[0005] Cortisol and other glucocorticoids can also act on the mineralocorticoid receptor (MR), in which case they are referred to as mineralocorticoids or mineralocorticoid recepter antagonists (MRAs). The mineralocorticoid receptor primarily regulates the salt concentration in the body. The MR can have substantially equal affinity for mineralocorticoids and glucocorticoids.

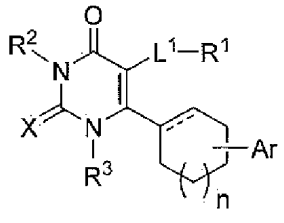
[0006] The biologic effects of cortisol, including those caused by hypercortisolemia, can be modulated at the GR level using receptor modulators, such as agonists, partial agonists and antagonists. Several different classes of agents are able to block the physiologic effects of GR-agonist binding. These antagonists include compositions which, by binding to GR, block the ability of an agonist to effectively bind to and/or activate the GR. One such known GR antagonist, mifepristone, has been found to be an effective anti-glucocorticoid agent in humans (Bertagna (1984) *J. Clin. Endocrinol. Metab.* **59**:25). Mifepristone binds to the GR with high affinity, with a dissociation constant (K_d) of 10^{-9} M (Cadepond (1997) *Annu. Rev. Med.* **48**:129).

[0007] In addition to cortisol, the biological effects of other steroids can be modulated at the GR level using receptor modulators, such as agonists, partial agonists and antagonists. When administered to subjects in need thereof, steroids can provide both intended therapeutic effects, *e.g.*, by stimulating glucocorticoid receptor transrepression, as well as negative side effects, *e.g.* by chronic glucocorticoid receptor transactivation.

[0008] What is needed in the art are new compositions and methods for modulating GR receptors to treat fatty liver disease. Surprisingly, the present invention meets these and other needs.

BRIEF SUMMARY

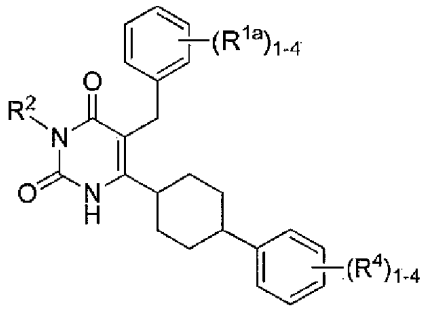
[0009] In one embodiment, the present disclosure provides a method of treating fatty liver disease. The method includes administering to a subject in need thereof, a therapeutically effective amount of a compound of Formula I, thereby treating the fatty liver disease, wherein the compound of Formula I has the structure:



(I).

In the compound of Formula I, the dashed line is absent or a bond. X is O or S. R^1 is cycloalkyl, heterocycloalkyl, aryl or heteroaryl, optionally substituted with from 1 to 3 R^{1a} groups. Each R^{1a} is independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkyl-OR^{1b}, halogen, C_{1-6} haloalkyl, C_{1-6} haloaloxy, -OR^{1b}, -$NR^{1b}R^{1c}$, -$C(O)R^{1b}$, -$C(O)OR^{1b}$, -$OC(O)R^{1b}$, -$C(O)NR^{1b}R^{1c}$, -$NR^{1b}C(O)R^{1c}$, -SO_2R^{1b}, -$SO_2NR^{1b}R^{1c}$, cycloalkyl, heterocycloalkyl, aryl or heteroaryl. R^{1b} and R^{1c} are each H or C_{1-6} alkyl. R^2 is H, C_{1-6} alkyl, C_{1-6} alkyl-OR^{1b}, C_{1-6} alkyl-$NR^{1b}R^{1c}$ or C_{1-6} alkylene-heterocycloalkyl. R^3 is H or C_{1-6} alkyl. Ar is aryl, optionally substituted with 1-4 R^4 groups. Each R^4 is H, C_{1-6} alkyl, C_{1-6} alkoxy, halogen, C_{1-6} haloalkyl or C_{1-6} haloalkoxy. L^1 is a bond or C_{1-6} alkylene. Subscript n is an integer from 0 to 3. Also included are the salts and isomers of the compounds recited herein.

[0009a] In one aspect of the present disclosure, there is provided a compound of Formula Id for use in treating fatty liver disease, wherein the compound of Formula Id has the structure:



(Id)

wherein

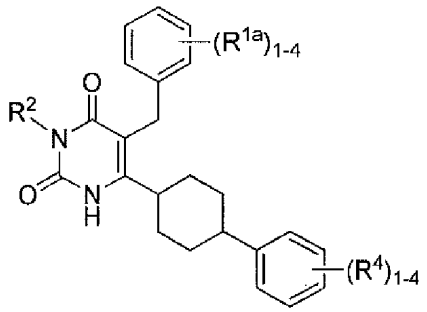
each R^{1a} is independently H, C_{1-6} alkyl, halogen, or C_{1-6} haloalkyl;

R^2 is H, or C_{1-6} alkyl; and

each R^4 is H, C_{1-6} alkyl, halogen, or C_{1-6} haloalkyl;

or is a salt or isomer thereof.

[0009b] In another aspect of the present disclosure, there is provided a use of a compound of Formula Id in the manufacture of a medicament for treating fatty liver disease, wherein the compound of Formula Id has the structure:



(Id)

wherein

each R^{1a} is independently H, C_{1-6} alkyl, halogen, or C_{1-6} haloalkyl;

R^2 is H, or C_{1-6} alkyl; and

each R^4 is H, C_{1-6} alkyl, halogen, or C_{1-6} haloalkyl;

and salts and isomers thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] **Figure 1** shows the percentage of fat (lipid droplets) in Oil Red O stained livers from mice that received a high fat diet and Compound 1 (60mg/kg/day) relative to control mice that received a high fat diet and vehicle.

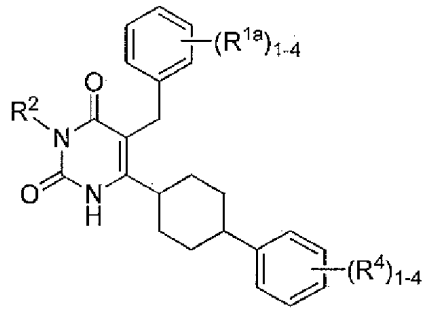
[0011] **Figure 2A and 2B** show Oil Red O staining of lipid droplets from livers from a mouse that received a high fat ("HF") diet and Compound 1 (Figure 2A) and a control mouse that received a high fat diet and vehicle (Figure 2B).

[0012] **Figure 3** shows the percentage of fat (lipid droplets) in Oil Red O stained livers from mice that received a high fat diet and either mifepristone or Compound 1 (60mg/kg/day) relative to control mice that received a high fat diet and vehicle. * $p<0.05$ "Compound 1" compared to "CTRL"

[0013] **Figure 4** shows triglyceride levels in livers of mice given a normal diet (the "CHOW" group), mice given a high fat diet for 3 weeks (the "HF-3wks" group), mice given a high fat diet for 6 weeks (the "HF-6wks" group), mice given a high fat diet and Compound 1 for 6 weeks (the "HF+118335-6wks"group), and mice given a high fat diet for 6 weeks with administration of Compound 1 only for the last 3 weeks (the "HF-118335 rev" group).

WHAT IS CLAIMED IS:

1. A compound of Formula Id for use in treating fatty liver disease, wherein the compound of Formula Id has the structure:



(Id)

wherein

each R^{1a} is independently H, C_{1-6} alkyl, halogen, or C_{1-6} haloalkyl;

R^2 is H, or C_{1-6} alkyl; and

each R^4 is H, C_{1-6} alkyl, halogen, or C_{1-6} haloalkyl;

or is a salt or isomer thereof.

2. The compound for use according to claim 1, wherein the fatty liver disease is alcohol related liver disease (ARLD) or nonalcoholic fatty liver disease (NAFLD).

3. The compound for use according to claim 2, wherein the alcohol related liver disease is alcohol fatty liver disease (AFL), alcoholic steatohepatitis (ASH) or alcoholic cirrhosis.

4. The compound for use according to claim 2, wherein the nonalcoholic fatty liver disease is nonalcoholic steatohepatitis (NASH) or nonalcoholic cirrhosis.

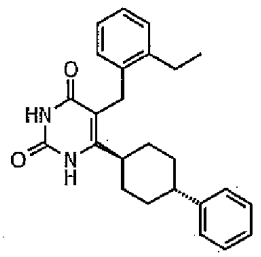
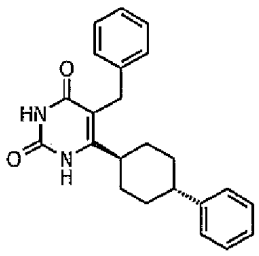
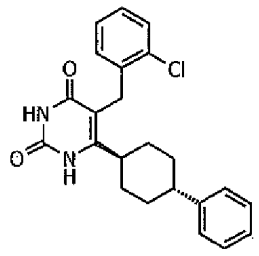
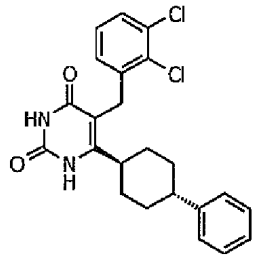
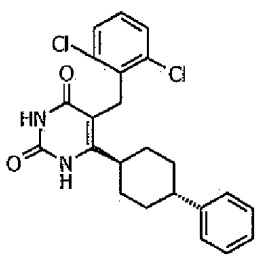
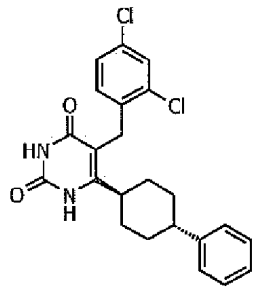
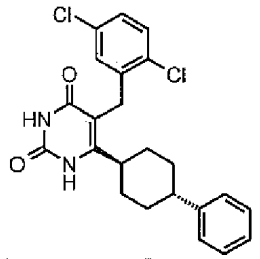
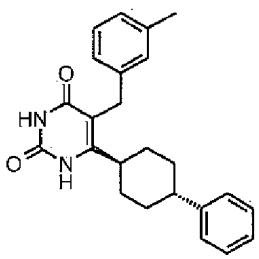
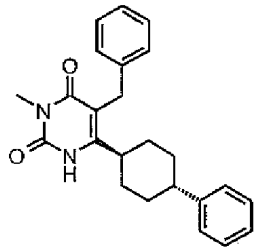
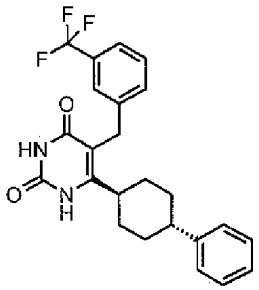
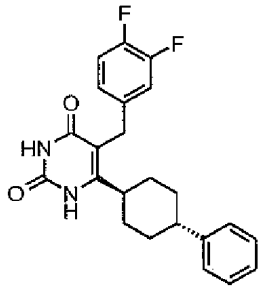
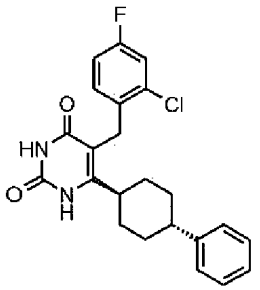
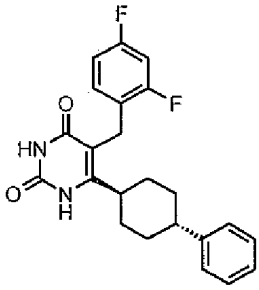
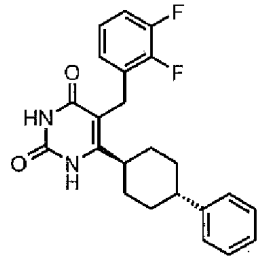
5. The compound for use according to any one of claims 1 to 4, wherein each R^{1a} is C_{1-6} haloalkyl.

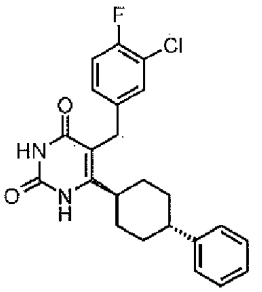
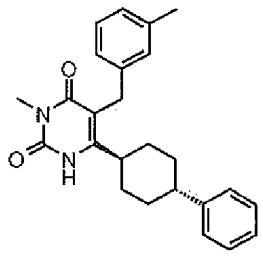
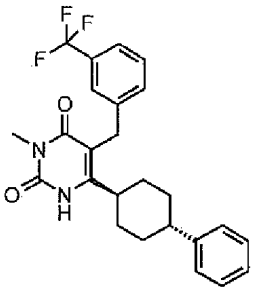
6. The compound for use according to any one of claims 1 to 5, wherein each R^{1a} is independently selected from the group consisting of H, Me, Et, F, Cl, or $-CF_3$.

7. The compound for use according to any one of claims 1 to 6, wherein each R^{1a} is $-CF_3$.

8. The compound for use according to any one of claims 1 to 7, wherein R^2 is H.

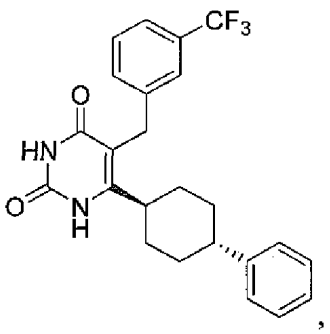
9. The compound for use according to any one of claims 1 to 8, wherein the compound is selected from the group consisting of:


,

,

,

,

,

,

,

,

,

,

,

,

,

,



, and


and salts thereof.

10. The compound for use according to any one of claims 1 to 9, wherein the compound has the formula:



or a salt thereof.

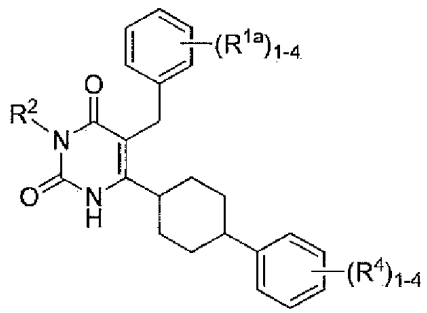
11. The compound for use according to any one of claims 1 to 10, wherein said compound is a glucocorticoid receptor antagonist.

12. The compound for use according to any one of claims 1 to 11, wherein said compound is a mineralocorticoid receptor antagonist.

13. The compound for use according to any one of claims 1 to 12, wherein said compound inhibits glucocorticoid binding to the glucocorticoid receptor and is a mineralocorticoid receptor antagonist.

14. The compound for use according to any one of claims 1 to 13, wherein said compound inhibits glucocorticoid binding to the glucocorticoid receptor with an inhibition constant (Ki) of between about 0.0001 nanomolar (nM) and about 1000 nM and is a mineralocorticoid receptor antagonist.

15. Use of a compound of Formula Id in the manufacture of a medicament for treating fatty liver disease, wherein the compound of Formula Id has the structure:



(Id)

wherein

each R^{1a} is independently H, C_{1-6} alkyl, halogen, or C_{1-6} haloalkyl;

R^2 is H, or C_{1-6} alkyl; and

each R^4 is H, C_{1-6} alkyl, halogen, or C_{1-6} haloalkyl;

or is a salt or isomer thereof.

16. The use of claim 15, wherein the fatty liver disease is alcohol related liver disease (ARLD) or nonalcoholic fatty liver disease (NAFLD).

17. The use of claim 16, wherein the alcohol related liver disease is alcohol fatty liver disease (AFL), alcoholic steatohepatitis (ASH) or alcoholic cirrhosis.

18. The use of claim 16, wherein the nonalcoholic fatty liver disease is nonalcoholic steatohepatitis (NASH) or nonalcoholic cirrhosis.

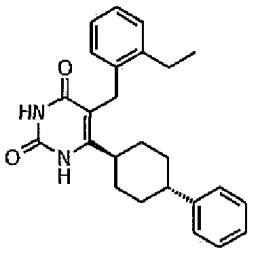
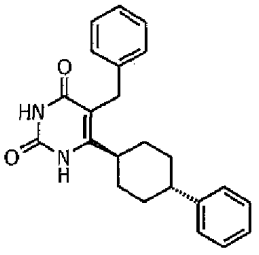
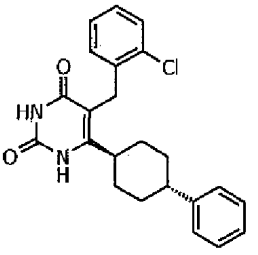
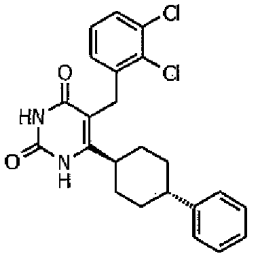
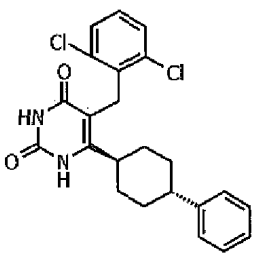
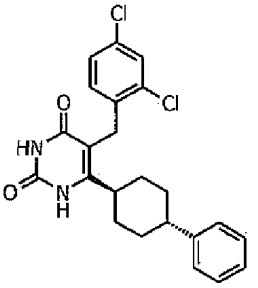
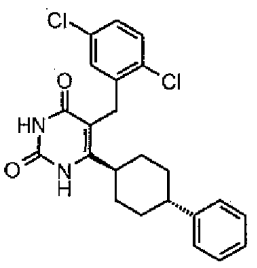
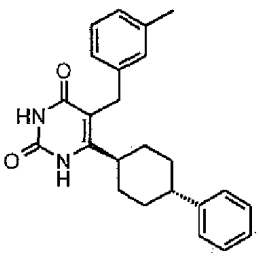
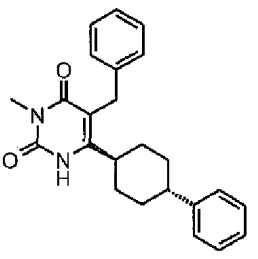
19. The use of any one of claims 15 to 18, wherein each R^{1a} is C_{1-6} haloalkyl.

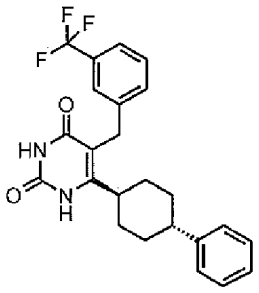
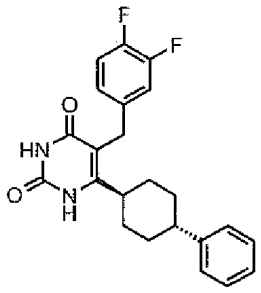
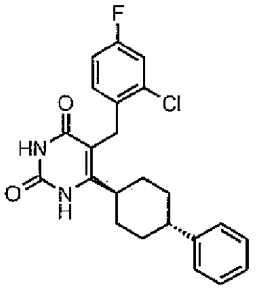
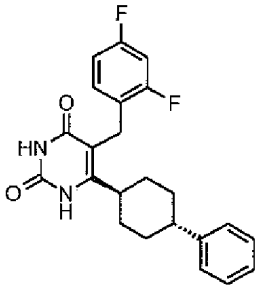
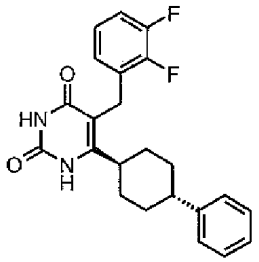
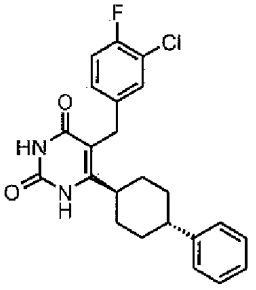
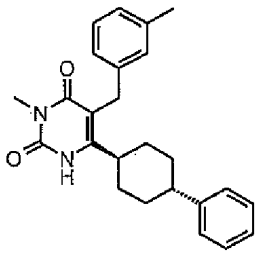
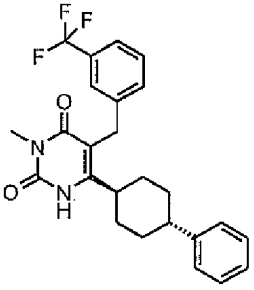
20. The use of any one of claims 15 to 19, wherein each R^{1a} is independently selected from the group consisting of H, Me, Et, F, Cl, or $-CF_3$.

21. The use of any one of claims 15 to 20, wherein each R^{1a} is $-CF_3$.

22. The use of any one of claims 15 to 21, wherein R^2 is H.

23. The use of any one of claims 15 to 22, wherein the compound is selected from the group consisting of:

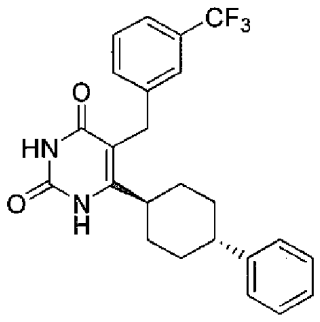

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

, and


and salts thereof.

5

24. The use of any one of claims 15 to 23, wherein the compound has the formula:



or a salt thereof.

25. The use according to any one of claims 15 to 24, wherein said compound is a glucocorticoid receptor antagonist.

26. The use according to any one of claims 15 to 25, wherein said compound is a mineralocorticoid receptor antagonist.

27. The use according to any one of claims 15 to 26, wherein said compound inhibits glucocorticoid binding to the glucocorticoid receptor and is a mineralocorticoid receptor antagonist.

28. The use according to any one of claims 15 to 27, wherein said compound inhibits glucocorticoid binding to the glucocorticoid receptor with an inhibition constant (Ki) of between about 0.0001 nanomolar (nM) and about 1000 nM and is a mineralocorticoid receptor antagonist.