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Señora Jefe de la
DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

EDIFICIO SISI Radicacion : 00065981 00000004
CARRERA 4 No. 7 Fecha (AMD): 2002-12-20 17:08:48
BOGOTA 8, COLC Trámite : 002 PATENTES D 1 REGISTRO/ 538 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Folios: 2 47-3611
10-4995

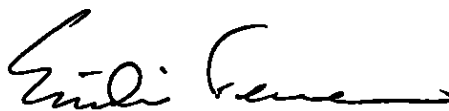
TRÁMITE : 002 EVENTO : 001 ACTUACIÓN : 538

Referencia : Expediente No. 00-065.981
Asunto : Solicitud de patente para: COMPOSICION FARMACEUTICA
Solicitante : TAKEDA CHEMICAL INDUSTRIES, LTD.
Fecha de solicitud : 01 de septiembre de 2000
Publicada en : la Gaceta No. 517 del 27 de junio de 2002

1. Yo, Emilio FERRERO, identificado como aparece al pie de mi firma, actuando como apoderado en el asunto de la referencia, atentamente, solicito se efectúe el examen de patentabilidad de la solicitud en referencia según lo establecido en el artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina. Para tal efecto presento junto con este escrito el recibo No. 02-80,897 por valor de \$318.000.00, que corresponde a la tasa fijada según lo dispuesto en la resolución No. 44691 del 31 de diciembre de 2001.

2. Ruego atentamente a la Señora Jefe se sirva ordenar que se anexe este recibo, para que se efectúe dicho examen y se continúe con el trámite de la solicitud.

Bogotá, 20 DIC 2002
Señora Jefe,


EMILIO FERRERO
T.P.A. No. 31.929

COLO 01763 801 006 0
JBP/JFR/ID-000118/WPCL1763

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SUPERINDUSTRIA Y COMERCIO

Radicacion : 00065981 00000004
 Fecha (AMD): 2002-12-20 17:08:48
 Tranite : 002 PATENTES D 1 REGISTRO/ 538 PETICION
 Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Folios: 2

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 02 - 80,897
 FECHA : DICIEMBRE 2 DE 2002

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	7030558	02/12/2002	28,771,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		112 PTC CAP-I EXAMEN DE PATENTIBILIDA	318,000.00
		TOTAL :	\$ 318,000.00

SON: TRESCIENTOS DIEZ Y OCHO MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Colo 01763-801-006 0

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020/
Bogotá, D.C.,

Doctor
Emilio Ferrero
Apoderado

Oficio N°

10999

REFERENCIA

Radicación	00 65981
Trámite	002
Evento	001
Actuación	430
Folios	011

Como resultado del examen de patentabilidad de la solicitud de patente de invención N° 00 65981, realizado según el artículo 45 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

Documentos estudiados:

- . Descripción: folios 500-571
- . Ejemplos: folios 571-577
- . Capítulo reivindicatorio estudiado: 578-677
- . Se reivindica prioridad presentada en Japón, el 03.09.99, bajo el número 1999/250443 y la número 2000/056021 de 28.02.00

Objeto de la invención

Según las reivindicaciones 1 a 24 de la presente solicitud, se refiere a una composición farmacéutica que comprende un sensibilizador de insulina en combinación con un compuesto de fórmula I, II, III, V o VI.

Clasificación internacional de patentes A 61 K 31/404

Excepciones a la patentabilidad

El art. 20d de la decisión 486 establece que *"No serán patentables los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales"*

2- Teniendo en cuenta lo anterior, el contenido de las reivindicaciones 13-17, que trata de "Un método para prevenir o tratar...", no es patentable.

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El artículo 14 de la decisión 486 de la comisión de la comunidad andina establece que: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*

El contenido de las reivindicaciones 18-24, que se refiere a "una utilización de un sensibilizador de insulina...", no se encuentra contemplado dentro de los objetos de patente, debido a que la legislación vigente contempla únicamente productos o procedimientos.

Claridad de la solicitud

El art. 30 de la decisión 486 establece que *"Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción"*

Teniendo en cuenta lo anterior, el término "sensibilizador de insulina" usado en las reivindicaciones 1-10 no corresponde a la definición de un compuesto, el cual debe ser definido por su fórmula química y no por el resultado a lograr.

El término "inferior" para alquilo debe ser especificado en los compuestos de fórmula I-VI, de acuerdo con la descripción.

Determinación del estado de la técnica:

Consultadas las fuentes de información con que cuenta este despacho, se encontraron los siguientes documentos, anteriores a la fecha de prioridad de la presente solicitud - 09.09.99-, relacionados con la materia de la presente solicitud:

Nº	Documento	Título	Fecha de publicación
1	US 5817689	"Derivados de indol que tienen un alquilo inferior sustituido por 2-fenil etanol amino en la posición 2 ó 3	06.10.98
2	US 5451677	"Fenil sulfonamidas sustituidas como agonistas beta 3 selectivos para el tratamiento de diabetes y obesidad"	19.09.95
3	WO 9901431	"Compuestos tricíclicos novedosos que tienen anillos saturados y composiciones que los contienen"	14.01.99
4	EP 0882707	"Compuestos tricíclicos novedosos y medicamentos que los contienen"	09.12.98

Evaluación de los requisitos de patentabilidad:

El artículo 14 de la decisión 486 de la comisión de la comunidad andina establece que: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*

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En cumplimiento del artículo 14 de la decisión 486 de la comisión de la comunidad andina, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Evaluación de la NOVEDAD

El artículo 16 de la decisión 486 contempla que *“Una invención se considerará nueva cuando no está comprendida en el estado de la técnica”*

La patente US 5817689 se relaciona con derivados de indol de fórmula (I) que son estimulantes potentes del receptor beta 3 y son útiles en el tratamiento de la obesidad y diabetes. Se revelan composiciones farmacéuticas que los contienen.

La patente US 5451677 publica fenilsulfonamidas sustituidas que son agonistas del receptor beta 3 y tienen actividad sobre la diabetes y la obesidad, finalmente se revelan sus métodos de preparación y composiciones que las contienen.

La publicación WO 9901431 revela compuestos de fórmula (I) que tienen agonismo sobre el receptor beta 3 y son eficaces para tratar y prevenir diabetes, obesidad hiperlipidemia, etc, se revelan composiciones que los contienen.

EP 0882707 revela compuestos de fórmula (I) que tienen agonismo sobre el receptor beta 3 y son eficaces para tratar y prevenir diabetes, obesidad hiperlipidemia, etc, se revelan composiciones que los contienen.

Comparando elemento por elemento, las composiciones de la 11-12 son iguales a las de las anterioridades citadas, debido a que se revelan los compuestos I-VI de la presente solicitud y composiciones que las contienen, y pueden afectar la novedad de la presente solicitud.

Lo anterior hace que el documento citado pueda afectar el nivel inventivo de la presente solicitud.

En conclusión los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
1	US 5817689	11-12	Novedad
2	US 5451677	11-12	Novedad
3	WO 9901431	11-12	Novedad
4	EP 0882707	11-12	Novedad

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

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Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo 5 del título primero de la Circular Única N° 10 de 2001


Álix Carmenza Céspedes de Vergel
Jefe de la División de Nuevas Creaciones

24 NOV. 2005

El anterior requerimiento fue notificado por fijación en lista, de fecha _____

CONCEPTO TÉCNICO Número 1813	EXAMINADOR TÉCNICO Código 202024
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US005817689A

United States Patent [19]

[11] Patent Number: 5,817,689

Kato et al.

[45] Date of Patent: Oct. 6, 1998

[54] **INDOLE DERIVATIVES HAVING A 2-PHENYL-ETHANOLAMINO-SUBSTITUTED LOWER ALKYL GROUP AT THE 2-OR 3-POSITION THEREOF**

[75] **Inventors:** Shiro Kato, Sakai; Hiroshi Harada, Suita; Yoshimi Hirokawa, Ikoma; Naoyuki Yoshida, Sakai; Hitoshi Kawashima, Osaka, all of Japan

[73] **Assignee:** Dainippon Pharmaceutical Co., Ltd., Osaka, Japan

[21] **Appl. No.:** 836,983

[22] **PCT Filed:** Nov. 27, 1995

[86] **PCT No.:** PCT/JP95/02400

§ 371 Date: May 29, 1997

§ 102(e) Date: May 29, 1997

[87] **PCT Pub. No.:** WO96/16938

PCT Pub. Date: Jun. 6, 1996

[30] **Foreign Application Priority Data**

Nov. 29, 1994 [JP] Japan 6-321402

[51] **Int. Cl.⁶** A61K 31/40; C07D 209/14

[52] **U.S. Cl.** 514/415; 514/411; 514/866; 514/909; 548/431; 548/506

[58] **Field of Search** 548/506, 431; 514/411, 415

[56] **References Cited**

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4,055,658 10/1977 Kreighbaum et al. 424/304

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Bobzin et al., "Aromatic Alkaloids from the Marine Sponge Chelonaplysilla", J. Org. Chem., 56, 4403-4407 (1991).

Chemical Abstract, 78, 431, 71665s (1973).

Clifton et al., "Arylethanolamines Derived from Salicylamide with α - and β -Adrenoceptor Blocking Activities. Preparation of Lebetalol, Its Enantiomers, and Related Salicylamides", 25, 670-679 (1982).

Jackman et al., "Some tryptamine derivatives: 1-aryloxy-3-[(2-indol-3'-ylethyl)amino]propan-2-ols", J. Pharm. Pharmacol., 17, 742-746 (1965).

Chemical Abstract, 96, 726, 142543k (1982).

Chemical Abstract, 109, 666, 128763n (1988).

Kato et al., CA 122:239540, May 8, 1995.

Patent Abstracts of Japan for JP 06345731, 1994.

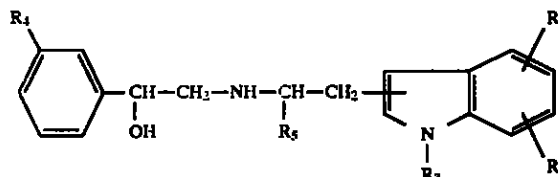
Primary Examiner—Joseph McKane

Assistant Examiner—Laura L. Stockton

Attorney, Agent, or Firm—Foley & Lardner

[57] **ABSTRACT**

An indole derivative of the formula:



wherein R_1 is lower alkoxy, lower alkoxy-carbonyl-lower alkoxy, carboxy-lower alkoxy, lower alkoxy-carbonyl, phenyl-lower alkoxy, lower alkyl being optionally substituted by hydroxy, di-lower alkylaminosulfonyl, etc., R_2 is hydrogen, halogen, lower alkoxy, lower alkoxy-carbonyl-lower alkoxy, carboxy-lower alkoxy, etc., R_3 is hydrogen or lower alkyl, R_4 is halogen or trifluoromethyl, R_5 is lower alkyl, or a salt thereof, these compounds being potent β_3 -adrenergic receptor-stimulating agent with excellent adrenoceptor selectivity, and being useful in the prophylaxis or treatment of obesity or diabetes mellitus.

25 Claims, No Drawings

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-continued

(A) DESCRIPTION: /desc = "chemically synthetic DNA"

(x 1) SEQUENCE DESCRIPTION: SEQ ID NO:3:

TTCTCGAGCC GGGGAATCCC ATGGGAC

27

(2) INFORMATION FOR SEQ ID NO:4:

(1) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(1 1) MOLECULE TYPE: other nucleic acid

(A) DESCRIPTION: /desc = "chemically synthetic DNA"

(x 1) SEQUENCE DESCRIPTION: SEQ ID NO:4:

ACACCTGCAG GTGAGGCTTC CAGGCGTCC

29

(2) INFORMATION FOR SEQ ID NO:5:

(1) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(1 1) MOLECULE TYPE: other nucleic acid

(A) DESCRIPTION: /desc = "chemically synthetic DNA"

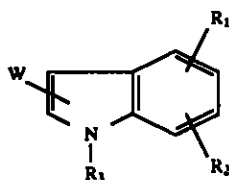
(x 1) SEQUENCE DESCRIPTION: SEQ ID NO:5:

TGTAAGCTTC TGCTTTACAG CAGTGAGTC

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We claim:

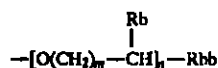
1. An indole derivative of the formula [I]:



wherein R_1 is a lower alkyl group being optionally substituted by a hydroxy group, a phenylsulfonylamino group, a lower alkylsulfonylamino group, a mono- or di-lower alkylaminosulfonyl group, or a group selected from the following (a) to (d), or combines with R_2 to form a methylenedioxy group, said methylenedioxy group being optionally substituted by a carboxyl group or a lower alkoxy-carbonyl group,

(a) a group of the formula: $-X-R_a$ (wherein X is O, S or NH, R_a is a hydrogen atom or a lower alkyl group, provided that when X is S, then R_a is a lower alkyl group);

(b) a group of the formula:

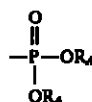


R_b (wherein R_b is a hydrogen atom, a lower alkyl group, a lower alkoxy-carbonyl group or a carboxyl group, R_{bb} is a lower alkoxy-carbonyl group or a carboxyl group, m is an integer of 0 to 3, and n is 0 or 1);

(c) a group of the formula: $-O(CH_2)_p-R_c$ (wherein R_c is a lower alkanoyl group, a hydroxy group, a cyano

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group, a phenyl group, a mono- or di-lower alkylaminocarbonyl group, or a group of the formula:



[II]

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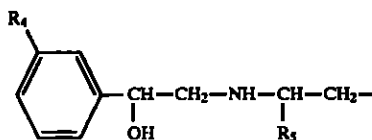
(wherein R_a is a hydrogen atom or a lower alkyl group), and p is an integer of 1 to 4); and

(d) a group of the formula: $-Y-(CH_2)_q-R_d$ (wherein Y is NH or S, R_d is a carboxyl group or a lower alkoxy-carbonyl group, and q is an integer of 1 to 4);

R_2 is a hydrogen atom, a halogen atom, a lower alkyl group being optionally substituted by a hydroxy group, a hydroxy group, a lower alkoxy group, or a group of the above (b) or (c), or combines with R_1 to form a methylenedioxy group, said methylenedioxy group being optionally substituted by a carboxyl group or a lower alkoxy-carbonyl group;

R_3 is a hydrogen atom or a lower alkyl group;

W is a group of the formula [II] which bonds to the 2- or 3-position of the indole nucleus:



[II]

wherein R_4 is a halogen atom or a trifluoromethyl group, and R_5 is a lower alkyl group, or a salt thereof.

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15. 2-[3-(7-Carboxymethoxyindol-3-yl)-2-propylamino]-1-(3-chlorophenyl)ethanol, or a salt thereof.

16. An optical isomer of 2-[3-(7-Carboxymethoxyindol-3-yl)-2-propylamino]-1-(3-chlorophenyl)ethanol, or a salt thereof.

17. A β 3-adrenergic receptor-stimulating composition, which comprises as an active ingredients a therapeutically effective amount of the indole derivative as set forth in claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

18. A composition for treatment of diabetes mellitus, which comprises as an active ingredient, a therapeutically effective amount of the indole derivative as set forth in claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

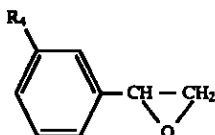
19. A composition for treatment of obesity, which comprises as an active ingredient, a therapeutically effective amount of the indole derivative as set forth in claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

20. A pharmaceutical composition which comprises the indole derivative set forth in claim 1 or a pharmaceutically acceptable salt and a pharmaceutically acceptable carrier or diluent.

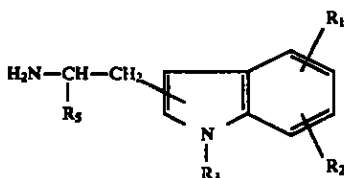
21. A method for treatment of diabetes mellitus in mammals, which comprises administering to said mammal a therapeutically effective amount of the indole derivative as set forth in claim 1, or a pharmaceutically acceptable salt thereof.

22. A method for treatment of obesity in mammals, which comprises administering to said mammal a therapeutically effective amount of the indole derivative as set forth in claim 1, or a pharmaceutically acceptable salt thereof.

23. A process for preparing the indole derivative of the formula I as set forth in claim 1 or a salt thereof, which comprises reacting a compound of the formula III:



wherein R_4 is a halogen atom or a trifluoromethyl group, with a compound of the formula IV:

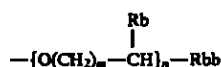


wherein R_1 is a lower alkyl group being optionally substituted by a hydroxy group, a phenylsulfonylamino group, a lower alkylsulfonylamino group, a mono- or di-lower alkylamino-sulfonyl group, or a group selected from the following (a) to (d), or combines with R_2 to form a methylenedioxy group, said methylenedioxy group being optionally substituted by a carboxyl group or a lower alkoxycarbonyl group,

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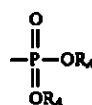
(a) a group of the formula: $-X-Ra$, wherein X is O, S or NH, Ra is a hydrogen atom or a lower alkyl group, provided that when X is S, then Ra is a lower alkyl group;

(b) a group of the formula:



wherein Rb is a hydrogen atom, a lower alkyl group, a lower alkoxycarbonyl group or a carboxyl group, Rbb is a lower alkoxycarbonyl group or a carboxyl group, m is an integer of 0 to 3, and n is 0 or 1;

(c) a group of the formula: $-O(CH2)_p-Rc$, wherein Rc is a lower alkanoyl group, a hydroxy group, a cyano group, a phenyl group, a mono- or di-lower alkylaminocarbonyl, or a group of the formula:

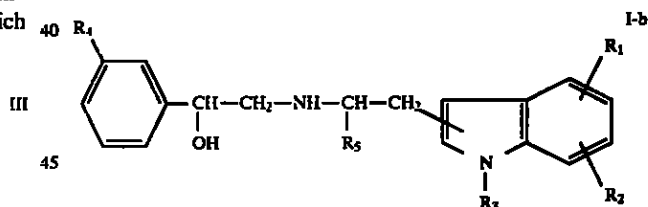


wherein R_1 is a hydrogen atom or a lower alkyl group, and p is an integer of 1 to 4;

(d) a group of the formula: $-Y-(CH2)_q-Rd$, wherein Y is NH or S, Rd is a carboxyl group or a lower alkoxycarbonyl group, and q is an integer of 1 to 4; and

R_2 is a hydrogen atom, a halogen atom, a lower alkyl group, being optionally substituted by a hydroxy group, a hydroxy group, a lower alkyl group, or a group of the above (b) or (c), or combines with R_1 to form a methylenedioxy group being optionally substituted by a carboxyl group; R_3 is a hydrogen atom or a lower alkyl group; and R_5 is a lower alkyl group, or a salt thereof.

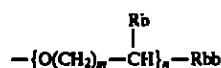
24. A process for preparing a compound of formula I-b:



wherein R_1 is a lower alkyl group being optionally substituted by a hydroxy group, a phenylsulfonylamino group, a lower alkylsulfonylamino group, a mono- or di-lower alkylaminosulfonyl group, or a group selected from the following (a)', (b)', (c)' and (d)', or combines with R_2 to form a methylenedioxy group, said methylenedioxy group being optionally substituted by a carboxyl group or a lower alkoxycarbonyl group,

(a)' a group of the formula $-X'-Ra$ wherein X' is O or S, Ra is a hydrogen atom or a lower alkyl group, provided that when X' is S, then Ra is a lower alkyl group;

(b) a group of the formula



wherein Rb is a hydrogen atom, a lower alkyl group, a lower alkoxycarbonyl group or a carboxyl group, Rbb

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US005451677A

United States Patent [19]

Fisher et al.

[11] Patent Number: 5,451,677

[45] Date of Patent: Sep. 19, 1995

[54] SUBSTITUTED PHENYL SULFONAMIDES AS SELECTIVE β 3 AGONISTS FOR THE TREATMENT OF DIABETES AND OBESITY

[75] Inventors: Michael H. Fisher, Ringoes; Robert J. Mathvink, Jersey City; Hyun O. Ok, Edison; Emma R. Parmee, Hoboken; Ann E. Weber, Scotch Plains, all of N.J.

[73] Assignee: Merck & Co., Inc., Rahway, N.J.

[21] Appl. No.: 168,105

[22] Filed: Dec. 15, 1993

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 15,689, Feb. 9, 1993, abandoned.

[51] Int. CL⁶ C07D 455/00; C07D 307/10; C07C 311/01

[52] U.S. CL 546/138; 546/290; 548/316.4; 548/469; 548/541; 549/33; 549/416; 549/475; 564/80; 564/82; 564/83; 564/84; 564/85; 564/86; 564/87; 564/88; 564/89; 564/90; 564/92; 564/96; 564/99

[58] Field of Search 514/604, 605; 564/80, 564/82, 83, 84, 85, 86, 87, 88, 89, 90, 92, 96, 99; 546/290, 138; 548/469, 541, 316.4; 549/33, 475, 416

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4,999,377 3/1991 Caulkett et al. 514/507
5,017,619 5/1991 Alig et al. 514/653
5,066,678 11/1991 Skidmore et al. 514/597
5,153,210 10/1992 Ainsworth et al. 514/369

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455006 4/1991 European Pat. Off. .
427480 5/1991 European Pat. Off. .
9000548 1/1990 WIPO .
90/15203 12/1990 WIPO .
WO94/03425 2/1994 WIPO .

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Lis, et al, Abstract to "Synthesis of novel (aryloxy) propanolamines and related compounds possessing both class II and class III antiarrhythmic activity" J. Med. Chem., (1990), 33(10), pp. 2883-2891.
Bloom, et al., J. Med. Chem., 35 3081-3084 (1992).
Still, et al., J. Org. Chem., 43, 2923 (1978).

Primary Examiner—José G. Dees
Assistant Examiner—Dwayne C. Jones
Attorney, Agent, or Firm—Mollie M. Yang; David L. Rose

[57] ABSTRACT

Substituted phenylsulfonamides are selective β ₃ adrenergic receptor agonists with very little β ₁ and β ₂ adrenergic receptor activity and as such the compounds are capable of increasing lipolysis and energy expenditure in cells. The compounds thus have potent activity in the treatment of Type II diabetes and obesity. The compounds can also be used to lower triglyceride levels and cholesterol levels or raise high density lipoprotein levels or to decrease gut motility. In addition, the compounds can be used to reduced neurogenic inflammation or as antidepressant agents. The compounds are prepared by coupling an aminocalkylphenyl-sulfonamide with an appropriately substituted alkyl epoxide. Compositions and methods for the use of the compounds in the treatment of diabetes and obesity and for lowering triglyceride levels and cholesterol levels or raising high density lipoprotein levels or for increasing gut motility are also disclosed.

18 Claims, No Drawings

compound of the formula (I) or pharmaceutically acceptable salt thereof. The compositions are formulated and administered in the same general manner as detailed below for treating diabetes and obesity. They may also contain other active ingredients known for use in the treatment of atherosclerosis and related conditions, for example fibrates such as clofibrate, bezafibrate and gemfibrozil; inhibitors of cholesterol biosynthesis such as HMG-CoA reductase inhibitors for example lovastatin, simvastatin and pravastatin; inhibitors of cholesterol absorption for example beta-sitosterol and (acyl CoA:cholesterol acyltransferase) inhibitors for example melinamide; anion exchange resins for example cholestyramine, colestipol or a dialkylaminoalkyl derivatives of a cross-linked dextran; nicotinic alcohol, nicotinic acid or a salt thereof; vitamin E; and thyromimetics.

The compounds of the instant invention also have the effect of reducing intestinal motility and thus find utility as aiding in the treatment of various gastrointestinal disorders such as irritable bowel syndrome. It has been proposed that the motility of non-sphincteric smooth muscle contraction is mediated by activity at β_3 adrenoceptors. The availability of a β_3 specific agonist, with little activity at β_1 and β_2 receptors will assist in the pharmacologic control of intestinal motility without concurrent cardiovascular effects. The instant compounds are administered generally as described below with dosages similar to those used for the treatment of diabetes and obesity.

It has also been found unexpectedly that the compounds which act as agonists at β_3 adrenoreceptors may be useful in the treatment of gastrointestinal disorders, especially peptic ulcerations, esophagitis, gastritis and duodenitis, (including that induced by *H. pylori*), intestinal ulcerations (including inflammatory bowel disease, ulcerative colitis, Crohn's disease and proctitis) and gastrointestinal ulcerations.

In addition, β_3 receptors have been indicated to have an effect on the inhibition of the release of neuropeptides in certain sensory fibers in the lung. As sensory nerves may play an important role in the neurogenic inflammation of airways, including cough, the instant specific β_3 agonists may be useful in the treatment of neurogenic inflammation, such as asthma, with minimal effects on the cardiopulmonary system.

β_3 adrenoreceptors are also able to produce selective antidepressant effects by stimulating the β_3 receptors in the brain and thus an additional contemplated utility of the compounds of this invention are as antidepressant agents.

The active compounds of the present invention may be orally administered as a pharmaceutical composition, for example, with an inert diluent, or with an assimilable edible carrier, or they may be enclosed in hard or soft shell capsules, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet. For oral therapeutic administration, which includes sublingual administration, these active compounds may be incorporated with excipients and used in the form of tablets, pills, capsules, ampules, sachets, elixirs, suspensions, syrups, and the like. Such compositions and preparations should contain at least 0.1 percent of active compound. The percentage of active compound in these compositions may, of course, be varied and may conveniently be between about 2 percent to about 60 percent of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that an effective dosage will

be obtained. The active compounds can also be administered intranasally as, for example, liquid drops or spray.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration, the condition being treated and the severity of the condition being treated.

When treating diabetes mellitus and/or hyperglycemia generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from about 0.1 milligram to about 1 milligram per kilogram of animal body weight, preferably given in divided doses two to six times a day, or in sustained release form. For most large mammals, the total daily dosage is from about 3.5 milligrams to about 140 milligrams, preferably from about 3.5 milligrams to about 5 milligrams. In the case of a 70 kg adult human, the total daily dose will generally be from about 7 milligrams to about 70 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response.

When treating obesity, in conjunction with diabetes and/or hyperglycemia, or alone, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from 1 milligram to about 10 milligrams per kilogram of animal body weight, preferably given in divided doses two to six times a day, or in sustained release form. For most large mammals, the total daily dosage is from about 35 milligrams to about 1,400 milligrams, preferably from about 35 milligrams to about 50 milligrams. In the case of a 70 kg adult human, the total daily dose will generally be from about 70 milligrams to about 700 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response.

The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

These active compounds may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example,

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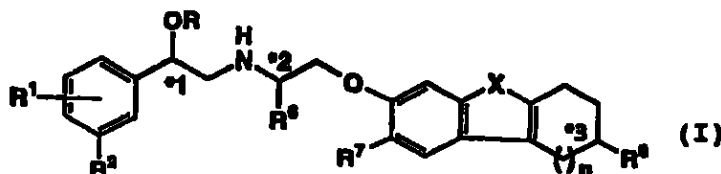
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(21) 国際出願番号 PCT/JP98/02680 (22) 国際出願日 1998年6月17日(17.06.98) (30) 優先権データ 特願平9/178197 1997年7月3日(03.07.97) JP (71) 出願人 (米国を除くすべての指定国について) 旭化成工業株式会社 (ASAHI KASEI KOGYO KABUSHIKI KAISHA)[JP/JP] 〒530-0004 大阪府大阪市北区堂島浜1丁目2番6号 Osaka, (JP) (72) 発明者 ; および (73) 発明者 / 出願人 (米国についてのみ) 三好詩郎(MIYOSHI, Shiro)[JP/JP] 〒416-0946 静岡県富士市五黄島843-8 Shizuoka, (JP) 小川行平(OGAWA, Kohei)[JP/JP] 〒411-0802 静岡県三島市東大場2-24-12 Shizuoka, (JP) (74) 代理人 弁理士 小林和憲(KOBAYASHI, Kazunori) 〒170-0004 東京都豊島区北大塚2丁目25番1号 太陽生命大塚ビル3階 Tokyo, (JP)		(81) 指定国 AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO特許 (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), ユーラシア特許 (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), 欧州特許 (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI特許 (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). 添付公開書類 国際調査報告書

(54)Title: NOVEL TRICYCLIC COMPOUNDS HAVING SATURATED RINGS AND MEDICINAL COMPOSITIONS CONTAINING THE SAME

(54)発明の名称 飽和環を含む新規な3環性化合物及びそれらを含む医薬組成物

(57) Abstract

Compounds represented by general formula (I) or their salts, having β_3 -adrenoceptor agonism and being efficacious when employed in drugs for treating and preventing diabetes, obesity, hyperlipemia, etc. wherein R represents hydrogen or methyl; R^1 represents hydrogen, halogeno, hydroxy, benzyloxy, amino or hydroxymethyl; R^2 represents hydrogen, hydroxymethyl, NHR^3 , $SO_2NR^4R^{4'}$, or nitro (wherein R^3 represents hydrogen, methyl, SO_2 , R^5 , formyl or $CONHR^6$; R^5 represents lower alkyl, benzyl or $NR^4R^{4'}$; R^4 and $R^{4'}$ may be the same or different and each represents hydrogen, lower alkyl or benzyl; and $R^{4'}$ represents hydrogen or lower alkyl); R^6 represents hydrogen or lower alkyl; n is 1 or 2; X represents secondary nitrogen, oxygen or sulfur; and when n is 1, then one of R^7 and R^8 represents hydrogen while another represents hydrogen, amino, acetylamino or hydroxy, or when n is 2, then R^8 represents hydrogen while R^7 represents hydrogen, amino, acetylamino or hydroxy.



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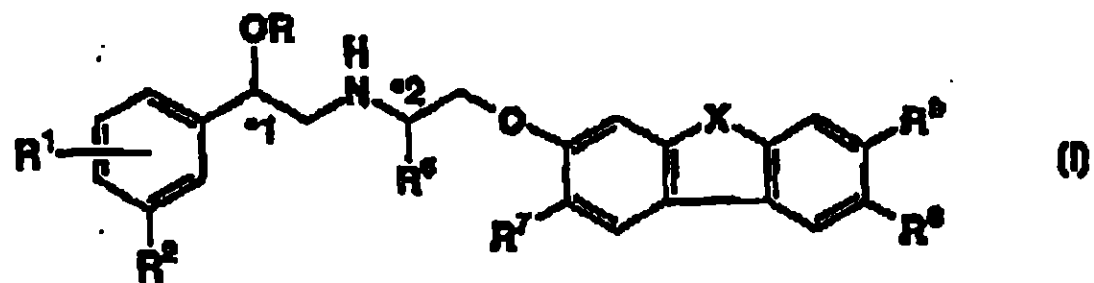
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(54) **NOVEL TRICYCLIC COMPOUNDS AND DRUG COMPOSITIONS CONTAINING THE SAME**

(57) Compounds represented by general formula (I) or salts thereof, a process for producing the same, and intermediates therefor, wherein R represents hydrogen or methyl; R¹ represents hydrogen, halogeno, hydroxy, benzyloxy, amino, or hydroxymethyl; R² represents hydrogen, hydroxymethyl, NHR³, SO₂NR⁴R⁴, or nitro; R⁶ represents hydrogen or lower alkyl; and X represents nitrogen, oxygen, sulfur, or methylene, provided that when X represents nitrogen, oxygen, or sulfur, then R⁹ represents hydrogen, one of R⁷ and R⁸ represents hydrogen, and the other thereof represents hydrogen, amino, acetylamino, or hydroxy, and when X represents methylene, then R⁷ and R⁸ each represents hydrogen and R⁹ represents hydrogen, amino, etc. They have a β-3 adrenaline receptor agonist and are useful as drugs for the treatment and prevention of diabetes, obesity, hyperlipemia, etc.



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