

URACIL COMPOUNDS

Cross-Reference to Related Patent Applications

This specification claims the benefit of priority to U.S. Provisional Patent Applications No. 63/599,664 (filed 16 November 2023) and 63/627,122 (filed 31 January 2024). The entire text of the
5 above-referenced patent applications are incorporated by reference into this specification.

Field

This specification relates to certain heteroaromatic compounds and pharmaceutically acceptable salts thereof that inhibit 17 β hydroxy steroid dehydrogenase 13 (17 β HSD13 or HSD17B13), and their use in treating diseases such as liver disease. This specification also relates to processes and
10 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,
15 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.

20 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 17 β HSD13 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
25 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 17 β HSD13 splice variant (rs72613567:TA) results in a truncated, unstable and enzymatically inactive protein and has thus been characterized as an 17 β HSD13 Loss of Function (LoF) variant (Ma et al, Hepatology 2019, 69(4), 1504-19). The association between the LoF 17 β HSD13
30 (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 17 β HSD13 (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 17 β HSD13LoF 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 17 β HSD13 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 17 β HSD13LoF variants conferring protection against liver disease risk and progression, inhibition of 17 β HSD13 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 17 β HSD13 inhibitors. Further, compounds of the disclosure may selectively inhibit 17 β HSD13 over 17 β HSD4 and/or 17 β HSD9.

Fifteen 17 β HSD (HSD17B) members have been identified in human. The sequence homology among the different members is rather low, but the overall structure seems conserved. 17 β -Hydroxysteroid dehydrogenases are mainly involved in sex hormone metabolism. Some 17 β HSD 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 17 β HSD13 inhibitor to avoid potential toxicity caused by off-target activity. This includes selectivity to other 17 β HSD members.

17 β HSD4/ D-bifunctional protein (DBP) is involved in fatty acid β -oxidation and steroid metabolism. 17 β HSD4 is ubiquitously expressed and play an important role in the inactivation of estrogens in a large series of peripheral tissues. Mutations in17 β HSD4 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 17 β HSD4 has been identified in Perrault syndrome, a recessive disorder characterized by ovarian dysgenesis in females, sensorineural

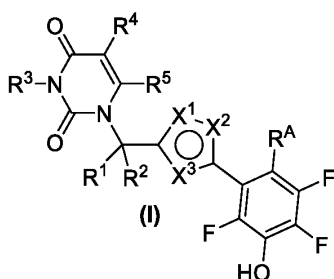
deafness in both males and females, and in some patients, neurological manifestations (Pierce et al. Am. J. Hum. Genet., 2010, 87, 282-8; and Chen et al. BMC Med Genet., 2017, 18, 91).

17 β HSD9/ 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 17 β HSD13 inhibitors. For example, the compounds of the specification may exhibit improved stability in colon to allow greater absorption in the human gastrointestinal tract, and/or improved metabolic stability. 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)



wherein,

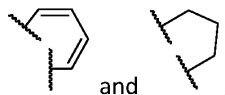
R^A is H, F or Cl,

one of X¹, X² and X³ is selected from NH, O and S and the other two of X¹, X² and X³ are independently selected from N and CR^Y, wherein each R^Y is independently H, -CN, or R^{XA}, wherein R^{XA} is independently C₁₋₃ alkyl optionally substituted with one to three F, either (i) R¹ and R² are independently selected from H, R⁶ and R⁷,

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

R^3 is R^{6A} or R^{7A} ,

either (i) R^4 is H, R^{6B} or R^{7B} , and R^5 is H, R^{6C} or R^{7C} ,



- 5 or (ii) R^4 and R^5 together form a group selected from each of R^6 , R^{6A} , R^{6B} and R^{6C} are independently C_{1-6} alkyl optionally substituted with one to three substituents independently selected from F and C_{3-6} cycloalkyl, and each of R^7 , R^{7A} , R^{7B} and R^{7C} are independently C_{3-6} cycloalkyl optionally substituted with one to three F,
- 10 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.

- 15 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.

- 20 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.

- 25 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.
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As used herein the term “alkyl” refers to both straight and branched chain saturated hydrocarbon radicals having the specified number of carbon atoms.

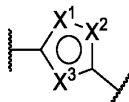
In this specification the prefix C_{x-y} , as used in terms such as “ C_{x-y} alkyl” and the like where x and y are integers, indicates the numerical range of carbon atoms that are present in the group. Examples of suitable C_{1-3} alkyl groups include methyl, ethyl, n-propyl, and i-propyl. Examples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

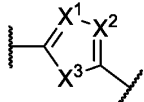
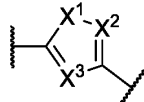
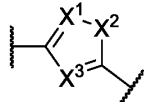
As used herein the term “cycloalkyl” refers to saturated cyclic hydrocarbon radicals having the specified number of carbon atoms. Examples of C_{3-6} cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

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

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

For the avoidance of doubt, the use of a circle within a 5 membered ring indicates that the 5

membered ring is an aromatic ring. By way of illustration only,  indicates an aromatic

ring selected from ,  and .

For the avoidance of doubt, the use of 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.

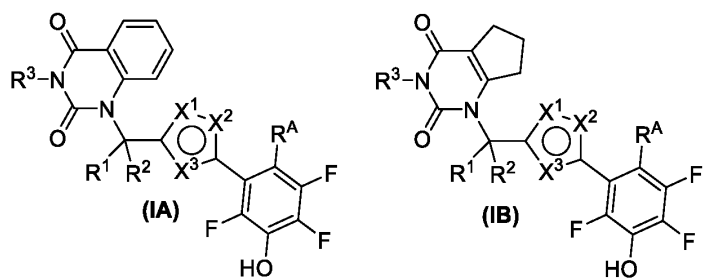
Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure is related.

- 5 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

- 10 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 (IA) or (IB)



- 15 or a pharmaceutically acceptable salt thereof.

In embodiments, there is provided a compound of Formula (I), (IA) or (IB), or a pharmaceutically acceptable salt thereof, wherein one of X¹, X² and X³ is O and the other two of X¹, X² and X³ are selected from N and CR^Y. In further embodiments, R^Y is H.

- In embodiments, there is provided a compound of Formula (I), (IA) or (IB), or a pharmaceutically acceptable salt thereof, wherein one of X¹, X² and X³ is S and the other two of X¹, X² and X³ are selected from N and CR^Y. In further embodiments, R^Y is H.

In embodiments, there is provided a compound of Formula (I), (IA) or (IB), or a pharmaceutically acceptable salt thereof, wherein one of X¹, X² and X³ is O and the other two of X¹, X² and X³ are both N.

In embodiments, there is provided a compound of Formula (I), (IA) or (IB), 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), (IA) or (IB), 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), (IA) or (IB), 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.

10 In embodiments, there is provided a compound of Formula (I), (IA) or (IB), 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), (IA) or (IB), 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), (IA) or (IB), 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,
- 20 (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,
- 25 (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,
- 30 (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 .

5 In embodiments, there is provided a compound of Formula (I), (IA) or (IB), 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,
 10 (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,
 15 (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,
 20 (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.

25 In embodiments, there is provided a compound of Formula (I), (IA) or (IB), 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), (IA) or (IB), 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), (IA) or (IB), 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), (IA) or (IB), 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.

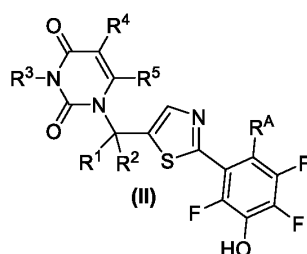
In embodiments, there is provided a compound of Formula (I), (IA) or (IB), or a pharmaceutically acceptable salt thereof, wherein X^1 is CR^Y , X^2 is N and X^3 is O. In further embodiments, each R^Y is H.

In embodiments, there is provided a compound of Formula (I), (IA) or (IB), 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.

- 5 In embodiments, there is provided a compound of Formula (I), (IA) or (IB), 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.

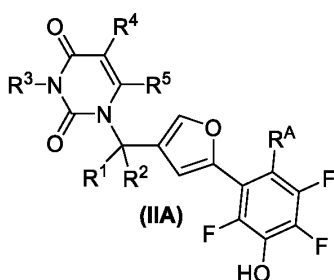
In embodiments, there is provided a compound of Formula (I), (IA) or (IB), or a pharmaceutically acceptable salt thereof, wherein X^1 is CR^Y , X^2 is N and X^3 is S. In further embodiments, each R^Y is H.

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



or a pharmaceutically acceptable salt thereof.

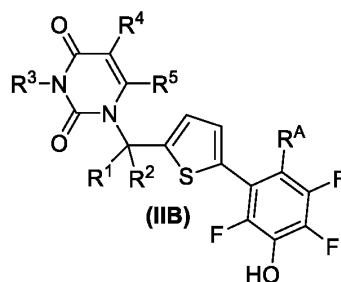
In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, that is a compound of Formula (IIA)



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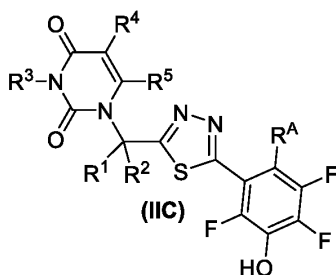
or a pharmaceutically acceptable salt thereof.

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)



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or a pharmaceutically acceptable salt thereof.

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

- 10 In embodiments, there is provided a compound of Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC), or a pharmaceutically acceptable salt thereof, wherein R^1 is H or CH_3 and R^2 is H.

In embodiments, there is provided a compound of Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC), or a pharmaceutically acceptable salt thereof, wherein R^1 is H and R^2 is H.

- 15 In embodiments, there is provided a compound of Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC), or a pharmaceutically acceptable salt thereof, wherein R^1 is R^6 , 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), (IA), (IB), (II), (IIA), (IIB) or (IIC), or a pharmaceutically acceptable salt thereof, wherein R^1 is R^7 , and R^2 is H. In further embodiments, R^1 is

- 20 C_{3-6} cycloalkyl and R^2 is H.

In embodiments, there is provided a compound of Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC), or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 are independently R^6 . 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 .

- 5 In embodiments, there is provided a compound of Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC), 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), (IA), (IB), (II), (IIA), (IIB) or (IIC), 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.
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- In embodiments, there is provided a compound of Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC), or a pharmaceutically acceptable salt thereof, wherein R^3 is C_{1-6} alkyl optionally substituted with one to three substituents independently selected from F and C_{3-6} cycloalkyl. In further embodiments, R^3 is C_{1-6} alkyl (i.e. unsubstituted C_{1-6} alkyl). In further embodiments, R^3 is C_{1-4} alkyl (i.e. unsubstituted C_{1-4} alkyl).
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In embodiments, there is provided a compound of Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC), or a pharmaceutically acceptable salt thereof, wherein R^3 is C_{3-6} cycloalkyl optionally substituted with one to three F. In further embodiments, R^3 is C_{3-6} cycloalkyl (i.e. unsubstituted C_{3-6} cycloalkyl).

- In embodiments, there is provided a compound of Formula (I), (II), (IIA), (IIB) or (IIC), or a pharmaceutically acceptable salt thereof, wherein R^4 is H, R^{6B} or R^{7B} , and R^5 is H, R^{6C} or R^{7C} . In further embodiments, R^4 is H, C_{1-6} alkyl or C_{3-6} cycloalkyl, and R^5 is H, C_{1-6} alkyl or C_{3-6} cycloalkyl. In further embodiments, R^4 is H or C_{1-4} alkyl, and R^5 is H or C_{1-4} alkyl. In further embodiments, R^4 is C_{1-4} alkyl, and R^5 is H. In further embodiments, R^4 is CH_3 , and R^5 is H.
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- In embodiments, there is provided a compound of Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC), wherein each R^6 is independently C_{1-6} alkyl optionally substituted with one to three F. In further embodiments, each R^6 is independently C_{1-4} alkyl optionally substituted with one to three F. In further embodiments, each R^6 is independently C_{1-4} alkyl. In further embodiments, each R^6 is independently CH_3 or CH_2CH_3 .
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- In embodiments, there is provided a compound of Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC), wherein R^{6A} is C_{1-6} alkyl optionally substituted with one to three F. In further embodiments, R^{6A} is C_{1-4} alkyl optionally substituted with one to three F. In further embodiments, R^{6A} is C_{1-4} alkyl. In further embodiments, R^{6A} is CH_3 .
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In embodiments, there is provided a compound of Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC), wherein R^{6B} is C_{1-6} alkyl optionally substituted with one to three F. In further embodiments, R^{6B} is C_{1-4} alkyl optionally substituted with one to three F. In further embodiments, R^{6B} is C_{1-4} alkyl. In further embodiments, R^{6B} is CH_3 .

- 5 In embodiments, there is provided a compound of Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC), wherein R^{6C} is C_{1-6} alkyl optionally substituted with one to three F. In further embodiments, R^{6C} is C_{1-4} alkyl optionally substituted with one to three F. In further embodiments, R^{6C} is C_{1-4} alkyl. In further embodiments, R^{6C} is CH_3 .

- In embodiments, there is provided a compound of Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC),
10 wherein each R^7 is independently C_{3-6} cycloalkyl optionally substituted with one to three F. In further embodiments, R^7 is C_{3-6} cycloalkyl.

In embodiments, there is provided a compound of Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC), wherein R^{7A} is C_{3-6} cycloalkyl optionally substituted with one to three F. In further embodiments, R^{7A} is C_{3-6} cycloalkyl.

- 15 In embodiments, there is provided a compound of Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC), wherein R^{7B} is C_{3-6} cycloalkyl optionally substituted with one to three F. In further embodiments, R^{7B} is C_{3-6} cycloalkyl.

- In embodiments, there is provided a compound of Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC), wherein R^{7C} is C_{3-6} cycloalkyl optionally substituted with one to three F. In further embodiments, R^{7C}
20 is C_{3-6} cycloalkyl.

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

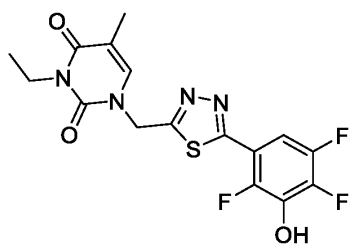
- 3-Ethyl-5-methyl-1-((5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methyl)pyrimidine-2,4(1H,3H)-dione,
25 3-Ethyl-5-methyl-1-((5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,3,4-thiadiazol-2-yl)methyl)pyrimidine-2,4(1H,3H)-dione,
3-Methyl-1-((5-(2,4,5-trifluoro-3-hydroxyphenyl)thiophen-2-yl)methyl)pyrimidine-2,4(1H,3H)-dione,
or
3-Methyl-1-((5-(2,4,5-trifluoro-3-hydroxyphenyl)furan-3-yl)methyl)pyrimidine-2,4(1H,3H)-dione,
30 or a pharmaceutically acceptable salt thereof.

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

3-Ethyl-5-methyl-1-((5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)ethyl)pyrimidine-2,4(1*H*,3*H*)-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 3-Ethyl-5-methyl-1-((5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,3,4-thiadiazol-2-

5 yl)methyl)pyrimidine-2,4(1*H*,3*H*)-dione

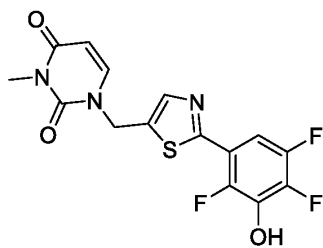


, or a pharmaceutically acceptable salt thereof.

In embodiments, there is provided a compound of Formula (I), that is 3-Ethyl-5-methyl-1-((5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,3,4-thiadiazol-2-yl)methyl)pyrimidine-2,4(1*H*,3*H*)-dione.

In embodiments, there is provided a pharmaceutically acceptable salt of a compound of Formula (I),
10 that is a pharmaceutically acceptable salt of 3-Ethyl-5-methyl-1-((5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,3,4-thiadiazol-2-yl)methyl)pyrimidine-2,4(1*H*,3*H*)-dione.

In embodiments, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt thereof, that is 3-Methyl-1-((2-(2,4,5-trifluoro-3-hydroxyphenyl)thiazol-5-yl)methyl)pyrimidine-2,4(1*H*,3*H*)-dione



15 , or a pharmaceutically acceptable salt thereof.

In embodiments, there is provided a compound of Formula (I), that is 3-Methyl-1-((2-(2,4,5-trifluoro-3-hydroxyphenyl)thiazol-5-yl)methyl)pyrimidine-2,4(1*H*,3*H*)-dione.

In embodiments, there is provided a pharmaceutically acceptable salt of a compound of Formula (I),
that is a pharmaceutically acceptable salt of is 3-Methyl-1-((2-(2,4,5-trifluoro-3-
20 hydroxyphenyl)thiazol-5-yl)methyl)pyrimidine-2,4(1*H*,3*H*)-dione.

A further feature is any of the embodiments described in the specification with the proviso that any of the specific Examples are individually disclaimed. A further feature is any of the embodiments

described in the specification with the proviso that any one or more of the compounds selected from the above list of Examples of compounds of the specification are individually disclaimed.

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

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

In embodiments, there is provided a pharmaceutical composition which comprises a compound of the Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC), 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), (IA), (IB), (II), (IIA), (IIB) or (IIC), or pharmaceutically acceptable salt thereof, wherein the compound of Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC), or pharmaceutically acceptable salt thereof is present within the composition with an enantiomeric excess (%ee) of $\geq 90\%$ and a diastereomeric excess (%de) of $\geq 90\%$.

The compound of Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC), 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), (IA), (IB), (II), (IIA), (IIB) or (IIC), 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), (IA), (IB), (II), (IIA), (IIB) or (IIC), and pharmaceutically acceptable salts thereof.

In further embodiments there is provided a compound of Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC), 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
5 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), (IA), (IB), (II), (IIA), (IIB) or (IIC) is, for example, a base addition salt. A base addition salt of a compound of Formula (I), (IA), (IB),
10 (II), (IIA), (IIB) or (IIC) 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
15 using a suitably basic organic amine (e.g., a choline or meglumine salt).

A suitable pharmaceutically acceptable salt of a compound of Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC) is, for example, an acid addition salt. An acid addition salt of a compound of Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC) 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
20 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.

25 A further suitable pharmaceutically acceptable salt of a compound of Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC) is, for example, a salt formed within a patient's body after administration of a compound of Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC) to the patient.

The compound of Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC), or pharmaceutically acceptable salt thereof, may be prepared as a co-crystal solid form. It is to be understood that a pharmaceutically
30 acceptable co-crystal of an compound of Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC), 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), (IA), (IB), (II), (IIA), (IIB) or (IIC), or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

5 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), (IA), (IB), (II), (IIA), (IIB) or (IIC), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

10 The pharmaceutical formulations of the compound of Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC), 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, 17th ed., Mack Publishing Company, Easton, PA., (1985).

15 In a further aspect there is provided a pharmaceutical composition comprising a compound of Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC), or a pharmaceutically acceptable salt thereof, for use in therapy as described herein.

As a result of their 17BHSD13 inhibitory activity, the compounds of Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC), and pharmaceutically acceptable salts thereof are expected to be useful in therapy, for
20 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), (IA), (IB), (II), (IIA), (IIB) or (IIC), 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), (IA), (IB), (II),
25 (IIA), (IIB) or (IIC), 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 steatohepatitis (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
30 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
5 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), (IA), (IB), (II), (IIA), (IIB) or (IIC), or a
10 pharmaceutically acceptable salt thereof, for use in providing an inhibitory effect on 17 β HSD13.

In embodiments, there is provided a compound of Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC), or a pharmaceutically acceptable salt thereof, for use in the treatment of a disease mediated by 17 β HSD13, such as liver disease (e.g. NASH).

In embodiments, there is provided a compound of Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC), or a
15 pharmaceutically acceptable salt thereof, for use in the treatment of fatty liver disease.

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

20 In embodiments, there is provided a compound of Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC), 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), (IA), (IB), (II), (IIA), (IIB) or (IIC), or a
25 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/m² to 40 kg/m². In further embodiments, the subject has a BMI of 30 kg/m² to 39.9 kg/m². In further embodiments, the patient has a BMI of at least 40 kg/m². In further embodiments, the patient is overweight. In further embodiments, the patient is obese.

In embodiments, there is provided a compound of Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC), 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), (IA), (IB), (II), (IIA), (IIB) or (IIC), 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), (IA), (IB), (II), (IIA), (IIB) or (IIC), 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), (IA), (IB), (II), (IIA), (IIB) or (IIC), 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), (IA), (IB), (II), (IIA), (IIB) or (IIC), 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), (IA), (IB), (II), (IIA), (IIB) or (IIC), 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), (IA), (IB), (II), (IIA), (IIB) or (IIC), 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), (IA), (IB), (II), (IIA), (IIB) or (IIC), 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
5 (rs738409 C>G) variant in PNPLA3.

In embodiments, there is provided a compound of Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC), 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
10 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), (IA), (IB), (II), (IIA), (IIB) or (IIC), or a pharmaceutically acceptable salt thereof, for use in the treatment of liver fibrosis. In further
15 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), (IA), (IB), (II), (IIA), (IIB) or (IIC), or a pharmaceutically acceptable salt thereof, for use in the treatment of cirrhosis. In further
20 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), (IA), (IB), (II), (IIA), (IIB) or (IIC), or a pharmaceutically acceptable salt thereof, for use in the treatment of liver inflammation. In further
25 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), (IA), (IB), (II), (IIA), (IIB) or (IIC), or a pharmaceutically acceptable salt thereof, for use in the treatment of hepatocellular carcinoma (HCC).

30 In embodiments, there is provided a compound of Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC), or a pharmaceutically acceptable salt thereof, for use in the treatment of alcoholic steatohepatitis (ASH).

In embodiments, there is provided a compound of Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC), 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), (IA), (IB), (II), (IIA), (IIB) or (IIC), or a pharmaceutically acceptable salt thereof, as described herein, in
5 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), (IA), (IB), (II), (IIA), (IIB) or (IIC), or a pharmaceutically acceptable salt thereof.

Terms such as “treating” or “treatment” refer to both (1) therapeutic measures that cure, slow
10 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.

15 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
20 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.

25 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), (IA), (IB), (II), (IIA), (IIB) or (IIC), 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
30 comprising administering to the patient an effective amount of a compound of Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC), 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
5 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), (IA), (IB), (II), (IIA), (IIB) or (IIC), or a pharmaceutically acceptable salt thereof, and a sodium-glucose transport protein 2 (SGLT2) inhibitor. In further
10 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), (IA), (IB), (II), (IIA), (IIB) or (IIC), or a pharmaceutically acceptable salt thereof, and metformin, or a pharmaceutically acceptable salt thereof.

15 In embodiments, there is provided a combination for use in the treatment of liver disease, such as NASH, comprising a compound of Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC), 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.

20 In embodiments, there is provided a combination for use in the treatment of liver disease, such as NASH, comprising a compound of Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC), 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.

25 In embodiments, there is provided a combination for use in the treatment of liver disease, such as NASH, comprising a compound of Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC), or a pharmaceutically acceptable salt thereof, and a PPAR agonist. In further embodiments, the PPAR agonist is a PPAR α agonist. In further embodiments, the PPAR agonist is a PPAR γ agonist. In further embodiments, the PPAR agonist is a PPAR α/γ agonist. In further embodiments, the PPAR agonist is selected from
30 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), (IA), (IB), (II), (IIA), (IIB) or (IIC), 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), (IA), (IB), (II), (IIA), (IIB) or (IIC), or a pharmaceutically acceptable salt thereof, and a ThrB agonist. In further embodiments, the ThrB agonist is resmetirom.

10 In embodiments, there is provided a combination for use in the treatment of liver disease, such as NASH, comprising a compound of Formula (I), (IA), (IB), (II), (IIA), (IIB) or (IIC), 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), (IA), (IB), (II), (IIA), (IIB) or (IIC) are primarily of value as therapeutic agents for use in patients, they are also useful whenever it is required to inhibit 17 β HSD13. 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

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

(i) operations were carried out at room temperature (rt), *i.e.* in the range 17 to 28°C and where needed under an atmosphere of an inert gas such as N₂;

(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 25 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
5 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;

10 (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 BIOATAGE SNAP cartridges (40–63 μm silica, 4–330 g), BIOATAGE 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 Colume Silica-CS
15 cartridges (80–330 g), or on reversed phase silica using Agela Technologies C-18, spherical cartridges (20–35 μm , 100 Å, 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
20 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
25 was purified by preparative HPLC on a XBRIDGE C18 ODB column (5 μm , 150×30 mm ID) using a gradient of MeCN in $\text{H}_2\text{O}/\text{NH}_4\text{HCO}_3$ (10 mM)+0.1% NH_4OH as mobile phase; **PrepMethod B** The compound was purified by preparative HPLC on a XSelect CSH Prep C18 OBD column (5 μm , 100×30 mm ID) using a gradient of MeCN in H_2O containing 0.1% FA as mobile phase; **PrepMethod C:** The compound was purified by preparative HPLC on a Kromasil C8 column (10 μm , 250×20 mm ID) using
30 a gradient of MeCN in $\text{H}_2\text{O}/\text{MeCN}/\text{FA}$ (95/5/0.2) as mobile phase; **PrepMethod D:** The compound was purified by preparative HPLC on a Kromasil C8 column (10 μm , 250×50 mm ID) using a gradient of MeCN in $\text{H}_2\text{O}/\text{MeCN}/\text{FA}$ (95/5/0.2) as mobile phase. **PrepMethod E:** The compound was purified

by preparative HPLC on a Phenomenex luna C18 column (10 μ m, 250×100 mm ID) using a gradient of MeCN in H₂O/TFA (0.1%) 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.

- 5 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 Na₂SO₄ 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
10 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-
15 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
20 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
25 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
30 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; 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

(xv) 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;

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

(xvii) 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 chemical structures of Examples and Intermediates where more than one
 5 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 for structures of Examples and Intermediates where all of the stereocenters are
 10 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 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
 15 two isomers containing one or more stereocenters with absolute unknown configuration;

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

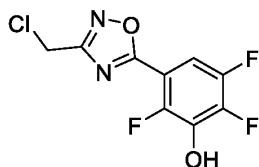
	AcOH	Acetic acid
	Art	Article
20	Aq	Aqueous
	bis(pinacolato)diboron 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane)	
	Calcd	Calculated
	DCM	Dichloromethane
	DIPEA	<i>N</i> -ethyl- <i>N</i> -isopropyl-propan-2-amine
25	DMF	<i>N,N</i> -dimethylformamide
	DMSO	Dimethyl sulfoxide
	dppb	1,4-bis(diphenylphosphino)butane
	e.g.	for example
	ESI	Electrospray ionization
30	etc.	et cetera
	Etl	Ethyl iodide
	EtOAc	Ethyl acetate

	EtOH	Ethanol
	FA	Formic acid
	(g)	gas
	HPLC	High performance liquid chromatography
5	HRMS	High resolution mass spectrometry
	ID	inner diameter
	i.e.	id est
	KI	Potassium iodide
	LCMS	Liquid Chromatography Mass Spectrometry
10	MeCN	Acetonitrile
	MeOH	Methanol
	MS	Mass spectrometry
	MsCl	Methanesulfonyl chloride
	m/z	mass spectrometry peak(s)
15	NaOt-Am	sodium 2-methylbutan-2-olate
	NMP	1-methylpyrrolidin-2-one
	NMR	Nuclear magnetic resonance
	Pd-118	[1,1'-Bis(di-tert-butylphosphino)ferrocene]dichloropalladium(II)
	Pd(dppf)Cl ₂	[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)
20	Pd(OAc) ₂	Palladium(II) acetate
	rt	Room temperature
	sat	Saturated
	SFC	Supercritical fluid chromatography
	TBAI	Tetrabutylammonium iodide
25	TEA	Triethylamine
	TFA	Trifluoroacetic acid
	THF	Tetrahydrofuran
	TLC	Thin layer chromatography
	UPLC	ultra performance liquid chromatography
30	UV	ultraviolet

Units

A	Angström
C	Celcius
cm	centimeter(s)

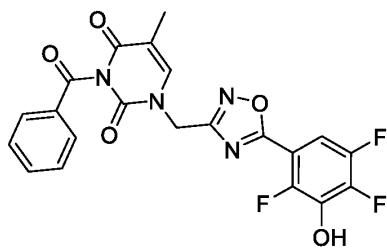
	g	gram
	h	hour(s)
	M	mole per liter
	mg	milligram
5	MHz	megahertz
	min	minute(s)
	mL	milliliter
	mm	millimeter
	mM	millimole per liter
10	mmol	millimole(s)
	μm	micrometer
	ppm	parts per million

Intermediate 1**15 3-(3-(Chloromethyl)-1,2,4-oxadiazol-5-yl)-2,5,6-trifluorophenol**

TEA (5.39 mL, 38.70 mmol) was added slowly to a solution of 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, and the reaction mixture was stirred at 25°C for 1 h. The reaction mixture was poured into NaHCO₃ (sat, aq, 200 mL), and extracted with DCM (3×100 mL). The combined organic layer was dried over Na₂SO₄, filtered and the filtrate was concentrated. The residue was dissolved in AcOH (20 mL) at 25°C and stirred at 100°C for 3 h. The solvent was removed under reduced pressure. The residue was diluted with NaHCO₃ (sat, aq, 200 mL) and extracted with EtOAc (3×100 mL). The combined organic layer was dried over Na₂SO₄, filtered, and evaporated. The residue was purified by straight phase flash chromatography on silica (gradient: 2–50% EtOAc in petroleum ether) to give the title compound (620 mg, 12%); MS (ESI) *m/z* [M+H]⁺ 263.

Intermediate 2

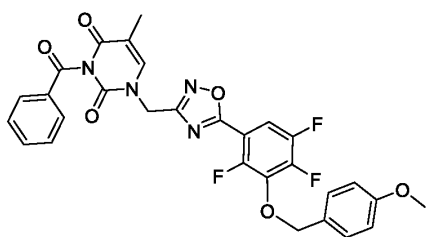
3-Benzoyl-5-methyl-1-((5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methyl)pyrimidine-2,4(1*H*,3*H*)-dione



K₂CO₃ (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), 3-benzoyl-5-methylpyrimidine-2,4(1H,3H)-dione (522 mg, 2.27 mmol) and NaI (85 mg, 0.57 mmol) in MeCN (5 mL) at 25°C, and the reaction 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 (180 mg, 35%) as a white solid; MS (ESI) *m/z* [M+H]⁺ 459.

Intermediate 3

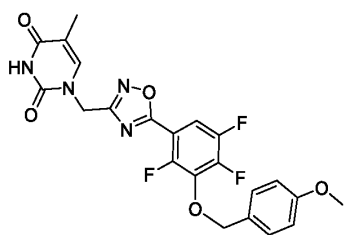
3-Benzoyl-5-methyl-1-((5-(2,4,5-trifluoro-3-((4-methoxybenzyl)oxy)phenyl)-1,2,4-oxadiazol-3-yl)methyl)pyrimidine-2,4(1H,3H)-dione



A mixture of 3-benzoyl-5-methyl-1-((5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methyl)pyrimidine-2,4(1H,3H)-dione **Intermediate 2** (150 mg, 0.33 mmol), K₂CO₃ (136 mg, 0.98 mmol) and 1-(chloromethyl)-4-methoxybenzene (61.5 mg, 0.39 mmol) in MeCN (5 mL) was stirred at 80°C for 6 h. The reaction mixture was filtered, and the filtrate was concentrated. The residue was purified by preparative TLC (EtOAc:petroleum ether, 3:1) to afford the title compound (110 mg, 58%) as a colourless oil; MS (ESI) *m/z* [M+H]⁺ 579.

Intermediate 4

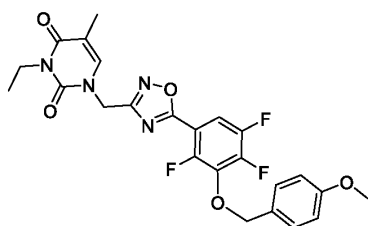
5-Methyl-1-((5-(2,4,5-trifluoro-3-((4-methoxybenzyl)oxy)phenyl)-1,2,4-oxadiazol-3-yl)methyl)pyrimidine-2,4(1H,3H)-dione



A mixture of 3-benzoyl-5-methyl-1-((5-(2,4,5-trifluoro-3-((4-methoxybenzyl)oxy)phenyl)-1,2,4-oxadiazol-3-yl)methyl)pyrimidine-2,4(1H,3H)-dione **Intermediate 3** (60 mg, 0.10 mmol) and 4 M NH₃ in MeOH (0.5 mL, 2.00 mmol) in MeOH (5 mL) was stirred at 60°C for 1 h. The reaction mixture was concentrated to afford the title compound (45 mg, 91%) as a colourless oil. MS (ESI) *m/z* [M+H]⁺ 475.

Intermediate 5

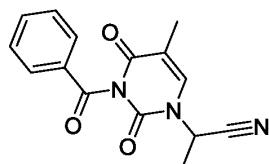
3-Ethyl-5-methyl-1-((5-(2,4,5-trifluoro-3-((4-methoxybenzyl)oxy)phenyl)-1,2,4-oxadiazol-3-yl)methyl)pyrimidine-2,4(1H,3H)-dione



A mixture of 5-methyl-1-((5-(2,4,5-trifluoro-3-((4-methoxybenzyl)oxy)phenyl)-1,2,4-oxadiazol-3-yl)methyl)pyrimidine-2,4(1H,3H)-dione **Intermediate 4** (50 mg, 0.11 mmol), EtI (18.1 mg, 0.12 mmol) and K₂CO₃ (29 mg, 0.21 mmol) in DMF (3 mL) was stirred at 60°C for 1 h. The mixture was filtered through a pad of CELITE. The crude product was purified by reversed phase flash chromatography on a C18 column (gradient: 5–72% MeCN in H₂O), to afford the title compound (20 mg, 38%) as a white solid; MS (ESI) *m/z* [M+H]⁺ 503.

Intermediate 6

2-(3-Benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)propanenitrile

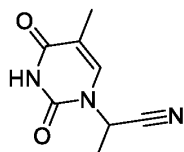


K₂CO₃ (360 mg, 2.61 mmol) was added to a mixture of 3-benzoyl-5-methylpyrimidine-2,4(1H,3H)-dione (500 mg, 2.17 mmol), 2-bromopropanenitrile (582 mg, 4.34 mmol) and NaI (163 mg, 1.09

mmol) in MeCN (15 mL) at 25°C. The resulting mixture was stirred at 60°C for 16 h. The reaction mixture was filtered, and the filtrate was concentrated. The residue was purified by preparative TLC (EtOAc:petroleum ether, 2:1), to afford the title compound (375 mg, 61%) as a pale yellow solid; MS (ESI) m/z $[M+H]^+$ 284.

5 Intermediate 7

2-(5-Methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)propanenitrile

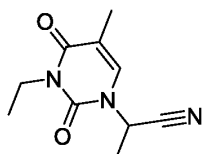


A mixture of 2-(3-benzoyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)propanenitrile

- Intermediate 6** (375 mg, 1.32 mmol) and 26% NH_4OH (aq, 892 mg, 6.62 mmol) in THF (15 mL) was stirred at 25°C for 1 h. The reaction mixture was concentrated to afford the title compound (233 mg, 98%) as a colorless oil; MS (ESI) m/z $[M-H]^-$ 178.

Intermediate 8

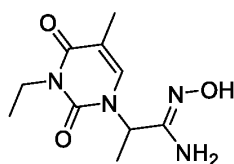
2-(3-Ethyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)propanenitrile



- A mixture of 2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)propanenitrile **Intermediate 7** (233 mg, 1.30 mmol), EtI (223 mg, 1.43 mmol) and K_2CO_3 (359 mg, 2.60 mmol) in DMF (6 mL) was stirred at 25°C for 16 h. The reaction mixture was filtered through a pad of CELITE. The crude product was purified by reversed phase flash chromatography on a C18-column (gradient: 0–17% MeCN in H_2O) to afford the title compound (246 mg, 91%) as a yellow solid; MS (ESI) m/z $[M+H]^+$ 208.

Intermediate 9

(Z)-2-(3-Ethyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-N'-hydroxypropanimidamide



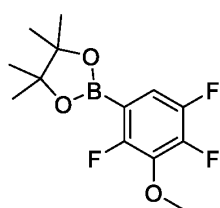
A mixture of 2-(3-ethyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)propanenitrile

Intermediate 8 (246 mg, 1.19 mmol) and 50% hydroxylamine (aq, 392 mg, 5.94 mmol) in EtOH (10 mL) was stirred at 25°C for 1 h. The reaction mixture was concentrated to afford the title compound

5 (280 mg, 98%) as a yellow oil; MS (ESI) m/z $[M+H]^+$ 241.

Intermediate 10

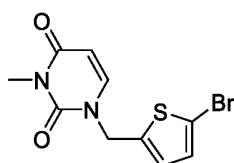
4,4,5,5-Tetramethyl-2-(2,4,5-trifluoro-3-methoxyphenyl)-1,3,2-dioxaborolane



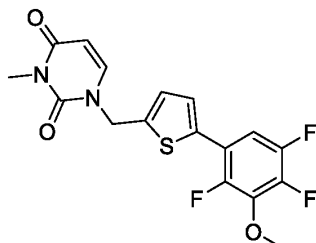
A mixture of 2,4,5-trifluoro-3-methoxybenzoic acid (2.40 g, 11.6 mmol), Pd(OAc)₂ (0.157 g, 0.70 mmol), bis(pinacolato)diboron (4.44 g, 17.5 mmol), pivalic anhydride (3.54 mL, 17.5 mmol), TEA (2.44 mL, 17.5 mmol) and dppb (0.596 g, 1.40 mmol) in 1,4-dioxane (60 mL) was stirred at 100°C for 48 h under a N₂(g) atmosphere. The mixture was cooled to rt and diluted with EtOAc (60 mL). 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, 15 67%) as a colourless oil; ¹H NMR (500 MHz, CDCl₃, 25°C) δ 1.35 (s, 12H), 4.01 (s, 3H), 7.20 (td, 1H).

Intermediate 11

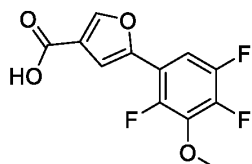
1-((5-Bromothiophen-2-yl)methyl)-3-methylpyrimidine-2,4(1H,3H)-dione



A solution of 2-bromo-5-(bromomethyl)thiophene (0.083 g, 0.32 mmol) in NMP (2 mL) was added to a stirred solution of 3-methylpyrimidine-2,4(1H,3H)-dione (0.041 g, 0.32 mmol) and sodium *tert*-pentoxide (0.036 g, 0.32 mmol) in NMP (1 mL), and the resulting mixture was stirred at rt for 1 h. The mixture was acidified with AcOH and purified by preparative HPLC, **PrepMethod C**, (gradient: 20–80%) to give the title compound (0.081 g, 83%) as a yellow solid; MS (ESI) m/z $[M+H]^+$ 303.

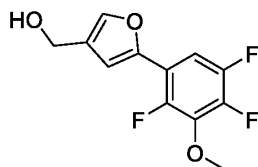
Intermediate 12**3-Methyl-1-((5-(2,4,5-trifluoro-3-methoxyphenyl)thiophen-2-yl)methyl)pyrimidine-2,4(1H,3H)-dione**

- 5 A mixture of 1-((5-bromothiophen-2-yl)methyl)-3-methylpyrimidine-2,4(1H,3H)-dione **Intermediate 11** (0.081 g, 0.27 mmol), 4,4,5,5-tetramethyl-2-(2,4,5-trifluoro-3-methoxyphenyl)-1,3,2-dioxaborolane **Intermediate 10** (0.101 g, 0.35 mmol), Pd-118 (0.010 g, 0.02 mmol) and 1.8M K₂CO₃ (aq, 0.598 mL, 1.08 mmol) in 1,4-dioxane (3 mL) was stirred at 60°C under a N₂(g) atmosphere for 1 h. The mixture was concentrated, and the residue dissolved in DCM and washed with H₂O. The
- 10 organic layer was concentrated, and the crude product was purified by straight phase flash chromatography on silica (gradient: 0–100% EtOAc in heptane) to give the title compound (0.078 g, 76%) as a white solid; MS (ESI) *m/z* [M+H]⁺ 383.

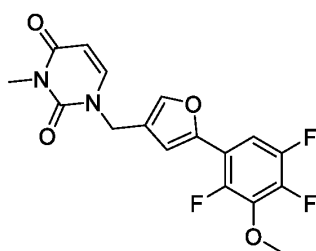
Intermediate 13**5-(2,4,5-Trifluoro-3-methoxyphenyl)furan-3-carboxylic acid**

- 15 A mixture of 5-bromofuran-3-carboxylic acid (0.400 g, 2.09 mmol), 4,4,5,5-tetramethyl-2-(2,4,5-trifluoro-3-methoxyphenyl)-1,3,2-dioxaborolane **Intermediate 10** (0.784 g, 2.72 mmol), Pd-118 (0.068 g, 0.10 mmol) and 1.8M K₂CO₃ (aq, 4.65 mL, 8.38 mmol) in 1,4-dioxane (20 mL) was stirred at 60°C under a N₂(g) atmosphere for 1 h, and then at 90°C for 1 h. The mixture was cooled to rt,
- 20 diluted with MeOH (50 mL), acidified with 4M HCl (10 mL) and filtered through CELITE. The filtrate was concentrated, and H₂O (≈20 mL) added was added to the residue. The crude product was filtered off and washed with H₂O. The resulting brown solid was dissolved in MeOH (3 mL), H₂O (6 mL) was added, and the crude product filtered off. The crude product was purified by preparative HPLC, **PrepMethod D**, (gradient: 50–80%) to give the title compound (0.059 g, 10%) as a beige solid;
- 25 MS (ESI) *m/z* [M+H]⁺ 271.

Intermediate 14

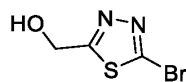
(5-(2,4,5-Trifluoro-3-methoxyphenyl)furan-3-yl)methanol

1M Isopropyl chloroformate in toluene (0.282 mL, 0.28 mmol) was added to a stirred solution of 5-(2,4,5-trifluoro-3-methoxyphenyl)furan-3-carboxylic acid **Intermediate 13** (0.059 g, 0.22 mmol) and TEA (0.039 mL, 0.28 mmol) in THF (2 mL), and the reaction mixture was stirred at rt for 30 min. The solids were filtered off and washed with THF (1 mL). The filtrate was added to a stirred solution of NaBH₄ (0.021 g, 0.54 mmol) in H₂O (0.600 mL), and the reaction mixture was stirred at rt for 30 min. H₂O and DCM were added and the phases were separated on a phase separator. The organic layer was concentrated, and the crude product was purified by straight phase flash chromatography on silica (gradient: 0–100% EtOAc in heptane) to give the title compound (0.038 g, 68%) as an off-white solid; ¹H NMR (500 MHz, CDCl₃, 25°C) δ 4.06 (t, 3H), 4.61 (d, 2H), 6.88 (d, 1H), 7.30 (ddd, 1H), 7.48 (s, 1H).

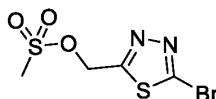
Intermediate 15**3-Methyl-1-((5-(2,4,5-trifluoro-3-methoxyphenyl)furan-3-yl)methyl)pyrimidine-2,4(1H,3H)-dione**

Methanesulfonic anhydride (0.051 g, 0.29 mmol) was added to a stirred solution of (5-(2,4,5-trifluoro-3-methoxyphenyl)furan-3-yl)methanol **Intermediate 14** (0.038 g, 0.15 mmol) and DIPEA (0.077 mL, 0.44 mmol) in DCM (1.5 mL), and the reaction mixture was stirred at rt for 1 h. DCM and 10% citric acid were added and the phases were separated. The aqueous layer was extracted with DCM, and the combined organic layers were passed through a phase separator and concentrated. The residue was dissolved in NMP (2 mL) and added to a stirred solution of 3-methylpyrimidine-2,4(1H,3H)-dione (0.024 g, 0.19 mmol) and sodium *tert*-pentoxide (0.021 g, 0.19 mmol) in NMP (1 mL). The reaction mixture was stirred at rt for 1 h. The mixture was acidified with AcOH and purified by preparative HPLC, **PrepMethod C**, (gradient: 20–80%) to give the title compound (0.039 g, 73%) as a white solid; MS (ESI) *m/z* [M+H]⁺ 367.

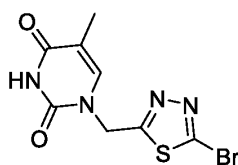
Intermediate 16

(5-Bromo-1,3,4-thiadiazol-2-yl)methanol

NaBH₄ (3.19 g, 84.2 mmol) was added to a solution of ethyl 5-bromo-1,3,4-thiadiazole-2-carboxylate (10.0 g, 42.1 mmol) in MeOH (100 mL) at 0°C. The mixture was stirred at 20°C for 1 h. 0.5 M HCl (200 mL) was added, and the reaction mixture was extracted with EtOAc (3×100 mL). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give crude title compound (6.7 g) as a white solid; MS (ESI) *m/z* [M+H]⁺ 195 and 197 (Br isotope pattern).

Intermediate 17**(5-Bromo-1,3,4-thiadiazol-2-yl)methyl methanesulfonate**

MsCl (7.87 g, 68.6 mmol, 5.33 mL) was added to a solution of (5-bromo-1,3,4-thiadiazol-2-yl)methanol **Intermediate 16** (6.70 g, 34.3 mmol) and TEA (10.4 g, 103 mmol, 14.3 mL) in THF (67 mL) at 0°C. The reaction mixture was stirred at 20°C for 1 h. Water (70 mL) was added, and the mixture was extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine (60 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give crude title compound (8.0 g) as a brown solid; MS (ESI) *m/z* [M+H]⁺ 273 and 275 (Br isotope pattern).

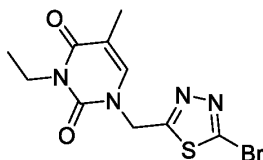
Intermediate 18**1-((5-Bromo-1,3,4-thiadiazol-2-yl)methyl)-5-methylpyrimidine-2,4(1H,3H)-dione**

Trimethylsilyl (*E*)-*N*-(trimethylsilyl)acetimidate (14.9 g, 73.2 mmol, 18.1 mL) and TBAI (2.16 g, 5.86 mmol) was added to a solution of (5-bromo-1,3,4-thiadiazol-2-yl)methyl methanesulfonate **Intermediate 17** (8.0 g, 29.3 mmol) and 5-methylpyrimidine-2,4(1H,3H)-dione (3.3 g, 26.4 mmol) in MeCN (56 mL). The reaction mixture was stirred at 80°C for 12 h. Water (100 mL) was added, and the mixture was extracted with EtOAc (3×80 mL). The combined organic layer was washed with brine

(100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give crude title compound (6.40 g) as a brown solid. MS (ESI) *m/z* [M+H]⁺ 303 and 305 (Br isotope pattern).

Intermediate 19

1-((5-Bromo-1,3,4-thiadiazol-2-yl)methyl)-3-ethyl-5-methylpyrimidine-2,4(1*H*,3*H*)-dione



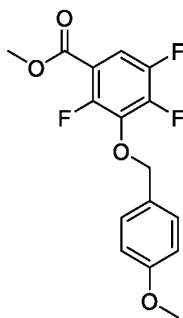
5

K₂CO₃ (5.84 g, 42.2 mmol) and EtI (4.94 g, 31.6 mmol, 2.53 mL) was added to a solution of 1-((5-bromo-1,3,4-thiadiazol-2-yl)methyl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione **Intermediate 18** (6.40 g, 21.1 mmol) in DMF (44.8 mL). The reaction mixture was stirred at 70°C for 2 h. Water (60 mL) was added, and the mixture was extracted with EtOAc (3×40 mL). The combined organic layer was washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give crude title compound (4.0 g) as a brown solid; MS (ESI) *m/z* [M+H]⁺ 331 and 333. (Br isotope pattern).

10

Intermediate 20

Methyl 2,4,5-trifluoro-3-((4-methoxybenzyl)oxy)benzoate



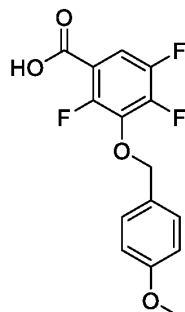
15

1-(Chloromethyl)-4-methoxybenzene (17.1 mL, 125 mmol) was added to methyl 2,4,5-trifluoro-3-hydroxybenzoate (23.5 g, 114 mmol) and K₂CO₃ (20.5 g, 148 mmol) in MeCN (350 mL) at rt, and the reaction mixture was stirred at 80°C for 15 h. The mixture was filtered through CELITE, and the filtrate was concentrated. The crude product was purified by straight phase flash chromatography on silica (gradient: 0–6% EtOAc in petroleum ether) to give the title compound (30.0 g, 81%) as a pale yellow liquid; ¹H NMR (300 MHz, CDCl₃) δ 3.82 (s, 3H), 3.95 (s, 3H), 5.18 (s, 2H), 6.88–6.94 (m, 2H), 7.34–7.40 (m, 2H), 7.48 (m, 1H).

20

Intermediate 21

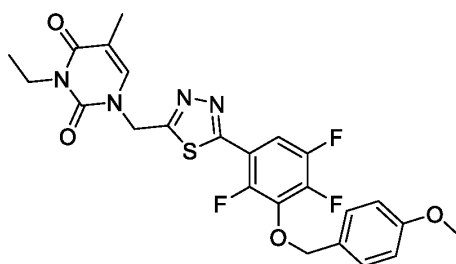
2,4,5-Trifluoro-3-((4-methoxybenzyl)oxy)benzoic acid



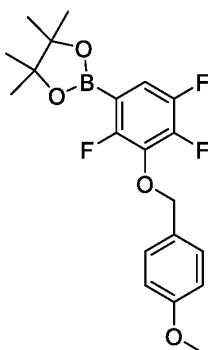
- 50% NaOH (aq, 20 mL, 381 mmol) was added to methyl 2,4,5-trifluoro-3-((4-methoxybenzyl)oxy)benzoate **Intermediate 20** (29 g, 89 mmol) in MeOH (100 mL) and H₂O (50 mL) at rt, and the reaction mixture was stirred at 60°C for 2 h. The mixture was poured into a mixture of water and ice (400 mL) and extracted with EtOAc (2×125 mL). The aqueous layer was acidified to pH3 with 6 M HCl (aq) and extracted with EtOAc (3×200 mL). The combined organic layer was dried over Na₂SO₄, filtered, and concentrated. The residue was triturated with EtOAc/petroleum ether (1:3, 30 mL) to give a solid which was collected by filtration and dried under vacuum to give the title compound (22.5 g, 81%) as a white solid; ¹H NMR (300 MHz, CDCl₃) δ 3.82 (s, 3H), 5.19 (s, 2H), 6.85–6.93 (m, 2H), 7.33–7.40 (m, 2H), 7.55 (m, 1H).

Intermediate 22

- 3-Ethyl-5-methyl-1-((5-(2,4,5-trifluoro-3-((4-methoxybenzyl)oxy)phenyl)-1,3,4-thiadiazol-2-yl)methyl)pyrimidine-2,4(1H,3H)-dione



Step a) 4,4,5,5-Tetramethyl-2-(2,4,5-trifluoro-3-((4-methoxybenzyl)oxy)phenyl)-1,3,2-dioxaborolane



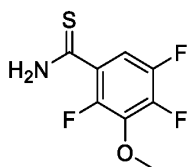
TEA (0.670 mL, 4.80 mmol) was added slowly to Pd(OAc)₂ (0.036 g, 0.16 mmol), 2,4,5-trifluoro-3-((4-methoxybenzyl)oxy)benzoic acid **Intermediate 21** (1.0 g, 3.2 mmol), pivalic anhydride (0.895 g, 4.80 mmol), dppb (0.137 g, 0.32 mmol) and bis(pinacolato)diboron (1.220 g, 4.80 mmol) in 1,4-dioxane
 5 (15 mL) at rt, and the reaction mixture was stirred at 160°C for 12 h. The reaction was quenched with NaHCO₃ (sat, aq, 150 mL) and extracted with EtOAc (3×100 mL). The combined organic layer was dried over Na₂SO₄, filtered and concentrated. The crude product was purified by straight phase flash chromatography on silica (gradient: 0–2% EtOAc in petroleum ether) to give the crude subtitle compound (0.450 g) as a pale yellow liquid.

10 **Step b) 3-Ethyl-5-methyl-1-((5-(2,4,5-trifluoro-3-((4-methoxybenzyl)oxy)phenyl)-1,3,4-thiadiazol-2-yl)methyl)pyrimidine-2,4(1H,3H)-dione**

A mixture of 1-((5-bromo-1,3,4-thiadiazol-2-yl)methyl)-3-ethyl-5-methylpyrimidine-2,4(1H,3H)-dione **Intermediate 19** (2.19 g, 6.61 mmol), 4,4,5,5-tetramethyl-2-(2,4,5-trifluoro-3-((4-methoxybenzyl)oxy)phenyl)-1,3,2-dioxaborolane **Intermediate 22 step a** (2.60 g, 6.61 mmol) and
 15 K₂CO₃ (1.83 g, 13.1 mmol) in dioxane (18.2 mL) was degassed and purged with N₂(g) (×3). Pd(dppf)Cl₂ (241 mg, 328 μmol) was added. The reaction mixture was degassed and purged with N₂(g) (×3), then stirred at 80°C for 12 h under a N₂(g) atmosphere. Water (20 mL) was added, and the mixture was extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give crude title compound (2.90
 20 g) as a brown oil; MS (ESI) *m/z* [M+H]⁺ 519.

Intermediate 23

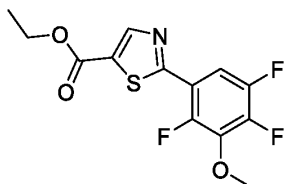
2,4,5-Trifluoro-3-methoxybenzothioamide



Lawesson's reagent (1.774 g, 4.39 mmol) was added to a solution of 2,4,5-trifluoro-3-methoxybenzamide (1.5 g, 7.31 mmol) in THF (30 mL) and the reaction mixture was heated at 50°C for 50 min. The reaction mixture was concentrated, and the residue was purified by straight phase
 5 flash chromatography on silica (0–20% EtOAc in heptane) to give the title compound (1.225 g, 76%) as a yellow solid; MS m/z (ESI) $[M-H]^-$ 220.1.

Intermediate 24

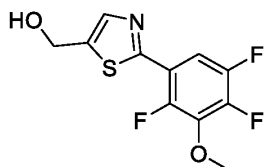
Ethyl 2-(2,4,5-trifluoro-3-methoxyphenyl)thiazole-5-carboxylate



A solution of 2,4,5-trifluoro-3-methoxybenzothioamide **Intermediate 23** (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
 15 pale orange solid; MS m/z (ESI) $[M+H]^+$ 318.1.

Intermediate 25

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



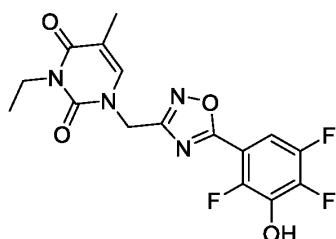
NaBH_4 (0.227 g, 5.99 mmol) was added to a stirred solution of ethyl 2-(2,4,5-trifluoro-3-methoxyphenyl)thiazole-5-carboxylate **Intermediate 24** (0.38 g, 1.20 mmol) in THF (4.5 mL) and MeOH (1.5 mL). The reaction mixture was stirred at 55 °C for 1 h. The reaction solution was cooled to rt and 3.8 M HCl (5 mL, aq) was added, and the mixture was stirred for 10 min. THF and MeOH
 20

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

5

Example 1

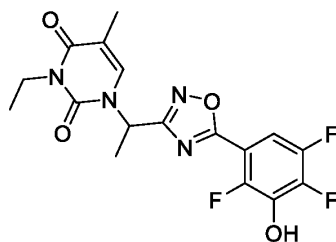
3-Ethyl-5-methyl-1-((5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methyl)pyrimidine-2,4(1H,3H)-dione



- 10 A solution of 3-ethyl-5-methyl-1-((5-(2,4,5-trifluoro-3-((4-methoxybenzyl)oxy)phenyl)-1,2,4-oxadiazol-3-yl)methyl)pyrimidine-2,4(1H,3H)-dione **Intermediate 5** (20 mg, 0.04 mmol) in TFA (1 mL) was stirred at 80°C for 3 h. The reaction mixture was concentrated, and the residue was purified by preparative HPLC, PrepMethod A (gradient: 9–25%), to give the title compound (5.8 mg, 38%) as a white solid; HRMS (ESI) m/z $[M+H]^+$ calcd for $C_{16}H_{14}F_3N_4O_4$: 383.0962, found: 383.0944; 1H NMR (300
- 15 MHz, CD_3OD) δ 1.21 (3H, t), 1.96 (3H, d), 4.02 (2H, q), 5.17 (2H, s), 6.83 (1H, ddd), 7.60 (1H, d).

Example 2

3-Ethyl-5-methyl-1-(1-(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)ethyl)pyrimidine-2,4(1H,3H)-dione

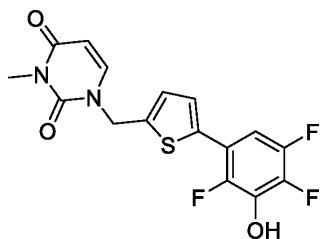


- 20 2,4,5-Trifluoro-3-hydroxybenzoyl chloride (329 mg, 1.56 mmol) was added slowly to a mixture of (Z)-2-(3-ethyl-5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-N'-hydroxypropanimidamide **Intermediate 9** (250 mg, 1.04 mmol) and TEA (0.435 mL, 3.12 mmol) in MeCN (15 mL) at 20°C. The

resulting solution was stirred at 20°C for 2 h. The reaction mixture was concentrated under vacuum, and the residue was dissolved in AcOH (15 mL). The resulting solution was stirred at 120°C for 3 h. The solution was partially concentrated under reduced pressure, and the residue was poured into NaHCO₃ (sat, aq 100 mL) and extracted with EtOAc (3×100 mL). The combined organic layer was dried over Na₂SO₄, filtered, and concentrated. The residue was purified by preparative TLC (EtOAc:petroleum ether, 1:1) and then by preparative HPLC, PrepMethod B (gradient: 41–52%), to afford the title compound (37 mg, 9%) as a white solid. HRMS (ESI) *m/z* [M+H]⁺ calcd for C₁₇H₁₆F₃N₄O₄: 397.1118, found: 397.1118; ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.10 (3H, t), 1.78 (3H, d), 1.84 (3H, s), 3.87 (2H, q), 5.94 (1H, q), 7.54–7.62 (1H, m), 7.67 (1H, s), 11.65 (1H, s).

10 Example 3

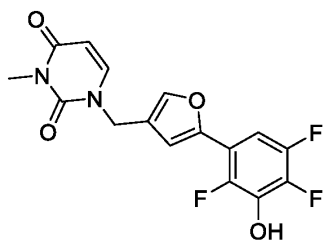
3-Methyl-1-((5-(2,4,5-trifluoro-3-hydroxyphenyl)thiophen-2-yl)methyl)pyrimidine-2,4(1*H*,3*H*)-dione



1M BBr₃ in DCM (1.63 mL, 1.63 mmol) was added to a stirred solution of 3-methyl-1-((5-(2,4,5-trifluoro-3-methoxyphenyl)thiophen-2-yl)methyl)pyrimidine-2,4(1*H*,3*H*)-dione **Intermediate 12** (0.078 g, 0.20 mmol) in DCM (4 mL) and the reaction mixture was stirred at rt for 2 h. The mixture was diluted with DCM and washed with H₂O. The phases were separated on a phase separator and the organic layer was concentrated. The residue was purified by preparative HPLC, **PrepMethod C**, (gradient: 30-70%) to give the title compound (0.003 g, 4%) as an off-white solid; HRMS (ESI) *m/z* [M+H]⁺ calcd for C₁₆H₁₂F₃N₂O₃S: 369.0516, found: 369.0520; ¹H NMR (500 MHz, CD₃OD) δ 3.31 (s, 3H), 5.15 (d, 2H), 5.77 (d, 1H), 7.01 (ddd, 1H), 7.16 (dd, 1H), 7.32 (dd, 1H), 7.71 (d, 1H).

Example 4

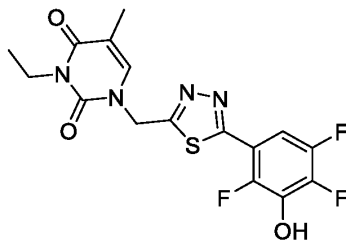
3-Methyl-1-((5-(2,4,5-trifluoro-3-hydroxyphenyl)furan-3-yl)methyl)pyrimidine-2,4(1*H*,3*H*)-dione



1M BBr₃ in DCM (0.43 mL, 0.43 mmol) was added to a stirred solution of 3-methyl-1-((5-(2,4,5-trifluoro-3-methoxyphenyl)thiophen-2-yl)methyl)pyrimidine-2,4(1*H*,3*H*)-dione **Intermediate 15** (0.039 g, 0.11 mmol) in DCM (2 mL) and the reaction mixture was stirred at rt for 30 min. The mixture was diluted with DCM and washed with H₂O. The phases were separated on a phase separator and the organic layer was concentrated. The residue was purified by preparative HPLC, **PrepMethod C**, (gradient: 30-70%) to give the title compound (0.029 g, 77%) as a white solid; HRMS (ESI) *m/z* [M+H]⁺ calcd for C₁₆H₁₂F₃N₂O₄: 353.0744, found: 353.0766; ¹H NMR (500 MHz, DMSO-*d*₆, 25°C) δ 3.16 (s, 3H), 4.80 (s, 2H), 5.73 (d, 1H), 6.89 (d, 1H), 7.11 – 7.20 (m, 1H), 7.81 (d, 1H), 7.84 (s, 1H), 11.13 (s, 1H).

Example 5

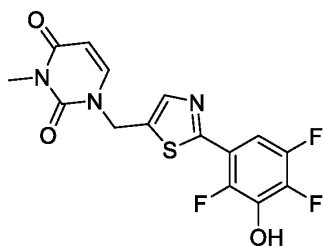
3-Ethyl-5-methyl-1-((5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,3,4-thiadiazol-2-yl)methyl)pyrimidine-2,4(1*H*,3*H*)-dione



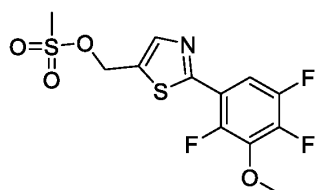
TFA (21.0 mL) was added to a solution of 3-ethyl-5-methyl-1-((5-(2,4,5-trifluoro-3-((4-methoxybenzyl)oxy)phenyl)-1,3,4-thiadiazol-2-yl)methyl)pyrimidine-2,4(1*H*,3*H*)-dione **Intermediate 22** (3.0 g, 5.79 mmol) and the reaction mixture was stirred at 25°C for 2 h. The mixture was concentrated under reduced pressure. The residue was purified by preparative HPLC, PrepMethod E (gradient: 20–50%) to give the title compound (172 mg, 7%) as a yellow solid; HRMS (ESI) *m/z* [M+H]⁺ calcd for C₁₆H₁₄F₃N₄O₃S: 399.0734, found: 399.0724; ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.50 (s, 1H), 7.80 (s, 1H), 7.65 (ddd, 1H), 5.43 (s, 2H), 3.86 (q, 2H), 1.83 (s, 3H), 1.09 (t, 3H).

Example 6

3-Methyl-1-((2-(2,4,5-trifluoro-3-hydroxyphenyl)thiazol-5-yl)methyl)pyrimidine-2,4(1*H*,3*H*)-dione

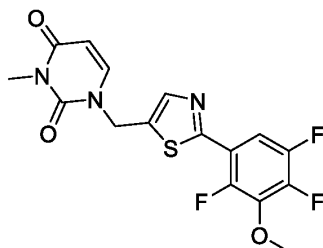


Step a) (2-(2,4,5-Trifluoro-3-methoxyphenyl)thiazol-5-yl)methyl methanesulfonate



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 25** (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 6 step b**.

Step b) 3-Methyl-1-((2-(2,4,5-trifluoro-3-methoxyphenyl)thiazol-5-yl)methyl)pyrimidine-2,4(1H,3H)-dione



10

A crude solution of (2-(2,4,5-trifluoro-3-methoxyphenyl)thiazol-5-yl)methyl methanesulfonate in DCM, **Example 6 step a**, was added to a stirred solution of 3-methylpyrimidine-2,4(1H,3H)-dione (40 mg, 0.32 mmol) and NaOt-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 6 step c**; MS (ESI) m/z $[M+H]^+$ 384.1.

15

Step c) 3-Methyl-1-((2-(2,4,5-trifluoro-3-hydroxyphenyl)thiazol-5-yl)methyl)pyrimidine-2,4(1H,3H)-dione

A solution of crude 3-methyl-1-((2-(2,4,5-trifluoro-3-methoxyphenyl)thiazol-5-yl)methyl)pyrimidine-2,4(1*H*,3*H*)-dione in NMP, **Example 6 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 (27 mg, 33 %) as a white solid; HRMS (ESI) m/z [M+H]⁺ calcd for C₁₅H₁₀F₃N₃O₃S: 370.0473, found: 370.0465; ¹H NMR (600 MHz, DMSO-*d*₆) δ 3.17 (3H, s), 5.21 (2H, s), 5.78 (1H, d), 7.5–7.62 (1H, m), 7.91 (1H, d), 8.04 (1H, s), 11.32 (1H, s).

***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
- 5 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.
- 10 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
- 15 100% 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
- 20 107.0. 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
- 25 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),
- 30 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 (t₀) and at 1.5 h (t₁) in a PHERASTAR FSX (BMG LABTECH). FI for each sample was calculated as FI at t₁ minus FI at t₀.

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

Inhibition of 17bHSD9 was measured in a cell-based assay with over expressed HSD17 β 9 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 μ L of culture media (DMEM with GLUTAMAX plus 10 % FBS). After the cells were allowed to attach for 6 h, 0.15 μ L of 10 concentration of compounds and 0.015 μ L 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 μ L of media was transferred using BRAVO dispensing robot (AGILENT) to a GREINER PP 384 well plate (781280) and 40 μ L 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 μ m, 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 IC₅₀ values.

Compound effect was calculated with the formula below;

$$\text{Compound \% effect} = -100 \times ((X - \text{min}) / (\text{max} - \text{min}))$$

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.

30

Metabolic stability (CL_{int})

Rat, human and cynomolgus hepatocyte metabolic stability was determined in accordance with or (for cynomolgus) in analogy with the method described by Jacobson *et al.** Cryopreserved hepatocytes at a concentration of 10^6 viable cells/mL were used. After thawing, hepatocytes were incubated for 10 min to warm to 37°C and test compounds, dissolved in acetonitrile, were added to
 5 give a final concentration of 1 μ M. At 0.5, 5, 15, 30, 45, 60, 80, 100 and 120 min, the incubation system was mixed and 20 μ L aliquots were transferred at each time point to wells in a separate plate filled with 80 μ L MeCN to stop the reaction. The quenching plate was then vortexed followed by centrifugation, and supernatants were analyzed by LC-MS/MS. Peak areas were determined from extracted ion chromatograms, and the *in vitro* intrinsic clearance (*in vitro* CL_{int}, in μ L/min/ 10^6 cells)
 10 of parent compound was calculated from the slope in the regression analysis of the natural logarithm of parent concentration vs time curve.

* Jacobson, L.; Middleton, B.; Holmgren, J.; Eirefelt, S.; Frojd, M.; Blomgren, A.; Gustavsson, L. An optimized automated assay for determination of metabolic stability using
 15 hepatocytes: assay validation, variance component analysis, and *in vivo* relevance. *Assay Drug Dev Technol* **2007**, 5 (3), 403–415. DOI: 10.1089/adt.2007.059.

Cynomolgus PK

The PK studies were conducted at Charles River Laboratories, UK. Compounds were tested in male
 20 cynomolgus monkeys (N=2) via infusion in the tail vein at the dose level of 0.5 mg/kg. Doses were selected based on previous rodent PK studies with at least 0.5 mg/kg intravenous dosing and 1 mg/kg oral dosing without any adverse events. Dosing formulation were 5% DMSO, 95% SBE-B-CD (30% w/v) in water. Following dosing, blood samples (ca 1 mL) were collected from the femoral or cephalic vein by venipuncture into tubes containing K2EDTA anticoagulant according to the following
 25 target times: Predose, 0.25 (15 min), 0.28 (17 min), 0.75 (45 min), 2.25, 4.25, 8.25 and 24.25 hours post start of infusion. Plasma samples were analysed using an established RGA2 LCMS/MS assay. The data shown in Tables 2 and 4 are the terminal half lives in plasma, estimated by fitting PK data with a 2-compartmental model.

Table 1

Example	17bHSD13 Enzyme assay IC ₅₀ (μ M)	17HSD17b4 Enzyme assay IC ₅₀ (μ M)	17bHSD1713 Cell assay IC ₅₀ (μ M, total)	17bHSD9 Cell assay IC ₅₀ (μ M, total)
1	0.105	>50	0.086	>50
2	0.294	>50	0.890	

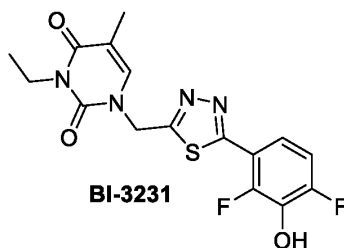
3	0.031	8.4	0.218	
4	0.033	>50	0.078	
5	0.015	>50	0.015	>50
6	0.022	43.9	0.037	>50

Table 2

Example	Rat Hep Clint ($\mu\text{L}/\text{min}/1\text{E}6$)	Hu Hep Clint ($\mu\text{L}/\text{min}/1\text{E}6$)	Cyno Hep Clint ($\mu\text{L}/\text{min}/1\text{E}6$)	Cyno PK (i.v) (plasma $t_{1/2}$, h)
1	5.5	4.9		
2	8.9	7.5		
3	15.5	72.8		
4	31.8	24.8		
5	9.7	5.9	18	1.7
6	16.8	7.9	19.3	6.5

Thamm et al., J Med Chem. 2023 Feb 23;66(4):2832-2850 (doi: 10.1021/acs.jmedchem.2c01884)

- 5 discloses BI-3231. Comparative data for BI-3231 is presented in Tables 3 and 4.

**Table 3**

	17bHSD13 Enzyme assay IC_{50} (μM)	17HSD17b4 Enzyme assay IC_{50} (μM)	17bHSD1713 Cell assay IC_{50} (μM , total)	17bHSD9 Cell assay IC_{50} (μM , total)
BI-3231	0.029	>50	0.007	>50

Table 4

Example	Rat Hep Clint	Hu Hep Clint	Cyno Hep Clint	Cyno PK (i.v)
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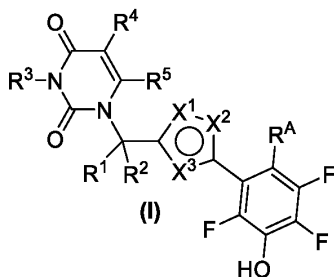
	($\mu\text{L}/\text{min}/1\text{E}6$)	($\mu\text{L}/\text{min}/1\text{E}6$)	($\mu\text{L}/\text{min}/1\text{E}6$)	(plasma $t_{1/2}$, h)
BI-3231	93.5	16.2	169	0.15

The data in Tables 1 to 4 may be from a single experiment or an average of two or more experiments.

- 5 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
- 10 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
- 15 combined to form sub-combinations thereof.

Claims

1. A compound of Formula (I)



wherein,

- 5 R^A is H, F or Cl,
 one of X¹, X² and X³ is selected from NH, O and S and the other two of X¹, X² and X³ are independently selected from N and CR^Y, wherein each R^Y is independently H, -CN, or R^{XA}, wherein R^{XA} is independently C₁₋₃ alkyl optionally substituted with one to three F,
 either (i) R¹ and R² are independently selected from H, R⁶ and R⁷,
 10 or (ii) R¹ and R² together with the carbon atom to which they are attached form a cyclopropane or cyclobutane ring,
 R³ is R^{6A} or R^{7A},
 either (i) R⁴ is H, R^{6B} or R^{7B}, and R⁵ is H, R^{6C} or R^{7C},
 or (ii) R⁴ and R⁵ together form a group selected from  and ,
 15 each of R⁶, R^{6A}, R^{6B} and R^{6C} are independently C₁₋₆ alkyl optionally substituted with one to three substituents independently selected from F and C₃₋₆ cycloalkyl, and
 each of R⁷, R^{7A}, R^{7B} and R^{7C} are independently C₃₋₆ cycloalkyl optionally substituted with one to three F,
 or a pharmaceutically acceptable salt thereof.

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

- (i) X¹ is N, X² is O and X³ is N,
 (ii) X¹ is N, X² is N and X³ is O,
 25 (iii) X¹ is CR^Y, X² is CR^Y and X³ is S,
 (iv) X¹ is O, X² is N and X³ is CR^Y,
 (v) X¹ is N, X² is O and X³ 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 ,
 5 (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,
 10 (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 .
- 15 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 .
- 20 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 in claim 1 or claim 2, wherein X^1 is N, X^2 is N and X^3 is S.
- 25 7. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 6, wherein R^A is H.
- 30 8. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 7, wherein R^1 is H or CH_3 and R^2 is H.
9. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 8, wherein R^3 is C_{1-4} alkyl, such as CH_3 or CH_2CH_3 .

10. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 9, wherein R⁴ is H, R^{6B} or R^{7B}, and R⁵ is H, R^{6C} or R^{7C}.
- 5 11. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in claim 10, wherein R⁴ is C₁₋₄ alkyl, such as CH₃ or CH₂CH₃.
12. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in claim 10, wherein R⁴ is H.
- 10 13. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 10 to 12, wherein R⁵ is H.
14. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in claim 1, that is
- 15 3-Ethyl-5-methyl-1-((5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methyl)pyrimidine-2,4(1H,3H)-dione,
 3-Ethyl-5-methyl-1-(1-(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)ethyl)pyrimidine-2,4(1H,3H)-dione,
 20 3-Ethyl-5-methyl-1-((5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,3,4-thiadiazol-2-yl)methyl)pyrimidine-2,4(1H,3H)-dione,
 3-Methyl-1-((5-(2,4,5-trifluoro-3-hydroxyphenyl)thiophen-2-yl)methyl)pyrimidine-2,4(1H,3H)-dione,
 3-Methyl-1-((5-(2,4,5-trifluoro-3-hydroxyphenyl)furan-3-yl)methyl)pyrimidine-2,4(1H,3H)-dione,
 3-Ethyl-5-methyl-1-((5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,3,4-thiadiazol-2-yl)methyl)pyrimidine-
 25 2,4(1H,3H)-dione, or
 3-Methyl-1-((2-(2,4,5-trifluoro-3-hydroxyphenyl)thiazol-5-yl)methyl)pyrimidine-2,4(1H,3H)-dione,
 or a pharmaceutically acceptable salt thereof.
15. A pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 14, and a pharmaceutically acceptable excipient.
- 30 16. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 14, or a pharmaceutical composition as claimed in claim 15, for use in therapy.

17. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 14, or a pharmaceutical composition as claimed in claim 15, for use in the treatment of liver disease.

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18. 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 14.

10 19. Use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 14, in the manufacture of a medicament for the treatment of liver disease.

20. A compound or pharmaceutical composition for use, method or use according to any one of claims 17 to 19, wherein the liver disease is selected from alcoholic liver disease, non-alcoholic liver
15 disease, NAFLD, NASH, liver fibrosis, cirrhosis, isolated steatosis, liver inflammation, alcoholic steatohepatitis (ASH), hepatitis C virus (HCV) and hepatocellular carcinoma (HCC).

21. A compound or pharmaceutical composition for use, method or use according to any one of claims 17 to 19, wherein the liver disease is NASH.

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