Accordingly compounds that modulate GPR40 are expected to have useful therapeutic properties especially in relation to metabolic conditions such as diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulemia, hypercholesteremia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, dyslipedemia, metabolic syndrome X, atherosclerosis, diabetic neuropathy, diabetic retinopathy, and hypoglycemia,

Compounds of this type may also be useful in the treatment of cognitive disorders, osteoporosis, inflammatory disorders, cardiovascular disease, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, sexual dysfunction, dermatopathy, dyspepsia, cancer and edema. As such there is significant interest in the development of compounds with this mode of action.

OBJECTS OF INVENTION

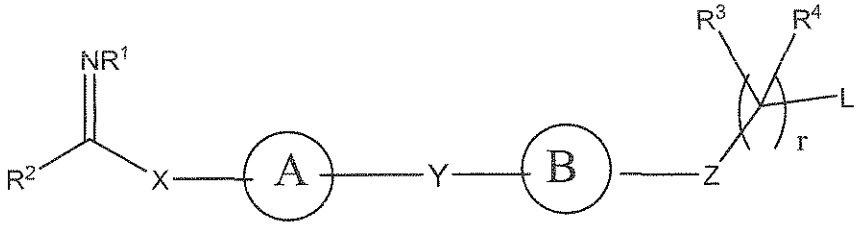
The principal object of the invention is to provide compounds that are modulators of GPR40 receptor activity. These compounds would be expected to be useful in the treatment of GPR40 related conditions.

A further object is to provide a pharmaceutical composition containing a compound that is a modulator of GPR40 receptor activity and a pharmaceutically acceptable excipient, diluent or carrier.

A further object is to provide a method of prevention or treatment of a condition associated with GPR40 receptor function in a mammal.

SUMMARY ~~OF INVENTION~~

The present ~~invention~~disclosure provides compounds of formula (I):



Formula (I)

wherein:

ring A is selected from the group consisting of optionally substituted C_3-C_{12}cycloalkyl, optionally substituted C_2-C_{12}heterocycloalkyl, an optionally substituted C_6-C_{10}arylfusedC_3-

each R^3, R^4, R^5 and R^6 is independently selected from the group consisting of H, halogen, CN, -NO_2, SH, CF_3, OH, CO_2H, $CONH_2$, OCF_3, optionally substituted C_1-C_{12}alkyl, optionally substituted C_1-C_{12}haloalkyl optionally substituted C_2-C_{12}alkenyl, optionally substituted C_2-C_{12}alkynyl, optionally substituted C_1-C_{12}alkyloxy, optionally substituted C_1-C_{12}haloalkyloxy, optionally substituted C_2-C_{10}heteroalkyl, optionally substituted C_3-C_{12}cycloalkyl, optionally substituted C_3-C_{12}cycloalkenyl, optionally substituted C_2-C_{12} heterocycloalkyl, optionally substituted C_2-C_{12} heterocycloalkenyl, optionally substituted C_6-C_{18}aryl, and optionally substituted C_1-C_{18}heteroaryl, or

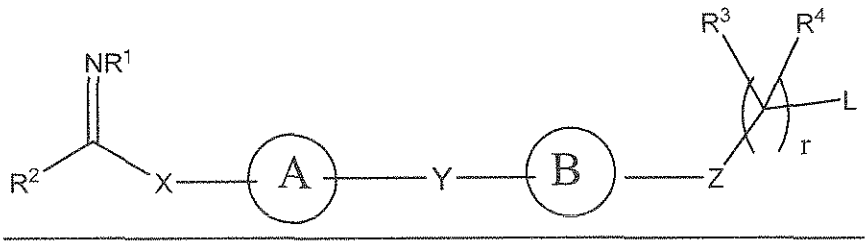
any two of R^3, R^4, R^5 and R^6 when taken together with the atoms to which they are attached may form an optionally substituted cyclic moiety or a double or triple bond between the atoms to which they are attached;

R^7 is selected from the group consisting of H, optionally substituted C_1-C_{12}alkyl, optionally substituted C_2-C_{12}alkenyl, optionally substituted C_2-C_{10}heteroalkyl, optionally substituted C_1-C_{12}haloalkyl, optionally substituted C_3-C_{12}cycloalkyl, optionally substituted C_6-C_{18}aryl, and optionally substituted C_1-C_{18}heteroaryl;

r is an integer selected from the group consisting of 0, 1 and 2;

or a pharmaceutically acceptable salt, N-oxide, or prodrug thereof.

In one aspect, there is provided a compound of formula (I):



Formula I

wherein:

ring A is an optionally substituted phenyl group;

ring B is an optionally substituted phenyl group;

X is a bond or a linking moiety containing from 1 to 8 atoms in the normal chain;

Y is a bond or a linking moiety containing from 1 to 8 atoms in the normal chain;

Z is a bond or is selected from the group consisting of optionally substituted C_6-C_{18}aryl, and optionally substituted C_1-C_{18}heteroaryl, -C(=O)-, -C(=NR^1)-, –(CR^5R^6)-, –(CR^5R^6)O-, –(CR^5R^6)S-, –(CR^5R^6)NR'- or is a heteroatomic group selected from the group consisting of S, O, P and NR" where R" is selected from the group consisting of H, optionally substituted C_1-C_{12}alkyl, optionally substituted C_2-C_{10}heteroalkyl, optionally substituted C_3-C_{12}cycloalkyl, optionally substituted C_6-C_{18}aryl, and optionally substituted C_1-C_{18}heteroaryl;

L is a group capable of releasing a cation or a salt thereof;

R^1 is selected from the group consisting of H, OR^7, optionally substituted C_1-C_{12}alkyl, optionally substituted C_1-C_{12}haloalkyl optionally substituted C_2-C_{12}alkenyl, optionally substituted C_2-C_{12}alkynyl, optionally substituted C_1-C_{12}alkyloxy, optionally substituted C_1-C_{12}haloalkyloxy, optionally substituted C_2-C_{10}heteroalkyl, optionally substituted C_3-C_{12}cycloalkyl, optionally substituted C_3-C_{12}cycloalkenyl, optionally substituted C_2-C_{12}heterocycloalkyl, optionally substituted C_2-C_{12}heterocycloalkenyl, optionally substituted C_6-C_{18}aryl, and optionally substituted C_1-C_{18}heteroaryl,

R^2 is H or a ring selected from the group consisting of an optionally substituted C_3-C_{12}cycloalkyl, optionally substituted C_2-C_{12}heterocycloalkyl, an optionally substituted C_6-C_{10}arylfusedC_3-C_6cycloalkyl, an optionally substituted C_1-C_{18}heteroarylfusedC_3-C_6cycloalkyl, optionally substituted C_6-C_{10}arylfusedC_2-C_{12}heterocycloalkyl, optionally substituted C_1-C_{18}heteroarylfused C_2-C_{12}heterocycloalkyl, optionally substituted C_6-C_{18}aryl and optionally substituted C_1-C_{18}heteroaryl;

each R^3, R^4, R^5 and R^6 is independently selected from the group consisting of H, halogen, CN, -NO_2, SH, CF_3, OH, CO_2H, $CONH_2$, OCF_3, optionally substituted C_1-C_{12}alkyl, optionally substituted C_1-C_{12}haloalkyl optionally substituted C_2-C_{12}alkenyl, optionally substituted C_2-C_{12}alkynyl, optionally substituted C_1-C_{12}alkyloxy, optionally substituted C_1-C_{12}haloalkyloxy, optionally substituted C_2-C_{10}heteroalkyl, optionally substituted C_3-C_{12}cycloalkyl, optionally substituted C_3-C_{12}cycloalkenyl, optionally substituted C_2-C_{12} heterocycloalkyl, optionally substituted C_2-C_{12} heterocycloalkenyl, optionally substituted C_6-C_{18}aryl, and optionally substituted C_1-C_{18}heteroaryl, or

any two of R^3, R^4, R^5 and R^6 when taken together with the atoms to which they are attached may form an optionally substituted cyclic moiety or a double or triple bond between the atoms to which they are attached;

R^7 is selected from the group consisting of H, optionally substituted C_1-C_{12}alkyl, optionally substituted C_2-C_{12}alkenyl, optionally substituted C_2-C_{10}heteroalkyl, optionally substituted C_1-C_{12}haloalkyl, optionally substituted C_3-C_{12}cycloalkyl, optionally substituted C_6-C_{18}aryl, and optionally substituted C_1-C_{18}heteroaryl;

r is 1;

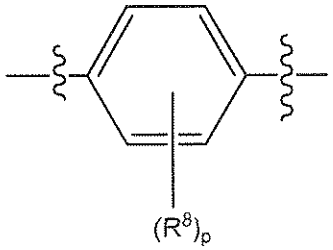
or a pharmaceutically acceptable salt, or N-oxide or prodrug thereof.

As with any group of structurally related compounds which possess a particular utility, certain embodiments of variables of the compounds of the Formula (I), are particularly useful in their end use application.

The moiety L may be any moiety or group that is capable of releasing a cation or a salt thereof. There are many potential groups of this type as would be apparent to a skilled addressee in the art. In some embodiments L is selected from the group consisting of -CO_2H, -SO_3H, -PO_3H, -SO_2NH_2, -$CONHSO_2CH_3$, and tetrazol-5-yl. In some embodiments L is CO_2H or a salt thereof.

In the compounds of the ~~invention~~disclosure r is an integer selected from the group consisting of 0, 1 and 2. In some embodiments r is 0. In some embodiments r is 1. In some embodiments r is 2.

In some embodiments ring B is an optionally substituted phenyl group of the formula IV:



Formula (IV)

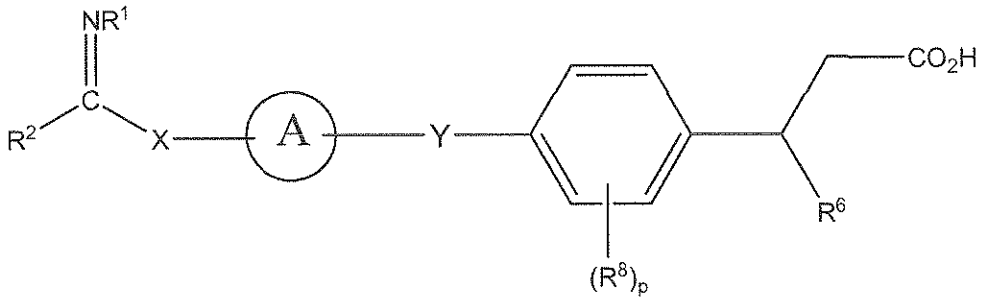
each R^8 is independently selected from the group consisting of H, halogen, OH, NH_2, NO_2, CN, C_1-C_{12}alkyl, C_1-C_{12}haloalkyl, C_1-C_{12}alkoxyl, and C_1-C_{12}haloalkoxyl,

wherein p is an integer selected from the group consisting of 0, 1, 2, 3 and 4.

In the compounds of the ~~invention~~disclosure p is an integer selected from the group consisting of 0, 1, 2, 3 and 4. In some embodiments p is 0. In some embodiments p is 1. In some embodiments p is 2. In some embodiments p is 3. In some embodiments p is 4.

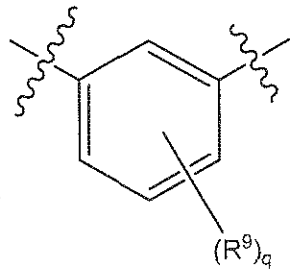
R^8 may be selected from a wide range of possible substituents as discussed above. In some embodiments each R^8 is independently selected from the group consisting of H, halogen, OH, NO_2, CN, C_1-C_{12}alkyl, C_1-C_{12}haloalkyl, C_1-C_{12}alkoxyl, and C_1-C_{12}haloalkoxyl. Exemplary R^8 substituents include F, Cl, Br, I, CH_3, CH_2CH_3, OH, OCH_3, CF_3, OCF_3, NO_2, NH_2, and CN.

In some embodiments L is CO_2H, r is 1, Z is $-(CR^5R^6)-$ and each of R^3, R^4, R^5 is H and ring B is an optionally substituted phenyl group of formula (IV). This provides compounds of formula (IVa).



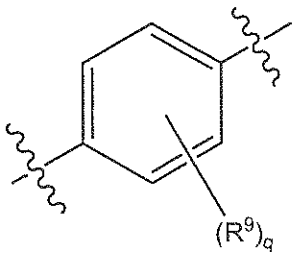
Formula (IVa)

In some embodiments ring A is an optionally substituted phenyl group. In some embodiments ring A is an optionally substituted phenyl group selected from the group consisting of formula (Va) and formula (Vb):



Formula (Va)

and

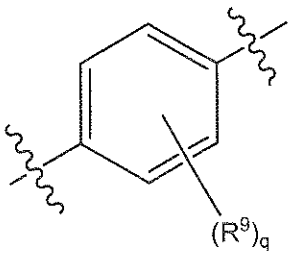


Formula (Vb)

wherein each R^9 is independently selected from the group consisting of H, halogen, OH, NH_2, NO_2, CN, C_1-C_{12}alkyl, C_1-C_{12}haloalkyl, C_1-C_{12}alkoxyl, and C_1-C_{12}haloalkoxyl;

wherein q is an integer selected from the group consisting of 0, 1,2, 3 and 4.

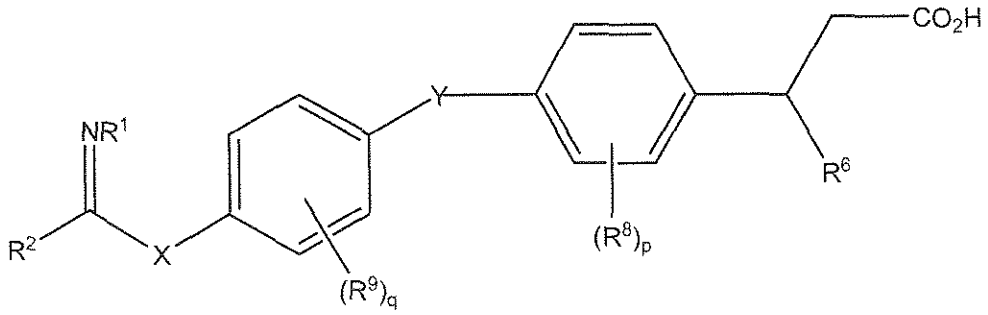
In certain embodiments ring A is an optionally substituted phenyl group of the formula:



wherein R^9 and q are as defined above.

In the compounds of the ~~invention~~disclosure q is an integer selected from the group consisting of 0, 1, 2, 3 and 4. In some embodiments q is 0. In some embodiments q is 1. In some embodiments q is 2. In some embodiments q is 3. In some embodiments q is 4.

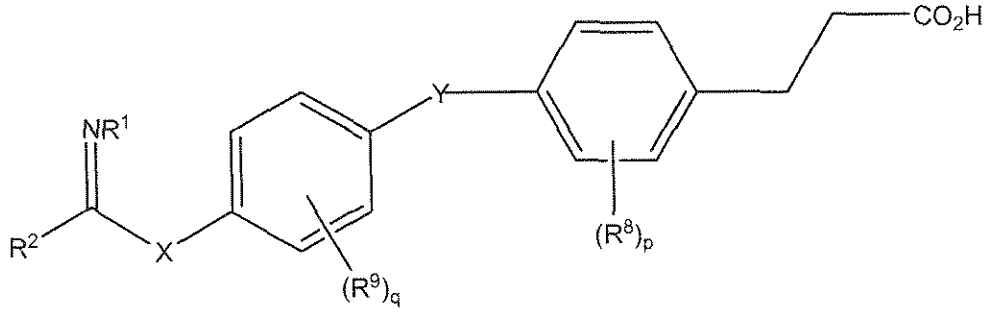
R^9 may be selected from a wide range of possible substituents as discussed above. In some embodiments each R^9 is independently selected from the group consisting of H, halogen, OH, NO_2, CN, C_1-C_{12}alkyl, C_1-C_{12}haloalkyl, C_1-C_{12}alkoxyl, and C_1-C_{12}haloalkoxyl.



Formula (Ve)

or a pharmaceutically acceptable salt or prodrug thereof where R^1, R^2, R^6, R^8, R^9, q, p, X, and Y are as defined above.

In some embodiments L is CO_2H, r is 1, Z is $-(CR^5R^6)-$ and each of R^3, R^4, R^5 and R^6 is H, ring B is an optionally substituted phenyl group of formula (IV) and ring A is an optionally substituted phenyl group of formula (Vb). This provides compounds of formula (Vf).



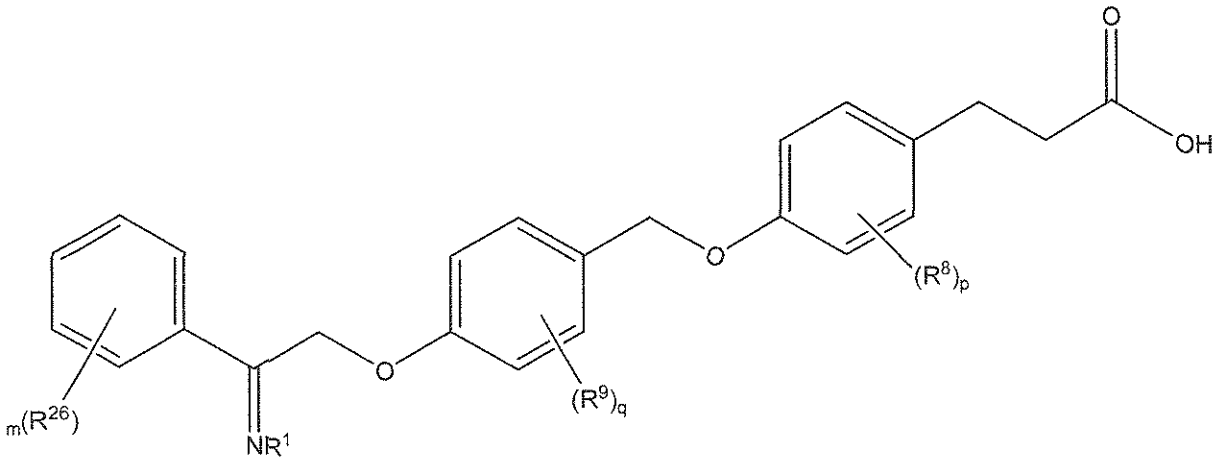
Formula (Vf)

or a pharmaceutically acceptable salt or prodrug thereof where R^1, R^2, R^8, R^9, q, p, X, and Y are as defined above.

In the compounds of the ~~invention~~disclosure X and Y are independently chosen such that they are a bond or there are between 1 and 8 atoms in the normal chain.

In some embodiments Y is selected from the group consisting of:

(a) a bond
(b) -O-
(c) -S-
(d) -S(=O)-
(e) $-S(=O)_2-$
(f) $-N(R^{10})-$,
(g) $-C(R^{10})_2-$,



Formula (IIXg)

or a pharmaceutically acceptable salt or prodrug thereof where R^1, R^8, R^9, R^{26}, m, q, and p, are as defined above.

As a result of the presence of the Oximino double bond the compounds of the ~~invention~~disclosure may exist as either the E or Z geometrical isomer. In some embodiments the compounds are in the E geometric form. In some embodiments the isomers are in the Z geometric form.

Many if not all of the variables discussed above may be optionally substituted. If the variable is optionally substituted then in some embodiments each optional substituent is independently selected from the group consisting of halogen, =O, =S, -CN, $-NO_2$, $-CF_3$, $-OCF_3$, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, heteroalkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, heteroarylalkyl, arylalkyl, cycloalkylalkenyl, heterocycloalkylalkenyl, arylalkenyl, heteroarylalkenyl, cycloalkylheteroalkyl, heterocycloalkylheteroalkyl, arylheteroalkyl, heteroarylheteroalkyl, hydroxy, hydroxyalkyl, alkyloxy, alkyloxyalkyl, alkyloxycycloalkyl, alkyloxyheterocycloalkyl, alkyloxyaryl, alkyloxyheteroaryl, alkyloxycarbonyl, alkylaminocarbonyl, alkenyloxy, alkynyloxy, cycloalkyloxy, cycloalkenyloxy, heterocycloalkyloxy, heterocycloalkenyloxy, aryloxy, phenoxy, benzyloxy, heteroaryloxy, arylalkyloxy, amino, alkylamino, acylamino, aminoalkyl, arylamino, sulfonylamino, sulfinylamino, sulfonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, sulfinyl, alkylsulfinyl, arylsulfinyl, aminosulfinylaminoalkyl, -C(=O)OH, $-C(=O)R^a$, $-C(=O)OR^a$, $C(=O)NR^aR^b$, $C(=NOH)R^a$, $C(=NR^a)NR^bR^c$, NR^aR^b, $NR^aC(=O)R^b$, $NR^aC(=O)OR^b$, $NR^aC(=O)NR^bR^c$, $NR^aC(=NR^b)NR^cR^d$, $NR^aSO_2R^b$,$-SR^a$, $SO_2NR^aR^b$, $-OR^a$, $OC(=O)NR^aR^b$, $OC(=O)R^a$ and acyl,

wherein R^a, R^b, R^c and R^d are each independently selected from the group consisting of H, C_1-C_{12}alkyl, C_1-C_{12}haloalkyl, C_2-C_{12}alkenyl, C_2-C_{12}alkynyl, C_1-C_{10} heteroalkyl, C_3-C_{12}cycloalkyl, C_3-C_{12}cycloalkenyl, C_1-C_{12}heterocycloalkyl, C_1-C_{12} heterocycloalkenyl, C_6-C_{18}aryl, C_1-C_{18}heteroaryl, and acyl, or any two or more of R^a, R^b, R^c and R^d, when taken together with the atoms to which they are attached form a heterocyclic ring system with 3 to 12 ring atoms.

In some embodiments each optional substituent is independently selected from the group consisting of: F, Cl, Br, =O, =S, -CN, -NO_2, alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, hydroxy, hydroxyalkyl, alkoxy, alkylamino, aminoalkyl, acylamino, phenoxy, alkoxyalkyl, benzyloxy, alkylsulfonyl, arylsulfonyl, aminosulfonyl, -C(O)OR^a, COOH, SH, and acyl.

In some embodiments each optional substituent is independently selected from the group consisting of: F, Br, Cl, =O, =S, -CN, methyl, trifluoro-methyl, ethyl, 2,2,2-trifluoroethyl, isopropyl, propyl, 2-ethyl-propyl, 3,3-dimethyl-propyl, butyl, isobutyl, 3,3-dimethyl-butyl, 2-ethyl-butyl, pentyl, 2-methyl-pentyl, pent-4-enyl, hexyl, heptyl, octyl, phenyl, NH_2, -NO_2, phenoxy, hydroxy, methoxy, trifluoro-methoxy, ethoxy, and methylenedioxy.

Alternatively, two optional substituents on the same moiety when taken together may be joined to form a fused cyclic substituent attached to the moiety that is optionally substituted. Accordingly the term optionally substituted includes a fused ring such as a cycloalkyl ring, a heterocycloalkyl ring, an aryl ring or a heteroaryl ring.

In addition to compounds of formula I, the embodiments disclosed are also directed to pharmaceutically acceptable salts, pharmaceutically acceptable N-oxides, pharmaceutically acceptable prodrugs, and pharmaceutically active metabolites of such compounds, and pharmaceutically acceptable salts of such metabolites.

In another aspect, there is provided a~~The invention also relates to~~ pharmaceutical compositions~~s~~ including a compound disclosed herein~~of the invention~~ and a pharmaceutically acceptable carrier, diluent or excipient.

In a further ~~aspect~~embodiment the present ~~invention~~disclosure provides a method of prevention or treatment of a condition associated with GPR40 receptor function in a mammal, the method comprising administering an effective amount of a compound of the ~~invention~~disclosure.

In yet an even further ~~aspect~~embodiment the ~~invention~~disclosure provides the use of a compound of the ~~invention~~disclosure in the preparation of a medicament for the treatment of a condition associated with GPR40 receptor function.

In another aspect, there is provided use of a compound disclosed herein in the manufacture of a medicament for preventing or treating a condition associated with GPR40 receptor function in a mammal, wherein the condition is selected from the group consisting of cognitive disorders, osteoporosis, inflammatory disorders, diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulemia, hypercholesteremia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, dyslipedemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer and edema.

In yet an even further ~~aspect~~embodiment the ~~invention~~disclosure provides the use of a compound of the ~~invention~~disclosure in the treatment of a condition associated with GPR40 receptor function.

In another aspect, there is provided a compound disclosed herein for use in the treatment of a condition associated with GPR40 receptor function in a mammal.

In some embodiments the condition is selected from the group consisting of cognitive disorders, osteoporosis, inflammatory disorders, diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulemia, hypercholesteremia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, dyslipedemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer and edema.

In some embodiments the condition is diabetes. In some embodiments the condition is type II diabetes.

These and other teachings of the ~~invention~~disclosure are set forth herein.

DETAILED DESCRIPTION OF THE INVENTION

In this specification a number of terms are used which are well known to a skilled addressee. Nevertheless for the purposes of clarity a number of terms will be defined.

As used herein, the term "unsubstituted" means that there is no substituent or that the only substituents are hydrogen.

The term "optionally substituted" as used throughout the specification denotes that the group may or may not be further substituted or fused (so as to form a condensed polycyclic system), with one or more non-hydrogen substituent groups. In certain embodiments the substituent groups are one or more groups independently selected from the group consisting of halogen, =O, =S, -CN, $-NO_2$, $-CF_3$, $-OCF_3$, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, heteroalkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, heteroarylalkyl, arylalkyl, cycloalkylalkenyl, heterocycloalkylalkenyl, arylalkenyl, heteroarylalkenyl, cycloalkylheteroalkyl, heterocycloalkylheteroalkyl, arylheteroalkyl, heteroarylheteroalkyl, hydroxy, hydroxyalkyl, alkyloxy, alkyloxyalkyl, alkyloxycycloalkyl, alkyloxyheterocycloalkyl, alkyloxyaryl,