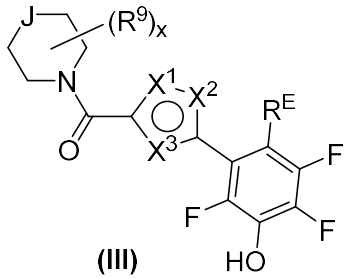
Claims

1. A compound Formula (III):



(III)

wherein

one of X^1, X^2 and X^3 is selected from NH, O and S and the other two of X^1, X^2 and X^3 are independently selected from N and CR^Y, wherein each R^Y is independently H, -CN, $-C(=O)N(R^7)_2$ or R^{XA}, wherein R^{XA} is independently C_{1-3} alkyl optionally substituted with one to three F;

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

x is selected from 0 to 3;

each R^9 is independently selected from R^3, R^4 and R^5;

R^E is H or halo,

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

each R^{3X} is independently C_{1-4} alkyl or C_{3-6} cycloalkyl, each of which are optionally substituted with one or more F;

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

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

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

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

each R^7 and R^{7B} are independently H, C_{1-4} alkyl or C_{3-6} cycloalkyl; and

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

or a pharmaceutically acceptable salt thereof.

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

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

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

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

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

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

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

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

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

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

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

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

4. A compound of Formula (III), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 3, wherein J is O.

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

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

7. A compound of Formula (III), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 6, wherein each R^5 is independently phenyl, each of which are optionally

substituted with one or more groups independently selected from OH, -CN, C_{1-4} alkoxy, -C(=O)OH, -C(=O)O(C_{1-4} alkyl), -C(=O)N(R^{7B})$_2$, R^{3X} and halo.

8. A compound of Formula (III), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 7, wherein R^E is H.

9. A compound of Formula (III), or a pharmaceutically acceptable salt thereof, as claimed in claim 1, that is selected from
((2*R*,6*S*)-2,6-Dimethylmorpholino)(5-(2,4,5-trifluoro-3-hydroxyphenyl)thiophen-2-yl)methanone,
(3-(2-Methoxyphenyl)pyrrolidin-1-yl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methanone,
(*R*)-(3-(4-Chlorophenyl)pyrrolidin-1-yl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)isoxazol-3-yl)methanone,
3-(4-(3-(4-Fluorophenoxy)propyl)piperazine-1-carbonyl)-5-(2,4,5-trifluoro-3-hydroxyphenyl)isoxazole-4-carbonitrile,
3-(4-(Pyridin-2-yl)piperazine-1-carbonyl)-5-(2,4,5-trifluoro-3-hydroxyphenyl)isoxazole-4-carbonitrile,
3-(4-(3-Methoxyphenyl)piperazine-1-carbonyl)-5-(2,4,5-trifluoro-3-hydroxyphenyl)isoxazole-4-carbonitrile,
5-(2,4,5-Trifluoro-3-hydroxyphenyl)-3-(4-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperazine-1-carbonyl)isoxazole-4-carbonitrile,
(S)-3-(3-(4-Chlorophenyl)pyrrolidine-1-carbonyl)-5-(2,4,5-trifluoro-3-hydroxyphenyl)isoxazole-4-carbonitrile,
3-((2*R*,6*S*)-2,6-Dimethylmorpholine-4-carbonyl)-5-(2,4,5-trifluoro-3-hydroxyphenyl)isoxazole-4-carbonitrile,
3-(4-(Benzo[*d*]oxazol-2-yl)piperazine-1-carbonyl)-5-(2,4,5-trifluoro-3-hydroxyphenyl)isoxazole-4-carbonitrile,
3-(4-(4-(4-Fluorophenyl)-2-oxo-2,3-dihydro-1*H*-imidazol-1-yl)piperidine-1-carbonyl)-5-(2,4,5-trifluoro-3-hydroxyphenyl)isoxazole-4-carbonitrile,
(*R*)-(3-Phenylpyrrolidin-1-yl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)thiophen-2-yl)methanone,
(3-Isopropylmorpholino)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methanone,
((3*R*,5*S*)-3,5-Dimethylmorpholino)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methanone,
((3*R*,5*S*)-3,5-Dimethylpiperidin-1-yl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methanone,

((2*R*,5*S*)-2,5-Dimethylpyrrolidin-1-yl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methanone,

Morpholino(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methanone,

Thiomorpholino(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methanone,

3-(4-(5-(2,4,5-Trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazole-3-carbonyl)piperazin-2-yl)benzonitrile,

Piperidin-1-yl(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methanone,

(*S*)-(5-(2,4,5-Trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)(2-(trifluoromethyl)morpholino)methanone,

(2-Isobutylmorpholino)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methanone,

(3,3-Dimethylmorpholino)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methanone,

(*R*)-(2-(Fluoromethyl)morpholino)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methanone,

((2*R*,5*R*)-2,5-Dimethylmorpholino)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methanone,

((2*S*,6*S*)-2,6-Dimethylmorpholino)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methanone,

(4-(4-Methoxyphenyl)piperazin-1-yl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methanone,

4-(1-(5-(2,4,5-Trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazole-3-carbonyl)piperidin-4-yl)benzonitrile,

(4-(3-(4-Fluorophenoxy)propyl)piperazin-1-yl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methanone,

(4-(Pyridin-2-yl)piperazin-1-yl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methanone,

(4-(3-Methoxyphenyl)piperazin-1-yl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methanone,

(4-(3-Chloro-5-(2-methyl-2*H*-tetrazol-5-yl)pyridin-2-yl)piperazin-1-yl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methanone,

(4-(2-((5-Bromopyridin-2-yl)oxy)ethyl)piperazin-1-yl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methanone,

(4-(Benzo[*d*]oxazol-2-yl)piperazin-1-yl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methanone,

(3-Propylpyrrolidin-1-yl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methanone,

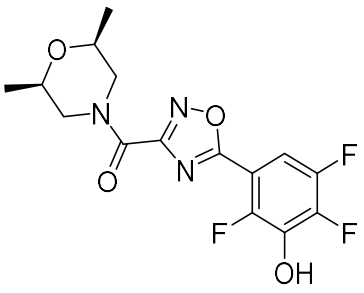
(4-Phenylpiperazin-1-yl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methanone,

2-(4-(5-(2,4,5-Trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazole-3-carbonyl)piperazin-1-yl)benzonitrile,

4-(4-(5-(2,4,5-Trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazole-3-carbonyl)piperazin-1-yl)benzonitrile,

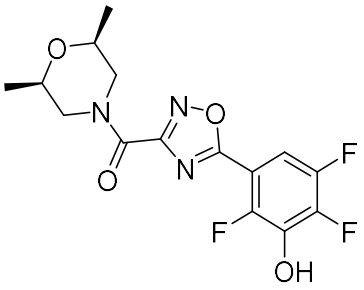
(4-(2-Methoxyphenyl)piperazin-1-yl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methanone,
((2*R*,6*S*)-2,6-Dimethylmorpholino)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methanone,
((2*R*,6*R*)-2,6-Dimethylmorpholino)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methanone,
((2*R*,6*S*)-2,6-Dimethylmorpholino)(5-(2,4,5-trifluoro-3-hydroxyphenyl)isoxazol-3-yl)methanone,
(*R*)-(3-(4-Chlorophenyl)pyrrolidin-1-yl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methanone,
(3-Phenylpyrrolidin-1-yl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methanone,
(*S*)-(3-(4-Chlorophenyl)pyrrolidin-1-yl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methanone,
(*R*)-(3-Phenylpyrrolidin-1-yl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)isoxazol-3-yl)methanone,
((2*S*,6*R*)-2,6-Dimethylmorpholino)(5-(2,4,5-trifluoro-3-hydroxy-6-iodophenyl)-1,2,4-oxadiazol-3-yl)methanone,
((2*R*,6*S*)-2,6-Dimethylmorpholino)(3-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-5-yl)methanone,
((3*R*,5*S*)-3,5-Dimethylpiperidin-1-yl)(3-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-5-yl)methanone,
(5-(2,4,5-Trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)(2,2,6-trimethylmorpholino)methanone,
((3*R*,5*S*)-3,5-Dimethylpiperazin-1-yl)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methanone,
((2*R*,6*S*)-2,6-Dimethylmorpholino)(2-(2,4,5-trifluoro-3-hydroxyphenyl)thiazol-5-yl)methanone,
rac-((2*R*,6*S*)-2-Ethyl-6-methylmorpholino)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methanone,
rac-((2*R*,6*S*)-2-isopropyl-6-methylmorpholino)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methanone, and
(5-(2-Bromo-3,4,6-trifluoro-5-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)((2R,6S)-2,6-dimethylmorpholino)methanone,
or a pharmaceutically acceptable salt thereof.

10. A compound of Formula (III), or a pharmaceutically acceptable salt thereof, as claimed in claim 1, that is ((2R,6S)-2,6-dimethylmorpholino)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methanone



or a pharmaceutically acceptable salt thereof.

11. A compound of Formula (III), as claimed in claim 10, that is ((2R,6S)-2,6-dimethylmorpholino)(5-(2,4,5-trifluoro-3-hydroxyphenyl)-1,2,4-oxadiazol-3-yl)methanone



.

12. A pharmaceutical composition comprising a compound of Formula (III), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 11, and a pharmaceutically acceptable excipient.

13. A compound of Formula (III), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 11, for use in therapy.

14. Use of a compound of Formula (III), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 11, in the manufacture of a medicament for the treatment of liver disease.

15. The use as claimed in claim 14, wherein the liver disease is selected from alcoholic liver disease, non-alcoholic liver disease, NAFLD, NASH, liver fibrosis, cirrhosis, isolated steatosis, liver inflammation, alcoholic steatohepatitis (ASH), hepatitis C virus (HCV) and hepatocellular carcinoma (HCC).

16. The use as claimed in claim 14 or claim 15, wherein the liver disease is liver fibrosis.

17. The use as claimed in claim 14 or claim 15, wherein the liver disease is cirrhosis.

18. The use of a combination in the manufacture of a medicament for the treatment of liver disease, wherein the combination comprises a compound of Formula (III) or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 11, and

(i) a glucagon-like peptide-1 receptor (GLP1) agonist,

(ii) a sodium-glucose transport protein 2 (SGLT2) inhibitor, or

(iii) a ThrB agonist.