# METHODS OF TREATING LIVER DISEASES

~~CROSS REFERENCE TO RELATED APPLICATIONS~~

~~[0001] This application claims priority to U.S. Provisional Patent Application Number 61/722,529 filed November 5, 2012 and U.S. Provisional Patent Application Number 61/779,396 filed March 13, 2013, both of which are incorporated by reference in their entireties.~~

## [0001] BACKGROUND

**[0002]** Fatty liver disease and liver fibrosis can be chronic liver diseases and represent a common and difficult clinical challenge of worldwide importance. Liver fibrosis is the excessive accumulation of extracellular matrix proteins including collagen that occurs in most types of chronic liver diseases. Advanced liver fibrosis results in cirrhosis, liver failure, and portal hypertension and often requires liver transplantation.

**[0003]** Non-alcoholic steatohepatitis (NASH) is a severe form of fatty liver disease that affects 2 to 5 percent of Americans. It resembles alcoholic liver disease but occurs in people who drink little or no alcohol. The major feature of NASH is excess fat contentin the liver, along with inflammation and liver damage. NASH can lead to liver cirrhosis, fibrosis, hepatocellular carcinoma, liver failure, liver-related death, and liver transplantation. NASH can also lead to an increased risk of cardiovascular disease.

**[0004]** Although NASH affects only 2-5 % of Americans, it is becoming prevalent, likely because of the greater number of Americans with obesity. Many people with NASH are middle-aged, obese, diabetic and/or have elevated blood cholesterol levels. However, NASH can occur in people without any apparent risk factor and can even occur in children. Currently, there are no specific therapies for treating NASH, although some studies suggest that diet, exercise and reducing alcohol intake may be useful in altering the course of the disease.

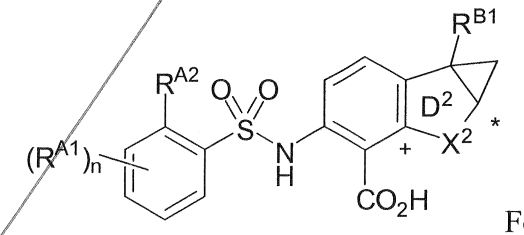
**[0005]** At present, the only curative treatment for end stage cirrhosis is transplantation, but limited availability of donor organs and the clinical condition of the potential recipient limit the applicability of this technique.

**[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-, $C_{1-6}$alkoxy$C_{1-6}$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 $R^P$;

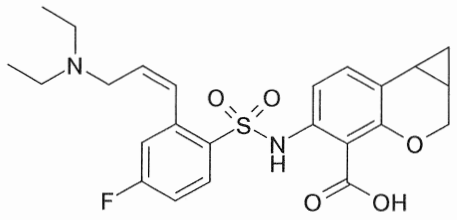
$R^i$ and $R^j$ are selected independently for each occurrence from the group consisting of hydrogen, $C_{1-4}$alkyl, $C_{3-6}$cycloalkyl, heterocyclyl and heterocyclylcarbonyl; wherein $C_{1-4}$alkyl and $C_{3-6}$cycloalkyl may be optionally substituted by one or more substituents selected from fluorine,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

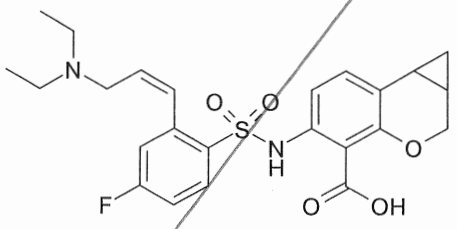
and pharmaceutically acceptable salts, stereoisomers, esters and prodrugs thereof.

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



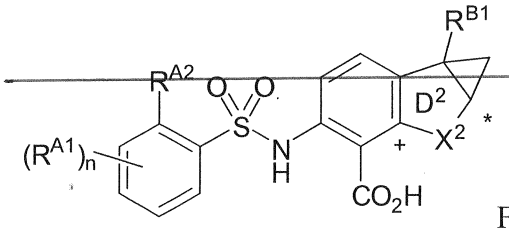
or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or substantially preventing fatty liver disease in a patient.

**[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-~~, $C_{1-6}$alkoxy$C_{1-6}$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-

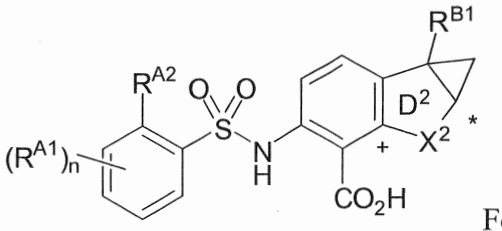
and $C_{1-6}$alkyl-$S(O)_2$-, $C_{1-6}$alkylcarbonyl- may optionally be substituted by one or more substituents selected from $R^P$;

$R^i$ 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-, $C_{1-6}$alkoxy$C_{1-6}$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-, $R^iR^j$N-carbonyl- and $R^iR^j$N-$SO_2$-; 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.

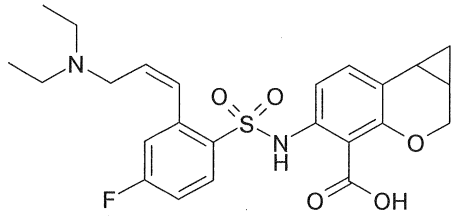
**[0013]** **Figure 6** indicates regulation of the expression of genes implicated in pathogenesis of fatty liver and fibrosis after treatment of obese mice with a disclosed compound.

**[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 one 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.

## 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.

species with slower rates of drug metabolism. Further, Compound A showed an anti-NASH effect and amelioration of glucose and lipid metabolism.

~~INCORPORATION BY REFERENCE~~

~~[00533] All publications and patents mentioned herein, including those items listed below, are hereby incorporated by reference in their entirety for all purposes as if each individual publication or patent was specifically and individually incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.~~

~~EQUIVALENTS~~

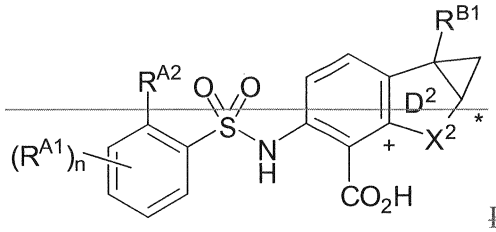
**[00534]** While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification. ~~The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.~~

~~[00535] Unless otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in this specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained by the present invention.~~

**[~~0053~~00535]** What is claimed is:

## CLAIMS

1. 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-, $C_{1-6}$alkoxy$C_{1-6}$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-$N(R^a)$-;

CLAIMS

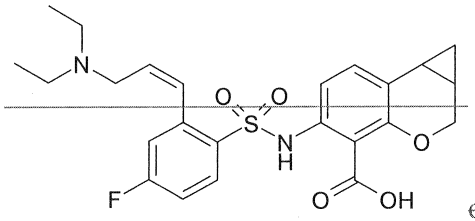
~~and pharmaceutically acceptable salts, stereoisomers, esters and prodrugs thereof.~~

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

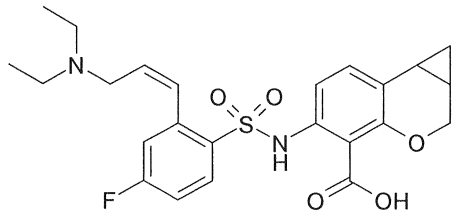
~~4. The use of any one of claims 1-3, wherein the compound is to be administered orally.~~

~~5. 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.~~

~~6~~1. 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.

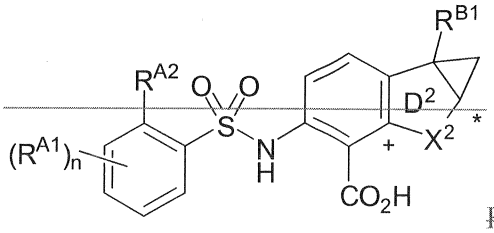
~~7. The use of claim 5, wherein the the compound is to be administered orally.~~

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

~~10~~2. The use of ~~any one of claims 1-9~~claim 1, 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 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-, $C_{1-6}$alkoxy$C_{1-6}$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

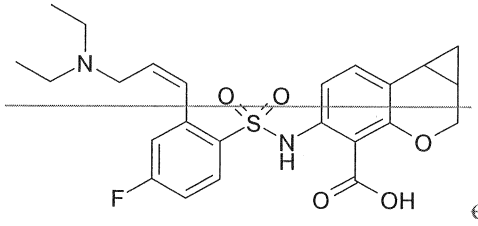
and $C_{1-6}$alkyl-$S(O)_2$-, $C_{1-6}$alkylcarbonyl- may optionally be substituted by one or more substituents selected from $R^p$;

$R^i$ 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-$N(R^a)$-;

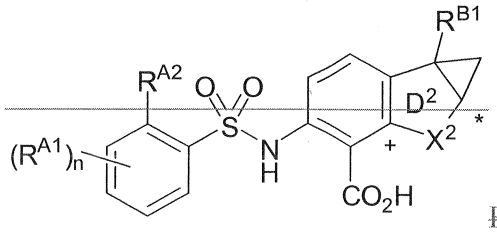
and pharmaceutically acceptable salts, stereoisomers, esters and prodrugs thereof.

12. The 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 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-, $C_{1-6}$alkoxy$C_{1-6}$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 $N(R^aR^b)$;

$R^{G1}$ 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-, $R^iR^j$N-carbonyl- and $R^iR^j$N-$SO_2$-; 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, $R^aR^b$N-, $R^aR^b$N-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, $R^aR^b$N-$C_{1-6}$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, $R^aR^b$N-, $R^aR^b$N-$SO_2$- and $R^aR^b$N-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 $R^aR^b$N-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, $R^iR^j$N-, $R^iR^j$N-carbonyl-, $R^iR^j$N-$SO_2$- and $R^iR^j$N-carbonyl-N($R^a$)-;

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

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

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