

BOGOTA - COLOMBIA
OFICINA FUNDADA EN 1941
APARTADO AEREO 12304
TEL: 57-1-3264270 57-1-6069700
FAX: 57-1-3264271 57-1-6069701
CABLES: LLOREDA
CALLE 72 No. 5-83 5º. PISO
www.lloredacamacho.com
jllico@lloredacamacho.com

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. _____ S. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-040337- -00001-0000

Fecha: 2008-04-14 16:25:02 Dep. 2020 NUECREACIONES
Folios: 1 PATENTE/11 Eje 379 FASE NACIONAL/11
Art 533 PETICION Folios: 2

Re: P1.-F. HOFFMANN-LA ROCHE AG.-Solicitud de Patente de
Invencción en Fase Nacional PCT para "ALQUIL-PIRIDINAS COMO
INHIBIDORES DE 11-BETA PARA LA DIABETES".-Clase C07D
213/76.-Expediente número 07-040.337.-

1. Me refiero a mi solicitud de patente de 23 de Abril de 2007.
2. De conformidad con lo dispuesto en el Artículo 5.2.12 de la Circular Externa No. 03 de 28 de Abril de 2003, y estando dentro del plazo de seis meses contados desde la fecha de la publicación de la solicitud en la Gaceta de la Propiedad Industrial número **581** de 31 de Octubre de 2007, solicito a ese Despacho proceder a realizar el examen de patentabilidad de la presente invención.
3. Me permito recordar a usted, que tal como se informó en el Petitorio de la invención, la presente solicitud corresponde a Capítulo II.
4. Anexo me permito acompañar recibo número 08-28.388, expedido por la Superintendencia de Industria y Comercio, que acredita el pago de la tasa que dicho examen causa.

Señor Superintendente,

ALICIA LLOREDA RICAURTE

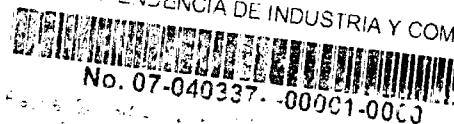
T.P. 53.215

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 28,388
FECHA : ABRIL 8 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LLOREDA Y CIA S. A	CONSIGNACION	BANCO DE BOGOTA	062754387	2756065	08/04/2008	11,999,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		114 PTC CAP-II EXAMEN DE PATENTIBILID	210,000.00
		TOTAL :	\$ 210,000.00

SON: DOSCIENTOS DIEZ MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 07-40337

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **581** DE

FECHA **31 DE OCTUBRE DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL **31 DE ENERO DE 2008**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO X

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
10 September 2004 (10.09.2004)

PCT

(10) International Publication Number
WO 2004/076413 A2

(51) International Patent Classification⁷: C07D

(21) International Application Number:
PCT/US2004/005555

(22) International Filing Date: 23 February 2004 (23.02.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/449,788 24 February 2003 (24.02.2003) US

(71) Applicant (for all designated States except US): ARENA PHARMACEUTICALS, INC. [US/US]; 6166 Nancy Ridge Drive, San Diego, CA 92121-3223 (US).

(72) Inventors; and

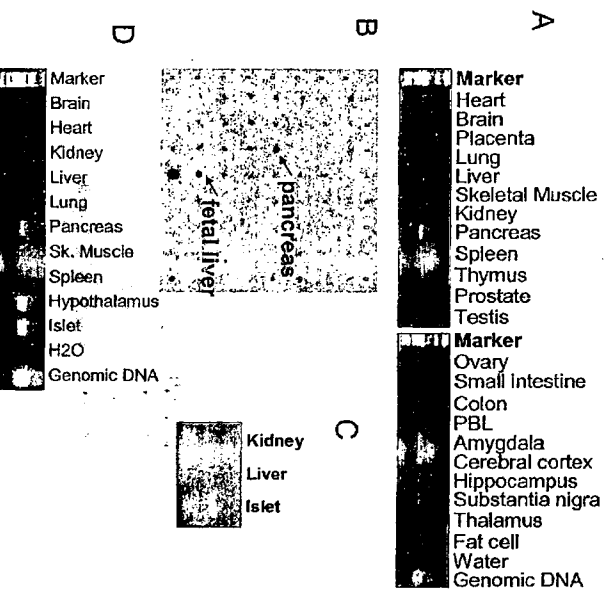
(75) Inventors/Applicants (for US only): JONES, Robert, M. [GB/US]; 10937 Corte luz del Sol, San Diego, CA 92130 (US). SEMPLE, Graeme [GB/US]; 15920 Camino Codorniz, San Diego, CA 92127 (US). CHOI, Jin, Sun, Karoline [US/US]; 9926 Scripps Westview Way, #251, San Diego, CA 92131 (US). XIONG, Yifeng [US/US];

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MY, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, ZW).

[Continued on next page]

(54) Title: SUBSTITUTED ARYL AND HETEROARYL DERIVATIVES AS MODULATORS OF GLUCOSE METABOLISM AND THE PROPHYLAXIS AND TREATMENT OF DISORDERS THEREOF



(57) Abstract: The present invention relates to certain substituted aryl and heteroaryl derivatives as shown in Formula (1a) that are modulators of metabolism. Accordingly, compounds of the present invention are useful in the prophylaxis or treatment of metabolic disorders and complications thereof, such as, diabetes and obesity.

WO 2004/076413 A2

**SUBSTITUTED ARYL AND HETEROARYL DERIVATIVES AS MODULATORS OF
GLUCOSE METABOLISM AND THE PROPHYLAXIS AND TREATMENT OF
DISORDERS THEREOF**

5

FIELD OF THE INVENTION

The present invention relates to certain substituted aryl and heteroaryl derivatives that are modulators of glucose metabolism. Accordingly, compounds of the present invention are useful in the prophylaxis or treatment of metabolic disorders and complications thereof, such as, diabetes and obesity.

10

BACKGROUND OF THE INVENTION

✓ Diabetes mellitus is a serious disease afflicting over 100 million people worldwide. In the United States, there are more than 12 million diabetics, with 600,000 new cases diagnosed each year.

15

Diabetes mellitus is a diagnostic term for a group of disorders characterized by abnormal glucose homeostasis resulting in elevated blood sugar. There are many types of diabetes, but the two most common are Type I (also referred to as insulin-dependent diabetes mellitus or IDDM) and Type II (also referred to as non-insulin-dependent diabetes mellitus or NIDDM).

20

The etiology of the different types of diabetes is not the same; however, everyone with diabetes has two things in common: overproduction of glucose by the liver and little or no ability to move glucose out of the blood into the cells where it becomes the body's primary fuel.

25

People who do not have diabetes rely on insulin, a hormone made in the pancreas, to move glucose from the blood into the cells of the body. However, people who have diabetes either don't produce insulin or can't efficiently use the insulin they produce; therefore, they can't move glucose into their cells. Glucose accumulates in the blood creating a condition called hyperglycemia, and over time, can cause serious health problems.

30

Diabetes is a syndrome with interrelated metabolic, vascular, and neuropathic components. The metabolic syndrome, generally characterized by hyperglycemia, comprises alterations in carbohydrate, fat and protein metabolism caused by absent or markedly reduced insulin secretion and/or ineffective insulin action. The vascular syndrome consists of abnormalities in the blood vessels leading to cardiovascular, retinal and renal complications. Abnormalities in the peripheral and autonomic nervous systems are also part of the diabetic syndrome.

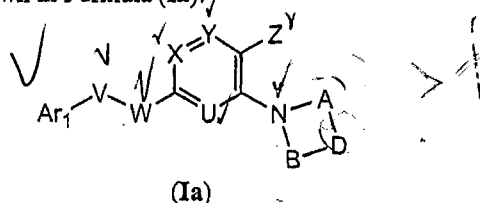
35

People with IDDM, which accounts for about 5% to 10% of those who have diabetes, don't produce insulin and therefore must inject insulin to keep their blood glucose levels normal.

- 5 -

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 invention is provided in the nucleotide sequence of Seq. ID.No:1 and the corresponding amino acid sequence in Seq. ID.No:2.

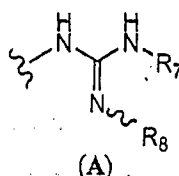
One aspect of the present invention encompasses certain substituted aryl and heteroaryl derivatives as shown in Formula (Ia):



wherein:

- 10 $\rightarrow$ A and B are independently C_{1-3} alkylene optionally substituted with 1 to 4 methyl groups;
- $\checkmark$ U is N or CR_1 ;
- D is O, S, S(O), S(O)₂, CR_2R_3 or NR_2 ;
- 15 $\rightarrow$ V is selected from the group consisting of C_{1-3} alkylene, ethynylene and C_{1-2} heteroalkylene optionally substituted with 1 to 4 substituents selected from the group consisting of C_{1-3} alkyl, C_{1-4} alkoxy, carboxy, cyano, C_{1-3} haloalkyl and halogen; or V
- $\rightarrow$ is absent;
- $\rightarrow$ W is $S(O)_2NR_4$, $-NR_4$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$; or W is absent;
- $\rightarrow$ X is N or CR_5 ;
- 20 $\rightarrow$ Y is N or CR_6 ;
- $\rightarrow$ Z is selected from the group consisting of H, C_{1-5} acyl, C_{1-5} acyloxy, C_{1-4} alkoxy, C_{1-6} 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} alkylthiourey, C_{1-4} alkylureyl, amino, carbo- C_{1-6} -alkoxy, carboxamide, carboxy, cyano, C_{4-8} diacylamino, C_{1-4} dialkylcarboxamide, C_{1-4} dialkylthiocarboxamide, C_{2-6} dialkylsulfonamide, C_{1-4} dialkylsulfonfylamino, formyl, C_{1-4} haloalkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkylcarboxamide, C_{1-4} haloalkylsulfinyl, C_{1-4} haloalkylsulfonyl,
- 25 $\rightarrow$ C_{1-4} haloalkylthio, halogen, aryl, heteroaryl, hydroxyl, hydroxylamino, nitro and tetrazolyl; or
- 30 Z is a group of Formula (A):

- 6 -



wherein:

R₇ is H, C₁₋₆ alkyl or C₃₋₆ cycloalkyl; andR₈ is H, nitro or cyano;

5 *Definition*

Ar₁ is aryl or heteroaryl optionally substituted with R₉, R₁₀, R₁₁, R₁₂ and R₁₃;
 R₁, R₅ and R₆ are independently selected from the group consisting of H, C₁₋₅
 acyloxy, C₂₋₆ alkenyl, C₁₋₄ alkoxy, C₁₋₈ alkyl, C₁₋₄ alkylcarboxamide, C₂₋₆ alkynyl, C₁₋₄
 alkylsulfonamide, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, C₁₋₄ alkylthio, C₁₋₄ alkylureyl,
 amino, C₁₋₄ alkylamino, C₂₋₈ dialkylamino, carboxamide, cyano, C₃₋₆ cycloalkyl, C₂₋₆
 dialkylcarboxamide, C₂₋₆ dialkylsulfonamide, halogen, C₁₋₄ haloalkoxy, C₁₋₄
 haloalkyl, C₁₋₄ haloalkylsulfinyl, C₁₋₄ haloalkylsulfonyl, C₁₋₄ haloalkylthio, hydroxyl
 and nitro;

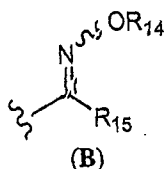
15 R₂ is selected from the group consisting of H, C₁₋₅ acyl, C₁₋₅ acyloxy, C₁₋₄
 alkoxy, C₁₋₈ alkyl, C₁₋₄ alkylcarboxamide, C₁₋₄ alkylthiocarboxamide, C₁₋₄
 alkylsulfinyl, C₁₋₄ alkylsulfonyl, C₁₋₄ alkylthio, amino, carbo-C₁₋₆-alkoxy,
 carboxamide, carboxy, cyano, C₃₋₆-cycloalkyl, C₂₋₆ dialkylcarboxamide, C₁₋₄
 haloalkoxy, C₁₋₄ haloalkyl, halogen, heteroaryl, hydroxyl and phenyl; and wherein C₁₋
 8 alkyl, heteroaryl and phenyl are optionally substituted with 1 to 5 substituents
 20 selected from the group consisting of C₁₋₅ acyl, C₁₋₅ acyloxy, C₁₋₄ alkoxy, C₁₋₈ alkyl,
 C₁₋₄ alkylamino, C₁₋₄ alkylcarboxamide, C₁₋₄ alkylthiocarboxamide, C₁₋₄
 alkylsulfonamide, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, C₁₋₄ alkylthio, C₁₋₄
 alkylthiourey, C₁₋₄ alkylureyl, amino, carbo-C₁₋₆-alkoxy, carboxamide, carboxy,
 cyano, C₃₋₆-cycloalkyl, C₃₋₆-cycloalkyl-C₁₋₃-heteroalkylene, C₂₋₈ dialkylamino, C₂₋₆
 25 dialkylcarboxamide, C₁₋₄ dialkylthiocarboxamide, C₂₋₆ dialkylsulfonamide, C₁₋₄
 alkylthiourey, C₁₋₄ haloalkoxy, C₁₋₄ haloalkyl, C₁₋₄ haloalkylsulfinyl, C₁₋₄
 haloalkylsulfonyl, C₁₋₄ haloalkyl, C₁₋₄ haloalkylthio, halogen, heterocyclic, hydroxyl,
 hydroxylamino and nitro; or

30 R₂ is -Ar₂-Ar₃ wherein Ar₂ and Ar₃ are independently aryl or heteroaryl
 optionally substituted with 1 to 5 substituents selected from the group consisting of
 H, C₁₋₅ acyl, C₁₋₅ acyloxy, C₁₋₄ alkoxy, C₁₋₈ alkyl, C₁₋₄ alkylcarboxamide, C₁₋₄
 alkylthiocarboxamide, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, C₁₋₄ alkylthio, amino,

- 7 -

carbo-C₁₋₆-alkoxy, carboxamide, carboxy, cyano, C₃₋₆-cycloalkyl, C₂₋₆
dialkylcarboxamide, C₁₋₄ haloalkoxy, C₁₋₄ haloalkyl, halogen, hydroxyl and nitro; or

R₂ is a group of Formula (B):

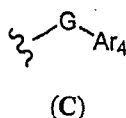


5

wherein:

R₁₄ is C₁₋₈ alkyl or C₃₋₆ cycloalkyl; and R₁₅ is F, Cl, Br or
CN; or

R₂ is a group of Formula (C):



10

wherein:

G is C=O, CR₁₆R₁₇, O, S, S(O), S(O)₂; where R₁₆ and R₁₇ are
independently H or C₁₋₈ alkyl; and

15

Ar₄ is phenyl or heteroaryl optionally substituted with 1 to 5
substituents selected from the group consisting of C₁₋₅ acyl, C₁₋₅
acyloxy, C₁₋₄ alkoxy, C₁₋₈ alkyl, C₁₋₄ alkylcarboxamide, C₁₋₄
alkylthiocarboxamide, C₁₋₄ alkylsulfonamide, C₁₋₄ alkylsulfinyl, C₁₋₄
alkylsulfonyl, C₁₋₄ alkylthio, C₁₋₄ alkylthiourey, C₁₋₄ alkylureyl,
amino, carbo-C₁₋₆-alkoxy, carboxamide, carboxy, cyano, C₃₋₆-
cycloalkyl, C₂₋₆ dialkylcarboxamide, C₁₋₄ dialkylthiocarboxamide, C₂₋
dialkylsulfonamide, C₁₋₄ alkylthiourey, C₁₋₄ haloalkoxy, C₁₋₄
haloalkyl, C₁₋₄ haloalkylsulfinyl, C₁₋₄ haloalkylsulfonyl, C₁₋₄
haloalkyl, C₁₋₄ haloalkylthio, halogen, heteroaryl, hydroxyl,
hydroxylamino and nitro;

20

25

R₃ is H, C₁₋₈ alkyl, C₁₋₄ alkoxy or hydroxyl;

~~R₄~~ is H or C₁₋₈ alkyl;

R₅ is selected from the group consisting of C₁₋₅ acyl, C₁₋₅ acyloxy, C₂₋₆

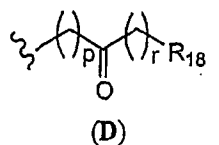
alkenyl, C₁₋₄ alkoxy, C₁₋₈ alkyl, C₁₋₄ alkylcarboxamide, C₂₋₆ alkynyl, C₁₋₄
alkylsulfonamide, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, C₁₋₄ alkylthio, C₁₋₄ alkylureyl,
amino, arylsulfonyl, carbo-C₁₋₆-alkoxy, carboxamide, carboxy, cyano, C₃₋₆ cycloalkyl,

30

- 8 -

C₂₋₆ dialkylcarboxamide, halogen, C₁₋₄ haloalkoxy, C₁₋₄ haloalkyl, C₁₋₄
 haloalkylsulfinyl, C₁₋₄ haloalkylsulfonyl, C₁₋₄ haloalkylthio, heterocyclic,
 heterocyclicsulfonyl, heteroaryl, hydroxyl, nitro, C₄₋₇ oxo-cycloalkyl, phenoxy,
 phenyl, sulfonamide and sulfonic acid, and wherein C₁₋₅ acyl, C₁₋₄ alkoxy, C₁₋₈ alkyl,
 5 C₁₋₄ alkylsulfonamide, alkylsulfonyl, arylsulfonyl, heteroaryl, phenoxy and phenyl are
 optionally substituted with 1 to 5 substituents selected independently from the group
 consisting of C₁₋₅ acyl, C₁₋₅ acyloxy, C₂₋₆ alkenyl, C₁₋₄ alkoxy, C₁₋₈ alkyl, C₁₋₄
 alkylcarboxamide, C₂₋₆ alkynyl, C₁₋₄ alkylsulfonamide, C₁₋₄ alkylsulfinyl, C₁₋₄
 alkylsulfonyl, C₁₋₄ alkylthio, C₁₋₄ alkylureyl, carbo-C₁₋₆-alkoxy, carboxamide,
 10 carboxy, cyano, C₃₋₆ cycloalkyl, C₂₋₆ dialkylcarboxamide, halogen, C₁₋₄ haloalkoxy,
 C₁₋₄ haloalkyl, C₁₋₄ haloalkylsulfinyl, C₁₋₄ haloalkylsulfonyl, C₁₋₄ haloalkylthio,
 heteroaryl, heterocyclic, hydroxyl, nitro and phenyl; or

R₉ is a group of Formula (D):



15

wherein:

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

R₁₈ is H, C₁₋₅ acyl, C₂₋₆ alkenyl, C₁₋₈ alkyl, C₁₋₄

alkylcarboxamide, C₂₋₆ alkynyl, C₁₋₄ alkylsulfonamide, carbo-C₁₋₆-
 alkoxy, carboxamide, carboxy, cyano, C₃₋₆ cycloalkyl, C₂₋₆

20

dialkylcarboxamide, halogen, heteroaryl or phenyl, and wherein the
 heteroaryl or phenyl optionally substituted with 1 to 5 substituents
 selected independently from the group consisting of C₁₋₄ alkoxy, C₁₋₈
 alkyl, amino, C₁₋₄ alkylamino, C₂₋₆ alkynyl, C₂₋₈ dialkylamino,
 halogen, C₁₋₄ haloalkoxy, C₁₋₄ haloalkyl and hydroxyl; and

25

R₁₀-R₁₃ are independently selected from the group consisting of C₁₋₅ acyl, C₁₋₅
 acyloxy, C₂₋₆ alkenyl, C₁₋₄ alkoxy, C₁₋₈ alkyl, C₁₋₄ alkylcarboxamide,
 C₂₋₆ alkynyl, C₁₋₄ alkylsulfonamide, C₁₋₄ alkylsulfinyl, C₁₋₄ alkylsulfonyl, C₁₋₄
 alkylthio, C₁₋₄ alkylureyl, amino, carbo-C₁₋₆-alkoxy, carboxamide, carboxy, cyano, C₃₋₆
 cycloalkyl, C₂₋₆ dialkylcarboxamide, halogen, C₁₋₄ haloalkoxy, C₁₋₄ haloalkyl, C₁₋₄
 haloalkylsulfinyl, C₁₋₄ haloalkylsulfonyl, C₁₋₄ haloalkylthio, hydroxyl and nitro; or

30

A-4

- 9 -

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

a pharmaceutically acceptable salt, hydrate or solvate thereof.

5 One aspect of the present invention encompasses N-oxides of substituted aryl and heteroaryl derivatives of Formula (Ia).

Some embodiments of the present invention include a pharmaceutical composition comprising at least one compound of the present invention in combination with a pharmaceutically acceptable carrier.

10 Some embodiments of the present invention include methods for prophylaxis or treatment of a metabolic disorder and/or complications thereof comprising administering to an individual in need of such prophylaxis or treatment a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

15 Some embodiments of the present invention include methods for controlling or decreasing weight gain comprising administering to an individual in need of such controlling or decreasing weight gain a therapeutically effective amount of a compound of the present invention or pharmaceutical composition thereof.

20 Some embodiments of the present invention include methods of modulating a RUP3 receptor comprising contacting the receptor with an effective amount of a compound of the present invention.

Some embodiments of the present invention include methods of modulating a RUP3 receptor in an individual comprising contacting the receptor with an effective amount of a compound of the present invention.

In some embodiments the compound is an agonist.

25 In some embodiments the compound is an inverse agonist.

Some embodiments of the present invention include methods of modulating a RUP3 receptor in an individual comprising contacting the receptor with a compound of the present invention wherein the modulation of the RUP3 receptor is prophylaxis or treatment of a metabolic disorder and/or complications thereof.

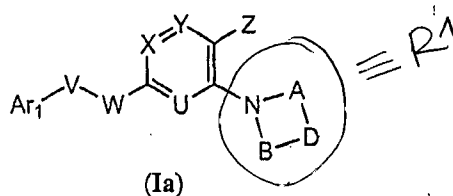
30 Some embodiments of the present invention include methods of modulating a RUP3 receptor in an individual comprising contacting the receptor with a compound of the present invention wherein the modulation of the RUP3 receptor controls or reduces weight gain of the individual.

- 20 -

PHARMACEUTICAL COMPOSITION shall mean a composition comprising at least one active ingredient, whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, and not limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

DETAILED DESCRIPTION

One aspect of the present invention encompasses certain substituted aryl and heteroaryl derivatives as shown in Formula (Ia):



or a pharmaceutically acceptable salt, hydrate or solvate thereof, wherein A, B, D, V, W, X, Y, Z, U, and Ar₁ are as described herein, *supra* and *infra*.

One aspect of the present invention encompasses N-oxides of certain substituted aryl and heteroaryl derivatives of Formula (Ia).

One aspect of the present invention encompasses certain substituted aryl and heteroaryl derivatives as shown in Formula (Ia) wherein:

→ A and B are both ethylene optionally substituted with 1 to 4 methyl groups;

U is N or CR₁;

→ D is CR₂R₃;

V is absent;

→ W is -S(O)₂NR₄, -NR₄, -O- or absent;

X is CR₅;

Y is CR₆;

Z is H or nitro;

→ Ar₁ is (aryl or heteroaryl) optionally substituted with R₉, R₁₀, R₁₁, R₁₂ and R₁₃;

R₁, R₅ and R₆ are each independently selected from the group consisting of H, halogen, and nitro;

R₂ is selected from the group consisting of H, C₁₋₅ acyl, C₁₋₈ alkyl, and heteroaryl; and wherein C₁₋₈ alkyl, and heteroaryl are optionally substituted with 1 to 5 substituents selected from the group consisting of C₁₋₄ alkoxy, C₁₋₈ alkyl, and halogen;

or

R₂ is a group of Formula (C), wherein G is S, S(O), S(O)₂; and Ar₄ is phenyl or heteroaryl optionally substituted with 1 to 5 substituents selected from the group consisting of C₁₋₄ alkoxy, C₁₋₈ alkyl, cyano, C₁₋₄ haloalkoxy, C₁₋₄ haloalkyl, and halogen;

→ R₃ is H;

→ R₄ is H or C₁₋₈ alkyl;

R₉ is selected from the group consisting of C₁₋₅ acyl, C₂₋₆ alkenyl, C₁₋₄ alkoxy, C₁₋₈ alkyl, C₁₋₄ alkylsulfonyl, amino, arylsulfonyl, carbo-C₁₋₆-alkoxy, carboxamide, carboxy, cyano, C₃₋₆ cycloalkyl, halogen, C₁₋₄ haloalkoxy, C₁₋₄ haloalkyl, heterocyclic, heteroaryl, hydroxyl, C₄₋₇ oxo-cycloalkyl, phenyl, and sulfonic acid, and wherein C₁₋₅ acyl, C₁₋₈ alkyl, arylsulfonyl, heteroaryl, and phenyl are optionally substituted with 1 to 5 substituents selected independently from the group consisting of C₁₋₄ alkoxy, C₁₋₈ alkyl, C₁₋₄ alkylsulfonyl, cyano, halogen, C₁₋₄ haloalkoxy, C₁₋₄ haloalkyl, heteroaryl, and hydroxyl; or

R₉ is a group of Formula (D) wherein "p" and "r" are independently 0, 1, 2 or 3; and R₁₈ is H, carbo-C₁₋₆-alkoxy, carboxy, heteroaryl or phenyl, and wherein the heteroaryl and phenyl are optionally substituted with 1 to 5 substituents selected independently from the group consisting of C₁₋₄ alkoxy, C₁₋₈ alkyl, halogen, C₁₋₄ haloalkoxy, and C₁₋₄ haloalkyl; and

R₁₀-R₁₃ are independently selected from the group consisting of C₁₋₄ alkoxy, C₁₋₈ alkyl, amino, cyano, halogen, C₁₋₄ haloalkoxy, C₁₋₄ haloalkyl, and hydroxyl; or a pharmaceutically acceptable salt, hydrate or solvate thereof.

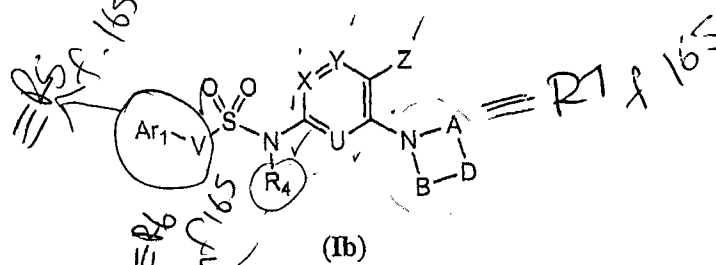
It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination.

As used herein, "substituted" indicates that at least one hydrogen atom of the chemical group is replaced by a non-hydrogen substituents or group. When a chemical group herein is "substituted" it may have up to the full valance of substitution; for example, a methyl group can be substituted by 1, 2, or 3 substituents, a methylene group can be substituted by 1 or 2 substituents, a phenyl group can be substituted by 1, 2, 3, 4, or 5 substituents, and the like.

- 22 -

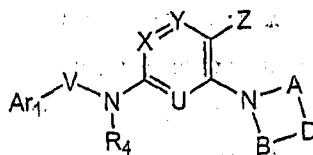
It is understood that certain groups used to describe compounds of the present invention contain a prefix designating the number of carbons in the particular group; for example, C₁₋₈ alkyl is understood to encompass a one (1) carbon alkyl (i.e., methyl) to eight (8) carbon alkyl groups.

One aspect of the present invention encompasses certain substituted aryl and heteroaryl derivatives as shown in Formula (Ia) wherein W is -S(O)₂NR₄- or -NR₄-. In some embodiments W is -S(O)₂NR₄- and compounds may be represented by Formula (Ib) as shown below:



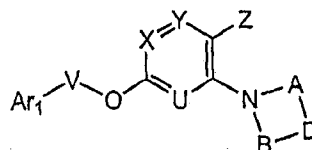
wherein each variable in Formula (Ib) has the same meaning as described herein. In some embodiments R₄ is H.

One aspect of the present invention encompasses certain substituted aryl and heteroaryl derivatives as shown in Formula (Ia) wherein W is -NR₄- and compounds may be represented by Formula (Ic) as shown below:



wherein each variable in Formula (Ic) has the same meaning as described herein. In some embodiments R₄ is H.

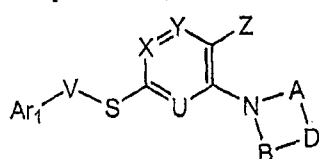
One aspect of the present invention encompasses certain substituted aryl and heteroaryl derivatives as shown in Formula (Ia) wherein W is -O-, an oxygen atom, and compounds may be represented by Formula (Id) as shown below:



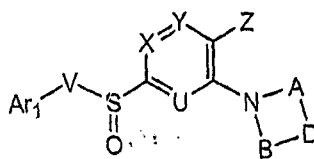
wherein each variable in Formula (Id) has the same meaning as described herein.

- 23 -

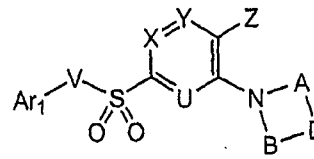
One aspect of the present invention encompasses certain substituted aryl and heteroaryl derivatives as shown in Formula (Ia) wherein W is S, S(O) or S(O)₂ and compounds may be represented by Formulae (Ie), (If) and (Ig) respectively as shown below:



(Ie)



(If)



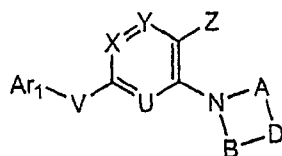
(Ig)

5

wherein each variable in Formula (Ie), (If) and (Ig) has the same meaning as described herein. In some embodiments W is -S-. In some embodiments W is -S(O)-. In some embodiments W is -S(O)₂-.

10

One aspect of the present invention encompasses certain substituted aryl and heteroaryl derivatives as shown in Formula (Ia) wherein W is absent. In some embodiments, compounds may be represented by Formula (Ih) as shown below:

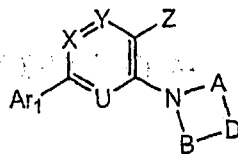


(Ih)

wherein each variable in Formula (Ih) has the same meaning as described herein.

15

In some embodiments, V is absent. In some embodiments compounds of the present invention are of Formula (Ih) wherein V is absent (i.e., both V and W are absent) and accordingly these compounds may be represented by Formula (Ii) as shown below:



(Ii)

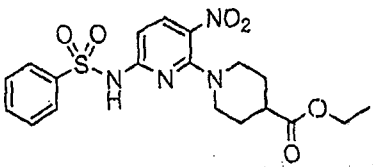
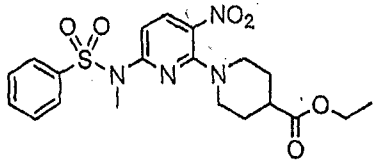
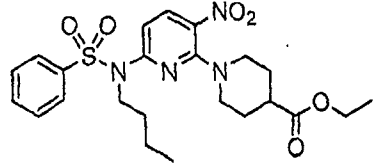
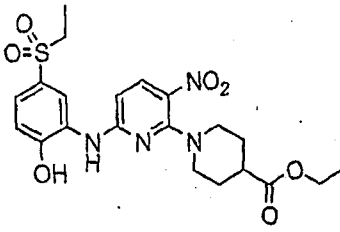
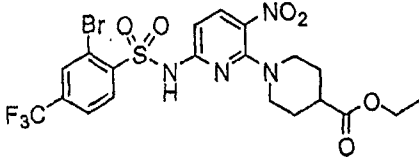
wherein each variable in Formula (Ii) has the same meaning as described herein.

20

One aspect of the present invention encompasses certain substituted aryl and heteroaryl derivatives as shown in Formula (Ia) wherein W is absent and V is ethynylene. Compounds may be represented by Formula (Ij) as shown below:

- 60 -

TABLE E

Cmpd#	Structure	Chemical Name
B1		6'-(Benzenesulfonylamino)-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester
B2		6'-(Benzenesulfonyl-methyl-amino)-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester
B3		6'-(Benzenesulfonyl-butyl-amino)-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester
B4		6'-(5-Ethanesulfonyl-2-hydroxy-phenylamino)-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester
B5		6'-(2-Bromo-4-trifluoromethyl-benzenesulfonylamino)-3'-nitro-3,4,5,6-tetrahydro-2H-[1,2']bipyridinyl-4-carboxylic acid ethyl ester

200

The resulting PCR reactions (15 μ l) were loaded on a 1.5% agarose gel to analyze the RT-PCR products, and a specific 547 base-pair DNA fragment representing rat **RUP3** was specifically amplified from cDNA of pancreas origin, revealing a similar expression profile with human. Of particular note, robust expression was seen in isolated islets and hypothalamus.

Example 3

RUP3 protein expression is restricted to β cell lineage of pancreatic islets (Figure 2).

A. A polyclonal anti-RUP3 antibody was prepared in rabbits (Figure 2A).

Rabbits were immunized with an antigenic peptide with sequence derived from rat **RUP3** ("rRUP3"). The peptide sequence was RGPERTRESAYHIVTISHPELDG (SEQ ID NO: 7) and shared 100% identity with mouse **RUP3** in the corresponding region. A cysteine residue was incorporated at the N-terminal end of this antigenic peptide to facilitate KLH crosslinking before injecting into rabbits. The resulting antisera ("anti-rRUP3") and the corresponding preimmune sera ("pre-rRUP3") were tested for immune reactivity to mouse **RUP3** in immunoblotting assays (lanes 1 through 4). In this assay, the GST-RUP3 fusion protein was readily recognized by the anti-rRUP3 antisera (lane 4), but not by the preimmune sera (lane 2). The immunoreactive signal could be efficiently eliminated when the immunoblotting assay was performed in the presence of excess antigenic peptide (lane 6).

B. RUP3 expression in insulin-producing β cells of pancreatic islets (Figure 2B).

Rat pancreas was perfused with 4% paraformaldehyde (PFA) in PBS and embedded in OCT embedding medium. Ten micron sections were prepared, fixed on glass slides, and immunostained with either pre-rRUP3 (Figure 2B, panel a) or with anti-rRUP3 antisera (Figure 2B, panels c and e) followed by secondary staining with donkey anti-rabbit IgG conjugated to the fluorochrome Cy-3. Each section was also co-immunostained with a monoclonal anti-insulin antibody (Santa Cruz, Figure 2B, panels b and d) in primary staining followed by a secondary staining with donkey anti-mouse IgG conjugated with FITC, or with a goat anti-glucagon antibody (Santa Cruz, Figure 2B, panel f) and donkey anti-goat IgG coupled to FITC. Immunofluorescent signals were examined under a fluorescent microscope. **RUP3** was found expressed in insulin producing cells (panels c and d), but not in glucagons producing cells (panels e and f). These data demonstrated that **RUP3** is expressed in β cells but not in β cells of the rat pancreatic islets. Analogous results were obtained when mouse pancreatic sections were investigated for **RUP3** expression.

Example 4**Functional Activities of RUP3 *In Vitro* (Figure 3).**

It was established that RUP3 stimulates the production of cAMP by cotransfection of 293 cells with: (1) a CRE-Luciferase reporter, wherein the ability to stimulate the production of firefly luciferase depends on increased cAMP in cells, and (2) an expression plasmid encoding the human form of RUP3 (Figure 3A). Note that cells co-transfected with an expression plasmid containing no RUP3 sequences ("CMV" in Figure 3A) produce very little luciferase activity, whereas cells transfected with an expression plasmid encoding RUP3 (Figure 3A) have at least a 10-fold increase in luciferase activity. This indicates that RUP3 stimulates the production of cAMP when introduced into 293 cells. This property of RUP3 is conserved across species, because hamster RUP3 stimulates luciferase activity when introduced into 293 cells in a manner analogous to that described for human RUP3 (Figure 3B).

It is established that, when cAMP is increased in insulin-producing cells of the pancreas, these cells exhibit an enhanced ability to secrete insulin when glucose concentrations rise. To test whether RUP3 might impart enhanced glucose-dependent insulin release, retrovirus containing human RUP3 was used to generate Tu6 cells that express high levels of RUP3. Tu6 cells produce insulin, but do not express appreciable levels of RUP3 and do not normally exhibit an increase in insulin release when increased glucose is present in the culture media. As shown in Figure 3C, Tu6 cells transduced with a control virus that contains no receptor are still able to produce insulin, but do not show an increase in insulin secretion when the concentration of glucose in the culture media is shifted from 1 mM to 16 mM. By contrast, Tu6 cells transduced with RUP3-containing retrovirus display significant glucose-dependent insulin secretion (Figure 3C).

Example 5**Functional Activities of RUP3 Agonists *In Vitro*.**

To demonstrate that RUP3 agonists stimulate endogenously expressed RUP3 in insulin-producing cells, two *in vitro* models can be used. In the first of these, RUP3 agonists are used to stimulate HIT-T15 cells, which express RUP3 at significant levels, as indicated in the Northern blot shown in Figure 4. Moreover, these cells are known to exhibit enhanced glucose-dependent insulin release when intracellular cAMP concentrations are elevated. In this example a RUP3 agonist can be evaluated for its ability to stimulate cAMP production in HIT cells in comparison to the level seen with the adenylyl cyclase activator forskolin. In this

- 86 -

assay Compound A30 has been shown to be a robust stimulator of cAMP in HIT-T15 cells. Furthermore, Compound A30 has also been shown to stimulate insulin secretion in HIT cells exposed to 15 mM glucose (at a level comparable to that seen with the adenylyl cyclase activator forskolin). This indicates that Compound A30 is a very robust potentiator of insulin secretion in HIT-T15 cells.

Isolated rat islets are the other *in vitro* model used to demonstrate the efficacy of RUP3 agonists. In this model, agents that induce cAMP are not expected to stimulate insulin secretion when glucose concentrations are low (e.g. 60 mg/dl). However, when glucose concentrations are increased (e.g. to 300 mg/dl), these agents are expected to enhance insulin secretion to levels above those seen with glucose alone. In this model Compound A30 (10 μ M) was shown to enhance glucose-dependent insulin release. Moreover, the level of enhancement can be compared to that seen with 25 nM GLP-1, a gut hormone known to act on islets in this manner.

Example 6

In vivo effects of RUP3 agonists on glucose homeostasis in mice.

A. Oral Glucose tolerance test (oGTT).

Male C57bl/6N mice at age of 8 weeks are fasted for 18 hours and randomly grouped (n=11) to receive a RUP3 agonist doses, or with control extendin-4 (ex-4, 1 μ g/kg), a GLP-1 peptide analog known to stimulate glucose-dependent insulin secretion. A test compound is delivered, such as for example, orally via a gavage needle (p.o. volume at 100 μ l). Control Ex-4 is delivered intraperitoneally. Thirty minutes after administration of test compound and control ex-4, mice are administered orally with dextrose at 5 g/kg dose. Levels of blood glucose are determined at the indicated time points using Glucometer Elite XL (Bayer).

B. Acute response of db mice to RUP3 agonist.

Male db mice (C57BL/KsOlaHsd-Lepr^{db}, diabetic, Harlan) at age of 10 weeks are randomly grouped (n=6) to receive vehicle (oral gavage), test compound, (such as for example 60 mg/kg, oral gavage), or Ex-4 (1 μ g/kg, intraperitoneally). After compound administration, food is removed and blood glucose levels are determined at selected times. Reduction in blood glucose at each time point is expressed as percentage of original glucose levels, averaged from six animals for each group. These animals had blood glucose levels (fed state) of 300-400 mg/dl, significantly higher than non-diabetic wild type animals. Treatment with Ex-4 significantly reduced glucose levels compared to vehicle control.

Example 7**Inhibition Of Food Intake In Normal Fed Male Sprague-Dawley Rats**

The *in vivo* activity of a test compound is assayed for its ability to regulate feeding behavior by measuring food consumption in normal fed rats during their dark cycle. Food intake is monitored over the dark phase since animals consume most of their food intake during the nocturnal period.

The test compound is assessed following acute administration. The study is based on a between-subject design (n=8 per group) and the effects of various doses of the test compound is compared to those of vehicle and a positive control. Rats [male Sprague-Dawley rats (220-300g)] naïve to drug treatment (i.e. never been exposed to drug prior to study). The anorectic drug d-fenfluramine (or, alternatively, exendin-4) serves as a positive control.

Prior to the study, the animals are weighed and separated into treatment groups in order to balance groups according to body weight. On the test day, animals are placed into individual cages for an hour. After this habituation period, animals are administered the test compound at doses, such as, 6.67, 20 and 60 mg/kg dissolved in 80% PEG400, 10% Tween 80 and 10% EtOH. The compound is administered intraperitoneally (volume of 1cc/kg) 30 min prior to the beginning of the dark phase. Animals are subsequently presented with a pre-weighed food cup with standard laboratory chow. Food consumption is determined by weighing the food cup at 2, 4, 6 and 22hr after the beginning of the dark cycle (i.e. lights off). Care is taken to collect all spillage. The food intake of animals in the different groups is monitored concurrently.

Food intake data is subjected to two-way repeated analysis of variance (ANOVA) with drug treatment as a between-subject factor and time as a repeated factor. Newman-Keuls tests are performed to assess whether differences between the vehicle mean and the drug-treated mean at each time point were significant. All statistical analyses are performed using Sigma Stat (version 2.0)

Example 8**CRE-Luciferase Assay in 293 Cells**

293 cells were plated in 96-well tissue culture plates at a concentration of 20,000 cells per well. The following day, the cells are transfected with a mixture of pCRE-Luc (Stratagene, Cat. # 219076), the indicated expression plasmid, and pEGFP-N1 (Clontech, Cat. # 6085-1) at a ratio of 5:1:0.25 using Lipofectamine Reagent (Invitrogen, Cat. #18324-020)

22A

according to the manufacturer's directions. pEGFP-N1 encodes a "green fluorescent protein" and was used as a control to determine that most cells were successfully transfected. After 24-48 hr, the cells were lysed *in situ* with 100 μ l/well reconstituted Luciferase buffer (Luciferase Reporter Gene Assay Kit, Packard, Cat. # 6016911), according to the manufacturer's directions. After a 10 minute incubation in the dark, luminescence was measured using a TRILUX 1450 Microbeta Counter (Wallac).

Example 9

Generation of Tu6/ RUP3 Stable Lines

To produce Tu6 cells that express RUP3 at high levels, a retrovirus bearing an expression cassette for RUP3 was generated. Briefly, RUP3 coding sequence was cloned into the retroviral vector pLNCX2 (Clontech, Cat # 6102-1). The amphotropic packaging cell line PT-67 (Clontech, K1060-D) was then transfected with either the parental vector pLNCX2 or pLNCX2/RUP3 using Lipofectamine and stable lines were established using guidelines provided by the PT-67 vendor. Retrovirus-containing supernatant was obtained by collecting media from the resultant stables according to the manufacturer's directions. Tu6 cells, in a 10 cm dish, were then infected with retrovirus by incubating in a solution of 1 ml viral supernatant/ 9 ml culture media containing 40 μ g/ml polybrene for 24 hours. The medium was then changed to culture media containing 300 μ g/ml G418. G418-resistant clones were ultimately created by virtue of the neomycin-resistance gene cassette present in the pLNCX2 vector, thus indicating the successful integration of retrovirus into the Tu6 genome. The expression of RUP3 in the Tu6/RUP3 G418-resistant colonies was confirmed by Northern blot.

Example 10

Insulin secretion, Tu6 Stables

To measure insulin secretion from rodent insulin-producing cell lines, cells were first cultured overnight in serum-free, glucose-deficient media. The following morning, the cells were then placed in the same media supplemented with either 1 mM or 16 mM glucose. After an incubation of 4 hours, the media was collected and analyzed for insulin content using a Rat Insulin Enzyme-Immunoassay (EIA) System (Amersham Pharmacia Biotech, Cat. # RPN 2567). Typically, the assay was performed using multiple dilutions of sample media in order to ensure that the sample measurements fell within the boundaries of the standard curve (generated using known amounts of insulin), as recommended by the manufacturer.