(Pondimin™) and dexfenfluramine (Redux™) have been reported to decrease food intake and body weight over a prolonged period (greater than 6 months). However, both products were withdrawn after reports of preliminary evidence of heart valve abnormalities associated with their use. Accordingly, there is a need for the development of a safer anti-obesity agent.

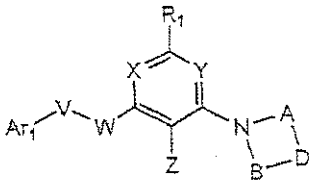
Obesity considerably increases the risk of developing cardiovascular diseases as well. Coronary insufficiency, atheromatous disease, and cardiac insufficiency are at the forefront of the cardiovascular complication induced by obesity. It is estimated that if the entire population had an ideal weight, the risk of coronary insufficiency would decrease by 25% and the risk of cardiac insufficiency and of cerebral vascular accidents by 35%. The incidence of coronary diseases is doubled in subjects less than 50 years of age who are 30% overweight. The diabetes patient faces a 30% reduced lifespan. After age 45, people with diabetes are about three times more likely than people without diabetes to have significant heart disease and up to five times more likely to have a stroke. These findings emphasize the inter-relations between risks factors for NIDDM and coronary heart disease and the potential value of an integrated approach to the prevention of these conditions based on the prevention of these conditions based on the prevention of obesity (Perry, I. J., et al., *BMJ* 310, 560-564 (1995)).

Diabetes has also been implicated in the development of kidney disease, eye diseases and nervous-system problems. Kidney disease, also called nephropathy, occurs when the kidney's "filter mechanism" is damaged and protein leaks into urine in excessive amounts and eventually the kidney fails. Diabetes is also a leading cause of damage to the retina at the back of the eye and increases risk of cataracts and glaucoma. Finally, diabetes is associated with nerve damage, especially in the legs and feet, which interferes with the ability to sense pain and contributes to serious infections. Taken together, diabetes complications are one of the nation's leading causes of death.

SUMMARY ~~OF THE INVENTION~~

The present disclosure~~invention~~ is drawn to compounds, which bind to and modulate the activity of a GPCR referred to herein as **RUP3**, and uses thereof. The term **RUP3**, as used herein, includes the human sequences found in GeneBank accession number XM_066873, naturally-occurring allelic variants, mammalian orthologs, and recombinant mutants thereof. A preferred human **RUP3** for use in screening and testing of the compounds of the disclosure~~invention~~ is provided in the nucleotide sequence of Seq. ID.No:1 and the corresponding amino acid sequence in Seq. ID.No:2.

In one aspect, there is provided a compound of Formula (**Ia**):



(**Ia**)

or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein:

A and B are independently C_{1-3} alkylene optionally substituted with 1 to 4 methyl groups;

D is CR_2R_3 or N-R_2;

V is absent;

W is NR_4 or O;

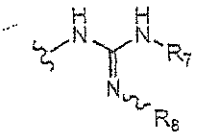
X is N;

Y is N;

Z is selected from the group consisting of C_{1-5} acyl, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, amino, cyano, C_{4-8} diacylamino, C_{2-6} dialkylsulfonamide, formyl, halogen, heterocyclic, and nitro wherein C_{1-8} alkyl and C_{1-5} acyl are each optionally substituted with 1 or 2 groups selected from the group consisting of C_{2-4} dialkylamino, hydroxy, and halogen; or

Z is selected from the group consisting of nitro, amino, formyl, $NHC(O)CF_3$, Br, $NHC(O)CH_3$, $N(C(O)CH_3)_2$, $N(S(O)_2CH_3)_2$, CH_3, [1,3]dioxolan-2-yl, CH_2OH, $CH_2N(CH_3)_2$, and $C(O)CH_3$; or

Z is a group of Formula (A):



(A)

wherein:

R_7 is H, C_{1-8} alkyl or C_{3-6} cycloalkyl; and

R_8 is H, nitro or nitrile;

Ar_1 is aryl or heteroaryl wherein each is optionally substituted with R_9-R_{13};

wherein the heteroaryl of Ar_1 is selected from the group consisting of pyridyl, benzofuranyl, pyrazinyl, pyridazinyl, pyrimidinyl, triazinyl, quinoline, benzoxazole, benzothiazole, 1H-benzimidazole, isoquinoline, quinazoline, quinoxaline, 1H-imidazolyl, [1,2,4]triazolyl, [1,2,3]triazolyl, pyrrolyl, pyrazolyl, 1H-pyrazolyl, imidazolyl, oxazolyl, [1,3,4]oxadiazolyl, [1,3,4]thiadiazolyl, [1,2,4]oxadiazolyl, [1,2,4]thiadiazolyl, tetrazolyl, 1,3-dioxo-1,3-dihydro-isoindolyl, and [1,2,3]thiadiazol-4-yl;

R_1 is selected from the group consisting of H, C_{1-4} alkoxy, C_{1-8} alkyl, C_{2-6} alkynyl, amino, C_{3-6} cycloalkyl, and C_{1-4} haloalkyl;

R_2 is selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, C_{3-6}-cycloalkyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, hydroxyl, CH_2OCH_2-cyclopropyl, CH_2OCH_2-cyclobutyl, CH_2OCH_2-cyclopentyl, CH_2OCH_2-cyclohexyl, $CH_2OCH_2CH_2$-cyclopropyl, $CH_2OCH_2CH_2$-cyclobutyl, $CH_2OCH_2CH_2$-cyclopentyl, $CH_2OCH_2CH_2$-cyclohexyl, $CH_2CH_2OCH_2$-cyclopropyl, $CH_2CH_2OCH_2$-cyclobutyl, $CH_2CH_2OCH_2$-cyclopentyl, $CH_2CH_2OCH_2$-cyclohexyl, $CH_2CH_2OCH_2CH_2$-cyclopropyl, $CH_2CH_2OCH_2CH_2$-cyclobutyl, $CH_2CH_2OCH_2CH_2$-cyclopentyl, and $CH_2CH_2OCH_2CH_2$-cyclohexyl; or

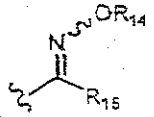
R_2 is C_{1-8} alkyl or heteroaryl, each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylsulfonyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, C_{3-6}-cycloalkyl, C_{3-6}-cycloalkyl-C_{1-3}-alkylene, C_{3-6}-cycloalkyl-C_{1-3}-heteroalkylene, and hydroxyl; or

R_2 is C_{1-8} alkyl, heteroaryl or phenyl each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl-C_{1-3}-heteroalkylene, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{1-4}

dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, halogen, heterocyclic, hydroxyl, hydroxylamino and nitro; or

R_2 is -Ar_2-Ar_3 wherein Ar_2 and Ar_3 are independently aryl or heteroaryl each optionally substituted with 1 to 5 substituents selected from the group consisting of H, C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl, C_{2-6} dialkylcarboxamide, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, hydroxyl and nitro; or

R_2 is a group of Formula (B):

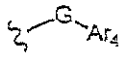


(B)

wherein:

R_{14} is C_{1-8} alkyl or C_{3-6} cycloalkyl; and R_{15} is F, Cl, Br or CN; or

R_2 is a group of Formula (C):



(C)

wherein:

G is C=O, $CR_{16}R_{17}$, O, S, S(O), or $S(O)_2$;

wherein

R_{16} and R_{17} are independently H or C_{1-8} alkyl; and

Ar_4 is phenyl or heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl, C_{2-6} dialkylcarboxamide, C_{1-4}

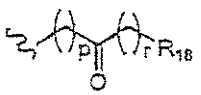
dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, halogen, heteroaryl, hydroxyl, hydroxylamino and nitro;

R_3 is H, C_{1-8} alkyl, C_{1-4} alkoxy, halogen or hydroxyl;

R_4 is H or C_{1-8} alkyl;

R_9 is selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, amino, arylsulfonyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylsulfonamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, heterocyclic, heterocyclicsulfonyl, heteroaryl, hydroxyl, nitro, C_{4-7} oxo-cycloalkyl, phenoxy, phenyl, sulfonamide and sulfonic acid, and wherein C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylsulfonamide, alkylsulfonyl, arylsulfonyl, heteroaryl, phenoxy and phenyl are each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, heteroaryl, heterocyclic, hydroxyl, nitro and phenyl; or

R_9 is a group of Formula (D):



(D)

wherein:

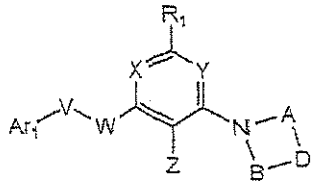
"p" and "r" are independently 0, 1, 2 or 3; and

R_{18} is H, C_{1-5} acyl, C_{2-6} alkenyl, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, heteroaryl or phenyl, and wherein the heteroaryl and phenyl are each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-4} alkoxy, amino, C_{1-4} alkylamino, C_{2-6} alkynyl, C_{2-8} dialkylamino, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl and hydroxyl; and

R_{10}-R_{13} are independently selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, hydroxyl and nitro; or

two adjacent R_{10}-R_{11} groups together with Ar_1 form a 5, 6 or 7 membered cycloalkyl, cycloalkenyl or heterocyclic group wherein the 5, 6 or 7 membered group is optionally substituted with halogen.

In another aspect, there is provided a compound of Formula (**Ia**):



(**Ia**)

or a pharmaceutically acceptable salt or hydrate thereof;

wherein:

A and B are independently C_{1-3} alkylene optionally substituted with 1 to 4 methyl groups;

D is CR_2R_3 or $N\text{-}R_2$;

V is absent;

W is NR_4 or O;

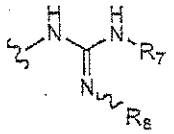
X is N;

Y is N;

Z is selected from the group consisting of C_{1-5} acyl, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, amino, cyano, C_{4-8} diacylamino, C_{2-6} dialkylsulfonamide, formyl, halogen, heterocyclic, and nitro wherein C_{1-8} alkyl and C_{1-5} acyl are each optionally substituted with 1 or 2 groups selected from the group consisting of C_{2-4} dialkylamino, hydroxy, and halogen; or

Z is selected from the group consisting of nitro, amino, formyl, $NHC(O)CF_3$, Br, $NHC(O)CH_3$, $N(C(O)CH_3)_2$, $N(S(O)_2CH_3)_2$, CH_3, [1,3]dioxolan-2-yl, CH_2OH, $CH_2N(CH_3)_2$, and $C(O)CH_3$; or

Z is a group of Formula (A):



(A)

wherein:

R_7 is H, C_{1-8} alkyl or C_{3-6} cycloalkyl; and

R_8 is H, nitro or nitrile;

Ar_1 is aryl or heteroaryl wherein each is optionally substituted with R_9-R_{13};

wherein the heteroaryl of Ar_1 is selected from the group consisting of pyridyl, benzofuranyl, pyrazinyl, pyridazinyl, pyrimidinyl, triazinyl, quinoline, benzoxazole, benzothiazole, 1H-benzimidazole, isoquinoline, quinazoline, quinoxaline, 1H-imidazolyl, [1,2,4]triazolyl, [1,2,3]triazolyl, pyrrolyl, pyrazolyl, 1H-pyrazolyl, imidazolyl, oxazolyl, [1,3,4]oxadiazolyl, [1,3,4]thiadiazolyl, [1,2,4]oxadiazolyl, [1,2,4]thiadiazolyl, tetrazolyl, 1,3-dioxo-1,3-dihydro-isoindolyl, and [1,2,3]thiadiazol-4-yl;

R_1 is selected from the group consisting of H, C_{1-4} alkoxy, C_{1-8} alkyl, C_{2-6} alkynyl, amino, C_{3-6} cycloalkyl, and C_{1-4} haloalkyl;

R_2 is selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, C_{3-6}-cycloalkyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, hydroxyl, CH_2OCH_2-cyclopropyl, CH_2OCH_2-cyclobutyl, CH_2OCH_2-cyclopentyl, CH_2OCH_2-cyclohexyl, $CH_2OCH_2CH_2$-cyclopropyl, $CH_2OCH_2CH_2$-cyclobutyl, $CH_2OCH_2CH_2$-cyclopentyl, $CH_2OCH_2CH_2$-cyclohexyl, $CH_2CH_2OCH_2$-cyclopropyl, $CH_2CH_2OCH_2$-cyclobutyl, $CH_2CH_2OCH_2$-cyclopentyl, $CH_2CH_2OCH_2$-cyclohexyl, $CH_2CH_2OCH_2CH_2$-cyclopropyl, $CH_2CH_2OCH_2CH_2$-cyclobutyl, $CH_2CH_2OCH_2CH_2$-cyclopentyl, and $CH_2CH_2OCH_2CH_2$-cyclohexyl; or

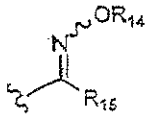
R_2 is C_{1-8} alkyl or heteroaryl, each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylsulfonyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, C_{3-6}-cycloalkyl, C_{3-6}-cycloalkyl-C_{1-3}-alkylene, C_{3-6}-cycloalkyl-C_{1-3}-heteroalkylene, and hydroxyl; or

R_2 is C_{1-8} alkyl, heteroaryl or phenyl each optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl-

C_{1-3}-heteroalkylene, C_{2-8} dialkylamino, C_{2-6} dialkylcarboxamide, C_{1-4} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, halogen, heterocyclic, hydroxyl, hydroxylamino and nitro; or

R_2 is -Ar_2-Ar_3 wherein Ar_2 and Ar_3 are independently aryl or heteroaryl each optionally substituted with 1 to 5 substituents selected from the group consisting of H, C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6}-cycloalkyl, C_{2-6} dialkylcarboxamide, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, halogen, hydroxyl and nitro; or

R_2 is a group of Formula (B):

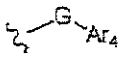


(B)

wherein:

R_{14} is C_{1-8} alkyl or C_{3-6} cycloalkyl; and R_{15} is F, Cl, Br or CN; or

R_2 is a group of Formula (C):



(C)

wherein:

G is C=O, $CR_{16}R_{17}$, O, S, S(O), or $S(O)_2$;

wherein

R_{16} and R_{17} are independently H or C_{1-8} alkyl; and

Ar_4 is phenyl or heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{1-4} alkylthiocarboxamide, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylthioureyl, C_{1-4} alkylureyl, amino, carbo-C_{1-6}-alkoxy, carboxamide, carboxy,

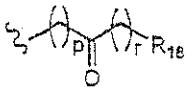
cyano, C_{3-6}-cycloalkyl, C_{2-6} dialkylcarboxamide, C_{1-4} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, halogen, heteroaryl, hydroxyl, hydroxylamino and nitro;

R_3 is H, C_{1-8} alkyl, C_{1-4} alkoxy, halogen or hydroxyl;

R_4 is H or C_{1-8} alkyl;

R_9 is selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, amino, arylsulfonyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylsulfonamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, heterocyclic, heterocyclicsulfonyl, heteroaryl, hydroxyl, nitro, C_{4-7} oxo-cycloalkyl, phenoxy, phenyl, sulfonamide and sulfonic acid, and wherein C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylsulfonamide, alkylsulfonyl, arylsulfonyl, heteroaryl, phenoxy and phenyl are each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, heteroaryl, heterocyclic, hydroxyl, nitro and phenyl; or

R_9 is a group of Formula (D):



(D)

wherein:

"p" and "r" are independently 0, 1, 2 or 3; and

R_{18} is H, C_{1-5} acyl, C_{2-6} alkenyl, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, heteroaryl or phenyl, and wherein the heteroaryl and phenyl are each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-4} alkoxy, amino, C_{1-4} alkylamino, C_{2-6} alkynyl, C_{2-8} dialkylamino, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl and hydroxyl; and

R_{10}-R_{13} are independently selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, hydroxyl and nitro; or

two adjacent R_{10}-R_{11} groups together with Ar_1 form a 5, 6 or 7 membered cycloalkyl, cycloalkenyl or heterocyclic group wherein the 5, 6 or 7 membered group is optionally substituted with halogen.

One embodiment~~aspect~~ of the present disclosure~~invention~~ encompasses 1,2,3-trisubstituted aryl and heteroaryl derivatives as shown in Formula (**Ia**):

wherein:

"p" and "r" are independently 0, 1, 2 or 3; and

R_{18} is H, C_{1-5} acyl, C_{2-6} alkenyl, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, heteroaryl or phenyl, and wherein the heteroaryl and phenyl are each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-4} alkoxy, amino, C_{1-4} alkylamino, C_{2-6} alkynyl, C_{2-8} dialkylamino, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl and hydroxyl; and

R_{10}-R_{13} are independently selected form the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, hydroxyl and nitro; or two adjacent R_{10}-R_{11} groups together with Ar_1 form a 5, 6 or 7 membered cycloalkyl, cycloalkenyl or heterocyclic group wherein the 5, 6 or 7 membered group is optionally substituted with halogen.

In one aspect, there is provided a pharmaceutical composition comprising at least one compound or pharmaceutically acceptable salt, hydrate or solvate thereof as defined herein and a pharmaceutically acceptable carrier.

Some embodiments of the present ~~invention~~disclosure include pharmaceutical compositions comprising at least one compound of the present ~~invention~~disclosure and a pharmaceutically acceptable carrier.

In one aspect, there is provided the method of producing a pharmaceutical composition comprising admixing at least one compound or pharmaceutically acceptable salt, hydrate or solvate thereof as defined herein and a pharmaceutically acceptable carrier.

Some embodiments of the present ~~invention~~disclosure include methods for prophylaxis or treatment of a metabolic disorder in an individual comprising administering to the individual a therapeutically effective amount of a compound of the present ~~invention~~disclosure or a pharmaceutical composition thereof.

Some embodiments of the present ~~invention~~disclosure include methods of controlling or decreasing weight gain of an individual comprising administering to the individual a therapeutically effective amount of a compound of the present ~~invention~~disclosure or pharmaceutical composition thereof.

Some embodiments of the present ~~invention~~disclosure include methods of modulating a **RUP3** receptor comprising contacting the receptor with a compound of the present ~~invention~~disclosure.

Some embodiments of the present ~~invention~~disclosure include methods of modulating a **RUP3** receptor in an individual comprising contacting the receptor with a compound of the present ~~invention~~disclosure. In some embodiments, the compound is an agonist. In some embodiments, the compound is an inverse agonist.

Some embodiments of the present ~~invention~~disclosure include methods of modulating a **RUP3** receptor in an individual comprising contacting the receptor with a compound of the present

~~invention~~disclosure wherein the modulation of the **RUP3** receptor is prophylaxis or treatment of a metabolic disorder.

Some embodiments of the present ~~invention~~disclosure include methods of modulating a **RUP3** receptor in an individual comprising contacting the receptor with a compound of the present ~~invention~~disclosure wherein the modulation of the **RUP3** receptor controls or reduces weight gain of the individual.

Some embodiments of the present ~~invention~~disclosure include the use of compounds of the present ~~invention~~disclosure for production of a medicament for use in prophylaxis or treatment of a metabolic disorder.

Some embodiments of the present ~~invention~~disclosure include the use of compounds of the present ~~invention~~disclosure for production of a medicament for use in controlling or decreasing weight gain in an individual.

In one aspect, there is provided the use of a compound or pharmaceutically acceptable salt, hydrate or solvate thereof as defined herein or a pharmaceutically composition thereof in the manufacture of a medicament for treatment of type II diabetes in an individual.

One ~~aspect~~embodiment of the present ~~invention~~disclosure pertains to compounds of the present ~~invention~~disclosure, as described herein, for use in methods of treatment of the human or animal body by therapy.

One ~~aspect~~embodiment of the present ~~invention~~disclosure pertains to compounds of the present ~~invention~~disclosure, as described herein, for use in methods of prophylaxis or treatment of a metabolic disorder of the human or animal body by therapy.

In some embodiments, the metabolic disorder is type I, type II diabetes, inadequate glucose tolerance, insulin resistance, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, dyslipidemia, syndrome X or metabolic syndrome.

One ~~aspect~~embodiment of the present ~~invention~~disclosure pertains to methods of producing a pharmaceutical compositions comprising admixing at least one compound of the present ~~invention~~disclosure and a pharmaceutically acceptable carrier.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A shows RT-PCR analysis of **RUP3** expression in human tissues. A total of twenty-two (22) human tissues were analyzed.

Figure 1B shows the cDNA Dot-Blot analysis of **RUP 3** expression in human tissues.

Figure 1C shows analysis of **RUP3** by RT-PCR with isolated huyman pancreatic islets of Langerhans.

Figure 1D shows analysis of **RUP3** expression with cDNAs of rat origin by RT-PCR.

Figure 2A shows a polyclonal anti-**RUP3** antibody prepared in Rabbits.

Figure 2B shows the expression of **RUP3** in insulin-producing β cells of pancreatic islets.

Figure 3 shows functional activities of **RUP3** *In vitro*.

Figure 4A shows a **RUP3** RNA blot.

cyano, C_{3-6}-cycloalkyl, C_{2-6} dialkylcarboxamide, C_{1-4} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} alkylthioureyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, halogen, heteroaryl, hydroxyl, hydroxylamino and nitro;

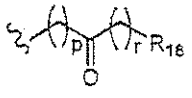
R_3 is H, C_{1-8} alkyl, C_{1-4} alkoxy, halogen or hydroxyl;

R_4 is H or C_{1-8} alkyl;

~~R_5 and R_6 are independently H, C_{1-8} alkyl or halogen;~~

R_9 is selected from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylamino, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, amino, arylsulfonyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylamino, C_{2-6} dialkylcarboxamide, C_{2-6} dialkylsulfonamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, heterocyclic, heterocyclicsulfonyl, heteroaryl, hydroxyl, nitro, C_{4-7} oxo-cycloalkyl, phenoxy, phenyl, sulfonamide and sulfonic acid, and wherein C_{1-5} acyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylsulfonamide, alkylsulfonyl, arylsulfonyl, heteroaryl, phenoxy and phenyl are each optionally substituted with 1 to 5 substituents selected independently from the group consisting of C_{1-5} acyl, C_{1-5} acyloxy, C_{2-6} alkenyl, C_{1-4} alkoxy, C_{1-8} alkyl, C_{1-4} alkylcarboxamide, C_{2-6} alkynyl, C_{1-4} alkylsulfonamide, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, C_{1-4} alkylthio, C_{1-4} alkylureyl, carbo-C_{1-6}-alkoxy, carboxamide, carboxy, cyano, C_{3-6} cycloalkyl, C_{2-6} dialkylcarboxamide, halogen, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl, C_{1-4} haloalkylthio, heteroaryl, heterocyclic, hydroxyl, nitro and phenyl; or

R_9 is a group of Formula (D):



(D)

wherein: