COMPOSITION OF COMPOUNDS THAT MODULATE CELL METABOLISM AND METHODS OF USE

~~NOVEL CELL METABOLISM MODULATING COMPOUNDS AND USES THEREOF~~

Cross Reference To Related Application Section~~Cross-Reference to Related Applications Section~~

This application is a Singapore national phase application of a PCT Application No. PCT/US2021/039470 filed on June 28, 2021, which claims priority to U.S. Provisional Patent Application S/N 63/045,079 filed on June 27, 2020, the entire contents of which are hereby incorporated by reference in ~~their~~ its entirety.

Field of the Embodiments

This invention relates to novel compounds for treatment or prophylaxis of diseases related to metabolism and inflammation, including, but not limited to, type-2 diabetes, obesity, cardiovascular disease, asthma, cancer and other diseases. Compounds in this invention particularly interact with fatty acid binding protein (FABP) 4 and improve glucose consumption in adipocytes.

Background of the Embodiments

FABPs are a family of proteins that reversibly bind free fatty acids and other lipid molecules and facilitate their transport in cells. To date, nine different FABP isoforms have been identified in mammals. FABP isoforms display differential expression patterns in different tissues. Fatty acid binding protein 4 (FABP4), also often referred to as aP2 in literature, is primarily expressed in adipocytes and macrophages, and mediates key metabolic and inflammatory pathways in these cells such as lipid storage and degradation, signaling and eicosanoid production. In addition, FABP4 is also secreted to plasma and has been proposed to act as an adipose-derived factor regulating systemic glucose homeostasis.

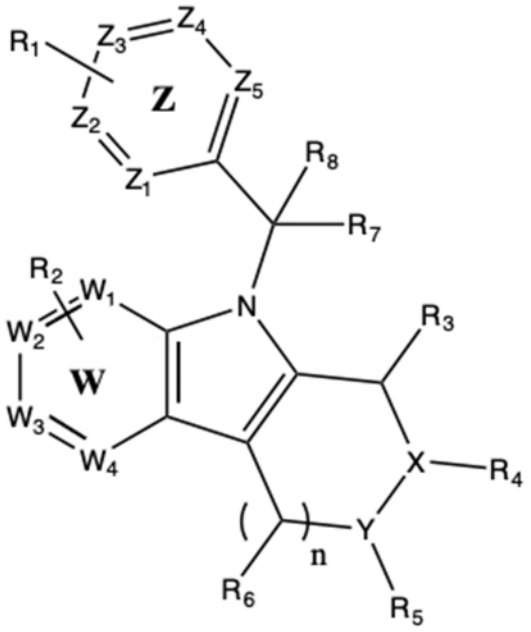
Genetic knockout studies in mice provided insights into tissue-specific and systemic functions of FABP4. Importantly, when mice bearing a homozygous deletion of the FABP4 gene

subjected to prolonged high-fat diet they gained weight comparable to wild-type but were protected from hyperglycemia and insulin-resistance (Hotamisligil et al., Science. 1996 Nov

Claims

What is claimed is:

1. A compound of Formula I ~~comprising~~:



Formula (I)

w~~W~~herein:

W_{1-4} and Z_1-Z_5 are each independently -C, -CH, ~~CH_2,~~ -O, S, or N;

X is independently CH_2, N or CHR_4;

Y is independently CH_2, or CHR_5;

n is a number between 0 and 3;

~~O~~one or more R_1's on the ring Z are independently selected from the group consisting of one or more of: CN, OH, COOH, OCH_3, CF_3, $CONH_2$, $B(OH)_2$, $B(OR)_2$, an acid isostere, a substituted amine, ethers, ~~and~~ a halogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted cyclic or heterocyclic, a substituted or unsubstituted cycloaryl or cyc~~h~~loheteroaryl, wherein the substituted cycloaryl or cyc~~h~~loheteroaryl may be substituted with one or more of hydrogen, CN, OH, COOH, OCH_3, CF_3, $CONH_2$, $B(OH)_2$, $B(OR)_2$, an acid isostere, a substituted amine, an ether~~s~~, ~~and~~ a halogen, a substituted or unsubstituted alkyl, a substituted or unsubstituted cyclic or heterocyclic, a substituted or unsubstituted cycloaryl or cyc~~h~~loheteroaryl, and SO_2NH_2;

~~O~~one or more R_2's on the ring W are independently selected from the group consisting of one or more of: CN, OH, CHF2, CH2F, CF_3, COOH, $CONH_2$, $B(OH)_2$, $B(OR)_2$, an acid isostere, a halogen, and a bicyclic heteroaryl;

R_7 is hydrogen, ~~or~~ CN, COOH, $CONH_2$, $B(OH)_2$, $B(OR)_2$ or an acid isostere;

R is alkyl;

R_3, R_4, R_5 or R_8, or R_6 when n is not zero, is each independently selected from:

(1) hydrogen;

(2) substituted or unsubstituted alkyl or ether having 1 to 12 carbon atoms,

(3) a substituted amine, or

(4) $-(CH_2)_m G$ ~~$-(CH_2)_m G,$~~ wherein m is 1 to 12 and G is independently ~~selected from~~:

(a) cycloalkyl containing 3 to 6 carbon atoms,

(b) aryl or heteroaryl,

(c) CF_3, CF_2H or CFH_2, or

(d) a heterocycle,

provided that R_3, R_4, R_5, R_8, or R_6 are not all hydrogen;

or pharmaceutically acceptable salts or stereoisomers thereof.

2. The compound according to claim 1, wherein R_1 and R_2 are both present and each is independently CN, COOH, or $CONH_2$.

3. The compound according to claim 1, wherein the Formula I ~~includes~~ comprises multiple R_1's and R_2's.

4. The compound according to claim 1, wherein at least one of R_3, R_4, R_5 R_8, or R_6 when n is not zero, is each independently alkyl having 4 carbon atoms.

5. The compound according to claim 1, wherein at least one of R_3, R_4, R_5 R_8, or R_6 when n is not zero, is each independently alkyl having 5 carbon atoms.

6. The compound according to claim 1, wherein at least one of R_3, R_4, R_5 R_8, or R_6 when n is not zero, is each independently alkyl having 6 carbon atoms.

~~7. The compound according to claim 1, wherein the ring Z contains Z_1-Z_4.~~

~~8. The compound according to claim 1, wherein the ring Z contains Z_1-Z_5.~~

~~9~~7. The compound according to claim 1, wherein at least one ~~the one or more~~ R_1~~'s on the ring Z~~ is ~~the~~ halogen.

~~10~~8. The compound according to claim 1, wherein at least one ~~the one or more~~ R_1 ~~'s on the ring Z~~ is ~~the~~ CN.

~~11~~9. The compound according to claim 1, wherein at least one ~~the one or more~~ R_1~~'s on the ring Z~~ is ~~the~~ CF_3.

~~12~~10. The compound according to claim 1, wherein at least one ~~the one or more~~ R_2~~'s on the ring W~~ is ~~the~~ halogen.

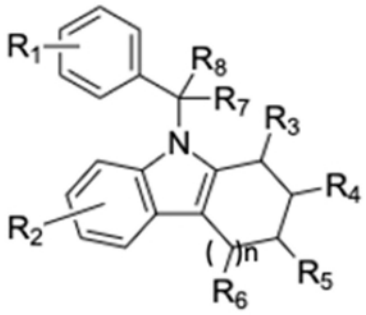
~~13~~11. The compound according to claim 1, wherein at least one ~~the one or more~~ R_1~~'s on the ring Z~~ comprise(s) ~~the~~ CN and/or ~~the~~ halogen.

~~14~~12. The compound according to claim 1, wherein at least one ~~the one or more~~ R_1~~'s on the ring Z~~ comprise(s) ~~the~~ CN and/or ~~the~~ halogen, and wherein at least one ~~the one or more~~ R_2's ~~on the ring W~~ comprise(s) another halogen.

~~15~~13. The compound according to claim ~~14~~12, wherein the R_1 halogen is identical to the R_2~~other~~ halogen.

~~16~~14. The compound according to claim ~~14~~12, wherein the R_1 halogen differs from the R_2~~other~~ halogen.

~~17~~15. A compound of Formula II ~~comprising~~:



Formula II

w~~W~~herein:

n = 0, 1, or 2;

R_1 is selected from the group consisting of: CN, COOH, $CONH_2$, $B(OH)_2$, $B(OR)_2$, an acid isostere, and a halogen;

R_2 is selected from the group consisting of: CN, COOH, $CONH_2$, $B(OH)_2$, $B(OR)_2$, an acid isostere, a halogen, and a bicyclic compound;

R_7 is hydrogen or CN, COOH, $CONH_2$, $B(OH)_2$, $B(OR)_2$ or an acid isostere;

R is alkyl;

R_3, R_4, R_5 or R_8, or R_6 when n is not zero, is each independently selected from:

(1) hydrogen;

(2) alkyl having 1 to 12 carbon atoms, or

(3) $-(CH_2)_m$ G, ~~$-(CH_2)_m$ G,~~ wherein m is 1 to 12 and G is independently ~~selected from~~:

(a) cycloalkyl containing 3 to 6 carbon atoms,

(b) aryl or heteroaryl, or

(c) CF_3, CF_2H or CFH_2;

provided that G is not a nitrogen or oxygen-containing group; and

provided that R3, R4, R5, R8, or R6 are not all hydrogen;

or pharmaceutically acceptable salts thereof.

~~18~~16. The compound according to claim ~~17~~15, wherein R_1 and R_2 are both present, and each is independently CN, COOH, or $CONH_2$.

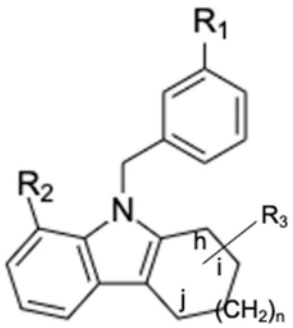
~~19~~17. The compound according to claim ~~17~~15, wherein the Formula II includes multiple R_1's and R_2's.

~~20~~18. The compound according to claim ~~17~~15, wherein at least one of R_3, R_4, R_5 R_8, or R_6 when n is not zero, is each independently alkyl having 4 carbon atoms.

~~21~~19. The compound according to claim ~~17~~15, wherein at least one of R_3, R_4, R_5 R_8, or R_6 when n is not zero, is each independently alkyl having 5 carbon atoms.

~~22~~20. The compound according to claim ~~17~~15, wherein at least one of R_3, R_4, R_5 R_8, or R_6 when n is not zero, is each independently alkyl having 6 carbon atoms.

~~23~~21. A compound of Formula III comprising:



~~W~~wherein:

n = 0, 1 or 2;

R_1 and R_2 are each independently CN, COOH or $CONH_2$;

R_3 is independently selected from:

(1) alkyl having 1 to 12 carbon atoms;

(2) ~~-~~$(CH_2)_mG$ ~~-(CH2)mG,~~ wherein m is 1 to 12 and G is independently ~~selected from~~:

(a) cycloalkyl containing 3 to 6 carbon atoms; or

(b) phenyl; ~~and~~

~~provided that G is not a nitrogen or oxygen-containing group;~~

or pharmaceutically acceptable salts thereof.

~~24~~22. A compound according to claim ~~23~~21, wherein n = 0 and R_3 is attached to the h-, i- or j-position.

~~25~~23. A compound according to claim ~~23~~21, wherein: n = 1 and R_3 is attached to the h-, i- or j-position.

~~26~~24. A compound according to claim ~~23~~21, wherein: n = 2 and R_3 is attached to the h-, i- or j-position.

~~27~~25. A compound according to claim ~~1, 17, or 23~~21, which is a pure optical isomer.

~~28~~26. A compound according to claim ~~23~~21, which is the (+)-isomer.

~~29~~27. A compound according to claim ~~23~~21, which is the (-) -isomer.

~~30~~28. A compound selected from the group consisting of: 5-[(3-cyanophenyl)methyl]-2-fluoro-7-hexyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 5-[(6-cyanopyridin-2-yl)methyl]-7-hexyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 5-[(6-carbamoylpyridin-2-yl)methyl]-7-hexyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 6-({4-carboxy-7-hexyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indol-5-yl}methyl)pyridine-2-carboxylic acid, 5-[(3-cyano-2-fluorophenyl)methyl]-7-hexyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 5-[(1,3-benzoxazol-6-yl)methyl]-7-hexyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 5-[(1,3-benzoxazol-5-yl)methyl]-7-hexyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 5-[(6-fluoropyridin-2-yl)methyl]-7-hexyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 5-[(2-fluoropyridin-4-yl)methyl]-7-hexyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 7-hexyl-5-{[6-(trifluoromethyl)pyridin-2-yl]methyl}-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 7-hexyl-5-{[2-(trifluoromethyl)pyridin-4-yl]methyl}-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 5-[(5-cyanopyridin-3-yl)methyl]-

7-hexyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 5-[(5-cyanothiophen-2-yl)methyl]-7-hexyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 5-[(4-cyanothiophen-2-yl)methyl]-7-hexyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 5-[(5-cyanofuran-2-yl)methyl]-7-hexyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 5-[(3,5-dimethyl-1,2-oxazol-4-yl)methyl]-7-hexyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 5-(3-cyanobenzoyl)-7-hexyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 5-[(1,3-benzoxazol-7-yl)methyl]-7-hexyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 5-[(5-cyanothiophen-3-yl)methyl]-7-hexyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 7-hexyl-5-[(1H-indol-4-yl)methyl]-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 5-[(3-carbamoylphenyl)methyl]-7-propyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 7-butyl-5-[(3-carbamoylphenyl)methyl]-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 7-butyl-5-[(3-cyanophenyl)methyl]-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 7-butyl-5-[(pyridin-3-yl)methyl]-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 7-butyl-5-[(3-methylphenyl)methyl]-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 7-butyl-5-[(3-methoxyphenyl)methyl]-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 7-butyl-5-[(3-chlorophenyl)methyl]-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 7-butyl-5-[(3-hydroxyphenyl)methyl]-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 7-butyl-5-[(2-methoxypyridin-4-yl)methyl]-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 7-butyl-5-[(4-carbamoylphenyl)methyl]-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 7-butyl-5-[(2-carbamoylphenyl)methyl]-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 7-butyl-5-[(4-methylphenyl)methyl]-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 7-butyl-5-[(2-cyanophenyl)methyl]-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 7-butyl-5-[(2-methylphenyl)methyl]-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 7-butyl-5-[(2-fluorophenyl)methyl]-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 5-[(3-carbamoylphenyl)methyl]-7-pentyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 5-[(3-cyanophenyl)methyl]-7-pentyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 5-[(3-carbamoylphenyl)methyl]-7-(2-phenylethyl)-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 5-[(3-cyanophenyl)methyl]-7-(2-

phenylethyl)-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 5-[(3-carbamoylphenyl)methyl]-7-hexyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 5-[(3-cyanophenyl)methyl]-7-hexyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 5-[(3-carbamoylphenyl)methyl]-7-octyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 5-[(3-cyanophenyl)methyl]-7-octyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 5-[(3-fluorophenyl)methyl]-7-hexyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 7-hexyl-5-[(pyridin-3-yl)methyl]-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 7-hexyl-5-[(3-methylphenyl)methyl]-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 7-hexyl-5-[(3-methoxyphenyl)methyl]-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 5-[(3-chlorophenyl)methyl]-7-hexyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 7-hexyl-5-[(2-methoxypyridin-4-yl)methyl]-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 5-[(3-carboxyphenyl)methyl]-7-hexyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 5-[(4-carbamoylphenyl)methyl]-7-hexyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 5-[(2-carbamoylphenyl)methyl]-7-hexyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 7-hexyl-5-[(4-methylphenyl)methyl]-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 5-[(4-cyanophenyl)methyl]-7-hexyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 5-[(2-cyanophenyl)methyl]-7-hexyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 7-hexyl-5-[(2-methylphenyl)methyl]-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 5-[(2-fluorophenyl)methyl]-7-hexyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 5-[(4-fluorophenyl)methyl]-7-hexyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 9-[(3-carbamoylphenyl)methyl]-2-hexyl-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 9-[(3-cyanophenyl)methyl]-2-hexyl-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 9-[(3-carboxyphenyl)methyl]-2-hexyl-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 9-[(3-fluorophenyl)methyl]-2-hexyl-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 2-hexyl-9-[(pyridin-3-yl)methyl]-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 2-hexyl-9-[(3-methylphenyl)methyl]-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 2-hexyl-9-[(3-methoxyphenyl)methyl]-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 9-[(3-chlorophenyl)methyl]-2-hexyl-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 2-hexyl-9-[(3-hydroxyphenyl)methyl]-2,3,4,9-tetrahydro-1H-

carbazole-8-carboxylic acid, 2-hexyl-9-[(2-methoxypyridin-4-yl)methyl]-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 9-[(3-carboxyphenyl)methyl]-2-hexyl-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 9-[(4-carbamoylphenyl)methyl]-2-hexyl-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 9-[(2-carbamoylphenyl)methyl]-2-hexyl-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 2-hexyl-9-[(4-methylphenyl)methyl]-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 9-[(4-cyanophenyl)methyl]-2-hexyl-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 9-[(2-cyanophenyl)methyl]-2-hexyl-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 2-hexyl-9-[(2-methylphenyl)methyl]-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 9-[(2-fluorophenyl)methyl]-2-hexyl-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 9-[(3-carbamoylphenyl)methyl]-2-(2-phenylethyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 9-[(3-cyanophenyl)methyl]-2-(2-phenylethyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 9-[(3-carbamoylphenyl)methyl]-4-(2-phenylethyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 9-[(3-cyanophenyl)methyl]-4-(2-phenylethyl)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 9-[(3-carbamoylphenyl)methyl]-2-propyl-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 9-[(3-cyanophenyl)methyl]-2-propyl-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 2-butyl-9-[(3-carbamoylphenyl)methyl]-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 9-[(3-carbamoylphenyl)methyl]-2-pentyl-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 9-[(3-cyanophenyl)methyl]-2-pentyl-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 1-butyl-9-[(3-carbamoylphenyl)methyl]-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 9-[(3-carbamoylphenyl)methyl]-1-(pentyloxy)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 9-[(3-cyanophenyl)methyl]-1-(pentyloxy)-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 1-butyl-9-[(3-cyanophenyl)methyl]-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 6-butyl-5-[(3-carbamoylphenyl)methyl]-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 6-butyl-5-[(3-cyanophenyl)methyl]-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 9-[(3-carbamoylphenyl)methyl]-1-ethyl-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 9-[(3-cyanophenyl)methyl]-1-ethyl-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 9-[(3-carboxyphenyl)methyl]-1-ethyl-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 9-[(3-carbamoylphenyl)methyl]-1-propoxy-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 9-[(3-carbamoylphenyl)methyl]-4-ethyl-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 4-[(3-carbamoylphenyl)methyl]-3-ethyl-1H,2H,3H,4H-cyclopenta[b]indole-5-carboxylic acid, 4-[(3-

cyanophenyl)methyl]-3-ethyl-1H,2H,3H,4H-cyclopenta[b]indole-5-carboxylic acid, 3-butyl-4-[(3-carbamoylphenyl)methyl]-1H,2H,3H,4H-cyclopenta[b]indole-5-carboxylic acid, 3-butyl-4-[(3-cyanophenyl)methyl]-1H,2H,3H,4H-cyclopenta[b]indole-5-carboxylic acid, 2-butyl-4-[(3-carbamoylphenyl)methyl]-1H,2H,3H,4H-cyclopenta[b]indole-5-carboxylic acid, 2-butyl-4-[(3-cyanophenyl)methyl]-1H,2H,3H,4H-cyclopenta[b]indole-5-carboxylic acid, 5-[(3-carbamoylphenyl)methyl]-10-ethyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 5-[(3-cyanophenyl)methyl]-10-ethyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 5-[(3-carbamoylphenyl)methyl]-10-propyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 5-[(3-cyanophenyl)methyl]-10-propyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 9-[(3-carboxyphenyl)methyl]-4-ethyl-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 9-[(3-carbamoylphenyl)methyl]-3-ethyl-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 10-butyl-5-[(3-carbamoylphenyl)methyl]-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 10-butyl-5-[(3-cyanophenyl)methyl]-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 5-[(3-carbamoylphenyl)methyl]-10-pentyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 5-[(3-cyanophenyl)methyl]-10-pentyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 4-[(3-carbamoylphenyl)methyl]-2-pentyl-1H,2H,3H,4H-cyclopenta[b]indole-5-carboxylic acid, 4-[(3-cyanophenyl)methyl]-2-pentyl-1H,2H,3H,4H-cyclopenta[b]indole-5-carboxylic acid, 9-[(3-carbamoylphenyl)methyl]-2-ethyl-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 9-[(3-carboxyphenyl)methyl]-2-ethyl-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 5-[(3-carbamoylphenyl)methyl]-7-ethyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 5-[(3-cyanophenyl)methyl]-7-ethyl-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, 9-[(3-cyanophenyl)methyl]-3-ethyl-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 9-[(3-carbamoylphenyl)methyl]-4-propyl-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 9-[(3-carbamoylphenyl)methyl]-3-propyl-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 9-[(3-cyanophenyl)methyl]-3-propyl-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 4-butyl-9-[(3-carbamoylphenyl)methyl]-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 4-butyl-9-[(3-cyanophenyl)methyl]-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 3-butyl-9-[(3-carbamoylphenyl)methyl]-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 3-butyl-9-[(3-cyanophenyl)methyl]-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 9-[(3-carbamoylphenyl)methyl]-4-pentyl-2,3,4,9-

tetrahydro-1H-carbazole-8-carboxylic acid, 9-[(3-cyanophenyl)methyl]-4-pentyl-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 9-[(3-carbamoylphenyl)methyl]-3-pentyl-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 9-[(3-cyanophenyl)methyl]-3-pentyl-2,3,4,9-tetrahydro-1H-carbazole-8-carboxylic acid, 4-[(3-carbamoylphenyl)methyl]-3-propyl-1H,2H,3H,4H-cyclopenta[b]indole-5-carboxylic acid, 4-[(3-cyanophenyl)methyl]-3-propyl-1H,2H,3H,4H-cyclopenta[b]indole-5-carboxylic acid, 2-({7-butyl-5-[(3-carbamoylphenyl)methyl]-5H,6H,7H,8H,9H,10H-cyclohepta[b]indol-4-yl}formamido)acetic acid, 2-({7-butyl-5-[(3-cyanophenyl)methyl]-5H,6H,7H,8H,9H,10H-cyclohepta[b]indol-4-yl}formamido)acetic acid, 7-butyl-5-[(3-carbamoylphenyl)methyl]-N-(2-hydroxyethyl)-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxamide, 7-butyl-5-[(3-cyanophenyl)methyl]-N-(2-hydroxyethyl)-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxamide, 7-butyl-5-[(3-fluorophenyl)methyl]-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, and 7-butyl-5-[(3-carboxyphenyl)methyl]-5H,6H,7H,8H,9H,10H-cyclohepta[b]indole-4-carboxylic acid, or pharmaceutically acceptable salts or stereoisomers thereof.

~~31~~29. A compound according to claim ~~30~~ 28 which is a pure optical isomer.

~~32~~30. Use of a compound of claims 1, 15, 21 or 28 in the manufacture of a medicament for ~~A method of~~ inhibiting the fatty acid binding protein FABP4 in a subject ~~in a mammal, which comprises administering to a mammal an effective amount of a compound of claim 1, 17 or 23~~.

~~33~~31. ~~A method~~The use according to claim ~~32~~30, wherein the subject is a human.

~~34. The compound according to claims 1, 17 or 23 for use in the prophylaxis or treatment of disorders acting on the fatty acid binding protein FABP4.~~

~~35. The compound according to claim 34, wherein the disorders are selected from type 2 diabetes, hyperglycemia, metabolic syndrome, obesity, atherosclerosis, intracranial atherosclerotic disease, non-alcoholic steatohepatitis, asthma, vascular dementia, multiple sclerosis, Alzheimer's disease, other chronic inflammatory and autoimmune/inflammatory diseases, chronic heart disease, polycystic ovary syndrome, preeclampsia, and cancer.~~

~~36~~32. A pharmaceutical composition comprising a compound according to claims 1, 15, 21 or 28 ~~17 or 23~~ as the active ingredient, in combination with a pharmaceutically acceptable diluent or carrier.

~~37~~33. A pharmaceutical composition comprising a compound according to claims 1, 15, 21 or 28 for use in the prophylaxis or treatment of disorders acting on the fatty acid binding protein FABP4.

~~38~~34. The pharmaceutical composition according to claim ~~37~~33, wherein the disorders are selected from the group consisting of: type 2 diabetes, hyperglycemia, metabolic syndrome, obesity, atherosclerosis, intracranial atherosclerotic disease, non-alcoholic steatohepatitis, asthma, vascular dementia, multiple sclerosis, Alzheimer's disease, other chronic inflammatory ~~and~~ or autoimmune/inflammatory diseases, chronic heart disease, polycystic ovary syndrome, preeclampsia, and cancer.

~~39~~35. The pharmaceutical composition according to any one of claim~~s~~ ~~36~~ 32 to ~~38~~34, further comprising an additional therapeutically active agent.

~~40~~36. Use of a compound according to claims 1, 15, 21 or 28 in the manufacture of a medicament ~~A method~~ for the prophylaxis or treatment of disorders acting on the fatty acid binding protein FABP4 in a subject~~, which comprises administering to a subject in need of such treatment an effective amount of a compound according to claims 1, 17, or 23~~.

~~41~~37. ~~A method~~The use according to claim ~~40~~36, wherein the subject is a human.

~~42~~38. The ~~method~~ use according to any one of claims ~~40~~ 36 and ~~41~~37, wherein the disorders are selected from the group consisting of: type 2 diabetes, hyperglycemia, metabolic syndrome, obesity, atherosclerosis, intracranial atherosclerotic disease, non-alcoholic steatohepatitis, asthma, vascular dementia, multiple sclerosis, Alzheimer's disease, other chronic inflammatory

~~and~~ or autoimmune/inflammatory diseases, chronic heart disease, polycystic ovary syndrome, preeclampsia, and cancer.

39. A compound according to claims 1, 15, 21 or 28 for use in therapy.

~~43. A method for inhibiting FABP4, which comprises administering to a subject in need of such treatment an effective amount of a compound according to claims 1, 17, or 23.~~

~~44. A method according to claim 43, wherein the subject is a human.~~

~~45. Use of a compound according to claims 1, 17, or 23 for the manufacture of a medicament for use in the prophylaxis or treatment of disorders acting on the fatty acid binding protein FABP4.~~

~~46. The use according to claim 45, wherein the disorders are selected from type 2 diabetes, hyperglycemia, metabolic syndrome, obesity, atherosclerosis, intracranial atherosclerotic disease, non-alcoholic steatohepatitis, asthma, vascular dementia, multiple sclerosis, Alzheimer's disease, other chronic inflammatory and autoimmune/inflammatory diseases, chronic heart disease, polycystic ovary syndrome, preeclampsia, and cancer.~~