



No. 06-108728- -00004-0000

Fecha: 2008-09-03 16:36:10 Dep: 2020 NULORLACIONE
Tra: 11 PATENTILYII Lve: 378 FASLNACIONALI
Act: 329 CIOINFORMACION Folios: 10

Superintendencia
de Industria y Comercio

FORMULARIO ÚNICO DE CORRECCIONES Y MODIFICACIONES

P2006/000200

SOLICITUD DE:

1

☐

Corrección de Error Material.

☒

Modificación a una Solicitud.

2

SOLICITANTE
(71)

Nombre: GLAXO GROUP LIMITED

Dirección: Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 ONN

Nacionalidad o Domicilio: Británica

Lugar de Constitución: Inglaterra

Teléfono: _____

Fax: _____

E-mail: _____

IDENTIFICACIÓN

C.C.

☐

NIT

☐

C.E.

☐

Otro

☐

Cual _____

Número _____

3

REPRESENTANTE
O APODERADO

Nombre: CARLOS R. OLARTE

Dirección: World Trade Center Torre A Calle 100 No. 8A-37 Piso 10. Bogotá

Teléfono: 601-7700 **Fax:** 601-7799

E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN

C.C.

☒

NIT

☐

C.E.

☐

Otro

☐

Cual _____

Número 79.782.747 Bta
TP 74.295

4

Número de expediente:
06-108.728

5

Descripción de la corrección o modificación solicitada VER PAGINA ADJUNTA.

6

Comprobante de pago No. 08-070,050

Fecha Sept 3, 2008

7

Anexos

☒

Comprobante de pago de la tasa.

☐

Poderes, si fuere el caso. Documento que soporta la cesión de Derechos.

☐

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

8

NOMBRE: CARLOS R. OLARTE

FIRMA: _____

C.C. 79.782.747 Bta T.P. 74.295

205
205

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NET 1000000000

RECIBO ORIGINAL DE DATA - LVE - 711000
FECHA 11 DE SEPTIEMBRE DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-108728-00004-0000

Fecha: 2008-09-03 16:38:10 Dep: 2029 NÚMERO APLICACIÓN
No. 11 PATENTILYII Lve. 378 FASE NACIONAL II
Art. 329 CTO INFORMACIÓN Folios: 10

***** C O N S E *****

DEPOSITANTE	TIPO PAIS	BANCO	CUENTA	VAL. PAIS	FECHA PAIS	VAL. PAIS
DEUTSCHE BANK AG	GERMANIA	BANCO DE SOROT	1000000000	1000000000	11-09-2008	1000000000

***** C O N S E *****

CANT. MONETARIO	CONCEPTO	TOTAL MONETARIO
1	500005-02-03 CAMBIO DE MODALIDAD Y MODIFICA	100,000,000
	100 MARCA Y LOGO ESPECIAL	100,000,000
	TOTAL	200,000,000

30000 CIENTO TRES MIL PESOS

[Handwritten signature]

RESPONSABLE :

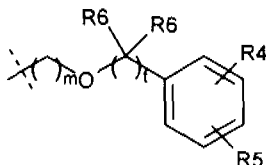
RECIBO DE DATA APLICADO AL EXPEDIENTE No.

206
206

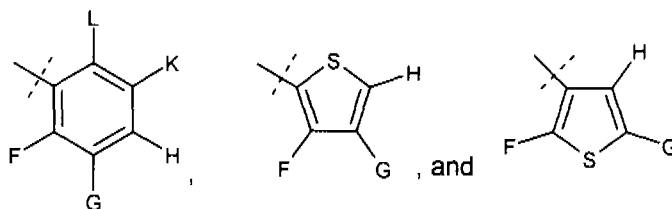
ANEXO EXPLICATIVO DEL CAPÍTULO REIVINDICATORIO MODIFICADO

En la Reivindicación 1:

- se limitó el alcance de R1 a un único radical:



- Los radicales R2 y R3 se limitaron a:



La Reivindicación 14 se limita a los compuestos de los ejemplos 3, 6, 7, 9, 10, 11, 28, 29, 34, 35, 39, 40, 41 a 46, 50, 66, 83 y 84.

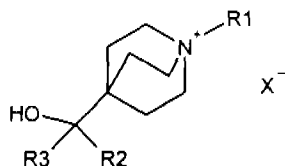
Se eliminaron los compuestos de los ejemplos 64 y 65.

En la Reivindicación 15 se reclama compuestos de los ejemplos 52 a 63.

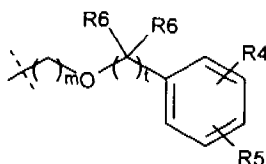
El compuesto de la Reivindicación 17 y 18 encuentra soporte en el ejemplo 84.

CAPÍTULO REIVINDICATORIO MODIFICADO

1. Un compuesto de fórmula (I) tal como se indica a continuación

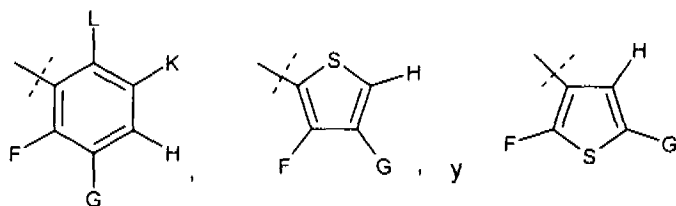


en donde:



R1 es

R2 y R3 son, independientemente, seleccionados del grupo compuesto por



F, G, H, K y L son independientemente seleccionados del grupo compuesto por hidrógeno, halógeno, alquilo C₁₋₄, alquilo C₁₋₄ halosustituido, alquilo C₁₋₄ hidroxisustituido y alcoxi C₁₋₄;

R4 y R5 son independientemente seleccionados del grupo compuesto por hidrógeno, halógeno, alquilo C₁₋₄, arilo, ciano, nitro, (CR₇R₇)pOR_b, y (CR₇R₇)pNR_bR_b; ó R4 y R5 unidos pueden formar un anillo saturado ó insaturado de 5 ó 6 miembros;

R6 se selecciona del grupo compuesto por hidrógeno y alquilo C₁₋₄;

R7 se selecciona del grupo compuesto por hidrógeno, alquilo C₁₋₄, alquilo C₁₋₄ halosustituido, y alquilo C₁₋₄ hidroxisustituido;

R_b se selecciona del grupo compuesto por hidrógeno, alquilo C₁₋₄ y arilo;

m es un número entero que tiene valores de 1 a 5

p es 0, 1 ó 2; y

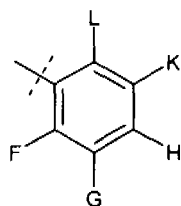
t es 0, 1 ó 2; y

X⁻ es un anión farmacéuticamente aceptable

2. El compuesto de acuerdo con la Reivindicación 1, en donde X⁻ se selecciona del grupo compuesto por cloruro, bromuro, yoduro, hidróxido, sulfato, nitrato, fosfato, acetato, trifluoroacetato, fumarato, citrato, tartrato, oxalato, succinato, mandelato, metansulfonato y p-toluensulfonato.

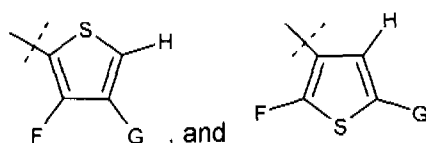
208
208

3. El compuesto de acuerdo con la Reivindicación 1 ó 2 en donde tanto R2 como R3 se seleccionan independientemente de:



4. El compuesto de acuerdo con la Reivindicación 3, en donde F, G, H, K y L son hidrógeno.

5. El compuesto de acuerdo con la Reivindicación 1 en donde tanto R2 como R3 se seleccionan independientemente del grupo compuesto por:



6. El compuesto de acuerdo con la Reivindicación 5 en donde F, G y H son hidrógeno.

7. El compuesto de acuerdo con la Reivindicación 1 ó 2 en donde R4 y R5 son hidrógeno.

8. El compuesto de acuerdo con la Reivindicación 1 ó 2 en donde m es 2, 3 ó 4.

9. El compuesto de acuerdo con la Reivindicación 1 ó 2 en donde t es 0 ó 1.

10. El compuesto de acuerdo con la Reivindicación 1 ó 2 en donde m es 2 y t es 1.

11. El compuesto de acuerdo con la Reivindicación 1 ó 2 en donde tanto R2 como R3 son fenil.

12. El compuesto de acuerdo con la Reivindicación 1 ó 2 en donde R4 y R5 son independientemente seleccionados del grupo compuesto por hidrógeno y halógeno.

13. El compuesto de acuerdo con la Reivindicación 1 ó 2 en donde F, G, H, K y L son independientemente seleccionados del grupo compuesto por hidrógeno, halógeno, metilo y metoxi.

14. El compuesto de acuerdo con la Reivindicación 1 ó 2 que es:

- bromuro de 4-[hidroxi(difenil)metil]-1-{2-[(feniloxi)etil]-1-azoniabencilo[2.2.2]octano;
- bromuro de 4-[hidroxi(difenil)metil]-1-{3-[(feniloxi)propil]-1-azoniabencilo[2.2.2]octano;
- bromuro de 4-[hidroxi(di-2-tienil)metil]-1-{2-[(feniloxi)etil]-1-azoniabencilo[2.2.2]octano;
- bromuro de 4-[hidroxi(di-2-tienil)metil]-1-{3-[(feniloxi)propil]-1-azoniabencilo[2.2.2]octano;

209
B.C.

- bromuro de 4-[hidroxi(difenil)metil]-1-{4-(feniloxi)butil}-1-azoniabicciclo[2.2.2]octano;
- bromuro de 4-[hidroxi(difenil)metil]-1-{4-[(fenilmetil)oxi]butil}-1-azoniabicciclo [2.2.2] octano;
- bromuro de 4-[hidroxi(difenil)metil]-1-{3-[(fenilmetil)oxi]propil}-1-azoniabicciclo [2.2.2] octano;
- bromuro de 1-{2-[(2,4dibromofenil)oxi]etil}-4-[hidroxi(difenil)metil]-1-azoniabicciclo [2.2.2] octano;
- bromuro de 4-[hidroxi(di-3-tienil)metil]-1-{2-[feniloxi]etil}-1-azoniabicciclo[2.2.2]octano;
- bromuro de 4-[hidroxi(di-3-tienil)metil]-1-{3-[feniloxi]propil}-1-azoniabicciclo[2.2.2]octano;
- bromuro de 4-[hidroxi(difenil)metil]-1-(3-{[2-(metiloxi)fenil]oxi}propil)-1- azoniabicciclo[2.2.2]octano;
- bromuro de 4-[hidroxi(difenil)metil]-1-{3-[(2-hidroxifenil)oxi]propil}-1- azoniabicciclo[2.2.2]octano;
- bromuro de 4-[hidroxi(difenil)metil]-1-{3-(2-naftaleniloxi)propil}-1- azoniabicciclo[2.2.2]octano;
- bromuro de 1-{3-[(3-clorofenil)oxi]propil}-4-[hidroxi(difenil)metil]-1- azoniabicciclo[2.2.2]octano;
- bromuro de 1-{3-[(4-bromofenil)oxi]propil}-4-[hidroxi(difenil)metil]-1- azoniabicciclo[2.2.2]octano;
- bromuro de 4-[hidroxi(difenil)metil]-1-{3-[(4-nitrofenil)oxi]propil}-1- azoniabicciclo[2.2.2]octano;
- bromuro de 1-{3-[(2-bromofenil)oxi]propil}-4-[hidroxi(difenil)metil]-1- azoniabicciclo[2.2.2]octano;
- bromuro de 4-[hidroxi(difenil)metil]-1-(3-{[4-(metiloxi)fenil]oxi}propil)-1- azoniabicciclo[2.2.2]octano;
- bromuro de 4-[hidroxi(difenil)metil]-1-{2-[(fenilmetil)oxi]etil}-1-azoniabicciclo[2.2.2]octano;
- bromuro de 1-{3-[(2-fluorofenil)oxi]propil}-4-[hidroxi(difenil)metil]-1- azoniabicciclo[2.2.2]octano;
- bromuro de 1-{3-[(3-fluorofenil)oxi]propil}-4-[hidroxi(difenil)metil]-1- azoniabicciclo[2.2.2]octano;
- bromuro de 1-{3-[(4-fluorofenil)oxi]propil}-4-[hidroxi(difenil)metil]-1- azoniabicciclo[2.2.2]octano;
- bromuro de 1-{3-(3-bifenililoxi)propil}-4-[hidroxi(difenil)metil]-1-azoniabicciclo[2.2.2]octano;
- bromuro de 1-{3-(4-bifenililoxi)propil}-4-[hidroxi(difenil)metil]-1-azoniabicciclo[2.2.2]octano;
- bromuro de 4-[hidroxi(difenil)metil]-1-{3-[(3-nitrofenil)oxi]propil}-1- azoniabicciclo[2.2.2]octano;
- bromuro de 4-[hidroxi(difenil)metil]-1-{3-[(2-metilfenil)oxi]propil}-1- azoniabicciclo[2.2.2]octano;

210
210

- bromuro de 1-(3-[[3-(dietilamino)fenil]oxi]propil)-4-[hidroxi(difenil)metil]-1-azoniabicyclo[2.2.2]octano;
- bromuro de 1-{3-[(4-cianofenil)oxi]propil}-4-[hidroxi(difenil)metil]-1-azoniabicyclo[2.2.2]octano;
- bromuro de 4-[hidroxi(difenil)metil]-1-[2-({[3-(metiloxi)fenil]metil}oxi)etil]-1-azoniabicyclo[2.2.2]octano;
- bromuro de 1-[2-({[4-(1,1-dimetiletil)fenil]metil}oxi)etil]-4-[hidroxi(difenil)metil]-1-azoniabicyclo[2.2.2]octano;
- bromuro de 1-(2-{{[4-fluorofenil]metil}oxi}etil)-4-[hidroxi(difenil)metil]-1-azoniabicyclo[2.2.2]octano;
- bromuro de 1-(2-{{[4-clorofenil]metil}oxi}etil)-4-[hidroxi(difenil)metil]-1-azoniabicyclo[2.2.2]octano;
- bromuro de 1-(2-{{[4-bromofenil]metil}oxi}etil)-4-[hidroxi(difenil)metil]-1-azoniabicyclo[2.2.2]octano;
- bromuro de 1-(2-{{[4-cianofenil]metil}oxi}etil)-4-[hidroxi(difenil)metil]-1-azoniabicyclo[2.2.2]octano;
- bromuro de 4-[hidroxi(difenil)metil]-1-{2-[(2-naftalenilmetil)oxi]etil}-1-azoniabicyclo[2.2.2]octano;
- bromuro de 1-(2-{{[3-fluorofenil]metil}oxi}etil)-4-[hidroxi(difenil)metil]-1-azoniabicyclo[2.2.2]octano; y
- bromuro de 4-[hidroxi(difenil)metil]-1-[2-[(1-metil-1-feniletil)oxi]etil]-1-azoniabicyclo[2.2.2]octano.

15. El compuesto de acuerdo con la Reivindicación 1 el cual es:

- bromuro de 4-[bis(4-fluorofenil)(hidroxi)metil]-1-[3-(feniloxi)propil]-1-azoniabicyclo[2.2.2]octano;
- bromuro de 4-[bis(4-fluorofenil)(hidroxi)metil]-1-{2-[(fenilmetil)oxi]etil}-1-azoniabicyclo[2.2.2]octano;
- bromuro de 4-(hidroxi{bis[3-(metiloxi)fenil]}metil)-1-[3-(feniloxi)propil]-1-azoniabicyclo[2.2.2]octano;
- bromuro de 4-(hidroxi{bis[3-(metiloxi)fenil]}metil)-1-{2-[(fenilmetil)oxi]etil}-1-azoniabicyclo[2.2.2]octano;
- bromuro de 4-(hidroxi{bis[4-(metiloxi)fenil]}metil)-1-[3-(feniloxi)propil]-1-azoniabicyclo[2.2.2]octano;
- bromuro de 4-(hidroxi{bis[4-(metiloxi)fenil]}metil)-1-{2-[(fenilmetil)oxi]etil}-1-azoniabicyclo[2.2.2]octano;
- bromuro de 4-[bis(3-fluorofenil)(hidroxi)metil]-1-[3-(feniloxi)propil]-1-azoniabicyclo[2.2.2]octano;

2H

- bromuro de 4-[bis(3-fluorofenil)(hidroxi)metil]-1-{2-[(fenilmetil)oxi]etil}-1-azoniabicyclo[2.2.2]octano;
- bromuro de 4-{hidroxi[bis(3-metilfenil)]metil}-1-[3-(feniloxi)propil]-1-azoniabicyclo[2.2.2]octano;
- bromuro de 4-{hidroxi[bis(3-metilfenil)]metil}-1-{2-[(fenilmetil)oxi]etil}-1-azoniabicyclo[2.2.2]octano;
- bromuro de 4-{hidroxi[bis(4-metilfenil)]metil}-1-[3-(feniloxi)propil]-1-azoniabicyclo[2.2.2]octano; y
- bromuro de 4-{hidroxi[bis(4-metilfenil)]metil}-1-{2-[(fenilmetil)oxi]etil}-1-azoniabicyclo[2.2.2]octano.

16. El compuesto de acuerdo con la Reivindicación 1 en donde X- es bromuro.

17. El compuesto de acuerdo con la Reivindicación 1 en donde X- es yoduro.

18. Una composición farmacéutica que comprende un compuesto de acuerdo con la Reivindicación 1 y un vehículo farmacéuticamente aceptable.

19. El compuesto el cual es bromuro de 4-[hidroxi(difenil)metil]-1-{2-[(fenilmetil)oxi]etil}-1-azoniabicyclo[2.2.2]octano.

20. Una composición farmacéutica que comprende un compuesto bromuro de 4-[hidroxi(difenil)metil]-1-{2-[(fenilmetil)oxi]etil}-1-azoniabicyclo[2.2.2]octano y un vehículo farmacéuticamente aceptable.

21. El uso de un compuesto de acuerdo con cualquiera de las Reivindicaciones 1 a 15 para la preparación de un medicamento para inhibir la unión de acetilcolina en un receptor de acetilcolina en el tracto respiratorio de un mamífero en necesidad del mismo, en donde el medicamento se administra por inhalación por la boca ó la nariz del mamífero.

22. El uso de un compuesto de acuerdo con cualquiera de las Reivindicaciones 1 a 15 para la preparación de un medicamento para inhibir la unión de acetilcolina en un receptor M3 muscarínico de acetilcolina en el tracto respiratorio de un mamífero en necesidad del mismo, en donde el medicamento se administra por inhalación por la boca ó la nariz del mamífero.

23. El uso de acuerdo con la Reivindicación 22 en donde la unión del receptor M3 muscarínico de acetilcolina es útil en el tratamiento de enfermedad pulmonar crónica obstructiva, bronquitis crónica, asma, obstrucción respiratoria crónica, fibrosis pulmonar, enfisema pulmonar ó rinitis alérgica.

212
4
212

24. El uso de acuerdo con la Reivindicación 22 en donde la administración es bucal.
25. El uso de acuerdo con la Reivindicación 22 en donde la administración es nasal.
26. El uso de acuerdo con la Reivindicación 26 en donde la administración se realiza mediante un dispensador de medicamentos seleccionado de un inhalador de polvo seco en un depósito, un inhalador de polvo seco de múltiples dosis, o un inhalador de dosis dosificadas.
27. El uso de bromuro de 4-[hidroxi(difenil)metil]-1-{2-[(fenilmetil)oxi]etil}-1-azoniabicyclo[2.2.2]octano para la preparación de un medicamento para el tratamiento de enfermedad pulmonar crónica obstructiva, bronquitis crónica, asma, obstrucción respiratoria crónica, fibrosis pulmonar, enfisema pulmonar ó rinitis alérgica en un humano en necesidad del mismo, en donde el medicamento se administra a dicho humano por inhalación bucal ó nasal.
28. El uso de acuerdo con la Reivindicación 26 en donde la administración se realiza mediante un dispensador de medicamentos seleccionado de un inhalador de polvo seco en un depósito, un inhalador de polvo seco de múltiples dosis, o un inhalador de dosis dosificadas.
29. El uso de acuerdo con la Reivindicación 27 ó 28 en donde la administración es nasal.
30. El uso de acuerdo con la Reivindicación 27 ó 28 en donde la administración es bucal.
31. El uso de bromuro de 4-[hidroxi(difenil)metil]-1-{2-[(fenilmetil)oxi]etil}-1-azoniabicyclo[2.2.2]octano para la preparación de un medicamento para inhibir la unión de acetilcolina a un receptor de acetilcolina en un mamífero en necesidad del mismo, en donde el medicamento se administra por inhalación nasal ó bucal en el mamífero.
32. El uso bromuro de 4-[hidroxi(difenil)metil]-1-{2-[(fenilmetil)oxi]etil}-1-azoniabicyclo[2.2.2]octano para la preparación de un medicamento que inhiba la unión de acetilcolina al receptor M3 muscarínico de acetilcolina en el tracto respiratorio de un mamífero en necesidad del mismo, en donde el medicamento es administrado por inhalación nasal ó bucal del mamífero.
33. El uso de acuerdo a la Reivindicación 31 ó 32 en donde la administración se realiza mediante un dispensador de medicamentos seleccionado de un inhalador de polvo seco en un depósito, un inhalador de polvo seco de múltiples dosis, o un inhalador de dosis dosificadas.

ZLB
2/3

34. Un anión farmacéuticamente aceptable de 4-[hidroxi(difenil)metil]-1-{2-[(fenilmetil)oxi]etil}-1-azoniabicyclo[2.2.2]octano.

35. Una composición farmacéutica que comprende un compuesto de acuerdo a la Reivindicación 34 y un vehículo farmacéuticamente aceptable.

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-108728

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **582** DE

FECHA **30 DE NOVIEMBRE DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL **27 DE FEBRERO DE 2008**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO X

215
215

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

202012
Bogotá, D.C., 04 de febrero de 2010

Apoderado: Carlos Reinaldo Olarte García

ASUNTO		Radicación	06-108728
Trámite	002	Evento	001
		Actuación	430
		Oficio	
		Folios	
Patente de Invención		☒	
Vía PCT (fase nacional)	☒	Cap. I	☒ Cap. II ☐
No. Sol. Internacional		PCT/US2005/014368	
Fecha de Presentación Internal.		27/abr/2005	

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

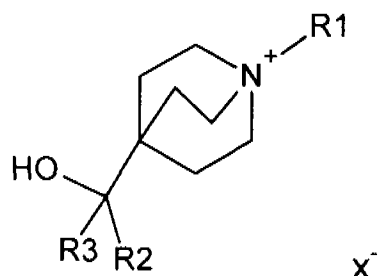
1. Documentos estudiados

- 1.1. Descripción: Folios: 104 a 167 Como se radicó inicialmente.
- 1.2. Reivindicaciones: Folios 168 a 180 Como se radicó inicialmente.
Folios 207 a 213 Modificaciones
- 1.3. Prioridad: Folio 1: US 60/565.623, 27/abr/2004

2. Objeto de la invención

Título de la solicitud: ANTAGONISTAS DEL RECEPTOR DE ACETILCOLINA MUSCARINICO.

La presente solicitud tiene por objeto los derivados de 4-(hidroximetil- disustituido)-1- alquilfenil-1-azoniabiciclo[2.2.2]octano de la fórmula Markush (I):



Se catalogó la invención, según la Clasificación Internacional de Patentes (IPC.):
C07D401/10, 471/14, A61K31/517, 31/41, 31/404, A61P29/00.

3. De la solicitud de Patente

3.1 El título de la solicitud no está de acuerdo con la materia descrita y reivindicada, toda vez que la solicitud trata de estructuras químicas.

3.2 Reivindicaciones (artículo 30 D 486 de la C.A.N.)

La reivindicación 34 no clara, se reclama un **anión**, que es un ion con carga eléctrica negativa, es decir, con exceso de electrones, el cual no puede subsistir aisladamente del catión, o sea, tal como está reclamada solamente puede existir en el papel. Por lo tanto se debe ajustar el capítulo reivindicatorio de tal manera que la materia reclamada tenga un soporte técnico real.

-la reivindicación 35 es inconsistente, ya que se hace referencia a que la "composición" comprenda un compuesto de acuerdo con la reivindicación 34 y la reivindicación 34 se refiere a un **anión**.

Por consiguiente el capítulo reivindicatorio carece de definición, claridad, concisión y falta de sustento por la descripción, exigidas en las reivindicaciones, por lo tanto no cumplen con el requisito de definición, claridad, concisión y/o sustento por la descripción de acuerdo al art. 30 de la Decisión 486 y/o art.22 Tratado PCT.

4. Reivindicaciones relativas a un uso o a un segundo uso (artículos 14 y 21 D 486 de la C.A.N.)

Las reivindicaciones 21 a 33 reclaman el uso de compuestos y de acuerdo con la legislación colombiana el uso no se considera para protección por patente, como se lee en el artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina "... Los Países Miembros otorgarán patentes para las invenciones sean de productos o procedimientos en todos los campos de la tecnología..."; aquí NO se hace alusión al uso.

Los usos o segundos usos no son patentables, de conformidad con la sentencia del TJAC 89-AI-2000, en general los usos no son patentables.

5. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el estado de la técnica fecha de presentación de la solicitud de la cual se reclama prioridad, 27/abr/2004.

Teniendo en cuenta la fecha indicada se realizó la búsqueda del estado de la técnica, en bases de datos en las que esta oficina tiene acceso libre, en búsqueda

217
217

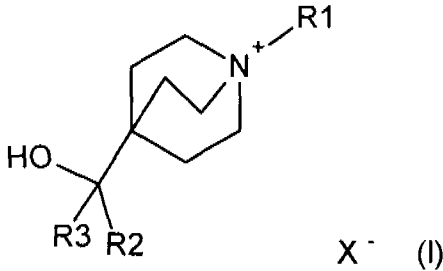
de documentos relacionados con la materia que se reclama como nueva e inventiva en presente solicitud, encontrándose los siguientes documentos más relevantes:

Nº	Documento	Título	Fecha de publicación*
D1	US 4748171	Cefem compounds having at the 3-position a (1,4-methylene-1-piperidinio)-methyl group or a (1-quinuclidinio)methyl group	3-may-1988
D2	US5008260	Cephem derivatives	16-abr-1991

12. Análisis de patentabilidad (según requisito) (artículo 14 D486)

12.1 Novedad (artículo 16 D486 de la C.A.N.)

La solicitud en estudio reclama los compuestos derivados de 4-(hidroximetil-disustituido)-1-alkilfenil-1-azoniabicyclo[2.2.2]octano, con fórmula:

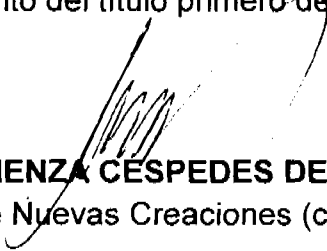


Las anterioridades D1 y D2 comprenden derivados de 4-(hidroximetil-disustituido)-1-alkilfenil-1-azoniabicyclo[2.2.2]octano, pero no coinciden con los compuestos reclamados en las reivindicaciones 1-20 (folios 207 a 211), por lo tanto la solicitud en estudio cumple con lo dispuesto en el artículo 16 D486 de la C.A.N.

6. Conclusión:

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de 60 días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


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

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

[54] CEPHEM COMPOUNDS HAVING AT THE 3-POSITION A (1,4-METHYLENE-1-PIPERIDINIO)-METHYL GROUP OR A (1-QUINUCLIDINIO)-METHYL GROUP

[75] Inventors: Hiroshi Yamauchi; Isao Sugiyama; Isao Saito; Seichiro Nomoto; Takashi Kamiya; Yoshimasa Machida; Shigeto Negi, all of Ibaraki, Japan

[73] Assignee: Eisai Co., Ltd., Tokyo, Japan

[21] Appl. No.: 818,824

[22] Filed: Jan. 14, 1986

[30] Foreign Application Priority Data

Jan. 14, 1985 [JP] Japan 60-3181
Apr. 11, 1985 [JP] Japan 60-75333
Sep. 9, 1985 [JP] Japan 60-174326

[51] Int. Cl.⁴ A61K 31/54; C07D 501/46
[52] U.S. Cl. 514/202; 540/222
[58] Field of Search 544/22; 514/202; 540/222

References Cited

U.S. PATENT DOCUMENTS

4,525,473 6/1985 Abaraki et al. 544/22

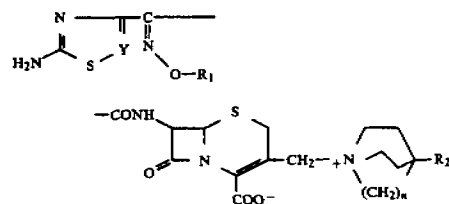
FOREIGN PATENT DOCUMENTS

0062321 10/1982 European Pat. Off. 544/22
03938 9/1985 PCT Int'l Appl. 544/22

Primary Examiner—Donald G. Daus
Assistant Examiner—Mark W. Noel
Attorney, Agent, or Firm—Wenderoth, Lind & Ponack

ABSTRACT

Described herein is a cephem derivative represented by the general formula:



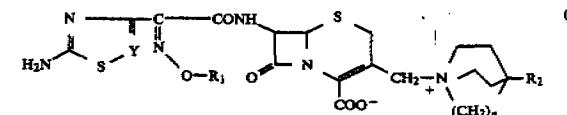
wherein n stands for 1 or 2, Y stands for CH or nitrogen atoms, R₁ represents a lower hydrocarbon group or a carboxyl-substituted, a carbamoyl-substituted, or a cyclopropyl-substituted lower alkyl group, and R₂ denotes hydroxyl group, a lower alkyl group, a hydroxy-substituted lower alkyl group, or carbamoyl group. The derivative is useful as an antibacterial agent. Also described herein are processes for the production of the derivative, antibacterial composition, intermediate of the derivative and process for the production thereof.

9 Claims, No Drawings

CEPHEM COMPOUNDS HAVING AT THE 3-POSITION A (1,4-METHYLENE-1-PIPERIDINIO)-METHYL GROUP OR A (1-QUINUCLIDINIO)-METHYL GROUP

DESCRIPTION OF THE INVENTION

The compounds of this invention are defined as follows:
5 A cephem derivative represented by the general formula:



BACKGROUND OF THE INVENTION

1. Field of the Invention
This invention relates to novel cephem derivatives useful as antibacterial agents, process for the production thereof, antibacterial composition, intermediates thereof and process thereof.

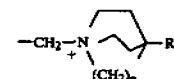
2. Description of the Prior Art

A number of compounds have heretofore been known which contain a substituted thiazolylacetamido group or substituted thiazolylacetamido group at the 7-position of the cephem skeleton. For example, the compounds may be disclosed in the following publications: Japanese Patent Application Laid-open Nos. 11600/1980, 105689/1980, 24389/1982, 81493/1982, 4789/1983, 41887/1983, 59992/1983, 149296/1981, 102293/1977, 116492/1977, 125190/1977, 154786/1979, 192394/1982, 219292/1984, 97982/1985, 197693/1985, 231683/85, etc.

Particularly, 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1-quinuclidinio)methyl-3-cephem-4-carboxylate is described in Japanese Patent Application Laid-open Nos. 219292/1984, 197693/1985, and 231683/1985. However, this compound can not be practically used from a clinical point of view, because its acute toxic value [LD₅₀ (mouse, intravenous injection)] amounts to about 100 mg/kg or less, and hence, the compound is very toxic.

SUMMARY OF THE INVENTION

The present inventors have found that cephem derivatives, each of which has the hereinafter-described group at the 3-position of the cephem skeleton, have excellent antibacterial activities, leading to completion of this invention:



wherein n stands for 1 or 2 and R₂ denotes hydroxyl group, a lower alkyl, a hydroxy-substituted lower alkyl group, or carbamoyl group.

An object of this invention is therefore to provide novel compounds useful as antibacterial agents, their production process and their use as an antibacterial composition.

Further object of this invention is to provide novel intermediates of the above cephem derivatives and the process for the production thereof.

wherein n stands for 1 or 2, Y stands for CH or nitrogen atom, R₁ represents a lower hydrocarbon group or a carboxyl-substituted, a carbamoyl-substituted, or a cyclopropyl-substituted lower alkyl group, and R₂ denotes hydroxyl group, a lower alkyl group, a hydroxy-substituted lower alkyl group, or carbamoyl group, or a pharmaceutically acceptable salt thereof.

As the lower hydrocarbon group represented by R₁ in the general formula (I), there may be mentioned lower alkyl groups such as methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl and sec-butyl; lower alkenyl groups such as vinyl and allyl; lower alkynyl groups such as propargyl; and the like. Examples of the carboxy-substituted lower alkyl group represented by R₁ may include carboxymethyl, 2-carboxy-ethyl, 3-carboxypropyl, 1-carboxyethyl, 1-carboxy-1-methylethyl, and the like. Exemplary carbamoyl-substituted lower alkyl groups represented by R₁ may include carbamoylmethyl, 2-carbamoyl-ethyl, 3-carbamoylpropyl, 1-carbamoyl-1-methylethyl, 1-carbamoyl-ethyl and the like. Exemplary cyclopropyl-substituted lower alkyl groups represented by R₁ may include cyclopropylmethyl, 2-cyclopropylethyl, and the like.

As exemplary hydroxy-substituted lower alkyl groups represented by R₂, there may be mentioned hydroxy-methyl, 2-hydroxyethyl, 1-hydroxyethyl, 3-hydroxypropyl and the like. Exemplary lower alkyl groups represented by R₂ may include methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl, and the like.

As non-toxic salts of the compounds of the general formula (I), may be mentioned their pharmaceutically-acceptable salts, for example, alkali metal salts such as sodium salts and potassium salts; alkaline earth metal salts such as calcium salts and magnesium salts; inorganic acid salts such as hydrochlorides, hydrobromides, hydroiodides, sulfates, carbonates and bicarbonates; organic carboxylates such as maleates, lactates and tartrates; organic sulfonates such as methanesulfonates, benzenesulfonates and toluenesulfonates; amino acid salts such as arginine salts, lysine salts, serine salts, aspartates and glutamates; amine salts such as trimethylamine salts, triethylamine salts, pyridine salts, procaine salts, picoline salts, dicyclohexylamine salts, N,N'-dibenzylethylenediamine salts, N-methylglucamine salts, diethanolamine salts, triethanolamine salts, tris(hydroxymethylamino)methane salts and phenethylbenzylamine salts; and the like.

Each of the compounds of the general formula (I), which pertains to the present invention, has its syn-isomer (Z) and anti-isomer (E) with respect to its configuration at the following moiety:

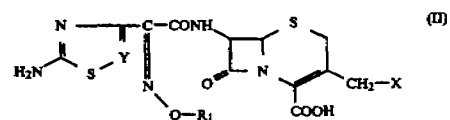


Although both isomers are included in the present invention, the syn-isomers are desired owing to their anti-bacterial activities.

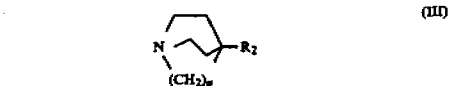
The compounds of this invention can be produced by the following processes.

I: First Process for Production:

The compounds of the general formula (I) and their pharmaceutically acceptable salts can be obtained by reacting a compound represented by the general formula:



wherein Y and R₁ have the same meanings as defined above and X represents a halogen atom, or a compound wherein the amino group and/or carboxyl group is/are protected by a protective group, or a salt thereof, with a compound represented by the general formula:



wherein n and R₂ have the same meanings as defined above, or with a salt thereof, followed by optionally removing the protective group.

As halogen atoms represented by X in the above general formula (II), there may be mentioned iodine atom, bromine atom and chlorine atom. Of these, iodine atom and bromine atom are particularly desired.

The above reaction may be carried out at a reaction temperature of -10° C. to 60° C. or preferably 0° C. to 40° C. As a reaction solvent, an anhydrous organic solvent is desired. As usable organic solvents, there may be mentioned lower alkylnitriles such as acetonitrile and propionitrile; halogenated lower alkyls such as chloromethane, methylene chloride and chloroform; ethers such as tetrahydrofuran and dioxane; amides such as N,N-dimethylformamide; esters such as ethyl acetate; ketones such as acetone; and hydrocarbons such as benzene; as well as mixed solvents thereof.

As the salts of the compounds of the general formulae (II) and (III) and the protective groups for the amino group and carboxyl group in the compounds of the general formula (II), those employed routinely may also be used so long as they do not impair the reaction.

For example, the formyl group, acetyl group, chloroacetyl group, dichloroacetyl group, t-butoxycarbonyl group, benzyloxycarbonyl group, trityl group, p-methoxybenzyl group, diphenylmethyl group and the like may be used as protective groups for amino group; and p-methoxybenzyl group, p-nitrobenzyl group, t-butyl group, methyl group, 2,2,2-trichloroethyl group, diphenylmethyl group, pivaloyloxymethyl group and the like as protective groups for carboxyl group. Fur-

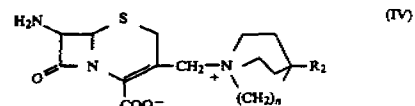
ther, use of a silylating agent such as bis(trimethylsilyl)acetamide, N-methyl-N-(trimethylsilyl)acetamide or N-methyl-N-(trimethylsilyl)trifluoroacetamide and the like is convenient because such a silylating agent can protect both amino and carboxyl groups at the same time.

As salts of the compounds of the general formulae (II) and (III), suitable selection may be made from their salts such as their alkali metal salts such as sodium salts and potassium salts; alkaline earth metal salts such as calcium salts and magnesium salts; ammonium salts; inorganic acid salts such as hydrochlorides, hydrobromides, sulfates, carbonates, hydroiodides and bicarbonates; organic carboxylates such as acetates, maleates, lactates and tartrates; organic sulfonates such as methanesulfonates, benzenesulfonates and toluenesulfonates; amine salts such as trimethylamine salts, triethylamine salts, pyridine salts, procaine salts, picoline salts, dicyclohexylamine salts, N,N'-dibenzylethylenediamine salts, N-methylglucamine salts, diethanolamine salts, triethanolamine salts, tris(hydroxymethylamino)methane salts and phenethylbenzylamine salts; amino acid salts such as arginine salts, aspartates, lysine salts, glutamates and serine salts; and the like.

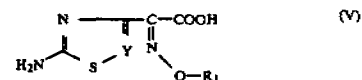
The removal of the protective group can be carried out by any conventional processes such as hydrolysis, reduction, and the like, depending on the types of the protective groups used.

II: Second Process for Production:

The compounds of the general formula (I) and their pharmaceutically acceptable salts can also be obtained by reacting a compound represented by the general formula:



wherein n and R₂ have the same meanings as defined above, or a compound wherein the group -COO- has been protected by a protective group, or a salt thereof, with a compound represented by the general formula:



wherein Y and R₁ have the same meanings as defined above, or a compound wherein the amino group has been protected by a protective group, or a reactive derivative at the carboxyl group thereof, or a salt thereof, and followed by optionally removing the protective group.

The process may be carried out in accordance with any conventional N-acylating reaction conditions. For example, the reaction may be performed in an inert solvent at a temperature of -50° C. to 50° C., preferably -20° C. to 30° C. in the presence or absence of a base. Examples of the inert solvent include acetone, tetrahydrofuran, N,N-dimethylformamide, N,N-dimethylacetamide, dioxane, dichloromethane, chloroform, benzene, toluene, acetonitrile, or the mixed solvents thereof. Examples of the base include N,N-dimethylani-

line, triethylamine, pyridine, N-methylmorpholine and the like.

In the case where the carboxylic acids (-COOH) represented by the general formula (V) are used in the process according to the present invention, the reaction is preferably carried out in the presence of a condensation agent such as N,N'-dicyclohexylcarbodiimide, N,N'-diethylcarbodiimide, N-cyclohexyl-N'-morpholinoethylcarbodiimide, trialkyl phosphite, ethyl polyphosphate, p-toluenesulfonic acid chloride and the like. Furthermore, in the case where such a reactive derivative at the carboxyl group in the general formula (V) is used, an example of the reactive derivative includes acid halides such as acid chloride, acid bromide and the like; symmetrical acid anhydrides; mixed acid anhydrides with carboxylic acid such as ethyl chloroacetate, trimethylacetic acid, thioacetic acid, diphenylacetic acid and the like; active esters with 2-mercaptopyridine, cyanomethanol, p-nitrophenol, 2,4-dinitrophenol, pentachlorophenol and the like; and active acid amides with saccharin and the like.

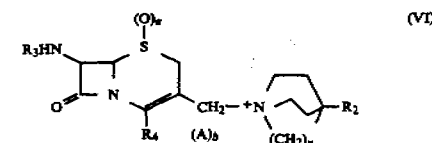
As the protective groups for -COO- of the compound of the general formula (IV), there can be similarly used the groups which were mentioned as the protective groups for carboxyl group of the compound of the aforesaid general formula (II).

As the protective group for the amino group of the compound of the general formula (V), there can be used the groups which were illustrated as the protective groups for the amino group of the compound of the above-mentioned general formula (II).

These protective groups can be removed by any conventional manner, such as hydrolysis, reduction, and the like, depending on the types of the protective groups used.

As the salts of the compounds of the formulae (IV) and (V), there may be suitably selected the salts which were illustrated as the salts of the compounds of the general formulae (II) and (III).

The novel compounds represented by the general formula:



wherein n and R₂ have the same meanings as defined above, a is 0 or 1, R₃ represents hydrogen atom or a protective group for the amino group, A denotes an anion, and b stands for 0, when R₄ denotes a group -COO-, and for 1, when R₄ represents a group -COOR₅ (R₅ being a protective group for the carboxyl group), or a salt thereof, inclusive of the compounds represented by the general formula (IV) are intermediates for the compounds represented by the general formula (I) of the present invention. These compounds are used for the production of the compounds of the present invention in accordance with the above-mentioned second process for the production.

Examples of R₃ being the protective group for the amino group in the compounds represented by said general formula (VI) include those employed usually in this field, for example, substituted or unsubstituted lower alkanoyl groups, such as formyl, acetyl, chloro-

acetyl, dichloroacetyl, propionyl, phenylacetyl, 2-thienylacetyl, 2-furylacetyl, phenoxyacetyl and the like; substituted or unsubstituted lower alkoxy carbonyl groups such as benzyloxycarbonyl, t-butoxycarbonyl, p-nitrobenzyloxycarbonyl and the like; substituted lower alkyl groups such as trityl, p-methoxybenzyl, diphenylmethyl and the like; and substituted silyl groups such as trimethylsilyl, t-butyl dimethylsilyl and the like.

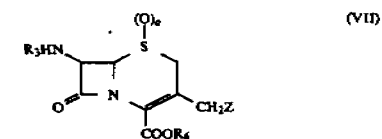
Examples of R₅ being the protective group for the carboxyl group include those employed usually in this field, for example, substituted or unsubstituted lower alkyl groups such as methyl, ethyl, propyl, t-butyl, 2,2,2-trichloroethyl, valeryloxymethyl, pivaloyloxymethyl, p-nitrobenzyl, p-methoxybenzyl, diphenylmethyl and the like; and substituted silyl groups such as trimethylsilyl, t-butyl dimethylsilyl and the like.

Examples of the anion in A include halogen ions such as chloro ion, bromo ion, iodo ion and the like; and inorganic acid ions such as sulfuric acid ion, nitric acid ion and the like.

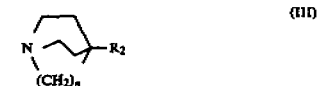
An example of salts of the compounds represented by the general formula (VI) includes inorganic acid salts such as hydrochloride, hydrobromide, hydroiodide, sulfate, carbonate, bicarbonate and the like; organic carboxylates such as, acetate, maleate, lactate, tartrate, trifluoroacetate and the like; organic sulfonates such as methanesulfonate, benzenesulfonate, toluenesulfonate and the like; and amino acid salts such as aspartate, glutamate and the like.

The compounds represented by the general formula (VI) can be produced in accordance with the following process.

A compound represented by the general formula:



wherein a and R₃ have the same meanings as defined above, R₆ denotes hydrogen atom or a protective group for the carboxyl group, and Z is a halogen atom or a lower alkanoyloxy group, or a salt thereof is reacted with a compound represented by the general formula:



wherein n and R₂ have the same meanings as defined above, or with a salt thereof, followed by, if necessary, removal of the protective group and/or reduction of the sulfoxide to obtain the compounds having the aforesaid general formula (VI) or the salts thereof.

In the case wherein Z in the general formula (VII) represents a halogen atom, the above reaction may be carried out in an inert solvent such as acetone, tetrahydrofuran, N,N-dimethylformamide, methylene chloride, chloroform, acetonitrile, and the like at a reaction temperature of -10° C. to 50° C.

219

United States Patent [19]

Yamauchi et al.

[11] Patent Number: 5,008,260

[45] Date of Patent: Apr. 16, 1991

[54] CEPHEM DERIVATIVES

[75] Inventors: Hiroshi Yamauchi; Isao Sugiyama;
Isao Saito; Seiichiro Nomoto; Takashi
Kamiya; Yoshimasa Machida; Shigeto
Negi, all of Ibaraki, Japan

[73] Assignee: Eisai Co., Ltd., Tokyo, Japan

[21] Appl. No.: 167,153

[22] Filed: Mar. 16, 1988

Related U.S. Application Data

[62] Division of Ser. No. 818,824, Jan. 14, 1986, Pat. No.
4,748,171.

[30] Foreign Application Priority Data

Jan. 14, 1985 [JP] Japan 60-3181
Apr. 11, 1985 [JP] Japan 60-75333
Aug. 9, 1985 [JP] Japan 60-174326

[51] Int. Cl.⁵ C07D 501/38; A61K 31/545

[52] U.S. Cl. 514/202; 540/222;
540/225

[58] Field of Search 514/202; 540/222, 225,
540/221

[56] References Cited

U.S. PATENT DOCUMENTS

4,525,473 6/1985 Aluraki et al. 514/202
4,698,336 10/1987 Saito et al. 540/222
4,748,171 5/1988 Yamauchi et al. 540/222
4,929,612 5/1990 Machida et al. 540/222

FOREIGN PATENT DOCUMENTS

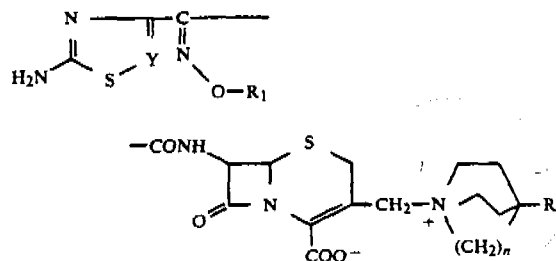
0062321 10/1982 European Pat. Off. 544/22
03938 9/1985 PCT Int'l Appl. 544/22

Primary Examiner—Nicholas S. Rizzo

Attorney, Agent, or Firm—Wenderoth, Lind & Ponack

[57] ABSTRACT

Described herein is a cephem derivative represented by the general formula:



wherein n stands for 1 or 2, Y stands for CH or nitrogen atom, R₁ represents a lower hydrocarbon group or a carboxyl-substituted, a carbamoyl-substituted, or a cyclopropyl-substituted lower alkyl group, and R₂ denotes hydroxyl group, a lower alkyl group, a hydroxy-substituted lower alkyl group, or carbamoyl group. The derivative is useful as an antibacterial agent. Also described herein are processes for the production of the derivative, antibacterial composition, intermediate of the derivative and process for the production thereof.

10 Claims, No Drawings

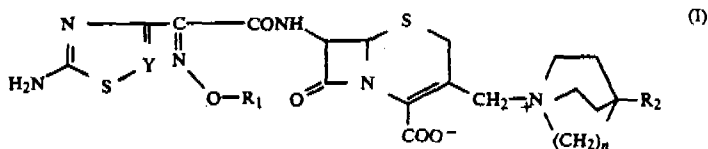
CEPHEM DERIVATIVES

This application is a division of Ser. No. 818,824 filed Jan. 14, 1986, now U.S. Pat. No. 4,748,171.

DESCRIPTION OF THE INVENTION

The compounds of this invention are defined as follows:

- 5 A cephem derivative represented by the general formula:



BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to novel cephem derivatives useful as antibacterial agents, process for the production thereof, antibacterial composition, intermediates thereof and process therefor.

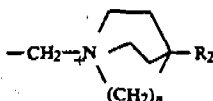
2. Description of the Prior Art

A number of compounds have heretofore been known which contain a substituted thiazolidylacetamido group or substituted thiazolylacetamido group at the 7-position of the cephem skeleton. For example, the compounds may be disclosed in the following publications: Japanese Patent Application Laid-open Nos. 11600/1980, 105689/1980, 24389/1982, 81493/1982, 4789/1983, 41887/1983, 59992/1983, 149296/1981, 102293/1977, 116492/1977, 125190/1977, 154786/1979, 192394/1982, 219292/1984, 97982/1985, 197693/1985, 231683/85, etc.

Particularly, 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1-quinuclidinio)methyl-3-cephem-4-carboxylate is described in Japanese Patent Application Laid-open Nos. 219292/1984, 197693/1985, and 231683/1985. However, this compound can not be practically used from a clinical point of view, because its acute toxic value [LD₅₀ (mouse, intravenous injection)] amounts to about 100 mg/kg or less, and hence, the compound is very toxic.

SUMMARY OF THE INVENTION

The present inventors have found that cephem derivatives, each of which has the hereinunderdescribed group at the 3-position of the cephem skeleton, have excellent antibacterial activities, leading to completion of this invention.



wherein n stands for 1 or 2 and R₂ denotes hydroxyl group, a lower alkyl, a hydroxy-substituted lower alkyl group, or carbamoyl group.

An object of this invention is therefore to provide novel compounds useful as antibacterial agents, their production process and their use as an antibacterial composition.

Further object of this invention is to provide novel intermediates of the above cephem derivatives and the process for the production thereof.

wherein n stands for 1 or 2, Y stands for CH or nitrogen atom, R₁ represents a lower hydrocarbon group or a carboxyl-substituted, a carbamoyl-substituted, or a cyclopropyl-substituted lower alkyl group, and R₂ denotes hydroxyl group, a lower alkyl group, a hydroxy-substituted lower alkyl group, or carbamoyl group, or a pharmaceutically acceptable salt thereof.

- 25 As the lower hydrocarbon group represented by R₁ in the general formula (I), there may be mentioned lower alkyl groups such as methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl and sec-butyl; lower alkenyl groups such as vinyl and allyl; lower alkynyl groups such as propargyl; and the like. Examples of the carboxy-substituted lower alkyl group represented by R₁ may include carboxymethyl, 2-carboxy-ethyl, 3-carboxypropyl, 1-carboxyethyl, 1-carboxy-1-methylethyl, and the like. Exemplary carbamoyl-substituted lower alkyl groups represented by R₁ may include carbamoylmethyl, 2-carbamoylethyl, 3-carbamoylpropyl, 1-carbamoyl-1-methylethyl, 1-carbamoylethyl and the like. Exemplary cyclopropyl-substituted lower alkyl groups represented by R₁ may include cyclopropylmethyl, 2-cyclopropylethyl, and the like.

- As exemplary hydroxy-substituted lower alkyl groups represented by R₂, there may be mentioned hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl, 3-hydroxypropyl and the like. Exemplary lower alkyl groups represented by R₂ may include methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl, and the like.

- As non-toxic salts of the compounds of the general formula (I), may be mentioned their pharmaceutically-acceptable salts, for example, alkali metal salts such as sodium salts and potassium salts; alkaline earth metal salts such as calcium salts and magnesium salts; inorganic acid salts such as hydrochlorides, hydrobromides, hydroiodides, sulfates, carbonates and bicarbonates; organic carboxylates such as maleates, lactates and tartrates; organic sulfonates such as methanesulfonates, benzenesulfonates and toluenesulfonates; amino acid salts such as arginine salts, lysine salts, serine salts, aspartates and glutamates; amine salts such as trimethylamine salts, triethylamine salts, pyridine salts, procaine salts, picoline salts, dicyclohexylamine salts, N,N'-dibenzylethylenediamine salts, N-methylglucamine salts, diethanolamine salts, triethanolamine salts, tris(hydroxymethylamino)methane salts and phenethylbenzylamine salts; and the like.

- 65 Each of the compounds of the general formula (I), which pertains to the present invention, has its syn-isomer (Z) and anti-isomer (E) with respect to its configuration at the following moiety:

line, triethylamine, pyridine, N-methylmorpholine and the like.

In the case where the carboxylic acids ($-\text{COOH}$) represented by the general formula (V) are used in the process according to the present invention, the reaction is preferably carried out in the presence of a condensation agent such as N,N'-dicyclohexylcarbodiimide, N,N'-diethylcarbodiimide, N-cyclohexyl-N'-morpholinoethylcarbodiimide, trialkyl phosphite, ethyl polyphosphate, p-toluenesulfonic acid chloride and the like. Furthermore, in the case where such a reactive derivative at the carboxyl group in the general formula (V) is used, an example of the reactive derivative includes acid halides such as acid chloride, acid bromide and the like; symmetrical acid anhydrides; mixed acid anhydrides with carboxylic acid such as ethyl chloro-carbonate, trimethylacetic acid, thioacetic acid, diphenylacetic acid and the like; active esters with 2-mercaptopyridine, cyanomethanol, p-nitrophenol, 2,4-dinitrophenol, pentachlorophenol and the like; and active acid amides with saccharin and the like.

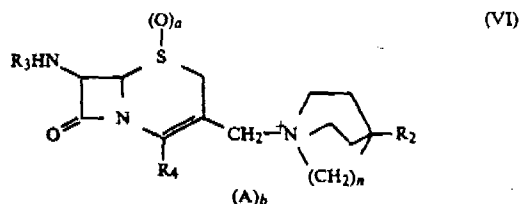
As the protective groups for $-\text{COO}-$ of the compound of the general formula (IV), there can be similarly used the groups which were mentioned as the protective groups for carboxyl group of the compound of the aforesaid general formula (II).

As the protective group for the amino group of the compound of the general formula (V), there can be used the groups which were illustrated as the protective groups for the amino group of the compound of the above-mentioned general formula (II).

These protective groups can be removed by any conventional manner, such as hydrolysis, reduction, and the like, depending on the types of the protective groups used.

As the salts of the compounds of the formulae (IV) and (V), there may be suitably selected the salts which were illustrated as the salts of the compounds of the general formulae (II) and (III).

The novel compounds represented by the general formula:



wherein n and R_2 have the same meanings as defined above, a is 0 or 1, R_3 represents hydrogen atom or a protective group for the amino group, A denotes an anion, and b stands for 0, when R_4 denotes a group $-\text{COO}-$, and for 1, when R_4 represents a group $-\text{COOR}_5$ (R_5 being a protective group for the carboxyl group), or a salt thereof, inclusive of the compounds represented by the general formula (IV) are intermediates for the compounds represented by the general formula (I) of the present invention. These compounds are used for the production of the compounds of the present invention in accordance with the above-mentioned second process for the production.

Examples of R_3 being the protective group for the amino group in the compounds represented by said general formula (VI) include those employed usually in this field, for example, substituted or unsubstituted

lower alkanoyl groups, such as formyl, acetyl, chloroacetyl, dichloroacetyl, propionyl, phenylacetyl, 2-thienylacetyl, 2-furylacetyl, phenoxyacetyl and the like; substituted or unsubstituted lower alkoxy carbonyl groups such as benzyloxycarbonyl, t-butoxycarbonyl, p-nitrobenzyloxycarbonyl and the like; substituted lower alkyl groups such as trityl, p-methoxybenzyl, diphenylmethyl and the like; and substituted silyl groups such as trimethylsilyl, t-butyldimethylsilyl and the like.

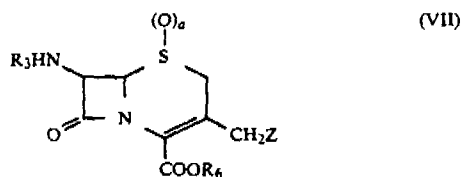
Examples of R_5 being the protective group for the carboxyl group include those employed usually in this field, for example, substituted or unsubstituted lower alkyl groups such as methyl, ethyl, propyl, t-butyl, 2,2,2-trichloroethyl, valeryloxymethyl, pivaloyloxymethyl, p-nitrobenzyl, p-methoxybenzyl, diphenylmethyl and the like; and substituted silyl groups such as trimethylsilyl, t-butyldimethylsilyl and the like.

Examples of the anion in A include halogen ions such as chloro ion, bromo ion, iodo ion and the like; and inorganic acid ions such as sulfuric acid ion, nitric acid ion and the like.

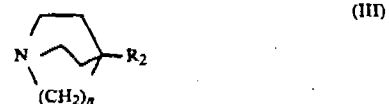
An example of salts of the compounds represented by the general formula (VI) includes inorganic acid salts such as hydrochloride, hydrobromide, hydroiodide, sulfate, carbonate, bicarbonate and the like; organic carboxylates such as, acetate, maleate, lactate, tartrate, trifluoroacetate and the like; organic sulfonates such as methanesulfonate, benzenesulfonate, toluenesulfonate and the like; and amino acid salts such as aspartate, glutamate and the like.

The compounds represented by the general formula (VI) can be produced in accordance with the following process.

A compound represented by the general formula:



wherein a and R_3 have the same meanings as defined above, R_6 denotes hydrogen atom or a protective group for the carboxyl group, and Z is a halogen atom or a lower alkanoyloxy group, or a salt thereof is reacted with a compound represented by the general formula:



wherein n and R_2 have the same meanings as defined above, or with a salt thereof, followed by, if necessary, removal of the protective group and/or reduction of the sulfoxide to obtain the compounds having the aforesaid general formula (VI) or the salts thereof.

In the case wherein Z in the general formula (VII) represents a halogen atom, the above reaction may be carried out in an inert solvent such as acetone, tetrahydrofuran, N, N-dimethylformamide, methylene chloride, chloroform, acetonitrile, and the like at a reaction temperature of -10°C. to 50°C.