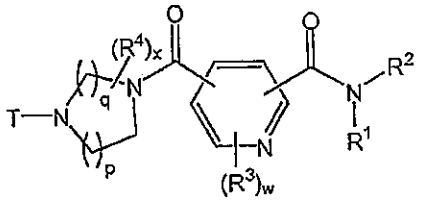
activated, AMPK switches on catabolic pathways (such as fatty acid oxidation and glycolysis) and switches off ATP-consuming pathways (such as lipogenesis). Adiponectin improves insulin sensitivity by directly stimulating glucose uptake in adipocytes and muscle and by increasing fatty acid oxidation in liver and muscle, resulting in reduced circulating fatty acid levels and reduced intracellular triglyceride contents. Moreover, adiponectin decreases glycogen concentration by reducing the activity of glycogen synthase. Adiponectin also plays a protective role against inflammation and atherosclerosis. It suppresses the expression of adhesion molecules in vascular endothelial cells and cytokine production from macrophages, thus inhibiting the inflammatory processes that occur during the early phases of atherosclerosis. What is needed are compounds, pharmaceutical compositions and methods of using them to treat disease states associated with circulating adiponectin levels, such as type II diabetes, atherosclerosis and cardiovascular disease.

[0004a] WO 2008/083124 A1 relates to certain N-substituted heterocycloalkyloxybenzamide derivatives and their use in activating the AMPK pathway and in the treatment of metabolism-related disorders and conditions.

SUMMARY

[0005] Disclosed herein are compounds having structural formula (I)



(I)

and pharmaceutically acceptable salts, prodrugs and *N*-oxides thereof (and solvates and hydrates thereof), wherein

R^1 is H, -(C_1-C_4 alkyl), -C(O)-(C_1-C_4 alkyl) or -C(O)O-(C_1-C_4 alkyl);

R^2 is -Hca, -Cak-N(R^9)-G-R^{22} or -(C_2-C_8 alkyl)-N(R^9)-R^{24} in which one or two carbons of the (C_2-C_8 alkyl) are optionally replaced by -O-, -S- or -N(R^9)- and R^{24} is -R^{23}, -G-R^{23} or -C(O)O-(C_1-C_6 alkyl) , provided that two consecutive carbons of the (C_2-C_8 alkyl) are not replaced by -O-;

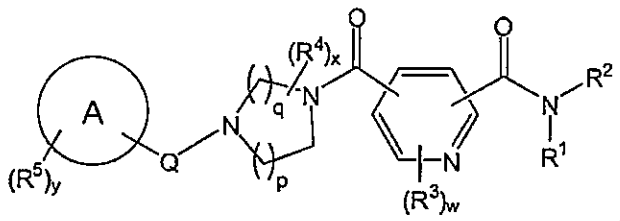
each R^3 is independently selected from -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_0-C_6 alkyl)-Ar, -(C_0-C_6 alkyl)-Het, -(C_0-C_6 alkyl)-Cak, -(C_0-C_6 alkyl)-Hca, -(C_0-C_6 alkyl)-L-R^7, -(C_0-C_6 alkyl)-NR^8R^9, -(C_0-C_6 alkyl)-OR^{10}, -(C_0-C_6 alkyl)-C(O)R^{10}, -(C_0-C_6 alkyl)-S(O)$_{0-2}R^{10}$, -halogen, -NO_2 and -CN;

w is 0, 1, 2 or 3;

each R^4 is independently selected from -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_0-C_6 alkyl)-Ar, -(C_0-C_6 alkyl)-Het, -(C_0-C_6 alkyl)-Cak, -(C_0-C_6 alkyl)-Hca, -(C_0-C_6

What is claimed is:

1. A compound having the structural formula



or a pharmaceutically acceptable salt, prodrug, or *N*-oxide thereof, wherein

R^1 is H, -(C_1-C_4 alkyl), -C(O)-(C_1-C_4 alkyl) or -C(O)O-(C_1-C_4 alkyl);

R^2 is -(optionally-substituted azetidin-3-yl), -(optionally substituted piperidin-4-yl), -(optionally substituted pyrrolidin-3-yl) or -(optionally-substituted azepan-4-yl), substituted at substituted at its 1-position with -(C_0-C_3 alkyl)-Ar, -(C_0-C_3 alkyl)-Het, C(O)-O(C_0-C_6 alkyl), -C(O)-Het, -C(O)-Ar, -S(O)$_2$-Het, -S(O)$_2$-Ar, -L-Ar, -L-Het, or -S(O)$_2$-O(C_0-C_6 alkyl);

each R^3 is independently selected from -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_0-C_6 alkyl)-L-R^7, -(C_0-C_6 alkyl)-NR^8R^9, -(C_0-C_6 alkyl)-OR^{10}, -(C_0-C_6 alkyl)-C(O)R^{10}, -(C_0-C_6 alkyl)-S(O)$_{0\text{-}2}R^{10}$, -halogen, -NO_2 and -CN;

w is 0, 1, 2 or 3;

each R^4 is independently selected from -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_0-C_6 alkyl)-L-R^7, -(C_0-C_6 alkyl)-NR^8R^9, -(C_0-C_6 alkyl)-OR^{10}, -(C_0-C_6 alkyl)-C(O)R^{10}, -(C_0-C_6 alkyl)-S(O)$_{0\text{-}2}R^{10}$, -halogen, -NO_2 and -CN, and two R^4 on the same carbon optionally combine to form oxo;

x is 0, 1, 2, 3 or 4;

p is 0, 1, 2, 3 or 4;

q is 2, 3 or 4;

the sum of p and q is 2, 3, 4, 5 or 6;

Q is -S(O)$_2$-, L or -(C_0-C_3 alkyl)-, in which each carbon of the -(C_0-C_3 alkyl)- is optionally and independently substituted with one or two R^{16};

the ring system denoted by "A" is heteroaryl or aryl;

each R^5 is independently selected from -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_0-C_6 alkyl)-L-R^7, -(C_0-C_6 alkyl)-NR^8R^9, -(C_0-C_6 alkyl)-OR^{10}, -(C_0-C_6 alkyl)-$C(O)R^{10}$, -(C_0-C_6 alkyl)-$S(O)_{0-2}R^{10}$, -halogen, -NO_2, -CN and -C(O)-Hca wherein the Hca contains a ring nitrogen atom through which it is bound to the -C(O)-; and

y is 0, 1, 2, 3 or 4;

in which

each L is independently selected from -$NR^9C(O)O$-, -$OC(O)NR^9$-, -$NR^9C(O)$-NR^9-, -$NR^9C(O)S$-, -$SC(O)NR^9$-, -$NR^9C(O)$-, -$C(O)$-NR^9-, -$NR^9C(S)O$-, -$OC(S)NR^9$-, -$NR^9C(S)$-NR^9-, -$NR^9C(S)S$-, -$SC(S)NR^9$-, -$NR^9C(S)$-, -$C(S)NR^9$-, -$SC(O)NR^9$-, -$NR^9C(S)$-, -$S(O)_{0-2}$-, -C(O)O, -OC(O)-, -C(S)O-, -OC(S)-, -C(O)S-, -SC(O)-, -C(S)S-, -SC(S)-, -OC(O)O-, -SC(O)O-, -OC(O)S-, -SC(S)O-, -OC(S)S-, -$NR^9C(NR^2)NR^9$-, -NR^9SO_2-, -SO_2NR^9- and -$NR^9SO_2NR^9$-,

each R^6, R^7, R^8 and R^{10} is independently selected from H, -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_0-C_6 alkyl)-L-(C_0-C_6 alkyl), -(C_0-C_6 alkyl)-NR^9-(C_0-C_6 alkyl), -(C_0-C_6 alkyl)-O-(C_0-C_6 alkyl), -(C_0-C_6 alkyl)-C(O)-(C_0-C_6 alkyl) and -(C_0-C_6 alkyl)-$S(O)_{0-2}$-(C_0-C_6 alkyl),

each R^9 is independently selected from -H, -(C_1-C_4 alkyl), -C(O)-(C_1-C_4 alkyl) and -C(O)O-(C_1-C_4 alkyl),

each R^{16} is independently selected from -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_0-C_6 alkyl)-L-R^7, -(C_0-C_6 alkyl)-NR^8R^9, -(C_0-C_6 alkyl)-OR^{10}, -(C_0-C_6 alkyl)-$C(O)R^{10}$, -(C_0-C_6 alkyl)-$S(O)_{0-2}R^{10}$, -halogen, -NO_2 and -CN, and optionally two of R^{16} on the same carbon combine to form oxo,

each R^{38} is independently selected from -H, -(C_1-C_4 alkyl), -C(O)-(C_1-C_4 alkyl) and -C(O)O-(C_1-C_4 alkyl),

each R^{22} and R^{23} is independently Ar or Het,

each Ar is an optionally substituted aryl,

each Het is an optionally substituted heteroaryl,

each Hca is an optionally substituted heterocycloalkyl, and

each alkyl is optionally substituted

in which optional substituents on saturated carbon atoms are selected from $-R^{60}$, halo, $-O^-M^+$, =O, $-OR^{70}$, $-SR^{70}$, $-S^-M^+$, =S, $-NR^{80}R^{80}$, $=NR^{70}$, =N-OR^{70}, trihalomethyl, $-CF_3$, -CN, -OCN, -SCN, -NO, $-NO_2$, $=N_2$, $-N_3$, $-SO_2R^{70}$, $-SO_2O^-M^+$, $-SO_2OR^{70}$, $-OSO_2R^{70}$, $-OSO_2O^-M^+$, $-OSO_2OR^{70}$, $-P(O)(O^-)_2(M^+)_2$, $-P(O)(OR^{70})O^-M^+$, $-P(O)(OR^{70})_2$, $-C(O)R^{70}$, $-C(S)R^{70}$, $-C(NR^{70})R^{70}$, $-C(O)O^-M^+$, $-C(O)OR^{70}$, $-C(S)OR^{70}$, $-C(O)NR^{80}R^{80}$, $-C(NR^{70})NR^{80}R^{80}$, $-OC(O)R^{70}$, $-OC(S)R^{70}$, $-OC(O)O^-M^+$, $-OC(O)OR^{70}$, $-OC(S)OR^{70}$, $-NR^{70}C(O)R^{70}$, $-NR^{70}C(S)R^{70}$, $-NR^{70}CO_2^-M^+$, $-NR^{70}CO_2R^{70}$, $-NR^{70}C(S)OR^{70}$, $-NR^{70}C(O)NR^{80}R^{80}$, $-NR^{70}C(NR^{70})R^{70}$ and $-NR^{70}C(NR^{70})NR^{80}R^{80}$;

optional substituents on unsaturated carbon atoms are selected from $-R^{60}$, halo, $-O^-M^+$, $-OR^{70}$, $-SR^{70}$, $-S^-M^+$, $-NR^{80}R^{80}$, trihalomethyl, $-CF_3$, -CN, -OCN, -SCN, -NO, $-NO_2$, $-N_3$, $-SO_2R^{70}$, $-SO_3^-M^+$, $-SO_3R^{70}$, $-OSO_2R^{70}$, $-OSO_3^-M^+$, $-OSO_3R^{70}$, $-PO_3^{-2}(M^+)_2$, $-P(O)(OR^{70})O^-M^+$, $-P(O)(OR^{70})_2$, $-C(O)R^{70}$, $-C(S)R^{70}$, $-C(NR^{70})R^{70}$, $-CO_2^-M^+$, $-CO_2R^{70}$, $-C(S)OR^{70}$, $-C(O)NR^{80}R^{80}$, $-C(NR^{70})NR^{80}R^{80}$, $-OC(O)R^{70}$, $-OC(S)R^{70}$, $-OCO_2^-M^+$, $-OCO_2R^{70}$, $-OC(S)OR^{70}$, $-NR^{70}C(O)R^{70}$, $-NR^{70}C(S)R^{70}$, $-NR^{70}CO_2^-M^+$, $-NR^{70}CO_2R^{70}$, $-NR^{70}C(S)OR^{70}$, $-NR^{70}C(O)NR^{80}R^{80}$, $-NR^{70}C(NR^{70})R^{70}$ and $-NR^{70}C(NR^{70})NR^{80}R^{80}$, and

optional substitutents on nitrogen atoms are selected from $-R^{60}$, $-O^-M^+$, $-OR^{70}$, $-SR^{70}$, $-S^-M^+$, $-NR^{80}R^{80}$, trihalomethyl, $-CF_3$, -CN, -NO, $-NO_2$, $-S(O)_2R^{70}$, $-S(O)_2O^-M^+$, $-S(O)_2OR^{70}$, $-OS(O)_2R^{70}$, $-OS(O)_2O^-M^+$, $-OS(O)_2OR^{70}$, $-P(O)(O^-)_2(M^+)_2$, $-P(O)(OR^{70})O^-M^+$, $-P(O)(OR^{70})(OR^{70})$, $-C(O)R^{70}$, $-C(S)R^{70}$, $-C(NR^{70})R^{70}$, $-C(O)OR^{70}$, $-C(S)OR^{70}$, $-C(O)NR^{80}R^{80}$, $-C(NR^{70})NR^{80}R^{80}$, $-OC(O)R^{70}$, $-OC(S)R^{70}$, $-OC(O)OR^{70}$, $-OC(S)OR^{70}$, $-NR^{70}C(O)R^{70}$, $-NR^{70}C(S)R^{70}$, $-NR^{70}C(O)OR^{70}$, $-NR^{70}C(S)OR^{70}$, $-NR^{70}C(O)NR^{80}R^{80}$, $-NR^{70}C(NR^{70})R^{70}$ and $-NR^{70}C(NR^{70})NR^{80}R^{80}$,

wherein

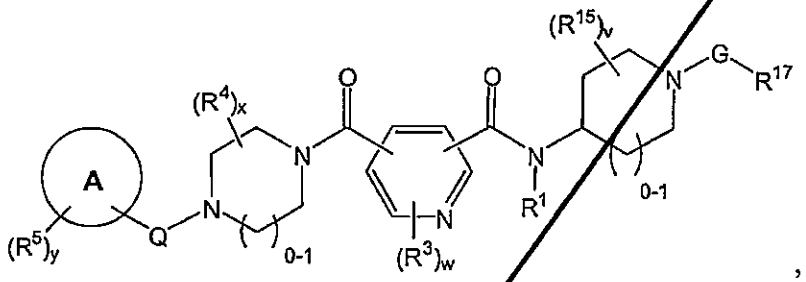
each R^{60} is H, alkyl or heteroalkyl

each R^{70} is H, alkyl or heteroalkyl

each R^{80} is H, alkyl or heteroalkyl or alternatively, two R^{80}'s, taken together with the nitrogen atom to which they are bonded, form a 5-, 6- or 7-membered heterocycloalkyl which may optionally include from 1 to 4 of the same or different additional heteroatoms selected from the group consisting of O, N and S, of which N may have -H or C_1-C_3 alkyl substitution

each M+ is a counterion with a net single positive charge.

2. A compound according to claim 1, having the structural formula



,

in which

Q and G are each independently a bond, $-CH_2-$, $-C(H)(R^{16})-$, $-C(R^{16})_2-$, L or $-S(O)_2-$;

v is 0, 1, 2, 3 or 4;

each R^{15} is independently selected from -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_0-C_6 alkyl)-L-R^7, -(C_0-C_6 alkyl)-NR^8R^9, -(C_0-C_6 alkyl)-OR^{10}, -(C_0-C_6 alkyl)-$C(O)R^{10}$, -(C_0-C_6 alkyl)-$S(O)_{0-2}R^{10}$, -halogen, $-NO_2$ and -CN, and two R^{15} on the same carbon optionally combine to form oxo;

R^{17} is Het or Ar optionally substituted with 1, 2 or 3 substituents independently selected from -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_0-C_6 alkyl)-L-R^7, -(C_0-C_6 alkyl)-NR^8R^9, -(C_0-C_6 alkyl)-OR^{10}, -(C_0-C_6 alkyl)-$C(O)R^{10}$, -(C_0-C_6 alkyl)-$S(O)_{0-2}R^{10}$, -halogen, $-NO_2$, -CN and -C(O)-Hca wherein the Hca contains a ring nitrogen atom through which it is bound to the -C(O)-.

3. A compound according to claim 2, wherein each R^{15} is independently selected from -(C_1-C_3 alkyl), -(C_1-C_3 haloalkyl), -(C_0-C_3 alkyl)-L-R^7, -(C_0-C_3 alkyl)-NR^8R^9, -(C_0-C_3 alkyl)-OR^{10}, -(C_0-C_3 alkyl)-$C(O)R^{10}$, -(C_0-C_3 alkyl)-$S(O)_{0-2}R^{10}$, -halogen, $-NO_2$ and -CN and two R^{15} on the same carbon optionally combine to form oxo, in which each R^7, R^8 and R^{10} is independently

selected from H, -(C_1-C_2 alkyl), -(C_1-C_2 haloalkyl), -(C_0-C_2 alkyl)-L-(C_0-C_2 alkyl), -(C_0-C_2 alkyl)-NR^9(C_0-C_2 alkyl), -(C_0-C_2 alkyl)-O-(C_0-C_2 alkyl), -(C_0-C_2 alkyl)-C(O)-(C_0-C_2 alkyl) and -(C_0-C_2 alkyl)-$S(O)_{0-2}$-(C_0-C_2 alkyl).

4. A compound according to any of claims 1-3, wherein each R^{16} is independently selected from -(C_1-C_3 alkyl), -(C_1-C_3 haloalkyl), -(C_0-C_3 alkyl)-L-R^7, -(C_0-C_3 alkyl)-NR^8R^9, -(C_0-C_3 alkyl)-OR^{10}, -(C_0-C_3 alkyl)-C(O)R^{10}, -(C_0-C_3 alkyl)-$S(O)_{0-2}R^{10}$, -halogen, -NO_2 and -CN, and two R^{16} on the same carbon optionally combine to form an oxo, in which each R^7, R^8 and R^{10} is independently selected from H, -(C_1-C_2 alkyl), -(C_1-C_2 haloalkyl), -(C_0-C_2 alkyl)-L-(C_0-C_2 alkyl), -(C_0-C_2 alkyl)-NR^9(C_0-C_2 alkyl), -(C_0-C_2 alkyl)-O-(C_0-C_2 alkyl), -(C_0-C_2 alkyl)-C(O)-(C_0-C_2 alkyl) and -(C_0-C_2 alkyl)-$S(O)_{0-2}$-(C_0-C_2 alkyl).

5. A compound according to any of claims 1-4, wherein Q has at most one R^{16} or an oxo substituted thereon.

6. A compound according to any of claims 1-4, wherein Q is an unsubstituted -(C_1-C_3 alkyl)-.

7. A compound according to any of claims 1-4, wherein Q is -CH_2-, a single bond, -C(O)-, -$S(O)_2$- or -$CH(CH_3)$-.

8. A compound according to any of claims 1-7, wherein y is 0.

9. A compound according to any of claims 1-7, wherein y is 1.

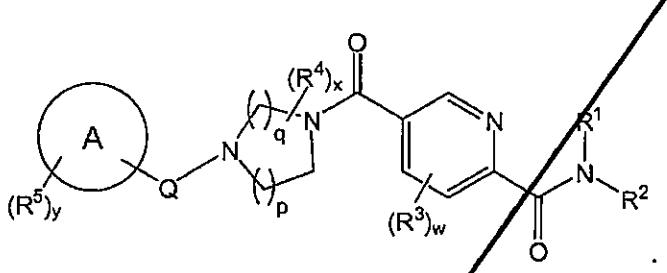
10. A compound according to any of claims 1-7, wherein each R^5 is independently selected from -(C_1-C_3 alkyl), -(C_1-C_3 haloalkyl), -(C_0-C_3 alkyl)-L-R^7, -(C_0-C_3 alkyl)-NR^8R^9, -(C_0-C_3 alkyl)-OR^{10}, -(C_0-C_3 alkyl)-C(O)R^{10}, -(C_0-C_3 alkyl)-$S(O)_{0-2}R^{10}$, -halogen, -NO_2 and -CN, in which each R^7, R^8 and R^{10} is independently selected from H, -(C_1-C_2 alkyl), -(C_1-C_2 haloalkyl), -(C_0-C_2 alkyl)-L-(C_0-C_2 alkyl), -(C_0-C_2 alkyl)-NR^9(C_0-C_2 alkyl), -(C_0-C_2 alkyl)-O-(C_0-C_2 alkyl), -(C_0-C_2 alkyl)-C(O)-(C_0-C_2 alkyl) and -(C_0-C_2 alkyl)-$S(O)_{0-2}$-(C_0-C_2 alkyl).

11. A compound according to any of claims 1-10, wherein the ring system denoted by "A" is a phenyl.

12. A compound according to any of claims 1-10, wherein the ring system denoted by "A" is a heteroaryl.

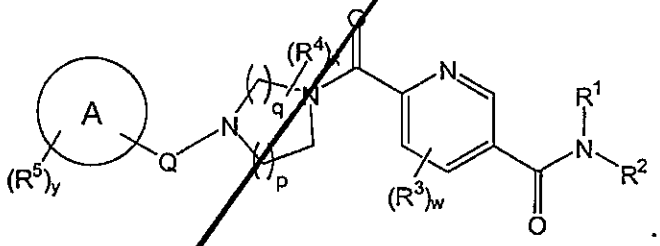
13. A compound according to any of claims 1-10, wherein the ring system denoted by "A" is a pyridyl, a thienyl, or a furanyl.

14. A compound according to any of claims 1-13, wherein the compound has the structural formula



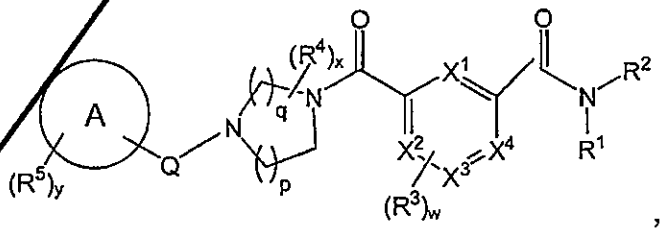
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15. A compound according to any of claims 1-13, wherein the compound has the structural formula



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16. A compound according to any of claims 1-13, wherein the compound has the structural formula



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in which one of X^1, X^2, X^3 and X^4 is N, and the others are carbons.

17. A compound according to any of claims 1-16, wherein the sum of p and q is 2 or 3.

18. A compound according to any of claims 1-17, wherein R^1 is H.

19. A compound according to any of claims 1-18, wherein R^2 is substituted at its 1-position with -(C_0-C_3 alkyl)-Ar or -(C_0-C_3 alkyl)-Het.

20. A compound according to any of claims 1-18, wherein R^2 is substituted at its 1-position with -C(O)-O(C_0-C_6 alkyl), -C(O)-Het, -C(O)-Ar, -$S(O)_2$-Het, -$S(O)_2$-Ar or -$S(O)_2$-O(C_0-C_6 alkyl).

21. A compound according to any of claims 1-18, wherein R^2 is substituted at its 1-position with -C(O)-NR^9-Het or -C(O)- NR^9-Ar.

22. A compound according to any of claims 1-21, wherein w is 0.

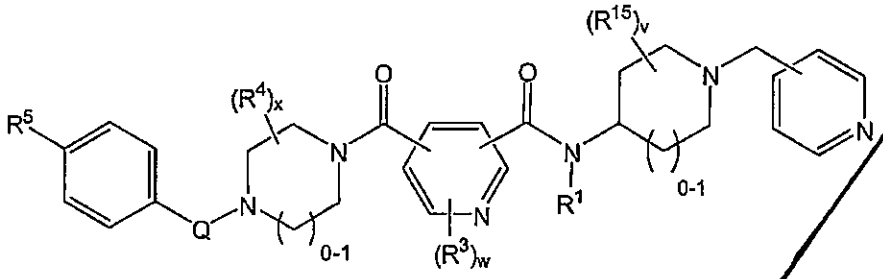
23. A compound according to any of claims 1-21, wherein w is at least 1 and at least one R^3 is selected from the group consisting of halo, cyano, -(C_1-C_4 fluoroalkyl), -O-(C_1-C_4 fluoroalkyl), -C(O)-(C_0-C_4 alkyl), -C(O)O-(C_0-C_4 alkyl), -C(O)N(C_0-C_4 alkyl)(C_0-C_4 alkyl), -$S(O)_2$O-(C_0-C_4 alkyl), NO_2 and -C(O)-Hca in which the Hca includes a nitrogen atom to which the -C(O)- is bound.

24. A compound according to any of claims 1-21, wherein each R^3 is independently selected from -(C_1-C_3 alkyl), -(C_1-C_3 haloalkyl), -(C_0-C_3 alkyl)-L-R^7, -(C_0-C_3 alkyl)-NR^8R^9, -(C_0-C_3 alkyl)-OR^{10}, -(C_0-C_3 alkyl)-C(O)R^{10}, -(C_0-C_3 alkyl)-$S(O)_{0-2}R^{10}$, -halogen, -NO_2 and -CN, in which each R^7, R^8 and R^{10} is independently selected from H, -(C_1-C_2 alkyl), -(C_1-C_2 haloalkyl), -(C_0-C_2 alkyl)-L-(C_0-C_2 alkyl), -(C_0-C_2 alkyl)-NR^9(C_0-C_2 alkyl), -(C_0-C_2 alkyl)-O-(C_0-C_2 alkyl), -(C_0-C_2 alkyl)-C(O)-(C_0-C_2 alkyl) and -(C_0-C_2 alkyl)-$S(O)_{0-2}$-(C_0-C_2 alkyl).

25. A compound according to any of claims 1-24 wherein x is 0.

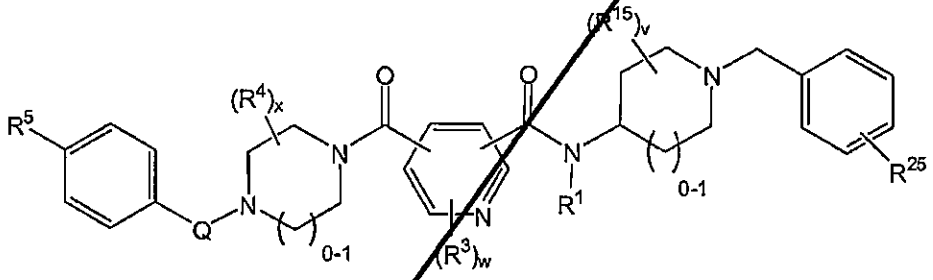
26. A compound according to any of claims 1-24, wherein each R^4 is independently selected from -(C_1-C_3 alkyl), -(C_1-C_3 haloalkyl), -(C_0-C_3 alkyl)-L-R^7, -(C_0-C_3 alkyl)-NR^8R^9, -(C_0-C_3 alkyl)-OR^{10}, -(C_0-C_3 alkyl)-C(O)R^{10}, -(C_0-C_3 alkyl)-$S(O)_{0-2}R^{10}$, -halogen, -NO_2 and -CN, in which each R^7, R^8 and R^{10} is independently selected from H, -(C_1-C_2 alkyl), -(C_1-C_2 haloalkyl), -(C_0-C_2 alkyl)-L-(C_0-C_2 alkyl), -(C_0-C_2 alkyl)-NR^9(C_0-C_2 alkyl), -(C_0-C_2 alkyl)-O-(C_0-C_2 alkyl), -(C_0-C_2 alkyl)-C(O)-(C_0-C_2 alkyl) and -(C_0-C_2 alkyl)-$S(O)_{0-2}$-(C_0-C_2 alkyl).

27. A compound according to any of claims 1-26, having the structural formula



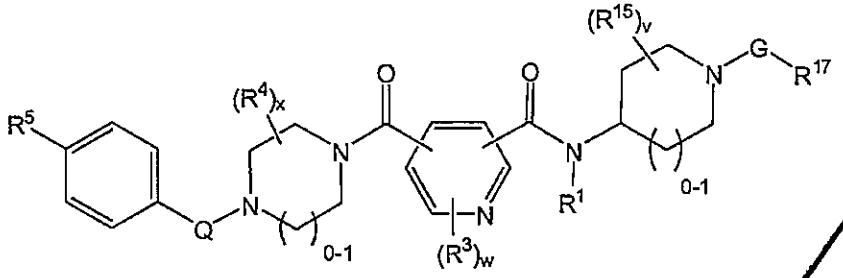
in which Q is a bond, -CH_2-, -C(H)(R^{16})-, -C(R^{16})$_2$-, L or -S(O)$_2$-; v is 0, 1, 2, 3 or 4; each R^{15} is independently selected from -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_0-C_6 alkyl)-L-R^7, -(C_0-C_6 alkyl)-NR^8R^9, -(C_0-C_6 alkyl)-OR^{10}, -(C_0-C_6 alkyl)-C(O)R^{10}, -(C_0-C_6 alkyl)-S(O)$_{0-2}R^{10}$, -halogen, -NO_2 and -CN, and two R^{15} on the same carbon optionally combine to form oxo.

28. A compound according to any of claims 1-26, having the structural formula



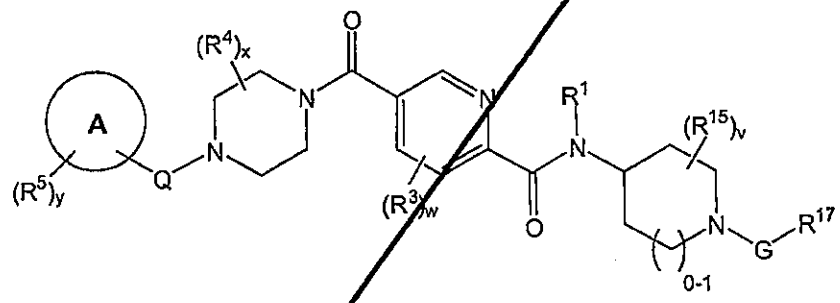
in which in which Q is a bond, -CH_2-, -C(H)(R^{16})-, -C(R^{16})$_2$-, L or -S(O)$_2$-; v is 0, 1, 2, 3 or 4; each R^{15} is independently selected from -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_0-C_6 alkyl)-L-R^7, -(C_0-C_6 alkyl)-NR^8R^9, -(C_0-C_6 alkyl)-OR^{10}, -(C_0-C_6 alkyl)-C(O)R^{10}, -(C_0-C_6 alkyl)-S(O)$_{0-2}R^{10}$, -halogen, -NO_2 and -CN, and two R^{15} on the same carbon optionally combine to form oxo; and R^{25} is selected from halo, cyano, -(C_1-C_4 haloalkyl), -O-(C_1-C_4 haloalkyl), -(C_1-C_4 alkyl), -O-(C_1-C_4 alkyl), -C(O)-(C_0-C_4 alkyl), -C(O)O-(C_0-C_4 alkyl), -C(O)N(C_0-C_4 alkyl)(C_0-C_4 alkyl), NO_2 and -C(O)-Hca in which the Hca contains a ring nitrogen atom through which it is bound to the -C(O)-.

29. A compound according to any of claims 1-26, having the structural formula

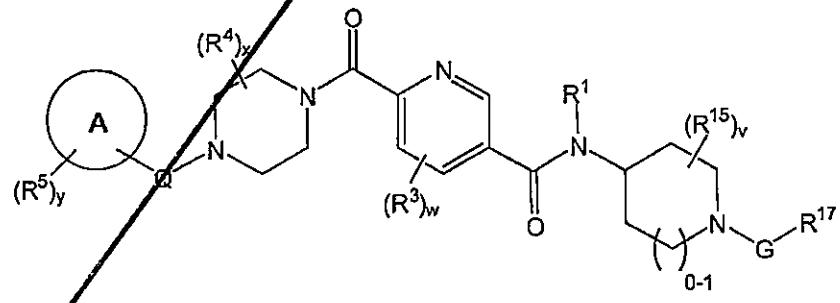


in which G is a bond, $-CH_2-$, $-C(H)(R^{16})-$, $-C(R^{16})_2-$, L or $-S(O)_2-$; v is 0, 1, 2, 3 or 4; each R^{15} is independently selected from $-(C_1-C_6$ alkyl), $-(C_1-C_6$ haloalkyl), $-(C_0-C_6$ alkyl)-L-R^7, $-(C_0-C_6$ alkyl)-NR^8R^9, $-(C_0-C_6$ alkyl)-OR^{10}, $-(C_0-C_6$ alkyl)-$C(O)R^{10}$, $-(C_0-C_6$ alkyl)-$S(O)_{0-2}R^{10}$, -halogen, $-NO_2$ and -CN, and two R^{15} on the same carbon optionally combine to form oxo; and Q is $-C(O)-$, $-S(O)_2-$ or $-C(O)-NH-$.

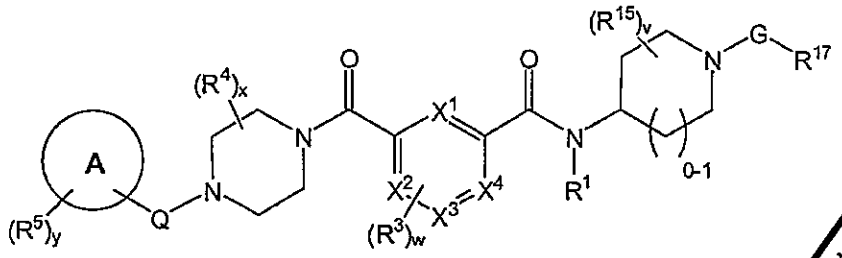
30. A compound according to any of claims 1-14 or 19, having the structural formula



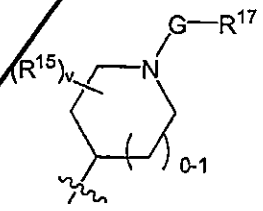
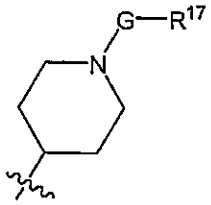
31. A compound according to any of claims 1-13, 15 or 19, having the structural formula

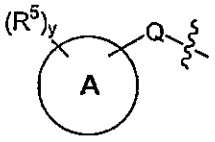


32. A compound according to any of claims 1-13, 16 or 19, having the structural formula



in which one of X^1, X^2, X^3 and X^4 is N, and the others are carbons.

33. A compound according to any of claims 2, 3 or 27-32, wherein the  moiety has the structure , in which G is $-CH_2-$, $-CH(CH_3)-$, $-C(O)-$, $-S(O)_2-$ or $-C(O)-NH-$.

34. A compound according to any of claims 1-33, wherein the  moiety is *p*-(trifluoromethyl)phenyl, *p*-fluorophenyl or *p*-cyanophenyl.

35. A compound according to any of claims 1-34, wherein w is 0, x is 0 and v is 0.

36. A compound according to claim 1, wherein the compound is

5-(4-(4-cyanobenzyl)piperazine-1-carbonyl)-*N*-(1-(4-cyanobenzyl)piperidin-4-yl)picolinamide;

N-(1-(4-cyanobenzyl)piperidin-4-yl)-5-(4-(4-fluorobenzyl)piperazine-1-carbonyl)picolinamide;

N-(1-(4-cyanobenzyl)piperidin-4-yl)-5-(4-(4-(trifluoromethyl)benzyl)piperazine-1-carbonyl)picolinamide

(S)-5-(4-(4-chlorophenyl)piperazine-1-carbonyl)-*N*-(1-(4-fluorobenzyl)pyrrolidin-3-yl)picolinamide;

(S)-5-(4-(4-chlorophenyl)piperazine-1-carbonyl)-*N*-(1-(pyridin-4-ylmethyl)pyrrolidin-3-yl)picolinamide;

(S)-5-(4-(4-chlorophenyl)piperazine-1-carbonyl)-*N*-(1-(4-cyanobenzyl)pyrrolidin-3-yl)picolinamide;

N-(1-(4-chlorobenzyl)pyrrolidin-3-yl)-5-(4-(4-chlorophenyl)piperazine-1-carbonyl)picolinamide; or

5-(4-(4-chlorophenyl)piperazine-1-carbonyl)-*N*-(1-(4-(trifluoromethyl)benzyl)pyrrolidin-3-yl)picolinamide.

37. A pharmaceutical composition comprising:

at least one pharmaceutically acceptable carrier, diluent or excipient; and

a compound according to any of claims 1-36 or a pharmaceutically acceptable salt, prodrug or *N*-oxide thereof.

38. A compound, pharmaceutically acceptable salt, prodrug or *N*-oxide according to any of claims 1-36, or an effective amount of a composition according to claim 37 for use in activating the AMPK pathway in a cell.

39. A compound, pharmaceutically acceptable salt, prodrug or *N*-oxide according to any of claims 1-36, or an effective amount of a composition according to claim 37 for use in increasing fatty acid oxidation in a cell.

40. A compound, pharmaceutically acceptable salt, prodrug or *N*-oxide according to any of claims 1-36, or an effective amount of a composition according to claim 37 for use in decreasing glycogen concentration in a cell.

41. A compound, pharmaceutically acceptable salt, prodrug or *N*-oxide according to any of claims 1-36, or an effective amount of a composition according to claim 37 for use in increasing glucose uptake in a cell.

42. A compound, pharmaceutically acceptable salt, prodrug or *N*-oxide according to any of claims 1-36, or an effective amount of a composition according to claim 37 for use in reducing triglyceride levels in a subject.

43. A compound, pharmaceutically acceptable salt, prodrug or *N*-oxide according to any of claims 1-36, or an effective amount of a composition according to claim 37 for use in treating type II diabetes in a subject.

44. A compound, pharmaceutically acceptable salt, prodrug or *N*-oxide according to any of claims 1-36, or an effective amount of a composition according to claim 37 for use in treating or preventing atherosclerosis or cardiovascular disease in a subject.

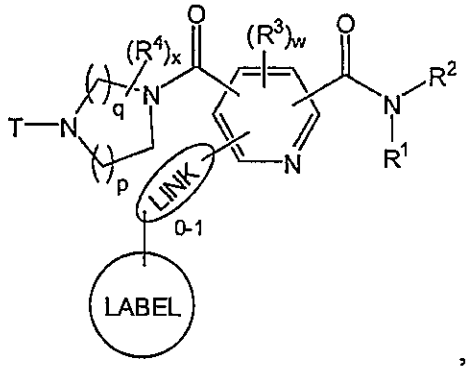
45. A compound, pharmaceutically acceptable salt, prodrug or *N*-oxide according to any of claims 1-36, or an effective amount of a composition according to claim 37 for use in up-regulating ceramidase function in a cell.

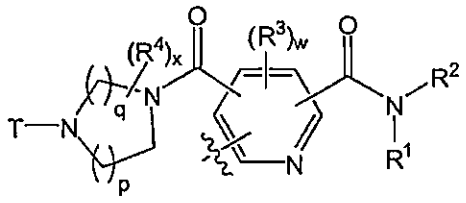
46. A compound, pharmaceutically acceptable salt, prodrug or *N*-oxide according to any of claims 1-36, or an effective amount of a composition according to claim 37 for use in decreasing ceramide concentration in a cell.

47. A compound, pharmaceutically acceptable salt, prodrug or *N*-oxide according to any of claims 1-36, or an effective amount of a composition according to claim 37 for use in treating or preventing a disorder in which cell proliferation is deficient or desired in a subject.

48. A compound, pharmaceutically acceptable salt, prodrug or *N*-oxide according to any of claims 1-36, or an effective amount of a composition according to claim 37 for use in treating or preventing a disease linked to elevated ceramide levels in a subject.

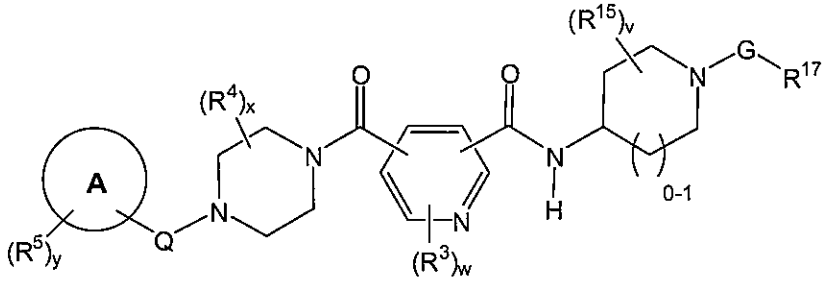
49. A labeled conjugate having the structural formula



in which the "LINK" moiety is a linker and is optional, and the "LABEL" moiety is a labeling agent, and the  moiety is as described in any of claims 1-34.

CLAIMS:

1. A compound having the structural formula



or a pharmaceutically acceptable salt, or *N*-oxide thereof, wherein

each R^3 is independently selected from -(C_1-C_3 alkyl), -(C_1-C_3 haloalkyl), -(C_0-C_3 alkyl)-L-R^7, -(C_0-C_3 alkyl)-NR^8R^9, -(C_0-C_3 alkyl)-OR^{10}, -(C_0-C_3 alkyl)-$C(O)R^{10}$, -(C_0-C_3 alkyl)-$S(O)_{0-2}R^{10}$, -halogen, -NO_2 and -CN;

w is 0, 1 or 2;

each R^4 is independently selected from -(C_1-C_3 alkyl), -(C_1-C_3 haloalkyl), -(C_0-C_3 alkyl)-L-R^7, -(C_0-C_3 alkyl)-NR^8R^9, -(C_0-C_3 alkyl)-OR^{10}, -(C_0-C_3 alkyl)-$C(O)R^{10}$, -(C_0-C_3 alkyl)-$S(O)_{0-2}R^{10}$, -halogen, -NO_2 and -CN, and two R^4 on the same carbon optionally combine to form oxo;

x is 0, 1 or 2;

Q is -CH_2-; a single bond; -$S(O)_2$-; -C(O)-; or -$CH(CH_3)$-;

the ring system denoted by "A" is monocyclic heteroaryl or phenyl;

each R^5 is independently selected from -(C_1-C_3 alkyl), -(C_1-C_3 haloalkyl), -(C_0-C_3 alkyl)-L-R^7, -(C_0-C_3 alkyl)-NR^8R^9, -(C_0-C_3 alkyl)-OR^{10}, -(C_0-C_3 alkyl)-$C(O)R^{10}$, -(C_0-C_3 alkyl)-$S(O)_{0-2}R^{10}$, -halogen, -NO_2 and -CN; and

y is 0, 1, 2, 3 or 4;

each R^{15} is independently selected -(C_1-C_3 alkyl), -(C_1-C_3 haloalkyl), -(C_0-C_3 alkyl)-L-R^7, -(C_0-C_3 alkyl)-NR^8R^9, -(C_0-C_3 alkyl)-OR^{10}, -(C_0-C_3 alkyl)-$C(O)R^{10}$, -(C_0-C_3 alkyl)-$S(O)_{0-2}R^{10}$, -halogen, -NO_2 and -CN and two R^{15} on the same carbon optionally combine to form oxo; and

v is 0, 1 or 2;

G is -CH_2-; a single bond; -$S(O)_2$-; -C(O)-; or -$CH(CH_3)$-;

R^{17} is phenyl or pyridyl, substituted with 0, 1, 2 or 3 substituents independently selected from -(C_1-C_3 alkyl), -(C_1-C_3 haloalkyl), -(C_0-C_3 alkyl)-L-R^7, -(C_0-C_3 alkyl)-NR^8R^9, -(C_0-C_3 alkyl)-OR^{10}, -(C_0-C_3 alkyl)-$C(O)R^{10}$, -(C_0-C_3 alkyl)-$S(O)_{0-2}R^{10}$, -halogen, -NO_2 and -CN, in which

each L is independently selected from -$NR^9C(O)O$-, -$OC(O)NR^9$-, -$NR^9C(O)$-NR^9-, -$NR^9C(O)S$-, -$SC(O)NR^9$-, -$NR^9C(O)$-, -$C(O)$-NR^9-, -$NR^9C(S)O$-, -$OC(S)NR^9$-, -$NR^9C(S)$-NR^9-, -$NR^9C(S)S$-, -$SC(S)NR^9$-, -$NR^9C(S)$-, -$C(S)NR^9$-, -$SC(O)NR^9$-, -$NR^9C(S)$-, -$S(O)_{0-2}$-, -C(O)O, -OC(O)-, -C(S)O-, -OC(S)-, -C(O)S-, -SC(O)-, -C(S)S-, -SC(S)-, -OC(O)O-, -SC(O)O-, -OC(O)S-, -SC(S)O-, -OC(S)S-, -$NR^9C(NR^2)NR^9$-, -NR^9SO_2-, -SO_2NR^9- and -$NR^9SO_2NR^9$-,

each R^7, R^8 and R^{10} is independently selected from H, -(C_1-C_2 alkyl), -(C_1-C_2 haloalkyl), -(C_0-C_2 alkyl)-L-(C_0-C_2 alkyl), -(C_0-C_2 alkyl)-NR^9(C_0-C_2 alkyl), -(C_0-C_2 alkyl)-O-(C_0-C_2 alkyl), -(C_0-C_2 alkyl)-C(O)-(C_0-C_2 alkyl) and -(C_0-C_2 alkyl)-$S(O)_{0-2}$-(C_0-C_2 alkyl), and

each R^9 is independently selected from -H, -(C_1-C_4 alkyl), -C(O)-(C_1-C_4 alkyl), -C(O)O-(C_1-C_4 alkyl)

and wherein each alkyl is saturated.

2. A compound according to claim 1, wherein Q is -CH_2-.

3. A compound according to claim 1, wherein Q is a single bond.

4. A compound according to any of claims 1-3, wherein y is 0.

5. A compound according to any of claims 1-3, wherein y is 1.

6. A compound according to any of claims 1-3, wherein y is not zero and at least one R^5 is halo, cyano, -(C_1-C_3 haloalkyl), -O-(C_1-C_2 haloalkyl), -(C_1-C_3 alkyl), -O-(C_1-C_2 alkyl), -C(O)-(C_0-C_2 alkyl), -C(O)O-(C_0-C_2 alkyl), -C(O)N(C_0-C_4 alkyl)(C_0-C_2 alkyl) or NO_2.

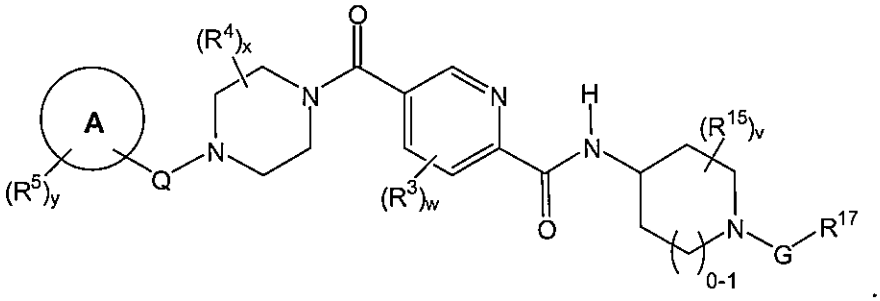
7. A compound according to any of claims 1-3, 5 and 6, wherein each R^5 is -(C_1-C_3 haloalkyl), -halogen or -CN.

8. A compound according to any of claims 1-7, wherein the ring system denoted by "A" is a phenyl.

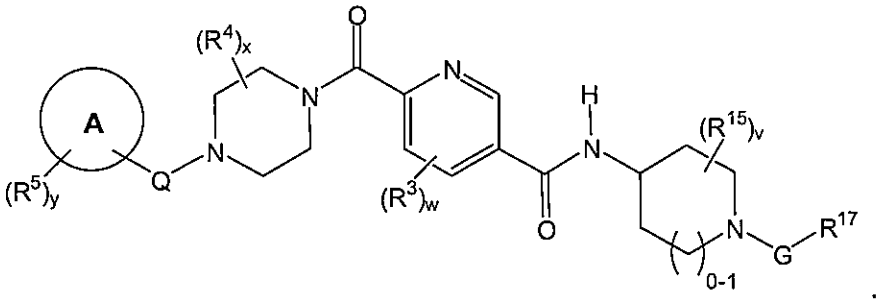
9. A compound according to any of claims 1-7, wherein the ring system denoted by "A" is a monocyclic heteroaryl.

10. A compound according to any of claims 1-7, wherein the ring system denoted by "A" is a pyridyl, a thienyl, or a furanyl.

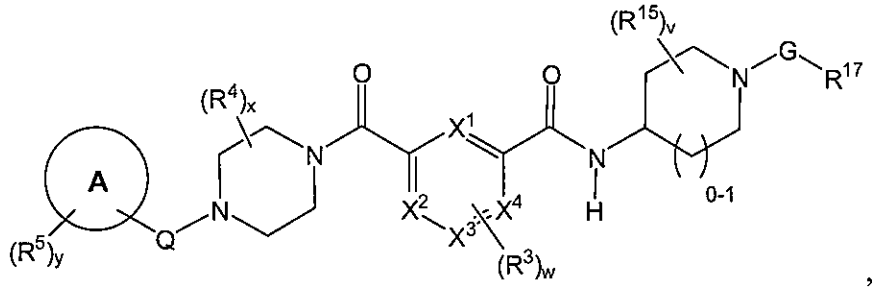
11. A compound according to any of claims 1-10, wherein the compound has the structural formula



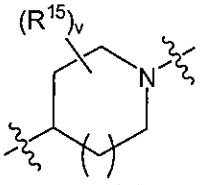
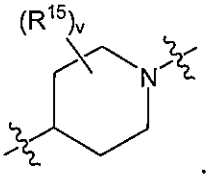
12. A compound according to any of claims 1-10, wherein the compound has the structural formula

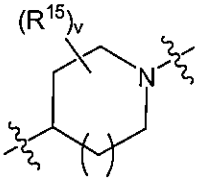
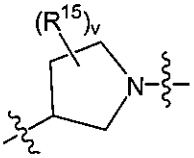


13. A compound according to any of claims 1-10, wherein the compound has the structural formula



in which one of X^1, X^2, X^3 and X^4 is N, and the others are carbons.

14. A compound according to any of claims 1-13 wherein the  moiety is .

15. A compound according to any of claims 1-13 wherein the  moiety is .

16. A compound according to any of claims 1-15, wherein w is 0.

17. A compound according to any of claims 1-15, wherein w is at least 1 and at least one R^3 is selected from the group consisting of halo, cyano, -(C_1-C_3 fluoroalkyl), -O-(C_1-C_2 fluoroalkyl), -C(O)-(C_0-C_2 alkyl), -C(O)O-(C_0-C_2 alkyl), -C(O)N(C_0-C_4 alkyl)(C_0-C_2 alkyl), -$S(O)_2$O-(C_0-C_2 alkyl) and NO_2.

18. A compound according to any of claims 1-15 or 17, wherein each R^3 is halo or -(C_1-C_3 alkyl).

19. A compound according to any of claims 1-18 wherein x is 0.

20. A compound according to any of claims 1-19, wherein R^{17} is phenyl substituted with 0, 1, 2 or 3 substituents independently selected from -(C_1-C_3 alkyl), -(C_1-C_3 haloalkyl), -(C_0-C_3 alkyl)-L-R^7, -(C_0-C_3 alkyl)-NR^8R^9, -(C_0-C_3 alkyl)-OR^{10}, -(C_0-C_3 alkyl)-C(O)R^{10}, -(C_0-C_3 alkyl)-$S(O)_{0-2}R^{10}$, -halogen, -NO_2 and -CN.

21. A compound according to any of claims 1-19, wherein R^{17} is phenyl substituted with 0, 1, 2 or 3 substituents independently selected from -(C_1-C_3 haloalkyl), -halogen and -CN.

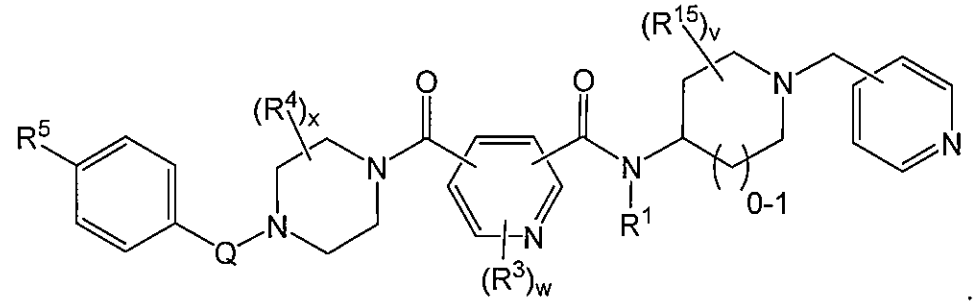
22. A compound according to any of claims 1-19 wherein R^{17} is pyridyl.

23. A compound according to any of claims 1-22 wherein G is -CH_2-.

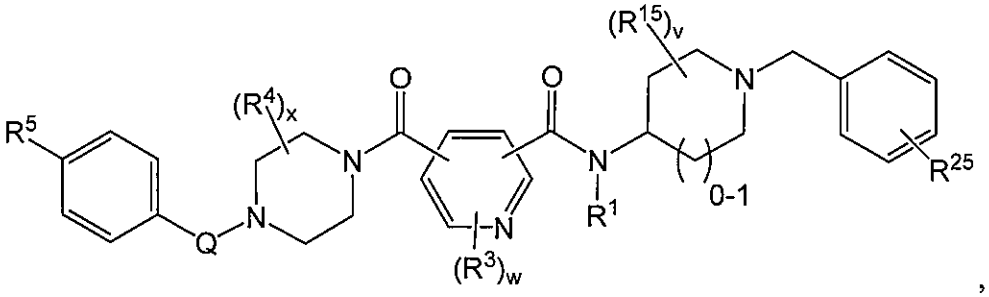
24. A compound according to any of claims 1-22 wherein G is -C(O)- or -$S(O)_2$-.

25. A compound according to any of claims 1-22, wherein v is 0.

26. A compound according to any of claims 1-3 and 5-25, having the structural formula

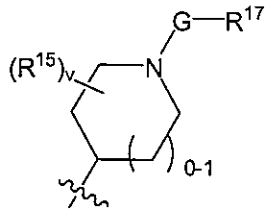


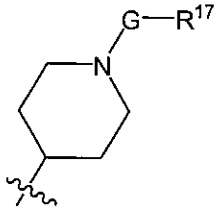
27. A compound according to any of claims 1-3 and 5-25, having the structural formula



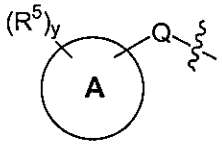
in which R^{25} is selected from halo, cyano, -(C_1-C_3 haloalkyl), -O-(C_1-C_2 haloalkyl), -(C_1-C_3 alkyl), -O-(C_1-C_2 alkyl), -C(O)-(C_0-C_2 alkyl), -C(O)O-(C_0-C_2 alkyl), -C(O)N(C_0-C_4 alkyl)(C_0-C_2 alkyl) and NO_2.

28. A compound according to any of claims 1-25, wherein Q is -C(O)- or -$S(O)_2$-.

29. A compound according to any of claims 1-14 and 16-28, wherein the 

moiety has the structure 

, in which G is -CH_2-, -$CH(CH_3)$-, -C(O)- or -$S(O)_2$-.

30. A compound according to any of claims 1-29, wherein the 

moiety is *p*-(trifluoromethyl)phenyl, *p*-fluorophenyl or *p*-cyanophenyl.

31. A compound according to any of claims 1-16 and 18-30, wherein w is 0, x is 0 and v is 0.

32. A compound according to any of claims 1-15 and 18-31, wherein

each R^3 is independently selected from -(C_1-C_3 alkyl), -(C_1-C_3 haloalkyl) and -halogen;

w is 0 or 1;

each R^4 is independently selected from, -halogen, and two R^4 on the same carbon optionally combine to form oxo;

the ring system denoted by "A" is phenyl; and

each R^{15} is independently selected from -halogen, and two R^{15} on the same carbon optionally combine to form oxo.

33. A compound according to claim 1, wherein the compound is

5-(4-(4-cyanobenzyl)piperazine-1-carbonyl)-*N*-(1-(4-cyanobenzyl)piperidin-4-yl)picolinamide;

N-(1-(4-cyanobenzyl)piperidin-4-yl)-5-(4-(4-fluorobenzyl)piperazine-1-carbonyl)picolinamide;

N-(1-(4-cyanobenzyl)piperidin-4-yl)-5-(4-(4-(trifluoromethyl)benzyl)piperazine-1-carbonyl)picolinamide

(S)-5-(4-(4-chlorophenyl)piperazine-1-carbonyl)-*N*-(1-(4-fluorobenzyl)pyrrolidin-3-yl)picolinamide;

(S)-5-(4-(4-chlorophenyl)piperazine-1-carbonyl)-*N*-(1-(pyridin-4-ylmethyl)pyrrolidin-3-yl)picolinamide;

(S)-5-(4-(4-chlorophenyl)piperazine-1-carbonyl)-*N*-(1-(4-cyanobenzyl)pyrrolidin-3-yl)picolinamide;

N-(1-(4-chlorobenzyl)pyrrolidin-3-yl)-5-(4-(4-chlorophenyl)piperazine-1-carbonyl)picolinamide; or

5-(4-(4-chlorophenyl)piperazine-1-carbonyl)-*N*-(1-(4-(trifluoromethyl)benzyl)pyrrolidin-3-yl)picolinamide.

34. A pharmaceutical composition comprising:

at least one pharmaceutically acceptable carrier, diluent or excipient; and

a compound according to any of claims 1-33 or a pharmaceutically acceptable salt or *N*-oxide thereof.

35. A compound, pharmaceutically acceptable salt or *N*-oxide according to any of claims 1-33, or an effective amount of a composition according to claim 34 for use in activating the AMPK pathway in a cell.

36. A compound, pharmaceutically acceptable salt or *N*-oxide according to any of claims 1-33, or an effective amount of a composition according to claim 34 for use in increasing fatty acid oxidation in a cell.

37. A compound, pharmaceutically acceptable salt or *N*-oxide according to any of claims 1-33, or an effective amount of a composition according to claim 34 for use in decreasing glycogen concentration in a cell.

38. A compound, pharmaceutically acceptable salt or *N*-oxide according to any of claims 1-33, or an effective amount of a composition according to claim 34 for use in increasing glucose uptake in a cell.

39. A compound, pharmaceutically acceptable salt or *N*-oxide according to any of claims 1-33, or an effective amount of a composition according to claim 34 for use in reducing triglyceride levels in a subject.

40. A compound, pharmaceutically acceptable salt or *N*-oxide according to any of claims 1-33, or an effective amount of a composition according to claim 34 for use in treating type II diabetes in a subject.

41. A compound, pharmaceutically acceptable salt or *N*-oxide according to any of claims 1-33, or an effective amount of a composition according to claim 34 for use in treating or preventing atherosclerosis or cardiovascular disease in a subject.

42. A compound, pharmaceutically acceptable salt or *N*-oxide according to any of claims 1-33, or an effective amount of a composition according to claim 34 for use in up-regulating ceramidase function in a cell.

43. A compound, pharmaceutically acceptable salt or *N*-oxide according to any of claims 1-33, or an effective amount of a composition according to claim 34 for use in decreasing ceramide concentration in a cell.

44. A compound, pharmaceutically acceptable salt or *N*-oxide according to any of claims 1-33, or an effective amount of a composition according to claim 34 for use in treating or preventing a disorder in which cell proliferation is deficient or desired in a subject.

45. A compound, pharmaceutically acceptable salt or *N*-oxide according to any of claims 1-33, or an effective amount of a composition according to claim 34 for use in treating or preventing a disease linked to elevated ceramide levels in a subject.