

Señores

DIVISIÓN DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá, D.C.

Folios: 2

SUPERINDUSTRIA Y COMERCIO

Radicacion : 00026001 00000002

Fecha (AMD): 2001-06-07 09:16:40

Tramite : 002 PATENTES D 1 REGISTRO/ 538 PETICION

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Re.: Código 02-01-538  
Expediente No. 00-26.001  
Solicitud de Patente  
**SMITHKLINE BEECHAM**  
**CORPORATION**

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En relación con el Expediente de la referencia por medio del presente escrito muy respetuosamente me permito solicitarles se sirvan proceder a efectuar el **EXAMEN DE PATENTABILIDAD** de la solicitud aquí contenida.

Para tal efecto acompaño el comprobante de pago por concepto de \$ 300.000.00, recibo No. 35.397/01-

De Ustedes Atentamente,

**GERMAN CASTILLO GRAU**

T.P. No. 2978 del C.S.J.



76 20

**Industria y Comercio****SUPERINTENDENCIA**

SUPERINDUSTRIA Y COMERCIO

Radicacion : 02026001 02020032

Folios: 2

Fecha (AMD): 2001-06-07 09:18:40

Tramite : 032 PATENTES D 1 REGISTRO/ 538 PETICION

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

BO OFICIAL DE CAJA : 01 - 35,397  
: JUNIO 6 DE 2001

## \*\*\*\*\* CONSIGNACION \*\*\*\*\*

| DEBITANTE              | TIPO PASO    | BANCO         | CUENTA      | No. PASO | FECHA PASO | Vr. PASO   |
|------------------------|--------------|---------------|-------------|----------|------------|------------|
| WILLO GRAU Y ASOCIADOS | CONSIGNACION | BANCO POPULAR | 050-00110-6 | 4066806  | 06/06/2001 | 645,708.00 |

## \*\*\*\*\* CONCEPTO \*\*\*\*\*

| RENTISTICO                | CONCEPTO                             | TOTAL CONCEPTO |
|---------------------------|--------------------------------------|----------------|
| 1 50005-01-01 SOLICITUDES | 85 EXAMEN DE PATENTABILIDAD DE INVEN | 300,000.00     |
|                           | TOTAL :                              | \$ 300,000.00  |

TRESCIENTOS MIL PESOS

RESPONSABLE :

BO DE CAJA APLICADO AL EXPEDIENTE No. \_\_\_\_\_

Carrera 13 No. 27-00 Pisos 5, 7 y 10  
Conmutador 382 0840  
Fax 350 5220  
E-mail: info@sic.gov.co  
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Bogotá, D.C., Colombia

77  
81  
2005-04-14  
375

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

2020  
Bogotá, D.C.,

Doctor  
GERMÁN CASTILLO GRAU  
(Apoderado)

|        |            |          |
|--------|------------|----------|
| ASUNTO | Radicación | 00026001 |
|        | Trámite    | 002      |
|        | Evento     | 001      |
|        | Actuación  | 430      |
|        | Oficio     | 12568    |
|        | Folios     | 020      |

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:

**Documentos estudiados:**

Los textos estudiados fueron la descripción (Folios: 4 a 29) y las reivindicaciones 1 a 12 (Folios: 30 a 32).

La presente solicitud reivindica prioridad americana N° US60.128687 de 09 de abril de 1999 y cumple con lo establecido en los artículos 9, 10 y 11 de la Decisión 486 de la Comisión de la Comunidad Andina.

**Objeto de invención:**

La presente solicitud se titula: "Triarilimidazoles".

El objeto de la presente solicitud se refiere a triarilimidazoles sustituidos con piridilo que son inhibidores del factor de crecimiento transformante, de la ruta que produce señales por medio de ("TGF")-beta, en particular de la fosforilación de smad2 o smad3 por el receptor de quinasa similar a activina o de tipo I ("ALK")-5, a los métodos para su preparación y a su empleo en medicina, concretamente en el tratamiento y la prevención de un estado de enfermedad mediado por esta ruta.

De acuerdo con la presente solicitud, TGF-beta1 es el miembro prototípico de una familia de citoquinas que incluye los TGF-beta, activinas, inhibinas, proteínas morfogenéticas óseas y la sustancia inhibidora Mülleriana, que producen señales a través de una familia de receptores de serina/treonina-quinasa transmembrana individuales. Estos receptores pueden dividirse en dos clases, los receptores de quinasa similares a activina (ALK) o de tipo I y los receptores de tipo II. Los receptores ALK se distinguen de los receptores de tipo II en que los receptores ALK (a) carecen de la cola intracelular rica en serina/treonina, (b) poseen dominios de serina/treonina-quinasa que son muy homólogos entre los receptores de tipo I y (c) comparten un fragmento de secuencia común denominado el dominio GS,

constituido por una región rica en restos de glicina y serina. El dominio GS están en el extremo amino terminal del dominio de quinasa intracelular y es crítico para activación por el receptor de tipo II. Varios estudios han indicado que la producción de señales por medio de TGF-beta necesita tanto receptores ALK como de tipo II. La activación del eje TGF-beta1 y la expansión de la matriz extracelular son factores precoces y persistentes que contribuyen al desarrollo y la progresión de la enfermedad renal crónica y la enfermedad vascular. Además, TGF-beta1 juega un papel en la formación de fibronetina e inhibidor 1 del activador de plasminógeno, componentes de los depósitos escleróticos, a través de la acción de fosforilación de smad3 por el receptor ALK5 de TGF-beta1.

Según la descripción, la fibrosis progresiva en el riñón y el sistema cardiovascular es una causa primordial de padecimiento y muerte y un factor importante que contribuye al costo del cuidado de la salud. TGF-beta1 y sus receptores están elevados en los vasos sanguíneos dañados y están indicados en la formación de la neoíntima después de angioplastia con globo. Se ha descubierto que una clase de triarilimidazoles sustituidos con 2-piridilo de fórmula I (ver folio: 30), funcionan como inhibidores no peptídicos, potentes y selectivos, de ALK5-quinasa y, por lo tanto, tienen utilidad en el tratamiento y la prevención de diversos estados de enfermedad mediados por mecanismos ALK5-quinasa, tales como enfermedad renal crónica, enfermedad renal aguda, curación de heridas, artritis, osteoporosis, enfermedad renal, insuficiencia cardíaca congestiva, úlceras, trastornos oculares, heridas corneales, nefropatía diabética, entre otros.

El objeto de la solicitud definido anteriormente se clasificó en la IPC A61K 31/435, 31/41.

### **Claridad de la solicitud:**

*El artículo 30 de la Decisión 486 de la Comisión de la Comunidad Andina establece que: "Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción.*

*Las reivindicaciones podrán ser independientes o dependientes. Una reivindicación será independiente cuando defina la materia que se desea proteger sin referencia a otra reivindicación anterior. Una reivindicación será dependiente cuando defina la materia que se desea proteger refiriéndose a una reivindicación anterior. Una reivindicación que se refiera a dos o más reivindicaciones anteriores se considerará una reivindicación dependiente múltiple."*

De acuerdo con lo anterior, hay términos ambiguos y muy generales tales como "opcionalmente", "halo", que no permiten que las reivindicaciones sean claras.

### **Excepciones de Patentabilidad:**

*El artículo 20 de la Decisión 486 se establece: "No serán patentables: a) las invenciones cuya explotación comercial en el territorio del País Miembro respectivo deba impedirse necesariamente para proteger el orden público o la moral. A estos efectos la explotación comercial de una invención no se considerará contraria al orden público o a la moral solo debido a la existencia de una disposición legal o administrativa que prohíba o que regule dicha explotación; b) las invenciones cuya explotación comercial en el País Miembro respectivo deba impedirse necesariamente para proteger la salud o la vida de las personas o de los animales, o para preservar los vegetales o el medio ambiente. A estos efectos la explotación comercial de una invención no se considerará contraria a la salud o la vida de las personas, de los animales, o para la preservación de los vegetales o del medio ambiente sólo por razón de existir una disposición legal o administrativa que prohíba o que regule dicha explotación; c) las plantas, los animales y los procedimientos esencialmente biológicos para la producción de plantas o animales que no sean procedimientos no biológicos o microbiológicos; d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los*



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seres humanos o a animales."

De acuerdo con lo anterior, la(s) reivindicación(es): 10 a 12 (Folio: 32 ), que se refieren a un método para inhibir la ruta que produce señales por medio de TGF-beta en mamíferos, no es (son) patentable(s).

#### Determinación del estado de la técnica:

*El artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de Patente o, en su caso, de la prioridad reconocida.*

*Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40".*

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es: 09/04/1999, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a esta.

Se hizo la búsqueda de documentos relevantes en el estado de la técnica, entendiendo como estado de la técnica la definición provista en el artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina y las excepciones fijadas en el artículo 17 de la misma.

Se encontró como anterioridades (documentos cuya fecha de publicación es anterior a la fecha de presentación de la primera solicitud de patente sobre la cual se reivindica prioridad o de la fecha de presentación de esta solicitud) que pueden afectar la patentabilidad del objeto de la presente solicitud:

| Nº | Documento   | Título                                                                                  | Fecha de Publicación |
|----|-------------|-----------------------------------------------------------------------------------------|----------------------|
| 1  | US 5656644  | Pyridyl imidazoles                                                                      | 12 de agosto de 1997 |
| 2  | WO 98/22109 | Triaryl substituted imidazoles as glucagon antagonists                                  | 28 de mayo de 1998   |
| 3  | US 5776954  | Substituted pyridyl pyrroles, compositions containing such compounds and methods of use | 7 de Julio de 1998   |
| 4  | GB 1381031  | Imidazole derivatives and processes for their production                                | 22 de enero de 1975  |

#### Evaluación de los requisitos de Patentabilidad:

*El Artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina el cual establece: "Los Países Miembros otorgarán Patentes para las invenciones, sean de producto o de procedimiento en todos los campos de la tecnología siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial".*

Se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación

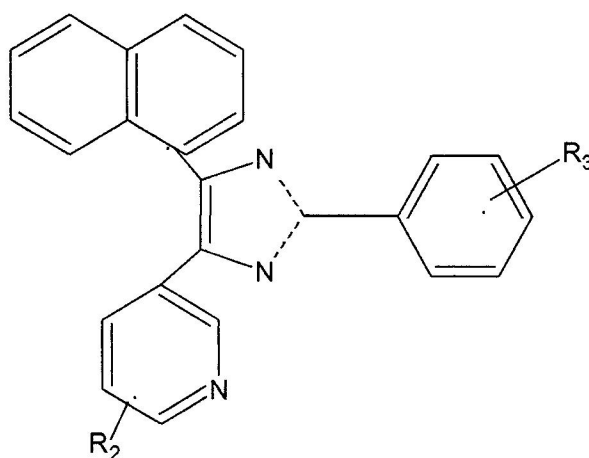
industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

### Evaluación de Nivel Inventivo:

*El artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica".*

El Nivel Inventivo se evaluó por comparación entre lo solicitado y encontrado en el estado de la técnica y que se relaciona con el objeto reivindicado y de acuerdo con la definición de nivel inventivo del Artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina.

La Solicitud de Patente Colombiana No. 00026001 menciona compuestos triarilimidazoles de fórmula I:



El documento **US 5656644** (folios: 86 a 88) menciona compuestos piridil imidazoles de fórmula I cuya diferencia con respecto a los compuestos de la presente solicitud es que la piridina está unida al resto de la molécula en posición 4 y no en posición 2 como aparece en la actual solicitud de patente.

El documento **WO 98/22109** (folios: 89 a 94) menciona compuestos triaril imidazoles sustituidos; cuya diferencia estructural con respecto a los compuestos de la presente solicitud se encuentra en que la piridina que forma parte de la misma está unida en la posición 4.

El documento **US 5776954** (folios: 95 a 97) se relaciona con compuestos derivados de piridil pirroles y composiciones que los contienen. Respecto a la estructura de los compuestos de la presente solicitud varía en el correspondiente de R<sub>1</sub> (en la anterioridad es R<sub>4</sub>).

El documento **GB 1381031** (folios: 98 a 100) se refiere a derivados de imidazol y la diferencia estructural en relación con los compuestos de la presente solicitud se encuentra en el grupo piridil sustituido de ésta (en la anterioridad es el grupo R<sub>3</sub> que es un fenilo).

La respuesta al problema técnico que se pretendía resolver, resulta obvia partiendo de las anterioridades en mención. Las diferencias estructurales son muy sutiles

tratándose de moléculas tan grandes como las presentadas en la actual solicitud. Como se observa, el objeto de esta solicitud podría resultar obvio para una persona del oficio normalmente versada en la materia y derivarse de manera evidente del estado de la técnica.

### **Evaluación de la Aplicación Industrial:**

*El artículo 19 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "Se considerará que una invención es susceptible de aplicación industrial, cuando su objeto pueda ser producido o utilizado en cualquier tipo de industria, entendiéndose por industria la referida a cualquier actividad productiva, incluidos los servicios".*

El objeto de la presente solicitud cumple con el requisito de Aplicación Industrial.

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

| Nº | Documento   | Reivindicaciones afectadas | Requisito que afecta |
|----|-------------|----------------------------|----------------------|
| 1  | US 5656644  | 1 a 9                      | Nivel Inventivo      |
| 2  | WO 98/22109 | 1 a 9                      | Nivel Inventivo      |
| 3  | US 5776954  | 1 a 9                      | Nivel Inventivo      |
| 4  | GB 1381031  | 1 a 9                      | 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 N° 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 14 ABR. 2005

|                                    |                                                |                                          |
|------------------------------------|------------------------------------------------|------------------------------------------|
| <b>CONCEPTO TÉCNICO</b><br>Nº: 483 | <b>EXAMINADOR TÉCNICO</b><br>Código N°: 202005 | <b>EXAMINADOR JURÍDICO</b><br>Código N°: |
|------------------------------------|------------------------------------------------|------------------------------------------|

# United States Patent [19]

Adams et al.

US005656644A

[11] Patent Number: 5,656,644

[45] Date of Patent: Aug. 12, 1997

[54] PYRIDYL IMIDAZOLES

[75] Inventors: Jerry Leroy Adams, Wayne; Timothy Francis Gallagher, Harleysville; John C. Lee, Radnor; John Richard White, Coatesville, all of Pa.

[73] Assignee: SmithKline Beecham Corporation, Philadelphia, Pa.

[21] Appl. No.: 277,804

[22] Filed: Jul. 20, 1994

[51] Int. Cl.<sup>6</sup> ..... C07D 401/04; A61K 31/44

[52] U.S. Cl. .... 514/341; 514/235.8; 514/306; 514/314; 514/397; 514/394; 546/274.1; 546/138; 546/167; 546/139; 546/269.1; 544/333; 544/360; 544/124; 548/313.4; 548/306.1

[58] Field of Search ..... 546/278, 269.1, 546/274.1, 138, 167, 139; 514/341, 235.8, 306, 314, 397, 394; 544/333, 124, 360; 548/313.4, 306.1

[56] References Cited

## U.S. PATENT DOCUMENTS

3,707,475 12/1972 Lombardino ..... 548/313.4  
3,772,441 11/1973 Lombardino ..... 548/313.4  
3,929,807 12/1975 Fitzi ..... 548/313.4  
3,940,486 2/1976 Fitzi ..... 548/313.4  
4,175,127 11/1979 Bender et al. .... 546/271

## FOREIGN PATENT DOCUMENTS

0 011 111 5/1980 European Pat. Off. .  
2221546 11/1972 Germany .

Primary Examiner—Jane Fan

Attorney, Agent, or Firm—Dara L. Dinner; Stephen Venetianer; Edward T. Lentz

[57] ABSTRACT

Novel 2,4,5-triaryl imidazole compounds and compositions for use in therapy.

13 Claims, No Drawings

| HPLC Method       |                                                      |
|-------------------|------------------------------------------------------|
| Column            | Altex Ultrasphere<br>10 mm I.D. x 25 cm              |
| Mobile Phase      | 70:30:0.1<br>water/acetonitrile/trifluoroacetic acid |
| Flow Rate         | 5 mL/min                                             |
| UV detection      | 210 nm                                               |
| Injection Volumes | 0.05-0.4 mL                                          |
| Retention Times   | 7.8 min Compound I<br>24 min Compound Ia             |

The pooled Compound I fractions totaled 32 mL in volume and the radioactive concentration was 1.52 mCi/mL (total 48.6 mCi). The pooled SB Compound Ia [<sup>3</sup>H] fractions (totaling 10.1 mCi) were evaporated to dryness and the residue was transferred quantitatively into a glass vial using 3.8 mL of absolute ethanol for further analysis.

An 8 mL (12.2 mCi) portion of Compound I was evaporated to dryness in vacuo at <35° C., then redissolved in 0.5 mL of mobile phase. The whole volume was injected into the HPLC system described above, and the appropriate peak was collected. Evaporation of the collected eluate in vacuo at <35° C. and transfer of the yellow residue into a vial with absolute ethanol provided a solution (3.8 mL, 2.44 mCi/mL) of Compound I. The portion of this solution used for NMR analyses was first evaporated to dryness using stream of nitrogen then taken up in CD<sub>3</sub>OD.

Analysis of 4-(4-Fluorophenyl)-2-(4-hydroxyphenyl)-3,5-t<sub>2</sub>-5-(4-pyridyl)imidazole, Compound I.

#### Radiochemical Purity by HPLC

| Method                  |                                                                |
|-------------------------|----------------------------------------------------------------|
| Column                  | Ultrasphere Octyl, 5 mm, 4.6 mm<br>I.D. x 25 cm, Beckman       |
| Mobile Phase            | 350:150:0.5 (v/v/v)<br>water/acetonitrile/trifluoroacetic acid |
| Flow Rate               | 1.0 mL/min                                                     |
| Mass detection          | UV at 210 nm                                                   |
| Radioactivity detection | Ramona-D radioactivity flow detector                           |
| Scintillator            | Tru-Count (Tru-Lab Supply Co.)                                 |
| Flow rate               | 5.0 mL/min                                                     |
| Cell volume             | 0.75 mL                                                        |
| Retention time          | 7.7 min                                                        |
| Result                  | 98.7                                                           |

#### Radioactive Concentration by Scintillation Counting

| Method       |                                             |
|--------------|---------------------------------------------|
| Scintillator | Ready Safe (Beckman Instruments, Inc.)      |
| Instrument   | TM Analytic model 6881                      |
| Efficiency   | Automated DPM calculation from quench curve |
| Result       | 2.44 mCi/mL                                 |

#### Specific Activity by Mass Spectrometry

| Method           |                                                                                                                                          |
|------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Method           | CI-MS, NH <sub>3</sub> reagent gas                                                                                                       |
| Result           | 20.0 Ci/mmol<br><sup>3</sup> H Distribution:<br>Unlabeled 44%<br>Single Label 43%<br>Double Label 13%<br><sup>3</sup> H NMR <sup>9</sup> |
| Method           |                                                                                                                                          |
| Instrument       | Brunker AM 400                                                                                                                           |
| Experiment       | Proton decoupled <sup>3</sup> H NMR<br>Proton non-decoupled <sup>3</sup> H NMR<br>Proton non-decoupled <sup>3</sup> H NMR                |
| Peak Referencing | Solvent Peak of methanol @ 3.3                                                                                                           |

-continued

|         |                                                                                          |
|---------|------------------------------------------------------------------------------------------|
| Solvent | Methanol-d <sub>4</sub>                                                                  |
| Result  | Tritium is incorporated exclusively on the carbon atoms ortho to aromatic hydroxyl group |

#### Analytical Summary

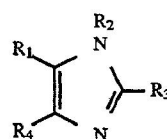
| Assay                                                            | Result                             |
|------------------------------------------------------------------|------------------------------------|
| 10 Radiochemical purity determined by HPLC                       | 98.7%                              |
| Radioactivity concentration determined by scintillation counting | 2.44 mCi/mL                        |
| Specific activity determined by mass spectrometry                | 20.0 Ci/mmol                       |
| 15 <sup>3</sup> H NMR                                            | agrees with the proposed structure |

Representative compounds of Formula (I), Examples 1 to 97, all have demonstrated a positive inhibitory activity in this binding assay.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is claimed is:

1. A compound of formula (I):



wherein:

R<sub>1</sub> is 4-pyridyl which is optionally substituted with one or two substituents each of which is independently selected from C<sub>1-4</sub> alkyl, halo, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> alkylthio, NH<sub>2</sub>, mono- or di-C<sub>1-6</sub>-alkylamino or N-heterocyclyl ring selected from pyrrolidine, piperidine, piperazine, morpholine, imidazolidine, and pyrazolidine;

R<sub>2</sub> is hydrogen;

n' is an integer having a value of 1 to 10;

m is 0, or the integer 1 or 2;

R<sub>3</sub> is Q-(Y<sub>1</sub>)<sub>n</sub>;

Q is an phenyl;

t is an integer of 1 to 3;

Z is oxygen or sulfur;

n is 0 or an integer from 1 to 10;

Y<sub>1</sub> is independently selected from -(CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>Y<sub>2</sub>;

Y<sub>2</sub> is OH, -NO<sub>2</sub>, -S(O)<sub>m</sub>R<sub>11</sub>, -S(O)<sub>m</sub>OR<sub>8</sub>, -S(O)<sub>m</sub>NR<sub>8</sub>R<sub>9</sub>, -NR<sub>8</sub>R<sub>9</sub>, -O(CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>NR<sub>8</sub>R<sub>9</sub>, -C(O)R<sub>8</sub>, -CO<sub>2</sub>R<sub>8</sub>, -CO<sub>2</sub>(CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>CONR<sub>8</sub>R<sub>9</sub>, -ZC(O)R<sub>8</sub>, -CN, -C(Z)NR<sub>8</sub>R<sub>9</sub>, -NR<sub>10</sub>C(Z)R<sub>8</sub>, -C(Z)NR<sub>8</sub>OR<sub>9</sub>, -NR<sub>10</sub>C(Z)NR<sub>8</sub>R<sub>9</sub>, -NR<sub>10</sub>S(O)<sub>m</sub>R<sub>11</sub>, -N(OR<sub>21</sub>)C(Z)NR<sub>8</sub>R<sub>9</sub>, -N(OR<sub>21</sub>)C(Z)R<sub>8</sub>, -C(=NOR<sub>21</sub>)R<sub>8</sub>, -NR<sub>10</sub>C(=NR<sub>15</sub>)SR<sub>11</sub>, -NR<sub>10</sub>C(=NR<sub>15</sub>)NR<sub>8</sub>R<sub>9</sub>, -NR<sub>10</sub>C(=CR<sub>14</sub>R<sub>24</sub>)SR<sub>11</sub>, -NR<sub>10</sub>C(=CR<sub>14</sub>R<sub>24</sub>)NR<sub>8</sub>R<sub>9</sub>, -NR<sub>10</sub>C(O)C(O)



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>(51) International Patent Classification <sup>6</sup> :</b><br><b>A61K 31/44, C07D 401/00</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | <b>A1</b> | <b>(11) International Publication Number:</b> <b>WO 98/22109</b><br><b>(43) International Publication Date:</b> 28 May 1998 (28.05.98)                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>(21) International Application Number:</b> PCT/US97/21020<br><b>(22) International Filing Date:</b> 17 November 1997 (17.11.97)<br><br><b>(30) Priority Data:</b><br>60/031,466 20 November 1996 (20.11.96) US<br>9700540.9 13 January 1997 (13.01.97) GB<br><br><b>(71) Applicant (for all designated States except US):</b> MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).<br><br><b>(72) Inventor; and</b><br><b>(75) Inventor/Applicant (for US only):</b> CHANG, Linda, L. [CA/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).<br><br><b>(74) Agent:</b> MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). |           | <b>(81) Designated States:</b> AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).<br><br><b>Published</b><br><i>With international search report.</i> |
| <b>(54) Title:</b> TRIARYL SUBSTITUTED IMIDAZOLES AS GLUCAGON ANTAGONISTS<br><br><b>(57) Abstract</b><br><br>2,4-Diaryl-5-pyridylimidazoles are glucagon antagonists. The compounds block the action of glucagon at its receptor. Thus, the compounds can be used in the prophylaxis or treatment of disease states in mammals mediated by elevated levels of glucagon. Examples of such disease states include diabetes, obesity, hypertension, and cachexia and the like.                                                                                                                                                                                          |           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |



$\text{NR}_8\text{R}_9$ ,  $-\text{NR}_{10}\text{C}(\text{O})\text{C}(\text{O})\text{OR}_{10}$ ,  $-\text{C}(=\text{NR}_{13})\text{NR}_8\text{R}_9$ ,  
 $-\text{C}(=\text{NOR}_{13})\text{NR}_8\text{R}_9$ ,  $-\text{C}(=\text{NR}_{13})\text{ZR}_{11}$ ,  $-\text{OC}(\text{Z})$   
 $\text{NR}_8\text{R}_9$ ,  $-\text{NR}_{10}\text{S}(\text{O})_m\text{CF}_3$ ,  $-\text{NR}_{10}\text{C}(\text{Z})\text{OR}_{10}$ , 5-( $\text{R}_{18}$ )  
 -1,2,4-oxadiazol-3-yl or 4-( $\text{R}_{12}$ )-5-( $\text{R}_{18}\text{R}_{19}$ )-4,5-  
 dihydro-1,2,4-oxadiazol-3-yl; provided that  $\text{Y}_1$  may  
 also be a halogen or  $\text{C}_{1-5}$  alkyl when  $t=2$  or 3;

$m'$  is an integer having a value of 1 or 2;

$\text{R}_4$  is phenyl, naphth-1-yl or naphth-2-yl which is option-  
 ally substituted by one or two substituents, each of  
 which is independently selected, and which, for a  
 4-phenyl, 4-naphth-1-yl or 5-naphth-2-yl substituent, is  
 halo, cyano,  $-\text{C}(\text{Z})\text{NR}_7\text{R}_{17}$ ,  $-\text{C}(\text{Z})\text{OR}_{23}$ ,  
 $-(\text{CR}_{10}\text{R}_{20})_m\text{COR}_{36}$ ,  $\text{SR}_5$ ,  $-\text{SOR}_5$ ,  $-\text{OR}_{36}$ , halo-  
 substituted- $\text{C}_{1-4}$  alkyl,  $\text{C}_{1-4}$  alkyl,  $-\text{ZC}(\text{Z})\text{R}_{36}$ ,  
 $-\text{NR}_{10}\text{C}(\text{Z})\text{R}_{23}$ , or  $-(\text{CR}_{10}\text{R}_{20})_m\text{NR}_{10}\text{R}_{20}$  and  
 which, for other positions of substitution, is halo,  
 cyano,  $-\text{C}(\text{Z})\text{NR}_{16}\text{R}_{26}$ ,  $-\text{C}(\text{Z})\text{OR}_8$ ,  $-(\text{CR}_{10}\text{R}_{20})_m$   
 $\text{COR}_8$ ,  $-\text{S}(\text{O})_m\text{R}_8$ ,  $-\text{OR}_8$ , halo-substituted- $\text{C}_{1-4}$   
 alkyl,  $-\text{C}_{1-4}$  alkyl,  $-(\text{CR}_{10}\text{R}_{20})_m\text{NR}_{10}\text{C}(\text{Z})\text{R}_8$ ,  
 $-\text{NR}_{10}\text{S}(\text{O})_m\text{R}_{11}$ ,  $-\text{NR}_{10}\text{S}(\text{O})_m\text{NR}_7\text{R}_{17}$   $-\text{ZC}(\text{Z})\text{R}_8$   
 or  $-(\text{CR}_{10}\text{R}_{20})_m\text{NR}_{16}\text{R}_{26}$ ;

wherein

$m''$  is 0 to 5 and  $m'''$  is 0 or 1;

$\text{R}_5$  is hydrogen,  $\text{C}_{1-4}$  alkyl,  $\text{C}_{2-4}$  alkenyl,  $\text{C}_{2-4}$  alkynyl or  
 $\text{NR}_7\text{R}_{17}$ , excluding the moieties  $-\text{SR}_5$  being  
 $-\text{SNR}_7\text{R}_{17}$  and  $-\text{SOR}_5$  being  $-\text{SOH}$ ;

$\text{R}_7$  and  $\text{R}_{17}$  is each independently selected from hydrogen  
 or  $\text{C}_{1-4}$  alkyl or  $\text{R}_7$  and  $\text{R}_{17}$  together with the nitrogen  
 to which they are attached form a heterocyclic ring  
 members which ring optionally contains an additional  
 heteroatom selected from oxygen, selected from  
 pyrrolidine, piperidine, piperazine, morpholine,  
 imidazolidine, and pyrazolidine;

$\text{R}_8$  is hydrogen or  $\text{R}_{11}$ ;

$\text{R}_9$  is hydrogen,  $\text{C}_{1-10}$  alkyl,  $\text{C}_{2-10}$  alkenyl,  $\text{C}_{2-10}$  alkynyl,  
 $\text{C}_{3-7}$  cycloalkyl,  $\text{C}_{5-7}$  cycloalkenyl, aryl, arylalkyl, or  
 $\text{R}_8$  and  $\text{R}_9$  may together with the nitrogen to which they  
 are attached form a heterocyclic ring selected from  
 pyrrolidine, piperidine, piperazine, morpholine,  
 imidazolidine, and pyrazolidine;

$\text{R}_{10}$  and  $\text{R}_{20}$  is each independently selected from hydro-  
 gen or  $\text{C}_{1-4}$  alkyl;

$\text{R}_{11}$  is  $\text{C}_{1-10}$  alkyl, halo-substituted  $\text{C}_{1-10}$  alkyl,  $\text{C}_{2-10}$   
 alkenyl,  $\text{C}_{2-10}$  alkynyl,  $\text{C}_{3-7}$  cycloalkyl,  $\text{C}_{5-7}$   
 cycloalkenyl, aryl, arylalkyl;

$\text{R}_{12}$  is hydrogen,  $-\text{C}(\text{Z})\text{R}_{13}$  or optionally substituted  $\text{C}_{1-4}$   
 alkyl, optionally substituted aryl, optionally substituted  
 aryl- $\text{C}_{1-4}$  alkyl, or  $\text{S}(\text{O})_2\text{R}_{25}$ ;

$\text{R}_{13}$  is hydrogen,  $\text{C}_{1-10}$  alkyl,  $\text{C}_{3-7}$  cycloalkyl, aryl,  
 aryl- $\text{C}_{1-10}$  alkyl;

$\text{R}_{14}$  and  $\text{R}_{24}$  is each independently selected from hydro-  
 gen, alkyl, nitro or cyano;

$\text{R}_{15}$  is hydrogen, cyano,  $\text{C}_{1-4}$  alkyl,  $\text{C}_{3-7}$  cycloalkyl or  
 aryl;

$\text{R}_{16}$  and  $\text{R}_{26}$  is each independently selected from hydro-  
 gen or optionally substituted  $\text{C}_{1-4}$  alkyl, optionally  
 substituted aryl or optionally substituted aryl- $\text{C}_{1-4}$   
 alkyl, or together with the nitrogen which they are  
 attached form a heterocyclic ring selected from  
 pyrrolidine, piperidine, piperazine, morpholine,  
 imidazolidine, and pyrazolidine;

$\text{R}_{18}$  and  $\text{R}_{19}$  is each independently selected from  
 hydrogen,  $\text{C}_{1-4}$  alkyl, substituted alkyl, optionally sub-  
 stituted aryl, optionally substituted arylalkyl or together

$\text{R}_{18}$  and  $\text{R}_{19}$  denote a double bonded oxygen or sulfur;  
 wherein the alkyl, aryl and arylalkyl groups are option-  
 ally substituted by halogen, hydroxy, hydroxy substi-  
 tuted  $\text{C}_{1-10}$  alkyl,  $\text{C}_{1-10}$  alkoxy,  $\text{S}(\text{O})_m$  alkyl, (wherein  
 $m$  is 0, 1 or 2),  $\text{NR}_7\text{R}_{17}$  group,  $\text{C}_{1-10}$  alkyl, cycloalkyl,  
 cycloalkyl alkyl, halo-substituted  $\text{C}_{1-10}$  alkyl, optionally  
 substituted aryl, optionally substituted arylalkyl,  
 wherein these aryl moieties may also be substituted one  
 to two times by halogen, hydroxy, hydroxy substituted  
 alkyl,  $\text{C}_{1-10}$  alkoxy,  $\text{S}(\text{O})_m$  alkyl,  $\text{NR}_7\text{R}_{17}$  group,  $\text{C}_{1-10}$   
 alkyl, or  $\text{CF}_3$ ;

$\text{R}_{21}$  is hydrogen, a pharmaceutically acceptable cation,  
 $\text{C}_{1-10}$  alkyl,  $\text{C}_{3-7}$  cycloalkyl, aryl, aryl  $\text{C}_{1-4}$  alkyl,  
 aroyl, or  $\text{C}_{1-10}$  alkanoyl;

$\text{R}_{22}$  is  $\text{R}_{10}$  or  $\text{C}(\text{Z})-\text{C}_{1-4}$  alkyl;

$\text{R}_{23}$  is  $\text{C}_{1-4}$  alkyl, halo-substituted- $\text{C}_{1-4}$  alkyl, or  $\text{C}_{3-5}$   
 cycloalkyl;

$\text{R}_{36}$  is hydrogen or  $\text{R}_{23}$ ;

$\text{R}_{25}$  is  $\text{C}_{1-10}$  alkyl,  $\text{C}_{3-7}$  cycloalkyl;

$\text{R}_{27}$  is hydrogen, cyano,  $\text{C}_{1-4}$  alkyl,  $\text{C}_{3-7}$  cycloalkyl, or  
 aryl;

or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1, wherein the  
 $\text{R}_1$ -4-pyridyl moiety is substituted by alkyl, amino, or mono-  
 or di-  $\text{C}_{1-6}$  alkylamino.

3. The compound according to claim 1 wherein  $\text{Y}_2$  is OH,  
 $-\text{S}(\text{O})_m\text{R}_{11}$ ,  $-\text{S}(\text{O})_m\text{NR}_8\text{R}_9$ , or  $-\text{NR}_8\text{R}_9$ .

4. The compound according to claim 1 wherein  $\text{R}_4$  is  
 optionally substituted phenyl, naphth-1-yl or naphth-2-yl  
 wherein the 4-phenyl, 4-naphth-1-yl or 5-naphth-2-yl moi-  
 ety are substituted by one or two substituents each indepen-  
 dently selected from halogen,  $-\text{SR}_5$ ,  $-\text{SOR}_5$ ,  $-\text{OR}_{36}$ , or  
 $-(\text{CR}_{10}\text{R}_{20})_m\text{NR}_{10}\text{R}_{20}$ , and for other positions of substi-  
 tution on these rings the substitution is halogen,  $-\text{S}(\text{O})_m\text{R}_8$ ,  
 $-\text{OR}_8$ ,  $-(\text{CR}_{10}\text{R}_{20})_m\text{NR}_{16}\text{R}_{26}$ ,  $-\text{NR}_{10}\text{C}(\text{Z})\text{R}_8$  and  
 $-\text{NR}_{10}\text{S}(\text{O})_m\text{R}_{11}$ .

5. The compound according to claim 4 wherein the  
 substituent in the 4-position for phenyl and naphth-1-yl and  
 on the 5-position in naphth-2-yl is fluoro, chloro,  $-\text{SR}_5$  or  
 $-\text{SOR}_5$ ; and 3-position substitution for phenyl and naphth-  
 1-yl is fluoro, chloro,  $-\text{OR}_8$ , amino,  $-\text{NHCO}(\text{C}_{1-10}$  alkyl);  
 and  $-\text{NR}_{10}\text{S}(\text{O})_m\text{R}_{11}$ .

6. The compound according to claim 5 wherein  $\text{R}_1$  is  
 4-pyridyl, or 2-alkyl-4-pyridyl.

7. The compound according to claim 3 wherein the  $\text{Y}_2$   
 group is substituted in the 4-position of the phenyl ring.

8. The compound according to claim 1 wherein  $\text{Y}_2$  is  
 methylsulfinyl, ethylsulfinyl, methylsulfonyl, N,N-  
 dimethylaminomethyl, N-benzyl-N-methylaminomethyl,  
 N-morpholinomethyl, methanesulfonamido,  
 sulphonamidomethyl, 5-methyl-4,5-dihydro-1,2,4-  
 oxadiazol-3-yl or 5,5-dimethyl-4,5-dihydro-1,2,4-  
 oxadiazol-3-yl.

9. The compound according to claim 1 which is:  
 2-(4-Cyanophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)-1H-  
 imidazole;

4-(4-Fluorophenyl)-2-(4-hydroxyphenyl)-5-(4-pyridyl)-  
 1H-imidazole;

4-[4-(4-Fluorophenyl)-5-(4-pyridyl)-1H-imidazol-2-yl]  
 benzoic acid;

2-(4-Aminomethylphenyl)-4-(4-fluorophenyl)-5-(4-  
 pyridyl)-1H-imidazole;

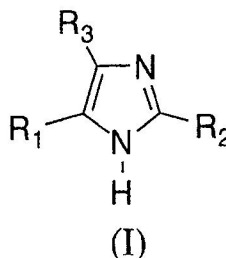
2-(3,5-Dibromo-4-hydroxyphenyl)-4-(4-fluorophenyl)-5-  
 (4-pyridyl)-1H-imidazole;

Ethyl 4-[4-(4-Fluorophenyl)-5-(4-pyridyl)]-1H-imidazol-  
 2-yl-benzoate;



WHAT IS CLAIMED IS:

1. A compound having the formula (I)



wherein

R<sub>1</sub> is 4-pyridyl, 4-pyrimidinyl or 4-quinolyl which is unsubstituted or substituted with one or two substituents each of which is independently selected from the group consisting of

- (1) halogen,
- (2) -CN,
- (3) C<sub>1</sub>-10 alkyl, wherein said alkyl is optionally substituted with from 1 to 5 halogen atoms,
- (4) -O-C<sub>1</sub>-10 alkyl,
- (5) -S-C<sub>1</sub>-10 alkyl,
- (6) -NR<sub>8</sub>R<sub>9</sub>, and
- (7) -NO<sub>2</sub>;

R<sub>2</sub> is phenyl, 1-naphthyl, 2-naphthyl or heteroaryl which is unsubstituted or substituted with one, two or three substituents each of which is independently selected from the group consisting of

- (1) C<sub>1</sub>-10 alkyl,
- (2) R<sub>4</sub>, and
- (3) C<sub>1</sub>-10 alkyl substituted with up to 5 groups independently selected from R<sub>4</sub>;

R<sub>3</sub> is phenyl, which is unsubstituted or substituted with one or two substituents each of which is independently selected from the group consisting of

- (1) C<sub>4</sub>-10 alkyl, wherein said alkyl is optionally substituted with from 1 to 5 halogen atoms,

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- 5
- (0)(2) -O-C<sub>3-10</sub> alkyl,  
(3) -O-C<sub>1-4</sub> alkylaryl,  
(4) -S-C<sub>2-10</sub> alkyl,  
(5) -S(O)<sub>m</sub>C<sub>3-10</sub> alkyl,  
(6) -C(O)C<sub>3-10</sub> alkyl,  
(7) -CO<sub>2</sub>C<sub>3-10</sub> alkyl,  
(8) -NR<sub>7</sub>R<sub>17</sub>,  
(9) *meta* -O-phenyl, which is optionally substituted with halo, C<sub>1-4</sub> alkyl, or C<sub>1-4</sub> alkoxy;
- 10 R<sub>4</sub> is
- 15
- (1) -OR<sub>8</sub>,  
(2) -NO<sub>2</sub>,  
(3) halogen  
(4) -S(O)<sub>m</sub>R<sub>11</sub>,  
(5) -SR<sub>8</sub>,  
(6) -S(O)<sub>m</sub>OR<sub>8</sub>,  
(7) -S(O)<sub>m</sub>NR<sub>8</sub>R<sub>9</sub>,  
(8) -NR<sub>8</sub>R<sub>9</sub>,  
(9) -O(CR<sub>10</sub>R<sub>20</sub>)<sub>p</sub>NR<sub>8</sub>R<sub>9</sub>,
- 20
- (10) -C(O)R<sub>8</sub>,  
(11) -CO<sub>2</sub>R<sub>8</sub>,  
(12) -CO<sub>2</sub>(CR<sub>10</sub>R<sub>20</sub>)<sub>n</sub>CONR<sub>8</sub>R<sub>9</sub>,  
(13) -ZC(O)R<sub>8</sub>,  
(14) -CN,
- 25
- (15) -C(Z)NR<sub>8</sub>R<sub>9</sub>,  
(16) NR<sub>10</sub>C(Z)R<sub>8</sub>,  
(17) -C(Z)NR<sub>8</sub>OR<sub>9</sub>,  
(18) NR<sub>10</sub>C(Z)NR<sub>8</sub>R<sub>9</sub>,  
(19) -NR<sub>10</sub>S(O)<sub>m</sub>R<sub>11</sub>,
- 30
- (20) -C(=NOR<sub>21</sub>)R<sub>8</sub>,  
(21) -NR<sub>10</sub>C(=NR<sub>15</sub>)SR<sub>11</sub>,  
(22) -NR<sub>10</sub>C(=NR<sub>15</sub>)NR<sub>8</sub>R<sub>9</sub>,  
(23) -NR<sub>10</sub>C(=CR<sub>14</sub>R<sub>24</sub>)SR<sub>11</sub>,  
(24) -NR<sub>10</sub>C(=CR<sub>14</sub>R<sub>24</sub>)NR<sub>8</sub>R<sub>9</sub>,

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- 5 (25)  $-\text{NR}_{10}\text{C}(\text{O})\text{C}(\text{O})\text{NR}_8\text{R}_9$ ,  
(26)  $-\text{NR}_{10}\text{C}(\text{O})\text{C}(\text{O})\text{OR}_{10}$ ,  
(27)  $-\text{C}(=\text{NR}_{13})\text{NR}_8\text{R}_9$ ,  
(28)  $-\text{C}(=\text{NOR}_{13})\text{NR}_8\text{R}_9$ ,  
(29)  $-\text{C}(=\text{NR}_{13})\text{ZR}_{11}$ ,  
(30)  $-\text{OC}(\text{Z})\text{NR}_8\text{R}_9$ ,  
(31)  $-\text{NR}_{10}\text{S}(\text{O})_m\text{CF}_3$ ,  
(32)  $-\text{NR}_{10}\text{C}(\text{Z})\text{OR}_{10}$ ,  
(33) 5-(R<sub>18</sub>)-1,2,4-oxadiazol-3-yl or  
10 (34) 4-(R<sub>12</sub>)-5-(R<sub>18</sub>R<sub>19</sub>)-4,5-dihydro-1,2,4-oxadiazol-3-yl;

R<sub>7</sub> and R<sub>17</sub> are each independently selected from hydrogen or C<sub>1-4</sub> alkyl provided that R<sub>7</sub> and R<sub>17</sub> are not both hydrogen; or R<sub>7</sub> and R<sub>17</sub> together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally  
15 contains an additional heteroatom selected from oxygen, sulfur or NR<sub>22</sub>;

R<sub>8</sub> and R<sub>9</sub> are independently selected from

- (1) hydrogen,  
(2) heterocyclyl,  
20 (3) heterocyclyl-C<sub>1-10</sub> alkyl, and  
(4) R<sub>11</sub>; or

R<sub>8</sub> and R<sub>9</sub> together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally  
25 contains an additional heteroatom selected from oxygen, sulfur or NR<sub>12</sub>;

R<sub>10</sub> and R<sub>20</sub> is each independently selected from hydrogen or C<sub>1-4</sub> alkyl;

- R<sub>11</sub> is (1) C<sub>1-10</sub> alkyl,  
(2) halo-substituted C<sub>1-10</sub> alkyl,  
(3) C<sub>2-10</sub> alkenyl,  
30 (4) C<sub>2-10</sub> alkynyl,  
(5) C<sub>3-7</sub> cycloalkyl,  
(6) C<sub>5-7</sub> cycloalkenyl,  
(7) aryl,  
(8) aryl-C<sub>1-10</sub> alkyl,

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- (9) heteroaryl or  
(10) heteroaryl-C<sub>1-10</sub> alkyl;  
R<sub>12</sub> is (1) hydrogen,  
(2) -C(Z)R<sub>13</sub>,  
5 (3) optionally substituted C<sub>1-4</sub> alkyl,  
(4) optionally substituted aryl C<sub>1-4</sub> alkyl, or  
(5) S(O)<sub>2</sub>R<sub>25</sub>;  
R<sub>13</sub> is (1) hydrogen, or  
(2) R<sub>25</sub>;  
10 R<sub>14</sub> and R<sub>24</sub> is each independently selected from  
(1) hydrogen,  
(2) C<sub>1-4</sub> alkyl,  
(3) nitro or  
(4) cyano;  
15 R<sub>15</sub> is (1) hydrogen,  
(2) cyano,  
(3) C<sub>1-4</sub> alkyl,  
(4) C<sub>3-7</sub> cycloalkyl or  
(5) aryl;  
20 R<sub>18</sub> and R<sub>19</sub> is each independently selected from  
(1) hydrogen,  
(2) C<sub>1-4</sub> alkyl,  
(3) substituted C<sub>1-4</sub> alkyl,  
(4) optionally substituted aryl,  
25 (5) optionally substituted aryl-C<sub>1-10</sub> alkyl or  
R<sub>18</sub> and R<sub>19</sub> together denote an oxo or thioxo;  
R<sub>21</sub> is (1) R<sub>13</sub>,  
(2) a pharmaceutically acceptable cation, or  
(3) aroyl, or  
30 (4) C<sub>1-10</sub> alkanoyl;  
R<sub>22</sub> is R<sub>10</sub> or C(Z)-C<sub>1-4</sub> alkyl;  
R<sub>25</sub> is (1) C<sub>1-10</sub> alkyl,  
(2) C<sub>3-7</sub> cycloalkyl,  
(3) heterocyclyl,

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- (4) aryl,  
(5) aryl C<sub>1-10</sub> alkyl,  
(6) heterocyclyl-C<sub>1-10</sub> alkyl,  
(7) heteroaryl or  
5 (8) heteroaryl C<sub>1-10</sub> alkyl;  
Z is oxygen or sulfur;  
m is 1 or 2;  
n is 1 to 10;  
p is 1 to 10; or  
10 a pharmaceutically acceptable salt thereof.

2. A compound of Claim 1  
wherein  
R<sub>1</sub> is 4-pyridyl which is unsubstituted or substituted with one or two  
15 substituents each of which is independently selected from the  
group consisting of  
(1) halogen,  
(2) -CN,  
(3) C<sub>1-10</sub> alkyl, wherein said alkyl is optionally  
20 substituted with from 1 to 5 halogen atoms,  
(4) -O-C<sub>1-10</sub> alkyl,  
(5) -S-C<sub>1-10</sub> alkyl,  
(6) -NR<sub>8</sub>R<sub>9</sub>, and  
(7) -NO<sub>2</sub>.

- 25 3. A compound of Claim 1  
wherein  
R<sub>2</sub> is phenyl, 1-naphthyl or 2-naphthyl each of which is unsubstituted or  
substituted with one, two or three groups each of which is  
30 independently selected from the group consisting of  
(1) C<sub>1-10</sub> alkyl,  
(2) R<sub>4</sub>, and  
(3) C<sub>1-10</sub> alkyl substituted with up to 5 groups  
independently selected from R<sub>4</sub>.

## de Laszlo et al.

[11] Patent Number: 5,776,954

[45] **Date of Patent:** **Jul. 7, 1998**

**[54] SUBSTITUTED PYRIDYL PYRROLES,  
COMPOSITIONS CONTAINING SUCH  
COMPOUNDS AND METHODS OF USE**

[75] **Inventors: Stephen E. de Laszlo, Rumson; Linda L. Chang, Wayne; Dooseop Kim, Westfield, all of N.J.; Nathan B. Mantlo, Lafayette, Colo.**

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

[21] Appl. No.: 742,428

[22] Filed: Oct. 30, 1996

[51] **Int. Cl.<sup>6</sup>** ..... **A61K 31/44; C07D 403/04**

[52] **U.S. Cl.** ..... **514/340**; 546/276.4; 546/278.4;  
546/278.7; 546/279.1; 546/194; 546/17;  
546/269.1; 544/360; 514/318; 514/279

[58] **Field of Search** ..... 546/276.4, 278.4,  
546/278.7, 279.1, 194, 17; 544/360, 340,  
318, 279

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*Primary Examiner—C. Warren Ivy*

*Assistant Examiner—Charanjit S. Aulakh*

Attorney, Agent, or Firm—Richard C. Billups; Mark R. Daniel

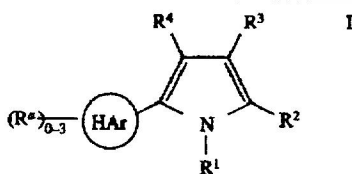
[57] **ABSTRACT**

The present invention addresses substituted pyridyl pyrroles, as well as compositions containing such compounds and methods of treatment. The compounds in the present invention are glucagon antagonists and inhibitors of the biosynthesis and action of TNF- $\alpha$  and IL1. The compounds block the action of glucagon at its receptors and thereby decrease the levels of plasma glucose. The instant pyrroles are also inhibitors of TNF- $\alpha$  and IL1 and may be used as antidiabetic agents as well as other cytokine mediated diseases. Cytokine mediated diseases refers to diseases or conditions in which excessive or unregulated production of one or more cytokines occurs. Interleukin-1 (IL-1) and Tumor Necrosis Factor (TNF) are cytokines produced by a variety of cells, which are involved in immunoregulation and other physiological conditions, such as inflammation.

### 39 Claims, No Drawings



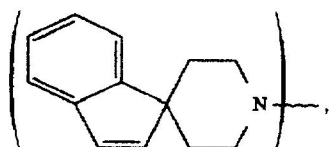
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Table of Compounds of Formula I with Gluc IC<sub>50</sub> < 2.0 uM and/or Streak IC<sub>50</sub> < 4 uM

| R1 | (R <sub>a</sub> ) <sub>0-3</sub> -HAr | R4                                      | R3   | R2                      |
|----|---------------------------------------|-----------------------------------------|------|-------------------------|
| H  | 4-Pyr                                 | 4-(2-(4-(F)-phenyl)-ethynyl)-phenyl     | H    | 4-Cl-Ph                 |
| H  | 4-Pyr                                 | 4-(2-(4-(ethyl)-phenyl)-ethynyl)-phenyl | H    | 4-Cl-Ph                 |
| H  | 4-Pyr                                 | 4-(2-(4-(butyl)-phenyl)-ethynyl)-phenyl | H    | 4-Cl-Ph                 |
| H  | 2-(F)-pyridin-5-yl                    | 4-F-Ph                                  | H    | 4-Cl-Ph                 |
| H  | 4-Pyr                                 | cyclohexyl                              | H    | 4-Cl-Ph                 |
| H  | 4-Pyr                                 | 4-F-Ph                                  | H    | 2-Br-Ph                 |
| H  | 4-Pyr                                 | 3-(CF <sub>3</sub> )-Ph                 | Me   | N-methyl-piperidin-4-yl |
| H  | 4-Pyr                                 | 3-(CF <sub>3</sub> )-Ph                 | Me   | piperidin-4-yl          |
| H  | 2-F-pyridin-5-yl                      | 4-F-Ph                                  | H    | 4-Cl-Ph                 |
| H  | 2-OH-pyridin-5-yl                     | 4-F-Ph                                  | H    | 4-Cl-Ph                 |
| H  | 4-Pyr                                 | 2-propoxy-4-(2-Ph-ethynyl)-Ph           | H    | 4-Cl-Ph                 |
| H  | 4-Pyr                                 | 4-(2-propenyl)-cyclohexen-1-yl          | H    | 4-Cl-Ph                 |
| H  | 4-Pyr                                 | N-(Cbz)-piperidin-4-yl                  | H    | 4-Cl-Ph                 |
| H  | 4-Pyr                                 | i-Propyl                                | H    | 4-Cl-Ph                 |
| H  | pyridazin-4-yl                        | 4-F-Ph                                  | H    | 4-Cl-Ph                 |
| H  | 4-Pyr                                 | 4-F-Ph                                  | H    | 2-CN-Ph                 |
| H  | 4-Pyr                                 | 2-CN-Ph                                 | H    | 4-Cl-Ph                 |
| H  | 4-Pyr                                 | 4-F-Ph                                  | n-Bu | 4-Cl-Ph                 |

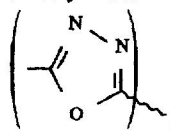
wherein: CO=carbonyl, Ph=phenyl, pyr=pyridyl, Pip=piperidinyl, OMe=methoxy, iPr=isopropyl, thioPh=thiophenyl, (A)=SO<sub>2</sub>NH<sub>2</sub>tBu, (B)=SO<sub>2</sub>NH<sub>2</sub>, (C)=SO<sub>2</sub>NHCO<sub>2</sub>nBu, (D)=tetrazol-5-yl, (E)=5-(n-Bu)-thiophen-2-yl, (G)=5-(Cl)-thiophen-2-yl, (J)=N-methyltetrazolyl, (M)=N-Boc-piperazin, (Q)=CO-spiroindane-1, (W)=CO-L-proline-OtBu, (X)=2-OH-Ph, (Y)=2-SO<sub>2</sub>NH<sub>2</sub>tBu-Ph, (Z)=piperidin-4-yl.

spiroindane-1 is:

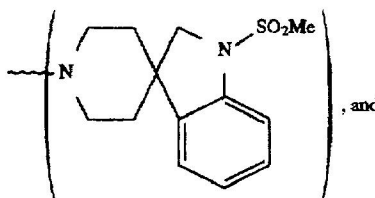


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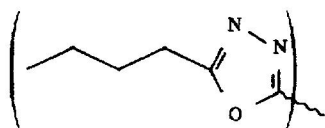
heterocycle-1 is:



spiroindane-1 is:

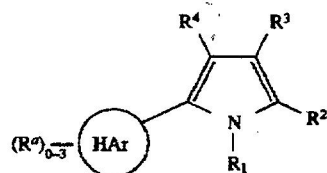


heterocycle-2 is:



What is claimed is:

1. A compound represented by formula I:



or a pharmaceutically acceptable salt, solvate, hydrate or tautomer thereof, wherein:



represents pyridyl which is unsubstituted or substituted with 1-3 R<sup>a</sup> groups;

each R<sup>a</sup> independently represents a member selected from the group consisting of: halo, aryl(R<sup>b</sup>)<sub>0-2</sub>, heteroaryl (R<sup>b</sup>)<sub>0-2</sub>, CF<sub>3</sub>, OCF<sub>3</sub>, CN, NO<sub>2</sub>, OR<sup>23</sup>, SR<sup>23</sup>, S(O)R<sup>23</sup>, SO<sub>2</sub>R<sup>21</sup>, NR<sup>20</sup>R<sup>23</sup>, NR<sup>20</sup>COR<sup>21</sup>, NR<sup>20</sup>CO<sub>2</sub>R<sup>21</sup>, NR<sup>20</sup>CONR<sup>20</sup>R<sup>23</sup>, NR<sup>20</sup>SO<sub>2</sub>R<sup>21</sup>, NR<sup>20</sup>C(NR<sup>20</sup>)NHR<sup>23</sup>, COR<sup>20</sup>, CO<sub>2</sub>R<sup>23</sup>, CONR<sup>20</sup>R<sup>23</sup>, SO<sub>2</sub>NR<sup>20</sup>CO<sub>2</sub>R<sup>21</sup>, SO<sub>2</sub>NR<sup>20</sup>COR<sup>21</sup>, SO<sub>2</sub>NR<sup>20</sup>CONR<sup>20</sup>R<sup>23</sup>, SO<sub>2</sub>NR<sup>20</sup>CO<sub>2</sub>R<sup>21</sup>OCONR<sup>20</sup>R<sup>23</sup>, OCONR<sup>20</sup>SO<sub>2</sub>R<sup>21</sup>, C(NR<sup>20</sup>)NR<sup>20</sup>R<sup>23</sup>, C(O)OCH<sub>2</sub>OC(O)R<sup>20</sup>, CONR<sup>20</sup>SO<sub>2</sub>R<sup>21</sup> and SO<sub>2</sub>NR<sup>20</sup>CO<sub>2</sub>R<sup>21</sup>;

when present, each R<sup>b</sup> independently represents a member selected from the group consisting of: halo, CF<sub>3</sub>, OCF<sub>3</sub>, CN, NO<sub>2</sub>, OR<sup>23</sup>, SR<sup>23</sup>, S(O)R<sup>23</sup>, SO<sub>2</sub>R<sup>21</sup>, NR<sup>20</sup>R<sup>23</sup>, NR<sup>20</sup>COR<sup>21</sup>, NR<sup>20</sup>CO<sub>2</sub>R<sup>21</sup>, NR<sup>20</sup>CONR<sup>20</sup>R<sup>23</sup>, NR<sup>20</sup>SO<sub>2</sub>R<sup>21</sup>, NR<sup>20</sup>C(NR<sup>20</sup>)NHR<sup>23</sup>, COR<sup>20</sup>, CO<sub>2</sub>R<sup>23</sup>, CONR<sup>20</sup>R<sup>23</sup>, SO<sub>2</sub>NR<sup>20</sup>R<sup>23</sup>, SO<sub>2</sub>NR<sup>20</sup>COR<sup>21</sup>, SO<sub>2</sub>NR<sup>20</sup>CONR<sup>20</sup>R<sup>23</sup>, SO<sub>2</sub>NR<sup>20</sup>CO<sub>2</sub>R<sup>21</sup>OCONR<sup>20</sup>R<sup>23</sup>, OCONR<sup>20</sup>SO<sub>2</sub>R<sup>21</sup>, C(NR<sup>20</sup>)NR<sup>20</sup>R<sup>23</sup>, C(O)OCH<sub>2</sub>OC(O)R<sup>20</sup>, CONR<sup>20</sup>SO<sub>2</sub>R<sup>21</sup>, and SO<sub>2</sub>NR<sup>20</sup>CO<sub>2</sub>R<sup>21</sup>;

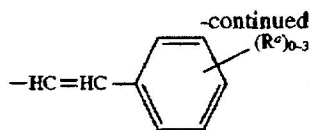
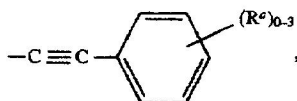
R<sup>1</sup> is selected from the group consisting of: H, aryl, C<sub>1-15</sub> alkyl, C<sub>3-15</sub> alkenyl, C<sub>3-15</sub> alkynyl and heterocyclyl, said alkyl, aryl, alkenyl, alkynyl and heterocyclyl being optionally substituted with from one to three members

selected from the group consisting of: aryl, heteroaryl, heterocyclyl, halo,  $\text{OR}^{23}$ ,  $\text{SR}^{23}$ ,  $\text{N}(\text{R}^{23})_2$ ,  $\text{S}(\text{O})\text{R}^{21}$ ,  $\text{SO}_2\text{R}^{21}$ ,  $\text{SO}_2\text{NR}^{20}\text{R}^{23}$ ,  $\text{SO}_2\text{NR}^{20}\text{COR}^{21}$ ,  $\text{SO}_2\text{NR}^{20}\text{CONR}^{20}\text{R}^{23}$ ,  $\text{NR}^{20}\text{COR}^{21}$ ,  $\text{NR}^{20}\text{CO}_2\text{R}^{21}$ ,  $\text{NR}^{20}\text{CONR}^{20}\text{R}^{23}$ ,  $\text{N}(\text{R}^{20})\text{C}(\text{NR}^{20})\text{NHR}^{23}$ ,  $\text{COR}^{20}$ ,  $\text{CO}_2\text{R}^{23}$ ,  $\text{CONR}^{20}\text{R}^{23}$ ,  $\text{CONR}^{20}\text{SO}_2\text{R}^{21}$ ,  $\text{NR}^{20}\text{SO}_2\text{R}^{21}$ ,  $\text{SO}_2\text{NR}^{20}\text{CO}_2\text{R}^{21}$ ,  $\text{OCONR}^{20}\text{R}^{23}$ ,  $\text{OCONR}^{20}\text{SO}_2\text{R}^{21}$ ,  $\text{OCONR}^{20}\text{R}^{23}$  and  $\text{C}(\text{O})\text{OCH}_2\text{OC}(\text{O})\text{R}^{20}$ ;

$\text{R}^2$  is selected from the group consisting of: aryl (with the proviso that aryl is not unsubstituted phenyl), heteroaryl (with the proviso that heteroaryl is not unsubstituted pyridyl),  $\text{C}_{7-15}$  alkenyl,  $\text{C}_{2-15}$  alkynyl,  $\text{CONR}^{20}\text{R}^{23}$ ,  $\text{SO}_2\text{R}^{21}$  (wherein  $\text{R}^{21}$  is not alkyl or  $\text{C}_{1-6}$  alkenyl),  $\text{SO}_2\text{N}(\text{R}^{20})_2$ ,  $\text{SO}_2\text{NR}^{20}\text{COR}^{21}$ ,  $\text{SO}_2\text{NR}^{20}\text{CON}(\text{R}^{20})_2$ ,  $\text{COR}^{20}$ ,  $\text{CO}_2\text{R}^{20}$  (wherein  $\text{R}^{20}$  is not  $\text{C}_{1-6}$  alkyl or hydrogen),  $\text{CONR}^{20}\text{SO}_2\text{R}^{21}$ ,  $\text{SO}_2\text{NR}^{20}\text{CO}_2\text{R}^{21}$  and heterocyclyl, said alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl being optionally substituted with from one to three members selected from the group consisting of: halo,  $\text{C}_{1-15}$  alkyl,  $\text{OCF}_3$ ,  $\text{CF}_3$ ,  $\text{CN}$ , aryl,  $\text{NO}_2$ , heteroaryl,  $\text{OR}^{20}$ ,  $\text{SR}^{20}$ ,  $\text{N}(\text{R}^{20})_2$ ,  $\text{S}(\text{O})\text{R}^{22}$ ,  $\text{SO}_2\text{R}^{22}$ ,  $\text{SO}_2\text{N}(\text{R}^{20})_2$ ,  $\text{SO}_2\text{NR}^{20}\text{COR}^{22}$ ,  $\text{SO}_2\text{NR}^{20}\text{CON}(\text{R}^{20})_2$ ,  $\text{NR}^{20}\text{COR}^{22}$ ,  $\text{NR}^{20}\text{CO}_2\text{R}^{22}$ ,  $\text{NR}^{20}\text{CON}(\text{R}^{20})_2$ ,  $\text{NR}^{22}\text{C}(\text{NR}^{22})\text{NHR}^{22}$ ,  $\text{COR}^{20}$ ,  $\text{CO}_2\text{R}^{20}$ ,  $\text{CON}(\text{R}^{20})_2$ ,  $\text{CONR}^{20}\text{SO}_2\text{R}^{22}$ ,  $\text{NR}^{20}\text{SO}_2\text{R}^{22}$ ,  $\text{SO}_2\text{NR}^{20}\text{CO}_2\text{R}^{22}$ ,  $\text{OCONR}^{20}\text{SO}_2\text{R}^{22}$ , and  $\text{OCONR}^{20}\text{R}^{23}$ ;

$\text{R}^3$  is selected from the group consisting of: H, aryl,  $\text{C}_{1-15}$  alkyl,  $\text{C}_{2-15}$  alkenyl,  $\text{C}_{2-15}$  alkynyl, halo,  $\text{NO}_2$ ,  $\text{CN}$ ,  $\text{CONR}^{20}\text{R}^{23}$ ,  $\text{SO}_2\text{R}^{21}$ ,  $\text{SO}_2\text{N}(\text{R}^{20})_2$ ,  $\text{SO}_2\text{NR}^{20}\text{COR}^{21}$ ,  $\text{SO}_2\text{NR}^{20}\text{CON}(\text{R}^{20})_2$ ,  $\text{COR}^{20}$ ,  $\text{CO}_2\text{R}^{20}$ ,  $\text{CONR}^{20}\text{SO}_2\text{R}^{21}$ ,  $\text{SO}_2\text{NR}^{20}\text{CO}_2\text{R}^{21}$  and heterocyclyl, said alkyl, alkenyl, alkynyl, aryl, and heterocyclyl being optionally substituted with from one to three members selected from the group consisting of: halo,  $\text{C}_{1-15}$  alkyl,  $\text{CF}_3$ ,  $\text{OCF}_3$ ,  $\text{CN}$ , aryl,  $\text{NO}_2$ , heteroaryl,  $\text{OR}^{23}$ ,  $\text{SR}^{23}$ ,  $\text{N}(\text{R}^{23})_2$ ,  $\text{S}(\text{O})\text{R}^{22}$ ,  $\text{SO}_2\text{R}^{22}$ ,  $\text{SO}_2\text{N}(\text{R}^{20})_2$ ,  $\text{SO}_2\text{NR}^{20}\text{COR}^{22}$ ,  $\text{SO}_2\text{NR}^{20}\text{CON}(\text{R}^{20})_2$ ,  $\text{NR}^{20}\text{COR}^{22}$ ,  $\text{NR}^{20}\text{CO}_2\text{R}^{22}$ ,  $\text{NR}^{20}\text{CON}(\text{R}^{20})_2$ ,  $\text{NR}^{22}\text{C}(\text{NR}^{22})\text{NHR}^{22}$ ,  $\text{COR}^{20}$ ,  $\text{CO}_2\text{R}^{20}$ ,  $\text{CON}(\text{R}^{20})_2$ ,  $\text{CONR}^{20}\text{SO}_2\text{R}^{22}$ ,  $\text{NR}^{20}\text{SO}_2\text{R}^{22}$ ,  $\text{SO}_2\text{NR}^{20}\text{CO}_2\text{R}^{22}$ ,  $\text{OCONR}^{20}\text{SO}_2\text{R}^{22}$ ,  $\text{OR}^{20}$  and  $\text{OCONR}^{20}\text{R}^{23}$ ;

$\text{R}^4$  is selected from the group consisting of  $\text{COR}^{20}$ ,  $\text{COOR}^{20}$ ,  $\text{CONR}^{20}\text{R}^{23}$ , aryl, heterocyclyl,  $\text{C}_{1-15}$  alkyl,  $\text{C}_{3-15}$  alkenyl,  $\text{C}_{3-15}$  alkynyl, said alkyl, alkenyl and alkynyl group optionally interrupted by 1-2 oxo or heteroatoms selected from O, S,  $\text{S}(\text{O})$ ,  $\text{SO}_2$  or  $\text{NR}^{24}$  and said  $\text{C}_{1-15}$  alkyl, aryl, heterocyclyl,  $\text{C}_{3-15}$  alkenyl,  $\text{C}_{3-15}$  alkynyl being optionally substituted with from 1-3 of  $\text{R}^{21}$ , halo, aryl( $\text{R}^a$ ) $_{0-3}$ , heteroaryl( $\text{R}^a$ ) $_{0-3}$ , heterocyclyl,  $\text{CN}$ ,  $\text{CF}_3$ ,  $\text{NO}_2$ ,  $\text{OR}^{23}$ ,  $\text{SR}^{23}$ ,  $\text{NR}^{20}\text{R}^{23}$ ,  $\text{S}(\text{O})\text{R}^{21}$ ,  $\text{SO}_2\text{R}^{21}$ ,  $\text{SO}_2\text{NR}^{20}\text{R}^{23}$ ,  $\text{SO}_2\text{NR}^{20}\text{COR}^{21}$ ,  $\text{OR}^{20}\text{CO}_2\text{R}^{23}$ ,  $\text{SO}_2\text{NR}^{20}\text{CONR}^{20}\text{R}^{23}$ ,  $\text{NR}^{20}\text{COR}^{21}$ ,  $\text{NR}^{20}\text{CO}_2\text{R}^{21}$ ,  $\text{NR}^{20}\text{CONR}^{20}\text{R}^{23}$ ,  $\text{N}(\text{R}^{20})\text{C}(\text{NR}^{20})\text{NHR}^{23}$ ,  $\text{CO}_2\text{R}^{23}$ ,  $\text{COR}^{20}$ ,  $\text{CONR}^{20}\text{R}^{23}$ ,  $\text{CONR}^{20}\text{SO}_2\text{R}^{21}$ ,  $\text{NR}^{20}\text{SO}_2\text{R}^{21}$ ,  $\text{SO}_2\text{NR}^{20}\text{CO}_2\text{R}^{21}$ ,  $\text{OCONR}^{20}\text{R}^{23}$ ,  $\text{OCONR}^{20}\text{SO}_2\text{R}^{21}$ ,  $\text{OCONR}^{20}\text{R}^{23}$ .



$-\text{C}\equiv\text{C}-\text{Heteroaryl}(\text{R}^a)_{0-3}$ ,  $-\text{HC}\equiv\text{HC}-\text{Heteroaryl}(\text{R}^a)_{0-3}$  and  $\text{C}(\text{O})\text{OCH}_2\text{OC}(\text{O})\text{R}^{20}$ ;

$\text{R}^{20}$  represents a member selected from the group consisting of: H,  $\text{C}_{1-15}$  alkyl,  $\text{C}_{3-15}$  alkenyl,  $\text{C}_{3-15}$  alkynyl, heterocyclyl, aryl and heteroaryl, said alkyl, alkenyl and alkynyl being optionally substituted with 1-3 groups selected from halo, aryl and heteroaryl;

$\text{R}^{21}$  represents a member selected from the group consisting of:  $\text{C}_{1-15}$  alkyl,  $\text{C}_{3-15}$  alkenyl,  $\text{C}_{3-15}$  alkynyl, aryl, heterocyclyl and heteroaryl; said alkyl, alkenyl or alkynyl being optionally interrupted by 1-2 heteroatoms selected from O, S,  $\text{S}(\text{O})$ ,  $\text{SO}_2$  or  $\text{NR}^{24}$  and said alkyl, alkenyl, alkynyl, aryl, heterocyclyl and heteroaryl being optionally substituted with from 1-3 of halo, heterocyclyl, heteroaryl, aryl( $\text{R}^a$ ) $_{0-2}$ , heteroaryl( $\text{R}^a$ ) $_{0-2}$ ,  $\text{CN}$ ,  $\text{OR}^{20}$ ,  $\text{O}((\text{CH}_2)_n\text{O})_m\text{R}^{20}$ ,  $\text{NR}^{20}((\text{CH}_2)_n\text{O})_m\text{R}^{20}$  wherein n represents an integer of from 1 to 4, and m represents an integer of from 1 to 4;  $\text{SR}^{20}$ ,  $\text{N}(\text{R}^{20})_2$ ,  $\text{S}(\text{O})\text{R}^{22}$ ,  $\text{SO}_2\text{R}^{22}$ ,  $\text{SO}_2\text{N}(\text{R}^{20})_2$ ,  $\text{SO}_2\text{NR}^{20}\text{COR}^{22}$ ,  $\text{SO}_2\text{NR}^{20}\text{CON}(\text{R}^{20})_2$ ,  $\text{NR}^{20}\text{COR}^{22}$ ,  $\text{NR}^{20}\text{CO}_2\text{R}^{22}$ ,  $\text{NR}^{20}\text{CON}(\text{R}^{20})_2$ ,  $\text{NR}^{22}\text{C}(\text{NR}^{22})\text{NHR}^{22}$ ,  $\text{CO}_2\text{R}^{20}$ ,  $\text{CON}(\text{R}^{20})_2$ ,  $\text{CONR}^{20}\text{SO}_2\text{R}^{22}$ ,  $\text{NR}^{20}\text{SO}_2\text{R}^{22}$ ,  $\text{SO}_2\text{NR}^{20}\text{CO}_2\text{R}^{22}$ ,  $\text{OCONR}^{20}\text{SO}_2\text{R}^{22}$ ,  $\text{OCONHR}^{20}\text{R}^{23}$  and  $\text{OCON}(\text{R}^{20})_2$ ;

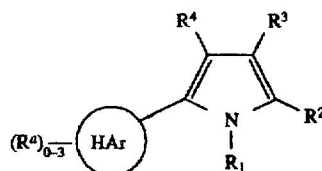
$\text{R}^{22}$  is selected from the group consisting of:  $\text{C}_{1-15}$  alkyl,  $\text{C}_{3-15}$  alkenyl,  $\text{C}_{3-15}$  alkynyl, heterocyclyl, aryl and heteroaryl, said alkyl, alkenyl, and alkynyl being optionally substituted with 1-3 halo, aryl or heteroaryl groups;

$\text{R}^{23}$  is  $\text{R}^{21}$  or H;

$\text{R}^{24}$  is selected from aryl,  $\text{COR}^{22}$ ,  $\text{CO}_2\text{R}^{22}$ ,  $\text{CON}(\text{R}^{20})_2$  and  $\text{SO}_2\text{R}^{22}$ ; and

when two  $\text{R}^{20}$  groups are present,  $\text{R}^{20}$  and  $\text{R}^{21}$  are present, or  $\text{R}^{20}$  and  $\text{R}^{23}$  are present, said two  $\text{R}^{20}$  groups,  $\text{R}^{20}$  and  $\text{R}^{21}$  or said  $\text{R}^{20}$  and  $\text{R}^{23}$  may be taken in combination with the atoms to which they are attached and any intervening atoms and represent heterocyclyl containing from 5-10 atoms, at least one atom of which is a heteroatom selected from O, S or N, said heterocyclyl optionally containing 1-3 additional N atoms and 0-1 additional O or S atom.

2. A compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:



represents pyridyl which is unsubstituted or substituted with 1-3  $\text{R}^a$  groups;

each  $\text{R}^a$  independently represents a member selected from the group consisting of: halo, aryl( $\text{R}^b$ ) $_{0-2}$ , heteroaryl

- (21) Application No. 19781/72 (22) Filed 28 April 1972  
 (31) Convention Application No. 6967/71 (32) Filed 11 May 1971  
 (31) Convention Application No. 4250/72 (32) Filed 22 March 1972 in  
 (33) Switzerland (CH)  
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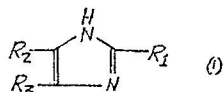
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#### (54) IMIDAZOLE DERIVATIVES AND PROCESSES FOR THEIR PRODUCTION

(71) We, CIBA-GEIGY AG, a body corporate organised according to the laws of Switzerland, of CH-4002 Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to imidazole derivatives which possess valuable pharmacological properties, processes for their manufacture, pharmaceutical preparations which contain the new imidazoles, and their use.

The invention provides imidazole derivatives of the general formula



wherein R<sub>1</sub> represents a lower alkyl group, a cycloalkyl group, or a phenyl which is optionally substituted by one or more halogen atoms, lower alkyl and lower alkoxy groups, and one of the groups R<sub>2</sub> and R<sub>3</sub> represents a phenyl group which is optionally substituted by one or more substituents selected from halogen atoms lower alkyl, hydroxy, lower alkoxy, lower alkylthio and lower alkylsulphonyl groups, and the other represents a 6-membered heteroaromatic radical containing 1 or 2 ring nitrogen atoms, and N - oxides thereof and salts of such compounds.

The compounds of the present invention possess valuable pharmacological properties, in particular anti-inflammatory, antinociceptive and antipyretic action with favourable therapeutic index.

The antiphlogistic action of the imidazole

derivatives of the invention when administered orally is shown, for example, in the Bolus alba oedema test on rats according to G. Wilhelmi, Jap. J. Pharmacol. 15, 187 (1965).

The analgesic action of the imidazole derivatives of the invention is demonstrated, for example, in mice according to the method described by E. Siegmund, R. Cadmus and G. Lu, Proc. Soc. Exp. Biol. Med. 95, 729 (1957). In this method, the amount of substance is determined which is necessary to prevent the syndrome caused by the intraperitoneal injection of 2 - phenyl - 1,4 - benzoquinone.

To determine the antipyretic action, a compound of the invention is administered perorally in suitable doses to rats which had been injected intramuscularly 16—18 hours previously with a suspension of 15% baker's yeast with 1% tragacanth and 1% sodium chloride in distilled water in an amount of 1 ml per 100 g body weight. The feverish temperatures induced by the yeast are taken rectally one hour and half an hour before the test substance is administered, and half-hourly at an interval of half an hour to 5 hours after the administration of the test substance. The maximum drop in temperature as well as the arithmetic average temperature fall during the 5 hours after the administration of the test substance are determined as basis of comparison contrasted with the average of the two measurements taken before the administration.

The imidazole derivatives of the invention are suitable as active substances which may be administered orally, rectally or parentally for the alleviation and relief of pains of varying origin, as well as for the treatment of

ethyl ester and 19.0 g of nicotinic acid ethyl ester;

- 5 *p* - chlorobenzyl - (3 - pyridyl) - ketone (oil), starting from 25.0 g of *p* - chlorophenylacetic acid ethyl ester and 19.0 g of nicotinic acid ethyl ester; *p* - methoxybenzyl - (4 - pyridyl) - ketone, m.p. 130—132°C, starting from 25.2 g of *p* - methoxyphenylacetic acid ethyl ester and 18.9 g of nicotinic acid ethyl ester;

- 10 *m* - methoxybenzyl - (3 - pyridyl) - ketone, b.p. 160—165°C/0.05 Torr, starting from 25.2 g of *m* - methoxyphenylacetic acid ethyl ester and 19.0 g of nicotinic acid ethyl ester.

- 15 b) 1 - (*o* - chlorophenyl) - 2 - (3 - pyridyl) - glyoxal

- The mixture of 13.2 g (0.057 mol) of *o* - chlorobenzyl - (3 - pyridyl) - ketone, 6.65 g (0.06 mol) of selenium dioxide and 50 ml of glacial acetic acid is boiled under reflux and subsequently filtered hot. The filtrate is evaporated in vacuo, the residue taken up in ethyl acetate and the solution filtered through a column filled with 450 g of silica gel. The filtrate is evaporated to leave as residue yellow crystals which melt at 50—52°C and are used direct for further processing.

The following glyoxals are manufactured analogously:

- 30 1 - (*p* - chlorophenyl) - 2 - (3 - pyridyl) - glyoxal, m.p. 80—82°, starting from 13.2 g of chlorobenzyl - (3 - pyridyl) - ketone and 6.65 g of selenium dioxide;

- 35 1 - (*m* - chlorophenyl) - 2 - (3 - pyridyl) - glyoxal, m.p. 55—57°, starting from 13.2 g of *m* - chlorobenzyl - (3 - pyridyl) - ketone and 6.65 g of selenium dioxide.

- 40 1 - (*o* - tolyl) - 2 - (3 - pyridyl) - glyoxal, b.p. 150°/0.01 Torr, starting from 32.0 g of *o* - xylyl - (3 - pyridyl) - ketone and 24.0 g of selenium dioxide;

- 45 1 - (*m* - tolyl) - 2 - (3 - pyridyl) - glyoxal, b.p. 160°/0.05 Torr, starting from 28.0 g of *m* - xylyl - (3 - pyridyl) - ketone and 16.0 g of selenium dioxide;

- 50 1 - (*p* - tolyl) - 2 - (3 - pyridyl) - glyoxal, m.p. 38—40°, starting from 42.0 g of *p* - xylyl - (3 - pyridyl) - ketone and 24.0 g of selenium dioxide;

- 55 1 - (*m* - methoxyphenyl) - 2 - (3 - pyridyl) - glyoxal, m.p. 48—50°, starting from 4.9 g of *m* - methoxybenzyl - (3 - pyridyl) - ketone and 2.6 g of selenium dioxide;

- 1 - (*p* - methoxyphenyl) - 2 - (4 - pyridyl) - glyoxal, m.p. 64—65°, starting from 4.9 g of *p* - methoxybenzyl - (4 - pyridyl) - ketone and 2.5 g of selenium dioxide.

- c) 2 - tert. butyl - 4(5) - (*o* - chlorophenyl) - 5(4) - (3 - pyridyl) - imidazole

- 60 The mixture of 9.83 g (0.04 mol) of 1 - (*o* - chlorophenyl) - 2 - (3 - pyridyl) - glyoxal, 3.79 g (0.044 mol) of pivalaldehyde,

20 g of ammonium acetate and 100 ml of glacial acetic acid is boiled under reflux for 24 hours and then, while stirring vigorously, poured into a mixture of 350 g of ice and 250 ml of concentrated aqueous ammonia solution. The crystal broth is extracted with ethyl acetate and the organic phase washed until neutral with saturated sodium chloride solution, dried with sodium sulphate and evaporated. The residue is recrystallised from toluene and dried in a high vacuum at 120°C to yield 2 - tert. butyl - 4 - (5) - (*o* - chlorophenyl) - 5 - (4) - (3 - pyridyl) - imidazole (m.p. 205—206°C).

The following compounds are manufactured analogously:

- 2 - tert. butyl - 4(5) - (*p* - chlorophenyl) - 5(4) - (3 - pyridyl) - imidazole, m.p. 241—244°C, starting from 9.83 g of 1 - (*p* - chlorophenyl) - 2 - (3 - pyridyl) - glyoxal and 3.79 g of pivalaldehyde;

- 2 - tert. butyl - 4(5) - (*m* - chlorophenyl) - 5(4) - (3 - pyridyl) - imidazole, m.p. 170—174°C, starting from 9.83 g of 1 - (*m* - chlorophenyl) - 2 - (3 - pyridyl) - glyoxal and 3.78 g of pivalaldehyde;

- 2 - tert. butyl - 4(5) - (*o* - tolyl) - 5(4) - (3 - pyridyl) - imidazole, m.p. 215—217°C, starting from 9.0 g of 1 - (*o* - tolyl) - 2 - (3 - pyridyl) - glyoxal and 3.79 g of pivalaldehyde;

- 2 - tert. butyl - 4(5) - (*m* - tolyl) - 5(4) - (3 - pyridyl) - imidazole, m.p. 170—171°C, starting from 9.0 g of 1 - (*m* - tolyl) - 2 - (3 - pyridyl) - glyoxal and 3.79 g of pivalaldehyde;

- 2 - tert. butyl - 4(5) - (*p* - tolyl) - 5(4) - (3 - pyridyl) - imidazole, m.p. 228—229°C, starting from 9.0 g of 1 - (*p* - tolyl) - 2 - (3 - pyridyl) - glyoxal and 3.79 g of pivalaldehyde;

- 2 - (*p* - chlorophenyl) - 4(5) - (*m* - tolyl) - 5(4) - (3 - pyridyl) - imidazole, m.p. 182—183°C, starting from 10.1 g of 1 - (*m* - tolyl) - 2 - (3 - pyridyl) - glyoxal and 6.4 g of *p* - chlorobenzaldehyde;

- 2 - tert. butyl - 4(5) - (*m* - methoxyphenyl) - 5(4) - (3 - pyridyl) - imidazole, m.p. 151—152°C, starting from 10.0 g of 1 - (*m* - methoxyphenyl) - 2 - (3 - pyridyl) - glyoxal and 3.6 g of pivalaldehyde;

- 2 - tert. butyl - 4(5) - (*p* - methylthio - phenyl) - 5(4) - (3 - pyridyl) - imidazole m.p. 199—200°C, starting from 11.0 g of 1 - (*p* - methylthio - phenyl) - 2 - (3 - pyridyl) - glyoxal and 3.64 g of pivalaldehyde.

### Example 3

- 2 - tert. butyl - 4(5) - phenyl - 5(4) - (3 - pyridyl) - imidazole

The mixture of 14.0 g (0.0664 mol) of 1 - phenyl - 2 - (3 - pyridyl) - glyoxal, 5.76 g (0.067 mol) of pivalaldehyde, 42 g of ammonium acetate and 110 ml of glacial

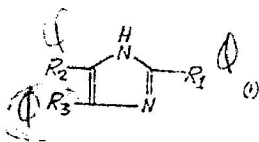
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acetate and 200 ml of glacial acetic acid is heated to the boil under reflux for 5 hours and then poured into a mixture of 300 ml of ice and 200 ml of concentrated aqueous ammonia solution. The suspension is extracted with ethyl acetate. The ethyl acetate solution is then washed with saturated sodium chloride solution, dried over sodium sulphate and evaporated under 11 Torr. The residue is chromatographed on 200 g of silica gel. The fractions 5 and 6, each eluted with 250 ml of ethyl acetate, contain the 2-tert. butyl 4(5) - (p - methylsulphonyl-phenyl) - 5(4) - (3 - pyridyl) - imidazole, which melts at 120-125°C (from toluene).

# WHAT WE CLAIM IS:—

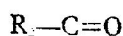
1. A process for the manufacture of an imidazole derivative of the general formula I

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in which  $R_1$  represents a lower alkyl group, a cycloalkyl group, or a phenyl group which is optionally substituted by one or more halogen atoms, lower alkyl and lower alkoxy groups, and one of the groups  $R_2$  and  $R_3$  represents a phenyl group which is optionally substituted by one or more substituents selected from halogen atoms, lower alkyl, hydroxy, lower alkoxy, lower alkylthio and lower alkylsulphonyl group, and the other represents a 6-membered heteroaromatic radical containing 1 or 2 ring nitrogen atoms, and of N-oxides thereof and salts of such compounds, wherein

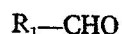
35 a) a substituted diketone of the general formula



(II)

a corresponding mono-oxime or N-oxide, is reacted with ammonia and an aldehyde of the general formula

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(III),

or

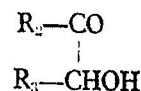
b) an amide of the general formula



(V)

45 is treated with ammonia, or

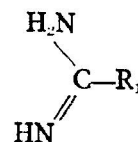
c) a reactive ester of an  $\alpha$ -hydroxy-ketone of the general formula



(IIa)

is reacted with an amidine of the general formula

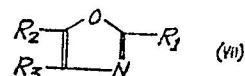
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(VI)

or with a salt thereof, or

d) an oxazole of the general formula



(VII)

is reacted with ammonia, and, if desired, a resulting compound is converted into an N-oxide or a resulting N-oxide is converted into the free compound, and/or, if desired, a resulting compound is converted into a salt or a resulting salt is converted into the free compound.

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2. A process for the manufacture of an imidazole derivative of the general formula I as defined in claim 1, in which  $R_1$  is a lower or cycloalkyl group, or a phenyl radical which is optionally monosubstituted by a fluorine, chlorine or bromine atom or a methyl, ethyl, methoxy or ethoxy group one of the groups  $R_2$  and  $R_3$  is a phenyl radical which is optionally monosubstituted by a chlorine atom or a methyl, hydroxy, methoxy, ethoxy, methylthio, ethylthio, methylsulphonyl or ethylsulphonyl group and the other is pyridyl or pyrazinyl, and acid addition salts of these compounds, wherein

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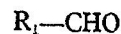
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a) a substituted diketone of the general formula II according to claim 1, in which  $R_2$  and  $R_3$  have the meanings given hereinabove, is treated with ammonia and an aldehyde of the general formula

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(III)

in which  $R_1$  has the meaning given hereinabove, or

b) an amide of the general formula V according to claim 1, in which  $R_1$ ,  $R_2$  and  $R_3$  have the meanings given hereinabove, is treated with ammonia, or

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c) a reactive ester of an  $\alpha$ -hydroxy-ketone of the general formula IIa according to claim 1, in which  $R_2$  and  $R_3$  have the meanings given hereinabove, is reacted with an amidine of the general formula VI according to claim

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# SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RADICACIÓN: 0-26001

EDICTO No. 10356

## LA SECRETARÍA GENERAL AD-HOC HACE SABER:

Que esta Superintendencia profirió Resolución No. 18464 de 29-JUL-2005. Que el contenido de la parte resolutive es como sigue: El Superintendente de Industria y Comercio.

### RESUELVE

**ARTICULO PRIMERO:** Negar el privilegio de patente de invención para la solicitud correspondiente a "TRIARILIMIDAZOLES".

**ARTICULO SEGUNDO:** Notificar personalmente el contenido de la presente resolución al doctor Germán Castillo Grau, o a quien haga sus veces, en su calidad de apoderado de

Smithkline Beecham Corporation., entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

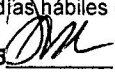
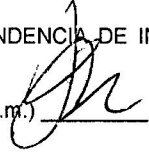
### NOTIFÍQUESE Y CUMPLASE

Dada en Bogotá, D.C., a los 29 JUL. 2005

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,

  
JAIRO RUBIO ESCOBAR

Para notificar a los interesados, se fija el presente EDICTO en lugar visible al público en la SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, por el término de (10) diez días hábiles contados a partir de las 8:30 a.m. de hoy.

Secretaría General Ad-Hoc 24-AGO-2005  Este edicto se desfija hoy 06-SEP-2005 a las cinco (5:00 p.m.) 

Secretaría General Ad-Hoc

EDICTO No. 10356