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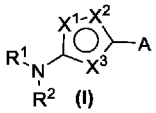
(54) Title: AMINO HETEROAROMATIC COMPOUNDS USEFUL IN THE TREATMENT OF LIVER DISEASES



(57) Abstract: The specification relates to compounds of Formula (I) and to pharmaceutically acceptable salts thereof, to processes and intermediates used for their preparation, to pharmaceutical compositions containing them and to their use in the treatment of diseases such as liver disease.

AMINO HETEROAROMATIC COMPOUNDS USEFUL IN THE TREATMENT OF LIVER DISEASES

CROSS-REFERENCE TO RELATED PATENT APPLICATION

This specification claims the benefit of priority to U.S. Provisional Patent Application No. 63/364,978 (filed 19 May 2022). The entire text of the above-referenced patent application is incorporated by reference into this specification.

This specification relates to certain amino heteroaromatic compounds and pharmaceutically acceptable salts thereof that inhibit 17β hydroxy steroid dehydrogenase 13 (17βHSD13 or HSD17B13), and their use in treating diseases such as liver disease. This specification also relates to processes and intermediate compounds involved in the preparation of the amino heteroaromatic compounds and to pharmaceutical compositions containing them.

Introduction

Non-alcoholic fatty liver disease (NAFLD) represents a spectrum of liver disease ranging from simple steatosis (non-alcoholic fatty liver), to non-alcoholic steatohepatitis (NASH) with or without fibrosis, to cirrhosis. Hepatic steatosis is defined as excess fat accumulation in the liver with greater than 5% induced by causes other than alcohol intake. NASH is defined by hepatic steatosis with inflammation and hepatocyte injury, with or without fibrosis. It is estimated that approximately 25% of the global population has NAFLD, and mortality due to NAFLD-related disease is expected to increase significantly through 2030.

To date, there are no approved treatments for NAFLD (such as NASH) and therapeutic interventions focus on addressing co-morbidities that contribute to the pathogenesis of NAFLD, including treating insulin resistance, obesity, type II diabetes mellitus, and dyslipidemia.

Recently, a variant in the 17βHSD13 gene, was associated in an allele dose-dependent manner with decreased serum aminotransferases levels, as well as a lower risk of liver disease, including alcoholic and non-alcoholic liver disease, cirrhosis and hepatocellular carcinoma (HCC) (Abul-Husn et al, N Engl J Med. 2018, 378(12), 1096-106, Wang et al, Eur Rev Med Pharmacol Sci, 2020, 24(17), 8997-9007). The 17βHSD13 splice variant (rs72613567:TA) results in a truncated, unstable and enzymatically inactive protein and has thus been characterized as an 17βHSD13 Loss of Function (LoF) variant (Ma et al, Hepatology 2019, 69(4), 1504-19). The association between the LoF 17βHSD13 (rs72613567:TA) and decreased disease severity has been replicated in additional cohorts with histologically proven NAFLD and was also associated with lower plasma transaminases, reduced risk of cirrhosis, HCC and liver related mortality in a study of 111612 individuals from the Danish general population (Gellert-Kristensen et al, Hepatology, 2020, 71(1), 56-66). Interestingly, the protective

effect of the LoF 17βHSD13 (rs72613567:TA) variant on plasma transaminases levels appears to be amplified by several key risk factors of liver disease such as obesity, alcohol consumption, as well as established genetic risk factors such as, but not limited to, the (rs738409 C>G) variant in patatin-like phospholipase domain-containing protein 3 (PNPLA3). Further, two additional 17βHSD13LoF variants (rs62305723) and (rs143404524) were also reported to confer protection from chronic liver disease progression (Kozlitina et al, N Engl J Med, 2018, 379(19), 1876-7). In general, the LoF 17βHSD13 protective variants has a stronger association with fibrosis and progression to advance liver disease but is not associated with steatosis.

Based on the genetic validation of 17βHSD13LoF variants conferring protection against liver disease risk and progression, inhibition of 17βHSD13 activity with small molecules inhibitors could be an effective therapeutic approach for treating liver diseases such as NAFLD (for example NASH, liver fibrosis, cirrhosis and isolated steatosis), liver inflammation, alcoholic steatohepatitis (ASH), hepatitis C virus (HCV) and hepatocellular carcinoma (HCC), such as in individuals harbouring several key risk factors of liver disease such as obesity, alcohol consumption, as well as established genetic risk factors such as the (rs738409 C>G) variant in PNPLA3.

The compounds of the disclosure provide an anti-liver disease effect by, as a minimum, acting as 17βHSD13 inhibitors. Further, compounds of the disclosure may selectively inhibit 17βHSD13 over 17βHSD4 and/or 17βHSD9.

Fifteen 17βHSD (HSD17B) members have been identified in human. The sequence homology among the different members is rather low, but the overall structure seems conserved. 17β-Hydroxysteroid dehydrogenases are mainly involved in sex hormone metabolism. Some 17βHSD enzymes also play key roles in cholesterol and fatty acid metabolism (Labrie et al. Journal of Molecular Endocrinology, 2000, 25, 1–16, Wen Su et al. Molecular and Cellular Endocrinology, 2019, 489, 119–125). A clean off-target profile is an advantage for a 17βHSD13 inhibitor to avoid potential toxicity caused by off-target activity. This includes selectivity to other 17βHSD members.

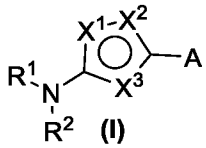
17βHSD4/ D-bifunctional protein (DBP) is involved in fatty acid β-oxidation and steroid metabolism. 17βHSD4 is ubiquitously expressed and play an important role in the inactivation of estrogens in a large series of peripheral tissues. Mutations in17βHSD4 are known to cause DBP deficiency, an autosomal-recessive disorder of peroxisomal fatty acid β-oxidation that is generally fatal within the first two years of life. A homozygous missense variant in 17βHSD4 has been identified in Perrault syndrome, a recessive disorder characterized by ovarian dysgenesis in females, sensorineural deafness in both males and females, and in some patients, neurological manifestations (Pierce et al. Am. J. Hum. Genet., 2010, 87, 282-8; and Chen et al. BMC Med Genet., 2017, 18, 91).

17βHSD9/ RDH5 (retinol dehydrogenase 5) is involved in retinoid metabolism. The enzyme is mainly expressed in the retinal pigment epithelium. The RDH5 gene encodes the enzyme that is a part of the visual cycle, the 11-cis retinol dehydrogenase, catalysing the reduction of 11-cis-retinol to 11-cis-retinal. RDH5 gene mutations cause a progressive cone dystrophy or macular dystrophy as well as night blindness. Fundus albipunctatus is a rare, congenital form of night blindness with rod system impairment, characterised by the presence of numerous small, white-yellow retinal lesions. This disorder is caused mostly by mutations in the RDH5 gene (Hotta et al. Am. J. Ophthalmol., 2003, 135, 917-9; and Skorczyk-Werner et al. J. Appl. Genet., 2015, 56, 317-27).

The compounds of the specification may also exhibit advantageous physical properties (for example, lower lipophilicity, higher aqueous solubility, higher permeability, lower plasma protein binding, and/or greater chemical stability), and/or favourable toxicity profiles (for example a decreased activity at hERG), and/or favourable metabolic or pharmacokinetic profiles, in comparison with other known 17βHSD13 inhibitors. Such compounds may therefore be especially suitable as therapeutic agents, such as for the treatment of liver disease.

General Description

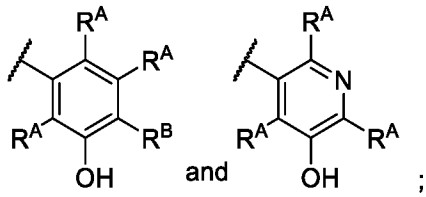
According to one aspect of the specification there is provided a compound of Formula (I);



(I)

wherein,

A is selected from



;

each R^A is independently selected from H, halo and $-OR^x$, wherein each R^X is independently C_{1-3} alkyl optionally substituted with one to three F;

R^B is halo, $-OCHF_2$ or $-OCF_3$;

one of X^1, X^2 and X^3 is selected from NH, O and S and the other two of X^1, X^2 and X^3 are independently selected from N and CH;

R^1 and R^2 are such that;

(i) R^1 is selected from R^8, R^{8A}, R^{4A} and R^{5A}, and R^2 is selected from R^{8B} and H; or

(ii) R^1 and R^2, taken together with the N atom to which they are attached, form a heterocycloalkyl ring, wherein the heterocycloalkyl ring is optionally substituted with one or more R^C, wherein each R^C is independently selected from F, R^3, R^4, -O(R^4), O(R^5), R^5, R^6, -OH, -CN, oxo and -C(=O)N(R^{7A})$_2$;

each R^3 is independently C_{1-4} alkyl or C_{3-6} cycloalkyl, each of which are optionally substituted with one or more groups independently selected from R^{4X}, R^{5x}, -O(R^{4X}), -O(R^{5X}) and F;

each R^{3X} is independently C_{1-4} alkyl or C_{3-6} cycloalkyl;

each R^4, R^{4A} and R^{4B} are independently monocyclic or bicyclic, 5 to 9 membered heteroaryl, each of which are optionally substituted with one or more groups independently selected from R^{4X}, -O(R^{4X}), R^{5X}, -O(R^{5X}), -OH, -CN, C_{1-4} alkoxy, -C(=O)OH, -C(=O)O(C_{1-4} alkyl), -C(=O)N(R^{7B})$_2$, R^3 and halo;

each R^5, R^{5A} and R^{5B} are independently phenyl, each of which are optionally substituted with one or more groups independently selected from R^{4X}, -O(R^{4X}), R^{5X}, -O(R^{5X}), -OH, -CN, C_{1-4} alkoxy, -C(=O)OH, -C(=O)O(C_{1-4} alkyl), -C(=O)N(R^{7B})$_2$, R^3 and halo;

each R^{4X} is independently monocyclic or bicyclic 5 to 9 membered heteroaryl, each of which are optionally substituted with one or more groups independently selected from -OH, -CN, C_{1-4} alkoxy, -C(=O)OH, -C(=O)N(R^{7B})$_2$, R^{3X} and halo;

each R^{5X} is independently phenyl, each of which are optionally substituted with one or more groups independently selected from -OH, -CN, C_{1-4} alkoxy, -C(=O)OH, -C(=O)N(R^{7B})$_2$, R^{3x} and halo;

each R^6 is independently C_{1-4} alkoxy optionally substituted with one or more groups independently selected from R^{4X}, R^{5x} and F;

each R^7, R^{7A}, R^{7B} and R^{7C} are independently H, R^{Z1} or R^{Z2}, wherein R^{Z1} is C_{1-4} alkyl optionally substituted with one or more C_{1-4} alkoxy or -C(=O)NH_2, and R^{Z2} is C_{3-6} cycloalkyl optionally substituted with one or more C_{1-4} alkoxy or -C(=O)NH_2;

R^8 is C_{1-4} alkyl substituted with one or more groups independently selected from R^{4B}, R^{5B}, F, -OH, -CN, C_{1-4} alkoxy, -C(=O)O(C_{1-4} alkyl) and -C(=O)N(R^{7C})$_2$;

R^{8A} is C_{3-6} cycloalkyl or adamantyl, each of which are optionally substituted with one or more groups independently selected from R^{4B}, R^{5B}, F, -OH, -CN, C_{1-4} alkoxy, -C(=O)O(C_{1-4} alkyl) and -C(=O)N(R^{7C})$_2$;

R^{8B} is C_{1-4} alkyl or C_{3-6} cycloalkyl, each of which are optionally substituted with one or more groups independently selected from R^{4B}, R^{5B}, F, -OH, -CN, C_{1-4} alkoxy, -C(=O)O(C_{1-4} alkyl) and -C(=O)N(R^{7C})$_2$;

wherein the heterocycloalkyl ring is a saturated, monocyclic or bicyclic, 4-8 membered ring comprising one N atom, and optionally one further heteroatom selected from N, O and S; and

wherein each heteroaryl is independently an aromatic ring containing one or more heteroatoms independently selected from N, O and S,

or a pharmaceutically acceptable salt thereof,

wherein the compound is not 2-(difluoromethoxy)-5-(5-((5-fluoroadamantan-2-yl)(methyl)amino)-1,3,4-oxadiazol-2-yl)phenol or 5-(3-(((1-cyclohexyl-1H-tetrazol-5-yl)methyl)(methyl)amino)-1,2,4-oxadiazol-5-yl)-2-fluorophenol.

In a further aspect there is provided a pharmaceutical composition comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In a further aspect there is provided a compound of Formula (I) or a pharmaceutically acceptable salt thereof, for use in therapy.

In a further aspect there is provided a compound of Formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment of liver disease.

In a further aspect there is provided the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament.

In a further aspect there is provided the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of liver disease.

In a further aspect there is provided a method of treating liver disease in a patient comprising administering to the patient an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

In a further aspect there is provided intermediates useful for the synthesis of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

Definitions

So that the present specification may be more readily understood, certain terms are explicitly defined below. In addition, definitions are set forth as appropriate throughout the detailed description.

As used herein the term "**alkyl**" refers to both straight and branched chain saturated hydrocarbon radicals having the specified number of carbon atoms.

In this specification the prefix C_{x-y}, as used in terms such as "C_{x-y} alkyl" and the like where x and y are integers, indicates the numerical range of carbon atoms that are present in the group. Examples of suitable C_{1-3} alkyl groups include methyl, ethyl, n-propyl, and i-propyl. Examples of suitable C_{1-4} alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl and t-butyl.

In this specification the prefix X-Y membered, as used in terms such as "X-Y membered ring" and the like where X and Y are integers, indicates the numerical range of atoms (i.e. carbon atoms and heteroatoms) that are present in the group.

As used herein the term "**alkoxy**" refers to a saturated group comprising the specified number of carbon atoms and one oxygen atom. For the avoidance of doubt, the alkoxy group may be a straight chain or a branched chain. Examples of suitable C_{1-3} alkoxy groups include methoxy (OMe), ethoxy (OEt), n-propoxy (O^nPr) and i-propoxy (O^iPr). Examples of suitable C_{1-4} alkoxy groups include methoxy (OMe), ethoxy (OEt), n-propoxy (O^nPr), i-propoxy (O^iPr), n-butoxy (O^nBu), i-butoxy (O^iBu), s-butoxy (O^sBu) and t-butoxy (O^tBu).

Unless otherwise stated, "**halo**" is selected from Cl, F, Br and I. In embodiments, halo is selected from Cl and F.

Unless otherwise stated, the term "**heterocycloalkyl ring**" refers to a saturated, monocyclic or bicyclic, 4-8 membered ring comprising one N atom, and optionally one further heteroatom selected from N, O and S. For the avoidance of doubt, the other atoms of the ring are carbon. A suitable 4 membered heterocycloalkyl group is azetidin-1-yl. A suitable 5 membered heterocycloalkyl group is pyrrolidin-1-yl. Examples of suitable 6 membered heterocycloalkyl groups include piperidin-1-yl, piperazin-1-yl, morpholin-4-yl and thiomorpholin-4-yl. Examples of suitable 7 membered heterocycloalkyl groups include azepan-1-yl, 1,4-diazepan-1-yl, 1,4-oxazepan-4-yl and 1,4-thiazepan-4-yl. Examples of suitable 8 membered heterocycloalkyl groups include azocan-1-yl, 1,4-diazocan-1-yl, 1,5-diazocan-1-yl ,1,4-oxazocan-4-yl, 1,5-oxazocan-5-yl, 1,4-thiazocanyl and 1,5-thiazocanyl.

The term "**heteroatom"** refers to N, O or S.

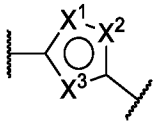
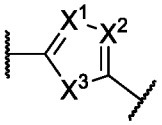
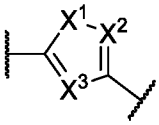
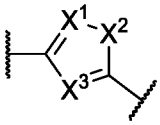
Unless otherwise stated, the term "**heteroaryl**" is an aromatic, monocyclic or bicyclic, 5 to 9 membered ring containing one or more heteroatoms independently selected from N, O and S. Where a compound of the disclosure comprises more than one heteroaryl groups, the heteroaryl groups may be the same or different. A heteroaryl may be a 5 or 6 membered monocyclic heteroaryl. Examples of suitable 5 membered heteroaryl groups include pyrrolyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, furazanyl, 1,3,4-thiadiazolyl and tetrazolyl. Examples of suitable 6 membered heteroaryl groups include pyridyl (such as 2-pyridyl, 3-pyridyl or 4-pyridyl), pyridazinyl, pyrimidinyl, pyrazinyl and 1,3,4-triazinyl. A heteroaryl may be a 9-membered bicyclic heteroaryl. Where a heteroaryl is bicyclic, one or both rings may be aromatic. Examples of a suitable 9-membered heteroaryl groups include indolyl, isoindolyl, benzofuranyl, isobenzofuranyl, indolinyl, isoindolinyl, benzothiophenyl,

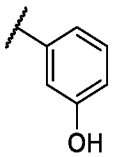
isobenzothiophenyl, indazolyl, benzimidazolyl, benzthiazolyl, purinyl, [1,2,4]triazolo[4,3-*b*]pyridazinyl (such as 6-[1,2,4]triazolo[4,3-*b*]pyridazinyl) and benzo[*d*]oxazolyl (such as 2-benzo[d]oxazolyl).

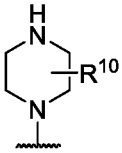
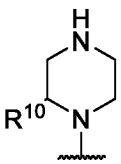
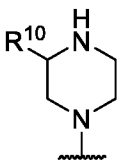
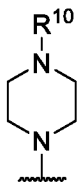
The term "**oxo**" refers to a oxygen atom forming a double bond (i.e. =O) to a suitable atom, such as carbon.

Unless specifically stated, the bonding of an atom or group may be any suitable atom of that group; for example, propyl includes prop-1-yl and prop-2-yl.

For the avoidance of doubt, where multiple substituents are independently selected from a given group, the selected substituents may comprise the same substituents or different substituents from within the given group.

For the avoidance of doubt, the use of a circle within a 5 membered ring indicates that the 5 membered ring is an aromatic ring. By way of illustration only,  indicates an aromatic ring selected from  ,  and  .

For the avoidance of doubt, the use of "⊥" in formulas of this specification denotes the point of attachment between different groups. By way of illustration only,  denotes a 3-hydroxyphenyl radical which is attached to a different group through the carbon atom *meta*- to the OH substituent.

For the avoidance of doubt, the use of a bond between a substituent and the centre of a ring denotes that the substituent may replace any hydrogen atom directly attached to the ring, whether that hydrogen atom be attached to a C or N atom. By way of illustration only,  indicates a group selected from  ,  and  .

Where any embodiment within this specification includes a group which is said to be "optionally substituted", then a further embodiment will include that embodiment wherein the said group is unsubstituted.

For the avoidance of doubt, where multiple substituents are independently selected from a given group, the selected substituents may comprise the same substituents or different substituents from within the given group.

Units, prefixes, and symbols are denoted in their International System of Units (SI) accepted form. Numeric ranges are inclusive of the numbers defining the range.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure is related. For example, the Concise Dictionary of Biomedicine and Molecular Biology, Juo, Pei-Show, 2nd ed., 2002, CRC Press; The Dictionary of Cell and Molecular Biology, 3rd ed., 1999, Academic Press; and the Oxford Dictionary of Biochemistry and Molecular Biology, Revised, 2000, Oxford University Press, provide one of skill with a general dictionary of many of the terms used in this disclosure.

Detailed Description

In one aspect there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as defined above.

In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from R^8, R^{8A}, R^{4A} and R^{5A}, and R^2 is selected from R^{8B} and H.

In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^1 is R^8, and R^2 is selected from R^{8B} and H.

In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^8 is C_{1-4} alkyl substituted with one or more groups (such as one to three groups) independently selected from R^{4B}, R^{5B}, F, -OH, -CN, C_{1-4} alkoxy, -C(=O)O(C_{1-4} alkyl) and -C(=O)N(R^{7C})$_2$. In further embodiments, R^8 is C_{1-4} alkyl substituted with one or two groups (such as one group) independently selected from R^{4B}, R^{5B}, F, -OH, -CN, C_{1-4} alkoxy, -C(=O)O(C_{1-4} alkyl) and -C(=O)N(R^{7C})$_2$. In further embodiments, R^8 is CH_3 substituted with one group selected from R^{4B}, R^{5B}, F, -OH, -CN, C_{1-4} alkoxy, -C(=O)O(C_{1-4} alkyl) and -C(=O)N(R^{7C})$_2$. In further embodiments, R^8 is CH_3 substituted with one group selected from monocyclic or bicyclic 5 to 9 membered heteroaryl and phenyl, wherein the 5 to 9 membered heteroaryl and phenyl are optionally substituted with one or more groups (such as one or two groups) selected from C_{1-4} alkyl, C_{3-6} cycloalkyl and phenyl. In further embodiments, R^8 is CH_3

substituted with monocyclic 5- membered heteroaryl, optionally substituted with one group selected from C_{1-4} alkyl, C_{3-6} cycloalkyl and phenyl.

In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^1 is R^{8A}, and R^2 is selected from R^{8B} and H.

In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^{8A} is C_{3-6} cycloalkyl or adamantyl, each of which are optionally substituted with one or more groups (such as one to three groups) independently selected from R^{4B}, R^{5B}, F, -OH, -CN, C_{1-4} alkoxy, -C(=O)O(C_{1-4} alkyl) and -C(=O)N(R^{7C})$_2$. In further embodiments, R^{8A} is adamantyl, optionally substituted with one to three F.

In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^1 is R^{4A}, and R^2 is selected from R^{8B} and H.

In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^{4A} is a monocyclic or bicyclic, 5 to 9 membered heteroaryl optionally substituted with one or more groups (such as one to three groups) independently selected from R^{4X}, -O(R^{4X}), R^{5X}, -O(R^{5X}), -OH, -CN, C_{1-4} alkoxy, -C(=O)OH, -C(=O)O(C_{1-4} alkyl) and -C(=O)N(R^{7B})$_2$, R^3 and halo. In further embodiments, R^{4A} is a monocyclic 5-membered heteroaryl optionally substituted with one or two groups (such as one group) independently selected from R^{4X}, -O(R^{4X}), R^{5X}, -O(R^{5X}), -OH, -CN, C_{1-4} alkoxy, -C(=O)OH, -C(=O)O(C_{1-4} alkyl) and -C(=O)N(R^{7B})$_2$, R^3 and halo. In further embodiments, R^{4A} is monocyclic 5- membered heteroaryl, optionally substituted with one group selected from C_{1-4} alkyl, C_{3-6} cycloalkyl and phenyl.

In embodiments, R^{5A} is phenyl, optionally substituted with one or more groups (such as one to three groups) independently selected from R^{4X}, -O(R^{4X}), R^{5X}, -O(R^{5X}), -OH, -CN, C_{1-4} alkoxy, -C(=O)OH, -C(=O)O(C_{1-4} alkyl), -C(=O)N(R^{7B})$_2$, R^3 and halo. In further embodiments, R^{5A} is phenyl, optionally substituted with one or two (such as one) groups independently selected from R^{4X}, -O(R^{4X}), R^{5X}, -O(R^{5X}), -OH, -CN, C_{1-4} alkoxy, -C(=O)OH, -C(=O)O(C_{1-4} alkyl), -C(=O)N(R^{7B})$_2$, R^3 and halo.

In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from R^8, R^{8A}, R^{4A} and R^{5A}, and R^2 is R^{8B}.

In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^{8B} is C_{1-4} alkyl or C_{3-6} cycloalkyl, each of which are optionally substituted with one or more groups (such as one to three groups) independently selected from R^{4B}, R^{5B}, F, -OH, -CN, C_{1-4} alkoxy, -C(=O)O(C_{1-4} alkyl) and -C(=O)N(R^{7C})$_2$. In further embodiments, is R^{8B} is C_{1-4} alkyl optionally substituted with one or two (such as one) groups independently selected from R^{4B}, R^{5B}, F, -OH, -CN,

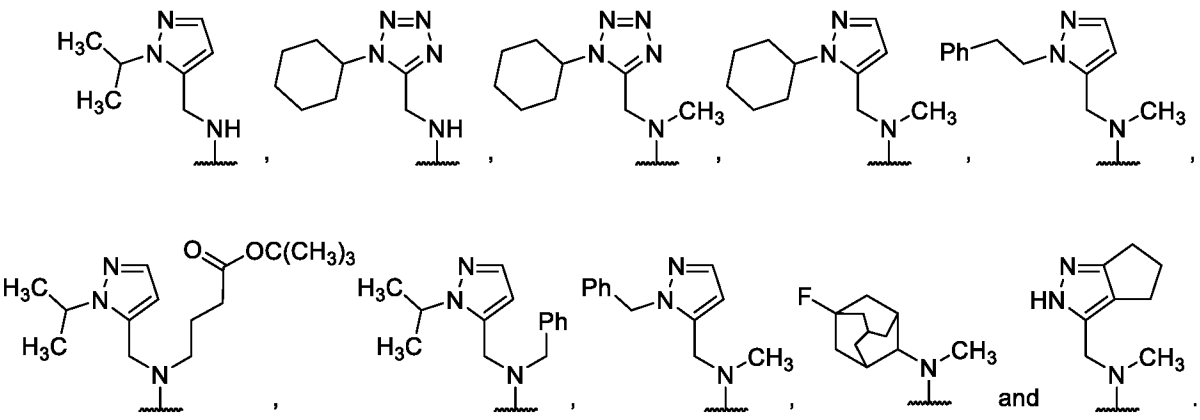
C_{1-4} alkoxy, -C(=O)O(C_{1-4} alkyl) and -C(=O)N(R^{7C})$_2$. In further embodiments, R^{8B} is C_{1-4} alkyl. In further embodiments, R^{8B} is CH_3, $CH(CH_3)_2$ or $C(CH_3)_3$.

In embodiments, each R^{4B} is independently monocyclic or bicyclic 5 to 9 membered heteroaryl, optionally substituted with one or more (such as one to three) groups independently selected from R^{4X}, -O(R^{4X}), R^{5X}, -O(R^{5X}), -OH, -CN, C_{1-4} alkoxy, -C(=O)OH, -C(=O)O(C_{1-4} alkyl), -C(=O)N(R^{7B})$_2$, R^3 and halo. In further embodiments, each R^{4B} is independently monocyclic or bicyclic 5 to 9 membered heteroaryl optionally substituted with one or more (such as one to three) groups independently selected from halo, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{1-4} alkoxy and CN. In further embodiments, each R^{4B} is independently monocyclic 5 membered heteroaryl optionally substituted with one or two groups independently selected from C_{1-4} alkyl and C_{3-6} cycloalkyl.

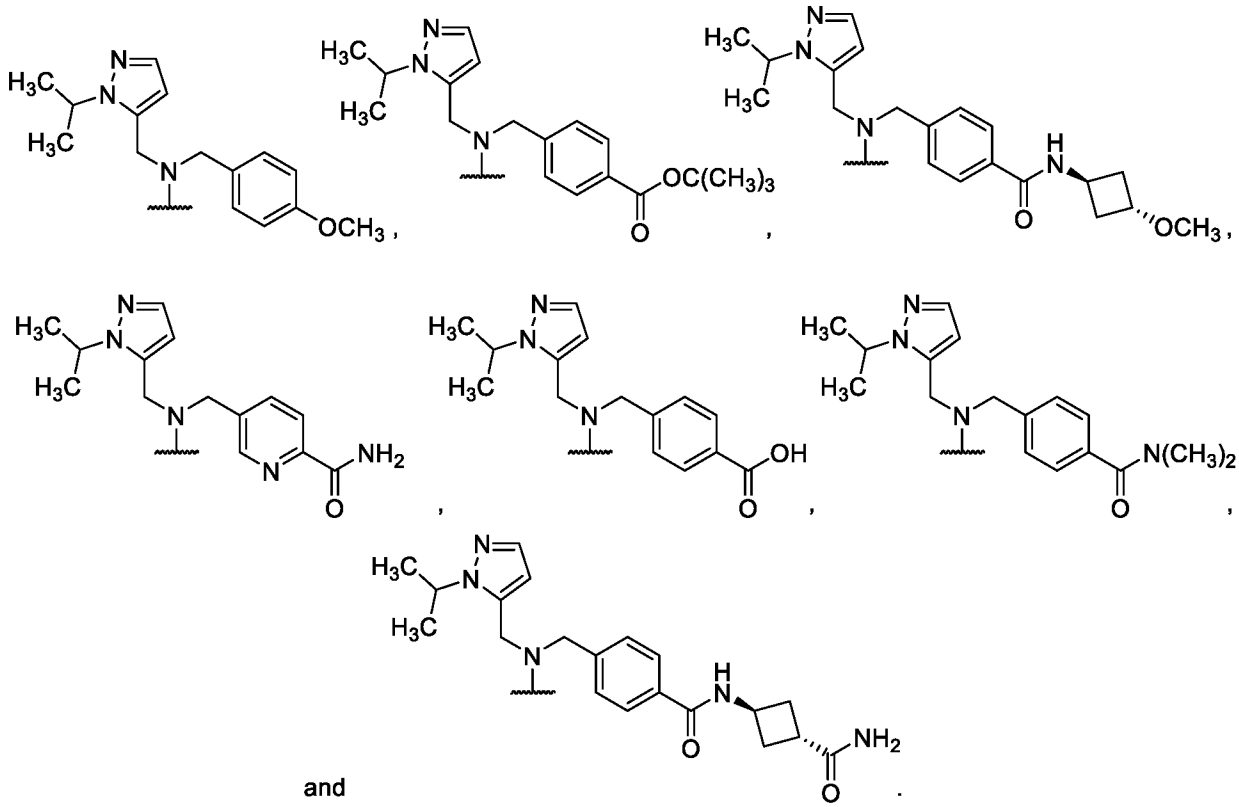
In embodiments, each R^{5B} is independently phenyl, optionally substituted with one or more (such as one to three) groups independently selected from R^{4X}, -O(R^{4X}), R^{5X}, -O(R^{5X}), -OH, -CN, C_{1-4} alkoxy, -C(=O)OH, -C(=O)O(C_{1-4} alkyl), -C(=O)N(R^{7B})$_2$, R^3 and halo. In further embodiments, each R^{5B} is independently phenyl optionally substituted with one or more (such as one to three) groups independently selected from halo, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{1-4} alkoxy, CN, C(=O)OH, -C(=O)O(C_{1-4} alkyl) and -C(=O)N(R^{7B})$_2$. In further embodiments, each R^{5B} is independently phenyl optionally substituted with one or two groups independently selected from C_{1-4} alkyl, C_{3-6} cycloalkyl, C(=O)OH, -C(=O)O(C_{1-4} alkyl) and -C(=O)N(R^{7B})$_2$.

In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^1 is R^{5A}, and R^2 is selected from R^{8B} and H.

In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein NR^1R^2 is selected from

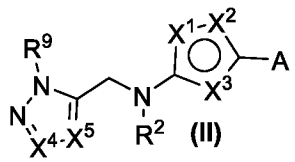


In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein NR^1R^2 is selected from



and

In embodiments, the compound of Formula (I) is a compound of Formula (II):



wherein

R^2 is selected from R^{8B} and H;

R^9 is R^3; and

X^4 and X^5 are independently N or CH,

or a pharmaceutically acceptable salt thereof.

In embodiments, there is provided a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein X^4 and X^5 are both N.

In embodiments, there is provided a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein X^4 and X^5 are both CH.

In embodiments, there is provided a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein R^9 is C_{1-4} alkyl or C_{3-6} cycloalkyl.

In embodiments, there is provided a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein R^2 is R^{8B}.

In embodiments, there is provided a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein R^2 is C_{1-4} alkyl optionally substituted with one group independently selected from R^{4B} and R^{5B}.

In embodiments, there is provided a compound of Formula (II), or a pharmaceutically acceptable salt thereof, wherein R^2 is C_{1-4} alkyl.

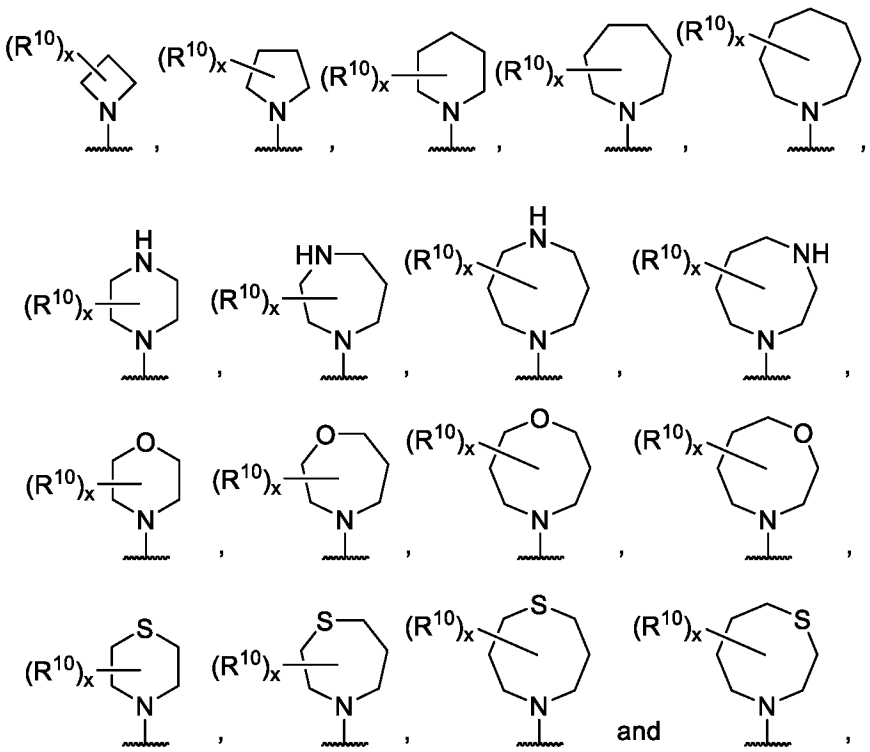
In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2, taken together with the N atom to which they are attached, form a heterocycloalkyl ring, wherein the heterocycloalkyl ring is optionally substituted with one or more R^C.

In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the heterocycloalkyl ring is a saturated, monocyclic, 4-8 membered ring comprising one N atom, and one further heteroatom selected from N, O and S (optionally substituted with one or more R^C). In further embodiments, the heterocycloalkyl ring is a saturated, monocyclic or bicyclic, 5-8 membered ring comprising one N atom, and one further heteroatom selected from N, O and S (optionally substituted with one or more R^C). In further embodiments, the heterocycloalkyl ring is a saturated, monocyclic 5 or 6 membered ring comprising one N atom and optionally one O atom (optionally substituted with one or more R^C).

In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the heterocycloalkyl ring is optionally substituted with one or more R^C. In further embodiments, the heterocycloalkyl ring is optionally substituted with one to three R^C. In further embodiments, the heterocycloalkyl ring is optionally substituted with one or two R^C.

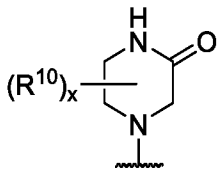
In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein each R^C is independently selected from F, R^3 , R^4, -O(R^4), -O(R^5), R^5, R^6, -OH, -CN and -C(=O)N(R^{7A})$_2$. In further embodiments, each R^C is independently selected from R^3, R^4 and R^5. In further embodiments, each R^C is independently R^5. In further embodiments, each R^C is independently R^3. In further embodiments, each R^C is independently C_{1-4} alkyl.

In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein NR^1R^2 is a group selected from



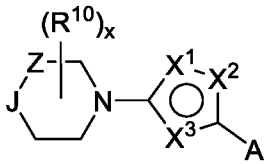
wherein x is selected from 0 to 3, and each R^{10} is independently selected from R^3, R^4 and R^5.

In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein NR^1R^2 is



wherein x is selected from 0 to 3, and each R^{10} is independently selected from R^3, R^4 and R^5.

In embodiments, the compound of Formula (I) is a compound of Formula (III):



(III)

wherein

J is selected from O, S, CH_2, NH and a covalent bond,

Z is such that

(i) where J is selected from O, S, CH_2 and a covalent bond, Z is selected from CH_2 and CH_2CH_2, and

(ii) where J is NH, Z is selected from CH_2, CH_2CH_2, and C(=O);

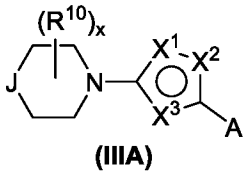
x is selected from 0 to 3; and

each R^{10} is independently selected from R^3, R^4 and R^5,

or a pharmaceutically acceptable salt thereof.

In embodiments, there is provided a compound of Formula (III), or a pharmaceutically acceptable salt thereof, wherein J is selected from O, S, CH_2 and a covalent bond, and Z is CH_2.

In embodiments, the compound of Formula (III) is a compound of Formula (IIIA):

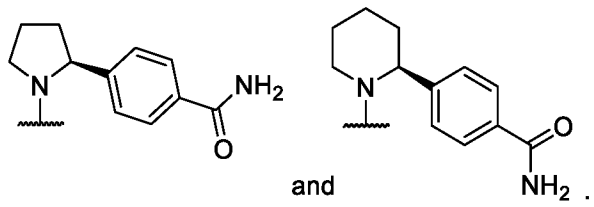


(IIIA),

wherein X^1, X^2, X^3, A, J, R^{10} and x are as defined for a compound of Formula (III). In further embodiments, J is CH_2.

In embodiments, there is provided a compound of Formula (III) or (IIIA), or a pharmaceutically acceptable salt thereof, wherein each R^{10} is independently R^3 or R^5. In further embodiments, each R^{10} is independently R^5. In further embodiments, each R^{10} is independently R^3. In further embodiments, each R^{10} is independently C_{1-4} alkyl.

In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein NR^1R^2 is a group selected from

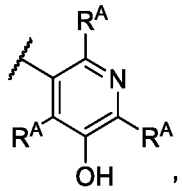


.

In embodiments, there is provided a compound of Formula (I), (II), (III) or (IIIA), or a pharmaceutically acceptable salt thereof, wherein each R^A is independently selected from H, halo and $-OR^x$, wherein each R^X is independently C_{1-3} alkyl optionally substituted with one to three F. In further embodiments, each R^A is independently selected from H, halo, C_{1-3} alkoxy, OCF_3 and $OCHF_2$. In further embodiments, each R^A is independently selected from H, F and Cl. In further embodiments, each R^A is independently selected from H and F.

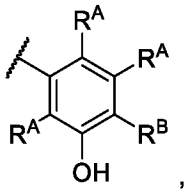
In embodiments, there is provided a compound of Formula (I), (II), (III) or (IIIA), or a pharmaceutically acceptable salt thereof, wherein one or more R^A is F. In further embodiments, two or more R^A is F. In further embodiments, each R^A is F.

In embodiments, there is provided a compound of Formula (I), (II), (III) or (IIIA), or a pharmaceutically acceptable salt thereof, wherein A is selected from



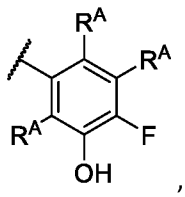
wherein R^A is as defined above.

In embodiments, there is provided a compound of Formula (I), (II), (III) or (IIIA), or a pharmaceutically acceptable salt thereof, wherein A is



wherein R^A and R^B are as defined above. In further embodiments, R^B is F, Cl or OCF_3. In further embodiments, R^B is F.

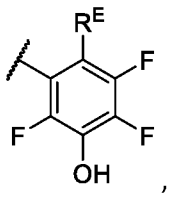
In embodiments, there is provided a compound of Formula (I), (II), (III) or (IIIA), or a pharmaceutically acceptable salt thereof, wherein A is



wherein R^A is as defined above

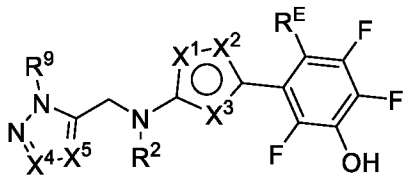
In embodiments, each R^A is independently H, F or Cl, such as H or F.

In embodiments, there is provided a compound of Formula (I), (II), (III) or (IIIA), or a pharmaceutically acceptable salt thereof, wherein A is



wherein R^E is H or halo.

In embodiments, there is provided a compound of Formula (I) which is a compound of Formula (IV):



(IV)

wherein

R^2 is R^{8A} or H;

R^9 is R^3,

X^4 and X^5 are independently N or CH; and

R^E is H or halo,

or a pharmaceutically acceptable salt thereof.

In embodiments, there is provided a compound of Formula (IV), or a pharmaceutically acceptable salt thereof, wherein X^4 and X^5 are both N.

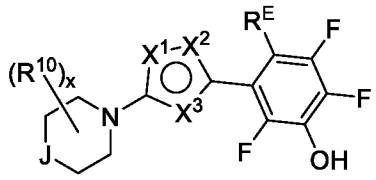
In embodiments, there is provided a compound of Formula (IV), or a pharmaceutically acceptable salt thereof, wherein X^4 and X^5 are both CH.

In embodiments, there is provided a compound of Formula (IV), or a pharmaceutically acceptable salt thereof, wherein R^9 is $C_{1\text{-}4}$ alkyl or $C_{3\text{-}6}$ cycloalkyl.

In embodiments, there is provided a compound of Formula (IV), or a pharmaceutically acceptable salt thereof, wherein R^2 is R^{8B}.

In embodiments, there is provided a compound of Formula (IV), or a pharmaceutically acceptable salt thereof, wherein R^2 is $C_{1\text{-}4}$ alkyl optionally substituted with one group independently selected from R^{4B} and R^{5B}. In further embodiments, R^2 is $C_{1\text{-}4}$ alkyl.

In embodiments, there is provided a compound of Formula (I) which is a compound of Formula (V):



(V)

wherein

J is selected from O, S, CH_2, NH and a covalent bond,

x is selected from 0 to 3; and

each R^{10} is independently selected from R^3, R^4 and R^5; and

R^E is H or halo,

or a pharmaceutically acceptable salt thereof.

In embodiments, there is provided a compound of Formula (V), or a pharmaceutically acceptable salt thereof, wherein, J is CH_2 or a covalent bond.

In embodiments, there is provided a compound of Formula (V), or a pharmaceutically acceptable salt thereof, wherein, x is 0, 1 or 2.

In embodiments, there is provided a compound of Formula (V), or a pharmaceutically acceptable salt thereof, wherein each R^{10} is independently R^3 or R^5. In further embodiments, each R^{10} is independently R^5. In further embodiments, each R^{10} is independently R^3. In further embodiments, each R^{10} is independently $C_{1\text{-}4}$ alkyl.

In embodiments, there is provided a compound of Formula (IV) or (V), or a pharmaceutically acceptable salt thereof, wherein R^E is H, F or Cl, such as H or F.

In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, wherein one of X^1, X^2 and X^3 is O and the other two of X^1, X^2 and X^3 are selected from N and CH.

In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, wherein one of X^1, X^2 and X^3 is S and the other two of X^1, X^2 and X^3 are selected from N and CH.

In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, wherein one of X^1, X^2 and X^3 is O and the other two of X^1, X^2 and X^3 are both N.

In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, wherein one of X^1, X^2 and X^3 is O, one of X^1, X^2 and X^3 is N, and one of X^1, X^2 and X^3 is CH.

In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, wherein one of X^1, X^2 and X^3 is S and the other two of X^1, X^2 and X^3 are both N.

In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, wherein one of X^1, X^2 and X^3 is S, one of X^1, X^2 and X^3 is N, and one of X^1, X^2 and X^3 is CH.

In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, wherein one of X^1, X^2 and X^3 is S and the other two of X^1, X^2 and X^3 are both CH.

In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, wherein

(i) X^1 is N, X^2 is O and X^3 is N,

(ii) X^1 is N, X^2 is N and X^3 is O;

(iii) X^1 is CH, X^2 is CH and X^3 is S;

(iv) X^1 is O, X^2 is N and X^3 is CH;

(v) X^1 is N, X^2 is O and X^3 is CH;

(vi) X^1 is CH, X^2 is N and X^3 is O;

(vii) X^1 is O, X^2 is N and X^3 is N;

(viii) X^1 is N, X^2 is N and X^3 is S;

(ix) X^1 is CH, X^2 is S and X^3 is CH; or

(x) X^1 is CH, X^2 is N and X^3 is S.

In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, wherein X^1 is N, X^2 is O and X^3 is N.

In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, wherein X^1 is N, X^2 is N and X^3 is O.

In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, wherein X^1 is N, X^2 is N and X^3 is S.

In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, wherein X^1 is N, X^2 is O and X^3 is CH.

In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, wherein X^1 is CH, X^2 is N and X^3 is O.

In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, wherein X^1 is CH, X^2 is S and X^3 is CH.

In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, wherein each R^3 is independently C_{1-4} alkyl or C_{3-6} cycloalkyl, each of which are optionally substituted with one or more (such as one to three) groups independently selected from R^{4X}, R^{5x}, -O(R^{4X}), -O(R^{5X}) and F. In further embodiments, each R^3 is independently C_{1-4} alkyl or C_{3-6} cycloalkyl.

In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, wherein each R^{3X} is independently C_{1-4} alkyl or C_{3-6} cycloalkyl. In further embodiments, each R^{3X} is C_{1-4} alkyl.

In embodiments, there is provided a compound of Formula (I), (III), (IIIA) or (V), or a pharmaceutically acceptable salt thereof, wherein each R^4 is independently monocyclic or bicyclic 5 to 9 membered heteroaryl (such as a monocyclic 5- or 6-membered heteroaryl), each of which are optionally substituted with one or more (such as one to three) groups independently selected from R^{4X}, -O(R^{4X}), R^{5X}, -O(R^{5X}), -OH, -CN, C_{1-4} alkoxy, -C(=O)OH, -C(=O)O(C_{1-4} alkyl), -C(=O)N(R^{7B})$_2$, R^3 and halo.

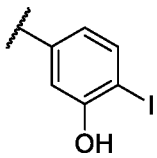
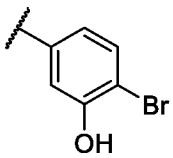
In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, wherein each R^{4X} is independently monocyclic or bicyclic 5 to 9 membered heteroaryl (such as a monocyclic 5- or 6-membered heteroaryl), each of which are optionally substituted with one or more (such as one to three) groups independently selected from -OH, -CN, C_{1-4} alkoxy, -C(=O)OH, -C(=O)N(R^{7B})$_2$, R^{3X} and halo.

In embodiments, there is provided a compound of Formula (I), (III), (IIIA) or (V), or a pharmaceutically acceptable salt thereof, wherein each R^5 is independently phenyl, optionally substituted with one or more (such as one to three) groups independently selected from R^{4X}, -O(R^{4X}), R^{5X}, -O(R^{5X}), -OH, -CN, C_{1-4} alkoxy, -C(=O)OH, -C(=O)O(C_{1-4} alkyl) and -C(=O)N(R^{7B})$_2$, R^3 and halo. In further embodiments, each R^5 is independently phenyl optionally substituted with one or more (such as one to three) groups independently selected from halo (such as F or Cl), C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{1-4} alkoxy and CN and C(=O)NH_2. In further embodiments, each R^5 is phenyl, optionally substituted with C(=O)NH_2.

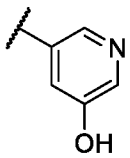
In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, wherein each R^{5X} is independently phenyl, optionally substituted with one or more (such as one to three) groups independently selected from -OH, -CN, C_{1-4} alkoxy, -C(=O)OH, -C(=O)N(R^{7B})$_2$, R^{3x} and halo. In further embodiments, each R^{5X} is independently phenyl optionally substituted with one or more (such as one to three) groups independently

selected from halo (such as F or Cl), C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{1-4} alkoxy and CN. In further embodiments, each R^{5X} is phenyl.

In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, wherein R^6 is C_{1-4} alkoxy optionally substituted with one or more groups (such as one to three groups) independently selected from R^{4X}, R^{5x} and F. In further embodiments, R^6 is C_{1-4} alkoxy optionally substituted with one or more (such as one to three) F. In further embodiments, R^6 is C_{1-4} alkoxy.

In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, with the proviso that when A is  or  and X^3 is N, that R^1 is selected from R^8, R^{8A}, R^{4A} and R^{5A}, and R^2 is selected from R^{8B} and H.

In embodiments, there is provided a compound of Formula (I), (III) or (IIIA), or a pharmaceutically acceptable salt thereof, with the proviso that the compound is other than 2-iodo-5-(3-(pyrrolidin-1-yl)-1,2,4-oxadiazol-5-yl)phenol, 2-bromo-5-(3-(4-methylpiperazin-1-yl)-1,2,4-oxadiazol-5-yl)phenol, 2-bromo-5-(3-(piperidin-1-yl)-1,2,4-oxadiazol-5-yl)phenol, 2-iodo-5-(3-(piperidin-1-yl)-1,2,4-oxadiazol-5-yl)phenol, 2-bromo-5-(3-(pyrrolidin-1-yl)-1,2,4-oxadiazol-5-yl)phenol, 2-bromo-5-(3-morpholino-1,2,4-oxadiazol-5-yl)phenol, 2-iodo-5-(3-morpholino-1,2,4-oxadiazol-5-yl)phenol, 5-(3-(azepan-1-yl)-1,2,4-oxadiazol-5-yl)-2-iodophenol, 5-(3-(azepan-1-yl)-1,2,4-oxadiazol-5-yl)-2-bromophenol and 2-iodo-5-(3-(4-methylpiperazin-1-yl)-1,2,4-oxadiazol-5-yl)phenol.

In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, with the proviso that when A is  and X^3 is N, that R^1 is selected from R^8, R^{8A}, R^{4A} and R^{5A}, and R^2 is selected from R^{8B} and H.

In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, with the proviso that the compound is other than 5-(5-(3-methylpiperazin-1-yl)-1H-1,2,4-triazol-3-yl)pyridin-3-ol, 5-(5-(1,4-diazepan-1-yl)-1H-1,2,4-triazol-3-yl)pyridin-3-ol, 5-(5-(3-methylpiperazin-1-yl)-1H-1,2,4-triazol-3-yl)pyridin-3-ol, 5-(5-(piperazin-1-yl)-1H-1,2,4-triazol-3-yl)pyridin-3-ol, 5-(5-(3,5-dimethylpiperazin-1-yl)-1H-1,2,4-triazol-3-yl)pyridin-3-ol, 5-(5-(3-methylpiperazin-1-yl)-1H-1,2,4-triazol-3-yl)pyridin-3-ol, 5-(3-(piperidin-1-yl)-1,2,4-oxadiazol-5-

yl)pyridin-3-ol, 5-(3-(4-methylpiperazin-1-yl)-1,2,4-oxadiazol-5-yl)pyridin-3-ol, 5-(3-morpholino-1,2,4-oxadiazol-5-yl)pyridin-3-ol, 5-(3-(azepan-1-yl)-1,2,4-oxadiazol-5-yl)pyridin-3-ol and 5-(3-(pyrrolidin-1-yl)-1,2,4-oxadiazol-5-yl)pyridin-3-ol.

In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the compound is selected from:

tert-butyl 4-((((1-isopropyl-1*H*-pyrazol-5-yl)methyl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)amino)methyl)benzoate,

4-((((1-isopropyl-1*H*-pyrazol-5-yl)methyl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)amino)methyl)benzoic acid,

4-((((1-isopropyl-1*H*-pyrazol-5-yl)methyl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)amino)methyl)-*N*,*N*-dimethylbenzamide,

4-((((1-isopropyl-1*H*-pyrazol-5-yl)methyl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)amino)methyl)-*N*-((1*r*,3*r*)-3-methoxycyclobutyl)benzamide,

N-((1*r*,3*r*)-3-carbamoylcyclobutyl)-4-((((1-isopropyl-1*H*-pyrazol-5-yl)methyl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)amino)methyl)benzamide,

2,3,6-trifluoro-5-(3-(((1-isopropyl-1*H*-pyrazol-5-yl)methyl)(4-methoxybenzyl)amino)-1,2,4-oxadiazol-5-yl)phenol,

5-((((1-isopropyl-1*H*-pyrazol-5-yl)methyl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)amino)methyl)picolinamide,

5-((((1-isopropyl-1*H*-pyrazol-5-yl)methyl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)amino)methyl)picolinic acid,

2-chloro-5-(3-(((1-cyclohexyl-*1H*-tetrazol-5-yl)methyl)(methyl)amino)-1,2,4-oxadiazol-5-yl)phenol,

5-(3-(((1-cyclohexyl-*1H*-tetrazol-5-yl)methyl)(methyl)amino)-1,2,4-oxadiazol-5-yl)pyridin-3-ol,

3-(3-(((1-cyclohexyl-*1H*-tetrazol-5-yl)methyl)(methyl)amino)-1,2,4-oxadiazol-5-yl)-2,5,6-trifluorophenol,

5-(3-(((1-cyclohexyl-*1H*-tetrazol-5-yl)methyl)amino)-1,2,4-oxadiazol-5-yl)-2-fluorophenol,

2,3,6-trifluoro-5-(3-(((1-isopropyl-*1H*-pyrazol-5-yl)methyl)amino)-1,2,4-oxadiazol-5-yl)phenol,

2,3,6-trifluoro-5-(3-(methyl((2,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl)methyl)amino)-1,2,4-oxadiazol-5-yl)phenol,

5-(5-(((1-cyclohexyl-*1H*-tetrazol-5-yl)methyl)(methyl)amino)-1,3,4-thiadiazol-2-yl)-2-fluorophenol,

2,3,6-trifluoro-5-(3-(methyl((1-phenethyl-*1H*-pyrazol-5-yl)methyl)amino)-1,2,4-oxadiazol-5-yl)phenol,

3-(3-(((1-benzyl-*1H*-pyrazol-5-yl)methyl)(methyl)amino)-1,2,4-oxadiazol-5-yl)-2,5,6-trifluorophenol,

5-(5-(((1-cyclohexyl-*1H*-tetrazol-5-yl)methyl)(methyl)amino)-1,3,4-oxadiazol-2-yl)-2-fluorophenol,

3-(3-(benzyl((1-isopropyl-*1H*-pyrazol-5-yl)methyl)amino)-1,2,4-oxadiazol-5-yl)-2,5,6-trifluorophenol,
4-(1-(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)piperidin-2-yl)benzamide,
4-(1-(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)pyrrolidin-2-yl)benzamide,
tert-butyl 4-(((1-isopropyl-*1H*-pyrazol-5-yl)methyl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)amino)butanoate,
5-(3-(((1-cyclohexyl-1*H*-pyrazol-5-yl)methyl)(methyl)amino)isoxazol-5-yl)-2-fluorophenol,
5-(5-(((1-cyclohexyl-1H-pyrazol-5-yl)methyl)(methyl)amino)isoxazol-3-yl)-2-fluorophenol,
2-fluoro-5-(5-(((1-isopropyl-1*H*-pyrazol-5-yl)methyl)amino)isoxazol-3-yl)phenol,
3-(3-(((1-cyclohexyl-1*H*-pyrazol-5-yl)methyl)(methyl)amino)-1,2,4-oxadiazol-5-yl)-2,5,6-trifluorophenol, and
5-(3-(((1-cyclohexyl-1*H*-pyrazol-5-yl)methyl)(methyl)amino)-1,2,4-oxadiazol-5-yl)-2-fluorophenol.

A further feature is any of the embodiments described in the specification with the proviso that any of the specific Examples are individually disclaimed. A further feature is any of the embodiments described in the specification with the proviso that any one or more of the compounds selected from the above list of Examples of compounds of the specification are individually disclaimed.

The compounds disclosed herein may contain one or more chiral centers. Accordingly, if desired, such compounds can be prepared or isolated as pure stereoisomers, i.e. as individual enantiomers, diastereoisomers, or as a stereoisomerically enriched mixture. All such stereoisomer (and enriched) mixtures are included within the scope of the embodiments, unless otherwise stated. Pure stereoisomers (or enriched mixtures) may be prepared using, for example, optically active starting materials or stereoselective reagents well-known in the art. Alternatively, racemic mixtures of such compounds can be separated using, for example, chiral column chromatography, chiral resolving agents and the like.

Unless stereochemistry is explicitly indicated in a chemical structure or chemical name, the chemical structure or chemical name is intended to embrace all possible stereoisomers, diastereoisomers, conformers, rotamers and tautomers of the compound depicted. For example, a compound containing a chiral carbon atom is intended to embrace both the (R) enantiomer and the (S) enantiomer, as well as mixtures of the enantiomers, including racemic mixtures; and a compound containing two chiral carbons is intended to embrace all enantiomers and diastereoisomers including (R,R), (S,S), (R,S) and (S,R).

In embodiments, there is provided a pharmaceutical composition which comprises a compound of the Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable excipient, optionally further comprising one or more

of the other stereoisomeric forms of the compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or pharmaceutically acceptable salt thereof, wherein the compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or pharmaceutically acceptable salt thereof is present within the composition with an enantiomeric excess (%ee) of ≥ 90% and a diastereomeric excess (%de) of ≥ 90%.

The compound of Formula (I), (II), (III), (IIIA), (IV) or (V), and pharmaceutically acceptable salts thereof, may be prepared, used or supplied in amorphous form, crystalline form, or semicrystalline form and any given compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or pharmaceutically acceptable salt thereof, may be capable of being formed into more than one crystalline / polymorphic form, including hydrated (e.g. hemi hydrate, a mono hydrate, a di hydrate, a tri hydrate or other stoichiometry of hydrate) and/or solvated forms. It is to be understood that the present specification encompasses any and all such solid forms of the compound of Formula (I), (II), (III), (IIIA), (IV) or (V), and pharmaceutically acceptable salts thereof.

In further embodiments there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), which is obtainable by the methods described in the 'Examples" section hereinafter.

The present specification is intended to include all isotopes of atoms occurring in the present compounds. Isotopes will be understood to include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include ^{13}C and ^{14}C. Isotopes of nitrogen include ^{15}N. Isotopes of fluorine include ^{18}F.

A suitable pharmaceutically acceptable salt of a compound of Formula (I), (II), (III), (IIIA), (IV) or (V) is, for example, a base addition salt. A base addition salt of a compound of Formula (I), (II), (III), (IIIA), (IV) or (V) may be formed by bringing the compound into contact with a suitable inorganic or organic base under conditions known to the skilled person. A base addition salt may for example be an alkali metal salt (such as a sodium, potassium, or lithium salt) or an alkaline earth metal salt (such as a calcium salt), which may be formed using an alkali metal or alkaline earth metal hydroxide or alkoxide (e.g., an ethoxide or methoxide). A base addition salt may also be formed using a suitably basic organic amine (e.g., a choline or meglumine salt).

A suitable pharmaceutically acceptable salt of a compound of Formula (I), (II), (III), (IIIA), (IV) or (V) is, for example, an acid addition salt. An acid addition salt of a compound of Formula (I), (II), (III), (IIIA), (IV) or (V) may be formed by bringing the compound into contact with a suitable inorganic or organic acid under conditions known to the skilled person. An acid addition salt may for example be formed using an inorganic acid selected from hydrochloric acid, hydrobromic acid, sulphuric acid and phosphoric acid. An acid addition salt may also be formed using an organic acid selected from

trifluoroacetic acid, citric acid, maleic acid, oxalic acid, acetic acid, formic acid, benzoic acid, fumaric acid, succinic acid, tartaric acid, lactic acid, pyruvic acid, methanesulfonic acid, benzenesulfonic acid and para-toluenesulfonic acid.

A further suitable pharmaceutically acceptable salt of a compound of Formula (I), (II), (III), (IIIA), (IV) or (V) is, for example, a salt formed within a patient's body after administration of a compound of Formula (I), (II), (III), (IIIA), (IV) or (V) to the patient.

The compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or pharmaceutically acceptable salt thereof, may be prepared as a co-crystal solid form. It is to be understood that a pharmaceutically acceptable co-crystal of an compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or pharmaceutically acceptable salts thereof, form an aspect of the present specification.

In a further aspect there is provided a pharmaceutical composition comprising a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

The term "pharmaceutical composition" refers to a preparation which is in such form as to permit the biological activity of the active ingredient, and which contains no additional components which are unacceptably toxic to a patient to which the composition would be administered. Such compositions can be sterile. A pharmaceutical composition according to the present specification will comprise a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. For example, the composition may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing). Such compositions may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents. An effective amount of the compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, will normally be present in the composition.

The compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, will normally be administered via the oral route though parenteral, intravenous, intramuscular, subcutaneous or in other injectable ways, buccal, rectal, vaginal, transdermal and/or nasal route and/or via inhalation, in the form of pharmaceutical preparations comprising the active

ingredient or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, in a pharmaceutically acceptable dosage form may be possible. Depending upon the disorder and patient to be treated and the route of administration, the compositions may be administered at varying doses.

The pharmaceutical formulations of the compound of Formula (I), (II), (III), (IIIA), (IV) or (V), described above may be prepared e.g. for parenteral, subcutaneous, intramuscular or intravenous administration.

The pharmaceutical formulations of the compound of Formula (I), (II), (III), (IIIA), (IV) or (V), described above may conveniently be administered in unit dosage form and may be prepared by any of the methods well-known in the pharmaceutical art, for example as described in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA., (1985).

Pharmaceutical formulations suitable for oral administration may comprise one or more physiologically compatible carriers and/or excipients and may be in solid or liquid form. Tablets and capsules may be prepared with binding agents; fillers; lubricants; and surfactants. Liquid compositions may contain conventional additives such as suspending agents; emulsifying agents; and preservatives Liquid compositions may be encapsulated in, for example, gelatin to provide a unit dosage form. Solid oral dosage forms include tablets, two-piece hard shell capsules and soft elastic gelatin (SEG) capsules. An exemplary oral composition would comprise a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), and at least one pharmaceutically acceptable excipient filled into a two-piece hard shell capsule or a soft elastic gelatin (SEG) capsule.

As a result of their 17BHSD13 inhibitory activity, the compounds of Formula (I), and pharmaceutically acceptable salts thereof are expected to be useful in therapy, for example in the treatment of diseases or medical conditions mediated at least in part by 17BHSD13, including liver disease, such as NASH.

In one aspect of the present specification there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, for use in therapy.

In one aspect of the present specification there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, for use in the treatment of liver disease. In embodiments, the liver disease is selected from alcoholic liver disease, non-alcoholic liver disease, NAFLD (such as NASH, liver fibrosis, cirrhosis, and isolated steatosis), liver inflammation, alcoholic steatoheptatis (ASH), hepatitis C virus (HCV) and hepatocellular carcinoma (HCC).

The term “therapy” is intended to have its normal meaning of dealing with a disease in order to entirely or partially relieve one, some or all of its symptoms, or to correct or compensate for the underlying pathology. The term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be interpreted in a corresponding manner.

The term “prophylaxis” is intended to have its normal meaning and includes primary prophylaxis to prevent the development of the disease and secondary prophylaxis whereby the disease has already developed and the patient is temporarily or permanently protected against exacerbation or worsening of the disease or the development of new symptoms associated with the disease.

The term “treatment” is used synonymously with “therapy”. Similarly the term “treat” can be regarded as “applying therapy” where “therapy” is as defined herein.

In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, for use in providing an inhibitory effect on 17βHSD13.

In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease mediated by 17βHSD13, such as liver disease (e.g. NASH).

In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, for use in the treatment of fatty liver disease.

In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, for use in the treatment of nonalcoholic Fatty Liver Disease (NAFLD), such as isolated steatosis, Nonalcoholic Steatohepatitis (NASH), liver fibrosis or cirrhosis. In further embodiments, the liver disease is end stage liver disease.

In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, for use in the treatment of liver disease, such as NASH, wherein the patient is also suffering from or susceptible to one or more conditions selected from the group consisting of obesity, dyslipidemia, insulin resistance, Type 2 diabetes, and renal insufficiency.

In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, for use in the treatment of liver disease, such as NASH, wherein the patient has a body mass index (BMI) of 27 kg/m^2 to 40 kg/m^2. In further embodiments, the subject has a BMI of 30 kg/m^2 to 39.9 kg/m^2. In further embodiments, the patient has a BMI of at

least 40 kg/m^2. In further embodiments, the patient is overweight. In further embodiments, the patient is obese.

In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, for use in the treatment of liver disease, such as NASH, wherein the patient is also suffering from or susceptible to dyslipidemia.

In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, for use in the treatment of liver disease, such as NASH, wherein the patient is also suffering from or susceptible to insulin resistance.

In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, for use in the treatment of liver disease, such as NASH, wherein the patient is also suffering from or susceptible to Type 2 diabetes.

In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, for use in the treatment of liver disease, such as NASH, wherein the patient is also suffering from or susceptible to renal insufficiency.

In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, for use in the treatment of liver disease, such as NASH, wherein the patient is also suffering from or susceptible to liver fibrosis. In further embodiments, the patient is (i) suffering from or susceptible to liver fibrosis, and (ii) suffering from or susceptible to one or more conditions selected from the group consisting of obesity, dyslipidemia, insulin resistance, Type 2 diabetes, and renal insufficiency.

In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, for use in the treatment of liver disease, such as NASH, wherein the patient is also suffering from or susceptible to cirrhosis. In further embodiments, the patient is (i) suffering from or susceptible to cirrhosis, and (ii) suffering from or susceptible to one or more conditions selected from the group consisting of obesity, dyslipidemia, insulin resistance, Type 2 diabetes, and renal insufficiency.

In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, for use in the treatment of NAFLD. In further embodiments, the NAFLD is Stage 1 NAFLD. In further embodiments, the NAFLD is Stage 2 NAFLD. In further embodiments, the NAFLD is Stage 3 NAFLD. In further embodiments, the NAFLD is Stage 4 NAFLD. See, e.g., "The Diagnosis and Management of Nonalcoholic Fatty Liver Disease: Practice

Guidance From the American Association for the Study of Liver Diseases," Hepatology, Vol. 67, No. 1, 2018.

In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, for use in the treatment of NAFLD, such as NASH. In further embodiments, the patient is obese. In further embodiments, the patient has alcoholic liver disease. In further embodiments, the patient has a genetic risk factor for liver disease, such as the (rs738409 C>G) variant in PNPLA3.

In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, for use in the treatment of NASH. In further embodiments, the NASH is Stage 1 NASH. In further embodiments, the NASH is Stage 2 NASH. In further embodiments, the NASH is Stage 3 NASH. In further embodiments, the NASH is Stage 4 NASH. In further embodiments, the patient is also suffering from or susceptible to one or more conditions selected from obesity, dyslipidemia, insulin resistance, Type 2 diabetes, and renal insufficiency.

In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, for use in the treatment of liver fibrosis. In further embodiments, the liver fibrosis is Stage 3 liver fibrosis. In further embodiments, the patient is also suffering from or susceptible to one or more conditions selected from obesity, dyslipidemia, insulin resistance, Type 2 diabetes, and renal insufficiency.

In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, for use in the treatment of cirrhosis. In further embodiments, the cirrhosis is stage F4 cirrhosis. In further embodiments, the patient is also suffering from or susceptible to one or more conditions selected from obesity, dyslipidemia, insulin resistance, Type 2 diabetes, and renal insufficiency.

In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, for use in the treatment of liver inflammation. In further embodiments, the inflammation is chronic inflammation. In further embodiments, the chronic inflammation is selected from the group consisting of rheumatoid arthritis, osteoarthritis, and Crohn's disease. In further embodiments, the chronic inflammation is rheumatoid arthritis.

In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, for use in the treatment of hepatocellular carcinoma (HCC).

In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, for use in the treatment of alcoholic steatoheptatis (ASH).

In embodiments, there is provided a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, for use in the treatment of hepatitis C virus (HCV).

In one aspect of the present specification there is provided the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as described herein, in the manufacture of a medicament, such as a medicament for the treatment of disease (e.g. NASH).

In one aspect of the present specification there is provided a method of treating disease, such as NASH, in a patient comprising administering to the patient an effective amount of a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof.

Terms such as “treating” or “treatment” refer to both (1) therapeutic measures that cure, slow down, lessen symptoms of, and/or halt progression of a diagnosed pathologic condition or disorder and (2) prophylactic or preventative measures that prevent and/or slow the development of a targeted pathologic condition or disorder. Thus, those in need of treatment include those already with the disorder; those prone to have the disorder; and those in whom the disorder is to be prevented.

The term "effective amount" means an amount of an active ingredient which is sufficient enough to significantly and positively modify the symptoms and/or conditions to be treated (e.g., provide a positive clinical response). The effective amount of an active ingredient for use in a pharmaceutical composition will vary with the particular condition being treated, the severity of the condition, the duration of the treatment, the nature of concurrent therapy, the particular active ingredient(s) being employed, the particular pharmaceutically-acceptable excipient(s)/carrier(s) utilized, and like factors within the knowledge and expertise of the attending physician.

The term “patient” refers to any animal (e.g., a mammal), including, but not limited to humans, non-human primates, rodents, and the like, which is to be the recipient of a particular treatment. Typically, the term “patient” refers to a human subject.

In embodiments, there is provided a method of treating disease in a patient comprising administering to the patient an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, wherein the disease is selected from isolated steatosis, NASH, liver fibrosis and cirrhosis.

In embodiments, there is provided a method of treating a 17βHSD13 mediated disease in a patient comprising administering to the patient an effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, such as NASH.

The compounds of the present disclosure may be used in the methods described above as either as single pharmacological agents or in combination with other pharmacological agents or techniques. Such combination therapies may be achieved by way of the simultaneous, sequential or separate dosing of the individual components of the treatment. These combination therapies (and corresponding combination products) employ the compounds of the present disclosure and the other pharmacological agent(s).

In embodiments, there is provided a combination for use in the treatment of liver disease, such as NASH, comprising a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, and a sodium-glucose transport protein 2 (SGLT2) inhibitor. In further embodiments, the SGLT2 inhibitor is selected from canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, luseogliflozin, and remogliflozin.

In embodiments, there is provided a combination for use in the treatment of liver disease, such as NASH, comprising a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, and metformin, or a pharmaceutically acceptable salt thereof.

In embodiments, there is provided a combination for use in the treatment of liver disease, such as NASH, comprising a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, and a glucagon-like peptide-1 receptor (GLP1) agonist. In further embodiments, the GLP1 agonist is selected from exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide, and semaglutide.

In embodiments, there is provided a combination for use in the treatment of liver disease, such as NASH, comprising a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, and a dipeptidyl peptidase 4 (DPP4) inhibitor agonist. In further embodiments, the DPP4 inhibitor is selected sitagliptin, vildagliptin, saxagliptin, linagliptin, gemigliptin, anagliptin, teneligliptin, alogliptin, trelagliptin, omarigliptin, evogliptin, gosogliptin, and dutogliptin.

In embodiments, there is provided a combination for use in the treatment of liver disease, such as NASH, comprising a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, and a PPAR agonist. In further embodiments, the PPAR agonist is a PPARα agonist. In further embodiments, the PPAR agonist is a PPARγ agonist. In further embodiments, the

PPAR agonist is a PPARα/γ agonist. In further embodiments, the PPAR agonist is selected from clofibrate, gemfibrozil, ciprofibrate, bezafibrate, and fenofibrate. In further embodiments, the PPAR agonist is a thiazolidinedione. In further embodiments, the thiazolidinedione is selected from pioglitazone, rosiglitazone, lobeglitazone, and rivoglitazone. In further embodiments, the PPAR agonist stimulates liver expression of FGF21.

In embodiments, there is provided a combination for use in the treatment of liver disease, such as NASH, comprising a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, and a Pan-PPAR agonist. In further embodiments, the Pan-PPAR agonist is lanifibranor.

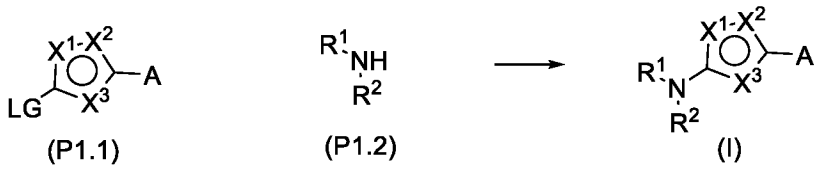
In embodiments, there is provided a combination for use in the treatment of liver disease, such as NASH, comprising a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, and a ThrB agonist. In further embodiments, the ThrB agonist is resmetirom.

In embodiments, there is provided a combination for use in the treatment of liver disease, such as NASH, comprising a compound of Formula (I), (II), (III), (IIIA), (IV) or (V), or a pharmaceutically acceptable salt thereof, and a FXR agonist. In further embodiments, the FXR agonist is obeticholic acid.

Although the compounds of the Formula (I) are primarily of value as therapeutic agents for use in patients, they are also useful whenever it is required to inhibit 17βHSD13. Thus, they are useful as pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents.

In one aspect of the present specification there is provided intermediates and methods useful for the synthesis of compounds of Formula (I), and pharmaceutically acceptable salts thereof. Schemes P1-P8 disclose intermediates and methods useful for the synthesis of compounds of Formula (I), wherein X^1, X^2, X^3, R^1, R^2 and A are defined as for a compound of Formula (I) herein, and LG are independently leaving groups, e.g. Cl or Br.

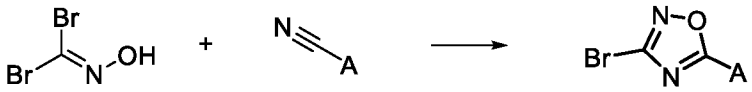
Scheme P1



(P1.1) (P1.2) (I)

A compound of Formula (P1.1) may be reacted with a compound of Formula (P1.2), in the presence of a suitable base, e.g. Cs_2CO_3, in a suitable solvent (e.g. *t*BuOH, DMF or dioxane) optionally at temperatures ranging from rt to 120 °C.

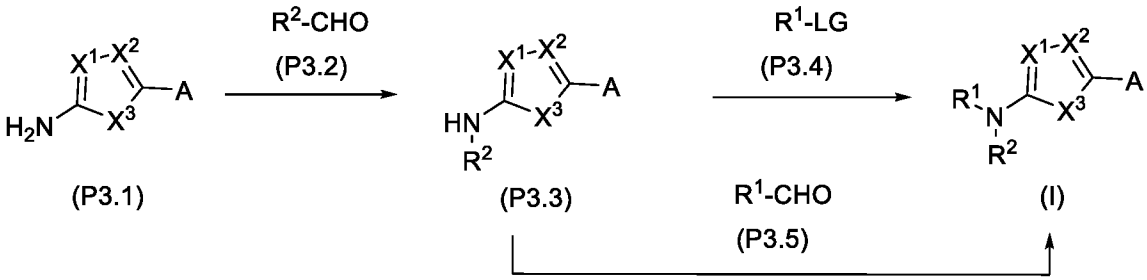
Scheme P2



(P2.1) (P2.2) (P2.3)

A compound of Formula (P2.3) may be synthesized by reacting a nitrile of Formula (P2.2) with dibromoformaldoxime (P2.1) in presence of a base (e.g. $NaHCO_3$), optionally in the presence of a solvent (e.g. toluene). Optionally, the temperature ranges from rt to reflux (such as 90 °C).

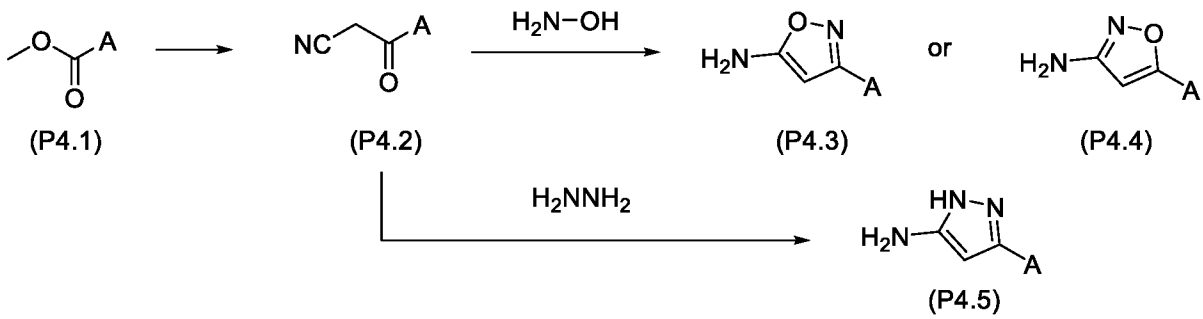
Scheme P3



(P3.1) (P3.3) (I)

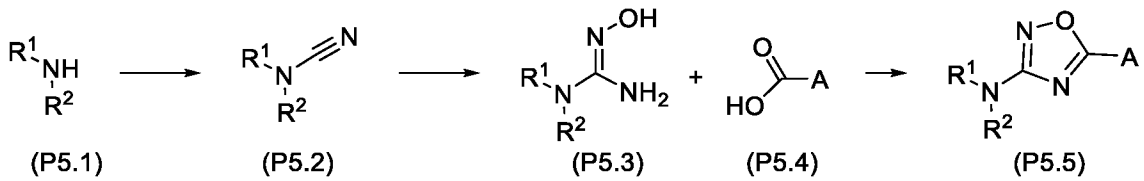
Compounds of Formula (P3.3) may be formed by reacting a compound of Formula (P3.1) with an aldehyde of Formula (P3.2) in presence of a reducing agent (e.g. $NaBH_4$) and an acid (e.g. formic acid) in a solvent (e.g. THF). A compound of Formula (P3.3) may be reacted with a compound of Formula (P3.4) in the presence of a base (e.g. C_2CO_3) in a suitable solvent (e.g. DMF), optionally at a temperature typically ranging from rt to 60 °C. Alternatively, certain compounds of Formula (I) may be formed by reacting a compound of Formula (P3.3) with an aldehyde of Formula (P3.5) in presence of a reducing agent (e.g. $NaBH_4$ or $NaB(OAc)_3$) and an acid (e.g. formic acid or acetic acid) in a solvent (e.g. THF).

Scheme P4



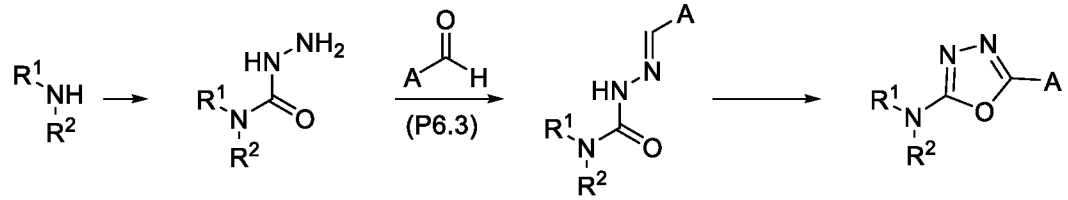
A compound of Formula (P4.2) may be formed from an ester of Formula (P4.1) by reaction with MeCN and a suitable base (e.g. NaH, $LiN(Si(CH_3)_3)_2$) in a solvent (e.g. THF), optionally in a temperature in the range -78 °C to 50 °C. A compound of Formula (P4.3) or (P4.4) may be formed by reacting a compound of Formula (P4.2) with hydroxylamine or a suitable salt thereof (such as HCl) in a solvent (such as EtOH, H_2O or mixtures thereof) in the presence of a suitable base (e.g. NaOH, $NaHCO_3$ or NaOAc), optionally at a temperature range between 60 to 120 °C. A compound of Formula (P4.5) may be formed by reacting a compound of Formula (P4.2) with hydrazine (such as hydrazine hydrate) in a solvent (such as EtOH or MeOH) optionally at a temperature range between 50 to 140 °C.

Scheme P5



A compound of Formula (P5.2) may be synthesized from a HCl salt of a suitable amine (P5.1) with a cyanide salt (e.g. $Zn(CN)_2$) and a halogenating agent, (e.g. *N*-chlorosuccinimide) in a mixture of MeCN and H_2O, optionally at a temperature ranging from rt to 80 °C. This may be transformed into a compound of Formula (P5.3) using hydroxylamine or a salt thereof (e.g. NH_3OHCl or $(NH_3OH)_2SO_4$) in a suitable solvent (e.g. EtOH or MeOH), in the presence of a base (e.g. $NaHCO_3$, DIPEA or TEA), optionally at temperature in the range rt to 60 °C. A compound of Formula (P5.5) may be formed by reacting a compound of Formula (P3.3) with a carboxylic acid of Formula (P5.4) using an amide coupling reagent (e.g. EDC/HOBt, T3P) in the presence of a base (e.g. DIPEA, $NaHCO_3$), using a suitable solvent (such as DMF), optionally at a temperature ranging from rt to 70 °C.

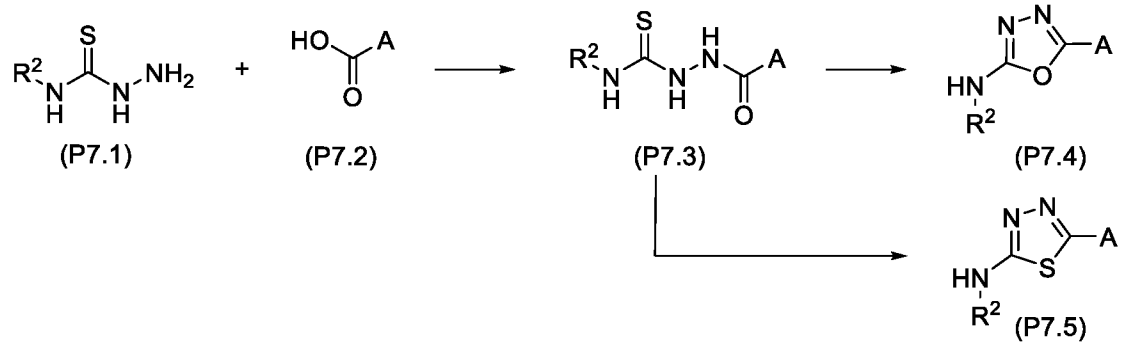
Scheme P6



(P6.1) (P6.2) (P6.4) (P6.5)

A compound of Formula (P6.2) may be synthesized by reaction of hydrazine or a protected derivative thereof (e.g. Boc-$NHNH_2$) with a di-activated carbonyl reagent (e.g. CDI) and an amine of Formula (P6.1) optionally in the presence of a base (e.g. TEA) in a solvent (e.g. DCM) optionally at rt. A compound of Formula (P6.2) may then be reacted with a suitable aldehyde of Formula (P6.3) in a solvent (such as MeOH) optionally in the presence of a base (such as NaOAc) to form a compound of Formula (P6.4). A compound of Formula (P6.5) may then be formed by reacting a compound of Formula (P6.4) by reaction with a suitable oxidation agent (e.g. I_2, Br_2 Chloramine T or PIDA) in a solvent such as MeOH, EtOH or HOAc in the presence of a suitable base (e.g. DBU or NaOAc) optionally at a temperature ranging from rt to 80 °C (such as rt).

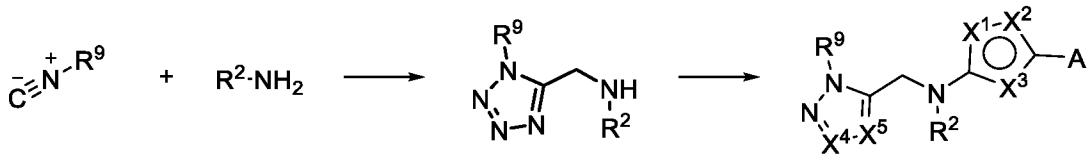
Scheme P7



(P7.1) (P7.2) (P7.3) (P7.4) (P7.5)

Compounds of Formula (P7.4) may be synthesized by heating a compound of Formula (P7.3), optionally in the presence of a carbodiimide reagent (e.g. EDC), in a solvent (e.g. DMF or DMSO) at a temperature ranging from 50 to 110 °C. Compounds of Formula (P7.5) may be synthesized by cyclization of a compound of Formula (P7.3) in presence of a strong acid (e.g. $MeSO_3H$ or H_2SO_4), optionally in a solvent (such as H_2O), optionally at a temperature in the range rt to 80 °C. Compounds of Formula (PP7.3) may be formed by standard methods known to person skilled in the art, e.g. reaction of a compound of Formula (PP7.1) with a carboxylic acid of Formula (P7.2) and a coupling reagent (e.g. EDC) optionally in the presence of a base (e.g. DIPEA) in a solvent (such as DMF), optionally at a temperature in the range 0 °C to rt. Compounds of Formula (P7.1) may be synthesized from the appropriate amine via a methods known to person skilled in the art.

Scheme P8



(P8.1) (P8.2) (P8.4) (II)

Compounds of Formula (P8.4) may be formed by reaction of a compound of Formula (P8.1) and a compound of Formula (P8.2) with a formaldehyde equivalent (e.g. paraformaldehyde) and TMS-N_3 in a solvent (such as EtOH or MeOH), optionally at a temperature in the range rt to 60 °C. Compounds of Formula (P8.4) may be transformed into compounds of Formula (II) by methods described in the schemes above.

It is understood that organic reactions described herein are performed according to laboratory practice known to person skilled in the art. It is understood that some of the reactions described herein may optionally be performed in different orders than laid out herein. It is understood that chiral isomers of compounds herein can be resolved at any stage in the synthetic process using chiral resolving agents described in the literature and known to person skilled in the art, or using chiral chromatography methods described in the literature and known to person skilled in the art, or as described further in the Examples.

It is understood that additional and/or other protective groups may optionally be needed in some of the steps described above, and it is further understood that a deprotection step therefore optionally may be performed, using method described in the literature and known to person skilled in the art. The protection and deprotection of functional groups is described in "Protective Groups in Organic Synthesis" 3rd Ed, T.W. Greene and P.G.M. Wutz, Wiley-Interscience (1999), which is incorporated herein by reference.

Examples

The specification will now be illustrated by the following non-limiting Examples in which, generally:

(i) operations were carried out at room temperature (rt), *i.e.* in the range 17 to 28°C and where needed under an atmosphere of an inert gas such as N_2;

(ii) where reactions refer to being degassed or purged, this can be performed for example by purging the reaction solvent with a constant flow of nitrogen for a suitable period of time (for example 5 to 10 min) or by repeatedly evacuating the vessel and backfill with appropriate inert atmosphere (for example nitrogen (g) or argon (g));

(iii) where reactions refer to the use of a microwave reactor, one of the following microwave reactors were used: BIOTAGE INITIATOR, PERSONAL CHEMISTRY EMRYS OPTIMIZER, PERSONAL CHEMISTRY SMITH CREATOR or CEM EXPLORER;

(iv) in general, the course of reactions was followed by thin layer chromatography (TLC) and/or analytical high performance liquid chromatography (HPLC or UPLC) which was usually coupled to a mass spectrometer (LCMS).

(v) when necessary, organic solutions were dried over anhydrous $MgSO_4$ or Na_2SO_4, or by using ISOLUTE Phase Separator, and workup procedures were carried out using traditional phase separating techniques. When a drying agent such as e.g. $MgSO_4$ or Na_2SO_4 is used for drying an organic layer, it is understood that said organic layer is filtered before concentration of said layer.

(vi), evaporations were carried out either by rotary evaporation *in vacuo* or in a GENEVAC HT-4 / EZ-2 or BIOTAGE V10;

(vii) unless otherwise stated, flash column chromatography was performed on straight phase silica, using either MERCK Silica Gel (Art. 9385) or prep-packed cartridges such as BIOTAGE SNAP cartridges (40-63 µm silica, 4–330 g), BIOTAGE SFÄR Silica HC D cartridges (20 µm, 10–100 g), INTERCHIM PURIFLASH cartridges (25 µm, 4–120 g), INTERCHIM PURIFLASH cartridges (50 µm, 25–330 g), GRACE GRACE RESOLV Silica Flash Cartridges (4–120 g) or AGELA FLASH Colum Silica-CS cartridges (80–330g), or on reversed phase silica using AGELA TECHNOLOGIES C-18, spherical cartridges (20–35µm, 100A, 80–330g), manually or automated using a GRACE REVELERIS X2 Flash system or similar system;

(viii) preparative reversed phase HPLC and preparative reversed phase SFC were performed using standard HPLC and SFC instruments, respectively, equipped with either a MS and/or UV triggered fraction collecting instrument, using either isocratic or a gradient of the mobile phase as described in the experimental section and using one of the following methods: **PrepMethod A:** The compound was purified by preparative HPLC on a KROMASIL C8 column (10 µm, 250×20 mm ID) using a gradient of MeCN in H_2O/MeCN/FA (95/5/0.2) as mobile phase; **PrepMethod B:** The compound was purified by preparative HPLC on a KROMASIL C8 column (10 µm, 250×50 mm ID) using a gradient of MeCN in H_2O/MeCN/FA (95/5/0.2) as mobile phase; **PrepMethod C:** The compound was purified by preparative HPLC on a WATERS SUNFIRE C18 ODB column (5 µm, 150×30 mm ID) using a gradient of MeCN in H_2O/FA (0.1 M) as mobile phase; **PrepMethod D:** The compound was purified by preparative HPLC on a WATERS SUNFIRE C18 ODB column (5 µm, 150×19 mm ID) using a gradient of MeCN in H_2O/FA (0.1 M) as mobile phase; **PrepMethod E:** The compound was purified by preparative HPLC on a XBRIDGE Prep OBD C18 column, (5 µm, 30×150 mm) using a gradient of

MeCN in H_2O/FA (0.1%) as mobile phase; **PrepMethod F**: The compound was purified by preparative HPLC on a YMC-ACTUS TRIART C18 column, (5 µm, 30×250 mm) using a gradient of MeCN in H_2O/NH_3(0.05%) as mobile phase; **PrepMethod G:** The compound was purified by preparative HPLC on a WATERS XSELECT CSH Fluoro Phenyl column, (5 µm, 100×10 mm ID) using a gradient of MeCN in H_2O/TFA (0.05%) as mobile phase; **PrepMethod H:** The compound was purified by preparative HPLC on a XBRIDGE C18 ODB column (5 µm, 150×30 mm ID) using a gradient of MeCN in H_2O/NH_4HCO_3 (10 mM)+0.1% NH_4OH as mobile phase; **PrepMethod I:** The compound was purified by preparative HPLC on a XBRIDGE SHIELD RP18 OBD column (5 µm, 150×30 mm ID) using a gradient of MeCN in H_2O/NH_4HCO_3 (10 mM) as mobile phase; **PrepMethod J:** The compound was purified by preparative HPLC on a XBRIDGE SHIELD RP18 OBD column (5 µm, 150×30 mm ID) using a gradient of MeCN in H_2O/NH_3 (0.05%) as mobile phase; **PrepMethod K:** The compound was purified by preparative SFC on a PHENOMENEX Luna Hilic column (5 µm, 250×30 mm ID) using a gradient of EtOH/FA (20 mM) in CO_2 as mobile phase; **PrepMethod L:** The compound was purified by preparative HPLC on a WATERS XSELECT CSH OBD column, (5 µm, 150×30 mm ID) using a gradient of MeCN in H_2O/FA (0.1%) as mobile phase; **PrepMethod M**: The compound was purified by preparative HPLC on a WATERS XSELECT CSH Prep C18 OBD column, (5 µm, 250×19 mm ID) using a gradient of MeOH in H_2O/FA (0.1%) as mobile phase; **PrepMethod N:** The compound was purified by preparative HPLC on a XBRIDGE C18 ODB column (5 µm, 250×19 mm ID) using a gradient of MeCN in H_2O/NH_4HCO_3 (10 mM)+0.1% NH_4OH as mobile phase; **PrepMethod O:** The compound was purified by preparative HPLC on a XBRIDGE C18 ODB column (5 µm, 150×30 mm ID) using a gradient of MeCN in H_2O/NH_4HCO_3 (10 mM) as mobile phase;

In some instances the compound may be dissolved in a solvent e.g. DMSO and filtered through a syringe filter prior to purification on preparative HPLC.

Relevant fractions were collected, combined and freeze-dried or evaporated to give the purified compound or relevant fractions were collected, combined and concentrated at reduced pressure, extracted with DCM or EtOAc, and the organic phase was dried either over Na_2SO_4 or by using a phase-separator, and then concentrated at reduced pressure to give the purified compound;

(ix) chiral preparative chromatography was carried out using HPLC or SFC on a standard HPLC or SFC instruments, respectively, and using either isocratic or gradient run with mobile phase as described in the experimental section;

(x) yields, where present, are not necessarily the maximum attainable, and when necessary, reactions were repeated if a larger amount of the reaction product was required;

(xi) where certain compounds were obtained as an acid-addition salt, for example a mono-hydrochloride salt or a di-hydrochloride salt, the stoichiometry of the salt was based on the number and nature of the basic groups in the compound, the exact stoichiometry of the salt was generally not determined, for example by means of elemental analysis data;

(xii) in general, the structures of the end-products of the Formula (I) were confirmed by nuclear magnetic resonance (NMR) and/or mass spectral techniques; proton NMR chemical shift values were measured on the delta scale using BRUKER AVANCE III 300, 400, 500 and 600 spectrometers, operating at ^{1}H frequencies of 300, 400, 500 and 600 MHz, respectively. The experiments were typically recorded at 25°C. Chemical shifts are given in parts per million with the solvent as internal standard. Protons on heteroatoms such as NH and OH protons are only reported when detected in NMR and can therefore be missing. In certain instances, protons can be masked or partially masked by solvent peaks and will therefore either be missing and not reported or reported as multiplets overlapping with solvent. The following abbreviations have been used (and derivatives thereof, e.g. dd, doublet of doublets, etc.): s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; qn, quintet; p, pentet. In some cases, the structures of the end-products of the Formula (I) might appear as rotamers in the NMR-spectrum, in which instances only peaks of the major rotamer are reported. In certain instances, the structures of the intermediates and/or the end-products of the Formula (I) might appear as rotamers in the NMR-spectrum, in which instances peaks of all rotamers are reported, and only the total number of protons are reported. The ratio of major vs minor rotamer is reported if known. Electrospray mass spectral data were obtained using a WATERS ACQUITY UPLC coupled to a Waters single quadrupole mass spectrometer or similar equipment, acquiring both positive and negative ion data, and generally, only ions relating to the parent structure are reported; high resolution electrospray mass spectral data were obtained using a WATERS XEVO qToF mass spectrometer or similar equipment, coupled to a WATERS ACQUITY UPLC, acquiring either positive and negative ion data, and generally, only ions relating to the parent structure are reported;

(xiii) intermediates were not necessarily fully purified but their structures and purity were assessed by TLC, analytical HPLC/UPLC, and/or NMR analysis and/or mass spectrometry;

(xiv) unless stated otherwise compounds containing an asymmetric carbon and/or sulfur atom were not resolved;

(xv) in general Examples and Intermediate compounds are named using CHEMDRAW PROFESSIONAL version 20.1.1.125 from PerkinElmer. CHEMDRAW PROFESSIONAL version 20.1.1.125 generates the names of chemical structures using the Cahn-Ingold-Prelog (CIP) rules for stereochemistry and follows IUPAC rules as closely as possible when generating chemical names. Stereoisomers are

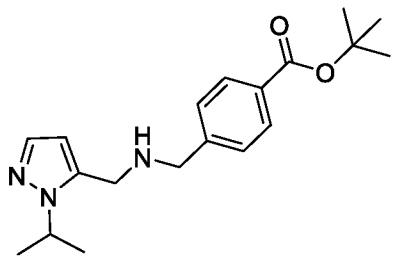
differentiated from each other by stereodescriptors cited in names and assigned in accordance with the CIP rules.;

(xvi) in addition to the ones mentioned above, the following abbreviations have been used:

AcOH	Acetic acid
Aq	Aqueous
Boc	*tert*-Butoxycarbonyl
t-Bu	*tert*-Butyl
t-BuOH	*tert*-Butanol
Brine	Saturated aqueous sodium chloride solution
Calcd	Calculated
CDI	di(1*H*-Imidazol-1-yl)methanone
DBU	2,3,4,6,7,8,9,10-octahydropyrimido[1,2-*a*]azepine
DCM	Dichloromethane
DIPEA	*N*-ethyl-*N*-isopropyl-propan-2-amine
DMF	*N*,*N*-dimethylformamide
DMSO	Dimethyl sulfoxide
EDC	3-(((ethylimino)methylene)amino)-*N*,*N*-dimethylpropan-1-amine
ESI	Electrospray ionization
EtOAc	Ethyl acetate
EtOH	Ethanol
eq	equivalents
FA	Formic acid
(g)	gas
HPLC	High performance liquid chromatography
HATU	(1-(Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium-3-oxo hexafluorophosphate
HOBt	1-hydroxybenzotriazole;hydrate
HRMS	High resolution mass spectrometry
ID	Inner diameter
$(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$	[4,4'-Bis(1,1-dimethylethyl)-2,2'-bipyridine-N1,N1']bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl-N]phenyl-C]Iridium(III) hexafluorophosphate [CAS No 870987-63-6]
MeCN	Acetonitrile
MeOH	Methanol
MS	Mass spectrometry

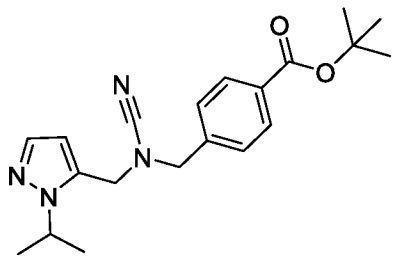
2-MeTHF	2-Methyltetrahydrofuran
m/z	mass spectrometry peak(s)
NCS	*N*-chlorosuccinimide
NMR	Nuclear magnetic resonance
PE	petroleum ether
Pd-C	Palladium on charcoal
PPh_3	Triphenylphosphane
rt	Room temperature
sat	Saturated
SFC	Supercritical fluid chromatography
T3P	propanephosphonic acid anhydride
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
UPLC	ultra performance liquid chromatography
UV	ultraviolet

Intermediate 1: *tert*-Butyl 4-((((1-isopropyl-1*H*-pyrazol-5-yl)methyl)amino)methyl)benzoate



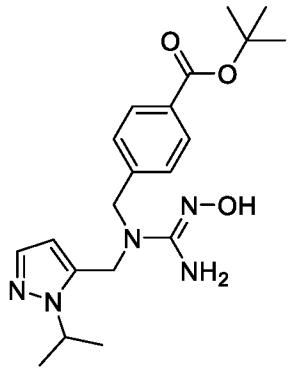
To a solution of (1-isopropyl-1*H*-pyrazol-5-yl)methanamine (0.808 g, 5.80 mmol) and *tert*-butyl 4-formylbenzoate (1.317 g, 6.38 mmol) in DCM (40 mL) was added AcOH (0.432 ml, 7.55 mmol). The reaction was stirred for 4 h at rt. Sodium triacetoxyborohydride (1.845 g, 8.71 mmol) was added and the reaction was stirred at rt for 16 h. Another 1.5 eq of sodium triacetoxyborohydride was added and the reaction was stirred for additional 2 h. The reaction was quenched with $NaHCO_3$ and extracted with DCM (×3). The combined organic phases were washed with brine, dried using a phase separator and concentrated. Crude material was purified by flash chromatography on silica (gradient: 0-100% EtOAc in heptane) to give the title compound (1.23 g, 64%) as a colourless oil; MS (ESI) *m/z* $[M+H]^+$ 330.4.

Intermediate 2: *tert*-Butyl 4-((*N*-((1-isopropyl-1*H*-pyrazol-5-yl)methyl)cyanamido)methyl)benzoate



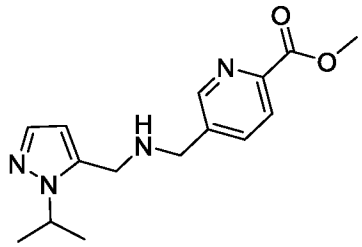
tert-Butyl 4-((((1-isopropyl-1*H*-pyrazol-5-yl)methyl)amino)methyl)benzoate **Intermediate 1** (1.23 g, 3.73 mmol) was dissolved in DCM (10 mL) and 4 M HCl in dioxane (1.867 ml, 7.47 mmol) was added. The reaction mixture was stirred for 5 min and evaporated. MeCN (31.9 mL) and water (3.55 mL) were added followed by $Zn(CN)_2$ (0.789 g, 6.72 mmol) and NCS (0.748 g, 5.60 mmol). The cloudy white reaction mixture was stirred at rt for 2 days. Water was added to the reaction mixture and the aqueous layer was extracted with DCM (×3). The combined organic layers were washed with brine, dried using an ISOLUTE phase separator and concentrated to give the crude title compound (1.4 g) as a transparent oil that became a solid when standing; MS (ESI) *m/z* $[M+H]^+$ 355.5.

Intermediate 3: *tert*-Butyl (*E*) 4-((2-hydroxy-1-((1-isopropyl-1*H*-pyrazol-5-yl)methyl)guanidino)methyl)benzoate



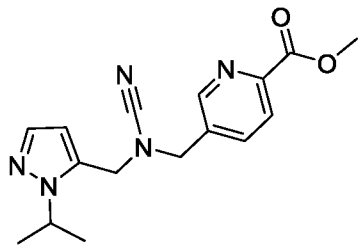
To a solution of *tert*-butyl 4-((*N*-((1-isopropyl-1*H*-pyrazol-5-yl)methyl)cyanamido)methyl)benzoate **Intermediate 2** (0.75 g, 2.12 mmol) in EtOH (15 mL) at rt was added $NaHCO_3$ (0.533 g, 6.35 mmol) followed by hydroxylamine HCl (0.221 g, 3.17 mmol). The resulting clear mixture was stirred at rt over night. The reaction mixture was filtered and the filtrat was concentrated under reduced pressure. EtOAc and 1M $NaHCO_3$ were added to the residue. The phases were separated and the organic phase was washed with brine and concentrated to give the title compound (0.796 g, 97%) as a transparent oil and as a mixture of isomers; MS (ESI) *m/z* $[M+H]^+$ 388.5.

Intermediate 4: Methyl 5-((((1-isopropyl-1*H*-pyrazol-5-yl)methyl)amino)methyl)picolinate



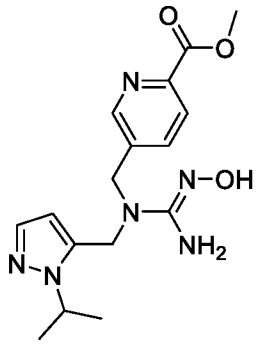
To a solution of (1-isopropyl-1*H*-pyrazol-5-yl)methanamine (0.329 g, 2.36 mmol) and methyl 5-formylpicolinate (0.432 g, 2.62 mmol) in DCM (23 mL) was added AcOH (0.176 ml, 3.07 mmol). The reaction was stirred for 3 h. Sodium triacetoxyhydroborate (0.751 g, 3.55 mmol) was added and the reaction was stirred at rt for 16 h. The reaction was quenched with 1 M $NaHCO_3$ and extracted with DCM (×3). The phases were separated using a phase separator. The combined organic layers were concentrated, and the crude material was purified by flash chromatography on silica (EtOAc:MeOH, 90:10) to give the title compound (0.6 g, 88%) as a transparent oil; MS (ESI) *m/z* $[M+H]^+$ 289.3.

Intermediate 5 : Methyl 5-((*N*-((1-isopropyl-1*H*-pyrazol-5-yl)methyl)cyanamido)methyl)picolinate



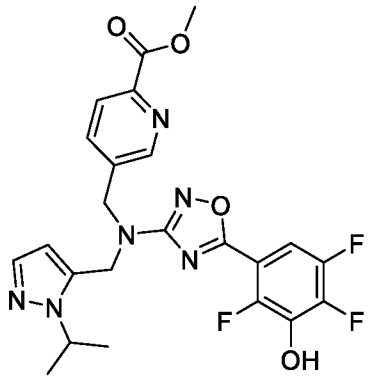
Methyl 5-((((1-isopropyl-1*H*-pyrazol-5-yl)methyl)amino)methyl)picolinate **Intermediate 4** (0.276 g, 0.96 mmol) was dissolved in DCM (4 mL) and 4 M HCl in dioxane (0.479 ml, 1.91 mmol) was added. The reaction mixture was stirred for 5 min and then evaporated. MeCN (8.18 mL) and water (0.909 mL) were added followed by $Zn(CN)_2$ (0.112 g, 0.96 mmol) and NCS (0.134 g, 1.01 mmol). The cloudy reaction mixture was stirred at rt over night. Water was added to the reaction mixture and the aqueous layer was extracted with DCM (×2). The combined organic layers were washed with brine, passed through a phase separator and concentrated to give crude title compound (0.329 g) as a yellow oil; MS (ESI) *m/z* $[M+H]^+$ 314.2.

Intermediate 6 : Methyl (*E*)-5-((2-hydroxy-1-((1-isopropyl-1*H*-pyrazol-5-yl)methyl)guanidino)methyl)picolinate



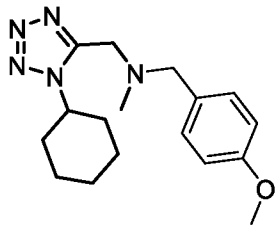
To a solution of methyl 5-((*N*-((1-isopropyl-1*H*-pyrazol-5-yl)methyl)cyanamido)methyl)picolinate **Intermediate 5** (0.329 g, 1.05 mmol) in EtOH (8 mL) at rt was added $NaHCO_3$ (0.265 g, 3.15 mmol) followed by hydroxylamine HCl (0.109 g, 1.57 mmol). The resulting mixture was stirred at rt over night. The reaction mixture was filtered and the filtrat was concentrated under reduced pressure. DCM and 1 M $NaHCO_3$ was added to the residue. The phases were separated using a phase separator and the organic phase was concentrated to give the crude title compound (0.340 g, 93%) as a transparent oil and as a mixture of isomers; MS (ESI) *m/z* $[M+H]^+$ 347.1.

Intermediate 7 : Methyl 5-((((1-isopropyl-1*H*-pyrazol-5-yl)methyl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)amino)methyl)picolinate



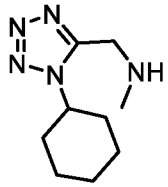
In a vial, 2,4,5-trifluoro-3-hydroxybenzoic acid (72 mg, 0.38 mmol), $NaHCO_3$ (79 mg, 0.94 mmol), HOBt (0.072 g, 0.38 mmol) and EDC (0.086 g, 0.45 mmol) were dissolved in DMF (1.5 mL) and stirred for 5 min. Then a solution of methyl (*E*)-5-((2-hydroxy-1-((1-isopropyl-1*H*-pyrazol-5-yl)methyl)guanidino)methyl)picolinate **Intermediate 6** (0.13 g, 0.38 mmol) in DMF (1.5 mL) was added to the activated acid solution. The reaction mixture was stirred for 30 min at rt, then at 70°C for 20 h. The crude product was cooled to rt, diluted with DMSO and purified by preparative HPLC, PrepMethod A (gradient 15-60%) to give the title compound (53 mg, 28%) as a white solid; MS (ESI) *m/z* $[M+H]^+$ 503.3.

Intermediate 8: 1-(1-Cyclohexyl-*1H*-tetrazol-5-yl)-*N*-(4-methoxybenzyl)-*N*-methylmethanamine



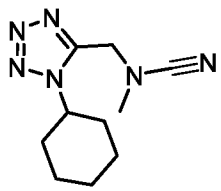
A mixture of paraformaldehyde (0.550 g, 18.32 mmol) and 1-(4-methoxyphenyl)-*N*-methylmethanamine (2.77 g, 18.32 mmol) in EtOH (40 mL) was stirred at rt until completion. Isocyanocyclohexane (2 g, 18.32 mmol) was added dropwise to the mixture at 0°C followed by azidotrimethylsilane (2.409 mL, 18.32 mmol). The resulting mixture was stirred at 60°C for 16 h. The solvent was removed under reduced pressure and the residue was purified by straight phase flash chromatography on silica, (gradient: 0–40% EtOAc in PE) to afford the title compound (4.30 g, 74%) as a colourless gum; MS *m/z* (ESI) $[M+H]^+$ 316.

Intermediate 9: 1-(1-Cyclohexyl-*1H*-tetrazol-5-yl)-*N*-methylmethanamine



Pd-C (0.145 g, 1.36 mmol) was added to 1-(1-cyclohexyl-1*H*-tetrazol-5-yl)-*N*-(4-methoxybenzyl)-N-methylmethanamine **Intermediate 8** (4.3 g, 13.63 mmol) in MeOH (50 mL) at 25°C under H_2(g). The resulting mixture was stirred at 25°C for 16 h. The mixture was filtered through a pad of CELITE and the filtrate was concentrated under reduced pressure to give the title compound (2.500 g, 94%) as a yellow oil; MS *m/z* (ESI) $[M+H]^+$ 196.

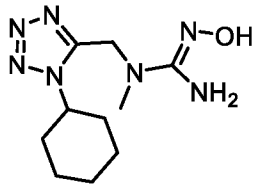
Intermediate 10: *N*-((1-Cyclohexyl-*1H*-tetrazol-5-yl)methyl)-*N*-methylcyanamide



1-(1-Cyclohexyl-*1H*-tetrazol-5-yl)-*N*-methylmethanamine **Intermediate 9** (200 mg, 0.61 mmol) was added to NCS (107 mg, 0.80 mmol) and $Zn(CN)_2$ (79 mg, 0.68 mmol) in MeCN (6 mL) and water (0.67 mL) at 25°C. The resulting mixture was stirred at 25°C for 16 h. The reaction mixture was diluted with DCM (50 mL), and washed sequentially with water (50 mL) and sat brine (50 mL). The organic layer

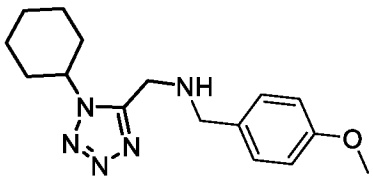
was dried over Na_2SO_4, filtered and evaporated to afford the title compound (50 mg, 37%) as a colorless oil; MS *m/z* (ESI) $[M+H]^+$ 221.

Intermediate 11: (*E*)-1-((1-Cyclohexyl-*1H*-tetrazol-5-yl)methyl)-2-hydroxy-1-methylguanidine



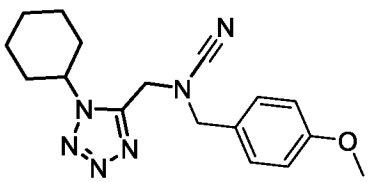
TEA (2.53 mL, 18.16 mmol) was added to a solution of *N*-((1-cyclohexyl-1*H*-tetrazol-5-yl)methyl)-*N*-methylcyanamide **Intermediate 10** (2 g, 9 mmol) and hydroxylamine HCl (0.694 g, 9.99 mmol) in MeOH (50 mL) at 25°C under a N_2(g) atmosphere. The resulting mixture was stirred at 60°C for 16 h. The solvent was removed under reduced pressure and the residue was purified by reversed phase flash chromatography on a C18 column (gradient: 0–20% MeCN in water containing 0.1% FA) to afford the title compound (0.650 g, 28%) as a white solid; MS *m/z* (ESI) $[M+H]^+$ 254.

Intermediate 12: 1-(1-Cyclohexyl-*1H*-tetrazol-5-yl)-*N*-(4-methoxybenzyl)methanamine



Paraformaldehyde (0.550 g, 18.32 mmol) and a solution of (4-methoxyphenyl)methanamine (2.51g, 18.32 mmol) in EtOH (20 mL) was stirred at rt until completion. Isocyanocyclohexane (2 g, 18.32 mmol) was added dropwise to the mixture at 0°C, followed by trimethylsilyl azide (2.111 g, 18.3 mmol). The resulting mixture was stirred at 60°C for 16 h. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography on silica, (gradient: 0–70% EtOAc in PE) to afford the title compound (3.90 g, 71%) as a colourless oil; MS *m/z* (ESI) $[M+H]^+$ 302.

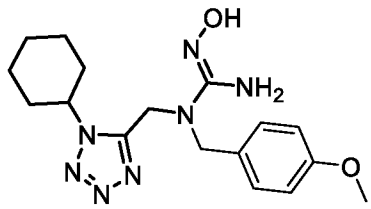
Intermediate 13: *N*-((1-Cyclohexyl-*1H*-tetrazol-5-yl)methyl)-*N*-(4-methoxybenzyl)cyanamide



$Zn(CN)_2$ (2.435 g, 20.74 mmol) was added to 1-(1-cyclohexyl-*1H*-tetrazol-5-yl)-*N*-(4-methoxybenzyl)methanamine **Intermediate 12** (2.5 g, 8.29 mmol) and NCS (1.440 g, 10.78 mmol) in

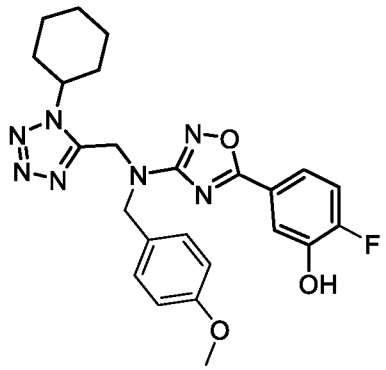
MeCN/H_2O (9:1, 20 mL) . The resulting mixture was stirred at 80°C for 4 h. The reaction mixture was diluted with EtOAc (1 L), and washed with sat brine (200 mL), The organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified by straight phase flash chromatography on silica, (gradient: 0–100% THF in PE) to afford the title compound (2.90 g) as a yellow solid; MS *m/z* (ESI) $[M+H]^+$ 327.

Intermediate 14: (*E*)-1-((1-Cyclohexyl-*1H*-tetrazol-5-yl)methyl)-2-hydroxy-1-(4-methoxybenzyl)guanidine



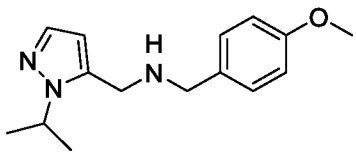
TEA (0.854 mL, 6.13 mmol) was added to a solution of *N*-((1-cyclohexyl-1*H*-tetrazol-5-yl)methyl)-*N*-(4-methoxybenzyl)cyanamide **Intermediate 13** (1 g, 3.06 mmol) and hydroxylamine HCl (0.319 g, 4.60 mmol) in MeOH (1 mL). The resulting mixture was stirred at 60°C for 3 h. The mixture was concentrated to afford the title compound (1.70 g) as a yellow solid; MS *m/z* (ESI) $[M+H]^+$ 360.

Intermediate 15: 5-(3-(((1-Cyclohexyl-*1H*-tetrazol-5-yl)methyl)(4-methoxybenzyl)amino)-1,2,4-oxadiazol-5-yl)-2-fluorophenol



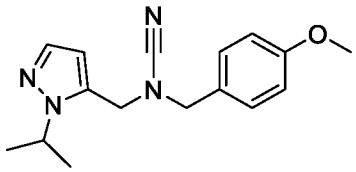
A mixture of 4-fluoro-3-hydroxybenzoic acid (1 g, 6.41 mmol), EDC (1.842 g, 9.61 mmol) and HOBt (1.471 g, 9.61 mmol) in DMF (3 mL) was stirred at rt for 10 min. (*E*)-1-((1-Cyclohexyl-*1H*-tetrazol-5-yl)methyl)-2-hydroxy-1-(4-methoxybenzyl)guanidine **Intermediate 14** (2.302 g, 6.41 mmol) was added and the resulting mixture was stirred at 80°C for 1 h. The reaction mixture was diluted with EtOAc (300 mL) and washed with sat NaCl (aq) (50 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford the title compound (0.80 g, 26%) as a yellow oil; MS *m/z* (ESI) $[M+H]^+$ 480.

Intermediate 16: 1-(1-Isopropyl-*1H*-pyrazol-5-yl)-*N*-(4-methoxybenzyl)methanamine



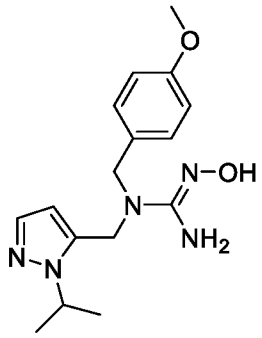
Titanium isopropoxide (2.057 g, 7.24 mmol) was added to 1-isopropyl-*1H*-pyrazole-5-carbaldehyde (1 g, 7.24 mmol) and (4-methoxyphenyl)methanamine (1.191 g, 8.68 mmol) in THF (20 mL) at 20°C and the reaction mixture was stirred at 20°C for 2 h. $NaBH_4$ (0.821 g, 21.71 mmol) was added and the resulting mixture was stirred at 25°C for 2 h. Water (20 mL) was added. The mixture was filtered through CELITE and the filter cake was washed with DCM (50 mL). The layers of the combined filtrates were separated and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford the title compound (1.800 g, 96%) as a colourless oil, which was used without further purification; MS *m/z* (ESI) $[M+H]^+$ 260.

Intermediate 17: *N*-((1-Isopropyl-*1H*-pyrazol-5-yl)methyl)-*N*-(4-methoxybenzyl)cyanamide



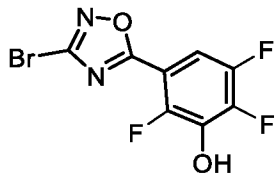
$Zn(CN)_2$ (0.598 g, 5.09 mmol) was added to NCS (0.803 g, 6.01 mmol) in a mixture of MeCN (12 mL) and water (1.2 mL) and the resulting mixture was stirred at 25°C for 1 h. 1-(1-Isopropyl-1*H*-pyrazol-5-yl)-*N*-(4-methoxybenzyl)methanamine **Intermediate 16** (1.2 g, 4.63 mmol) was added and the resulting mixture was stirred at 25°C for 16 h. The reaction mixture was concentrated, diluted with EtOAc (100 mL), and washed with water (2×100 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified by preparative TLC (EtOAc:DCM, 1:1), to afford the title compound (1 g, 76%) as a colourless oil; MS *m/z* (ESI) $[M+H]^+$ 285.

Intermediate 18: (*E*)-2-Hydroxy-1-((1-isopropyl-1*H*-pyrazol-5-yl)methyl)-1-(4-methoxybenzyl)guanidine



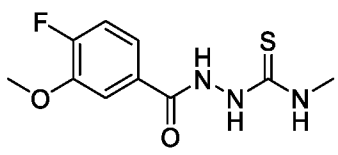
$NaHCO_3$ (0.591 g, 7.03 mmol) was added to hydroxylamine HCl (0.293 g, 4.22 mmol) and *N*-((1-isopropyl-*1H*-pyrazol-5-yl)methyl)-*N*-(4-methoxybenzyl)cyanamide **Intermediate 17** (1 g, 3.52 mmol) in EtOH (10 mL) at 20°C and the resulting solution was stirred at 20°C for 16 h. The reaction mixture was filtered through CELITE. The solvent was removed under reduced pressure to afford the title compound (1.100 g, 99%) as a colourless oil; MS *m/z* (ESI) $[M+H]^+$ 318.

Intermediate 19: 3-(3-Bromo-1,2,4-oxadiazol-5-yl)-2,5,6-trifluorophenol



$NaHCO_3$ (374 mg, 4.45 mmol) was added to a solution of 2,4,5-trifluoro-3-hydroxybenzonitrile (241 mg, 1.39 mmol) in toluene (21 mL). Hydroxycarbonimidic dibromide (564 mg, 2.78 mmol) was added portion wise over 1.5 h at 90°C. The reaction mixture was stirred at 90°C for 16 h. Additional dibromoformaldoxime (282 mg) and $NaHCO_3$ (117 mg) were added and the stirring was continued at 95°C for 5 h. The reaction mixture was cooled to rt, the white precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by straight phase flash chromatography on silica (gradient: 0–20% of EtOAc:heptane) to afford the title compound (0.156 g, 38%, 57% purity) as a white gummy solid; MS *m/z* (ESI) $[M-H]^-$ 292.9 and 294.9.

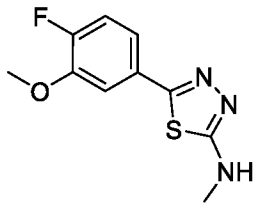
Intermediate 20: 2-(4-Fluoro-3-methoxybenzoyl)-*N*-methylhydrazine-1-carbothioamide



A mixture of 4-fluoro-3-methoxybenzoic acid (2 g, 11.76 mmol) and EDC (3.38 g, 17.63 mmol) in DMF (20 mL) was stirred at rt for 5 min. Then *N*-methylhydrazinecarbothioamide (1.36 g, 12.93 mmol) was added and the resulting mixture was stirred at rt for 1 h. The reaction mixture was poured into

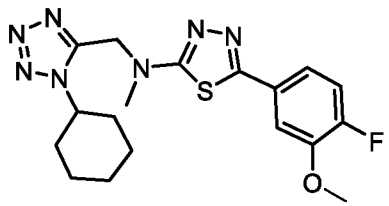
water (500 mL) and extracted with EtOAc (3 ×200 mL). The combined organic layer was dried over Na_2SO_4, filtered and evaporated. The solid was washed with EtOAc (10 mL) and oven dried to afford the title compound (1.100 g, 36%) as a white solid; MS *m/z* (ESI) $[M+H]^+$ 258.

Intermediate 21: 5-(4-Fluoro-3-methoxyphenyl)-*N*-methyl-1,3,4-thiadiazol-2-amine



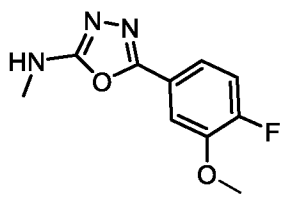
A mixture of 2-(4-fluoro-3-methoxybenzoyl)-*N*-methylhydrazine-1-carbothioamide **intermediate 20** (1 g, 3.9 mmol) in 80% H_2SO_4 (aq, 20 mL) was stirred at rt for 16 h. The reaction mixture was poured into ice water (100 mL), neutralised with sat $NaHCO_3$ and extracted with EtOAc (3×100 mL). The combined organic layer was dried over Na_2SO_4, filtered and evaporated to afford the title compound (900 mg, 80%) as a white solid; MS *m/z* (ESI) $[M+H]^+$ 240.

Intermediate 22: *N*-((1-Cyclohexyl-*1H*-tetrazol-5-yl)methyl)-5-(4-fluoro-3-methoxyphenyl)-*N*-methyl-1,3,4-thiadiazol-2-amine



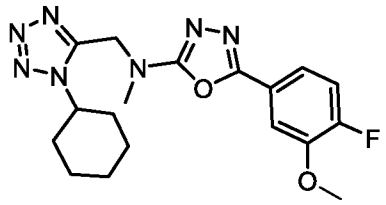
A mixture of 5-(chloromethyl)-1-cyclohexyl-*1H*-tetrazole (100 mg, 0.50 mmol), 5-(4-fluoro-3-methoxyphenyl)-*N*-methyl-1,3,4-thiadiazol-2-amine **Intermediate 21** (119 mg, 0.50 mmol) and Cs_2CO_3 (487 mg, 1.49 mmol) in DMF (5 mL) was stirred at rt for 1 h. The reaction mixture was poured into water (50 mL), extracted with EtOAc (3×50 mL), and the combined organic layer was dried over Na_2SO_4, filtered and evaporated. The crude product was purified by reversed phase flash chromatography on a C18 column (gradient: 0–100% MeOH in water containing 0.1% NH_4HCO_3) to afford the title compound (150 mg, 75%) as a white solid; MS *m/z* (ESI) $[M+H]^+$ 404.

Intermediate 27: 5-(4-Fluoro-3-methoxyphenyl)-*N*-methyl-1,3,4-oxadiazol-2-amine



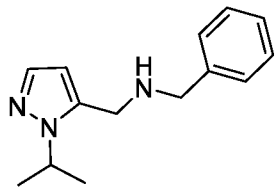
A mixture of 4-fluoro-3-methoxybenzoic acid (2 g, 12 mmol) and EDC (3.38 g, 17.63 mmol) in DMF (20 mL) under a N_2(g) atmosphere was stirred at rt for 5 min. *N*-Methylhydrazinecarbothioamide (15.5 mg, 0.15 mmol) was added and the resulting mixture was stirred at 80°C for 1 h. The reaction mixture was diluted with water (100 mL), and washed with EtOAc (3x150 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated. The solid was triturated with EtOAc (10 mL) to afford the title compound (0.9 g, 34%) as a white solid; MS *m/z* (ESI) $[M+H]^+$ 224.

Intermediate 28: *N*-((1-Cyclohexyl-*1H*-tetrazol-5-yl)methyl)-5-(4-fluoro-3-methoxyphenyl)-*N*-methyl-1,3,4-oxadiazol-2-amine



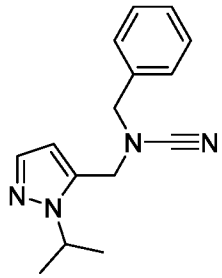
A mixture of 5-(chloromethyl)-1-cyclohexyl-*1H*-tetrazole (100 mg, 0.50 mmol), 5-(4-fluoro-3-methoxyphenyl)-*N*-methyl-1,3,4-oxadiazol-2-amine **Intermediate 27** (111 mg, 0.50 mmol) and Cs_2CO_3 (487 mg, 1.49 mmol) in DMF (5 mL) was stirred at 60°C for 1 h. The crude product was purified by reversed phase flash chromatography on a C18 column (gradient: 0–100% MeOH in water) to afford the title compound (160 mg, 83%) as a white solid; MS *m/z* (ESI) $[M+H]^+$ 388.

Intermediate 29 *N*-Benzyl-1-(1-isopropyl-*1H*-pyrazol-5-yl)methanamine



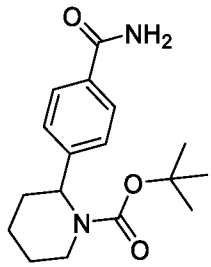
AcOH (82 µl, 1.44 mmol) followed by sodium triacetoxyborohydride (609 mg, 2.87 mmol) was added to a solution of (1-isopropyl-*1H*-pyrazol-5-yl)methanamine (200 mg, 1.44 mmol) and benzaldehyde (161 µL, 1.58 mmol) in DCM (14.12 mL) and the reaction mixture was stirred at rt for 3 h. The reaction was quenched with $NaHCO_3$ (20 mL) and extracted with DCM (3x30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by straight phase flash chromatography on silica (gradient: 0–5% MeOH in EtOAc) to afford the title compound (0.223 g, 68%) as a colourless oil; MS *m/z* (ESI) $[M+H]^+$ 230.2.

Intermediate 30: *N*-Benzyl-*N*-((1-isopropyl-*1H*-pyrazol-5-yl)methyl)cyanamide



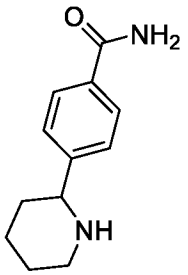
A solution of *N*-benzyl-1-(1-isopropyl-*1H*-pyrazol-5-yl)methanamine HCl **Intermediate 29** (129 mg, 0.49 mmol) in MeCN (2 mL) and water (0.25 mL) was added to a solution of $Zn(CN)_2$ (103 mg, 0.87 mmol) and NCS (97 mg, 0.73 mmol) in MeCN (2 mL) and water (0.25 mL). The reaction mixture was stirred at rt for 40 h. Water (30 mL) was added to the reaction mixture and the aqueous layer was extracted with DCM (3×30 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated to afford the title compound (0.121 g, 98%); MS *m/z* (ESI) $[M+H]^+$ 255.2.

Intermediate 31: *tert*-Butyl 2-(4-carbamoylphenyl)piperidine-1-carboxylate



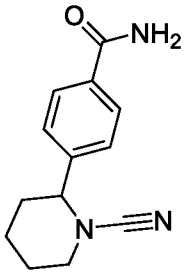
$(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ (0.045 g, 0.04 mmol) was added to 1-(*tert*-butoxycarbonyl)piperidine-2-carboxylic acid (2.78 g, 12.14 mmol), 4-iodobenzamide (1 g, 4.05 mmol), nickel chloride, dimethoxyethane adduct (0.089 g, 0.40 mmol), 4,4'-di-*tert*-butyl-2,2'-dipyridyl (0.163 g, 0.61 mmol) and Cs_2CO_3 (3.96 g, 12.14 mmol) in DMF (30 mL) at 20°C. The reaction mixture was purged with N_2(g) for 20 min. The resulting solution was stirred at 20°C for 16 h and irradiated at 365 nm in a Penn, Photoreactor m2. The reaction mixture was quenched with water (50 mL) and extracted with EtOAc (3×50 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified by reversed phase flash chromatography on a C18 column (gradient 0 –60% MeCN in water) to afford the title compound (0.570 g, 46%) as a white solid; MS *m/z* (ESI) $[M+H\text{-Boc}]^+$ 205.

Intermediate 32: 4-(Piperidin-2-yl)benzamide



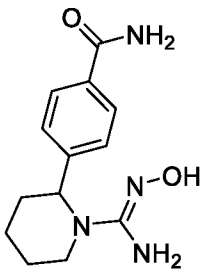
4 M HCl in 1,4-dioxane (2259 µl, 9.03 mmol) was added to *tert*-butyl 2-(4-carbamoylphenyl)piperidine-1-carboxylate **Intermediate 31** (550 mg, 1.81 mmol) in 1,4-dioxane (20 mL). The resulting mixture was stirred at 20°C for 16 h. The solvent was removed under reduced pressure. The residue was purified by reversed phase flash chromatography on a C18 column (gradient: 0–60% MeCN in water) to afford the title compound (0.350 g, 87%) as a white solid; MS *m/z* (ESI) $[M+H]^+$ 205.

Intermediate 33: 4-(1-Cyanopiperidin-2-yl)benzamide



The intermediate was synthesized and purified analogous to the procedure described for **Intermediate 30** starting from 4-(piperidin-2-yl)benzamide **Intermediate 32** (500 mg, 1.91 mmol) to afford the title compound (0.320 g, 84%) as a white solid; MS *m/z* (ESI) $[M+H]^+$ 230.

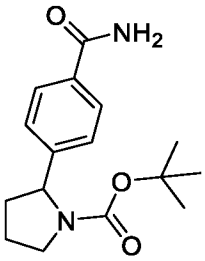
Intermediate 34: (*E*)-4-(1-(*N*'-hydroxycarbamimidoyl)piperidin-2-yl)benzamide



$NaHCO_3$ (454 mg, 5.41 mmol) was added to 4-(1-cyanopiperidin-2-yl)benzamide **Intermediate 33** (310 mg, 1.35 mmol) and hydroxylammonium chloride (188 mg, 2.70 mmol) in EtOH (20 mL). The resulting mixture was stirred at 25°C for 16 h. The reaction was quenched with water (50 mL), and the mixture was extracted with EtOAc (3×100 mL). The combined organic layer was dried over

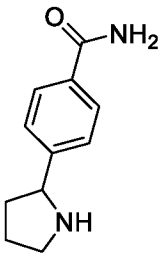
Na_2SO_4, filtered and evaporated. The crude product was purified by reversed phase flash chromatography on a C18 column (gradient: 0–60% MeCN in water), to afford the title compound (0.300 g, 85%) as a pale yellow solid; MS *m/z* (ESI) $[M+H]^+$ 263.

Intermediate 35 *tert*-Butyl 2-(4-carbamoylphenyl)pyrrolidine-1-carboxylate



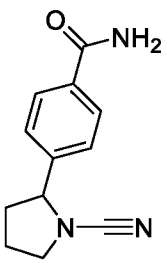
The title compound was synthesized and purified analogous to the procedure described for **Intermediate 31** starting from (*tert*-butoxycarbonyl)-*D*-proline (400 mg, 1.86 mmol) to afford the title compound (0.200 g, 56%) as a white solid; MS *m/z* (ESI) $[M-t\text{Bu}]^+$ 235.

Intermediate 36: 4-(Pyrrolidin-2-yl)benzamide



tert-Butyl (*S*)-2-(4-carbamoylphenyl)pyrrolidine-1-carboxylate **Intermediate 35** (200 mg, 0.69 mmol) was added to a mixture of TFA (2 mL) and DCM (2 mL) at 20°C. The resulting solution was stirred at 20°C for 3 h. The solvent was removed under reduced pressure to afford the TFA salt of the title compound (0.190 g, 91%) as a yellow oil. MS *m/z* (ESI) $[M+H]^+$ 191.

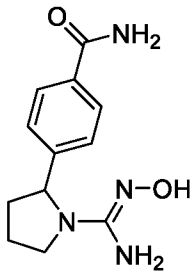
Intermediate 37: 4-(1-Cyanopyrrolidin-2-yl)benzamide



The title compound was synthesized analogous to the procedure described for **Intermediate 30** starting from 4-(pyrrolidin-2-yl)benzamide 2,2,2-trifluoroacetate **Intermediate 36** (190 mg, 0.54

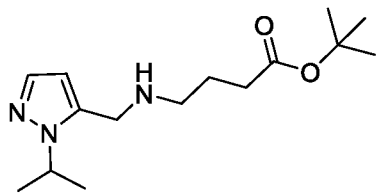
mmol). The reaction mixture was filtered through CELITE to afford the title compound (0.115 g, 99%) as a white solid; MS *m/z* (ESI) $[M+Na]^+$ 238.

Intermediate 38: (*E*)-4-(1-(*N*'-hydroxycarbamimidoyl)pyrrolidin-2-yl)benzamide



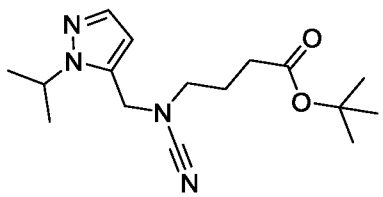
The title compound was synthesized analogous to the procedure described for **Example 20 step a** starting from 4-(1-cyanopyrrolidin-2-yl)benzamide **Intermediate 37** (115 mg, 0.53 mmol) to afford the title compound as a white solid; MS *m/z* (ESI) $[M+H]^+$ 249.

Intermediate 39: *tert*-Butyl 4-(((1-isopropyl-*1H*-pyrazol-5-yl)methyl)amino)butanoate



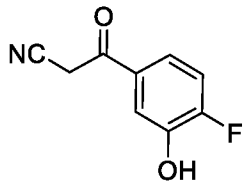
AcOH (133 µl, 2.32 mmol) followed by sodium triacetoxyborohydride (460 mg, 2.17 mmol) was added to a solution of 1-isopropyl-*1H*-pyrazole-5-carbaldehyde (200 mg, 1.45 mmol) and *tert*-butyl 4-aminobutanoate (346 mg, 2.17 mmol) in DCM (14 mL) and the reaction was stirred at rt for 16 h. Additional sodium triacetoxyborohydride (1.5 eq) was added and the reaction mixture was stirred for 1 h. The reaction was quenched with $NaHCO_3$ (20 mL) and extracted with DCM (3×30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by normal phase flash chromatography on silica (gradient: 0–60% EtOAc in heptane) to give the title compound (0.245 g, 60%) as a colorless oil; MS *m/z* (ESI) $[M+H]^+$ 282.3.

Intermediate 40: *tert*-Butyl 4-(*N*-((1-isopropyl-1*H*-pyrazol-5-yl)methyl)cyanamido)butanoate



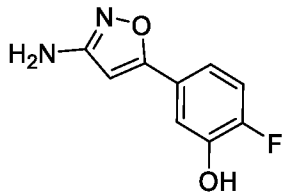
4 M HCl in dioxane (304 µl, 1.22 mmol) was added to *tert*-butyl 4-(((1-isopropyl-1*H*-pyrazol-5-yl)methyl)amino)butanoate **Intermediate 39** (190 mg, 0.68 mmol) in DCM (10 mL). The solution was stirred for 5 min and concentrated under vacuum. The residue was dissolved in MeCN (5.80 mL) and water (0.645 mL) followed by the addition of $Zn(CN)_2$ (143 mg, 1.22 mmol) and NCS (135 mg, 1.01 mmol). The reaction mixture was stirred at rt for 40 h. Water (30 mL) was added to the reaction mixture and the aqueous layer was extracted with DCM (3×30 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and concentrated to give the title compound (0.209 g); MS *m/z* (ESI) $[M+H]^+$ 307.

Intermediate 41: Ethyl 4-cyano-5-(4-fluoro-3-hydroxyphenyl)isoxazole-3-carboxylate



MeCN (0.62 mL, 1.18 mmol) was added to a stirred suspension of NaH (60% in oil, 0.094 g, 2.35 mmol) in THF (1 mL), and the resulting mixture was stirred at rt for 10 min. Methyl 4-fluoro-3-hydroxybenzoate (0.100 g, 0.59 mmol) was added, and the resulting mixture was heated to 50°C for 70 h. H_2O was added, the mixture was acidified with 3.8M HCl and extracted with EtOAc. The organic layer was concentrated, and the residue was purified by straight phase flash chromatography on silica (gradient: 0–100% EtOAc in heptane) to give the title compound as a white solid (0.075g, 71%); MS (ESI) *m/z* $[M-H]^-$ 311.

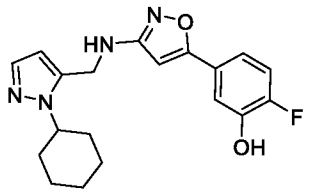
Intermediate 42: 5-(3-Aminoisoxazol-5-yl)-2-fluorophenol



NaOH (0.098 g, 2.5 mmol) was added to a mixture of ethyl 4-cyano-5-(4-fluoro-3-hydroxyphenyl)isoxazole-3-carboxylate **Intermediate 41** (0.400 g, 2.23 mmol) and hydroxylammonium chloride (0.186 g, 2.68 mmol) in H_2O (2 mL) and EtOH (2 mL) at 25°C, and the resulting mixture was stirred at 65°C for 16 h. The reaction mixture was acidified with HCl to pH 2, and the mixture was heated at 80°C for 4 h. The reaction mixture was concentrated, diluted with EtOAc, and washed with water. The organic layer was dried over Na_2SO_4, filtered and concentrated.

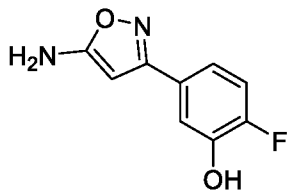
The residue was purified by preparative TLC (PE:EtOAc 1:2) to give the title compound as a yellow solid (0.200 g, 46%); MS (ESI) *m/z* $[M+H]^+$ 195.

Intermediate 43: 5-(3-(((1-Cyclohexyl-1*H*-pyrazol-5-yl)methyl)amino)isoxazol-5-yl)-2-fluorophenol



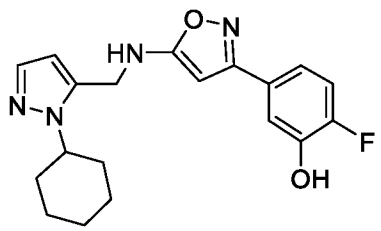
FA (0.5 mL, 13 mmol) was added to 5-(3-aminoisoxazol-5-yl)-2-fluorophenol **Intermediate 42** (0.180 g, 0.93 mmol) and 1-cyclohexyl-1*H*-pyrazole-5-carbaldehyde (0.165 g, 0.93 mmol) in MeOH (2 mL) at 60°C under a N_2(g) atmosphere, and the resulting mixture was stirred for 4 h. $NaBH_4$ (0.035 g, 0.93 mmol) was added, and the reaction mixture was stirred at 25°C for 1 h. The reaction mixture was concentrated, diluted with EtOAc (20 mL), and washed with H_2O (30 mL) . The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative TLC (PE/EtOAc 1:1) to give the title compound as a white solid (0.080 g, 24%); MS (ESI) *m/z* $[M+H]^+$ 357.

Intermediate 44 5-(5-Aminoisoxazol-3-yl)-2-fluorophenol



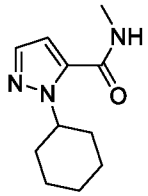
NaOH (1.00 g, 25.1 mmol) was added to a mixture of ethyl 4-cyano-5-(4-fluoro-3-hydroxyphenyl)isoxazole-3-carboxylate **Intermediate 41** (1.5 g, 8.4 mmol) and hydroxylammonium chloride (1.16 g, 16.8 mmol) in EtOH (20 mL), and the resulting mixture was stirred at 80°C for 4 h. The reaction mixture was acidified with 2M HCl, poured into H_2O (50 mL) and extracted with EtOAc (2×25 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative TLC (PE/EtOAc 1:2) to give the title compound as an orange solid (0.832 g, 51%); MS (ESI) *m/z* $[M+H]^+$ 195.

Intermediate 45: 5-(5-(((1-Cyclohexyl-1*H*-pyrazol-5-yl)methyl)amino)isoxazol-3-yl)-2-fluorophenol



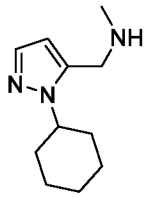
5-(5-Aminoisoxazol-3-yl)-2-fluorophenol **Intermediate 44** (0.218 g, 1.12 mmol) was added to 1-cyclohexyl-1*H*-pyrazole-5-carbaldehyde (0.200 g, 1.12 mmol) in THF (8 mL) and FA (2 mL). The resulting mixture was stirred at 25°C for 1 h. $NaBH_4$ (42 mg, 1.12 mmol) was added and the resulting mixture was stirred at 25°C for 2 h. The solvent was removed under reduced pressure, and the residue was purified by reversed phase flash chromatography on a C18 column (gradient: 0–60% MeCN in H_2O/FA (0.1%)) to give the title compound as a white solid (0.150 g, 38%); MS (ESI) *m/z* $[M+H]^+$ 357.

Intermediate 46: 1-Cyclohexyl-*N*-methyl-1*H*-pyrazole-5-carboxamide



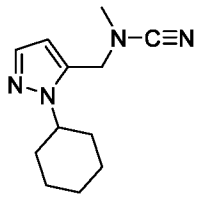
Ethyl 1-cyclohexyl-1*H*-pyrazole-5-carboxylate *J.Enzyme Inhib Med Chem (2018), 33(1), 144-1452* (900 mg , 4.05 mmol) was added to methylamine (40 wt% in H_2O, 10 mL, 4.05 mmol) and the reaction mixture was stirred at 60°C for 16 h. The mixture was concentrated at reduced pressure to give the title compound (750 mg, 89%) as a white solid; MS (ESI) *m/z* $[M+H]^+$ 208.

Intermediate 47: 1-(1-Cyclohexyl-1*H*-pyrazol-5-yl)-*N*-methylmethanamine



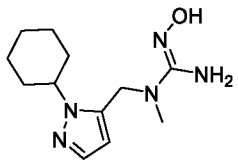
$LiAlH_4$ (2.5 M in THF, 4.05 mL, 10.13 mmol) was added dropwise to 1-cyclohexyl-*N*-methyl-1*H*-pyrazole-5-carboxamide **Intermediate 46** (700 mg, 3.38 mmol) and anhydrous $AlCl_3$ (450 mg, 3.38 mmol) in THF (20 mL) at 0°C, and the reaction mixture was stirred at 60°C for 3 h. The reaction was quenched with MeOH (20 mL).The reaction mixture was filtered, and the solvent was removed under reduced pressure. The crude product was purified by reversed phase flash chromatography on a C18 column, (gradient: 0–100% MeOH in H_2O (0.1%NH_4HCO_3)) to give the title compound (500 mg, 77%) as a yellow oil; MS (ESI) *m/z* $[M+H]^+$ 194.

Intermediate 48: *N*-((1-Cyclohexyl-1*H*-pyrazol-5-yl)methyl)-*N*-methylcyanamide



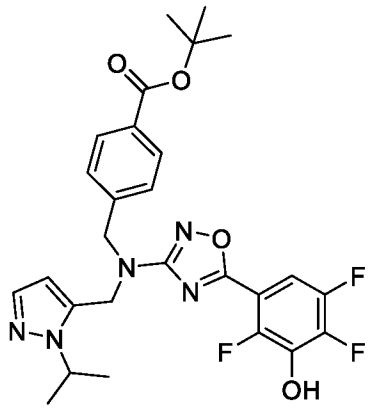
$Zn(CN)_2$ (456 mg, 3.88 mmol) was added to a mixture of 1-(1-cyclohexyl-1*H*-pyrazol-5-yl)-*N*-methylmethanamine **Intermediate 47** (500 mg, 2.59 mmol) and NCS (449 mg, 3.36 mmol) in MeCN/H_2O (9:1, 10 mL), and the reaction mixture was stirred at 25°C for 16 h. The reaction mixture was filtered through silica, and the filtrate was concentrated at reduced pressure. The crude product was purified by straight phase flash chromatography on silica (gradient: 0–100% EtOAc in PE) to give the title compound (300 mg, 53%) as a white solid; MS (ESI) *m/z* $[M+H]^+$ 219.

Intermediate 49: (*E*)-1-((1-Cyclohexyl-1*H*-pyrazol-5-yl)methyl)-2-hydroxy-1-methylguanidine



TEA (383 µl, 2.75 mmol) was added to a solution of *N*-((1-cyclohexyl-1*H*-pyrazol-5-yl)methyl)-*N*-methylcyanamide **Intermediate 48** (300 mg, 1.37 mmol) and hydroxylammonium chloride (143 mg, 2.06 mmol) in MeOH (5 mL), and the reaction mixture was stirred at 60°C for 16 h. The reaction mixture was concentrated at reduced pressure to give the title compound (300 mg, 87%) as a yellow solid; MS (ESI) *m/z* $[M+H]^+$ 252.

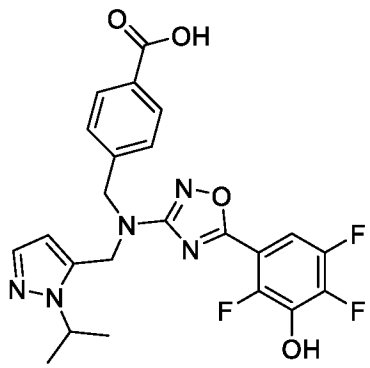
Example 1: *tert*-Butyl 4-((((1-isopropyl-1*H*-pyrazol-5-yl)methyl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)amino)methyl)benzoate



In a vial 2,4,5-trifluoro-3-hydroxybenzoic acid (0.307 g, 1.60 mmol), $NaHCO_3$ (0.336 g, 4.00 mmol), HOBt (0.306 g, 1.60 mmol) and EDC (0.368 g, 1.92 mmol) were dissolved in DMF (5.33 mL) and

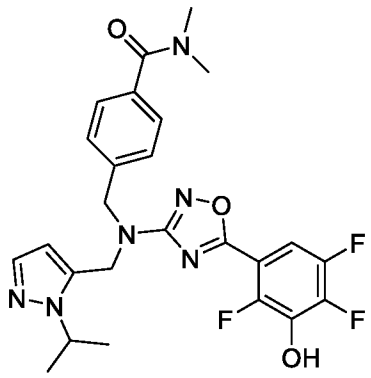
stirred for 5 min. Then a solution of *tert*-butyl (*E*) 4-((2-hydroxy-1-((1-isopropyl-1*H*-pyrazol-5-yl)methyl)guanidino)methyl)benzoate **Intermediate 3** (0.620 g, 1.60 mmol) in DMF (5.33 mL) was added to the activated acid solution. The reaction mixture was stirred for 30 min at rt, then at 70°C for 20 h. The reaction mixture was diluted with EtOAc and quenched with NH_4Cl (aq). The phases were separated. The water phase was extracted with EtOAc (×3). The combined organic layers were washed with 1 M $NaHCO_3$, 1 M $KHSO_4$ and brine, dried using a phase separator and concentrated under reduced pressure. The crude product was dissolved in DMSO and purified by preparative HPLC, PrepMethod B (gradient 40-85%) to give the title compound (0.335 g, 39%) as a yellow oil; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{27}H_{29}F_3N_5O_4$: 544.2166, found: 544.2184; ^1H NMR (500 MHz, $CDCl_3$) δ 1.42 (6H, d), 1.59 (9H, s), 4.46–4.59 (1H, m), 4.63 (4H, d), 6.12 (1H, d), 7.27–7.31 (2H, m), 7.39–7.49 (1H, m), 7.52 (1H, d), 7.92–8 (2H, m).

Example 2: 4-((((1-Isopropyl-1*H*-pyrazol-5-yl)methyl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)amino)methyl)benzoic acid



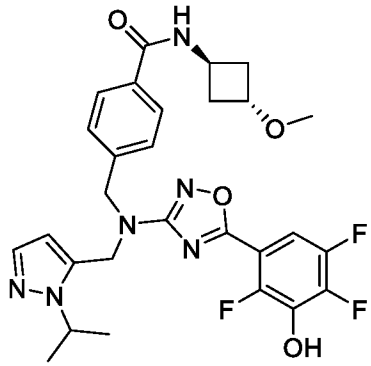
To a solution of *tert*-butyl 4-((((1-isopropyl-1*H*-pyrazol-5-yl)methyl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)amino)methyl)benzoate **Example 1** (155 mg, 0.29 mmol) in DCM (1.426 mL) was added TFA (1.426 mL) and the reaction was stirred at rt for 1 h. Volatiles were removed in vacuo and the crude was further azeotroped with MeCN (×4). The residue was dissolved in EtOAc and washed with water (×3). The organic phase was dried using a phase separator and evaporated. The crude material was redissolved in MeCN/water and freeze dried to give the title compound (134 mg, 78%) as a yellow solid. ^{19}F NMR indicated product to TFA 1:1. Part of the solid compound (35 mg) was purified by preparative HPLC, PrepMethod C (gradient 5-95%), to give 16.5 mg of the title compound; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{21}F_3N_5O_4$: 488.1540, found: 488.1558; ^1H NMR (600 MHz, DMSO-d_6) δ 7.83 – 7.98 (m, 2H), 7.44 – 7.59 (m, 1H), 7.31 – 7.44 (m, 3H), 6.13 – 6.23 (m, 1H), 4.69 – 4.8 (m, 2H), 4.54 – 4.69 (m, 3H), 1.25 – 1.37 (m, 6H).

Example 3: 4-((((1-Isopropyl-1*H*-pyrazol-5-yl)methyl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)amino)methyl)-*N*,*N*-dimethylbenzamide



4-((((1-Isopropyl-1*H*-pyrazol-5-yl)methyl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)amino)methyl)benzoic acid 2TFA **Example 2** (38 mg, 0.05 mmol), HATU (40 mg, 0.11 mmol) and DMF (0.3 mL) were mixed in a vial. DIPEA (56 µl, 0.32 mmol) was added followed by dimethylamine HCl (11 mg, 0.13 mmol). The resulting yellow solution was stirred at rt for 2 h. The reaction solution was diluted with DMSO, filtered and purified by preparative HPLC, PrepMethod D (gradient 5-95%) to give the title compound (24 mg, 87%); HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{25}H_{26}F_3N_6O_3$: 515.2012, found: 515.1988; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.30 (6H, d), 2.93 (6H, d), 4.52–4.66 (3H, m), 4.72 (2H, s), 6.16 (1H, d), 7.29–7.34 (2H, m), 7.34–7.37 (2H, m), 7.39 (1H, d), 7.48–7.59 (1H, m), 11.57 (1H, s).

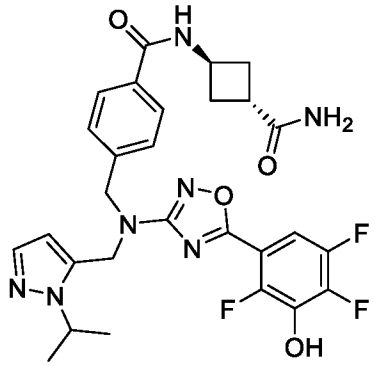
Example 4: 4-((((1-Isopropyl-1*H*-pyrazol-5-yl)methyl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)amino)methyl)-*N*-((1*r*,3*r*)-3-methoxycyclobutyl)benzamide



4-((((1-Isopropyl-1*H*-pyrazol-5-yl)methyl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)amino)methyl)benzoic acid 2TFA **Example 2** (36 mg, 0.05 mmol), HATU (38 mg, 0.10 mmol) and DMF (0.3 mL) were mixed in a vial. DIPEA (53 µl, 0.30 mmol) was added followed by (1*r*,3*r*)-3-methoxycyclobutan-1-amine HCl (17 mg, 0.12 mmol) and the resulting yellow solution was stirred at rt for 2 h. The reaction solution was diluted with DMSO, filtered and purified by preparative HPLC, PrepMethod D (gradient 5-95%) to give the title compound (20 mg, 68%); HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{30}F_3N_6O_4$: 571.2274, found: 571.2290; ^{1}H NMR (600 MHz, DMSO-d_6,) δ 1.27 (6H, d),

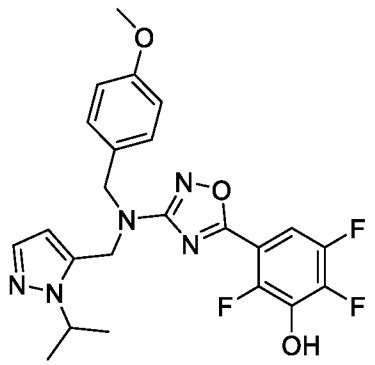
2.13–2.28 (4H, m), 3.11 (3H, s), 3.9–4 (1H, m), 4.3–4.46 (1H, m), 4.5–4.64 (3H, m), 4.68 (2H, s), 6.13 (1H, d), 7.23–7.33 (2H, m), 7.35 (1H, d), 7.42–7.59 (1H, m), 7.65–7.86 (2H, m), 8.55 (1H, d).

Example 5: *N*-((1*r*,3*r*)-3-Carbamoylcyclobutyl)-4-((((1-isopropyl-1*H*-pyrazol-5-yl)methyl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)amino)methyl)benzamide



4-((((1-Isopropyl-1*H*-pyrazol-5-yl)methyl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)amino)methyl)benzoic acid 2TFA **Example 2** (35 mg, 0.05 mmol), HATU (37 mg, 0.10 mmol) and DMF (0.3 mL) were mixed in a vial. DIPEA (51 µl, 0.29 mmol) was added followed by (1*r*,3*r*)-3-aminocyclobutane-1-carboxamide HCl (17 mg, 0.11 mmol) and the resulting yellow solution was stirred at rt for 2 h. The reaction solution was diluted with DMSO, filtered and purified by preparative HPLC, PrepMethod D (gradient 5-95%) to give the title compound (16 mg, 57%); HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{28}H_{29}F_3N_7O_4$: 584.2228, found: 584.2214; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.30 (6H, d), 2.16–2.3 (2H, m), 2.33–2.41 (2H, m), 2.82–2.93 (1H, m), 4.47–4.56 (1H, m), 4.56–4.65 (3H, m), 4.72 (2H, s), 6.17 (1H, d), 6.76 (1H, s), 7.22 (1H, s), 7.29–7.37 (2H, m), 7.39 (1H, d), 7.47–7.57 (1H, m), 7.78–7.81 (2H, m), 8.57 (1H, d).

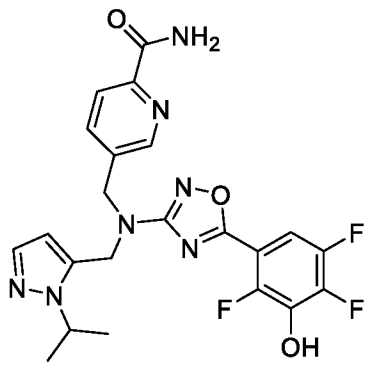
Example 6: 2,3,6-Trifluoro-5-(3-(((1-isopropyl-1*H*-pyrazol-5-yl)methyl)(4-methoxybenzyl)amino)-1,2,4-oxadiazol-5-yl)phenol



In a vial, 2,4,5-trifluoro-3-hydroxybenzoic acid (61 mg, 0.32 mmol), $NaHCO_3$ (67 mg, 0.80 mmol), HOBt (61 mg, 0.32 mmol) and EDC (74 mg, 0.38 mmol) were dissolved in DMF (1.5 mL) and stirred

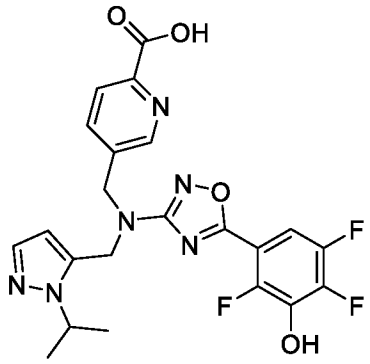
for 5 min. A solution of (*E*)-2-hydroxy-1-((1-isopropyl-1*H*-pyrazol-5-yl)methyl)-1-(4-methoxybenzyl)guanidine **Intermediate 18** (0.102 g, 0.32 mmol) in DMF (1.5 mL) was added to the activated acid solution. The reaction mixture was stirred for 30 min at rt, then at 70°C for 20 h. The reaction mixture was diluted with EtOAc and the reaction was quenched with NH_4Cl. The organic layer was washed with 1 M $NaHCO_3$ and the phases were separated. The combined organic layers were washed with 1 M $KHSO_4$ and brine, dried using a phase separator and concentrated under reduced pressure. The crude product was dissolved in DMSO (2 mL) and purified by preparative HPLC, PrepMethod C (gradient 5-95%) to give the title compound (45 mg, 30%); HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{23}H_{23}F_3N_5O_3$: 474.1748, found: 474.1750; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.30 (6H, d), 3.72 (3H, s), 4.48 (2H, s), 4.51–4.6 (1H, m), 4.62 (2H, s), 6.15 (1H, d), 6.83–6.93 (2H, m), 7.15–7.25 (2H, m), 7.39 (1H, d), 7.45–7.56 (1H, m).

Example 7: 5-((((1-Isopropyl-1*H*-pyrazol-5-yl)methyl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)amino)methyl)picolinamide



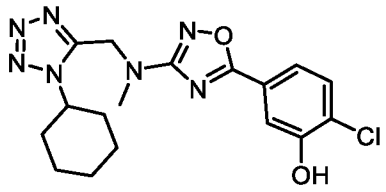
HATU (42.0 mg, 0.11 mmol) was added to a stirred solution of 5-((((1-isopropyl-1*H*-pyrazol-5-yl)methyl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)amino)methyl)picolinic acid **Example 8** (27 mg, 0.06 mmol) and DIPEA (58 µl, 0.33 mmol) in DMF (0.6 mL) at rt and the resulting solution was stirred for ~1 min. NH_4Cl (17.74 mg, 0.33 mmol) was added and the stirring was continued at rt over night. The reaction solution was diluted with DMSO and filtered. The filter cake was washed with DMSO and the combined filtrates were purified by preparative HPLC, PrepMethod A (gradient 15-55%) to give the title compound (22 mg, 82%) as a white solid; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{21}F_3N_7O_3$: 488.1652, found: 488.1656; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.30 (6H, d), 4.55–4.65 (1H, m), 4.68 (2H, s), 4.79 (2H, s), 6.21 (1H, d), 7.40 (1H, d), 7.45–7.57 (1H, m), 7.57–7.71 (1H, m), 7.83 (1H, dd), 7.97 (1H, dd), 8.02–8.18 (1H, m), 8.49 (1H, dd), 11.59 (1H, s).

Example 8 : 5-((((1-Isopropyl-1*H*-pyrazol-5-yl)methyl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)amino)methyl)picolinic acid



LiOH (9.5 mg, 0.40 mmol) dissolved in water (0.5 mL) was added to methyl 5-((((1-isopropyl-1*H*-pyrazol-5-yl)methyl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)amino)methyl)picolinate **Intermediate 7** (50 mg, 0.10 mmol) in THF (0.55 mL) at rt. The reaction mixture was stirred at 50°C for 1.5 h. The reaction mixture was cooled to rt, diluted with EtOAc and acidified with 1 M HCl. The organic phase was separated. The water phase was extracted with EtOAc. The combined organic layers were washed with brine, passed through a phase separator and concentrated to give the crude title compound (47 mg, 97%) as a transparent glas. Part of the crude (approximately15 mg) was purified by preparative HPLC, PrepMethod A (gradient 15-55%) to give the title compound (10 mg) as a white solid; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{20}F_3N_6O_4$: 489.1492, found: 489.1490; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.30 (6H, d), 4.57–4.65 (1H, m), 4.68 (2H, s), 4.79 (2H, s), 6.21 (1H, d), 7.33–7.48 (2H, m), 7.82 (1H, dd), 7.98 (1H, d), 8.56 (1H, d).

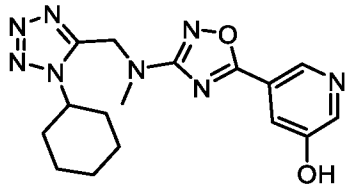
Example 9: 2-Chloro-5-(3-(((1-cyclohexyl-*1H*-tetrazol-5-yl)methyl)(methyl)amino)-1,2,4-oxadiazol-5-yl)phenol



(*E*)-1-((1-Cyclohexyl-1*H*-tetrazol-5-yl)methyl)-2-hydroxy-1-methylguanidine **Intermediate 11** (100 mg, 0.39 mmol) was added to 4-chloro-3-hydroxybenzoic acid (82 mg, 0.47 mmol), EDC (91 mg, 0.47 mmol), HOBt (66 mg, 0.43 mmol) and $NaHCO_3$ (83 mg, 0.99 mmol) in DMF (5 mL) at 25°C under a N_2(g) atmosphere. The resulting mixture was stirred at 80°C for 16 h. The reaction mixture was diluted with EtOAc (20 mL) and washed sequentially with water (20 mL) and sat brine (2×20 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified by reversed phase flash chromatography on a C18 column (gradient: 0–75% MeOH in water (0.1% FA)) to afford the title compound (40 mg, 26%) as a white solid; HRMS (ESI) *m/z* $[M+H]^+$ calcd for C17 H21 Cl N7 O2: 390.1440, found: 390.1426; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.18–1.43 (3H, m), 1.65 (1H, d),

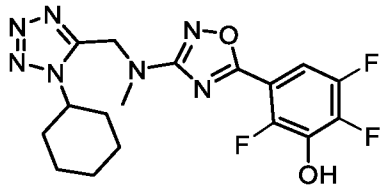
1.74–1.89 (4H, m), 1.98 (2H, d), 3.06 (3H, s), 4.52–4.64 (1H, m), 5.02 (2H, s), 7.45 (1H, dd), 7.54–7.63 (2H, m), 10.92 (1H, s).

Example 10: 5-(3-(((1-Cyclohexyl-*1H*-tetrazol-5-yl)methyl)(methyl)amino)-1,2,4-oxadiazol-5-yl)pyridin-3-ol



(*E*)-1-((1-Cyclohexyl-1*H*-tetrazol-5-yl)methyl)-2-hydroxy-1-methylguanidine **Intermediate 11** (100 mg, 0.39 mmol), 5-hydroxynicotinic acid (66 mg, 0.47 mmol), EDC (83 mg, 0.43 mmol), $NaHCO_3$ (83 mg, 0.99 mmol) and HOBt (63 mg, 0.41 mmol) were suspended in DMF (5 mL) under a N_2(g) atmosphere. The resulting mixture was stirred at 60°C for 16 h. The reaction mixture was diluted with EtOAc (100 mL) and washed sequentially with water (2×50 mL) and sat brine (2×50 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified by preparative HPLC, PrepMethod E, (gradient: 30–50%) to afford the title compound (0.021 g, 15%) as a white solid; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{21}N_8O_2$: 357.1782, found: 357.1778; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.13–1.46 (3H, m), 1.6–1.7 (1H, m), 1.71–1.9 (4H, m), 1.93–2.07 (2H, m), 3.09 (3H, s), 4.53–4.65 (1H, m), 5.03 (2H, s), 7.67 (1H, dd), 8.38 (1H, d), 8.65 (1H, d), 10.62 (1H, s).

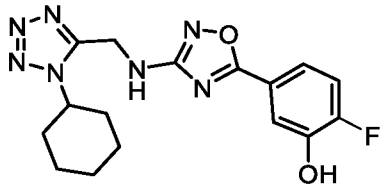
Example 11: 3-(3-(((1-Cyclohexyl-*1H*-tetrazol-5-yl)methyl)(methyl)amino)-1,2,4-oxadiazol-5-yl)-2,5,6-trifluorophenol



(*E*)-1-((1-Cyclohexyl-1*H*-tetrazol-5-yl)methyl)-2-hydroxy-1-methylguanidine **Intermediate 11** (100 mg, 0.39 mmol), 2,4,5-trifluoro-3-hydroxybenzoic acid (91 mg, 0.47 mmol), EDC (83 mg, 0.43 mmol), $NaHCO_3$ (83 mg, 0.99 mmol) and HOBt (63.5 mg, 0.41 mmol) were suspended in DMF (5 mL) under a N_2(g) atmosphere. The resulting mixture was stirred at 60°C for 16 h. The reaction mixture was diluted with EtOAc (100 mL) and washed sequentially with water (2×50 mL) and sat brine (2×50 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified by preparative HPLC, PrepMethod E**,** (gradient: 40–58%) to afford the title compound (0.076 g, 47%) as a white solid; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{19}F_3N_7O_2$: 410.1546, found: 410.1566; ^{1}H NMR

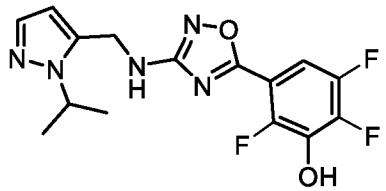
(300 MHz, DMSO-d_6) δ 1.16–1.44 (3H, m), 1.59–1.7 (1H, m), 1.73–1.87 (4H, m), 1.94–2.03 (2H, m), 3.08 (3H, s), 4.52–4.65 (1H, m), 5.02 (2H, s), 7.43–7.53 (1H, m).

Example 12: 5-(3-(((1-Cyclohexyl-*1H*-tetrazol-5-yl)methyl)amino)-1,2,4-oxadiazol-5-yl)-2-fluorophenol



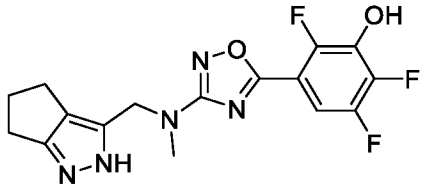
TFA (5 mL) was added to 5-(3-(((1-cyclohexyl-1*H*-tetrazol-5-yl)methyl)(4-methoxybenzyl)amino)-1,2,4-oxadiazol-5-yl)-2-fluorophenol **Intermediate 15** (400 mg, 0.83 mmol), and the resulting mixture was stirred at rt for 4 h. The mixture was concentrated and the residue was purified by preparative HPLC, PrepMethod F, (isocratic: 45%) to afford the title compound (0.023 g, 8%) as a white solid; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{19}FN_7O_2$: 360.1578, found: 360.1558; ^{1}H NMR (400 MHz, DMSO-*d6*) δ 1.17–1.33 (1H, m), 1.33–1.49 (2H, m), 1.61–1.71 (1H, m), 1.74–1.90 (4H, m), 1.96–2.07 (2H, m), 4.51–4.64 (1H, m), 4.72 (2H, d), 7.31–7.40 (1H, m), 7.40–7.47 (1H, m), 7.56 (1H, dd), 7.86 (1H, t), 10.59 (1H, s).

Example 13: 2,3,6-Trifluoro-5-(3-(((1-isopropyl-*1H*-pyrazol-5-yl)methyl)amino)-1,2,4-oxadiazol-5-yl)phenol



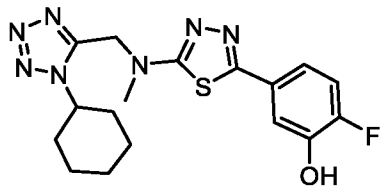
A solution of 2,3,6-trifluoro-5-(3-(((1-isopropyl-1H-pyrazol-5-yl)methyl)(4-methoxybenzyl)amino)-1,2,4-oxadiazol-5-yl)phenol **Example 6** (200 mg, 0.42 mmol) in TFA (1 mL) was stirred at 70°C for 2 h. The solvent was removed under reduced pressure and the residue was purified by preparative HPLC, PrepMethod G, (gradient: 34–45%) to afford the title compound (0.054 g, 33%) as a white solid; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{15}H_{15}F_3N_5O_2$: 354.1172, found: 354.1162; ^{1}H NMR (300 MHz, DMSO-*d6*) δ 1.37 (6H, d), 4.40 (2H, d), 4.55–4.69 (1H, m), 6.17 (1H, d), 7.34 (1H, d), 7.45 (1H, ddd), 7.67 (1H, t), 11.54 (1H, s).

Example 14: 2,3,6-Trifluoro-5-(3-(methyl((2,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl)methyl)amino)-1,2,4-oxadiazol-5-yl)phenol



To a solution of *N*-methyl-1-(2,4,5,6-tetrahydrocyclopenta[*c*]pyrazol-3-yl)methanamine dihydrochloride (19 mg, 0.09 mmol) in *t*-BuOH (0.7 mL) was added a solution of 3-(3-bromo-1,2,4-oxadiazol-5-yl)-2,5,6-trifluorophenol **Intermediate 19** (45 mg, 0.09 mmol, 57% purity) in *t*-BuOH (1.1 mL) followed by Cs_2CO_3 (169 mg, 0.52 mmol). The reaction mixture was heated in a sealed tube at 115°C for 16 h. The reaction was cooled to rt and diluted with DCM (5 mL) and sat NH_4Cl (aq, 5 mL). The organic layer was separated and the aqueous layer was further extracted with DCM (4×5 mL). The combined organic layers were filtered through a phase separator and concentrated under reduce pressure. The residue was purified by preparative HPLC, PrepMethod C, (gradient: 5–95%) to afford the title compound (1 mg, 3%) as a white solid; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{15}F_3N_5O_2$: 366.1172, found: 366.1166; ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.21 – 2.33 (6H, m), 2.87 (3H, s), 4.46 (2H, s), 7.08 (1H, s).

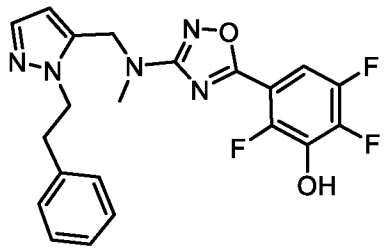
Example 15: 5-(5-(((1-Cyclohexyl-*1H*-tetrazol-5-yl)methyl)(methyl)amino)-1,3,4-thiadiazol-2-yl)-2-fluorophenol



BBr_3 (1 M in DCM) (0.991 mL, 0.99 mmol) was added dropwise to *N*-((1-cyclohexyl-*1H*-tetrazol-5-yl) methyl)-5-(4-fluoro-3-methoxyphenyl)-*N*-methyl-1,3,4-thiadiazol-2-amine **Intermediate 22** (80 mg, 0.20 mmol) in DCM (5 mL) at 0°C. The resulting mixture was stirred at rt for 1 h. The reaction was quenched with water (50 mL), and the mixture was neutralised with sat $NaHCO_3$ and extracted with DCM (3×50 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated. The crude product was purified by preparative HPLC, PrepMethod H (gradient: 30–45%) to afford the title compound (28 mg, 36%) as a white solid; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{21}FN_7OS$: 390.1506, found: 390.1510

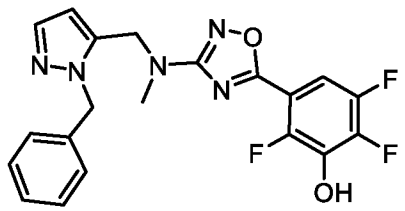
^{1}H NMR (400 MHz, DMSO-d_6) δ 1.2–1.46 (3H, m), 1.64–1.72 (1H, m), 1.74–1.87 (4H, m), 1.97–2.04 (2H, m), 3.23 (3H, s), 4.57–4.68 (1H, m), 5.18 (2H, s), 7.12–7.19 (1H, m), 7.21–7.28 (1H, m), 7.38–7.46 (1H, m), 10.31 (1H, s).

Example 17: 2,3,6-Trifluoro-5-(3-(methyl((1-phenethyl-*1H*-pyrazol-5-yl)methyl)amino)-1,2,4-oxadiazol-5-yl)phenol



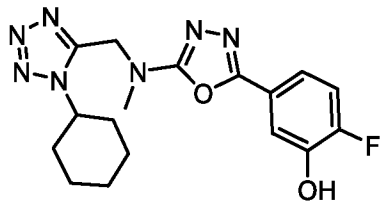
A solution of 3-(3-bromo-1,2,4-oxadiazol-5-yl)-2,5,6-trifluorophenol **Intermediate 19** (47 mg, 0.09 mmol, purity 57%) in *t*-BuOH (1 mL) was added to a solution of *N*-methyl-1-(1-phenethyl-*1H*-pyrazol-5-yl)methanamine (29 mg, 0.14 mmol) in *t*-BuOH (0.7 mL) followed by Cs_2CO_3 (179 mg, 0.55 mmol). The reaction mixture was heated in a sealed tube at 115°C for 16 h. The reaction was cooled to rt and diluted with DCM (5 mL) and sat NH_4Cl (aq, 5 mL). The organic layer was separated and the aqueous layer (pH 7) was further extracted with DCM (4×5 mL). The combined organic layers were passed through a phase separator and concentrated under reduced pressure. The residue was dissolved in DMSO (2 mL) and purified by preparative HPLC, PrepMethod C, (gradient: 5–95%), to afford the title compound (2.7 mg, 7%); HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{21}H_{19}F_3N_5O_2$: 430.1486, found: 430.1496; ^{1}H NMR (600 MHz, DMSO) δ 2.78 (3H, s), 2.99 (2H, t), 4.32 (2H, t), 4.44 (2H, s), 6.17 (1H, d), 7.02 (2H, d), 7.12–7.2 (3H, m), 7.28–7.35 (1H, m), 7.43 (1H, d).

Example 18: 3-(3-(((1-Benzyl-*1H*-pyrazol-5-yl)methyl)(methyl)amino)-1,2,4-oxadiazol-5-yl)-2,5,6-trifluorophenol



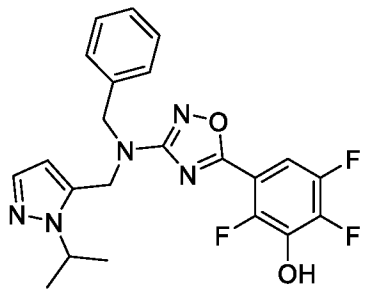
The title compound was synthesized and purified analogous to the procedure described in **Example 17** starting from 1-(1-benzyl-*1H*-pyrazol-5-yl)-*N*-methylmethanamine, 2HCl (45 mg, 0.16 mmol) and 3-(3-bromo-1,2,4-oxadiazol-5-yl)-2,5,6-trifluorophenol **Intermediate 19** (57 mg, 0.11 mmol) to afford the title compound (2 mg, 4%); HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{17}F_3N_5O_2$: 416.1328, found: 416.1330; ^{1}H NMR (600 MHz, DMSO) δ 2.82 (3H, s), 4.65 (2H, s), 5.41 (2H, s), 6.30 (1H, d), 6.98–7.02 (2H, m), 7.2–7.24 (1H, m), 7.24–7.28 (2H, m), 7.28–7.33 (1H, m), 7.46 (1H, d).

Example 19: 5-(5-(((1-Cyclohexyl-*1H*-tetrazol-5-yl)methyl)(methyl)amino)-1,3,4-oxadiazol-2-yl)-2-fluorophenol

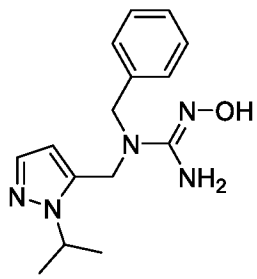


BBr_3 in DCM (1 M, 1.678 mL, 1.68 mmol) was added dropwise to *N*-((1-cyclohexyl-1*H*-tetrazol-5-yl)methyl)-5-(4-fluoro-3-methoxyphenyl)-*N*-methyl-1,3,4-oxadiazol-2-amine **Intermediate 28** (130 mg, 0.34 mmol) in DCM (5 mL) at 0°C. The resulting mixture was stirred at rt for 1 h. The reaction was quenched with water (50 mL), neutralised with sat $NaHCO_3$ and extracted with DCM (3×50 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated to afford a yellow solid. The crude product was purified by preparative HPLC, PrepMethod J (gradient:23–32%), to afford the title compound (30 mg, 24%) as a white solid; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{21}FN_7O_2$: 374.1736, found: 374.1732; ^1H NMR (400 MHz, DMSO-d_6) δ 1.19–1.44 (3H, m), 1.62–1.7 (1H, m), 1.75–1.87 (4H, m), 1.95–2.03 (2H, m), 3.16 (3H, s), 4.52–4.63 (1H, m), 5.09 (2H, s), 7.29–7.34 (2H, m), 7.44–7.49 (1H, m), 10.41 (1H, s).

Example 20: 3-(3-(Benzyl((1-isopropyl-*1H*-pyrazol-5-yl)methyl)amino)-1,2,4-oxadiazol-5-yl)-2,5,6-trifluorophenol



Step a) (*E*)-1-Benzyl-2-hydroxy-1-((1-isopropyl-*1H*-pyrazol-5-yl)methyl)guanidine



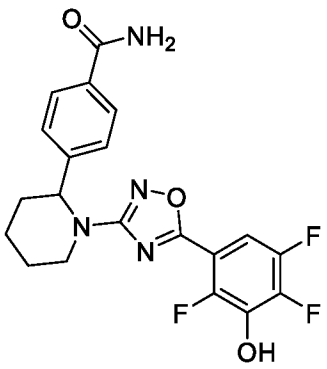
$NaHCO_3$ (159 mg, 1.89 mmol) followed by hydroxylamine HCl (98 mg, 1.42 mmol) were added to a solution of *N*-benzyl-*N*-((1-isopropyl-*1H*-pyrazol-5-yl)methyl)cyanamide **Intermediate 30** (120 mg, 0.47 mmol) in EtOH (4.7 mL) at rt and the resulting mixture was stirred at rt for 1.75 h. The reaction

mixture was filtered and the filtrate was concentrated under reduced pressure to afford the title compound, half of which (0.235 mmol) was used in step b; MS *m/z* (ESI) $[M+H]^+$ 288.3.

Step b) 3-(3-(Benzyl((1-isopropyl-*1H*-pyrazol-5-yl)methyl)amino)-1,2,4-oxadiazol-5-yl)-2,5,6-trifluorophenol

A mixture of 2,4,5-trifluoro-3-hydroxybenzoic acid (0.045 g, 0.24 mmol), $NaHCO_3$ (0.049 g, 0.59 mmol), HOBt hydrate (0.036 g, 0.24 mmol) and EDC (0.054 g, 0.28 mmol) in DMF (1.3 mL) was stirred for 5 min under a N_2(g) atmosphere. A solution of (*E*)-1-benzyl-2-hydroxy-1-((1-isopropyl-*1H*-pyrazol-5-yl)methyl)guanidine **Example 20 Step a** (0.235 mmol) in DMF (1.0 mL) was added and the reaction mixture was stirred at rt for 30 min, then at 70°C for 20 h. The reaction was quenched with sat. NH_4Cl (aq, 20 mL) and extracted with DCM (3×30 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was dissolved in DMSO (2.0 mL) and purified by preparative HPLC, PrepMethod K, (gradient: 5–95%) to afford the title compound (0.014 g, 13%); HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{21}F_3N_5O_2$: 444.1642, found: 444.1650; ^{1}H NMR (600 MHz, DMSO) δ 1.29 (6H, d), 4.54–4.6 (3H, m), 4.67 (2H, s), 6.15 (1H, d), 7.24–7.29 (3H, m), 7.3–7.35 (2H, m), 7.39 (1H, d), 7.48 (1H, ddd).

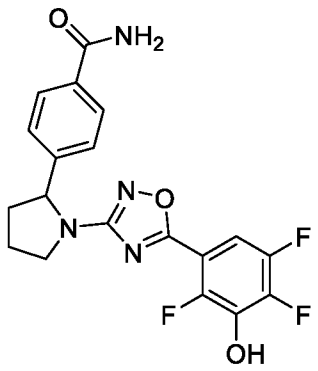
Example 21: 4-(1-(5-(2,4,5-Trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)piperidin-2-yl)benzamide



(*E*)-4-(1-(*N*'-Hydroxycarbamimidoyl)piperidin-2-yl)benzamide **Intermediate 34** (500 mg, 1.91 mmol) was added to 2,4,5-trifluoro-3-hydroxybenzoic acid (439 mg, 2.29 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide HCl (731 mg, 3.81 mmol), HOBt monohydrate (515 mg, 3.81 mmol) and $NaHCO_3$ (641 mg, 7.62 mmol) in DMF (15 mL). The resulting mixture was stirred at 25°C for 16 h. The reaction was quenched with water (50 mL) and extracted with EtOAc (3×100 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated. The crude product was purified by preparative HPLC, PrepMethod L, (gradient: 43–56%) to afford the title compound (0.027 g, 3%) as a white solid; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{18}F_3N_4O_3$: 419.1326, found: 419.1342; ^{1}H NMR (400

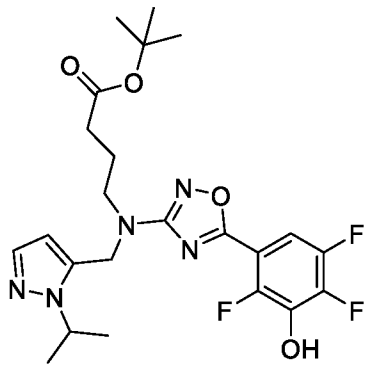
MHz, DMSO) δ 1.25–1.4 (1H, m), 1.54–1.7 (3H, m), 1.93–2.04 (1H, m), 2.28–2.36 (1H, m), 3.17–3.24 (1H, m), 3.89–3.97 (1H, m), 5.29–5.34 (1H, m), 7.31 (1H, s), 7.35 (2H, d), 7.43–7.5 (1H, m), 7.85 (2H, d), 7.92 (1H, s), 11.54 (1H, s).

Example 22: 4-(1-(5-(2,4,5-Trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)pyrrolidin-2-yl)benzamide

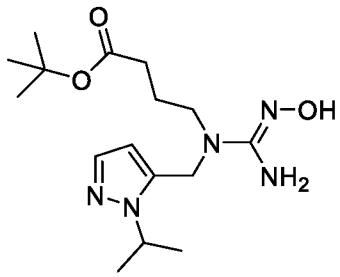


2,4,5-Trifluoro-3-hydroxybenzoic acid (93 mg, 0.48 mmol) was added to a mixture of EDC (185 mg, 0.97 mmol), HOBt (131 mg, 0.97 mmol) and $NaHCO_3$ (122 mg, 1.45 mmol) in DMF (1.2 mL) and the reaction mixture was stirred at 20°C for 1 h. (*E*)-4-(1-(N'-Hydroxycarbamimidoyl)pyrrolidin-2-yl)benzamide **Intermediate 38** (120 mg, 0.48 mmol) was added and the resulting solution was stirred at 70°C for 16 h. The process was repeated once more using (*E*)-4-(1-(*N*'-hydroxycarbamimidoyl)pyrrolidin-2-yl)benzamide **Intermediate 38** (40 mg, 0.16 mmol). The reaction mixtures were combined and concentrated. The residue was diluted with EtOAc (50 mL), and washed with water (50 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated. The crude product was purified by preparative HPLC, PrepMethod L, (gradient 36-50%) to afford the title compound (0.036 g, 14%) as a white solid. HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{16}F_3N_4O_3$: 405.1168, found: 405.1168; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.78–1.93 (1H, m), 1.93–2.06 (2H, m), 2.38–2.49 (1H, m), 3.55–3.69 (1H, m), 3.74–3.87 (1H, m), 4.96 (1H, dd), 7.22–7.43 (4H, m), 7.81 (2H, d), 7.92 (1H, s), 11.54 (1H, s).

Example 23: *tert*-Butyl 4-(((1-isopropyl-*1H*-pyrazol-5-yl)methyl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)amino)butanoate



Step a) tert-Butyl (*E*)-4-(2-hydroxy-1-((1-isopropyl-1*H*-pyrazol-5-yl)methyl)guanidino)butanoate



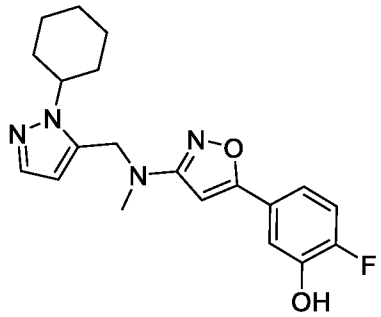
$NaHCO_3$ (0.228 g, 2.72 mmol) followed by hydroxylamine HCl (0.142 g, 2.04 mmol) were added to a solution of *tert*-butyl 4-(*N*-((1-isopropyl-*1H*-pyrazol-5-yl)methyl)cyanamido)butanoate **Intermediate 40** (0.208 g, 0.68 mmol) in EtOH (6.8 mL) at rt. The resulting mixture was stirred at rt for 1.75 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to afford the title compound as a mixture of *N*-hydroxyguanidine isomers 3:1. The crude product was used as such in step b; MS *m/z* (ESI) $[M+H]^+$ 340.5.

Step b) *tert*-Butyl 4-(((1-isopropyl-*1H*-pyrazol-5-yl)methyl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)amino)butanoate

A solution of 2,4,5-trifluoro-3-hydroxybenzoic acid (0.131 g, 0.68 mmol), $NaHCO_3$ (0.143 g, 1.70 mmol), HOBt (0.104 g, 0.68 mmol) and EDC (0.156 g, 0.82 mmol) in DMF (1.3 mL) was stirred for 5 min under a N_2(g) atmosphere. A solution of crude tert-butyl (*E*)-4-(2-hydroxy-1-((1-isopropyl-1*H*-pyrazol-5-yl)methyl)guanidino)butanoate **Example 23 Step a** (0.68 mmol) in DMF (1.0 mL) was added, and the reaction mixture was stirred at rt for 30 min and then at 70°C for 20 h. The reaction was quenched with NH_4Cl (20 mL) and extracted with DCM (3×30 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduce pressure.The residue was dissolved in DMSO (4.0 mL) and purified by preparative HPLC, PrepMethod B, (gradient: 30–100%) to afford the title compound (0.100 g, 30%) as a white solid; HRMS (ESI) *m/z*

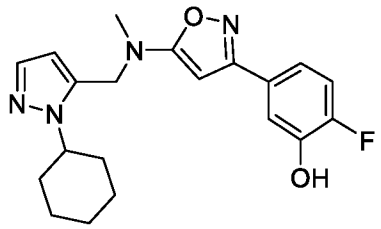
[M+H]+ calcd for $C_{23}H_{29}F_3N_5O_4$: 496.2166, found: 496.2172; ^{1}H NMR (500 MHz, DMSO) δ 1.34 (6H, d), 1.37 (9H, s), 1.73–1.81 (2H, m), 2.20 (2H, t), 3.32–3.36 (overlapping with solvent, m), 4.56–4.65 (1H, m), 4.69 (2H, s), 6.17 (1H, d), 7.38 (1H, d), 7.50 (1H, ddd), 11.59 (1H, s).

Example 24: 5-(3-(((1-Cyclohexyl-1*H*-pyrazol-5-yl)methyl)(methyl)amino)isoxazol-5-yl)-2-fluorophenol



Paraformaldehyde (0.013 g, 0.45 mmol) was added to 5-(3-(((1-cyclohexyl-1*H*-pyrazol-5-yl)methyl)amino)isoxazol-5-yl)-2-fluorophenol **Intermediate 43** (0.080 mg, 0.22 mmol) in THF (0.75 mL) and FA (0.25 mL), and the resulting mixture was stirred at 25°C for 1 h. $NaBH_4$ (0.029 g, 0.76 mmol) was added, and the stirring continued at 25°C for 4 h. The reaction mixture was concentrated, diluted with EtOAc, and washed with H_2O . The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC, PrepMethod M, (gradient: 63-79%) to give the title compound compound as a white solid (0.027 g, 33%); HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{24}FN_4O_2$: 371.1878, found: 371.1886: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.09 – 1.33 (m, 3H), 1.60 (d, 1H), 1.68 – 1.83 (m, 6H), 2.80 (s, 3H), 4.15 (p, 1H), 4.55 (s, 2H), 6.12 (d, 1H), 6.85 (s, 1H), 7.20 – 7.49 (m, 4H), 10.28 (s, 1H).

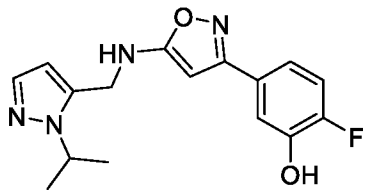
Example 25: 5-(5-(((1-Cyclohexyl-1*H*-pyrazol-5-yl)methyl)(methyl)amino)isoxazol-3-yl)-2-fluorophenol



Paraformaldehyde (0.076 g, 2.53 mmol) was added to 5-(5-(((1-cyclohexyl-1*H*-pyrazol-5-yl)methyl)amino)isoxazol-3-yl)-2-fluorophenol **Intermediate 45** (0.090 mg, 0.25 mmol) in THF (8 mL) and FA (2 mL), and the resulting mixture was stirred at 25°C for 1 h. $NaBH_4$ (0.029 g, 0.76 mmol) was added, and the stirring continued at 25°C for 12 h. H_2O (20 mL) was added, and the mixture was

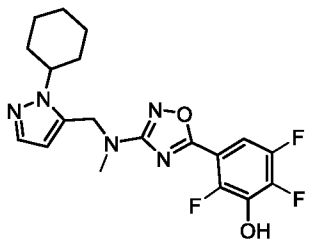
extracted with EtOAc (3 x 20 mL). The combined organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified by preparative HPLC, PrepMethod N, (gradient: 55–72%) to give the title compound compound as a white solid (4 mg, 5%); HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{20}H_{24}FN_4O_2$: 371.1878, found: 371.1874: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.10 – 1.34 (m, 3H), 1.61 (d, 1H), 1.69 – 1.83 (m, 6H), 2.89 (s, 3H), 4.12 (m, 1H), 4.64 (s, 2H), 5.76 (s, 1H), 6.17 (d, 1H), 7.13 – 7.41 (m, 4H), 10.13 (s, 1H).

Example 26: 2-Fluoro-5-(5-(((1-isopropyl-1*H*-pyrazol-5-yl)methyl)amino)isoxazol-3-yl)phenol



FA (0.25 mL, 6.52 mmol) was added to 1-isopropyl-1*H*-pyrazole-5-carbaldehyde (100 mg, 0.72 mmol) and 5-(5-aminoisoxazol-3-yl)-2-fluorophenol **Intermediate 44** (0.141 mg, 0.72 mmol) in THF (1 mL) and the resulting mixture was stirred at 30°C for 4 h. $NaBH_4$ (0.055 mg, 1.45 mmol) was added and the stirring was continued for 2 h. H_2O was added and the mixture was extracted with EtOAc (2×20 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative TLC (PE/EtOAc 1:1), and then by preparative HPLC, PrepMethod L, (gradient: 3140%) to give the title compound compound as a white solid (10 mg, 4%); HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{18}FN_4O_2$: 317.1408, found: 317.1404: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H), 7.81 (t, 1H), 7.39 – 7.11 (m, 4H), 6.24 (d, 1H), 5.55 (s, 1H), 4.59 (p, 1H), 4.40 (d, 2H), 1.37 (d, 6H).

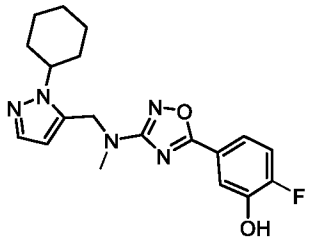
Example 27: 3-(3-(((1-Cyclohexyl-1*H*-pyrazol-5-yl)methyl)(methyl)amino)-1,2,4-oxadiazol-5-yl)-2,5,6-trifluorophenol



2,4,5-Trifluoro-3-hydroxybenzoic acid (42 mg, 0.22 mmol) was dissolved in 2-MeTHF (6 mL) and cooled to 0°C. DIPEA (104 µl, 0.60 mmol), T3P in EtOAc (50%, 237 µl, 0.40 mmol) and (*E*)-1-((1-cyclohexyl-1*H*-pyrazol-5-yl)methyl)-2-hydroxy-1-methylguanidine **Intermediate 49** (50 mg, 0.20 mmol) were added and the reaction mixture was stirred at rt overnight and then heated at 80°C for 90 min. The reaction mixture was diluted with EtOAc and washed with sat $NaHCO_3$ (aq), water and

brine. The organic phase was passed through a phase-separator and concentrated in vacuo, and the residue was purified by preparative HPLC, PrepMethod D, (gradient: 5–90%), to give the title compound (2.8 mg, 3.5%); HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{21}F_3N_5O_2$: 408.1642, found: 408.1640; ^{1}H NMR (600 MHz, DMSO-d_6) δ 0.79–0.96 (3H, m), 1.24–1.3 (1H, m), 1.4–1.51 (6H, m), 2.60 (3H, s), 3.9–3.99 (1H, m), 4.42 (2H, s), 5.92 (1H, d), 7.09 (1H, d), 7.1–7.16 (1H, m), 7.86 (1H, s).

Example 28: 5-(3-(((1-Cyclohexyl-1*H*-pyrazol-5-yl)methyl)(methyl)amino)-1,2,4-oxadiazol-5-yl)-2-fluorophenol



A solution of 4-fluoro-3-hydroxybenzoic acid (124 mg, 0.80 mmol), EDC (229 mg, 1.19 mmol) and HOBt (183 mg, 1.19 mmol) in DMF (3 mL) was stirred at rt for 10 min. 1-((1-Cyclohexyl-1*H*-pyrazol-5-yl)methyl)-2-hydroxy-1-methylguanidine **Intermediate 49** (60 mg, 0.24 mmol) was added and the reaction mixture was stirred at 80°C for 1 h. The reaction mixture was diluted with EtOAc (300 mL), and washed with sat brine (50 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated and the crude product was purified by preparative HPLC, PrepMethod O, (gradient 40–50%) to give the title compound (65 mg, 22%) as a white solid; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{23}FN_5O_2$: 372.1830, found: 372.1832; ^{1}H NMR (CD_3OD, 300 MHz) δ 1.23 (3H, s), 1.61 (1H, s), 1.81 (6H, s), 2.92 (3H, s), 4.28 – 4.42 (1H, m), 4.77 (2H, s), 6.29 (1H, d), 7.19 – 7.31 (1H, m), 7.45 (1H, d), 7.52 – 7.63 (1H, m), 7.60 – 7.69 (1H, m).

***In vitro* 17bHSD13 enzyme assay**

10 concentration of compounds (0.2 µl) in DMSO was added to GREINER PP 384 well plate (781280) using ECHO dispensing (BECKMAN COULTER) followed by 20 µl of recombinant 17bHSD13 (N2-K300). The enzyme reaction was initiated by addition, using CERTUS-FLEX dispenser (GYGER), of 20 µl of substrate solution containing NAD (SIGMA, N1511) and Estradiol (SIGMA, E8875). After each addition plates were centrifuged for 1 min at 150x g (EPPENDORF, 5810R, A-4-81). Final assay conditions were 80 nM of 17bHSD13, 0.5 mM of NAD, 20 µM Estradiol and various concentrations of compound in buffer (5 mM EDTA (TEKNOVA E0306), 0.01% DDM (AFFYMETRIX D310) in 50mM Tris-

Cl, pH 7.4). After 2.5 h the reaction were stopped by addition of 20 µl of 0.6 % Formic acid (MERCK 5.33002) and samples were analyzed using LC-MS/MS.

SCIEX LC-MS/MS system: Sample was injected with CTC analytical injector, SHIMATZU LC pumps LC20 and analyzed on the SCIEX API 5000 LCMSMS system with the following settings. Samples were chromatographed on a WATERS, SYMMETRY, C8, 3.5 µm, 2.1x 50 mm) column at constant flow rate of 0.5 mL/min. The mobile phases consist of A (water with 0.2% formic acid) and B (acetonitrile with 0.2% formic acid). The LC gradient profile is as follows: 50% B during 0 to 0.5 min, a linear increase to 100% B during 0.5 to 1 min, hold at 100% B during 1 to 1.6 min then back to 50% B from 1.6 to 2 min. The run time was 2 min with retention times of approximately 0.8 and 1.07 min for Estradiol and Estrone, respectively. Detection was performed on a API 5000 LC/MS/MS system with a triple quadrupole mass spectrometer, a TURBO V ion source, in multiple reaction monitoring (MRM) mode at positive polarity with APCI probe. The MRM pairs were m/z 273.1 to m/z 107.0 and m/z 271.3 to 107.0. for Estradiol and Estrone, respectively. The dwell times were 100 ms for each transition and a depolarization and collision energy of 100 and 40, respectively. Data from MS signals was using area under curve (AUC). Ratio = Estrone/(Estrone + Estradiol)

***In vitro* 17bHSD13 cell assay**

Inhibition of 17bHSD13 was measured in a cell-based assay with over expressed HSD17β13 in HEK293S cells, measuring estradiol to estrone conversion by LCMS/MS.

Cells were plated in 384 well plates (GREINER CELL culture plate 384w black/clear Poly-D-Lysine) at 10 K c/w in 30 µl of culture media (DMEM with GLUTAMAX plus 10 % FBS). After the cells were allowed to attach for 6 h, 0.15 µl of 10 concentration of compounds and 0.03 µl of 10 mM Estradiol (SIGMA, E8875) in DMSO, was added using ECHO dispensing (BECKMAN COULTIER). After 18 h of cell culturing for 20 µl of media was transferred using BRAVO dispensing robot (AGILENT) to a GREINER PP 384 well plate (781280) and 40 µl of 50 % acetonitrile was added. Samples were analyzed using LC-MS/MS.

SCIEX LC-MS/MS system: Sample was injected with CTC analytical injector, SHIMATZU LC pumps LC20 and analysed on the SCIEX API 5000 LCMSMS system with the following settings. Samples were chromatographed on a WATERS, symmetry, C8, 3.5 µm, 2.1x 50 mm) column at constant flow rate of 0.5 mL/min. The mobile phases consist of A (water with 0.2% formic acid) and B (acetonitrile with 0.2% formic acid). The LC gradient profile is as follows: 50% B during 0 to 0.5 min, a linear increase to 100% B during 0.5 to 1 min, hold at 100% B during 1 to 1.6 min then back to 50% B from 1.6 to 2 min. The run time was 2 min with retention times of approximately 0.8 and 1.07 min for Estradiol

and Estrone, respectively. Detection was performed on a API 5000 LC/MS/MS system with a triple quadrupole mass spectrometer, a TURBO V ion source, in multiple reaction monitoring (MRM) mode at positive polarity with APCI probe. The MRM pairs were m/z 273.1 to m/z 107.0 and m/z 271.3 to 107.0. for Estradiol and Estrone, respectively. The dwell times were 100 ms for each transition and a depolarization and collision energy of 100 and 40, respectively. Data from MS signals was using area under curve (AUC). Ratio = Estrone/(Estrone + Estradiol)

***In vitro* 17bHSD4 enzyme assay**

10 concentration of compounds (0.2 µl) in DMSO was added to GREINER FLUOTRAC 200 384 well plate (781076) using ECHO dispensing (BECKMAN COULTER). 80 nl of 10 mM Estradiol (SIGMA, E8875) was added using Echo dispensing. The enzyme reaction was initiated by addition, using MULTIDROP COMBI dispensing (THERMO FISHER), of 40 µl of a mix containing recombinant 17bHSD4 (M1-N311) and NAD. Final assay conditions were 40 nM of 17bHSD4, 0.125 mM of NAD, 15 µM Estradiol and various concentrations of compound in buffer (5 mM EDTA (TEKNOVA E0306), 0.01% DDM (AFFYMETRIX D310) in 50mM Tris-Cl, pH 7.4). After each addition plates were centrifuged for 1 min at 150x g (EPPENDORF, 5810R, A-4-81). NADH formation was measured by fluorescence intensity (FI) (Ex360/Em460) at time zero (t_0) and at 1.5 h (t_1) in a PHERASTAR FSX (BMG LABTECH). FI for each sample was calculated as FI at t_1 minus FI at t_0.

***In vitro* 17bHSD9 cell assay**

Inhibition of 17bHSD9 was measured in a cell-based assay with over expressed HSD17β9 in HEK293S cells, measuring retinol to retinal conversion by LCMS/MS.

Cells were plated in 384 well plates (GREINER CELL culture plate 384w black/clear Poly-D-Lysine) at 10 K c/w in 30 µl of culture media (DMEM with GLUTAMAX plus 10 % FBS). After the cells were allowed to attach for 6 h, 0.15 µl of 10 concentration of compounds and 0.015 µl of 10 mM all-trans-retinol (CAYMAN CHEMICAL, 20241) in DMSO, was added using ECHO dispensing (BECKMAN COULTIER). After 18 h of cell culturing for 20 µl of media was transferred using BRAVO dispensing robot (AGILENT) to a GREINER PP 384 well plate (781280) and 40 µl of 50 % acetonitrile was added. Samples were analyzed using LC-MS/MS.

SCIEX LC-MS/MS system: Sample was injected with CTC analytical injector, SHIMATZU LC pumps LC20 and analysed on the SCIEX API 5000 LCMSMS system with the following settings. Samples were chromatographed on a WATERS, symmetry, C8, 3.5 µm, 2.1x 50 mm) column at constant flow rate of 0.5 mL/min. The mobile phases consists of A (water with 0.2% formic acid) and B (acetonitrile with 0.2% formic acid). The LC gradient profile is as follows: 50% B during 0 to 0.1 min, a linear increase to

100% B during 0.1 to 0.8 min, hold at 100% B during 0.8 to 1.5 min then back to 50% B from 1.5 to 1.6 min and hold during run time. The run time was 2 min with retention times of approximately 1,54 and 1.62 min for Retinol and Retinal, respectively. Detection was performed on a API 5000 LC/MS/MS system with a triple quadrupole mass spectrometer, a TURBO V ion source, in multiple reaction monitoring (MRM) mode at positive polarity with ESI probe. The MRM pairs were m/z 269.3 to m/z 93.0 and m/z 285.2 to 161.0. for Retinol and Retinal, respectively. The dwell times were 100 ms for each transition and a depolarization and collision energy of 50 and 25, respectively. Data from MS signals was using area under curve (AUC). Ratio = Retinal/(Retinal+ Retinol).

Data analysis

GENEDATA SCREENER was used for curve fitting and calculation of IC_{50} values.

Compound effect was calculated with the formula below;

Compound % effect = -100 x ((X-min)/(max-min))

where X represents the effect in the presence of test compound, min is DMSO and max is the maximum inhibition of enzyme using a known inhibitor as control.

Table 1

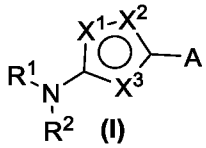
Example	17bHSD13 Enzyme assay IC_{50} (µM)	17HSD17b4 Enzyme assay IC_{50} (µM)	17bHSD1713 Cell assay IC_{50} (µM)	17bHSD9 Cell assay IC_{50} (µM)
1	0.036	2.3	1.69	2.9
2	0.090	10.7	>26	>50
3	0.063		2.20	
4	0.048		1.92	>50
5	0.057		>50	>50
6	0.049		1.41	>50
7	0.131	9.9	2.12	
8	0.190		>50	
9	0.053	4.6	0.86	
10	0.349	5.0	2.68	
11	0.033	14.0	0.42	1.8
12	0.031	29.3	0.10	3.6
13	0.075	20.3	1.42	
14	0.050	41.8	1.58	

15	0.138	>50	0.45	
17	0.037	14.0	1.76	3.8
18	0.078		1.60	
19	0.464		2.39	
20	0.124	7.6	2.53	
21	0.081	5.4	7.84	>50
22	0.271	35.9	19.03	>50
23	0.033	16.1	0.81	
24	0.112	>50	0.32	
25	0.138	14.9	0.32	
26	0.628	>50	4.14	
27	0.058	15.6	1.58	
28	0.057		0.58	

The above description of illustrative embodiments is intended only to acquaint others skilled in the art with the Applicant's specification, its principles, and its practical application so that others skilled in the art may readily adapt and apply the specification in its numerous forms, as they may be best suited to the requirements of a particular use. This description and its specific examples, while indicating embodiments of this specification, are intended for purposes of illustration only. This specification, therefore, is not limited to the illustrative embodiments described in this specification, and may be variously modified. In addition, it is to be appreciated that various features of the specification that are, for clarity reasons, described in the context of separate embodiments, also may be combined to form a single embodiment. Conversely, various features of the specification that are, for brevity reasons, described in the context of a single embodiment, also may be combined to form sub-combinations thereof.

Claims

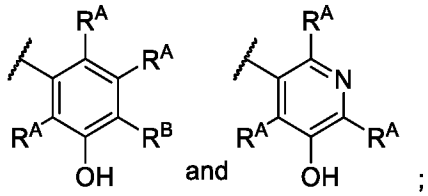
1. A compound of Formula (I);



(I)

wherein,

A is selected from



;

each R^A is independently selected from H, halo and $-OR^X$, wherein each R^X is independently C_{1-3} alkyl optionally substituted with one to three F;

R^B is halo, $-OCHF_2$ or $-OCF_3$;

one of X^1, X^2 and X^3 is selected from NH, O and S and the other two of X^1, X^2 and X^3 are independently selected from N and CH;

R^1 and R^2 are such that;

(i) R^1 is selected from R^8, R^{8A}, R^{4A} and R^{5A}, and R^2 is selected from R^{8B} and H; or

(ii) R^1 and R^2, taken together with the N atom to which they are attached, form a heterocycloalkyl ring, wherein the heterocycloalkyl ring is optionally substituted with one or more R^C, wherein each R^C is independently selected from F, R^3, R^4, $-O(R^4)$, $O(R^5)$, R^5, R^6, -OH, -CN, oxo and $-C(=O)N(R^{7A})_2$;

each R^3 is independently C_{1-4} alkyl or C_{3-6} cycloalkyl, each of which are optionally substituted with one or more groups independently selected from R^{4X}, R^{5x}, $-O(R^{4X})$, $-O(R^{5X})$ and F;

each R^{3X} is independently C_{1-4} alkyl or C_{3-6} cycloalkyl;

each R^4, R^{4A} and R^{4B} are independently monocyclic or bicyclic, 5 to 9 membered heteroaryl, each of which are optionally substituted with one or more groups independently selected from R^{4X}, $-O(R^{4X})$, R^{5X}, $-O(R^{5X})$, -OH, -CN, C_{1-4} alkoxy, $-C(=O)OH$, $-C(=O)O(C_{1-4}$ alkyl), $-C(=O)N(R^{7B})_2$, R^3 and halo;

each R^5, R^{5A} and R^{5B} are independently phenyl, each of which are optionally substituted with one or more groups independently selected from R^{4X}, $-O(R^{4X})$, R^{5X}, $-O(R^{5X})$, -OH, -CN, C_{1-4} alkoxy, $-C(=O)OH$, $-C(=O)O(C_{1-4}$ alkyl), $-C(=O)N(R^{7B})_2$, R^3 and halo;

each R^{4X} is independently monocyclic or bicyclic 5 to 9 membered heteroaryl, each of which are optionally substituted with one or more groups independently selected from -OH, -CN, C_{1-4} alkoxy, $-C(=O)OH$, $-C(=O)N(R^{7B})_2$, R^{3X} and halo;

each R^{5X} is independently phenyl, each of which are optionally substituted with one or more groups independently selected from -OH, -CN, C_{1-4} alkoxy, -C(=O)OH, -C(=O)N(R^{7B})$_2$, R^{3x} and halo;

each R^6 is independently C_{1-4} alkoxy optionally substituted with one or more groups independently selected from R^{4X}, R^{5x} and F;

each R^7, R^{7A}, R^{7B} and R^{7C} are independently H, R^{Z1} or R^{Z2}, wherein R^{Z1} is C_{1-4} alkyl optionally substituted with one or more C_{1-4} alkoxy or -C(=O)NH_2, and R^{Z2} is C_{3-6} cycloalkyl optionally substituted with one or more C_{1-4} alkoxy or -C(=O)NH_2;

R^8 is C_{1-4} alkyl substituted with one or more groups independently selected from R^{4B}, R^{5B}, F, -OH, -CN, C_{1-4} alkoxy, -C(=O)O(C_{1-4} alkyl) and -C(=O)N(R^{7C})$_2$;

R^{8A} is C_{3-6} cycloalkyl or adamantyl, each of which are optionally substituted with one or more groups independently selected from R^{4B}, R^{5B}, F, -OH, -CN, C_{1-4} alkoxy, -C(=O)O(C_{1-4} alkyl) and -C(=O)N(R^{7C})$_2$;

R^{8B} is C_{1-4} alkyl or C_{3-6} cycloalkyl, each of which are optionally substituted with one or more groups independently selected from R^{4B}, R^{5B}, F, -OH, -CN, C_{1-4} alkoxy, -C(=O)O(C_{1-4} alkyl) and -C(=O)N(R^{7C})$_2$;

wherein the heterocycloalkyl ring is a saturated, monocyclic or bicyclic, 4-8 membered ring comprising one N atom, and optionally one further heteroatom selected from N, O and S; and

wherein each heteroaryl is independently an aromatic ring containing one or more heteroatoms independently selected from N, O and S,

or a pharmaceutically acceptable salt thereof,

wherein the compound is not 2-(difluoromethoxy)-5-(5-((5-fluoroadamantan-2-yl)(methyl)amino)-1,3,4-oxadiazol-2-yl)phenol or 5-(3-(((1-cyclohexyl-1H-tetrazol-5-yl)methyl)(methyl)amino)-1,2,4-oxadiazol-5-yl)-2-fluorophenol.

2. A compound of Formula (I) or a pharmaceutically acceptable salt thereof, as claimed in claim 1, wherein

(i) X^1 is N, X^2 is O and X^3 is N;

(ii) X^1 is N, X^2 is N and X^3 is O;

(iii) X^1 is CH, X^2 is CH and X^3 is S;

(iv) X^1 is O, X^2 is N and X^3 is CH;

(v) X^1 is N, X^2 is O and X^3 is CH;

(vi) X^1 is CH, X^2 is N and X^3 is O;

(vii) X^1 is O, X^2 is N and X^3 is N;

(viii) X^1 is N, X^2 is N and X^3 is S;

(ix) X^1 is CH, X^2 is S and X^3 is CH; or

(x) X^1 is CH, X^2 is N and X^3 is S.

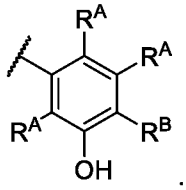
3 A compound of Formula (I) or a pharmaceutically acceptable salt thereof, as claimed in claim 1, wherein one of X^1, X^2 and X^3 is O and the other two of X^1, X^2 and X^3 are independently selected from N and CH.

4 A compound of Formula (I) or a pharmaceutically acceptable salt thereof, as claimed in claim 1, wherein X^1 is N, X^2 is O and X^3 is N.

5. A compound of Formula (I) or a pharmaceutically acceptable salt thereof, as claimed any one of claims 1 to 4, wherein each R^A is independently H or halo.

6. A compound of Formula (I) or a pharmaceutically acceptable salt thereof, as claimed any one of claims 1 to 4, wherein each R^A is independently H or F.

7. A compound of Formula (I) or a pharmaceutically acceptable salt thereof, as claimed any one of claims 1 to 6, wherein A is



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8. A compound of Formula (I) or a pharmaceutically acceptable salt thereof, as claimed any one of claims 1 to 7, wherein R^B is F.

9. A compound of Formula (I) or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 8, wherein each R^3 is independently C_{1-4} alkyl optionally substituted with one to three F.

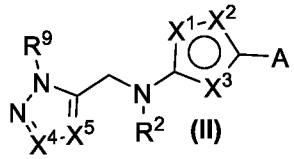
10. A compound of Formula (I) or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 9, wherein each R^4, R^{4A} and R^{4B} are independently monocyclic 5 or 6 membered heteroaryl, each of which are optionally substituted with one or more groups independently selected from OH, -CN, C_{1-4} alkoxy, -C(=O)OH, -C(=O)O(C_{1-4} alkyl), -C(=O)N(R^{7B})$_2$, R^{3X} and halo.

11. A compound of Formula (I) or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 10, wherein each R^5, R^{5A} and R^{5B} is independently phenyl, each of which are optionally substituted with one or more groups independently selected from OH, -CN, C_{1-4} alkoxy, -C(=O)OH, -C(=O)O(C_{1-4} alkyl), -C(=O)N(R^{7B})$_2$, R^{3X} and halo.

12. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 11, wherein R^1 is selected from R^8, R^{8A}, R^{4A} and R^{5A}, and R^2 is selected from R^{8B} and H.

13. A compound of Formula (I) or a pharmaceutically acceptable salt thereof, as claimed in claim 12, wherein R^1 is C_{1-4} alkyl, substituted with one R^{4B} or R^{5B}.

14. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 13, that is a compound of Formula (II):



(II)

wherein

R^2 is selected from R^{8B} and H;

R^9 is R^3; and

X^4 and X^5 are independently N or CH,

or a pharmaceutically acceptable salt thereof.

15. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in claim 14, wherein X^4 and X^5 are both N.

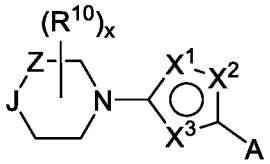
16. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in claim 14 or 15, wherein R^9 is C_{1-4} alkyl or C_{3-6} cycloalkyl.

17. A compound of Formula (I) or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 14 to 16, wherein R^2 is R^{8B}.

18. A compound of Formula (I) or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 14 to 17 wherein R^2 is C_{1-4} alkyl optionally substituted with one group independently selected from R^{4B} and R^{5B}.

19. A compound of Formula (I) or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 14 to 17, wherein R^2 is C_{1-4} alkyl.

20. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 11, that is a compound of Formula (III):



(III)

wherein

J is selected from O, S, CH_2, NH and a covalent bond,

Z is such that

(i) where J is selected from O, S, CH_2 and a covalent bond, Z is selected from CH_2 and CH_2CH_2, and

(ii) where J is NH, Z is selected from CH_2, CH_2CH_2, and C(=O);

x is selected from 0 to 3; and

each R^{10} is independently selected from R^3, R^4 and R^5,

or a pharmaceutically acceptable salt thereof.

21. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in claim 22, wherein J is selected from O, S, CH_2 and a covalent bond, and Z is CH_2.

22. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in claim 20 or 21, wherein each R^{10} is independently R^5.

23. A pharmaceutical composition comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 22, and a pharmaceutically acceptable excipient.

24. A compound of Formula (I) or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 22, for use in therapy.

25. A compound of Formula (I) or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 22, for use in the treatment of NASH.

26. A method of treating NASH in a patient comprising administering to the patient a compound of Formula (I) or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 22.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2023/063423

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/04 C07D413/12 C07D413/14 C07D417/12 A61K31/4245
A61K31/433 A61P1/16
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
C07D A61P A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 9 212 151 B2 (AMITECH THERAPEUTIC SOLUTIONS INC [US]) 15 December 2015 (2015-12-15)	1-13
A	column 84 - column 93	14-26

X	KR 2015 0049698 A (UNIV DONGGUK IND ACAD COOP [KR]; KOREA RES INST CHEM TECH [KR]) 8 May 2015 (2015-05-08)	1-13
A	paragraph [0121]	14-26

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[x] Further documents are listed in the continuation of Box C.
[x] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 July 2023	14/07/2023

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

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2023/063423

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KUMAR SIGALAPALLI DILEP ET AL: "Microwave-Assisted TBHP-Mediated Synthesis of 2-Amino-1,3,4-oxadiazoles in Water", CHEMISTRYSELECT, vol. 5, no. 42, 13 November 2020 (2020-11-13), pages 13248-13258, XP093061563, DE ISSN: 2365-6549, DOI: 10.1002/slct.202003516 Retrieved from the Internet: URL:https://onlinelibrary.wiley.com/doi/full-xml/10.1002/slct.202003516>	1-13
A	page 13249	14-26

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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PCT/EP2023/063423

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