO₄) and concentrated in vacuo to give methyl 2-(4-(2-cyano-6-fluoro-4-(2-(6-(trifluoromethyl)pyridin-2-yl)acetamido)phenyl)-1H-pyrazol-1-yl)-2-methylpropanoate. UPLC-MS-2: Rt = 1.03 min; MS m/z [M+H]⁺ = 490.2.

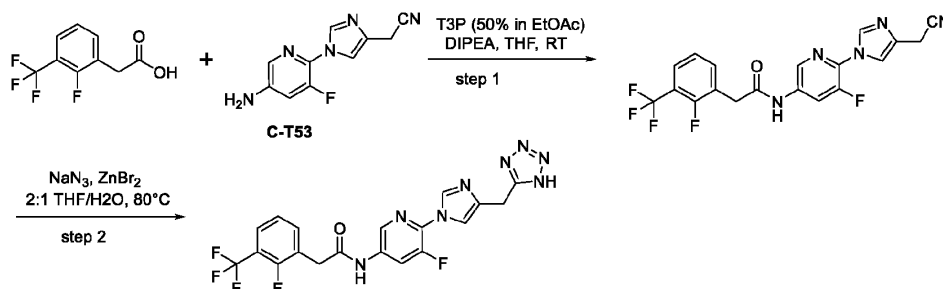
Step 2: Methyl 2-(4-(2-cyano-6-fluoro-4-(2-(6-(trifluoromethyl)pyridin-2-yl)acetamido)phenyl)-1H-pyrazol-1-yl)-2-methylpropanoate (step 1, 330 mg, 0.634 mmol) was dissolved in 10 ml
10 hydrazine solution (1M in EtOH) and stirred for 4 d at 80°C and then concentrated in vacuo. The residue was purified on silica gel [DCM/MeOH(+2% 7N NH₃ in MeOH)] to give N-(3-cyano-5-fluoro-4-(1-(1-hydrazineyl-2-methyl-1-oxopropan-2-yl)-1H-pyrazol-4-yl)phenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide. UPLC-MS-2: Rt = 0.80 min; MS m/z [M+H]⁺ = 490.5.

Step 3: N-(3-Cyano-5-fluoro-4-(1-(1-hydrazineyl-2-methyl-1-oxopropan-2-yl)-1H-pyrazol-4-yl)phenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide (step 2, 25 mg, 0.046 mmol) was
15 dissolved in 0.5 ml EtOH. Ethyl acetimidate hydrochloride (16 mg, 0.129 mmol) and NaOH (5 mg, 0.125 mmol) were added and the reaction mixture was stirred 80°C for 4 d. After that, the reaction mixture was diluted with EtOAc and washed with H₂O and brine, dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by RP-HPLC-2 (Eluent A: H₂O+7.3mM
20 NH₄OH, B: ACN+7.3mM NH₄OH, Gradient: 20 to 50% B in 22.5 min hold 2.5 min) and lyophilisation of the relevant fractions to give:

Example 36: N-(3-Cyano-5-fluoro-4-(1-(2-(5-methyl-4H-1,2,4-triazol-3-yl)propan-2-yl)-1H-pyrazol-4-yl)phenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide. ¹H NMR (600 MHz, DMSO-d₆)
δ 13.53 (s, 1H), 10.82 (s, 1H), 8.09 (dd, 1H), 8.04 (s, 1H), 7.89 - 7.79 (m, 4H), 7.75 (d, 1H), 4.03
25 (d, 2H), 2.31 (s, 3H), 1.99 - 1.89 (m, 6H). UPLC-MS-2: Rt = 0.88 min; MS m/z [M+H]⁺ = 513.2.
and

Example 37: N-(3-Cyano-5-fluoro-4-(1-(2-(5-methyl-1,3,4-oxadiazol-2-yl)propan-2-yl)-1H-pyrazol-4-yl)phenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide. ¹H NMR (600 MHz, DMSO-d₆)
δ 10.85 (s, 1H), 8.39 (s, 1H), 8.09 (t, 1H), 7.90 - 7.85 (m, 3H), 7.83 (d, 1H), 7.76 (d, 1H), 4.04 (s,
30 2H), 2.47 (s, 3H), 2.03 (s, 6H). MS-2: Rt = 0.91 min; MS m/z [M+H]⁺ = 514.3.

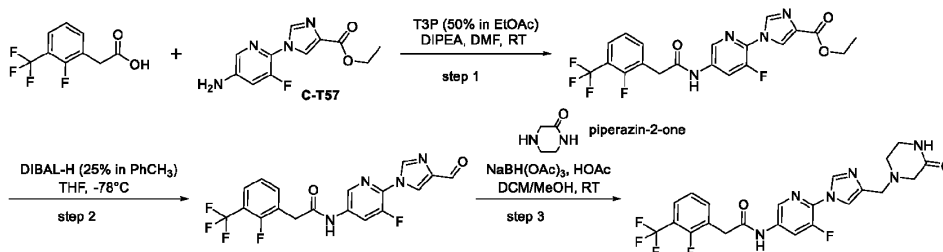
Example 38: N-(6-(4-((1H-Tetrazol-5-yl)methyl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide



Step 1: 2-(2-Fluoro-3-(trifluoromethyl)phenyl)acetic acid [CAS No. 194943-83-4] (243 mg, 1.093 mmol) and Intermediate C-T53 (254 mg, 0.994 mmol) were dissolved in 8 ml THF, DIPEA (0.521 ml, 2.98 mmol) and T3P (50% in EtOAc) (0.888 ml, 1.491 mmol) were added. This mixture was stirred at RT for 30 min. Then the reaction mixture was diluted with EtOAc, washed with H₂O (3x) and with brine, dried (Na₂SO₄) and concentrated in vacuo. The residue was triturated with EtOAc/petroleum ether 1:9 in ultrasound bath. The precipitate was filtered and washed with petroleum ether, then dried to give N-(6-(4-(cyanomethyl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide. UPLC-MS-2: Rt = 0.93 min; MS m/z [M+H]⁺ = 422.3.

Step 2: N-(6-(4-(Cyanomethyl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide (step 1, 100 mg, 0.237 mmol), NaN₃ (30.9 mg, 0.475 mmol) and ZnBr₂ (53.4 mg, 0.237 mmol) were suspended in 3 ml 2:1 THF/water and stirred at 80°C for 20 h. After that the reaction mixture was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na₂SO₄) and concentrated in vacuo. The residue was suspended in 5:1 DCM/IPA and then treated with 5% aq. citric acid. The organic phase was filtered over a phase separator filled with Na₂SO₄ and concentrated in vacuo to give crude product which was purified by RP-HPLC 3 (Eluent A: H₂O+0.1% HCOOH, B: ACN+0.1% HCOOH 98:2 to 0:100) to give N-(6-(4-((1H-tetrazol-5-yl)methyl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide. ¹H NMR (600 MHz, DMSO-d₆) δ 10.97 (s, 1H), 8.48 (d, 1H), 8.37 (s, 1H), 8.30 (dd, 1H), 7.77 (t, 1H), 7.72 (d, 2H), 7.41 (t, 1H), 4.29 (s, 2H), 3.95 (s, 2H). UPLC-MS-2: Rt = 0.85/0.86 min; MS m/z [M+H]⁺ = 465.2.

Example 39: 2-(2-Fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-((3-oxopiperazin-1-yl)methyl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide

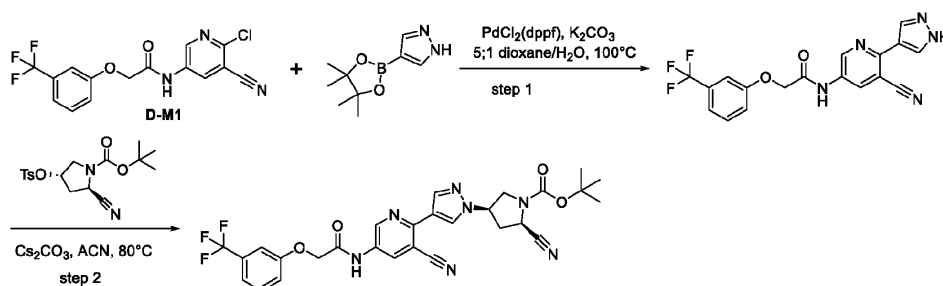


Step 1: T3P (50% in EtOAc) (3.42 ml, 5.40 mmol) and DIPEA (1.25 ml, 7.20 mmol) were added to a solution of 2-(2-fluoro-3-(trifluoromethyl)phenyl)acetic acid [CAS No. 194943-83-4] (0.80 g, 3.60 mmol) and Intermediate C-T57 (0.90 g, 3.60 mmol) in DMF (15 ml). After stirring at RT for 12 h, the reaction mixture was diluted with ice-H₂O and stirred for 10 min. The resulting precipitate was filtered, washed with H₂O and dried under vacuum to give ethyl 1-(3-fluoro-5-(2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamido)pyridin-2-yl)-1H-imidazole-4-carboxylate. HPLC-MS-3: Rt = 1.66 min; MS m/z [M+H]⁺ = 455.1.

Step 2: DIBAL-H (25% in PhCH₃) (0.56 ml, 0.99 mmol) was added dropwise to a solution of ethyl 1-(3-fluoro-5-(2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamido)pyridin-2-yl)-1H-imidazole-4-carboxylate (step 1, 0.15 g, 0.33 mmol) in THF (10 ml) at -78°C. After 1 h, the reaction mixture was diluted with sat. aq. NH₄Cl and EtOAc. The separated organic layer was washed with brine (2x), dried (Na₂SO₄) and concentrated under reduced pressure to give 2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-formyl-1H-imidazol-1-yl)pyridin-3-yl)acetamide. HPLC-MS-3: Rt = 0.40 min; MS m/z [M+H]⁺ = 411.1.

Step 3: HOAc (0.216 g, 0.36 mmol) was added dropwise to a solution of 2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-formyl-1H-imidazol-1-yl)pyridin-3-yl)acetamide (step 2, 0.15 g, 0.36 mmol) and piperazin-2-one (0.548 g, 0.54 mmol) in DCM/MeOH (10 ml). After stirring at RT for 30 min, NaBH(OAc)₃ (0.152 g, 0.72 mmol) was added and the mixture stirred for another 12 h. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between EtOAc and H₂O. The organic layer was washed with brine (2x), dried (Na₂SO₄) and concentrated under reduced pressure and the residue was purified by RP-HPLC-5 (Eluent A: H₂O+0.1% HCOOH, B: ACN) to give 2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-((3-oxopiperazin-1-yl)methyl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide. ¹H NMR (300 MHz, CD₃OD) δ 8.45 (d, 1H), 8.36 (dd, 1H), 8.34 (m, 1H), 7.77 (s, 1H), 7.61-7.73 (m, 2H), 7.35 (t, 1H), 3.93 (s, 2H), 3.68 (s, 2H), 3.18 (s, 2H), 2.72-2.84 (m, 2H). HPLC-MS-1: Rt = 1.32 min; MS m/z [M+H]⁺ 495.0.

Example 40: tert-Butyl (2R,4R)-2-cyano-4-(4-(3-cyano-5-(2-(3-(trifluoromethyl)phenoxy)acetamido)pyridin-2-yl)-1H-pyrazol-1-yl)pyrrolidine-1-carboxylate



Step 1: PdCl₂(dppf) (309 mg, 0.422 mmol) was added to a solution of Intermediate D-M1 (1.5 g, 4.22 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole [CAS No. 269410-08-4]

(1.23 g, 6.33 mmol) and K_2CO_3 (1.75 g, 12.65 mmol) in 5:1 dioxane/ H_2O (12 ml) and the mixture was stirred under N_2 atmosphere at $100^\circ C$. After 6 h, the reaction mixture was poured into H_2O and extracted with DCM (4x). The combined organic layers were washed with brine (2x), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was triturated in 4:1

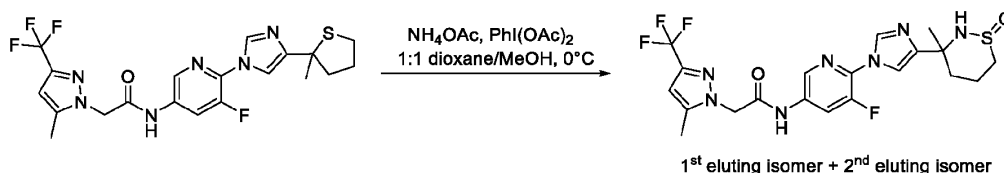
- 5 EtOAc/petroleum ether and filtered. The filter cake was dried under vacuum to give N-(5-cyano-6-(1H-pyrazol-4-yl)pyridin-3-yl)-2-(3-(trifluoromethyl)phenoxy)acetamide. HPLC-MS-4: R_t = 0.91 min; MS m/z $[M+H]^+$ = 388.0.

- Step 2:** Cs_2CO_3 (421 mg, 1.29 mmol) was added to a solution of N-(5-cyano-6-(1H-pyrazol-4-yl)pyridin-3-yl)-2-(3-(trifluoromethyl)phenoxy)acetamide (step 1, 250 mg, 0.645 mmol) and tert-butyl (2R,4S)-2-cyano-4-(tosyloxy)pyrrolidine-1-carboxylate (284 mg, 0.775 mmol) in ACN (10 ml) and the mixture was heated to $80^\circ C$. After 16 h, the reaction mixture was concentrated. The residue was diluted with H_2O and extracted with EtOAc (3x). The combined organic layers were washed with brine (2x), dried (Na_2SO_4) and concentrated under reduced pressure and the residue was purified first by RP-HPLC (basic conditions) and then by preparative TLC (1:2
- 15 petroleum ether/EtOAc) to give tert-butyl (2R,4R)-2-cyano-4-(4-(3-cyano-5-(2-(3-(trifluoromethyl)phenoxy)acetamido)pyridin-2-yl)-1H-pyrazol-1-yl)pyrrolidine-1-carboxylate. 1H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, 1H), 8.63 (d, 1H), 8.46 (s, 1H), 8.42 (s, 2H), 7.57-7.51 (m, 1H), 7.39 (d, 1H), 7.30 (br s, 1H), 7.22 (dd, 1H), 5.00 (m, 1H), 4.74 (s, 2H), 4.68 (m, 1H), 4.17-3.93 (m, 2H), 3.06-2.85 (m, 2H), 1.56 (m, 9H). HPLC-MS-4: R_t = 1.01 min; MS m/z $[M+H]^+$ =
- 20 582.2.

Note: tert-butyl (2R,4S)-2-cyano-4-(tosyloxy)pyrrolidine-1-carboxylate was obtained using the following procedure.

- Et_3N (0.85 ml, 6.12 mmol) and $TsCl$ (700 mg, 3.67 mmol) were added to a solution of tert-butyl (2R,4S)-2-cyano-4-hydroxypyrrolidine-1-carboxylate [CAS No. 1613482-42-0] (650 mg, 3.06 mmol) and DMAP (37 mg, 0.306 mmol) in DCM (10 ml) at RT. After 2 h, the reaction mixture was poured into H_2O and extracted with DCM (3x). The combined organic layers were washed with brine (2x), dried (Na_2SO_4) and concentrated under reduced pressure to give tert-butyl (2R,4S)-2-cyano-4-(tosyloxy)pyrrolidine-1-carboxylate. HPLC-MS-4: R_t = 0.91 min; MS m/z
- 30 $[M+H]^+$ = 367.1.

Example 41: N-(5-Fluoro-6-(4-(3-methyl-1-oxido-1,2-thiazinan-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide

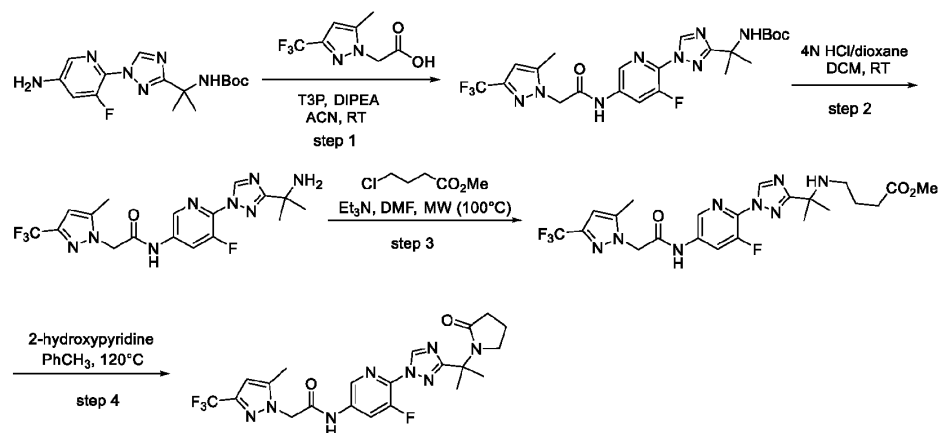


NH₄OAc (37.8 mg, 491 μ mol) and (diacetoxyiodo)benzene (94.9 mg, 294.6 μ mol) were added to a solution of Example 109 (46 mg, 98.19 μ mol) in 1:1 dioxane/MeOH (3 ml). After stirring for 10 min, the mixture was treated with Si-Thiol resin (500 mg) and then stirred at 0°C for 30 min followed by 1 h at RT. The reaction mixture was filtered and the filtrate concentrated under reduced pressure and the residue was purified by RP-HPLC-3 (mobile phase: H₂O+0.2% HCOOH/ACN 95:5 to 0:100) to give the diastereomers of N-(5-fluoro-6-(4-(3-methyl-1-oxido-1,2-thiazinan-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide.

Example 41a: 1st eluting isomer: ¹H NMR (600 MHz, DMSO-*d*₆) δ 11.09 (br s, 1H), 8.47 (d, 1H), 8.28 (dd, 1H), 8.15 (m, 1H), 7.96 (m, 1H), 6.57 (s, 1H), 6.56 (s, 1H), 5.18 (s, 2H), 2.69 (m, 1H), 2.42 (m, 1H), 2.33 (m, 1H), 2.31 (s, 3H), 2.15 (m, 1H), 1.60-1.71 (m, 2H), 1.35 (s, 3H). UPLC-MS-8: Rt = 0.79 min; MS m/z [M+H]⁺ 500.2.

Example 41b: 2nd eluting isomer: ¹H NMR (600 MHz, DMSO-*d*₆) δ 11.08 (br s, 1H), 8.47 (d, 1H), 8.26 (dd, 1H), 8.20 (m, 1H), 7.55 (s, 1H), 6.57 (s, 1H), 6.17 (s, 1H), 5.18 (s, 2H), 2.72 (m, 1H), 2.55-2.59 (m, 2H), 2.31 (s, 3H), 1.96-2.08 (m, 2H), 1.81 (m, 1H), 1.77 (s, 3H). UPLC-MS-8: Rt = 0.85 min; MS m/z [M+H]⁺ 500.2.

Example 42: N-(5-Fluoro-6-(3-(2-(2-oxopyrrolidin-1-yl)propan-2-yl)-1H-1,2,4-triazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide



Step 1: To a solution of Intermediate C-T7 (350.0 mg, 1.009 mmol) in ACN (6.00 ml) were added 2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid [CAS No. 345637-71-0] (315.1 mg, 1.514 mmol), DIPEA (391.4 mg, 527 μ L, 3.028 mmol) and T3P (50% in EtOAc) (1.285 g, 1.194 ml, 2.019 mmol) and the reaction mixture was stirred at RT for 2 h. Further DIPEA (391.4 mg, 527 μ L, 3.028 mmol), T3P (50% in EtOAc) (1.285 g, 1.194 ml, 2.019 mmol) and 2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid (315.1 mg, 1.514 mmol) were added and the mixture was continued to stir for 2.5 h at RT. The reaction mixture was diluted with EtOAc, washed with an aqueous saturated solution of NaHCO₃, phases were separated and the aqueous layer was extracted with EtOAc (2x). The combined organic layers were washed with

brine, dried using a phase separator and evaporated. The crude product was purified by silica gel column chromatography eluting with a gradient of EtOAc (0-100%) in cyclohexane.

Fractions containing the desired product were combined and evaporated to give tert-butyl (2-(1-(3-fluoro-5-(2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)pyridin-2-yl)-1H-1,2,4-triazol-3-yl)propan-2-yl)carbamate. ¹H NMR (600 MHz, DMSO-d₃) δ 11.14 (s, 1H), 8.95 (s, 1H), 8.51 (d, 1H), 8.29 (dd, 1H), 7.06 (s, 1H), 6.57 (s, 1H), 5.19 (s, 2H), 2.32 (s, 3H), 1.55 (s, 6H), 1.32 (s, 9H). UPLC-MS-8: Rt = 1.11 min; MS m/z [M+H]⁺ 527.3.

Step 2: A solution of tert-butyl (2-(1-(3-fluoro-5-(2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)pyridin-2-yl)-1H-1,2,4-triazol-3-yl)propan-2-yl)carbamate (step 1, 486 mg, 0.775 mmol) and HCl (4M/dioxane) (565.4 mg, 3.877 ml, 4.000 molar, 20 eq, 15.51 mmol) in DCM (3 ml) was stirred at RT for 2 h. The reaction mixture was evaporated to dryness. The residue was dissolved in H₂O and aqueous layer was basified with an aqueous saturated solution of NaHCO₃ and extracted with DCM (2x). The combined organic layers were dried using a phase separator and evaporated to give N-(6-(3-(2-aminopropan-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide. ¹H NMR (600 MHz, DMSO-d₃) δ 11.17 (s, 1H), 8.97 (s, 1H), 8.52 (d, 1H), 8.29 (dd, 1H), 6.56 (s, 1H), 5.19 (s, 2H), 2.32 (s, 3H), 1.43 (s, 6H). UPLC-MS-8: Rt = 0.59 min; MS m/z [M+H]⁺ 427.1.

Step 3: A solution of N-(6-(3-(2-aminopropan-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (step 2, 100 mg, 0.213 mmol), Et₃N (149 ul, 1.067 mmol) and methyl 4-chlorobutanoate (28.6 ul, 0.235 mmol) in DMF (1.5 ml) was stirred at 100°C under microwave irradiation. Additional Et₃N (149 ul, 1.067 mmol) and methyl 4-chlorobutanoate (28.6 ul, 0.235 mmol) were added after 1 h and after 5 h. After stirring overnight at 100°C (heating block), the reaction mixture was diluted with EtOAc and washed with H₂O and brine. The organic layer was dried (phase separator) and concentrated under reduced pressure and the residue was purified first by RP-HPLC-3 (mobile phase: H₂O+0.1%TFA/ACN 95:5 to 0:100) and then by RP-HPLC-3 (mobile phase: H₂O+0.1%NH₄OH/ACN 95:5 to 0:100). The product-containing fractions were combined, diluted with sat. aq. NaHCO₃ and extracted with DCM (3x). The combined organic layers were dried (phase separator) and concentrated under reduced pressure to give methyl 4-((2-(1-(3-fluoro-5-(2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)pyridin-2-yl)-1H-1,2,4-triazol-3-yl)propan-2-yl)amino)butanoate. UPLC-MS-8: Rt = 0.66 min; MS m/z [M+H]⁺ 527.3.

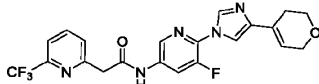
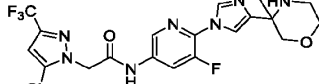
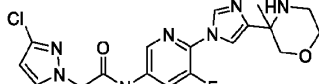
Step 4: A solution of methyl 4-((2-(1-(3-fluoro-5-(2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)pyridin-2-yl)-1H-1,2,4-triazol-3-yl)propan-2-yl)amino)butanoate (step 3, 52 mg, 97.78 umol) and 2-hydroxypyridine (18.6 mg, 195.6 umol) in toluene was stirred at 120°C for 72 h. The reaction mixture was cooled to RT, diluted with DCM and washed with sat. aq. NaHCO₃ and brine. The organic layer was dried (phase separator) and concentrated under reduced pressure and the residue was purified by RP-HPLC-3 (mobile phase: H₂O+0.1%TFA/ACN 95:5

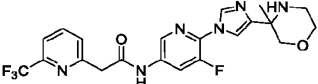
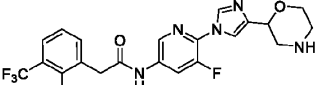
to 0:100). The product-containing fractions were combined, diluted with sat. aq. NaHCO₃ and extracted with DCM (3x). The combined organic layers were dried (phase separator) and concentrated under reduced pressure to give N-(5-fluoro-6-(3-(2-(2-oxopyrrolidin-1-yl)propan-2-yl)-1H-1,2,4-triazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide.

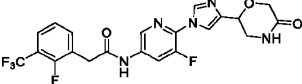
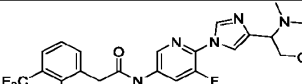
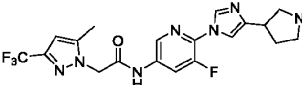
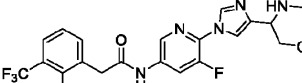
- 5 ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.17 (br s, 1H), 8.96 (d, 1H), 8.51 (d, 1H), 8.30 (dd, 1H), 6.57 (s, 1H), 5.19 (s, 2H), 3.53 (t, 2H), 2.32 (s, 3H), 2.14-2.21 (m, 2H), 1.86-1.96 (m, 2H), 1.69 (s, 6H). UPLC-MS-8: Rt = 0.88 min; MS m/z [M+H]⁺ 495.1.

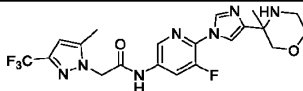
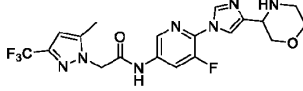
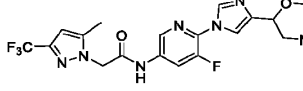
The following examples were prepared using methods similar to Examples 1-42 from

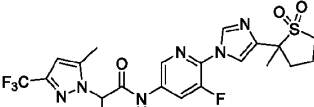
- 10 intermediates which are either commercially available or were obtained by methods described herein.

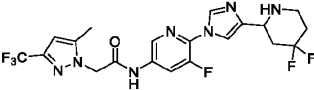
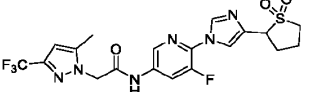
Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
43	 N-(6-(4-(3,6-Dihydro-2H-pyran-4-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide	Analogous to Example 10 from Intermediate D-T3 and using PdCl ₂ (dppf).DC M/K ₃ PO ₄ /6:1 dioxane/H ₂ O	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.95 (br s, 1H), 8.49 (d, 1H), 8.29 (dd, 1H), 8.23 (m, 1H), 8.10 (t, 1H), 7.83 (d, 1H), 7.77 (d, 1H), 7.69 (s, 1H), 6.40 (m, 1H), 4.18-4.26 (m, 2H), 4.07 (s, 2H), 3.76-3.83 (m, 2H), 2.35-2.43 (m, 2H). UPLC-MS-2: Rt = 0.92 min; MS m/z [M+H] ⁺ 448.3.
44 – rac 44a - 1 st eluting isomer 44b - 2 nd eluting isomer	 2-(5-Chloro-3-(trifluoromethyl)-1H-pyrazol-1-yl)-N-(5-fluoro-6-(4-(3-methylmorpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide	Analogous to Example 11 from Intermediate C-T3 and 2-(5-chloro-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid [CAS No. 922516-24-3] using first C-SFC-6 (mobile phase: CO ₂ /(MeOH+0.05%NH ₃) 50-70%)	1 st eluting isomer ¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ 11.17 (s, 1H), 8.47 (d, 1H), 8.25 (dd, 1H), 8.21 (t, 1H), 7.62 (t, 1H), 7.14 (s, 1H), 5.30 (s, 2H), 3.90 (d, 1H), 3.53 (dt, 1H), 3.51 - 3.46 (m, 1H), 3.40 (d, 1H), 2.74 (ddd, 1H), 2.69 (dt, 1H), 1.24 (s, 3H). UPLC-MS-8: Rt = 0.71 min; MS m/z [M+H] ⁺ 488.0. C-SFC-5 (mobile phase: CO ₂ /(MeOH+0.05%NH ₃) 50/50): Rt = 2.37 min. 2 nd eluting isomer C-SFC-5 (mobile phase: CO ₂ /(MeOH+0.05%NH ₃) 50/50): Rt = 4.47 min.
45	 2-(3-Chloro-5-(trifluoromethyl)-1H-pyrazol-1-yl)-N-(5-fluoro-6-(4-(3-methylmorpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide	Side product of Example 44 from Intermediate C-T3 and 2-(5-chloro-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ 11.12 (s, 1H), 8.45 (d, 1H), 8.24 (dd, 1H), 8.20 (t, 1H), 7.61 (t, 1H), 7.25 (s, 1H), 5.26 (s, 2H), 3.90 (d, 1H), 3.55 - 3.51 (m, 1H), 3.51 - 3.46 (m, 1H), 3.40 (d, 1H), 2.74 (ddd, 1H), 2.71 - 2.65 (m, 1H), 1.24 (s, 3H).

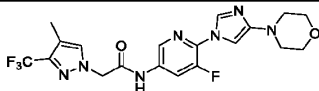
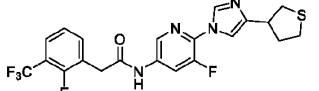
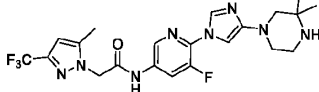
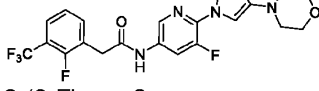
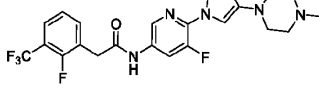
Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
	methylmorpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide	[CAS No. 922516-24-3] (contained some 2-(3-chloro-5-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid) using first C-SFC-6 (mobile phase: CO ₂ /(MeOH+0.05%NH ₃) 50-70%) and then C-SFC-6 (mobile phase: CO ₂ /(MeOH+0.05%NH ₃) 40-44%)	UPLC-MS-8: Rt = 0.71 min; MS m/z [M+H] ⁺ 488.0. C-SFC-5 (mobile phase: CO ₂ /(MeOH+0.05%NH ₃) 50/50): Rt = 0.99 min.
46 – rac 46a – 1st eluting isomer 46b – 2nd eluting isomer	 N-(5-Fluoro-6-(4-(3-methylmorpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide	Analogous to Example 11 from Intermediate C-T3 and 2-(6-(trifluoromethyl)pyridin-2-yl)acetic acid [CAS No. 1000565-32-1] using C-SFC-11 (mobile phase: CO ₂ /(MeOH+0.05%NH ₃) 60:40)	1 st eluting isomer ¹ H NMR (600 MHz, DMSO-d ₆) δ 10.95 (s, 1H), 8.48 (d, 1H), 8.29 (dd, 1H), 8.19 (t, 1H), 8.10 (t, 1H), 7.83 (dd, 1H), 7.77 (d, 1H), 7.61 (t, 1H), 4.07 (s, 2H), 3.90 (d, 1H), 3.53 (dt, 1H), 3.51 - 3.45 (m, 1H), 3.40 (d, 1H), 2.74 (ddd, 1H), 2.71 - 2.66 (m, 1H), 1.24 (s, 3H). UPLC-MS-8: Rt = 0.58 min; MS m/z [M+H] ⁺ 465.1. C-SFC-5 (mobile phase: CO ₂ /(MeOH+0.05%NH ₃) 55/45): Rt = 1.31 min. 2 nd eluting isomer C-SFC-5 (mobile phase: CO ₂ /(MeOH+0.05%NH ₃) 55/45): Rt = 1.81 min.
47 (rac) 47a - 1st eluting isomer 47b – 2nd eluting isomer	 2-(2-Fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(morpholin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide	Analogous to Example 11 from Intermediate C-M5 and 2-(2-fluoro-3-(trifluoromethyl)phenyl)acetic acid [CAS No. 194943-83-4] using C-SFC-12 (mobile phase: CO ₂ /(MeOH+0.05%NH ₃) 60:40)	1 st eluting isomer ¹ H NMR (600 MHz, DMSO-d ₆) δ 10.95 (s, 1H), 8.47 (d, 1H), 8.28 (dd, 1H), 8.17 (t, 1H), 7.77 (t, 1H), 7.72 (t, 1H), 7.57 (s, 1H), 7.41 (t, 1H), 4.40 (d, 1H), 3.95 (s, 2H), 3.81 (d, 1H), 3.58 (m, 1H), 3.03 (d, 1H), 2.79 – 2.68 (m, 3H). UPLC-MS-2: Rt = 0.72 min; MS m/z [M+H] ⁺ 468.1. C-SFC-5 (mobile phase: CO ₂ /(IPA+0.05%NH ₃) 65/35): Rt = 2.79 min. 2 nd eluting isomer

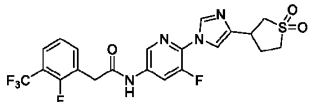
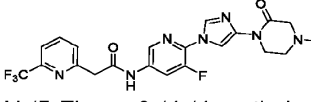
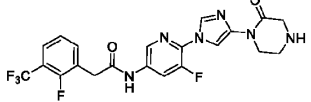
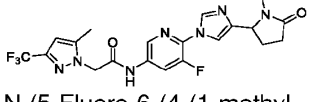
Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
			C-SFC-5 (mobile phase: CO ₂ /(IPA+0.05%NH ₃) 65/35): Rt = 4.48 min.
48 (rac)	 2-(2-Fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(5-oxomorpholin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide	Analogous to Example 11 from Intermediate C-T4 and 2-(2-fluoro-3-(trifluoromethyl)phenyl)acetic acid [CAS No. 194943-83-4]	¹ H NMR (600 MHz, DMSO-d ₆) δ 10.98 (s, 1H), 8.48 (d, 1H), 8.29 (dd, 1H), 8.23 (s, 1H), 8.12 (d, 1H), 7.77 (t, 1H), 7.74 (s, 1H), 7.72 (t, 1H), 7.41 (t, 1H), 4.80 (dd, 1H), 4.17 (d, 1H), 4.10 (d, 1H), 3.95 (s, 2H), 3.58 (dd, 1H), 3.44 - 3.42 (m, 1H). UPLC-MS-2: Rt = 0.86 min; MS m/z [M+H] ⁺ 482.1.
49	 2-(2-Fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(4-methylmorpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide	Analogous to Example 13 from Intermediate A-M5 and Intermediate C-M7	¹ H NMR (600 MHz, DMSO-d ₆) δ 10.97 (s, 1H), 8.48 (d, 1H), 8.29 (dd, 1H), 8.18 (t, 1H), 7.79 - 7.74 (m, 1H), 7.72 (t, 1H), 7.61 (d, 1H), 7.41 (t, 1H), 3.95 (s, 2H), 3.78 (d, 1H), 3.70 - 3.66 (m, 1H), 3.60 (td, 1H), 3.46 (dd, 1H), 3.12 (dd, 1H), 2.75 (dt, 1H), 2.23 (td, 1H), 2.07 (s, 3H). UPLC-MS-2: Rt = 0.73 min; MS m/z [M+H] ⁺ 482.1.
50	 N-(5-Fluoro-6-(4-(pyrrolidin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide	Analogous to Example 11 from Intermediate C-T5 and 2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid [CAS No. 345637-71-0]	¹ H NMR (600 MHz, DMSO-d ₆) δ 11.07 (s, 1H), 8.45 (d, 1H), 8.26 (dd, 1H), 8.16 (s, 1H), 7.50 (s, 1H), 6.57 (s, 1H), 5.17 (s, 2H), 3.17 - 3.07 (m, 2H), 2.93 - 2.81 (m, 2H), 2.73 (dd, 1H), 2.31 (s, 3H), 2.06 - 1.99 (m, 1H), 1.83 - 1.76 (m, 1H). UPLC-MS-2: Rt = 0.62 min; MS m/z [M+H] ⁺ 438.2
24 (rac) 51a - 1 st eluting isomer 51b - 2 nd eluting isomer	 2-(2-Fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(morpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide	Analogous to Example 11 from Intermediate C-T2 and 2-(2-fluoro-3-(trifluoromethyl)phenyl)acetic acid [CAS No. 194943-83-4] using C-HPLC-2 (mobile phase: n-heptane/DCM:EtOH +0.05%NH ₃ 65:30:5)	1 st eluting isomer C-HPLC-1 (mobile phase: n-heptane/DCM:EtOH +0.05%NH ₃ (65:30:5)): Rt = 31.08 min. 2 nd eluting isomer ¹ H NMR (600 MHz, DMSO-d ₆) δ 10.97 (s, 1H), 8.47 (d, 1H), 8.28 (dd, 1H), 8.18 (t, 1H), 7.77 (t, 1H), 7.72 (t, 1H), 7.56 (s, 1H), 7.41 (t, 1H), 3.95 (s, 2H), 3.89 (dd, 1H), 3.79 (dd, 1H), 3.70 (dt, 1H), 3.41 (ddd, 1H), 3.29 (dd, 1H), 2.86 - 2.79 (m, 2H), 2.68 (s, 1H). UPLC-MS-2: Rt = 0.74 min; MS m/z [M+H] ⁺ 468.1. C-HPLC-1 (mobile phase: n-

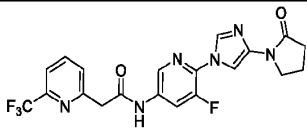
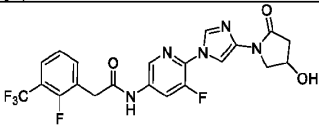
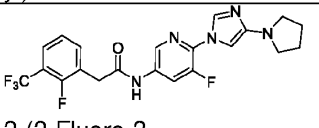
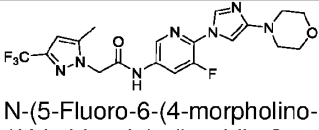
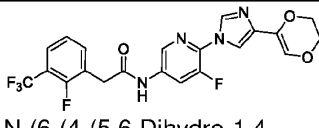
Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
			heptane/DCM:EtOH +0.05%NH ₃ (65:30:5): Rt = 37.32 min.
52 – rac 52a - 1 st eluting isomer 52b – 2 nd eluting isomer	 N-(5-Fluoro-6-(4-(3-methylmorpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide	Analogous to Example 11 from Intermediate C-T3 and 2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid [CAS No. 345637-71-0] using C-SFC-11 (mobile phase: CO ₂ /MeOH +0.05%NH ₃ 50: 50)	1 st eluting isomer ¹ H NMR (600 MHz, DMSO-d ₆) δ 11.08 (s, 1H), 8.47 (d, 1H), 8.27 (dd, 1H), 8.21 (t, 1H), 7.63 (s, 1H), 6.57 (s, 1H), 5.18 (s, 2H), 3.90 (d, 1H), 3.57 - 3.46 (m, 2H), 3.41 (d, 1H), 2.78 - 2.66 (m, 2H), 2.31 (d, 3H), 1.25 (s, 3H). UPLC-MS-8: Rt = 0.58 min; MS m/z [M+H] ⁺ 468.2. C-SFC-5 (mobile phase: CO ₂ /MeOH +0.05%NH ₃ (50: 50)): Rt = 1.51 min. 2 nd eluting isomer C-SFC-5 (mobile phase: CO ₂ /MeOH +0.05%NH ₃ (50: 50)): Rt = 2.71 min.
11 – rac 53a – 1 st eluting isomer 53b - 2 nd eluting isomer	 N-(5-Fluoro-6-(4-(morpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide	Analogous to Example 11 from Intermediate C-T2 and 2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid [CAS No. 345637-71-0] using C-SFC-13 (mobile phase: CO ₂ /EtOH +0.05%NH ₃ 50: 50)	1 st eluting isomer ¹ H NMR (600 MHz, DMSO-d ₆) δ 11.09 (s, 1H), 8.47 (d, 1H), 8.26 (dd, 1H), 8.19 (s, 1H), 7.58 (s, 1H), 6.57 (s, 1H), 5.18 (s, 2H), 3.89 (dd, 1H), 3.79 (dd, 1H), 3.73 - 3.66 (m, 1H), 3.44 - 3.39 (m, 1H), 3.31 - 3.27 (m, 1H), 2.89 - 2.80 (m, 2H), 2.31 (s, 3H). UPLC-MS-2: Rt = 0.59 min; MS m/z [M+H] ⁺ 454.2. C-SFC-5 (mobile phase: CO ₂ /EtOH +0.05%NH ₃ (65: 35)): Rt = 2.71 min. 2 nd eluting isomer UPLC-MS-2: Rt = 0.59 min; MS m/z [M+H] ⁺ 454.2. C-SFC-5 (mobile phase: CO ₂ /EtOH +0.05%NH ₃ (65: 35)): Rt = 2.71 min.
54 – rac 54a – 1 st eluting isomer 54b - 2 nd eluting isomer	 N-(5-Fluoro-6-(4-(morpholin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide	Analogous to Example 11 from Intermediate C-M5 and 2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid [CAS No. 345637-71-0]	1 st eluting isomer ¹ H NMR (400 MHz, DMSO-d ₆) δ 11.10 (s, 1H), 8.47 (d, 1H), 8.26 (dd, 1H), 8.18 (t, 1H), 7.57 (s, 1H), 6.57 (s, 1H), 5.18 (s, 2H), 4.38 (dd, 1H), 3.79 (dt, 1H), 3.59 - 3.52 (m, 1H), 3.00 (dd, 1H), 2.74 - 2.68 (m, 3H), 2.31 (s, 3H). UPLC-MS-2: Rt = 0.60 min; MS m/z [M+H] ⁺ 454.2. C-SFC-5

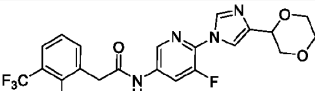
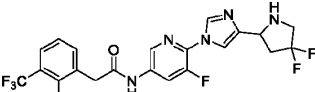
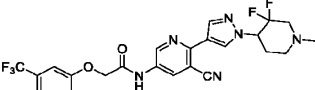
Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
		using C-SFC-10 (mobile phase: CO ₂ /IPA +0.05%NH ₃ 55:45)	(mobile phase: CO ₂ /IPA +0.05%NH ₃ (60:40)): Rt = 1.53 min. 2 nd eluting isomer UPLC-MS-2: Rt = 0.59 min; MS m/z [M+H] ⁺ 454.2. C-SFC-5 (mobile phase: CO ₂ /IPA +0.05%NH ₃ (60:40)): Rt = 2.43 min.
55 – rac 55a - 1 st eluting isomer 55b – 2 nd eluting isomer 55c – 3 rd eluting isomer 55d – 4 th eluting isomer	 N-(5-Fluoro-6-(4-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)propanamide	Analogous to Example 1 using Intermediate C-M1 and 2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)propanoic acid [CAS No. 1005566-34-6] using C-SFC-9 (mobile phase: CO ₂ /MeOH +0.05%NH ₃ 78:22)	1 st eluting isomer ¹ H NMR (400 MHz, DMSO-d ₆) δ 10.86 (s, 1H), 8.50 (d, 1H), 8.31 (dd, 1H), 8.26 (t, 1H), 7.82 (d, 1H), 6.58 (s, 1H), 5.33 (q, 1H), 3.28 – 3.21 (m, 1H), 3.21 – 3.13 (m, 1H), 2.75 – 2.66 (m, 1H), 2.31 (s, 3H), 2.27 – 2.18 (m, 1H), 2.18 – 2.07 (m, 2H), 1.77 (d, 3H), 1.65 (s, 3H). UPLC-MS-2: Rt = 0.82 min; MS m/z [M+H] ⁺ 515.3. C-SFC-7 (mobile phase: CO ₂ /MeOH +0.05%NH ₃ (78:22)): Rt = 1.73 min. 2 nd eluting isomer ¹ H NMR (400 MHz, DMSO-d ₆) δ 10.85 (s, 1H), 8.50 (d, 1H), 8.31 (dd, 1H), 8.26 (t, 1H), 7.82 (t, 1H), 6.58 (s, 1H), 5.33 (q, 1H), 3.27 – 3.21 (m, 1H), 3.21 – 3.13 (m, 1H), 2.76 – 2.67 (m, 1H), 2.31 (s, 3H), 2.27 – 2.19 (m, 1H), 2.17 – 2.07 (m, 2H), 1.77 (d, 3H), 1.65 (s, 3H). UPLC-MS-2: Rt = 0.82 min; MS m/z [M+H] ⁺ 515.3. C-SFC-7 (mobile phase: CO ₂ /MeOH +0.05%NH ₃ (78:22)): Rt = 2.05 min. 3 rd eluting isomer ¹ H NMR (400 MHz, DMSO-d ₆) δ 10.86 (s, 1H), 8.50 (d, 1H), 8.31 (dd, 1H), 8.26 (t, 1H), 7.82 (t, 1H), 6.58 (s, 1H), 5.33 (q, 1H), 3.27 – 3.21 (m, 1H), 3.20 – 3.13 (m, 1H), 2.76 – 2.67 (m, 1H), 2.31 (s, 3H), 2.28 – 2.18 (m, 1H), 2.16 – 2.08 (m, 2H), 1.77 (d, 3H), 1.65 (s, 3H). UPLC-MS-2: Rt = 0.82 min; MS m/z [M+H] ⁺ 515.3. C-SFC-7 (mobile phase:

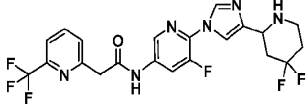
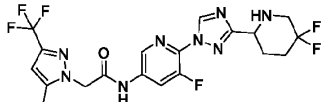
Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
			CO₂/MeOH +0.05%NH₃ (78:22): Rt = 2.73 min. 4th eluting isomer ¹H NMR (400 MHz, DMSO-d₆) δ 10.86 (s, 1H), 8.50 (d, 1H), 8.31 (dd, 1H), 8.26 (t, 1H), 7.82 (t, 1H), 6.58 (s, 1H), 5.33 (q, 1H), 3.27 – 3.21 (m, 1H), 3.20 – 3.13 (m, 1H), 2.76 – 2.67 (m, 1H), 2.31 (s, 3H), 2.28 – 2.18 (m, 1H), 2.16 – 2.08 (m, 2H), 1.77 (d, 3H), 1.65 (s, 3H). UPLC-MS-2: Rt = 0.82 min; MS m/z [M+H]⁺ 515.3. C-SFC-7 (mobile phase: CO₂/MeOH +0.05%NH₃ (78:22)): Rt = 5.01 min.
56 – rac 56a - 1st eluting isomer 56b - 2nd eluting isomer	 N-(6-(4-(4,4-difluoropiperidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide	Analogous to Example 11 using Intermediate C-T8 and 2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid [CAS No. 345637-71-0] using C-HPLC-6 (mobile phase: heptane+DEA/EtOH+0.05%NH₃ 50:50)	1st eluting isomer ¹H NMR (600 MHz, DMSO-d₆) δ 11.09 (s, 1H), 8.48 (d, 1H), 8.26 (dd, 1H), 8.22 (d, 1H), 7.62 (s, 1H), 6.57 (s, 1H), 5.18 (s, 2H), 3.78 – 3.72 (m, 1H), 3.14 – 3.06 (m, 1H), 2.72 (t, 1H), 2.34 – 2.30 (m, 4H), 2.03 – 1.94 (m, 1H), 1.93 – 1.79 (m, 2H). UPLC-MS-2: Rt = 0.73 min; MS m/z [M+H]⁺ 488.1. C-HPLC-5 (mobile phase: heptane+DEA/EtOH+DEA 50:50): Rt = 6.35 min. 2nd eluting isomer C-HPLC-5 (mobile phase: heptane+DEA/EtOH+DEA 50:50): Rt = 9.00 min.
57 – rac 57a - 1st eluting isomer 57b - 2nd eluting isomer	 N-(6-(4-(1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide	Analogous to Example 1 using Intermediate C-T9 and 2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid [CAS No. 345637-71-0] using C-SFC-6 (mobile phase: CO₂/MeOH +0.05%NH₃ (65:35))	1st eluting isomer C-SFC-14 (mobile phase: CO₂/MeOH +0.05%NH₃ (65:35)): Rt = 1.56 min. 2nd eluting isomer ¹H NMR (400 MHz, DMSO-d₆) δ 11.12 (s, 1H), 8.49 (d, 1H), 8.32 – 8.23 (m, 2H), 7.82 (d, 1H), 6.57 (s, 1H), 5.18 (s, 2H), 4.36 (dd, 1H), 3.27 – 3.21 (m, 1H), 3.13 – 3.05 (m, 1H), 2.49 – 2.45 (m, 1H), 2.43 – 2.36 (m, 1H), 2.31 (s, 3H), 2.28 – 2.22 (m, 1H), 2.14 – 2.05 (m, 1H). UPLC-MS-2: Rt = 0.75 min; MS m/z [M+H]⁺ 487.1. C-SFC-14 (mobile phase:

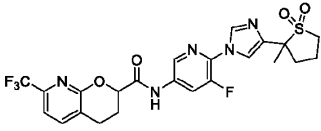
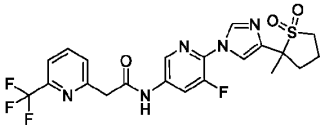
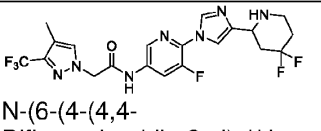
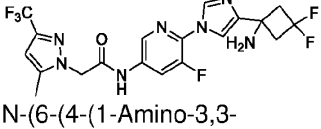
Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
			CO ₂ /MeOH +0.05%NH ₃ (65:35): Rt = 2.22 min.
58	 N-(5-Fluoro-6-(4-morpholino-1H-imidazol-1-yl)pyridin-3-yl)-2-(4-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide	Analogous to Example 5 using Intermediate C-T10 and 2-(4-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid [CAS No. 1823464-54-5]	¹ H NMR (600 MHz, DMSO-d ₆) δ 11.00 (s, 1H), 8.45 (d, 1H), 8.22 (dd, 1H), 8.06 (t, 1H), 7.81 (s, 1H), 6.98 (t, 1H), 5.15 (s, 2H), 3.76 - 3.66 (m, 4H), 3.08 - 2.98 (m, 4H), 2.16 - 2.10 (m, 3H). UPLC-MS-2: Rt = 0.91 min; MS m/z [M+H] ⁺ 454.2.
59	 2-(2-Fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(tetrahydrothiophen-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide	Analogous to Example 5 using Intermediate C-T11 and 2-(2-fluoro-3-(trifluoromethyl)phenyl)acetic acid [CAS No. 194943-83-4]	¹ H NMR (600 MHz, DMSO-d ₆) δ 10.94 (s, 1H), 8.47 (d, 1H), 8.28 (dd, 1H), 8.18 (t, 1H), 7.79 - 7.75 (m, 1H), 7.74 - 7.70 (m, 1H), 7.60 (q, 1H), 7.41 (t, 1H), 3.95 (s, 2H), 3.38 - 3.34 (m, 1H), 3.09 (dd, 1H), 2.93 (dd, 1H), 2.89 - 2.85 (m, 2H), 2.32 - 2.25 (m, 1H), 2.13 - 2.04 (m, 1H). UPLC-MS-2: Rt = 1.20 min; MS m/z [M+H] ⁺ 469.2.
60	 N-(6-(4-(3,3-Dimethylpiperazin-1-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide	Analogous to Example 9 using Intermediate D-M4 and 2,2-dimethylpiperazine	¹ H NMR (600 MHz, DMSO-d ₆) δ 8.41 (d, 1H), 8.23 (dd, 1H), 8.01 (t, 1H), 6.88 (s, 1H), 6.55 (s, 1H), 5.14 (s, 2H), 2.90 (dd, 2H), 2.86 - 2.80 (m, 2H), 2.73 (s, 2H), 2.31 (s, 3H), 1.74 (d, 1H), 1.10 (s, 6H). UPLC-MS-2: Rt = 0.65 min; MS m/z [M+H] ⁺ 481.2.
61	 2-(2-Fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-morpholino-1H-imidazol-1-yl)pyridin-3-yl)acetamide	Analogous to Example 9 using Intermediate D-T2 and morpholine	¹ H NMR (600 MHz, DMSO-d ₆) δ 10.92 (s, 1H), 8.45 (d, 1H), 8.26 (dd, 1H), 8.05 (t, 1H), 7.76 (t, 1H), 7.72 (t, 1H), 7.41 (t, 1H), 6.97 (t, 1H), 3.94 (s, 2H), 3.75 - 3.66 (m, 4H), 3.08 - 2.99 (m, 4H). UPLC-MS-2: Rt = 1.00 min; MS m/z [M+H] ⁺ 468.4.
62	 2-(2-Fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(4-methylpiperazin-1-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide	Analogous to Example 9 using Intermediate D-T2 and 1-methylpiperazine	¹ H NMR (600 MHz, DMSO-d ₆) δ 10.91 (s, 1H), 8.44 (d, 1H), 8.25 (dd, 1H), 8.03 (t, 1H), 7.76 (t, 1H), 7.74 - 7.70 (m, 1H), 7.41 (t, 1H), 6.93 (t, 1H), 3.94 (s, 2H), 3.05 (t, 4H), 2.42 (t, 4H), 2.21 (s, 3H). UPLC-MS-2: Rt = 0.78 min; MS m/z [M+H] ⁺ 481.5.

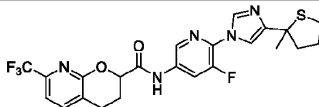
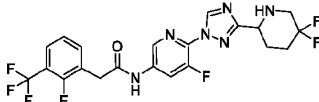
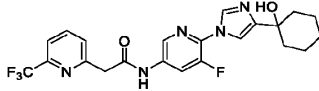
Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
63 - rac 63a – 1 st eluting isomer 63b – 2 nd eluting isomer	 N-(6-(4-(1,1-Dioxidotetrahydrothiophen-3-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 1/Steps 2-3 using Example 59 and mCPBA, DCM at 0°C. C-SFC-6 (mobile phase: CO ₂ /iPrOH +0.05%NH ₃ (50:50))	1 st eluting isomer C-SFC-14 (mobile phase: CO ₂ /iPrOH +0.05%NH ₃ (50:50)): Rt = 1.37 min. 2 nd eluting isomer ¹ H NMR (400 MHz, DMSO-d ₆) δ 10.97 (s, 1H), 8.48 (d, 1H), 8.29 (dd, 1H), 8.23 (t, 1H), 7.77 (t, 1H), 7.74 - 7.70 (m, 1H), 7.69 (q, 1H), 7.41 (t, 1H), 3.95 (s, 2H), 3.71 - 3.63 (m, 1H), 3.49 (dd, 1H), 3.30 - 3.26 (m, 1H), 3.21 - 3.15 (m, 2H), 2.48 - 2.43 (m, 1H), 2.30 - 2.19 (m, 1H). UPLC-MS-2: Rt = 0.92 min; MS m/z [M+H] ⁺ 501.1. C-SFC-14 (mobile phase: CO ₂ / iPrOH +0.05%NH ₃ (50:50)): Rt = 2.45 min.
64	 N-(5-Fluoro-6-(4-(4-methyl-2-oxopiperazin-1-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide	Analogous to Example 18 using Intermediate D-T3 and 4-methylpiperazin-2-one	¹ H NMR (600 MHz, DMSO-d ₆) δ 10.98 (s, 1H), 8.49 (d, 1H), 8.31 (dd, 1H), 8.19 (t, 1H), 8.12 - 8.05 (m, 2H), 7.83 (d, 1H), 7.77 (d, 1H), 4.07 (s, 2H), 3.91 (t, 2H), 3.17 (d, 2H), 2.74 (t, 2H), 2.28 (s, 3H). UPLC-MS-2: Rt = 0.56 min; MS m/z [M+H] ⁺ 478.3.
65	 2-(2-Fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(2-oxopiperazin-1-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide	Analogous to Example 18 using Intermediate D-T2 and tert-butyl 3-oxopiperazine-1-carboxylate followed by Boc-deprotection using TFA, DCM, RT, 30 min.	¹ H NMR (600 MHz, DMSO-d ₆) δ 10.97 (s, 1H), 8.48 (d, 1H), 8.30 (dd, 1H), 8.18 (t, 1H), 8.09 (t, 1H), 7.77 (t, 1H), 7.72 (t, 1H), 7.41 (t, 1H), 3.95 (s, 2H), 3.86 (t, 2H), 3.43 (s, 2H), 3.02 (t, 2H). UPLC-MS-2: Rt = 0.77 min; MS m/z [M+H] ⁺ 481.5.
66 - rac 66a – 1 st eluting isomer 66b – 2 nd eluting isomer	 N-(5-Fluoro-6-(4-(1-methyl-5-oxopyrrolidin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide	Analogous to Example 1/Steps 1 and 3 using Intermediate C-T12 and 2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid [CAS No. 345637-71-0]. C-SFC-16 (mobile	1 st eluting isomer ¹ H NMR (600 MHz, DMSO-d ₆) δ 11.17 (s, 1H), 8.48 (d, 1H), 8.30 - 8.25 (m, 2H), 7.76 (t, 1H), 6.57 (s, 1H), 5.19 (s, 2H), 4.64 - 4.59 (m, 1H), 2.56 (s, 3H), 2.47 - 2.41 (m, 1H), 2.31 (s, 3H), 2.30 - 2.25 (m, 2H), 2.10 - 2.04 (m, 1H). UPLC-MS-2: Rt = 0.77 min; MS m/z [M+H] ⁺ 466.1. C-SFC-15 (mobile phase:

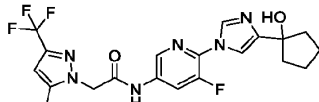
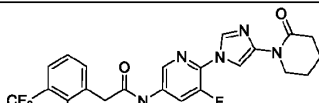
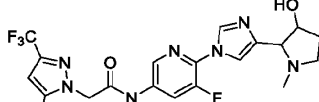
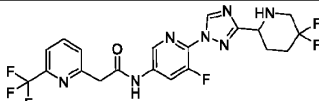
Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
		phase: CO ₂ /iPrOH +0.05%NH ₃ (63:37)	CO ₂ /iPrOH+0.05%NH ₃ (60:40)); Rt = 1.81 min. 2 nd eluting isomer C-SFC-15 (mobile phase: CO ₂ /iPrOH+0.05%NH ₃ (60:40)); Rt = 2.47 min.
67	 N-(5-Fluoro-6-(4-(2-oxopyrrolidin-1-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide	Analogous to Example 18 using Intermediate D-T3 and pyrrolidin-2-one	¹ H NMR (600 MHz, DMSO-d ₆) δ 8.45 (d, 1H), 8.37 (dd, 1H), 8.19 (s, 1H), 8.14 (s, 1H), 8.02 (t, 1H), 7.72 (t, 2H), 4.10 - 4.01 (m, 4H), 2.61 (t, 2H), 2.25 (p, 2H). UPLC-MS-2: Rt = 0.81 min; MS m/z [M+H] ⁺ 449.4.
68	 2-(2-Fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(4-hydroxy-2-oxopyrrolidin-1-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide	Analogous to Example 18 using Intermediate D-T2 and 4-hydroxypyrrolidin-2-one	¹ H NMR (600 MHz, DMSO-d ₆) δ 10.97 (s, 1H), 8.48 (d, 1H), 8.31 (dd, 1H), 8.17 (t, 1H), 7.97 (t, 1H), 7.77 (t, 1H), 7.74 - 7.70 (m, 1H), 7.41 (t, 1H), 5.34 (d, 1H), 4.43 (td, 1H), 4.02 (dd, 1H), 3.95 (s, 2H), 3.81 (dd, 1H), 2.81 (dd, 1H), 2.27 (dd, 1H). UPLC-MS-2: Rt = 0.86 min; MS m/z [M+H] ⁺ 482.3.
69	 2-(2-Fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(pyrrolidin-1-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide	Analogous to Example 9 using Intermediate D-T2 and pyrrolidine	¹ H NMR (600 MHz, DMSO-d ₆) δ 8.45 - 8.41 (m, 1H), 8.31 (dd, 1H), 8.10 (d, 1H), 7.73 - 7.68 (m, 1H), 7.66 (t, 1H), 7.37 (t, 1H), 6.90 (t, 1H), 3.94 (d, 2H), 3.25 (td, 4H), 2.03 - 1.97 (m, 4H). UPLC-MS-2: Rt = 0.74 min; MS m/z [M+H] ⁺ 470.5.
70	 N-(5-Fluoro-6-(4-morpholino-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide	Analogous to Example 9 using Intermediate D-M4 and morpholine	¹ H NMR (600 MHz, DMSO-d ₆) δ 11.06 (s, 1H), 8.44 (d, 1H), 8.24 (dd, 1H), 8.06 (t, 1H), 6.98 (t, 1H), 6.57 (s, 1H), 5.17 (s, 2H), 3.75 - 3.67 (m, 4H), 3.06 - 2.98 (m, 4H), 2.33 - 2.28 (m, 3H). UPLC-MS-2: Rt = 0.86 min; MS m/z [M+H] ⁺ 454.2.
71	 N-(6-(4-(5,6-Dihydro-1,4-dioxin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-(4,4,5,5-tetramethyl-1,3-dioxol-2-yl)ethyl)acetamide	Analogous to Example 10 using 2-(5,6-dihydro-1,4-dioxin-2-yl)-4,4,5,5-tetramethyl-	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.93 (s, 1H), 8.47 (d, 1H), 8.27 (dd, 1H), 8.23 - 8.18 (m, 1H), 7.81 - 7.68 (m, 2H), 7.52 - 7.47 (m, 1H), 7.41 (t, 1H), 6.76 (s, 1H), 4.22 - 4.15 (m, 2H), 4.15 - 4.06 (m, 2H), 3.95 (s, 2H).

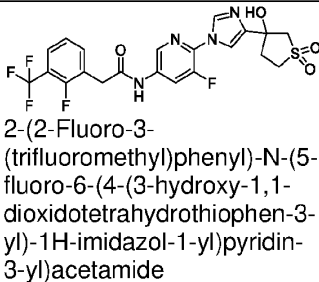
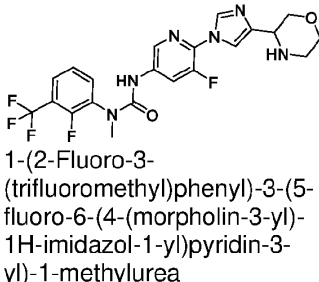
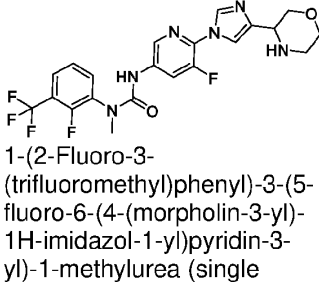
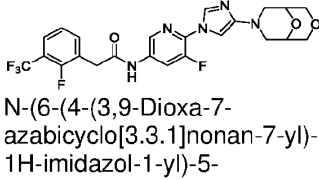
Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
	fluoro-3-(trifluoromethyl)phenyl)acetamide	1,3,2-dioxaborolane [CAS No. 1046811-97-5]	UPLC-MS-2: Rt = 1.06 min; MS m/z [M+H] ⁺ 467.2.
72 – rac 72a – 1st eluting isomer 72b – 2nd eluting isomer	 N-(6-(4-(1,4-Dioxan-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 21 using Example 71 followed by C-SFC-19 (mobile phase: CO ₂ /(MeOH+0.05%NH ₃) 80/20)	1 st eluting isomer ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.96 (s, 1H), 8.50 – 8.45 (m, 1H), 8.28 (dd, 1H), 8.22 – 8.17 (m, 1H), 7.81 – 7.68 (m, 2H), 7.67 – 7.62 (m, 1H), 7.41 (t, 1H), 4.57 (dd, 1H), 3.94 (s, 2H), 3.87 (dd, 1H), 3.81 (dd, 1H), 3.77 – 3.67 (m, 2H), 3.64 – 3.51 (m, 2H). UPLC-MS-2: Rt = 0.95 min; MS m/z [M+H] ⁺ 469.2. C-SFC-15 (mobile phase: CO ₂ /(MeOH+0.05%NH ₃) 80/20): Rt = 3.72 min. 2 nd eluting isomer C-SFC-15 (mobile phase: CO ₂ /(MeOH+0.05%NH ₃) 80/20): Rt = 4.10 min.
73 – rac 73a – 1st eluting isomer 73b – 2nd eluting isomer	 N-(6-(4-(4,4-Difluoropyrrolidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 25 using 2-(2-fluoro-3-(trifluoromethyl)phenyl)acetic acid [CAS No. 194943-83-4] and Intermediate C-T18 using C-SFC-21 ((mobile phase: CO ₂ /(EtOH+0.05%NH ₃) 55/45)	1 st eluting isomer ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.93 (s, 1H), 8.50 – 8.45 (m, 1H), 8.28 (dd, 1H), 8.23 – 8.18 (m, 1H), 7.81 – 7.67 (m, 2H), 7.65 (s, 1H), 7.41 (t, 1H), 4.40 – 4.28 (m, 1H), 3.95 (s, 2H), 3.33 – 3.28 (m, 1H), 3.23 – 3.03 (m, 2H), 2.63 – 2.52 (m, 1H), 2.45 – 2.27 (m, 1H). UPLC-MS-8: Rt = 0.88 min; MS m/z [M+H] ⁺ 488.1. C-SFC-5 (mobile phase: CO ₂ /(EtOH+0.05%NH ₃) 70/30): Rt = 2.45 min. 2 nd eluting isomer C-SFC-5 (mobile phase: CO ₂ /(EtOH+0.05%NH ₃) 70/30): Rt = 3.71 min.
74	 N-(5-Cyano-6-(1-(3,3-difluoro-1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)pyridin-3-yl)-2-(3-(trifluoromethyl)phenoxy)acetamide	Analogous to Example 15 using Example 3 and NaCNBH ₃	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.64 (s, 1H), 9.00 (d, 1H), 8.54 (d, 1H), 8.45 (s, 1H), 8.20 (s, 1H), 7.58 (t, 1H), 7.41 – 7.32 (m, 3H), 5.01 – 4.87 (m, 3H), 3.25 – 3.10 (m, 1H), 2.99 – 2.89 (m, 1H), 2.53 – 2.36 (m, 2H), 2.34 – 2.23 (m, 4H), 2.13 – 2.06 (m,

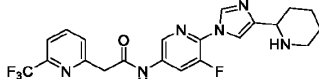
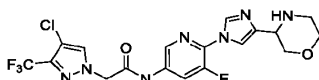
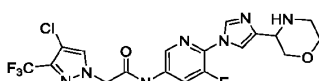
Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
			1H). UPLC-MS-2: Rt = 0.87 min; MS m/z [M+H] ⁺ 521.2.
75 – rac 75a – 1st eluting isomer 75b - 2nd eluting isomer	 N-(6-(4-(4,4-difluoropiperidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide	Analogous to Example 2 using Intermediate C-T8 and 2-(6-(trifluoromethyl)pyridin-2-yl)acetic acid [CAS No. 1000565-32-1]. C-SFC-18 (mobile phase: CO₂/iPrOH +0.05%NH₃ (48:52) after step 1 (racemate of Boc-protected following Boc deprotection gives 1st eluting isomer and 2nd eluting isomer	1st eluting isomer ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ 10.94 (s, 1H), 8.49 (s, 1H), 8.28 (dd, 1H), 8.20 (s, 1H), 8.09 (t, 1H), 7.82 (d, 1H), 7.76 (d, 1H), 7.61 (s, 1H), 4.07 (s, 2H), 3.77 (dd, 1H), 3.14 – 3.06 (m, 1H), 2.80 – 2.68 (m, 1H), 2.38 – 2.27 (m, 1H), 2.04 – 1.95 (m, 1H), 1.95 – 1.76 (m, 2H). UPLC-MS-8: Rt = 0.75 min; MS m/z [M+H]⁺ 485.1. 2nd eluting isomer ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ 10.94 (s, 1H), 8.49 (s, 1H), 8.28 (dd, 1H), 8.20 (s, 1H), 8.09 (t, 1H), 7.82 (d, 1H), 7.76 (d, 1H), 7.62 (s, 1H), 4.07 (s, 2H), 3.82 – 3.76 (m, 1H), 3.15 – 3.06 (m, 1H), 2.79 – 2.68 (m, 1H), 2.36 – 2.26 (m, 1H), 2.04 – 1.96 (m, 1H), 1.95 – 1.77 (m, 2H). UPLC-MS-8: Rt = 0.66 min; MS m/z [M+H]⁺ 485.1.
76 - rac 76a - 1st eluting isomer 76b - 2nd eluting isomer	 N-(6-(3-(5,5-difluoropiperidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide	Analogous to Example 2 using Intermediate C-T15. C-SFC-6 (mobile phase: CO₂/MeOH +0.05%NH₃ (85:15) after step 1 (racemate of Boc-protected intermediate) followed by Boc deprotection gives 1st eluting isomer and 2nd eluting isomer	1st eluting isomer ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ 11.15 (s, 1H), 9.05 (s, 1H), 8.52 (d, 1H), 8.30 (dd, 1H), 6.57 (s, 1H), 5.19 (s, 2H), 4.00 (d, 1H), 3.19 – 3.09 (m, 1H), 3.04 – 2.92 (m, 1H), 2.75 – 2.59 (m, 1H), 2.32 (s, 3H), 2.22 – 2.12 (m, 1H), 2.12 – 1.98 (m, 2H), 1.93 – 1.82 (m, 1H). UPLC-MS-2: Rt = 0.74 min; MS m/z [M+H]⁺ 489.2. 2nd eluting isomer ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ 11.15 (s, 1H), 9.05 (s, 1H), 8.52 (d, 1H), 8.30 (dd, 1H), 6.57 (s, 1H), 5.19 (s, 2H), 4.00 (d, 1H), 3.18 – 3.09 (m, 1H), 3.05 – 2.91 (m, 1H), 2.74 – 2.58 (m, 1H), 2.32 (s, 3H), 2.21 – 2.12 (m, 1H), 2.12 – 2.00 (m, 2H), 1.93 – 1.82 (m, 1H). UPLC-MS-8: Rt = 0.77 min; MS m/z [M+H]⁺ 489.2.

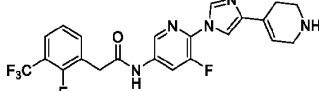
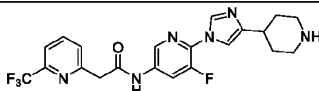
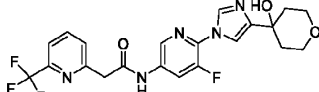
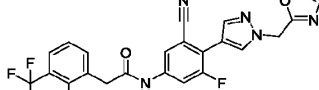
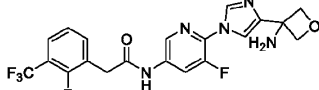
Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
77 (mixt. of diastereoisomers)	 N-(5-Fluoro-6-(4-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-7-(trifluoromethyl)-3,4-dihydro-2H-pyrano[2,3-b]pyridine-2-carboxamide	Analogous to Example 1 using Intermediate C-M1 and Intermediate A-M3 without chiral separation (mixture of diastereoisomers).	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.83 (s, 1H), 8.65 – 8.60 (m, 1H), 8.38 (dd, 1H), 8.30 – 8.25 (m, 1H), 7.88 – 7.81 (m, 2H), 7.48 (d, 1H), 5.15 (dd, 1H), 3.29 – 3.12 (m, 2H), 3.04 – 2.94 (m, 1H), 2.94 – 2.83 (m, 1H), 2.78 – 2.68 (m, 1H), 2.38 – 2.28 (m, 1H), 2.28 – 2.04 (m, 4H), 1.65 (s, 3H). UPLC-MS-2: Rt = 0.83 min; MS m/z [M+H] ⁺ 540.3.
78 - rac 78a - 1st eluting isomer 78b – 2 nd eluting isomer	 N-(5-Fluoro-6-(4-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide	Analogous to Example 1 using Intermediate C-M1 and 2-(6-(trifluoromethyl)pyridin-2-yl)acetic acid [CAS No. 1000565-32-1]. C-SFC-6 (mobile phase: CO ₂ /MeOH +0.05%NH ₃ (57:43)	1 st eluting isomer C-SFC-14 (mobile phase: CO ₂ /MeOH+0.05%NH ₃) 55/45): Rt = 1.56 min. 2 nd eluting isomer ¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ 10.99 (s, 1H), 8.50 (d, 1H), 8.31 (dd, 1H), 8.27 – 8.24 (m, 1H), 8.10 (t, 1H), 7.85 – 7.80 (m, 2H), 7.77 (d, 1H), 4.07 (s, 2H), 3.28 – 3.13 (m, 2H), 2.76 – 2.65 (m, 1H), 2.28 – 2.19 (m, 1H), 2.16 – 2.07 (m, 2H), 1.65 (s, 3H). UPLC-MS-8: Rt = 0.79 min; MS m/z [M+H] ⁺ 498.2. C-SFC-14 (mobile phase: CO ₂ /MeOH+0.05%NH ₃) 55/45): Rt = 2.26 min.
79	 N-(6-(4-(4,4-Difluoropiperidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(4-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide	Analogous to Example 11 using Intermediate C-T8 and 2-(4-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid [CAS No. 1823464-54-5]	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.02 (s, 1H), 8.51 – 8.46 (m, 1H), 8.25 (dd, 1H), 8.22 – 8.18 (m, 1H), 7.84 – 7.78 (m, 1H), 7.65 – 7.59 (m, 1H), 5.16 (s, 2H), 3.75 (d, 1H), 3.16 – 3.05 (m, 1H), 2.78 – 2.68 (m, 1H), 2.31 (m, 1H), 2.15 – 2.10 (m, 3H), 2.06 – 1.66 (m, 3H). UPLC-MS-2: Rt = 0.73 min; MS m/z [M+H] ⁺ 488.3.
80	 N-(6-(4-(1-Amino-3,3-difluorocyclobutyl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-fluoropyridin-3-yl)-2-(5-fluoropyridin-3-yl)-2-(5-fluoropyridin-3-yl)acetamide	Analogous to Example 11 using Intermediate C-T16	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.06 (s, 1H), 8.51 – 8.45 (m, 1H), 8.30 – 8.21 (m, 2H), 7.72 – 7.67 (m, 1H), 6.56 (s, 1H), 5.18 (s, 2H), 3.15 – 2.99 (m, 2H), 2.72 – 2.57 (m, 2H), 2.42 (s, 2H), 2.34 – 2.29 (m, 3H). UPLC-MS-8: Rt = 0.63 min; MS m/z [M+H] ⁺ 474.1.

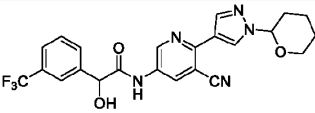
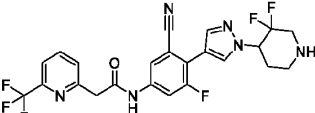
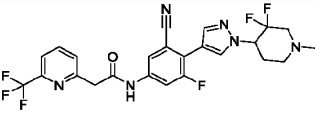
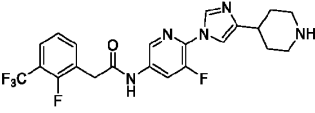
Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
	methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide		
81 (mixture of diastereoisomers)	 N-(5-Fluoro-6-(4-(2-methyltetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-7-(trifluoromethyl)-3,4-dihydro-2H-pyrano[2,3-b]pyridine-2-carboxamide	Analogous to Example 5 using Intermediate C-M1 and Intermediate A-M3 (mixture of diastereoisomers).	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.80 (s, 1H), 8.61 – 8.56 (m, 1H), 8.35 (dd, 1H), 8.23 – 8.17 (m, 1H), 7.85 (d, 1H), 7.59 (t, 1H), 7.48 (d, 1H), 5.18 – 5.11 (m, 1H), 3.05 – 2.94 (m, 3H), 2.94 – 2.82 (m, 1H), 2.44 – 2.36 (m, 1H), 2.35 – 2.27 (m, 1H), 2.22 – 2.13 (m, 1H), 2.13 – 2.04 (m, 2H), 1.95 – 1.85 (m, 1H), 1.71 (s, 3H). UPLC-MS-2: Rt = 1.19 min; MS m/z [M+H] ⁺ 508.1
82 - rac 82a – 1 st eluting isomer 82b – 2 nd eluting isomer	 N-(6-(3-(5,5-Difluoropiperidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-(trifluoromethyl)phenyl)acetamide	Analogous to Example 2 using Intermediate C-T15 and 2-(2-fluoro-3-(trifluoromethyl)phenyl)acetic acid [CAS No. 194943-83-4]. C-SFC-20 (mobile phase: CO ₂ /MeOH +0.05%NH ₃ (75:25) after step 1 (racemate of Boc-protected intermediate). Followed by Boc deprotection 1 st eluting isomer and 2 nd eluting isomer	1st eluting isomer ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ 11.02 (s, 1H), 9.03 (s, 1H), 8.52 (d, 1H), 8.32 (dd, 1H), 7.77 (t, 1H), 7.72 (t, 1H), 7.41 (t, 1H), 4.00 (d, 1H), 3.97 (s, 2H), 3.18 – 3.08 (m, 1H), 3.04 – 2.92 (m, 1H), 2.74 – 2.58 (m, 1H), 2.21 – 2.12 (m, 1H), 2.12 – 1.99 (m, 2H), 1.94 – 1.82 (m, 1H). UPLC-MS-8: Rt = 0.94 min; MS m/z [M+H]⁺ 503.1. 2nd eluting isomer ¹H NMR (600 MHz, DMSO-<i>d</i>₆) δ 11.02 (s, 1H), 9.03 (s, 1H), 8.52 (d, 1H), 8.31 (dd, 1H), 7.81 – 7.75 (m, 1H), 7.72 (t, 1H), 7.41 (t, 1H), 4.02 – 3.98 (m, 1H), 3.96 (s, 2H), 3.18 – 3.09 (m, 1H), 3.04 – 2.93 (m, 1H), 2.78 – 2.59 (m, 1H), 2.22 – 2.12 (m, 1H), 2.12 – 2.00 (m, 2H), 1.94 – 1.82 (m, 1H). UPLC-MS-8: Rt = 0.95 min; MS m/z [M+H]⁺ 503.1.
83	 N-(5-Fluoro-6-(4-(1-hydroxycyclohexyl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide	Analogous to Example 5 using Intermediate C-T17 and 2-(6-(trifluoromethyl)pyridin-2-yl)acetic acid [CAS No. 1000565-32-1].	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.93 (s, 1H), 8.50 – 8.45 (m, 1H), 8.28 (dd, 1H), 8.15 (t, 1H), 8.10 (t, 1H), 7.83 (d, 1H), 7.77 (d, 1H), 7.53 – 7.48 (m, 1H), 4.60 (s, 1H), 4.07 (s, 2H), 1.92 – 1.80 (m, 2H), 1.74 – 1.60 (m, 4H), 1.59 – 1.50 (m, 1H), 1.48 – 1.39 (m, 2H), 1.30 – 1.19 (m, 1H). UPLC-MS-2: Rt = 0.94 min; MS m/z [M+H] ⁺ 464.4.

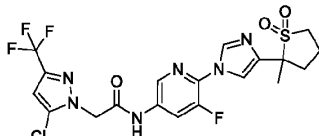
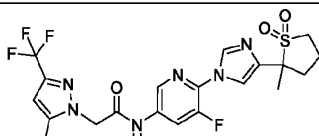
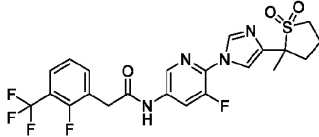
Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
84	 N-(5-Fluoro-6-(4-(1-hydroxycyclopentyl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide	Analogous to Example 5 using Intermediate C-T19 and 2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid [CAS No. 345637-71-0].	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.05 (s, 1H), 8.47 (d, 1H), 8.25 (dd, 1H), 8.20 – 8.14 (m, 1H), 7.55 – 7.50 (m, 1H), 6.57 (s, 1H), 5.18 (s, 2H), 4.77 (s, 1H), 2.32 (s, 3H), 2.05 – 1.93 (m, 2H), 1.86 – 1.64 (m, 6H). UPLC-MS-8: Rt = 0.92 min; MS m/z [M+H] ⁺ 453.1.
85	 2-(2-Fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(2-oxopiperidin-1-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide	Analogous to Example 18 using Intermediate D-T2 and piperidin-2-one [CAS No. 675-20-7].	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.94 (s, 1H), 8.48 (s, 1H), 8.30 (d, 1H), 8.16 (s, 1H), 8.07 (s, 1H), 7.83 – 7.57 (m, 2H), 7.41 (s, 1H), 4.05 – 3.85 (m, 4H), 2.44 – 2.24 (m, 2H), 1.87 (s, 2H), 1.78 (s, 2H). UPLC-MS-2: Rt = 1.02 min; MS m/z [M+H] ⁺ 480.4.
86	 N-(5-Fluoro-6-(4-(3-hydroxy-1-methylpyrrolidin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (trans isomer)	Analogous to step 1 & 2 of Example 26 using Intermediate C-M9	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ 11.08 (s, 1H), 8.47 (d, 1H), 8.26 (dd, 1H), 8.23 – 8.18 (m, 1H), 7.57 (d, 1H), 6.57 (s, 1H), 5.18 (s, 2H), 4.90 (d, 1H), 4.25 – 4.19 (m, 1H), 3.02 (d, 1H), 2.99 – 2.92 (m, 1H), 2.49 – 2.42 (m, 1H), 2.31 (s, 3H), 2.17 (s, 3H), 2.11 – 2.00 (m, 1H), 1.60 – 1.53 (m, 1H). UPLC-MS-8: Rt = 0.56 min; MS m/z [M+H] ⁺ 468.3.
87 - rac 87a – 1 st eluting isomer 87b – 2 nd eluting isomer	 N-(6-(3-(5,5-Difluoropiperidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide	Analogous to Example 2 using Intermediate C-T15 and 2-(6-(trifluoromethyl)pyridin-2-yl)acetic acid [CAS No. 1000565-32-1]. C-SFC-20 (mobile phase: CO ₂ /MeOH +0.05%NH ₃ (80:20) after step 1 (racemate of Boc-protected intermediate); Followed by Boc deprotection 1 st eluting isomer and 2 nd eluting isomer	1 st eluting isomer ¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ 11.06 (s, 1H), 9.04 (s, 1H), 8.53 (d, 1H), 8.32 (dd, 1H), 8.10 (t, 1H), 7.83 (d, 1H), 7.77 (d, 1H), 4.09 (s, 2H), 4.00 (d, 1H), 3.17 – 3.09 (m, 1H), 3.04 – 2.92 (m, 1H), 2.67 (s, 1H), 2.22 – 2.13 (m, 1H), 2.12 – 1.99 (m, 2H), 1.92 – 1.84 (m, 1H). UPLC-MS-8: Rt = 0.73 min; MS m/z [M+H] ⁺ 486.2. 2 nd eluting isomer ¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ 11.06 (s, 1H), 9.04 (s, 1H), 8.53 (d, 1H), 8.32 (dd, 1H), 8.10 (t, 1H), 7.83 (d, 1H), 7.77 (d, 1H), 4.09 (s, 2H), 4.03 – 3.97 (m, 1H), 3.17 – 3.09 (m, 1H), 3.04 – 2.92 (m, 1H), 2.64 (s, 1H), 2.21

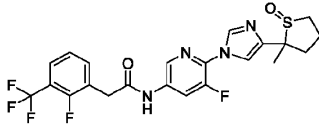
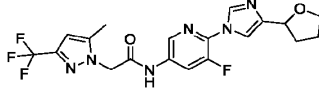
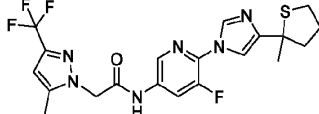
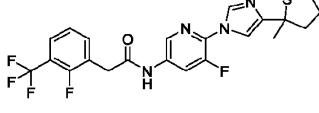
Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
			– 2.12 (m, 1H), 2.12 – 1.99 (m, 2H), 1.93 – 1.80 (m, 1H). UPLC-MS-8: Rt = 0.73 min; MS m/z [M+H] ⁺ 486.2.
88 – rac 88a – 1st eluting isomer 88b – 2nd eluting isomer	 2-(2-Fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(3-hydroxy-1,1-dioxidotetrahydrothiophen-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide	Analogous to Example 5 using Intermediate C-T20 and 2-(2-fluoro-3-(trifluoromethyl)phenyl)acetic acid [CAS No. 194943-83-4] followed by C-SFC-22 (mobile phase: CO ₂ /MeOH +0.05%NH ₃ (70:30))	1 st eluting isomer C-SFC-23 (mobile phase: CO ₂ /MeOH +0.05%NH ₃ (70:30)): Rt = 1.57 min. 2 nd eluting isomer ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.96 (s, 1H), 8.51 – 8.46 (m, 1H), 8.29 (dd, 1H), 8.27 – 8.24 (m, 1H), 7.81 – 7.70 (m, 2H), 7.70 – 7.66 (m, 1H), 7.41 (t, 1H), 6.12 (s, 1H), 3.95 (s, 2H), 3.51 (d, 1H), 3.38 – 3.31 (m, 3H), 2.61 – 2.54 (m, 1H), 2.41 – 2.31 (m, 1H). UPLC-MS-2: Rt = 0.85 min; MS m/z [M+H] ⁺ 517.1. C-SFC-23 (mobile phase: CO ₂ /MeOH +0.05%NH ₃ (70:30)): Rt = 2.16 min.
89	 1-(2-Fluoro-3-(trifluoromethyl)phenyl)-3-(5-fluoro-6-(4-(morpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-1-methylurea	Analogous to Example 27 using Intermediate C-T2 (Peak 1)	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ 9.13 (br s, 1H), 8.41 (br s, 1H), 8.06-8.19 (m, 2H), 7.86 (br s, 1H), 7.77 (br s, 1H), 7.55 (br s, 1H), 7.49 (m, 1H), 3.89 (m, 1H), 3.81 (m, 1H), 3.71 (m, 1H), 3.39-3.47 (m, 2H), 2.84 (br s, 2H). UPLC-MS-8: Rt = 0.70 min; MS m/z [M+H] ⁺ 483.2.
90	 1-(2-Fluoro-3-(trifluoromethyl)phenyl)-3-(5-fluoro-6-(4-(morpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-1-methylurea (single enantiomer)	Analogous to Example 27 using Intermediate C-T2 (Peak 2)	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ 9.12 (s, 1H), 8.41 (m, 1H), 8.14 (m, 1H), 8.12 (m, 1H), 7.86 (m, 1H), 7.77 (m, 1H), 7.54 (s, 1H), 7.49 (m, 1H), 3.89 (m, 1H), 3.79 (m, 1H), 3.70 (m, 1H), 3.41 (m, 1H), 2.83 (br s, 2H). UPLC-MS-8: Rt = 0.66 min; MS m/z [M+H] ⁺ 483.1.
91	 N-(6-(4-(3,9-Dioxabicyclo[3.3.1]nonan-7-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-(trifluoromethyl)phenyl)acetic acid	Analogous to Example 5 using Intermediate C-T22 and 2-(2-fluoro-3-(trifluoromethyl)phenyl)acetic acid	¹ H NMR (400 MHz, DMSO) δ 10.87 (s, 1H), 8.45 (s, 1H), 8.32 – 8.18 (m, 1H), 8.04 (s, 1H), 7.90 – 7.58 (m, 2H), 7.50 – 7.33 (m, 1H), 6.87 (s, 1H), 3.94 (s, 2H), 3.90 – 3.73 (m, 6H), 3.70 – 3.58 (m, 2H), 3.06 – 2.90 (m,

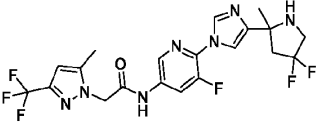
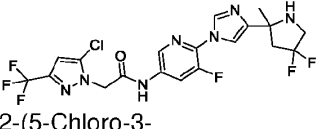
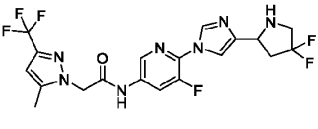
Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
	fluoro-3-(trifluoromethyl)phenyl)acetamide	[CAS No. 194943-83-4].	2H). UPLC-MS-2: Rt = 0.91 min; MS m/z [M+H] ⁺ 510.2.
92 – rac 92a – 1st eluting isomer 92b – 2nd eluting isomer	 N-(5-Fluoro-6-(4-(piperidin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide	Analogous to Example 25 using Intermediate C-T23 (rac) and 2-(6-(trifluoromethyl)pyridin-2-yl)acetic acid [CAS No. 1000565-32-1] using C-SFC-25 (mobile phase: CO ₂ /MeOH +0.05%NH ₃ (65:35 to 60:40 gradient))	1 st eluting isomer C-SFC-5 (mobile phase: CO ₂ /MeOH +0.05%NH ₃ (60:40)): Rt = 2.33 min. 2 nd eluting isomer ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.94 (s, 1H), 8.50 – 8.45 (m, 1H), 8.27 (dd, 1H), 8.18 – 8.13 (m, 1H), 8.13 – 8.05 (m, 1H), 7.86 – 7.80 (m, 1H), 7.76 (d, 1H), 7.48 (s, 1H), 4.07 (s, 2H), 3.59 – 3.52 (m, 1H), 3.04 – 2.96 (m, 1H), 2.68 – 2.58 (m, 1H), 2.39 (s, 1H), 1.95 – 1.88 (m, 1H), 1.82 – 1.74 (m, 1H), 1.57 – 1.50 (m, 1H), 1.46 – 1.28 (m, 3H). UPLC-MS-2: Rt = 0.49 min; MS m/z [M+H] ⁺ 449.5. C-SFC-5 (mobile phase: CO ₂ /MeOH +0.05%NH ₃ (60:40)): Rt = 3.35 min.
93	 2-(4-Chloro-3-(trifluoromethyl)-1H-pyrazol-1-yl)-N-(5-fluoro-6-(4-(morpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide	Analogous to Example 11 using Intermediate C-T2 (Peak 1) and 2-(4-chloro-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid [CAS No. 1006446-52-1].	(Ent-1) ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.06 (s, 1H), 8.50 – 8.45 (m, 1H), 8.37 – 8.32 (m, 1H), 8.24 (dd, 1H), 8.21 – 8.17 (m, 1H), 7.61 – 7.55 (m, 1H), 5.25 (s, 2H), 3.89 (dd, 1H), 3.80 (dd, 1H), 3.75 – 3.66 (m, 1H), 3.49 – 3.37 (m, 1H), 3.33 – 3.25 (m, 1H), 2.91 – 2.79 (m, 2H), 2.71 (s, 1H). UPLC-MS-8: Rt = 0.78 min; MS m/z [M+H] ⁺ 474.0.
94	 2-(4-Chloro-3-(trifluoromethyl)-1H-pyrazol-1-yl)-N-(5-fluoro-6-(4-(morpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide (single enantiomer)	Analogous to Example 11 using Intermediate C-T2 (Peak 2) and 2-(4-chloro-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid [CAS No. 1006446-52-1].	(Ent-2) ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.06 (s, 1H), 8.50 – 8.45 (m, 1H), 8.37 – 8.32 (m, 1H), 8.24 (dd, 1H), 8.21 – 8.17 (m, 1H), 7.60 – 7.55 (m, 1H), 5.25 (s, 2H), 3.89 (dd, 1H), 3.80 (dd, 1H), 3.75 – 3.66 (m, 1H), 3.47 – 3.36 (m, 1H), 3.33 – 3.25 (m, 1H), 2.91 – 2.80 (m, 2H), 2.69 (s, 1H). UPLC-MS-8: Rt = 0.68 min; MS m/z [M+H] ⁺ 474.1.

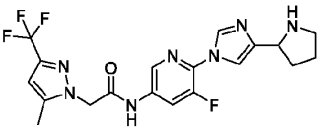
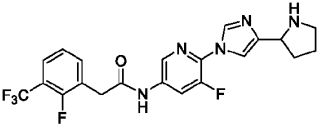
Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
95	 2-(2-Fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(1,2,3,6-tetrahydropyridin-4-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide	Analogous to Example 3 using Intermediate D-T2 and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate [CAS No. 286961-14-6].	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ 11.04 (s, 1H), 8.51 (d, 1H), 8.37 – 8.22 (m, 2H), 7.83 (s, 1H), 7.75 (dt, 2H), 7.41 (t, 1H), 6.51 – 6.32 (m, 1H), 3.96 (s, 2H), 3.88 – 3.64 (m, 2H), 3.31 (t, 2H), 2.61 (qd, 2H). UPLC-MS-2: Rt = 0.77 min; MS m/z [M+H] ⁺ 464.3.
96	 N-(5-Fluoro-6-(4-(piperidin-4-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide	Analogous to Example 11 using Intermediate C-T26 and 2-(6-(trifluoromethyl)pyridin-2-yl)acetic acid [CAS No. 1000565-32-1].	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.94 (s, 1H), 8.49 – 8.44 (m, 1H), 8.27 (dd, 1H), 8.17 – 8.05 (m, 2H), 7.83 (d, 1H), 7.76 (d, 1H), 7.39 (s, 1H), 4.06 (s, 2H), 3.02 – 2.93 (m, 2H), 2.63 – 2.53 (m, 3H), 2.29 – 1.94 (m, 1H), 1.90 – 1.81 (m, 2H), 1.52 – 1.37 (m, 2H). UPLC-MS-2: Rt = 0.51 min; MS m/z [M+H] ⁺ 449.4.
97	 N-(5-Fluoro-6-(4-(4-hydroxytetrahydro-2H-pyran-4-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide	Analogous to Example 5 using Intermediate C-T27 and 2-(6-(trifluoromethyl)pyridin-2-yl)acetic acid [CAS No. 1000565-32-1].	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.95 (s, 1H), 8.48 (d, 1H), 8.29 (dd, 1H), 8.21 – 8.16 (m, 1H), 8.10 (t, 1H), 7.83 (d, 1H), 7.77 (d, 1H), 7.59 – 7.53 (m, 1H), 4.97 (s, 1H), 4.07 (s, 2H), 3.79 – 3.69 (m, 2H), 3.67 – 3.58 (m, 2H), 2.13 – 1.99 (m, 2H), 1.60 (d, 2H). UPLC-MS-2: Rt = 0.69 min; MS m/z [M+H] ⁺ 466.1.
98	 N-(3-Cyano-5-fluoro-4-(1-(oxazol-2-ylmethyl)-1H-pyrazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 28 using Intermediate C-T28.	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ 10.83 (s, 1H), 8.35 (s, 1H), 8.12 (d, 1H), 7.90 (s, 1H), 7.89 – 7.83 (m, 2H), 7.78 – 7.68 (m, 2H), 7.40 (t, 1H), 7.24 (d, 1H), 5.66 (s, 2H), 3.92 (s, 2H). UPLC-MS-2: Rt = 1.00 min; MS m/z [M+H] ⁺ 488.2.
99	 N-(6-(4-(3-Amino-oxetan-3-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-(trifluoromethyl)phenyl)acetamide	Analogous to Example 11 using Intermediate C-T29 and 2-(2-(trifluoromethyl)phenyl)acetic acid [CAS No. 1000565-32-1].	¹ H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.48 (d, 1H), 8.33 – 8.23 (m, 2H), 7.81 – 7.66 (m, 3H), 7.41 (t, 1H), 4.82 (d, 2H), 4.51 (d, 2H), 3.95 (s, 2H), 2.88 (s, 2H). UPLC-MS-8: Rt = 0.73 min; MS m/z [M+H] ⁺ 454.3.

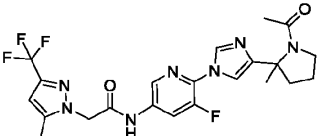
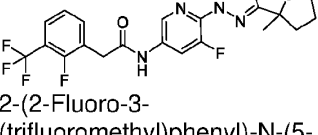
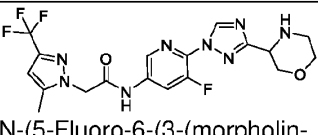
Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
	fluoro-3-(trifluoromethyl)phenyl)acetamide	(trifluoromethyl)phenyl)acetic acid [CAS No. 194943-83-4].	
100	 N-(5-Cyano-6-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)pyridin-3-yl)-2-hydroxy-2-(3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 28 using Intermediate C-M10 and 2-hydroxy-2-(3-(trifluoromethyl)phenyl)acetic acid [CAS No. 349-10-0].	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ 10.64 (s, 1H), 9.11 (d, 1H), 8.59 (d, 1H), 8.50 (d, 1H), 8.15 (d, 1H), 7.88 (d, 1H), 7.83 (d, 1H), 7.73 – 7.66 (m, 1H), 7.63 (t, 1H), 6.95 (s, 1H), 5.53 (dd, 1H), 5.34 (s, 1H), 3.95 (dtd, 1H), 3.67 (ddd, 1H), 2.21 – 2.02 (m, 1H), 2.02 – 1.87 (m, 2H), 1.79 – 1.63 (m, 1H), 1.56 (tt, 2H). UPLC-MS-2: Rt = 1.06 min; MS m/z [M-H] ⁻ 470.2.
101	 N-(3-Cyano-4-(1-(3,3-difluoropiperidin-4-yl)-1H-pyrazol-4-yl)-5-fluorophenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide	Analogous to Example 6 using Intermediate B-M3 and D-T4.	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.84 (s, 1H), 8.19 (s, 1H), 8.09 (t, 1H), 7.94 – 7.90 (m, 1H), 7.90 – 7.85 (m, 2H), 7.83 (d, 1H), 7.76 (d, 1H), 5.06 – 4.90 (m, 1H), 4.05 (s, 2H), 3.24 – 3.13 (m, 1H), 3.09 – 3.01 (m, 1H), 2.98 – 2.83 (m, 1H), 2.75 – 2.66 (m, 1H), 2.64 – 2.54 (m, 1H), 2.35 – 2.21 (m, 1H), 2.11 – 2.02 (m, 1H). UPLC-MS-2: Rt = 0.68 min; MS m/z [M+H] ⁺ 509.2.
102	 N-(3-Cyano-4-(1-(3,3-difluoro-1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)-5-fluorophenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide	Analogous to Example 15 using Example 101 and NaCNBH ₃	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.84 (s, 1H), 8.22 (s, 1H), 8.09 (t, 1H), 7.94 – 7.91 (m, 1H), 7.90 – 7.85 (m, 2H), 7.83 (d, 1H), 7.76 (d, 1H), 4.97 – 4.81 (m, 1H), 4.05 (s, 2H), 3.22 – 3.11 (m, 1H), 2.97 – 2.90 (m, 1H), 2.52 – 2.36 (m, 2H), 2.32 – 2.22 (m, 4H), 2.13 – 2.04 (m, 1H). UPLC-MS-2: Rt = 0.79 min; MS m/z [M+H] ⁺ 523.3.
103	 2-(2-Fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(piperidin-4-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide	Analogous to Example 21 using Example 95 without HOAc.	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ 10.93 (s, 1H), 8.46 (d, 1H), 8.27 (dd, 1H), 8.15 (t, 1H), 7.74 (dt, 2H), 7.50 – 7.35 (m, 2H), 3.95 (s, 2H), 3.10 – 2.94 (m, 2H), 2.69 – 2.56 (m, 3H), 1.93 – 1.79 (m, 2H), 1.47 (dd, 2H). UPLC-MS-2: Rt = 0.75 min; MS m/z [M-H] ⁻ 466.3.

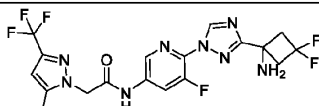
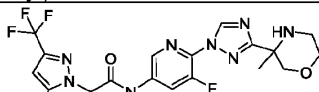
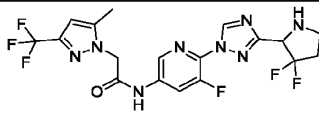
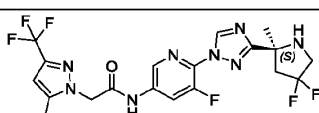
Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
104 – rac 104a – 1st eluting isomer 104b – 2nd eluting isomer	 2-(5-Chloro-3-(trifluoromethyl)-1H-pyrazol-1-yl)-N-(5-fluoro-6-(4-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide	Analogous to Example 1 using 2-(5-chloro-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid [CAS No. 922516-24-3] using C-SFC-22 (mobile phase: CO₂/MeOH +0.05%NH₃ (70:30))	1st eluting isomer C-SFC-5 (mobile phase: CO₂/MeOH +0.05%NH₃ (70:30)): Rt = 1.76 min. 2nd eluting isomer ¹H NMR (600 MHz, DMSO-d₆) δ 11.20 (s, 1H), 8.49 (d, 1H), 8.30 - 8.25 (m, 2H), 7.83 (d, 1H), 7.14 (s, 1H), 5.30 (s, 2H), 3.28 - 3.21 (m, 1H), 3.17 (ddd, 1H), 2.76 - 2.67 (m, 1H), 2.23 (dddd, 1H), 2.17 - 2.08 (m, 2H), 1.65 (s, 3H). UPLC-MS-2: Rt = 0.91 min; MS m/z [M+H]⁺ 521.2. C-SFC-5 (mobile phase: CO₂/MeOH +0.05%NH₃ (70:30)): Rt = 2.41 min.
105 – rac 105a – 1st eluting isomer 105b – 2nd eluting isomer	 N-(5-Fluoro-6-(4-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide	Analogous to Example 1 using 2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid [CAS No. 345637-71-0] using C-SFC-29 (mobile phase: CO₂/MeOH +0.05%NH₃ (65:35))	1st eluting isomer C-SFC-14 (mobile phase: CO₂/MeOH +0.05%NH₃ (65:35)): Rt = 1.43 min. 2nd eluting isomer ¹H NMR (600 MHz, DMSO-d₆) δ 11.11 (s, 1H), 8.49 (d, 1H), 8.33 - 8.20 (m, 2H), 7.83 (s, 1H), 6.57 (s, 1H), 5.19 (s, 2H), 3.27 - 3.14 (m, 2H), 2.72 (dd, 1H), 2.31 (s, 3H), 2.26 - 2.20 (m, 1H), 2.14 (dd, 2H), 1.65 (s, 3H). UPLC-MS-2: Rt = 0.82 min; MS m/z [M+H]⁺ = 501.2. C-SFC-14 (mobile phase: CO₂/MeOH +0.05%NH₃ (65:35)): Rt = 1.98 min.
106 – rac 106a – 1st eluting isomer 106b – 2nd eluting isomer confirmed by x-ray	 2-(2-Fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide	Analogous to Example 1 using 2-(2-fluoro-3-(trifluoromethyl)phenyl)acetic acid [CAS No. 194943-83-4] using C-SFC-30 (mobile phase: CO₂/MeOH +0.05%NH₃ (65:35)) KKM222 = 1st eluting isomer and GUE677 =	(R-enantiomer) 1st eluting isomer C-SFC-14 (mobile phase: CO₂/MeOH +0.05%NH₃ (65:35)): Rt = 1.46 min. (S-enantiomer) 2nd eluting isomer ¹H NMR (600 MHz, DMSO-d₆) δ 10.97 (s, 1H), 8.49 (d, 1H), 8.31 (dd, 1H), 8.26 (t, 1H), 7.82 (t, 1H), 7.77 (t, 1H), 7.72 (t, 1H), 7.41 (t, 1H), 3.95 (s, 2H), 3.26 - 3.15 (m, 2H), 2.73 - 2.69 (m, 1H), 2.23 (tq, 1H), 2.16 - 2.09 (m, 2H), 1.65 (s, 3H). UPLC-MS-

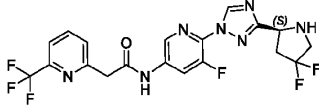
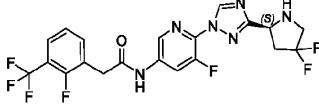
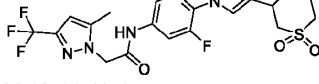
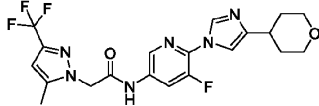
Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
		2 nd eluting isomer	2: Rt = 0.97 min; MS m/z [M+H] ⁺ = 515.2. C-SFC-14 (mobile phase: CO ₂ /MeOH +0.05%NH ₃ (65:35)): Rt = 2.07 min.
107	 2-(2-Fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(2-methyl-1-oxidotetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide	Obtained as an additional product in the synthesis of Example 106	¹ H NMR (600 MHz, DMSO-d ₆) δ 10.97 (s, 1H), 8.49 (d, 1H), 8.30 (dd, 1H), 8.25 (t, 1H), 7.77 (t, 1H), 7.72 (t, 2H), 7.41 (t, 1H), 3.95 (s, 2H), 3.46 (ddd, 1H), 2.67 (dt, 2H), 2.33 (tt, 1H), 2.15 - 2.04 (m, 2H), 1.43 (s, 3H). UPLC-MS-2: Rt = 0.94 min; MS m/z [M+H] ⁺ = 499.2.
108 – rac 108a – 1st eluting isomer 108b – 2nd eluting isomer	 N-(5-Fluoro-6-(4-(2-methyl-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide	Analogous to Example 5 using Intermediate C-T30 and 2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid [CAS No. 345637-71-0] followed by C-SFC-17 (mobile phase: CO ₂ /MeOH +0.05%NH ₃ (65:35))	1 st eluting isomer ¹ H NMR (600 MHz, DMSO-d ₆) δ 11.11 (s, 1H), 8.46 (d, 1H), 8.26 (dd, 1H), 8.19 (t, 1H), 7.62 - 7.58 (m, 1H), 6.57 (s, 1H), 5.17 (s, 2H), 4.84 (t, 1H), 3.88 (td, 1H), 3.73 (td, 1H), 2.31 (d, 3H), 2.19 - 2.10 (m, 1H), 2.05 - 1.85 (m, 3H). UPLC-MS-2: Rt = 0.92 min; MS m/z [M+H] ⁺ = 439. C-SFC-15 (mobile phase: CO ₂ /MeOH +0.05%NH ₃ (65:35)): Rt = 1.43 min. 2 nd eluting isomer C-SFC-15 (mobile phase: CO ₂ /MeOH +0.05%NH ₃ (65:35)): Rt = 2.93 min.
109	 N-(5-Fluoro-6-(4-(2-methyltetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide	Analogous to Example 5 using 2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid [CAS No. 345637-71-0] and Intermediate C-M1	¹ H NMR (600 MHz, DMSO-d ₆) δ 11.08 (s, 1H), 8.46 (d, 1H), 8.26 (dd, 1H), 8.20 (s, 1H), 7.58 (t, 1H), 6.57 (s, 1H), 5.18 (s, 2H), 2.98 (td, 2H), 2.42 - 2.39 (m, 1H), 2.31 (s, 3H), 2.15 - 2.03 (m, 2H), 1.91 (ddd, 1H), 1.71 (s, 3H). UPLC-MS-2: Rt = 1.23 min; MS m/z [M+H] ⁺ = 483.2.
110	 2-(2-fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(2-methyl-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide	Analogous to Example 5 using 2-(2-fluoro-3-(trifluoromethyl)phenyl)acetic acid	¹ H NMR (600 MHz, DMSO-d ₆) δ 10.94 (s, 1H), 8.46 (d, 1H), 8.28 (dd, 1H), 8.18 (t, 1H), 7.74 (dt, 2H), 7.57 (d, 1H), 7.41 (t, 1H), 3.95 (s, 2H), 2.98 (td, 2H), 2.39

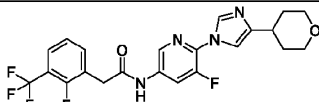
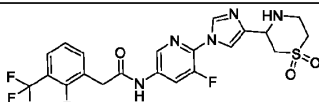
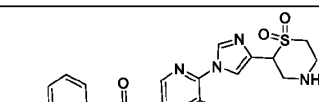
Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
	2-(2-Fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(2-methyltetrahydrothiophen-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide	[CAS No. 194943-83-4] and Intermediate C-M1	(td, 1H), 2.14 - 2.04 (m, 2H), 1.90 (ddd, 1H), 1.71 (s, 3H). UPLC-MS-2: Rt = 1.25 min; MS m/z [M+H] ⁺ = 483.2.
111 – rac 111a – 1st eluting isomer 111b – 2nd eluting isomer	 N-(6-(4-(4,4-Difluoro-2-methylpyrrolidin-2-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide	Analogous to Example 25 using Intermediate C-T31 using C-SFC-31 (mobile phase: CO ₂ /EtOH +0.05%NH ₃ (83:17 to 80:20))	1st eluting isomer ¹H NMR (600 MHz, DMSO-d₆) δ 11.10 (s, 1H), 8.46 (d, 1H), 8.27 (dd, 1H), 8.22 (t, 1H), 7.63 (t, 1H), 6.57 (s, 1H), 5.17 (s, 2H), 3.26 (dq, 1H), 3.19 (d, 2H), 2.78 (ddd, 1H), 2.31 (d, 3H), 2.25 (ddd, 1H), 1.45 (s, 3H). UPLC-MS-8: Rt = 0.69 min; MS m/z [M+H]⁺ = 488. C-SFC-7 (mobile phase: CO₂/EtOH +0.05%NH₃ (80:20)): Rt = 1.94 min. 2nd eluting isomer C-SFC-7 (mobile phase: CO₂/EtOH +0.05%NH₃ (80:20)): Rt = 2.31 min.
112	 2-(5-Chloro-3-(trifluoromethyl)-1H-pyrazol-1-yl)-N-(6-(4-(4,4-difluoro-2-methylpyrrolidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)acetamide	Analogous to Example 25 using 2-(5-chloro-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid [CAS No. 922516-24-3] and Intermediate B-M17 using C-SFC-31 (mobile phase: CO ₂ /EtOH +0.05%NH ₃ (80:20 to 77:23))	¹H NMR (600 MHz, DMSO-d₆) δ 11.19 (s, 1H), 8.46 (d, 1H), 8.25 (dd, 1H), 8.22 (t, 1H), 7.64 (d, 1H), 7.14 (s, 1H), 5.29 (s, 2H), 3.19 (d, 3H), 2.78 (ddd, 1H), 2.25 (ddd, 1H), 1.45 (s, 3H). UPLC-MS-8: Rt = 0.78 min, MS m/z [M+H]⁺ = 508.0/510.0. C-SFC-7 (mobile phase: CO₂/EtOH +0.05%NH₃ (80:20)): Rt = 3.03 min. C-SFC-7 (mobile phase: CO₂/EtOH +0.05%NH₃ (80:20)): Rt = 2.43 min.
113 – rac 113a – 1st eluting isomer 113b – 2nd eluting isomer	 N-(6-(4-(4,4-Difluoropyrrolidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide	Analogous to Example 25 using Intermediate C-T18 using C-SFC-26 (mobile phase: CO ₂ /IPA +0.05%NH ₃ (50:50))	1st eluting isomer ¹H-NMR (600 MHz, DMSO-d₆) δ 11.10 (s, 1H), 8.47 (d, 1H), 8.27 (dd, 1H), 8.23 (t, 1H), 7.66 (q, 1H), 6.57 (s, 1H), 5.18 (s, 2H), 4.33 (q, 1H), 3.29 (d, 1H), 3.11 (d, 2H), 2.59 - 2.51 (m, 1H), 2.42 - 2.32 (m, 1H), 2.31 (d, 3H). UPLC-MS-2 : Rt = 0.61 min; MS m/z [M+H]⁺ = 474.3. C-SFC-5

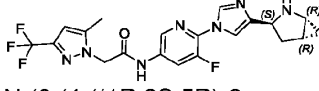
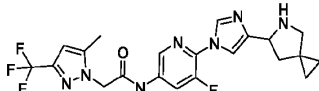
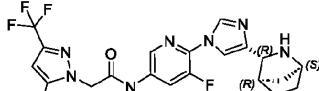
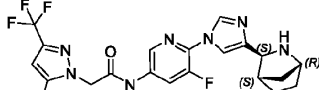
Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
	methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide		(mobile phase: CO ₂ /IPA +0.05%NH ₃ (70:30)): Rt = 1.77 min. 2 nd eluting isomer C-SFC-5 (mobile phase: CO ₂ /IPA +0.05%NH ₃ (70:30)): Rt = 2.65 min.
114- rac 114a – 1 st eluting isomer 114b – 2 nd eluting isomer	 N-(5-Fluoro-6-(4-(pyrrolidin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide	Analogous to Example 25 using Intermediate C-T32 using C-SFC-32 (mobile phase: CO ₂ /MeOH +0.05%NH ₃ (55:45))	1 st eluting isomer C-SFC-15 (mobile phase: CO ₂ /MeOH +0.05%NH ₃ (60:40)): Rt = 1.70 min. 2 nd eluting isomer ¹ H NMR (600 MHz, DMSO-d ₆) δ 11.09 (s, 1H), 8.49 - 8.42 (m, 1H), 8.26 (d, 1H), 8.17 (s, 1H), 7.55 (s, 1H), 6.57 (s, 1H), 5.18 (s, 2H), 4.03 (s, 1H), 2.97 (s, 1H), 2.79 (s, 1H), 2.31 (s, 3H), 1.99 (s, 1H), 1.72 (s, 3H). UPLC-MS-2: Rt = 0.62 min; MS m/z [M+H] ⁺ = 438.4. C-SFC-15 (mobile phase: CO ₂ /MeOH +0.05%NH ₃ (60:40)): Rt = 2.98 min
115 – rac 115a – 1 st eluting isomer 115b – 2 nd eluting isomer	 2-(2-Fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(pyrrolidin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide	Analogous to Example 25 using 2-(2-fluoro-3-(trifluoromethyl)phenyl)acetic acid [CAS No. 194943-83-4] and Intermediate C-T32 using C-SFC-33 (mobile phase: CO ₂ /MeOH +0.05%NH ₃ (60:40 to 45:55))	1 st eluting isomer C-SFC-7 (mobile phase: CO ₂ /MeOH +0.05%NH ₃ (60:40)): Rt = 0.84 min. 2 nd eluting isomer ¹ H NMR (600 MHz, DMSO-d ₆) δ 10.93 (s, 1H), 8.46 (d, 1H), 8.27 (dd, 1H), 8.16 (s, 1H), 7.77 (t, 1H), 7.72 (t, 1H), 7.54 (s, 1H), 7.41 (t, 1H), 4.03 (t, 1H), 3.95 (s, 2H), 2.97 (dt, 1H), 2.79 (dt, 1H), 2.04 - 1.95 (m, 1H), 1.79 - 1.66 (m, 3H). UPLC-MS-2: Rt = 0.85 min; MS m/z [M+H] ⁺ = 452.4. C-SFC-7 (mobile phase: CO ₂ /MeOH +0.05%NH ₃ (60:40)): Rt = 2.13 min.

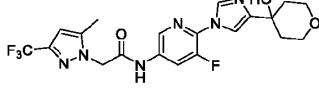
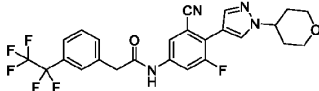
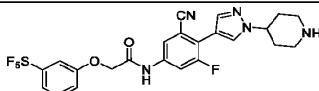
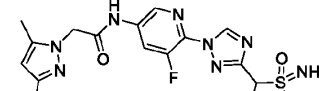
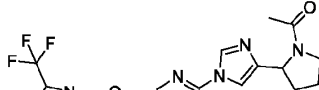
Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
116	 N-(6-(4-(1-Acetyl-2-methylpyrrolidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide	Analogous to Example 12 using Example 150	¹ H NMR (600 MHz, DMSO-d ₆) δ 11.08 (s, 1H), 8.46 (s, 1H), 8.26 (d, 1H), 8.13 (s, 1H), 7.43 (d, 1H), 6.76 – 6.48 (m, 1H), 5.43 – 5.10 (m, 2H), 3.61 (d, 2H), 2.36 – 2.28 (m, 3H), 2.18 (s, 1H), 2.00 – 1.58 (m, 9H). UPLC-MS-8: Rt = 0.92 min; MS m/z [M+H] ⁺ = 494.3.
117 – rac 117a – 1st eluting isomer 117b – 2nd eluting isomer	 2-(2-Fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(3-(2-methyl-1,1-dioxidotetrahydrothiophen-2-yl)-1H-1,2,4-triazol-1-yl)pyridin-3-yl)acetamide	Analogous to Example 5 using Intermediate C-T33 and 2-(2-fluoro-3-(trifluoromethyl)phenyl)acetic acid [CAS No. 194943-83-4] followed by C-SFC-34 (mobile phase: CO ₂ /MeOH +0.1%NH ₄ OH (50:50))	1st eluting isomer ¹H NMR (600 MHz, DMSO-d₆) δ 11.06 (s, 1H), 9.13 (s, 1H), 8.53 (d, 1H), 8.35 (dd, 1H), 7.77 (t, 1H), 7.73 (t, 1H), 7.41 (t, 1H), 3.97 (s, 2H), 3.30 (d, 1H), 3.23 (ddd, 1H), 2.94 (dt, 1H), 2.35 – 2.28 (m, 1H), 2.25 – 2.19 (m, 1H), 2.16 (dt, 1H), 1.73 (s, 3H). UPLC-MS-8: Rt = 0.98 min; MS m/z [M+H]⁺ = 516.2. C-SFC-7 (mobile phase: CO₂/MeOH +0.05%NH₃ (75:25)): Rt = 1.61 min. 2nd eluting isomer C-SFC-7 (mobile phase: CO₂/MeOH +0.05%NH₃ (75:25)): Rt = 2.02 min.
118 – rac 118a – 1st eluting isomer 118b – 2nd eluting isomer	 N-(5-Fluoro-6-(3-(morpholin-3-yl)-1H-1,2,4-triazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide	Analogous to Example 25 using Intermediate C-T34 using C-SFC-35 (mobile phase: CO ₂ /MeOH +0.05%NH ₃ (60:40))	1st eluting isomer ¹H NMR (600 MHz, DMSO-d₆) δ 11.18 (s, 1H), 9.05 (s, 1H), 8.52 (d, 1H), 8.30 (dd, 1H), 6.57 (s, 1H), 5.20 (s, 2H), 3.98 (dd, 1H), 3.94 (dd, 1H), 3.71 (dt, 1H), 3.57 (t, 1H), 3.46 (td, 1H), 2.91 – 2.80 (m, 2H), 2.73 (s, 1H), 2.32 (s, 3H). UPLC-MS-8: Rt = 0.49 min; MS m/z [M+H]⁺ = 455.2. C-SFC-15 (mobile phase: CO₂/MeOH +0.05%NH₃ (65:35)): Rt = 2.12 min. 2nd eluting isomer C-SFC-15 (mobile phase: CO₂/MeOH +0.05%NH₃ (65:35)): Rt = 2.80 min.

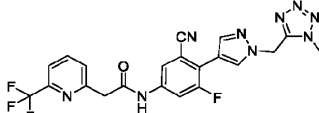
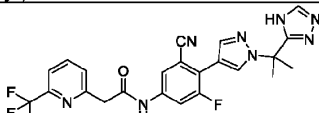
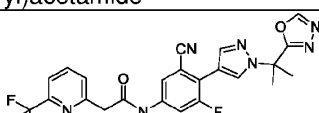
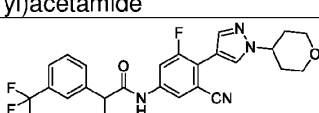
Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
119	 N-(6-(3-(1-Amino-3,3-difluorocyclobutyl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide	Analogous to Example 11 using Intermediate C-T35	¹ H NMR (600 MHz, DMSO-d ₆) δ 11.17 (s, 1H), 9.07 (s, 1H), 8.52 (d, 1H), 8.31 (dd, 1H), 6.57 (s, 1H), 5.19 (s, 2H), 3.18 (td, 2H), 2.78 (td, 2H), 2.55 (s, 2H), 2.32 (s, 3H). UPLC-MS-8: Rt = 0.68 min; MS m/z [M+H] ⁺ = 475.2.
120 – rac 120a – 1 st eluting isomer 120b – 2 nd eluting isomer	 N-(5-Fluoro-6-(3-(3-methylmorpholin-3-yl)-1H-1,2,4-triazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide	Analogous to Example 25 using Intermediate C-T36 using C-SFC-33 (mobile phase: CO ₂ /MeOH +0.05%NH ₃ (75:25))	1 st eluting isomer ¹ H NMR (600 MHz, DMSO-d ₆) δ 11.18 (s, 1H), 9.03 (d, 1H), 8.52 (d, 1H), 8.31 (dd, 1H), 6.57 (s, 1H), 5.20 (s, 2H), 4.16 (d, 1H), 3.57 (dt, 1H), 3.51 - 3.45 (m, 1H), 3.42 (d, 1H), 2.92 (ddd, 1H), 2.76 (s, 1H), 2.67 (dt, 1H), 2.35 - 2.29 (m, 3H), 1.23 (s, 3H). UPLC-MS-8: Rt = 0.53 min; MS m/z [M+H] ⁺ = 469.3. C-SFC-7 (mobile phase: CO ₂ /MeOH +0.05%NH ₃ (75:25)): Rt = 1.39 min. 2 nd eluting isomer C-SFC-7 (mobile phase: CO ₂ /MeOH +0.05%NH ₃ (75:25)): Rt = 2.71 min.
121 – rac 121a – 1 st eluting isomer 121b – 2 nd eluting isomer	 N-(6-(3-(3,3-Difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide	Analogous to Example 25 using Intermediate C-T37 using C-SFC-36 (mobile phase: CO ₂ /IPA +0.05%NH ₃ (63:37))	1 st eluting isomer ¹ H-NMR (600 MHz, DMSO-d ₆) δ 11.19 (s, 1H), 9.11 (s, 1H), 8.53 (d, 1H), 8.31 (dd, 1H), 6.57 (s, 1H), 5.20 (s, 2H), 4.40 (dd, 1H), 3.31 - 3.27 (m, 1H), 3.10 - 2.99 (m, 1H), 2.39 - 2.33 (m, 2H), 2.32 (s, 3H). UPLC-MS-8: Rt = 0.72 min; MS m/z [M+H] ⁺ = 475. C-SFC-15 (mobile phase: CO ₂ /MeOH +0.05%NH ₃ (63:37)): Rt = 1.37 min. 2 nd eluting isomer C-SFC-15 (mobile phase: CO ₂ /MeOH +0.05%NH ₃ (63:37)): Rt = 2.30 min.
122		Analogous to Example 11 using Intermediate C-T38	¹ H NMR (600 MHz, DMSO-d ₆) δ 11.17 (s, 1H), 9.05 (s, 1H), 8.52 (d, 1H), 8.31 (dd, 1H), 6.57 (s, 1H), 5.20 (s, 2H), 4.81 (s, 0H), 3.28 - 3.19 (m, 3H), 2.97 - 2.87

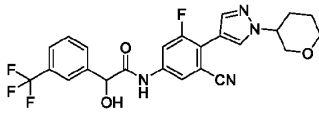
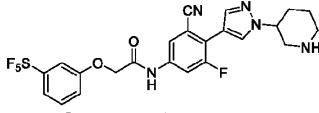
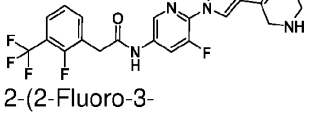
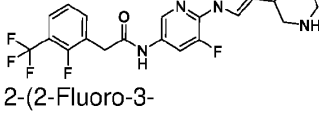
Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
	(S)-N-(6-(3-(4,4-Difluoro-2-methylpyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide		(m, 1H), 2.32 (s, 4H), 1.56 (s, 3H). UPLC-MS-8: Rt = 0.83 min; MS m/z [M+H] ⁺ = 489.1.
123	 (S)-N-(6-(3-(4,4-Difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide	Analogous to Example 11 using Intermediate C-T40 and 2-(6-(trifluoromethyl)pyridin-2-yl)acetic acid [CAS No. 1000565-32-1].	¹ H NMR (600 MHz, DMSO-d ₆) δ 11.05 (s, 1H), 9.06 (s, 1H), 8.53 (d, 1H), 8.313 (dd, 1H), 8.10 (t, 1H), 7.83 (d, 1H), 7.77 (d, 1H), 4.51 (q, 1H), 4.09 (s, 2H), 3.30 (s, 1H), 3.17 (t, 1H), 2.66 (ddt, 1H), 2.55 (td, 1H). UPLC-MS-8: Rt = 0.68 min; MS m/z [M+H] ⁺ = 472.1.
124	 (S)-N-(6-(3-(4,4-Difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 11 using Intermediate C-T40 and 2-(2-fluoro-3-(trifluoromethyl)phenyl)acetic acid [CAS No. 194943-83-4]	¹ H NMR (600 MHz, DMSO-d ₆) δ 11.08 (s, 1H), 9.06 (s, 1H), 8.53 (d, 1H), 8.32 (dd, 1H), 7.77 (t, 1H), 7.72 (t, 1H), 7.41 (t, 1H), 4.51 (q, 1H), 3.97 (s, 2H), 3.29 (s, 1H), 3.17 (td, 1H), 2.66 (ddt, 1H), 2.59 - 2.52 (m, 1H). UPLC-MS-8: Rt = 0.99 min; MS m/z [M+H] ⁺ = 472.1.
125 – rac 125a – 1 st eluting isomer 125b – 2 nd eluting isomer	 N-(6-(4-(1,1-Dioxidothiomorpholin-3-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide	Analogous to Example 32 using Intermediate C-T42 using C-SFC-11 (mobile phase: CO ₂ /IPA +0.05%NH ₃ (50:50))	1 st eluting isomer C-SFC-5 (mobile phase: CO ₂ /IPA +0.05%NH ₃ (50:50)): Rt = 1.50 min. 2 nd eluting isomer ¹ H NMR (600 MHz, DMSO-d ₆) δ 11.10 (s, 1H), 8.48 (d, 1H), 8.27 (dd, 1H), 8.24 (t, 1H), 7.69 (q, 1H), 6.57 (s, 1H), 5.18 (s, 2H), 4.11 (ddd, 1H), 3.39 (td, 1H), 3.14 – 2.98 (m, 4H), 2.76 (s, 1H), 2.31 (d, 3H). UPLC-MS-2: Rt = 0.62 min, MS m/z [M+H] ⁺ = 502. C-SFC-5 (mobile phase: CO ₂ /IPA +0.05%NH ₃ (50:50)): Rt = 2.58 min.
126	 N-(5-fluoro-6-(4-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide	Analogous to Example 5 using Intermediate C-T43 and 2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid	¹ H NMR (600 MHz, DMSO-d ₆) δ 11.07 (s, 1H), 8.46 (d, 1H), 8.26 (dd, 1H), 8.18 (t, 1H), 7.46 (q, 1H), 6.57 (s, 1H), 5.18 (s, 2H), 3.90 (ddd, 2H), 3.43 (td, 2H), 2.78 (tt, 1H), 2.31 (s, 3H), 1.86

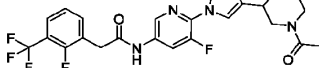
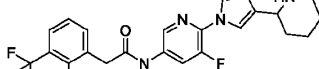
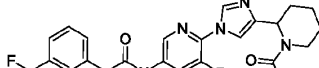
Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
	3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide	pyrazol-1-yl)acetic acid [CAS No. 345637-71-0]	(ddq, 2H), 1.62 (dtd, 2H). UPLC-MS-2: Rt = 0.86 min; MS m/z [M+H] ⁺ = 453.3.
127	 2-(2-Fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(tetrahydro-2H-pyran-4-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide	Analogous to Example 5 using Intermediate C-T43 and 2-(2-fluoro-3-(trifluoromethyl)phenyl)acetic acid [CAS No. 194943-83-4]	¹ H NMR (600 MHz, DMSO-d ₆) δ 10.93 (s, 1H), 8.46 (t, 1H), 8.27 (dt, 1H), 8.16 (d, 1H), 7.76 (t, 1H), 7.72 (t, 1H), 7.50 - 7.43 (m, 1H), 7.41 (t, 1H), 3.94 (s, 2H), 3.92 - 3.86 (m, 2H), 3.43 (tt, 2H), 2.78 (tt, 1H), 1.86 (ddt, 2H), 1.68 - 1.56 (m, 2H). UPLC-MS-2: Rt = 1.01 min; MS m/z [M+H] ⁺ = 467.3.
128 – rac 128a – 1 st eluting isomer 128b – 2 nd eluting isomer	 N-(6-(4-(1,1-Dioxidothiomorpholin-3-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 32 using Intermediate C-T42 and 2-(2-fluoro-3-(trifluoromethyl)phenyl)acetic acid [CAS No. 194943-83-4] using C-SFC-37 (mobile phase: CO ₂ /IPA +0.05%NH ₃ (65:35))	1 st eluting isomer ¹ H NMR (600 MHz, DMSO-d ₆) δ 10.96 (s, 1H), 8.48 (d, 1H), 8.29 (dd, 1H), 8.23 (d, 1H), 7.77 (t, 1H), 7.72 (t, 1H), 7.68 (s, 1H), 7.41 (t, 1H), 4.16 - 4.05 (m, 1H), 3.95 (s, 2H), 3.43 - 3.36 (m, 1H), 3.12 - 2.99 (m, 4H), 2.76 (s, 1H). UPLC-MS-2: Rt = 0.81 min; MS m/z [M+H] ⁺ = 516. C-SFC-7 (mobile phase: CO ₂ /IPA +0.05%NH ₃ (65:35)): Rt = 1.14 min. 2 nd eluting isomer C-SFC-7 (mobile phase: CO ₂ /IPA +0.05%NH ₃ (65:35)): Rt = 1.74 min.
129 – rac 129a – 1 st eluting isomer 129b – 2 nd eluting isomer	 N-(6-(4-(1,1-Dioxidothiomorpholin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 32 using Intermediate C-T41 and 2-(2-fluoro-3-(trifluoromethyl)phenyl)acetic acid [CAS No. 194943-83-4] using C-SFC-38 (mobile phase: CO ₂ /IPA +0.05%NH ₃ (48:52))	1 st eluting isomer C-SFC-14 (mobile phase: CO ₂ /IPA +0.05%NH ₃ (50:50)): Rt = 1.40 min. 2 nd eluting isomer ¹ H NMR (600 MHz, DMSO-d ₆) δ 10.97 (s, 1H), 8.49 (d, 1H), 8.31 (dd, 1H), 8.28 (t, J = 1H), 7.80 - 7.75 (m, 2H), 7.72 (t, 1H), 7.41 (t, 1H), 4.30 (dd, 1H), 3.95 (s, 2H), 3.40 - 3.36 (m, 1H), 3.28 (dd, 1H), 3.25 - 3.15 (m, 2H), 3.07 (d, 2H), 1.27 - 1.22 (m, 1H). UPLC-MS-2: Rt = 0.76 min; MS m/z [M+H] ⁺ = 516. C-SFC-14 (mobile phase: CO ₂ /IPA +0.05%NH ₃ (50:50)): Rt = 2.73 min.

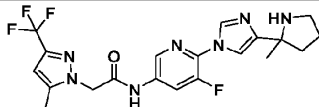
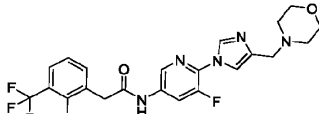
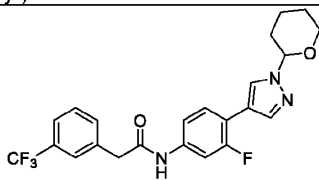
Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
130	 N-(6-(4-((1R,3S,5R)-2-Azabicyclo[3.1.0]hexan-3-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide	Analogous to Example 11 using Intermediate C-T44	¹ H NMR (600 MHz, DMSO) δ 11.08 (s, 1H), 8.46 (d, 1H), 8.25 (dd, 1H), 8.17 (s, 1H), 7.53 (s, 1H), 6.57 (s, 1H), 5.18 (s, 2H), 3.90 (t, 1H), 2.81 (s, 1H), 2.31 (s, 3H), 2.10 (dd, 1H), 1.83 (td, 1H), 1.39 (dq, 1H), 0.67 (d, 1H), 0.32 (d, 1H). UPLC-MS-8: Rt = 0.58 min; MS m/z [M+H] ⁺ = 450.2.
131 – rac 131a – 1st eluting isomer 131b – 2nd eluting isomer	 N-(6-(4-(5-Azaspiro[2.4]heptan-6-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide	Analogous to Example 25 using Intermediate C-T45 using C-SFC-39 (mobile phase: CO ₂ /MeOH +0.05%NH ₃ (45:55))	¹ st eluting isomer ¹ H NMR (600 MHz, DMSO-d ₆) δ 11.14 (s, 1H), 8.45 (s, 1H), 8.27 (d, 1H), 8.19 (s, 1H), 7.59 (s, 1H), 6.56 (s, 1H), 5.17 (s, 2H), 4.24 (s, 1H), 2.95 – 2.82 (m, 1H), 2.75 (s, 1H), 2.31 (s, 3H), 1.91 (s, 2H), 1.24 (s, 1H), 0.57 (d, 1H), 0.53 (t, 2H), 0.48 (s, 1H). UPLC-MS-2: Rt = 0.62 min; MS m/z [M+H] ⁺ = 464. C-SFC-7 (mobile phase: CO ₂ /IPA +0.05%NH ₃ (65:35)): Rt = 1.29 min. ² nd eluting isomer C-SFC-7 (mobile phase: CO ₂ /IPA +0.05%NH ₃ (65:35)): Rt = 2.66 min.
132	 N-(6-(4-((1S,3R,4R)-2-Azabicyclo[2.2.1]heptan-3-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide	Analogous to Example 11 using Intermediate C-T46	¹ H NMR (600 MHz, DMSO-d ₆) δ 11.09 (s, 1H), 8.46 (s, 1H), 8.25 (d, 1H), 8.18 (d, 1H), 7.52 (d, 1H), 6.57 (t, 1H), 5.18 (q, 2H), 3.80 (s, 1H), 3.45 (s, 1H), 2.41 (s, 1H), 2.31 (t, 3H), 1.58 (d, 3H), 1.51 - 1.43 (m, 2H), 1.15 (s, 1H). UPLC-MS-2: Rt = 0.62 min; MS m/z [M+H] ⁺ = 464.3.
133	 N-(6-(4-((1R,3S,4S)-2-Azabicyclo[2.2.1]heptan-3-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide	Analogous to Example 11 using Intermediate C-T47	¹ H NMR (600 MHz, DMSO-d ₆) δ 11.07 (s, 1H), 8.46 (d, 1H), 8.25 (dd, 1H), 8.18 (s, 1H), 7.51 (s, 1H), 6.57 (s, 1H), 5.18 (s, 2H), 3.81 (s, 1H), 3.46 (s, 1H), 2.41 (s, 1H), 2.31 (s, 3H), 1.60 (d, 3H), 1.46 (d, 2H), 1.15 (d, 1H). UPLC-MS-2: Rt = 0.63 min; MS m/z [M+H] ⁺ = 464.3.

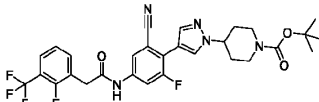
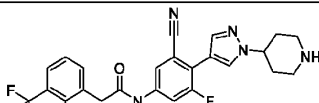
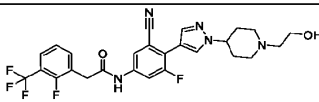
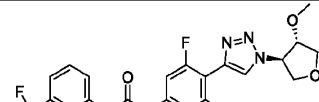
Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
134	 N-(5-Fluoro-6-(4-(4-hydroxytetrahydro-2H-pyran-4-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide	Analogous to Example 5 using Intermediate C-T27 and 2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid [CAS No. 345637-71-0]	¹ H NMR (500 MHz, DMSO-d ₆) δ 11.06 (s, 1H), 8.48 (d, 1H), 8.26 (dd, 1H), 8.19 (d, 1H), 7.57 (d, 1H), 6.56 (s, 1H), 5.18 (s, 2H), 4.96 (s, 1H), 3.74 (td, 2H), 3.63 (dt, 2H), 2.32 (s, 3H), 2.07 (ddd, 2H), 1.61 (d, 2H). UPLC-MS-8: Rt = 0.79 min; MS m/z [M+H] ⁺ = 468.9.
135	 N-(3-Cyano-5-fluoro-4-(1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)phenyl)-2-(3-(perfluoroethyl)phenyl)acetamide	Analogous to Example 5 using Intermediate C-M3 and Intermediate A-M1	¹ H NMR (600 MHz, DMSO-d ₆) δ 10.75 (s, 1H), 8.24 (d, 1H), 7.92 - 7.80 (m, 3H), 7.69 - 7.64 (m, 2H), 7.63 (s, 2H), 4.52 (tt, 1H), 3.97 (dt, 2H), 3.87 (s, 2H), 3.52 - 3.42 (m, 2H), 2.03 - 1.95 (m, 4H). UPLC-MS-2: Rt = 1.18 min; MS m/z [M+H] ⁺ = 523.2.
136	 N-(3-Cyano-5-fluoro-4-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)phenyl)-2-(3-(pentafluorophenyl)phenoxy)acetamide	Analogous to Example 11 using Intermediate A-M2 and Intermediate C-T49 and using 4N HCl/dioxane in Step 2	¹ H NMR (600 MHz, DMSO-d ₆) δ 10.56 (s, 1H), 8.21 (s, 1H), 7.95 (dd, 2H), 7.86 (d, 1H), 7.59 (t, 1H), 7.57 - 7.51 (m, 2H), 7.36 (dd, 1H), 4.90 (s, 2H), 4.31 (tt, 1H), 3.04 (dt, 2H), 2.59 (td, 2H), 2.16 (s, 1H), 1.97 (ddd, 2H), 1.81 (qd, 2H). UPLC-MS-2: Rt = 0.92 min; MS m/z [M+H] ⁺ = 546.3.
137	 N-(5-Fluoro-6-(3-(1-imino-1-oxidotetrahydro-1H-1λ⁶-thiophen-2-yl)-1H-1,2,4-triazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide	Analogous to Example 35/Steps 1-2 using 2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid [CAS No. 345637-71-0]	¹ H NMR (600 MHz, DMSO-d ₆) δ 11.22 (s, 1H), 9.25 - 9.04 (m, 1H), 8.54 (t, 1H), 8.32 (dt, 1H), 6.57 (s, 1H), 5.20 (s, 2H), 4.50 - 4.38 (m, 1H), 4.17 - 3.40 (m, 1H), 3.24 - 3.01 (m, 2H), 2.64 - 2.51 (m, 2H), 2.37 - 2.06 (m, 6H). UPLC-MS-9: Rt = 3.21 min; MS m/z [M+H] ⁺ = 487.
138 – rac 138a – 1st eluting isomer 138b – 2nd eluting isomer	 N-(6-(4-(1-Acetylpyrrolidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide	Analogous to Example 12 using Example 114 racemic mixture using C-SFC-13 (mobile phase: CO ₂ /MeOH + 0.05%NH ₃ (65:35))	1 st eluting isomer ¹ H NMR (600 MHz, DMSO-d ₆) δ 11.11 (d, 1H), 8.46 (s, 1H), 8.25 (d, 2H), 7.65 - 7.37 (m, 1H), 6.57 (d, 1H), 5.36 - 5.12 (m, 2H), 5.13 - 4.94 (m, 1H), 3.64 (s, 2H), 2.38 - 2.27 (m, 3H), 2.14 - 1.93 (m, 4H), 1.92 (s, 3H). UPLC-MS-8: Rt = 0.86 min; MS m/z [M+H] ⁺ = 480.4. C-SFC-5 (mobile phase:

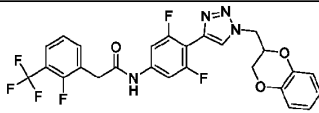
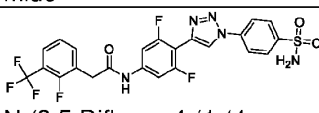
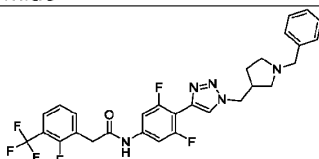
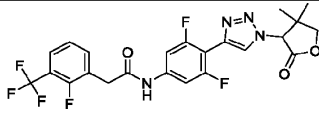
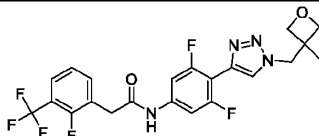
Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
			CO ₂ /MeOH+0.05%NH ₃ (65:35)): Rt = 1.66 min. 2 nd eluting isomer C-SFC-5 (mobile phase: CO ₂ /MeOH+0.05%NH ₃ (65:35)): Rt = 2.68 min.
139	 N-(3-Cyano-5-fluoro-4-(1-((1-methyl-1H-tetrazol-5-yl)methyl)-1H-pyrazol-4-yl)phenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide	Analogous to Example 5 using Intermediate C-T51 and 2-(6-(trifluoromethyl)pyridin-2-yl)acetic acid [CAS No. 1000565-32-1]	¹ H NMR (600 MHz, DMSO-d ₆) δ 10.85 (s, 1H), 8.44 (d, 1H), 8.09 (t, 1H), 7.91 (q, 1H), 7.89 - 7.85 (m, 2H), 7.83 (dd, 1H), 7.76 (d, 1H), 5.93 (s, 2H), 4.09 (s, 3H), 4.04 (s, 2H). UPLC-MS-2: Rt = 0.77 min; MS m/z [M+H] ⁺ = 486.2.
140	 N-(4-(1-(2-(4H-1,2,4-Triazol-3-yl)propan-2-yl)-1H-pyrazol-4-yl)-3-cyano-5-fluorophenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide	Analogous to Example 36/37 using ethyl formimidate in Step 3	¹ H NMR (600 MHz, DMSO-d ₆) δ 13.99 (s, 1H), 10.82 (s, 1H), 8.40 (s, 1H), 8.09 (t, 1H), 8.05 (s, 1H), 7.87 - 7.80 (m, 4H), 7.75 (d, 1H), 4.03 (s, 2H), 1.98 (s, 6H). UPLC-MS-2: Rt = 0.88 min; MS m/z [M+H] ⁺ = 499.3.
141	 N-(4-(1-(2-(1,3,4-Oxadiazol-2-yl)propan-2-yl)-1H-pyrazol-4-yl)-3-cyano-5-fluorophenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide	Analogous to Example 36/37 using ethyl trimethyl orthoformate hydrochloride and 0.1eq. PPTS in toluene at 110°C in Step 3	¹ H NMR (600 MHz, DMSO-d ₆) δ 10.85 (s, 1H), 9.24 (s, 1H), 8.43 (s, 1H), 8.09 (t, 1H), 7.91 - 7.85 (m, 3H), 7.83 (d, 1H), 7.76 (d, 1H), 4.05 (s, 2H), 2.07 (s, 6H). UPLC-MS-2: Rt = 0.89 min; MS m/z [M+H] ⁺ = 500.2.
142	 N-(3-Cyano-5-fluoro-4-(1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)phenyl)-2-hydroxy-2-(3-(trifluoromethyl)phenyl)acetic acid	Analogous to Example 28 using Intermediate C-M3 and 2-hydroxy-2-(3-(trifluoromethyl)phenyl)acetic acid [CAS No. 349-10-0].	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.59 (s, 1H), 8.25 - 8.20 (m, 1H), 8.12 - 8.01 (m, 2H), 7.93 - 7.74 (m, 3H), 7.72 - 7.58 (m, 2H), 6.98 - 6.93 (m, 1H), 5.31 (d, 1H), 4.58 - 4.46 (m, 1H), 3.97 (dt, 2H), 3.47 (td, 2H), 1.99 (td, 4H). UPLC-MS-2: Rt = 1.02 min; MS m/z [M+H] ⁺ = 489.2.

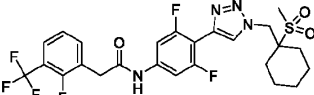
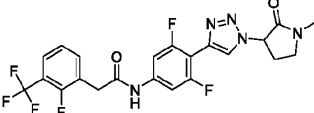
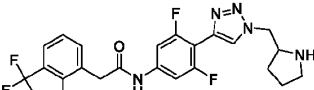
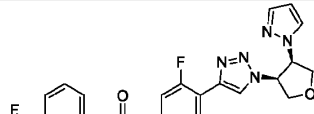
Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
143	 N-(3-Cyano-5-fluoro-4-(1-(tetrahydro-2H-pyran-3-yl)-1H-pyrazol-4-yl)phenyl)-2-hydroxy-2-(3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 28 using Intermediate C-T54 and 2-hydroxy-2-(3-(trifluoromethyl)phenyl)acetic acid [CAS No. 349-10-0].	¹ H NMR (600 MHz, DMSO-d ₆) δ 10.57 (s, 1H), 8.26 (s, 1H), 8.10 (d, 1H), 8.06 (dt, 1H), 7.90 - 7.85 (m, 2H), 7.82 (d, 1H), 7.69 (d, 1H), 7.62 (t, 1H), 6.94 (s, 1H), 5.31 (s, 1H), 4.41 (tt, 1H), 3.99 (dd, 1H), 3.84 - 3.75 (m, 1H), 3.66 (ddd, 1H), 3.49 - 3.41 (m, 1H), 2.19 - 2.14 (m, 1H), 2.14 - 2.00 (m, 1H), 1.78 - 1.70 (m, 1H), 1.70 - 1.57 (m, 1H). UPLC-MS-2: Rt = 1.02 min; MS m/z [M+H] ⁺ = 489.2.
144	 N-(3-Cyano-5-fluoro-4-(1-(piperidin-3-yl)-1H-pyrazol-4-yl)phenyl)-2-(3-(pentafluoro-λ⁶-sulfanyl)phenoxy)acetamide	Analogous to Example 11 using Intermediate A-M2 and Intermediate C-T55	¹ H NMR (600 MHz, DMSO-d ₆) δ 10.56 (s, 1H), 8.26 (d, 1H), 7.99 - 7.93 (m, 2H), 7.86 (d, 1H), 7.59 (t, 1H), 7.56 - 7.52 (m, 2H), 7.36 (dd, 1H), 4.89 (s, 2H), 4.24 (tt, 1H), 3.17 (ddd, 1H), 2.86 (dt, 1H), 2.78 (dd, 1H), 2.48 - 2.45 (m, 1H), 2.11 (dd, 1H), 1.91 (qd, 1H), 1.71 (dt, 1H), 1.56 - 1.45 (m, 1H). UPLC-MS-2: Rt = 0.93 min; MS m/z [M+H] ⁺ = 546.2.
145	 2-(2-Fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(1,2,5,6-tetrahydropyridin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide	Analogous to Example 3 using Intermediate D-T2 and tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate [CAS No. 885693-20-9] and using BrettPhosPd-G3 in Step 1 and 4N HCl/dioxane in Step 2	¹ H NMR (400 MHz, CD ₃ OD) δ 8.53 (s, 1H), 8.47 (d, 1H), 8.35 (dd, 1H), 8.35 (m, 1H), 7.86 (s, 1H), 7.62-7.72 (m, 2H), 7.35 (t, 1H), 6.59 (m, 1H), 4.00-4.04 (m, 2H), 3.91-3.94 (m, 2H), 3.36 (m, 2H), 2.53-2.62 (m, 2H). HPLC-MS-5: Rt = 0.77 min; MS m/z [M+H] ⁺ = 464.2.
146	 2-(2-Fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(piperidin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide	Analogous to Example 21 using Example 145 and EtOH without HOAc	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.99 (s, 1H), 8.48 (d, 1H), 8.33 (s, 1H), 8.28 (dd, 1H), 8.17 (m, 1H), 7.69-7.80 (m, 2H), 7.50 (s, 1H), 7.41 (t, 1H), 3.95 (s, 2H), 3.05 (m, 1H), 2.76 (m, 1H), 2.59-2.65 (m, 2H), 2.01 (m, 2H), 1.72 (m, 1H), 1.56 (m, 2H). HPLC-

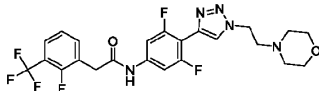
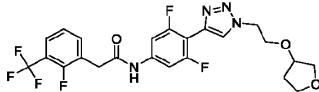
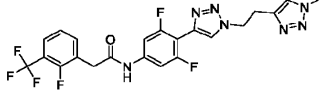
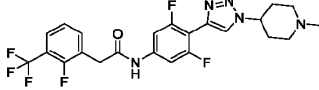
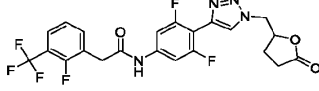
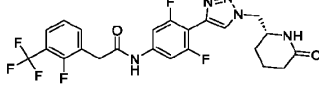
Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
			MS-7: Rt = 1.32 min; MS m/z [M+H] ⁺ = 466.0.
147 - rac 147a – 1 st eluting isomer 147b – 2 nd eluting isomer	 N-(6-(4-(1-Acetylpiperidin-3-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 12 using Example 146 and Ac₂O/pyridine using C-HPLC-8 (mobile phase: hexane/(1:1 EtOH/MeOH +0.1%HCOOH))	MS-7: Rt = 1.32 min; MS m/z [M+H]⁺ = 466.0. 1st eluting isomer C-HPLC-9: (mobile phase: hexane/(80:20 EtOH/MeOH +0.1%HCOOH) 70:30) Rt = 5.89 min. 2nd eluting isomer ¹H NMR (400 MHz, CD₃OD) δ 8.44 (m, 1H), 8.33 (dt, 1H), 8.29 (m, 1H), 7.60-7.71 (m, 3H), 7.35 (t, 1H), 4.36-4.60 (m, 1H), 3.92 (s, 2H), 3.82-4.15 (m, 1H), 3.24 (m, 0.5H), 2.98 (m, 0.5H), 2.83 (m, 1H), 2.10-2.22 (m, 4H), 1.75-1.90 (m, 2H), 1.60 (m, 1H). HPLC-MS-5: Rt = 0.77 min; MS m/z [M+H]⁺ = 508.1. C-HPLC-9: (mobile phase: hexane/(80:20 EtOH/MeOH +0.1%HCOOH) 70:30) Rt = 6.64 min.
148 – rac 148a – 1 st eluting isomer 148b – 2 nd eluting isomer	 2-(2-Fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(piperidin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide	Analogous to Example 10 and Example 21 using tert-butyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydropyridine-1(2H)-carboxylate [CAS No. 865245-32-5] and BrettPhosPd-G3 followed by N-Boc deprotection with 4N HCl/dioxane and C-HPLC	1st eluting isomer C-HPLC-9: (mobile phase: hexane/(50:50 IPA/MeOH +0.1%Et₂NH) 85:15) Rt = 9.42 min. 2nd eluting isomer ¹H NMR (400 MHz, CD₃OD) δ 8.47 (m, 1H), 8.38 (m, 1H), 8.36 (dd, 1H), 7.88 (s, 1H), 7.62-7.71 (m, 2H), 7.35 (t, 1H), 4.33 (dd, 1H), 3.93 (s, 2H), 3.43 (m, 1H), 3.18 (m, 1H), 2.24 (m, 1H), 1.93-2.10 (m, 3H), 1.70-1.84 (m, 2H). HPLC-MS-5: Rt = 0.72 min; MS m/z [M+H]⁺ = 466.1. C-HPLC-9: (mobile phase: hexane/(50:50 IPA/MeOH +0.1%Et₂NH) 85:15) Rt = 10.32 min.
149	 N-(6-(4-(1-Acetylpiperidin-2-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 12/Step 1 using Example 148 (racemate) and Ac₂O/pyridine	¹H NMR (400 MHz, CD₃OD) δ 8.45 (m, 1H), 8.28-8.38 (m, 2H), 7.57-7.72 (m, 3H), 7.35 (t, 1H), 5.88 (m, 0.5H), 5.22 (m, 0.5H), 4.48 (m, 0.5H), 3.92 (d, 2H), 3.81 (m, 0.5H), 3.24 (m, 0.5H), 2.71 (m, 0.5H), 2.38 (m, 1H), 2.21/2.22 (s, 3H), 1.76-2.07 (m,

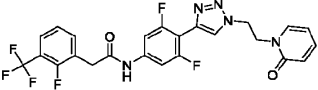
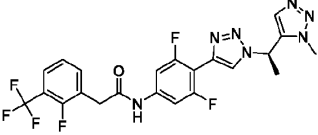
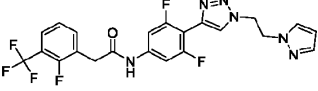
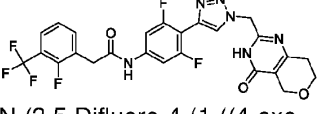
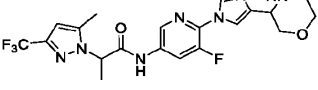
Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
	(trifluoromethyl)phenyl)acetamide		2H), 1.41-1.75 (m, 4H). HPLC-MS-5: Rt = 0.82 min; MS m/z [M+H] ⁺ = 508.1.
150 – rac 150a – 1 st eluting isomer 150b – 2 nd eluting isomer	 N-(5-Fluoro-6-(4-(2-methylpyrrolidin-2-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide	Analogous to Example 25 using Intermediate C-T56 using C-SFC-31 (mobile phase: CO ₂ /EtOH +0.05%NH ₃ (60:40))	1 st eluting isomer C-SFC-7 (mobile phase: CO ₂ /EtOH+0.05%NH ₃ (60:40)): Rt = 0.84 min. 2 nd eluting isomer ¹ H NMR (600 MHz, DMSO-d ₆) δ 11.10 (s, 1H), 8.45 (s, 1H), 8.26 (d, 1H), 8.16 (s, 1H), 7.53 (s, 1H), 6.57 (s, 1H), 5.17 (s, 2H), 2.84-2.95 (m, 2H), 2.31 (s, 3H), 2.08 (m, 1H), 1.75 (m, 1H), 1.57-1.70 (m, 2H), 1.37 (s, 3H), 1.23 (s, 1H). UPLC-MS-2: Rt = 0.67 min; MS m/z [M+H] ⁺ = 452.4. C-SFC-7 (mobile phase: CO ₂ /EtOH+0.05%NH ₃ (60:40)): Rt = 2.99 min.
151	 2-(2-Fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(morpholinomethyl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide	Analogous to Example 39 using morpholine in Step 3	¹ H NMR (300 MHz, CD ₃ OD) δ 8.45 (d, 1H), 8.35 (dd, 1H), 8.31 (s, 1H), 7.74 (s, 1H), 7.61-7.72 (m, 2H), 7.35 (t, 1H), 3.93 (s, 2H), 3.66-3.75 (m, 4H), 3.58 (s, 2H), 2.50-2.62 (m, 4H). HPLC-MS-1: Rt = 1.02 min; MS m/z [M+H] ⁺ = 482.2.
152	 N-(3-Fluoro-4-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)phenyl)-2-(3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 10 using Intermediate D-M3/Step 1 and 1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole [CAS No. 1003846-21-6] using PdCl ₂ (dppf) and K ₂ CO ₃	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.46 (s, 1H), 8.21 (d, 1H), 7.90 (d, 1H), 7.54-7.73 (m, 6H), 7.32 (dd, 1H), 5.44 (dd, 1H), 3.94 (m, 1H), 3.81 (s, 2H), 3.64 (m, 1H), 2.12 (m, 1H), 1.88-2.00 (m, 2H), 1.68 (m, 1H), 1.50-1.59 (m, 2H). HPLC-MS: Rt 2.53 min; MS m/z [M+H] ⁺ 448.0.

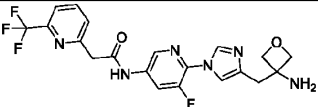
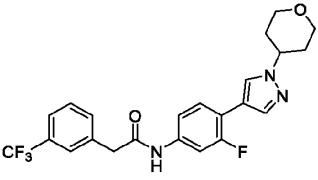
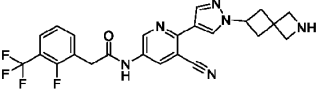
Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
153	 tert-Butyl 4-(4-(2-cyano-6-fluoro-4-(2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamido)phenyl)-1H-pyrazol-1-yl)piperidine-1-carboxylate	Analogous to Example 5 using Intermediate C-T49 and 2-(2-fluoro-3-(trifluoromethyl)phenyl)acetic acid [CAS No. 194943-83-4]	¹ H NMR (400 MHz, CD ₃ OD) δ 8.17 (s, 1H), 7.93 (m, 1H), 7.85 (dd, 1H), 7.80 (m, 1H), 7.61-7.70 (m, 2H), 7.34 (t, 1H), 4.47 (m, 1H), 4.17-4.28 (m, 2H), 3.89 (s, 2H), 2.86-3.09 (m, 2H), 2.08-2.15 (m, 2H), 1.91-2.04 (m, 2H), 1.48 (s, 9H). HPLC-MS-2: Rt 1.89 min; MS m/z [M-56+H] ⁺ 534.3.
154	 N-(3-Cyano-5-fluoro-4-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide (TFA-salt)	From Example 153 using TFA/DCM/RT	¹ H NMR (400 MHz, CD ₃ OD) δ 8.19 (s, 1H), 7.97 (s, 1H), 7.87 (d, 1H), 7.82 (s, 1H), 7.60-7.71 (m, 2H), 7.35 (t, 1H), 4.65 (m, 1H), 3.90 (s, 2H), 3.52-3.66 (m, 2H), 3.15-3.28 (m, 2H), 2.24-2.45 (m, 4H). HPLC-MS-1: Rt 1.37 min; MS m/z [M-56+H] ⁺ 489.8.
155	 N-(3-Cyano-5-fluoro-4-(1-(1-(2-hydroxyethyl)piperidin-4-yl)-1H-pyrazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 31 using Example 154 and 2-bromoethan-1-ol	¹ H NMR (400 MHz, CD ₃ OD) δ 8.47 (s, 1H), 8.19 (s, 1H), 7.96 (m, 1H), 7.86 (d, 1H), 7.81 (m, 1H), 7.61-7.71 (m, 2H), 7.35 (t, 1H), 4.54 (m, 1H), 3.89 (s, 2H), 3.85 (t, 2H), 3.53-3.62 (m, 2H), 3.10 (t, 2H), 2.95-3.06 (m, 2H), 2.27-2.43 (m, 4H). HPLC-MS-1: Rt 1.36 min; MS m/z [M-56+H] ⁺ 533.8.
156	 N-(3,5-Difluoro-4-(1-(2-hydroxy-1-(1-methoxycyclobutyl)ethyl)-1H-1,2,3-triazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 7 using 2-azido-2-(1-methoxycyclobutyl)ethan-1-ol [CAS No. 1803570-54-8]	¹ H NMR (500 MHz, DMSO-d ₆) δ 10.73 (s, 1H), 8.25 (s, 1H), 7.67-7.77 (m, 2H), 7.37-7.48 (m, 3H), 4.84-4.94 (m, 2H), 3.91-4.08 (m, 2H), 3.90 (s, 2H), 3.19 (s, 3H), 2.34 (m, 1H), 2.16 (m, 1H), 2.06 (m, 1H), 1.59-1.73 (m, 2H), 1.49 (m, 1H). HPLC-MS-8: Rt 1.34 min; MS m/z [M+H] ⁺ 529.2.
157	 N-(3,5-Difluoro-4-(1-((3R,4S)-4-methoxytetrahydrofuran-3-yl)-1H-1,2,3-triazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 7 using (3R,4S)-3-azido-4-methoxytetrahydrofuran	¹ H NMR (500 MHz, DMSO-d ₆) δ 10.79 (s, 1H), 8.43 (s, 1H), 7.67-7.77 (m, 2H), 7.34-7.46 (m, 3H), 4.34 (m, 1H), 4.11-4.20 (m, 2H), 4.08 (dd, 1H), 3.88 (s, 2H), 3.77 (dd, 1H), 3.42 (m, 1H), 3.35 (s, 3H).

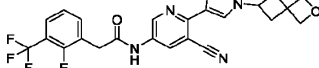
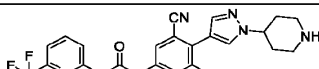
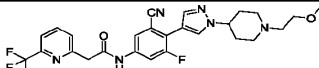
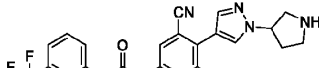
Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
	yl)-1H-1,2,3-triazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide		HPLC-MS-8: Rt 1.32 min; MS m/z [M+H] ⁺ 501.1.
158	 N-(4-(1-((2,3-dihydrobenzo[b][1,4]dioxin-2-yl)methyl)-1H-1,2,3-triazol-4-yl)-3,5-difluorophenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 7 using 2-(azidomethyl)-2,3-dihydrobenzo[b][1,4]dioxine [CAS No. 128318-80-9]	¹ H NMR (500 MHz, DMSO-d ₆) δ 10.76 (s, 1H), 8.40 (s, 1H), 7.68-7.77 (m, 2H), 7.43 (d, 2H), 7.39 (t, 1H), 6.78-6.91 (m, 4H), 4.69-4.87 (m, 3H), 4.40 (d, 1H), 4.01 (m, 1H), 3.89 (s, 2H). HPLC-MS-8: Rt 1.45 min; MS m/z [M+H] ⁺ 549.2.
159	 N-(3,5-difluoro-4-(1-(4-sulfamoylphenyl)-1H-1,2,3-triazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 7 using 4-azidobenzenesulfonamide [CAS No. 36326-86-0]	HPLC-MS-8: Rt 1.35 min; MS m/z [M+H] ⁺ 555.9.
160	 N-(4-(1-((1-benzylpyrrolidin-3-yl)methyl)-1H-1,2,3-triazol-4-yl)-3,5-difluorophenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 7 using 3-(azidomethyl)-1-benzylpyrrolidine [CAS No. 218293-49-3]	¹ H NMR (500 MHz, DMSO-d ₆) δ 10.76 (s, 1H), 8.39 (s, 1H), 7.67-7.77 (m, 2H), 7.37-7.47 (m, 3H), 7.24-7.40 (m, 4H), 7.19 (m, 1H), 4.30-4.43 (m, 2H), 3.88 (s, 2H), 3.52 (s, 2H), 2.69 (m, 1H), 2.37-2.55 (m, 2H), 2.30 (m, 1H), 1.84 (m, 1H), 1.52 (m, 1H). HPLC-MS-8: Rt 0.97 min; MS m/z [M+H] ⁺ 574.0.
161	 N-(4-(1-(4,4-dimethyl-2-oxotetrahydrofuran-3-yl)-1H-1,2,3-triazol-4-yl)-3,5-difluorophenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 7 using 3-azido-4,4-dimethyldihydrofuran-2(3H)-one [CAS No. 1824188-89-7]	¹ H NMR (500 MHz, DMSO-d ₆) δ 10.77 (s, 1H), 8.47 (s, 1H), 7.65-7.77 (m, 2H), 7.45 (d, 2H), 7.38 (t, 1H), 5.92 (s, 1H), 4.26 (s, 2H), 3.90 (s, 2H), 1.24 (s, 3H), 0.82 (s, 3H). HPLC-MS-8: Rt 1.36 min; MS m/z [M+H] ⁺ 513.3.
162	 N-(4-(1-(3-(azidomethyl)-3-methyloxetane)-1H-1,2,3-triazol-4-yl)-3,5-difluorophenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 7 using 3-(azidomethyl)-3-methyloxetane	¹ H NMR (500 MHz, DMSO-d ₆) δ 10.76 (s, 1H), 8.43 (s, 1H), 7.66-7.76 (m, 2H), 7.43 (d, 2H), 7.38 (t, 1H), 4.68 (s, 2H), 4.58 (d, 2H), 4.27 (d, 2H), 3.90 (s, 2H),

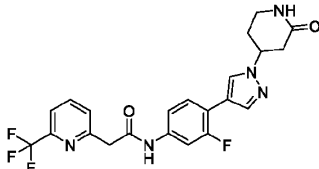
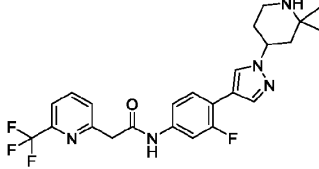
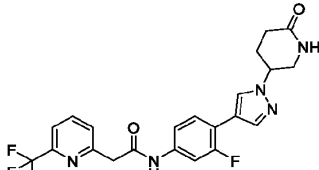
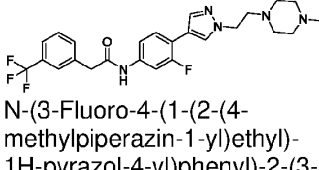
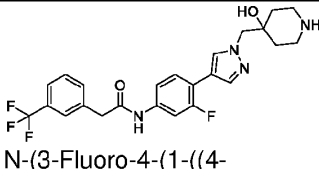
Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
	N-(3,5-Difluoro-4-(1-((3-methyloxetan-3-yl)methyl)-1H-1,2,3-triazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	[CAS No. 90683-29-7]	1.15 (s, 3H). HPLC-MS-8: Rt 1.30 min; MS m/z [M+H] ⁺ 485.1.
163	 N-(3,5-Difluoro-4-(1-((1-(methylsulfonyl)cyclohexyl)methyl)-1H-1,2,3-triazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 7 using 1-(azidomethyl)-1-(methylsulfonyl)cyclohexane [CAS No. 1934576-76-7]	¹ H NMR (500 MHz, DMSO-d ₆) δ 10.74 (s, 1H), 8.30 (s, 1H), 7.65-7.78 (m, 2H), 7.43 (d, 2H), 7.38 (t, 1H), 4.99 (s, 2H), 3.88 (s, 2H), 2.84 (s, 3H), 1.60-1.89 (m, 9H), 1.23 (m, 1H). HPLC-MS-8: Rt 1.36 min; MS m/z [M+H] ⁺ 575.0.
164	 N-(3,5-Difluoro-4-(1-(1-methyl-2-oxopyrrolidin-3-yl)-1H-1,2,3-triazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 7 using 3-azido-1-methylpyrrolidin-2-one [CAS No. 33693-59-3]	HPLC-MS-8: Rt 1.24 min; MS m/z [M+H] ⁺ 498.1.
165	 N-(3,5-Difluoro-4-(1-(pyrrolidin-2-ylmethyl)-1H-1,2,3-triazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 7 using 2-(azidomethyl)pyrrolidine [CAS No. 288083-80-7]	HPLC-MS-8: Rt 1.15 min; MS m/z [M+H] ⁺ 484.2.
166	 N-(4-(1-((3S,4R)-4-(1H-pyrazol-1-yl)tetrahydrofuran-3-yl)-1H-1,2,3-triazol-4-yl)-3,5-difluorophenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 7 using 1-((3R,4S)-4-azidotetrahydrofuran-3-yl)-1H-pyrazole [CAS No. 2138050-98-1]	¹ H NMR (500 MHz, DMSO-d ₆) δ 10.74 (s, 1H), 8.30 (s, 1H), 7.65-7.78 (m, 2H), 7.43 (d, 2H), 7.38 (t, 1H), 4.99 (s, 2H), 3.88 (s, 2H), 2.84 (s, 3H), 1.60-1.89 (m, 9H), 1.23 (m, 1H). HPLC-MS-8: Rt 1.28 min; MS m/z [M+H] ⁺ 537.2.

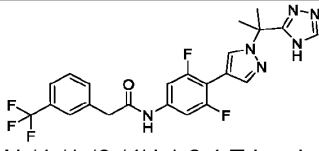
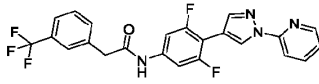
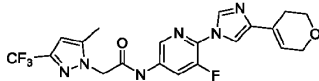
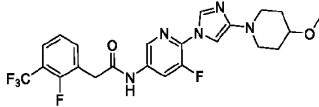
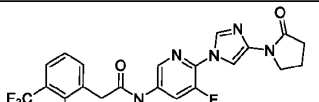
Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
167	 N-(3,5-Difluoro-4-(1-(2-morpholinoethyl)-1H-1,2,3-triazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 7 using 4-(2-azidoethyl)morpholine [CAS No. 660395-39-1]	¹ H NMR (500 MHz, DMSO-d ₆) δ 10.76 (s, 1H), 8.38 (s, 1H), 7.64-7.77 (m, 2H), 7.44 (d, 2H), 7.39 (t, 1H), 4.52 (t, 2H), 3.88 (s, 2H), 3.47-3.53 (m, 4H), 2.78 (t, 2H), 2.37-2.42 (m, 4H). HPLC-MS-8: Rt 1.03 min; MS m/z [M+H] ⁺ 514.2.
168	 N-(3,5-Difluoro-4-(1-(2-(tetrahydrofuran-3-yl)oxy)ethyl)-1H-1,2,3-triazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 7 using 3-(2-azidoethoxy)tetrahydrofuran [CAS No. 2126178-96-7]	¹ H NMR (500 MHz, DMSO-d ₆) δ 10.76 (s, 1H), 8.32 (s, 1H), 7.67-7.78 (m, 2H), 7.42 (d, 2H), 7.38 (t, 1H), 4.58 (t, 2H), 4.10 (s, 1H), 3.87 (s, 2H), 3.80 (s, 2H), 3.52-3.62 (m, 4H), 1.84 (m, 1H), 1.75 (m, 1H). HPLC-MS-8: Rt 1.29 min; MS m/z [M+H] ⁺ 515.1.
169	 N-(3,5-Difluoro-4-(1-(2-(1-methyl-1H-1,2,3-triazol-4-yl)ethyl)-1H-1,2,3-triazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 7 using 4-(2-azidoethyl)-1-methyl-1H-1,2,3-triazole [CAS No. 1909326-98-2]	¹ H NMR (500 MHz, DMSO-d ₆) δ 10.75 (s, 1H), 8.34 (s, 1H), 7.80 (s, 1H), 7.65-7.74 (m, 2H), 7.43 (d, 2H), 7.39 (t, 1H), 4.72 (t, 2H), 3.95 (s, 3H), 3.90 (s, 2H), 3.25 (t, 2H). HPLC-MS-8: Rt 1.23 min; MS m/z [M+H] ⁺ 510.1.
170	 N-(3,5-Difluoro-4-(1-(1-methylpiperidin-4-yl)-1H-1,2,3-triazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 7 using 4-azido-1-methylpiperidine [CAS No. 1175146-68-5]	¹ H NMR (400 MHz, CD ₃ OD) δ 8.33 (s, 1H), 7.60-7.71 (m, 2H), 7.44 (d, 2H), 7.34 (t, 1H), 4.82 (m, 1H), 3.89 (s, 2H), 3.38-3.47 (m, 2H), 2.86-3.00 (m, 2H), 2.73 (s, 3H), 2.31-2.47 (m, 4H). HPLC-MS-2: Rt 0.37 min; MS m/z [M+H] ⁺ 498.2.
171	 N-(3,5-Difluoro-4-(1-((5-oxotetrahydrofuran-2-yl)methyl)-1H-1,2,3-triazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 7 using 5-(azidomethyl)dihydrofuran-2(3H)-one [CAS No. 179532-81-1]	¹ H NMR (500 MHz, DMSO-d ₆) δ 10.74 (s, 1H), 8.30 (s, 1H), 7.65-7.78 (m, 2H), 7.43 (d, 2H), 7.38 (t, 1H), 4.96 (m, 1H), 4.67-4.81 (m, 2H), 3.89 (s, 2H), 2.26-2.40 (m, 2H), 1.98 (m, 1H). HPLC-MS-8: Rt 1.27 min; MS m/z [M+H] ⁺ 499.2.
172	 N-(3,5-Difluoro-4-(1-((R)-6-azidomethyl)pyrrolidin-2-yl)-1H-1,2,3-triazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 7 using (R)-6-(azidomethyl)pip	¹ H NMR (500 MHz, DMSO-d ₆) δ 10.77 (s, 1H), 8.35 (s, 1H), 7.67-7.78 (m, 2H), 7.60 (s, 1H), 7.42 (d, 2H), 7.38 (t, 1H), 4.55 (dd,

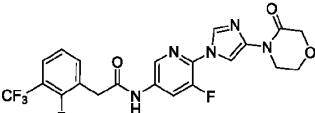
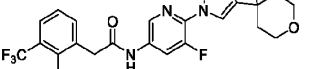
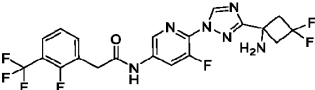
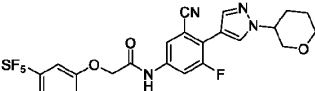
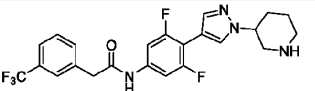
Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
	(R)-N-(3,5-Difluoro-4-(1-((6-oxopiperidin-2-yl)methyl)-1H-1,2,3-triazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	eridin-2-one [CAS No. 1807939-24-7]	¹ H), 4.45 (m, 1H), 3.92 (s, 2H), 3.79 (m, 1H), 2.08 (m, 1H), 1.99 (m, 1H), 1.61-1.73 (m, 2H), 1.56 (m, 1H), 1.25 (m, 1H). HPLC-MS-8: Rt 1.22 min; MS m/z [M+H] ⁺ 512.1.
173	 N-(3,5-Difluoro-4-(1-(2-(2-oxopyridin-1(2H)-yl)ethyl)-1H-1,2,3-triazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 7 using 1-(2-azidoethyl)pyridin-2(1H)-one [CAS No. 1249203-09-5]	HPLC-MS-8: Rt 1.46 min; MS m/z [M+H] ⁺ 522.0.
174	 (R)-N-(3,5-Difluoro-4-(1-(1-(1-methyl-1H-1,2,3-triazol-5-yl)ethyl)-1H-1,2,3-triazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 7 using (R)-5-(1-azidoethyl)-1-methyl-1H-1,2,3-triazole [CAS No. 1909286-88-9]	¹ H NMR (500 MHz, DMSO-d ₆) δ 10.76 (s, 1H), 8.54 (s, 1H), 7.93 (s, 1H), 7.66-7.78 (m, 2H), 7.42 (d, 2H), 7.38 (t, 1H), 6.33 (m, 1H), 3.89 (s, 3H), 3.87 (s, 2H), 1.95 (d, 3H). HPLC-MS-8: Rt 1.26 min; MS m/z [M+H] ⁺ 510.1.
175	 N-(4-(1-(2-(1H-Pyrazol-1-yl)ethyl)-1H-1,2,3-triazol-4-yl)-3,5-difluorophenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 7 using 1-(2-azidoethyl)-1H-pyrazole [CAS No. 689157-81-1]	HPLC-MS-8: Rt 1.36 min; MS m/z [M+H] ⁺ 495.2.
176	 N-(3,5-Difluoro-4-(1-((4-oxo-3,5,7,8-tetrahydro-4H-pyrano[4,3-d]pyrimidin-2-yl)methyl)-1H-1,2,3-triazol-4-yl)phenyl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 7 using 2-(azidomethyl)-3,5,7,8-tetrahydro-4H-pyrano[4,3-d]pyrimidin-4-one [CAS No. 1419953-82-4]	¹ H NMR (500 MHz, DMSO-d ₆) δ 12.85 (br s, 1H), 10.73 (s, 1H), 8.48 (s, 1H), 7.64-7.77 (m, 2H), 7.42 (d, 2H), 7.38 (t, 1H), 5.55 (s, 2H), 4.33 (s, 2H), 3.91 (s, 2H), 3.79 (t, 2H). HPLC-MS-8: Rt 1.21 min; MS m/z [M+H] ⁺ 565.2.
177 2 nd eluting peak		Analogous to Example 25 using Intermediate C-	UPLC-MS-8: Rt = 0.63 min; MS m/z [M+H] ⁺ 468.0. C-HPLC-12 (mobile phase: TBME/(EtOH+0.1%Et ₂ NH)/(MeO

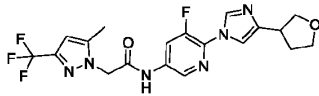
Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
	N-(5-Fluoro-6-(4-(morpholin-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)propanamide	T2 and 2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)propanoic acid [CAS No. 1005566-34-6] using first C-HPLC-11 (mobile phase: TBME/EtOH/Me OH (85:10:5)) and then RP-HPLC-1 (mobile phase: H ₂ O/ACN 100:0 to 0:100)	H+0.1%Et ₂ NH) (85:10:5)) ; Rt = 11.05 min.
178	 N-(6-(4-((3-Aminooxetan-3-yl)methyl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide	Analogous to Example 35/Steps 1-2 using Intermediate C-T58 and 2-(6-(trifluoromethyl)pyridin-2-yl)acetic acid [CAS No. 1000565-32-1]	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.19 (s, 1H), 8.52 (d, 1H), 8.31 (dd, 1H), 8.19 (s, 1H), 8.09 (t, 1H), 7.82 (d, 1H), 7.77 (d, 1H), 7.66 (s, 1H), 4.49 (d, 2H), 4.39 (d, 2H), 4.08 (s, 2H), 2.87 (s, 2H).
179	 N-(3-Fluoro-4-(1-(tetrahydro-2H-pyran-4-yl)-1H-pyrazol-4-yl)phenyl)-2-(3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 10 using Intermediate D-M3/Step 1 and 1-(tetrahydro-2H-pyran-4-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole [CAS No. 1040377-03-4] with PdCl ₂ (dppf) and K ₂ CO ₃	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 10.43 (s, 1H), 8.15 (s, 1H), 7.85 (s, 1H), 7.53-7.74 (m, 6H), 7.31 (d, 1H), 4.37-4.44 (m, 1H), 3.90-4.04 (m, 2H), 3.80 (s, 2H), 3.40-3.54 (m, 2H), 1.91-2.04 (m, 4H). HPLC-MS: Rt 2.48 min; MS m/z [M+H] ⁺ 448.1.
180	 N-(6-(1-(2-Azaspiro[3.3]heptan-6-yl)-1H-pyrazol-4-yl)-5-cyanopyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 3 using Intermediate D-T7 and Intermediate B-T39 with PdCl ₂ (dppf).DCM and Cs ₂ CO ₃	¹ H NMR (400 MHz, CD ₃ OD) δ 8.86 (d, 1H), 8.49 (d, 1H), 8.37 (s, 1H), 8.26 (s, 1H), 7.61-7.72 (m, 2H), 7.35 (t, 1H), 4.89 (m, 1H), 4.22 (s, 2H), 4.18 (s, 2H), 3.92 (s, 2H), 2.80-2.97 (m, 4H). HPLC-MS-7: Rt 1.35 min; MS m/z [M+H] ⁺ 485.1.

Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
	(trifluoromethyl)phenyl)acetamide (TFA salt)		
181	 N-(6-(1-(2-Oxaspiro[3.3]heptan-6-yl)-1H-pyrazol-4-yl)-5-cyanopyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 10 using Intermediate D-T7 and Intermediate B-T40 with PdCl ₂ (dppf).DC M and Cs ₂ CO ₃	¹ H NMR (400 MHz, CD ₃ OD) δ 9.11 (s, 1H), 9.03 (s, 1H), 8.99 (d, 1H), 8.64 (d, 1H), 7.61-7.73 (m, 2H), 7.36 (t, 1H), 5.32 (m, 1H), 4.85 (s, 2H), 3.95 (s, 2H), 3.72 (s, 2H), 2.73-2.82 (m, 2H), 2.11-2.20 (m, 2H). HPLC-MS-7: Rt 1.34 min; MS m/z [M+H] ⁺ 485.9.
182	 N-(3-Cyano-5-fluoro-4-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)phenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide (TFA salt)	Analogous to Example 11 using Intermediate C-T49 and 2-(6-(trifluoromethyl)pyridin-2-yl)acetic acid [CAS No. 1000565-32-1]	HPLC-MS-2: Rt 0.23 min; MS m/z [M+H] ⁺ 473.2.
183	 N-(3-Cyano-5-fluoro-4-(1-(1-(2-methoxyethyl)piperidin-4-yl)-1H-pyrazol-4-yl)phenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide	Analogous to Example 31 using Example 182 and 1-chloro-2-methoxyethane [CAS No. 627-42-9]	¹ H NMR (400 MHz, CDCl ₃) δ 10.46-10.39 (m, 1H), 7.93-8.04 (m, 3H), 7.68-7.80 (m, 3H), 7.53 (d, 1H), 4.61 (br s, 1H), 4.00 (s, 3H), 3.51-3.82 (m, 4H), 3.30-3.35 (m, 4H), 2.98 (m, 1H), 2.61-2.67 (m, 2H), 2.37-2.40 (m, 2H). HPLC-MS-2: Rt 0.46 min; MS m/z [M+H] ⁺ 531.3.
184	 N-(3-Cyano-5-fluoro-4-(1-(pyrrolidin-3-yl)-1H-pyrazol-4-yl)phenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide (TFA salt)	Analogous to Example 11 using Intermediate C-T13 and 2-(6-(trifluoromethyl)pyridin-2-yl)acetic acid [CAS No. 1000565-32-1]	¹ H NMR (400 MHz, CD ₃ OD) δ 8.22 (s, 1H), 8.00-8.06 (m, 2H), 7.88 (dd, 1H), 7.83 (s, 1H), 7.68-7.76 (m, 2H), 5.35 (m, 1H), 4.04 (s, 2H), 3.81 (m, 1H), 3.66-3.76 (m, 2H), 3.52 (m, 1H), 2.58 (m, 1H), 2.42 (m, 1H). HPLC-MS-1: Rt 1.31 min; MS m/z [M+H] ⁺ 459.0.
185	 N-(3-Fluoro-4-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)phenyl)-2-(3-(trifluoromethyl)phenyl)acetamide (HCl salt)	Analogous to Example 6 using Intermediate D-M3/Step 1 with PdCl ₂ (dppf) and K ₂ CO ₃ in Step 1 and 4N HCl/dioxane in Step 2	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.74 (s, 1H), 9.21 (m, 1H), 8.94 (m, 1H), 8.13 (d, 1H), 7.91 (s, 1H), 7.53-7.77 (m, 6H), 7.37 (dd, 1H), 4.52-4.61 (m, 1H), 3.84 (s, 2H), 3.39 (m, 2H), 3.06 (m, 2H), 2.10-2.30 (m, 4H). HPLC-MS-4: Rt 0.83 min; MS m/z [M+H] ⁺ 447.1.

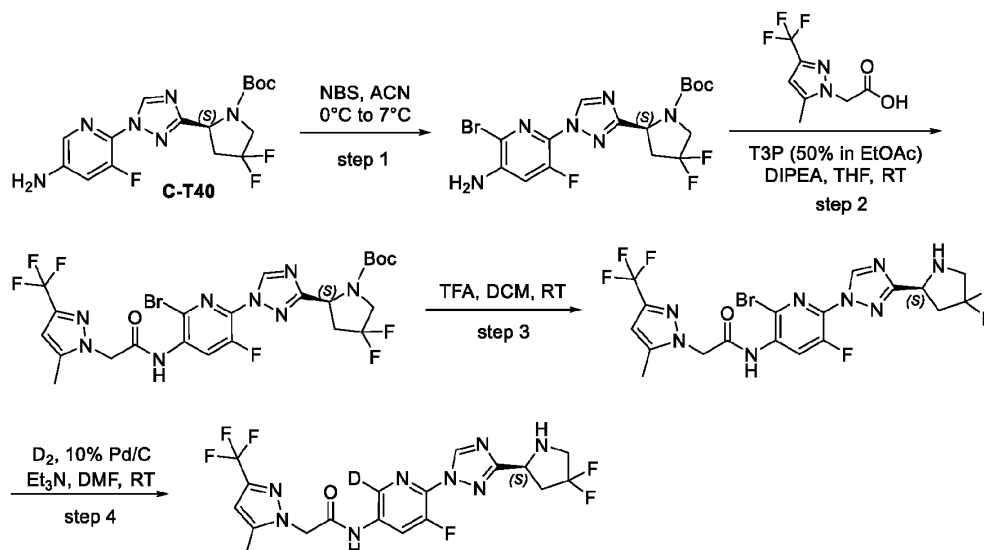
Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
186	 N-(3-Fluoro-4-(1-(2-oxopiperidin-4-yl)-1H-pyrazol-4-yl)phenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide	Analogous to Example 10 using Intermediate D-T8 and Intermediate B-T41 with PdCl ₂ (dppf) and K ₂ CO ₃	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.53 (s, 1H), 8.17 (d, 1H), 8.09 (t, 1H), 7.90 (s, 1H), 7.82 (d, 1H), 7.75 (d, 1H), 7.61-7.71 (m, 3H), 7.33 (dd, 1H), 4.75 (m, 1H), 3.90-4.18 (m, 2H), 3.04-3.28 (m, 2H), 2.64-2.73 (m, 2H), 2.05-2.22 (m, 2H). HPLC-MS-4: Rt 0.88 min; MS m/z [M+H] ⁺ 462.2
187	 N-(4-(1-(2,2-Dimethylpiperidin-4-yl)-1H-pyrazol-4-yl)-3-fluorophenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide (TFA salt)	Analogous to Example 6 using Intermediate D-T8 and Intermediate B-T42 with PdCl ₂ (dppf) and K ₂ CO ₃	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.54 (s, 1H), 8.81 (br s, 1H), 8.55 (br s, 1H), 8.14 (d, 1H), 8.09 (t, 1H), 7.93 (s, 1H), 7.82 (d, 1H), 7.75 (d, 1H), 7.63-7.71 (m, 2H), 7.33 (dd, 1H), 4.84 (m, 1H), 4.01 (s, 2H), 3.18-3.31 (m, 2H), 1.98-2.25 (m, 4H), 1.39 (d, 6H). HPLC-MS-4: Rt 0.80 min; MS m/z [M+H] ⁺ 476.1.
188	 N-(3-Fluoro-4-(1-(6-oxopiperidin-3-yl)-1H-pyrazol-4-yl)phenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide	Analogous to Example 10 using Intermediate D-T8 and Intermediate B-T43 with PdCl ₂ (dppf) and K ₂ CO ₃	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.52 (s, 1H), 8.19 (d, 1H), 8.09 (t, 1H), 7.90 (s, 1H), 7.82 (d, 1H), 7.75 (d, 1H), 7.63-7.71 (m, 2H), 7.58 (s, 1H), 7.33 (dd, 1H), 4.60-4.77 (m, 1H), 4.01 (s, 2H), 3.49-3.61 (m, 2H), 2.13-2.41 (m, 4H). HPLC-MS-4: Rt 0.88 min; MS m/z [M+H] ⁺ 462.2.
189	 N-(3-Fluoro-4-(1-(2-(4-methylpiperazin-1-yl)ethyl)-1H-pyrazol-4-yl)phenyl)-2-(3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 6 using Intermediate D-M3/Step 1 and Intermediate B-T45	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.43 (br s, 1H), 8.07-8.11 (m, 1H), 7.83 (s, 1H), 7.55-7.72 (m, 6H), 7.31 (dd, 1H), 4.23 (t, 2H), 3.80 (s, 2H), 2.70 (t, 2H), 2.20-2.48 (m, 8H), 2.12 (s, 3H). HPLC-MS: Rt 2.18 min; MS m/z [M+H] ⁺ 490.1.
190	 N-(3-Fluoro-4-(1-(4-hydroxypiperidin-4-yl)methyl)-1H-pyrazol-4-yl)phenyl)-2-(6-(trifluoromethyl)pyridin-2-yl)acetamide	Analogous to Example 6 using Intermediate D-M3/Step 1 and Intermediate B-T44 with (Ph ₃ P) ₄ Pd in Step 1 and 4N	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.81 (s, 1H), 9.02 (br s, 1H), 8.65 (br s, 1H), 8.07 (d, 1H), 7.89 (s, 1H), 7.52-7.78 (m, 6H), 7.39 (dd, 1H), 4.17 (s, 2H), 3.84 (s, 2H), 3.06-3.23 (m, 2H), 3.00 (q, 2H), 1.66-1.83 (m, 2H), 1.56 (d, 2H). HPLC-MS-4: Rt 0.83 min; MS m/z [M+H] ⁺ 477.2.

Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
	yl)phenyl)-2-(3-(trifluoromethyl)phenyl)acetamide (HCl salt)	HCl/dioxane in Step 2	
191	 N-(4-(1-(2-(4H-1,2,4-Triazol-3-yl)propan-2-yl)-1H-pyrazol-4-yl)-3,5-difluorophenyl)-2-(3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 10 using Intermediate D-T1 and Intermediate B-T27 with PdCl ₂ (dtbpf) and Na ₂ CO ₃	¹ H NMR (400 MHz, DMSO-d ₆) δ 13.98 (s, 1H), 10.63 (s, 1H), 8.39 (s, 1H), 7.91 (s, 1H), 7.77 (d, 1H), 7.70 (s, 1H), 7.56-7.67 (m, 3H), 7.34-7.45 (m, 2H), 3.82 (s, 2H), 1.97 (s, 6H). HPLC-MS: Rt 2.26 min; MS m/z [M+H] ⁺ 491.1.
192	 N-(3,5-Difluoro-4-(1-(pyridin-2-yl)-1H-pyrazol-4-yl)phenyl)-2-(3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 18 using Intermediate D-M5 and 2-bromopyridine with L-proline/DMF	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.76 (br s, 1H), 8.89 (s, 1H), 8.52 (d, 1H), 8.17 (s, 1H), 7.95-8.08 (m, 2H), 7.71 (s, 1H), 7.55-7.68 (m, 3H), 7.49 (d, 2H), 7.41 (ddd, 1H), 3.85 (s, 2H). HPLC-MS: Rt 2.49 min; MS m/z [M+H] ⁺ 459.1.
193	 N-(6-(4-(3,6-Dihydro-2H-pyran-4-yl)-1H-imidazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide	Analogous to Example 10 using Intermediate D-M4 with PdCl ₂ (dppf).DC M and K ₃ PO ₄	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.07 (s, 1H), 8.48 (d, 1H), 8.27 (dd, 1H), 8.25 (s, 1H), 7.70 (s, 1H), 6.57 (s, 1H), 6.40 (s, 1H), 5.18 (s, 2H), 4.22 (m, 2H), 3.80 (t, 2H), 2.35-2.42 (m, 2H), 2.31 (s, 3H). UPLC-MS-2: Rt = 0.93 min; MS m/z [M+H] ⁺ = 451.0.
194	 2-(2-Fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(4-methoxypiperidin-1-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide	Analogous to Example 24 using Intermediate D-T2 and 4-methoxypiperidine with NaOtBu/DMA	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.88 (s, 1H), 8.44 (d, 1H), 8.24 (dd, 1H), 8.01 (m, 1H), 7.67-7.80 (m, 2H), 7.40 (t, 1H), 6.92 (s, 1H), 3.94 (s, 2H), 3.39-3.48 (m, 2H), 3.29 (m, 1H), 3.26 (s, 3H), 2.71-2.80 (m, 2H), 1.87-1.96 (m, 2H), 1.44-1.56 (m, 2H). UPLC-MS-2: Rt = 1.07 min; MS m/z [M+H] ⁺ = 496.4.
195	 2-(2-Fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(2-oxopyrrolidin-1-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide	Analogous to Example 18 using Intermediate D-T2	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.97 (s, 1H), 8.48 (d, 1H), 8.30 (dd, 1H), 8.17 (s, 1H), 7.97 (s, 1H), 7.68-7.81 (m, 2H), 7.41 (t, 1H), 3.95 (s, 2H), 3.91 (t, 2H), 2.44-2.49 (m, 2H), 2.05-2.16 (m, 2H). UPLC-MS-2: Rt = 1.00 min; MS m/z [M+H] ⁺ = 466.4.

Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
196	 2-(2-Fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(3-oxomorpholino)-1H-imidazol-1-yl)pyridin-3-yl)acetamide	Analogous to Example 18 using Intermediate D-T2 and morpholin-3-one	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.96 (s, 1H), 8.49 (d, 1H), 8.31 (dd, 1H), 8.21 (s, 1H), 8.09 (s, 1H), 7.69-7.81 (m, 2H), 7.41 (t, 1H), 4.25 (s, 2H), 3.96-4.02 (m, 4H), 3.95 (s, 2H). UPLC-MS-2: Rt = 0.94 min; MS m/z [M+H] ⁺ = 482.3.
197	 2-(2-Fluoro-3-(trifluoromethyl)phenyl)-N-(5-fluoro-6-(4-(4-hydroxytetrahydro-2H-pyran-4-yl)-1H-imidazol-1-yl)pyridin-3-yl)acetamide	Analogous to Example 5 using Intermediate C-T27 and 2-(2-fluoro-3-(trifluoromethyl)phenyl)acetic acid [CAS No. 194943-83-4]	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.92 (s, 1H), 8.47 (d, 1H), 8.28 (dd, 1H), 8.18 (m, 1H), 7.69-7.80 (m, 2H), 7.56 (m, 1H), 7.41 (t, 1H), 4.96 (s, 1H), 3.95 (s, 2H), 3.68-3.79 (m, 2H), 3.58-3.68 (m, 2H), 2.01-2.13 (m, 2H), 1.56-1.65 (m, 2H). UPLC-MS-2: Rt = 0.86 min; MS m/z [M+H] ⁺ = 483.5.
198	 N-(6-(3-(1-Amino-3,3-difluorocyclobutyl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(2-fluoro-3-(trifluoromethyl)phenyl)acetamide	Analogous to Example 11 using Intermediate C-T35 and 2-(2-fluoro-3-(trifluoromethyl)phenyl)acetic acid [CAS No. 194943-83-4]	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.04 (br s, 1H), 9.05 (s, 1H), 8.53 (d, 1H), 8.33 (dd, 1H), 7.77 (t, 1H), 7.72 (t, 1H), 7.41 (t, 1H), 3.97 (s, 2H), 3.13-3.23 (m, 2H), 2.73-2.83 (m, 2H), 2.52 (br s, 2H). UPLC-MS-8: Rt = 0.85 min; MS m/z [M+H] ⁺ = 489.3.
199	 N-(3-Cyano-5-fluoro-4-(1-(tetrahydro-2H-pyran-3-yl)-1H-pyrazol-4-yl)phenyl)-2-(3-(pentafluoro-λ⁶-sulfaneyl)phenoxy)acetamide	Analogous to Example 5 using Intermediate A-M2 and Intermediate C-T54	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.57 (s, 1H), 8.29 (s, 1H), 7.94-7.98 (m, 2H), 7.89 (s, 1H), 7.59 (t, 1H), 7.52-7.56 (m, 2H), 7.36 (dd, 1H), 4.89 (s, 2H), 4.42 (m, 1H), 4.00 (dd, 1H), 3.80 (m, 1H), 3.67 (dd, 1H), 3.46 (dt, 1H), 2.17 (m, 1H), 2.11 (m, 1H), 1.75 (m, 1H), 1.66 (m, 1H). UPLC-MS-2: Rt = 1.19 min; MS m/z [M+H] ⁺ = 547.2.
200	 N-(3,5-Difluoro-4-(1-(piperidin-3-yl)-1H-pyrazol-4-yl)phenyl)-2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)-1H-pyrazol-1-yl	Analogous to Example 6 using tert-butyl 3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)-1H-pyrazol-1-yl	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.79 (s, 1H), 8.32 (s, 1H), 8.17 (s, 1H), 7.82 (s, 1H), 7.71 (s, 1H), 7.55-7.67 (m, 3H), 7.40-7.49 (m, 2H), 4.37-4.50 (m, 1H), 3.84 (s, 2H), 3.38-3.39 (m, 1H), 2.97-3.10 (m, 2H), 2.68 (dt, 1H),

Example	Structure	Method, Intermediate(s) and Chiral Separation Conditions	Characterizing Data
	(trifluoromethyl)phenyl)acetamide (HCOOH salt)	yl)piperidine-1-carboxylate [CAS No. 1092563-74-0]	2.07-2.18 (m, 1H), 1.97 (ddd, 1H), 1.74-1.85 (m, 1H), 1.56-1.72 (m, 1H). HPLC-MS: Rt = 2.04 min; MS m/z [M+H] ⁺ = 465.0.
201	 N-(5-Fluoro-6-(4-(tetrahydrofuran-3-yl)-1H-imidazol-1-yl)pyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (TFA-salt)	Analogous to Example 10 and Example 21 using Intermediate D-M4 and 2-(2,5-dihydrofuran-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [CAS No. 212127-80-5] with PdCl ₂ (dppf)/K ₃ P O ₄ and NH ₄ HCO ₂ /EtOH	¹ H NMR (600 MHz, DMSO-d ₆) δ 11.15 (s, 1H), 8.73 (br s, 1H), 8.50 (d, 1H), 8.30 (dd, 1H), 7.78 (s, 1H), 6.57 (s, 1H), 5.19 (s, 2H), 3.99 (t, 1H), 3.87 (td, 1H), 3.79 (q, 1H), 3.69 (d, 1H), 3.68 (d, 1H), 2.31 (s, 3H), 2.25 (m, 1H), 2.06 (m, 1H). UPLC-MS-2: Rt = 0.86 min; MS m/z [M+H] ⁺ = 439.3.

Example 202: (S)-N-(6-(3-(4,4-Difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-d-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide



- 5 Step 1: A solution of NBS (175 mg, 0.9835 mmol) in ACN (1.5 ml) was added to a solution of tert-butyl (S)-2-(1-(5-amino-3-fluoropyridin-2-yl)-1H-1,2,4-triazol-3-yl)-4,4-difluoropyrrolidine-1-carboxylate (Intermediate C-T40, 360 mg, 0.9366 mmol) in ACN (8 ml) under Ar at 0°C. After 1

h, the temperature had risen to 7°C. The reaction mixture was quenched with H₂O and extracted with EtOAc. The organic layer was washed with brine, dried (Na₂SO₄) and concentrated in vacuo. The residue was purified on silica gel (cyclohexane/EtOAc 100:0 to 50:50) to afford tert-butyl (S)-2-(1-(5-amino-6-bromo-3-fluoropyridin-2-yl)-1H-1,2,4-triazol-3-yl)-4,4-difluoropyrrolidine-1-carboxylate. UPLC-MS-8: Rt = 0.97 min; [M+H]⁺ = 463.2/465.2.

Step 2: DIPEA (415 µl, 2.38 mmol) and then T3P (50% in EtOAc) (708 µl, 1.19 mmol) was added to a solution of tert-butyl (S)-2-(1-(5-amino-6-bromo-3-fluoropyridin-2-yl)-1H-1,2,4-triazol-3-yl)-4,4-difluoropyrrolidine-1-carboxylate (step 1, 375 mg, 0.793 mmol) and 2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid [CAS No. 345637-71-0] (191 mg, 0.873 mmol) in THF (8 ml) at 0°C. The cooling bath was removed, and the reaction mixture was stirred at RT for 20 h. The reaction mixture was diluted with EtOAc, quenched with H₂O and washed with 10% citric acid (2x), H₂O, sat. aq. NaHCO₃ and brine. The organic layer was dried (Na₂SO₄) and concentrated in vacuo. The residue was purified first on silica gel [cyclohexane/(3:1 TBME/EtOH) 100:0 to 50:50] and then via RP-HPLC-4 (mobile phase: (H₂O+0.1%TFA)/ACN 80/20 to 10/90) to afford tert-butyl (S)-2-(1-(6-bromo-3-fluoro-5-(2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)pyridin-2-yl)-1H-1,2,4-triazol-3-yl)-4,4-difluoropyrrolidine-1-carboxylate. UPLC-MS-8: Rt = 1.26 min; [M+H]⁺ = 653.1/655.1.

Step 3: TFA (1 ml, 12.98 mmol) was added to a solution of tert-butyl (S)-2-(1-(6-bromo-3-fluoro-5-(2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)pyridin-2-yl)-1H-1,2,4-triazol-3-yl)-4,4-difluoropyrrolidine-1-carboxylate (step 2, 320 mg, 0.485 mmol) in DCM (5 ml) at RT. After 2 h, the reaction mixture was concentrated in vacuo. The residue was partitioned between EtOAc and sat. aq. NaHCO₃. The organic layer was washed with sat. aq. NaHCO₃ and brine, dried (Na₂SO₄) and concentrated in vacuo. The residue was diluted with 1:1 EtOAc/heptane and concentrated in vacuo to afford (S)-N-(2-bromo-6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide. UPLC-MS-8: Rt = 0.81 min; [M+H]⁺ = 553.0/555.0.

Step 4: Et₃N (30 µl, 0.215 mmol) and 10% Pd/C (20 mg) were added to a solution of (S)-N-(2-bromo-6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (step 3, 22 mg, 0.0394 mmol) in DMF (2 ml). The mixture was degassed with freeze (liquid nitrogen)-thaw cycles (2x), then frozen again and purged with deuterium from a D₂-line. The mixture was stirred under a D₂ atmosphere at RT for 90 min. The mixture was diluted with EtOAc and filtered over a membrane filter. The filtrate was washed with H₂O (3x) and brine, dried (Na₂SO₄) and concentrated in vacuo. The residue was dissolved in MeOH and concentrated in vacuo. The residue was purified via RP-HPLC-3 (mobile phase: (H₂O+0.1%TFA)/ACN 90/10 to 60/40). The product-containing fractions were quenched with sat. aq. NaHCO₃ and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried (Na₂SO₄) and concentrated in vacuo. The residue was diluted with heptane,

sonicated and then concentrated in vacuo to afford (S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide. ¹H NMR (400 MHz, DMSO-d₆) δ 11.17 (s, 1H), 9.07 (s, 1H), 8.30 (dd, 1H), 6.57 (d, 1H), 5.20 (s, 2H), 4.52 (q, 1H), 3.38 (s, 1H), 3.10-3.24 (m, 2H), 2.53-2.73 (m, 2H), 2.32 (s, 3H). UPLC-MS-8: Rt = 0.70 min; [M+H]⁺ = 476.2.

Example 203: Preparation methods and characterization of the monohydrate crystalline form of (S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide

Preparation methods of (S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide monohydrate

The monohydrate form of (S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide was obtained using the following method:

(S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (**33a**) (3.5 g) was weighed into a 250 ml reactor, followed by the addition of 140 ml of MeOH/H₂O (33:67 ratio). The mixture was slurried for 24 h at RT. The solid was then obtained by filtration (Buchner funnel) and washed (3x) with MeOH/H₂O (33:67 ratio). The solid was then dried under vacuum (< 100 mbar) at RT to obtain the monohydrate form of (S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide

Characterization of (S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide monohydrate

A: XRPD analysis

A representative XRPD diffractogram of the (S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide monohydrate is shown in Figure 1 and the corresponding reflection list (peak list) from 12 to 30° 2-Theta and relative peak intensities are provided in Table 1 below.

Table 1

Peak	Angle (° 2-Theta)	d Value	Rel. Intensity
1	12.36	7.15	9.4%
2	16.90	5.24	100.0%
3	17.49	5.07	28.5%
4	19.21	4.62	6.4%
5	20.15	4.40	5.9%
6	21.77	4.08	9.2%
7	23.01	3.86	12.6%

8	23.47	3.79	4.1%
9	25.91	3.44	19.2%
10	29.88	2.99	15.6%

Table 1: Reflection (peak) positions of the (S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide monohydrate in the range from 12 to 30° 2-Theta; A typical precision of the 2-Theta values is in the range of ± 0.2° 2-Theta, preferably of ± 0.1° 2-Theta. The most characteristic XRPD peaks are bold and in italics.

B: Differential scanning calorimetry (DSC) analysis

(S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide monohydrate was investigated by DSC using a Mettler Toledo DSC1/DSC3+ STARe System instrument. A sample of approximately 1-10 mg was heated in an aluminum pan with pierced lid from 20 to 350°C at a rate of 10°C/min. Nitrogen (40 ml/min) was used as purge gas. The DSC curve of (S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide monohydrate is shown in Figure 2 where an endothermic peak with an onset temperature of about 175.4 °C and a peak temperature of about 176.8 °C is obtained.

C: Thermogravimetric analysis (TGA) analysis

(S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide monohydrate was investigated by TGA using a Mettler Toledo TGA/DSC3+ STARe System instrument. A sample of approximately 1-10 mg was heated in an aluminum pan. The lid was auto-pierced at the beginning of the measurement. The sample was heated from 20 to 350°C at a rate of 10°C/min. Nitrogen (20 ml/min) was used as purge gas. The TGA curve is shown in Figure 3, where 3.56% mass loss is observed prior to the sample melting.

Biological Data

Lipolysis Assay

Patatin-like phospholipase domain-containing 3 (PNPLA3) is a triacylglyceride (TAG) hydrolase, locating on the lipid droplet (LD) membrane. The point mutation PNPLA3I148M (G/G genotype) is genetically associated with progressive fatty liver disease. PNPLA3I148M has reduced lipid hydrolase activity and accumulates on hepatic LDs, where it can interfere with normal LD function resulting in steatosis and steatohepatitis in patients as well as animal models of non-alcoholic steatohepatitis (NASH). PNPLA3I148M negatively regulates lipolysis by competitively binding CGI58 and thereby inhibiting PNPLA2 function. Compounds which bind to PNPLA3I148M, and release CGI58, thus restore PNPLA2-mediated cellular lipolysis. A cellular assay using human hepatocytes overexpressing PNPLA3I148M was used to identify compounds which restore (i.e. normalize) PNPLA2-mediated cellular lipolysis. The assay read-

out is based on measuring the reduction of remaining deuterated oleic acid containing TAGs by LC-MS.

List of abbreviations

Abbreviation	Description
AC	Active control
AC ₅₀	Active concentration 50%
Amax	Maximum value on a fitted curve at any concentration (Helios terminology)
ATCC	American Type Culture Collection
BSA	Bovine serum albumin
CRC	Concentration response curve
c/w	Cells per well
Data(Cmax)	The average value of data points in a concentration response curve at highest concentration (Helios terminology)
d9-OA	Deuterated Oleic Acid
DMSO	Dimethylsulfoxide
f.c.	Final concentration
FCS	Fetal calf serum
FFA	Free Fatty Acid
Huh7	Human hepatocyte cell line Huh7
LC-MS	Liquid Chromatography Mass Spectrometry
ISTD	Internal Standard
LD	Lipid Droplets
LDV	Low dead volume
LMW	Low molecular weight
NC	Neutral control
PBS	Phosphate buffered saline
PP	Polypropylene
rhu	Recombinant human
RT	Room temperature
S/B	Signal to background
SD	Standard deviation
TAG	Triglycerides (17:0)
wp	Well plate

5

Methods

Table 2: Materials

Material	Company	Cat number
DMEM	GIBCO	31966-021
DMEM (no phenol red)	GIBCO	21063-029
FBS (Heat Inactivated)	GIBCO	A3161001
Hepes	GIBCO	15630-080
Blasticidin		
Penicillin/Streptomycin	GIBCO	15140-122
OptiMEM	GIBCO	31985-062
PBS	GIBCO	10010-023
NaOH		
Trypsin-EDTA 0.25%	GIBCO	25200-056
Transfection reagent	FuGene	EZ31A
70 uM cell strainer	BD Falcon	352350
PCR Plate	Eppendorf	0030128.508
BSA (fatty acid free)	Biowest	P6156-100gr
d9-Oleic Acid	Avanti Polar Lipids	8618090-10mg
Butanol	Sigma	537993
Isopropanol	BioSolve	0016264101BS
H ₂ O (LCMS grade)	Honeywell	14263
Methanol	Honeywell	14262
Triglyceride (17:0_17:0_17:0)	Sigma	T2151-100MG
Black clear bottom 384wp, plastic	Greiner	781091

Table 3: Instruments

Instrument	Company
Vanquish, TSQ-Quantum (LC-MS)	Thermo
384/ 1536wp Multidrop dispenser	Thermo
CyBi 384-well dispenser	Cybio
Echo acoustic dispenser	LabCyte
Cell counter	Invitrogen
Incubator	Liconic

Table 4: Buffer and media

Name	Composition
Growth Medium	DMEM + 10% FBS Heat Inactivated + 1% P/S + 1% Hepes
Assay Medium	DMEM (No phenol red) + 2% BSA

Name	Composition
Extraction Solution	Butanol + 100 ng/ml Triglycerides f.c

Cell culture

HUH7-hPNPLA3(I148M)-RFP overexpressing cells were cultured in DMEM, 10% heat inactivated FBS, Pen/Strep and 10 mM Hepes containing 10 µg/ml Blasticidin. The cells were
 5 passed twice a week. The cells were seeded at a density of 3×10^6 /150 cm² flask if the cells were cultured for 4 d, and 5×10^6 /150 cm² flask if cultured for 3 d.

On day one of the assay, 9 million of HUH7-PNPLA3(I148M)-RFP cells were seeded in 9.75 ml of growth medium in a T75 cm² flask and cultured for about 6 h in 5% CO₂/37°C incubator. After 6 h incubation, add 250 µl of a 8mM d9-OA (prepared as described below) to each 75 cm²
 10 flask.

8mM d9-OA was prepared following the protocol below:

d9-OA glass tubes were centrifuged in a ml Falcon tube (50 mL) and then broken within the Falcon tube. A 200 mM solution of d9-OA was then prepared by adding 515 µl of 0.2 M NaOH
 15 to 30 mg of d9-OA. The solution was then incubated at 72°C for 30 min with 1000 rpm shaking. A 16 mM d9-OA in DMEM+20% BSA solution was then prepared by dilution of the 200 mM d9-OA solution with the addition of 5.92 mL of DMEM+20%BSA to the 515 µl of d9-OA in NaOH. Finally, 8mM d9-OA in 10% BSA was obtained by adding 6.43 ml of DMEM no phenol red.

20 Compound preparation

A 10 mM solution of the test compound was diluted in 50 µl Assay medium (DMEM no phenol Red + 2% BSA) to give a final compound concentration in the assay plate in the range of 10 µM - 31.4 nM, containing 0.05% DMSO for a 10-point CRC. Neutral control compounds were obtained similarly.

25

Cell suspension preparation

The cells in each T75 cm² flask were washed with PBS (GIBCO, 10010-023) and detached with 1 mL 0.25%Trypsin/EDTA (GIBCO, 25200-056) in a 5% CO₂/37°C incubator for 5 min. Then 9 mL of assay medium (DMEM + 2% BSA), was added and the cell suspension was passed
 30 through a 70 µm cell strainer. The cells were centrifuged at 1000 rpm for 5 min in a Eppendorf 5810 R centrifuge and the supernatant discarded. The cells were resuspended in 7.5 mL assay medium and the cells density was adjusted to about 2.5×10^5 /ml by dilution.

50 µl of the cell suspension were added to each well of the prepared compound plates to give about 12500 cells/well. The cells were then incubated with the test compound titration for
 35 24 h at 37°C.

TAG extraction

Following treatment with test compound for 24 h, the culture medium was removed from plate wells and 50 µl of butanol containing 100 ng/ml TAG 17:0_17:0_17:0 (ISTD) was added to each plate well. The plates were sealed, followed by shaking at 600 rpm for 30 minutes. The plates were then centrifuged at 2000 rpm for 10 min at room temperature. 40 µl of supernatant was transferred from each well to new 240 µl low-binding Eppendorf deep-well plates.

TAG measurement

The quantity of d9-OA containing TAGs and ISTD were then measured by LCMS using the conditions below:

UPLC	WATERS UPLC Acquity
Column	Agilent Zorbax 300SB-C8; 3.5 µm; 50 mm x 1.0 mm
Column temperature	40 °C
Mobile phase	A: H ₂ O 80 % + 20% MeOH, 5mM NH ₄ Ac, 0.1% HCOOH B: 100 % Isopropanol, 5mM NH ₄ AC, 0.1% HCOOH
Flow	150 µl/min
Gradient (%B)	0 min 65 % B 0.1 min: 65 % B, 1 min 85 % B 2.3 min 95 % B 3 min 95 % B 3.1 min 65 % B
Equilibration time	1.5 min
Injection	2.5 µL
MS	TSQ Quantum Access Max; Thermo
Ionization mode	+ESI
SRM	<i>m/z</i> 866.70 --> <i>m/z</i> 579.30 ; 0.1 s/Da
neutral loss	308.30 Da <i>m/z</i> 810-940 in 0.5 s; Q1 Peak Width [FWHM]: 0.7 Da 26 V collision energy

Data analysis

Test compound activity was obtained by measuring the reduction of remaining d9-OA containing TAG with LC-MS.

$$\text{Relative d9-TAG Level (\%)} = \frac{\text{Sample} - \text{Ave}_-}{\text{Ave}_+ - \text{Ave}_-}$$

+ : positive control (DMSO)

- : negative control (cell free)

The in-vitro activities of the exemplified compounds is given in Table 5, where the AC₅₀ represents the concentration of compound needed to give a 50% decrease in TAG levels

5 relative to the control.

Table 5: Tabulated in vitro PNPLA3I148M activities

Example No.	Lipolysis AC ₅₀ (nM)	Example No.	Lipolysis AC ₅₀ (nM)
1	n.d.	89	****
1a	**	90	***
1b	****	91	***
1c	*	92	*****
1d	*****	92a	*****
2	n.d.	92b	***
2a	**	93	*****
2b	**	94	****
3	*****	95	*****
4	****	96	*****
4a	****	97	*****
4b	*****	98	*****
5	****	99	*****
6	****	100	*****
7	****	101	*****
8	n.d.	102	*****
8a	*****	103	*****
8b	*	104	n.d.
9	***	104a	***
10	***	104b	**
11	***	105	**
12	n.d.	105a	***
12a	****	105b	**
12b	***	106	**
13	****	106a	***
13a	****	106b	***
13b	****	107	***
14	*****	108	***
15	*****	108a	**
16	*****	108b	***
17	**	109	***
18	***	110	***

Example No.	Lipolysis AC ₅₀ (nM)	Example No.	Lipolysis AC ₅₀ (nM)
19	****	111	**
20	***	111a	**
21	***	111b	**
22	***	112	***
23	*****	113	***
24	***	113a	**
25	n.d.	113b	**
25a	*****	114	n.d.
25b	*****	114a	****
26	**	114b	****
26a	**	115	n.d.
26b	***	115a	*****
27	***	115b	****
28	****	116	*****
29	****	117	n.d.
30	*****	117a	**
31	*****	117b	***
32	***	118	n.d.
32a	***	118a	***
32b	***	118b	***
33	n.d.	119	**
33a	**	120	n.d.
33b	****	120a	***
34	***	120b	***
35	*****	121	n.d.
35a	*****	121a	***
35b	***	121b	***
35c	****	122	***
35d	***	123	***
36	*****	124	***
37	*****	125	n.d.
38	*****	125a	***
39	*****	125b	**
40	*****	126	***
41	n.d.	127	****
41a	***	128	n.d.
41b	***	128a	***
42	***	128b	***
43	****	129	n.d.

Example No.	Lipolysis AC ₅₀ (nM)	Example No.	Lipolysis AC ₅₀ (nM)
44	n.d.	129a	***
44a	***	129b	***
44b	****	130	***
45	*****	131	n.d.
46	n.d.	131a	***
46a	***	131b	***
46b	*****	132	***
47	****	133	****
47a	****	134	***
47b	***	135	****
48	*****	136	**
49	*****	137	****
50	*****	138	n.d.
51a	***	138a	***
51b	***	138b	****
52	n.d.	139	*****
52a	***	140	*****
52b	***	141	*****
53a	***	142	*****
53b	***	143	*****
54	n.d.	144	*****
54a	***	145	*****
54b	***	146	*****
55	***	147	**
55a	*****	147a	***
55b	*****	147b	**
55c	*	148	n.d.
55d	*****	148a	*****
56	***	148b	****
56a	**	149	***
56b	**	150	***
57	**	150a	*****
57a	***	150b	****
57b	**	151	****
58	***	152	****
59	***	153	****
60	***	154	*****
61	***	155	*****
62	****	156	*****

Example No.	Lipolysis AC ₅₀ (nM)	Example No.	Lipolysis AC ₅₀ (nM)
63	****	157	*****
63a	***	158	*****
63b	***	159	*****
64	****	160	*****
65	****	161	*****
66	*****	162	*****
66a	*****	163	*****
66b	*****	164	*****
67	*****	165	*****
68	*****	166	*****
69	*****	167	*****
70	**	168	*****
71	****	169	*****
72	***	170	*****
72a	**	171	*****
72b	**	172	*****
73	**	173	*****
73a	***	174	*****
73b	***	175	*****
74	*****	176	*****
75	**	177	*****
75a	***	178	*****
75b	**	179	*****
76	n.d.	180	*****
76a	**	181	*****
76b	***	182	*****
77	**	183	*****
78	n.d.	184	*****
78a	***	185	*****
78b	**	186	*****
79	**	187	****
80	**	188	****
81	**	189	*****
82	n.d.	190	*****
82a	***	191	*****
82b	**	192	***
83	**	193	***
84	***	194	***
85	***	195	***

Example No.	Lipolysis AC ₅₀ (nM)	Example No.	Lipolysis AC ₅₀ (nM)
86	***	196	***
87	n.d.	197	***
87a	****	198	***
87b	***	199	***
88	***	200	***
88a	****	201	***
88b	***	202	n.d.

Note: * EC₅₀ < 0.5 nM; ** EC₅₀ 0.5 nM to 5 nM; *** EC₅₀ >5 nM to 50 nM

**** EC₅₀ >50 nM to 100 nM; ***** EC₅₀ >100 nM to 500 nM

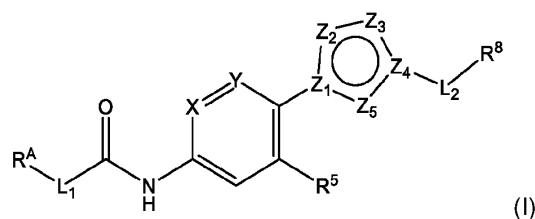
***** EC₅₀ >500 nM to 1000 nM; ***** EC₅₀ >1000 nM

n.d. not determined

5

Claims

1. A compound of Formula (I), or a pharmaceutically acceptable salt thereof,



wherein:

- 5 -X=Y- is -CR^x=CR^y-, -CR^x=N- or -N=CR^y-;
 R^x is H, D, halogen or C₁-C₄alkyl;
 R^y is H, D, halogen, -CN, C₁-C₄alkyl, C₁-C₄fluoroalkyl or C₁-C₄alkoxy;
 R⁵ is H, halogen, -CN, C₁-C₄alkyl, C₁-C₄fluoroalkyl or C₁-C₄alkoxy;
 R^A is:
- 10 (i) phenyl which is unsubstituted or is substituted with 1, 2, 3 or 4 R¹ groups;
 (ii) a partially saturated 9-, 10-, 11- or 12-membered bicyclic carbocyclyl which is
 unsubstituted or is substituted with 1 to 4 R¹ groups;
 (iii) a 5- or 6- membered monocyclic heteroaryl having 1, 2, 3 or 4 ring members
 independently selected from N, NR⁴, O and S, wherein the monocyclic
 15 heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 R¹ groups;
 or
 (iv) a partially saturated 8-, 9-, 10-, 11- or 12-membered fused bicyclic heterocyclyl
 having 1, 2, 3 or 4 ring members independently selected from N, NR⁴, O and S,
 wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with 1,
 20 2, 3 or 4 R¹ groups;
- each R¹ is independently selected from the group consisting of halogen, C₁-C₄alkyl, C₂-
 C₄alkenyl, C₂-C₄alkynyl, C₁-C₄alkoxy, C₁-C₄alkoxycarbonyl, C₃-C₆cycloalkyl, C₁-
 C₄fluoroalkyl, C₁-C₄fluoroalkoxy, pentafluorosulfanyl, C₁-C₄hydroxyalkyl, C₁-
 C₄thioalkyl, azido, diC₁-C₄alkylamino, diC₁-C₄alkylaminocarbonyl, D, CD₃, cyano,
 25 formyl, phenyl and a 5- to 6-membered heterocycloalkyl comprising 1 or 2 ring
 members independently selected from N, NR⁴, O and S;
- L₁ is a bond, -(CR²R³)_p-, -(CR²R³)_p-NR⁴-, -(CR²R³)_p-O-, -NR⁴(CR²R³)_q-, -(CR²R³)_qNR⁴-, -
 O-(CR²R³)_p- or -S-(CR²R³)_p-;
- R² is H, D, halogen or C₁-C₄alkyl;
- 30 R³ is H, D, halogen, C₁-C₄alkyl C₁-C₄alkoxy, OH, amino or *t*-Boc-amino;
 or R² and R³, together with the C atom to which they are attached, are linked to form C₃-
 C₄cycloalkyl which is unsubstituted or is substituted with a single substituent selected
 from C₁-C₄alkyl and oxo;
 each R⁴ is independently selected from the group consisting of H and C₁-C₄alkyl;

p is 1, 2 or 3;

q is 0, 1 or 2;

Z₁ is N or C; Z₂ is N or CR^z; Z₃ is N or CR^z; Z₄ is N or C; Z₅ is N or CR^z;

wherein each R^z is independently selected from the group consisting of H,

5 halogen, C₁-C₄alkyl and C₁-C₄fluoroalkyl; and provided that at least two, and not more than four, of Z₁, Z₂, Z₃, Z₄ and Z₅ are N;

L₂ is a bond, -(CR⁶R⁷)_n- or -(CR⁶R⁷)_nO-*, where the * indicates the point of attachment to R⁸;

each R⁶ is independently selected from the group consisting of H, C₁-C₄alkyl, C₁-C₄fluoroalkyl and C₁-C₄hydroxyalkyl;

each R⁷ is independently selected from the group consisting of H, C₁-C₄alkyl, C₁-C₄fluoroalkyl and C₁-C₄hydroxyalkyl;

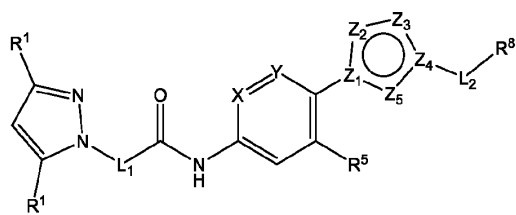
or R⁶ and R⁷, together with the C atom to which they are attached, are linked to form C₃-C₆cycloalkyl, oxetanyl, tetrahydrofuranyl or tetrahydropyranyl;

15 n is 1, 2 or 3;

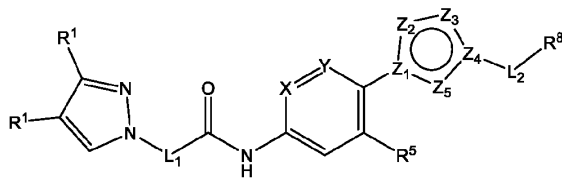
R⁸ is:

- (i) 4-, 5- or 6-membered heterocycloalkyl having 1, 2 or 3 ring members independently selected from N, NR⁹, O and S, wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents each independently selected from -OH, -CN, -N(R¹⁰)₂, halogen, C₁-C₄fluoroalkyl, C₁-C₄alkyl, C₁-C₄alkoxy, oxo and a 5- or 6- membered monocyclic heteroaryl having 1, 2, 3 or 4 ring members independently selected from N, NR⁹, O and S, wherein the monocyclic heteroaryl is unsubstituted;
- 20 (ii) 4-, 5- or 6-membered heterocycloalkyl wherein one ring member is S(=O)₂, S(=O) or S(=O)(=NH), and wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from -OH, C₁-C₄alkyl and oxo;
- 25 (iii) 4-, 5- or 6-membered heterocycloalkyl wherein one ring member is S(=O)₂ or S(=O), and 1, 2 or 3 other ring members are independently selected from N, NR⁹ and O, and wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents each independently selected from C₁-C₄alkyl and oxo;
- 30 (iv) a partially saturated 5- or 6-membered heterocyclyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents independently selected from -OH, C₁-C₄alkyl, and oxo;
- 35 (v) a partially saturated 5- or 6-membered heterocyclyl wherein one ring member is S(=O)₂ and 1, 2 or 3 other ring members are independently selected from N, NR⁹, O and S, wherein the partially saturated heterocyclyl is unsubstituted or is

- substituted with 1, 2, 3 or 4 substituents independently selected from -OH, C₁-C₄alkyl, and oxo;
- (vi) a 5- or 6- membered monocyclic heteroaryl having 1, 2, 3 or 4 ring members independently selected from N, NR⁹, O and S, wherein the monocyclic heteroaryl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents each independently selected from -OH, C₁-C₄alkoxy and C₁-C₄alkyl;
- (vii) a 6- or 7-membered fused bicyclic heterocyclyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from -OH, -N(R¹⁰)₂, C₁-C₄alkyl-NH₂, halogen, C₁-C₄alkyl, and oxo;
- (viii) a partially saturated 8-, 9-, 10-, 11- or 12-membered fused bicyclic heterocyclyl having 1, 2, 3 or 4 ring members independently selected from N, NR⁹, O and S, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from -OH, -N(R¹⁰)₂, C₁-C₄alkyl-NH₂, halogen, C₁-C₄alkyl, and oxo;
- (ix) a 6-, 7-, 8-, 9- or 10- membered spiro bicyclic heterocycloalkyl having 1, 2 or 3 ring members independently selected from N, NR⁹, O and S, wherein the spiro bicyclic heterocycloalkyl is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from -OH, -N(R¹⁰)₂, C₁-C₄alkyl-NH₂, halogen, C₁-C₄alkyl, and oxo;
- (x) a 6- membered heterocycloalkyl having 1 to 2 ring members independently selected from N, NR⁹, O and S, wherein the heterocycloalkyl has a C₁-C₃alkyl bridge or a -CH₂OCH₂- bridge;
- (xi) phenyl which is unsubstituted or is substituted with 1, 2, 3 or 4 substituents, each independently selected from -S(=O)₂N(R¹⁰)₂, -OH, -N(R¹⁰)₂, C₁-C₄alkyl-NH₂, halogen and C₁-C₄alkyl;
- or
- (xii) C₄-C₈cycloalkyl which is unsubstituted or is substituted with 1, 2, 3 or 4 substituents independently selected from -OH, -N(R¹⁰)₂, -S(=O)₂R¹⁰, C₁-C₄alkyl-NH₂, halogen, C₁-C₄alkoxy, C₁-C₄alkyl, and oxo;
- R⁹ is H, C₁-C₄alkyl, benzyl, C₁-C₄alkyl-OR¹⁰, -C(=O)OR¹⁰ or -C(=O)R¹⁰, and
- R¹⁰ is H or C₁-C₄alkyl.
2. The compound of Formula (I) of claim 1 having the structure if Formula (I-a) or Formula (I-b), or a pharmaceutically acceptable salt thereof,

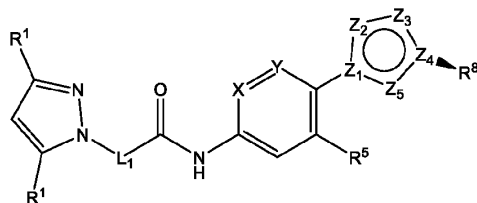


(I-a)

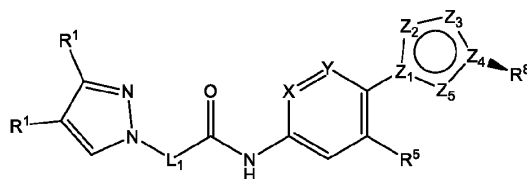


(I-b).

3. The compound of Formula (I) of claim 1 having the structure of Formula (I-c) or Formula (I-d), or a pharmaceutically acceptable salt thereof,



(I-c)



(I-d).

4. The compound of any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein:

-X=Y- is -CR^x=CR^y-, -CR^x=N- or -N=CR^y-;

R^x is H, D, or halogen;

R^y is H, D, halogen or -CN;

R⁵ is halogen or -CN;

each R¹ is independently selected from the group consisting of halogen, D, CD₃, C₁-

C₄alkyl, C₁-C₄fluoroalkyl, C₁-C₄fluoroalkoxy, C₃-C₆cycloalkyl and pentafluorosulfanyl;

L₁ is -(CR²R³)_p-, -NR⁴(CR²R³)_q- or -O-(CR²R³)_p-;

R² is H, D or halogen;

R³ is H, D, halogen, OH or C₁-C₄alkyl;

or R² and R³, together with the C atom to which they are attached, are linked to form C₃-

C₄cycloalkyl which is unsubstituted

R⁴ is H or C₁-C₄alkyl;

p is 1;

q is 0;

Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is N;
 or Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is CR^z;
 or Z₁ is C, Z₂ is CR^z, Z₃ is N, Z₄ is N and Z₅ is CR^z;
 or Z₁ is C, Z₂ is N, Z₃ is N, Z₄ is N and Z₅ is CR^z;

5 each R^z is H;

L₂ is a bond, -(CR⁶R⁷)_n- or -(CR⁶R⁷)_nO-*, where the * indicates the point of attachment to R⁸;

each R⁶ is independently selected from the group consisting of H, C₁-C₄alkyl, C₁-C₄fluoroalkyl and C₁-C₄hydroxyalkyl;

10 each R⁷ is independently selected from the group consisting of H, C₁-C₄alkyl, C₁-C₄fluoroalkyl and C₁-C₄hydroxyalkyl;

or R⁶ and R⁷, together with the C atom to which they are attached, are linked to form tetrahydropyranyl;

n is 1 or 2;

15 R⁸ is:

- (i) 4-, 5- or 6-membered heterocycloalkyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2 or 3 substituents each independently selected from -OH, -CN, -N(R¹⁰)₂, halogen, C₁-C₄fluoroalkyl, C₁-C₄alkyl, C₁-C₄alkoxy, oxo and a 5- or 6- membered monocyclic heteroaryl having 1 or 2 ring members independently selected from N and NR⁹, wherein the monocyclic heteroaryl is unsubstituted;
- 20 (ii) 5- membered heterocycloalkyl wherein one ring member is S(=O)₂, S(=O) or S(=O)(=NH), and wherein the heterocycloalkyl is unsubstituted or is substituted with a substituent selected from -OH and C₁-C₄alkyl;
- 25 (iii) 6-membered heterocycloalkyl wherein one ring member is S(=O)₂ or S(=O), and one other ring member is selected from N, NR⁹ and O, and wherein the heterocycloalkyl is unsubstituted or is substituted with a substituent selected from C₁-C₄alkyl;
- 30 (iv) a partially saturated 6-membered heterocyclyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with an oxo;
- (v) a partially saturated 6-membered heterocyclyl wherein one ring member is S(=O)₂ and one other ring member is selected from N, NR⁴, and O, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with an oxo;
- 35 (vi) a 5- or 6- membered monocyclic heteroaryl having 1, 2, 3 or 4 ring members independently selected from N, NR⁹ and O, wherein the monocyclic heteroaryl is

- unsubstituted or is substituted with a substituent selected from -OH, C₁-C₄alkoxy and C₁-C₄alkyl;
- (vii) a 6- membered fused bicyclic heterocyclyl having 1 ring member selected from N and NR⁹, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with an oxo;
- (viii) a partially saturated 10- membered fused bicyclic heterocyclyl having 1, 2, or 3 ring members independently selected from N, NR⁹, and O, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with an oxo;
- (ix) a 7- membered spiro bicyclic heterocycloalkyl having 1 ring member selected from N, NR⁹, and O, wherein the spiro bicyclic heterocycloalkyl is unsubstituted;
- (x) a 6- membered heterocycloalkyl having 1 to 2 ring members independently selected from N, NR⁹ and O, wherein the heterocycloalkyl has a C₁-C₃alkyl bridge or a -CH₂OCH₂- bridge;
- (xi) phenyl which is substituted with -S(=O)₂N(R¹⁰)₂;
- or
- (xii) C₄-C₈cycloalkyl which is substituted with 1, 2 or 3 substituents independently selected from -OH, -N(R¹⁰)₂, -S(=O)₂R¹⁰, C₁-C₄alkyl-NH₂, halogen and C₁-C₄alkoxy;
- R⁹ is H, C₁-C₄alkyl, benzyl, C₁-C₄alkyl-OR¹⁰, -C(=O)OR¹⁰ or -C(=O)R¹⁰, and
- R¹⁰ is H or C₁-C₄alkyl.
5. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein:
- X=Y- is -CR^x=CR^y- or -CR^x=N-;
- R^x is H;
- R^y is H, halogen or -CN;
- R⁵ is halogen or -CN;
- each R¹ is independently selected from the group consisting of halogen, C₁-C₄alkyl, C₁-C₄fluoroalkyl and pentafluorosulfanyl;
- L₁ is -(CR²R³)_p-, -NR⁴(CR²R³)_q- or -O-(CR²R³)_p-;
- R² is H;
- R³ is H, OH or C₁-C₄alkyl;
- R⁴ is H or C₁-C₄alkyl;
- p is 1;
- q is 0;
- Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is N;
- or Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is CR^z;
- or Z₁ is C, Z₂ is CR^z, Z₃ is N, Z₄ is N and Z₅ is CR^z;

or Z₁ is C, Z₂ is N, Z₃ is N, Z₄ is N and Z₅ is CR^z;

each R^z is H;

L₂ is a bond, -(CR⁶R⁷)_n- or -(CR⁶R⁷)_nO-*, where the * indicates the point of attachment to R⁸;

5 each R⁶ is independently selected from the group consisting of H, C₁-C₄alkyl, and C₁-C₄hydroxyalkyl;

each R⁷ is independently selected from the group consisting of H, C₁-C₄alkyl, and C₁-C₄hydroxyalkyl;

n is 1 or 2;

10 R⁸ is:

- (i) 4-, 5- or 6-membered heterocycloalkyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2 or 3 substituents each independently selected from -OH, -CN, -N(R¹⁰)₂, halogen, C₁-C₄fluoroalkyl, C₁-C₄alkyl, C₁-C₄alkoxy, oxo and a 5- or 6- membered monocyclic heteroaryl having 1 or 2 ring members independently selected from N and NR⁹, wherein the monocyclic heteroaryl is unsubstituted;
- 15 (ii) 5- membered heterocycloalkyl wherein one ring member is S(=O)₂, S(=O) or S(=O)(=NH), and wherein the heterocycloalkyl is unsubstituted or is substituted with a substituent selected from -OH and C₁-C₄alkyl;
- 20 (iii) 6-membered heterocycloalkyl wherein one ring member is S(=O)₂ or S(=O), and one other ring member is selected from N, NR⁹ and O, and wherein the heterocycloalkyl is unsubstituted or is substituted with a substituent selected from C₁-C₄alkyl;
- 25 (iv) a partially saturated 6-membered heterocyclyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with an oxo;
- (v) a partially saturated 6-membered heterocyclyl wherein one ring member is S(=O)₂ and one other ring member is selected from N, NR⁴, and O, wherein the partially saturated heterocyclyl is unsubstituted or is substituted with an oxo;
- 30 (vi) a 5- or 6- membered monocyclic heteroaryl having 1, 2, 3 or 4 ring members independently selected from N, NR⁹ and O, wherein the monocyclic heteroaryl is unsubstituted or is substituted with a substituent selected from -OH, C₁-C₄alkoxy and C₁-C₄alkyl;
- 35 (vii) a 6- membered fused bicyclic heterocyclyl having 1 ring member selected from N and NR⁹, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with an oxo;

- (viii) a partially saturated 10- membered fused bicyclic heterocyclyl having 1, 2, or 3 ring members independently selected from N, NR⁹, and O, wherein the fused bicyclic heterocyclyl is unsubstituted or is substituted with an oxo;
- (ix) a 7- membered spiro bicyclic heterocycloalkyl having 1 ring member selected from N, NR⁹, and O, wherein the spiro bicyclic heterocycloalkyl is unsubstituted;
- (x) a 6- membered heterocycloalkyl having 1 to 2 ring members independently selected from N, NR⁹ and O, wherein the heterocycloalkyl has a C₁-C₃alkyl bridge or a -CH₂OCH₂- bridge;
- (xi) phenyl which is substituted with -S(=O)₂N(R¹⁰)₂;
- or
- (xii) C₄-C₈cycloalkyl which is substituted with 1, 2 or 3 substituents independently selected from -OH, -N(R¹⁰)₂, -S(=O)₂R¹⁰, C₁-C₄alkyl-NH₂, halogen and C₁-C₄alkoxy;
- R⁹ is H, C₁-C₄alkyl, benzyl, C₁-C₄alkyl-OR¹⁰, -C(=O)OR¹⁰ or -C(=O)R¹⁰,
- and
- R¹⁰ is H or C₁-C₄alkyl.
6. The compound of any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein:
- X=Y- is -CR^x=N-;
- R^x is H;
- R⁵ is halogen;
- each R¹ is independently selected from the group consisting of halogen, C₁-C₄alkyl and C₁-C₄fluoroalkyl
- L₁ is -(CR²R³)_p-;
- R² is H;
- R³ is H, or C₁-C₄alkyl;
- p is 1;
- Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is N;
- or Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is CR^z;
- or Z₁ is C, Z₂ is CR^z, Z₃ is N, Z₄ is N and Z₅ is CR^z;
- or Z₁ is C, Z₂ is N, Z₃ is N, Z₄ is N and Z₅ is CR^z;
- each R^z is H;
- L₂ is a bond or -(CR⁶R⁷)_n-;
- each R⁶ is independently selected from the group consisting of H and C₁-C₄alkyl;
- each R⁷ is independently selected from the group consisting of H and C₁-C₄alkyl;
- n is 1 or 2;
- R⁸ is:

- (i) 4-, 5- or 6-membered heterocycloalkyl having 1 or 2 ring members independently selected from N, NR⁹, O and S, wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2 or 3 substituents each independently selected from -OH, halogen, C₁-C₄fluoroalkyl, C₁-C₄alkyl, and oxo;
- 5 (ii) 5- membered heterocycloalkyl wherein one ring member is S(=O)₂, or S(=O)(=NH), and wherein the heterocycloalkyl is unsubstituted or is substituted with a substituent selected from C₁-C₄alkyl;
- (iii) 6-membered heterocycloalkyl wherein one ring member is S(=O)₂ or S(=O), and one other ring member is selected from N, NR⁹ and O, and wherein the
10 heterocycloalkyl is unsubstituted or is substituted with a substituent selected from C₁-C₄alkyl;
- (iv) a partially saturated 6-membered heterocyclyl having 1 or 2 ring members independently selected from O and S, wherein the partially saturated heterocyclyl is unsubstituted;
- 15 (v) a partially saturated 6-membered heterocyclyl wherein one ring member is S(=O)₂ and one other ring member is O, wherein the partially saturated heterocyclyl is unsubstituted;
- (vi) a 5- membered monocyclic heteroaryl having 3 ring members independently selected from N, and O, wherein the monocyclic heteroaryl is unsubstituted;
- 20 (vii) a 6- membered fused bicyclic heterocyclyl having 1 ring member selected from NR⁹, wherein the fused bicyclic heterocyclyl is unsubstituted;
- (viii) a 7- membered spiro bicyclic heterocycloalkyl having 1 ring member selected from N, NR⁹, and O, wherein the spiro bicyclic heterocycloalkyl is unsubstituted;
- (ix) a 6- membered heterocycloalkyl having 1 ring members selected from NR⁹,
25 wherein the heterocycloalkyl has a C₁-C₃alkyl bridge;
- or
- (x) C₄-C₈cycloalkyl which is substituted with 1, 2 or 3 substituents independently selected from -OH, -N(R¹⁰)₂, C₁-C₄alkyl-NH₂ and halogen;
- R⁹ is H, C₁-C₄alkyl, or -C(=O)R¹⁰,
30 and
R¹⁰ is H or C₁-C₄alkyl.

7. The compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein:

- X=Y- is -CR_x=N-;
- 35 R^x is H;
- R⁵ is F;
- each R¹ is independently selected from the group consisting of F, Cl, methyl and -CF₃;
- L₁ is -(CR²R³)_p-;

R^2 is H;

R^3 is H or methyl;

p is 1;

Z_1 is N, Z_2 is CR^z , Z_3 is N, Z_4 is C and Z_5 is N;

5 or Z_1 is N, Z_2 is CR^z , Z_3 is N, Z_4 is C and Z_5 is CR^z ;

each R^z is H;

L_2 is a bond or $-(CR^6R^7)_n-$;

each R^6 is independently selected from the group consisting of H and methyl;

each R^7 is independently selected from the group consisting of H and methyl;

10 n is 1 or 2;

R^8 is:

- (i) 4-, 5- or 6-membered heterocycloalkyl having 1 or 2 ring members independently selected from N, NR^9 , O and S, wherein the heterocycloalkyl is unsubstituted or is substituted with 1, 2 or 3 substituents each independently selected from -OH, F, CF_3 , methyl and oxo;
 - 15 (ii) 5- membered heterocycloalkyl wherein one ring member is $S(=O)_2$ or $S(=O)(=NH)$, and wherein the heterocycloalkyl is unsubstituted or is substituted with a methyl;
 - (iii) 6-membered heterocycloalkyl wherein one ring member is $S(=O)_2$ or $S(=O)$, and one other ring member is selected from N, NR^9 and O, and wherein the heterocycloalkyl is unsubstituted or is substituted with a methyl,
 - 20 (iv) a partially saturated 6-membered heterocyclyl having 1 or 2 ring members independently selected from O and S, wherein the partially saturated heterocyclyl is unsubstituted;
 - 25 (v) a partially saturated 6-membered heterocyclyl wherein one ring member is $S(=O)_2$ and one other ring member is and O, wherein the partially saturated heterocyclyl is unsubstituted;
 - (vi) a 5- membered monocyclic heteroaryl having 3 ring members independently selected from N and O, wherein the monocyclic heteroaryl is unsubstituted;
 - 30 (vii) a 6- membered fused bicyclic heterocyclyl having 1 ring member selected from NR^9 , wherein the fused bicyclic heterocyclyl is unsubstituted;
 - (viii) a 7- membered spiro bicyclic heterocycloalkyl having 1 ring member selected from NR^9 , and O, wherein the spiro bicyclic heterocycloalkyl is unsubstituted;
 - (ix) a 6- membered heterocycloalkyl having 1 ring members selected from NR^9 ,
 - 35 wherein the heterocycloalkyl has a C_1 - C_3 alkyl bridge;
- or
- (x) cyclobutyl, cyclopentyl, or cyclohexyl which is substituted with 1, 2 or 3 substituents independently selected from -OH, $-NH_2$, $-CH_2NH_2$, and F;

and

R⁹ is H, methyl or -C(=O)CH₃.

8. The compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein:

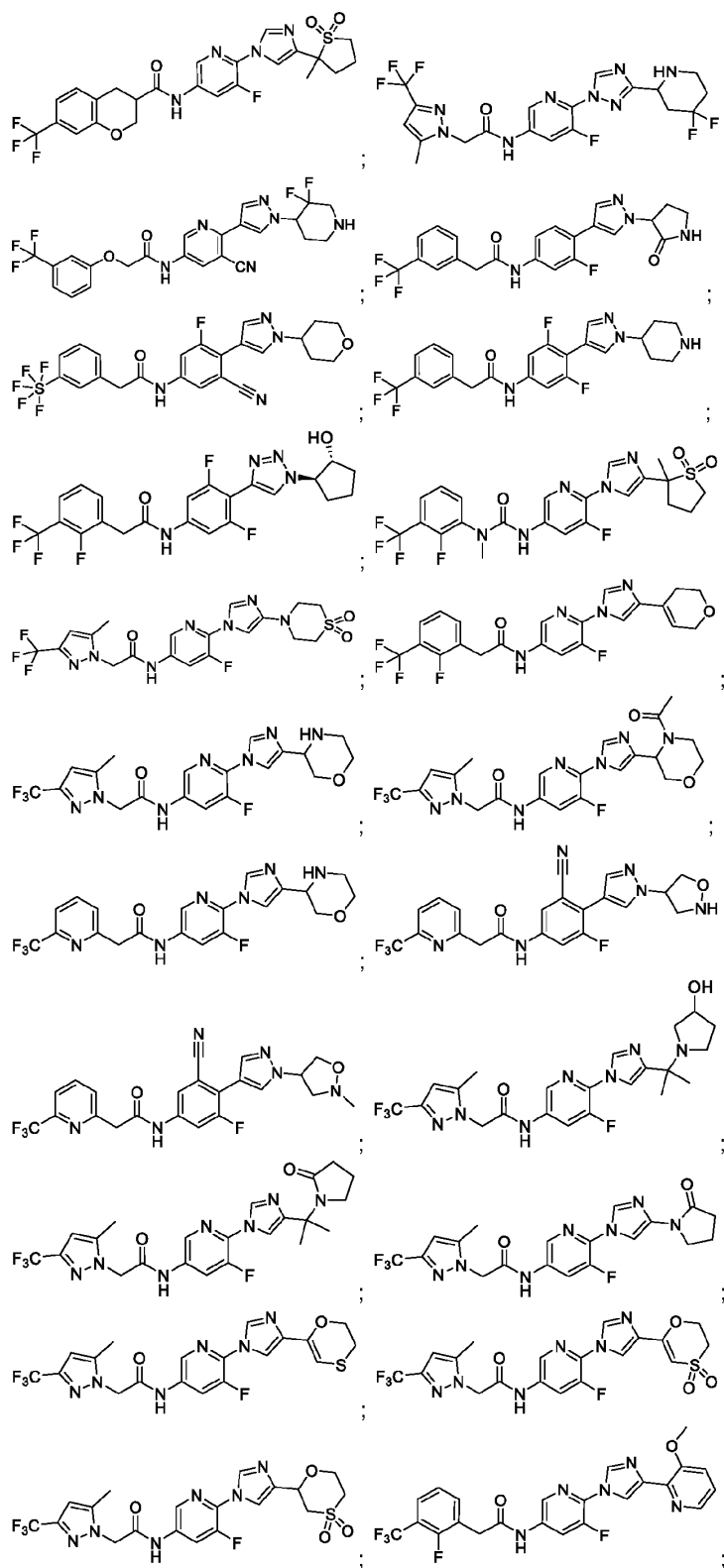
- 5 -X=Y- is -CR^x=N-;
 R^x is H;
 R⁵ is halogen;
 each R¹ is independently selected from the group consisting of halogen, C₁-C₄alkyl and
 C₁-C₄fluoroalkyl;
 10 L₁ is -(CR²R³)_p-;
 R² is H;
 R³ is H;
 p is 1;
 Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is N;
 15 each R^z is H;
 L₂ is a bond;
 R⁸ is pyrrolidinyl which is substituted with 1 or 2 substituents, each independently
 selected from halogen and C₁-C₄fluoroalkyl.

9. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein:

- 20 -X=Y- is -CR^x=N-;
 R^x is H;
 R⁵ is F;
 each R¹ is independently selected from the group consisting of F, Cl, methyl, and CF₃;
 25 L₁ is -(CR²R³)_p-;
 R² is H;
 R³ is H;
 p is 1;
 Z₁ is N, Z₂ is CR^z, Z₃ is N, Z₄ is C and Z₅ is N;
 30 each R^z is H;
 L₂ is a bond;
 R⁸ is pyrrolidinyl which is substituted with 1 or 2 substituents, each independently
 selected from F and CF₃.

10. The compound of claim 1, or a pharmaceutically acceptable salt thereof, selected from:

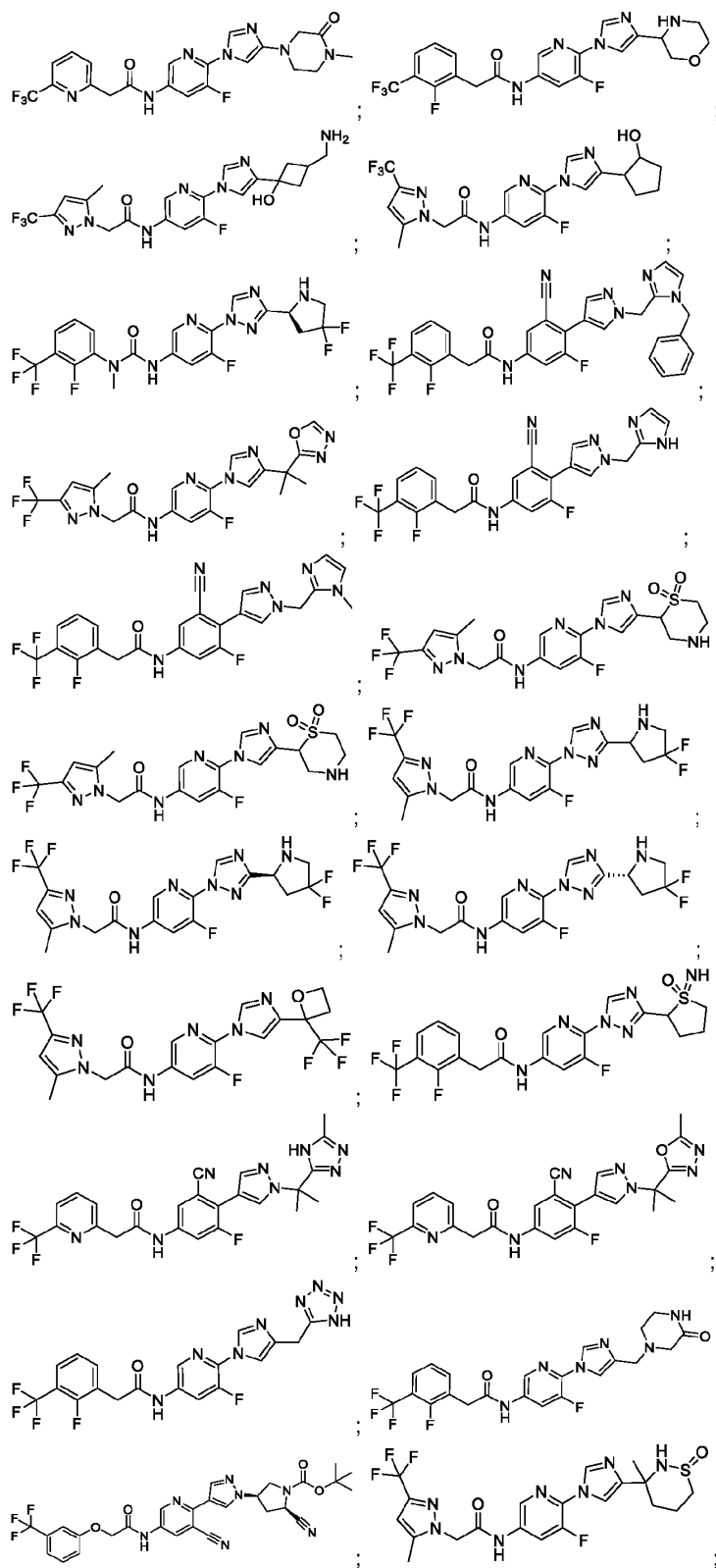
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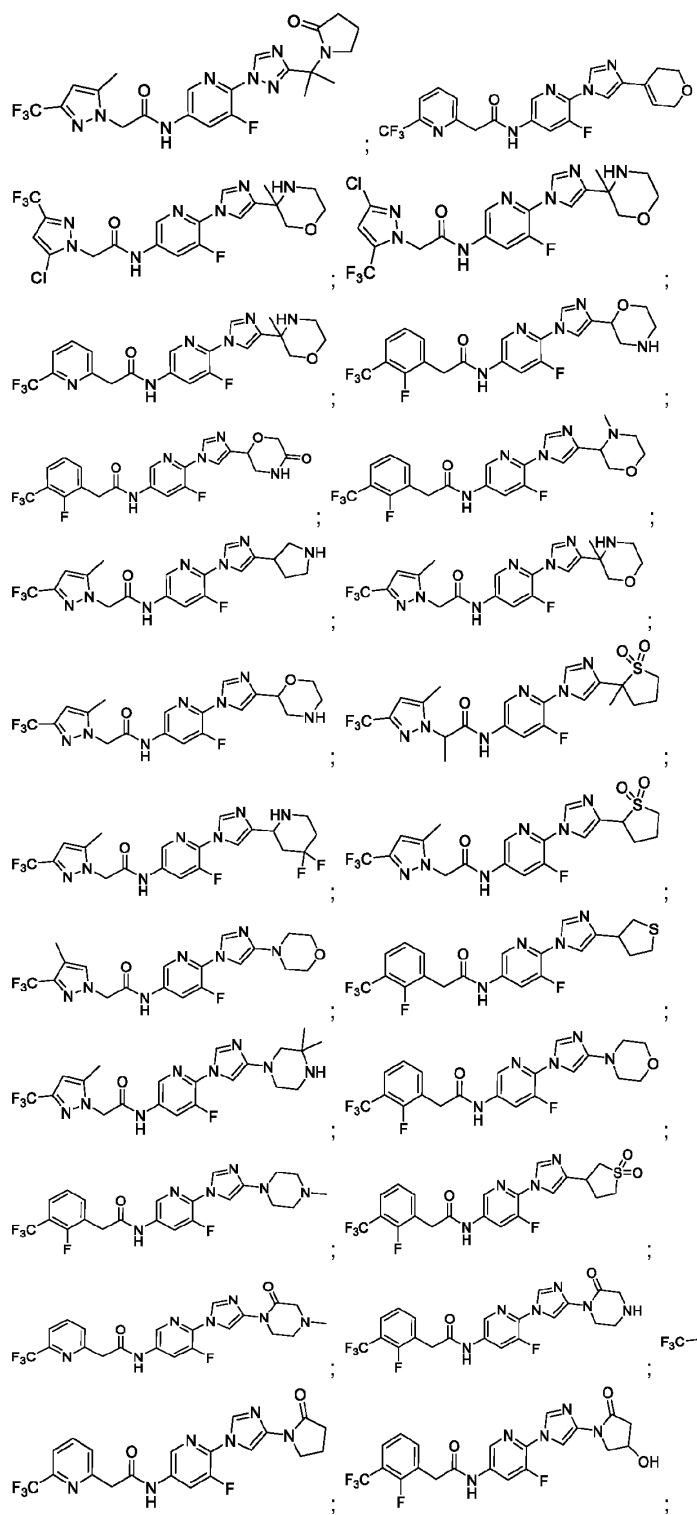
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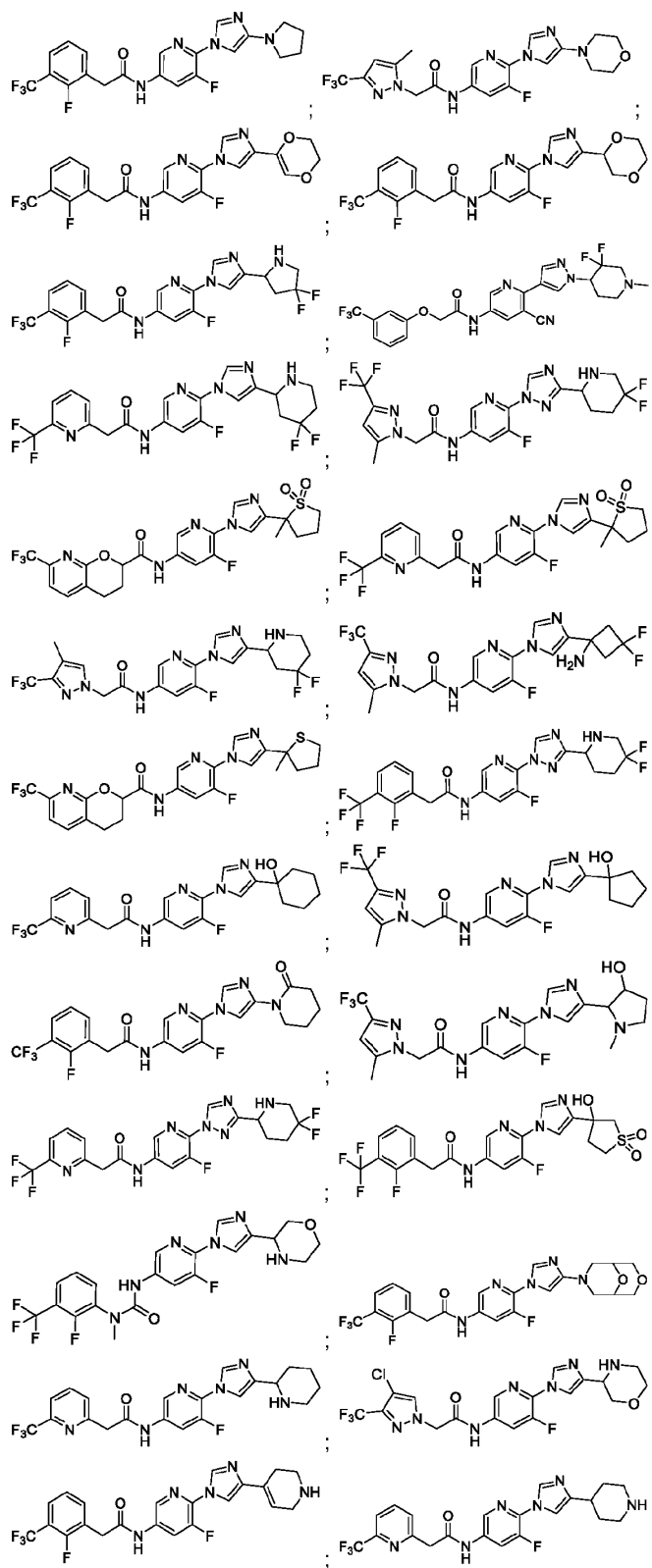
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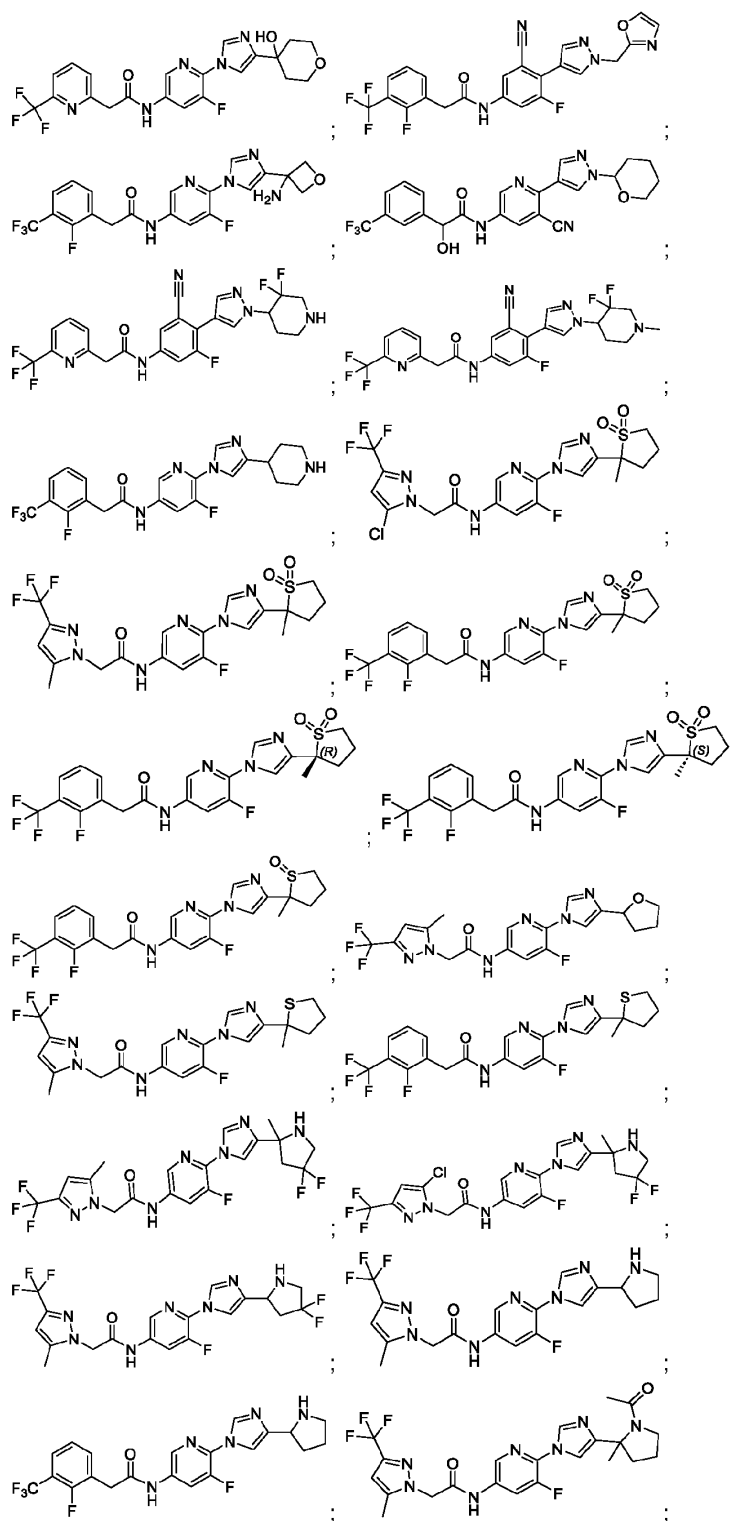
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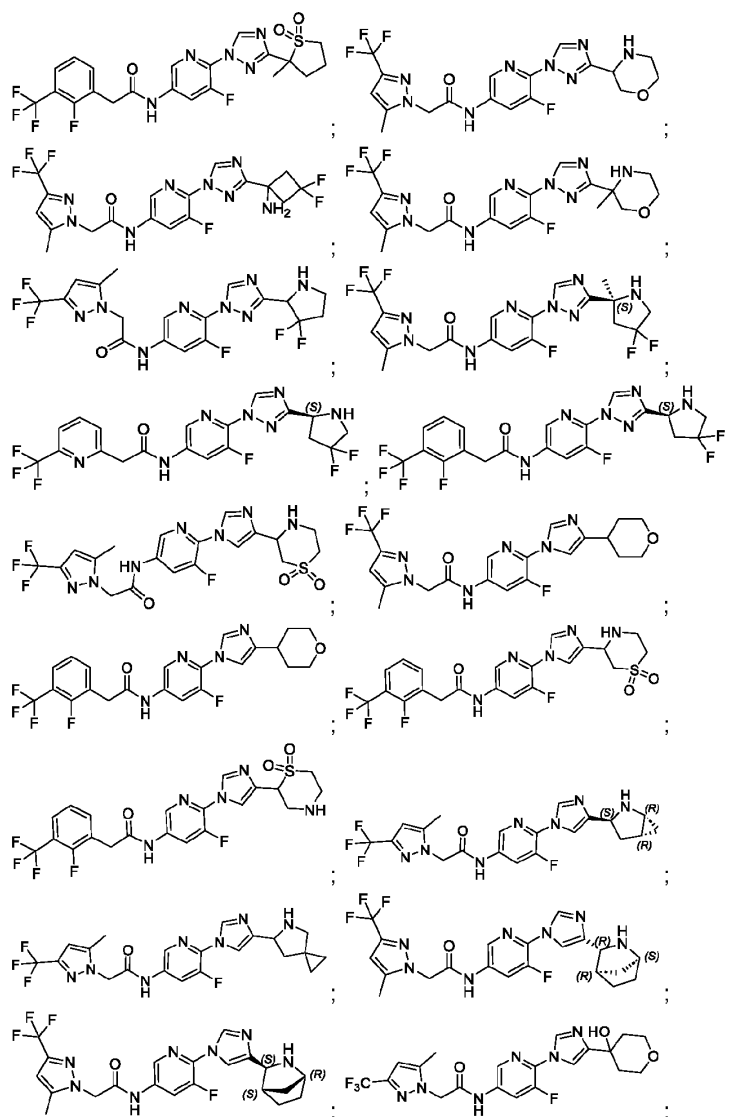


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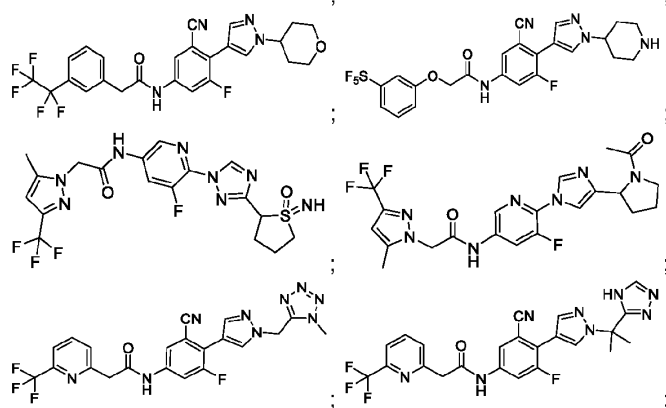
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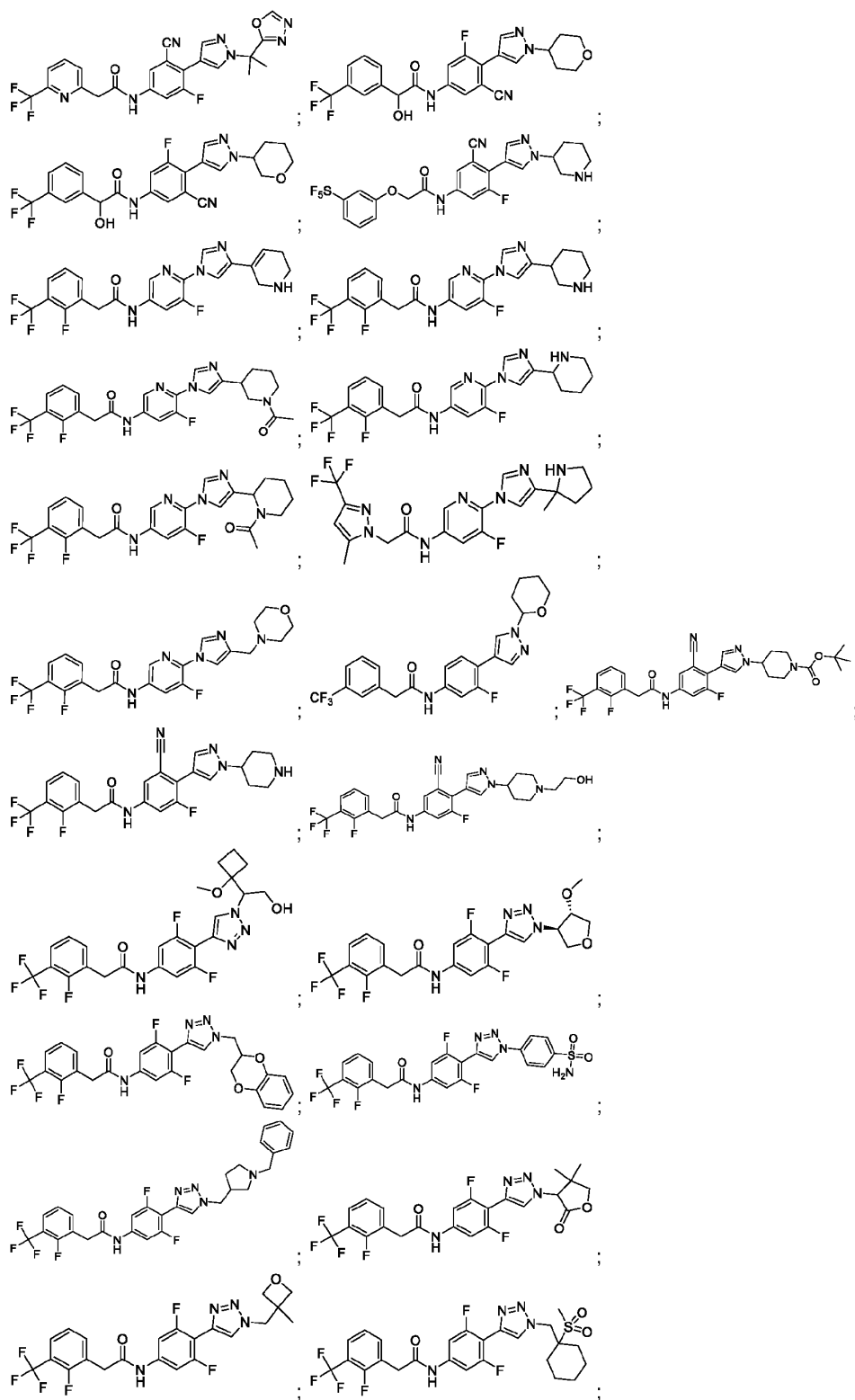
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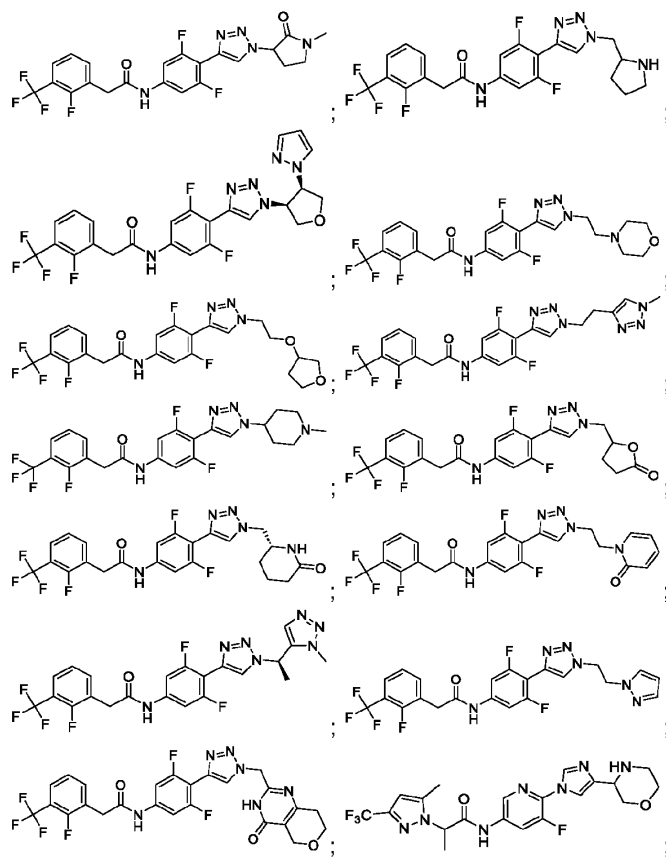


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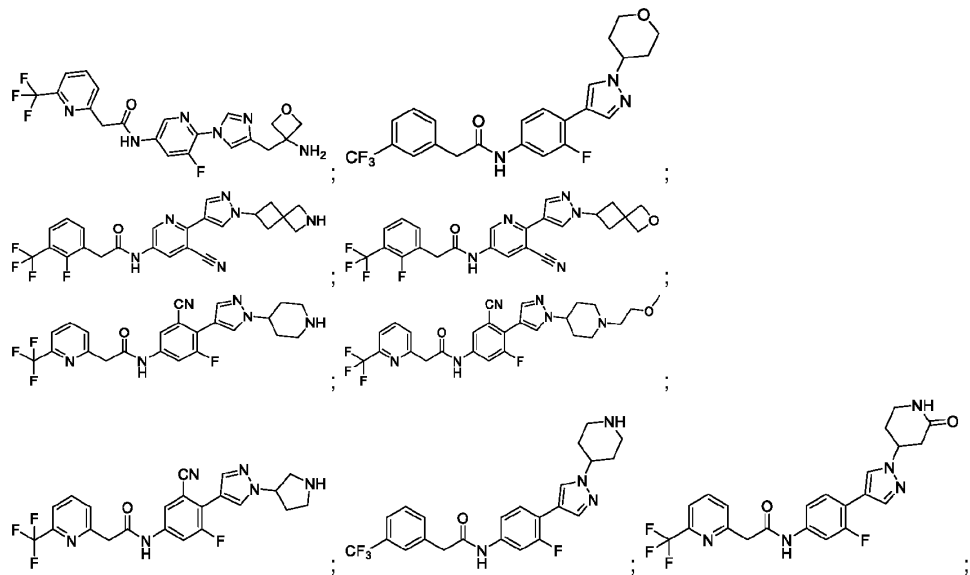


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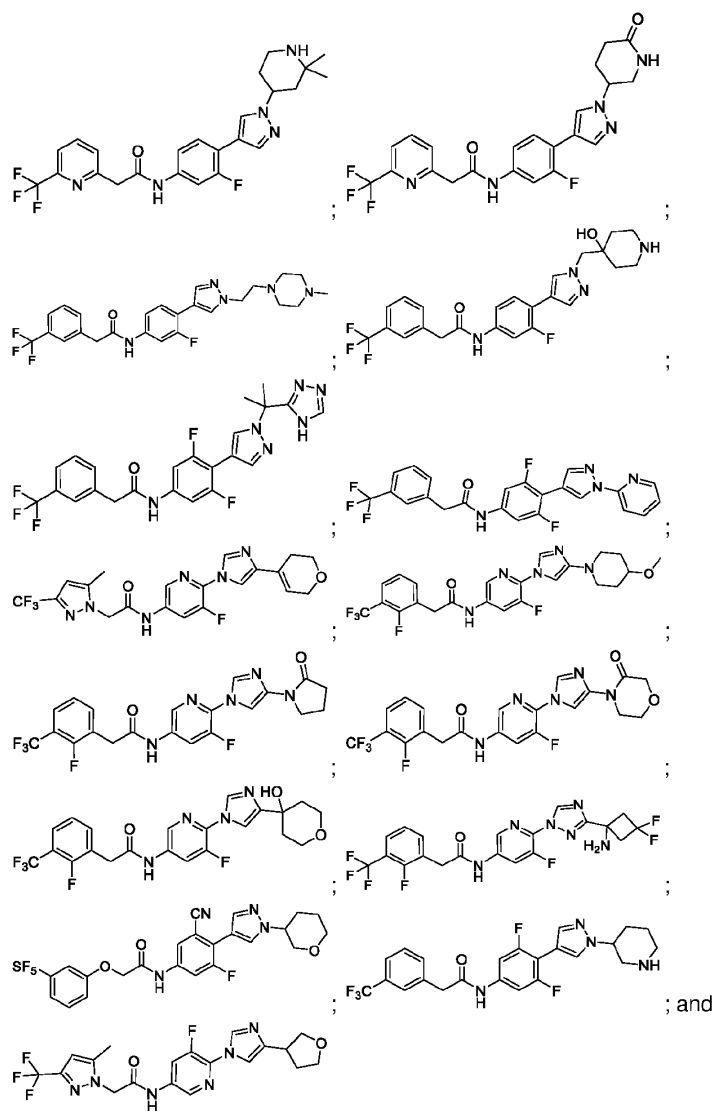
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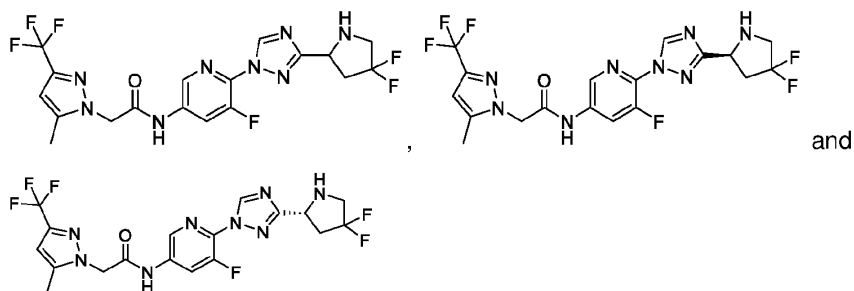
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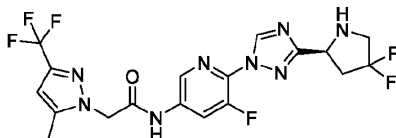


10 11. The compound of claim 1, or a pharmaceutically acceptable salt thereof, selected from:



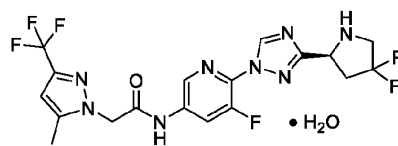
12. A pharmaceutical composition comprising a compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable carriers.
13. A pharmaceutical composition comprising a compound of any one of claims 1 to 11, or a pharmaceutically acceptable acid addition salt thereof, and one or more pharmaceutically acceptable carriers.
14. A method for treating a PNPLA3I148M associated disease comprising administering to a subject in need thereof a compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof.
15. A method for treating a PNPLA3I148M associated disease by normalizing lipolysis, wherein the method comprises administering to a subject in need thereof of a compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof.
16. Use of a compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, for the treatment of a PNPLA3I148M associated disease.
17. Use of a compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a PNPLA3I148M associated disease.
18. The method of claims 14 to 15 or the use of claims 16 to 17, wherein the PNPLA3I148M associated disease is a liver disease.
19. The method of claims 14 to 15 or the use of claims 16 to 17, wherein the PNPLA3I148M associated disease is a metabolic dysfunction-associated steatotic liver disease (MASLD).
20. The method of claims 14 to 15 or the use of claims 16 to 17, wherein the PNPLA3I148M associated disease is a nonalcoholic fatty liver disease (NAFLD).
21. The method of claims 14 to 15 or the use of claims 16 to 17, wherein the PNPLA3I148M associated disease is metabolic dysfunction–associated steatohepatitis (MASH), nonalcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH), cirrhosis with liver fibrosis or hepatocellular carcinoma (HCC).
22. The method of claims 14 to 15 or the use of claims 16 to 17, wherein the PNPLA3I148M associated disease is metabolic dysfunction–associated steatohepatitis (MASH).
23. A method for normalizing lipolysis by administering to a subject in need thereof of a compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof.
24. A method for normalizing lipolysis by disrupting a PNPLA3I148M-ABHD5 complex, wherein the method comprises administering to a subject in need thereof a compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof.

25. The compound of Formula (I) of claim 1, wherein the compound is (S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide and has the structure



- 5 26. The compound of claim 23, which is crystalline (S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide.
27. The compound of claim 24, which is characterized by having a powder X-ray diffractogram comprising at least four reflections at 2-Theta angles selected from the group consisting of
 10 (12.36 $\pm$ 0.2)°, (16.90 $\pm$ 0.2)°, (17.49 $\pm$ 0.2)°, (19.21 $\pm$ 0.2)°, (20.15 $\pm$ 0.2)°, (21.77 $\pm$ 0.2)°, (23.01 $\pm$ 0.2)°, (23.47 $\pm$ 0.2)°, (25.91 $\pm$ 0.2)° and (29.88 $\pm$ 0.2)°, when measured at a temperature in the range of from 20 to 40 °C with Cu-Kalpha radiation having a wavelength of 0.15406 nm.
- 15 28. The compound of claim 25, which is characterized by having a powder X-ray diffractogram comprising reflections at 2-Theta angles of (16.90 $\pm$ 0.2)°, (17.49 $\pm$ 0.2)°, (23.01 $\pm$ 0.2)°, (25.91 $\pm$ 0.2)° and (29.88 $\pm$ 0.2)°, when measured at a temperature in the range of from 20 to 40 °C with Cu-Kalpha radiation having a wavelength of 0.15406 nm.
29. The compound of any one of claims 24 to 26, which is characterized by having a differential scanning calorimetry curve comprising an endothermic peak having a peak temperature of
 20 (176.8 °C $\pm$ 0.5) °C, when measured at a heating rate of 10°C/min.
30. The compound of any one of claims 24 to 27, which is characterized by having a thermogravimetric analysis curve showing a mass loss of not more than 3.56 weight%, based on the weight of the (S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide monohydrate,
 25 when heated from 20°C to 350°C at a rate of 10°C/min.
31. The compound of any one of claims 24 to 28, which is (S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide monohydrate.

32. The compound of any one of claims 24 to 28, which is (S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-



yl)acetamide monohydrate and has the structure

33. The compound of claim 23, wherein the compound is amorphous (S)-N-(6-(3-(4,4-difluoropyrrolidin-2-yl)-1H-1,2,4-triazol-1-yl)-5-fluoropyridin-3-yl)-2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide.