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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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Solicitud de Patente PCT entrada fase nacional para: **DERIVADOS DE N-((3-OXO-2,3-DIHIDRO-1H-ISOINDOL-1-IL)ACETIL)GUANIDINA EN CALIDAD DE INHIBIDORES DE NHE-1 PARA EL TRATAMIENTO DE INFARTO Y LA ANGINA DE PECHO**

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. 9902 notificado el 28 de agosto de 2009 atentamente me permito dar repuesta al mismo de la siguiente manera:

Nivel inventivo

Ese Despacho considera que los compuestos de la presente solicitud constituyen una serie bioisótera de la primer serie de guanadinas con actividad sobre el intercambiador Na^+/H^+ NHE. Considera además que las diferencias en cuanto a la estructura anular no demuestran una ventaja técnica comparativa que evidencia una ventaja en términos del efecto técnico.

En respuesta a las objeciones hechas por su Despacho, el solicitante respetuosamente considera que ninguno de los documentos citados por el señor examinador afectaría el nivel inventivo de los compuestos de la solicitud. Pongo a consideración de su despacho las siguientes aclaraciones que sustentan la actividad inventiva de la solicitud:

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El documento D1 enseña los compuestos Cariporide y Eriporide, los cuales son benzoilguanidinas sustituidas e inhibidores de NHE1, D2 divulga el compuesto Zoniporide (pirazol carbonil guanidina sustituida) como inhibidores de NHE1 y D3 divulga arilguanidinas adicionales, particularmente pirazina o piridil carbonilo guanidinas y benzoilguanidinas sustituidas como inhibidores de NHE1.

Todos los compuestos descritos en los documentos D1, D2 y D3 son compuestos en los cuales el residuo carbonil guanidina está unido a un sistema de anillo aromático, en consecuencia, estos compuestos son arilguanidinas. Por el contrario los compuestos de la presente solicitud son alcanil guanidinas, en las cuales la carbonil guanidina está unida al residuo pirrolona de un anillo isoindolona por medio de un puente de metileno. Entonces, claramente la carbonil guanidina no está unida a un anillo aromático y los compuestos de la invención no son arilguanidinas. Por lo tanto, partiendo de las enseñanzas de D1, D2 y D3, la persona versada en la materia técnica no derivaría de manera evidente que los compuestos de la invención los cuales difieren significativamente en su estructura y propiedades químicas con respecto a los compuestos de las anterioridades, tendrían excelente actividad inhibitoria de NHE1.

Teniendo en cuenta que las estructuras químicas de los compuestos cotejados difieren significativamente, los documentos citados por el señor examinador no dan indicación alguna que sugiera cómo modificar las estructuras presentadas en dichos documentos con el objeto de obtener los compuestos inhibidores de NHE1 reivindicados por el solicitante.

Cumplido así con lo dispuesto, respetuosamente solicito que se otorgue el privilegio de patente a la presente invención toda vez que ésta cumple con el requisito de nivel inventivo estipulado por el Artículo 18 de la Decisión 486.

De la Señora Jefe,



Luis Patiño Leyva
C.C. No. 2.920.616 de Bogotá
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(18)



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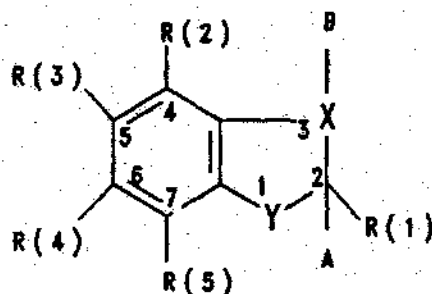
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(54) **Benzokondensierte 5-Ringheterocyclen, Verfahren zu ihrer Herstellung, ihre Verwendung als Medikament, ihre Verwendung als Diagnostikum, sowie sie enthaltendes Medikament.**

(57) **Beschrieben werden benzokondensierte 5-Ringheterocyclen der Formel I**



(1),

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mit X gleich N oder CR(6); Y gleich Sauerstoff, S oder NR(7); A und B gemeinsam eine Bindung oder beide Wasserstoff, sofern gleichzeitig X gleich CR(6) und Y gleich NR(7) sind;
einer der Substituenten R(1) bis R(6) eine -CO-N = C(NH₂)₂-Gruppe; die jeweils anderen Substituenten R(1) bis R(6) H, Hal, Alkyl;
bis zu zwei der anderen Substituenten R(1) bis R(6) CN, NO₂, N₃, (C₁-C₄)-Alkyloxy, CF₃; bis zu einem der

und saluretischen Wirkung begleitet auftritt und diese Nebenwirkungen bei der Behandlung von Herzrhythmusstörungen unerwünscht sind.

Hinweise auf antiarrhythmische Eigenschaften des Amilorids wurden auch bei Experimenten an isolierten Tierherzen erhalten (Eur. Heart J. 9 (suppl. 1): 167 (1988) (book of abstracts)). So wurde beispielsweise an Rattenherzen gefunden, daß ein künstlich ausgelöstes Kammerflimmern durch Amilorid völlig unterdrückt werden konnte. Noch potenter als Amilorid war in diesem Modell das oben erwähnte Amiloridderivat Ethylisopropylamilorid.

In der Europäischen Offenlegungsschrift 416 499 werden Benzoylguanidine mit antiarrhythmischen Eigenschaften beschrieben.

In der US-Patentschrift 3 780 027 werden ebenfalls Acylguanidine beschrieben, die sich grundlegend von den hier beschriebenen erfindungsgemäßen Verbindungen I dadurch unterscheiden, daß es sich um trisubstituierte Benzoylguanidine handelt, die sich in ihrem Substitutionsmuster von im Handel befindlichen Diuretika, wie Bumetanid und Furosemid, ableiten und eine für die angestrebte saldiuretische Wirkung wichtige Aminogruppe in Position 2 bzw. 3 zur Carbonylguanidengruppe tragen. Entsprechend wird für diese Verbindungen eine starke saldiuretische Wirksamkeit berichtet.

Es war daher überraschend, daß die erfindungsgemäßen Verbindungen keine unerwünschten und nachteiligen saldiuretischen, jedoch sehr gute antiarrhythmische Eigenschaften aufweisen, weshalb sie zum Behandeln von Krankheiten, wie sie beispielsweise bei Sauerstoffmangelerscheinungen auftreten, geeignet sind. Die Verbindungen sind infolge ihrer pharmakologischen Eigenschaften als antiarrhythmische Arzneimittel mit cardioprotektiver Komponente zur Infarktprophylaxe und der Infarktbehandlung sowie zur Behandlung der angina pectoris hervorragend geeignet, wobei sie auch präventiv die pathophysiologischen Vorgänge beim Entstehen ischämisch induzierter Schäden, insbesondere bei der Auslösung ischämisch induzierter Herzarrhythmien, inhibieren oder stark vermindern. Wegen ihrer schützenden Wirkungen gegen pathologische hypoxische und ischämische Situationen können die erfindungsgemäßen Verbindungen der Formel I infolge Inhibition des zellulären Na^+/H^+ -Austauschmechanismus als Arzneimittel zur Behandlung aller akuten oder chronischen durch Ischämie ausgelösten Schäden oder dadurch primär oder sekundär induzierten Krankheiten verwendet werden. Dies betrifft ihre Verwendung als Arzneimittel für operative Eingriffe, z.B. bei Organ-Transplantationen, wobei die Verbindungen sowohl für den Schutz der Organe im Spender vor und während der Entnahme, zum Schutz abnehmener Organe beispielsweise bei Behandlung mit oder deren Lagerung in physiologischen Bedürfnissen, wie auch bei der Überführung in den Empfängerorganismus verwendet werden können. Die Verbindungen sind ebenfalls wertvolle, protektiv wirkende Arzneimittel bei der Durchführung angioplastischer operativer Eingriffe beispielsweise am Herzen wie auch an peripheren Gefäßen. Entsprechend ihrer protektiven Wirkung gegen ischämisch induzierte Schäden sind die Verbindungen auch als Arzneimittel zur Behandlung von Ischämien des Nervensystems, insbesondere des ZNS, geeignet, wobei sie z.B. zur Behandlung des Schlaganfalls oder des Hirnödems geeignet sind. Darüberhinaus eignen sich die erfindungsgemäßen Verbindungen der Formel I ebenfalls zur Behandlungen von Formen des Schocks, wie beispielsweise des allergischen, cardiogenen, hypovolämischen und des bakteriellen Schocks.

Darüber hinaus zeichnen sich die erfindungsgemäßen Verbindungen der Formel I durch starke inhibierende Wirkung auf die Proliferationen von Zellen, beispielsweise der Fibroblasten-Zellproliferation und der Proliferation der glatten Gefäßmuskulzellen, aus. Deshalb können die Verbindungen der Formel I als wertvolle Therapeutika für Krankheiten infrage, bei denen die Zellproliferation eine primäre oder sekundäre Ursache darstellt, und können deshalb als Antifibrosklerotika, Mittel gegen diabetische Spätkomplikationen, Krebserkrankungen, fibrotische Erkrankungen wie Lungenfibrose, Leberfibrose oder Nierenfibrose, Organhypertrophien und -hyperplasien, insbesondere bei Prostatahyperplasie bzw. Prostatahypertrophie verwendet werden.

Die erfindungsgemäßen Verbindungen sind wirkungsvolle Inhibitoren des zellulären Natrium-Proteinen-Antiporters (Na^+/H^+ -Exchanger), der bei zahlreichen Erkrankungen (Essentielle Hypertonie, Atherosklerose, Diabetes usw.) auch in solchen Zellen erhöht ist, die Messungen leicht zugänglich sind, wie beispielsweise in Erythrocyten, Thrombocyten oder Leukozyten. Die erfindungsgemäßen Verbindungen eignen sich deshalb als hervorragende und einfache wissenschaftliche Werkzeuge, beispielsweise in ihrer Verwendung als Diagnostika zur Bestimmung und Unterscheidung bestimmter Formen der Hypertonie, aber auch der Atherosklerose, des Diabetes, proliferativer Erkrankungen usw.. Darüber hinaus sind die Verbindungen der Formel I für die präventive Therapie zur Verhinderung der Genese des Bluthochdrucks, beispielsweise der essentiellen Hypertonie, geeignet.

Die Erfindung betrifft weiterhin ein Verfahren zur Herstellung der Verbindungen I, dadurch gekennzeichnet, daß man

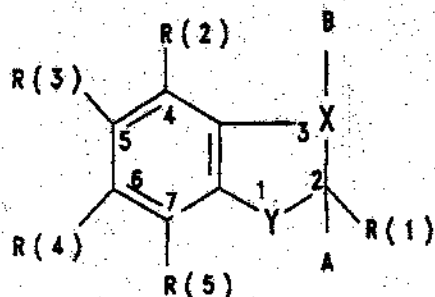
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Ergebnisse

Inhibition des Na ⁺ /H ⁺ -Exchangers:	
Beispiel	IC ₅₀ mol/l
52	4×10^{-8}
53	5×10^{-8}
54	2×10^{-7}
61	3×10^{-7}
69	5×10^{-8}
86	3×10^{-8}
104	2×10^{-7}
106	5×10^{-8}

Patentansprüche

1. Benzokondensierte 5-Ringheterocyclen der Formel 1



worin bedeuten:

X N, CR(6),

Y Sauerstoff, S, NR(7),

A, B gemeinsam eine Bindung
oder

beide Wasserstoff, sofern gleichzeitig X gleich CR(6) und Y gleich NR(7) sind,

einer der Substituenten R(1) bis R(6) eine -CO-N = C(NH₂)₂-Gruppe, die jeweils anderen Substituenten R(1) bis R(6)

Wasserstoff, F, Cl, Br, I, (C₁-C₆)-Alkyl,

bis zu zwei der anderen Substituenten R(1) bis R(6).

CN, NO₂, N₃, (C₁-C₄)-Alkyloxy, CF₃,

bis zu einem der anderen Substituenten

R(6)-C_nH_{2n+1}-Z-

n Null bis 10,

wobei die Alkylkette -C_nH_{2n+1}- geradkettig oder verzweigt ist und wobei ein C-Atom durch ein Sauerstoff- oder S-Atom oder durch ein N-Atom ersetzt sein kann,

R(6) Wasserstoff, (C₂-C₆)-Alkenyl, (C₃-C₁₀)-Cycloalkyl,

das unsubstituiert oder durch 1 bis 4 Methylgruppen oder eine OH-Gruppe substituiert ist, oder eine Ethylengruppe -CH = CH- enthalten kann, und worin eine Methylengruppe durch ein Sauerstoff- oder S-Atom oder durch ein N-Atom ersetzt sein kann, Phenyl,

unsubstituiert oder substituiert durch 1 bis 3 Substituenten ausgewählt aus der Gruppe bestehend aus F, Cl, Br, I, CF₃, CH₃-S(O)₂-

- s Null, 1, 2,
R(9)-W_Y-
5 R(9) H, Methyl, Ethyl,
W gleich Sauerstoff, NR(10),
R(10) H, Methyl,
Y Null, 1,
C_mF_{2m+1}-
10 m 1 bis 3,
1- oder 2-Naphthyl, Pyridyl, Chinolyl, Isochinolyl,
Z -CO-, -CH₂-, -[CR(11)(OH)]_q-
q 1, 2, 3,
R(11) H, Methyl;
15 Sauerstoff, -NR(12)-,
R(12) H, Methyl,
-S(O)₂-,
s Null, 1, 2,
-SO₂-NR(13)-,
20 R(13) H, (C₁-C₄)-Alkyl,
R(7) Wasserstoff, (C₁-C₁₀)-Alkyl, (C₂-C₁₀)-Alkenyl, R(8)-C_nH_{2n}-,
sowie deren pharmazeutisch verträgliche Salze.

2. Verbindungen der Formel I nach Anspruch 1, dadurch gekennzeichnet, daß darin bedeuten:

- 25 X CR(6), N,
Y NR(7),
A, B gemeinsam eine Bindung
oder
beide Wasserstoff, sofern gleichzeitig X gleich CR(6) und Y gleich NR(7) sind,
30 und die Reste R(1) bis R(7) die angegebene Bedeutung besitzen.

3. Verbindungen der Formel I nach Anspruch 1, dadurch gekennzeichnet, daß darin bedeuten:

- X CR(6), N, Y NR(7),
A, B gemeinsam eine Bindung
35 oder
beide Wasserstoff, sofern gleichzeitig X gleich CR(6) und Y gleich NR(7) sind,
einer der Substituenten R(1) bis R(6) eine -CO-N = C(NH₂)₂-Gruppe, und die jeweils anderen
Substituenten R(1) bis R(6)
Wasserstoff, F, Cl, Br, I, (C₁-C₆)-Alkyl,
40 bis zu zwei der anderen Substituenten R(1) bis R(6)
CF₃, (C₁-C₄)-Alkyloxy,
bis zu einem der anderen Substituenten R(1) bis R(6) CN, NO₂, N₃, R(8)-C_nH_{2n}-Z-,
n Null bis 4, wobei die Alkylkette -C_nH_{2n}- geradkettig oder verzweigt sein kann und ein C-
Atom durch ein Sauerstoff oder S-Atom oder durch ein N-Atom ersetzt sein kann,
45 R(8) Wasserstoff, (C₂-C₆)-Alkenyl, (C₅-C₈)-Cycloalkyl;
das unsubstituiert ist oder durch 1 - 2 Methylgruppen oder eine OH-Gruppe substitu-
iert, und worin eine Methylengruppe durch ein Sauerstoff- oder S-Atom oder durch ein N-
Atom ersetzt sein kann,
Phenyl,
50 das unsubstituiert ist oder substituiert mit 1 bis 3 Substituenten ausgewählt aus der
Gruppe bestehend aus F, Cl, Br, I, CF₃, CH₃-S(O)₂-
s Null, 1, 2,
R(9)-W_Y-
R(9) H, Methyl, Ethyl,
55 W Sauerstoff, NR(10),
R(10) H, Methyl,
y Null, 1,
C_mF_{2m+1}-

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- m 1 bis 3,
Pyridyl, Chinolyl, Isochinolyl
Z -CO-, -CH₂-, Sauerstoff, -NR(12)-,
R(12) H, Methyl,
5 -S(O)₂-,
s Null, 1, 2,
-SO₂-NR(13)-,
R(13) H, (C₁-C₆)-Alkyl,
R(7) Wasserstoff, (C₁-C₆)-Alkyl, (C₂-C₄)-Alkenyl, R(8)-C_nH_{2n}-.

4. Verbindungen der Formel I nach Anspruch 1, dadurch gekennzeichnet, daß darin bedeuten:

- X CR(6),
Y NR(7),
A, B gemeinsam eine Bindung
15 oder

beide Wasserstoff, sofern gleichzeitig X gleich CR(6) und Y gleich NR(7) sind,

und R(1) -CO-N= C(NH₂)₂

und die jeweils anderen Substituenten R(2) bis R(6)

Wasserstoff, F, Cl, Br,

20 bis zu zwei der Substituenten R(2) bis R(6)

CF₃, (C₁-C₂)-Alkyloxy,

bis zu einem der Substituenten R(2) bis R(6)

R(8)-C_nH_{2n}-Z-,

25 n Null, 1, 2,

wobei die Alkylkette -C_nH_{2n}- geradkettig oder verzweigt ist und wobei ein C-Atom durch ein Sauerstoff- oder S-Atom oder durch ein N-Atom ersetzt sein kann,

R(8) Wasserstoff, Phenyl,

das unsubstituiert ist oder substituiert mit 1 bis 3 Substituenten ausgewählt aus der Gruppe bestehend aus F, Cl, CF₃, CH₃-S(O)₂-,

30 s Null, 2,

R(9)-W_y-,

R(9) H, Methyl,

W Sauerstoff,

y Null, 1,

35 Pyridyl, Chinolyl, Isochinolyl,

Z -CO-, -CH₂-, -S(O)₂-, Sauerstoff,

s Null, 1, 2,

und

R(7) (C₁-C₆)-Alkyl, (C₂-C₄)-Alkenyl, R(8)-C_nH_{2n}-.

5. Verbindung der Formel I nach Anspruch 1, dadurch gekennzeichnet, daß sie ausgewählt ist aus der Gruppe bestehend aus

5-Chlor-1-methyl-2-indolylcarbonyl-guanidin-hydrochlorid,

5-Chlor-1-ethyl-2-indolylcarbonyl-guanidin-hydrochlorid,

45 3-Chlor-1-methyl-2-indolylcarbonyl-guanidin-hydrochlorid,

3,5-Dichlor-1-methyl-2-indolylcarbonyl-guanidin-hydrochlorid,

5-Fluor-1-methyl-2-indolylcarbonyl-guanidin-hydrochlorid,

3-Chlor-5-fluor-1-methyl-2-indolylcarbonyl-guanidin-hydrochlorid,

4,6-Dichlor-1,3-dimethyl-2-indolylcarbonyl-guanidin-hydrochlorid,

50 2-Phenoxy-1-phenylindol-3-carbonsäureguanidid Methansulfonsäuresalz,

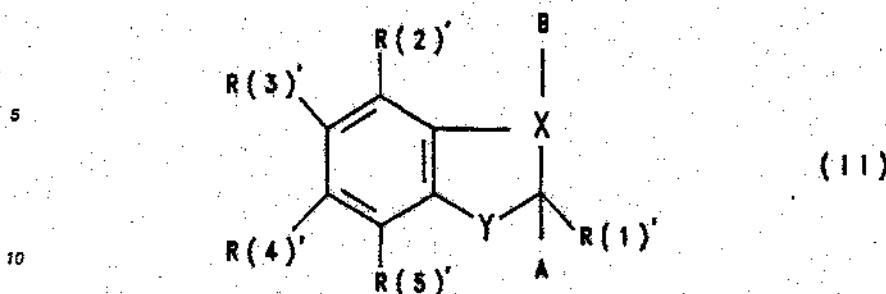
2-Chlor-1-phenylindol-3-carbonsäureguanidid Methansulfonsäuresalz,

1-Methylindol-2-carbonsäureguanidid-hydrochlorid,

5-Fluor-1-methylindol-2-carbonsäureguanidid-hydrochlorid.

6. Verfahren zur Herstellung einer Verbindung der Formel I nach Anspruch 1, dadurch gekennzeichnet, daß man eine Verbindung der Formel II

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75 worin einer der Substituenten R(1)' bis R(5)' eine -CO-L-Gruppe bedeutet und L für eine leicht nucleophil substituierbare leaving group steht, und die jeweils anderen Substituenten R(1)' bis R(5)' die angegebene Bedeutung besitzen, mit Guanidin unter Bildung der in Formel I angegebenen Acylguanidingruppe, -CO-N = C(NH₂)₂, umsetzt, und daß man gegebenenfalls in das pharmazeutisch verträgliche Salz überführt.

- 20
7. Verwendung einer Verbindung I nach Anspruch 1 zur Herstellung eines Medikaments zur Behandlung von Arrhythmien.
- 25 8. Methode zum Behandeln von Arrhythmien, dadurch gekennzeichnet, daß man eine wirksame Menge einer Verbindung I nach Anspruch 1 mit den üblichen Zusatzstoffen versetzt und in einer geeigneten Darreichungsform verabreicht.
- 30 9. Verwendung einer Verbindung I nach Anspruch 1 zur Herstellung eines Medikaments zur Behandlung oder Prophylaxe des Herzinfarktes.
10. Verwendung einer Verbindung I nach Anspruch 1 zur Herstellung eines Medikaments zur Behandlung oder Prophylaxe der Angina Pectoris.
- 35 11. Verwendung einer Verbindung I nach Anspruch 1 zur Herstellung eines Medikaments zur Behandlung oder Prophylaxe von ischämischen Zuständen des Herzens.
- 40 12. Verwendung einer Verbindung I nach Anspruch 1 zur Herstellung eines Medikaments zur Behandlung oder Prophylaxe von ischämischen Zuständen des peripheren und zentralen Nervensystems und des Schlaganfalls.
13. Verwendung einer Verbindung I nach Anspruch 1 zur Herstellung eines Medikaments zur Behandlung oder Prophylaxe von ischämischen Zuständen peripherer Organe und Gliedmaßen.
- 45 14. Verwendung einer Verbindung I nach Anspruch 1 zur Herstellung eines Medikaments zur Behandlung von Schockzuständen.
15. Verwendung einer Verbindung I nach Anspruch 1 zur Herstellung eines Medikaments zum Einsatz bei chirurgischen Operationen und Organtransplantationen.
- 50 16. Verwendung einer Verbindung I nach Anspruch 1 zur Herstellung eines Medikaments zur Konservierung und Lagerung von Transplantaten für chirurgische Maßnahmen.
- 55 17. Verwendung einer Verbindung I nach Anspruch 1 zur Herstellung eines Medikaments zur Behandlung von Krankheiten, bei denen die Zellproliferation eine primäre oder sekundäre Ursache darstellt, und somit ihre Verwendung als Antiatherosklerotika, Mittel gegen Diabetische Spätkomplikationen, Krebserkrankungen, fibrotische Erkrankungen wie Lungenfibrose, Leberfibrose oder Nierenfibrose, Prostatahyperplasie.

United States Patent [19]

Lai et al.

US005416094A

[11] Patent Number: 5,416,094

[45] Date of Patent: May 16, 1995

[54] ANTIARRHYTHMIC AND
CARDIOPROTECTIVE SUBSTITUTED
1,2-DISOQUINOLINES, MEDICAMENT
CONTAINING THEM, AND THEIR USE FOR
COMBATING HEART FAILURES

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[73] Assignee: Hoechst Aktiengesellschaft,
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[21] Appl. No.: 126,200

[22] Filed: Sep. 24, 1993

[30] Foreign Application Priority Data
Sep. 28, 1993 [EP] European Pat. Off. 92116335

[51] Int. Cl.⁶ C07D 217/12; A61K 31/47

[52] U.S. Cl. 514/307; 546/140;
546/141; 546/143; 546/144; 546/146; 546/128;
544/333; 544/363; 514/233.5; 514/255;
514/256; 514/308; 514/309; 514/310

[58] Field of Search 546/146, 140, 141, 143,
546/144, 145; 544/128, 333, 363; 514/233.5,
255, 256, 307, 308, 309, 310

References Cited

U.S. PATENT DOCUMENTS

3,780,027 12/1973 Crago et al. 546/494
4,360,611 4/1981 Hartmann et al. 546/146
4,322,418 3/1982 Lohr et al. 546/146
4,673,682 6/1987 Kopp et al. 514/307

FOREIGN PATENT DOCUMENTS

0005231 11/1979 European Pat. Off. 546/146
0105210 4/1984 European Pat. Off. 546/146
4154768 5/1992 Japan 546/146

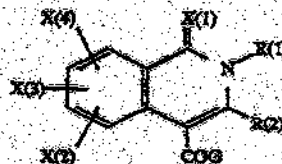
OTHER PUBLICATIONS

European Search Report dated Jan. 11, 1994 for corresponding EP Application No. 93 11 5081.

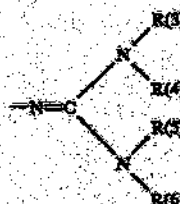
Primary Examiner—C. Warren Ivy
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Attorney, Agent, or Firm—Finnegan, Henderson,
Farabow, Garrett & Dunner

ABSTRACT

Described are guanidinocarbonyl isoquinolines of the formula I,



wherein R(1) is hydrogen, (amino) (cyclo) (aryl)alk(enyl) (heteroaryl); R(2) is hydrogen, halogen, alkyl, or aryl; G is a radical of the formula VII:

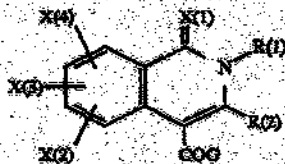


X(2), X(3) and X(4) are hydrogen, halogen, nitro, amino, alkyl, sulfonamide, (mono) (di) (lower alkyl) (amino), benzyl, hydroxy; X(1) hydrogen, oxygen, sulfur and NR(7)R(8), and their pharmaceutically acceptable salts; described is also a process for their preparation, their use as medicaments, and medicaments containing them for treating congestive heart failure, and arrhythmic conditions as well as cardioprotective agents in mammals.

1 Claim, No Drawings

**ANTIARRHYTHMIC AND CARDIOPROTECTIVE
SUBSTITUTED ISOQUINOLINES,
MEDICAMENT CONTAINING THEM, AND
THEIR USE FOR COMBATING HEART FAILURES**

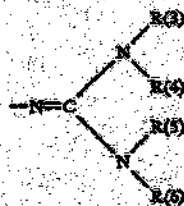
The invention relates to isoquinolines of the formula I:



wherein

R(1) is hydrogen, alkyl, cycloalkyl, arylalkyl, alkenyl, substituted amino alkyl or an aryl or heteroaryl ring, which rings are unsubstituted or substituted with one to three groups including halogen, nitro, amino, mono(lower alkyl)amino, di(lower alkyl)amino, lower alkyl, lower alkoxy, benzyloxy, phenoxy, hydroxy, or trifluoromethyl.

R(2) is hydrogen, halogen, alkyl, or aryl which may be unsubstituted or may have one to three groups including halogen, nitro, amino, mono(lower alkyl)amino, di(lower alkyl)amino, lower alkyl, lower alkoxy, benzyloxy, phenoxy, a hydroxy, G is a radical of the formula VII



X(2), X(3) and X(4) individually or collectively are selected from hydrogen, halogen, nitro, amino, alkyl, sulfonamide, mono(lower alkyl)amino, di(lower alkyl)amino, lower alkyl, benzyloxy, hydroxy and a combination thereof.

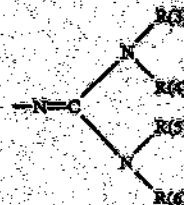
X(1) is two hydrogen atoms, oxygen, sulfur or NR(7), in which R(7) is hydrogen, alkyl, cycloalkyl, arylalkyl, alkenyl, substituted amino alkyl or an aryl or heteroaryl ring, which rings are unsubstituted or substituted with one to three groups including halogen, nitro, amino, mono(lower alkyl)amino, di(lower alkyl)amino, lower alkyl, lower alkoxy, benzyloxy, phenoxy, hydroxy, or trifluoromethyl.

in which substituents any alkyl chain or alkenyl chain may be interrupted by oxygen, sulfur or NR(8), wherein R(8) is hydrogen, alkyl, cycloalkyl, arylalkyl, alkenyl, substituted amino alkyl or an aryl or heteroaryl ring, which rings are unsubstituted or substituted with one to three groups including halogen, nitro, amino, mono(lower alkyl)amino, di(lower alkyl)amino, lower alkyl, lower alkoxy, benzyloxy, phenoxy, hydroxy, or trifluoromethyl, and their pharmaceutically acceptable salts.

Preferred are compounds I in which

R(1) is aryl or heteroaryl with no substitution or substituted with one to three groups including halogen, nitro, amino, mono(lower alkyl)amino,

di(lower alkyl)amino, lower alkyl, lower alkoxy, benzyloxy, phenoxy, hydroxy, or trifluoromethyl, R(2) is hydrogen, or alkyl, G is a radical of the formula VII:



with R(3), R(4), R(5) and R(6) being hydrogen, X(2), X(3) and X(4) individually or collectively are selected from hydrogen, halogen, nitro, amino, alkyl, sulfonamide, mono(lower alkyl)amino, di(lower alkyl)amino, lower alkyl, benzyloxy, hydroxy and a combination thereof,

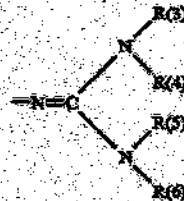
X(1) is oxygen.

Particularly preferred are compounds I wherein:

R(1) is lower alkyl, lower alkoxy, or a phenyl, naphthyl, or pyridyl ring the rings being unsubstituted or substituted with one to three groups including halogen, nitro, amino, mono(lower alkyl)amino, di(lower alkyl)amino, lower alkyl, lower alkoxy, benzyloxy, phenoxy, hydroxy, or trifluoromethyl,

R(2) is hydrogen,

G is a radical of the formula VII:



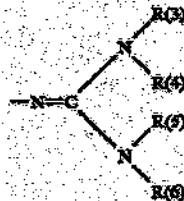
with R(3), R(4), R(5) and R(6) being hydrogen, X(2), X(3) and X(4) individually or collectively are hydrogen, halogen, nitro, amino, alkyl, sulfonamide, mono(lower alkyl)amino, di(lower alkyl)amino, lower alkyl, benzyloxy, hydroxy and a combination thereof, and

X(1) is oxygen.

Most preferred are compounds wherein

R(1) is lower alkyl, lower alkoxy, or phenyl, naphthyl or pyridyl rings the rings being unsubstituted or substituted with Cl.

R(2) is hydrogen, G is a radical of the formula VII:



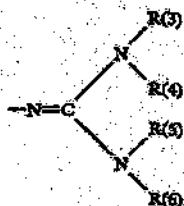
with R(3), R(4), R(5) and R(6) being hydrogen, X(2), X(3) and X(4) individually or collectively are hydrogen, halogen, nitro, amino, alkyl, sulfon-

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mide, mono(lower alkyl)amino, di(lower alkyl)amino, lower alkyl, benzyloxy, hydroxy and a combination thereof, and

X(1) is oxygen.

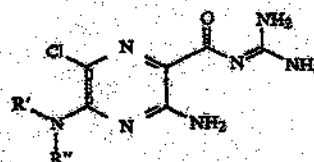
As used throughout the specification and the claims, the term "alkyl" refers to a straight or branched chain hydrocarbon radical containing no unsaturation and having 1 to 6 carbon atoms such as methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 1-pentyl, 2-pentyl, 3-hexyl and the like. Further it is possible to interrupt the chain by O, S or NR(8). The term "alkenyl" refers to straight or branched chain hydrocarbons with at least one unsaturation and having 3-6 carbon atoms such as allyl, isopropenyl, isobutenyl and the like; this chain may be interrupted by oxygen, sulfur or NR(8). The term "lower" as applied to any of the aforementioned groups refers to a group having a carbon skeleton containing up to and including 6-carbon atoms. The term "cycloalkyl" refers to a substituted or unsubstituted saturated or unsaturated cyclic carbon skeleton of 3-8 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl and like. The term "halogen" refers to F, Cl, Br or I. The term "aryl" includes substituted and unsubstituted phenyl and heteroaromatics. The notation "heterocycles", includes hetero aromatics such as pyridyl, thienyl, furyl, indolyl, quinolyl, isquinolyl, pyrimidyl, triazolyl, benzothiazolyl and the like, saturated heterocycles such as pyrrolidines, piperidines, morpholines and piperazines. Guanidino refers to unsubstituted $-N=C(NH_2)_2$ and its tautomeric forms and substituted guanidino refers to a radical of the formula VII:



wherein R(3), R(4), R(5), R(6) may be individually or collectively hydrogen, lower alkyl, acyl, aryl, or cycloalkyls. Alkyl and cycloalkyls are as defined earlier; acyl may be a branched or straight chain acyl group of C_1-C_6 units. NR(3)R(4) or NR(5)R(6) may be the part of a heterocyclic structure such as piperidine, pyrrolidine, morpholine or piperazines and the like. The term "arylalkyl" is a group which has a substituted phenyl connected through an alkyl group, for substituted phenyl is defined earlier, similarly alkyl may be a chain of carbon C_1-C_6 both straight or branched. Above substituted guanidino may also exist in a tautomeric form. R(7) and R(8) carry the same meaning as for R(1). All isomers, tautomers, and stereoisomers are included.

Compounds of the formula I carry a substituted acylguanidine in its skeleton. Amiloride a pyrazine with an acylguanidine may be as a representative, it is a potassium sparing diuretic. Several derivatives of amiloride are reported, dimethylamiloride or ethylisopropylamiloride are well known derivatives in this series

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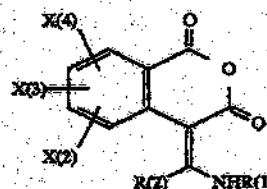


Amiloride: R' and R'' = H
Dimethylamiloride: R' and R'' = CH₃
Ethylisopropylamiloride R' = Et R'' = i-Pr.

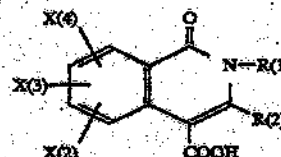
Amiloride has antiarrhythmic properties [Circulation 79, 1257 (1989)]. Its weak antiarrhythmic properties associated with hypotensive and saluretic action restricts its wide use, as these side effects are detrimental in the treatment of cardiac arrhythmias. The amiloride derivative ethylisopropylamiloride [(Eur. Heart J. 9 (Suppl.1): 167 (1988)](book of abstracts) was found to suppress completely an artificially induced ventricular fibrillation.

In U.S. Pat. No. 3 780 027 acylguanidines are claimed. They have no structural resemblance to the inventive compounds. These compounds have strong saluretic action as they are derived from commercially available diuretics such as bumetanide and furosemide, further these compounds carry an amino group, which is important for saluretic action.

It was very surprising that the compounds according to the invention show very good antiarrhythmic properties without saluretic properties. Due to this pharmacological effect, the compounds are ideally suitable as antiarrhythmic pharmaceuticals having a cardioprotective component for infarct prophylaxis and infarct treatment and also for the treatment of angina pectoris. The invention also relates to the process for the preparation of compounds of formula I. The synthesis of compounds of formula I was carried out by using an intermediate of formula II,

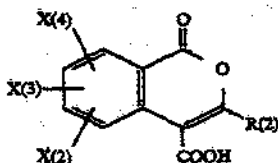


which in turn is made through a reported method (Otto. S. Wolfbeis, Liebigs. Ann. Chem. 1981, 819-827). 5-Methylthiomophthalic acid used for the preparation of compounds of formula II was made from 2,4-dimethylbenzoic acid by a similar method reported in the literature (G. B. Henderson and R. A. Hill, J. C. S., Perkin Trans. I, p. 1111, 1962). Compounds of formula II are converted into isoquinolones of formula III,



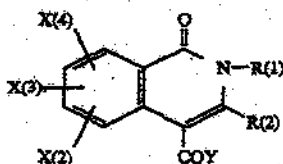
on treatment with 10% NaOH or on treatment with an acid (C. D. Patil, G. S. Sadana and K. D. Deodhar; J.

Ind. chem Soc; 67, 654-656, 1990 and the references therein). Compounds of the formula III may also be prepared directly by condensation of the formula VI

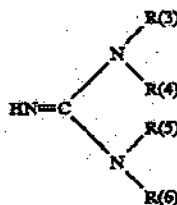


(M. Kimura; I. Waki; Y. Deguchi; K. Anemiyama and T. Maeda. Chem. Pharm. Bull. Jap. 31, 1277, 1983) with primary amine $\text{NH}_2\text{R}(1)$. Values of $\text{R}(1)$, $\text{R}(2)$, $\text{X}(2)$, $\text{X}(3)$ and $\text{X}(4)$ for formula II, III, IV and VI have the same meaning as defined above for formula I. The majority of the compounds reported here are unknown.

The invention also relates to a process for the preparation of compounds of formula I, which comprises: reacting compounds of formula IV



with either free guanidine or with a compound of formula V



in which $\text{R}(3)$, $\text{R}(4)$, $\text{R}(5)$ and $\text{R}(6)$ have values as defined earlier and Y is a leaving group, which can be easily displaced by a nucleophile.

The activated acid derivatives of the formula IV in which Y is an alkoxy group, preferably a methoxy group, an activated phenoxy group, a phenylthio, methylthio, 2-pyridylthio group or a nitrogen heterocycle, such as imidazolyl, which can be prepared from acid chloride (formula IV; $\text{Y}=\text{Cl}$) which in turn can be prepared from acid, formula III on treatment with thionyl chloride. Other activating ester methods can be used, which are known in the peptide area to activate the acid for coupling reaction. The imidazolides of formula IV, $\text{Y}=\text{imidazolides}$, can also be prepared from a compound of formula III by treating it with 1,1-Carbonyldiimidazole [C. Staab, Angew. Chem. Int. (Ed. Eng. 1 351-367 (1962)]. Compound of formula IV ($\text{Y}=\text{Cl}$) on treatment with the compound of formula V under Schotten-Baumann condition, also gave compound of formula I. Other mixed anhydrides related to formula IV may be prepared, such as with ClCOOEt , tosyl chloride, triethylphosphoryl chloride in the presence of triethylamine or any other base in an inert solvent. Activation of the COOH group in the compounds of the formula III can also be achieved with DCC (dicyclohexylcarbodiimide). Other methods of

preparation of activated carboxylic acid derivative of formula IV type are given with indication of source literature in J. March, Advanced Organic Chemistry, 3rd Edition (John Wiley & Son, 1985), p. 330. Coupling reaction between compounds of formula III and V can be conducted in a variety of ways in protic or aprotic polar solvents, but inert organic solvents are preferred. In this connection methanol, THF, DMF, N-methylpyrrolidone, hexamethyl phosphoric acid triamide (HMPA), etc., at from room temperature up to the boiling point of these solvents have proved suitable for the reaction of the Formula IV ($\text{Y}=\text{OMe}$) with guanidine. Reactions of compound IV with salt free guanidine are advantageously carried out in aprotic inert solvents such as THF, dimethoxy ethane, DMF or dioxane. However water can also be used as a solvent. In the case where a compound of formula III is directly treated with Carbonyldiimidazole for activating the carboxy group, aprotic polar solvents such as DMF, or dimethoxy ethane are used, followed by the addition of a compound of formula V.

Compounds of the formula I may be converted into pharmacologically acceptable acid addition salts.

Acids useful for preparing the pharmaceutically acceptable acid addition salts of the invention include inorganic acid such as hydrochloric, hydrobromic, sulfuric, nitric, phosphoric and perchloric acids, as well as organic acids such as tartaric, citric, acetic, succinic, maleic, fumaric, methanesulfonic and oxalic acids.

The active compounds of the present invention may be administered orally, parenterally, intravenously, rectally or by inhalation, the preferred administration being dependent on the specific clinical need of the disorder.

In this connection, the compounds of formula I can be used alone or together with pharmaceutical auxiliaries, and indeed both in veterinary and in human medicine.

Which auxiliaries are suitable for the desired pharmaceutical formulation is familiar to the person skilled in the art on the basis of his expert knowledge. In addition to solvents, gel-forming agents, suppository bases, tablet auxiliaries and other active compound carriers, antioxidants, dispersants, emulsifiers, defoaming agents, flavor correctors, preservatives, solubilizers or colorants, for example, can be used.

For a form for oral use, the active compounds are mixed with the additives suitable for this purpose, such as excipients, stabilizers or inert diluents and are brought into the forms suitable of administration, such as tablets, coated tablets, hard gelatin capsules, aqueous, alcoholic or oily solutions, by the customary methods. Inert carriers which can be used are, for example, gum arabic, magnesium, magnesium carbonate, potassium phosphate, lactose, glucose or starch, in particular cornstarch. In this case, preparation can take place both as dry and as moist granules. Suitable oily excipients or solvents are, for example, vegetable or animal oils, such as sunflower oil or cod liver oil.

For subcutaneous or intravenous administration, the active compounds, as desired with the substances customary for this purpose such as solubilizers, emulsifiers or other auxiliaries, are brought into solution, suspension or emulsion. Possible solvents are, for example: water, physiological saline solution or alcohols, for example ethanol, propanol, glycerol, in addition also sugar solutions such as glucose or mannitol solutions, or

alternatively, a mixture of the various solvents mentioned.

Pharmaceutical formulations suitable for administration in the form of aerosols or sprays are, for example, solutions, suspensions or emulsions of the active compound of the formula I in a pharmaceutically acceptable solvent, such as, in particular, ethanol or water, or a mixture of such solvents. If required, the formulation may also contain other pharmaceutical auxiliaries such as surfactants, emulsifiers and stabilizers and also a propellant gas. Such a preparation customarily contains the active compound in a concentration of about 0.1 to 10, in particular of about 0.3 to 3% by weight.

The dosage of the active compound of the formula I to be administered and the frequency of administration depend on the potency and duration of action of the compounds used; and additionally 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 dose of a compound of the formula I in a patient of about 75 kg weight is at least 0.001 mg, preferably 0.01 mg to at most 10 mg, preferably at most 1 mg. In acute outbreaks of the illness, for example immediately after suffering a cardiac infarct, still higher and above all, more frequent dosages may also be necessary, for example up to 4 individual doses per day. In particular on i.v. use, for example in an infarct patient in the intensive care unit, up to 100 mg per day may be necessary.

A few representative compounds of the formula I according to the invention or their physiologically tolerable salts shown below in Table I can be prepared analogously to the procedures given in the exemplary embodiments:

Table I

- 1) 2-(3,4-Dimethoxyphenyl)-4-guanidinocarbonyl-1(2H)-isoquinolinone. Hydrochloride monohydrate, m.p. 205°-206° C.,
- 2) 2-(3-Methoxyphenyl)-4-guanidinocarbonyl-1(2H)-isoquinolinone. Hydrochloride, m.p. 238°-240° C.,
- 3) 2-(4-Methoxyphenyl)-4-guanidinocarbonyl-1(2H)-isoquinolinone. Hydrochloride-hemihydrate, m.p. 249°-250° C.,
- 4) 2-(3,5-Dimethoxyphenyl)-4-guanidinocarbonyl-1(2H)-isoquinolinone. Hydrochloride-sesquihydrate, m.p. 260°-262° C.,
- 5) 2-(4-isopropylphenyl)-4-guanidinocarbonyl-1(2H)-isoquinolinone. Hydrochloride-Hydrate, m.p. 198°-200° C.,
- 6) 2-(4-Chlorophenyl)-4-guanidinocarbonyl-1(2H)-isoquinolinone. Hydrochloride-Hydrate, m.p. 195°-197° C.,
- 7) 2-(3,4-Dimethylphenyl)-4-guanidinocarbonyl-1(2H)-isoquinolinone. Hydrochloride-Hemihydrate, m.p. 248°-249° C.,
- 8) 2-(4-Fluorophenyl)-4-guanidinocarbonyl-1(2H)-isoquinolinone. Hydrochloride-Hemihydrate, m.p. 247°-248° C.,
- 9) 2-(4-Ethoxyphenyl)-4-guanidinocarbonyl-1(2H)-isoquinolinone. Hydrochloride-Hemihydrate, m.p. 205°-207° C.,
- 10) 2-(4-Cyclohexylphenyl)-4-guanidinocarbonyl-1(2H)-isoquinolinone. Hydrochloride, m.p. 253°-254° C.,

- 11) 2-(2,4-Dimethylphenyl)-4-guanidinocarbonyl-1(2H)-isoquinolinone. Hydrochloride-Dihydrate, m.p. 218°-220° C.,
- 12) 2-(2,5-Dimethylphenyl)-4-guanidinocarbonyl-1(2H)-isoquinolinone. Hydrochloride-hydrate, m.p. 210°-211° C.,
- 13) 2-(4-Methylphenyl)-4-guanidinocarbonyl-1(2H)-isoquinolinone. Hydrochloride-Hemihydrate, m.p. 245°-246° C.,
- 14) 2-(2-Methylphenyl)-4-guanidinocarbonyl-1(2H)-isoquinolinone. Hydrochloride, m.p. 274°-275° C.,
- 15) 2-(3,5-Dimethylphenyl)-4-guanidinocarbonyl-1(2H)-isoquinolinone. Hydrochloride, m.p. 281°-282° C.,
- 16) 2-(3-Methylphenyl)-4-guanidinocarbonyl-1(2H)-isoquinolinone. Hydrochloride, m.p. 269°-270° C.,
- 17) 2-(2-Naphthyl)-4-guanidinocarbonyl-1(2H)-isoquinolinone. Hydrochloride, m.p. 217°-219° C.,
- 18) 6, 7-Dimethoxy-2-(3,4-dimethylphenyl)-4-guanidinocarbonyl-1(2H)-isoquinolinone. Hydrochloride, m.p. 270°-271° C.,
- 19) 6,7-Dimethoxy-2-(3-methoxyphenyl)-4-guanidinocarbonyl-1(2H)-isoquinolinone. Hydrochloride, m.p. 259°-263° C.,
- 20) 2-(3,4-Dimethylphenyl)-4-guanidinocarbonyl-6-methyl-1(2H)-isoquinolinone hydrochloride hemihydrate. m.p. 305°-306° C.,
- 21) 4-Guanidinocarbonyl-6-methyl-2-(2-methylphenyl)-1(2H)-isoquinolinone hydrochloride. m.p. 303°-305° C.,
- 22) 4-Guanidinocarbonyl-6-methyl-2-(4-methoxyphenyl)-1(2H)-isoquinolinone hydrochloride hemihydrate. m.p. 251°-253° C.,
- 23) 2-(3,5-Dimethoxyphenyl)-4-guanidinocarbonyl-6-methyl-1(2H)-isoquinolinone hydrochloride sesquihydrate. m.p. 261°-263° C.,
- 24) 4-Guanidinocarbonyl-2-(3-methoxyphenyl)-6-methyl-1(2H)-isoquinolinone hydrochloride hemihydrate. m.p. 262°-264° C.,
- 25) 4-Guanidinocarbonyl-6-methyl-2-(3-methylphenyl)-1(2H)-isoquinolinone hydrochloride. m.p. 288°-290° C.,
- 26) 4-Guanidinocarbonyl-6-methyl-2-phenyl-1(2H)-isoquinolinone hydrochloride. m.p. 282°-283° C.,
- 27) 2-(4-Chlorophenyl)-4-guanidinocarbonyl-6-methyl-1(2H)-isoquinolinone hydrochloride monohydrate. m.p. 273°-275° C.,
- 28) 4-Guanidinocarbonyl-6-methyl-2-(2-naphthyl)-1(2H)-isoquinolinone hydrochloride. m.p. 270°-271° C.,
- 29) 2-(2,4-Dimethylphenyl)-4-guanidinocarbonyl-6-methyl-1(2H)-isoquinolinone hydrochloride. m.p. 219°-220° C.,
- 30) 4-Guanidinocarbonyl-6-methyl-2-(2,4,6-trimethylphenyl)-1(2H)-isoquinolinone hydrochloride sesquihydrate. m.p. 261°-262° C.,
- 31) 4-Guanidinocarbonyl-2-(2-methoxyphenyl)-6-methyl-1(2H)-isoquinolinone hydrochloride hemihydrate. m.p. 284°-285° C.,
- 32) 2-(2,6-Dimethylphenyl)-4-guanidinocarbonyl-6-methyl-1(2H)-isoquinolinone hydrochloride hemihydrate. m.p. 283° C.,
- 33) 4-Guanidinocarbonyl-6-methyl-2-(3,4,5-trimethoxyphenyl)-1(2H)-isoquinolinone hydrochloride dihydrate. m.p. 250° C.,
- 34) 2-(4-Bromophenyl)-4-guanidinocarbonyl-6-methyl-1(2H)-isoquinolinone hydrochloride hemihydrate. m.p. 259-260.

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- 35) 2-(4-Fluorophenyl)-4-guanidinocarbonyl-6-methyl-1(2H)-isoquinolinone hydrochloride. m.p. 260°-261° C.
- 36) 2-(4-Fluorophenylmethyl)-4-guanidinocarbonyl-6-methyl-1(2H)-isoquinolinone hydrochloride. m.p. 251°-252° C.
- 37) 4-Guanidinocarbonyl-6-methyl-2-phenylmethyl-1(2H)-isoquinolinone hydrochloride. m.p. 257°-258° C.
- 38) 2-(4-Chlorophenylmethyl)-4-guanidinocarbonyl-6-methyl-1(2H)-isoquinolinone hydrochloride hemihydrate. m.p. 265° C.
- 39) 2-(2-Fluorophenyl)-4-guanidinocarbonyl-6-methyl-1(2H)-isoquinolinone hydrochloride monohydrate. m.p. 275° C.
- 40) 4-Guanidinocarbonyl-6-methyl-2-(4-nitrophenyl)-1(2H)-isoquinolinone hydrochloride monohydrate. m.p. 262°-263° C.
- 41) 2-(3,4-Dimethoxyphenylmethyl)-4-guanidinocarbonyl-6-methyl-1(2H)-isoquinolinone hydrochloride hemihydrate. m.p. 228°-230° C.
- 42) 2-Cyclopentyl-4-guanidinocarbonyl-6-methyl-1(2H)-isoquinolinone hydrochloride. m.p. 253°-254° C.
- 43) 4-Guanidinocarbonyl-6-methyl-2-(1-methylethyl)-1(2H)-isoquinolinone hydrochloride. m.p. 258°-259° C.
- 44) 2-(4-Bromo-2,6-dimethylphenyl)-4-guanidinocarbonyl-6-methyl-1(2H)-isoquinolinone hydrochloride. m.p. 251°-252° C.
- 45) 2-(3,4-Dichlorophenylmethyl)-4-guanidinocarbonyl-6-methyl-1(2H)-isoquinolinone hydrochloride. m.p. 251°-252° C.
- 46) 4-Guanidinocarbonyl-6-methyl-2-[4-(1-piperazinophenyl)]-1(2H)-isoquinolinone dihydrochloride dihydrate. m.p. >360° C.
- 47) 2-(3-Fluorophenyl)-4-guanidinocarbonyl-6-methyl-1(2H)-isoquinolinone hydrochloride. m.p. 278°-280° C.
- 48) 2-Phenyl-4-guanidinocarbonyl-1(2H)-isoquinolinone hydrochloride hemihydrate. m.p. 251°-255° C.
- 49) 2-(3,4,5-Trimethoxyphenyl)-4-guanidinocarbonyl-1(2H)-isoquinolinone hydrochloride dihydrate. m.p. 264°-269° C.
- 50) 2-(2-Chloro-4-methyl)-4-guanidinocarbonyl-1(2H)-isoquinolinone hydrochloride hemihydrate. m.p. 220°-225° C.
- 51) 2-(2,4-Dimethoxyphenyl)-4-guanidinocarbonyl-1(2H)-isoquinolinone hydrochloride sesquihydrate. m.p. 216° C.
- 52) 6,7-Dimethoxy-2-(2-naphthyl)-4-guanidinocarbonyl-1(2H)-isoquinolinone hydrochloride sesquihydrate. m.p. 277°-280° C.
- 53) 6,7-Dimethoxy-2-(3-methoxyphenyl)-4-guanidinocarbonyl-1(2H)-isoquinolinone hydrochloride hydrate. m.p. 259°-263° C.
- 54) 2-(4-*t*-Butylphenyl)-4-guanidinocarbonyl-1(2H)-isoquinolinone hydrochloride hydrate m.p. 230°-235° C.
- 55) 2-Ethyl-4-guanidinocarbonyl-1(2H)-isoquinolinone hydrochloride hydrate. m.p. 264°-269° C.
- 56) 2-(2-Ethoxyphenyl)-4-guanidinocarbonyl-1(2H)-isoquinolinone hydrochloride hydrate. m.p. 204°-206° C.
- 57) 2-Isopropyl-4-guanidinocarbonyl-1(2H)-isoquinolinone hydrochloride. m.p. 248°-273° C.
- 58) 2-Cyclopentyl-4-guanidinocarbonyl-1(2H)-isoquinolinone hydrochloride. m.p. 244°-249° C.

- 59) 2-Propyl-4-guanidinocarbonyl-1(2H)-isoquinolinone hydrochloride. m.p. 248°-254° C.
- 60) 2-(4-N,N-Dimethylphenyl)-4-guanidinocarbonyl-1(2H)-isoquinolinone hydrochloride hydrate. m.p. 225°-227° C.
- 61) 2-iso-Butyl-4-guanidinocarbonyl-1(2H)-isoquinolinone hydrochloride hydrate. m.p. 242°-244° C.
- 62) 2-(2-Methyl-6-pyridyl)-4-guanidinocarbonyl-1(2H)-isoquinolinone dihydrochloride hemihydrate. m.p. 219°-221° C.
- 63) 2-(2,3-Dihydro-1,5-dimethyl-2-phenyl-3-oxo-4-pyrazolyl)-4-guanidinocarbonyl-1(2H)-isoquinolinone hydrochloride dihydrate. m.p. 212°-213° C.
- 65) 2-(2-Methoxyphenyl)-4-guanidinocarbonyl-1(2H)-isoquinolinone hydrochloride. m.p. 268°-269° C.
- 66) 2-(3-Chlorophenyl)-4-guanidinocarbonyl-1(2H)-isoquinolinone hydrochloride hydrate. m.p. 269°-270° C.
- 67) 2-Cyclohexyl-4-guanidinocarbonyl-1(2H)-isoquinolinone hydrochloride sesquihydrate. m.p. 189°-190° C.
- 68) 4-Guanidinocarbonyl-2-(3-hydroxyphenyl)-1(2H)-isoquinolinone hydrochloride sesquihydrate. m.p. 219°-221° C.
- 69) 2-(5-Fluoro-2-methylphenyl)-4-guanidinocarbonyl-1(2H)-isoquinolinone hydrochloride hydrate. m.p. 214°-216° C.
- 70) 4-Guanidinocarbonyl-2-(1-naphthyl)-1(2H)-isoquinolinone hydrochloride sesquihydrate. m.p. 231°-232° C.
- 71) 2-[2-(3,4-Dimethoxyphenylethyl)]-4-guanidinocarbonyl-1(2H)-isoquinolinone hydrochloride hemihydrate. m.p. 282°-283° C.
- 72) 2-(2,4-Dichlorophenyl)-4-guanidinocarbonyl-1(2H)-isoquinolinone hydrochloride hydrate. m.p. 254°-255° C.
- 73) 4-Guanidinocarbonyl-2-(2,4,6-trimethylphenyl)-1(2H)-isoquinolinone hydrochloride hemihydrate. m.p. 280°-282° C.
- 74) 4-Guanidinocarbonyl-2-(5-methylisoxazol-3-yl)-1(2H)-isoquinolinone hydrochloride hemihydrate. m.p. 253°-255° C.
- 75) 2-(2,6-Difluorophenyl)-4-guanidinocarbonyl-1(2H)-isoquinolinone hydrochloride. m.p. 261°-262° C.
- 76) 2-(3,4-Dichlorobenzyl)-4-guanidinocarbonyl-1(2H)-isoquinolinone hydrochloride. m.p. 255°-257° C.
- 77) 2-(4-Fluorobenzyl)-4-guanidinocarbonyl-1(2H)-isoquinolinone hydrochloride. m.p. 263°-264° C.
- 78) 2-(4-Chlorobenzyl)-4-guanidinocarbonyl-1(2H)-isoquinolinone hydrochloride hydrate. m.p. 249°-250° C.

Experimental Section

The representative example 2-(2-Methylphenyl)-4-guanidinocarbonyl-1(2H)-isoquinolinone (S. No. 14 of formula I—Table I) is defined; other compounds were also synthesized using such/other sequences.

A. Synthesis of compound with formula II.

a: 4-(2-Methylphenyl) aminomethylene homophthalic anhydride:

Homophthalic anhydride (2.4 g), triethylorthoformate (11 ml) and *o*-toluidine (1.6 g) were mixed and refluxed for 40 min. The reaction mixture was cooled, diluted with ethanol and petroleum ether to give a solid. The solid was filtered washed with pet ether; yield 2.05 g; mp 289°-290° C.,

IR (KBr) in cm^{-1} , 1700, 1665 and 1510. Anal. calcd. for: $\text{C}_{17}\text{H}_{13}\text{NO}_3$; C, 73.11%; H, 4.69%; N, 5.01%. Found: C, 72.58%; H, 4.75%; N, 4.93%.

B. Synthesis of compounds with formula III.

a. 2-(2-Methylphenyl)-4-carboxy-1(2H)-isoquinolinone:

4-(2-Methylphenyl)aminomethylene homophthalic anhydride (1.85 g), ethyl alcohol (25 ml) and sodium hydroxide (1.3 g) were mixed and heated on a steam bath for 1 hour. The reaction mixture was diluted with water and acidified with diluted hydrochloric acid. The separated solid was filtered and washed with water and dried. Traces of impurities by flash chromatography using 1% MeOH- CHCl_3 as the eluant.

Yield 844 mg; mp 307°-308° C.

IR(KBr) in cm^{-1} , 3040-3100 (broad); 1720, 1635, NMR(CDCl_3 +TFA) δ : 2.2 (s, 3H, Ar- CH_3); 7.2-7.4 (m, 4H, Ar-H); 7.6-8.0 (m, 2H, Ar-H); 8.32 (s, 1H, H-3); 8.48 (d, J=7.7Hz, 1H, H-5); 8.88 (d, J=7.7Hz, 1H, H-8).

	C %	H %	N %
Anal. Calcd. for $\text{C}_{17}\text{H}_{13}\text{NO}_3$:	73.11	4.69	5.01
Found:	72.69	4.78	4.99

C. Synthesis of compounds with formula I.

a. 2-(2-Methylphenyl)-4-guanidinocarbonyl-1(2H)-isoquinolinone.

2-(2-Methylphenyl)-4-carboxy-1(2H)-isoquinolinone (0.78 g) was dissolved in dry DMF (12 ml), 1,1-Carbonyldiimidazole (500 mg) was added and the reaction mixture stirred at room temperature for 3 hrs., the resultant solution was transferred to a flask containing free guanidine (0.95 g). The reaction mixture was further stirred at room temperature for overnight. Excess solvent was removed under vacuum. The residue was triturated with water and the separated solid was filtered, washed with water and dried. Yield 787 mg;

The compound was converted into hydrochloride salt. Yield 746 mg; mp 274°-275° C.

IR(KBr) in cm^{-1} ; 3350-2900; 1700; 1670 and 1620. NMR(DMSO- d_6) in δ : 2.2 (s, 3H, Ar- CH_3); 7.44 (brs, 4H, Ar-H); 7.56-7.96 (m, 2H, Ar-H); 8.04-8.60 [m, 7H, Ar-H(3); NH_2 (4)], 12.23 (brs, 1H, H-Cl).

	C %	H %	N %	Cl %
Anal. Calcd. for $\text{C}_{18}\text{H}_{17}\text{N}_4\text{O}_2\text{Cl}$:	60.59	4.80	15.70	9.93
Found:	60.53	4.75	15.51	10.05

Pharmacological methods to evaluate antiarrhythmic and cardioprotective action:

1. Reperfusion induced arrhythmias in isolated rat heart.

Wistar rats of either sex, weighing 280-300 g were used in this experiment. The heart was excised and perfused with physiological solution according to Langendorff method. The perfusate was gassed with 95% oxygen and 5% carbon dioxide gas mixture at 37° C. A silicon balloon catheter was introduced the left ventricle through the left auricle for recording left ventricular pressure (LVP) and left ventricular dp/dt max. (LV dp/dt max). The heart was perfused for an initial 20 min period (control perfusion). Acute regional ischemia was then induced in the left anterior descending coronary artery for 15 min (ischemic period). Thereafter,

the occlusion was reopened and cardiac functions were monitored for 30 min. (reperfusion period).

The following parameters such as LVP, LV dp/dt max, heart rate, coronary flow, ventricular fibrillation (VF) duration were recorded continuously on Nihon-Kohden polygraph system. Epicardial ECG was monitored on BPL monitor throughout the experiment.

All test compounds were dissolved in distilled water or DMSO (100%) and added in different concentrations into perfusate. The protective effect of the compound was assessed from reduction in VF duration and reversal of cardiac contractility. The results of the representative compounds are cited in the table II. The instant compounds of the series, at 0.1 μM -1.0 μM dose, as compared to control heart, significantly reduced the duration of reperfusion induced arrhythmias (Ref. Table II).

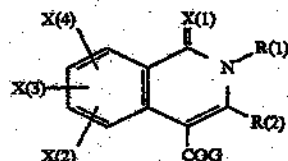
TABLE II

Reperfusion induced arrhythmias in isolated rat heart.				
*S.No.	n	Dose μM	Ventricular Fibrillation Duration (Min) M $\pm$ S.E.	
Control	8	—	26.25 $\pm$ 3.75	
2	7	1	3.14 $\pm$ 2.65	
4	6	1	10.11 $\pm$ 6.29	
7	7	0.1	4.32 $\pm$ 4.28	
13	7	0.1	12.86 $\pm$ 6.03	
14	4	0.1	7.5 $\pm$ 7.5	

*S.No.: Refers to numbers in the Table I.

We claim:

1. An isoquinoline compound of the formula I:



wherein:

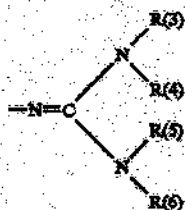
R(1) is hydrogen, (C₁-C₆)-alkyl, (C₃-C₆)-cycloalkyl, phenyl- (C₁-C₆)-alkyl, (C₃-C₆)-alkenyl, substituted (C₁-C₆)-alkyl-amino or a phenyl, naphthyl, pyridyl, thienyl, furyl, indolyl, quinolyl, isoquinolyl, pyrimidyl, triazolyl, benzothiazolyl, pyrrolidinyl, piperidinyl, morpholinyl, or piperazinyl ring, the rings being unsubstituted or substituted with one to three substituents selected from the group consisting of F, Cl, Br, I, nitro, amino, mono-(C₁-C₆)-alkyl-amino, di-(C₁-C₆)-alkyl-amino, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy, benzyloxy, phenoxy, hydroxy, and trifluoromethyl;

R(2) is hydrogen, F, Cl, Br, I, (C₁-C₆)-alkyl, or phenyl which is unsubstituted or is substituted by one to three substituents selected from the group consisting of F, Cl, Br, I, nitro, amino, mono-(C₁-C₆)-alkyl-amino, di-(C₁-C₆)-alkyl-amino, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy, benzyloxy, phenoxy and hydroxy;

G is a radical of the formula VII:

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X(2), X(3) and X(4) are individually or collectively hydrogen, F, Cl, Br, I, nitro, amino, alkyl, sulfonamide, mono-(C₁-C₆)-alkyl-amino, di-(C₁-C₆)-alkyl-amino, (C₁-C₆)-alkyl, benzyloxy, or hydroxy; and

X(1) is hydrogen, oxygen, sulfur or NR(7), in which R(7) is hydrogen, (C₁-C₆)-alkyl, (C₃-C₆)-cycloalkyl, phenyl-(C₁-C₆)-alkyl, (C₃-C₆)-alkenyl, substituted (C₁-C₆)- or a phenyl, pyridyl, thienyl, furyl, indolyl, quinolyl, isoquinolyl, pyrimidyl, triazolyl, benzothiazolyl, pyrrolidinyl, piperidinyl, morpholinyl, or piperazinyl ring, which rings are unsubstituted or substituted with one to three substituents selected from the group consisting of F, Cl, Br, I, nitro, amino, mono-(C₁-C₆)-alkyl-amino, di-(C₁-C₆)-alkyl-amino, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy, benzyloxy, phenoxy, hydroxy, and trifluoromethyl, in which substituents any alkyl chain or alkenyl chain may be interrupted by oxygen, sulfur or NR(8) wherein R(8) is hydrogen, (C₁-C₆)-alkyl, (C₃-C₆)-cycloalkyl, phenyl-(C₁-C₆)-alkyl, (C₃-C₆)-alkenyl, substituted (C₁-C₆)-alkyl-amino or a phenyl, pyridyl, thienyl, furyl, indolyl, quinolyl, isoquinolyl, pyrimidyl, triazolyl, benzothiazolyl, pyrrolidinyl, piperidinyl, morpholinyl or piperazinyl ring, which rings are unsubstituted or substituted with one to three substituents selected from the group consisting of F, Cl, Br, I, nitro, amino, mono-(C₁-C₆)-alkyl-amino, di-(C₁-C₆)-alkyl-amino, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy, benzyloxy, phenoxy, hydroxy and trifluoromethyl,

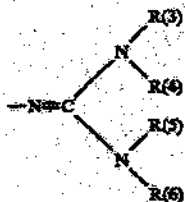
or a pharmaceutically acceptable salt thereof.

2. A compound of the formula I as claimed in claim 1 in which:

R(1) is phenyl, naphthyl, pyridyl, thienyl, furyl, indolyl, quinolyl, isoquinolyl, pyrimidyl, triazolyl, benzothiazolyl, pyrrolidinyl, piperidinyl, morpholinyl, or piperazinyl, unsubstituted or substituted with one to three substituents selected from the group consisting of F, Cl, Br, I, nitro, amino, mono-(C₁-C₆)-alkyl-amino, di-(C₁-C₆)-alkyl-amino, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy, benzyloxy, phenoxy, hydroxy and trifluoromethyl;

R(2) is hydrogen, or (C₁-C₆)-alkyl;

G is a radical of the formula VII:



R(3), R(4), R(5) and R(6) are hydrogen;

X(2), X(3) and X(4) are individually or collectively hydrogen, F, Cl, Br, I, nitro, amino, (C₁-C₆)-alkyl, sulfonamide, mono-(C₁-C₆)-alkyl-amino, di-

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(C₁-C₆)-alkyl-amino, (C₁-C₆)-alkyl, benzyloxy or hydroxy; and

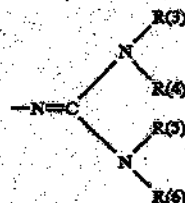
X(1) is oxygen.

3. A compound of the formula I as claimed in claim 1 wherein:

R(1) is (C₁-C₆)-alkyl, (C₁-C₆)-alkyloxy, or a phenyl, naphthyl, or pyridyl ring, the rings being unsubstituted or substituted with one to three substituents selected from the group consisting of F, Cl, Br, I, nitro, amino, mono-(C₁-C₆)-alkyl-amino, di-(C₁-C₆)-alkyl-amino, (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy benzyloxy, phenoxy, hydroxy and trifluoromethyl;

R(2) is hydrogen;

G is a radical of the formula VII:



with R(3), R(4), R(5) and R(6) being hydrogen; X(2), X(3) and X(4) are individually or collectively hydrogen, F, Cl, Br, I, nitro, amino, alkyl, sulfonamide, mono-(C₁-C₆)-alkyl-amino, di-(C₁-C₆)-alkyl-amino, (C₁-C₆)-alkyl, benzyloxy or hydroxy; and

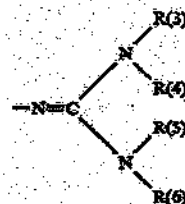
X(1) is oxygen.

4. A compound of the formula I as claimed in claim 1 wherein:

R(1) is (C₁-C₆)-alkyl, (C₁-C₆)-alkyloxy, or a phenyl, naphthyl or pyridyl ring, the rings being unsubstituted or substituted with Cl;

R(2) is hydrogen;

G is a radical of the formula VII:



with R(3), R(4), R(5) and R(6) being hydrogen; X(2), X(3) and X(4) are individually or collectively hydrogen, F, Cl, Br, I, nitro, amino, (C₁-C₆)-alkyl, sulfonamide, mono-(C₁-C₆)-alkyl-amino, di-(C₁-C₆)-alkyl-amino, (C₁-C₆)-alkyl, benzyloxy or hydroxy; and

X(1) is oxygen.

5. A medicament pharmaceutical composition for combating or preventing heart failure or ischemic conditions of the heart which comprises an effective amount of a compound of the formula I as claimed in claim 1 together with a pharmaceutically acceptable auxiliary.

6. A method of treating or preventing heart failures which comprises administering an effective amount of a compound of the formula I as claimed in claim 1.

7. A method of treating or preventing ischemic conditions of the heart which comprises administering an effective amount of a compound of the formula I as claimed in claim 1.

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(22) 1994/08/02
(43) 1995/02/04

(51) Int.Cl. ⁵ C07D-209/42; C07D-235/06; C07D-249/18; C07D-277/68;
C07D-307/84; C07D-333/70; C07D-401/04; C07D-403/12;
C07D-409/04; A61K-031/33

(19) (CA) APPLICATION FOR CANADIAN PATENT (12)

(54) Benze-Fused Heterocyclic Compounds with a 5-Membered Ring, Process for Their Preparation, Their Use as Medicaments, Their Use as Diagnostic Agents, and Medicaments Containing Them

(72) Lang, Hans-Jochen - Germany (Federal Republic of) ;
Welchert, Andreas - Germany (Federal Republic of) ;
Schwark, Jan-Robert - Germany (Federal Republic of) ;
Scholz, Wolfgang - Germany (Federal Republic of) ;
Aibus, Udo - Germany (Federal Republic of) ;
Crause, Peter - Germany (Federal Republic of) ;

(71) Hoechst Aktiengesellschaft - Germany (Federal Republic of) ;

(30) (DE) P 43 26 005.5 1993/08/03
(DE) P 44 14 316.8 1994/04/25

(57) 19 Claims

Notice: This application is as filed and may therefore contain an incomplete specification.



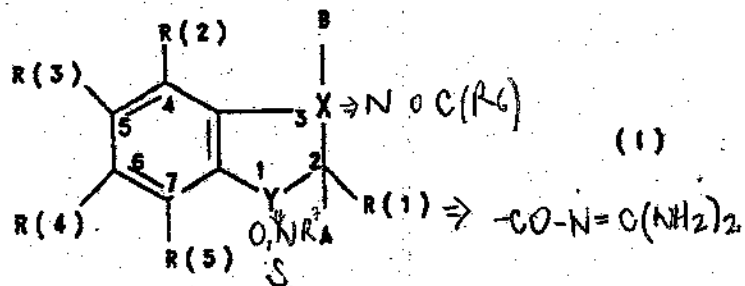
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THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A benzo-fused heterocyclic compound having a 5-membered ring, of the formula 1



in which:

X is N or CR(6),

Y is oxygen, S or NR(7),

A and B together are a bond

or

are both hydrogen, if, at the same time, X is

CR(6) and Y is NR(7),

one of the substituents R(1) to R(6) is a -CO-N=C(NH₂)₂ group,

the other respective substituents R(1) to R(6) are hydrogen, F, Cl, Br, I or (C₁-C₆)-alkyl,

up to two of the other substituents R(1) to R(6) are CN, NO₂, N₃, (C₁-C₄)-alkoxy or CF₃,

up to one of the other substituents is

R(8)-C_nH_{2n}-Z-,

n is zero to 10,

wherein the alkylene chain -C_nH_{2n}- is straight-chain or branched and

wherein a carbon atom can be replaced by an oxygen or S atom or by an N atom,

R(8) is hydrogen, (C₂-C₆)-alkenyl, (C₃-C₁₀)-cycloalkyl,

which is unsubstituted or substituted by 1 to 4 methyl groups or an OH group, or can contain an

ethylene group $-\text{CH}=\text{CH}-$, and wherein
a methylene group can be replaced by
an oxygen or S atom or by an N atom,
phenyl,

5 which is unsubstituted or
substituted by 1 to 3 substituents
from the group consisting of F, Cl,
Br, I, CF_3 , $\text{CH}_3-\text{S}(\text{O})_s-$,

10 s is zero, 1 or 2,
 $\text{R}(9)-\text{W}_y-$,
R(9) is H, methyl or ethyl,
W is oxygen or $\text{NR}(10)$,
R(10) is H or methyl,
y is zero or 1,

15 $\text{C}_m\text{F}_{2m+1}$,
m is 1 to 3,
1- or 2-naphthyl, pyridyl, quinolyl or
isoquinolyl,

20 Z is $-\text{CO}-$, $-\text{CH}_2-$, $-\text{[CR}(11)(\text{OH})]_q-$
q is 1, 2 or 3,
R(11) is H or methyl,
oxygen, $-\text{NR}(12)-$,
R(12) is H or methyl,
 $-\text{S}(\text{O})_s-$,

25 s is zero, 1 or 2,
 $-\text{SO}_2-\text{NR}(13)-$,
R(13) is H or (C_1-C_4) -alkyl,

R(7) is hydrogen, $(\text{C}_1-\text{C}_{10})$ -alkyl, $(\text{C}_2-\text{C}_{10})$ -alk-
enyl or $\text{R}(8)-\text{C}_n\text{H}_{2n}-$.

30 or a pharmaceutically tolerated salt thereof.

2. A compound of the formula I as claimed in claim 1,
in which:

X is $\text{CR}(6)$ or N,

Y is $\text{NR}(7)$,

35 A and B together are a bond

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20+

Example 34:

5,6-Dichloro-1-methyl-1H-benzimidazol-2-yl-carbonyl-guanidine hydrochloride,

Melting point 274°C. (decomposition)

5 Example 35:

3-Indolylcarbonyl-guanidine hydrochloride,

Melting point 270°C. (decomposition)

Example 36:

5-Indolylcarbonyl-guanidine hydrochloride,

10 Melting point 258°C. (decomposition)

Example 37:

1-Benzyl-3-indolylcarbonyl-guanidine hydrochloride,

Melting point 256°C. (decomposition)

Example 38:

15 4-Indolylcarbonyl-guanidine hydrochloride,

Melting point 270°C. (decomposition)

Example 39:

1-Methyl-3-indolylcarbonyl-guanidine hydrochloride,

Melting point 250°C. (decomposition)

20 Example 40:

1-(2-N,N-Dimethylaminoethyl)-3-indolylcarbonyl-guanidine dihydrochloride,

Melting point 250°C. (decomposition)

Example 41:

25 1-Methyl-2-indolylcarbonyl-guanidine hydrochloride,

Melting point 280°C.

Example 42:

2-Indolylcarbonyl-guanidine hydrochloride,

Melting point 310 - 312°C.

Example 43:

5-Chloro-2-indolylcarbonyl-guanidine hydrochloride,
Melting point 317 - 320°C.

Example 44:

- 5 5-Methoxy-2-indolylcarbonyl-guanidine hydrochloride,
Melting point 292°C.

Example 45:

- 5-Chloro-1-methyl-2-indolylcarbonyl-guanidine hydro-
chloride,
10 Melting point 269°C.

Example 46:

1-(3,4-Dichlorobenzyl)-2-indolylcarbonyl-guanidine
hydrochloride,
Melting point 195°C.

Example 47:

1-(2-N,N-Dimethylaminoethyl)-2-indolylcarbonyl-guanidine
dihydrochloride,
Melting point 255°C. (decomposition)

Example 48:

- 20 1-Benzyl-2-indolylcarbonyl-guanidine hydrochloride,
Melting point 229°C.

Example 49:

1-Ethyl-2-indolylcarbonyl-guanidine hydrochloride,
Melting point 200 - 201°C.

Example 50:

25 1-Benzyl-5-chloro-2-indolylcarbonyl-guanidine hydro-
chloride,
Melting point 198°C.

Example 51:

- 30 5-Chloro-1-(2-N,N-dimethylaminoethyl)-2-indolylcarbonyl-
guanidine dihydrochloride,

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Melting point 255°C. (decomposition)

Example 52:

5-Chloro-1-ethyl-2-indolylcarbonyl-guanidine hydro-
chloride,

5 Melting point 255°C.

Example 53:

5-Chloro-1-propyl-2-indolylcarbonyl-guanidine hydro-
chloride,

Melting point 255°C.

10 Example 54:

5-Chloro-1-butyl-2-indolylcarbonyl-guanidine hydro-
chloride,

Melting point 222°C.

Example 55:

15 5-Hydroxy-1-methyl-2-indolylcarbonyl-guanidine hydro-
chloride,

Melting point 288°C.

Example 56:

20 3,5-Dichloro-1-(2-N,N-dimethylaminoethyl)-2-indolyl-
carbonyl-guanidine dihydrochloride,

Melting point 246°C.

Example 57:

5-Methoxy-1-methyl-2-indolylcarbonyl-guanidine hydro-
chloride,

25 Melting point 227°C.

Example 58:

3-Chloro-1-methyl-2-indolylcarbonyl-guanidine hydro-
chloride,

Melting point 216°C.

30 Example 59:

3-Chloro-2-indolylcarbonyl-guanidine hydrochloride,

Melting point 222°C.

Example 60:

3,5-Dichloro-1-(4-picolyl)-2-indolylcarbonyl-guanidine
hydrochloride,

5 Melting point 220°C.

Example 61:

5-Chloro-1-(4-picolyl)-2-indolylcarbonyl-guanidine
hydrochloride,

Melting point 287°C.

10 Example 62:

5-Chloro-1,3-dimethyl-2-indolylcarbonyl-guanidine hydro-
chloride,

Melting point 258°C.

Example 63:

15 5,7-Dichloro-1,3-dimethyl-2-indolylcarbonyl-guanidine
hydrochloride,

Melting point 307°C.

Example 64:

20 4,6-Dichloro-1,3-dimethyl-2-indolylcarbonyl-guanidine
hydrochloride,

Melting point 296°C.

Example 65:

5-Chloro-1-methyl-3-phenyl-2-indolylcarbonyl-guanidine
hydrochloride,

25 Melting point 288°C.

Example 66:

3-Bromo-1-methyl-2-indolylcarbonyl-guanidine hydro-
chloride,

Melting point 208 - 210°C.

30 Example 67:

5-Fluoro-1-methyl-2-indolylcarbonyl-guanidine

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

2020
Bogotá, D.C., 18/02/2010

Abogado
Luis Patiño Leyva
(Apoderado)

ASUNTO

Radicación **04 120497**
Trámite 002
Evento 001
Actuación 430
Oficio 2628
Folios 011

Patente de Invención ☒ Patente de Modelo de Utilidad ☐
Vía Nacional ☐
Vía PCT (fase nacional) ☒ Cap. I ☐ Cap. II ☒

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: 85 a 198
- 1.2. Reivindicaciones: Folios: 199 a 212
Folios: 291 a 297 Memorial de 15/07/2008
- 1.3. Datos PCT: Solicitud Internacional: PCT/EP03/05279
Capítulo II
Fecha Sol. Internacional: 20/05/2003
Publicación. Internacional: WO03/101450
Fecha Pub. Internacional: 11/12/2003
Fecha Inicio Fase Nacional: 03/01/2005
Solicitud Nacional: CO 04 120497
Fecha Sol. Nacional: 30/11/2004
- 1.4. Prioridad: FR0206783 de 03/06/2002
- 1.5. Respuesta del solicitante: Folios: 286 a 297 Memorial de 15/07/2008
Folios: 318 a 319 Memorial de 23/11/2009

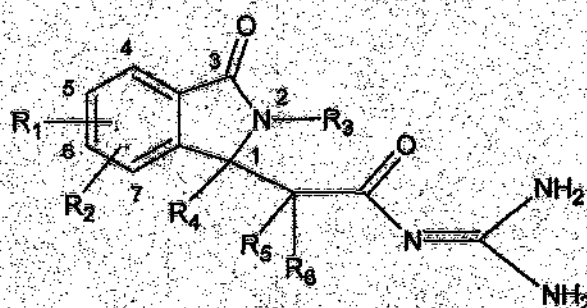
2. Objeto de la invención

Título de la solicitud

Derivados de N-((3-oxo-2,3-dihidro-1H-isoindol-1-il)acetil)guanidina en calidad de inhibidores de NHE-1 para el tratamiento del infarto y la angina de pecho

Reivindicaciones

Reivindicaciones 1 a 4: Se reivindican los compuestos de fórmula (I):



Especialmente, se reclama protección para las especies químicas:

N-[2-(2-isobutil-3-oxo-2,3-dihidro-1H-isoindol-1-il)-2-metilpropionil]guanidina
N-[(2-isobutil-7-metil-3-oxo-2,3-dihidro-1H-isoindol-1-il)acetil]guanidina
N-[5-cloro-3-oxo-2-(3,3,3-trifluoropropil)-2,3-dihidro-1H-isoindol-1-il)acetil]guanidina

Entre otros.

Reivindicaciones 5 y 6: Se reivindican las composiciones farmacéuticas que contienen compuestos de fórmula (I).

Reivindicación 7: Se reivindica el proceso para la obtención de los compuestos de fórmula (I) caracterizado porque comprende las siguientes etapas:

- Un hidruro complejo se hace reaccionar con una ftalimida de fórmula (II).
- El producto obtenido se hace reaccionar luego con un alcóxicarbonilmetileno-trifenilfosforano en tolueno, o con un fosfonoacetato de triálquilo y una base.
- El producto obtenido se hace reaccionar con cloruro de guanidino y una base o con guanidina.

Reivindicación 8: Se reivindica el proceso para la obtención de los compuestos de fórmula (I) caracterizado porque comprende las siguientes etapas:

- Un compuesto de fórmula (III) se hace reaccionar con un alcóxicarbonilmetileno-trifenilfosforano en tolueno o con un fosfonoacetato de triálquilo y una base.
- El producto obtenido se hace reaccionar con una amina de la fórmula R_3NH_2 y una carbodilimida.
- El producto obtenido se hace reaccionar con cloruro de guanidino y una base o con guanidina.

Reivindicación 9: Se reivindica el proceso para la obtención de los compuestos de fórmula (I) caracterizado porque comprende las siguientes etapas:

- a) Una ftalimida se hace reaccionar con haluro de alquilmagnesio con un reactivo de alquil-litio en un éter
- b) El producto obtenido se hace reaccionar con un alcoxycarbonilmetileno-trifenilfosforano en tolueno o con 1-etoxi-1-trimetilsiloxietileno y un ácido de Lewis
- c) El producto obtenido se hace reaccionar con cloruro de guanidinio y una base o con guanidina.

Reivindicación 10: Se reivindica el proceso para la obtención de los compuestos de fórmula (I) caracterizado porque comprende las siguientes etapas:

- a) El compuesto de fórmula (IV) se hace reaccionar en presencia de diisopropilamidiuro de litio
- b) El producto obtenido se hace reaccionar con cloruro de guanidinio y una base o con guanidina en un alcohol.

Sustento Descriptivo

La invención se refiere a nuevos compuestos de isoindolinona de la fórmula (I) que son adecuados como medicamentos anti-arrítmicos con un componente cardioprotector para la profilaxis del infarto y el tratamiento del infarto y la angina de pecho. Los compuestos también inhiben de una manera preventiva los procesos patofisiológicos asociados al daño inducido por isquemia, en particular el desencadenamiento de arritmias cardíacas inducidas por isquemia y de la insuficiencia cardíaca.

Los inhibidores del NHE1 de la fórmula (I) tienen un importante efecto antiinflamatorio y pueden utilizarse en la inhibición de los mediadores de la inflamación, además exhiben un efecto reductor de las lipoproteínas del suero factor de riesgo esencial para el desarrollo de lesiones vasculares arterioescleróticas.

- Una vez catalogada la invención ésta se clasificó en la sección: A 61 K ³¹/4035 de la **Clasificación Internacional de Patentes**.

3. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es: 03/06/2002, se procedió a efectuar la búsqueda de documentos relacionados en el estado de la técnica con fecha de publicación anterior a ésta.

N°	Documento	Título	Fecha de Publicación
D1	XP002238283	"Potent and selective inhibition of the human Na ⁺ /K ⁺ exchanger isoform NHE1 by a novel aminoguanidine derivative T-162559"	11/04/2001
D2	Artículo 1	"Discovery of Zoniporide: A potent and selective sodium-hydrogen exchanger type 1 (NHE-1) inhibitor with high aqueous solubility"	Enero de 2001

Nº	Documento	Título	Fecha de Publicación
D3	Artículo 2	"Synthesis and Biological evaluation of aroylguanidines related to amiloride as inhibitors of the human platelet Na^+/H^+ exchanger"	Enero de 2002
D4	EP0639573	"Benzokondensierte 5-Ringheterocyclus, Verfahren zu ihrer Herstellung, ihre Verwendung als Medikament, ihre Verwendung als Diagnostikum, sowie sie enthaltendes Medikament"	28/07/1994
D5	US5416094	"Antiarrhythmic and cardioprotective substituted -1(2H)isoquinolines, medicament containing them, and their use for combating heart failures"	16/05/1995

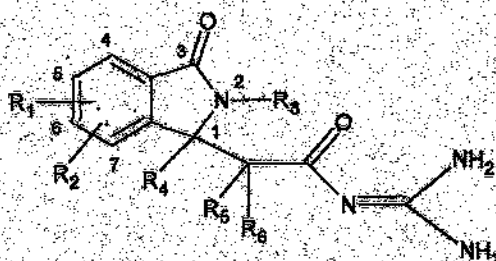
Anterioridad D1 en los Folios 276 a 283, D2 y D3 en los folios 298 a 309 y anterioridades D4 y D5 en los folios 320 a 333.

4. Análisis de patentabilidad (artículo 14 D. 486)

4.1 Nivel inventivo (artículo 18 D. 486)

El nivel inventivo del objeto reclamado se evaluó por comparación entre las características esenciales de los compuestos definidos en el pliego reivindicatorio y los elementos estructurales anticipados por el arte previo.

- Se reivindican compuestos derivados del núcleo de la fórmula (I):



Especialmente, se reclama protección para las especies químicas:

N-[2-(2-isobutil-3-oxo-2,3-dihidro-1H-isoindol-1-il)-2-metilpropionil]guanidina
 N-[(2-isobutil-7-metil-3-oxo-2,3-dihidro-1H-isoindol-1-il)acetil]guanidina
 N-[5-cloro-3-oxo-2-(3,3,3-trifluoropropil)-2,3-dihidro-1H-isoindol-1-il)acetil]guanidina

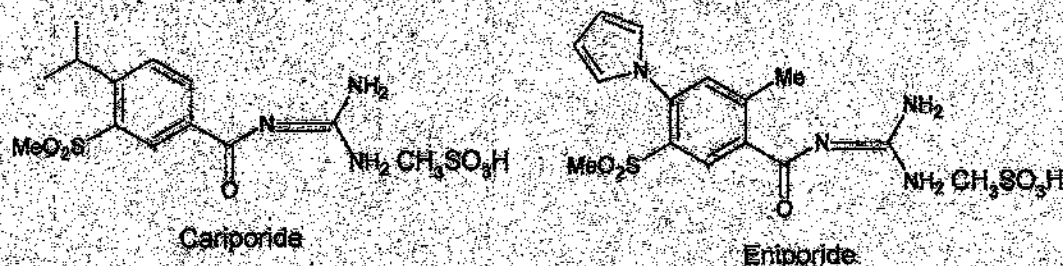
Entre otros,

- El estado del arte previo a la invención presenta las siguientes estructuras:

Anterioridad D1:

La publicación D1 revela derivados de aminoguanidina que presentan actividad como inhibidores selectivos de la isoforma NHE-1 intercambiador Na^+/H^+ . Dentro de los

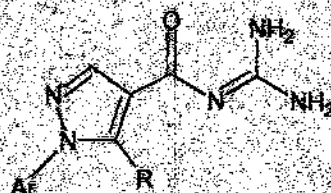
compuestos que se encuentran revelados en el folio 277 se encuentran las especies químicas Cariporide y Eniporide:



Anterioridad D2:

La publicación D2 hace referencia a la actividad selectiva de Zoniporide como inhibidor de la actividad del intercambiador Na^+/H^+ NHE en especial, de los subtipos NHE-1 y NHE-2.

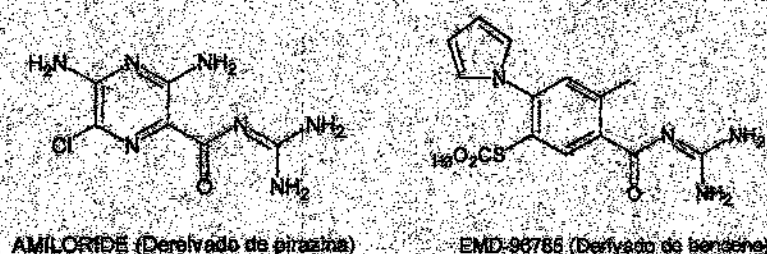
El compuesto zoniporide y sus análogos estructurales se derivan de la estructura de fórmula 3:

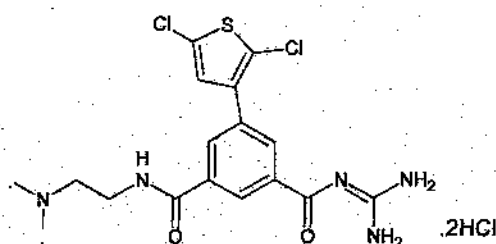


Compuesto	R	Ar	NHE-1 IC50(nM) ^a	NHE-2 IC50(nM) ^c	NHE-1 vs NHE-2 ^d
3 ^a	Me	Fenil	830	3900	5
3b	Ciclopropil	Fenil	350	12,800	37
3c	Ciclopropil	1-nafil	180	16,300	102
3d (Zoniporide)	Ciclopropil	5-quinolinil	59	12,000	203
3e	Me	5-quinolinil	860	41,600	48
1a (Cariporide)			560	28,700	51
1b (Eniporide)			140	9200	66

Anterioridad D3:

La publicación D3 hace referencia a compuestos con estructura análoga a la reivindicada, denominados derivados de aroilguanidinas con actividad inhibidora del intercambiador Na^+/H^+ . En particular, se presenta el compuesto amiloride y otras estructuras similares que a continuación se relacionan:



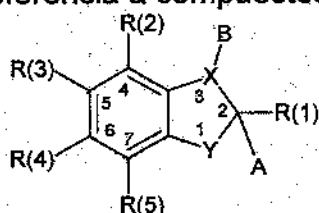


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En el folio 308 de la anterioridad **D3** se establece que de acuerdo con el estudio efectuado sobre la intercambiabilidad de grupos sobre la estructura del compuesto amiloride se consiguen iguales resultados cuando el anillo es de piridina o cuando el anillo es de benceno, sin que esta situación modifique la potencia inhibitoria del intercambiador Na^+/H^+ NHE.

Anterioridad D4:

La publicación **D4** hace referencia a compuestos que presentan la estructura:



Donde:

X es N o CR(6)

Y es O, S o NR(7)

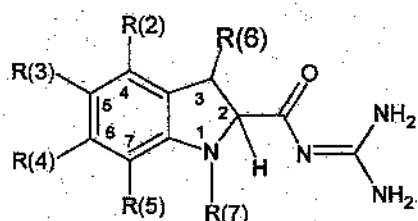
A y B son un puente o son -H

Uno de los sustituyentes R(1) a R(6) es el grupo: $-\text{CO}-\text{N}=\text{C}(\text{NH}_2)_2$

Y los demás sustituyentes R(1) a R(6) son -H, Cl, Br, I o alquilo C_{1-6}

R(7) es -H, alquilo C_{1-10} , alquenilo C_{2-10} o R(8)- C_nH_{2n} .

Es decir, se obtienen compuestos con las siguientes características químicas y funcionales:



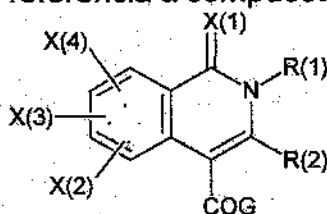
Algunas de las especies químicas más representativas del antecedente son:

Clorhidrato de 1-(2-N,N-dimetilaminoetil)-3-indolilcarbonyl-guanidina

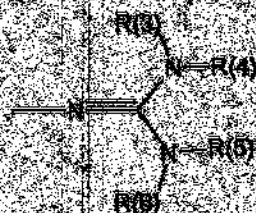
Clorhidrato de 5-cloro-1-(2-N,N-dimetilaminoetil)-2-indolilcarbonyl-guanidina

Anterioridad D5:

La publicación **D5** hace referencia a compuestos con la siguiente estructura anular:



Donde:



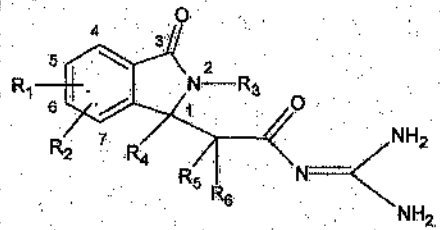
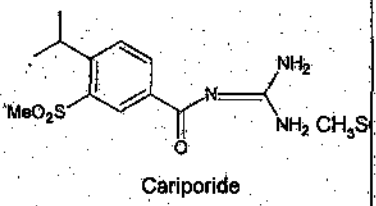
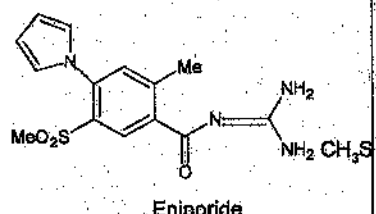
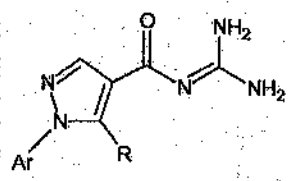
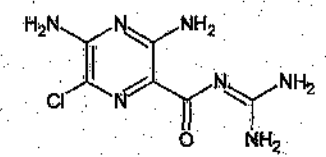
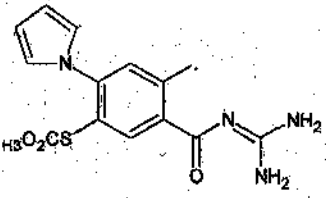
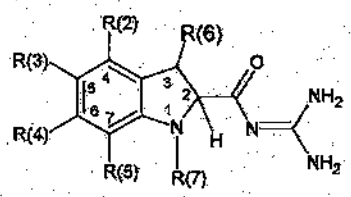
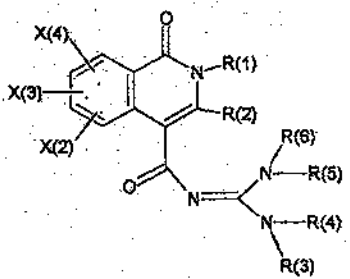
G es un radical de fórmula (VII)

R(1) es -H, alquilo C₁₋₆, cicloalquilo C₃₋₆

R(2) es -H, F, Cl, Br, I, alquilo C₁₋₆ o fenilo

X(2), X(3) y X(4) son de manera independiente o conjunta -H, F, Cl, Br, I, nitro, amino, alquilo, sulfonamida, monoalquil C₁₋₆ amino.

Comparación estructural:

Materia Reivindicada	D1	D2	D3	D4	D5
	 Cariporide  Eniporide		 AMILORIDE (Derivado de pirazina)  EMD-96785 (Derivado de benceno)		

Diferencias Técnicas:

Al evaluar los elementos característicos de los compuestos reivindicados con respecto a las enseñanzas del estado de la técnica reveladas en los antecedentes D1, D2, D3, D4 ó D5 fue posible concluir lo siguiente:

Con respecto al documento D1 la diferencia estriba en que los derivados de guanidina Cariporide y Eniporide no presentan núcleo de isoindolinona sino de benceno.

Con respecto al documento D2 que presenta derivados de guanidina la diferencia estriba en que el núcleo es un anillo de cinco miembros de pirazol, mientras que en el caso de los compuestos reivindicados el anillo central es de isoindolinona.

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Con relación a las enseñanzas reveladas por el documento **D3** la diferencia estriba en que estos compuestos presentan como anillo central estructuras de benceno y pirazina, sin embargo no presentan núcleos fusionados de isoindolinona.

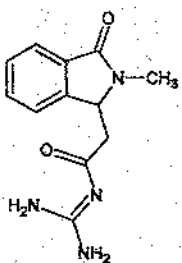
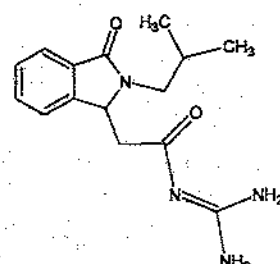
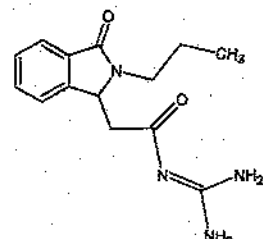
Con respecto al documento **D4** la diferencia estriba en que la estructura definida en el pliego reivindicatorio es de isoindolil-3-ona, mientras que en el caso de la publicación corresponde a indol.

Con respecto al documento **D5** la diferencia estriba en que la estructura anular que define los compuestos de la invención es de isoindolil-3-ona, mientras que en el caso del antecedente corresponde a isoquinolin-2-ona.

Del problema técnico objetivo y del efecto inesperado:

De acuerdo con el sustento descriptivo de la solicitud los compuestos que presentan núcleo de isoindol-acetil-guanidina son agentes antiarrítmicos porque inhiben la actividad del intercambiador Na^+/H^+ NHE-1. Y con el nuevo diseño estructural que aporta la solicitud mediante los folios 291 a 297 se pretende generar una alternativa terapéutica para el manejo de la arritmia cardíaca.

Para demostrar las ventajas que evidencian los compuestos el solicitante adjunta una tabla con las respuestas de actividad IC_{50} para los ejemplos 1 a 56b, dentro de los que se encuentran estructuras como:

Compuestos	IC_{50}
Ejemplo 1 	74
Ejemplo 2 	59
Ejemplo 5 	92

Al respecto es preciso señalar que la diferencia en cuanto a la estructura anular de isoindolinona y su intercambio por anillos de benceno y pirazina no demuestran una ventaja técnica comparativa que evidencie una ventaja inesperada en términos del efecto técnico. Por el contrario, los valores de IC_{50} de algunos de los ejemplos que acompañan el capítulo descriptivo, como es el caso de las estructuras 1, 2 y 5 demuestran que se requiere la misma concentración para inhibir la actividad del intercambiador NHE-1 que el compuesto Zoniporide, el cual, forma parte del estado del arte próximo a la invención, por lo que para esta Superintendencia es claro que la materia reivindicada carece del requisito de altura inventiva, toda vez que una persona versada en ciencias farmacéuticas se encontraba en capacidad de derivar los elementos estructurales característicos de los compuestos reclamados con base en las enseñanzas que en conjunto revelan las publicaciones [D4 y D1] o [D4 y D2] o [D4 y D3] o [D4 y D5].

Y por otra parte, los datos de actividad reportados por el señor solicitante en la memoria descriptiva no evidencian un efecto técnico inesperado o un salto cualitativo en la regla técnica, toda vez que no superan la efectividad terapéutica para núcleos como el de Zoniporide, para el que la publicación científica D2 precisa concentración mínima inhibitoria de menor magnitud que las reportadas para el núcleo de isoindolil-3-ona.

Además, en virtud de las enseñanzas de las publicaciones D4 o D5 se evidencia la existencia de más de una serie bioisómera para los derivados de guanidina con actividad sobre el intercambiador Na^+/H^+ NHE y en razón a la comparación efectuada y a la similitud estructural es posible concluir que los compuestos no cumplen con las disposiciones normativas del artículo 18 de la Decisión 486 relacionadas con el nivel inventivo.

5. Conclusión:

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

N°	Documento N°	Reivindicaciones Afectadas	Requisito que Afecta
D1	XP002238283	1 a 10	Nivel Inventivo
D2	Artículo 1	1 a 10	Nivel Inventivo
D3	Artículo 2	1 a 10	Nivel Inventivo
D4	EP0639573	1 a 10	Nivel Inventivo
D5	US5416094	1 a 10	Nivel Inventivo

6. Respuesta a los argumentos del solicitante:

Mediante memorial de fecha 23/11/2009 el señor solicitante argumenta lo siguiente:

"ninguno de los documentos citados por el señor examinador afectaría el nivel inventivo de los compuestos de la solicitud"

"(...) D1 enseña los compuestos Cariporide y Eriporide, los cuales son benzoilguanidinas sustituidas e inhibidores de NHE1, D2 divulga el compuesto Zoniporide (pirazol carbonil guanidina sustituida) como inhibidores de NHE1 y D3 divulga arilguanidinas adicionales, particularmente pirazina o piridil carbonilo guanidas y benzoilguanidinas sustituidas como inhibidores de NHE1".

"Todos los compuestos descritos en los documentos D1, D2 y D3 son compuestos en los cuales el residuo carbonil guanidina está unido a un sistema de anillo aromático, en consecuencia, estos compuestos son arilguanidinas. Por el contrario los compuestos de la

presente solicitud son alcanolil guanidinas, en las cuales la carbonil guanidina está unida al residuo pirrolona de un anillo isoindolona por medio de un puente de metileno. Entonces, claramente la carbonil guanidina no está unida a un anillo aromático y los compuestos de la invención no son arilguanidinas. Por lo tanto, partiendo de las enseñanzas de D1, D2 y D3, la persona versada en la materia técnica no derivaría de manera evidente que los compuestos de la invención los cuales difieren significativamente en su estructura y propiedades químicas con respecto a los compuestos de las anterioridades, tendrían excelente actividad inhibitoria de NHE1".

Al respecto es preciso señalar que la diferencia mencionada por el señor solicitante no es la causa de un efecto técnico inesperado o sorprendente en términos de actividad farmacológica, toda vez que aún sin que exista un átomo de carbono intermedio (grupo metileno) entre la estructura arilica o heterocíclica y la estructura carbonil-guanidina la actividad se conserva y con resultados de concentración mínima inhibitoria IC_{50} farmacológicamente superiores que los reportados por el señor solicitante en el capítulo descriptivo.

Así las cosas, al combinar las enseñanzas de cualquiera de los documentos D1, D2 o D3 con la reportada en la publicación D4 es posible derivar tanto los elementos estructurales como la actividad antiarrítmica, por lo que una persona versada en ciencias farmacéuticas se encontraba en capacidad de anticipar las características que definen la materia reivindicada en los folios 291 a 297, ya que en el documento D4 se presentan anillos heterocíclicos tipo indol sustituidos por carbonil-guanidina con actividad antiarrítmica.

Y por otra parte, la publicación D5 presenta isoquinolin-2-onas sustituidas por carbonil-guanidinas, a las que también se ha reportado actividad sobre el intercambiador sodio/ H^+ por lo que tal y como se reivindican los compuestos de isoindolin-3-onas como inhibidores de NHE1 y alternativa terapéutica para el manejo de la angina de pecho es claro que existen anticipaciones técnicas cercanas y farmacológicamente superiores que permitirían a una persona versada en ciencias farmacéuticas derivar los elementos esenciales de la serie bioisómera reclamada.

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 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 N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Directora de Nuevas Creaciones (o)

El anterior requerimiento fue notificado por fijación en lista, de fecha
26 FEB. 2010

CONCEPTO TÉCNICO No. 802

EXAMINADOR TÉCNICO
Código No. 202044