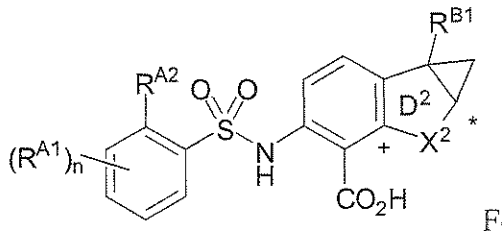
[0006] MetAP2 encodes a protein that functions at least in part by enzymatically removing the amino terminal methionine residue from certain newly translated proteins such as glyceraldehyde-3-phosphate dehydrogenase (Warder *et al.* (2008) J Proteome Res 7:4807). Increased expression of the MetAP2 gene has been historically associated with various forms of cancer. Molecules inhibiting the enzymatic activity of MetAP2 have been identified and have been explored for their utility in the treatment of various tumor types (Wang et al. (2003) Cancer Res. 63:7861) and infectious diseases such as microsporidiosis, leishmaniasis, and malaria (Zhang et al. (2002) J. Biomed. Sci. 9:34). Notably, inhibition of MetAP2 activity in obese and obese-diabetic animals leads to a reduction in body weight in part by increasing the oxidation of fat and in part by reducing the consumption of food (Rupnick et al. (2002) Proc. Natl. Acad. Sci. USA 99:10730).

SUMMARY

[0007] This disclosure is directed in part to, for example, methods of treating non-alcoholic steatohepatitis NASH and associated disorders (e.g., fibrosis) by administering compounds which may be modulators of MetAP2, such as disclosed compounds. In an embodiment, the disclosure is directed to methods of reducing cholesterol (e.g., total cholesterol in plasma) in a patient in need thereof.

[0007a] In a first aspect of the present disclosure, there is provided a use of a compound of Formula IV in the manufacture of a medicament for treating or substantially preventing a fatty liver disease or liver fibrosis in a patient:



Formula IV

D^2 is a 5-7 membered partially unsaturated heterocyclic or carbocyclic ring;

X^2 is selected from the group consisting of: $^{+}$-$C(R^{D1}R^{D2})$-*, $^{+}$-W^1-*, $^{+}$-$C(R^{D1}R^{D2})$-$C(R^{D5}R^{D6})$-*, $^{+}$-W^2-$C(R^{D5}R^{D6})$-*, $^{+}$-W^2-C(O)-*, $^{+}$-$C(R^{D1}R^{D2})$-W^4-*, $^{+}$-$C(R^{D1}R^{D2})$-$C(R^{D3}R^{D4})$-$C(R^{D5}R^{D6})$-*, $^{+}$-W^2-$C(R^{D3}R^{D4})$-$C(R^{D5}R^{D6})$-*, $^{+}$-W^2-C(O)-$C(R^{D5}R^{D6})$-*, $^{+}$-$C(R^{D1}R^{D2})$-W^3-$C(R^{D5}R^{D6})$-*, $^{+}$-$C(R^{D1}R^{D2})$-W^3-C(O)-*, $^{+}$-$C(R^{D1}R^{D2})$-$C(R^{D3}R^{D4})$-W^4-* and $^{+}$-$C(R^{D1}R^{D2})$-C(O)-W^4-*; wherein the $^{+}$ and * indicate the attachment points of X^2 as indicated in Formula IV;

W^1 is selected from the group consisting of O, S or $N(R^{N1})$;

W^2 is selected from the group consisting of O or $N(R^{N2})$;

W^3 is selected from the group consisting of O or $N(R^{N3})$;

W^4 is selected from the group consisting of O or $N(R^{N4})$;

R^{B1} is selected from the group consisting of H, F, OH, CN, C_{1-2}alkoxy or C_{1-3}alkyl; wherein C_{1-3}alkyl and C_{1-2}alkoxy are optionally substituted by a group selected from OH, C_{1-2}alkoxy, CN or one or more fluorine atoms;

R^{A1} is selected, independently for each occurrence, from the group consisting of hydrogen, hydroxyl, cyano, halogen, C_{1-4}alkyl or C_{1-3}alkoxy; wherein C_{1-4}alkyl, or C_{1-3}alkoxy may be optionally substituted by one or more fluorines;

n is 0, 1, or 2;

R^{A2} is selected from the group consisting of hydrogen, R^iR^jN-, heterocyclyl, heterocyclyloxy and heterocyclyl-(NR^a)-; wherein said heterocyclyl may optionally be substituted by one or more substituents selected from R^g and wherein if said heterocyclyl contains a –NH moiety that nitrogen may optionally be substituted by one or more groups R^h; or

R^{A2} is selected from the group consisting of: C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, C_{3-6}alkenyloxy, C_{3-6}alkynyloxy, C_{3-6}cycloalkoxy, C_{1-6}alkyl-$S(O)_w$- (wherein w is 0, 1 or 2), C_{1-6}alkyl-$N(R^a)$-, C_{1-6}alkyl-$N(R^a)$-carbonyl-, C_{1-6}alkylcarbonyl-$N(R^a)$-, C_{1-6}alkyl-$N(R^a)$-carbonyl-$N(R^a)$-, C_{1-6}alkyl-$N(R^a)$-SO_2-, C_{1-6}alkyl-SO_2-$N(R^a)$-, C_{1-6}alkoxycarbonyl-$N(R^a)$-, C_{1-6}alkylcarbonyl-$N(R^a)$-C_{1-6}alkyl-, C_{1-6}alkyl-$N(R^a)$-carbonyl-C_{1-6}alkyl-, C_{1-6}alkoxyC_{1-6}alkyl-; wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, C_{3-6}alkenyloxy, C_{3-6}alkynyloxy, C_{3-6}cycloalkoxy, C_{1-6}alkyl-$S(O)_w$-, C_{1-6}alkyl-$N(R^a)$-, C_{1-6}alkyl-$N(R^a)$-carbonyl-, C_{1-6}alkylcarbonyl-$N(R^a)$-, C_{1-6}alkyl-$N(R^a)$-carbonyl-$N(R^a)$-, C_{1-6}alkyl-$N(R^a)$-SO_2-, C_{1-6}alkyl-SO_2-$N(R^a)$-, C_{1-6}alkoxycarbonyl-$N(R^a)$-, C_{1-6}alkylcarbonyl-$N(R^a)C_{1-6}$alkyl-, C_{1-6}alkyl-$N(R^a)$-carbonyl-C_{1-6}alkyl-, C_{1-6}alkoxy-C_{1-6}alkyl may optionally be substituted by R^p, phenyl, phenoxy, heteroaryl, heteroaryloxy, heteroaryl-(NR^a)-, heterocyclyl, heterocyclyloxy or heterocyclyl-$N(R^a)$-; and wherein said heteroaryl or phenyl may optionally be substituted with one or more substituents selected from R^f; and wherein said heterocyclyl may optionally be substituted by one or more substituents selected from R^g; and wherein if said heterocyclyl contains a –NH moiety that nitrogen may optionally be substituted by one or more groups R^h;

R^{D1} and R^{D2} are each independently selected from the group consisting of hydrogen, fluorine, hydroxyl, C_{1-2}alkyl or C_{1-2}alkoxy; wherein the C_{1-2}alkyl and C_{1-2}alkoxy may optionally be substituted by one or more fluorine atoms or a group selected from cyano or hydroxyl;

R^{D3} and R^{D4} are each independently selected from the group consisting of hydrogen, fluorine, hydroxyl, cyano, C_{1-3}alkyl or C_{1-3}alkoxy; wherein the C_{1-3} alkyl and C_{1-3} alkoxy may optionally be substituted by one or more fluorine atoms or a group selected from cyano, hydroxyl or $N(R^aR^b)$;

R^{D5} and R^{D6} are each independently selected from the group consisting of hydrogen, fluorine, hydroxyl, cyano, C_{1-2}alkyl or C_{1-2}alkoxy; wherein the C_{1-2}alkyl and C_{1-2}alkoxy may optionally be substituted by a substituent or substituents selected from the group consisting of: one or more fluorine atoms,cyano, hydroxyl or $N(R^aR^b)$;

R^{C1} is selected from the group consisting of hydrogen, halogen, C_{1-2}alkyl or C_{1-2}alkoxy; wherein the C_{1-2}alkyl or C_{1-2}alkoxy may optionally be substituted by one or more fluorine atoms;

R^{C2} is selected from the group consisting of hydrogen, halogen, hydroxyl, cyano, C_{1-2}alkyl or C_{1-2}alkoxy; wherein the C_{1-2}alkyl and C_{1-2}alkoxy may optionally be substituted by one or more fluorine atoms or a group selected from cyano, hydroxyl or $N(R^aR^b)$;

R^{N1} is selected from the group consisting of hydrogen or C_{1-2}alkyl;

R^{N2} is selected from the group consisting of hydrogen or C_{1-2}alkyl;

R^{N3} is selected from the group consisting of hydrogen, C_{1-3}alkyl or C_{1-2}alkylcarbonyl; wherein the C_{1-3}alkyl and C_{1-2}alkylcarbonyl may optionally be substituted by a substituent or substituents selected from the group consisting of: one or more fluorines, cyano, hydroxyl or $N(R^aR^b)$;

R^{N4} is selected from the group consisting of hydrogen, C_{1-3}alkyl or C_{1-2}alkylcarbonyl; wherein the C_{1-3}alkyl and C_{1-2}alkylcarbonyl may optionally be substituted by a substituent or substituents selected from the group consisting of: one or more fluorines, cyano, hydroxyl or $N(R^aR^b)$;

R^a and R^b are independently selected, for each occurrence, from the group consisting of hydrogen and C_{1-3}alkyl; wherein C_{1-3}alkyl may optionally be substituted by one or more substituents selected from fluorine, cyano, oxo and hydroxyl;

or R^a and R^b, together with the nitrogen to which they are attached, may form a 4-6 membered heterocyclic ring, which may have an additional heteroatom selected from O, S, or N; wherein the 4-6 membered heterocyclic ring may optionally be substituted by one or more substituents selected from the group consisting of fluorine, cyano, oxo or hydroxyl;

R^f is independently selected, for each occurrence, from the group consisting of R^p, hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkyl-$S(O)_w$-, (wherein w is 0, 1 or 2), C_{1-6}alkylcarbonyl-$N(R^a)$- and C_{1-6}alkoxycarbonyl-$N(R^a)$-; wherein C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkyl-$S(O)_w$-, C_{1-6}alkylcarbonyl-$N(R^a)$-, C_{1-6}alkoxycarbonyl-$N(R^a)$- may be optionally substituted by one or more substituents selected from R^p;

R^g is independently selected for each occurrence from the group consisting of R^p, hydrogen, oxo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, C_{1-6}alkyl-$S(O)_w$-, (wherein w is 0, 1 or 2), C_{1-6}alkylcarbonyl-$N(R^a)$- and C_{1-6}alkoxycarbonyl-$N(R^a)$-; wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, C_{1-6}alkyl-$S(O)_w$-, C_{1-6}alkylcarbonyl-$N(R^a)$-, C_{1-6}alkoxycarbonyl-$N(R^a)$- may be optionally substituted by one or more substituents selected from R^p;

R^h is independently selected for each occurrence from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkyl-$S(O)_2$-, C_{1-6}alkoxycarbonyl-, R^iR^jN-carbonyl- and R^iR^jN-SO_2-; wherein C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl C_{3-6}cycloalkyl and C_{1-6}alkyl-$S(O)_2$-, C_{1-6}alkylcarbonyl- may optionally be substituted by one or more substituents selected from R^p;

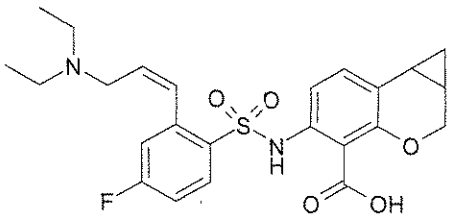
R^i and R^j are selected independently for each occurrence from the group consisting of hydrogen, C_{1-4}alkyl, C_{3-6}cycloalkyl, heterocyclyl and heterocyclylcarbonyl; wherein C_{1-4}alkyl and C_{3-6}cycloalkyl may be optionally substituted by one or more substituents selected from fluorine, hydroxyl, cyano, R^aR^bN-, R^aR^bN-carbonyl- and C_{1-3}alkoxy and wherein heterocyclyl and heterocyclylcarbonyl may be optionally substituted by one or more substituents selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, halo-C_{1-6}-alkyl, hydroxyl-C_{1-6}-alkyl, R^aR^bN-C_{1-6}alkyl- and C_{1-6}-alkoxy-C_{1-6}-alkyl group; and wherein if said heterocyclyl or heterocyclylcarbonyl contains a –NH moiety that nitrogen may optionally be substituted by one or more groups C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkyl-$S(O)_2$- and C_{1-6}-alkylcarbonyl;or R^i and R^j taken together with the nitrogen to which they are attached form a 4-7 membered heterocyclic ring, which may have an additional heteroatom selected from O, S, or N; wherein the 4-7 membered heterocyclic ring may be optionally substituted on carbon by

one or more substituents selected from the group consisting of fluorine, hydroxyl, oxo, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, R^aR^bN-, R^aR^bN-SO_2- and R^aR^bN-carbonyl-; wherein said C_{1-6}alkyl or C_{1-6}alkoxy may optionally be substituted by fluorine, hydroxyl or cyano; and wherein the 4-7 membered heterocyclic ring may be optionally substituted on nitrogen by one or more substituents selected from the group consisting of C_{1-6}alkyl and R^aR^bN-carbonyl-; and wherein said C_{1-6}alkyl may be optionally substituted by one or more substituents selected from the group consisting of fluorine, hydroxyl, cyano;

R^P is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, cyano, C_{1-6}alkoxy, R^iR^jN-, R^iR^jN-carbonyl-, R^iR^jN-SO_2- and R^iR^jN-carbonyl-$N(R^a)$-;

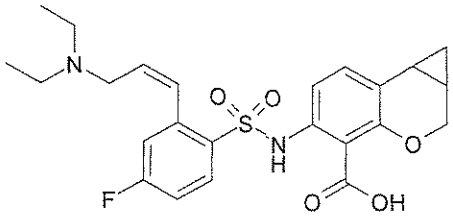
and pharmaceutically acceptable salts, stereoisomers, esters and prodrugs thereof.

[0007b] In a second aspect of the present disclosure, there is provided a use of a compound represented by



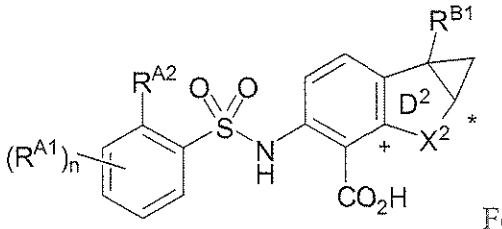
or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or substantially preventing fatty liver disease in a patient.

[0007c] In a third aspect of the present disclosure, there is provided a use of a compound represented by



or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or substantially preventing liver fibrosis in a patient.

[0007d] In a fourth aspect of the present disclosure, there is provided a use of a compound of Formula IV in the manufacture of a medicament for reducing total plasma cholesterol in a patient:



Formula IV

D^2 is a 5-7 membered partially unsaturated heterocyclic or carbocyclic ring;

X^2 is selected from the group consisting of: $^{+}$-$C(R^{D1}R^{D2})$-*, $^{+}$-W^1-*, $^{+}$-$C(R^{D1}R^{D2})$-$C(R^{D5}R^{D6})$-*, $^{+}$-W^2-$C(R^{D5}R^{D6})$-*, $^{+}$-W^2-C(O)-*, $^{+}$-$C(R^{D1}R^{D2})$-W^4-*, $^{+}$-$C(R^{D1}R^{D2})$-$C(R^{D3}R^{D4})$-$C(R^{D5}R^{D6})$-*, $^{+}$-W^2-$C(R^{D3}R^{D4})$-$C(R^{D5}R^{D6})$-*, $^{+}$-W^2-C(O)-$C(R^{D5}R^{D6})$-*, $^{+}$-$C(R^{D1}R^{D2})$-W^3-$C(R^{D5}R^{D6})$-*, $^{+}$-$C(R^{D1}R^{D2})$-W^3-C(O)-*, $^{+}$-$C(R^{D1}R^{D2})$-$C(R^{D3}R^{D4})$-W^4-* and $^{+}$-$C(R^{D1}R^{D2})$-C(O)-W^4-*; wherein the $^{+}$ and * indicate the attachment points of X^2 as indicated in Formula IV;

W^1 is selected from the group consisting of O, S or $N(R^{N1})$;

W^2 is selected from the group consisting of O or $N(R^{N2})$;

W^3 is selected from the group consisting of O or $N(R^{N3})$;

W^4 is selected from the group consisting of O or $N(R^{N4})$;

R^{B1} is selected from the group consisting of H, F, OH, CN, C_{1-2}alkoxy or C_{1-3}alkyl; wherein C_{1-3}alkyl and C_{1-2}alkoxy are optionally substituted by a group selected from OH, C_{1-2}alkoxy, CN or one or more fluorine atoms;

R^{A1} is selected, independently for each occurrence, from the group consisting of hydrogen, hydroxyl, cyano, halogen, C_{1-4}alkyl or C_{1-3}alkoxy; wherein C_{1-4}alkyl, or C_{1-3}alkoxy may be optionally substituted by one or more fluorines;

n is 0, 1, or 2;

R^{A2} is selected from the group consisting of hydrogen, R^iR^jN-, heterocyclyl, heterocyclyloxy and heterocyclyl-(NR^a)-; wherein said heterocyclyl may optionally be substituted by one or more substituents selected from R^g and wherein if said heterocyclyl contains a –NH moiety that nitrogen may optionally be substituted by one or more groups R^h; or

R^{A2} is selected from the group consisting of: C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, C_{3-6}alkenyloxy, C_{3-6}alkynyloxy, C_{3-6}cycloalkoxy, C_{1-6}alkyl-$S(O)_w$- (wherein w is 0, 1 or 2), C_{1-6}alkyl-$N(R^a)$-, C_{1-6}alkyl-$N(R^a)$-carbonyl-, C_{1-6}alkylcarbonyl-$N(R^a)$-, C_{1-6}alkyl-$N(R^a)$-carbonyl-$N(R^a)$-, C_{1-6}alkyl-$N(R^a)$-SO_2-, C_{1-6}alkyl-SO_2-$N(R^a)$-, C_{1-}

$_{6}$alkoxycarbonyl-N(R^a)-, C_{1-6}alkylcarbonyl-N(R^a)-C_{1-6}alkyl-, C_{1-6}alkyl-N(R^a)-carbonyl-C_{1-6}alkyl-, C_{1-6}alkoxyC_{1-6}alkyl-; wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, C_{3-6}alkenyloxy, C_{3-6}alkynyloxy, C_{3-6}cycloalkoxy, C_{1-6}alkyl-$S(O)_w$-, C_{1-6}alkyl-N(R^a)-, C_{1-6}alkyl-N(R^a)-carbonyl-, C_{1-6}alkylcarbonyl-N(R^a)-, C_{1-6}alkyl-N(R^a)-carbonyl-N(R^a)-, C_{1-6}alkyl-N(R^a)-SO_2-, C_{1-6}alkyl-SO_2-N(R^a)-, C_{1-6}alkoxycarbonyl-N(R^a)-, C_{1-6}alkylcarbonyl-N(R^a)C_{1-6}alkyl-, C_{1-6}alkyl-N(R^a)-carbonyl-C_{1-6}alkyl-, C_{1-6}alkoxy-C_{1-6}alkyl may optionally be substituted by R^p, phenyl, phenoxy, heteroaryl, heteroaryloxy, heteroaryl-(NR^a)-, heterocyclyl, heterocyclyloxy or heterocyclyl-N(R^a)-; and wherein said heteroaryl or phenyl may optionally be substituted with one or more substituents selected from R^f; and wherein said heterocyclyl may optionally be substituted by one or more substituents selected from R^g; and wherein if said heterocyclyl contains a –NH moiety that nitrogen may optionally be substituted by one or more groups R^h;

R^{D1} and R^{D2} are each independently selected from the group consisting of hydrogen, fluorine, hydroxyl, C_{1-2}alkyl or C_{1-2}alkoxy; wherein the C_{1-2}alkyl and C_{1-2}alkoxy may optionally be substituted by one or more fluorine atoms or a group selected from cyano or hydroxyl;

R^{D3} and R^{D4} are each independently selected from the group consisting of hydrogen, fluorine, hydroxyl, cyano, C_{1-3}alkyl or C_{1-3}alkoxy; wherein the C_{1-3} alkyl and C_{1-3} alkoxy may optionally be substituted by one or more fluorine atoms or a group selected from cyano, hydroxyl or N(R^aR^b);

R^{D5} and R^{D6} are each independently selected from the group consisting of hydrogen, fluorine, hydroxyl, cyano, C_{1-2}alkyl or C_{1-2}alkoxy; wherein the C_{1-2}alkyl and C_{1-2}alkoxy may optionally be substituted by a substituent or substituents selected from the group consisting of: one or more fluorine atoms,cyano, hydroxyl or N(R^aR^b);

R^{C1} is selected from the group consisting of hydrogen, halogen, C_{1-2}alkyl or C_{1-2}alkoxy; wherein the C_{1-2}alkyl or C_{1-2}alkoxy may optionally be substituted by one or more fluorine atoms;

R^{C2} is selected from the group consisting of hydrogen, halogen, hydroxyl, cyano, C_{1-2}alkyl or C_{1-2}alkoxy; wherein the C_{1-2}alkyl and C_{1-2}alkoxy may optionally be substituted by one or more fluorine atoms or a group selected from cyano, hydroxyl or N(R^aR^b);

R^{N1} is selected from the group consisting of hydrogen or C_{1-2}alkyl;

R^{N2} is selected from the group consisting of hydrogen or C_{1-2}alkyl;

R^{N3} is selected from the group consisting of hydrogen, C_{1-3}alkyl or C_{1-2}alkylcarbonyl; wherein the C_{1-3}alkyl and C_{1-2}alkylcarbonyl may optionally be substituted by a substituent or substituents selected from the group consisting of: one or more fluorines, cyano, hydroxyl or $N(R^aR^b)$;

R^{N4} is selected from the group consisting of hydrogen, C_{1-3}alkyl or C_{1-2}alkylcarbonyl; wherein the C_{1-3}alkyl and C_{1-2}alkylcarbonyl may optionally be substituted by a substituent or substituents selected from the group consisting of: one or more fluorines, cyano, hydroxyl or $N(R^aR^b)$;

R^a and R^b are independently selected, for each occurrence, from the group consisting of hydrogen and C_{1-3}alkyl; wherein C_{1-3}alkyl may optionally be substituted by one or more substituents selected from fluorine, cyano, oxo and hydroxyl;

or R^a and R^b, together with the nitrogen to which they are attached, may form a 4-6 membered heterocyclic ring, which may have an additional heteroatom selected from O, S, or N; wherein the 4-6 membered heterocyclic ring may optionally be substituted by one or more substituents selected from the group consisting of fluorine, cyano, oxo or hydroxyl;

R^f is independently selected, for each occurrence, from the group consisting of R^P, hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkyl-$S(O)_w$-, (wherein w is 0, 1 or 2), C_{1-6}alkylcarbonyl-$N(R^a)$- and C_{1-6}alkoxycarbonyl-$N(R^a)$-; wherein C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkyl-$S(O)_w$-, C_{1-6}alkylcarbonyl-$N(R^a)$-, C_{1-6}alkoxycarbonyl-$N(R^a)$- may be optionally substituted by one or more substituents selected from R^P;

R^g is independently selected for each occurrence from the group consisting of R^P, hydrogen, oxo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, C_{1-6}alkyl-$S(O)_w$-, (wherein w is 0, 1 or 2), C_{1-6}alkylcarbonyl-$N(R^a)$- and C_{1-6}alkoxycarbonyl-$N(R^a)$-; wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, C_{1-6}alkyl-$S(O)_w$-, C_{1-6}alkylcarbonyl-$N(R^a)$-, C_{1-6}alkoxycarbonyl-$N(R^a)$- may be optionally substituted by one or more substituents selected from R^P;

R^h is independently selected for each occurrence from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkyl-$S(O)_2$-, C_{1-6}alkoxycarbonyl-, R^iR^jN-carbonyl- and R^iR^jN-SO_2-; wherein C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl C_{3-6}cycloalkyl

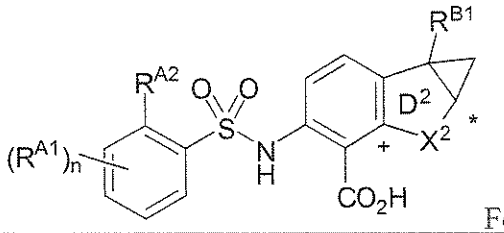
and C_{1-6}alkyl-$S(O)_2$-, C_{1-6}alkylcarbonyl- may optionally be substituted by one or more substituents selected from R^p;

R^i and R^j are selected independently for each occurrence from the group consisting of hydrogen, C_{1-4}alkyl, C_{3-6}cycloalkyl, heterocyclyl and heterocyclylcarbonyl; wherein C_{1-4}alkyl and C_{3-6}cycloalkyl may be optionally substituted by one or more substituents selected from fluorine, hydroxyl, cyano, R^aR^bN-, R^aR^bN-carbonyl- and C_{1-3}alkoxy and wherein heterocyclyl and heterocyclylcarbonyl may be optionally substituted by one or more substituents selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, halo-C_{1-6}-alkyl, hydroxyl-C_{1-6}-alkyl, R^aR^bN-C_{1-6}alkyl- and C_{1-6}-alkoxy-C_{1-6}-alkyl group; and wherein if said heterocyclyl or heterocyclylcarbonyl contains a –NH moiety that nitrogen may optionally be substituted by one or more groups C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkyl-$S(O)_2$- and C_{1-6}-alkylcarbonyl;or R^i and R^j taken together with the nitrogen to which they are attached form a 4-7 membered heterocyclic ring, which may have an additional heteroatom selected from O, S, or N; wherein the 4-7 membered heterocyclic ring may be optionally substituted on carbon by one or more substituents selected from the group consisting of fluorine, hydroxyl, oxo, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, R^aR^bN-, R^aR^bN-SO_2- and R^aR^bN-carbonyl-; wherein said C_{1-6}alkyl or C_{1-6}alkoxy may optionally be substituted by fluorine, hydroxyl or cyano; and wherein the 4-7 membered heterocyclic ring may be optionally substituted on nitrogen by one or more substituents selected from the group consisting of C_{1-6}alkyl and R^aR^bN-carbonyl-; and wherein said C_{1-6}alkyl may be optionally substituted by one or more substituents selected from the group consisting of fluorine, hydroxyl, cyano;

R^p is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, cyano, C_{1-6}alkoxy, R^iR^jN-, R^iR^jN-carbonyl-, R^iR^jN-SO_2- and R^iR^jN-carbonyl-$N(R^a)$-;

and pharmaceutically acceptable salts, stereoisomers, esters and prodrugs thereof.

[0007e] In a fifth aspect of the present disclosure, there is provided a use of a compound of Formula IV in the manufacture of a medicament for decreasing whole blood HbA_{1c} or lowering the plasma level of HbA_{1c} in a patient:



Formula IV

D^2 is a 5-7 membered partially unsaturated heterocyclic or carbocyclic ring;

X^2 is selected from the group consisting of: $^{+}$-$C(R^{D1}R^{D2})$-*, $^{+}$-W^1-*, $^{+}$-$C(R^{D1}R^{D2})$-$C(R^{D5}R^{D6})$-*, $^{+}$-W^2-$C(R^{D5}R^{D6})$-*, $^{+}$-W^2-C(O)-*, $^{+}$-$C(R^{D1}R^{D2})$-W^4-*, $^{+}$-$C(R^{D1}R^{D2})$-$C(R^{D3}R^{D4})$-$C(R^{D5}R^{D6})$-*, $^{+}$-W^2-$C(R^{D3}R^{D4})$-$C(R^{D5}R^{D6})$-*, $^{+}$-W^2-C(O)-$C(R^{D5}R^{D6})$-*, $^{+}$-$C(R^{D1}R^{D2})$-W^3-$C(R^{D5}R^{D6})$-*, $^{+}$-$C(R^{D1}R^{D2})$-W^3-C(O)-*, $^{+}$-$C(R^{D1}R^{D2})$-$C(R^{D3}R^{D4})$-W^4-* and $^{+}$-$C(R^{D1}R^{D2})$-C(O)-W^4-*; wherein the $^{+}$ and * indicate the attachment points of X^2 as indicated in Formula IV;

W^1 is selected from the group consisting of O, S or $N(R^{N1})$;

W^2 is selected from the group consisting of O or $N(R^{N2})$;

W^3 is selected from the group consisting of O or $N(R^{N3})$;

W^4 is selected from the group consisting of O or $N(R^{N4})$;

R^{B1} is selected from the group consisting of H, F, OH, CN, C_{1-2}alkoxy or C_{1-3}alkyl; wherein C_{1-3}alkyl and C_{1-2}alkoxy are optionally substituted by a group selected from OH, C_{1-2}alkoxy, CN or one or more fluorine atoms;

R^{A1} is selected, independently for each occurrence, from the group consisting of hydrogen, hydroxyl, cyano, halogen, C_{1-4}alkyl or C_{1-3}alkoxy; wherein C_{1-4}alkyl, or C_{1-3}alkoxy may be optionally substituted by one or more fluorines;

n is 0, 1, or 2;

R^{A2} is selected from the group consisting of hydrogen, R^iR^jN-, heterocyclyl, heterocyclyloxy and heterocyclyl-(NR^a)-; wherein said heterocyclyl may optionally be substituted by one or more substituents selected from R^g and wherein if said heterocyclyl contains a –NH moiety that nitrogen may optionally be substituted by one or more groups R^h; or

R^{A2} is selected from the group consisting of: C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, C_{3-6}alkenyloxy, C_{3-6}alkynyloxy, C_{3-6}cycloalkoxy, C_{1-6}alkyl-$S(O)_w$- (wherein w is 0, 1 or 2), C_{1-6}alkyl-$N(R^a)$-, C_{1-6}alkyl-$N(R^a)$-carbonyl-, C_{1-6}alkylcarbonyl-$N(R^a)$-, C_{1-6}alkyl-$N(R^a)$-carbonyl-$N(R^a)$-, C_{1-6}alkyl-$N(R^a)$-SO_2-, C_{1-6}alkyl-SO_2-$N(R^a)$-, C_{1-6}alkoxycarbonyl-$N(R^a)$-, C_{1-6}alkylcarbonyl-$N(R^a)$-C_{1-6}alkyl-, C_{1-6}alkyl-$N(R^a)$-carbonyl-C_{1-6}alkyl-, C_{1-6}alkoxyC_{1-6}alkyl-; wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, C_{3-6}alkenyloxy, C_{3-6}alkynyloxy, C_{3-6}cycloalkoxy, C_{1-6}alkyl-$S(O)_w$-, C_{1-6}alkyl-$N(R^a)$-, C_{1-6}alkyl-$N(R^a)$-carbonyl-, C_{1-6}alkylcarbonyl-$N(R^a)$-, C_{1-6}alkyl-$N(R^a)$-carbonyl-$N(R^a)$-, C_{1-6}alkyl-$N(R^a)$-SO_2-, C_{1-6}alkyl-SO_2-$N(R^a)$-, C_{1-6}alkoxycarbonyl-$N(R^a)$-, C_{1-6}alkylcarbonyl-$N(R^a)C_{1-6}$alkyl-, C_{1-6}alkyl-$N(R^a)$-carbonyl-C_{1-6}alkyl-, C_{1-6}alkoxy-C_{1-6}alkyl may optionally be

substituted by R^p, phenyl, phenoxy, heteroaryl, heteroaryloxy, heteroaryl-(NR^a)-, heterocyclyl, heterocyclyloxy or heterocyclyl-$N(R^a)$-; and wherein said heteroaryl or phenyl may optionally be substituted with one or more substituents selected from R^f; and wherein said heterocyclyl may optionally be substituted by one or more substituents selected from R^g; and wherein if said heterocyclyl contains a –NH moiety that nitrogen may optionally be substituted by one or more groups R^h;

R^{D1} and R^{D2} are each independently selected from the group consisting of hydrogen, fluorine, hydroxyl, C_{1-2}alkyl or C_{1-2}alkoxy; wherein the C_{1-2}alkyl and C_{1-2}alkoxy may optionally be substituted by one or more fluorine atoms or a group selected from cyano or hydroxyl;

R^{D3} and R^{D4} are each independently selected from the group consisting of hydrogen, fluorine, hydroxyl, cyano, C_{1-3}alkyl or C_{1-3}alkoxy; wherein the C_{1-3} alkyl and C_{1-3} alkoxy may optionally be substituted by one or more fluorine atoms or a group selected from cyano, hydroxyl or $N(R^aR^b)$;

R^{D5} and R^{D6} are each independently selected from the group consisting of hydrogen, fluorine, hydroxyl, cyano, C_{1-2}alkyl or C_{1-2}alkoxy; wherein the C_{1-2}alkyl and C_{1-2}alkoxy may optionally be substituted by a substituent or substituents selected from the group consisting of: one or more fluorine atoms,cyano, hydroxyl or $N(R^aR^b)$;

R^{C1} is selected from the group consisting of hydrogen, halogen, C_{1-2}alkyl or C_{1-2}alkoxy; wherein the C_{1-2}alkyl or C_{1-2}alkoxy may optionally be substituted by one or more fluorine atoms;

R^{C2} is selected from the group consisting of hydrogen, halogen, hydroxyl, cyano, C_{1-2}alkyl or C_{1-2}alkoxy; wherein the C_{1-2}alkyl and C_{1-2}alkoxy may optionally be substituted by one or more fluorine atoms or a group selected from cyano, hydroxyl or $N(R^aR^b)$;

R^{N1} is selected from the group consisting of hydrogen or C_{1-2}alkyl;

R^{N2} is selected from the group consisting of hydrogen or C_{1-2}alkyl;

R^{N3} is selected from the group consisting of hydrogen, C_{1-3}alkyl or C_{1-2}alkylcarbonyl; wherein the C_{1-3}alkyl and C_{1-2}alkylcarbonyl may optionally be substituted by a substituent or substituents selected from the group consisting of: one or more fluorines, cyano, hydroxyl or $N(R^aR^b)$;

R^{N4} is selected from the group consisting of hydrogen, C_{1-3}alkyl or C_{1-2}alkylcarbonyl; wherein the C_{1-3}alkyl and C_{1-2}alkylcarbonyl may optionally be substituted by a substituent or substituents selected from the group consisting of: one or more fluorines, cyano, hydroxyl or $N(R^aR^b)$;

R^a and R^b are independently selected, for each occurrence, from the group consisting of hydrogen and C_{1-3}alkyl; wherein C_{1-3}alkyl may optionally be substituted by one or more substituents selected from fluorine, cyano, oxo and hydroxyl;

or R^a and R^b, together with the nitrogen to which they are attached, may form a 4-6 membered heterocyclic ring, which may have an additional heteroatom selected from O, S, or N; wherein the 4-6 membered heterocyclic ring may optionally be substituted by one or more substituents selected from the group consisting of fluorine, cyano, oxo or hydroxyl;

R^f is independently selected, for each occurrence, from the group consisting of R^P, hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkyl-$S(O)_w$-, (wherein w is 0, 1 or 2), C_{1-6}alkylcarbonyl-$N(R^a)$- and C_{1-6}alkoxycarbonyl-$N(R^a)$-; wherein C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkyl-$S(O)_w$-, C_{1-6}alkylcarbonyl-$N(R^a)$-, C_{1-6}alkoxycarbonyl-$N(R^a)$- may be optionally substituted by one or more substituents selected from R^P;

R^g is independently selected for each occurrence from the group consisting of R^P, hydrogen, oxo, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, C_{1-6}alkyl-$S(O)_w$-, (wherein w is 0, 1 or 2), C_{1-6}alkylcarbonyl-$N(R^a)$- and C_{1-6}alkoxycarbonyl-$N(R^a)$-; wherein C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, C_{1-6}alkyl-$S(O)_w$-, C_{1-6}alkylcarbonyl-$N(R^a)$-, C_{1-6}alkoxycarbonyl-$N(R^a)$- may be optionally substituted by one or more substituents selected from R^P;

R^h is independently selected for each occurrence from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkyl-$S(O)_2$-, C_{1-6}alkoxycarbonyl-, R^iR^jN-carbonyl- and R^iR^jN-SO_2-; wherein C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl C_{3-6}cycloalkyl and C_{1-6}alkyl-$S(O)_2$-, C_{1-6}alkylcarbonyl- may optionally be substituted by one or more substituents selected from R^P;

R^i and R^j are selected independently for each occurrence from the group consisting of hydrogen, C_{1-4}alkyl, C_{3-6}cycloalkyl, heterocyclyl and heterocyclylcarbonyl; wherein C_{1-4}alkyl and C_{3-6}cycloalkyl may be optionally substituted by one or more substituents selected from fluorine, hydroxyl, cyano, R^aR^bN-, R^aR^bN-carbonyl- and C_{1-3}alkoxy and wherein heterocyclyl

and heterocyclylcarbonyl may be optionally substituted by one or more substituents selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, halo-C_{1-6}-alkyl, hydroxyl-C_{1-6}-alkyl, R^aR^bN-C_{1-6}alkyl- and C_{1-6}-alkoxy-C_{1-6}-alkyl group; and wherein if said heterocyclyl or heterocyclylcarbonyl contains a –NH moiety that nitrogen may optionally be substituted by one or more groups C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkyl-$S(O)_2$- and C_{1-6}-alkylcarbonyl;or R^i and R^j taken together with the nitrogen to which they are attached form a 4-7 membered heterocyclic ring, which may have an additional heteroatom selected from O, S, or N; wherein the 4-7 membered heterocyclic ring may be optionally substituted on carbon by one or more substituents selected from the group consisting of fluorine, hydroxyl, oxo, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, R^aR^bN-, R^aR^bN-SO_2- and R^aR^bN-carbonyl-; wherein said C_{1-6}alkyl or C_{1-6}alkoxy may optionally be substituted by fluorine, hydroxyl or cyano; and wherein the 4-7 membered heterocyclic ring may be optionally substituted on nitrogen by one or more substituents selected from the group consisting of C_{1-6}alkyl and R^aR^bN-carbonyl-; and wherein said C_{1-6}alkyl may be optionally substituted by one or more substituents selected from the group consisting of fluorine, hydroxyl, cyano;

R^p is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, cyano, C_{1-6}alkoxy, R^iR^jN-, R^iR^jN-carbonyl-, R^iR^jN-SO_2- and R^iR^jN-carbonyl-$N(R^a)$-;

and pharmaceutically acceptable salts, stereoisomers, esters and prodrugs thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0008] **Figure 1** indicates a disclosed compound targets the liver based on the presence of tissue biomarkers.

[0009] **Figure 2** shows the results from a body weight change study in obese mice 10 days after administration of a disclosed compound versus fumagillin or vehicle.

[0010] **Figure 3** shows the results from a mouse study examining the effect of once a day or twice a day administration of a disclosed compound.

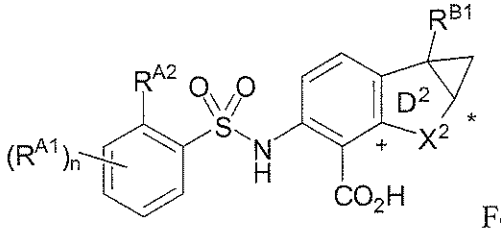
[0011] **Figure 4** indicates the reduction in the level of plasma insulin after administration of a disclosed compound.

[0012] **Figure 5** shows a reduction in liver and mesenteric fat pad weight in an animal model.

[0013] **Figure 6** indicates regulation of the expression of genes implicated in pathogenesis of fatty liver and fibrosis after treatment of obese mice with a disclosed compound.

CLAIMS

1. Use of a compound of Formula IV in the manufacture of a medicament for ~~A method of~~ treating or substantially preventing a fatty liver disease or liver fibrosis in a patient ~~comprising administering to a patient in need thereof a therapeutically effective amount of compound represented by~~:



Formula IV

D^2 is a 5-7 membered partially unsaturated heterocyclic or carbocyclic ring;

X^2 is selected from the group consisting of: $^{+}$-$C(R^{D1}R^{D2})$-*, $^{+}$-W^1-*, $^{+}$-$C(R^{D1}R^{D2})$-$C(R^{D5}R^{D6})$-*, $^{+}$-W^2-$C(R^{D5}R^{D6})$-*, $^{+}$-W^2-C(O)-*, $^{+}$-$C(R^{D1}R^{D2})$-W^4-*, $^{+}$-$C(R^{D1}R^{D2})$-$C(R^{D3}R^{D4})$-$C(R^{D5}R^{D6})$-*, $^{+}$-W^2-$C(R^{D3}R^{D4})$-$C(R^{D5}R^{D6})$-*, $^{+}$-W^2-C(O)-$C(R^{D5}R^{D6})$-*, $^{+}$-$C(R^{D1}R^{D2})$-W^3-$C(R^{D5}R^{D6})$-*, $^{+}$-$C(R^{D1}R^{D2})$-W^3-C(O)-*, $^{+}$-$C(R^{D1}R^{D2})$-$C(R^{D3}R^{D4})$-W^4-* and $^{+}$-$C(R^{D1}R^{D2})$-C(O)-W^4-*; wherein the $^{+}$ and * indicate the attachment points of X^2 as indicated in Formula IV;

W^1 is selected from the group consisting of O, S or $N(R^{N1})$;

W^2 is selected from the group consisting of O or $N(R^{N2})$;

W^3 is selected from the group consisting of O or $N(R^{N3})$;

W^4 is selected from the group consisting of O or $N(R^{N4})$;

R^{B1} is selected from the group consisting of H, F, OH, CN, C_{1-2}alkoxy or C_{1-3}alkyl; wherein C_{1-3}alkyl and C_{1-2}alkoxy are optionally substituted by a group selected from OH, C_{1-2}alkoxy, CN or one or more fluorine atoms;

R^{A1} is selected, independently for each occurrence, from the group consisting of hydrogen, hydroxyl, cyano, halogen, C_{1-4}alkyl or C_{1-3}alkoxy; wherein C_{1-4}alkyl, or C_{1-3}alkoxy may be optionally substituted by one or more fluorines;

n is 0, 1, or 2;

R^{A2} is selected from the group consisting of hydrogen, R^iR^jN-, heterocyclyl, heterocyclyloxy and heterocyclyl-(NR^a)-; wherein said heterocyclyl may optionally be substituted by one or more substituents selected from R^g and wherein if said heterocyclyl

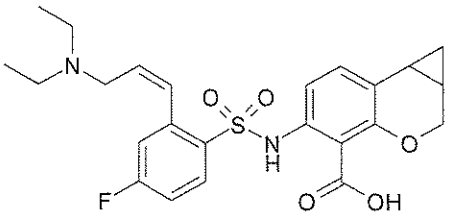
and pharmaceutically acceptable salts, stereoisomers, esters and prodrugs thereof.

2. The ~~method~~ use of claim 1, wherein the fatty liver disease is selected from the group consisting of: non-alcoholic steatohepatitis, liver cirrhosis, focal fatty liver, or hepatocellular carcinoma.

3. The use ~~method~~ of claim 1 or 2, wherein the patient is a human.

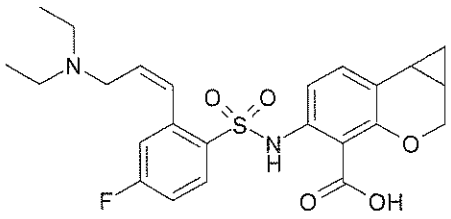
4. The use ~~method~~ of any one of claims 1-3, wherein the compound is to be administered orally.

5. Use of a ~~A method of treating or substantially preventing fatty liver disease comprising administering to a patient in need thereof a therapeutically effective amount of the~~ compound represented by



or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or substantially preventing fatty liver disease in a patient.

6. Use of a ~~A method of treating or substantially preventing liver fibrosis comprising administering to a patient in need thereof a therapeutically effective amount of the~~ compound represented by



or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or substantially preventing liver fibrosis in a patient.

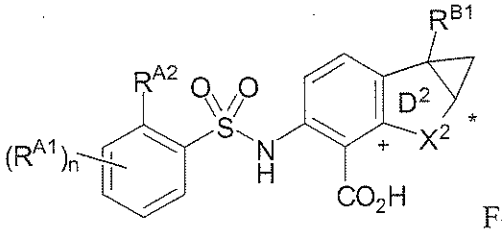
7. The ~~method~~ use of claim 5, wherein the the compound is to be administered orally.

8. The use ~~method~~ of claim 5 or 6, wherein the fatty liver disease is selected from the group consisting of: non-alcoholic steatohepatitis, liver cirrhosis, focal fatty liver, or hepatocellular carcinoma.

9. The use ~~method~~ of any one of claims 1-8, wherein the compound is to be administered in a once daily or twice daily dosage.

10. The use ~~method~~ of any one of claims 1-9, wherein the dose of the compound is less than about 10 mg/kg.

11. Use of a compound of Formula IV in the manufacture of a medicament for ~~A method of~~ reducing total plasma cholesterol in a patient ~~in need therefor comprising administering to a patient in a therapeutically effective amount of compound represented by~~:



Formula IV

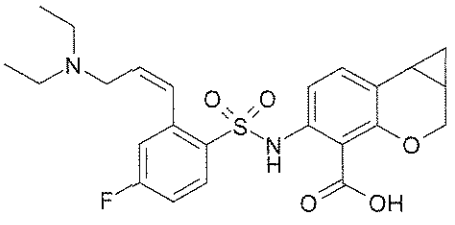
and C_{1-6}alkyl-$S(O)_2$-, C_{1-6}alkylcarbonyl- may optionally be substituted by one or more substituents selected from R^P;

R^i and R^j are selected independently for each occurrence from the group consisting of hydrogen, C_{1-4}alkyl, C_{3-6}cycloalkyl, heterocyclyl and heterocyclylcarbonyl; wherein C_{1-4}alkyl and C_{3-6}cycloalkyl may be optionally substituted by one or more substituents selected from fluorine, hydroxyl, cyano, R^aR^bN-, R^aR^bN-carbonyl- and C_{1-3}alkoxy and wherein heterocyclyl and heterocyclylcarbonyl may be optionally substituted by one or more substituents selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, halo-C_{1-6}-alkyl, hydroxyl-C_{1-6}-alkyl, R^aR^bN-C_{1-6}alkyl- and C_{1-6}-alkoxy-C_{1-6}-alkyl group; and wherein if said heterocyclyl or heterocyclylcarbonyl contains a –NH moiety that nitrogen may optionally be substituted by one or more groups C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkyl-$S(O)_2$- and C_{1-6}-alkylcarbonyl;or R^i and R^j taken together with the nitrogen to which they are attached form a 4-7 membered heterocyclic ring, which may have an additional heteroatom selected from O, S, or N; wherein the 4-7 membered heterocyclic ring may be optionally substituted on carbon by one or more substituents selected from the group consisting of fluorine, hydroxyl, oxo, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, R^aR^bN-, R^aR^bN-SO_2- and R^aR^bN-carbonyl-; wherein said C_{1-6}alkyl or C_{1-6}alkoxy may optionally be substituted by fluorine, hydroxyl or cyano; and wherein the 4-7 membered heterocyclic ring may be optionally substituted on nitrogen by one or more substituents selected from the group consisting of C_{1-6}alkyl and R^aR^bN-carbonyl-; and wherein said C_{1-6}alkyl may be optionally substituted by one or more substituents selected from the group consisting of fluorine, hydroxyl, cyano;

R^P is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, cyano, C_{1-6}alkoxy, R^iR^jN-, R^iR^jN-carbonyl-, R^iR^jN-SO_2- and R^iR^jN-carbonyl-$N(R^a)$-;

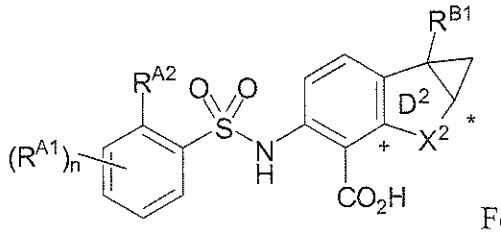
and pharmaceutically acceptable salts, stereoisomers, esters and prodrugs thereof.

12. The ~~method~~ use of claim 11, wherein the compound is represented by



or a pharmaceutically acceptable salt thereof.

13. Use of a compound of Formula IV in the manufacture of a medicament for ~~A method of~~ decreasing whole blood HbA_{1c} or lowering the plasma level of HbA_{1c} in a patient ~~in need thereof, comprising administering to the patient a therapeutically effective amount of compound represented by~~:



Formula IV

D^2 is a 5-7 membered partially unsaturated heterocyclic or carbocyclic ring;

X^2 is selected from the group consisting of: $^+$-$C(R^{D1}R^{D2})$-*, $^+$-W^1-*, $^+$-$C(R^{D1}R^{D2})$-$C(R^{D5}R^{D6})$-*, $^+$-W^2-$C(R^{D5}R^{D6})$-*, $^+$-W^2-C(O)-*, $^+$-$C(R^{D1}R^{D2})$-W^4-*, $^+$-$C(R^{D1}R^{D2})$-$C(R^{D3}R^{D4})$-$C(R^{D5}R^{D6})$-*, $^+$-W^2-$C(R^{D3}R^{D4})$-$C(R^{D5}R^{D6})$-*, $^+$-W^2-C(O)-$C(R^{D5}R^{D6})$-*, $^+$-$C(R^{D1}R^{D2})$-W^3-$C(R^{D5}R^{D6})$-*, $^+$-$C(R^{D1}R^{D2})$-W^3-C(O)-*, $^+$-$C(R^{D1}R^{D2})$-$C(R^{D3}R^{D4})$-W^4-* and $^+$-$C(R^{D1}R^{D2})$-C(O)-W^4-*; wherein the $^+$ and * indicate the attachment points of X^2 as indicated in Formula IV;

W^1 is selected from the group consisting of O, S or $N(R^{N1})$;

W^2 is selected from the group consisting of O or $N(R^{N2})$;

W^3 is selected from the group consisting of O or $N(R^{N3})$;

W^4 is selected from the group consisting of O or $N(R^{N4})$;

R^{B1} is selected from the group consisting of H, F, OH, CN, C_{1-2}alkoxy or C_{1-3}alkyl; wherein C_{1-3}alkyl and C_{1-2}alkoxy are optionally substituted by a group selected from OH, C_{1-2}alkoxy, CN or one or more fluorine atoms;

R^{A1} is selected, independently for each occurrence, from the group consisting of hydrogen, hydroxyl, cyano, halogen, C_{1-4}alkyl or C_{1-3}alkoxy; wherein C_{1-4}alkyl, or C_{1-3}alkoxy may be optionally substituted by one or more fluorines;

n is 0, 1, or 2;

R^{A2} is selected from the group consisting of hydrogen, R^iR^jN-, heterocyclyl, heterocyclyloxy and heterocyclyl-(NR^a)-; wherein said heterocyclyl may optionally be substituted by one or more substituents selected from R^g and wherein if said heterocyclyl contains a –NH moiety that nitrogen may optionally be substituted by one or more groups R^h; or

$_{6}$alkylcarbonyl-N(R^a)-, C_{1-6}alkoxycarbonyl-N(R^a)- may be optionally substituted by one or more substituents selected from R^P;

R^h is independently selected for each occurrence from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkyl-$S(O)_2$-, C_{1-6}alkoxycarbonyl-, R^iR^jN-carbonyl- and R^iR^jN-SO_2-; wherein C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl C_{3-6}cycloalkyl and C_{1-6}alkyl-$S(O)_2$-, C_{1-6}alkylcarbonyl- may optionally be substituted by one or more substituents selected from R^P;

R^i and R^j are selected independently for each occurrence from the group consisting of hydrogen, C_{1-4}alkyl, C_{3-6}cycloalkyl, heterocyclyl and heterocyclylcarbonyl; wherein C_{1-4}alkyl and C_{3-6}cycloalkyl may be optionally substituted by one or more substituents selected from fluorine, hydroxyl, cyano, R^aR^bN-, R^aR^bN-carbonyl- and C_{1-3}alkoxy and wherein heterocyclyl and heterocyclylcarbonyl may be optionally substituted by one or more substituents selected from C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, halo-C_{1-6}-alkyl, hydroxyl-C_{1-6}-alkyl, R^aR^bN-C_{1-6}alkyl- and C_{1-6}-alkoxy-C_{1-6}-alkyl group; and wherein if said heterocyclyl or heterocyclylcarbonyl contains a –NH moiety that nitrogen may optionally be substituted by one or more groups C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkyl-$S(O)_2$- and C_{1-6}-alkylcarbonyl;or R^i and R^j taken together with the nitrogen to which they are attached form a 4-7 membered heterocyclic ring, which may have an additional heteroatom selected from O, S, or N; wherein the 4-7 membered heterocyclic ring may be optionally substituted on carbon by one or more substituents selected from the group consisting of fluorine, hydroxyl, oxo, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, R^aR^bN-, R^aR^bN-SO_2- and R^aR^bN-carbonyl-; wherein said C_{1-6}alkyl or C_{1-6}alkoxy may optionally be substituted by fluorine, hydroxyl or cyano; and wherein the 4-7 membered heterocyclic ring may be optionally substituted on nitrogen by one or more substituents selected from the group consisting of C_{1-6}alkyl and R^aR^bN-carbonyl-; and wherein said C_{1-6}alkyl may be optionally substituted by one or more substituents selected from the group consisting of fluorine, hydroxyl, cyano;

R^P is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, cyano, C_{1-6}alkoxy, R^iR^jN-, R^iR^jN-carbonyl-, R^iR^jN-SO_2- and R^iR^jN-carbonyl-N(R^a)-;

and pharmaceutically acceptable salts, stereoisomers, esters and prodrugs thereof.

14. The ~~method~~ use of claim 13, wherein the patient has a diabetic condition.

15. The ~~method~~ use of any one of claims 1-14, wherein the patient is not obese.