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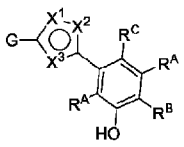
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(54) Title: HETEROAROMATIC 17BETA HYDROXY STEROID DEHYDROGENASE 13 INHIBITORS



(I)

(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.

HETEROAROMATIC 17BETA HYDROXY STEROID DEHYDROGENASE 13 INHIBITORS

Cross-Reference to Related Patent Application

This specification claims the benefit of priority to U.S. Provisional Patent Application No. 63/599,661 (filed 16 November 2023). The entire text of the above-referenced patent application is incorporated by reference into this specification.

Field

This specification relates to certain 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 amido heteroaromatic compounds and to pharmaceutical compositions containing them.

Background

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

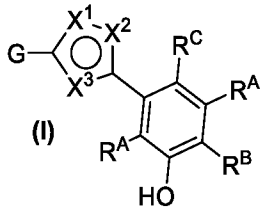
deafness in both males and females, and in some patients, neurological manifestations (Pierce et al. Am. J. Hum. Genet., 2010, 87, 282-8; and Chen et al. BMC Med Genet., 2017, 18, 91).

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. For example, the compounds of the specification may exhibit improved stability in colon to allow greater absorption in the human gastrointestinal tract. Such compounds may therefore be especially suitable as therapeutic agents, such as for the treatment of liver disease.

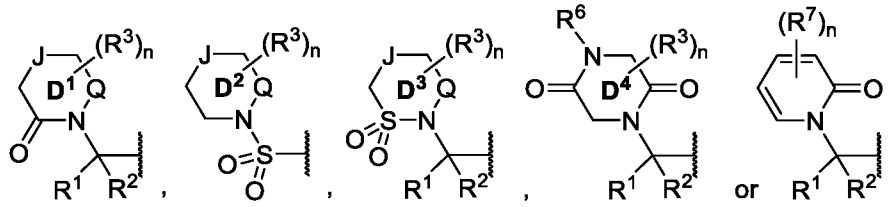
General Description

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



(I)

wherein,

G is 

each R^A is independently selected from H, F and Cl,

R^B is F or Cl,

R^C is H, F or Cl,

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 CR^Y, wherein each R^Y is independently H, -CN, or R^{XA}, wherein R^{XA} is independently C_{1-3} alkyl optionally substituted with one to three F,

either (i) R^1 and R^2 are independently selected from H, R^4 and R^5,

or (ii) R^1 and R^2 together with the carbon atom to which they are attached form a cyclopropane or cyclobutane ring,

each R^3 is independently R^{4A}, R^{5A} or -OH,

each of R^4 and R^{4A} are independently C_{1-6} alkyl optionally substituted with one to three F, and

each of R^5 and R^{5A} are independently C_{3-6} cycloalkyl optionally substituted with one to three F,

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

each R^7 is independently selected from R^{4A}, R^{5A}, -O(R^{4A}) -O(R^{5A}), -OH, -CN, and halo,

n is 0, 1, 2 or 3,

J is O, CH_2 or a covalent bond,

Q is CH_2 or C(=O),

and wherein optionally (i) one carbon atom of ring D^1, D^2, D^3 or D^4 is attached to a C_{2-5} alkylene group to form a spirocyclic ring, or (ii) two carbon atoms of ring D^1, D^2, D^3 or D^4 are attached to a C_{1-5} alkylene group to form a bridged or fused ring, wherein one CH_2 group of said C_{2-5} alkylene group and C_{1-5} alkylene group may be optionally replaced by an oxygen group,

or a pharmaceutically acceptable salt thereof.

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. Examples of suitable C_{1-6} alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl and t-butyl, n-pentyl and n-hexyl.

As used herein the term "**alkylene**" refers to both straight and branched chain saturated hydrocarbon bivalent radicals having the specified number of carbon atoms with two points of attachment to adjacent atoms/groups. Examples of suitable C_{1-5} alkylene groups include, but are not limited to, $-CH_2-$, $-CH(CH_3)-$, $-CH(CH_2CH_3)-$, $-C(CH_3)_2-$, $-CH_2CH_2-$, $-CH(CH_3)CH_2-$, $-CH(CH_2CH_3)CH_2-$, $-C(CH_3)_2CH_2-$, $-CH(CH_3)CH(CH_3)-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$,$-C(CH_3)(CH_3)CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH(CH_3)CH_2CH_2CH_2-$, $-CH_2CH(CH_3)CH_2CH_2-$ and $-CH_2CH_2CH_2CH_2CH_2-$. Examples of suitable C_{2-5} alkylene groups include, but are not limited to, $-CH_2CH_2-$, $-CH(CH_3)CH_2-$, $-CH(CH_2CH_3)CH_2-$, $-C(CH_3)_2CH_2-$, $-CH(CH_3)CH(CH_3)-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$,$-C(CH_3)(CH_3)CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH(CH_3)CH_2CH_2CH_2-$, $-CH_2CH(CH_3)CH_2CH_2-$ and $-CH_2CH_2CH_2CH_2CH_2-$. In embodiments, one CH_2 group of a C_{1-5} alkylene group may be optionally replaced by an oxygen group. Examples of suitable C_{1-5} alkylene groups with a CH_2 group replaced by an oxygen group include, but are not limited to, $-O-$, $-OCH_2-$, $-CH(CH_3)O-$, $-CH(CH_2CH_3)O-$, $-C(CH_3)_2O-$, $-OCH_2CH_2-$, $-CH_2OCH_2-$, $-OCH_2CH_2CH_2-$, $-CH_2OCH_2CH_2-$, $-OCH_2CH_2CH_2CH_2-$, $-CH_2OCH_2CH_2CH_2-$ and $-CH_2CH_2OCH_2CH_2-$. In embodiments, one CH_2 group of a C_{2-5} alkylene group may be optionally

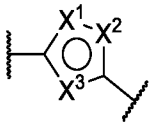
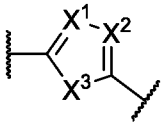
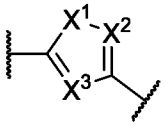
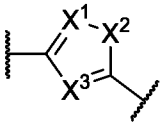
replaced by an oxygen group. Examples of suitable C_{2-5} alkylene groups with a CH_2 group replaced by an oxygen group include, but are not limited to, $-CH_2O-$, $-CH(CH_3)O-$, $-CH(CH_2CH_3)O-$, $-C(CH_3)_2O-$, $-OCH_2CH_2-$, $-CH_2OCH_2-$, $-OCH_2CH_2CH_2-$, $-CH_2OCH_2CH_2-$, $-OCH_2CH_2CH_2CH_2-$, $-CH_2OCH_2CH_2CH_2-$ and $-CH_2CH_2OCH_2CH_2-$.

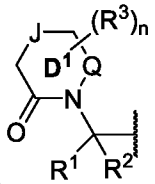
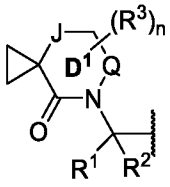
As used herein the term "**cycloalkyl**" refers to saturated cyclic hydrocarbon radicals having the specified number of carbon atoms. Examples of C_{3-6} cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

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

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 label "D1", "D2", "D3" or "D4", in the centre of a ring indicates that said ring is "ring D1", "ring D2", "ring D3" or "ring D4" respectively. By way of illustration only, an example of ring D1  attached to a C_2 alkylene group to form a spirocyclic ring is .

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.

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.

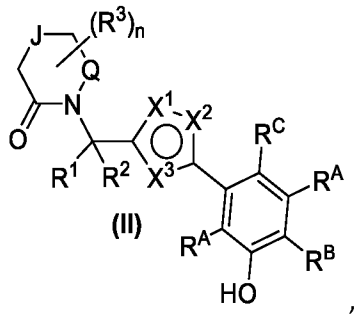
Units, prefixes, and symbols are denoted in their International System of Units (SI) accepted form. Numeric ranges are inclusive of the numbers defining the range.

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, that is a compound of Formula (II)

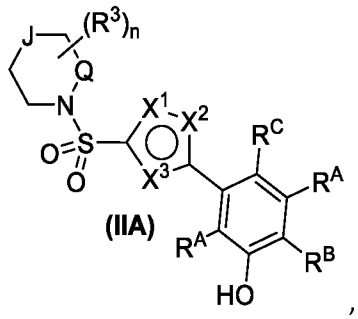


(II)

,

or a pharmaceutically acceptable salt thereof.

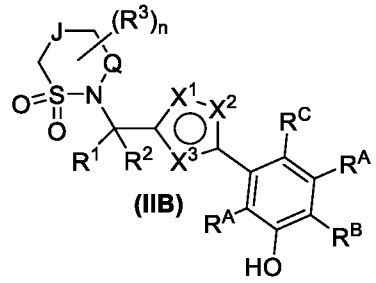
In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, that is a compound of Formula (IIA)



,

or a pharmaceutically acceptable salt thereof.

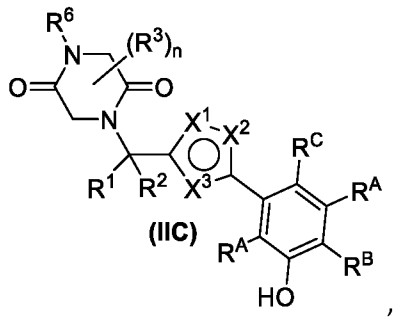
In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, that is a compound of Formula (IIB)



,

or a pharmaceutically acceptable salt thereof.

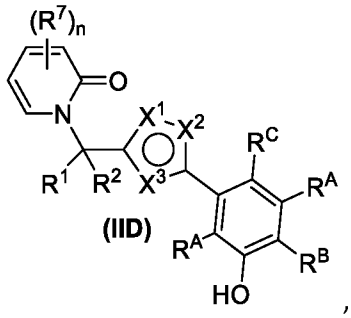
In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, that is a compound of Formula (IIC)



,

or a pharmaceutically acceptable salt thereof.

In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, that is a compound of Formula (IID)



(IID),

or a pharmaceutically acceptable salt thereof.

In embodiments, there is provided a compound of Formula (I), (II), (IIA), (IIB), (IIC) or (IID), or a pharmaceutically acceptable salt thereof, wherein each R^Y is independently H, -CN, or R^{XA}, wherein R^{XA} is independently C_{1-3} alkyl optionally substituted with one to three F. In further embodiments R^{XA} is independently C_{1-3} alkyl (i.e. C_{1-3} alkyl is unsubstituted). In further embodiments, each R^Y is independently H.

In embodiments, there is provided a compound of Formula (I), (II), (IIA), (IIB), (IIC) or (IID), 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 CR^Y. In further embodiments, R^Y is H.

In embodiments, there is provided a compound of Formula (I), (II), (IIA), (IIB), (IIC) or (IID), 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 CR^Y. In further embodiments, R^Y is H.

In embodiments, there is provided a compound of Formula (I), (II), (IIA), (IIB), (IIC) or (IID), 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), (IIA), (IIB), (IIC) or (IID), 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 CR^Y. In further embodiments, R^Y is H or -CN.

In embodiments, there is provided a compound of Formula (I), (II), (IIA), (IIB), (IIC) or (IID), 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), (IIA), (IIB), (IIC) or (IID), 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 CR^Y. In further embodiments, R^Y is H.

In embodiments, there is provided a compound of Formula (I), (II), (IIA), (IIB), (IIC) or (IID), 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 CR^Y. In further embodiments, each R^Y is H.

In embodiments, there is provided a compound of Formula (I), (II), (IIA), (IIB), (IIC) or (IID), 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 CR^Y. In further embodiments, each R^Y is H.

In embodiments, there is provided a compound of Formula (I), (II), (IIA), (IIB), (IIC) or (IID), 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 CR^Y, X^2 is CR^Y and X^3 is S,
(iv) X^1 is O, X^2 is N and X^3 is CR^Y,
(v) X^1 is N, X^2 is O and X^3 is CR^Y,
(vi) X^1 is CR^Y, 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 CR^Y, X^2 is S and X^3 is CR^Y,
(x) X^1 is CR^Y, X^2 is N and X^3 is S,
(xi) X^1 is CR^Y, X^2 is O and X^3 is CR^Y,
(xii) X^1 is CR^Y, X^2 is CR^Y and X^3 is N,
(xiii) X^1 is N, X^2 is CR^Y and X^3 is S,
(xiv) X^1 is CR^Y, X^2 is S and X^3 is N,
(xv) X^1 is S, X^2 is N and X^3 is CR^Y,
(xvi) X^1 is CR^Y, X^2 is O and X^3 is N,
(xvii) X^1 is O, X^2 is CR^Y and X^3 is CR^Y, or
(xviii) X^1 is N, X^2 is S and X^3 is CR^Y.

In embodiments, there is provided a compound of Formula (I), (II), (IIA), (IIB), (IIC) or (IID), 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,

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

(xi) X^1 is CH, X^2 is O and X^3 is CH,

(xii) X^1 is CH, X^2 is CH and X^3 is N,

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

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

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

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

(xvii) X^1 is O, X^2 is CH and X^3 is CH, or

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

In embodiments, there is provided a compound of Formula (I), (II), (IIA), (IIB), (IIC) or (IID), 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), (IIA), (IIB), (IIC) or (IID), 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), (IIA), (IIB), (IIC) or (IID), 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), (IIA), (IIB), (IIC) or (IID), or a pharmaceutically acceptable salt thereof, wherein X^1 is N, X^2 is O and X^3 is CR^Y. In further embodiments, R^Y is H.

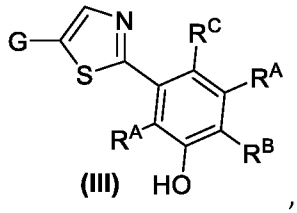
In embodiments, there is provided a compound of Formula (I), (II), (IIA), (IIB), (IIC) or (IID), or a pharmaceutically acceptable salt thereof, wherein X^1 is CR^Y, X^2 is N and X^3 is O. In further embodiments, R^Y is H.

In embodiments, there is provided a compound of Formula (I), (II), (IIA), (IIB), (IIC) or (IID), or a pharmaceutically acceptable salt thereof, wherein X^1 is CR^Y, X^2 is CR^Y and X^3 is S. In further embodiments, each R^Y is H.

In embodiments, there is provided a compound of Formula (I), (II), (IIA), (IIB), (IIC) or (IID), or a pharmaceutically acceptable salt thereof, wherein X^1 is CR^Y, X^2 is O and X^3 is CR^Y. In further embodiments, each R^Y is H.

In embodiments, there is provided a compound of Formula (I), (II), (IIA), (IIB), (IIC) or (IID), or a pharmaceutically acceptable salt thereof, wherein X^1 is CR^Y, X^2 is N and X^3 is S. In further embodiments, R^Y is H.

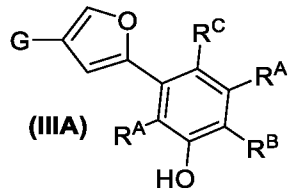
In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, that is a compound of Formula (III)



(III) ,

or a pharmaceutically acceptable salt thereof.

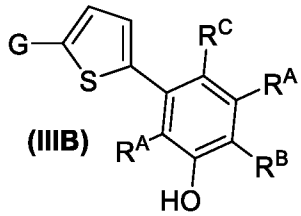
In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, that is a compound of Formula (IIIA)



(IIIA)

or a pharmaceutically acceptable salt thereof.

In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, that is a compound of Formula (IIIB)



(IIIB)

or a pharmaceutically acceptable salt thereof.

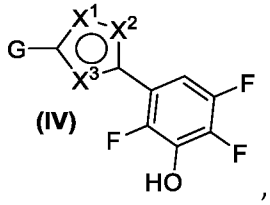
In embodiments, there is provided a compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IIIA) or (IIIB), or a pharmaceutically acceptable salt thereof, wherein each R^A is independently H or F. In further embodiments, each R^A is F.

In embodiments, there is provided a compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IIIA) or (IIIB), or a pharmaceutically acceptable salt thereof, wherein R^B is F.

In embodiments, there is provided a compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IIIA) or (IIIB), or a pharmaceutically acceptable salt thereof, wherein R^C is H or F. In further embodiments, R^C is H.

In embodiments, there is provided a compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IIIA) or (IIIB), or a pharmaceutically acceptable salt thereof, wherein each R^A is F, R^B is F and R^C is H.

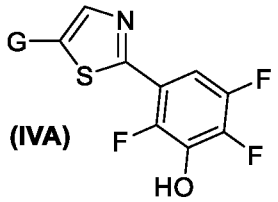
In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, that is a compound of Formula (IV)



(IV) ,

or a pharmaceutically acceptable salt thereof.

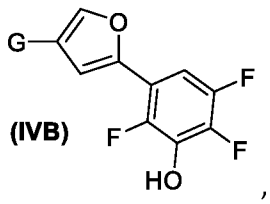
In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, that is a compound of Formula (IVA)



(IVA) ,

or a pharmaceutically acceptable salt thereof.

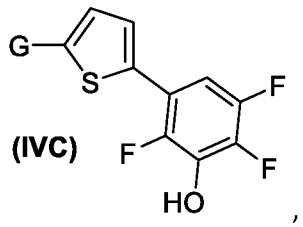
In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, that is a compound of Formula (IVB)



(IVB) ,

or a pharmaceutically acceptable salt thereof.

In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, that is a compound of Formula (IVC)



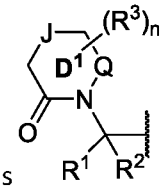
(IVC) ,

or a pharmaceutically acceptable salt thereof.

In embodiments, there is provided a compound of Formula (I), (II), (IIA), (IIB), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein J is O. In alternative embodiments, J is CH_2. In alternative embodiments, J is a covalent bond.

In embodiments, there is provided a compound of Formula (I), (II), (IIA), (IIB), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein Q is CH_2. In alternative embodiments, Q is C(=O).

In embodiments, there is provided a compound of Formula (I), (II), (IIA), (IIB), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein J is O and Q is CH_2. In alternative embodiments, J is CH_2 and Q is CH_2. In alternative embodiments, J is a covalent bond and Q is CH_2.

In embodiments, there is provided a compound of Formula (I), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein G is 

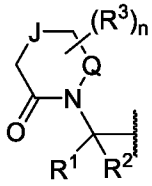
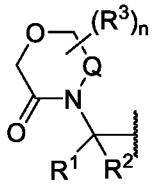
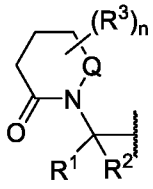
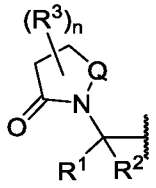
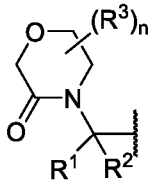
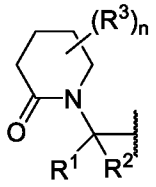
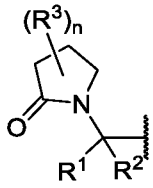
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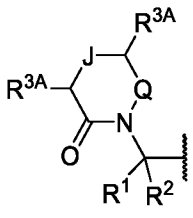
In embodiments, there is provided a compound of Formula (I), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein one carbon atom of ring D^1 is attached to a C_{2-5} alkylene group to form a spirocyclic ring, and wherein one CH_2 group of said C_{2-5} alkylene group may be optionally replaced by an oxygen group.

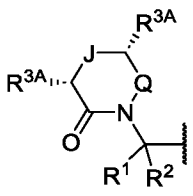
In embodiments, there is provided a compound of Formula (I), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein one carbon atom of ring D^1 is attached to a C_{2-5} alkylene group to form a spirocyclic ring.

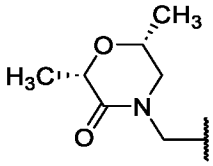
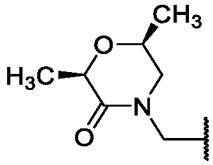
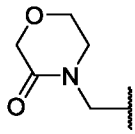
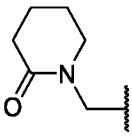
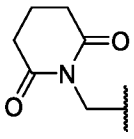
In embodiments, there is provided a compound of Formula (I), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein two carbon atoms of ring D^1 are attached to a C_{1-5} alkylene group to form a bridged or fused ring, and wherein one CH_2 group of said C_{1-5} alkylene group may be optionally replaced by an oxygen group.

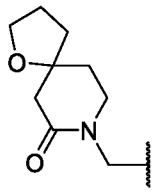
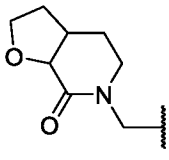
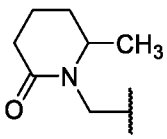
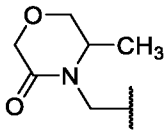
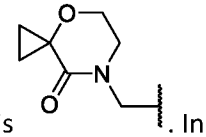
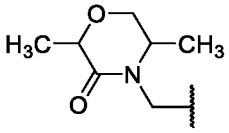
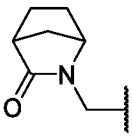
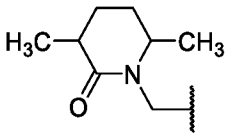
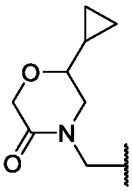
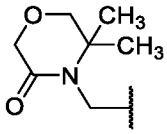
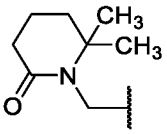
In embodiments, there is provided a compound of Formula (I), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein two carbon atoms of ring D^1 are attached to a C_{1-5} alkylene group to form a bridged or fused ring.

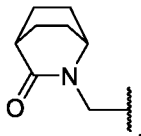
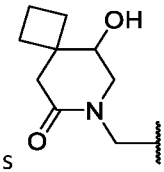
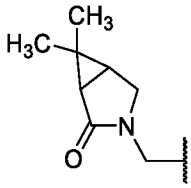
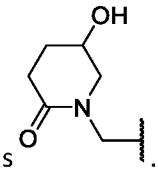
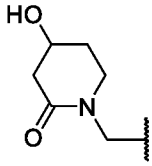
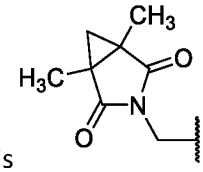
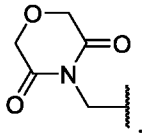
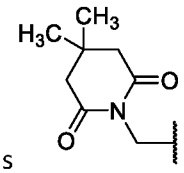
In embodiments, there is provided a compound of Formula (I), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein G is . In further embodiments, G is . In further embodiments, G is . In further embodiments, G is . In further embodiments, G is . In further embodiments, G is . In further embodiments, G is .

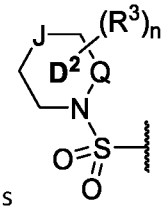
In embodiments, there is provided a compound of Formula (I), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein G is , wherein each R^{3A} is independently H, R^{4A} or R^{5A}.

In embodiments, there is provided a compound of Formula (I), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein G is , wherein each R^{3A} is independently H, R^{4A} or R^{5A}.

In embodiments, there is provided a compound of Formula (I), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein G is . In alternative embodiments, G is . In alternative embodiments, G is . In alternative embodiments, G is . In alternative embodiments, G is .

In embodiments, there is provided a compound of Formula (I), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein G is . In alternative embodiments, G is . In alternative embodiments, G is . In alternative embodiments, G is . In alternative embodiments, G is . In alternative embodiments, G is . In alternative embodiments, G is . In alternative embodiments, G is . In alternative embodiments, G is . In alternative embodiments, G is . In alternative embodiments, G is .

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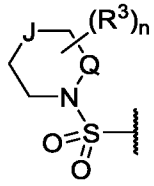
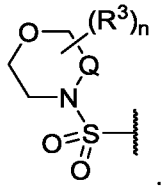
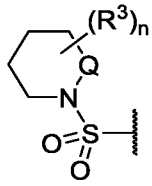
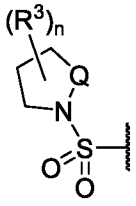
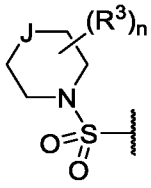
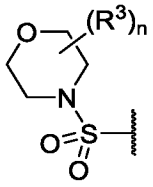
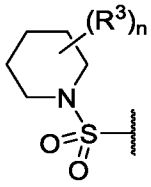
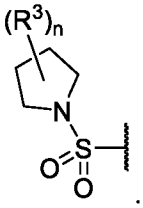
In embodiments, there is provided a compound of Formula (I), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein G is .

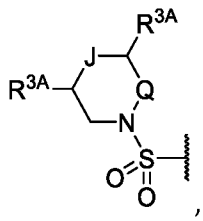
In embodiments, there is provided a compound of Formula (I), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein one carbon atom of ring D^2 is attached to a $C_{2\text{-}5}$ alkylene group to form a spirocyclic ring, and wherein one CH_2 group of said $C_{2\text{-}5}$ alkylene group may be optionally replaced by an oxygen group.

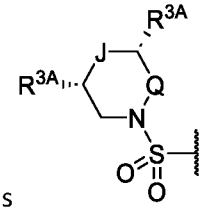
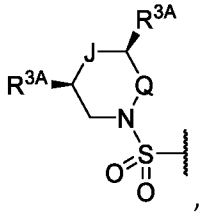
In embodiments, there is provided a compound of Formula (I), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein one carbon atom of ring D^2 is attached to a $C_{2\text{-}5}$ alkylene group to form a spirocyclic ring.

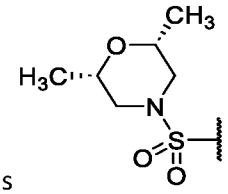
In embodiments, there is provided a compound of Formula (I), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein two carbon atoms of ring D^2 are attached to a $C_{1\text{-}5}$ alkylene group to form a bridged or fused ring, and wherein one CH_2 group of said $C_{1\text{-}5}$ alkylene group may be optionally replaced by an oxygen group.

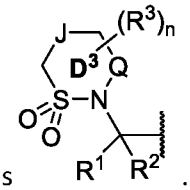
In embodiments, there is provided a compound of Formula (I), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein two carbon atoms of ring D^2 are attached to a $C_{1\text{-}5}$ alkylene group to form a bridged or fused ring.

In embodiments, there is provided a compound of Formula (I), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein G is . In further embodiments, G is . In further embodiments, G is . In further embodiments, G is . In further embodiments, G is . In further embodiments, G is . In further embodiments, G is . In further embodiments, G is .

In embodiments, there is provided a compound of Formula (I), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein G is , wherein each R^{3A} is independently H, R^{4A} or R^{5A}.

In embodiments, there is provided a compound of Formula (I), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein G is  or , wherein each R^{3A} is independently H, R^{4A} or R^{5A}.

In embodiments, there is provided a compound of Formula (I), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein G is .

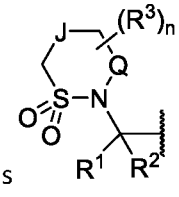
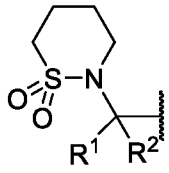
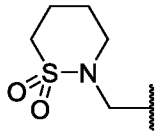
In embodiments, there is provided a compound of Formula (I), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein G is .

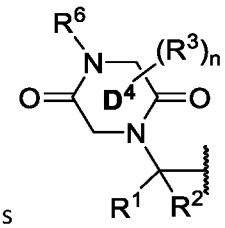
In embodiments, there is provided a compound of Formula (I), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein one carbon atom of ring D^3 is attached to a $C_{2\text{-}5}$ alkylene group to form a spirocyclic ring, and wherein one CH_2 group of said $C_{2\text{-}5}$ alkylene group may be optionally replaced by an oxygen group.

In embodiments, there is provided a compound of Formula (I), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein one carbon atom of ring D^3 is attached to a $C_{2\text{-}5}$ alkylene group to form a spirocyclic ring.

In embodiments, there is provided a compound of Formula (I), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein two carbon atoms of ring D^3 are attached to a $C_{1\text{-}5}$ alkylene group to form a bridged or fused ring, and wherein one CH_2 group of said $C_{1\text{-}5}$ alkylene group may be optionally replaced by an oxygen group.

In embodiments, there is provided a compound of Formula (I), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein two carbon atoms of ring D^3 are attached to a $C_{1\text{-}5}$ alkylene group to form a bridged or fused ring.

In embodiments, there is provided a compound of Formula (I), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein G is . In further embodiments, G is . In further embodiments, G is .

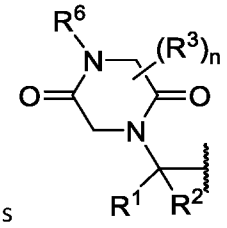
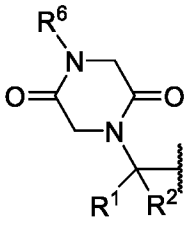
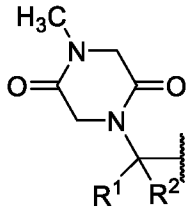
In embodiments, there is provided a compound of Formula (I), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein G is .

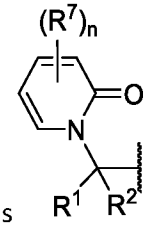
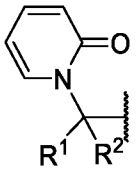
In embodiments, there is provided a compound of Formula (I), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein one carbon atom of ring D^4 is attached to a $C_{2\text{-}5}$ alkylene group to form a spirocyclic ring, and wherein one CH_2 group of said $C_{2\text{-}5}$ alkylene group may be optionally replaced by an oxygen group.

In embodiments, there is provided a compound of Formula (I), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein one carbon atom of ring D^4 is attached to a $C_{2\text{-}5}$ alkylene group to form a spirocyclic ring.

In embodiments, there is provided a compound of Formula (I), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein two carbon atoms of ring D^4 are attached to a $C_{1\text{-}5}$ alkylene group to form a bridged or fused ring, and wherein one CH_2 group of said $C_{1\text{-}5}$ alkylene group may be optionally replaced by an oxygen group.

In embodiments, there is provided a compound of Formula (I), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein two carbon atoms of ring D^4 are attached to a $C_{1\text{-}5}$ alkylene group to form a bridged or fused ring.

In embodiments, there is provided a compound of Formula (I), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein G is . In further embodiments, G is . In further embodiments, G is .

In embodiments, there is provided a compound of Formula (I), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein G is . In further embodiments, G is .

In embodiments, there is provided a compound of Formula (I), (II), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 are independently selected from H, R^4 and R^5.

In embodiments, there is provided a compound of Formula (I), (II), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein R^1 is H and R^2 is H.

In embodiments, there is provided a compound of Formula (I), (II), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein R^1 is R^4, and R^2 is H. In further embodiments, R^1 is C_{1-6} alkyl and R^2 is H. In further embodiments, R^1 is C_{1-4} alkyl and R^2 is H. In further embodiments, R^1 is CH_3 and R^2 is H.

In embodiments, there is provided a compound of Formula (I), (II), (IIB), (IIC), (IID), (III), (IIIA),(IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein R^1 is R^5, and R^2 is H. In further embodiments, R^1 is C_{3-6} cycloalkyl and R^2 is H.

In embodiments, there is provided a compound of Formula (I), (II), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 are independently R^4. In further embodiments, R^1 and R^2 are independently C_{1-6} alkyl. In further embodiments, R^1 and R^2 are independently C_{1-4} alkyl. In further embodiments, R^1 is CH_3 and R^2 is CH_3.

In embodiments, there is provided a compound of Formula (I), (II), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 together with the carbon atom to which they are attached form a cyclopropane or cyclobutane ring.

In embodiments, there is provided a compound of Formula (I), (II), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 together with the carbon atom to which they are attached form a cyclopropane ring.

In embodiments, there is provided a compound of Formula (I), (II), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 together with the carbon atom to which they are attached form a cyclobutane ring.

In embodiments, there is provided a compound of Formula (I), (II), (IIA), (IIB), (IIC), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein each R^3 is independently R^{4A}. In further embodiments, each R^3 is independently C_{1-6} alkyl. In further embodiments, each R^3 is independently C_{1-4} alkyl. In further embodiments, each R^3 is CH_3.

In embodiments, there is provided a compound of Formula (I), (II), (IIA), (IIB), (IIC), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein each R^3 is independently R^{5A}. In further embodiments, each R^3 is independently C_{3-6} cycloalkyl.

In embodiments, there is provided a compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID) (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein n is 0. In alternative embodiments, n is 1. In alternative embodiments, n is 2. In alternative embodiments, n is 3.

In embodiments, there is provided a compound of Formula (I), (II), (IIA), (IIB), (IIC), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein n is 2 and each R^3 is independently C_{1-4} alkyl. In further embodiments, n is 2 and each R^3 is CH_3.

In embodiments, there is provided a compound of Formula (I), (II), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein each R^4 is independently C_{1-6} alkyl optionally substituted with one to three F. In further embodiments, each R^4 is independently C_{1-6} alkyl (i.e. C_{1-6} alkyl is unsubstituted). In further embodiments, each R^4 is

independently C_{1-4} alkyl optionally substituted with one to three F. In further embodiments, each R^4 is independently C_{1-4} alkyl (i.e. C_{1-4} alkyl is unsubstituted). In further embodiments, each R^4 is CH_3.

In embodiments, there is provided a compound of Formula (I), (II), (IIA), (IIB), (IIC), (III), (IIIA). (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein each R^{4A} is independently C_{1-6} alkyl optionally substituted with one to three F. . In further embodiments, each R^{4A} is independently C_{1-6} alkyl (i.e. C_{1-6} alkyl is unsubstituted). In further embodiments, each R^{4A} is independently C_{1-4} alkyl optionally substituted with one to three F. In further embodiments, each R^{4A} is independently C_{1-4} alkyl (i.e. C_{1-4} alkyl is unsubstituted). In further embodiments, each R^{4A} is CH_3.

In embodiments, there is provided a compound of Formula (I), (II), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein each R^5 is independently C_{3-6} cycloalkyl optionally substituted with one to three F. In further embodiments, each R^5 is independently C_{3-6} cycloalkyl.

In embodiments, there is provided a compound of Formula (I), (II), (IIA), (IIB), (IIC), (III), (IIIA) (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein each R^{5A} is independently C_{3-6} cycloalkyl optionally substituted with one to three F. In further embodiments, each R^{5A} is independently C_{3-6} cycloalkyl.

In embodiments, there is provided a compound of Formula (I), (IIC), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, wherein R^6 is C_{1-6} alkyl, C_{3-6} cycloalkyl or H. In further embodiments, R^6 is C_{1-6} alkyl. In further embodiments, R^6 is CH_3.

In embodiments, there is provided a compound of Formula (I), (IID), (III), (IIIA), (IIIB), or a pharmaceutically acceptable salt thereof, wherein each R^7 is independently C_{1-6} alkyl, C_{3-6} cycloalkyl, -O(C_{1-6} alkyl) -O(C_{3-6} cycloalkyl), -OH, -CN, and halo. In embodiments, wherein each R^7 is independently C_{1-6} alkyl, -O(C_{1-6} alkyl), -OH, -CN, F and Cl. In embodiments, wherein each R^7 is independently C_{1-4} alkyl, -O(C_{1-4} alkyl), -OH, -CN, F and Cl.

In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, with the proviso that the compound is not 1-((3-(4-fluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-5-yl)methyl)piperidin-2-one.

In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, that is

(2R,6S)-2,6-Dimethyl-4-((5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methyl)morpholin-3-one,

(2S,6R)-2,6-Dimethyl-4-((5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methyl)morpholin-
4-((5-(2,4,5-Trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methyl)morpholin-3-one,
1-((5-(2,4,5-Trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methyl)piperidin-2-one,
1-((5-(2,4,5-Trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methyl)piperidine-2,6-dione,
3-(4-(((2R,6S)-2,6-Dimethylmorpholino)sulfonyl)furan-2-yl)-2,5,6-trifluorophenol,
2-((5-(2,4,5-Trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methyl)-1,2-thiazinane 1,1-dioxide,
5-Hydroxy-1-((5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methyl)piperidin-2-one, or
6-Cyclopropyl-4-((5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methyl)morpholin-3-one,
or a pharmaceutically acceptable salt thereof.

In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, that is
1-((2-(2,4,5-Trifluoro-3-hydroxyphenyl)thiazol-5-yl)methyl)piperidine-2,6-dione,
6-Cyclopropyl-4-((2-(2,4,5-trifluoro-3-hydroxyphenyl)thiazol-5-yl)methyl)morpholin-3-one,
(1R,5S)-3-((2-(2,4,5-Trifluoro-3-hydroxyphenyl)thiazol-5-yl)methyl)-3-azabicyclo[3.1.0]hexane-2,4-
dione,
(1R,5S)-3-((2-(2,4,5-Trifluoro-3-hydroxyphenyl)thiazol-5-yl)methyl)-3-azabicyclo[3.2.0]heptane-2,4-
dione,
1-((2-(2,4,5-Trifluoro-3-hydroxyphenyl)thiazol-5-yl)methyl)pyrrolidine-2,5-dione, or
3-((2-(2,4,5-Trifluoro-3-hydroxyphenyl)thiazol-5-yl)methyl)oxazolidine-2,4-dione,
or a pharmaceutically acceptable salt thereof.

In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, that is
2,6-Dimethyl-4-((5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methyl)morpholin-3-one,
2,6-Dimethyl-4-((5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methyl)morpholin-4-((5-
(2,4,5-Trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methyl)morpholin-3-one,
1-((5-(2,4,5-Trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methyl)piperidin-2-one,
1-((5-(2,4,5-Trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methyl)piperidine-2,6-dione,
3-(4-((2,6-Dimethylmorpholino)sulfonyl)furan-2-yl)-2,5,6-trifluorophenol,
2-((5-(2,4,5-Trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methyl)-1,2-thiazinane 1,1-dioxide,
5-Hydroxy-1-((5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methyl)piperidin-2-one,
6-Cyclopropyl-4-((5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methyl)morpholin-3-one,
1-((2-(2,4,5-Trifluoro-3-hydroxyphenyl)thiazol-5-yl)methyl)piperidine-2,6-dione,
6-Cyclopropyl-4-((2-(2,4,5-trifluoro-3-hydroxyphenyl)thiazol-5-yl)methyl)morpholin-3-one,
3-((2-(2,4,5-Trifluoro-3-hydroxyphenyl)thiazol-5-yl)methyl)-3-azabicyclo[3.1.0]hexane-2,4-dione,

3-((2-(2,4,5-Trifluoro-3-hydroxyphenyl)thiazol-5-yl)methyl)-3-azabicyclo[3.2.0]heptane-2,4-dione,
1-((2-(2,4,5-Trifluoro-3-hydroxyphenyl)thiazol-5-yl)methyl)pyrrolidine-2,5-dione, or
3-((2-(2,4,5-Trifluoro-3-hydroxyphenyl)thiazol-5-yl)methyl)oxazolidine-2,4-dione,
or a pharmaceutically acceptable salt thereof.

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 I 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or pharmaceutically acceptable salt thereof, wherein the compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), and pharmaceutically acceptable salts thereof.

In further embodiments there is provided a compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or pharmaceutically acceptable salts thereof, 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC) is, for example, a base addition salt. A base addition salt of a compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC) 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC) is, for example, an acid addition salt. An acid addition salt of a compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC) 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC) is, for example, a salt formed within a patient's body after administration of a compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC) to the patient.

The compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

The pharmaceutical formulations of the compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC),or a pharmaceutically acceptable salt thereof, described above may be prepared e.g. for parenteral, subcutaneous, intramuscular or intravenous administration.

The pharmaceutical formulations of the compound of Formula (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, 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, [1]7th ed., Mack Publishing Company, Easton, PA., (1985).

As a result of their 17BHSD13 inhibitory activity, the compounds of (I), (II), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (II), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (II), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (II), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), or a pharmaceutically acceptable salt thereof, and a dipeptidyl peptidase 4 (DPP4) inhibitor. 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC), 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), (II), (IIA), (IIB), (IIC), (IID), (III), (IIIA), (IIIB), (IV), (IVA), (IVB) or (IVC) 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.

Examples

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

(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 GRACERESOLV Silica Flash Cartridges (4–120 g) or Agela Flash Colum Silica-CS cartridges (80–330 g), or on reversed phase silica using Agela Technologies C-18, spherical cartridges (20–35 µm, 100 A, 80–330 g), manually or automated using a Grace REVELERIS X2 Flash system or similar system;

(viii) preparative TLC was performed on glass-backed silica plates (20×20 cm) covered with a 1 mm thick silica gel (particle size of 10–40 µm), in a glass chamber, using the appropriate solvent or solvent mixtures as eluant as stated in the experimental description;

(ix) preparative reverse phase HPLC and preparative reverse 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 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 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 XBRIDGE Shield RP18 OBD column (5µm, 150x30 mm ID) using a gradient of MeCN in water (containing 10 mmol/L NH_4HCO_3+0.05%NH_3 in H_2O); **PrepMethod D:** The compound purified by preparative HPLC on a Kromasil C8 column (10 µm, 250×20 mm ID) using a gradient of MeCN in H2O/MeCN/FA (95/5/0.2) 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.

(x) 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;

(xi) 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;

(xii) 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;

(xiii) 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 ^1H frequencies of 300, 400, 500 and 600 MHz, respectively. The experiments were typically recorded at 25°C. Chemical shifts are given in ppm 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 a more equal relationship, in such instances the peaks of such rotamers are either reported as multiplets, if the signals of said rotamers are partially overlapping, or as individual peaks, if the signals of said rotamers are well separated and only the total number of protons are reported. The ratio of major vs minor rotamer is reported if known.

(xiv) 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;

(xv) 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

(xvi) 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;

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

(xviii) in general Examples and Intermediate compounds are named using ChemDraw Professional version 22.2.0 from PerkinElmer. ChemDraw Professional version 22.2.0 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.

ChemDraw is optionally using labels in the graphical representation of stereocenters such as '&' and 'or' to describe the configuration of the stereochemical centers present in the structure. A number following the '&' and 'or' flag is assigned to each stereocenter present in the structure. The numbers are incremented automatically to indicate that stereocenters may vary independently to each other.

In general, for chemical structures of Examples and Intermediates where more than one stereocenter is present and said stereocenters have a fixed relative configuration, the same number is used after the label '&' and 'or' to indicate that said stereocenters forms a group. A third stereocenter present in the same chemical structure, that varies independently to the former stereocenters, is designated with a unique new number following the label '&' and 'or'.

In general chemical structures of Examples and Intermediates containing the label '&' at a stereocenter, means the configuration of such Example or Intermediate at that stereocenter is a mixture of both (*R*) and (*S*); and a label 'or' means the configuration of such Example or Intermediate at that stereocenter is either (*S*) or (*R*). Absolute, unspecified, '&', and 'or' stereocenters can all be present in a single structure.

In general, for chemical structures of Examples and Intermediates where only one stereocenter is present and said stereocenter is racemic, no flag is designated to the stereocenter and the structure is drawn with a straight bond at said stereocenter.

In general for structures of Examples and Intermediates where all of the stereocenters are designated as '&', the structure is named with a “rac-” prefix. For structures of Examples and

Intermediates where all of the stereocenters are designated as 'or', the structure is named with a "rel-" prefix.

In general, for chemical structures of Examples and Intermediates where more than one stereocenter is present and said stereocenters have a fixed relative configuration, the same number is used after the label '&' and 'or' to indicate that said stereocenters forms a group. A third stereocenter present in the same chemical structure, that varies independently to the former stereocenters, is designated with a unique new number following the label '&' and 'or'.

In general the label "Isomer 1" corresponds to the first eluted isomer, and "Isomer 2" corresponds to the second eluted isomer, on a given chiral HPLC column and eluent, and are used to distinguish two isomers containing one or more stereocenters with absolute unknown configuration;

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

AcOH	Acetic acid
Aq	Aqueous
Art	Article
bis(pinacolato)diboron	4,4,4',4',5,5,5',5'-Octamethyl-2,2'-bi-1,3,2-dioxaborolane
Calcd	Calculated
DCM	Dichloromethane
DIPEA	*N*-ethyl-*N*-isopropyl-propan-2-amine
DMF	*N*,*N*-dimethylformamide
DMSO	Dimethyl sulfoxide
dppb	1,4-Bis(diphenylphosphino)butane
EDC	3-(((ethylimino)methylene)amino)-*N*,*N*-dimethylpropan-1-amine
e.g.	for example
ESI	Electrospray ionization
etc.	et cetera
EtOAc	Ethyl acetate
FA	Formic acid
(g)	gas
HPLC	High performance liquid chromatography
HOBt	1-hydroxybenzotriazole;hydrate
HRMS	High resolution mass spectrometry
ID	innter diameter

i.e.	id est
LCMS	Liquid Chromatography Mass Spectrometry
MeCN	Acetonitrile
MeOH	Methanol
MS	Mass spectrometry
MTBE	methyl tert-butyl ether
m/z	mass spectrometry peak(s)
NaO*t*-Am	sodium 2-methylbutan-2-olate
NBS	*N*-bromosuccinimide
NMP	1-methylpyrrolidin-2-one
NMR	Nuclear magnetic resonance
$Pd(OAc)_2$	Palladium(II) acetate
rt	Room temperature
sat	Saturated
SFC	Supercritical fluid chromatography
TEA	Triethylamine
TFA	trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
UPLC	ultra performance liquid chromatography
UV	ultraviolet
vs	versus
XPhos	2-dicyclohexylphosphino-2',4',6'-tri-iso-propyl-1,1'-biphenyl
XPhos Pd G3	(2-Dicyclohexylphosphino-2’,4’,6’-triisopropyl-1,1’-biphenyl)[2-(2’-amino-1,1’-biphenyl)]palladium(II) methanesulfonate, XPhos-G3-Palladacycle. (CAS Registry Number 1445085-55-1)

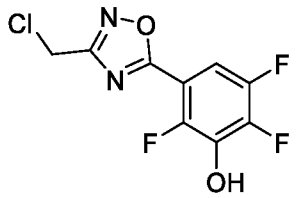
Units

A	Angström
C	Celcius
cm	centimeter(s)
g	gram
h	hour(s)
M	mole per liter
mg	milligram

MHz	megaherz
min	minute(s)
mL	milliliter
mm	millimeter
mmol	millimole(s)
µm	micrometer
µL	Microlitre
ppm	parts per million

Intermediate 1

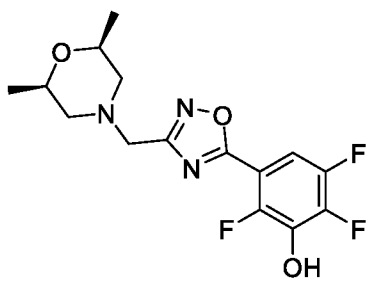
3-(3-(Chloromethyl)-1,2,4-oxadiazol-5-yl)-2,5,6-trifluorophenol



TEA (5.39 mL, 38.70 mmol) was added slowly to 2,4,5-trifluoro-3-hydroxybenzoyl chloride (6.11 g, 29.0 mmol) and 2-chloro-*N*-hydroxyacetimidamide (2.1 g, 19.4 mmol) in DCM (20 mL) at 25°C. The resulting solution was stirred at 25°C for 1 h. The reaction mixture was poured into $NaHCO_3$ (sat, aq, 200 mL), and extracted with DCM (3×100 mL). The combined organic layer was dried over Na_2SO_4, filtered and the filtrate was concentrated. The residue was dissolved in AcOH (20 mL) at 25°C, and the resulting solution was stirred at 100°C for 3 h. The solvent was partially removed under reduced pressure and the residue was poured into $NaHCO_3$ (sat, aq, 200 mL) and extracted with EtOAc (3×100 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by straight phase flash chromatography on silica (gradient: 2–50% EtOAc in heptane) to give the title compound (620 mg, 56%); MS (ESI) *m/z* $[M-H]^-$ 262.9.

Intermediate 2

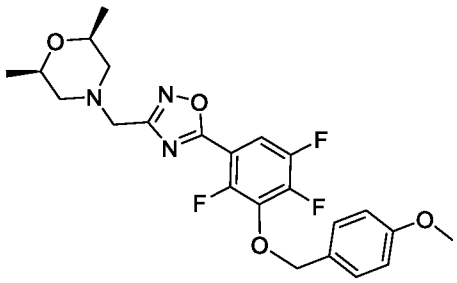
3-(3-(((2*S*,6*R*)-2,6-Dimethylmorpholino)methyl)-1,2,4-oxadiazol-5-yl)-2,5,6-trifluorophenol



K_2CO_3 (188 mg, 1.36 mmol) was added to 3-(3-(chloromethyl)-1,2,4-oxadiazol-5-yl)-2,5,6-trifluorophenol **Intermediate 1** (300 mg, 1.13 mmol), (2*S*,6*R*)-2,6-dimethylmorpholine (131 mg, 1.13 mmol) and NaI (85 mg, 0.57 mmol) in MeCN (5 mL) at 25°C. The resulting mixture was stirred at 25°C for 16 h. The reaction mixture was filtered, and the filtrate was concentrated. The residue was purified by preparative TLC (EtOAc:petroleum ether, 1:1), to afford the title compound (160 mg, 41%) as a pale yellow gum; MS (ESI) *m/z* $[M+H]^+$ 344.

Intermediate 3

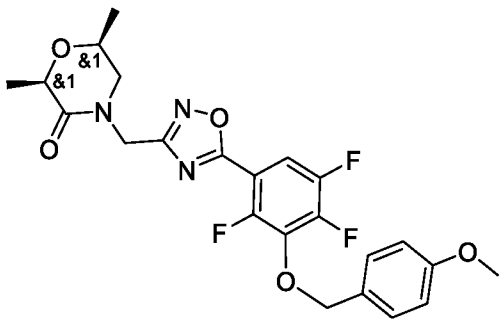
(2*S*,6*R*)-2,6-Dimethyl-4-((5-(2,4,5-trifluoro-3-((4-methoxybenzyl)oxy)phenyl)-1,2,4-oxadiazol-3-yl)methyl)morpholine



3-(3-(((2*S*,6*R*)-2,6-Dimethylmorpholino)methyl)-1,2,4-oxadiazol-5-yl)-2,5,6-trifluorophenol **Intermediate 2** (160 mg, 0.47 mmol), 1-(chloromethyl)-4-methoxybenzene (stabilized with $CaCO_3$) (88 mg, 0.56 mmol) and K_2CO_3 (193 mg, 1.40 mmol) in MeCN (5 mL) was stirred at 80°C for 16 h. The reaction mixture was filtered, and the filtrate was concentrated. The residue was purified by preparative TLC (EtOAc:petroleum ether, 1:2), to afford the title compound (112 mg, 51.9%) as a pale yellow gum; MS (ESI) *m/z* $[M+H]^+$ 464.

Intermediate 4

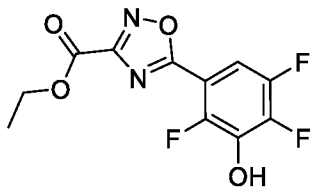
***rac*-(2*R*,6*S*)-2,6-Dimethyl-4-((5-(2,4,5-trifluoro-3-((4-methoxybenzyl)oxy)phenyl)-1,2,4-oxadiazol-3-yl)methyl)morpholin-3-one**



I_2 (1.97 g, 7.77 mmol) was added to (2*S*,6*R*)-2,6-dimethyl-4-((5-(2,4,5-trifluoro-3-((4-methoxybenzyl)oxy)phenyl)-1,2,4-oxadiazol-3-yl)methyl)morpholine **Intermediate 3** (160 mg, 0.35 mmol) and $NaHCO_3$ (870 mg, 10.36 mmol) in THF (10 mL) and water (4 mL) at 25°C. The resulting mixture was stirred at 25°C for 3 h. The reaction mixture was added to a mixture of $Na_2S_2O_3$ (sat, aq, 100 mL) and $NaHCO_3$ (sat, aq, 100 mL). The mixture was extracted with DCM (2×100 mL), and the combined organic layer was washed with $NaHCO_3$ (sat, aq, 100 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by preparative TLC (EtOAc:petroleum ether, 1:1), to afford the title compound (101 mg, 61%) as a pale yellow solid; MS (ESI) *m/z* $[M+H]^+$ 478.

Intermediate 5

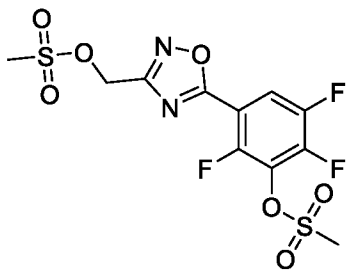
Ethyl 5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazole-3-carboxylate



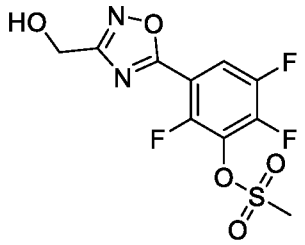
EDC (43.5 g, 227 mmol) and HOBt (15.34 g, 114 mmol) were added to ethyl (*Z*)-2-amino-2-(hydroxyimino)acetate (15 g, 113 mmol), 2,4,5-trifluoro-3-hydroxybenzoic acid (21.81 g, 113 mmol) and $NaHCO_3$ (28.6 g, 340.6 mmol) in DMF (150 mL) under a N_2(g) atmosphere. The resulting solution was stirred at 100°C for 1 h. The reaction mixture was filtered through CELITE, and the filtrate was concentrated, diluted with DCM (300 mL) and washed with water (300 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by reversed phase flash chromatography on a C18 column (gradient 50–60% MeCN in water (0.5% FA)) to give the title compound (7.0 g, 21%) as a white solid; MS (ESI) *m/z* $[M+H]^+$ 289.

Intermediate 6

(5-(2,4,5-Trifluoro-3-((methylsulfonyl)oxy)phenyl)-1,2,4-oxadiazol-3-yl)methyl methanesulfonate



Step 1: 2,3,6-Trifluoro-5-(3-(hydroxymethyl)-1,2,4-oxadiazol-5-yl)phenyl methanesulfonate



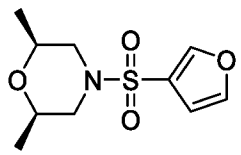
$NaBH_4$ (1.18 g, 31.2 mmol) was added to a stirred solution of ethyl 5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazole-3-carboxylate **Intermediate 5** (3.0 g, 10.4 mmol) in MeOH (60 mL), and the resulting mixture was stirred at rt for 15 min. A second portion of $NaBH_4$ (1.18 g, 31.2 mmol) was added and the reaction mixture was stirred at rt for 15 min. 3.8 M HCl (60 mL) was added, and the reaction mixture was stirred at rt for 15 min. The reaction mixture was concentrated, and the remaining aqueous solution was diluted with water and extracted with EtOAc. The organic layer was concentrated to give the subtitle compound (2.82 g); MS (ESI) *m/z* $[M+H]^+$ 247.1.

Step 2: (5-(2,4,5-trifluoro-3-((methylsulfonyl)oxy)phenyl)-1,2,4-oxadiazol-3-yl)methyl methanesulfonate

2,3,6-Trifluoro-5-(3-(hydroxymethyl)-1,2,4-oxadiazol-5-yl)phenyl methanesulfonate **Intermediate 6 Step a)** (2.54 g) was dissolved in DCM (100 mL). DIPEA (9.06 mL, 52.0 mmol) and methanesulfonic anhydride (5.43 g, 31.2 mmol) were added and the reaction mixture was stirred at rt for 30 min. 3.8 M HCl (100 mL) was added, and the phases were separated. The aqueous layer was extracted with DCM, and the combined organic layer was passed through a phase separator and concentrated. The residue was purified by straight phase flash chromatography on silica (gradient: 40–70% EtOAc in heptane) to give the title compound (3.70 g, 88%) as an off-white solid; MS (ESI) *m/z* $[M+H]^+$ 403.

Intermediate 7

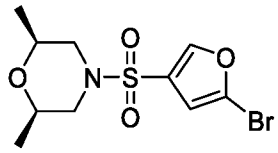
(2*R*,6*S*)-4-(Furan-3-ylsulfonyl)-2,6-dimethylmorpholine



(2*R*,6*S*)-2,6-Dimethylmorpholine (747 mg, 6.48 mmol) was added slowly to a solution of furan-3-sulfonyl chloride (900 mg, 5.40 mmol) and TEA (1.506 mL, 10.81 mmol) in DCM (10 mL) at 0°C. The reaction mixture was allowed to reach rt and the solution 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: 0–100% MeCN in water) to afford the title compound (1.04 g, 78%) as a yellow oil; MS (ESI) *m/z* $[M+H]^+$ 246.

Intermediate 8

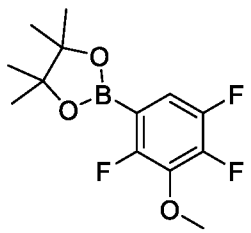
(2*R*,6*S*)-4-((5-Bromofuran-3-yl)sulfonyl)-2,6-dimethylmorpholine



NBS (710 mg, 3.99 mmol) was added dropwise to a stirred solution of (2*R*,6*S*)-4-(furan-3-ylsulfonyl)-2,6-dimethylmorpholine **Intermediate 7** (815 mg, 3.32 mmol) anhydrous DMF (20 mL) at 0°C. The resulting solution was stirred at 60°C for 2.5 h. The reaction mixture was stirred at 60°C for 2.5 h and then cooled to 0°C. NBS (710 mg, 3.99 mmol) was added dropwise at 0°C and the reaction mixture was then heated at 60°C for 2.5 h. The reaction mixture was cooled again to 0°C and NBS (710 mg, 3.99 mmol) was added dropwise at 0°C. The reaction mixture was heated at 60°C for 2.5 h. The reaction mixture was diluted with water (200 mL) and extracted with EtOAc (3×150 mL). The combined organic layer was washed with brine (sat, 3×200 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by reversed phase flash chromatography on a C18-column (gradient: 10–100% MeCN in water) and then by preparative TLC (EtOAc:petroleum ether, 1:4), to afford the title compound (525 mg, 49 %) as a white solid; MS (ESI) *m/z* $[M+H]^+$ 324/326.

Intermediate 9

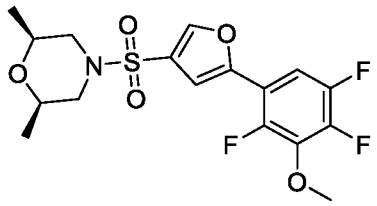
4,4,5,5-Tetramethyl-2-(2,4,5-trifluoro-3-methoxyphenyl)-1,3,2-dioxaborolane



A mixture of 2,4,5-trifluoro-3-methoxybenzoic acid (2.40 g, 11.6 mmol), $Pd(OAc)_2$ (0.157 g, 0.70 mmol), bis(pinacolato)diboron (4.44 g, 17.5 mmol), pivalic anhydride (3.54 mL, 17.5 mmol), TEA (2.44 mL, 17.5 mmol) and dppb (0.596 g, 1.40 mmol) in 1,4-dioxane (60 mL) was stirred at 100°C for 48 h under a N_2(g) atmosphere. The mixture was cooled to rt and diluted with EtOAc (60 mL). The solids were filtered off and the filtrate was concentrated. The crude product was purified by straight phase flash chromatography on silica (gradient: 0–6% EtOAc in heptane) to give the title compound (2.25 g, 67%) as a colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (s, 12H), 4.01 (s, 3H), 7.20 (td, 1H).

Intermediate 10

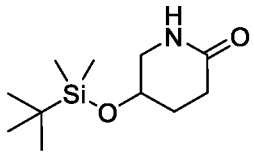
(2*R*,6*S*)-2,6-Dimethyl-4-((5-(2,4,5-trifluoro-3-methoxyphenyl)furan-3-yl)sulfonyl)morpholine



K_3PO_4 (802 mg, 3.78 mmol) was added to (2*R*,6*S*)-4-((5-bromofuran-3-yl)sulfonyl)-2,6-dimethylmorpholine **Intermediate 8** (490 mg, 1.51 mmol), 4,4,5,5-tetramethyl-2-(2,4,5-trifluoro-3-methoxyphenyl)-1,3,2-dioxaborolane **Intermediate 9** (1.31 g, 4.53 mmol), XPhos Pd G3 (383 mg, 0.45 mmol) and XPhos (216 mg, 0.45 mmol) in THF (10 mL) and water (2 mL) at 25°C. The reaction mixture was stirred under a N_2(g) atmosphere at 60°C for 2 h. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (3×100 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by preparative TLC (EtOAc:petroleum ether, 1:4), to afford the title compound (448 mg, 73%) as a white solid; MS (ESI) *m/z* $[M+H]^+$ 406.

Intermediate 11

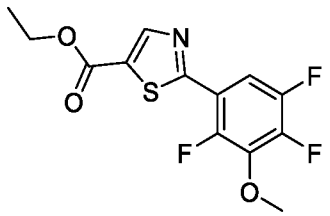
5-((*tert*-Butyldimethylsilyl)oxy)piperidin-2-one



tert-Butylchlorodimethylsilane (0.564 mL, 3.26 mmol) was added to a mixture of 5-hydroxypiperidin-2-one (302 mg, 2.62 mmol) and 1*H*-imidazole (357 mg, 5.25 mmol) in anhydrous NMP (3 mL) at rt and the resulting solution was stirred at rt overnight. The solution was diluted with MTBE (40 mL) and washed with water (3×15 mL), dried over Na_2SO_4, filtered and concentrated to give the title compound (485 mg, 81%) as a white solid; MS *m/z* (ESI) $[M+H]^+$ 230.

Intermediate 12

Ethyl 2-(2,4,5-trifluoro-3-methoxyphenyl)thiazole-5-carboxylate

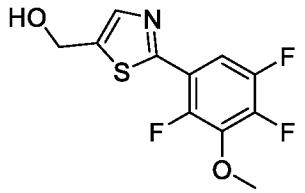


A solution of 2,4,5-trifluoro-3-methoxybenzothioamide *WO2023222850 A1* (1.095 g, 4.95 mmol) and ethyl 2-chloro-3-oxopropanoate (0.820 g, 5.45 mmol) in toluene (25 mL) was heated at 105–110°C

for 4 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by straight phase flash chromatography on silica, (0–30% EtOAc in heptane) to give an orange solid which was further purified by trituration with heptane to give the title compound (282 mg, 18%) as a pale orange solid; MS *m/z* (ESI) $[M+H]^+$ 318.1.

Intermediate 13

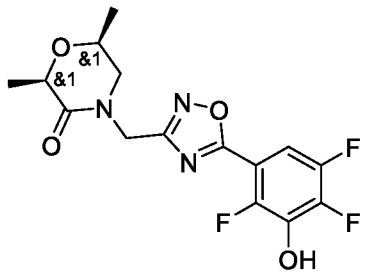
(2-(2,4,5-Trifluoro-3-methoxyphenyl)thiazol-5-yl)methanol



$NaBH_4$ (0.227 g, 5.99 mmol) was added to a stirred solution of ethyl 2-(2,4,5-trifluoro-3-methoxyphenyl)thiazole-5-carboxylate **Intermediate 12** (0.38 g, 1.20 mmol) in THF (4.5 mL) and MeOH (1.5 mL). The reaction mixture was stirred at 55 °C for 1 h. The reaction solution was cooled to rt and 3.8 M HCl (5 mL, aq) was added, and the mixture was stirred for 10 min. THF and MeOH was evaporated off, and the remaining water residue was extracted with 150 mL EtOAc (×2). The combined organic layers were washed with water (20 mL), passed through a phase separator, and concentrated under reduced pressure to give the title compound (0.33 g, 100 %) as a white solid; MS (ESI) *m/z* $[M+H]^+$ 276.1

Example 1

rac-(2*R*,6*S*)-2,6-Dimethyl-4-((5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methyl)morpholin-3-one

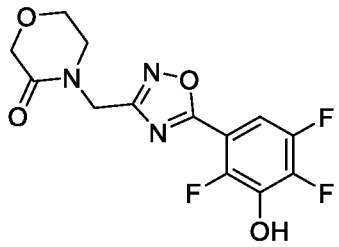


A solution of 4 M HCl in dioxane (0.359 mL, 2.51 mmol) and *rac*-(2*R*,6*S*)-2,6-dimethyl-4-((5-(2,4,5-trifluoro-3-((4-methoxybenzyl)oxy)phenyl)-1,2,4-oxadiazol-3-yl)methyl)morpholin-3-one **Intermediate 4** (80 mg, 0.17 mmol) in 1,4-dioxane (10 mL) was stirred at 60°C for 3 h. The reaction mixture was concentrated and the residue was purified by preparative HPLC, PrepMethod A (gradient: 6–27%), to afford the title compound (30 mg, 50%) as a white solid; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{15}H_{15}F_3N_3O_4$: 358.1008, found: 358.1004; ^1H NMR (500 MHz, DMSO-d_6) δ 1.14 (3H,

d), 1.27 (3H, d), 3.29–3.40 (2H, m), 3.91–4.00 (1H, m), 4.20 (1H, q), 4.62 (1H, d), 4.74 (1H, d), 7.1–7.17 (1H, m).

Example 2

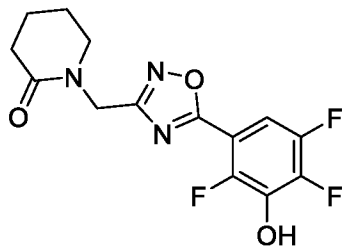
4-((5-(2,4,5-Trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methyl)morpholin-3-one



(5-(2,4,5-Trifluoro-3-((methylsulfonyl)oxy)phenyl)-1,2,4-oxadiazol-3-yl)methyl methanesulfonate **Intermediate 6** (100 mg, 0.25 mmol) was added to a stirred suspension of morpholin-3-one (55.3 mg, 0.55 mmol) and NaO*t*-Am (60 mg, 0.55 mmol) in NMP (3 mL) and the resulting suspension was stirred at rt for 1.5 h. AcOH (0.043 mL, 0.75 mmol) was added followed by water (0.1 mL) and the mixture was filtered through a syringe filter (Glass Acrodisk 25 mm, 1.0 µm). The filtrate was purified by preparative HPLC, PrepMethod B (gradient: 15–55%), to give the title compound (59 mg, 72%) as a white solid; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{13}H_{11}F_3N_3O_4$: 330.0696, found: 330.0684; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.49–3.55 (2H, m), 3.85–3.9 (2H, m), 4.12 (2H, s), 4.79 (2H, s), 7.59 (1H, ddd), 11.64 (1H, s).

Example 3

1-((5-(2,4,5-Trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methyl)piperidin-2-one

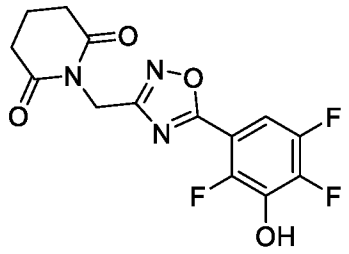


A solution of (5-(2,4,5-trifluoro-3-((methylsulfonyl)oxy)phenyl)-1,2,4-oxadiazol-3-yl)methyl methanesulfonate **Intermediate 6** (75 mg, 0.19 mmol) in NMP (0.7 mL) was added to a stirred suspension of piperidin-2-one (47 mg, 0.41 mmol) and NaO*t*-Am (45.2 mg, 0.41 mmol) in NMP (1.3 mL) and the resulting solution was stirred at rt for 20 min. AcOH (32 µL, 0.56 mmol) was added followed by water (0.1 mL) and the mixture was filtered through a syringe filter (Glass Acrodisk 25 mm, 1.0 µm). The filtrate was purified by preparative HPLC, PrepMethod B (gradient: 15–55%), to give the title compound (29 mg, 47%) as a white solid; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{14}H_{13}F_3N_3O_3$:

328.0904, found: 328.0926; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.71–1.82 (4H, m), 2.29 (2H, t), 3.43 (2H, t), 4.72 (2H, s), 7.5–7.59 (1H, m), 11.64 (1H, s).

Example 4

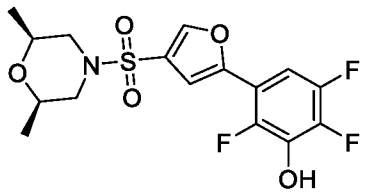
1-((5-(2,4,5-Trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methyl)piperidine-2,6-dione



(5-(2,4,5-Trifluoro-3-((methylsulfonyl)oxy)phenyl)-1,2,4-oxadiazol-3-yl)methyl methanesulfonate **Intermediate 6** (100 mg, 0.25 mmol) was added to a stirred suspension of piperidine-2,6-dione (62 mg, 0.55 mmol) and NaO*t*-Am (60 mg, 0.55 mmol) in anhydrous NMP (3 mL) and the resulting suspension was stirred at rt overnight. AcOH (0.043 mL, 0.75 mmol) was added followed by water (0.1 mL) and the mixture was filtered through a syringe filter (Glass Acrodisk 25 mm, 1.0 µm). The filtrate was purified by preparative HPLC PrepMethod B (gradient: 15–55%), to give the title compound (47 mg, 55%) as a white solid; HRMS (ESI) *m/z* $[M+H]^+$ +calcd for $C_{14}H_{11}F_3N_3O_4$: 342.0696, found: 342.0690; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.90 (2H, p), 2.71 (4H, t), 5.04 (2H, s), 7.54 (1H, ddd), 11.64 (1H, s).

Example 5

3-(4-(((2*R*,6*S*)-2,6-Dimethylmorpholino)sulfonyl)furan-2-yl)-2,5,6-trifluorophenol

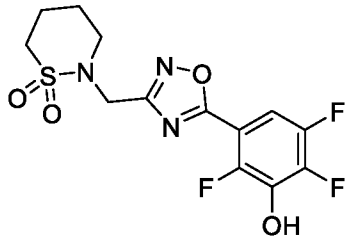


A solution of (2*S*,6*R*)-2,6-dimethyl-4-((5-(2,4,5-trifluoro-3-methoxyphenyl)furan-3-yl)sulfonyl)morpholine **Intermediate 10** (317 mg, 0.78 mmol) in methanesulfonic acid (10 mL) was stirred at 25°C for 30 min. *rac*-D-Methionine (467 mg, 3.13 mmol) was added portion wise and the resulting solution was stirred at 60°C for 18 h. The reaction mixture was very carefully poured into $NaHCO_3$ (sat, aq, 100 mL) and extracted with EtOAc (3×150 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by preparative TLC (EtOAc:petroleum ether, 1:1) and then by preparative HPLC PrepMethod C (gradient 15–35%), to

afford the title compound (55 mg, 18%) as a white solid; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{17}F_3NO_5S$: 390.0618, found: 390.0650; ^1H NMR (300 MHz, $CDCl_3$) δ 1.19 (6H, d), 2.14 (2H, dd), 3.54–3.62 (2H, m), 3.67–3.83 (2H, m), 6.92–6.99 (1H, m), 7.19 (1H, ddd), 7.93 (1H, d).

Example 6

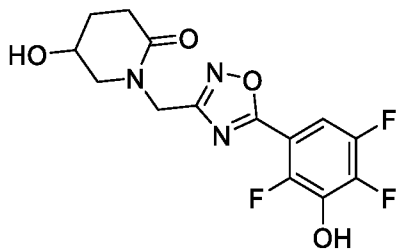
2-((5-(2,4,5-Trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methyl)-1,2-thiazinane 1,1-dioxide



NaO*t*-Am (60.2 mg, 0.55 mmol) was added to a solution of 1,2-thiazinane 1,1-dioxide (74 mg, 0.55 mmol) in anhydrous NMP (1.5 mL) and the resulting mixture was stirred at rt for 2 min. (5-(2,4,5-Trifluoro-3-((methylsulfonyl)oxy)phenyl)-1,2,4-oxadiazol-3-yl)methyl methanesulfonate **Intermediate 6** (100 mg, 0.25 mmol) was added and the reaction mixture was stirred at rt for 1 h. AcOH (43 µL, 0.75 mmol) was added followed by water (0.1 mL) and the mixture was filtered through a syringe filter (Glass Acrodisk 25 mm, 0.45 µm). The filtrate was purified by preparative HPLC, PrepMethod B, (gradient: 20–60%), to give the title compound (54 mg, 60%) as a white solid; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{13}H_{13}F_3N_3O_4S$: 364.0574, found: 364.0588; ^1H NMR (DMSO-d_6) δ: 1.56–1.65 (2H, m), 2.00–2.09 (2H, m), 3.22 (2H, t), 3.43 (2H, t), 4.54 (2H, s), 7.55–7.64 (1H, m), 11.67 (1H, s)

Example 7

5-Hydroxy-1-((5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methyl)piperidin-2-one

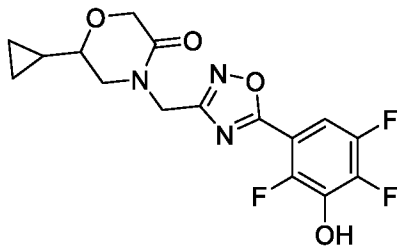


(5-(2,4,5-Trifluoro-3-((methylsulfonyl)oxy)phenyl)-1,2,4-oxadiazol-3-yl)methyl methanesulfonate **Intermediate 6** (100 mg, 0.25 mmol) was added to a stirred suspension of of 5-((*tert*-butyldimethylsilyl)oxy)piperidin-2-one **Intermediate 11** (125 mg, 0.55 mmol) and NaO*t*-Am (60 mg, 0.55 mmol) in NMP (3 mL) and the reaction mixture was stirred at rt for 2 h. NaO*t*-Am (27 mg, 0.25

mmol) was added and the reaction mixture was stirred for 2 h. The reaction mixture was poured into 0.05 M $KHSO_4$ (aq, 20 mL) and extracted with MTBE (40 mL). The organic layer was washed with water (2×15 mL), dried over Na_2SO_4, filtered and concentrated. The residue was dissolved in 90% TFA (aq, 2 mL) and stirred at rt for 1 h. The solution was concentrated, and the residue was purified by preparative HPLC , PrepMethod B (gradient: 10–50%) to give the title compound (42 mg, 50%) as a white solid; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{14}H_{13}F_3N_3O_4$: 344.0852, found: 344.0852; ^1H NMR (500 MHz, DMSO-d_6) δ 1.69–1.79 (1H, m), 1.82–1.92 (1H, m), 2.26 (1H, dt), 2.37–2.46 (1H, m), 3.27 (1H, dd), 3.54 (1H, dd), 3.96–4.01 (1H, m), 4.59 (1H, d), 4.79 (1H, d), 5.08 (1H, s), 7.52–7.61 (1H, m), 11.65 (1H, s).

Example 8

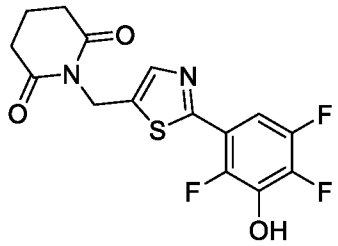
6-Cyclopropyl-4-((5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methyl)morpholin-3-one



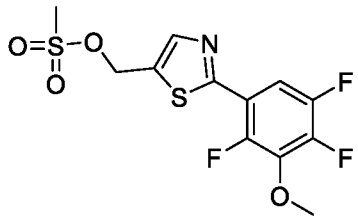
(5-(2,4,5-Trifluoro-3-((methylsulfonyl)oxy)phenyl)-1,2,4-oxadiazol-3-yl)methyl methanesulfonate **Intermediate 6** (100 mg, 0.25 mmol) was added to a stirred suspension 6-cyclopropylmorpholin-3-one (77 mg, 0.55 mmol) and NaO*t*-Am (60 mg, 0.55 mmol) in NMP (3 mL) and the reaction mixture was stirred at rt for 3 h. AcOH (85 µL, 1.49 mmol) was added and the solution was filtered through a syringefilter (Glass Acrodisk 25 mm, 1.0 µm). The filter was washed with DMSO (0.5 mL) and the combined filtrates were purified by preparative HPLC, PrepMethod D (gradient: 25–65%), to give the title compound (39 mg, 43%) as an off white solid; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{15}F_3N_3O_4$: 370.1008, found: 370.0992; ^1H NMR (DMSO-d_6) δ 0.26–0.40 (2H, m), 0.44–0.54 (2H, m), 0.89–0.99 (1H, m), 3.23 (1H, td), 3.48–3.55 (2H, m), 4.08 (1H, d), 4.17 (1H, d), 4.68 (1H, d), 4.88 (1H, d), 7.59 (1H, ddd), 11.64 (1H, s).

Example 9

1-((2-(2,4,5-Trifluoro-3-hydroxyphenyl)thiazol-5-yl)methyl)piperidine-2,6-dione

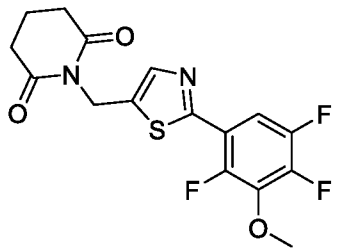


Step a) 2-(2,4,5-Trifluoro-3-methoxyphenyl)thiazol-5-yl)methyl methanesulfonate



Methanesulfonic anhydride (0.171 g, 0.98 mmol) was added to a stirred solution of (2-(2,4,5-trifluoro-3-methoxyphenyl)thiazol-5-yl)methanol **Intermediate 13** (0.180 g, 0.65 mmol) and DIPEA (0.343 mL, 1.96 mmol) in DCM (6 mL). The reaction mixture was stirred at rt for 30 min to give a solution of crude subtitle compound that was used directly in **Example 9 step b).**

Step b) 1-((2-(2,4,5-Trifluoro-3-methoxyphenyl)thiazol-5-yl)methyl)piperidine-2,6-dione



A crude solution of (2-(2,4,5-trifluoro-3-methoxyphenyl)thiazol-5-yl)methyl methanesulfonate in DCM, **Example 9 step a**) was added to a stirred solution of piperidine-2,6-dione (37 mg, 0.33 mmol) and NaO*t*-Am (70 mg, 0.64 mmol) in NMP (2 mL). The reaction mixture was stirred at rt for 2 h. AcOH (0.074 mL, 1.30 mmol) was added, and the DCM was evaporated under reduced pressure to give a solution of crude subtitle compound in NMP that was used directly in **Example 9 step c)**; MS (ESI) *m/z* $[M+H]^+$ 371.1.

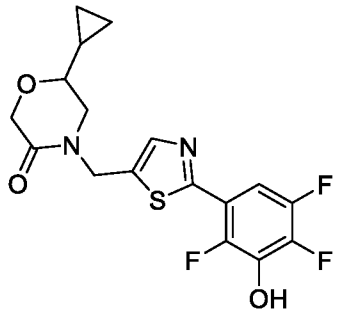
Step c) 1-((2-(2,4,5-Trifluoro-3-hydroxyphenyl)thiazol-5-yl)methyl)piperidine-2,6-dione

A solution of crude 1-((2-(2,4,5-trifluoro-3-methoxyphenyl)thiazol-5-yl)methyl)piperidine-2,6-dione in NMP, **Example 9 step b),** and KI (717 mg, 4.32 mmol) was diluted with NMP (2 mL) and heated at 130 °C for 2 h. The reaction mixture was stirred at rt overnight. The mixture was diluted with DMSO, filtered and purified by preparative HPLC, **PrepMethod D** (gradient: 20-60%) to give the title compound (21 mg, 27 %) as a white solid; HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{15}H_{12}F_3N_2O_3S$: 355.0358, found: 355.0366.

The following **Examples 10-14** were prepared from **Intermediate 13** and the appropriate amine in an analogues manner as described for **Example 9**.

Example 10

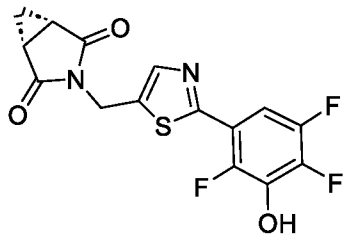
6-Cyclopropyl-4-((2-(2,4,5-trifluoro-3-hydroxyphenyl)thiazol-5-yl)methyl)morpholin-3-one



HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{17}H_{16}F_3N_2O_3S$: 383.0672, found: 383.0678

Example 11

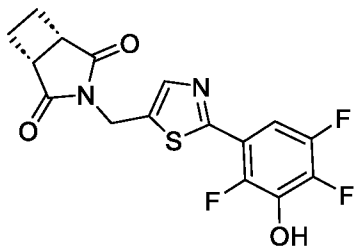
(1*R*,5*S*)-3-((2-(2,4,5-Trifluoro-3-hydroxyphenyl)thiazol-5-yl)methyl)-3-azabicyclo[3.1.0]hexane-2,4-dione



HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{15}H_{10}F_3N_2O_3S$: 355.0358, found: 355.0376

Example 12

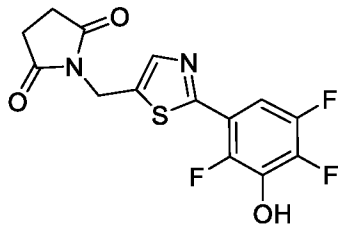
(1*R*,5*S*)-3-((2-(2,4,5-Trifluoro-3-hydroxyphenyl)thiazol-5-yl)methyl)-3-azabicyclo[3.2.0]heptane-2,4-dione



HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{12}F_3N_2O_3S$: 369.0516, found: 369.0504

Example 13

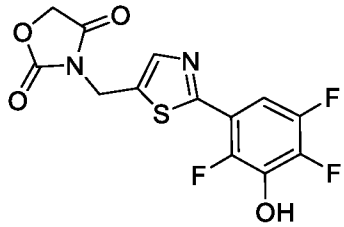
1-((2-(2,4,5-Trifluoro-3-hydroxyphenyl)thiazol-5-yl)methyl)pyrrolidine-2,5-dione



HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{14}H_{10}F_3N_2O_3S$: 343.0358, found: 343.0364

Example 14

3-((2-(2,4,5-Trifluoro-3-hydroxyphenyl)thiazol-5-yl)methyl)oxazolidine-2,4-dione



HRMS (ESI) *m/z* $[M+H]^+$ calcd for $C_{13}H_8F_3N_2O_4S$: 345.0152, found: 345.0148

***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	0.533	>50	0.43	
2	1.146	>50	8.97	
3	0.299	>50	0.86	
4	0.291	>50	0.75	
5	0.089	>50	0.38	27.3
6	1.426	>50	4.37	
7	2.927	>50	>50	
8	0.077	>50	0.44	>50
9	0.044	>50	0.21	
10	0.048	>50	0.55	>15.8
11	0.126	25.6	0.45	
12	0.103	>50	0.39	
13	0.212	20.1	0.56	
14	0.351		4.33	

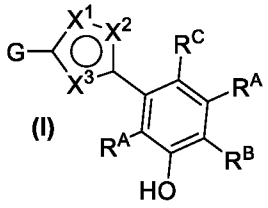
The data in Table 1 may be from a single experiment or an average of two or more experiments.

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.

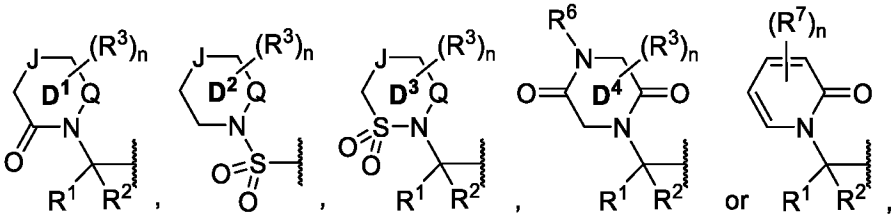
Claims

1. A compound of Formula (I)



(I)

wherein,

G is  ,

each R^A is independently selected from H, F and Cl,

R^B is F or Cl,

R^C is H, F or Cl,

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 CR^Y, wherein each R^Y is independently H, -CN, or R^{XA}, wherein R^{XA} is independently C_{1-3} alkyl optionally substituted with one to three F,

either (i) R^1 and R^2 are independently selected from H, R^4 and R^5,

or (ii) R^1 and R^2 together with the carbon atom to which they are attached form a cyclopropane or cyclobutane ring,

each R^3 is independently R^{4A}, R^{5A} or -OH,

each of R^4 and R^{4A} are independently C_{1-6} alkyl optionally substituted with one to three F, and

each of R^5 and R^{5A} are independently C_{3-6} cycloalkyl optionally substituted with one to three F,

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

each R^7 is independently selected from R^{4A}, R^{5A}, -O(R^{4A}) -O(R^{5A}), -OH, -CN, and halo,

n is 0, 1, 2 or 3,

J is O, CH_2 or a covalent bond,

Q is CH_2 or C(=O),

and wherein optionally (i) one carbon atom of ring D^1, D^2, D^3 or D^4 is attached to a C_{2-5} alkylene group to form a spirocyclic ring, or (ii) two carbon atoms of ring D^1, D^2, D^3 or D^4 are attached to a C_{1-5} alkylene group to form a bridged or fused ring, wherein one CH_2 group of said C_{2-5} alkylene group and C_{1-5} alkylene group may be optionally replaced by an oxygen group,

or a pharmaceutically acceptable salt thereof.

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 CR^Y, X^2 is CR^Y and X^3 is S,

(iv) X^1 is O, X^2 is N and X^3 is CR^Y,

(v) X^1 is N, X^2 is O and X^3 is CR^Y,

(vi) X^1 is CR^Y, 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 CR^Y, X^2 is S and X^3 is CR^Y,

(x) X^1 is CR^Y, X^2 is N and X^3 is S,

(xi) X^1 is CR^Y, X^2 is O and X^3 is CR^Y,

(xii) X^1 is CR^Y, X^2 is CR^Y and X^3 is N,

(xiii) X^1 is N, X^2 is CR^Y and X^3 is S,

(xiv) X^1 is CR^Y, X^2 is S and X^3 is N,

(xv) X^1 is S, X^2 is N and X^3 is CR^Y,

(xvi) X^1 is CR^Y, X^2 is O and X^3 is N,

(xvii) X^1 is O, X^2 is CR^Y and X^3 is CR^Y, or

(xviii) X^1 is N, X^2 is S and X^3 is CR^Y.

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

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

5. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in claim 1 or claim 2, wherein X^1 is CR^Y, X^2 is CR^Y and X^3 is S.

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

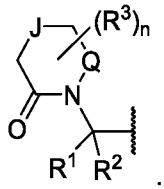
7. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed any one of claims 1 to 6, wherein each R^A is F.

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 any one of claims 1 to 8, wherein R^C is H.

10. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 9, wherein R^1 is H or CH_3 and R^2 is H.

11. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 10, wherein G is



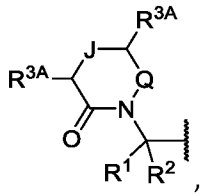
.

12. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 11, wherein J is O.

13. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 12, wherein Q is CH_2.

14. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 13, wherein each R^3 is independently C_{1-4} alkyl.

15. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 13, wherein G is



wherein each R^{3A} is independently H, R^{4A} or R^{5A}.

16. A pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 15, and a pharmaceutically acceptable excipient.

17. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 15, for use in therapy.

18. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 15, for use in the treatment of liver disease.

19. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 15, for use in the treatment of a liver disease selected from alcoholic liver disease, non-alcoholic liver disease, NAFLD, NASH, liver fibrosis, cirrhosis, isolated steatosis, liver inflammation, alcoholic steatohepatitis (ASH), hepatitis C virus (HCV) and hepatocellular carcinoma (HCC).

20. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 15, for use in the treatment of NASH.

21. A method of treating liver disease 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 15.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2024/061419

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D413/06 A61P1/16 C07D413/12 C07D417/06 A61K31/54
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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	THAMM SVEN ET AL: "Discovery of a Novel Potent and Selective HSD17B13 Inhibitor, BI-3231, a Well-Characterized Chemical Probe Available for Open Science", JOURNAL OF MEDICINAL CHEMISTRY, vol. 66, no. 4, 2 February 2023 (2023-02-02), pages 2832-2850, XP093064026, US ISSN: 0022-2623, DOI: 10.1021/acs.jmedchem.2c01884 Retrieved from the Internet: URL:https://pubs.acs.org/doi/pdf/10.1021/acs.jmedchem.2c01884> page 2832, left column, line 1 - page 2833, left column, line 5; tables 2, 3 ----- -/--	1-21

[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
20 February 2025	06/03/2025

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	Kleidernigg, Oliver

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2024/061419

C(Continuation). **DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	WO 2023/222850 A1 (ASTRAZENECA AB [SE]) 23 November 2023 (2023-11-23) claims 1-33	1-21

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2024/061419

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2023222850 A1	23-11-2023	AU 2023274003 A1	02-01-2025
		CN 119173506 A	20-12-2024
		DO P2024000239 A	30-12-2024
		EP 4514782 A1	05-03-2025
		IL 316898 A	01-01-2025
		TW 202411224 A	16-03-2024
		US 2023373983 A1	23-11-2023
		US 2025011311 A1	09-01-2025
		WO 2023222850 A1	23-11-2023