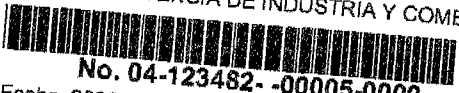


CASTELLANOS & Co.
ABOGADOS
Calle 94 A No. 7 A - 09
Bogotá, D.C., COLOMBIA

Señora
Jefe de la División de Nuevas Creaciones
Superintendencia de Industria y Comercio
Ministerio de Comercio, Desarrollo Industria y Turismo
E. S. D.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 04-123482-00005-0000
Fecha: 2008-12-23 14:36:07 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALI
Act. 444 RESPUESTAREQUE Folios: 8

Ref.: Expediente No. **04.123.482**
Solicitud de Patente PCT entrada fase nacional para: **BENZOILGUANIDINAS
CICLOALQUILDERIVADAS FLUORADAS Y SU USO COMO MEDICAMENTO**
Solicitante: **SANOFI-AVENTIS DEUTSCHLAND GmbH**

RESPUESTA A EXAMEN DE FONDO

LUIS PATIÑO LEIVA, mayor de edad, identificado y domiciliado como aparece al pie de mi firma, en atención a su oficio No. 12187 notificado el 26 de septiembre de 2008, atentamente me permito dar respuesta al mismo de la siguiente manera:

Reivindicaciones de Uso

Las reivindicaciones 6 a 12 que se refieren al uso de un compuesto han sido eliminadas del capítulo reivindicatorio. En consecuencia, la objeción en cuestión debe tenerse como superada.

Nivel Inventivo

Argumenta su Despacho que ambos compuestos tanto de la anterioridad como de la presente solicitud tienen la misma actividad farmacológica y que una persona versada en la materia sabría que un heteroarilo sustituido por flúor y un cicloalquilo sustituido por flúor pueden ser bioisómeros, es decir, que no van a influir en un cambio importante de actividad farmacológica como en la presente solicitud que no cambió la actividad de las benzoliguanidinas ya conocidas en el estado de la técnica.

Con el fin de superar la objeción por falta de nivel inventivo, pongo a consideración del señor examinador los siguientes argumentos que demuestran que los compuestos de la invención no habrían sido sugeridos por una persona versada en la materia en vista de las enseñanzas del documento D1.

El documento D1 revela benzoliguanidinas como inhibidores NHE los cuales pueden estar sustituidos con nitro-heteroarilo (C1-C9) opcionalmente sustituidos con flúor. Sin embargo, dicho documento no revela ni un solo ejemplo en el cual el compuesto nitro-heteroarilo (C1-C9) se encuentre sustituido por flúor.

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Bogotá, D.C., COLOMBIA

Por otra parte, nada de lo revelado en D1 sugiere a una persona versada en la materia a modificar los compuestos allí reivindicados de tal forma que se obtengan los compuestos de la presente invención los cuales presentan un **grupo cicloalquilo fluorado**.

Es más, una persona versada en la materia sabe que **compuestos aromáticos** del tipo nitro-heteroarilo (C1-C9) no se pueden comparar con grupos cicloalquilos **no aromáticos** como el grupo cicloalquilo fluorado acá reivindicado. De hecho, es conocido en el arte que tanto los grupos aromáticos como los no aromáticos presentan diferencias **estructurales, químicas y biológicas**.

En consecuencia, una persona versada en la materia no tendría motivación para cambiar el anillo **nitro-heteroarilo (C1-C9)** revelado en D1 por un **grupo cicloalquilo fluorado** como el acá reivindicado y que además se obtuviera actividad inhibitoria NHE1 tal como se describe en la presente invención.

Finalmente, solicito a su Despacho conceder el privilegio de patente a la presente invención toda vez que las objeciones planteadas por su Despacho han sido superadas.

Anexos

- Nuevo capítulo reivindicatorio
- Formulario de modificaciones
- Recibo de pago

De la Señora Jefe,



Luis Patiño Leyva

C.C. No. 2.930.616 de Bogotá

T.P.A. No. 2698 del C. Sup. de la Judicatura

Calle 94A # 7A-09

Teléfonos: 6107420

23 DIC. 2008

FÓRMULARIO ÚNICO DE CORRECCIONES Y MODIFICACIONES

①

SOLICITUD DE:



Corrección de Error Material



Modificación a una solicitud

②

SOLICITANTE

Nombre: **SANOFI-AVENTIS DEUTSCHLAND GmbH**

Dirección: **Brünigstrasse
Alemania**

Domicilio: **Brünigstrasse
Alemania**

Lugar de Constitución: **Alemania**

Teléfono:

Fax:

E-mail:

IDENTIFICACIÓN

C.C.



NIT



C.E.



Otro



Cual

Número

③

REPRESENTANTE
O APODERADO

Nombre: **LUIS PATIÑO LEYVA**

Dirección: **Carrera 11A No. 94-76 Oficina 308**

Teléfono: **616 19 48** Fax: **616 39 76**

E-mail: **gustavo_hollmann@etb.net.co**

IDENTIFICACIÓN

C.C.



NIT



C.E.



Otro



Cual

Número

2.930.616

TPA

2698

④

Número de Expediente:

04.123.482

⑤

Descripción de la corrección o modificación solicitada:

Presento nuevo pliego reivindicatorio sobre el cual se debe realizar el examen de patentabilidad

⑥

Comprobante de pago No.

08-95.947

Fecha

Diciembre 11 de 2008

⑦

Anexos:



Comprobante de pago de la tasa.



Poderes si fuere el caso, junto con la sustitución de los mismos a mi favor.



Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas



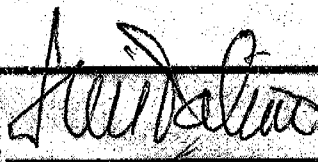
Nuevo capítulo reivindicatorio

⑧

NOMBRE

LUIS PATIÑO LEIVA

FIRMA



CC 2.930.616 de Bogotá - TPA 2698 CSJ

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página -

23 DIC. 2008

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 95,947
FECHA : DICIEMBRE 11 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 04-123482- -00005-0000

Fecha: 2008-12-23 14:36:07 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALI
Act. 444 RESPUESTAREQUE Folios: 8

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
ALVARO CASTELLANOS	CONSIGNACION	BANCO DE BOGOTA	062754387	81246244	11/12/2008	2,088,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03	CAMBIO DE MODALIDAD Y MODIFICA	
12		MARCAS Y LEMAS COMERCIALES	103,000.00
		TOTAL :	\$ 103,000.00

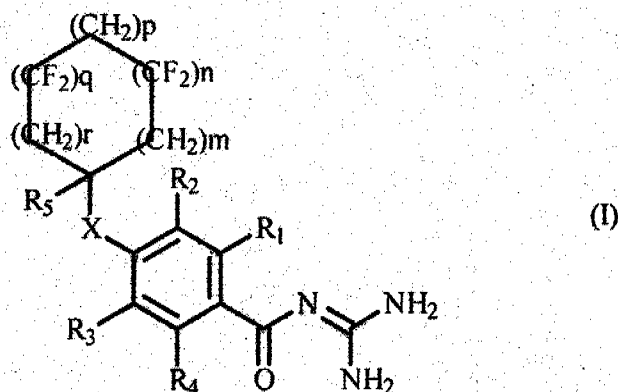
SON: CIENTO TRES MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.

REIVINDICACIONES

1. Una benzoilguanidina cicloalquilderivada fluorada de la fórmula I



en la que los significados son:

X oxígeno, azufre o NR6;

R6 hidrógeno, alquilo que tiene 1, 2, 3 ó 4 átomos de carbono o $(CH_2)_k-CF_3$;

k 0, 1, 2 ó 3;

m cero, 1, 2 ó 3;

n cero, 1, 2 ó 3;

p cero, 1, 2 ó 3;

q 1, 2 ó 3;

r cero, 1, 2 ó 3;

donde el total de m, n, p, q y r es al menos 2;

R1 hidrógeno, alquilo que tiene 1, 2, 3 ó 4 átomos de carbono, F, Cl, -OR(7),

-NR(8)R(9) o $-C_sF_{2s+1}$;

R(7), R(8) y R(9),

independientemente uno del otro, hidrógeno, alquilo que tiene 1, 2 ó 3 átomos de carbono o $(CH_2)_t-CF_3$;

s 1, 2, 3, ó 4;

t 0, 1, 2, 3 ó 4;

R2 hidrógeno, F, Cl, alquilo que tiene 1, 2, 3 ó 4 átomos de carbono o CF_3 ;

R3 hidrógeno, F, Cl, alquilo que tiene 1, 2, 3 ó 4 átomos de carbono, CF_3 o SO_uR10 ;

u cero, 1 ó 2;

R10 alquilo que tiene 1, 2, 3 ó 4 átomos de carbono o NR11R12;

R11 y R12 independientemente uno del otro, hidrógeno o alquilo que tiene 1, 2, 3 ó 4 átomos de carbono;

R4 hidrógeno, alquilo que tiene 1, 2, 3, ó 4 átomos de carbono, F, Cl, -OR(13),

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-NR(14)R(15) o $-C_vF_{2v+1}$;

R(13), R(14) y R(15),

independientemente uno del otro, hidrógeno, alquilo que tiene 1, 2 ó 3 átomos de carbono o $(CH_2)_wCF_3$;

v 1, 2, 3 ó 4;

w 0, 1, 2, 3, ó 4;

R5 hidrógeno o F;

y sus sales aceptables farmacéuticamente.

2. Un compuesto de la fórmula I como se reivindica en la reivindicación 1, en la que los significados son:

X oxígeno, azufre o NR6;

R6 hidrógeno, metilo o CH_2CF_3 ;

m cero, 1 ó 2;

n cero, 1 ó 2;

p cero, 1 ó 2;

q 1 ó 2;

r cero, 1 ó 2;

donde el total de m, n, p, q y r es al menos 2;

R1 hidrógeno, metilo, F, Cl, -OR(7), -NR(8)R(9) o $-CF_3$;

R(7), R(8) y R(9),

independientemente uno del otro, hidrógeno, metilo, CF_3 o CH_2CF_3 ;

R2 hidrógeno, F, Cl, metilo o CF_3 ;

R3 hidrógeno, F, Cl, alquilo que tiene 1, 2, 3 ó 4 átomos de carbono, CF_3 , SO_2CH_3 o SO_2NH_2 ;

R4 hidrógeno, metilo, F, Cl, -OR(13), -NR(14)R(15) o $-CF_3$;

R(13), R(14) y R(15),

independientemente uno del otro, hidrógeno, metilo, CF_3 o CH_2CF_3 ;

R5 hidrógeno o F;

y sus sales aceptables farmacéuticamente.

3. Un compuesto de la fórmula I como se reivindica en la reivindicación 1 ó 2, en la que los significados son:

X oxígeno, azufre o NR6;

R6 hidrógeno, metilo o CH_2CF_3 ;

m cero ó 1;

n cero, 1 ó 2;

p cero ó 1;

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q 1 ó 2;

r cero ó 1;

donde el total de m, n, p, q y r es al menos 2;

R1 hidrógeno, metilo, F, Cl, -OR(7), -NR(8)R(9) o -CF₃;

R(7), metilo, CF₃ o CH₂-CF₃;

R(8) y R(9),

independientemente uno del otro, hidrógeno, metilo o CH₂-CF₃;

R2 hidrógeno, F o Cl;

R3 CF₃, SO₂CH₃ o SO₂NH₂;

R4 hidrógeno;

R5 hidrógeno o F;

y sus sales aceptables farmacéuticamente.

4. Un compuesto de la fórmula I como se reivindica en una o más de las reivindicaciones 1, 2 y 3, seleccionado del grupo:

N-[4-(3,3-difluorociclobutoxi)-5-metanosulfonil-2-metilbenzoil]-guanidina,

N-[4-(3,3-difluorociclobutilamino)-5-metanosulfonil-2-metilbenzoil]-guanidina,

N-[4-[(3,3-difluorociclobutil)metilamino)-5-metanosulfonil-2-metilbenzoil]-guanidina y

N-[4-[(3,3-difluorociclobutil)metilamino)-5-etanosulfonil-2-metilbenzoil]-guanidina

y sus sales aceptables farmacéuticamente.

5. Un compuesto de la fórmula I y/o sus sales aceptables farmacéuticamente como se reivindica en una o más de las reivindicaciones 1 a 4, para usar como medicamento.

6. Una medicina para uso humano, veterinario y/o fitoprotector que comprende una cantidad eficaz de al menos un compuesto de la fórmula I y/o las sales aceptables farmacéuticamente como se reivindica en una o más de las reivindicaciones 1 a 4, junto con soportes y aditivos aceptables farmacéuticamente.

7. Una medicina para uso humano, veterinario y/o fitoprotector que comprende una cantidad eficaz de al menos un compuesto de la fórmula I y/o las sales aceptables farmacéuticamente como se reivindica en una o más de las reivindicaciones 1 a 4, junto con soportes y aditivos aceptables farmacéuticamente en combinación con otros ingredientes o medicamentos activos farmacológicamente.

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US005869531A

United States Patent [19]

Weichert et al.

[11] **Patent Number:** **5,869,531**

[45] **Date of Patent:** **Feb. 9, 1999**

[54] **FLUOROALKYL SUBSTITUTED
BENZOYLGUANIDINES**

[75] **Inventors:** **Andreas Weichert**, Egelsbach;
Heinz-Werner Kleemann,
Bischofsheim; **Hans-Jochen Lang**,
Hofheim; **Jan-Robert Schwark**,
Frankfurt; **Udo Albus**, Florstadt;
Wolfgang Scholz, Eschborn, all of
Germany

[73] **Assignee:** **Hoechst Aktiengesellschaft**, Frankfurt
am Main, Germany

[21] **Appl. No.:** **525,095**

[22] **Filed:** **Sep. 8, 1995**

[30] **Foreign Application Priority Data**

Sep. 9, 1994 [DE] Germany 44 32 105.8

[51] **Int. Cl.⁶** **A61K 31/155**; C07C 233/64;
C07C 279/02

[52] **U.S. Cl.** **514/618**; 514/634; 564/162;
564/183; 564/230

[58] **Field of Search** 564/162, 183,
564/230; 514/618, 634

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,780,027 12/1973 Cragoe, Jr. et al. .
5,091,394 2/1992 Englert et al. 564/85
5,373,024 12/1994 Lang et al. 514/618

FOREIGN PATENT DOCUMENTS

B-55229 8/1994 Australia .
A-602-522 6/1994 European Pat. Off. .
A-604-852 7/1994 European Pat. Off. .

Primary Examiner—José G. Dees

Assistant Examiner—Barbara Badio

Attorney, Agent, or Firm—Finnegan, Henderson, Farabow,
Garrett & Dunner, L.L.P.

[57] **ABSTRACT**

Disclosed are 4-(2'-trifluoromethylethyl)benzoylguanidine
and 3-methylsulfonyl-4-(2'-trifluoromethylethyl)
benzoylguanidine. Also disclosed are pharmaceutical com-
positions and the use of the compounds in the treatment of
disorders induced by ischemia.

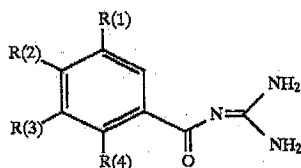
3 Claims, No Drawings

5,869,531

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FLUOROALKYL SUBSTITUTED
BENZOYLGUANIDINES

The invention relates to benzoylguanidines of the formula I



in which:

- R(1) is hydrogen, F, Cl, Br, I, CN, NO₂, OH, (C₁-C₆)-alkyl, (C₃-C₆)-cycloalkyl, O_a-(CH₂)_b-(CF₂)_c-CF₃;
a is zero or 1;
b is zero, 1 or 2;
c is zero, 1, 2 or 3; or
R(1) R(5)-SO_m or R(6)R(7)N-SO₂-;
m is zero, 1 or 2;
R(5) and R(6) independently of one another are (C₁-C₄)-alkyl, (C₃-C₆)-alkenyl, CF₃ or -C_nH_{2n}-R(8);
n is zero, 1, 2, 3 or 4;
R(7) is hydrogen or (C₁-C₄)-alkyl;
R(8) is (C₃-C₆)-cycloalkyl or phenyl, which is not substituted or is substituted by 1-3 substituents selected from the group consisting of F, Cl, CF₃, methyl, methoxy and NR(9)R(10);
R(9) and R(10) independently of one another are hydrogen or (C₁-C₄)-alkyl; or
R(6) is H;
or R(6) and R(7) together are 4 or 5 methylene groups, of which one CH₂ group can be replaced by oxygen, S, NH, N-CH₃ or N-benzyl, or
R(1) is -SR(11), -OR(11) or -CR(11)R(12)R(13);
R(11) is -C_pH_{2p}-(C₃-C₆)-cycloalkyl, -(C₁-C₉)-heteroaryl or phenyl, the aromatic systems being unsubstituted or substituted by 1-3 substituents selected from the group consisting of F, Cl, CF₃, CH₃, methoxy, hydroxyl, amino, methylamino and dimethylamino;
R(12) and R(13) independently of one another are defined as R(11) or are hydrogen or (C₁-C₄)-alkyl;
p is zero, 1 or 2; or
R(1) is phenyl, naphthyl, biphenyl or (C₁-C₉)-heteroaryl, the latter linked via C or N, which are unsubstituted or substituted by 1-3 substituents selected from the group consisting of F, Cl, CF₃, CH₃, methoxy, hydroxyl, amino, methylamino and dimethylamino;
R(2) is -CF₂R(14), -CH[R(15)] [R(16)], -CF[CF₂]-CF₃]-[R(15)], -C[(CF₂)_r-CF₃]=CR(15)R(16);
R(14) is (C₁-C₄)-alkyl or (C₃-C₆)-cycloalkyl;
R(15) and R(16) independently of one another are hydrogen or (C₁-C₄)-alkyl;
q is zero, 1 or 2;
r is zero, 1 or 2;
R(3) is defined as R(1);
R(4) is hydrogen, (C₁-C₃)-alkyl, F, Cl, Br, I, CN or -(CH₂)_s-(CF₂)_t-CF₃;

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s is zero or 1;
t is zero, 1 or 2;

and their pharmaceutically tolerable salts.

Preferred compounds of the formula I are those in which:

- R(1) is H, F, Cl, Br, CN, (C₁-C₄)-alkyl, (C₃-C₆)-cycloalkyl, O_a-(CF₂)_c-CF₃;
a is zero or 1;
c is zero, 1, 2 or 3; or
R(1) is R(5)-SO_m or R(6)R(7)N-SO₂-;
m is zero, 1 or 2;
R(5) and R(6) independently of one another are (C₁-C₄)-alkyl, (C₃-C₆)-alkenyl, CF₃ or -C_nH_{2n}-R(8);
n is zero or 1;
R(7) is hydrogen or (C₁-C₄)-alkyl;
R(8) is (C₃-C₆)-cycloalkyl or phenyl, which is unsubstituted or substituted by 1-3 substituents selected from the group consisting of F, Cl, CF₃, methyl, methoxy and NR(9)R(10);
R(9) and R(10) are hydrogen or (C₁-C₄)-alkyl; or
R(6) is hydrogen; or
R(6) and R(7) together are 4 or 5 methylene groups, of which one CH₂ group can be replaced by oxygen, S, NH, N-CH₃ or N-benzyl, or
R(1) is -OR(11);
R(11) is -C_pH_{2p}-(C₃-C₆)-cycloalkyl, -(C₁-C₉)-heteroaryl or phenyl, the aromatic systems being unsubstituted or substituted by 1-3 substituents selected from the group consisting of F, Cl, CF₃, CH₃, methoxy, hydroxyl, amino, methylamino and dimethylamino;
f is zero or 1; or
R(1) is phenyl, naphthyl, biphenyl or (C₁-C₉)-heteroaryl, the latter linked via C or N, and which are unsubstituted or substituted by 1-3 substituents selected from the group consisting of F, Cl, CF₃, CH₃, methoxy, hydroxyl, amino, methylamino and dimethylamino;
R(2) is -CF₂R(14), -CF[R(15)] [R(16)], -CF[CF₂]-CF₃]-[R(15)], -C[(CF₂)_r-CF₃]=CR(15)R(16);
R(14) is (C₁-C₄)-alkyl or (C₃-C₆)-cycloalkyl;
R(15) and R(16) independently of one another are hydrogen or (C₁-C₄)-alkyl;
q is zero, 1 or 2;
r is zero, 1 or 2;
R(3) is defined as R(1);
R(4) is H, (C₁-C₃)-alkyl, F, Cl, Br, CN or CF₃;
and their pharmaceutically tolerable salts.
Particularly preferred compounds of the formula I are those in which:
R(1) is hydrogen, F, Cl, Br, (C₁-C₄)-alkyl, (C₃-C₆)-cycloalkyl, O_a-(CF₂)_c-CF₃;
a is zero or 1;
c is zero or 1; or
R(1) is R(5)-SO₂;
R(5) is (C₁-C₄)-alkyl or CF₃; or
R(1) is -OR(11);
R(11) is (C₄-C₆)-cycloalkyl, quinolyl, isoquinolyl, pyridyl, in each case bonded via C or N, or phenyl, which is unsubstituted or substituted by 1-3 substituents selected from the group consisting of F,

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Cl, CF₃, CH₃, methoxy, hydroxyl, amino, methylamino and dimethylamino; or
 R(1) is quinolyl, isoquinolyl, pyridyl, in each case bonded via C or N,
 or phenyl,

which is unsubstituted or substituted by 1-3 substituents selected from the group consisting of F, Cl, CF₃, CH₃, methoxy, hydroxyl, amino, methylamino and dimethylamino;

R(2) is —CF₂R(14), —CF[R(15)] [R(16)], —CF(CF₃) [R(15)], —C(CF₃)=CR(15)R(16);

R(14) is (C₁-C₄)-alkyl or (C₃-C₆)-cycloalkyl;

R(15) and R(16)

independently of one another are hydrogen or (C₁-C₄)-alkyl;

R(3) is hydrogen, F, Cl, Br, I, —SO₂Me or CF₃;

R(4) is hydrogen, methyl, F, Cl or —CF₃;

and their pharmaceutically tolerable salts.

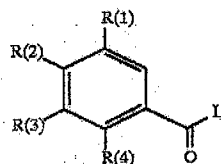
(C₁-C₆)-Heteroaryl is understood as meaning radicals which are derived from phenyl or naphthyl, in which one or more CH groups are replaced by N and/or in which at least two adjacent CH groups (with formation of a five-membered aromatic ring) are replaced by S, NH or O. In addition, one or both atoms of the condensation site of bicyclic radicals (such as in indoliziny) can also be N atoms.

(C₁-C₆)-Heteroaryl includes, in particular, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, indazolyl, quinolyl, isoguinolyl, phthalazinyl, quinoxalinyl, quinazolinyl, cinnolinyl.

If one of the substituents R(1) to R(4) contains one or more centers of asymmetry, these can have either the S or R configuration. The compounds can be present as optical isomers, as diastereomers, as racemates or as mixtures thereof.

The designated alkyl radicals can be either straight-chain or branched.

The invention furthermore relates to a process for the preparation of the compound I which comprises reacting a compound of the formula II



in which R(1) to R(4) have the meaning indicated and L is a leaving group which can readily be substituted nucleophilically, with guanidine.

The activated acid derivatives of the formula II in which L is an alkoxy group, preferably a methoxy group, a phenoxy group, phenylthio, methylthio or 2-pyridylthio group, or a nitrogen heterocycle, preferably 1-imidazolyl, are advantageously obtained in a manner known per se from the underlying carbonyl chlorides (formula II, L=Cl), which for their part can in turn be prepared in a manner known per se from the underlying carboxylic acids (formula II, L=OH), for example using thionyl chloride.

Besides the carbonyl chlorides of the formula II (L=Cl), further activated acid derivatives of the formula II can be prepared in a manner known per se directly from the underlying benzoic acid derivatives (formula II, L=OH), for example the methyl esters of the formula II where L=OCH₃, by treatment with gaseous HCl in methanol, the imada-

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zolides of the formula II by treatment with carbonyldiimidazole [L=imidazolyl, Staab, Angew. Chem. Int. Ed. Engl. 1, 351-367 (1962)], the mixed anhydrides II with Cl—COOC₂H₅ or tosyl chloride in the presence of triethylamine in an inert solvent, and also the activation of benzoic acids with dicyclohexyl-carbodiimide (DCC) or with O-(cyano(ethoxycarbonyl)-methylene)amino]-1,1,3,3-tetramethyluronium tetrafluoroborate ("TOTU") [Proceedings of the 21st European Peptide Symposium, Peptides 1990, Editors E. Giralt and D. Andreu, Escom, Leiden, 1991]. A number of suitable methods for the preparation of activated carboxylic acid derivatives of the formula II are indicated under details of source literature in J. March, Advanced Organic Chemistry, Third Edition (John Wiley & Sons, 1985), p. 350.

The reaction of an activated carboxylic acid derivative of the formula II with guanidine is carried out in a manner known per se in a protic or aprotic polar but inert organic solvent. In this case, in the reaction of the methyl benzoates (II, L=OMe) with guanidine, methanol, isopropanol or THF from 20° C. to the boiling point of these solvents have proven suitable. In most reactions of compounds II with salt-free guanidine, the reaction was advantageously carried out in aprotic inert solvents such as THF, dimethoxyethane or dioxane. However, water can also be used as a solvent in the reaction of II with guanidine when using a base such as, for example, NaOH.

If L=Cl, the reaction is advantageously carried out with addition of an acid scavenger, e.g. in the form of excess guanidine for binding the halohydric acid.

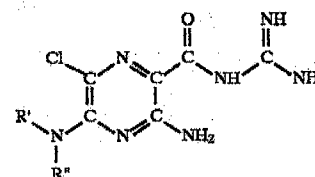
Some of the underlying benzoic acid derivatives of the formula II are known and described in the literature. The unknown compounds of the formula II can be prepared by methods known from the literature. The benzoic acids obtained are reacted by one of the process variants described above to give the compounds I according to the invention.

The introduction of some substituents in the 2-, 3-, 4- and 5-position takes place by literature-known methods of palladium-mediated cross-coupling of aryl halides or aryl triflates with, for example, organostannanes, organoboronic acids or organoboranes or organocopper or organozinc compounds.

In general, benzoylguanidines I are weak bases and can bind acid with the formation of salts. Possible acid addition salts are salts of all pharmacologically tolerable acids, for example halides, in particular hydrochlorides, lactates, sulfates, citrates, tartrates, acetates, phosphates, methylsulfonates and p-toluenesulfonates.

The compounds I are substituted acylguanidines.

The most prominent representative of the acylguanidines is the pyrazine derivative amiloride, which is used as a potassium-sparing diuretic in therapy. Numerous other compounds of the amiloride type are described in the literature, such as, for example, dimethylamiloride or ethylisopropylamiloride.



Amiloride: R', R''=H

Dimethylamiloride: R', R''=CH₃

Ethylisopropylamiloride: R'=C₂H₅, R''=CH(CH₃)₂



US005696167A

United States Patent [19]

Gericke et al.

[11] Patent Number: 5,696,167
[45] Date of Patent: Dec. 9, 1997

[54] 4-MERCAPTOBENZOYLGUANIDINE
DERIVATIVES

5,292,755 3/1994 Englert et al. 514/331

FOREIGN PATENT DOCUMENTS

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[21] Appl. No.: 593,863

[22] Filed: Jan. 30, 1996

[30] Foreign Application Priority Data

Jan. 31, 1995 [DE] Germany 195 02 895.3

[51] Int. Cl.⁶ C07C 323/65; A61K 31/18

[52] U.S. Cl. 514/618; 564/430; 564/440

[58] Field of Search 564/440, 430;
514/618

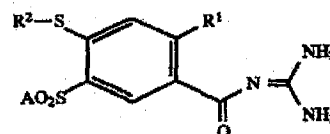
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U.S. PATENT DOCUMENTS

5,091,394 2/1992 Englert et al. 514/331

[57] ABSTRACT

4-Mercaptobenzoylguanidines of the formula I



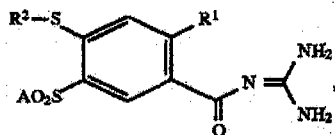
in which A, R₁, R₂ and R₃ have the meanings given, and the physiologically unobjectionable salts thereof exhibit antiarrhythmic properties and are active as inhibitors of the cellular Na⁺/H⁺ antiporter.

15 Claims, No Drawings

4-MERCAPTOBENZOYLGUANIDINE DERIVATIVES

SUMMARY OF THE INVENTION

The invention relates to ortho-substituted 4-mercaptobenzoylguanidine derivatives of the formula I



in which

R¹ is A, CF₃, CH₂F, CHF₂ or C₂F₅,

R² is H, A, C₃₋₇-cycloalkyl Ph or Het,

Het is a mono- or dicyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 nitrogen, oxygen and/or sulfur atoms, which heterocycle is attached via N or C, which can be unsubstituted or mono- di- or trisubstituted by Hal, CF₃, A, OH, OA, SH, SA, NH₂, NHA, NA₂, CN, NO₂ and/or carbonyl oxygen, i.e., a carbon atom in the heterocyclic ring can be double bonded to an extra cyclic oxygen atom,

A is alkyl having from 1 to 6 carbon atoms,

Hal is F, Cl, Br or I, and

Ph is unsubstituted phenyl or phenyl which is mono-, di- or trisubstituted by A, OA, NH₂, NHA, NA₂, F, Cl, Br and/or CF₃,

and the physiologically acceptable salts thereof.

An object of the invention was to discover novel compounds having valuable properties, in particular those compounds which can be used for preparing medicaments. It has been found that the compounds of formula I and their physiologically unobjectionable salts possess valuable pharmacological properties while being well tolerated.

The novel compounds are inhibitors of the cellular Na⁺/H⁺ antiporter, i.e. are active compounds which inhibit the cellular Na⁺/H⁺ exchange mechanism (Düsing et al., Med. Klin. 87, 378-384 (1992)) and thus represent good antiarrhythmic agents which are particularly suitable for treating arrhythmias which occur as a result of lack of oxygen.

The best-known active compound of the acylguanidine group is amiloride. However, this substance exhibits primarily a hypotensive and saluretic effect, which is undesirable when treating disturbances of cardiac rhythm, in particular, whereas the anti-arrhythmic properties are only very weakly expressed.

In addition to this, structurally similar compounds are known, for example, from EP 04 16 499, equivalent to U.S. Pat. Nos. 5,091,394 and 5,292,755.

The invention relates to compounds of the formula I and to physiologically unobjectionable salts thereof.

The novel substances of the present application exhibit a good cardioprotective effect and are therefore particularly suitable for the treatment of infarction, for infarction prophylaxis and for treating angina pectoris. Furthermore, the substances counteract all types of pathological hypoxic and ischaemic damage, so that the disorders which are caused primarily or secondarily by such damage can be treated. The active compounds are also well suited to preventive applications.

Because of the protective effects of these substances in pathological, hypoxic or ischaemic situations, there are further possibilities for using these compounds in association with surgical interventions, for protecting organs which

are from time to time less well supplied, in the course of organ transplants, for protecting the organs which are being removed, in association with angioplastic vascular or cardiac interventions, in association with ischaemias of the nervous system, in the therapy of conditions of shock, and for the prophylactic prevention of essential hypertension.

In addition, the compounds can also be employed as therapeutic agents in diseases arising from cell proliferation, such as arteriosclerosis, late complications in diabetes, tumour diseases, fibrotic diseases, in particular of the lungs, liver and kidneys, and also organ hypertrophies and hyperplasias. Furthermore, the substances are suitable for diagnostic use in order to diagnose diseases which are accompanied by an increased activity of the Na⁺/H⁺ antiporter, for example in erythrocytes, thrombocytes or leucocytes.

All of the compounds of the invention have all of the above effects, to a finite extent. The effects of the compounds can be ascertained using methods which are known per se, as described, for example, by N. Escobales and J. Figuroa in J. Membrane Biol. 120, 41-49 (1991) or by L. Counillon, W. Scholz, H. J. Lang and J. Pouyssegur in Mol. Pharmacol. 44, 1041-1045 (1993).

Examples of suitable experimental animals are mice, rats, guinea pigs, dogs, cats, monkeys or pigs.

The compounds can, therefore, be used as pharmaceutical active compounds in human and veterinary medicine. They can also be used as intermediates for preparing further pharmaceutical active compounds.

In the given formulae, A is a branched or unbranched alkyl group having 1-6, preferably 1-4, in particular 1, 2 or 3 carbon atoms, specifically methyl for preference, with ethyl, propyl, isopropyl, butyl and isobutyl also being preferred and sec-butyl, tert-butyl, pentyl, isopentyl (3-methylbutyl), hexyl and isohexyl (4-methylpentyl) being additionally preferred.

R¹ is preferably A, especially methyl or ethyl.

R² is A, phenyl, 2-, 3- or 4-chlorophenyl, 2-, 3- or 4-fluorophenyl or Het. With particular preference, Het is—besides the definitions given below—pyridyl, pyrimidyl, triazolyl, thiazolyl or the partially or completely hydrogenated derivatives of these radicals, which can also be substituted as indicated.

Ph is preferably phenyl which is unsubstituted or is monosubstituted by F, Cl, Br, A, OA, NH₂, NHA, NA₂ or CF₃.

Hal is preferably F, Cl or Br.

Het preferably contains 5-7 atoms (including heteroatoms), and is preferably 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, and also preferably 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-triazol-1-, -3- or -5-yl, 1- or 5-tetrazolyl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-thiadiazol-2- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 2-, 3-, 4-, 5- or 6-2H-thiopyran-2-, 3- or 4-4H-thiopyran-3- or 4-pyridazinyl, pyrazinyl, 2-, 3-, 4-, 5-, 6- or 7-benzofuryl, 2-, 3-, 4-, 5-, 6- or 7-benzothiophenyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzisothiazolyl, 2-, 4-, 5-, 6- or 7-benz-2,1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isquinolyl, 1-, 2-, 3-, 4- or 9-carbazolyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8- or 9-acridinyl, 3-, 4-, 5-, 6-, 7- or 8-cinnolinyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl. The heterocyclic radicals can also be partially or completely hydroge-

nated. Thus Het can also, for example, be 2,3-dihydro-2-, -3-, -4- or -5-furyl, 2,5-dihydro-2-, -3-, -4- or -5-furyl, tetrahydro-2- or -3-furyl, 1,3-dioxolan-4-yl, tetrahydro-2- or -3-thienyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 2,5-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 1-, 2- or 3-pyrrolidinyl, tetrahydro-1-, -2- or -4-imidazolyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrazolyl, tetrahydro-1-, -3- or -4-pyrazolyl, 1,4-dihydro-1-, -2-, -3- or -4-pyridyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5- or -6-pyridyl, 1,2,3,6-tetrahydro-1-, -2-, -3-, -4-, -5- or -6-pyridyl, 1-, 2-, 3- or 4-piperidyl, 2-, 3- or 4-morpholinyl, tetrahydro-2-, -3- or -4-pyranyl, 1,4-dioxanyl, 1,3-dioxane-2-, -4- or -5-yl, hexahydro-1-, -3- or -4-pyridazinyl, hexahydro-1-, -2-, -4- or -5-pyrimidinyl, 1-, 2- or 3-piperazinyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-quinolyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-isoquinolyl.

It applies generally that all the radicals, for example A, which may occur two or more times in the molecule can be identical or different, i.e. independent of each other.

The invention relates accordingly, in particular, to those compounds of the formula I in which at least one of the said radicals has one of the abovementioned preferred meanings. Some preferred groups of compounds can be expressed by the following formulae Ia to Ih, which correspond to the formula I and in which the radicals which are not more precisely described have the meaning given in the case of the formula I, but in which

in Ia R¹ is methyl or ethyl;

in Ib R¹ is methyl or ethyl and R² is A;

in Ic R¹ is methyl or ethyl and R² is 2-thiazolyl, 4,5-dihydro-thiazol-2-yl, 1,2,4-triazol-3-yl or 1,2,4-(4-methyltriazol-3-yl);

in Id R¹ is methyl or ethyl, and R² is imidazolyl, pyridyl or pyrimidinyl;

in Ie R¹ is methyl or ethyl, and R² is pyridyl or pyrimidinyl;

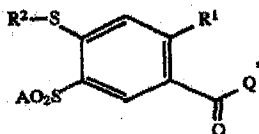
in If R¹ is methyl or ethyl and R² is phenyl, fluorophenyl or chlorophenyl;

in Ig R¹ is methyl or ethyl and R² is methyl, ethyl, propyl, isopropyl or butyl;

in Ih R¹ is methyl or ethyl and R² is cyclohexyl or cyclopentyl.

Furthermore, particular preference is given to those compounds which have preferred meanings as cited under Ia to Ih but in which, in addition, —SO₂A is methylsulfonyl.

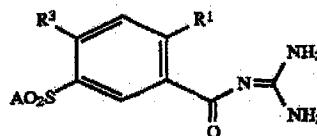
The invention also relates to a process for preparing the compounds of the formula I according to claim 1, and the salts thereof, characterized in that a compound of the formula II



in which R¹, R² and A have the meanings given above and

Q is Cl, Br, OA, O—CO—A, O—CO—Ph, OH or another reactive esterified OH group or a leaving group which can readily be substituted nucleophilically,

is reacted with guanidine, or in that a benzoylguanidine of the formula III



in which R¹ and A have the meanings given above and R² is F, Cl, Br, I or another suitable leaving group, is reacted with a compound of the formula IV



in which

R² has the meanings given,

or with a salt-like compound which can be derived therefrom, or with a thiolate, or in that a compound which otherwise corresponds to the formula I but which contains, instead of one or more hydrogen atoms, one or more reducible groups and/or one or more additional C—C and/or C—N bonds, is treated with a reducing agent,

or in that a compound which otherwise corresponds to the formula I but which contains, instead of one or more hydrogen atoms, one or more solvolyzable groups is treated with a solvolyzing agent and/or in that a base of the formula I which is obtained is converted by treatment with an acid into one of its salts.

The compounds of the formula I are otherwise prepared by methods which are known, per se, as are described in the literature (for example in the standard works such as Houben-Weyl, Methoden der organischen Chemie [Methods of organic chemistry], Georg-Thieme-Verlag, Stuttgart; Organic Reactions, John Wiley & Sons, Inc., New York; and in the abovementioned patent application), under reaction conditions which are known and suitable for the reactions mentioned. In this context, use can also be made of variants which are known per se but which have not been mentioned in any more detail.

If desired, the starting compounds can also be formed in situ, such that they are not isolated from the reaction mixture but are instead immediately subjected to further reaction to give the compounds of the formula I.

Preferably, compounds of the formula I are prepared by reacting an activated carboxylic acid derivative of the formula II, where Q is particularly preferably Cl or —O—CH₃, with guanidine. Reaction variants are also particularly suitable in which the free carboxylic acid II (Q=OH) is converted, in a manner known per se, into the particular activated derivative which is then directly, without intermediate isolation, reacted with guanidine. Methods in which intermediate isolation can be dispensed with are, for example, activation with carbonyldiimidazol, dicyclohexylcarbodiimide or the Mukayama variant (Angew. Chem. 91, 788-812 (1979)).

The carboxylic acids of the formula II are prepared, for example, by nucleophilic aromatic substitution starting from appropriate benzoic acid derivatives with corresponding thiols or thiophenols. The reaction takes place in analogy to the reaction of compounds III and IV, described below.

The reaction of a reactive carboxylic acid derivative of the formula II with guanidine takes place in a manner known per se, preferably in a protic or aprotic polar or apolar inert organic solvent.

Suitable solvents are listed below for the reaction of the compounds III and IV. Particularly preferred solvents, however, are methanol, THF, dimethoxyethane, dioxane, water or mixtures which can be prepared therefrom.

Example C: solution

A solution is prepared from 1 g of an active compound of the formula I, 9.38 g of $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$, 28.48 g of $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$ and 0.1 g of benzalkonium chloride in 940 ml of double-distilled water. The solution is adjusted to a pH of 6.8, made up to 1 l and sterilized by irradiation. This solution can be used in the form of eyedrops.

Example D: ointment

500 mg of an active compound of the formula I are mixed with 99.5 g of petroleum jelly under aseptic conditions.

Example E: tablets

A mixture of 1 kg of active compound of the formula I, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is pressed in a customary manner to give tablets such that each tablet contains 10 mg of active compound.

Example F: coated tablets

In analogy to Example E, tablets are pressed which are subsequently coated in a customary manner with a coating comprising sucrose, potato starch, talc, tragacanth and colourant.

Example G: capsules

Hard gelatin capsules are filled in a customary manner with 2 kg of active compound of the formula I such that each capsule contains 20 mg of the active compound.

Example H: ampoules

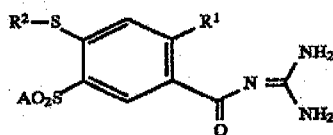
A solution of 1 kg of active compound of the formula I in 60 l of double-distilled water is sterilized by filtration and dispensed into ampoules, which are lyophilized under sterile conditions and sealed in a sterile manner. Each ampoule contains 10 mg of active compound.

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention and, without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

What is claimed is:

1. 4-Mercaptobenzoylguanidines of the formula I



in which

R^1 is A, CF_3 , CH_2F , CHF_2 or C_2F_5 ,

R^2 is H, A, C_{3-7} -cycloalkyl or Ph,

Het is a mono- or dicyclic saturated, unsaturated or aromatic heterocycle having 1 to 4 nitrogen, oxygen and/or sulfur atoms, which heterocycle is attached via N or C, which can be unsubstituted or mono-, di- or trisubstituted by Hal, CF_3 , A, OH, OA, SH, SA, NH_2 , NHA, NA_2 , CN, NO_2 and/or carbonyl oxygen,

A is C_{1-6} -alkyl,

Hal is F, Cl, Br or I, and

Ph is unsubstituted phenyl or phenyl which is mono-, di- or trisubstituted by A, OA, NH_2 , NHA, NA_2 , F, Cl, Br and/or CF_3 ,

or a physiologically acceptable salt thereof.

2. A compound according to claim 1, wherein R^1 is CF_3 , CH_2F , CHF_2 or C_2F_5 .

3. A compound according to claim 1, wherein R^1 is methyl or ethyl.

4. A compound according to claim 1, wherein R^1 is methyl or ethyl and R^2 is A.

5. A compound according to claim 1, wherein R^1 is methyl or ethyl and R^2 is phenyl, fluorophenyl or chlorophenyl.

6. A compound according to claim 1, wherein R^1 is methyl or ethyl and R^2 is methyl, ethyl, propyl, isopropyl or butyl.

7. A compound according to claim 1, wherein R^1 is methyl or ethyl and R^2 is cyclohexyl or cyclopentyl.

8. A compound according to claim 1, wherein R^1 is methyl.

9. A compound according to claim 1, which is

(a) N-diaminomethylene-2-methyl-4-methylthio-5-methylsulfonylbenzamide;

(b) N-diaminomethylene-2-methyl-4-isopropylthio-5-methylsulfonylbenzamide;

(c) N-diaminomethylene-2-methyl-4-phenylthio-5-methylsulfonylbenzamide;

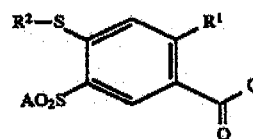
(d) N-diaminomethylene-2-methyl-4-cyclohexylthio-5-methylsulfonylbenzamide;

(e) N-diaminomethylene-2-methyl-4-(3-chlorophenylthio)-5-methylsulfonylbenzamide;

or a physiologically acceptable salt thereof.

10. A process for the preparation of aminobenzoylguanidine derivatives of formula I according to claim 1, or salts thereof, comprising

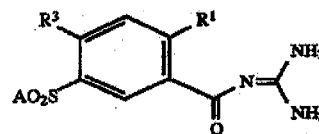
(a) reacting a compound of formula II



in which

Q is Cl, Br, OA, $\text{O}-\text{CO}-\text{A}$, $\text{O}-\text{CO}-\text{Ph}$, OH, a reactive esterified OH group or a leaving group which can readily be substituted nucleophilically, with guanidine.

(b) reacting a benzoylguanidine of formula III



in which

R^3 is F, Cl, Br, I or a leaving group, is reacted with a compound of the formula IV



with a salt-like compound which can be derived therefrom, or with a thiolate,

(c) treating a compound which otherwise corresponding to formula I but which contains, instead of one or more hydrogen atoms, one or more reducible groups and/or one or more additional C-C and/or C-N bonds, with a reducing agent,

(d) treating a compound which otherwise corresponds to formula I but which contains, instead of one or more hydrogen atoms, one or more solvolysable groups with a solvolysing agent, or

(e) converting a compound of formula I by treatment with an acid into one of its salts.



US005866610A

United States Patent [19]

Lang et al.

[11] Patent Number: 5,866,610

[45] Date of Patent: Feb. 2, 1999

[54] SUBSTITUTED BENZOYLGUANIDINES,
PROCESS FOR THEIR PREPARATION,
THEIR USE AS A PHARMACEUTICAL AS
INHIBITORS OF THE CELLULAR NA⁺/H⁺
EXCHANGE OR AS A DIAGNOSTIC, AND
PHARMACEUTICAL CONTAINING THEM

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[73] Assignee: Hoechst Aktiengesellschaft, Frankfurt
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[21] Appl. No.: 683,141

[22] Filed: Jul. 18, 1996

Related U.S. Application Data

[63] Continuation of Ser. No. 391,272, Feb. 21, 1995, abandoned,
which is a continuation of Ser. No. 198,812, Feb. 18, 1994,
abandoned.

[30] Foreign Application Priority Data

Feb. 20, 1993 [DE] Germany 43 05 250.9

[51] Int. Cl.⁶ A61K 31/165; C07C 233/65

[52] U.S. Cl. 514/617; 514/614; 514/615;
514/619; 514/622; 514/821; 558/415; 564/161;
564/163; 564/165; 564/166; 564/167

[58] Field of Search 564/147, 149,
564/237, 241, 161, 163, 165, 166, 167;
514/614, 615, 634, 821, 524, 617, 619,
622; 558/615

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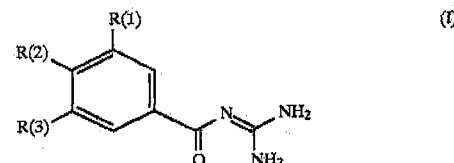
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Primary Examiner—Shailendra Kumar
Attorney, Agent, or Firm—Finnegan, Henderson, Farabow,
Garrett & Dunner, L.L.P.

[57] ABSTRACT

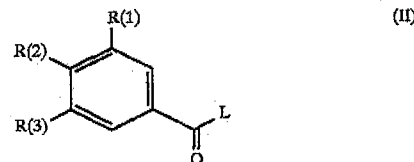
Substituted benzoylguanidines, process for their
preparation, their use as a pharmaceutical or diagnostic, and
pharmaceutical containing them.

Described are benzoylguanidines of the formula I



where R(1) to R(3) are H, Hal, (cyclo)alkyl, N₃, CN or OH,
alkyloxy, phenyl, phenoxy or benzoyl, and their pharmaco-
logically acceptable salts, but with the exception of the
compounds benzoylguanidine, 4-chlorobenzoylguanidine,
3,4-dichlorobenzoylguanidine and 3- or
4-methylbenzoylguanidine.

They are obtained by reacting a compound II



with guanidine, L being a leaving group.

6 Claims, No Drawings

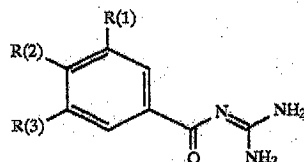
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**SUBSTITUTED BENZOYLGUANIDINES,
PROCESS FOR THEIR PREPARATION,
THEIR USE AS A PHARMACEUTICAL AS
INHIBITORS OF THE CELLULAR NA⁺/H⁺
EXCHANGE OR AS A DIAGNOSTIC, AND
PHARMACEUTICAL CONTAINING THEM**

This application is a continuation of application Ser. No. 08/391,272, filed Feb. 21, 1995 abandoned, which is a continuation of prior application Ser. No. 08/198,812, filed Feb. 18, 1994, abandoned, which application is entirely incorporated herein by reference.

The invention relates to benzoylguanidines of the formula I



in which:

R(1), R(2), R(3) are hydrogen, F, Cl, Br, I or (C₁-C₁₂)-alkyl,

one of the substituents R(1), R(2) or R(3) is N₃, CN, OH or (C₁-C₁₀)-alkyloxy, if at least one of the remaining substituents R(1), R(2) or R(3) is a sufficiently lipophilic alkyl radical having 3 to 12 carbon atoms,

or one of the substituents R(1), R(2) or R(3) is R(4)—C_nH_{2n}—O_m where m is zero or 1, n is zero, 1, 2 or 3,

R(4) is C_pF_{2p+1}

where p is 1, 2 or 3 if n is zero or 1, or

R(4) is (C₃-C₁₂)-cycloalkyl, phenyl, pyridyl, quinolyl or isoquinolyl, the aromatic and heteroaromatic ring systems being unsubstituted or substituted by a substituent selected from the group comprising F, Cl, CF₃, methyl, methoxy or NR(5)R(6), where R(5) and R(6) are hydrogen or (C₁-C₄)-alkyl,

or one of the substituents R(1), R(2) or R(3) is —C=CR(5), —C[R(6)]=CR(5),

R(5) is

phenyl which is unsubstituted or substituted by 1-3 substituents selected from the group comprising F, Cl, CF₃, methyl, methoxy, hydroxyl, amino, methylamino or dimethylamino,

(C₁-C₆)-heteroaryl, which is unsubstituted or substituted as phenyl,

(C₁-C₆)-alkyl, which is unsubstituted or substituted by 1-3 OH, or

(C₃-C₈)-cycloalkyl,

R(6) is hydrogen or methyl,

and the pharmacologically acceptable salts thereof, where, if R(4) is pyridyl, quinolyl or isoquinolyl, m and n must not simultaneously be zero, and with the exception of the compounds benzoylguanidine, 4-chlorobenzoylguanidine, 3,4-dichlorobenzoylguanidine, and 3- or 4-methylbenzoylguanidine.

Preferred compounds are those in which

R(1), R(2), R(3) are hydrogen, F, Cl, Br or (C₁-C₈)-alkyl one of the substituents R(1), R(2) or R(3) is OH or (C₁-C₆)-alkyloxy, if at least one of the remaining substituents R(1), R(2) or R(3) is a sufficiently lipophilic alkyl radical having 3 to 6 carbon atoms,

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or one of the substituents R(1), R(2) or R(3) is R(4)—C_nH_{2n}—O_m where

m is zero or 1,

n is zero, 1, 2 or 3,

R(4) is C_pF_{2p+1}

where p is 1 if n is zero or 1, or

R(4) is (C₃-C₇)-cycloalkyl, phenyl, pyridyl, quinolyl or isoquinolyl, the aromatic and heteroaromatic ring systems being unsubstituted or substituted by a substituent selected from the group comprising

F, Cl, CF₃, methyl or methoxy,

or one of the substituents R(1), R(2) or R(3) is —C=CR(5),

R(5) is phenyl or (C₁-C₄)-alkyl,

which is unsubstituted or substituted by OH,

and the pharmacologically acceptable salts thereof, where, if R(4) is pyridyl, quinolyl or isoquinolyl, m and n must not simultaneously be zero, and with the exception of the compounds benzoylguanidine, 4-chlorobenzoylguanidine, 3,4-dichlorobenzoylguanidine and 3- or 4-methylbenzoylguanidine.

Particularly preferred are 3-trifluoromethylbenzoylguanidine hydrochloride, 3,5-bistrifluoromethylbenzoylguanidine hydrochloride, 3-methyl-5-trifluoromethylbenzoylguanidine hydrochloride, 4-fluoro-3-trifluoromethylbenzoylguanidine hydrochloride, 4-(4-fluorophenoxy)-3-trifluoromethylbenzoylguanidine hydrochloride, 5-fluoro-3-trifluoromethylbenzoylguanidine hydrochloride, 3-chloro-4-isopropylbenzoylguanidine hydrochloride, 4-tert-butyl-3-methoxybenzoylguanidine hydrochloride, 3-tert-butyl-4-hydroxybenzoylguanidine hydrochloride, 3-tert-butyl-4-isopropylbenzoylguanidine hydrochloride and the pharmacologically acceptable salts thereof.

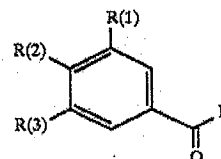
If one of the substituents R(1) to R(3) contains an asymmetric centre, then the invention also embraces S- and R-configured compounds. The compounds can be in the form of optical isomers, diastereomers, racemates or mixtures of these.

The alkyl radicals mentioned can be either straight-chain or branched.

(C₁-C₆)-heteroaryl is to be understood as meaning, in particular radicals which are derived from phenyl or naphthyl and in which one or more CH groups are replaced by nitrogen and/or in which at least two adjacent CH groups (on the formation of a five-membered aromatic ring) are replaced by S, NH or O. Moreover, it is also possible for one or both atoms of the condensation site of bicyclic radicals (such as in indoliziny) to be nitrogen atoms.

Heteroaryl is, in particular, furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, indazolyl, quinolyl, isoquinolyl, phthalazinyl, quinoxalinyl, quinazolinyl, cinnolinyl.

The invention furthermore relates to a process for the preparation of a compound I, which comprises reacting a compound of the formula II



in which R(1) to R(3) have the abovementioned meaning and L is a leaving group which can readily be substituted by a nucleophile, with guanidine.

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The activated acid derivatives of the formula II in which L is an alkoxy group, preferably a methoxy group, a phenoxy group, a phenylthio, methylthio or 2-pyridylthio group, or a nitrogen heterocycle, preferably 1-imidazolyl, are obtained advantageously, in a manner known per se, from the carboxylic acid chlorides on which they are based (formula II, L=Cl), which, in turn, can be prepared from the carboxylic acids on which they are based (formula II, L=OH), in a manner known per se, for example using thionyl chloride.

In addition to the carboxylic acid chlorides of the formula II (L=Cl), further activated acid derivatives of the formula II can also be prepared in a manner known per se directly from the benzoic acid derivatives on which they are based (formula II, L=OH), for example the methyl esters of the formula II where L=OCH₃ by treating them with gaseous HCl in methanol, the imidazolides of the formula II by treating them with carbonyldiimidazole (L=1-imidazolyl, Staab, Angew. Chem. Int. Ed. Engl. 1, 351-367 (1962)), the mixed anhydrides II using Cl-COOC₂H₅ or tosyl chloride in the presence of triethylamine in an inert solvent, and benzoic acids can be activated using dicyclohexylcarbodiimide (DCC) or using O-[(cyano(ethoxycarbonyl)methylene)amino]-1,1,3,3-tetramethyluronium tetrafluoroborate ("TOTU") [Proceedings of the 21st European Peptide Symposium, Peptides 1990, Editors E. Giralt and D. Andreu, Escom, Lieden, 1991]. A series of suitable methods for the preparation of activated carboxylic acid derivatives of the formula II is given in J. March, Advanced Organic Chemistry, Third Edition (John Wiley & Sons, 1985), p. 350, where the references are cited.

An activated carboxylic acid derivative of the formula I is reacted with guanidine in a manner known per se, in a protic or aprotic polar, but inert, organic solvent. Substances which have proven themselves in the reaction of the methyl benzoates (II, L=OMe) with guanidine are methanol or THP between 20° C. and the boiling point of these solvents. In most reactions of compounds II with salt-free guanidine, the procedure was advantageously carried out in aprotic inert solvents, such as THF, dimethoxyethane or dioxane. If a base, such as, for example, NaOH is used as solvent, water can also be used in the reaction of II and III.

If L is Cl, the process is carried out advantageously with the addition of an acid scavenger, for example in the form of excess guanidine, to bind the hydrohalic acid.

Some of the basic benzoic acid derivatives of the formula II are known and described in the literature. The unknown compounds of the formula II can be prepared by methods known from the literature.

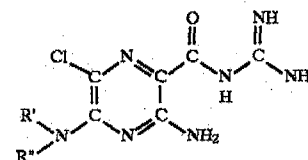
Carboxylic acids or their esters of the formula II (for example L=—OH or —O-methyl) where R(2) has the meaning of halogen or R(3) has the meaning of nitro can act as useful starting compounds for other carboxylic acids of the formula II, it being possible for the halogen in the position R(2) to be exchanged very conveniently in a known manner for a large number of nucleophilic reagents, such as phenols or alcohols R(4)—C_nH_{2n}—OH or their alkali metal salts giving the corresponding benzoic acid derivatives. Equally, nitro groups can be reduced to the corresponding aminobenzoic acid by means of Sandmeyer or Ullmann reactions and then lead to the desired, in particular halogen-substituted, benzoic acid derivatives. In many cases, chlorine, bromine or iodine can also be introduced into a particular benzoic acid in a manner known per se by direct halogenation using a Friedel-Crafts catalyst.

In general, benzoylguanidines I are weak bases and can bind acid with the formation of salts. Suitable acid addition

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salts are salts of all pharmacologically acceptable acids, for example halides, in particular hydrochlorides, lactates, sulfates, citrates, tartrates, acetates, phosphates, methylsulfonates and p-toluenesulfonates.

The compounds I are substituted acylguanidines. The best known representative of the acylguanidines is the pyrazine derivative amiloride, which is used in therapy as a potassium-sparing diuretic. A large number of other compounds of the amiloride type are described in the literature, such as, for example, dimethylamiloride or ethylisopropylamiloride.



Amiloride: R', R''=H

Dimethylamiloride: R', R''=CH₃

Ethylisopropylamiloride: R'=C₂H₅, R''=CH(CH₃)₂

Moreover, studies have been published which suggest that amiloride has antiarrhythmic properties (Circulation 79, 1257-63 (1989). However, a broad use as an antiarrhythmic is prevented by the fact that this effect is only weakly pronounced and accompanied by a hypotensive and saluretic activity, and these side effects are undesired in the treatment of cardiac arrhythmias.

Results obtained in experiments with isolated animal hearts have also suggested that amiloride has antiarrhythmic properties (Eur. Heart J. 9 (suppl.1): 167 (1988) (book of abstracts). For example, it has been found on rats' hearts that an artificially induced ventricular fibrillation could be suppressed completely by amiloride. The abovementioned amiloride derivative ethylisopropylamiloride was even more potent than amiloride in this model.

European Offenlegungsschrift 416,499 (HOE 89/F 288) describes benzoylguanidines which have a hydrogen atom in the position which corresponds to the radical R(1).

German Offenlegungsschrift 3,502,629 discloses benzoylguanidines which are substituted in the m-position with a phenoxy group and which always have at least two substituents in the phenoxy group. These compounds are used in crop protection.

The publication Kumamoto, Pharm. Bull [1966], pages 7-13, describes a few substituted benzoylguanidines which can be used as anticancer agents.

U.S. Pat. No. 3,780,027 claims acylguanidines which are similar to the compounds of the formula I with regard to the structure and which are derived from commercially available loop diuretics, such as bumetanide. Accordingly, powerful salidiuretic activity is reported for these compounds.

It was therefore surprising that the compounds according to the invention have no undesired and disadvantageous salidiuretic, but very good antiarrhythmic, properties, such as, for example, in the case of oxygen deficiency symptomis. Due to their pharmacological properties, the compounds are outstandingly suitable for use as antiarrhythmic pharmaceuticals with a cardioprotective component for the prophylaxis and treatment of infarctions and for the treatment of angina pectoris, and they also preventively inhibit, or greatly reduce, the pathophysiological processes involved in ischemically induced damage, in particular when ischemically induced cardiac arrhythmias are triggered. Due to their protective activities against pathological, hypoxic and ischemic situations, the compounds of the formula I accord-

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ing to the invention can be used, due to inhibition of the cellular Na^+/H^+ exchange mechanism, as pharmaceuticals for the treatment of all acute or chronic, ischemia-triggered types of damage or diseases which are primarily or secondarily induced thereby. This applies to their use as pharmaceuticals for invasive treatment, for example in the case of organ transplants, where the compounds can be used not only for protecting the organs in the donor before and during removal, for the protection of removed organs, for example when they are treated with, or stored in, physiological bath fluids, but also when they are transferred into the acceptor organism. The compounds are also valuable protective pharmaceuticals for carrying out invasive angioplastic treatment, for example on the heart or on peripheral blood vessels. Due to their protective activity against ischemically induced types of damage, the compounds are also suitable for use as pharmaceuticals for the treatment of ischemias of the nervous system, in particular of the central nervous system, where they are suitable, for example, for the treatment of apoplexy or of cerebral edema. Moreover, the compounds of the formula I according to the invention are also suitable for the treatment of forms of shock, such as, for example, allergic, cardiogenic, hypovolemic and bacterial shock.

Moreover, the compounds of the formula I according to the invention are distinguished by powerful inhibitory action on cell proliferations, for example fibroblast cell proliferation and proliferation of the smooth vascular muscle cells. This is why the compounds of the formula I are suitable as valuable therapeutic agents for diseases in which cell proliferation is a primary or secondary cause, and they can therefore be used as antiatherosclerotics, agents against late complications in diabetes, cancers, fibrotic disorders, such as pulmonary fibrosis, hepatic fibrosis or renal fibrosis, organ hypertrophias and hyperplasias, in particular in prostatic hyperplasia or prostatic hypertrophy.

The compounds according to the invention are valuable inhibitors of the cellular sodium proton antiporter (Na^+/H^+ exchanger), which is elevated in a large number of diseases (essential hypertension, atherosclerosis, diabetes and the like) even in those cells which are readily accessible to measurements, such as in erythrocytes, thrombocytes or leukocytes. The compounds according to the invention are therefore suitable as outstanding and simple scientific tools, for example in their use as diagnostics for determining, and distinguishing between certain forms of hypertension, but also of atherosclerosis, diabetes, proliferative diseases, and the like. Moreover, the compounds of formula I are suitable for preventive therapy for preventing the genesis of hypertension, such as of essential hypertension.

Moreover, the compounds are distinguished by an inhibition of the hydrochloric acid production of the parietal cells of the stomach, and they can therefore be used as pharmaceuticals for the treatment of gastrointestinal diseases. Such gastrointestinal disorders and diseases of the esophagus are, for example, gastric and intestinal ulcers and reflux esophagitis.

Pharmaceuticals which contain a compound I can be administered orally, parenterally, intravenously, rectally or by inhaling, the preferred way of administration being dependent on the particular symptom of the disease. The compounds I can be used by themselves or together with pharmaceutical auxiliaries, and they can be employed both in veterinary medicine and human medicine.

A person skilled in the art knows, on the basis of his expert knowledge, which auxiliaries are suitable for the desired pharmaceutical formulation. Auxiliaries which can be used in addition to solvents, gel-formers, bases for

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suppositories, tableting auxiliaries, and other excipients for active substances are, for example, antioxidants, dispersants, emulsifiers, antifoamers, flavor improvers, preservatives, solubilizers or colorants.

For an oral dosage form, the active compounds together with the additives suitable for this purpose, such as carriers, stabilizers or inert diluents, are mixed and formulated by customary methods to give suitable dosage forms, such as tablets, sugar-coated tablets, hard gelatin capsules, or aqueous, alcoholic or oily solutions. Inert excipients which may be used are, for example, gum arabic, magnesia, magnesium carbonate, potassium phosphate, lactose, glucose or starch, in particular maize starch. Dry granules or moist granules can be used for the preparation. Examples of oily excipients or examples of solvents are vegetable or animal oils, such as sunflower oil or codliver oil.

For subcutaneous or intravenous administration, the active compounds, if desired together with the substances which are customary for this purpose, such as solubilizers, emulsifiers or other auxiliaries, are dissolved, suspended or emulsified. Examples of suitable solvents are: water, physiological saline, or alcohols, for example ethanol, propanol, glycerol, and also sugar solutions, such as glucose or mannitol solutions, or else a mixture of the various solvents which have been mentioned above.

Pharmaceutical formulations which are suitable for administration in the form of aerosols or sprays are, for example, solutions, suspensions or emulsions of the active substance of the formula I in a pharmaceutically acceptable solvent, such as, in particular, ethanol or water, or else in a mixture of such solvents.

If required, the formulation can also contain other pharmaceutical auxiliaries, such as surfactants, emulsifiers and stabilizers, and a propellant gas. The concentration of active substances in such a preparation is generally from about 0.1 to 10, in particular from about 0.3 to 3, % by weight.

The dose of the active substance of the formula I to be administered and the frequency of the administration will depend on the potency and duration of action of the compounds used; in addition also on the nature and severity of the disease to be treated and on the sex, age, weight and individual responsiveness of the mammal to be treated.

On average, the daily dosage rate of a compound of the formula I in the case of a patient of approximately 75 kg will be at least 0.001 mg/kg, preferably 0.01 mg/kg, up to not more than 10 mg/kg, preferably 1 mg/kg, of body weight. If the disease is acute, such as immediately after suffering a cardiac infarction, even higher, and in particular, more frequent, doses may also be required, for example up to 4 single doses per day. Up to 200 mg per day may be required, in particular for intravenous administration, such as in the case of a patient who has suffered an infarction and is under intensive care.

EXPERIMENTAL PART

General Protocol for the Preparation of Benzoyleguanidines (I) from Benzoic Acids (II, $\text{L}=\text{OH}$)

0.01 mol of the benzoic acid derivative of the formula II is dissolved or suspended in 60 ml of anhydrous tetrahydrofuran (THF), and 1.78 g (0.011 mol) of carbonyldiimidazole are then added. After the reaction solution has been stirred for 2 hours at room temperature, 2.95 g (0.05 mol) of guanidine are introduced. After the mixture has been stirred overnight, the THF is distilled off under reduced pressure (Rotavapor), water is added, the pH is brought to 6-7 using

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

2020

Bogotá, D.C.,

Abogado

LUIS PATIÑO LEIVA

(Apoderado)

ASUNTO

Radicación 04123482

Trámite 002

Evento 001

Actuación 430

Oficio 0667

Folios 018

Patente de Invención

☒

Patente de Modelo de Utilidad

☐

Vía Nacional

☐

Vía PCT (fase nacional)

☒

Cap. I

☐

Cap. II

☒

No. Sol. Internacional

PCT/EP03/05738

Fecha de Presentación Internacional 2-06-2003

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados:

1.1. Descripción:

(Folios: 37 a 59) como se radicó inicialmente.
Modificaciones (Folios: 103 a 124).

1.2. Reivindicaciones:

1 a 13 (Folios: 60 a 65) como se radicó inicialmente. Modificadas 1 a 14 (Folios: 125 a 130). Modificadas 1 a 7 (folios: 148 a 150).

1.3. Rta. del Solicitante: Folios: 144 y 145.

1.4. Prioridad:

13/06/2002, DE 10226462.7.

2. Análisis de la Prioridad:

La prioridad de la presente solicitud corresponde al objeto reivindicado.

3. Objeto de la invención:

La presente solicitud se titula: "Benzoilguanidinas cicloalquilderivadas fluoradas y su uso como medicamento".

El objeto de la presente solicitud se refiere a compuestos de fórmula I, que son derivados de benzoilguanidina cicloalquilderivadas fluoradas; los compuestos pueden existir como isómeros ópticos, como diastereoisómeros, como racematos o como mezclas de ellos. La solicitud comprende todas las formas tautómeras de los compuestos de las fórmulas I y II.

Las benzoilguanidinas de la fórmula I son generalmente bases débiles y son capaces de unirse a ácidos para formar sales. Los compuestos de la fórmula I son acilguanidinas sustituidas e inhiben el antiporte celular sodio-protón (intercambiador Na^+/H^+ , NHE). Los compuestos de la solicitud, se distinguen por tener normalmente propiedades ADME favorables (absorción, distribución, metabolismo, excreción) comparados con benzoilguanidinas conocidas, junto con actividad excelente en la inhibición del intercambio Na^+/H^+ ; estas propiedades convenientes son dependientes del grupo cicloalquilo fluorado.

Los inhibidores de NHE de la solicitud son adecuados para el tratamiento de enfermedades causadas por isquemia y por reperfusión. Los compuestos son adecuados como medicamentos antiarrítmicos. Son adecuados para profilaxis del infarto y tratamiento del infarto y para el tratamiento de angina pectoris, casos en los que también inhiben preventivamente o reducen mucho los procesos patofisiológicos asociados con el desarrollo de daño inducido por isquemia.

En el capítulo reivindicatorio se reclama lo siguiente:

Reivindicaciones 1 a 5 (folios: 148 a 150): Una benzoilguanidina cicloalquilderivada fluorada de la fórmula I y sus sales aceptables farmacéuticamente.

Reivindicaciones 6 y 7 (folio: 150): Una medicina para uso humano, veterinario y/o fitoprotector que comprende una cantidad eficaz de al menos un compuesto de la fórmula I y/o las sales aceptables farmacéuticamente junto con soportes y aditivos aceptables farmacéuticamente.

El problema planteado en esta solicitud es la necesidad de compuestos inhibidores del antiporte celular sodio-protón (intercambiador Na^+/H^+ , NHE).

La solución propuesta por la presente solicitud consiste en compuestos derivados de benzoilguanidinas cicloalquil derivados de fórmula I.

El objeto de la solicitud definido anteriormente se clasificó en la IPC C07C 317/46.

4. Determinación del Estado de la Técnica:

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

Fecha de presentación de la solicitud prioritaria 13 de junio de 2002.

Teniendo en cuenta la fecha indicada, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a esta.

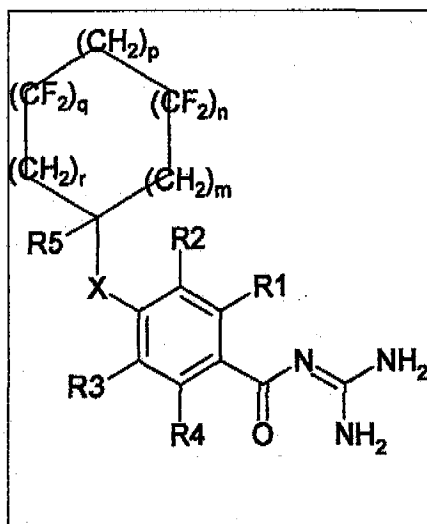
Se encontró como anterioridades que pueden afectar la patentabilidad del objeto de la presente solicitud:

Nº	Documento	Título	Fecha de Publicación
D1	ES 2096840	Benzoilguanidinas sustituidas, procedimiento para su preparación, su uso como medicamento o agente para diagnóstico, así como medicamento que las contiene	16 de marzo de 1997
D2	US 5869531	Fluoroalkyl substituted benzoylguanidines	9 de febrero de 1999
D3	US 5696167	4-mercaptobenzoylguanidine derivatives	9 de diciembre de 1997
D4	US 5866610	Substituted benzoylguanidines, process for their preparation, their use as a pharmaceutical as inhibitors of the celular Na ⁺ /H ⁺ Exchange or as a diagnostic, and pharmaceutical containing them	2 de febrero de 1999

5. Análisis de patentabilidad (artículo 14 D486)

5.1. Nivel inventivo (artículo 18 D486)

La presente Solicitud de Patente reivindica lo siguiente: derivados de benzoilguanidinas cicloalquil derivados, de fórmula I, que son inhibidores del intercambiador Na⁺/H⁺:

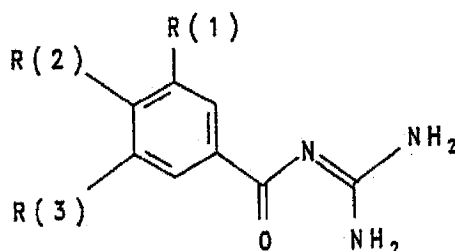


Donde:

- X es oxígeno, azufre o NR₆. R₆ es hidrógeno, alquilo que tiene 1, 2, 3 o 4 átomos de carbono o (CH₂)_k-CF₃
- Donde k es 0, 1, 2 o 3; m es cero, 1, 2 o 3; n es cero, 1, 2 o 3; p es cero, 1, 2 o 3; q es 1, 2 o 3; r es cero, 1, 2 o 3.
- R₁ es hidrógeno, alquilo que tiene 1, 2, 3 o 4 átomos de carbono, F, Cl, OR₇, -NR₈R₉ o C₈F_{2s+1}
- R₂ es hidrógeno, F, Cl, alquilo que tiene 1, 2, 3 o 4 átomos de carbono o CF₃.

- R_3 es hidrógeno, F, Cl, alquilo que tiene 1, 2, 3 o 4 átomos de carbono, CF_3 o SO_2R_{10} ; u es cero, 1 o 2.
- R_4 es hidrógeno alquilo que tiene 1, 2, 3 o 4 átomos de carbono, F, Cl, $-OR_{13}$.
- R_5 es hidrógeno o F.

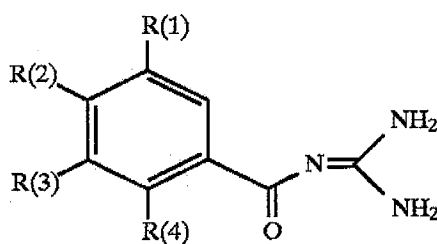
La anterioridad ES 2096840 (folios: 133 a 138), menciona benzoilguanidinas sustituidas que son inhibidoras del antiportador celular sodio-protones (intercambiador Na^+/H^+) para el tratamiento de enfermedades como: aterosclerosis, diabetes, enfermedades proliferativas, fibrosis pulmonar, acción protectora en la realización de intervenciones angioplásticas operativas, por ejemplo en el corazón.



Donde R^2 significa nitrógeno-heteroarilo C_{1-9} y que puede estar sustituido por 1-3 sustituyentes seleccionados de: F, Cl, CF_3 , CH_3 , metoxi, hidroxilo, entre otros.

Como se puede observar, el documento ES 2096840 menciona compuestos derivados de benzoilguanidinas que tienen en la posición de R^2 un anillo heteroarilo que puede estar sustituido hasta en 3 posiciones por flúor, mientras que en la presente solicitud, en esa misma posición se encuentra un cicloalquilo que puede estar sustituido por flúor hasta en dos posiciones. Ambos compuestos, tanto de la anterioridad como de la presente solicitud, tienen la misma actividad farmacológica.

El documento US 5869531 (folios: 152 a 154) se relaciona con benzoilguanidinas fluoroalquil-sustituidas de fórmula I, y se usan para el tratamiento de enfermedades inducidas por isquemia:

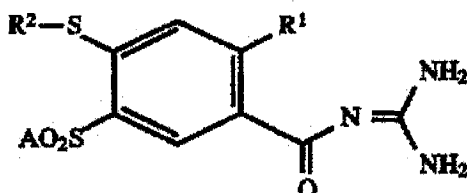


En donde:

- R_1 es hidrógeno, F, Cl, Br, I, CN, entre otros.
- R_2 es CF_2R_{14} , $CF(R_{15}R_{16})$, $CF(CF_2)_qCF_3$, R_{15} , $C(CF_2)(CF_3)=CR_{15}R_{16}$, donde: R_{14} es alquil C_{1-4} , cicloalquil C_{3-6} ; R_{15} y R_{16} son independientemente uno del otro hidrógeno o alquil C_{1-4} .
- R_3 es R_1
- R_4 es hidrógeno, alquil C_{1-3} , F, Cl, Br, I, CN o $(CH_2)_s-(CF_2)-CF_3$; donde s es 0 o 1 y t es 1 o 2.

En este documento US 5869531 se evidencia que en la posición R_2 (correspondiente a X-cicloalquilo en la presente solicitud) puede haber un cicloalquilo o un alquilo sustituido por el grupo CF_2 , como se encuentra en la solicitud en estudio.

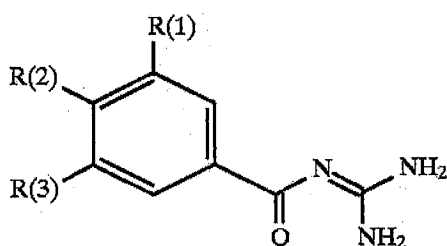
La anterioridad US 5696167 (folios: 155 a 158) se refiere a derivados de 4-mercaptobenzoilguanidina como inhibidores del intercambio Na^+/H^+ , para el tratamiento de enfermedades del ritmo cardiaco:



Donde:

- R_1 es A, CF_3 , CH_2F , CHF_2 o C_2F_5 .
- R_2 es H, A, cicloalquil C_{3-7} , fenil o Het.
- Het es heterociclo saturado, insaturado o aromático, mono o dicíclico, que tiene 1 a 4 átomos de nitrógeno, oxígeno o azufre, puede estar sustituido por Hal, CF_3 , A, OH, OA, SH, SA, NH_2 , NHA, NA_2 , entre otros.
- A es alquilo de 1 a 6 carbonos.
- Hal es F, Cl, Br o I.
- Fenilo puede estar sustituido con A, OA, NH_2 , NHA, NA_2 , F, Cl, Br y/o CF_3 .

El documento US 5866610 (folios: 159 a 162) se relaciona con benzoilguanidinas sustituidas que tienen un mecanismo de inhibición del intercambio de Na^+/H^+ , por lo cual tienen propiedades como cardioprotectores para el tratamiento de enfermedades tipo arritmia, angina, etc.



En donde:

- R_1 , R_2 , R_3 son hidrógeno, F, Cl, Br, I o alquil C_{1-12} ; o uno de R_1 , R_2 o R_3 es $R_4-C_nH_{2n}-O_m$, donde m es cero o 1, n es cero, 1, 2 o 3; R_4 es C_pF_{2p+1} , donde p es 1, 2 o 3 si n es cero o 1.

Al realizar los reemplazos respectivos en los significados de los sustituyentes, resultan compuestos muy semejantes a compuestos de la presente solicitud; por ejemplo, R_2 puede ser CF_2-CH_2-O- que corresponde a CF_2-CH_2-X- en la solicitud en estudio, cuando X es oxígeno y r, m, n son cero y q es 1. R_1 y R_3 son hidrógeno que corresponden a R_2 y R_3 en la presente solicitud y significan hidrógeno.

Estas anterioridades demuestran con claridad que ya era conocido en el estado del arte que los compuestos benzoilguanidinas sustituidos tienen actividad para el tratamiento de enfermedades cardiovasculares, como por ejemplo las arritmias, isquemia, angina, etc., y que su núcleo principal es el responsable de esta actividad y no sus sustituyentes.

De otro lado, estas anterioridades evidencian que los compuestos benzoilguanidinas pueden estar sustituidos con cicloalquilo no sustituido o sustituido por flúor, tal como pueden estarlo compuestos de la presente solicitud, conservando su actividad farmacológica. También estos compuestos pueden estar sustituidos con un alquilo sustituido a la vez por flúor, donde dicho alquilo va unido al grupo benzoilguanidina a través de un oxígeno, tal como se muestra en la presente solicitud.

Este tipo de compuestos también pueden estar sustituidos con un fenilo o heterociclo no sustituido o sustituido por flúor. Si bien los compuestos de la presente solicitud no están sustituidos por estos grupos, pero en su lugar, se puede encontrar un cicloalquilo sustituido por flúor, se reitera que es sabido por una persona medianamente versada en la materia, que un anillo heteroarilo sustituido por flúor y un cicloalquilo sustituido por flúor pueden ser bioisómeros, es decir, que no van a influir en un cambio importante de actividad farmacológica, como sucede con el objeto de la presente solicitud que no cambió la actividad de las benzoilguanidinas ya conocidas en el estado de la técnica.

De hecho, a lo largo de la presente solicitud, no se observan datos que demuestren una ventaja técnica frente a lo que se conocía o un efecto técnico inesperado. Por lo tanto, sería obvio para una persona medianamente versada en la materia, reemplazar un heteroarilo sustituido con flúor por un cicloalquilo sustituido con flúor sin que se altere la actividad farmacológica de las benzoilguanidinas.

El problema técnico planteado en esta solicitud: la necesidad de compuestos inhibidores del antiporte celular sodio-protón (intercambiador Na^+/H^+ , NHE), se había resuelto previamente mediante compuestos derivados de benzoilguanidinas sustituidas ya conocidos(as). Por esta razón se considera que las sustituciones de las benzoilguanidinas reivindicadas en la presente solicitud son evidentes para una persona medianamente versada en la materia.

Las reivindicaciones 1 y sus dependientes de esta solicitud no mencionan una característica que conceda un efecto inesperado o especial a los compuestos y medicina que los contiene, que pueda considerarse como un aporte a la técnica, así que son obvios para una persona versada en la materia.

Además, puesto que D1-D2, D2-D3 y D2-D4 divulgaban previamente derivados de benzoilguanidina como inhibidores de NHE (folios: 133 a 138, 152 a 162), una persona conocedora de la materia motivada por tal sugerencia lograría el objeto de esta solicitud compuestos derivados de benzoilguanidina (folios: 148 a 150); de manera que para una persona medianamente versada en la materia sería obvio utilizar este documento. Por lo cual puede no haber Nivel Inventivo.

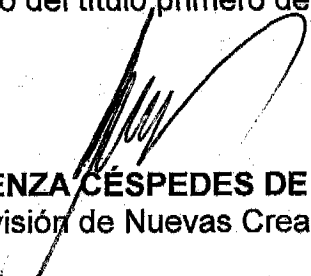
6. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento Nº	Reivindicaciones afectadas	Requisito que afecta
D1	ES 2096840	1 a 7	Nivel Inventivo
D2	US 5869531	1 a 7	Nivel Inventivo
D3	US 5696167	1 a 7	Nivel Inventivo
D4	US 5866610	1 a 7	Nivel Inventivo

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.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única Nº 10 de 2001.


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 23 ENE 2009

CONCEPTO TÉCNICO No. 143	EXAMINADOR TÉCNICO Código No. 202005
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