

Doctor

José Luis Salazar

Jefe de División de Nuevas Creaciones

SUPERINTENDENCIA DE INDUSTRIA Y C

E. S.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-000418- -00008-0000

Fecha: 2013-07-03 16:01:43  
Tra. 11 PATENTEIYII  
Act. 523 RESPUESTADep. 2020 DIR.NUEVASCR  
Eve: 378 FASENACIONALI  
Folios: 33

Referencia: Expediente No. 09.000.418

Solicitud de Patente de Invención titulada: "Compuestos de fosfonato y fosfinato como activadores de glucocinasa"

Solicitante: Bristol-Myers Squibb Company

**RESPUESTA AL AUTO NOTIFICADO POR FIJACIÓN EN LISTA NO. 008**  
**DEL 19 DE FEBRERO DE 2013, OFICIO NO. 2568 (EXAMEN DE FONDO)**

ÁLVARO CORREA ORDÓÑEZ, mayor de edad y vecino de Bogotá D.C., identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad en referencia, doy respuesta al auto emanado por ese Despacho dentro del término de prórroga solicitado en mi memorial 09-000418-00007-0000 de fecha 17 de mayo de 2013:

**1. Modificación a una solicitud en trámite**

De conformidad con el artículo 34 de la Decisión 486 que permite al solicitante modificar su solicitud en cualquier momento del trámite sin que se presente ampliación a la materia originalmente presentada me permito presentar un nuevo pliego reivindicatorio conformado por 8 reivindicaciones.

**2. Respuesta a las observaciones del examinador**

**2.1. Reivindicaciones relativas a un uso o a un segundo uso**

El examinador establece que las reivindicaciones 10 a 12 no son patentables.

Con el fin de atender a la anterior observación, se cancelaron dichas reivindicaciones.

## 2.2. Título de la invención

Su Despacho menciona que el título comprende aspectos que no son objeto de patentabilidad como es el uso de los compuestos reivindicados.

Con el propósito de atender a la anterior observación se modifica el título como sigue:

“Compuestos de fosfonato y fosfinato como activadores de glucocinasa”

Con el nuevo título se da por superada la anterior observación.

## 2.3 Claridad del pliego reivindicatorio

### 2.3.1 Término "éster de profármaco"

Su Despacho menciona que la reivindicación 1 no es clara cuando emplea el término "éster de profármaco".

Atendiendo la sugerencia del examinador dicho término se ha cancelado.

### 2.3.2 Reivindicaciones 1,2,3,4 y 6

Su Despacho establece que las reivindicaciones 1,2,3,4 y 6 no son claras, ni concisas puesto que los radicales como por ejemplo, alquilo, amino, heteroarilo, alquinilo no definen los átomos de carbono, y para los "hetero" no se definen los heteroátomos que los conforman.

Como se informó anteriormente se presenta un nuevo pliego reivindicatorio modificado el cual define claramente los radicales.

### 2.3.3 Reivindicación 9

Su Despacho establece que la reivindicación 9 no es clara cuando emplea los términos

agente anti-diabético, agente anti-hiperglicémico, agente anti-hiperinsulinémico, agente anti-retinopático (...) supresor de apetito, agente mejorador de memoria... entre otros porque define los componentes de la composición por su función pero no por un compuesto como tal. El examinador sugiere que se restrinja el alcance de la reivindicación a componentes específicos.

Su Despacho podrá notar que se incluyó como agente anti-diabético la insulina y análogos de insulina. Los otros agentes se encuentran claramente definidos en la memoria descriptiva originalmente presentada.

Por ejemplo, desde la página 77 se mencionan los ejemplos de agentes anti-diabéticos adecuados.

En la página 80 se menciona los agentes anti-isquémicos adecuados. En la página 87 se mencionan ejemplos de agentes anti-hipertensivos como bloqueadores beta adrenérgicos, bloqueadores del canal de calcio y los agentes anti-cáncer se mencionan en la página 90. Por lo tanto, si se encuentra sustento en la descripción de dichos agentes.

#### 2.4 Unidad de invención

Su Despacho establece que la solicitud no cumple con el requisito de unidad de invención porque se refiere a 11 grupos inventivos. Menciona además que el grupo inventivo 4 se sugiere en el documento WO2004/063194, el cual da a conocer tiazolil-amidas como activadores de glucocinasa. El examinador sugiere presentar divisionales o limitar la solicitud inicial a una sola invención.

Con el fin de atender a la anterior observación, se presenta un nuevo pliego reivindicatorio cuyos compuestos se dirigen al mismo concepto inventivo en que estos son amida-fosfonatos (o fosfinatos) los cuales tienen actividad del activador glucocinasa y estos son útiles para el tratamiento de la diabetes Tipo II.

#### 2.5 Determinación del Estado de la Técnica

Por último, el examinador menciona que el estado de la técnica se determinó con base en la fecha de presentación de la solicitud de prioridad 6 de julio de 2006 y no se encontraron documentos que anticipen el objeto de esta solicitud.

Teniendo en cuenta lo anterior, se concluye que su Despacho reconoce la novedad y el nivel inventivo de la presente solicitud.

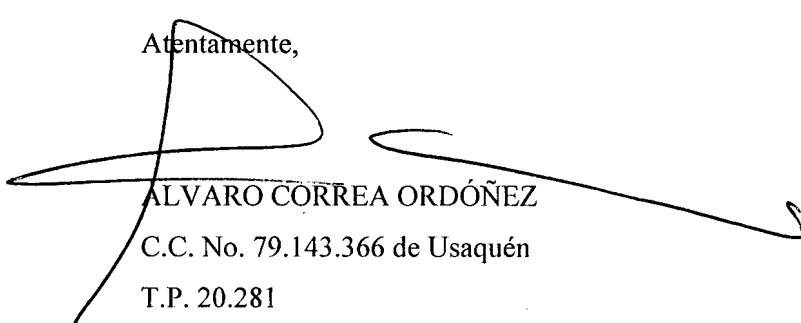
En este orden de ideas, tenemos que la invención propuesta por el solicitante cumple con los requisitos de patentabilidad y de esta manera es susceptible de ostentar el título de patente de invención.

**3. Solicitudes concedidas en otros países para esta misma invención.**

A manera informativa, pongo en conocimiento del Examinador que las patentes US No. 7,910,747 y la US No. 8,153,677 equivalentes a la presente solicitud colombiana han sido otorgadas. Aún cuando entiendo que estas decisiones de ninguna manera obligan al Despacho para decidir de igual forma, considero que por tratarse de una pregunta fáctica la determinación de la existencia de novedad, nivel inventivo y aplicación industrial, las decisiones de otras oficinas de patentes constituyen un antecedente persuasivo en la materia.

En virtud de lo anterior, solicito que se acepten las razones expuestas en el presente documento y en consecuencia, se otorgue el privilegio de patente de invención para el invento que se tramita en este expediente.

Atentamente,



ALVARO CORREA ORDÓÑEZ

C.C. No. 79.143.366 de Usaquén

T.P. 20.281

Anexos:        -    Capítulo reivindicatorio modificado conformado por 8  
                      reivindicaciones  
                      -    Copia de las carátulas de las patentes US No. 7,910,747 y la US  
                              No. 8,153,677

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## REIVINDICACIONES MODIFICADAS

1. Un compuesto, caracterizado porque tiene la estructura:



en donde el grupo

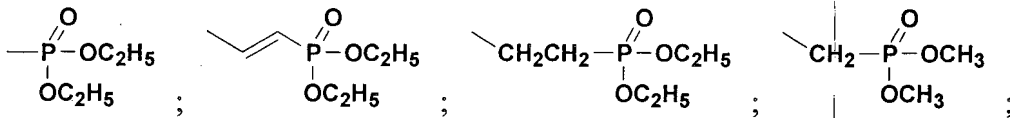


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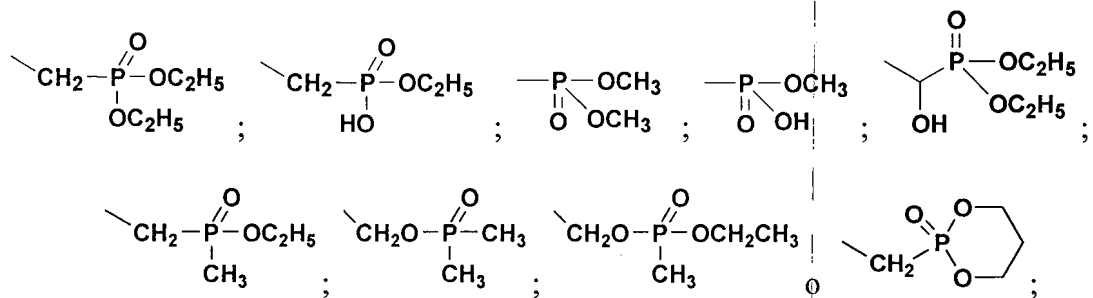


sustituido por  $R_4$  y opcionalmente sustituido con uno o dos sustituyentes  $R_5$  y  $R_6$ ;

20  $R_4$  se selecciona del grupo que consiste de



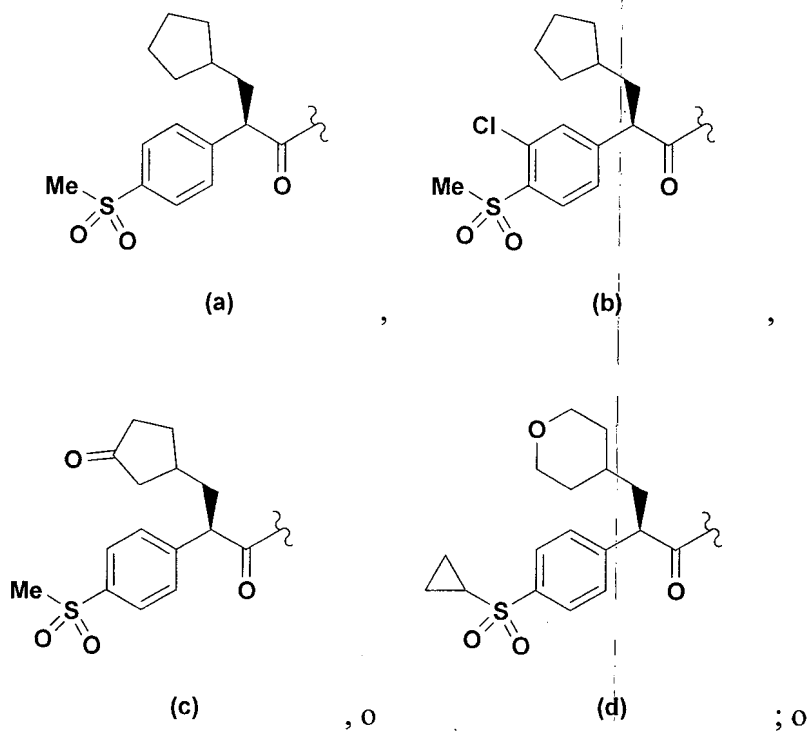
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- 5 R5 y R6 son iguales o diferentes y se seleccionan del grupo que consiste de hidrógeno, alquilo C1-8, halógeno y carboxi, o está ausente;

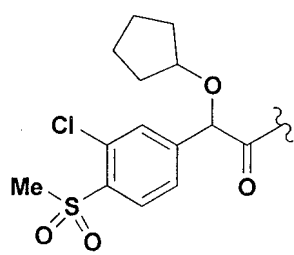
Y-X-CO- es

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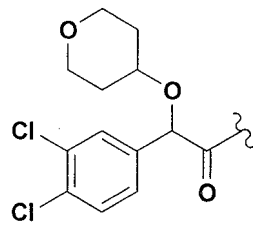


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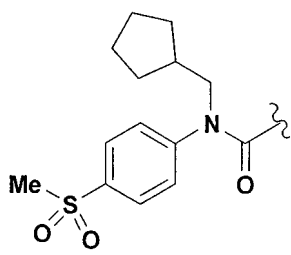


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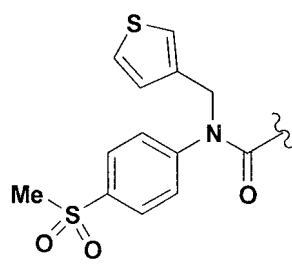


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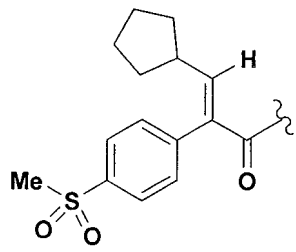


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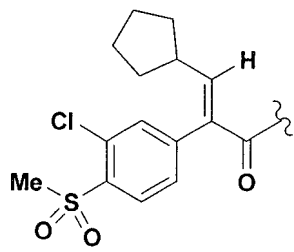


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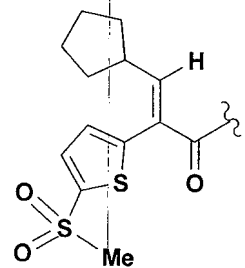
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(i)



(j)

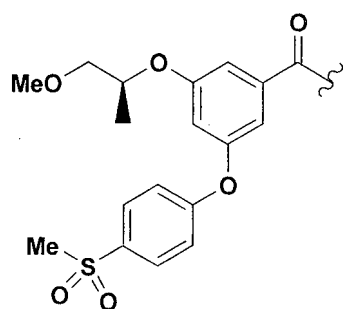


(k)

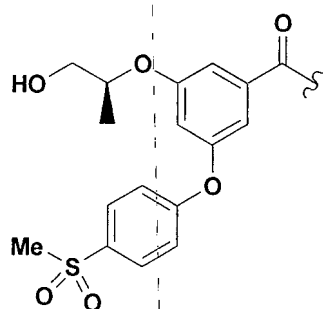
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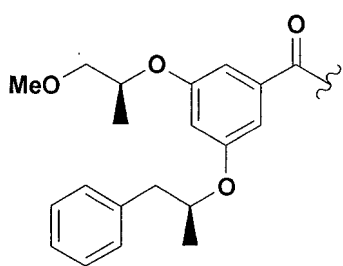
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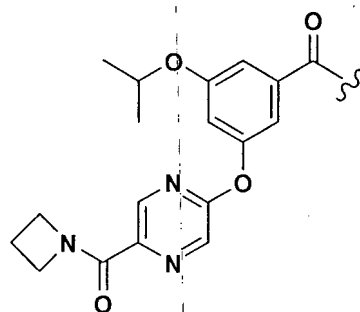
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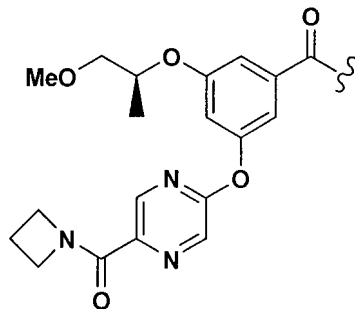
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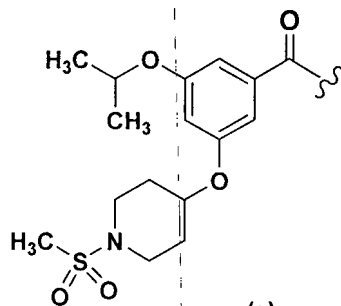
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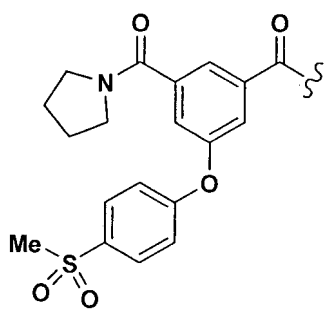
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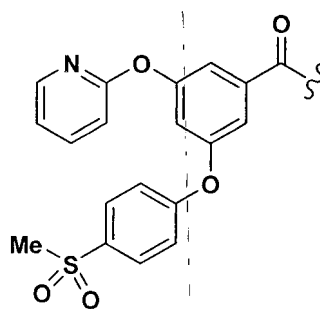
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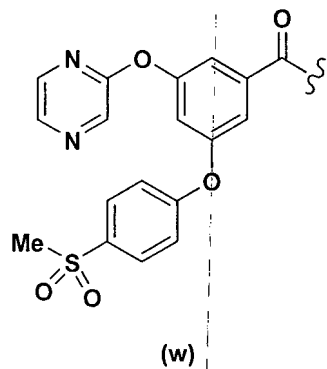
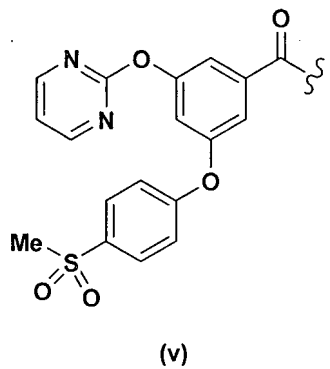


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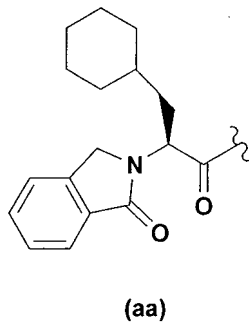
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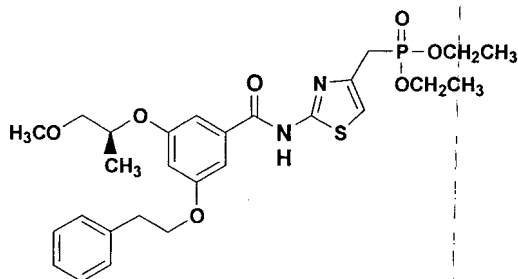
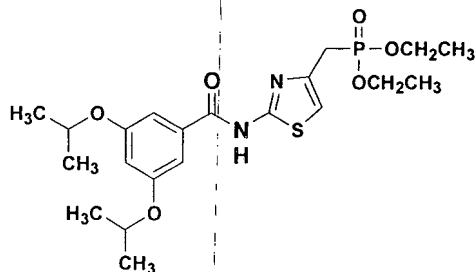
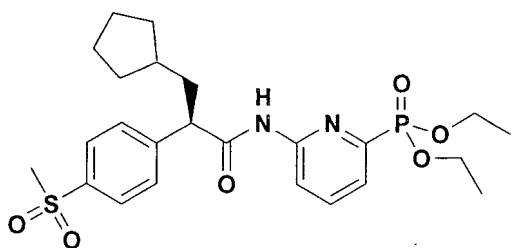
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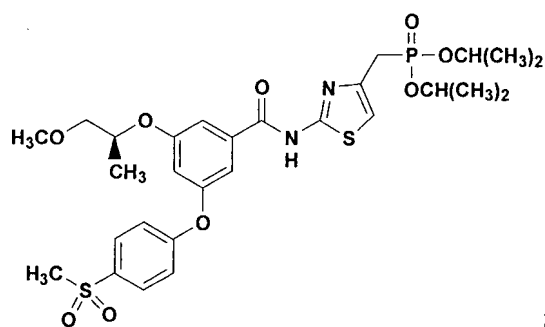
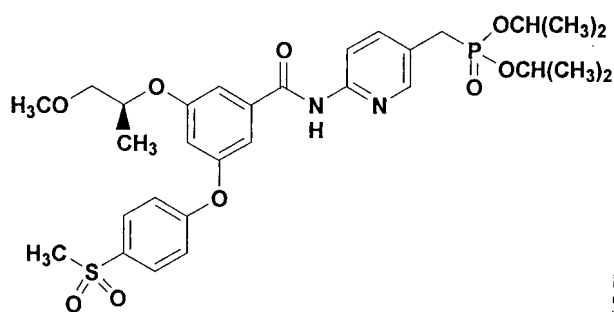
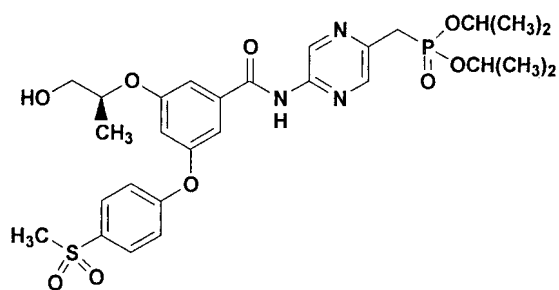
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un compuesto seleccionado de

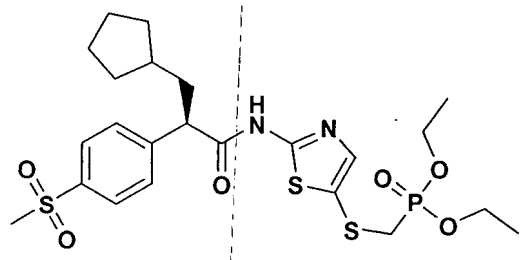
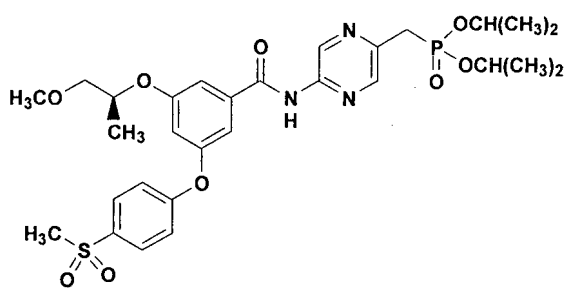


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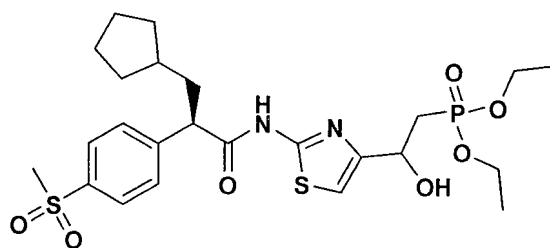
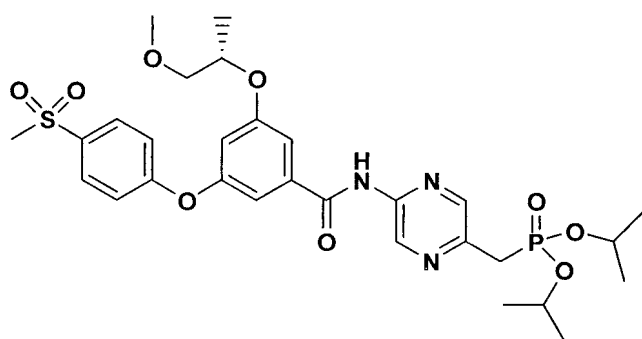
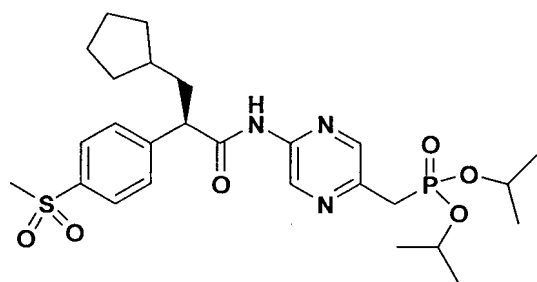
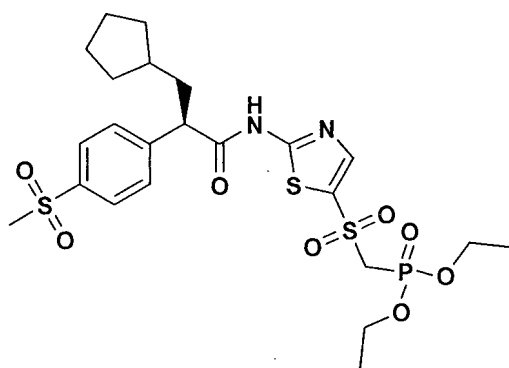
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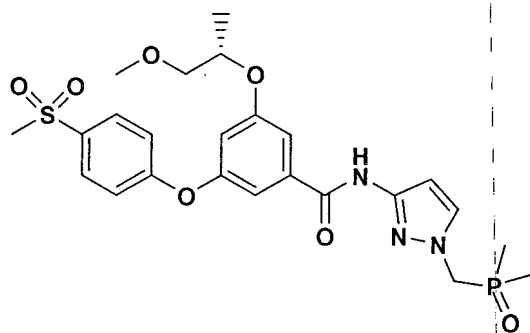
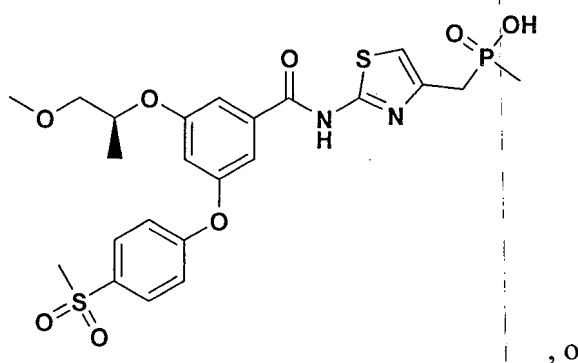
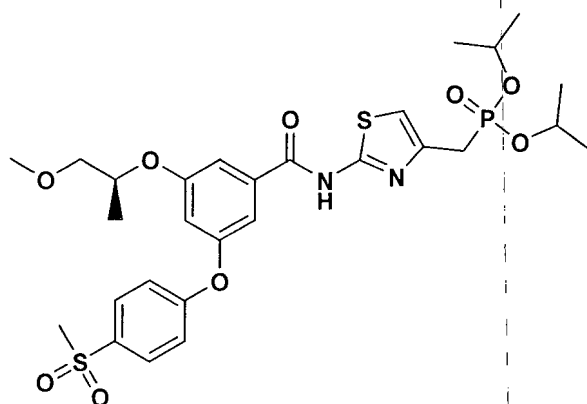


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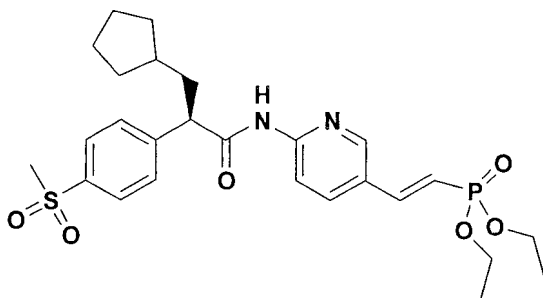
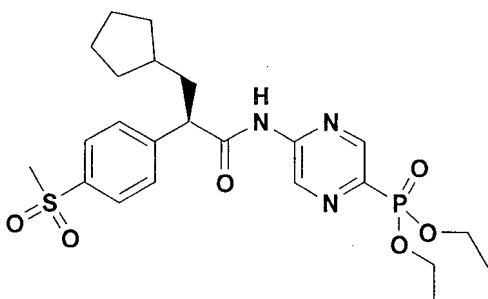
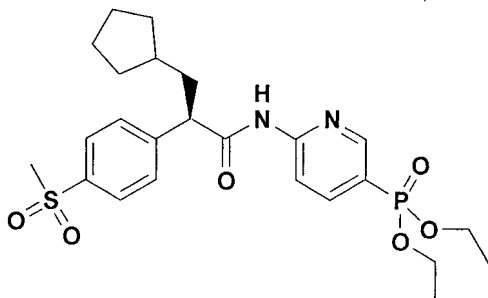
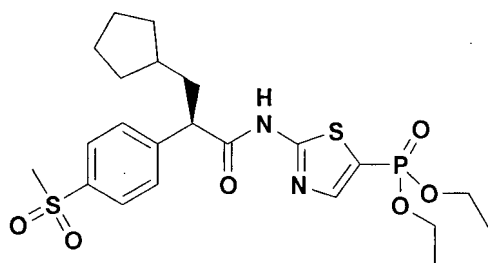


5 todos los esteroisómeros de los mismos, o una sal farmacéuticamente aceptable de los mismos.

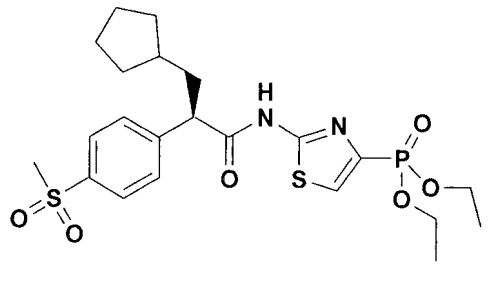
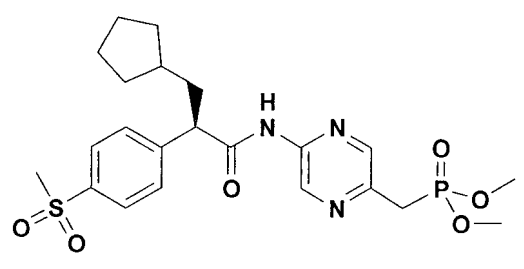
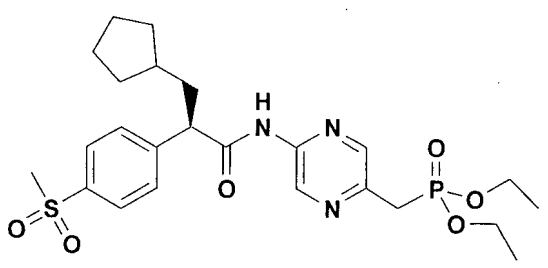
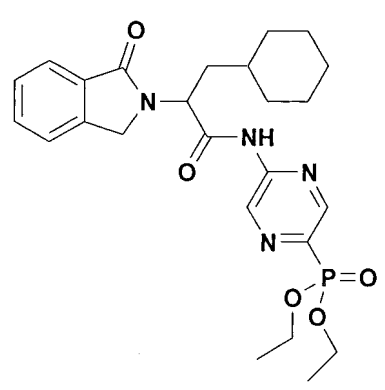
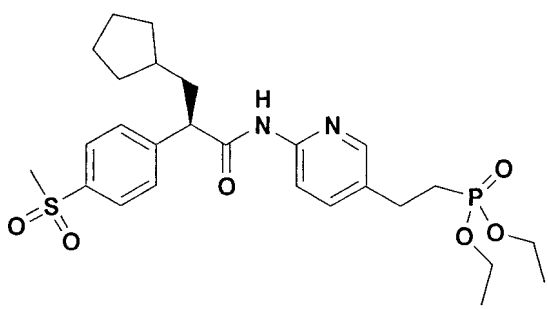
2. El compuesto tal como se definió en la reivindicación 1 en donde  $R_5$  y  $R_6$  son cada uno H.

3. El compuesto tal como se definió en la reivindicación 1 donde el compuesto es

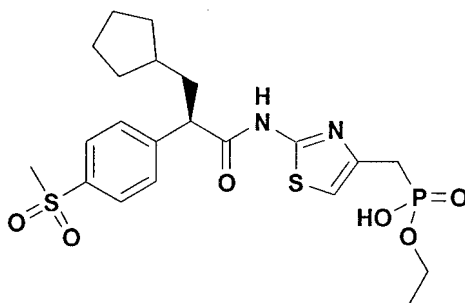
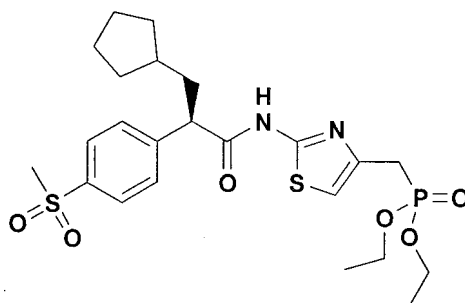
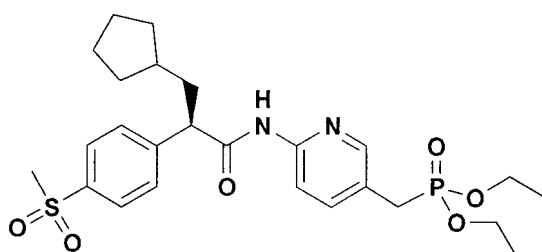
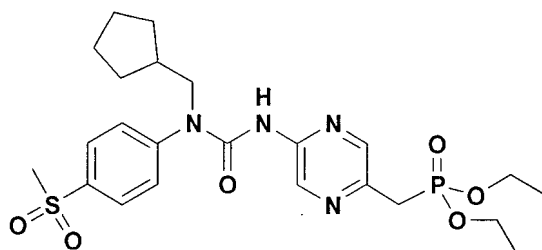
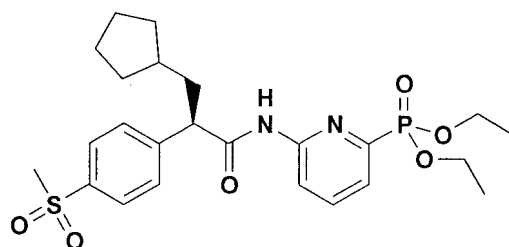
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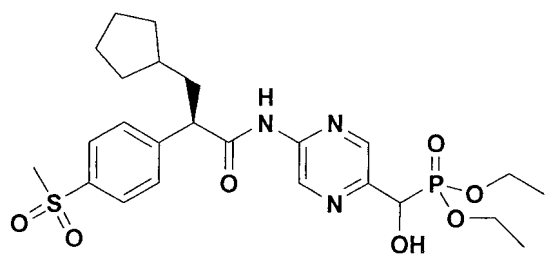
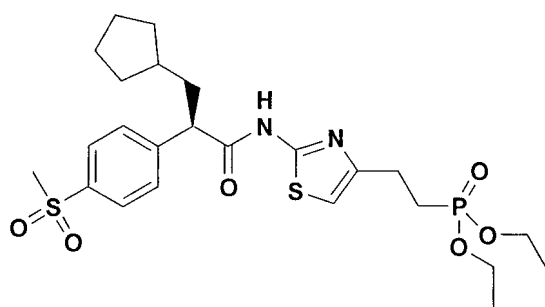
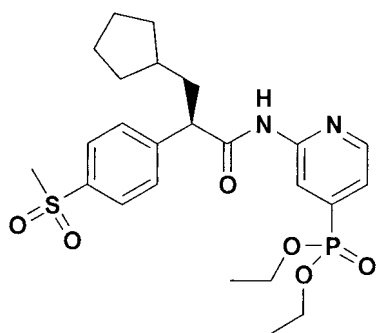
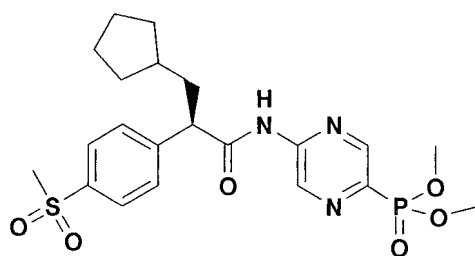
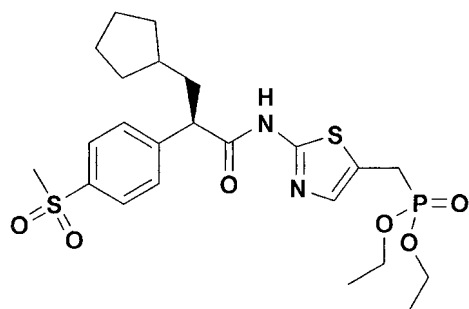
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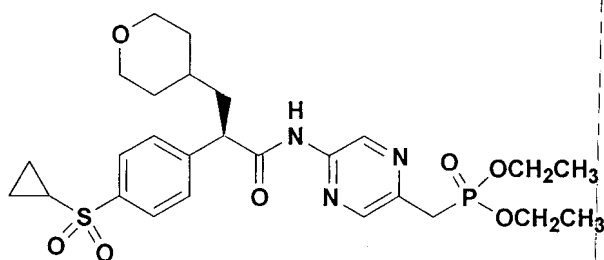
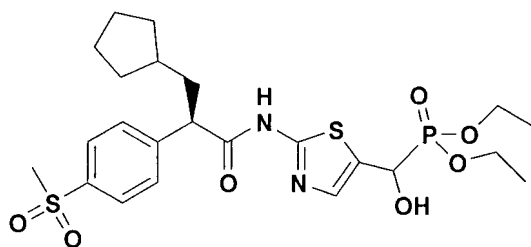
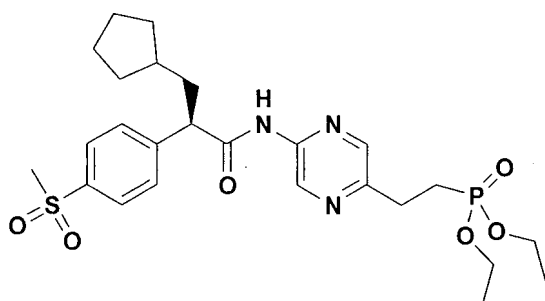
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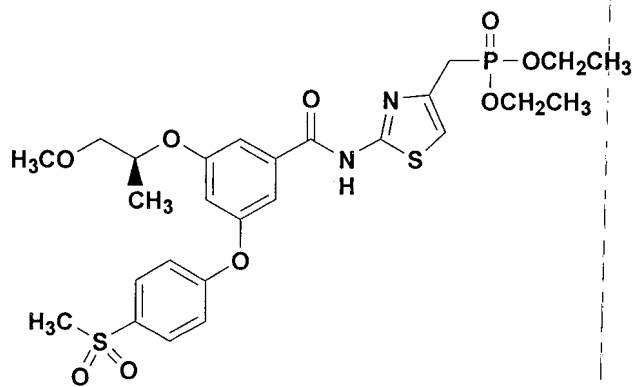
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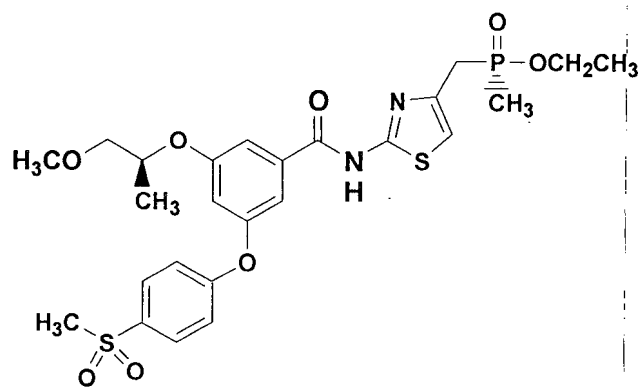
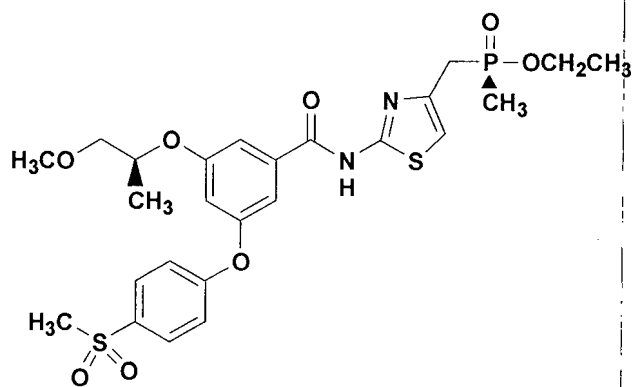
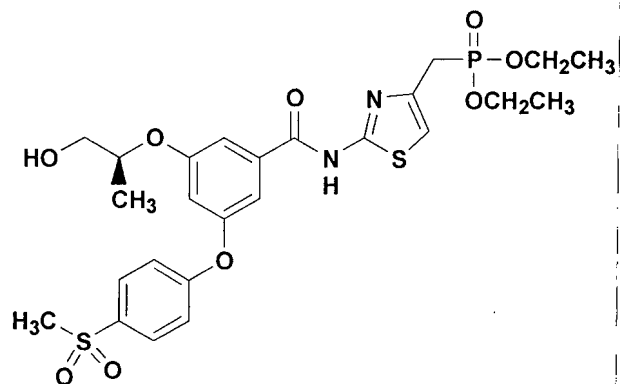
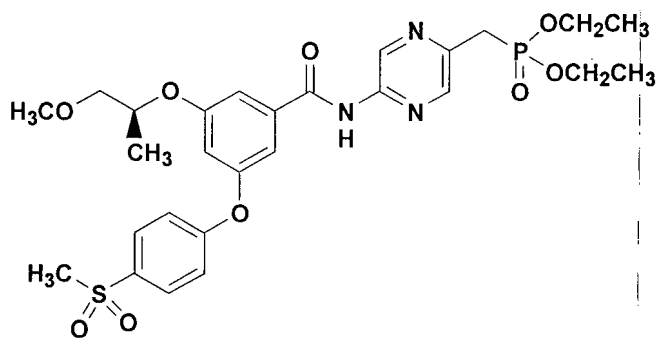
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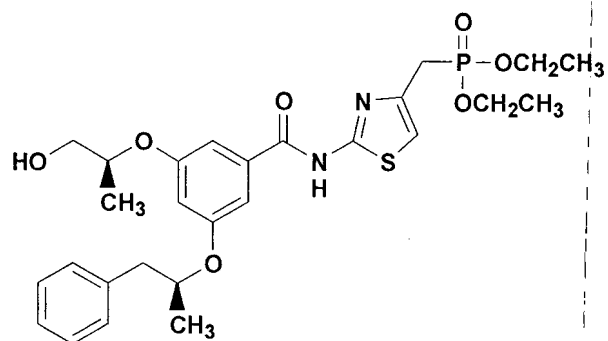
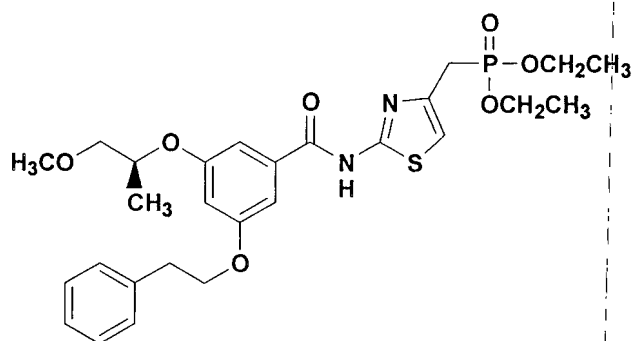
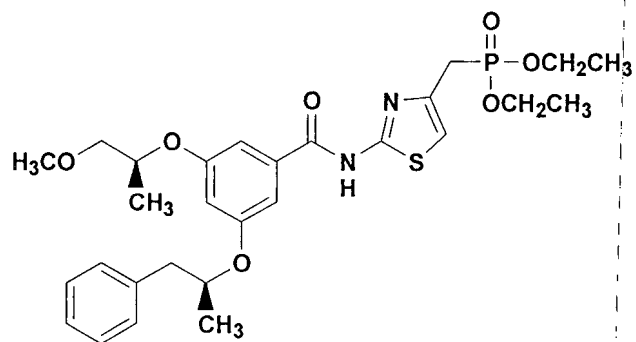
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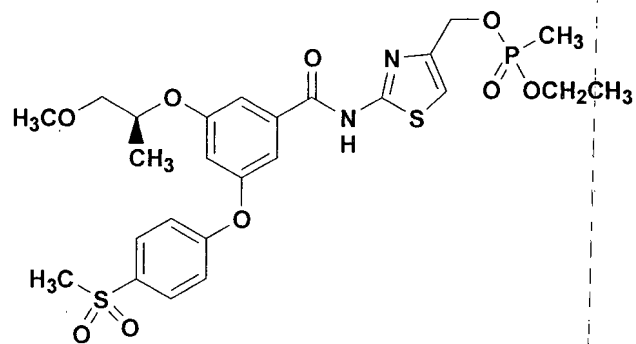
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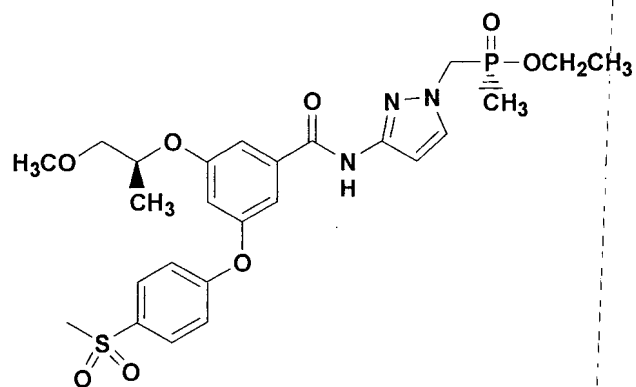
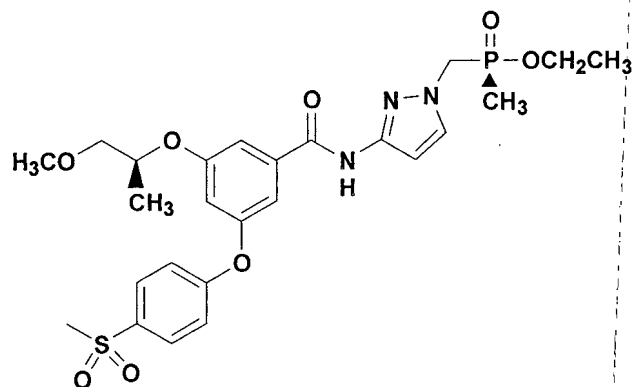
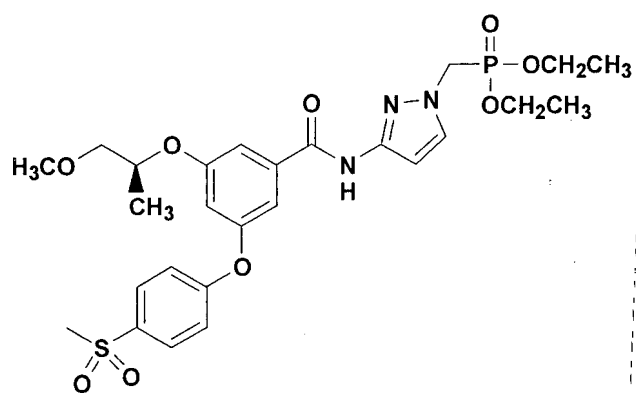
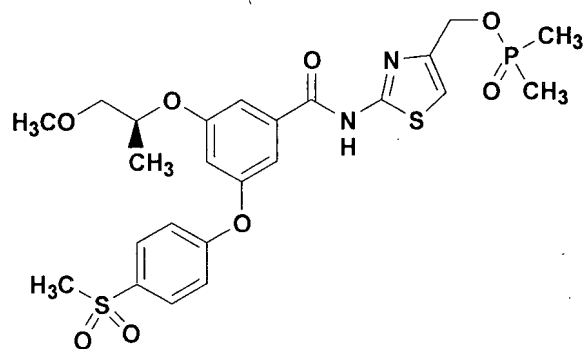
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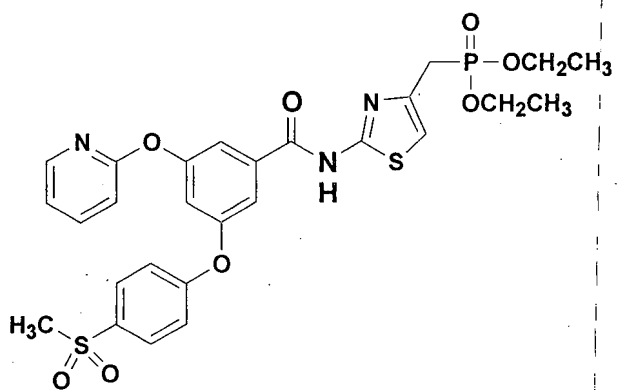
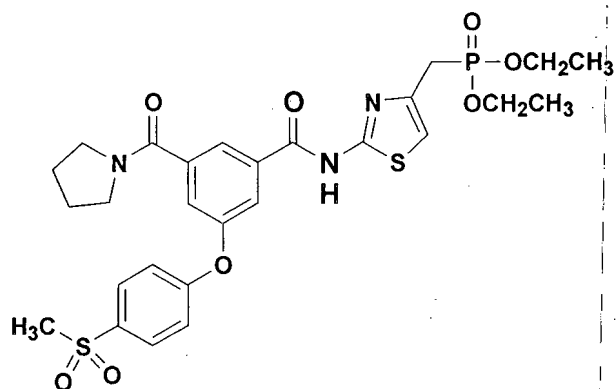
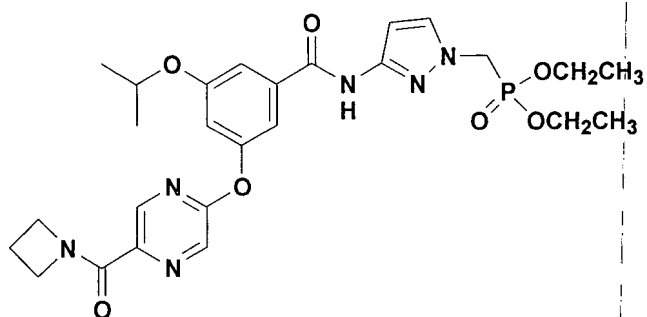
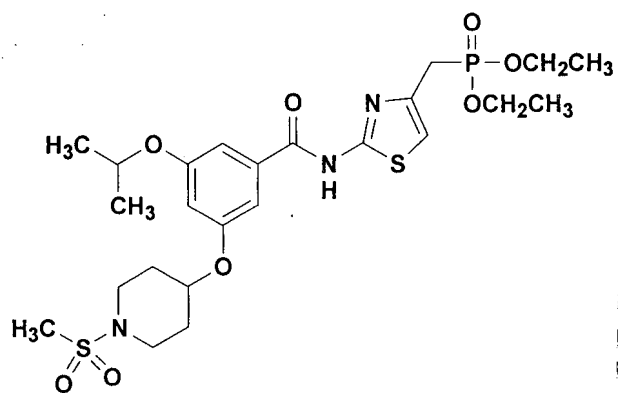
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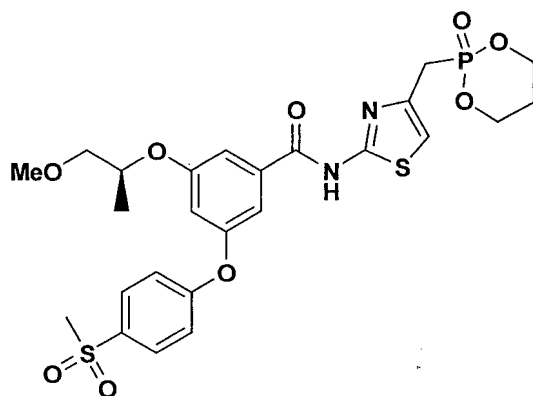
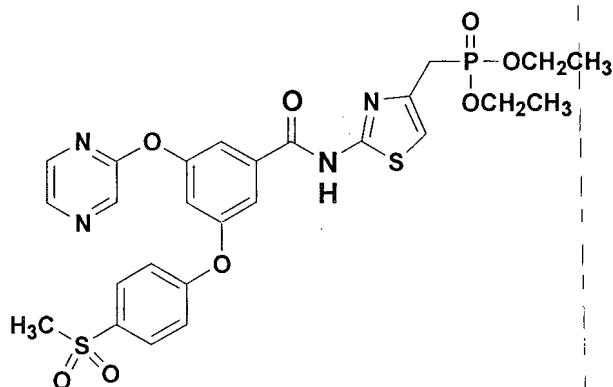
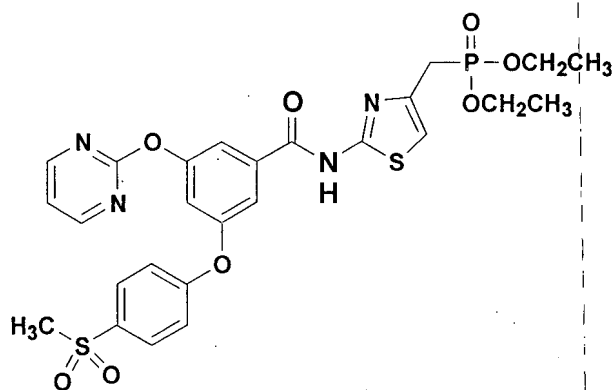


- 16 -



- 17 -





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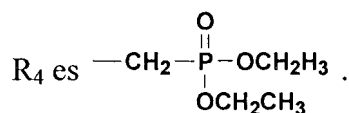
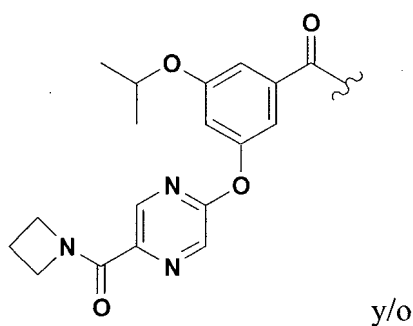
4. Una Composición farmacéutica, caracterizada porque comprende un compuesto de conformidad con la reivindicación 1 y otro agente terapéutico el cual es un agente anti-diabético tales como insulina y análogos de insulina, agente anti-hiperglicémico, agente anti-hiperinsulinémico, agente anti-

10

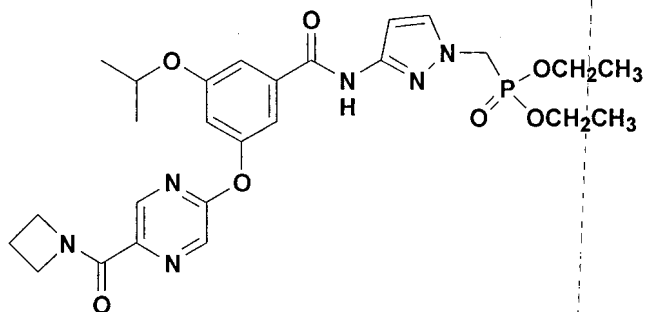
retinopático, agente anti-neuropático, agente anti-  
 nefropático, agente anti-ateroesclerótico, agente anti-  
 infeccioso, agente anti-isquémico, agente anti-hipertensivo,  
 agente anti-obesidad, agente anti-dislipidémico, agente anti-  
 5 hiperlipidémico, agente anti-hipertrigliceridémico, agente  
 anti-hipercolesterolémico, agente anti-isquémico, agente  
 anti-cáncer, agente anti-citotóxico, agente anti-restenótico,  
 agente anti-pancreático, agente que disminuye el lípido,  
 agente supresor del apetito, agente potenciador de la memoria  
 10 o agente cognitivo y un portador farmacéuticamente aceptable  
 del mismo.

5. El compuesto de conformidad con la reivindicación 1,  
 caracterizado porque Y-X-CO es

15

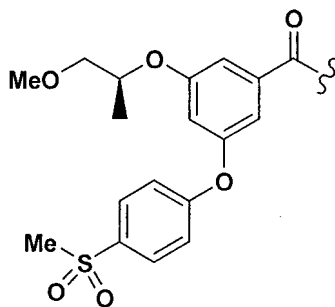


6. Un compuesto, caracterizado porque tiene la  
 20 estructura.

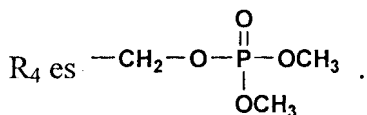


o una sal del mismo farmacéuticamente aceptable.

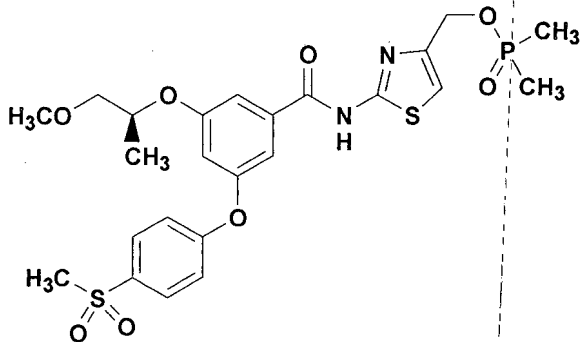
7. El compuesto de conformidad con la reivindicación  
5 1, caracterizado porque Y-X-CO es:



y/o



8. Un compuesto, caracterizado porque tiene la estructura



10

o una sal del mismo farmacéuticamente aceptable.



US007910747B2

(12) **United States Patent**  
**Ryono et al.**

(10) **Patent No.:** **US 7,910,747 B2**  
(45) **Date of Patent:** **Mar. 22, 2011**

(54) **PHOSPHONATE AND PHOSPHINATE  
PYRAZOLYLAMIDE GLUCOKINASE  
ACTIVATORS**

(75) Inventors: **Denis E. Ryono**, Princeton, NJ (US);  
**Peter T. W. Cheng**, Princeton, NJ (US);  
**Scott A. Bolton**, Newtown, PA (US);  
**Sean Chen**, Princeton, NJ (US); **Yan  
Shi**, Flourtown, PA (US); **Wei Meng**,  
Pennington, NJ (US); **Joseph A. Tino**,  
Lawrenceville, NJ (US)

(73) Assignee: **Bristol-Myers Squibb Company**,  
Princeton, NJ (US)

(\*) Notice: Subject to any disclaimer, the term of this  
patent is extended or adjusted under 35  
U.S.C. 154(b) by 0 days.

(21) Appl. No.: **11/769,964**

(22) Filed: **Jun. 28, 2007**

(65) **Prior Publication Data**  
US 2008/0009465 A1 Jan. 10, 2008

**Related U.S. Application Data**

(60) Provisional application No. 60/818,912, filed on Jul. 6,  
2006.

(51) **Int. Cl.**  
**C07D 231/00** (2006.01)

(52) **U.S. Cl.** ..... **548/375.1; 544/408; 548/953;**  
549/475

(58) **Field of Classification Search** ..... **544/408;**  
548/375.1, 953; 549/475  
See application file for complete search history.

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2006/0135578 A1\* 6/2006 Momose et al. .... 514/374

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WO WO 2006/016194 2/2006  
WO WO 2006/040528 4/2006  
WO WO 2006/040529 4/2006

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WO WO 2007/017649 2/2007  
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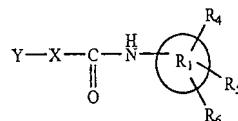
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enhanced antihyperglycaemic and insulinotropic actions",  
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Guertin, K.R. et al., "Small molecule glucokinase activators as glu-  
cose lowering agents: A new paradigm for diabetes therapy", Current  
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Johnson, D. et al., "Glucose-dependent Modulation of Insulin Secre-  
tion and Intracellular Calcium Ions by GKA50—a Glucokinase Acti-  
vator", Diabetes, 56, pp. 1694-1702 (2007).

(Continued)

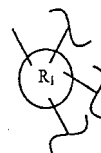
*Primary Examiner* — James O Wilson  
*Assistant Examiner* — Douglas M Willis  
(74) *Attorney, Agent, or Firm* — Maureen S. Gibbons;  
Burton Rodney

(57) **ABSTRACT**

Pyrazoloamides are provided which are phosphonate and  
phosphinate glucokinase activators that are useful in treating  
diabetes and related diseases and have the structure



wherein



is a pyrazoyl ring;

R<sub>4</sub> is —(CH<sub>2</sub>)<sub>n</sub>—Z—(CH<sub>2</sub>)<sub>m</sub>—PO(OR<sub>7</sub>)(OR<sub>8</sub>),  
—(CH<sub>2</sub>)<sub>n</sub>Z—(CH<sub>2</sub>)<sub>m</sub>—PO(OR<sub>7</sub>)R<sub>9</sub>, or  
—(CH<sub>2</sub>)<sub>n</sub>Z—(CH<sub>2</sub>)<sub>m</sub>—PO(R<sub>9</sub>)(R<sub>10</sub>);

R<sub>5</sub> and R<sub>6</sub> are independently selected from H, alkyl and  
halogen;

Y is R<sub>3</sub>(CH<sub>2</sub>)<sub>s</sub>, wherein R<sub>3</sub> is aryl, s is 0, X is a bond; and  
n, Z, m, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, and R<sub>7</sub> are as defined herein;  
or a pharmaceutically acceptable salt thereof.

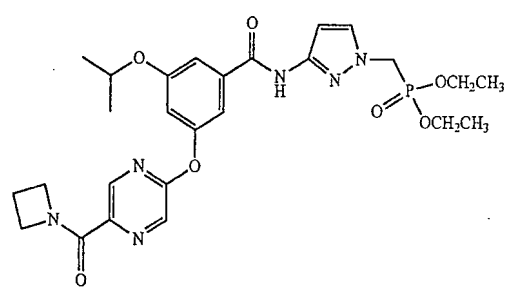
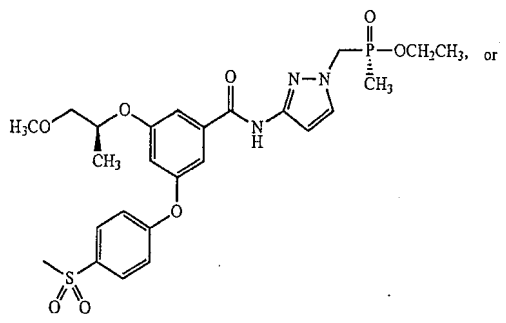
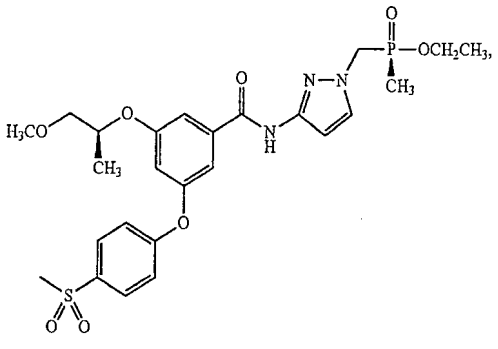
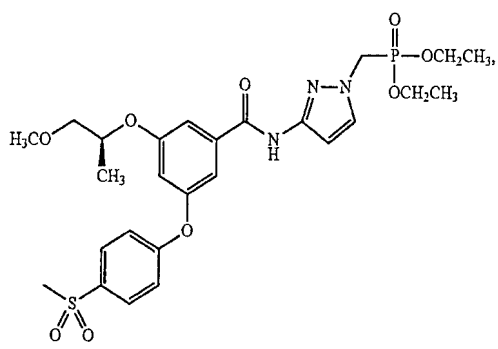
**3 Claims, No Drawings**

US 7,910,747 B2

279

What is claimed is:

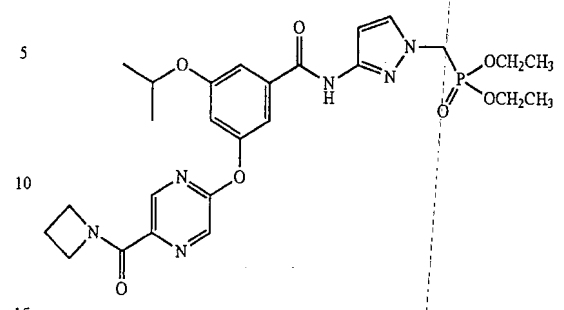
1. A compound selected from:



or a stereoisomer of any of the preceding compounds or a pharmaceutically acceptable salt thereof.

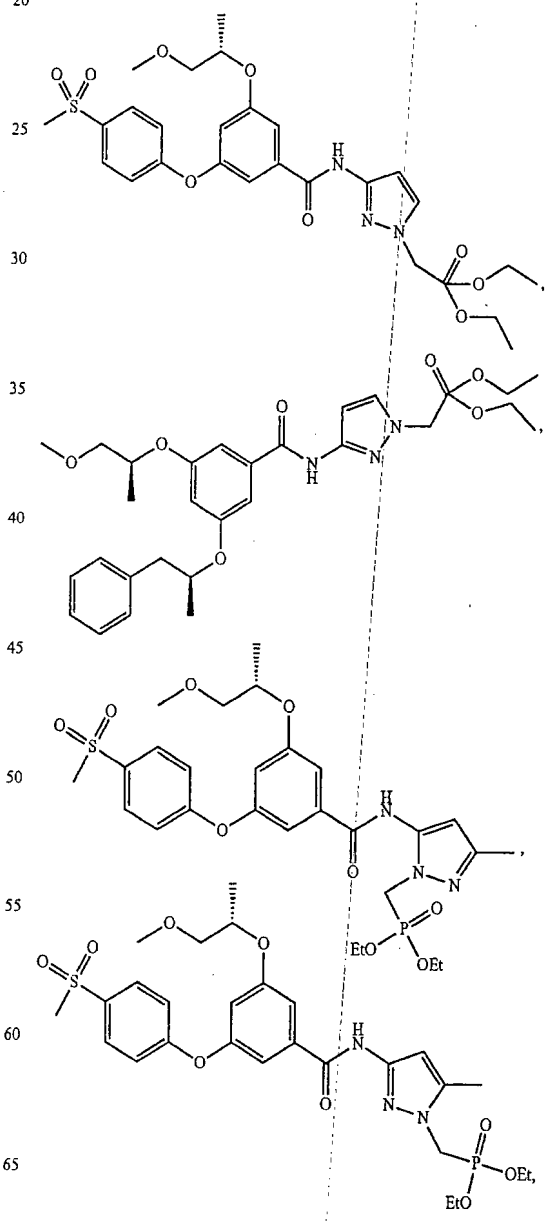
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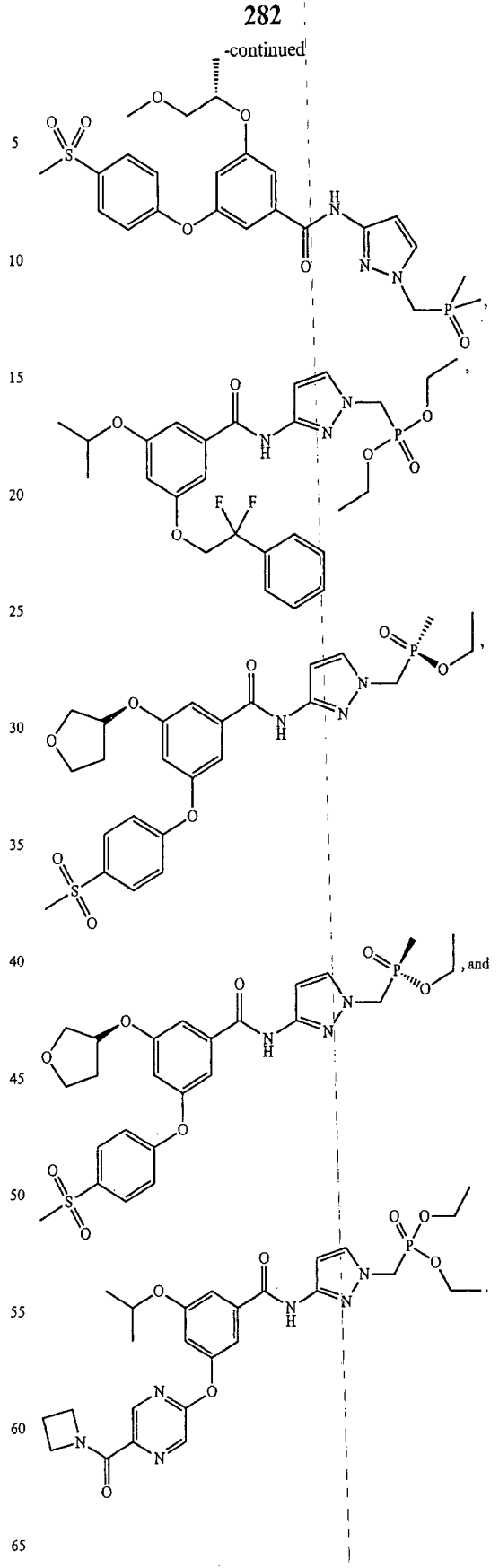
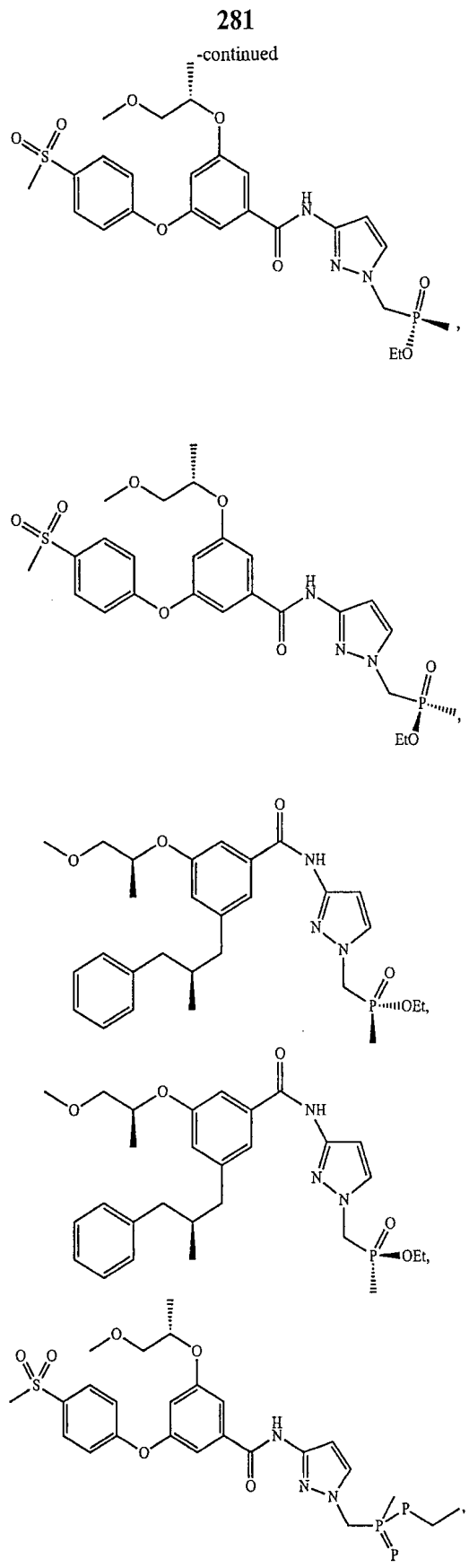
2. A compound having the structure:



or a pharmaceutically acceptable salt thereof.

3. A compound selected from the group consisting of the following structures or their pharmaceutically acceptable salts:





\* \* \* \* \*

UNITED STATES PATENT AND TRADEMARK OFFICE  
**CERTIFICATE OF CORRECTION**

PATENT NO. : 7,910,747 B2  
 APPLICATION NO. : 11/769964  
 DATED : March 22, 2011  
 INVENTOR(S) : Denis Ryono et al.

Page 1 of 2

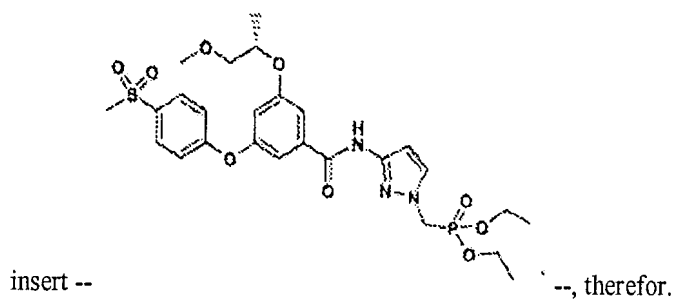
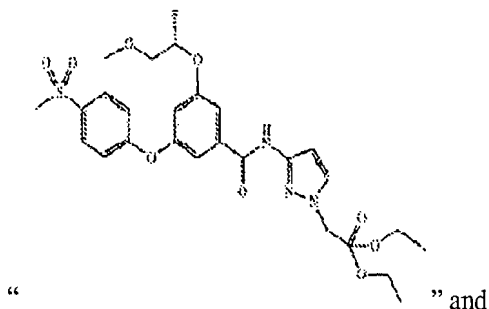
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Abstract:

Title Page, col. 2, line 7, delete "pyrazoyl" and insert -- pyrazolyl --, therefor;  
 Title Page, col. 2, line 13, delete "aryl," and insert -- aryl, --, therefor.

In the Claims:

Claim 3, col. 280, line 18, delete "acceptavle" and insert -- acceptable --, therefor.  
 Claim 3, col. 280, lines 20-34, delete



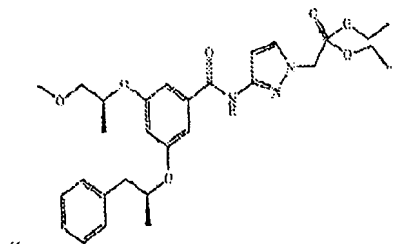
Signed and Sealed this  
 Eighteenth Day of October, 2011

*David J. Kappos*

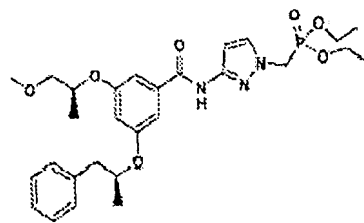
David J. Kappos  
 Director of the United States Patent and Trademark Office

In the Claims:

Claim 3, col. 280, line 35-44, delete

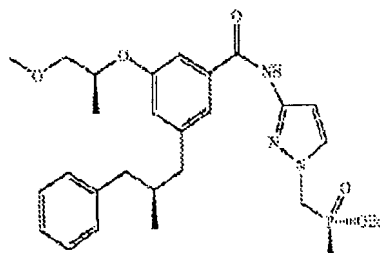


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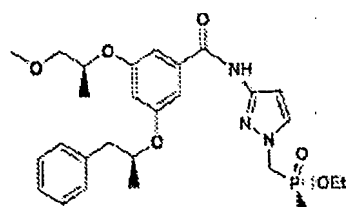


--, therefor.

Claim 3, col. 281, line 33-43, delete

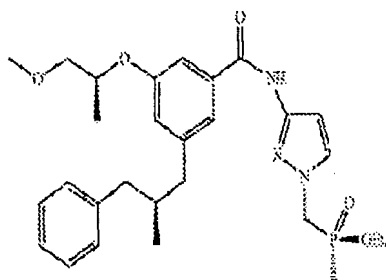


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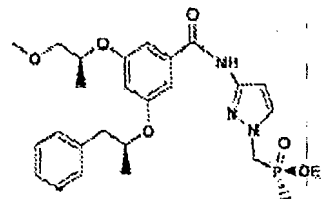


--, therefor.

Claim 3, col. 281, line 44-54, delete

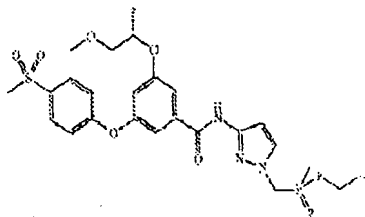


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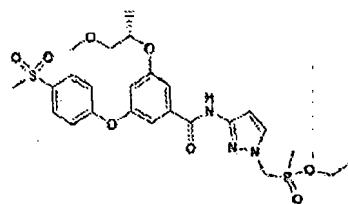


--, therefor.

Claim 3, col. 281, line 55-65, delete



” and insert --



--, therefor.



US008153677B2

(12) **United States Patent**  
**Ryono et al.**

(10) **Patent No.:** **US 8,153,677 B2**  
(45) **Date of Patent:** **\*Apr. 10, 2012**

(54) **SUBSTITUTED PYRAZOLYLAMIDE  
COMPOUNDS USEFUL AS GLUCOKINASE  
ACTIVATORS**

(75) **Inventors:** **Denis E. Ryono**, Minneapolis, MN (US);  
**Peter T. W. Cheng**, Princeton, NJ (US);  
**Scott A. Bolton**, Newtown, PA (US);  
**Sean Chen**, Princeton, NJ (US); **Yan**  
**Shi**, Flourtown, PA (US); **Wei Meng**,  
Pennington, NJ (US); **Joseph A. Tino**,  
Lawrenceville, NJ (US); **Richard B.**  
**Sulsky**, West Trenton, NJ (US)

(73) **Assignee:** **Bristol-Myers Squibb Company**,  
Princeton, NJ (US)

(\*) **Notice:** Subject to any disclaimer, the term of this  
patent is extended or adjusted under 35  
U.S.C. 154(b) by 0 days.

This patent is subject to a terminal dis-  
claimer.

(21) **Appl. No.:** **13/012,351**

(22) **Filed:** **Jan. 24, 2011**

(65) **Prior Publication Data**  
US 2011/0118211 A1 May 19, 2011

**Related U.S. Application Data**

(63) Continuation of application No. 11/769,964, filed on  
Jun. 28, 2007, now Pat. No. 7,910,747.

(60) Provisional application No. 60/818,912, filed on Jul. 6,  
2006.

(51) **Int. Cl.**  
**A61K 31/415** (2006.01)

(52) **U.S. Cl.** ..... 514/407; 548/375.1

(58) **Field of Classification Search** ..... 514/407;  
548/375.1

See application file for complete search history.

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2006/0135578 A1 6/2006 Momose et al.

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| WO | WO 2005/080360   | 9/2005  |

|    |                |         |
|----|----------------|---------|
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| WO | WO 2005/121110 | 12/2005 |
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| WO | WO 2006/016178 | 2/2006  |
| WO | WO 2006/016194 | 2/2006  |
| WO | WO 2006/040528 | 4/2006  |
| WO | WO 2006/040529 | 4/2006  |
| WO | WO 2006/058923 | 6/2006  |
| WO | WO 2007/007040 | 1/2007  |
| WO | WO 2007/007041 | 1/2007  |
| WO | WO 2007/007042 | 1/2007  |
| WO | WO 2007/017649 | 2/2007  |
| WO | WO 2007/060448 | 5/2007  |

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Johnson, D. et al., "Glucose-dependent Modulation of Insulin Secretion and Intracellular Calcium Ions by GKA50—a Glucokinase Activator", *Diabetes*, 56, pp. 1694-1702 (2007).  
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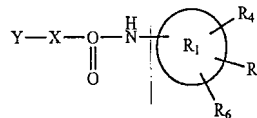
*Primary Examiner* — James O Wilson

*Assistant Examiner* — Douglas M Willis

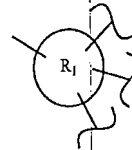
(74) *Attorney, Agent, or Firm* — Gary D. Greenblatt

(57) **ABSTRACT**

Compounds are provided which are phosphonate and phosphinate activators and thus are useful in treating diabetes and related diseases and have the structure



wherein



is a heteroaryl ring;

$R_4$  is  $-(CH_2)_n-Z-(CH_2)_m-PO(OR_7)(OR_8)$ ,

$-(CH_2)_n-Z-(CH_2)_m-OPO(OR_7)R_9$ ,

$-(CH_2)_n-Z-(CH_2)_m-OPO(R_9)(R_{10})$ , or

$-(CH_2)_n-Z-(CH_2)_m-PO(R_9)(R_{10})$ ;

$R_5$  and  $R_6$  are independently selected from hydrogen, alkyl and halogen;

$Y$  is  $R_7(CH_2)_s$  or is absent; and

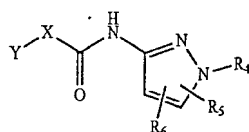
$X$ ,  $n$ ,  $Z$ ,  $m$ ,  $R_4$ ,  $R_5$ ,  $R_6$ ,  $R_7$ , and  $s$  are as defined herein;

or a pharmaceutically acceptable salt thereof. A method for treating diabetes and related diseases employing the above compounds is also provided.

**17 Claims, No Drawings**

What is claimed is:

1. A compound having the structure:

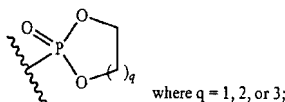


or a pharmaceutically acceptable salt thereof, wherein:

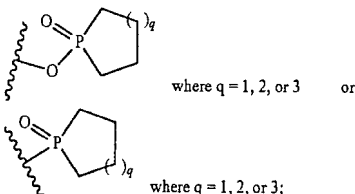
$R_4$  is selected from the group consisting of:  
 $-(CH_2)_n-Z-(CH_2)_m-PO(OR_7)(OR_8)$ ,  
 $-(CH_2)_n-Z-(CH_2)_m-PO(OR_7)R_9$ , and  
 $-(CH_2)_n-Z-(CH_2)_m-PO-(R_9)R_{10}$ ;

$R_7$  and  $R_8$  are the same or different and are independently selected from alkyl, or

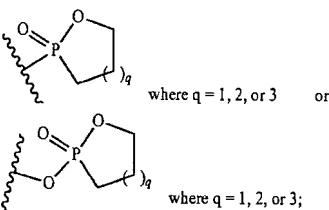
$R_7$  and  $R_8$  can be cyclized into a ring



$R_9$  and  $R_{10}$  are the same or different and are independently selected from the group consisting of alkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl;  
or  $R_9$  and  $R_{10}$  can be cyclized into a ring



or  $R_7$  and  $R_9$  can be cyclized into a ring



$Z$  is a single bond, alkylene, or alkenylene wherein said alkylene or alkenylene may be optionally substituted with hydroxy, alkoxy, aminoalkyl, aminoaralkyl, aminoheteroaralkyl, aminoaryl, aminoheteroaryl, or carboxy;

$m$  is zero, 1 or 2;

$n$  is 1 or 2;

$R_5$  and  $R_6$  are the same or different and are selected from the group consisting of hydrogen, alkyl, halogen and carboxy;

$X$  is a single bond;

$Y$  is  $R_3-(CH_2)_s-$ ;

$s$ =zero; and

$R_3$  is phenyl substituted with zero, 1, or 2 substituent groups independently selected:

(a)  $-OR^a$  wherein  $R^a$  is:

(i) alkyl, wherein said alkyl may be further substituted with at least one of halo, alkoxy or phenyl;

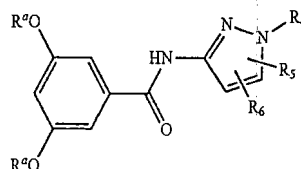
(ii) phenyl, optionally substituted with  $-SO_2R^c$  wherein  $R^c$  is alkyl;

(iii) a 4 to 7 membered heterocycle optionally substituted with  $-SO_2R^c$  wherein  $R^c$  is alkyl;

(iv) pyridinyl or pyrazinyl, optionally substituted with  $-C(=O)NR^dR^b$  or  $-SO_2R^c$  wherein  $R^d$  and  $R^b$  may join together with the N to which they are attached to form a 4- to 7-membered heterocycle and  $R^c$  is alkyl; and/or

(b)  $-C(=O)R^a$  wherein  $R^a$  is a 4- to 7-membered heterocycle.

2. The compound according to claim 1 having the structure:



or a pharmaceutically acceptable salt thereof; wherein:

$R_3$  is phenyl substituted with zero, 1, or 2 substituent groups independently selected:

(a)  $-OR^a$  wherein  $R^a$  is:

(i) alkyl, wherein said alkyl may be further substituted with at least one of halo, alkoxy or phenyl;

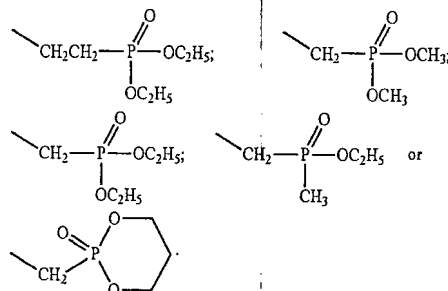
(ii) phenyl, optionally substituted with  $-SO_2R^c$  wherein  $R^c$  is alkyl; or

(iii) pyridinyl or pyrazinyl, optionally substituted with  $-C(=O)NR^dR^b$  or  $-SO_2R^c$  wherein  $R^d$  and  $R^b$  may join together with the N to which they are attached to form a 4- to 7-membered heterocycle and  $R^c$  is alkyl.

3. The compound according to claim 2 or a pharmaceutically acceptable salt thereof, wherein  $R_4$  is  $-(CH_2)_n-Z-(CH_2)_m-PO(OR_7)R_9$ .

4. The compound according to claim 2 or a pharmaceutically acceptable salt thereof, wherein  $R_4$  is  $-(CH_2)_n-Z-(CH_2)_m-PO-(R_9)R_{10}$ .

5. The compound according to claim 2 or a pharmaceutically acceptable salt thereof, wherein  $R_4$  is:



6. The compound according to claim 2 or a pharmaceutically acceptable salt thereof, wherein  $R_4$  is  $-(CH_2)_n-Z-(CH_2)_m-PO(OR_7)(OR_8)$ .

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7. The compound according to claim 6 or a pharmaceutically acceptable salt thereof, wherein:

Z is a single bond;

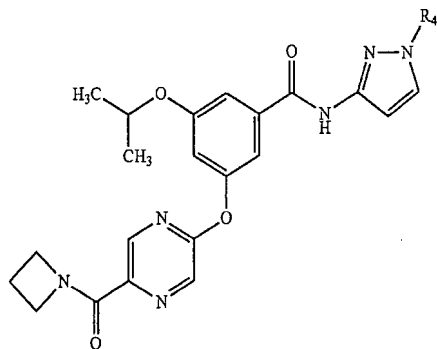
m is zero;

n is 1 or 2;

R<sub>7</sub> is alkyl; and

R<sub>8</sub> is alkyl.

8. The compound according to claim 1 having the structure:

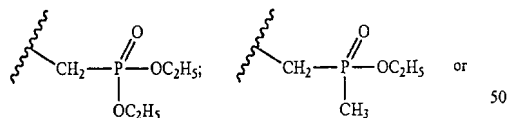
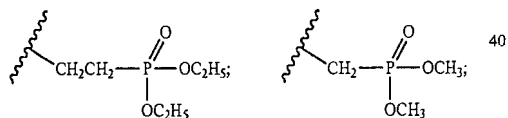


or a pharmaceutically acceptable salt thereof.

9. The compound according to claim 8 or a pharmaceutically acceptable salt thereof, wherein R<sub>4</sub> is  $-(CH_2)_nZ-$  (CH<sub>2</sub>)<sub>m</sub>-PO(OR<sub>7</sub>)R<sub>9</sub>.

10. The compound according to claim 8 or a pharmaceutically acceptable salt thereof, wherein R<sub>4</sub> is  $-(CH_2)_nZ-$  (CH<sub>2</sub>)<sub>m</sub>-PO-(R<sub>9</sub>)R<sub>10</sub>.

11. The compound according to claim 8 or a pharmaceutically acceptable salt thereof, wherein R<sub>4</sub> is:



12. The compound according to claim 8 or a pharmaceutically acceptable salt thereof, wherein R<sub>4</sub> is  $-(CH_2)_nZ-$  (CH<sub>2</sub>)<sub>m</sub>-PO(OR<sub>7</sub>)(OR<sub>8</sub>).

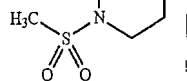
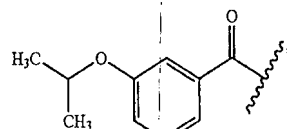
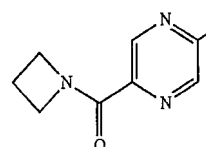
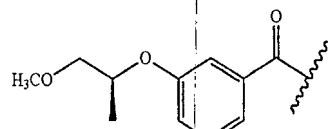
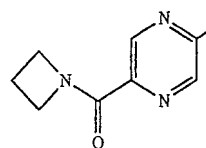
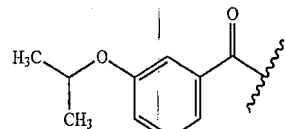
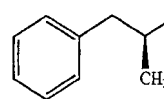
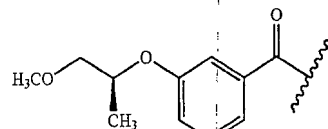
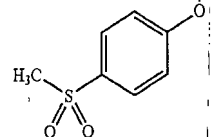
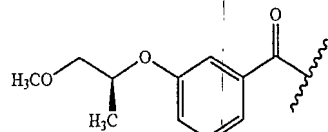
13. The compound according to claim 12 or a pharmaceutically acceptable salt thereof, wherein:

R<sub>7</sub> is alkyl; and

R<sub>8</sub> is alkyl.

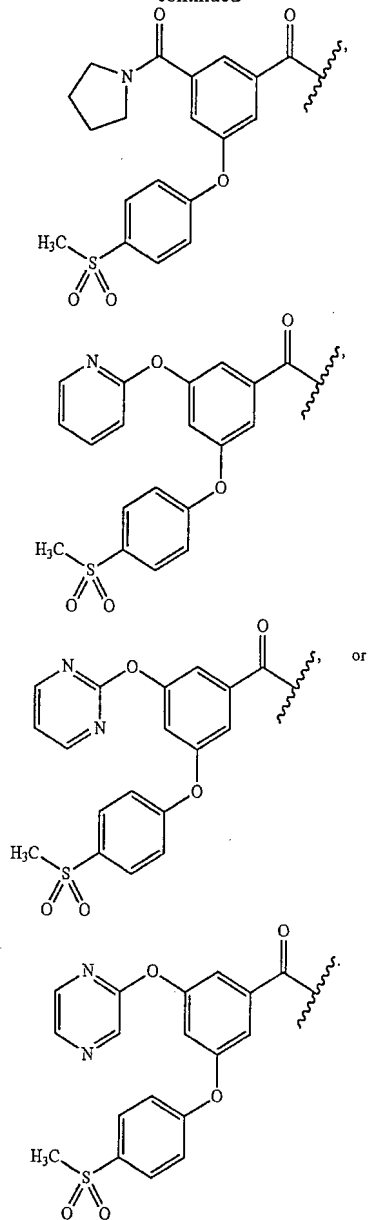
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14. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein Y-X-CO- is:

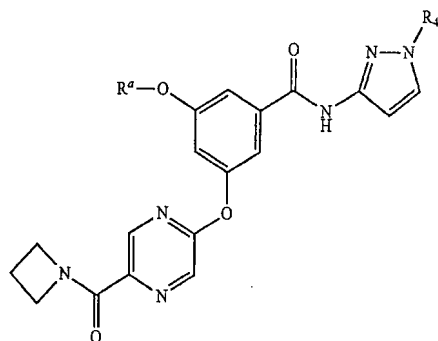


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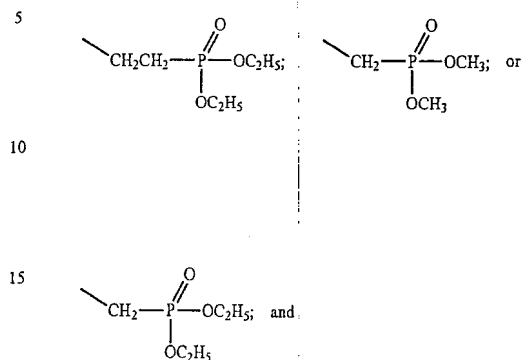


15. The compound according to claim 1 having the structure:



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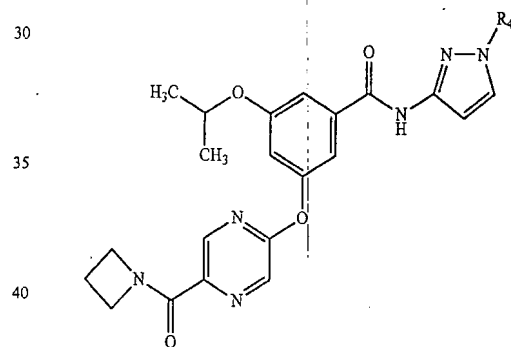
or a pharmaceutically acceptable salt thereof, wherein:  
wherein  $R_4$  is:



$R^a$  is  $C_{1-4}$  alkyl.

16. A pharmaceutical composition comprising a compound as according to claim 1 or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

17. The pharmaceutical composition according to claim 16, wherein said compound according to claim 1 is:



or a pharmaceutically acceptable salt thereof, wherein  $R_4$  is:

