

No. 11-003597-00005-0000

Fecha: 2011-12-16 11:17:05 Dep. 2020 DIR.NUEVASCR  
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII  
Act. 400 OPOSIOBSERVTER Folios: 33

Act. 400 OPOSIOBSERVTER Folios: 32

**FORMULARIO ÚNICO DE OPOSICIÓN**

①

**OPOSICIÓN A:**

- |                                                                        |                                                  |
|------------------------------------------------------------------------|--------------------------------------------------|
| <input checked="" type="checkbox"/> Patente de Invención.              | <input type="checkbox"/> Marca Colectiva.        |
| <input type="checkbox"/> Patente de Modelo de Utilidad.                | <input type="checkbox"/> Marca de Certificación. |
| <input type="checkbox"/> Diseño Industrial.                            | <input type="checkbox"/> Lema Comercial.         |
| <input type="checkbox"/> Esquema de Trazado para Circuitos Integrados. |                                                  |
| <input type="checkbox"/> Marcas de Productos o Servicios.              |                                                  |

②

**SOLICITUD  
PUBLICADA**

Número del expediente: 11-003.597

Solicitante: ABBOTT HEALTHCARE PRODUCTS B.V.

Apoderado: MARGARITA CASTELLANOS ABONDANO

Título de la nueva creación o denominación del signo: "FORMULACIÓN  
FARMACÉUTICA DE EPROSARTAN"

Gaceta: 633

③ **OPOSICIÓN PRESENTADA POR:**

**SOLICITANTE**

Nombre: **LABORATORIOS SYNTHESIS  
S.A.S.**

Dirección: **Carrera 44 N° 20 C 73**

Nacionalidad o Domicilio: **COLOMBIA**  
Lugar de Constitución: **BOGOTA**

Teléfono: **3692222** Fax: **3693542**  
E-mail:

**IDENTIFICACIÓN**

C.C. ☐ NIT ☒

C.E. ☐ Otro ☐

Cual

Número 860.000.760-1

**REPRESENTANTE  
O APODERADO**

Nombre: **ELIANA ISAURA MORENO  
BOHORQUEZ**

Dirección: **CARRERA 104 N°119-95 OF 104**

Teléfono: **2131213** Fax: **6121979**  
E-mail: **negocios@optimum-co.com**

**IDENTIFICACIÓN**

C.C. ☒ NIT ☐

C.E. ☐ Otro ☐

Cual

Número 51.975.664 TP 83823

④ **FUNDAMENTOS DE LA OPOSICIÓN:**

Art.14, 16, 18, 20 y 30 de la Decisión 486 de la CAN

Causal: No cumple con los requisitos de patentabilidad.

Signo opositor: \_\_\_\_\_

Justificación: \_\_\_\_\_

La presente solicitud no cumple con los requisitos de patentabilidad dado que lo  
revelado, ya se encontraba en el estado de la técnica o es posible derivarlo de la  
misma tal y como se demostrará en el capítulo "Fundamento de Hechos".

⑤ Comprobante de pago No. \_\_\_\_\_

Fecha \_\_\_\_\_

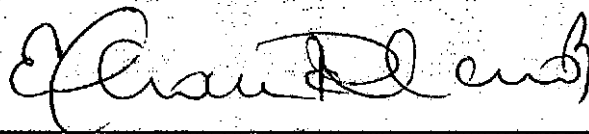
⑥ ANEXOS

- ☒ Comprobante de pago de la tasa.
- ☒ Poderes, si fuere el caso.
- ☒ Pruebas de los fundamentos de la oposición.
- ☐ Documentos que acrediten el legítimo interés, si fuere el caso.
- ☒ Documento que acredite la existencia y representación legal de las partes, cuando sean personas jurídicas.

⑦

NOMBRE: ELIANA ISAURA MORENO BOHORQUEZ

FIRMA: \_\_\_\_\_



C.C. 51'975.664

TP. 83823

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO  
NIT : 800.176.089-2  
- / -



RECIBO DE CAJA

No. 11 - 107715

Bogotá D.C., Noviembre 02 de 2011 - 15:51:23

RECIBIDO DE : LABORATORIOS SYNTHESIS S.A.S.

NI 860.000.760

\*\*\* Soporte del Pago \*\*\*

| TIPO PAGO    | BANCO           | CUENTA    | No. PAGO  | FECHA PAGO | VR. PAGO     |
|--------------|-----------------|-----------|-----------|------------|--------------|
| CONSIGNACION | BANCO DE BOGOTA | 062754387 | 430324134 | 01/11/2011 | 3.040.000.00 |

\*\*\* Conceptos Pagados \*\*\*

| CANT. | RENTISTICO                                              | CONCEPTO                      | Vr. UNDITARIO | Vr. CONCEPTO |
|-------|---------------------------------------------------------|-------------------------------|---------------|--------------|
| 1     | 50005-01-04 PRESENTACION DE OBSERVACIONES A SOLICITUDES | 12 MARCAS Y LEMAS COMERCIALES | 304.000.00    | 304.000.00   |
|       |                                                         |                               |               | \$304.000.00 |

SON: \*\*TRESCIENTOS CUATRO MIL PESOS MONEDA CORRIENTE\*\*

Responsable: \_\_\_\_\_

Recibo de Caja Aplicado al Expediente No. \_\_\_\_\_

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 11-003597- -00005-0000

Fecha: 2011-12-16 11:17:05

Dep. 2020 DIR.NUEVASCR

Tra. 11 PATENTEIYII

Eve: 379 FASENACIONALII

Act. 400 OPOSIOBSERVTER

Folios: 33

Act. 400 OPOSIOBSERVTER Folios: 32

Sede Centro: Carrera 13 No. 27 - 00 Pisos 3,4,5 y 10 Bogotá, D.C.- Colombia

Web: [www.sic.gov.co](http://www.sic.gov.co) e-mail: [info@sic.gov.co](mailto:info@sic.gov.co) Conmutador: (571) 5870000 Fax: (571) 5870284 Línea: 018000-910165 Call Center: (571) 6513240

Noviembre 2 de 2011 - 15:51:24

Señor Director,  
DIRECCIÓN DE NUEVAS CREACIONES  
Superintendencia de Industria y Comercio  
E. S. D.

Referencia : Expediente N° 11 03597  
Asunto : Oposición a la solicitud de patente de Invención titulada  
"FORMULACION FARMACEUTICA DE EPROSARTAN."  
Solicitante : ABBOTT HEALTHCARE PRODUCTS B.V  
Opositora : LABORATORIOS SYNTHESIS S.A.S.

Publicada en la Gaceta de la Propiedad Industrial  
N° 633 del 20 de Octubre de 2011

Yo, **ELIANA ISaura MORENO BOHORQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad **LABORATORIOS SYNTHESIS S.A.S.** conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Bogotá, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada "**FORMULACION FARMACEUTICA DE EPROSARTAN**", cuyo titular es **ABBOTT HEALTHCARE PRODUCTS B.V.**, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

### 1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en

particular EPROSARTAN. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

## 2. FUNDAMENTOS DE HECHOS

2.1. La solicitud objeto de la presente fue presentada el 14 de enero de 2011, reivindicando prioridad bajo la solicitud US20080080067 del 2008-07-11; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 633 del 20 de Octubre de 2011, cuya publicación internacional corresponde a la WO2010003996 del 2010-01-14.

2.2. La solicitud colombiana 11 03597 objeto de la presente oposición, se refiere a una formulación farmacéutica que comprende eprosartan ácido, en la forma de una formulación de liberación inmediata.

2.3. Ahora bien, con base en el artículo 14 de la Decisión 486 de la CAN consagra lo siguiente: *“Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial”*. Así las cosas, las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afecta la patentabilidad de la presente solicitud:

- D1: EP0955294 publicada el 10 de noviembre de 1999.

2.4. Así entonces, el documento D1 de forma particular en la página dos, párrafo 1, en la página 8 y el ejemplo 94, se refiere a antagonistas de los receptores de angiotensina II que son útiles en la regulación de la hipertensión y el tratamiento de la insuficiencia cardíaca congestiva, insuficiencia renal y glaucoma, a composiciones farmacéuticas que incluyen los antagonistas, y los métodos de uso de estos compuestos para producir antagonismo del receptor de angiotensina II en mamíferos.

2.5. Por lo tanto, este documento objeto de oposición a la luz del documento D1 carece evidentemente de ALTURA INVENTIVA.

2.6. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 11 03597 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con uno de los tres requisitos necesarios para su protección.

2.7. Que por consiguiente, respecto a la solicitud pretendida se tiene que:

2.8. CARENCIA DE ALTURA INVENTIVA. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *“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.”*. A la fecha de prioridad, 11 de julio de 2008, a partir del documento D1, un experto en la materia puede llegar de manera evidente a una formulación farmacéutica que comprende un antagonista de los receptores de la angiotensina II (ARA-II) como eprosartan, en la forma de una formulación de liberación inmediata, sobre lo cual busca protección en el capítulo reivindicatorio.

2.9. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *“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.”*. La solicitud pretendida no cumple con uno de los tres requisitos de patentabilidad.

2.10. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada **“FORMULACION FARMACEUTICA DE EPROSARTAN”**, cuyo titular es **ABBOTT HEALTHCARE PRODUCTS B.V.**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 633 del 20 de Octubre de 2011.

### 3. PRUEBAS

De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes:

- D1: EP0955294 publicada el 10 de noviembre de 1999.

### 4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

- 4.1. Numeral 1 del artículo 586 del Código de Comercio.
- 4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.
- 4.3. En las demás normas concordantes.

### 5. ANEXOS

Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

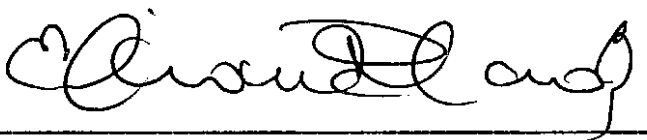
1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de **LABORATORIOS SYNTHESIS S.A.S.**
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:

- D1: EP0955294 publicada el 10 de noviembre de 1999.

**6. NOTIFICACIONES**

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 N° 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,



**ELIANA ISAURA MORENO BOHORQUEZ**

C.C. 51'975.664 de Bogotá

T.P.A. 83823 del C.S. de la J.

**PODER ESPECIAL**

Yo, , **ORLANDO MUÑOZ MARTINEZ**, mayor de edad y vecino de la ciudad de Bogotá (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **LABORATORIOS SYNTHESIS S.A.S.** sociedad legalmente constituida y domiciliada en la ciudad de Bogotá (Colombia), por el presente documento otorgo a la doctora **ELIANA ISAURA MORENO BOHÓRQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del C.S. de la J., poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. 11 003.597, titulada **"FORMULACIÓN FARMACÉUTICA DE EPROSARTAN"**, cuyo titular **ABBOTT HEALTHCARE PRODUCTS B.V.** publicada en la gaceta No. 633 del 20 de octubre de 2011.

Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de la oposición, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados. Asimismo quedan autorizados para impugnar administrativa todo lo que fuere resuelto en el expediente a que se hace expresa referencia en el presente poder, con todas las facultades generales y específicas que fuera requerido para ella.

De la misma manera, además de las facultades que le confiere la naturaleza del presente mandato, se encuentran facultados para recibir, desistir, transigir, sustituir, y reasumir el presente poder, incoar acciones, interponer recursos y demás facultades conferidas por la ley.

Dado y Firmado en Bogotá (Colombia) a los 07 días del mes de diciembre de 2011.

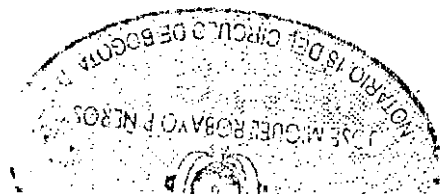
**LABORATORIOS SYNTHESIS S.A.S.**



Cédula de ciudadanía No. 8.317.044 de Medellín

NIT: 860.000.760-1

**Representante Legal**



DECLARACION DE RECONOCIMIENTO

Compareció ante el Notario 18 del Circulo de Buenos Aires

Don Orlando Munoz Martinez

quien es

Expediente N° 8317044 y

declara que

aparece en el presente documento

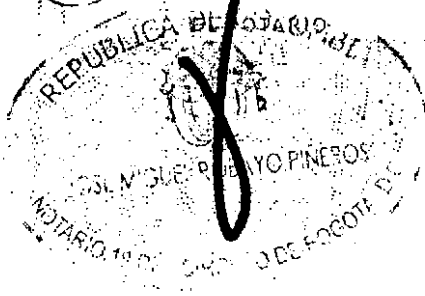
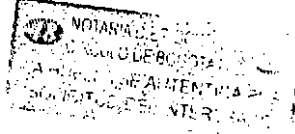
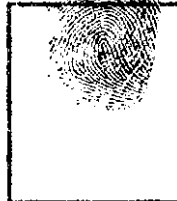
con su nombre y que el contenido del mismo

es cierto.

07 DIC 2011

NOTARIO

*[Handwritten signature]*





\*01\*



\* 1 1 3 4 8 8 6 0 4 \*

10

CAMARA DE COMERCIO DE BOGOTA

SEDE NORTE

12 DE DICIEMBRE DE 2011 HORA 10:22:07

R033271429

PAGINA: 1 de 5

\* \* \* \* \*

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O INSCRIPCION DE DOCUMENTOS

LA CAMARA DE COMERCIO DE BOGOTA, CON FUNDAMENTO EN LAS MATRICULAS E INSCRIPCIONES DEL REGISTRO MERCANTIL

CERTIFICA:

NOMBRE : LABORATORIOS SYNTHESIS S A S

N.I.T. : 860000760-1

DOMICILIO : BOGOTA D.C.

CERTIFICA:

MATRICULA NO: 00008059 DEL 23 DE MARZO DE 1972

CERTIFICA:

DIRECCION DE NOTIFICACION JUDICIAL : CRA 44 NO 20C 73

MUNICIPIO : BOGOTA D.C.

EMAIL DE NOTIFICACION JUDICIAL : synthe@synthesis.com.co

DIRECCION COMERCIAL : CRA 44 NO 20C 73

MUNICIPIO : BOGOTA D.C.

EMAIL COMERCIAL : synthe@synthesis.com.co

CERTIFICA:

CONSTITUCION: ESCRITURA PUBLICA NO.2078, NOTARIA 8 BOGOTA, DEL 27 DE JULIO DE 1.950, INSCRITA EL 10 DE AGOSTO DE 1.950, BAJO EL NO. 21.766 DEL LIBRO RESPECTIVO ACLARADA POR ESCRITURA NO. 3608 DEL 8 DE OCTUBRE DE 1.956 NOTARIA 8 DE BOGOTA INSCRITA EN ESTA - CAMARA DE COMERCIO EL 19 DE OCTUBRE DE 1.956 BAJO EL NO. 35.547 DEL LIBRO RESPECTIVO, SE CONSTITUYO LA SOCIEDAD DENOMINADA: "LABORATORIOS BALBAG".

CERTIFICA:

QUE POR ESCRITURA PUBLICA NUMERO 3997 OTORGADA EN LA NOTARIA 8 DE BOGOTA EL 24 DE NOVIEMBRE DE 1.952, INSCRITA EN ESTA CAMARA DE COMERCIO EL 1 DE DICIEMBRE DE 1.952, BAJO EL NUMERO 26.158 DEL LIBRO RESPECTIVO, LA SOCIEDAD CAMBIO SU NOMBRE DE: "LABORATORIOS --- BALBAG" POR EL DE "LABORATORIO SYNTHESIS" E INTRODUJO OTRAS REFORMAS.

CERTIFICA :

QUE POR ESCRITURA PUBLICA NUMERO 6491 OTORGADA EN LA NOTARIA 1. - DE BOGOTA EL 24 DE DICIEMBRE DE 1.981, INSCRITA EN ESTA CAMARA DE COMERCIO EL 12 DE MARZO DE 1.982, BAJO EL NUMERO 113.297 DEL LIBRO IX, LA SOCIEDAD CAMBIO SU NOMBRE DE "LABORATORIOS SYNTHESIS - BALAVOINE Y CIA. S.C.A" POR EL DE "LABORATORIOS SYNTHESIS LTDA. Y CIA. S.C.A" E INTRODUJO OTRAS REFORMAS.

CERTIFICA:

QUE POR ESCRITURA PUBLICA NUMERO 8580 OTORGADA EN LA NOTARIA 3 DE BOGOTA EL 4 DE DICIEMBRE DE 1.973, INSCRITA EN ESTA CAMARA DE COMERCIO EL 7 DE ENERO DE 1.974, BAJO EL NUMERO 14.478 DEL LIBRO IX, LA SOCIEDAD SE TRASFORMO DE LIMITADA EN COMANDITA POR ACCIONES BAJO EL NOMBRE DE LABORATORIOS SYNTHESIS BALAVOINE Y CIA. S.C.A.

**CERTIFICA:**

QUE POR ACTA NO. 117 DE LA ASAMBLEA DE ACCIONISTAS, DEL 30 DE ABRIL DE 2010, INSCRITA EL 10 DE JUNIO DE 2010 BAJO EL NÚMERO 1390261 DEL LIBRO IX, LA SOCIEDAD DE LA REFERENCIA SE TRANSFORMO DE SOCIEDAD EN COMANDITA POR ACCIONES A SOCIEDAD POR ACCIONES SIMPLIFICADA BAJO EL NOMBRE DE: LABORATORIOS SYNTHESIS S.A.S.

**CERTIFICA:**

QUE POR E.P. NO.5.435 DEL 17 DE SEPTIEMBRE DE 1.996, NOTARIA PRIMERA DE SANTAFE DE BOGOTA, INSCRITA EL 30 DE SEPTIEMBRE DE 1.996, BAJO EL NO.556.909 DEL LIBRO IX, ADICIONADA POR LOS REGISTROS 557 146 DEL 1 DE OCTUBRE DE 1.996, Y 557.301 DEL 2 DE OCTUBRE DE 1996 DEL LIBRO IX, LA SOCIEDAD DE LA REFERENCIA COMUNICO QUE SE FUSIONO, ABSORBIENDO A LA SOCIEDAD "SYNTHESIS VETERINARIA LTDA Y CIA S C A"

**CERTIFICA:**

QUE POR E.P. NO.1024 DEL 28 DE FEBRERO DE 1997, DE LA NOTARIA 1. DE SANTAFE DE BOGOTA, INSCRITA EL 31 DE MARZO DE 1997, BAJO EL NUMERO 579245 DEL LIBRO IX, CELEBRO ACUERDO DE FUSIÓN CON LA SOCIEDAD PRODUCTOS DIETÉTICAS DIETESYN S.A, DONDE LA SOCIEDAD DE LA REFERENCIA FUE LA ABSORBENTE.

**CERTIFICA:**

QUE POR ACTA NO. 120 DE LA ASAMBLEA DE ACCIONISTAS DEL 29 DE JULIO DE 2010, INSCRITA EL 19 DE NOVIEMBRE DE 2010 BAJO EL NUMERO 01429837 DEL LIBRO IX, LA SOCIEDAD DE LA REFERENCIA (ABSORBENTE) ABSORBE MEDIANTE FUSIÓN A LAS SOCIEDADES INMUNOSYN SAS Y GYNOPHARM SAS LAS CUALES SE DISUELVEN SIN LIQUIDARSE.

**CERTIFICA:**

**REFORMAS:**

| ESCRITURAS NO. | FECHA        | NOTARIA      | INSCRIPCION              |
|----------------|--------------|--------------|--------------------------|
| 4471           | 18-XII-1.956 | 8 BTA.       | 22-XII-1.956 NO. 36.077  |
| 3322           | 31-XII-1.958 | 8 BTA.       | 12-I-1.959 NO. 42.034    |
| 2322           | 22-IX-1.961  | 8 BTA.       | 29-IX-1.961 NO. 51.161   |
| 290            | 2-II-1.967   | 6 BTA.       | 24-II-1.967 NO. 71.304   |
| 8545           | 16-XII-1.967 | 6 BTA.       | 26-I-1.968 NO. 75.041    |
| 4679           | 20-XII-1.967 | 8 BTA.       | 26-I-1.968 NO. 75.042    |
| 3010           | 14-V-1.968   | 6 BTA.       | 30-V-1.968 NO. 76.244    |
| 2931           | 4-V-1.970    | 6 BTA.       | 18-V-1.970 NO. 84.983    |
| 5656           | 13-VII-1.970 | 6 BTA.       | 13-VIII-1.970 NO. 86.126 |
| 3487           | 15-VII-1.971 | 3 BTA.       | 29-VII-1.971 NO. 90.980  |
| 4638           | 10-VII-1.984 | 11 BTA.      | 27-VIII-1.984 NO.157.001 |
| 1443           | 14-III-1.985 | 11 BTA.      | 26- III-1.985 NO.167.627 |
| 724            | 11- II-1.985 | 1 BTA.       | 21- II-1.985 NO.165.940  |
| 4836           | 11-VIII-1986 | 1 BTA.       | 23- IX -1.986 NO.197.784 |
| 5659           | 15- IX -1986 | 1 BTA.       | 23- IX -1.986 NO.197.784 |
| 6326           | 16- X -1987  | 1 BTA.       | 23- X -1.987 NO.221.604  |
| 5164           | 21-VIII-1990 | 1 BTA.       | 3- IX -1.990 NO.303.579  |
| 9244           | 23-XII- 1991 | 1 STAFE.BTA. | 8-I -1.992 NO.351.255    |
| 8145           | 15- X - 1992 | 1 STAFE.BTA. | 16- X-1.992 NO.382.488   |
| 1374           | 26- III-1993 | 1 STAFE.BTA. | 19- III-1993 NO.399972   |
| 3120           | 01-VI-1.995  | 1A.STAFE BTA | 23-VI- 1.995 NO.498.060  |
| 5435           | 17-IX-1.996  | 1A.STAFE BTA | 30-IX- 1.996 NO.556.909  |
| 5435           | 17-IX-1.996  | 1A.STAFE BTA | 01- X- 1.996 NO.557.146  |
| 5435           | 17-IX-1.996  | 1A.STAFE BTA | 02- X- 1.996 NO.557.301  |
| 5942           | 7-X -1.996   | 1A.STAFE BTA | 11- X- 1.996 NO.558.222  |
| 6305           | 24-X--1.996  | 1A.STAFE BTA | 07-XI--1.996 NO.561.207  |
| 6929           | 25-XI-1.996  | 1A.STAFE BTA | 12-XII-1.996 NO.565.961  |
| 787            | 19-II-1.997  | 1A.STAFE BTA | 25-II -1.997 NO.575.141  |



\*01\*

CAMARA DE COMERCIO DE BOGOTA

SEDE NORTE

12 DE DICIEMBRE DE 2011 HORA 10:22:07

R033271429

PAGINA: 2 de 5

\* \* \* \* \*

1024

28-II-1.997 1A.STAFE BTA 31-III-1.997 NO.579.245

CERTIFICA:

REFORMAS:

| E.P. NO. | FECHA      | NOTARIA | CIUDAD      | FECHA      | NO. INSC. |
|----------|------------|---------|-------------|------------|-----------|
| 0007110  | 1997/10/28 | 0001    | BOGOTA D.C. | 1997/11/06 | 00609204  |
| 0001896  | 1998/03/16 | 0001    | BOGOTA D.C. | 1998/04/01 | 00628368  |
| 0002924  | 1998/04/21 | 0001    | BOGOTA D.C. | 1998/05/18 | 00634309  |
| 0002377  | 2000/06/14 | 0001    | BOGOTA D.C. | 2000/06/20 | 00733626  |
| 0000SIN  | 2004/06/22 | 0000    | BOGOTA D.C. | 2004/06/28 | 00940785  |
| 117      | 2010/04/30 | 0000    | BOGOTA D.C. | 2010/06/10 | 01390261  |
| 120      | 2010/08/18 | 0000    | BOGOTA D.C. | 2010/08/26 | 01409241  |
| 120      | 2010/08/30 | 0000    | BOGOTA D.C. | 2010/09/13 | 01413659  |
| 120      | 2010/07/29 | 0000    | BOGOTA D.C. | 2010/11/19 | 01429837  |
| 139      | 2011/06/07 | 0000    | BOGOTA D.C. | 2011/06/20 | 01489422  |
| 146      | 2011/10/24 | 0000    | BOGOTA D.C. | 2011/11/30 | 01531828  |

CERTIFICA:

VIGENCIA: QUE LA SOCIEDAD NO SE HALLA DISUELTA. DURACION HASTA EL 27 DE JULIO DE 2040

CERTIFICA:

OBJETO SOCIAL: EL OBJETO DE LA SOCIEDAD ES EL EJERCICIO DE TODAS LAS ACTIVIDADES COMERCIALES PARA: 1) LA IMPORTACIÓN, EXPORTACIÓN, FABRICACIÓN, COMERCIALIZACIÓN, DISTRIBUCIÓN Y VENTA DE PRODUCTOS FARMACÉUTICOS, HIGIÉNICOS, VETERINARIOS E IMPLEMENTOS MÉDICOS. 2) CUALQUIER OTRA ACTIVIDAD LÍCITA DE COMERCIO RELACIONADA CON SU OBJETO SOCIAL PRINCIPAL Y TODO LO QUE SE RELACIONA CON LA IMPORTACIÓN DE LOS BIENES Y EQUIPOS NECESARIOS PARA EL DESARROLLO DE SU OBJETO SOCIAL. 3) TENER LA REPRESENTACIÓN EN COLOMBIA DE EMPRESAS O SOCIEDADES ESTABLECIDAS FUERA DEL TERRITORIO COLOMBIANO, CUYO OBJETO SEA SIMILAR O COMPLEMENTARIO. EN DESARROLLO DE SU OBJETO SOCIAL PRINCIPAL, LA SOCIEDAD PODRÁ ADELANSTAR Y CELEBRAR LOS SIGUIENTES ACTOS Y CONTRATOS: A) EXPORTAR E IMPORTAR, AGENCIAR, DISTRIBUIR, COMERCIALIZAR, COMPRAR O VENDER A COMISIÓN O CONSIGNACIÓN O DE CUALQUIER OTRA FORMA O MODALIDAD, TODA CLASE DE EQUIPOS, APARATOS, BIENES AL POR MAYOR O AL DETAL, Y SERVICIOS RELACIONADOS CON SU ACTIVIDAD. B) GRAVAR EN CUALQUIER FORMA LOS BIENES DE SU PROPIEDAD MUEBLES O INMUEBLES, DAR EN PRENDA LOS PRIMEROS O HIPOTECAR LOS SEGUNDOS PARA GARANTIZAR OBLIGACIONES DE LA SOCIEDAD. C) CONSTITUIR APODERADOS QUE LE REPRESENTEN, ASOCIARSE CON OTRAS COMPAÑÍAS DE LA MISMA O PARECIDA NATURALEZA Y EN GENERAL REALIZAR TODA CLASE DE OPERACIONES COMERCIALES O CIVILES Y EJECUTAR O CELEBRAR TODA CLASE DE CONTRATOS O ACTOS DEL MISMO ORDEN, YA SEAN INDUSTRIALES, COMERCIALES O FINANCIEROS ENCAMINADOS A ALCANZAR LOS FINES QUE SE PROPONEN. D) ADQUIRIR, ENAJENAR, ADMINISTRAR, RECIBIR O DAR EN ARRENDATARIO O A CUALQUIER TÍTULO, TODA CLASE DE BIENES MUEBLES E INMUEBLES. E) INTERVENIR ANTE TERCEROS O ANTE LOS ACCIONISTAS MISMOS COMO ACREEDORA O COMO DEUDORA

EN TODA CLASE DE OPERACIONES DE CRÉDITO, DANDO O RECIBIENDO LAS GARANTÍAS DEL CASO, CUANDO HAYA LUGAR A ELLAS; F) EFECTUAR CUALQUIER CLASE DE OPERACIONES DE CRÉDITO ACTIVO O PASIVO, TALES COMO CONSTITUIR DEPÓSITOS, EFECTUAR PRESTAMOS. OTORGAR O RECIBIR DOCUMENTOS NEGOCIABLES, GIRAR, ACEPTAR, ENDOSAR, ASEGURAR Y NEGOCIAR EN GENERAL TÍTULOS VALORES RECIBIRLOS EN PAGO; G) CELEBRAR Y EJECUTAR EN GENERAL TODOS LOS ACTOS Y CONTRATOS PREPARATORIOS, COMPLEMENTARIOS O ACCESORIOS DE TODOS LOS ANTERIORES, LOS QUE SE RELACIONEN CON LA EXISTENCIA Y FUNCIONAMIENTO DE LA SOCIEDAD, Y LOS QUE SEAN CONDUCTENTES AL BUEN LOGRO DE LOS FINES SOCIALES.

CERTIFICA:

CAPITAL:

\*\* CAPITAL AUTORIZADO \*\*

VALOR : \$22,000,000,000.00  
NO. DE ACCIONES : 22,000,000.00  
VALOR NOMINAL : \$1,000.00

\*\* CAPITAL SUSCRITO \*\*

VALOR : \$20,362,200,000.00  
NO. DE ACCIONES : 20,362,200.00  
VALOR NOMINAL : \$1,000.00

\*\* CAPITAL PAGADO \*\*

VALOR : \$20,362,200,000.00  
NO. DE ACCIONES : 20,362,200.00  
VALOR NOMINAL : \$1,000.00

CERTIFICA:

REPRESENTACION LEGAL: LA SOCIEDAD CONTARÁ CON UN GERENTE, QUIEN TENDRÁ DOS SUPLENTE DENOMINADOS SUBGERENTES, QUIENES LO REEMPLAZARÁN EN LAS FALTAS OCASIONALES, TEMPORALES O ABSOLUTAS DE AQUÉL.

CERTIFICA:

\*\* NOMBRAMIENTOS \*\*

QUE POR ACTA NO. 127 DE ASAMBLEA DE ACCIONISTAS DEL 12 DE NOVIEMBRE DE 2010, INSCRITA EL 23 DE NOVIEMBRE DE 2010 BAJO EL NUMERO 01430759 DEL LIBRO IX, FUE (RON) NOMBRADO (S):

NOMBRE

IDENTIFICACION

GERENTE

PALACIOS LUIS ALBERTO

C.E. 000000000319788

QUE POR ACTA NO. 117 DE ASAMBLEA DE ACCIONISTAS DEL 30 DE ABRIL DE 2010, INSCRITA EL 10 DE JUNIO DE 2010 BAJO EL NUMERO 01390261 DEL LIBRO IX, FUE (RON) NOMBRADO (S):

NOMBRE

IDENTIFICACION

SUBGERENTE

MUÑOZ MARTINEZ ORLANDO

C.C. 000000008317044

QUE POR ACTA NO. 139 DE ASAMBLEA DE ACCIONISTAS DEL 7 DE JUNIO DE 2011, INSCRITA EL 20 DE JUNIO DE 2011 BAJO EL NUMERO 01489425 DEL LIBRO IX, FUE (RON) NOMBRADO (S):

NOMBRE

IDENTIFICACION

SUBGERENTE

PICART LAURENZ FRANCISCO JAVIER

C.E. 00000000E399661

CERTIFICA:

FACULTADES DEL REPRESENTANTE LEGAL: EL GERENTE DE LA SOCIEDAD TIENE A SU CARGO LA ADMINISTRACIÓN INMEDIATA DE LA SOCIEDAD, ASÍ COMO LA REPRESENTACIÓN LEGAL DE LA MISMA Y EN TAL VIRTUD LE ESTÁN ASIGNADAS LAS SIGUIENTES FUNCIONES Y ATRIBUCIONES: A) LLEVAR LA REPRESENTACIÓN DE LA ENTIDAD, TANTO JUDICIAL COMO EXTRAJUDICIALMENTE. B) EJECUTAR LOS



\* \* \* \* \*

ACUERDOS Y DECISIONES DE LA ASAMBLEA GENERAL DE ACCIONISTAS. C) CONSTITUIR, PARA CASOS ESPECIALES, APODERADOS JUDICIALES O EXTRAJUDICIALES. D) CELEBRAR LOS ACTOS, OPERACIONES Y CONTRATOS CONDUCTANTES AL BUEN LOGRO DEL OBJETO DE LA SOCIEDAD. E) CUIDAR DE LA RECAUDACIÓN E INVERSIÓN DE LOS FONDOS DE LA SOCIEDAD. F) PRESENTAR A LA REUNIÓN ORDINARIA ANUAL DE LA ASAMBLEA GENERAL DE ACCIONISTAS, EL INVENTARIO Y LOS ESTADOS FINANCIEROS DE PROPÓSITO GENERAL DE FIN DE EJERCICIO, JUNTO CON UN INFORME ESCRITO RELACIONADO CON LA SITUACIÓN Y LA MARCHA DE LA ENTIDAD. G) CREAR LOS EMPLEADOS NECESARIOS PARA LA DEBIDA MARCHA DE LA SOCIEDAD, SEÑALAR SUS FUNCIONES Y ASIGNACIONES Y HACER LOS NOMBRAMIENTOS CORRESPONDIENTES. H) CONVOCAR A LA ASAMBLEA GENERAL CUANDO PROCEDA HACERLO CONFORME A LA LEY O A ESTOS ESTATUTOS. I) PRESENTAR A LA ASAMBLEA GENERAL DE ACCIONISTAS, CUANDO ASÍ LO SOLICITE, ESTADOS FINANCIEROS MENSUALES DE PRUEBA E INFORMES. J) EJERCER LAS FUNCIONES QUE LE DELEGUE LA ASAMBLEA GENERAL DE ACCIONISTAS. K) CUMPLIR Y HACER QUE SE CUMPLAN EN OPORTUNIDAD Y DEBIDAMENTE TODAS LAS EXIGENCIAS DE LAS LEYES EN RELACIÓN CON EL FUNCIONAMIENTO Y LAS ACTIVIDADES DE LA INSTITUCIÓN. L) LAS DEMÁS QUE LE CORRESPONDAN CONFORME A LA LEY Y A ESTOS ESTATUTOS. EL GERENTE DE LA SOCIEDAD DEBERÁ CONTAR CON AUTORIZACIÓN PREVIA DE LA ASAMBLEA GENERAL DE ACCIONISTAS, CUANDO PRETENDA SUSCRIBIR EN NOMBRE DE LA SOCIEDAD (I) ACTOS O CONTRATOS PARA ADQUIRIR, ENAJENAR, RECIBIR O DAR EN ARRENDAMIENTO O A CUALQUIER OTRO TÍTULO, TODA CLASE DE BIENES INMUEBLES DE LA SOCIEDAD O BIENES MUEBLES DIFERENTES A LOS PRODUCTOS COMERCIALIZADOS ORDINARIAMENTE POR LA SOCIEDAD, ASÍ COMO (II) ACTOS O CONTRATOS, INDEPENDIENTE DE SU OBJETO, QUE SUPERE EN CUANTÍA EL EQUIVALENTE A 300 SMLMV (TRESCIENTOS SALARIOS MÍNIMOS MENSUALES LEGALES VIGENTES).

CERTIFICA:

QUE POR ESCRITURA PUBLICA NO. 3511 DE LA NOTARIA 18 DE BOGOTA D.C., DEL 8 DE SEPTIEMBRE DE 2010, INSCRITA EL 1 DE OCTUBRE DE 2010 BAJO EL NO. 00018604 DEL LIBRO V, COMPARECIO JOSE ANTONIO JAIME ESCOBAR IDENTIFICADO CON CEDULA DE CIUDADANÍA NO. 19.262.407 DE BOGOTA, EN SU CALIDAD DE GERENTE DE LABORATORIOS SYNTHESIS LTDA., POR MEDIO DE LA PRESENTE ESCRITURA PUBLICA, CONFIERE PODER GENERAL AL A OLGA VICTORIA PRIETO ZAMORA, IDENTIFICADA CON CEDULA DE CIUDADANÍA NO. 52.780.303 DE BOGOTA PARA QUE EN NOMBRE DE LA SOCIEDAD LABORATORIOS SYNTHESIS S.A.S., PROMUEVA Y DEFIENDA LOS INTERESES DE LA SOCIEDAD JUDICIAL Y EXTRAJUDICIALMENTE, EN TODA ESPECIE DE GESTIONES Y ACTUACIONES ANTE LAS AUTORIDADES ADMINISTRATIVAS O JURISDICCIONALES Y EN ESPECIAL PARA: A. DILIGENCIAR Y SUSCRIBIR LOS DOCUMENTOS NECESARIOS PARA EL REGISTRO DE INVERSIONES EXTRANJERAS ANTE LAS AUTORIDADES COLOMBIANAS. B. TRANSIGIR, DESISTIR Y APELAR A DECISIONES DE ÁRBITROS O DE AMIGABLES COMPONEDORES EN LAS CUESTIONES EN QUE TENGA INTERÉS FRENTE A TERCEROS, A LOS ASOCIADOS MISMOS O A SUS ADMINISTRADORES. C.

~~ADELANTAR CUALQUIER TIPO DE TRÁMITE ANTE EL INSTITUTO DE VIGILANCIA DE~~  
MEDICAMENTOS Y ALIMENTOS INVIMA O A LA ENTIDAD QUE HAGA SUS VECES. D.  
RECIBIR NOTIFICACIÓN DE TODAS LAS PROVIDENCIAS QUE SE EXPIDAN DENTRO  
DE LOS DIFERENTES TRÁMITES E INTERPONER LOS RECURSOS PROPIOS DE LA VÍA  
GUBERNATIVA. E. REPRESENTAR Y VIGILAR ANTE LOS FUNCIONARIOS, OFICINAS  
Y DEPENDENCIAS DEL INSTITUTO DE VIGILANCIA DE MEDICAMENTOS Y ALIMENTOS  
INVIMA O A LA ENTIDAD QUE HAGA SUS VECES, TODAS LAS SOLICITUDES QUE  
CONTENGAN TRÁMITES A NOMBRE DE LABORATORIOS SYNTHESIS S.A.S. F.  
SOLICITAR, OBTENER, REVISAR Y MODIFICAR REGISTROS SANITARIOS. G.  
OBTENER ANTE LAS OFICINAS Y AUTORIDADES NACIONALES QUE CORRESPONDAN Y  
EN ESPECIAL DE LA DIVISIÓN DE PROPIEDAD INDUSTRIAL DE LA  
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, REGISTROS DE MARCAS,  
RENOVACIÓN DE REGISTROS MARCARIOS, ANOTACIÓN DE TRASPASOS Y CAMBIO DE  
NOMBRE, PRESENTACIÓN Y TRÁMITE DE OPOSICIONES, PRESENTACIÓN Y TRÁMITE  
DE RECURSOS POR LA VÍA GUBERNATIVA Y DEMÁS DILIGENCIAS RELACIONADAS, A  
CUYO EFECTO LA FACULTA PARA DAR ANTE DICHAS AUTORIDADES, PARA ELEVAR  
SOLICITUDES, FORMULAR DESCRIPCIONES, APELACIONES Y RECLAMOS, SOLICITAR  
TESTIMONIO, RECIBIR, DESISTIR, SUSTITUIR, CANCELAR, TRANSIGIR,  
RENUNCIAR, ACEPTAR NOTIFICACIONES Y NOMBRAR APODERADOS JUDICIALES Y  
EXTRAJUDICIALES. H. ADQUIRIR MARCAS, PATENTES, PROCEDIMIENTOS DE  
FABRICACIÓN, EXPLOTADAS EN CUALQUIER FORMA, YA SEA UTILIZÁNDOLOS  
DIRECTAMENTE O PERMITIENDO SU EXPLOTACIÓN POR OTRAS PERSONAS NATURALES  
O JURÍDICAS CONTRA EL PAGO DE REGALÍAS O PARTICIPACIONES. I. CELEBRAR  
Y EJECUTAR EN GENERAL TODOS LOS ACTOS Y CONTRATOS PREPARATORIOS,  
COMPLEMENTARIOS O ACCESORIOS DE TODOS LOS ANTERIORES, LOS QUE SE  
RELACIONEN CON LA EXISTENCIA Y FUNCIONAMIENTO DE LA SOCIEDAD, Y LOS  
QUE SEAN CONDUCENTES AL BUEN LOGRO DE LOS FINES SOCIALES. J. RECIBIR  
NOTIFICACIONES DE CUALESQUIERA TIPO DE ACTOS EMANADOS DE LAS  
AUTORIDADES ADMINISTRATIVAS O JUDICIALES. K. PRESENTAR RECURSOS POR LA  
VÍA ADMINISTRATIVA O JUDICIAL, RENUNCIAR A TÉRMINOS, DESISTIR,  
CONCILIAR, TRANSIGIR Y MODIFICAR. L. ELEVAR PETICIONES Y SOLICITAR  
INFORMACIÓN A LAS AUTORIDADES ADMINISTRATIVAS Y JURISDICCIONALES. M.  
PRESENTAR DEMANDAS ANTE LAS AUTORIDADES ADMINISTRATIVAS Y JUDICIALES.  
N. SUSTITUIR EL PRESENTE PODER Y REVOCAR TAL SUSTITUCIÓN DENTRO DE LA  
REPÚBLICA DE COLOMBIA.

CERTIFICA:

\*\* REVISOR FISCAL \*\*

QUE POR CERTIFICACION DE REVISOR FISCAL DEL 4 DE OCTUBRE DE 2011,  
INSCRITA EL 10 DE OCTUBRE DE 2011 BAJO EL NUMERO 01519171 DEL LIBRO  
IX, FUE (RON) NOMBRADO (S):

| NOMBRE                      | IDENTIFICACION       |
|-----------------------------|----------------------|
| REVISOR FISCAL PRINCIPAL    |                      |
| ARCILA SABOGAL DIANA YAMILE | C.C. 000000052828052 |

QUE POR DOCUMENTO PRIVADO DE REVISOR FISCAL DEL 28 DE JUNIO DE 2010,  
INSCRITA EL 8 DE JULIO DE 2010 BAJO EL NUMERO 01397034 DEL LIBRO IX,  
FUE (RON) NOMBRADO (S):

| NOMBRE                      | IDENTIFICACION       |
|-----------------------------|----------------------|
| REVISOR FISCAL SUPLENTE     |                      |
| PRADA SANCHEZ NUBIA MARCELA | C.C. 000001032358923 |

QUE POR ACTA NO. 119 DE ASAMBLEA DE ACCIONISTAS DEL 22 DE JUNIO DE  
2010, INSCRITA EL 8 DE JULIO DE 2010 BAJO EL NUMERO 01397026 DEL LIBRO  
IX, FUE (RON) NOMBRADO (S):

| NOMBRE                          | IDENTIFICACION         |
|---------------------------------|------------------------|
| REVISOR FISCAL PERSONA JURIDICA |                        |
| DELOITTE & TOUCHE LTDA          | N.I.T. 000008600058134 |

CERTIFICA:



\* \* \* \* \*

RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011

ULTIMO AÑO RENOVADO : 2011

\*\*\*\*\*  
NOMBRE : MASCOTT

MATRICULA NO : 00664622 DE 18 DE SEPTIEMBRE DE 1995

RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011

ULTIMO AÑO RENOVADO : 2011  
\*\*\*\*\*

NOMBRE : ONCOPHARM

MATRICULA NO : 00625764 DE 13 DE DICIEMBRE DE 1994

RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011

ULTIMO AÑO RENOVADO : 2011  
\*\*\*\*\*

NOMBRE : GASTROPHARM

MATRICULA NO : 00621442 DE 2 DE NOVIEMBRE DE 1994

RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011

ULTIMO AÑO RENOVADO : 2011  
\*\*\*\*\*

NOMBRE : GYNECOPHARM

MATRICULA NO : 00621245 DE 1 DE NOVIEMBRE DE 1994

RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011

ULTIMO AÑO RENOVADO : 2011  
\*\*\*\*\*

NOMBRE : ENTEROPHARM

MATRICULA NO : 00621244 DE 1 DE NOVIEMBRE DE 1994

RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011

ULTIMO AÑO RENOVADO : 2011  
\*\*\*\*\*

NOMBRE : EQUIPHARMA

MATRICULA NO : 00556630 DE 21 DE JULIO DE 1993

RENOVACION DE LA MATRICULA : EL 14 DE MARZO DE 2011

ULTIMO AÑO RENOVADO : 2011  
\*\*\*\*\*

CERTIFICA:

DE CONFORMIDAD CON LO ESTABLECIDO POR LA LEY 962 DE 2005, LOS ACTOS DE REGISTRO AQUI CERTIFICADOS QUEDAN EN FIRME CINCO (5) DIAS HABILES DESPUES DE LA FECHA DE INSCRIPCION, SIEMPRE QUE NO SEAN OBJETO DE RECURSOS EN LA VIA GUBERNATIVA.

\* \* \* EL PRESENTE CERTIFICADO NO CONSTITUYE PERMISO DE \* \* \*  
\* \* \* FUNCIONAMIENTO EN NINGUN CASO \* \* \*

SEÑOR EMPRESARIO, SI SU EMPRESA TIENE ACTIVOS INFERIORES A 30.000 SMLMV Y UNA PLANTA DE PERSONAL DE MENOS DE 200 TRABAJADORES, USTED TIENE DERECHO A RECIBIR UN DESCUENTO EN EL PAGO DE LOS PARAFISCALES DE 75% EN EL PRIMER AÑO DE CONSTITUCION DE SU EMPRESA, DE 50% EN EL SEGUNDO AÑO Y DE 25% EN EL TERCER AÑO. LEY 590 DE 2000 Y DECRETO 525 DE 2009.

RECUERDE INGRESAR A [www.supersociedades.gov.co](http://www.supersociedades.gov.co) PARA VERIFICAR SI SU EMPRESA ESTA OBLIGADA A REMITIR ESTADOS FINANCIEROS. EVITE SANCIONES.

EL SECRETARIO DE LA CAMARA DE COMERCIO,

\*\*\*\*\*  
\*\*\*\*\*  
\*\*\*\*\*  
\*\*\*\*\*



**\*01\***

CAMARA DE COMERCIO DE BOGOTA

VALOR : \$ 3,700

Wanda

# ANEXO

(12)

EUROPEAN PATENT APPLICATION

(43) Date of publication:  
10.11.1999 Bulletin 1999/45

(21) Application number: 99115614.2

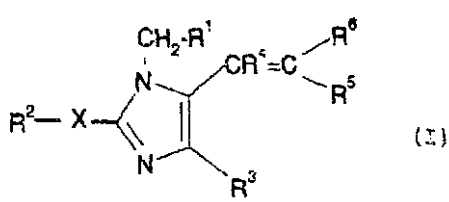
(22) Date of filing: 07.06.1990

(51) Int. Cl.<sup>6</sup>: C07D 233/58, C07D 233/70,  
C07D 233/82, C07D 401/12,  
C07D 403/12, C07D 405/12,  
C07D 409/12, A61K 31/415

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <div>(84) Designated Contracting States:<br/>AT BE CH DE DK ES FR GB GR IT LI LU NL SE</div> <div>(30) Priority: 14.06.1989 US 366079<br/>06.04.1990 US 506412</div> <div>(62) Document number(s) of the earlier application(s) in<br/>accordance with Art. 76 EPC:<br/>90306204.0 / 0 403 159</div> <div>(71) Applicant:<br/>SMITHKLINE BEECHAM CORPORATION<br/>Philadelphia Pennsylvania 19101 (US)</div> <div>(72) Inventors:<br/>• Finkelstein, Joseph Alan<br/>Philadelphia, PA 19151 (US)</div> | <div>• Keenan, Richard McCulloch<br/>Malvern, pA 19355 (US).</div> <div>• Weinstein, Joseph<br/>Phoenixville, PA 19460 (US)</div> <div>(74) Representative:<br/>Blakey, Alison Jane et al<br/>Smithkline Beecham,<br/>Corporate Intellectual Property,<br/>Two New Horizons Court<br/>Brentford, Middlesex, TW8 9EP (GB)</div> <div>Remarks:<br/>This application was filed on 06 - 08 - 1999 as a<br/>divisional application to the application mentioned<br/>under INID code 62.</div> |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

(54) Imidazolyl-alkenoic acid

(57) Angiotensin II receptor antagonists having the  
formula (I):



which are useful in regulating hypertension and in the treatment of congestive heart failure, renal failure, and glaucoma, pharmaceutical compositions including these antagonists, and methods of using these compounds to produce angiotensin II receptor antagonism in mammals.

EP 0 955 294 A2

## Description

[0001] The present invention relates to new imidazolyl-alkenoic acids which are angiotensin II receptor antagonists and are useful in regulating hypertension induced or exacerbated by angiotensin II, and in the treatment of congestive heart failure, renal failure, and glaucoma. This invention also relates to pharmaceutical compositions containing these compounds and methods for using these compounds as antagonists of angiotensin II, as antihypertensive agents and as agents for treating congestive heart failure, renal failure, and glaucoma.

## BACKGROUND OF THE INVENTION

[0002] The class of peptide pressor hormone known as angiotensin is responsible for a vasopressor action that is implicated in the etiology of hypertension in man. Inappropriate activity of the renin-angiotensin systems appears to be a key element in essential hypertension, congestive heart failure and in some forms of renal disease. In addition to a direct action on arteries and arterioles, angiotensin II (All), being one of the most potent endogenous vasoconstrictors known, exerts stimulation on the release of aldosterone from the adrenal cortex. Therefore, the renin-angiotensin system, by virtue of its participation in the control of renal sodium handling, plays an important role in cardiovascular homeostasis.

[0003] Interruption of the renin-angiotensin system with converting enzyme inhibitors, such as captopril, has proved to be clinically useful in the treatment of hypertension and congestive heart failure (Abrams, W.B., et al., (1984), *Federation Proc.*, **43**, 1314). The most direct approach towards inhibition of the renin-angiotensin system would block the action of All at the receptor. Compelling evidence suggests that All also contributes to renal vasoconstriction and sodium retention that is characteristic of a number of disorders such as heart failure, cirrhosis and complications of pregnancy (Hollenberg, N.K., (1984), *J. Cardiovas. Pharmacol.*, **6**, S176). In addition, recent animal studies suggest that inhibition of the renin-angiotensin system may be beneficial in halting or slowing the progression of chronic renal failure (Anderson, S., et al., (1985), *J. Clin. Invest.*, **76**, 612). Also, a recent patent application (South African Patent Application No. 87/01,653) claims that All antagonists are useful as agents for reducing and controlling elevated intraocular pressure, especially glaucoma, in mammals.

[0004] The compounds of this invention inhibit, block and antagonize the action of the hormone All, and are therefore useful in regulating and moderating angiotensin induced hypertension, congestive heart failure, renal failure and other disorders attributed to the actions of All. When compounds of this invention are administered to mammals, the elevated blood pressure due to All is reduced and other manifestations based on All intercession are minimized and controlled. Compounds of this invention are also expected to exhibit diuretic activity.

[0005] Recognition of the importance of blocking and inhibiting the actions of All has stimulated other efforts to synthesize antagonists of All. The following references have disclosed imidazole derivatives which are described as having All blocking activity and useful as hypotensive agents.

[0006] Furukawa et al, U.S. Patent 4,340,598 discloses imidazol-5-yl acetic acids and imidazol-5-yl-propanoic acids. Specifically, the discloser includes 1-benzyl-2-n-butyl-5-chloroimidazole-4-acetic acid and 1-benzyl-2-phenyl-5-chloroimidazole-4-propanoic acid.

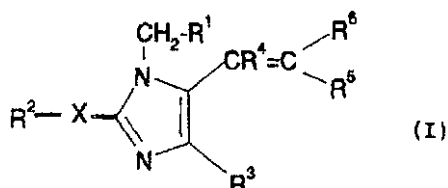
[0007] Furukawa, et al., U.S. Patent 4,355,040 discloses substituted imidazole-5-acetic acid derivatives. A compound specifically disclosed is 1-(2-chlorobenzyl)-2-n-butyl-4-chloroimidazole-5-acetic acid.

[0008] Carini et al. in EP 253,310 disclose certain imidazolylpropenoic acids. Two intermediates described in this patent are ethyl 3-[1-(4-nitrobenzyl)-2-butyl-4-chloroimidazol-5-yl]propenoate and ethyl 3-[2-butyl-4-chloro-1-(4-aminobenzyl)imidazol-5-yl]propenoate.

[0009] Also, Wareing, in PCT/EP 86/00297, discloses as intermediates certain imidazolylpropenoate compounds. On page 62, Formula (CX) is ethyl 3-[1-(4-fluorophenyl)-4-isopropyl-2-phenyl-1H-imidazol-5-yl]-2-propenoate.

## DESCRIPTION OF THE INVENTION

[0010] The present invention relates to blockers of angiotensin II receptors represented by the following Formula (I):



10 in which:

$R^1$  is phenyl, biphenyl, naphthyl, or adamantylmethyl, which are unsubstituted or substituted by one to three substituents selected from Cl, Br, F, I,  $C_1$ - $C_4$ alkyl, nitro,  $CO_2R^7$ , tetrazol-5-yl,  $C_1$ - $C_4$ alkoxy, hydroxy,  $SC_1$ - $C_4$ alkyl,  $SO_2NHR^7$ ,  $NHSO_2R^7$ ,  $SO_3H$ ,  $CONR^7R^7$ , CN,  $SO_2C_1$ - $C_4$ alkyl, or  $C_nF_{2n+1}$ , wherein n is 1-3;

$R^2$  is  $C_2$ - $C_{10}$ alkyl,  $C_3$ - $C_{10}$ alkenyl,  $C_3$ - $C_{10}$ alkynyl,  $C_3$ - $C_6$ cycloalkyl, or  $(CH_2)_0$ -phenyl unsubstituted or substituted by one to three substituents selected from  $C_1$ - $C_4$ alkyl nitro, Cl, Br, F, I, hydroxy,  $C_1$ - $C_4$ alkoxy,  $NR^7R^7$ ,  $CO_2R^7$ , CN, or  $CONR^7R^7$ ;

X is a single bond, S, or O;

$R^3$  is hydrogen, Cl, Br, F, I, CHO, hydroxymethyl,  $COOR^7$ ,  $CONR^7R^7$ ,  $NO_2$ , or  $C_nF_{2n+1}$ , wherein n is 1-3;

$R^4$  and  $R^5$  are independently hydrogen,  $C_1$ - $C_6$ alkyl, thienyl-Y, furyl-Y, pyrazolyl-Y, imidazolyl-Y, pyrrolyl-Y, triazolyl-Y, oxazolyl-Y, isoxazolyl-Y, thiazolyl-Y, pyridyl-Y, or tetrazolyl-Y, except that  $R^4$  and  $R^5$  are not both selected from hydrogen and  $C_1$ - $C_6$ alkyl and each heterocyclic ring is unsubstituted or substituted by  $C_1$ - $C_4$ alkyl,  $C_1$ - $C_4$ alkoxy, Cl, Br, F, I,  $NR^7R^7$ ,  $CO_2R^7$ ,  $SO_2NHR^7$ ,  $SO_3H$ , or  $CONR^7R^7$ ;

Y is a single bond, O, S, or  $C_1$ - $C_6$ alkylene which is straight or branched or optionally substituted by phenyl or benzyl, wherein each of the aryl groups is unsubstituted or substituted by halo,  $NO_2$ ,  $CF_3$ ,  $C_1$ - $C_4$ alkyl,  $C_1$ - $C_4$ alkoxy, CN, or  $CO_2R^7$ ;

$R^6$  is -Z- $COOR^8$  or -Z- $CONR^7R^7$ ;

Z is a single bond, vinyl,  $-CH_2-O-CH_2-$ , methylene optionally substituted by  $C_1$ - $C_4$ alkyl, one or two benzyl groups, thienylmethyl, or furylmethyl, or  $-C(O)NHCHR^9$ , wherein  $R^9$  is H,  $C_1$ - $C_6$ alkyl, phenyl, benzyl, thienylmethyl, or furylmethyl;

each  $R^7$  independently is hydrogen,  $C_1$ - $C_4$ alkyl, or  $(CH_2)_m$ phenyl, wherein m is 0-4; and

$R^8$  is hydrogen,  $C_1$ - $C_6$ alkyl, or 2-di( $C_1$ - $C_6$ alkyl)-amino-2-oxoethyl; or a pharmaceutically acceptable salt thereof.

[0011] Preferably, one of  $R^4$  and  $R^5$  is hydrogen or  $C_1$ - $C_6$ alkyl.

[0012] Preferred compounds of this invention are represented by Formula (I) when:

$R^1$  is phenyl unsubstituted or substituted by one to three substituents selected from chloro, fluoro, trifluoromethyl, nitro, methyl, methoxy, hydroxy, sulfamido, carboxy, carbo $C_1$ - $C_4$ alkoxy, carbamoyl, cyano, or tetrazol-5-yl;

X is a single bond;

$R^2$  is  $C_2$ - $C_6$ alkyl;

$R^3$  is hydrogen, chloro, fluoro, or trifluoromethyl;

$R^4$  is hydrogen or  $C_1$ - $C_6$ alkyl;

$R^5$  is thienylmethyl, furylmethyl, imidazolylmethyl, or pyridylmethyl, each of which is optionally substituted by methyl or methoxy; and

$R^6$  is  $COOH$ ,  $COOC_{1-2}$ alkyl, or  $CONH_2$ ; or a pharmaceutically acceptable salt thereof.

[0013] The E isomers (trans stereochemistry of the  $R^6$  group and imidazole group) are generally more active and thus, are preferred over the Z isomers (cis).

[0014] As used herein, the terms alkyl, alkenyl, alkoxy and alkynyl mean carbon chains which are branched or unbranched with the length of the chain determined by the descriptor preceding the term.

[0015] Particular compounds of the invention include, but are not limited to, the following:

(E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid,

(E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-furyl)methyl-2-propenoic acid,

(E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(4-pyridyl)methyl-2-propenoic acid,

(E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(3-thienyl)methyl-2-propenoic acid,

(E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(5-methyl-2-thienyl)methyl-2-propenoic acid,

(E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(4-imidazolyl)methyl-2-propenoic acid,  
 (E)-3-[2-n-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid,  
 (E)-3-[2-n-butyl-1-[(2-nitrophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid,  
 (E)-3-[2-n-butyl-1-[(2-cyanophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid,  
 5 (E)-3-[2-n-butyl-1-[(4-methoxy-3-methylphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid,  
 (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(5-methoxy-2-thienyl)methyl-2-propenoic acid,  
 (E)-3-[2-n-butyl-1-[(2,3-dichlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid,  
 (E)-3-[2-n-butyl-1-[(4-carboxy-2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid,  
 (E)-3-[2-n-butyl-1-[(4-carboxy-3-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid,  
 10 (E)-3-[2-n-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid,  
 (E)-3-[2-n-butyl-1-[(4-carbomethoxyphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid; and  
 (E)-3-[2-n-butyl-1-[(2-trifluoromethylphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid; or a  
 pharmaceutically acceptable salt thereof.

15 [0016] The invention also relates to pharmaceutical compositions comprising a pharmaceutical carrier and an effective amount of a compound of Formula (I).

[0017] Also included in the present invention are methods for antagonizing angiotensin II receptors which comprises administering to a subject in need thereof an effective amount of a compound of Formula (I). methods of producing anti-hypertensive activity and methods of treating congestive heart failure, glaucoma, and renal failure by administering  
 20 these compounds are also included in this invention.

[0018] The compounds of this invention are prepared by procedures described herein and illustrated by the examples. Reagents, protecting groups and functionality on the imidazole and other fragments of the molecule must be consistent with the proposed chemical transformations. Steps in the synthesis must be compatible with the functional groups and the protecting groups on the imidazole and other parts of the molecule.

25 [0019] The starting materials, 2-R<sup>2</sup>X-imidazole, are known to the art (*J. Org. Chem.* 45:4038, 1980) or are synthesized by known procedures. For example, imidazole is converted to 2-n-butylimidazole by reacting imidazole with triethylorthoformate and p-toluenesulfonic acid to give 1-diethoxyorthoamide imidazole and then treating with n-butyl lithium to give the 2-lithium derivative of the orthoamide and alkylating with n-butyl iodide in a suitable solvent, such as tetrahydrofuran (THF).

30 [0020] The following procedure is useful for the preparation of compounds of Formula (I) particularly where R<sup>1</sup> is 2-chlorophenyl, R<sup>2</sup> is n-butyl, R<sup>3</sup> is hydrogen, chloro, or CF<sub>3</sub>, R<sup>4</sup> is hydrogen, R<sup>5</sup> is as described in Formula (I), R<sup>6</sup> is COOR<sup>8</sup> and R<sup>8</sup> is hydrogen, methyl, or ethyl.

[0021] The 1-R<sup>1</sup>CH<sub>2</sub>-group is incorporated onto the 2-R<sup>2</sup>X-imidazole by known procedures, for example, by reaction with an R<sup>1</sup>-CH<sub>2</sub> halide, mesylate or acetate, such as 2-chlorobenzyl bromide, in a suitable solvent, such as dimethylformamide (DMF), in the presence of a suitable acid acceptor, such as sodium alkylate, potassium or sodium carbonate,  
 35 or a metal hydride, preferably sodium hydride at a reaction temperature of 25°C to 100°C, preferably 50°C. The resulting 1-R<sup>1</sup>CH<sub>2</sub>-2-R<sup>2</sup>X imidazole is hydroxymethylated in the 5-position, for example, by reacting with formaldehyde in the presence of sodium acetate in acetic acid to provide the 1-R<sup>1</sup>CH<sub>2</sub>-2-R<sup>2</sup>X-5-hydroxymethylimidazole intermediates.

[0022] Alternatively, the 1-R<sup>1</sup>CH<sub>2</sub>-2-R<sup>2</sup>X-5-hydroxymethylimidazole intermediates are prepared by reacting an imido ether, R<sup>2</sup>-C(=NH)-O-alkyl, such as valeramide methyl ether, with dihydroxyacetone in liquid ammonia under pressure to give 2-R<sup>2</sup>-5-hydroxymethylimidazole. This intermediate is reacted with acetic anhydride to give 1-acetyl-5-acetoxymethyl-2-R<sup>2</sup>-imidazole. The diacetate intermediate is N-alkylated, for example, using 2-chlorobenzyl triflate and the resulting 1-R<sup>1</sup>CH<sub>2</sub>-2-R<sup>2</sup>-5-acetoxymethylimidazole is treated with aqueous base, such as 10% sodium hydroxide solution, to give the 1-R<sup>1</sup>CH<sub>2</sub>-2-R<sup>2</sup>-5-hydroxymethylimidazole intermediate.

45 [0023] Alternatively, the 2-R<sup>1</sup>S-imidazole compounds are prepared by the following procedure. Benzylamines, substituted by one to three substituents selected from halo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, CN, NO<sub>2</sub>, CF<sub>3</sub>, CO<sub>2</sub>C<sub>1-6</sub>alkyl, SC<sub>1-4</sub>alkyl, or SO<sub>2</sub>C<sub>1-4</sub>alkyl, are alkylated with a C<sub>1-6</sub>alkyl chloroacetate, for example methyl chloroacetate, in the presence of a base, such as triethylamine, in a suitable solvent, such as dimethylformamide. The resulting alkylaminoalkyl ester compounds are N-formulated with formic acid in the presence of a suitable solvent, such as xylenes, followed by C-formulation of  
 50 the carbon alpha to both the amino and the ester groups. Reaction of this intermediate with acidic thiocyanate, preferably potassium thiocyanate, in an inert organic solvent, such as C<sub>1-4</sub>alkyl alcohol produces 1-RCH<sub>2</sub>-2-mercapto-5-alkanoate ester imidazole compounds. The free thio group of the ester imidazole is reacted with a halo-R<sup>10</sup> compound, wherein R<sup>10</sup> is C<sub>2-10</sub>alkyl, C<sub>3-10</sub>alkenyl, C<sub>3-10</sub>alkynyl, C<sub>3-6</sub>cycloalkyl or an optionally substituted (CH<sub>2</sub>)<sub>0-8</sub>Ph, preferably propyl bromide, in the presence of a suitable base, such as sodium carbonate, in an appropriate solvent, such as  
 55 ethyl acetate. The ester is reduced to the hydroxymethyl-imidazole intermediate by reduction with a suitable reagent, preferably diisobutyl aluminum hydride, in an appropriate solvent, such as tetrahydrofuran, at a temperature of -78°C to 25°C, preferably at less than -10°C.

[0024] The hydroxymethyl group of the hereinbefore prepared intermediate is oxidized to an aldehyde by treatment

with a suitable reagent, such as anhydrous chromic acid-silica gel in tetrahydrofuran or, preferably, with activated manganese dioxide, in a suitable solvent, such as benzene or toluene, or preferably methylene chloride, at a temperature of 25°C to 140°C, preferably at 25°C. The 1-R<sup>1</sup>CH<sub>2</sub>-2-R<sup>2</sup>X-imidazol-5-carboxaldehydes are reacted with an appropriate phosphonate, such as those listed in Table I (Examples 2-5). The phosphonates are prepared, for example, from trialkyl phosphonoacetates by alkylation with an appropriate halide, mesylate or acetate in the presence of a suitable base, such as sodium hydride, in a suitable solvent, preferably glyme at a reaction temperature of 25°C to 110°C, preferably at 55°C, to provide, for example, the phosphonates listed in Table I. The reaction of the imidazol-5-carboxaldehydes with the phosphonates is performed in the presence of a suitable base, such as a metal alkoxide, lithium hydride or preferably sodium hydride, in a suitable solvent, such as ethanol, methanol, ether, dioxane, tetrahydrofuran, or preferably glyme, at a reaction temperature of 10°C to 50°C, preferably at 25°C, to provide a variable mixture of trans and cis, e.g., (E) and (Z), 1-R<sup>1</sup>CH<sub>2</sub>-2-R<sup>2</sup>X-5-CH=C(R<sup>5</sup>)-(COO-alkyl)-imidazoles. These isomers are readily separated by chromatography over silica gel in suitable solvent systems, preferably hexane in ethyl acetate mixtures. The esters are hydrolyzed to the acids, 1-R<sup>1</sup>-CH<sub>2</sub>-2-R<sup>2</sup>X-5-CH=C(R<sup>5</sup>)COOH-imidazoles, using bases, such as potassium hydroxide, lithium hydroxide or sodium hydroxide, in a suitable solvent system, such as, for example, aqueous alcohols or diglyme. The trans and cis structures of the acids are readily determined by NMR by the NOE protocol, as well as by the biological activities since, generally, the trans (E) isomeric acids are the more potent isomers.

[0025] Alternatively, the 1-R<sup>1</sup>CH<sub>2</sub>-2-R<sup>2</sup>X-imidazol-5-carboxaldehydes are prepared by the following procedure. Starting 2-R<sup>2</sup>X-imidazol-4-carboxaldehydes are reacted with an N-alkylating protecting reagent, such as chloromethyl pivalate (POM-Cl), in the presence of a base, such as dimethylformamide, at a temperature of 20°C to 50°C, preferably at 25°C, to give N-alkylation (e.g., POM-derivation) on the least hindered nitrogen atom of the imidazole nucleus. The 1-R<sup>1</sup>CH<sub>2</sub>-group is incorporated onto the imidazole by N-alkylation of the above prepared aldehyde with a halomethylbenzene compounds, such as methyl 4-bromomethyl-3-chlorobenzoate, at a temperature of 80°C to 125°C, preferably at 100°C. The protecting group on the 3-nitrogen of the imidazole ring is removed by base hydrolysis, for example using a biphasic mixture of ethyl acetate and aqueous sodium carbonate, to give 1-R<sup>1</sup>CH<sub>2</sub>-2-R<sup>2</sup>X-imidazole-5-carboxaldehyde compounds. The Formula (I) compounds can be prepared from these 5-carboxaldehyde compounds by the methods described above.

[0026] Compounds of Formula (I), wherein R<sup>6</sup> is COOR<sup>6</sup>, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are as described in Formula (I), and R<sup>8</sup> is H, methyl or ethyl, are also prepared by the following procedure.

[0027] The 2-R<sup>2</sup>X-imidazole starting materials are reacted with trimethylsilylethoxymethyl (SEM) chloride to give 1-(trimethylsilyl)ethoxymethyl-2-R<sup>2</sup>-imidazole. The reaction is carried out, for example, in the presence of sodium hydride in a solvent such as dimethylformamide. The 5-tributyltin derivatives are prepared by lithiation with, for example, butyllithium in a suitable solvent, preferably diethyl ether, followed by treatment of the lithio imidazole derivative with a tributyltin halide, preferably tri-n-butyltin chloride, at -10°C to 35°C, preferably at 25°C. The 1-SEM-2-R<sup>2</sup>-5-tributyltinimidazole is coupled with an α,β-unsaturated acid ester having a leaving group on the β-position, such as a halide or trifluoromethanesulfonyloxy group, for example, BrCR<sup>4</sup>=C(R<sup>5</sup>)(COOalkyl), in the presence of a phosphine ligand, such as bis(diphenylphosphino)propane, or triphenylphosphine and a palladium (II) compound, or preferably tetrakis(triphenylphosphine)-palladium(0), with or without a base, such as tributylamine, at a temperature of 50°C to 150°C, preferably at 120°C. Both the (E) and (Z) olefinic isomers are prepared by this procedure, and the isomeric esters are readily separated by chromatography over silica gel. The 1-SEM group from the (E) and (Z) isomers is hydrolyzed with acid, for example, aqueous hydrochloric, in a suitable alcoholic solvent, such as methanol or ethanol, and the 1-unsubstituted imidazole derivatives are converted to the 1-t-butoxycarbonyl (t-BOC) imidazoles with di-t-butyl dicarbonate (Hoppe-Seyler's Z. Physiol. Chem., (1976), 357, 1651). The t-BOC esters are alkylated and hydrolyzed with, for example, 2-chlorobenzyl-O-triflate in the presence of a suitable base, preferably diisopropylethylamine, in a suitable solvent, preferably methylene chloride, to afford the 1-(2-chlorophenyl)methylimidazole derivatives (esters). The (E) and (Z) isomers are hydrolyzed to the (E) and (Z) acids by the method described above.

[0028] Compounds of Formula (I) are also prepared by the following procedure. The 1-R<sup>1</sup>CH<sub>2</sub>-2-R<sup>2</sup>X-imidazole-5-carboxaldehydes, prepared as described above, are reacted with a substituted half-acid, half-ester derivative of a malonate, such as ethyl 2-carboxy-3-(2-thienyl)propionate, in the presence of a base, such as piperidine, in a suitable solvent, such as toluene, at a temperature of 80°C to 110°C, preferably at 100°C. The resulting 1-R<sup>1</sup>CH<sub>2</sub>-2-R<sup>2</sup>X-5-CH=C(R<sup>5</sup>)COO alkylimidazoles are hydrolyzed to the corresponding Formula (I) acid compounds by alkaline hydrolysis as described above.

[0029] Compounds of Formula (I) in which R<sup>1</sup> is 2-chlorophenyl, R<sup>2</sup> is n-butyl, R<sup>3</sup> is H, Cl, or CF<sub>3</sub>, R<sup>4</sup> is methyl, R<sup>5</sup> is as described in Formula (I), R<sup>6</sup> is COOR<sup>6</sup> and other parameters are as described above are prepared as follows. The 1-R<sup>1</sup>CH<sub>2</sub>-2-R<sup>2</sup>X-imidazol-5-carboxaldehydes, prepared as described above, are converted to the corresponding alcohols with an organo-metallic derivative or Grignard reagent, preferably methyl lithium, in a suitable solvent, such as tetrahydrofuran. The alcohol is oxidized, for example, using manganese dioxide to give the ketone. The olefinic esters are prepared from the ketone by reaction with appropriate phosphonates to give the (E) and/or (Z) isomers which are readily separated. The acids are prepared from the esters by alkaline hydrolysis as described above.

[0030] Compounds of Formula (I) in which  $R^3$  is H, Cl,  $CH_2OH$ , or  $CF_3$  are prepared as follows. The 1- $R^1$ - $CH_2$ -2- $R^2X$ -imidazol-5-carboxaldehydes are treated with the lithium derivatives of a substituted ethyl or methyl ester. These lithio derivatives are prepared from the reaction of lithium diisopropylamide in a suitable solvent, preferably tetrahydrofuran, with an acid ester, such as  $ROOC-CH_2-Y-(2-thienyl)$ , to generate the  $\alpha$ -lithio derivatives at  $-78^\circ C$  to  $-10^\circ C$ , preferably at  $-78^\circ C$ , which are then treated with the imidazol-carboxaldehyde. The intermediate  $\beta$ -hydroxy group of the imidazol ester is converted to a mesylate or an acetate and the mesylate, or preferably the acetate, is heated in a suitable solvent, such as toluene, with one to two equivalents of 1,8-diazo-bicyclo[5.4.0]undec-7-ene, at 50 to  $110^\circ C$ , preferably at  $80^\circ C$ , to afford ester compounds of Formula (I) such as 3-(imidazol-5-yl)-2-(2-thienyl)methyl-2-propenoic acid esters. The (E) isomer is the predominate olefinic isomer. The acids are prepared from the esters by the method described above.

[0031] Compounds of Formula (I), wherein  $R^1$  is 2-chlorophenyl,  $R^2$  is n-butyl,  $R^3$  is H, Cl,  $CF_3$ , or  $CH_2OH$ ,  $R^4$  is H,  $R^5$  is heterocyclic or a substituted heterocyclic group as described in Formula (I) and  $R^6$  is  $COOH$ , may be prepared by heating 1- $R^1$ - $CH_2$ -2- $R^2X$ -imidazol-5-carboxaldehydes at  $50^\circ C$  to  $180^\circ C$ , preferably at  $140^\circ C$ , with an appropriate substituted heterocyclic acetic acid and with acetic anhydride and potassium carbonate to provide unsaturated acids of formula (I) such as 3-[2-n-butyl-1-(2-chlorophenyl)methyl-1H-imidazol-5-yl]-2- $R^5$ -2-propenoic acid. The trans olefinic acid is the principal product.

[0031] Compounds of Formula (I) in which  $R^5$  is  $Z-COOR^8$  where Z is an optionally substituted methylene group are prepared by reducing the trans or (E) isomers of 2-(imidazol-5-yl)-2-propenoic acid esters (prepared as described above) with an appropriate hydride reagent, preferably diisobutylaluminum hydride, in a suitable solvent, such as tetrahydrofuran, to provide the unsaturated alcohol compounds. These compounds are reacted with ethyl chloroformate, for example, with a base, preferably triethylamine, in a suitable solvent, such as tetrahydrofuran, to give 5-EtOOCOCH<sub>2</sub>CR<sup>5</sup>=CR<sup>4</sup>-imidazols which are reacted with carbon monoxide in the presence of a phosphine ligand, preferably triphenyl-phosphine with palladium (II) acetate, in a suitable solvent, preferably tetrahydrofuran, at a temperature of  $25^\circ C$  to  $100^\circ C$ , preferably at  $40^\circ C$ , to give the 5-EtOOCOCH<sub>2</sub>CR<sup>5</sup>=CR<sup>4</sup>-imidazols. The corresponding acids are prepared from these ethyl esters by base hydrolysis as described above.

[0032] Compounds of Formula (I) in which Z is  $-CH_2COOR^8$  having additional substitution on the carbon  $\alpha$  to the carboxylate group are prepared by converting 5-EtOOCOCH<sub>2</sub>CR<sup>5</sup>=CH<sup>4</sup>-imidazols to the lithium derivative of the ester with a lithium dialkylamide, preferably lithium diisopropylamide, and then treating with an alkylating agent, such as methyl halide, benzyl bromide, or heterocyclic methyl halide, to provide the mono-alkylated product compounds or the dialkylated product compounds. The acid compounds are prepared from the esters by base hydrolysis.

[0033] Compounds of Formula (I) in which  $R^5$  is  $Z-COOR^8$  where Z is  $-CH_2-O-CH_2-$  are prepared from unsaturated alcohol compounds, which had been obtained by the reduction of the Formula (I) propenoic acid esters. The alcohol is reacted with an appropriate hydride reagent, such as sodium hydride, in a suitable solvent, such as glyme, followed by reaction with an alkylating reagent, such as methyl bromoacetate, to give 5-MeOOCOCH<sub>2</sub>-O-CH<sub>2</sub>CR<sup>5</sup>=CR<sup>4</sup>-imidazols. The corresponding acids are prepared from these esters by base hydrolysis as described above.

[0034] Compounds of Formula (I) in which  $R^5$  is  $Z-COOR^8$  where Z is  $-C(O)NHCHR^9$  are prepared from the Formula (I) propenoic acid compounds. These acids are reacted with an appropriately substituted amino acid, such as glycine methyl ester hydrochloride or phenylalanine methyl ester hydrochloride, in the presence of an amide-forming reagent, such as N-hydroxysuccinimide and dicyclohexylcarbodiimide, in the presence of a base, for example triethylamine, in a suitable solvent, such as tetrahydrofuran, at a temperature of  $20^\circ C$  to  $50^\circ C$ , preferably at  $35^\circ C$ . The 5- $C_1$ -alkylOOCOCHR<sup>9</sup>NHC(O)-CH<sub>2</sub>CR<sup>5</sup>=CR<sup>4</sup>-imidazols are converted to their corresponding acids by base hydrolysis as described above.

[0035] Compounds of Formula (I) in which the  $R^1$  substituent is substituted by hydroxy are formed from Formula (I) compounds in which the  $R^1$  group is substituted by  $C_1$ - $C_4$ alkoxy using an ether-cleaving reagent, such as boron tribromide or hydrobromic acid.

[0036] Compounds of Formula (I) in which the  $R^1$  substituent is substituted by carboxy are formed from Formula (I) compounds in which the  $R^1$  group is substituted by  $CO_2C_1$ - $C_4$ alkyl using basic hydrolysis or ethanol, or using acidic hydrolysis, such as aqueous hydrochloric acid.

[0037] Compounds of Formula (I) in which the  $R^1$  substituent is substituted by a tetrazol-5-yl group are prepared from the corresponding carboxy compounds. For example, Formula (I) acid compounds are reacted with a halogenating agent, such as thionyl chloride, in a suitable solvent, for example benzene, to give the corresponding acid halide compounds. The acid halides are then converted to primary amide compounds in a reaction with concentrated ammonia. Subsequent dehydration of the amides with oxalyi chloride/dimethylformamide in acetonitrile/dimethylformamide yields the nitrile compounds, which are the immediate precursors to the Formula (I) tetrazole compounds. Tetrazole formation is accomplished by reacting the nitriles with azide, preferably aluminum azide prepared in situ by the reaction of sodium azide with aluminum chloride, in a suitable solvent, for example tetrahydrofuran. The Formula (I) compounds in which  $R^5$  is  $-Z-CO_2H$  are prepared from these Formula (I) tetrazole ester compounds by basic hydrolysis as described above.

[0038] Pharmaceutically acceptable acid addition salts of compounds of Formula (I) are formed with appropriate

organic or inorganic acids by methods known in the art. For example, the base is reacted with a suitable inorganic or organic acid in an aqueous miscible solvent such as ethanol with isolation of the salt by removing the solvent or in an aqueous immiscible solvent when the acid is soluble therein, such as ethyl ether or chloroform, with the desired salt separating directly or isolated by removing the solvent. Representative examples of suitable acids are maleic, fumaric, benzoic, ascorbic, pantoic, succinic, bismethylene-salicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, hydrochloric, hydrobromic, sulfuric, cyclohexyl-sulfamic, phosphoric and nitric acids.

[0039] Pharmaceutically acceptable base addition salts of compounds of Formula (I) in which R<sup>8</sup> is H are prepared by known methods from organic and inorganic bases, including nontoxic alkali metal and alkaline earth bases, for example, calcium, lithium, sodium, and potassium hydroxide; ammonium hydroxide, and nontoxic organic bases, such as triethylamine, butylamine, piperazine, and (tri-hydroxymethyl)-methylamine.

[0040] Angiotensin II antagonist activity of the compounds of Formula (I) is assessed by *in vitro* and *in vivo* methods. *In vitro* antagonist activity is determined by the ability of the compounds to compete with <sup>125</sup>I-angiotensin II for binding to vascular angiotensin II receptors and by their ability to antagonize the contractile response to angiotensin II in the isolated rabbit aorta. *In vivo* activity is evaluated by the efficacy of the compounds to inhibit the pressor response to exogenous angiotensin II in conscious rats and to lower blood pressure in a rat model of renin dependent hypertension.

#### Binding

[0041] The radioligand binding assay is a modification of a method previously described in detail (Gunther et al., *Circ. Res.* 47:278, 1980). A particular fraction from rat mesenteric arteries is incubated in Tris buffer with 80 pM of <sup>125</sup>I-angiotensin II with or without angiotensin II antagonists for 1 hour at 25°C. The incubation is terminated by rapid filtration and receptor bound <sup>125</sup>I-angiotensin II trapped on the filter is quantitated with a gamma counter. The potency of angiotensin II antagonists is expressed as the IC<sub>50</sub> which is the concentration of antagonist needed to displace 50% of the total specifically bound angiotensin II. Exemplary of the IC<sub>50</sub> of compounds of the invention (E isomers) is about 0.1 nM to about 100 μM.

#### Aorta

[0042] The ability of the compounds to antagonize angiotensin II induced vasoconstriction is examined in the rabbit aorta. Ring segments are cut from the rabbit thoracic aorta and suspended in organ baths containing physiological salt solution. The ring segments are mounted over metal supports and attached to force displacement transducers which are connected to a recorder. Cumulative concentration response curves to angiotensin II are performed in the absence of antagonist or following a 30-minute incubation with antagonist. Antagonist disassociation constants (K<sub>B</sub>) are calculated by the dose ratio method using the mean effective concentrations. Exemplary of the K<sub>B</sub> of compounds of the invention (E isomers) is about 0.1 nM to about 30 μM.

#### Inhibition of pressor response to angiotensin II in conscious rats

[0043] Rats are prepared with indwelling femoral arterial and venous catheters and a stomach tube (Gellai et al., *Kidney Int.* 15:419, 1979). Two to three days following surgery the rats are placed in a restrainer and blood pressure is continuously monitored from the arterial catheter with a pressure transducer and recorded on a polygraph. The change in mean arterial pressure in response to intravenous injections of 250 mg/kg angiotensin II is compared at various time points prior to and following the administration of the compounds intravenously or orally at doses of 0.1 to 300 mg/kg. The dose of compound needed to produce 50% inhibition of the control response to angiotensin II (IC<sub>50</sub>) is used to estimate the potency of the compounds. The IC<sub>50</sub> of (E)-3-[2-n-butyl-1-((2-chlorophenyl)methyl)-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid is 3.60 mg/kg i.v. and 44.00 mg/kg orally.

#### Antihypertensive activity

[0044] The antihypertensive activity of the compounds is measured by their ability to reduce mean arterial pressure in conscious rats made renin-dependent hypertensive by ligation of the left renal artery (Cangiano et al., *J. Pharmacol. Exp. Ther.* 208:310, 1979). Renal artery ligated rats are prepared with indwelling catheters as described above. Seven to eight days following renal artery ligation, the time at which plasma renin levels are highest, the conscious rats are placed in restrainers and mean arterial pressure is continuously recorded prior to and following the administration of the compounds intravenously or orally. The dose of compound needed to reduce mean arterial pressure by 30 mm Hg (IC<sub>50</sub>) is used as an estimate of potency. The IC<sub>50</sub> of (E)-3-[2-n-butyl-1-((2-chlorophenyl)methyl)-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid is 1.80 mg/kg i.v. and 8.0 mg/kg orally.

[0045] The intraocular pressure lowering effects employed in this invention may be measured by the procedure described by Watkins, et al., *J. Ocular Pharmacol.*, 1 (2): 161-168 (1985).

[0046] The compounds of Formula (I) are incorporated into convenient dosage forms, such as injectable preparations, or for orally active compounds, capsules or tablets. Solid or liquid pharmaceutical carriers are employed. Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Liquid carriers include syrup, peanut oil, olive oil, saline, and water. Similarly, the carrier or diluent may include any prolonged release material, such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies widely but, preferably, will be from about 25 mg to about 1 g per dosage unit. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion, soft gelatin capsule, sterile injectable liquid, such as an ampoule, or an aqueous or nonaqueous liquid suspension.

[0047] For topical ophthalmologic administration, the pharmaceutical compositions adapted include solutions, suspensions, ointments, and solid inserts. Typical pharmaceutically acceptable carriers are, for example, water, mixtures of water and water-miscible solvents such as lower alkanols or vegetable oils, and water soluble ophthalmologically acceptable non-toxic polymers, for example, cellulose derivatives such as methyl cellulose. The pharmaceutical preparation may also contain non-toxic auxiliary substances such as emulsifying, preserving wetting, and bodying agents, as for example, polyethylene glycols; antibacterial components, such as quaternary ammonium compounds; buffering ingredients, such as alkali metal chloride; antioxidants, such as sodium metabisulfite; and other conventional ingredients, such as sorbitan monolaurate.

[0048] Additionally, suitable ophthalmic vehicles may be used as carrier media for the present purpose including conventional phosphate buffer vehicle systems.

[0049] The pharmaceutical preparation may also be in the form of a solid insert. For example, one may use a solid water soluble polymer as the carrier for the medicament. Solid water insoluble inserts, such as those prepared from ethylene vinyl acetate copolymer, may also be utilized.

[0050] The pharmaceutical preparations are made following conventional techniques of a pharmaceutical chemist involving mixing, granulating, and compressing, when necessary, for tablet forms, or mixing, filling and dissolving the ingredients, as appropriate, to give the desired oral, parenteral, or topical products.

[0051] Doses of the compounds of Formula (I) in a pharmaceutical dosage unit as described above will be an efficacious, nontoxic quantity selected from the range of 0.01 - 200 mg/kg of active compound, preferably 1 - 100 mg/kg. The selected dose is administered to a human patient in need of angiotensin II receptor antagonism from 1-6 times daily, orally, rectally, topically, by injection, or continuously by infusion. Oral dosage units for human administration preferably contain from 1 to 500 mg of active compound. Preferably, lower dosages are used for parenteral administration. Oral administration, at higher dosages, however, also can be used when safe and the active compound in an amount selected from 0.0001 to 0.1 (w/v%), preferably from 0.0001 to 0.01. As a topical dosage unit form, an amount of active compound from between 50 ng to 0.05 mg, preferably 50 ng to 5 µg, is applied to the human eye.

[0052] The method of this invention of antagonizing angiotensin II receptors in mammals, including humans, comprises administering to a subject in need of such antagonism an effective amount of a compound of Formula (I). The method of this invention of producing antihypertensive activity and the method of treating congestive heart failure, glaucoma, and renal failure comprise administering a compound of Formula (I) to a subject in need thereof an effective amount to produce said activity.

[0053] Contemplated equivalents of Formula (I) compounds are compounds otherwise corresponding thereto wherein substituents have been added to any of the unsubstituted positions of the Formula (I) compounds provided such compounds have the pharmaceutical utility of Formula (I) compounds.

[0054] The following examples illustrate preparation of compounds and pharmaceutical compositions of this invention. The examples are not intended to limit the scope of this invention as described hereinabove and as claimed below.

#### Example 1

(E)-3-[2-n-Butyl-1-(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic Acid

#### [0055]

##### (i) 2-n-butyl-1-(2-chloro-phenyl)methyl-1H-imidazole

Imidazole was converted to the 1-diethoxyorthoamide derivative by the method of Curtis and Brown, *J. Org. Chem.*, (1980), 45, 20. Imidazole (12.8 g, 0.19 mol) and 118.4 g (0.8 mol) of triethylorthoformate were reacted in the presence of 1 g of p-toluenesulfonic acid to give 20.6 (61%), bp 65-70°C (0.1 mm) of 1-diethoxyorthoamide imidazole. This product (24.0 g, 0.14 mol) was dissolved in dry tetrahydrofuran (250 mL), cooled to -40°C and n-butyl lithium (0.14 mol, 56.4 mL of 2.5 M in hexane) was added at -40°C to -35°C. After 15 minutes n-butyl iodide (31.1 g, 0.169 mol) was added at -40°C, and the reaction was stirred overnight at ambient temperature. The reaction was

Example 89

E-3-[2-n-Butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoxy Acetic Acid

- 5 [0154] To a suspension of sodium hydride (53 mg, 2.3 mmol) in 5 mL of glyme was added portionwise (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenol (0.802 mg, 2.0 mmol, prepared as described in Example 17). After stirring for 30 minutes, methyl bromoacetate (3.35 mg, 2.2 mmol) was added dropwise. The reaction was stirred overnight at room temperature and then the mixture was poured into ice-water. The product was extracted into ethyl acetate (3x). The combined organic extracts were washed with water and brine and dried with anhydrous magnesium sulfate. The solvent was removed in vacuo. The residue was chromatographed on silica gel eluting with hexane/ethyl acetate (4:6) to give 2.44 mg (26%) of the ester of the title compound as an oil.
- 10 [0155] The ester was saponified by base as described in Example 1, iv, Method A(c); mp 141-142°C (ethyl acetate/methanol).

15 Example 90

E-3-[2-n-Butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenyl Glycine

- 20 [0156] To a solution of (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid (0.5 g, 1.2 mmol prepared in Example 1) in tetrahydrofuran (12 mL) was added N-hydroxysuccinimide (0.153, 1.33 mmol), followed by dicyclohexylcarbodiimide (0.249 g, 1.2 mmol) in 5 mL of tetrahydrofuran. The reaction mixture was heated at 35°C for one hour and then glycine methyl ester hydrochloride (0.197 g, 1.57 mmol) and triethylamine (0.22 mL, 1.57 mmol) were added. The reaction was stirred at room temperature overnight. The mixture was diluted with 20 mL of ethyl acetate and the solids were filtered. The filtrate was concentrated to dryness and the residue was chromatographed on silica gel eluting with ethyl acetate/hexane (4:6) to give 0.258 g (44%) of the ester-amide as an oil.
- 25 [0157] The ester was saponified to the title acid compound by base, as described in Example 1 (iv, Method A(c); mp 175-177°C.

Example 91

30

(E)-3-[2-n-Butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenamide

- [0158] (E)-3-[2-n-Butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid, prepared in Example 1, was treated with thionyl chloride and then ammonium hydroxide, as described in Example 54, to give the title compound; mp 184-185°C.
- 35

Example 92

(E)-3-[2-n-Butyl-1-[(2-trifluoromethylphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenamide

40

- [0159] (E)-3-[2-n-Butyl-1-[(2-trifluoromethylphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid, prepared in Example 58, was treated with thionyl chloride and then ammonium hydroxide, as described in Example 54, to give the title compound; mp 207-208°C.

45 Example 93

Ethyl (E)-3-[2-n-butyl-1-[(4-carbomethoxyphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propanoate

50

- [0160] The title compound was prepared following the procedure of Example 1 (iv, Method B) using 2-n-butyl-1-[(4-carbomethoxyphenyl)methyl]imidazole-5-aldehyde, prepared by the method described for the preparation of 2-n-butyl-1-[(4-carboethoxy-2-chlorophenyl)methyl]imidazole-5-aldehyde in Example 42, and ethyl 3-(2-thienyl)propanoate; mp 130-132°C.

Example 94

55

- [0161] An oral dosage form for administering orally active Formula (I) compounds is produced by screening, mixing and filling into hard gelatin capsules the ingredients in proportions, for example, as shown below.

| Ingredients                                                                                         | Amounts |
|-----------------------------------------------------------------------------------------------------|---------|
| (E)-3-[2-n-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid | 100 mg  |
| magnesium stearate                                                                                  | 10 mg   |
| lactose                                                                                             | 100 mg  |

#### Example 95

[0162] The sucrose calcium sulfate dihydrate and orally active Formula (I) compounds are mixed and granulated with a 10% gelatin solution. The wet granules are screened, dried, mixed with the starch, talc and stearic acid, screened and compressed into a tablet.

| Ingredients                                                                                                  | Amounts |
|--------------------------------------------------------------------------------------------------------------|---------|
| (E)-3-[2-n-butyl-1-[(4-carboxy-2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid | 75 mg   |
| calcium sulfate dihydrate                                                                                    | 100 mg  |
| sucrose                                                                                                      | 15 mg   |
| starch                                                                                                       | 8 mg    |
| talc                                                                                                         | 4 mg    |
| stearic acid                                                                                                 | 2 mg    |

#### Example 96

[0163] (E)-3-[2-n-Butyl-1-[(4-carboxy-3-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid, 50 mg, is dispersed in 25 mL of normal saline to prepare an injectable preparation.

#### Example 97

[0164] A topical ophthalmological solution for administering Formula (I) compounds is produced by mixing under sterile conditions the ingredients in proportions, for example, as shown below.

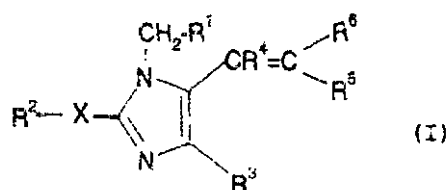
| Ingredients                                                                                       | Amounts (mg/mL) |
|---------------------------------------------------------------------------------------------------|-----------------|
| (E)-3-[2-n-butyl-1-[2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid | 1.0             |
| dibasic sodium phosphate                                                                          | 10.4            |
| monobasic sodium phosphate                                                                        | 2.4             |
| chlorobutanol                                                                                     | 5.0             |
| hydroxypropanol methylcellulose                                                                   | 5.0             |
| sterile water                                                                                     | q.s.ad 1.0mL    |
| 1.0 N sodium hydroxide                                                                            | q.s.ad pH 7.4   |

[0165] It is to be understood that the invention is not limited to the embodiments illustrated hereabove and the right

to the illustrated embodiments and all modifications coming within the scope of the following claims is reserved.

# Claims

1. A compound of the formula (I):



in which:

R<sup>1</sup> is phenyl, biphenyl, naphthyl, or adamantylmethyl, which are unsubstituted or substituted by one to three substituents selected from Cl, Br, F, I, C<sub>1</sub>-C<sub>4</sub> alkyl, nitro, CO<sub>2</sub>R<sup>7</sup>, tetrazol-5-yl, C<sub>1</sub>-C<sub>4</sub>alkoxy, hydroxy, SC<sub>1</sub>-C<sub>4</sub>alkyl, SO<sub>2</sub>NHR<sup>7</sup>, NHSO<sub>2</sub>R<sup>7</sup>, SO<sub>3</sub>H, CONR<sup>7</sup>R<sup>7</sup>, CN, SO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub>alkyl, or C<sub>n</sub>F<sub>2n+1</sub>, wherein n is 1-3;

R<sup>2</sup> is C<sub>2</sub>-C<sub>10</sub>alkyl, C<sub>2</sub>-C<sub>10</sub>alkenyl, C<sub>3</sub>-C<sub>10</sub>alkynyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or (CH<sub>2</sub>)<sub>0-8</sub>phenyl unsubstituted or substituted by one to three substituents selected from C<sub>1</sub>-C<sub>4</sub>alkyl, nitro, Cl, Br, F, I, hydroxy, C<sub>1</sub>-C<sub>4</sub>alkoxy, NR<sup>7</sup>R<sup>7</sup>, CO<sub>2</sub>R<sup>7</sup>, CN, or CONR<sup>7</sup>R<sup>7</sup>;

X is a single bond, S, or O;

R<sup>3</sup> is hydrogen, Cl, Br, F, I, CHO, hydroxymethyl, COOR<sup>7</sup>, CONR<sup>7</sup>R<sup>7</sup>, NO<sub>2</sub>, or C<sub>n</sub>F<sub>2n+1</sub>, wherein n is 1-3;

R<sup>4</sup> and R<sup>5</sup> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, thienyl-Y, furyl-Y, pyrazolyl-Y, imidazolyl-Y, pyrrolyl-Y, triazolyl-Y, oxazolyl-Y, isoxazolyl-Y, thiazolyl-Y, pyridyl-Y, or tetrazolyl-Y, except that R<sup>4</sup> and R<sup>5</sup> are not both selected from hydrogen and 1-C<sub>6</sub>alkyl and each heterocyclic ring is unsubstituted or substituted by C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, Cl, Br, F, I, NR<sup>7</sup>R<sup>7</sup>, CO<sub>2</sub>R<sup>7</sup>, SO<sub>2</sub>NHR<sup>7</sup>, SO<sub>3</sub>H, or CONR<sup>7</sup>R<sup>7</sup>;

Y is a single bond, O, S, or C<sub>1</sub>-C<sub>6</sub>alkyl which is straight or branched or optionally substituted by phenyl or benzyl, wherein each of the aryl groups is unsubstituted or substituted by halo, NO<sub>2</sub>, CF<sub>3</sub>, C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, CN, or CO<sub>2</sub>R<sup>7</sup>;

R<sup>6</sup> is -Z-COOR<sup>8</sup> or -Z-CONR<sup>7</sup>R<sup>7</sup>;

Z is a single bond, vinyl, -CH<sub>2</sub>-O-CH<sub>2</sub>-, methylene optionally substituted by C<sub>1</sub>-C<sub>4</sub>alkyl, one or two benzyl groups, thienylmethyl, or furylmethyl, or -C(O)NHCHR<sup>9</sup>-, wherein R<sup>9</sup> is H, C<sub>1</sub>-C<sub>6</sub>alkyl, phenyl, benzyl, thienylmethyl, or furylmethyl;

each R<sup>7</sup> independently is hydrogen, C<sub>1</sub>-C<sub>4</sub>alkyl, or (CH<sub>2</sub>)<sub>m</sub>phenyl, wherein m is 0-4; and

R<sup>8</sup> is hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, or 2-di(C<sub>1</sub>-C<sub>6</sub>alkyl)-amino-2-oxoethyl; or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 in which one of R<sup>4</sup> and R<sup>5</sup> is hydrogen or C<sub>1</sub>-C<sub>6</sub>alkyl.

3. A compound according to claim 1 or 2 in which:

R<sup>1</sup> is phenyl unsubstituted or substituted by one to three substituents selected from chloro, fluoro, trifluoromethyl, nitro, methyl, methoxy, hydroxy, sulfamido, carboxy, carboxy-C<sub>1</sub>-C<sub>4</sub>alkoxy, carbamoyl, cyano, or tetrazol-5-yl;

X is a single bond;

R<sup>2</sup> is C<sub>2</sub>-C<sub>8</sub>alkyl;

R<sup>3</sup> is hydrogen, chloro, fluoro, or trifluoromethyl;

R<sup>4</sup> is hydrogen or C<sub>1</sub>-C<sub>6</sub>alkyl;

R<sup>5</sup> is thienylmethyl, furylmethyl, imidazolylmethyl, or pyridylmethyl, each of which is optionally substituted by methyl or methoxy; and

R<sup>6</sup> is COOH, COOC<sub>1-2</sub>alkyl, or CONH<sub>2</sub>.

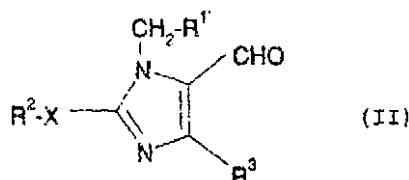
4. A compound according to any one of claims 1 to 3 which is the E (trans) isomer.

5. A compound according to claim 1 which is:

(E)-3-[2-n-butyl-1-[(4-carboxy-3-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid;  
 (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid;  
 (E)-3-[2-n-butyl-1-[(4-carboxy-2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid;  
 (E)-3-[2-n-butyl-1-[(4-carbomethoxyphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid;  
 (E)-3-[2-n-hexyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid;  
 (E)-3-[2-n-propyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid;  
 (E)-3-[2-n-butyl-1-[(2-nitrophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid;  
 (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-furyl)methyl-2-propenoic acid;  
 (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(4-imidazolyl)methyl-2-propenoic acid;  
 (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(3-thienyl)methyl-2-propenoic acid;  
 (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(5-methyl-2-thienyl)methyl-2-propenoic acid;  
 (E)-3-[2-n-butyl-1-[(2-cyanophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid;  
 (E)-3-[2-n-butyl-1-[(4-methoxy-3-methylphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid;  
 (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(4-pyridyl)methyl-2-propenoic acid;  
 (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(5-methoxy-2-thienyl)methyl-2-propenoic acid;  
 (E)-3-[2-n-butyl-1-[(2,3-dichlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid; or  
 (E)-3-[2-n-butyl-1-[(2-trifluoromethylphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid; or  
 a pharmaceutically acceptable salt thereof.

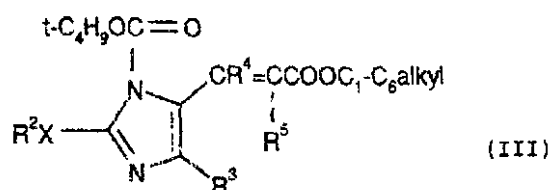
6. A compound according to any one of claims 1 to 5 for use as a medicament.
7. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 5 and a pharmaceutically acceptable carrier.
8. A process for preparing a compound of the formula (I) or a pharmaceutically acceptable salt thereof as defined in claim 1, which process comprises:

a) reacting a compound of the formula (II):

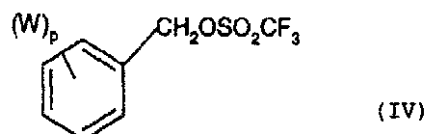


wherein  $\text{R}^2$ ,  $\text{R}^3$ , and X are as defined in claim 1, and  $\text{R}^1$  as defined in claim 1, except that the substituents on the  $\text{R}^1$  group do not include tetrazol-5-yl, OH, or  $\text{CO}_2\text{H}$ , with  $(\text{C}_1\text{-C}_4\text{alkoxy})_2\text{P}(\text{O})\text{CH}(\text{R}^5)\text{-COOC}_1\text{-C}_6\text{alkyl}$ , wherein  $\text{R}^5$  is as defined in claim 1, in the presence of a base; or

b) reacting a compound of the formula (III):

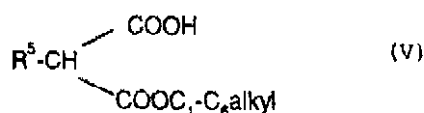


wherein  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$ ,  $\text{R}^5$ , and X are as defined in claim 1, with a compound of the formula (IV):



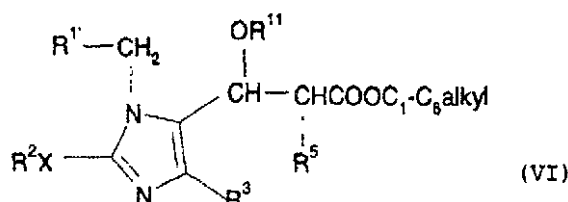
wherein W is Cl, Br, F, I, C<sub>1</sub>-C<sub>4</sub>alkyl, nitro, CO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, SC<sub>1</sub>-C<sub>4</sub>alkyl, CN, SO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub>alkyl, SO<sub>2</sub>NHR<sup>7</sup>, NHSO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub>alkyl, or C<sub>n</sub>F<sub>2n+1</sub>, n is 1-3, p is 0-3, and R<sup>7</sup> is hydrogen, C<sub>1</sub>-C<sub>4</sub>alkyl, or (CH<sub>2</sub>)<sub>0-4</sub>phenyl; or

c) reacting a compound of the formula (II) as hereinbefore defined with a compound of the formula (V):



wherein R<sup>5</sup> is as defined in claim 1, in the presence of a base; or

d) reacting a compound of the formula (VI):



wherein R<sup>2</sup>, R<sup>3</sup>, R<sup>5</sup>, and X are as defined in claim 1, R<sup>1</sup> is R<sup>1</sup> as defined in claim 1, except that the substituents on the R<sup>1</sup> group do not include tetrazol-5-yl, OH, or CO<sub>2</sub>H and R<sup>11</sup> is COCH<sub>3</sub> or SO<sub>2</sub>CH<sub>3</sub>, with a base; or

e) reacting a compound of the formula (II) as hereinbefore defined with an appropriate heterocyclic acetic acid in acetic anhydride in the presence of a base; and thereafter:

(i) for formula (I) compounds in which Z is -CH<sub>2</sub>-O-CH<sub>2</sub>-, reducing the formula (I) ester hereinbefore prepared, followed by reaction with a C<sub>1</sub>-C<sub>6</sub>alkyl haloacetate or;

(ii) for formula (I) compounds in which Z is -C(O)NHCHR<sup>9</sup> - wherein R<sup>9</sup> is H, C<sub>1</sub>-C<sub>4</sub>alkyl, phenyl, benzyl, thienylmethyl, or furylmethyl, hydrolyzing the formula (I) ester compounds hereinbefore prepared, followed by reaction with an appropriately substituted amino acid, in the presence of an amide-forming reagent; or

(iii) for formula (I) compounds in which Z is a methylene group, reducing the formula (I) ester compounds hereinbefore prepared, followed by reaction with a C<sub>1</sub>-C<sub>6</sub>alkyl chloroformate and then reaction with carbon monoxide in the presence of a phosphine ligand; or

(iv) for formula (I) compounds in which Z is a methylene group substituted by C<sub>1</sub>-C<sub>4</sub>alkyl, benzyl, thienylmethyl, or furylmethyl, reacting the formula (I) ester compounds wherein Z is a methylene group prepared above with a lithium dialkylamide followed by reaction with an alkylating agent; and thereafter where necessary:

(i) for formula (I) compounds in which the R<sup>1</sup> group is substituted by hydroxy, deprotecting the formula (I)

compounds in which the  $R^1$  group is substituted by  $C_1$ - $C_4$ alkoxy; or

(ii) for formula (I) compounds in which the  $R^1$  group is substituted by carboxy, hydrolyzing the formula (I) compounds in which the  $R^1$  group is substituted by  $CO_2C_{1-4}$ alkyl; or

(iii) for formula (I) compounds in which  $R^1$  group is substituted by a tetrazol-5-yl group, treating the formula (I) compound in which the  $R^1$  group is substituted by carboxy, with a halogenating agent, followed by conversion to the primary amide in a reaction with ammonia, dehydration with oxalylchloride/dimethylformamide and reaction with azide; or

(iv) for formula (I) compounds in which  $R^6$  is  $-Z-COOH$ , hydrolyzing the formula (I) compounds in which  $R^6$  is  $-Z-COOC_{1-6}$ alkyl; or

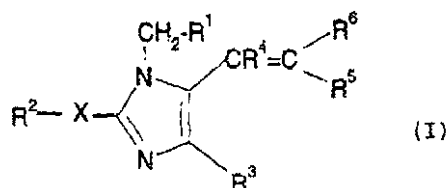
(v) for formula (I) compounds in which  $R^6$  is  $-Z-CONR^7R^7$  wherein  $R^7$  is hydrogen,  $C_1$ - $C_4$ alkyl, or  $(CH_2)_0$ - $_4$ phenyl, treating the formula (I) compounds in which  $R^6$  is  $-Z-COOH$  with a halogenating agent, followed by reaction with an appropriately substituted amine; and thereafter optionally forming a pharmaceutically acceptable salt.

9. The use of a compound of the formula (I) or a pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 5 in the manufacture of a medicament for treatment of diseases in which angiotensin II receptor antagonism is a factor.

10. The use of a compound of the formula (I) or a pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 5 in the manufacture of a medicament for the treatment of hypertension, congestive heart failure or renal failure.

#### Claims for the following Contracting States: ES, GR

1. A process for preparing a compound of the formula (I):



in which:

$R^1$  is phenyl, biphenyl, naphthyl, or adamantylmethyl, which are unsubstituted or substituted by one to three substituents selected from Cl, Br, F, I,  $C_1$ - $C_4$ alkyl nitro,  $CO_2R^7$ , tetrazol-5-yl,  $C_1$ - $C_4$ alkoxy, hydroxy,  $SC_{1-6}$ alkyl,  $SO_2NHR^7$ ,  $NHSO_2R^7$ ,  $SO_3H$ ,  $CONR^7R^7$ , CN,  $SO_2C_{1-4}$ alkyl, or  $C_nF_{2n+1}$ , wherein n is 1-3;

$R^2$  is  $C_2$ - $C_{10}$ alkyl,  $C_3$ - $C_{10}$ alkenyl,  $C_3$ - $C_{10}$ alkynyl,  $C_3$ - $C_6$ cycloalkyl, or  $(CH_2)_0$ - $_4$ phenyl unsubstituted or substituted by one to three substituents selected from  $C_1$ - $C_4$ alkyl, nitro, Cl, Br, F, I, hydroxy,  $C_1$ - $C_4$ alkoxy,  $NR^7R^7$ ,  $CO_2R^7$ , CN, or  $CONR^7R^7$ ;

X is a single bond, S, or O;

$R^3$  is hydrogen, Cl, Br, F, I, CHO, hydroxymethyl,  $COOR^7$ ,  $CONR^7R^7$ ,  $NO_2$ , or  $C_nF_{2n+1}$ , wherein n is 1-3;

$R^4$  and  $R^5$  are independently hydrogen,  $C_1$ - $C_6$ alkyl, thienyl-Y, furyl-Y, pyrazolyl-Y, imidazolyl-Y, pyrrolyl-Y, triazolyl-Y, oxazolyl-Y, isoxazolyl-Y, thiazolyl-Y, pyridyl-Y, or tetrazolyl-Y, except that  $R^4$  and  $R^5$  are not both selected from hydrogen and  $C_1$ - $C_6$ alkyl and each heterocyclic ring is unsubstituted or substituted by  $C_1$ - $C_4$ alkyl,  $C_1$ - $C_4$ alkoxy, Cl, Br, F, I,  $NR^7R^7$ ,  $CO_2R^7$ ,  $SO_2NHR^7$ ,  $SO_3H$ , or  $CONR^7R^7$ ;

Y is a single bond, C, S, or  $C_1$ - $C_6$ alkyl which is straight or branched or optionally substituted by phenyl or benzyl, wherein each of the aryl groups is unsubstituted or substituted by halo,  $NO_2$ ,  $CF_3$ ,  $C_1$ - $C_4$ alkyl,  $C_1$ - $C_4$ alkoxy, CN, or  $CO_2R^7$ ;

$R^6$  is  $-Z-COOR^6$  or  $-Z-CONR^7R^7$ ;

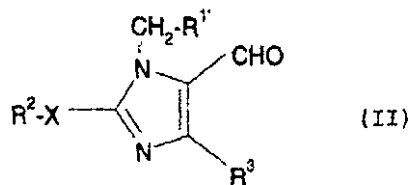
Z is a single bond, vinyl,  $-CH_2-O-CH_2-$ , methylene optionally substituted by  $C_1$ - $C_4$ alkyl, one or two benzyl

groups, thienylmethyl, or furylmethyl, or  $-\text{C}(\text{O})\text{NHCHR}^9$ , wherein  $\text{R}^9$  is H,  $\text{C}_1\text{-C}_6$ alkyl, phenyl, benzyl, thienylmethyl, or furylmethyl;

each  $\text{R}^7$  independently is hydrogen,  $\text{C}_1\text{-C}_4$ alkyl, or  $(\text{CH}_2)_m$ phenyl, wherein m is 0-4; and  $\text{R}^8$  is hydrogen,  $\text{C}_1\text{-C}_6$ alkyl, or 2-di( $\text{C}_1\text{-C}_6$ alkyl)-amino-2-oxoethyl; or a pharmaceutically acceptable salt thereof.

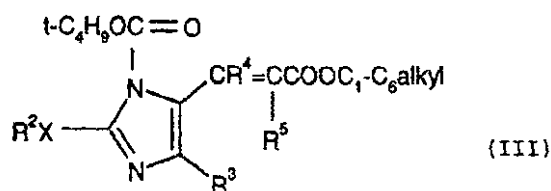
which process comprises:

a) reacting a compound of the formula (II):

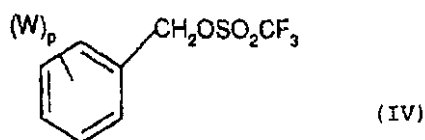


wherein  $\text{R}^2$ ,  $\text{R}^3$ , and X are as defined in claim 1, and  $\text{R}^1$  as defined in claim 1, except that the substituents on the  $\text{R}^1$  group do not include tetrazol-5-yl, OH, or  $\text{CO}_2\text{H}$ , with  $(\text{C}_1\text{-C}_4\text{alkoxy})_2\text{P}(\text{O})\text{CH}(\text{R}^5)\text{-COOC}_1\text{-C}_6\text{alkyl}$ , wherein  $\text{R}^5$  is as defined in claim 1, in the presence of a base; or

b) reacting a compound of the formula (III):

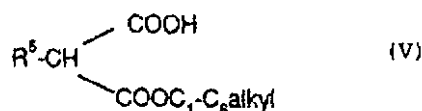


wherein  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$ ,  $\text{R}^5$ , and X are as defined in claim 1, with a compound of the formula (IV):



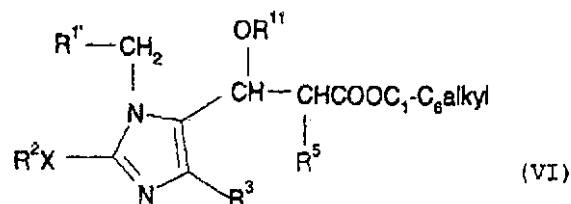
wherein W is Cl, Br, F, I,  $\text{C}_1\text{-C}_4$ alkyl, nitro,  $\text{CO}_2\text{C}_1\text{-C}_4$ alkyl,  $\text{C}_1\text{-C}_4$ alkoxy,  $\text{SC}_1\text{-C}_4$ alkyl, CN,  $\text{SO}_2\text{C}_1\text{-C}_4$ alkyl,  $\text{SO}_2\text{NHR}^7$ ,  $\text{NHSO}_2\text{C}_1\text{-C}_4$ alkyl, or  $\text{C}_n\text{F}_{2n+1}$ , n is 1-3, p is 0-3, and  $\text{R}^7$  is hydrogen,  $\text{C}_1\text{-C}_4$ alkyl, or  $(\text{CH}_2)_0\text{-}_4$ phenyl; or

c) reacting a compound of the formula (II) as hereinbefore defined with a compound of the formula (V):



wherein  $\text{R}^5$  is as defined in claim 1, in the presence of a base; or

d) reacting a compound of the formula (VI):



wherein  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^5$ , and  $\text{X}$  are as defined in claim 1,  $\text{R}^1$  is  $\text{R}^1$  as defined in claim 1, except that the substituents on the  $\text{R}^1$  group do not include tetrazol-5-yl, OH, or  $\text{CO}_2\text{H}$  and  $\text{R}^{11}$  is  $\text{COCH}_3$  or  $\text{SO}_2\text{CH}_3$ , with a base; or

e) reacting a compound of the formula (II) as hereinbefore defined with an appropriate heterocyclic acetic acid in acetic anhydride in the presence of a base; and thereafter:

(i) for formula (I) compounds in which  $\text{Z}$  is  $-\text{CH}_2\text{---O---CH}_2-$ , reducing the formula (I) ester hereinbefore prepared, followed by reaction with a  $\text{C}_1\text{---C}_6$ alkyl haloacetate or;

(ii) for formula (I) compounds in which  $\text{Z}$  is  $-\text{C}(\text{O})\text{NHCHR}^9$  - wherein  $\text{R}^9$  is H,  $\text{C}_1\text{---C}_4$ alkyl, phenyl, benzyl, thienylmethyl, or furylmethyl, hydrolyzing the formula (I) ester compounds hereinbefore prepared, followed by reaction with an appropriately substituted amino acid, in the presence of an amide-forming reagent; or

(iii) for formula (I) compounds in which  $\text{Z}$  is a methylene group, reducing the formula (I) ester compounds hereinbefore prepared, followed by reaction with a  $\text{C}_1\text{---C}_6$ alkyl chloroformate and then reaction with carbon monoxide in the presence of a phosphine ligand; or

(iv) for formula (I) compounds in which  $\text{Z}$  is a methylene group substituted by  $\text{C}_1\text{---C}_4$ alkyl, benzyl, thienylmethyl, or furylmethyl, reacting the formula (I) ester compounds wherein  $\text{Z}$  is a methylene group prepared above with a lithium dialkylamide followed by reaction with an alkylating agent; and thereafter where necessary.

(i) for formula (I) compounds in which the  $\text{R}^1$  group is substituted by hydroxy, deprotecting the formula (I) compounds in which the  $\text{R}^1$  group is substituted by  $\text{C}_1\text{---C}_4$ alkoxy; or

(ii) for formula (I) compounds in which the  $\text{R}^1$  group is substituted by carboxy, hydrolyzing the formula (I) compounds in which the  $\text{R}^1$  group is substituted by  $\text{CO}_2\text{C}_1\text{---C}_4$ alkyl; or

(iii) for formula (I) compounds in which  $\text{R}^1$  group is substituted by a tetrazol-5-yl group, treating the formula (I) compound in which the  $\text{R}^1$  group is substituted by carboxy, with a halogenating agent, followed by conversion to the primary amide in a reaction with ammonia, dehydration with oxalylchloride/dimethylformamide and reaction with azide; or

(iv) for formula (I) compounds in which  $\text{R}^6$  is  $-\text{Z---COOH}$ , hydrolyzing the formula (I) compounds in which  $\text{R}^6$  is  $-\text{Z---COOC}_1\text{---C}_6$ alkyl; or

(v) for formula (I) compounds in which  $\text{R}^6$  is  $-\text{Z---CONR}^7\text{R}^7$  wherein  $\text{R}^7$  is hydrogen,  $\text{C}_1\text{---C}_4$ alkyl, or  $(\text{CH}_2)_0\text{---}4$ phenyl, treating the formula (I) compounds in which  $\text{R}^6$  is  $-\text{Z---COOH}$  with a halogenating agent, followed by reaction with an appropriately substituted amine; and thereafter optionally forming a pharmaceutically acceptable salt.

2. A process according to claim 1 in which one of  $\text{R}^4$  and  $\text{R}^5$  is hydrogen or  $\text{C}_1\text{---C}_6$ alkyl.

3. A process according to claim 1 or 2 wherein:

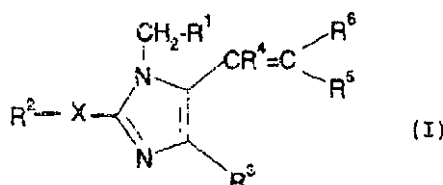
R<sup>1</sup> is phenyl unsubstituted or substituted by one to three substituents selected from chloro, fluoro, trifluoromethyl, nitro, methyl, methoxy, hydroxy, sulfamido, carboxy, carboC<sub>1</sub>-C<sub>4</sub>alkoxy, carbamoyl, cyano, or tetrazol-5-yl;  
 X is a single bond;  
 R<sup>2</sup> is C<sub>2</sub>-C<sub>8</sub>alkyl;  
 R<sup>3</sup> is hydrogen, chloro, fluoro, or trifluoromethyl;  
 R<sup>4</sup> is hydrogen or C<sub>1</sub>-C<sub>6</sub>alkyl;  
 R<sup>5</sup> is thienylmethyl, furylmethyl, imidazolylmethyl, or pyridylmethyl, each of which is optionally substituted by methyl or methoxy; and  
 R<sup>6</sup> is COOH, COOC<sub>1-2</sub>alkyl, or CONH<sub>2</sub>.

4. A process according to any one of claims 1 to 3 wherein the compound of formula (I) is the E (trans) isomer.

5. A process according to claim 1 wherein the compound of formula (I) is:

(E)-3-[2-n-butyl-1-[(4-carboxy-3-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid;  
 (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid;  
 (E)-3-[2-n-butyl-1-[(4-carboxy-2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid;  
 (E)-3-[2-n-butyl-1-[(4-carbomethoxyphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid;  
 (E)-3-[2-n-hexyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid;  
 (E)-3-[2-n-propyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid;  
 (E)-3-[2-n-butyl-1-[(2-nitrophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid;  
 (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-furyl)methyl-2-propenoic acid;  
 (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(4-imidazolyl)methyl-2-propenoic acid;  
 (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(3-thienyl)methyl-2-propenoic acid;  
 (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(5-methyl-2-thienyl)methyl-2-propenoic acid;  
 (E)-3-[2-n-butyl-1-[(2-cyanophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid;  
 (E)-3-[2-n-butyl-1-[(4-methoxy-3-methylphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid;  
 (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(4-pyridyl)methyl-2-propenoic acid;  
 (E)-3-[2-n-butyl-1-[(2-chlorophenyl)methyl]-1H-imidazol-5-yl]-2-(5-methoxy-2-thienyl)methyl-2-propenoic acid;  
 (E)-3-[2-n-butyl-1-[(2-dichlorophenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid; or  
 (E)-3-[2-n-butyl-1-[(2-trifluoromethylphenyl)methyl]-1H-imidazol-5-yl]-2-(2-thienyl)methyl-2-propenoic acid; or  
 a pharmaceutically acceptable salt thereof.

6. A compound of the formula (I):



in which:

R<sup>1</sup> is phenyl, biphenyl, naphthyl, or adamantylmethyl, which are unsubstituted or substituted by one to three substituents selected from Cl, Br, F, I, C<sub>1</sub>-C<sub>4</sub>alkyl, nitro, CO<sub>2</sub>R<sup>7</sup>, tetrazol-5-yl, C<sub>1</sub>-C<sub>4</sub>alkoxy, hydroxy, SC<sub>1</sub>-C<sub>4</sub>alkyl, SO<sub>2</sub>NHR<sup>7</sup>, NHSO<sub>2</sub>R<sup>7</sup>, SO<sub>3</sub>H, CONR<sup>7</sup>R<sup>7</sup>, CN, SO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub>alkyl, or C<sub>n</sub>F<sub>2n+1</sub>, wherein n is 1-3;  
 R<sup>2</sup> is C<sub>2</sub>-C<sub>10</sub>alkyl, C<sub>3</sub>-C<sub>10</sub>alkenyl, C<sub>3</sub>-C<sub>10</sub>alkynyl, C<sub>3</sub>-C<sub>6</sub>cycloalkyl, or (CH<sub>2</sub>)<sub>0-8</sub>phenyl unsubstituted or substituted by one to three substituents selected from C<sub>1</sub>-C<sub>4</sub>alkyl, nitro, Cl, Br, F, I, hydroxy, C<sub>1</sub>-C<sub>4</sub>alkoxy, NR<sup>7</sup>R<sup>7</sup>, CO<sub>2</sub>R<sup>7</sup>, CN or CONR<sup>7</sup>R<sup>7</sup>;  
 X is a single bond, S, or O;  
 R<sup>3</sup> is hydrogen, Cl, Br, F, I, CHO, hydroxymethyl, COOR<sup>7</sup>, CONR<sup>7</sup>R<sup>7</sup>, NO<sub>2</sub>, or C<sub>n</sub>F<sub>2n+1</sub>, wherein n is 1-3;  
 R<sup>4</sup> and R<sup>5</sup> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, thienyl-Y, furyl-Y, pyrazolyl-Y, imidazolyl-Y, pyrrolyl-Y, triazolyl-Y, oxazolyl-Y, isoxazolyl-Y, thiazolyl-Y, pyridyl-Y, or tetrazolyl-Y, except that R<sup>4</sup> and R<sup>5</sup> are not both selected from hydrogen and C<sub>1</sub>-C<sub>6</sub>alkyl and each heterocyclic ring is unsubstituted or substituted by C<sub>1</sub>-

C<sub>4</sub>alkyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, Cl, Br, F, I, NR<sup>7</sup>R<sup>7</sup>, CO<sub>2</sub>R<sup>7</sup>, SO<sub>2</sub>NHR<sup>7</sup>, SO<sub>3</sub>H, or CONR<sup>7</sup>R<sup>7</sup>;

Y is a single bond, O, S, or C<sub>1</sub>-C<sub>6</sub>alkyl which is straight or branched or optionally substituted by phenyl or benzyl, wherein each of the aryl groups is unsubstituted or substituted by halo, NO<sub>2</sub>, CF<sub>3</sub>, C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, CN, or CO<sub>2</sub>R<sup>7</sup>;

R<sup>6</sup> is -Z-COOR<sup>8</sup> or -Z-CONR<sup>7</sup>R<sup>7</sup>;

Z is a single bond, vinyl, -CH<sub>2</sub>-O-CH<sub>2</sub>-, methylene optionally substituted by C<sub>1</sub>-C<sub>4</sub>alkyl, one or two benzyl groups, thienylmethyl, or furylmethyl, or -C(O)NHCHR<sup>9</sup>-, wherein R<sup>9</sup> is H, C<sub>1</sub>-C<sub>6</sub>alkyl, phenyl, benzyl, thienylmethyl, or furylmethyl;

each R<sup>7</sup> independently is hydrogen, C<sub>1</sub>-C<sub>4</sub>alkyl, or (CH<sub>2</sub>)<sub>m</sub>phenyl, wherein m is 0-4; and

R<sup>8</sup> is hydrogen, C<sub>1</sub>-C<sub>6</sub>alkyl, or 2-di(C<sub>1</sub>-C<sub>6</sub>alkyl)-amino-2-oxoethyl; or a pharmaceutically acceptable salt thereof.

7. A compound according to claim 6 for use as a medicament.

8. A pharmaceutical composition which comprises a compound according to claim 6 and a pharmaceutically acceptable carrier.

9. The use of a compound of the formula (I) or a pharmaceutically acceptable salt thereof as defined in claim 6 in the manufacture of a medicament for treatment of diseases in which angiotensin II receptor antagonism is a factor.

10. The use of a compound of the formula (I) or a pharmaceutically acceptable salt thereof as defined in claim 6 in the manufacture of a medicament for the treatment of hypertension, congestive heart failure or renal failure.