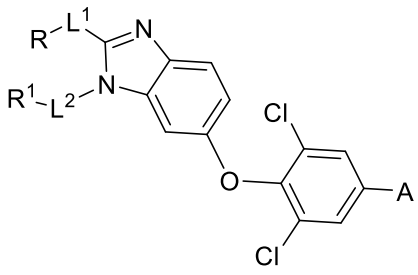
THR beta, and preferably those that avoid the undesirable effects associated with agonism of THR alpha and/or preferentially distributed in liver, and maintain the beneficial effects of thyroid hormones, *e.g.*, for the treatment for patients with non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), metabolic syndrome, dyslipidemia, hypertriglyceridemia, or hypercholesterolemia.

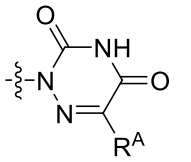
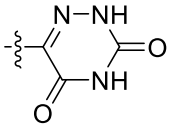
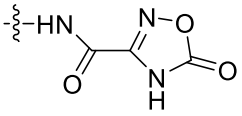
SUMMARY

[0004a] In an aspect of the present disclosure, there is provided a compound of formula (I):



(I)

or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of each of the foregoing, wherein:

A is  ,  , or  , wherein R^A is H or -CN;

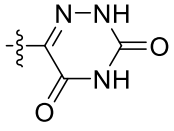
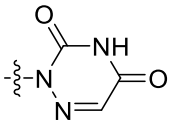
L^1 is a bond, -NR'-, -O-, -S-, or -$S(O)_2$-, wherein R' is H or C_1-C_6 alkyl;

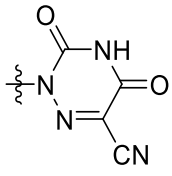
L^2 is a bond or -$S(O)_2$-;

R^1 is H, C_1-C_6 alkyl, C_6-C_{10} aryl, 3-12 membered heterocyclyl, 5-12 membered heteroaryl, or C_3-C_6 cycloalkyl, wherein the C_1-C_6 alkyl, C_6-C_{10} aryl, 3-12 membered heterocyclyl, 5-12 membered heteroaryl, and C_3-C_6 cycloalkyl are each independently optionally substituted by 1-5 R^2 groups;

R is H, C_1-C_6 alkyl, C_6-C_{10} aryl, 3-12 membered heterocyclyl, 5-12 membered heteroaryl, or C_3-C_6 cycloalkyl, wherein the C_1-C_6 alkyl, C_6-C_{10} aryl, 3-12 membered heterocyclyl, 5-12 membered heteroaryl, and C_3-C_6 cycloalkyl are each independently optionally substituted by 1-5 R^2 groups; and

each R^2 is independently halogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl-OH, -NH_2, -CN, or hydroxyl, provided that

when L^1 is a bond and R is H, then A is  or , and

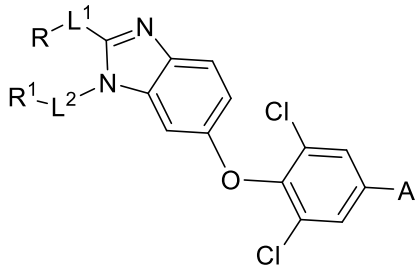
when L^1 is -O-, R is H, and A is , then R^1 is C_2-C_6 alkyl, C_6-C_{10} aryl, 3-12 membered heterocyclyl, 5-12 membered heteroaryl, or C_3-C_6 cycloalkyl, wherein the C_2-C_6 alkyl, C_6-C_{10} aryl, 3-12 membered heterocyclyl, 5-12 membered heteroaryl, and C_3-C_6 cycloalkyl are each independently optionally substituted by 1-5 R^2 groups.

[0004b] In another aspect of the present disclosure, there is provided a pharmaceutical composition, comprising the compound disclosed herein, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of each of the foregoing, and a pharmaceutically acceptable excipient.

[0004c] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of each of the foregoing, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating a disorder ameliorated by activation of thyroid hormone receptor beta in a patient in need thereof.

[0004d] In another aspect of the present disclosure, there is provided a disclosed herein, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of each of the foregoing, or the pharmaceutical composition disclosed herein, for use in therapy.

[0005] In some examples, provided herein is a compound of formula (I):



(I)

or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of any of the foregoing, wherein L^1, L^2, R, R^1, and A are as disclosed herein.

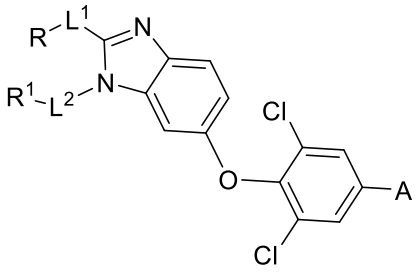
[0006] In some examples, provided herein is a pharmaceutical composition comprising a compound provided herein and a pharmaceutically acceptable excipient.

[0007] In some examples, provided herein is a method of agonizing thyroid hormone receptor beta (THR beta) comprising contacting either an effective amount of a compound provided herein, or an effective amount of a pharmaceutical composition provided herein, with the THR beta.

[0008] In some examples, provided herein is a method of treating a disorder which is ameliorated by activation of THR beta in a patient, comprising administering to the patient a therapeutically effective amount of a compound provided herein, or a therapeutically effective amount of a composition provided herein. In some examples, the disorder is non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), metabolic syndrome, dyslipidemia, hypertriglyceridemia, or hypercholesterolemia. In some examples, the disorder is NASH.

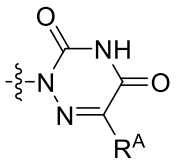
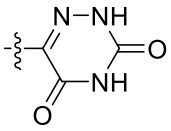
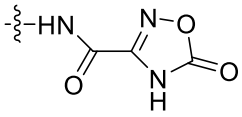
CLAIMS

1. A compound of formula (I):



(I)

or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of each of the foregoing, wherein:

A is  ,  , or  , wherein R^A is H or -CN;

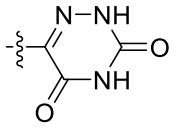
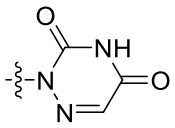
L^1 is a bond, -NR'-, -O-, -S-, or -$S(O)_2$-, wherein R' is H or C_1-C_6 alkyl;

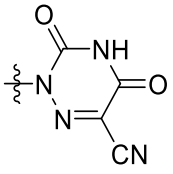
L^2 is a bond or -$S(O)_2$-;

R^1 is H, C_1-C_6 alkyl, C_6-C_{10} aryl, 3-12 membered heterocyclyl, 5-12 membered heteroaryl, or C_3-C_6 cycloalkyl, wherein the C_1-C_6 alkyl, C_6-C_{10} aryl, 3-12 membered heterocyclyl, 5-12 membered heteroaryl, and C_3-C_6 cycloalkyl are each independently optionally substituted by 1-5 R^2 groups;

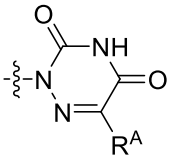
R is H, C_1-C_6 alkyl, C_6-C_{10} aryl, 3-12 membered heterocyclyl, 5-12 membered heteroaryl, or C_3-C_6 cycloalkyl, wherein the C_1-C_6 alkyl, C_6-C_{10} aryl, 3-12 membered heterocyclyl, 5-12 membered heteroaryl, and C_3-C_6 cycloalkyl are each independently optionally substituted by 1-5 R^2 groups; and

each R^2 is independently halogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_1-C_6 haloalkyl, C_1-C_6 alkyl-OH, -NH_2, -CN, or hydroxyl, provided that

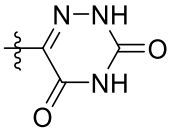
when L^1 is a bond and R is H, then A is  or  , and

when L^1 is -O-, R is H, and A is , then R^1 is C_2-C_6 alkyl, C_6-C_{10} aryl, 3-12 membered heterocyclyl, 5-12 membered heteroaryl, or C_3-C_6 cycloalkyl, wherein the C_2-C_6 alkyl, C_6-C_{10} aryl, 3-12 membered heterocyclyl, 5-12 membered heteroaryl, and C_3-C_6 cycloalkyl are each independently optionally substituted by 1-5 R^2 groups.

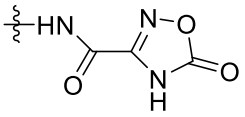
2. The compound of claim 1, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of each of the foregoing, wherein

A is .

3. The compound of claim 1, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of each of the foregoing, wherein

A is .

4. The compound of claim 1, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of each of the foregoing, wherein

A is .

5. The compound of any one of claims 1-4, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of each of the foregoing, wherein L^1 is a bond.

6. The compound of any one of claims 1-4, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of each of the foregoing, wherein L^1 is -NR'-.

7. The compound of any one of claims 1-4, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of each of the foregoing, wherein L^1 is -O-.

8. The compound of any one of claims 1-4, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of each of the foregoing, wherein L^1 is -S-.

9. The compound of any one of claims 1-4, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of each of the foregoing, wherein L^1 is $-S(O)_2-$.

10. The compound of any one of claims 1-9, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of each of the foregoing, wherein L^2 is a bond.

11. The compound of any one of claims 1-9, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of each of the foregoing, wherein L^2 is $-S(O)_2-$.

12. The compound of any one of claims 1-11, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of each of the foregoing, wherein R is H.

13. The compound of any one of claims 1-11, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of each of the foregoing, wherein R is C_1-C_6 alkyl optionally substituted by 1-3 R^2 groups.

14. The compound of any one of claims 1-11, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of each of the foregoing, wherein R is methyl or ethyl, each of which is optionally substituted by 1-3 R^2 groups.

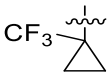
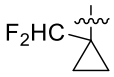
15. The compound of any one of claims 1-14, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of each of the foregoing, wherein R^1 is H.

16. The compound of any one of claims 1-14, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of each of the foregoing, wherein R^1 is C_1-C_6 alkyl which is optionally substituted by 1-5 R^2 groups.

17. The compound of any one of claims 1-14, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of each of the foregoing, wherein R^1 is methyl, ethyl, isopropyl, or t-butyl.

18. The compound of any one of claims 1-14, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of each of the foregoing, wherein R^1 is C_3-C_6 cycloalkyl optionally substituted by 1-5 R^2 groups.

19. The compound of any one of claims 1-14, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of each of the foregoing, wherein R^1 is cyclopropyl or cyclobutyl, each of which is optionally substituted by 1 R^2 group.

20. The compound of any one of claims 1-14, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of each of the foregoing, wherein R^1 is , , , or .

21. The compound of claim 1, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of each of the foregoing, wherein the compound is selected from the compounds in Table 1.

22. A pharmaceutical composition, comprising the compound of any one of claims 1-21, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of each of the foregoing, and a pharmaceutically acceptable excipient.

23. Use of a compound of any one of claims 1-21, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of each of the foregoing, or the pharmaceutical composition of claim 22, in the manufacture of a medicament for treating a disorder ameliorated by activation of thyroid hormone receptor beta in a patient in need thereof.

24. The use of claim 23, wherein the disorder is non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), metabolic syndrome, dyslipidemia, hypertriglyceridemia, or hypercholesterolemia.

25. The use of claim 24, wherein the disorder is NASH.

26. A compound of any one of claims 1-21, or a tautomer or stereoisomer thereof, or a pharmaceutically acceptable salt of each of the foregoing, or the pharmaceutical composition of claim 22, for use in therapy.