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As. 93.344

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 04-022003- -00006-0000

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Act. 444 RESPUESTAREQUE Folios: 10

Señora

JEFE DE DIVISIÓN DE NUEVAS CREACIONES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
E. S. D.

REF: Expediente No. 04 022.003 – solicitud de patente de invención a favor
de ASTRAZENECA AB

Respuesta a oficio No. 13855 del 2 de noviembre de 2007

JUAN PABLO CADENA SARMIENTO, portador de la tarjeta profesional No. 57.492 del C.S.J., obrando como apoderado de la sociedad ASTRAZENECA AB, según lo acredita el documento de poder presentado ante esa División, me permito dar respuesta a las observaciones de carácter técnico y jurídico, relacionadas con la patentabilidad, para la concesión de la patente de acuerdo con la Decisión 486 según el concepto técnico No. 1864 notificado por fijación en lista de fecha 02 de noviembre de 2007

Con el fin de superar las objeciones relacionadas con la claridad de la solicitud presentadas por el señor examinador, se anexa un nuevo capítulo reivindicatorio con 1 – 17 reivindicaciones, el cual reemplaza en su totalidad el capítulo reivindicatorio presentado anteriormente y no anexa materia nueva ni amplía el alcance de la presente solicitud.

EL nuevo capítulo reivindicatorio anexo subsana completamente las objeciones presentadas por el señor examinador, relacionadas con la falta de claridad del mismo. En primer lugar el nuevo capítulo reivindicatorio se dirige a una única estructura y especifica aun más los sustituyentes dentro de la misma.

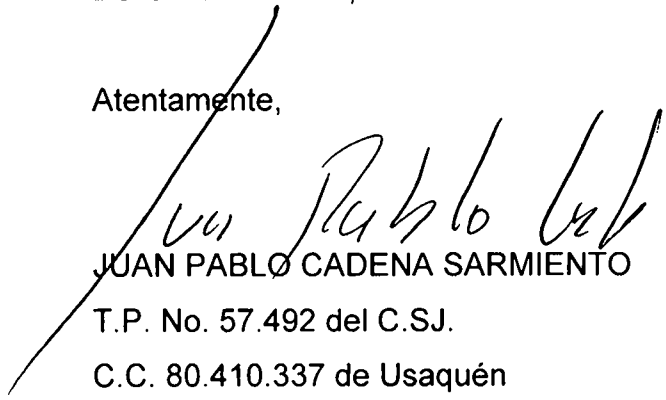
El nuevo capítulo reivindicatorio se dirige a los compuestos de fórmula (IIb) divulgados en la página 29 de la solicitud. Así mismo, se elimina el uso de las expresiones "profarmaco", "sal" y "solvato" y se completa la traducción del capítulo reivindicatorio, eliminando todas aquellas palabras que quedaban en inglés.

El nuevo capítulo anexo también subsana la objeción por falta de unidad de invención al referirse a una estructura única y al delimitar con mayor claridad los sustituyentes empleados. Por último, se elimina las reivindicaciones relativas al uso, subsanando así la objeción presentada por el señor examinador.

En vista de lo anterior, respetuosamente solicitamos el retiro de las objeciones a la presente solicitud, sobre la base de los argumentos y el nuevo capítulo reivindicatorio presentados ya que, en opinión del solicitante, la presente invención cumple con los requisitos de novedad, altura inventiva y aplicabilidad industrial de la Decisión 486.

De la Señora Jefe,

Atentamente,



JUAN PABLO CADENA SARMIENTO

T.P. No. 57.492 del C.SJ.

C.C. 80.410.337 de Usaquén

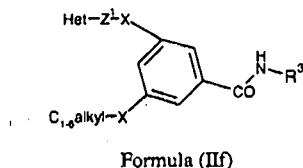
Carrera 7 No. 71-21, Torre B, Of. 402

Bogotá, Enero 30 de 2008

CH
anexos

Reivindicaciones

1. Un compuesto de fórmula (IIf):



en donde:

Het es un heterociclilo monocíclico, y los grupos het y C₁₋₆ alquilo son opcionalmente sustituidos independiente con 3 grupos seleccionados de R⁴ y el grupo C₁₋₆ alquilo opcionalmente contiene un enlace doble;

cada X es un enlazante seleccionado independientemente de:

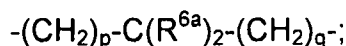
-O-Z-, -O-Z-O-Z-, -C(O)O-Z-, OC(O)-Z-, -S-Z-, -SO-Z-, -SO₂-Z-, -N(R⁶)-Z-,
 , -N(R⁶)SO₂-Z-, -SO₂N(R⁶)-Z-, -CH=CH-Z-, C≡C-Z-, -N(R⁶)-CO-Z-,
 CON(R⁶)-Z-, -C(O)N(R⁶)S(O)₂-Z-, -S(O)₂N(R⁶)C(O)-Z-, -C(O)-Z-, -Z-,
 C(O)-Z-O-Z-, -N(R⁶)-C(O)-Z-O-Z-, -O-Z-N(R⁶)-Z-, -O-C(O)-Z-O-Z-;

cada Z es independientemente un enlace directo, C₂₋₆ alquilenos o un grupo de fórmula -(CH₂)_p-C(R^{6a})₂-(CH₂)_q-;

cada R⁴ es elegido independientemente de halo, -CH_{3-a}F_a, CN, NH₂, C₁₋₆ alquilo, -OC₁₋₆ alquilo, -COOH, -C(O)OC₁₋₆ alquilo, OH o fenilo opcionalmente sustituido por C₁₋₆ alquilo y -C(O)OC₁₋₆ alquilo,

o R⁵-X¹, donde X¹ se independientemente como se define X arriba y R⁵ se selecciona de hidrógeno, C₁₋₆ alquilo, -CH_{3-a}-F_a, fenilo, naftilo, heterociclilo o C₃₋₇ cicloalquilo; y R⁵ es opcionalmente sustituido por uno o más sustituyentes seleccionados de: halo, C₁₋₆ alquilo, -OC₁₋₆ alquilo, -CH_{3-a}F_a, CN, OH, NH₂, COOH, o -C(O)OC₁₋₆ alquilo,

cada Z¹ es independientemente un enlace directo, C₂₋₆ alquilenos o un grupo de fórmula



R³ es heterociclilo, en donde el átomo en la posición 2 del anillo de heterociclilo relativo al grupo amida, al que está unido R³, es un nitrógeno sp² hibridado, y R³ está opcionalmente sustituido por hasta 2 grupos R⁷;

R⁶ se selecciona independientemente de hidrógeno, C₁₋₆ alquilo o C₂₋₄ alquil-O-C₁₋₄ alquilo;

R^{6a} se selecciona independientemente de hidrógeno, halo, C₁₋₆ alquilo o -C₂₋₄ alquil-O-C₁₋₄ alquilo;

cada R^7 se selecciona independientemente de:

C_{1-6} alquilo, C_{2-6} alquenilo, C_{2-6} alquinilo, $(CH_2)_{0-3}$ arilo, $(CH_2)_{0-3}$ heterociclilo, $(CH_2)_{0-3}C_{3-7}$ cicloalquilo, OH, C_{1-6} alquil-halo, OC_{1-6} alquilo, $(CH_2)_{0-3}S(O)_{0-2}R^8$, SH, SO_3H , tioxo, NH_2 , CN, $(CH_2)_{0-3}NHSO_2R^8$, $(CH_2)_{0-3}COOH$, $(CH_2)_{0-3}O-(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}C(O)(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}C(O)OR^8$, $(CH_2)_{0-3}C(O)NH_2$, $(CH_2)_{0-3}C(O)NH(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}NH(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}NHC(O)(CH_2)_{0-3}R^8$, $(CH_2)_{0-3}C(O)NHSO_2-R^8$ y $(CH_2)_{0-3}SO_2NHC(O)-R^8$ en donde una cadena de alquilo, un anillo de cicloalquilo o un anillo de heterociclilo dentro de R^7 es opcionalmente sustituido por uno o más sustituyentes seleccionados independientemente de: C_{1-4} alquilo, OH, halo, CN, NH_2 , N- C_{1-4} alquilamino, N,N-di- C_{1-4} alquilamino y OC_{1-4} alquilo;

R^8 se selecciona de hidrógeno, C_{1-6} alquilo, arilo, heterociclilo, C_{3-7} cicloalquilo, OH, C_{1-6} alquil-OH, COOH, $C(O)OC_{1-6}$ alquilo, $N(R^6)C_{1-6}$ alquilo, $N(R^6)C_{1-6}$ alquilo, OC_{1-6} alquilo, C_{0-6} alquilOC(O) C_{1-6} alquilo, $C(OH)(C_{1-6}$ alquil) C_{1-6} alquilo; en donde una cadena de alquilo o un anillo de arilo, heterociclilo o cicloalquilo dentro de R^8 es opcionalmente sustituido por uno o más sustituyentes seleccionados independientemente de: C_{1-4} alquilo, OH, halo, CN, NH_2 , -NH- C_{1-4} alquilo, -N-di-(C_{1-4} alquil) y OC_{1-4} alquilo;

cada a es independientemente 1, 2 o 3;

p es un entero entre 0 y 3;

q es un entero entre 0 y 3;

y $p + q < 4$;

con la condición que:

- (i) cuando R^3 es 2-piridilo y X es diferente de $-Z-$, $-C(O)-Z-$, $-N(R^6)-C(O)-Z-O-Z-$ o $-O-Z-N(R^6)-Z-$, entonces R^3 no puede estar mono-sustituido en la posición 5 con un grupo R^7 seleccionado de COOH o $C(O)OC_{1-6}$ alquilo;
- (ii) una cadena de alquilo sin ramificar, sin sustituir no puede exceder la longitud de C_{1-6} alquilo.
- (iii) solo un grupo X puede ser $-NHC(O)-$;
- (iv) cuando X es independientemente seleccionado de $-C(O)NH-$, $-NHC(O)-$, $-O-$, $S(O_2)NH-$ o un enlace directo entre un grupo X es $-NHC(O)$, Het- Z^1 se selecciona de 4,5-dihidro-5-oxo-pirazolilo, tienilo o piridilo y Het- Z^1 es opcionalmente sustituido por R^4 entonces R^3 no puede ser tiazola sin sustituir, 4,5-dihidro-5-oxo-pirazolilo sustituido por triclorofenol, 4,5,6,7-tetrahidro-benzo[b]tiofeno sustituido por triclorofenol, 4,5,6,7-tetrahidro-

benzo[b]tiofeno sustituido por etoxycarbonilo o piridilo independiente y opcionalmente sustituido por metilo, etoxi, o propilcarbonilamino;

(v) cuando R^3 es 2-piridilo, X es Z o $-C(O)-Z-O-Z-$, y (uno) Z se selecciona tal que X es por lo tanto un enlace directo, $-(CH_2)_{1-4}-$, $-CH=CH-Z$, o $-C(O)O-Z-$, entonces R^3 no puede estar mono-sustituido en la posición 5 con un grupo R^7 seleccionado de $COOH$ o $C(O)OC_{1-6}$ alquilo.

2. Un compuesto de acuerdo con la reivindicación 1, en donde Het se selecciona de isoxazolilo, pirrolidinilo, 2-pirrolidonilo, 2,5-dioxopirrolidinilo, morfolino, tetrahidrofuranilo, piperidilo, piperazinilo, tiomorfolino, tetrahidropiranilo, tienilo, imidazolilo, 1,2,4-triazolilo, 1,3,4-triazolilo, indolilo, tiazolilo, tiadiazolilo, pirazinilo, piradizinilo y piridilo.

3. Un compuesto de acuerdo con la reivindicación 1 o la reivindicación 2, en donde R^3 se selecciona de tiazol, benzotiazol, tiadiazol, piridina, pirazina, pirazol, imidazol, pirimidina, oxazol e indol.

4. Un compuesto de acuerdo con la reivindicación 1, en donde Z es un enlace directo, $-CH_2-$ o $-C(CH_3)_2-$.

5. Un compuesto de acuerdo con la reivindicación 4, en donde Z es un enlace directo.

6. Un compuesto de acuerdo con la reivindicación 1, en donde Z^1 se selecciona de un enlace directo, $-(CH_2)_{1-2}$, y un grupo de fórmula $-(CH_2)_p-C(R^{6a})_2-(CH_2)_q-$, en donde R^{6a} se selecciona independientemente de hidrógeno y C_{1-4} alquilo.

7. Un compuesto de acuerdo con la reivindicación 6, en donde Z^1 es un enlace directo, $-CH_2-$ o $-(CH_2)_2-$.

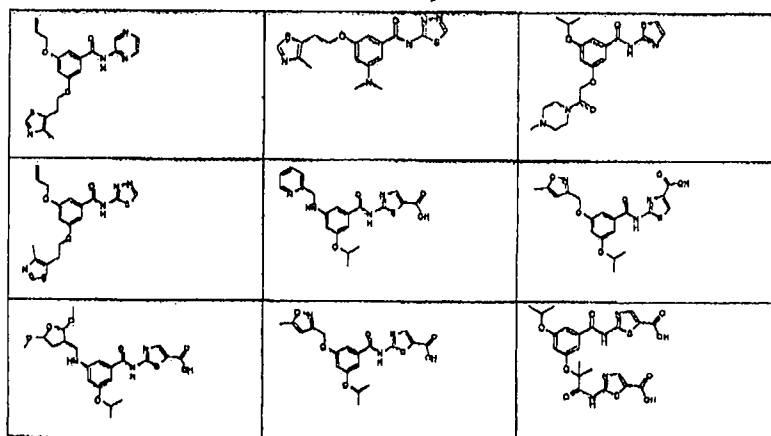
8. Un compuesto de acuerdo con la reivindicación 1, en donde cada X se selecciona independientemente de:

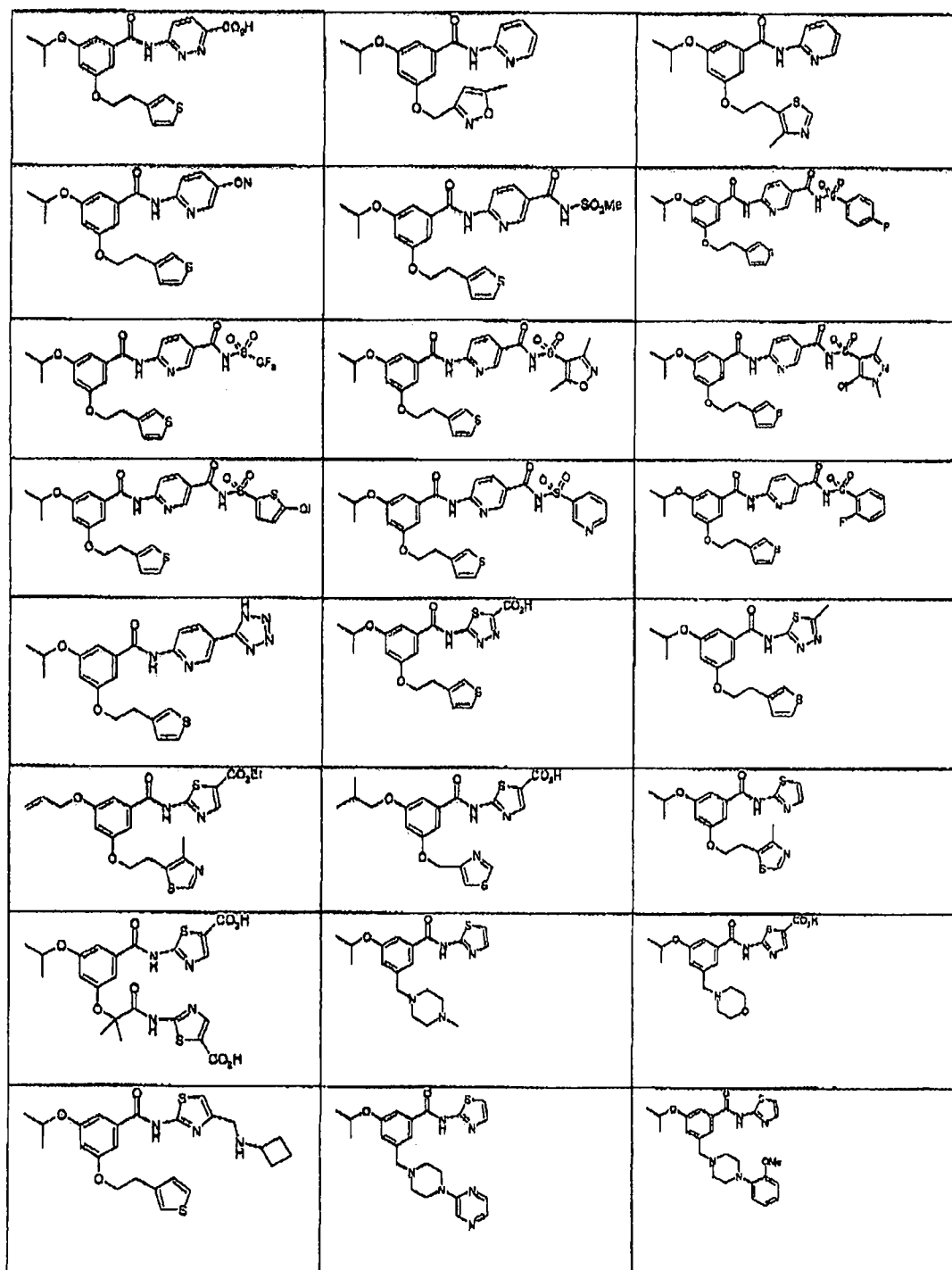
$-Z-$, $-CH=CH-Z-$, $-O-Z-$, $-C(O)-Z-$, $-C(O)O-Z-$, $OC(O)-Z-$, $-C(O)-Z-O-Z-$, $-O-C(O)-Z-O-Z-$, $-S-Z-$, $-SO-Z-$, $-SO_2-Z-$, $-N(R^6)-Z-$, $-N(R^6)CO-Z-$, $-CON(R^6)-Z-$, $-N(R^6)-C(O)-Z-O-Z-$, $-SO_2N(R^6)-Z-$, $-N(R^6)SO_2-Z-$ y $-O-Z-N(R^6)-Z-$.

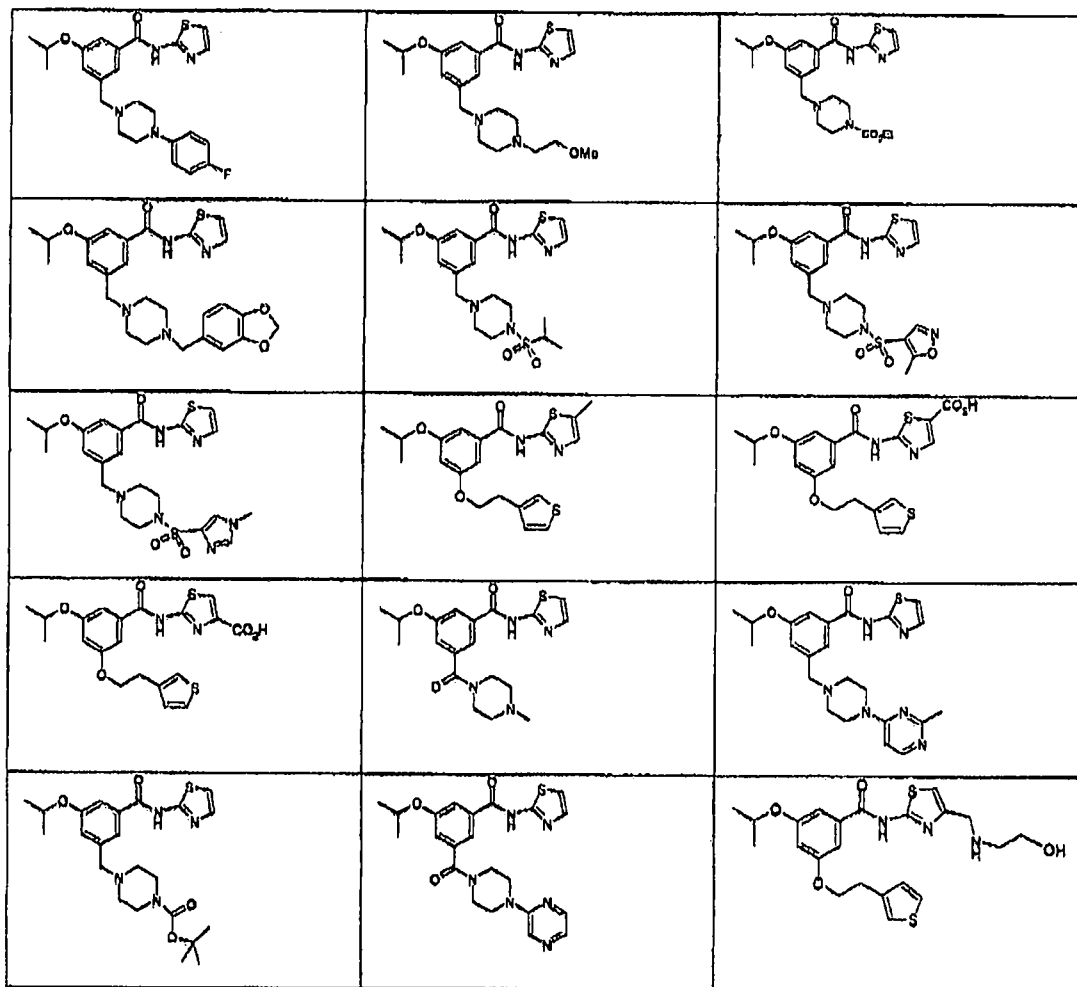
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9. Un compuesto de acuerdo con la reivindicación 8, en donde X se selecciona de $-Z-$, $CH=CH-Z-$, $-C(O)-Z-$, $-C(O)O-Z-$, $-C(O)-Z-O-Z-$, $-N(R^6)-Z-$, y $-N(R^6)CO-Z-$.
10. Un compuesto de acuerdo con la reivindicación 9, en donde cada X se selecciona de: $-CH=CH-Z-$, $-O-Z-$ y $-C(O)-Z-$.
11. Un compuesto de acuerdo con la reivindicación 10, en donde X es $-O-Z-$.
12. Un compuesto de acuerdo con la reivindicación 1, en donde cada R^4 se selecciona independientemente de halo, CH_3-aF_a , OCH_3-aF_a , CN, C_{1-6} alquilo, OC_{1-6} alquilo, $COOH$, $C(O)OC_{1-6}$ alquilo, $(CH_2)_{0-3}COOH$, $O(CH_2)_{0-3}COOH$, CO-fenilo, $CONH_2$, $CONH$ -fenilo, SO_2NH_2 , SO_2C_{1-6} alquilo, OH, y fenilo opcionalmente sustituido con C_{1-6} alquilo o $C(O)OC_{1-6}$ alquilo.
13. Un compuesto de acuerdo con la reivindicación 1, en donde R^3 esta sin sustituir o esta sustituido por uno del grupo R^7 .
14. Un compuesto de acuerdo con la reivindicación 1, en donde R^7 se selecciona independientemente de OH, CN, NH_2 , SO_3H , tioxo, halo, C_{1-4} alquilo, C_{1-4} alquil-OH, $O-C_{1-4}$ alquilo, C_{1-4} alquil-halo, $(CH_2)_{0-1}COOH$, $(CH_2)_{0-1}C(O)OR^8$, $(CH_2)_{0-1}NH(CH_2)_{0-2}R^8$, $(CH_2)_{0-1}NHC(O)(CH_2)_{0-2}R^8$, $(CH_2)_{0-1}C(O)NH(CH_2)_{0-2}R^8$, $-(CH_2)_{0-2}S(O)_{0-2}R^8$, $-(CH_2)_{0-1}NH SO_2R^8$.
15. Un compuesto de acuerdo con la reivindicación 8, en donde el compuesto se selecciona de:



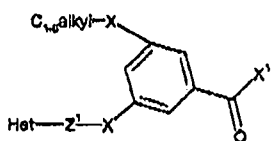




16. Una composición farmacéutica que comprende un compuesto de acuerdo con la reivindicación 1, junto con un diluyente o portador farmacéuticamente aceptable.

17. Un proceso para la preparación de un compuesto de fórmula (IIf), como se define en la reivindicación 1, el cual comprende:

a) la reacción de un compuesto de fórmula (IIIa) con un compuesto de fórmula (IIIb),



Formula (IIIa)

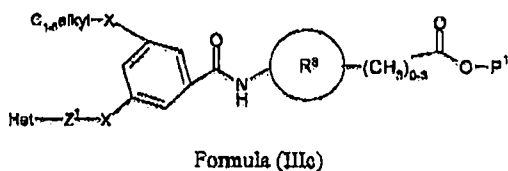


Formula (IIIb);

o

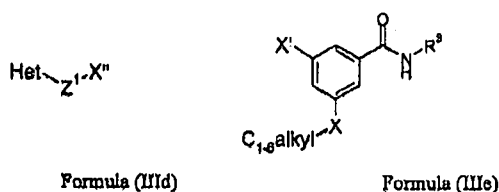
en donde X^1 es un grupo saliente.

- b) para compuestos de fórmula (IIf) donde R^3 está sustituido con $-(CH_2)_0-3CO_2H$, la desprotección de un compuesto de fórmula (IIIc),



en donde p es un grupo protector;

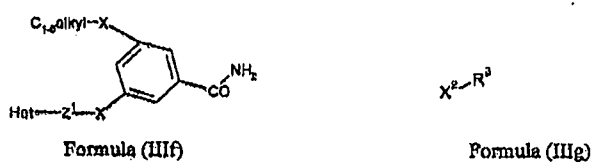
- c) la reacción de un compuesto de fórmula (IIId) con un compuesto de fórmula (IIIe),



en donde x' y X'' comprenden grupos que cuando reaccionan juntos forman el grupo X;

- d) para un compuesto de fórmula (IIf) en donde X o X^1 es $-SO-Z-$ o $-SO_2-Z-$, la oxidación de compuesto correspondiente de fórmula (IIf) en donde X o X^1 es respectivamente $-S-Z-$;

- e) la reacción de un compuesto de fórmula (IIIf) con un compuesto de fórmula (IIIg),



en donde X^2 es un grupo saliente;
y en adelante, de ser necesario:

- i) convertir un compuesto de fórmula (IIf) en otro compuesto de fórmula (IIf);
- ii) remover cualquier grupo protector.

[54] BENZAMIDE DERIVATIVES

[75] Inventors: Roger E. Ford, Gidea Park; Philip Knowles, Rayleigh; Edward Lunt, Westcliff-on-Sea; Stuart M. Marshall, Stanford-le-Hope; Anthony J. H. Summers, London, all of England

[73] Assignee: May & Baker Limited, Essex, England

[21] Appl. No.: 848,032

[22] Filed: Nov. 3, 1977

[30] Foreign Application Priority Data

Nov. 5, 1976 [GB] United Kingdom 46174/76

[51] Int. Cl.² A61K 31/41; C07D 257/06

[52] U.S. Cl. 424/269; 260/308 D

[58] Field of Search 260/308 D; 424/269

[56] References Cited

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3,342,826 9/1967 Miller et al. 260/326.47
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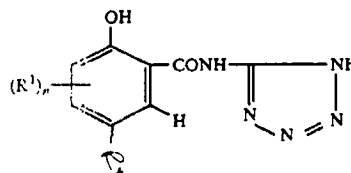
Primary Examiner—Nicholas S. Rizzo

Assistant Examiner—D. B. Springer

Attorney, Agent, or Firm—Stevens, Davis, Miller & Mosher

[57] ABSTRACT

Benzamide derivatives of the formula:-



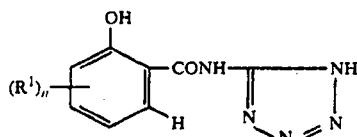
wherein R¹ represents a fluorine, chlorine or bromine atom, or an alkyl, alkoxy, alkylthio, alkylsulphonyl, alkanoylamino, alkylamino or alkylsulphamoyl group, each such group containing from 1 to 6 carbon atoms, a dialkylsulphamoyl, dialkylamino or dialkylcarbamoyl group (wherein the two alkyl groups may be the same or different and each contains from 1 to 4 carbon atoms), an alkanoyl, alkoxycarbonyl, alkoxycarbonylamino or alkylcarbamoyl group containing from 2 to 6 carbon atoms, or a hydroxy, formyl, nitro, trifluoromethyl, aryl, benzyloxycarbonylamino, amino, sulphamoyl, cyano, tetrazol-5-yl, carboxy, carbamoyl or aroyl group, and n represents an integer 1, 2 or 3, are new compounds, possessing pharmacological properties, in particular properties of value in the treatment of respiratory disorders manifested by the interaction of tissue-fixed antibodies with specific antigens.

32 Claims, No Drawings

BENZAMIDE DERIVATIVES

This invention relates to new therapeutically useful benzamide derivatives, to processes for their preparation and to pharmaceutical compositions containing them.

As a result of research and experimentation, it has been found that the new benzamide derivatives represented by the general formula:



[wherein R¹ represents a fluorine, chlorine or bromine atom, or a straight- or branched-chain alkyl, alkoxy, alkylthio, alkylsulphonyl, alkanoylamino, alkylamino or alkylsulphamoyl group, each such group containing from 1 to 6 carbon atoms, a dialkylsulphamoyl, dialkylamino or dialkylcarbamoyl group (wherein the two alkyl groups may be the same or different and each contains from 1 to 4 carbon atoms), a straight- or branched-chain alkanoyl, alkoxycarbonyl, alkoxycarbonylamino or alkylcarbamoyl group containing from 2 to 6 carbon atoms, or a hydroxy, formyl, nitro, trifluoromethyl, aryl (e.g. phenyl), benzyloxycarbonylamino, amino, sulphamoyl, cyano, tetrazol-5-yl, carboxy, carbamoyl or aroyl (e.g. benzoyl) group, and n represents an integer 1, 2 or 3, preferably 1 or 2, the substituents R¹ being the same or different when n represents 2 or 3] and pharmaceutically acceptable salts thereof, possess valuable pharmacological properties.

It will be understood by those skilled in the art that each of the hydrogen atoms depicted in general formula I in the moieties OH, CONH and NH may give rise to tautomerism and that all the resulting tautomeric forms may be present to a greater or lesser degree and are in a state of dynamic equilibrium with each other. Furthermore, the substituents R¹ may contain chiral centres and thus give rise to optical isomerism. The present invention embraces all optical isomers of general formula I and all tautomers of compounds of general formula I and mixtures thereof.

The present invention includes pharmaceutically acceptable salts of compounds of formula I with pharmaceutically acceptable bases. By the term "pharmaceutically acceptable salts" is meant salts the cations of which are relatively innocuous to the animal organism when used in therapeutic doses so that the beneficial pharmacological properties of the parent compounds of general formula I are not vitiated by side effects ascribable to those cations. Suitable salts include the alkali metal, e.g. sodium and potassium, and ammonium salts and salts of amines known in the art to be pharmaceutically acceptable, e.g. ethylene diamine, choline, diethanolamine, triethanolamine, octadecylamine, diethylamine, triethylamine, 2-amino-2-(hydroxymethyl)propane-1,3-diol and 1-(3,4-dihydroxyphenyl)-2-isopropylaminoethanol.

Pharmaceutically acceptable salts may be prepared by the reaction together of a compound of formula I and the appropriate base, that is to say a base as described immediately hereinbefore, for example at an elevated temperature, with or without an appropriate solvent, preferably followed by recrystallization from

an appropriate solvent, for example a hydroxylic solvent, e.g. water, of the salt so formed.

In this specification when reference is made to compounds of formula I reference is also intended to their pharmaceutically acceptable salts, where the context so permits.

The benzene derivatives of the present invention possess valuable pharmacological properties, in particular properties of value in the treatment of respiratory disorders manifested by the interaction of tissue-fixed antibodies with specific antigens, such as allergic bronchial asthma.

Individual compounds of formula I of particular importance include the following:

2-hydroxy-4-nitro-N-(tetrazol-5-yl)benzamide;	AA
2-hydroxy-5-(N,N-dimethylsulphamoyl)-N-(tetrazol-5-yl)benzamide;	AB
2-hydroxy-5-(N-methyl-N-isopropylsulphamoyl)-N-(tetrazol-5-yl)benzamide;	AC
5-chloro-2-hydroxy-N-(tetrazol-5-yl)benzamide;	AL
2-hydroxy-3,5-dinitro-N-(tetrazol-5-yl)benzamide;	AE
2,5-dihydroxy-N-(tetrazol-5-yl)benzamide;	AF
2-hydroxy-5-methyl-N-(tetrazol-5-yl)benzamide;	AG
2-hydroxy-3-methyl-N-(tetrazol-5-yl)benzamide;	AH
2-hydroxy-3-nitro-N-(tetrazol-5-yl)benzamide;	AI
2,4-dihydroxy-N-(tetrazol-5-yl)benzamide;	AJ
2-hydroxy-4-methyl-N-(tetrazol-5-yl)benzamide;	AK
3-bromo-2-hydroxy-N-(tetrazol-5-yl)benzamide;	AL
3-chloro-2-hydroxy-N-(tetrazol-5-yl)benzamide;	AM
2-hydroxy-3-propoxy-N-(tetrazol-5-yl)benzamide;	AN
2-hydroxy-5-nitro-N-(tetrazol-5-yl)benzamide;	AO
2-hydroxy-5-methoxy-N-(tetrazol-5-yl)benzamide;	AP
5-(N,N-dibutylsulphamoyl)-2-hydroxy-N-(tetrazol-5-yl)benzamide;	AQ
3-acetyl-2-hydroxy-5-methyl-N-(tetrazol-5-yl)benzamide;	AR
3-ethoxy-2-hydroxy-N-(tetrazol-5-yl)benzamide;	AS
2-hydroxy-4-methoxy-N-(tetrazol-5-yl)benzamide;	AT
3-acetyl-5-chloro-2-hydroxy-N-(tetrazol-5-yl)benzamide;	AU
5-acetyl-2-hydroxy-N-(tetrazol-5-yl)benzamide;	AV
3,5-diacetyl-2,4-dihydroxy-N-(tetrazol-5-yl)benzamide;	AW
4-chloro-2-hydroxy-N-(tetrazol-5-yl)benzamide;	AX
3,5-dibromo-2-hydroxy-N-(tetrazol-5-yl)benzamide;	AY
5-acetylamino-2-hydroxy-N-(tetrazol-5-yl)benzamide;	AZ
4-tert-butyl-2-hydroxy-N-(tetrazol-5-yl)benzamide;	BA
4-acetylamino-2-hydroxy-N-(tetrazol-5-yl)benzamide;	BB
4-trifluoromethyl-2-hydroxy-N-(tetrazol-5-yl)benzamide;	BC
4-fluoro-2-hydroxy-N-(tetrazol-5-yl)benzamide;	BD
2-hydroxy-3-methoxy-N-(tetrazol-5-yl)benzamide;	BE
2-hydroxy-5-methylthio-N-(tetrazol-5-yl)benzamide;	BF
2-hydroxy-5-phenyl-N-(tetrazol-5-yl)benzamide;	BG
5-fluoro-2-hydroxy-N-(tetrazol-5-yl)benzamide;	BH
2-hydroxy-3-methylthio-N-(tetrazol-5-yl)benzamide;	BI
2-hydroxy-3-methylsulphonyl-N-(tetrazol-5-yl)benzamide;	BJ
2-hydroxy-3,5-bis(methylsulphonyl)-N-(tetrazol-5-yl)benzamide;	BK
5-formyl-2-hydroxy-N-(tetrazol-5-yl)benzamide;	BL
5-bromo-2-hydroxy-N-(tetrazol-5-yl)benzamide;	BM
2-hydroxy-4-methylthio-N-(tetrazol-5-yl)benzamide;	BN
2-hydroxy-5-methylsulphonyl-N-(tetrazol-5-yl)benzamide;	BO
2-hydroxy-4-methylsulphonyl-N-(tetrazol-5-yl)benzamide;	BP
5-benzyloxycarbonylamino-2-hydroxy-N-(tetrazol-5-yl)benzamide;	BQ
4-benzyloxycarbonylamino-2-hydroxy-N-(tetrazol-5-yl)benzamide;	BR
5-amino-2-hydroxy-N-(tetrazol-5-yl)benzamide;	BS
3-(N-tert-butylsulphamoyl)-2-hydroxy-5-methyl-N-(tetrazol-5-yl)benzamide;	BT
3-acetyl-2-hydroxy-5-sulphamoyl-N-(tetrazol-5-yl)benzamide;	BU
5-trifluoromethyl-2-hydroxy-N-(tetrazol-5-yl)benzamide;	BV
3-acetyl-5-ethyl-2-hydroxy-N-(tetrazol-5-yl)benzamide;	BW
3-acetyl-2-hydroxy-4,5-dimethyl-N-(tetrazol-5-yl)benzamide;	BX
3-acetyl-5-sec-butyl-2-hydroxy-N-(tetrazol-5-yl)benzamide;	BY
3-acetyl-5-tert-butyl-2-hydroxy-N-(tetrazol-5-yl)benzamide;	BZ
3-acetyl-2-hydroxy-N-(tetrazol-5-yl)benzamide;	CA
3-acetyl-5-bromo-2-hydroxy-N-(tetrazol-5-yl)benzamide;	CB
3-acetyl-5-fluoro-2-hydroxy-N-(tetrazol-5-yl)benzamide;	

-continued

benzamide;	CC
3-acetyl-2-hydroxy-5-propyl-N-(tetrazol-5-yl)benzamide;	CD
2-hydroxy-5-methyl-3-propionyl-N-(tetrazol-5-yl)-	
benzamide;	CE
5-ethyl-2-hydroxy-3-propionyl-N-(tetrazol-5-yl)-	
benzamide;	CF
3-butyl-5-ethyl-2-hydroxy-N-(tetrazol-5-yl)benzamide;	CG
3-formyl-2-hydroxy-N-(tetrazol-5-yl)benzamide;	CH
3-formyl-2-hydroxy-5-methyl-N-(tetrazol-5-yl)benzamide;	CI
3-cyano-2-hydroxy-N-(tetrazol-5-yl)benzamide;	CJ
5-cyano-2-hydroxy-N-(tetrazol-5-yl)benzamide;	CK
1-cyano-2-hydroxy-5-methyl-N-(tetrazol-5-yl)benzamide;	CL
2-hydroxy-5-methyl-3,N-bis(tetrazol-5-yl)benzamide;	CM
3-N-(tetrazol-5-yl)carbamoylsalicylic acid;	CN
3-tert-butylcarbamoyl-2-hydroxy-N-(tetrazol-5-yl)-	
benzamide;	CO
2-hydroxy-3-dimethylamino-N-(tetrazol-5-yl)benzamide;	CP
5-acetyl-2-hydroxy-3-nitro-N-(tetrazol-5-yl)benzamide;	CQ
3-benzoyl-2-hydroxy-5-methyl-N-(tetrazol-5-yl)-	
benzamide and	CR
3acetyl-2-hydroxy-5-nitro-N-(tetrazol-5-yl)benzamide,	CS
and their pharmaceutically acceptable salts.	

The letters of the alphabet AA to CS are assigned to the compounds for easy reference later in the specification, for example in the following Tables.

Preferred compounds of general formula I are those wherein R¹ represents a fluorine, chlorine or bromine atom, or a straight- or branched-chain alkyl, alkoxy, alkylthio, alkylsulphonyl, alkanoylamino or alkylsulphamoyl group, each such group containing from 1 to 6 carbon atoms, a dialkylsulphamoyl or dialkylamino group (wherein the two alkyl groups may be the same or different and each contains from 1 to 4 carbon atoms), a straight- or branched-chain alkanoyl or alkylcarbamoyl group containing from 2 to 6 carbon atoms, or a hydroxy, formyl, nitro, trifluoromethyl, phenyl, benzyloxycarbonylamino, amino, sulphamoyl, cyano, tetrazol-5-yl, carboxy or benzoyl group, and n is as hereinbefore defined, and more particularly those such compounds wherein n represents 1 or 2, and their pharmaceutically acceptable salts.

Compounds within general formula I wherein one of the substituents R¹ on the phenyl ring is a nitro, cyano, alkanoyl (e.g. acetyl, propionyl or butyryl), formyl or tetrazol-5-yl group, any other substituent(s) R¹ present (preferably not more than one) being as hereinbefore defined, and their pharmaceutically acceptable salts, are of particular importance. Within that class compounds AE, AI, AO, BL, BU, BY, BZ, CC, CG, CH, CJ, CK, CQ, and especially compounds AR, BW, CA, CD, CE, CF, CM and CS, are of outstanding importance. Compounds AN, AP, BB, BF, BR and, especially, BE outside that class are also of outstanding importance.

In pharmacological tests the benzamide derivatives of general formula I suppress the passive cutaneous anaphylactic (PCA) reaction resulting from combination of tissue-fixed reaginic antibodies with the appropriate antigenic material (termed reagin-allergen combination) and carried out in an essentially similar manner to that described by Ogilvie [Nature (Lond.), (1964), 204, 91-92; Immunology, (1967), 12, 112-131]. In the method used to test these compounds sera were obtained from rats which had been infected with larvae of the nematode parasite *Nippostrongylus brasiliensis*; as a result of the parasitic infestation reaginic antibodies are elaborated in the host mammal and are found in sera removed from such animals. Other, non-infected, rats received intradermal injections of appropriate dilutions of such sera and were then given the allergenic material along with Evans' blue dye intravenously forty-eight hours later.

The allergenic material consisted of supernatant fluid after centrifugation of homogenates of adult *Nippostrongylus brasiliensis* worms which had been macerated in Tyrode's solution. The sites of PCA reactions were visualised by the effusion of Evan's blue dye from the circulation into those areas as a result of increased capillary permeability caused by the release of biologically-active substances from cells where reagin-allergen combination had occurred. The new compounds when given intravenously to the rats just before injection of allergen, or administered orally thirty minutes before intravenous injection of allergen, were able to prevent the development of the PCA reaction, as shown below in Table I, Table II and Table III.

Table I shows the intravenous dose, expressed in mg/kg animal body weight, which produces 100% inhibition of the PCA reaction (ED100).

Table II shows the percentage inhibition of the PCA reaction produced by an oral dose of 100 mg/kg animal body weight.

Table III shows the oral dose, expressed in mg/kg animal body weight, which produces 50% inhibition of the PCA reaction (ED50).

TABLE I

Compound	AA	AB	AC	AD	AE	AF	AG	AH	AI
ED100	10	2	5	1	0.05	1	1	0.5	0.5
Compound	AJ	AK	AL	AM	AN	AO	AP	AR	AS
ED100	10	10	10	5	0.5	0.2	0.5	0.1	1
Compound	AT	AU	AV	AW	AY	AZ	BA	BB	BD
ED100	5	2	10	5	5	10	10	1	10
Compound	BE	BF	BG	BH	BI	BJ	BK	BL	BM
ED100	0.2	0.5	10	1	20	20	10	0.5	5
Compound	BN	BO	BQ	BR	BS	BU	BV	BW	BX
ED100	10	5	5	0.5	5	0.5	2	0.1	20
Compound	BY	BZ	CA	CB	CC	CD	CE	CF	CG
ED100	0.5	0.5	0.1	2	0.2	0.1	0.05	0.05	0.1
Compound	CH	CI	CJ	CK	CL	CM	CN	CO	CP
ED100	0.5	2	0.5	0.2	2	0.05	1	5	2
Compound	CQ	CR	CS						
ED100	0.2	1	0.1						

TABLE II

Compound	AA	AC	AD	AE	AH	AI	AJ	AK
% inhibition	18	20	94	80	82	68	38	32
Compound	AL	AM	AN	AO	AP	AR	AS	AT
% inhibition	69	82	87	48	75	42	76	8
Compound	AU	AV	AW	AY	BA	BB	BD	BE
% inhibition	71	16	84	65	37	26	75	62
Compound	BH	BJ	BK	BL	BM	BN	BO	BS
% inhibition	94	64	29	25	46	8	63	35
Compound	BU	BV	BW	BY	BZ	CA	CB	CC
% inhibition	86	90	51	43	59	64	66	62
Compound	CD	CE	CF	CG	CH	CI	CJ	CK
% inhibition	64	99	41	55	75	70	50	89
Compound	CL	CM	CN	CO	CP	CQ	CR	CS
% inhibition	26	64	43	26	68	56	22	54

TABLE III

Com-	AD	AE	AH	AI	AL	AM	AN	AO
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The active compound or compounds may also be administered by methods known for the inhalation of drugs which are not themselves gaseous under normal conditions of administration. Thus, a solution of the compound or compounds in a suitable pharmaceutically acceptable solvent, for example water, can be nebulized by a mechanical nebulizer, for example a Wright Nebulizer, to give an aerosol of finely-divided liquid particles suitable for administration for inhalation orally or nasally. The solutions may contain stabilizing agents and buffering agents to give an isotonic character, e.g. sodium chloride, sodium citrate and citric acid.

Means for producing self-propelling compositions for generating aerosols for the administration of medicaments are, for example, described in detail in U.S. Pat. Nos. 2,868,691 and 3,095,355.

The compound or compounds may also be administered orally by inhalation in the form of a dry micronised powder, which may be diluted with one or more suitable pharmaceutically acceptable inert solid diluents selected from, for example, lycopodium, boric acid, starch, bismuth subcarbonate and heavy magnesium carbonate.

The pharmaceutical compositions of the present invention may contain, in addition to the compound or compounds of formula I, one or more substances known per se to have bronchodilating actions in man, for example, isoprenaline, salbutamol and prostaglandin E₁ (PGE₁).

It is highly desirable that the aerosols or micronised powders should have a particle size less than about 10 microns and preferably less than 5 microns, for example, between 0.5 and 3 microns, to ensure effective distribution to very narrow bronchioles. Preferably, administration is by means of devices enabling controlled quantities of the active ingredients to be administered, for example by means of metered valves.

The dose of the compounds of general formula I employed depends upon the desired therapeutic effect, the route of administration and the duration of the treatment. In the adult, the doses are generally between 0.02 and 4 mg/kg body weight per day by administration by inhalation in divided doses, and generally between 4 and 2000, preferably between 4 and 400 mg/kg body weight per day by oral administration.

The following Composition Examples illustrate pharmaceutical compositions according to the present invention.

COMPOSITION EXAMPLE 1

Micromilled 2-hydroxy-3-methoxy-N-(tetrazol-5-yl)benzamide (600 mg) and emulsifier YN (150 mg; a mixture of ammonium compounds of phosphatidic acids derived from rape seed oil) were placed in an aluminium vial (20 ml capacity). Trichloromonofluoromethane (2.7 g), dichlorodifluoromethane (9.4 g) and dichlorotetrafluoroethane (4.4 g) were then added, to give a total volume of 12.5 ml. The vial was sealed with a metered valve delivering a dose of 0.05 ml. Each dose (generated from 0.05 ml of suspension) of aerosol released from the pressurized pack thus obtained contained 2.4 mg of 2-hydroxy-3-methoxy-N-(tetrazol-5-yl)benzamide.

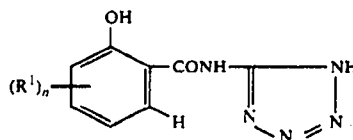
COMPOSITION EXAMPLE 2

Capsules for oral administration were made up in the usual manner by filling No. 2 size gelatine capsules each with 255 mg of the following composition:

3-acetyl-2-hydroxy-5-methyl-N-(tetrazol-5-yl)benzamide	150 mg
lactose	50 mg
starch	50 mg
magnesium stearate	2.5 mg
aerosil	2.5 mg

We claim:

1. A compound of the formula:



wherein R¹ represents a fluorine, chlorine or bromine atom, or an alkyl, alkoxy, alkylthio, alkylsulphonyl, alkanoylamino, alkylamino or alkylsulphamoyl group, each such group containing from 1 to 6 carbon atoms, a dialkylsulphamoyl, dialkylamino or dialkylcarbamoyl group wherein the two alkyl groups may be the same or different and each contains from 1 to 4 carbon atoms, an alkanoyl, alkoxy, carbonyl, alkoxy, carbonylamino or alkylcarbamoyl group containing from 2 to 6 carbon atoms, or a hydroxy, formyl, nitro, trifluoromethyl, phenyl, benzyloxycarbonylamino, amino, sulphamoyl, cyano, tetrazol-5-yl, carboxy, carbamoyl or benzoyl group, and n represents 1 or 2, the substituents R¹ being in the 3- and 5-positions when n represents 2, and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 wherein R¹ represents a fluorine, chlorine or bromine atom, an alkyl, alkoxy, alkylthio, alkylsulphonyl or alkanoylamino group, each such group containing from 1 to 6 carbon atoms, a dialkylsulphamoyl group wherein the two alkyl groups may be the same or different and each contains from 1 to 4 carbon atoms, an alkanoyl group containing from 2 to 6 carbon atoms, or a hydroxy, formyl, nitro, trifluoromethyl or phenyl group, and n represents 1 or 2, the substituents R¹ being in the 3- and 5-positions when n represents 2, and pharmaceutically acceptable salts thereof.

3. A compound according to claim 1 wherein R¹ represents a fluorine, chlorine or bromine atom, or an alkyl, alkoxy, alkylthio, alkylsulphonyl, alkanoylamino or alkylsulphamoyl group, each such group containing from 1 to 6 carbon atoms, a dialkylsulphamoyl or dialkylamino group wherein the two alkyl groups may be the same or different and each contains from 1 to 4 carbon atoms, an alkanoyl or alkylcarbamoyl group containing from 2 to 6 carbon atoms, or a hydroxy, formyl, nitro, trifluoromethyl, phenyl, benzyloxycarbonylamino, amino, sulphamoyl, cyano, tetrazol-5-yl, carboxy or benzoyl group, and n represents 1 or 2, the substituents R¹ being in the 3- and 5-positions when n represents 2, and pharmaceutically acceptable salts thereof.

4. A compound according to claim 1 wherein one of the substituents R¹ on the phenyl ring of the compounds of the general formula depicted in claim 1 is a nitro, cyano, alkanoyl, formyl or tetrazol-5-yl group, any other substituent R¹ present on the phenyl ring being as defined in claim 1, and pharmaceutically acceptable salts thereof.

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5. A compound according to claim 1 which is 3-acetyl-2-hydroxy-5-methyl-N-(tetrazol-5-yl)benzamide and pharmaceutically acceptable salts thereof.

6. A compound according to claim 1 which is 2-hydroxy-3-methoxy-N-(tetrazol-5-yl)benzamide and pharmaceutically acceptable salts thereof.

7. A compound according to claim 1 which is 3-acetyl-5-ethyl-2-hydroxy-N-(tetrazol-5-yl)benzamide and pharmaceutically acceptable salts thereof.

8. A compound according to claim 1 which is 3-acetyl-2-hydroxy-N-(tetrazol-5-yl)benzamide and pharmaceutically acceptable salts thereof.

9. A compound according to claim 1 which is 3-acetyl-2-hydroxy-5-propyl-N-(tetrazol-5-yl)benzamide and pharmaceutically acceptable salts thereof.

10. A compound according to claim 1 which is 2-hydroxy-5-methyl-3-propionyl-N-(tetrazol-5-yl)benzamide and pharmaceutically acceptable salts thereof.

11. A compound according to claim 1 which is 5-ethyl-2-hydroxy-3-propionyl-N-(tetrazol-5-yl)benzamide and pharmaceutically acceptable salts thereof.

12. A compound according to claim 1 which is 2-hydroxy-5-methyl-3,N-bis(tetrazol-5-yl)benzamide and pharmaceutically acceptable salts thereof.

13. A compound according to claim 1 which is 3-acetyl-2-hydroxy-5-nitro-N-(tetrazol-5-yl)benzamide and pharmaceutically acceptable salts thereof.

14. A compound according to claim 1 which is 2-hydroxy-3,5-dinitro-N-(tetrazol-5-yl)benzamide and pharmaceutically acceptable salts thereof.

15. A compound according to claim 1 which is 2-hydroxy-3-nitro-N-(tetrazol-5-yl)benzamide and pharmaceutically acceptable salts thereof.

16. A compound according to claim 1 which is 2-hydroxy-3-propoxy-N-(tetrazol-5-yl)benzamide and pharmaceutically acceptable salts thereof.

17. A compound according to claim 1 which is 2-hydroxy-5-nitro-N-(tetrazol-5-yl)benzamide and pharmaceutically acceptable salts thereof.

18. A compound according to claim 1 which is 2-hydroxy-5-methoxy-N-(tetrazol-5-yl)benzamide and pharmaceutically acceptable salts thereof.

19. A compound according to claim 1 which is 4-acetylamino-2-hydroxy-N-(tetrazol-5-yl)benzamide and pharmaceutically acceptable salts thereof.

20. A compound according to claim 1 which is 2-hydroxy-5-methylthio-N-(tetrazol-5-yl)benzamide and pharmaceutically acceptable salts thereof.

21. A compound according to claim 1 which is 5-formyl-2-hydroxy-N-(tetrazol-5-yl)benzamide and pharmaceutically acceptable salts thereof.

22. A compound according to claim 1 which is 4-benzoyloxycarbonylamino-2-hydroxy-N-(tetrazol-5-yl)benzamide and pharmaceutically acceptable salts thereof.

23. A compound according to claim 1 which is 3-acetyl-2-hydroxy-5-sulphamoyl-N-(tetrazol-5-yl)benzamide and pharmaceutically acceptable salts thereof.

24. A compound according to claim 1 which is 3-acetyl-5-sec-butyl-2-hydroxy-N-(tetrazol-5-yl)benzamide and pharmaceutically acceptable salts thereof.

25. A compound according to claim 1 which is 3-acetyl-5-tert-butyl-2-hydroxy-N-(tetrazol-5-yl)benzamide and pharmaceutically acceptable salts thereof.

26. A compound according to claim 1 which is 3-acetyl-5-fluoro-2-hydroxy-N-(tetrazol-5-yl)benzamide and pharmaceutically acceptable salts thereof.

27. A compound according to claim 1 which is 3-butyryl-5-ethyl-2-hydroxy-N-(tetrazol-5-yl)benzamide and pharmaceutically acceptable salts thereof.

28. A compound according to claim 1 which is 3-formyl-2-hydroxy-N-(tetrazol-5-yl)benzamide and pharmaceutically acceptable salts thereof.

29. A compound according to claim 1 which is 3-cyano-2-hydroxy-N-(tetrazol-5-yl)benzamide and pharmaceutically acceptable salts thereof.

30. A compound according to claim 1 which is 5-cyano-2-hydroxy-N-(tetrazol-5-yl)benzamide and pharmaceutically acceptable salts thereof.

31. A compound according to claim 1 which is 5-acetyl-2-hydroxy-3-nitro-N-(tetrazol-5-yl)benzamide and pharmaceutically acceptable salts thereof.

32. A pharmaceutical composition useful in the treatment of respiratory disorders manifested by the interaction of tissue-fixed antibodies with specific antigens which comprises as active ingredient, an effective amount of a compound as claimed in claim 1, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutical carrier.

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2020
Bogotá D C

Doctor(a)
RAMIRO CASTRO DUQUE.
Apoderado(a)

REFERENCIA:	Radicación N°	04-22003
	Solicitud internacional	PCT/GB02/03745
	Fecha límite fase nacional	17/03/2004
	Trámite	011
	Evento	379
	Actuación	416
	Oficio N°	574
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en los artículos 26 y 27 de la Decisión 486, de la Comisión de la Comunidad Andina, y en las demás disposiciones vigentes sobre la materia, se envía el extracto de la solicitud a la oficina de comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial, conforme lo establece el artículo 40 de la Decisión 486.

Cúmplase
Dado en Bogotá D C, 12 JUL. 2005

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe División de Nuevas Creaciones