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Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S D.

Re: P1.-**ASTRAZENECA AB**.- Solicitud de Patente de Invención para **"NUEVOS ACIDOS AMINOPROPILFOSFINICOS".-** Clase A61.-Expediente número 00-093.167.-

1. Me refiero a mi solicitud arriba mencionada de fecha 6 de Diciembre de 2000.

2. Anexos me permito presentar a usted:

(1) Copia autentica, debidamente legalizada hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 392393 de 23 de Noviembre de 2000, de la solicitud de patente presentada para el invento arriba nombrado **respecto de la cual reclamo prioridad,** a saber la solicitud sueca número 9904508-0 de 9 de Diciembre de 1999, junto con su traducción, también debidamente legalizada hasta por el Ministerio de Relaciones exteriores bajo el número 486724 de 6 de Diciembre de 2000, correspondiente a las legalizaciones y reivindicaciones de dicho documento;

(2) Copia autentica, debidamente legalizada hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 392392 de 23 de Noviembre de 2000, de la solicitud de patente presentada para el invento arriba nombrado **respecto de la cual reclamo prioridad,** a saber la solicitud sueca número 0003640-0 de 9 de Octubre de 2000, junto con su traducción, también debidamente legalizada

hasta por el Ministerio de Relaciones exteriores bajo el número 486723 de 6 de Diciembre de 2000, correspondiente a las legalizaciones y reivindicaciones de dicho documento;

(3) Copia debidamente autenticada por el Notario Sexto del Circulo de Bogotá, de los documentos que acreditan la calidad de Traductor Oficial de la señora María Luisa Brigard de Restrepo quien elaboró la traducción de las legalizaciones y reivindicaciones de las solicitudes suecas número 9904508-0 y 0003640-0 de 9 de Diciembre de 1999 y 9 de Octubre de 2000 respectivamente;

(4) Documento que acredita el traspaso que los autores del invento de la referencia hacen a favor de mi representando, de sus derechos sobre el mismo, debidamente legalizado hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 490025 de 12 de Diciembre de 2000;

(5) Traducción Oficial No. 365/12-00, debidamente legalizada hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 580710 de 20 de Diciembre de 2000, correspondiente a las legalizaciones de dicho documento de traspaso;

(6) Documento que acredita el traspaso que el autor del invento de la referencia hace a favor de mi representando, de sus derechos sobre el mismo, debidamente legalizado hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 490020 de 12 de Diciembre de 2000; y

(7) Traducción Oficial No. 8185, debidamente legalizada hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 494068 de 15 de Diciembre de 2000, correspondiente a las legalizaciones de dicho documento de traspaso.

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3. Ruego a usted tomar atenta nota de lo anterior y proceder de conformidad.

Señor Superintendente,

JOSE ANTONIO LLOREDA
T.P. 10.784
Código 231

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REPUBLICA DE COLOMBIA
MINSTERIO DE RELACIONES EXTERIORES

EL SUSCRITO JEFE DEL AREA DE LEGALIZACIONES DEL MINISTERIO DE RELACIONES EXTERIORES

C E R T I F I C A

Que revisados los registros que se llevan en la oficina de Legalizaciones aparece la firma de la señora **MARIA LUISA DE BRIGARD DE RESTREPO**, como traductora e intérprete oficial para los idiomas **INGLES - ESPAÑOL, ESPAÑOL-INGLES,** según resolución 0793 del 21 de marzo de 1958

La anterior certificación se expide a solicitud de la interesada quien se identificó con cédula de ciudadanía No. 20.024.691 expedida en Santa Fe de Bogotá.

Dada en Santa Fe de Bogotá, D.C. a los veinticinco (25) días de marzo de 1999

CARLOS GUILLERMO DIAZ BUITRAGO
Jefe Area de Legalizaciones

EL NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE BOGOTA, HAGO CONSTAR QUE ESTA COPIA FOTOSTATICA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
23 OCT 2000
JUAN MANUEL ROTERO MEDINA
NOTARIO

Astra
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09

TRADUCCION OFICIAL No. 5.786

de un documento escrito en INGLES, el cual para su identificación se sella con el sello del Traductor al mismo tiempo que la presente. -

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TRADUCCION OFICIAL No. 5.786
María Luisa Brigard de Restrepo
Intérprete Oficial
Res. No. 0793 del Min. de Justicia

PRV

DIRECCION NACIONAL DE PATENTES Y REGISTRO

Certificado

Por el presente se certifica que la anexa es una copia fiel de los documentos registrados originalmente ante la Oficina de Patentes y Registro en relación con la siguiente solicitud de patente.

La solicitud fue registrada originalmente en inglés.

(71) Solicitante(s) Astra AB, Södertälje SE

(21) Solicitud de patente número 9904508-0

(86) Fecha de registro 9-12-1999

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Estocolmo, 20-10-2000

Por la Oficina de Patentes y Registro

(Firma)

Therese Friberger

Derechos 170:-

TRADUCCION OFICIAL No. 5.786

María Luisa Briceño de Restrepo
Intérprete Oficial
en Otras del Min. de Justicia

EN ESPAÑOL, las autenticaciones de la firma anterior hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 392393 de fecha 23 de noviembre del 2.000

MINISTERIO DE RELACIONES EXTERIORES
CUYA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS.
486724

REIVINDICACIONES

1. Un compuesto acorde con la fórmula I

en donde

HO SE ASUME RESPONSABILIDAD EN EL TEXTO
JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.
2000 DIC -6

R_1 representa hidrógeno, hidroxi, alquilo inferior, alcoxi inferior o halógeno;

R_2 representa hidroxi, mercapto, halógeno o un grupo oxo;

R_3 representa hidrógeno, alquilo inferior (opcionalmente sustituído con hidroxi, mercapto, alcoxi inferior, tioalcoxi inferior o arilo);

R_4 representa hidrógeno, alquilo inferior (opcionalmente sustituído con arilo), o arilo;

y sales farmaceuticamente aceptables y los esteroisómeros del mismo,

con la excepción de:

i) el racemato de ácido (3-amino-2-hidroxipropil)fosforoso, y

ii) ácido (2*R/S*, 3*R*)-(3-amino-2-hidroxibutil)fosforoso.

2. Un compuesto acorde con la reivindicación 1 en el que

R_1 representa hidrógeno;

R_2 representa flúor, hidroxi o un grupo oxo;

R_3 representa hidrógeno;

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R_4 representa hidrógeno;

con la excepción del racemato de ácido (3-amino-2-hidroxipropil)fosforoso.

3. Acido (3-amino-2-fluoropropil)fosforoso o una sal farmaceuticamente aceptable o los esteroisómeros del mismo.

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TRADUCCION OFICIAL No.
María Luisa Brigard de Restrepo
Intérprete Oficial
Real Cédula de Juramento

4. Acido (3-amino-2-oxopropil)fosforoso o una sal farmaceuticamente aceptable o los esteroisómeros del mismo.

5. Acido (*S*)-(3-amino-2-hidroxipropil)fosforoso o una sal farmaceuticamente aceptable o los esteroisómeros del mismo.

6. Un compuesto acorde con la reivindicación 1 para usarlo en terapia.

7. Uso de un compuesto acorde con cualquiera de las reivindicaciones 1 a 5 para la fabricación de un medicamento para la inhibición de relajaciones transitorias del esfínter esofágeo inferior.

8. Uso de un compuesto acorde con cualquiera de las reivindicaciones 1 a 5 para la fabricación de un medicamento para el tratamiento de enfermedad de reflujo gastro-esofágeo.

9. Uso de un compuesto acorde con cualquiera de las reivindicaciones 1 a 5 para la

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fabricación de un medicamento para el tratamiento de regurgitación en infantes.

10. Uso de un compuesto acorde con cualquiera de las reivindicaciones 1 a 5 para la fabricación de un medicamento para asma relacionada o no con GORD, eructos, tos, dolor, adicción a la cocaína, hipo, IBS, dispepsia, emesis o nocicepción.

11. Un método para el tratamiento de relajaciones transitorias del esfínter esofágeo inferior que consiste en tratar a un paciente que sufre de dicho estado con una preparación farmacéutica que comprende un compuesto de la fórmula I.

12. Un método para el tratamiento de enfermedad de reflujo gastro-esofágeo que consiste en tratar a un paciente que sufre de dicho estado con una preparación farmacéutica que comprende un compuesto de la fórmula I.

13. Un método para el tratamiento de regurgitación en infantes que consiste en tratar a un paciente que sufre de dicho estado con una preparación farmacéutica que comprende un compuesto de la fórmula I.

14. Un método para el tratamiento de asma relacionada o no con GORD, eructos, tos, dolor, adicción a la cocaína, hipo, IBS, dispepsia, emesis o nocicepción. que consiste en tratar a un paciente que sufre de dicho estado con una preparación farmacéutica que comprende un compuesto de la fórmula I.

15. Una preparación farmacéutica que comprende como ingrediente activo una

cantidad terapeuticamente aceptable del compuesto de cualquiera de las reivindicaciones 1 a 5, opcionalmente en asociación con diluentes, excipientes o portadores inertes.

16. Una preparación farmacéutica acorde con la reivindicación 15 para usarla en la inhibición de relajaciones transitorias del esfínter esofágeo inferior.

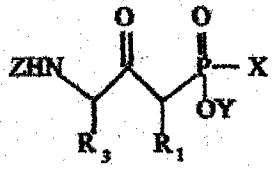
17. Una preparación farmacéutica acorde con la reivindicación 15 para usarla en el tratamiento de enfermedad de reflujo gastro-esofágeo.

18. Una preparación farmacéutica acorde con la reivindicación 15 para usarla en el tratamiento de regurgitación en infantes.

19. Un procedimiento para la preparación de un compuesto de la fórmula I acorde con la reivindicación 1,

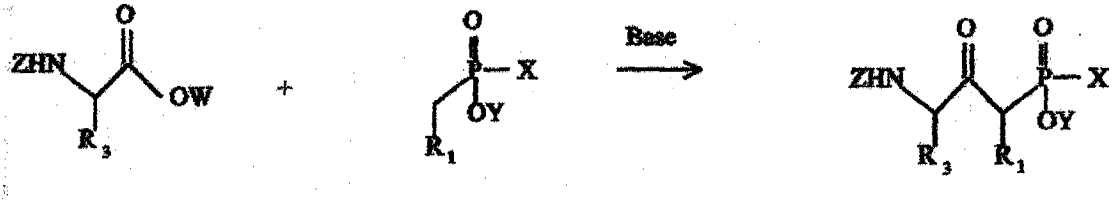
en el que

a) un compuesto de la fórmula II



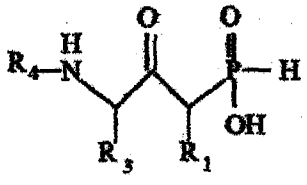
(II)

en donde R_1 y R_3 corresponden a las definiciones dadas arriba en la fórmula I, X es hidrógeno o un grupo protector tal como $-CCH_3(OCH_2CH_3)_2$, Z es un grupo protector tal como t-butiloxicarbonilo y Y es hidrógeno o un grupo protector tal como alquilo inferior. y ese compuesto de la fórmula II puede haber sido sintetizado mediante reacción de condensación de acuerdo con el Esquema 1 empleando un éster de aminoácido N- protegido en el que R_3 corresponde a la definición dada arriba, W es un grupo protector tal como alquilo inferior y Z corresponde a la definición dada en la fórmula II, y un derivado de ácido fosfínico protegido en el que R_1 corresponde a la definición dada arriba en la fórmula I, X y Y corresponden a las definiciones dadas en la fórmula II, y una base tal como diisopropilamida de litio,



Esquema 1

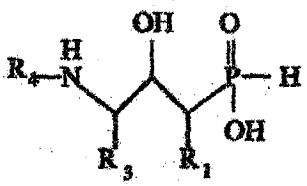
se convierten opcionalmente mediante una reacción de N-alquilación con el fin de introducir R_4, si se desea que R_4 no sea igual a hidrógeno, y luego una reacción hidrolítica para obtener un compuesto de la fórmula III



(III)

en donde R_1, R_3 y R_4 corresponden a las definiciones dadas arriba en la fórmula I, y, si se desea, un compuesto resultante se convierte en otro compuesto de la fórmula III, una mezcla resultante de isómeros se separa en los isómeros individuales y/o una sal resultante obtenida en este proceso se convierte en el compuesto libre de la fórmula III o en otra sal y/o, si se desea, un compuesto libre resultante de la fórmula III se convierte en una sal que corresponda a la definición anterior;

o un compuesto de la fórmula II se convierte, mediante una reacción reductora, opcionalmente una reacción de N-alquilación si se desea que R_4 no sea igual a hidrógeno, y finalmente una reacción hidrolítica para obtener un compuesto de la fórmula IV

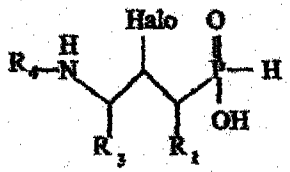


(IV)

en donde R_1, R_3 y R_4 corresponden a las definiciones dadas arriba en la fórmula I, y, si se desea, un compuesto resultante se convierte en otro compuesto de la fórmula IV, una mezcla resultante de isómeros se separa en los isómeros individuales y/o una sal resultante obtenida en este proceso se convierte en el compuesto libre de la fórmula IV o en otra sal y/o, si se desea, un compuesto libre resultante de la fórmula IV se convierte en una sal que corresponda a la definición anterior;

o un compuesto de la fórmula II se convierte, mediante una reacción reductora seguida por una reacción de desoxohalogenación, opcionalmente una reacción de N-alquilación, para

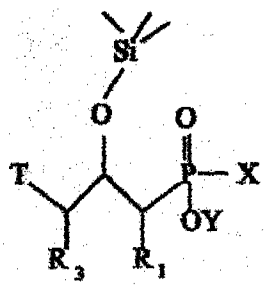
introducir R_4 si se desea que R_4 no sea igual a hidrógeno, y finalmente una reacción hidrolítica para obtener un compuesto de la fórmula V



(V)

en donde R_1, R_3 y R_4 corresponden a las definiciones dadas arriba en la fórmula I y Halo es un átomo de halógeno, y, si se desea, un compuesto resultante se convierte en otro compuesto de la fórmula V, una mezcla resultante de isómeros se separa en los isómeros individuales y/o una sal resultante obtenida en este proceso se convierte en el compuesto libre de la fórmula V o en otra sal y/o, si se desea, un compuesto libre resultante de la fórmula V se convierte en una sal que corresponda a la definición anterior;

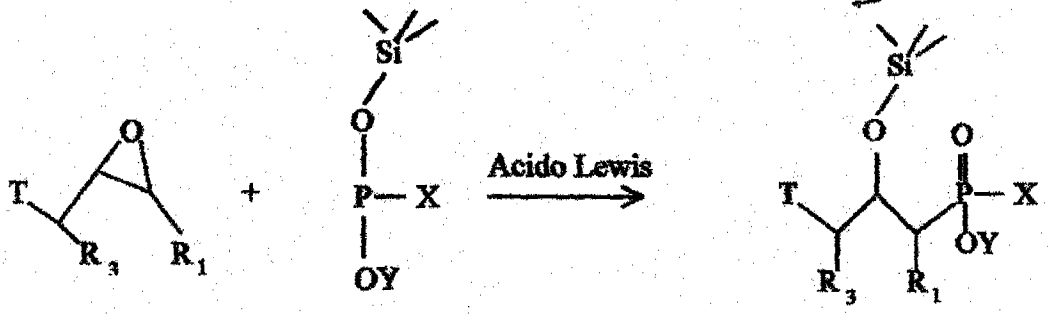
o b) un compuesto de la fórmula VI



(VI)

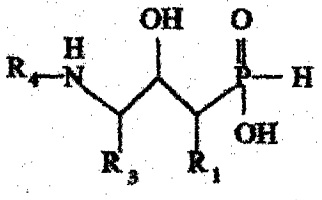
en donde R_1 y R_3 corresponden a las definiciones dadas arriba en la fórmula I, X es hidrógeno o un grupo protector tal como $-CCH_3(OCH_2CH_3)_2$, T es un grupo que puede convertirse en un grupo $-NH_2$, y Y es hidrógeno o un grupo protector tal como alquilo

inferior, y ese compuesto de la fórmula VI puede haber sido sintetizado mediante una reacción de condensación de acuerdo con el Esquema 2 empleando un derivado de 2,3-epoxipropilo, tal como un derivado de 2,3-epoxipropilamina o un derivado de epiclorohidrina N-protegido adecuado, en el que R_1 y R_3 corresponden a las definiciones dadas arriba en la fórmula I, y un derivado de ácido fosfínico protegido adecuado activado mediante O-sililación, en donde X y Y corresponden a las definiciones dadas en la fórmula VI, y un ácido Lewis tal como $ZnCl_2$ anhidro,



Esquema 2

se convierte mediante una reacción en la que el grupo trimetilsililo es reemplazado por un grupo hidrógeno, una reacción en la que el grupo T definido en la fórmula VI se convierte en -NHR_4 en donde R_4 corresponde a la definición dada en la fórmula I, y finalmente una reacción hidrolítica para obtener un compuesto de la fórmula VII



(VII)

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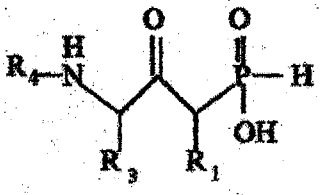
en donde R_1, R_3 y R_4 corresponden a las definiciones dadas arriba en la fórmula I, y si se desea, un compuesto resultante se convierte en otro compuesto de la fórmula VII, una mezcla resultante de isómeros se separa en los isómeros individuales y/o una sal resultante obtenida en este proceso se convierte en el compuesto libre de la fórmula VII o en otra sal y/o, si se desea, un compuesto libre resultante de la fórmula VII se convierte en una sal que corresponda a la definición anterior;

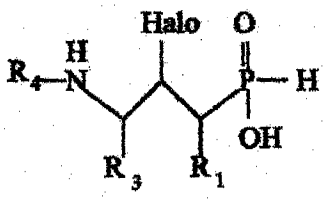
o un compuesto de la fórmula VI se convierte, mediante una reacción en la que el grupo trimetilsililo es reemplazado por hidrógeno, una reacción de oxidación, una reacción en la que el grupo T definido en la fórmula VI se convierte en $-NHR_4$ en donde R_4 corresponde a la definición dada en la fórmula I, y finalmente una reacción hidrolítica para obtener un compuesto de la fórmula VIII



(VIII)

en donde R_1, R_3 y R_4 corresponden a las definiciones dadas arriba en la fórmula I, y si se desea, un compuesto resultante se convierte en otro compuesto de la fórmula VIII, una mezcla resultante de isómeros se separa en los isómeros individuales y/o una sal resultante obtenida en este proceso se convierte en el compuesto libre de la fórmula VIII o en otra sal y/o, si se desea, un compuesto libre resultante de la fórmula VIII se convierte en una sal que corresponda a la definición anterior;

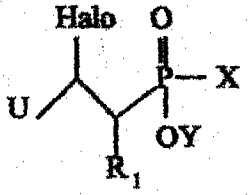
o un compuesto de la fórmula VI se convierte, mediante una reacción en la que el grupo trimetilsililo es reemplazado por hidrógeno, una reacción de oxohalogenación, una reacción en la que el grupo T definido en la fórmula VI se convierte en $-NHR_4$ en donde R_4 corresponde a la definición dada en la fórmula I, y finalmente una reacción hidrolítica para obtener un compuesto de la fórmula IX



(IX)

en donde R_1, R_3 y R_4 corresponden a las definiciones dadas arriba en la fórmula I, y Halo es un átomo de halógeno, y si se desea, un compuesto resultante se convierte en otro compuesto de la fórmula IX, una mezcla resultante de isómeros se separa en los isómeros individuales y/o una sal resultante obtenida en este proceso se convierte en el compuesto libre de la fórmula IX o en otra sal y/o, si se desea, un compuesto libre resultante de la fórmula IX se convierte en una sal que corresponda a la definición anterior;

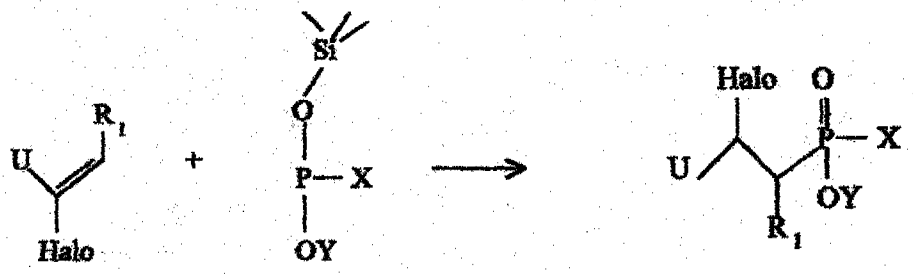
o c) un compuesto de la fórmula XI



(XI)

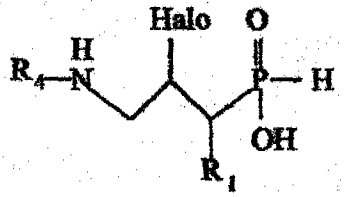
en donde R_1 y R_3 corresponden a las definiciones dadas arriba en la fórmula I, X es

hidrógeno o un grupo protector tal como $-CCH_3(OCH_2CH_3)_2$, U es un grupo que retira electrones, tal como -CN o CO_2Et que puede convertirse en un grupo $-CH_2NH_2$, y Y es hidrógeno o un grupo protector tal como alquilo inferior y Halo es un átomo de halógeno, y ese compuesto de la fórmula XI puede haber sido sintetizado mediante una reacción de adición de acuerdo con el Esquema 3 empleando un compuesto insaturado en el que R_1 corresponde a la definición dada arriba en la fórmula I, U y halo corresponden a las definiciones dadas en la fórmula XI, y un derivado de ácido fosfínico protegido adecuado activado mediante O-sililación, en donde X y Y corresponden a las definiciones dadas en la fórmula XI,



Esquema 3

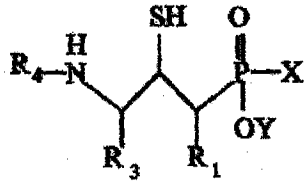
se convierte, mediante una reacción en la que el grupo U se convierte en $-NHR_4$ en donde R_4 corresponde a la definición dada arriba en la fórmula I, y una reacción hidrolítica para obtener un compuesto de la fórmula XII



(XII)

en donde R_1 y R_4 corresponden a las definiciones dadas arriba en la fórmula I, y Halo es un átomo de halógeno, y si se desea, un compuesto resultante se convierte en otro compuesto de la fórmula XII, una mezcla resultante de isómeros se separa en los isómeros individuales y/o una sal resultante obtenida en este proceso se convierte en el compuesto libre de la fórmula XII o en otra sal y/o, si se desea, un compuesto libre resultante de la fórmula XII se convierte en una sal que corresponda a la definición anterior;

o d) un compuesto de la fórmula XIII

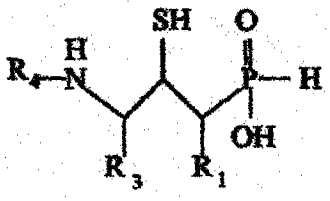


(XIII)

en donde R_1, R_3 y R_4 corresponden a las definiciones dadas arriba en la fórmula I, X es hidrógeno o un grupo protector tal como $-CCH_3(OCH_2CH_3)_2$, y Y es hidrógeno o un grupo protector tal como alquilo inferior, y ese compuesto de la fórmula XIII puede haber sido sintetizado mediante una reacción de adición de acuerdo con el Esquema 4 tratando un derivado de ácido fosfínico insaturado en el que R_1 R_3 y R_4 corresponden a las definiciones dadas arriba en la fórmula I, con H_2S, un ion mercaptido (HS) o un compuesto de mercapto protegido tal como bencilotiol caso en el cual el grupo protector se remueve luego

Esquema 4

se convierte mediante una reacción hidrolítica para obtener un compuesto de la fórmula XIV,



(XIV)

en donde R_1, R_3 y R_4 corresponden a las definiciones dadas arriba en la fórmula I, y si se desea, un compuesto resultante se convierte en otro compuesto de la fórmula XIV, una mezcla resultante de isómeros se separa en los isómeros individuales y/o una sal resultante obtenida en este proceso se convierte en el compuesto libre de la fórmula XIV o en otra sal y/o, si se desea, un compuesto libre resultante de la fórmula XIV se convierte en una sal que corresponda a la definición anterior.

20. 3-[(dietoximetil)(etoxi)fosforil]-2-fluoropropanoato de etilo.

21. (3-amino-2-fluoro-3-oxopropil)(dietoximetil)fosfinato de etilo.

22. (*R*)-(3-cloro-2-hidroxipropil)(1,1-dietoxietil)fosfinato de etilo.

23. (*S*)-(3-amino-2-hidroxipropil)(1,1-dietoxietil)fosfinato de etilo.

24. (*S*)-(3-cloro-2-hidroxipropil)(1,1-dietoxietil)fosfinato de etilo.

25. (*R*)-(3-amino-2-hidroxipropil)(1,1-dietoxietil)fosfinato de etilo.

26. (3-amino-2-oxopropil)(1,1-dietoxietil)fosfinato.

ES TRADUCCION FIEL Y COMPLETA, de la cual queda copia en los archivos de esta oficina de traducciones, para su confrontación y a la que me remito.

Derechos de Traducción: $144.000,oo

BOGOTA, 24 DE NOVIEMBRE DEL 2000.

TRADUCCION OFICIAL No. 5786

María Luisa Brigard de Restrepo
Intérprete Oficial
Res. No. 0783 del Min. de Justicia

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The application was originally filed in English.

(71) *Sökande* / *Applicant (s)* — *AstraZeneca AB, Södertälje SE*

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Stockholm, 2000-10-20

För Patent- och registreringsverket
For the Patent- and Registration Office

Therese Friberger

Therese Friberger

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21

EL CONSULADO DE COLOMBIA EN ESTOCOLMO, SUECIA

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ANNE-MARIE BONDE

88 86

NEW COMPOUNDS

Field of the invention

The present invention is related to novel compounds having affinity to one or more $GABA_B$ receptors, as well as to their pharmaceutically acceptable salts and stereoisomers. The invention is also related to processes for their preparation, pharmaceutical compositions containing said therapeutically active compounds and to the use of said active compounds in therapy.

Background and prior art

Reflux

Gastro-oesophageal reflux disease (GORD) is the most prevalent upper gastrointestinal tract disease. Current therapy has aimed at reducing gastric acid secretion, or at reducing oesophageal acid exposure by enhancing oesophageal clearance, lower oesophageal sphincter tone and gastric emptying. The major mechanism behind reflux has earlier been considered to depend on a hypotonic lower oesophageal sphincter. However recent research (e.g. *Holloway & Dent (1990) Gastroenterol. Clin. N. Amer. 19, 517-535*) has shown that most reflux episodes occur during transient lower oesophageal sphincter relaxations, hereinafter referred to as TLOSR, i.e. relaxations not triggered by swallows. It has also been shown that gastric acid secretion usually is normal in patients with GORD.

Consequently, there is a need for compounds which reduce the incidence of TLOSR and thereby prevent reflux.

Pharmaceutical compositions comprising a local anaesthetic, adapted to inhibit relaxation of the lower oesophageal sphicter are disclosed in WO 87/04077 and in US 5,036,057. Recently $GABA_B$-receptor agonists have been shown to inhibit TLOSR which is disclosed in WO 98/11885.

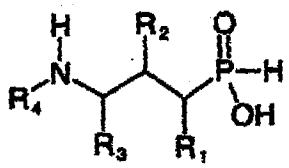
$GABA_B$ receptor agonists

GABA (4-aminobutanoic acid) is an endogenous neurotransmitter in the central and peripheral nervous systems. Receptors for GABA have traditionally been divided into $GABA_A$ and $GABA_B$ receptor subtypes. $GABA_B$ receptors belong to the superfamily of G-protein coupled receptors. $GABA_B$ receptor agonists are being described as being of use in the treatment of CNS disorders, such as muscle relaxation in spinal spasticity, cardiovascular disorders, asthma, gut motility disorders such as irritable bowel syndrome (IBS) and as prokinetic and anti-tussive agents. $GABA_B$ receptor agonists have also been disclosed as useful in the treatment of emesis (WO 96/11680) and recently, as mentioned above, in the inhibition of TLOSR (WO 98/11885).

The most studied $GABA_B$ receptor agonist is baclofen (4-amino-3-(chlorophenyl)butanoic acid) disclosed in the Swiss patent No. CH 449, 046. Baclofen has for several years been used as an antispastic agent. EP 0356128 describes the use of the specific compound (3-aminopropyl)methyl phosphinic acid, as a potent $GABA_B$ receptor agonist, in therapy. EP 0181833 discloses substituted 3-aminopropyl phosphinic acids (or more correctly 3-aminopropyl phosphonous acids) which are found to have very strong affinities towards $GABA_B$ receptor sites. In analogy to baclofen, the compounds can be used as for instance muscle relaxants. EP 0399949 discloses derivatives of (3-aminopropyl)methyl phosphinic acid which are described as potent $GABA_B$ receptor agonists. These compounds are stated to be useful as muscle relaxants. EP 0463969 and FR 2722192 are both applications related to 4-aminobutanoic acid derivatives having different heterocyclic substituents at the β-carbon of the butyl chain. Structure-activity relationships of several phosphinic acid analogues with respect to their affinities to the $GABA_B$ receptor as well as their muscle relaxant effect are discussed in *J. Med. Chem.* (1995), 38, 3297-3312. The conclusion in said article is that considerably stronger muscle relaxation could be achieved with the (S)-enantiomer of (3-amino-2-hydroxypropyl)methyl phosphinic acid than with baclofen without the occurrence of unwanted CNS effects.

Outline of the invention

The present invention provides novel compounds of the formula I



(I)

wherein

R_1 represents hydrogen, hydroxy, lower alkyl, lower alkoxy or halogen;

R_2 represents hydroxy, mercapto, halogen, or an oxo group;

R_3 represents hydrogen, lower alkyl (optionally substituted with hydroxy, mercapto, lower alkoxy, lower thioalkoxy or aryl);

R_4 represents hydrogen, lower alkyl (optionally substituted with aryl), or aryl;

and pharmaceutically acceptable salts and the stereoisomers thereof,

with the exceptions of:

i) the racemate of (3-amino-2-hydroxypropyl)phosphonous acid, and

ii) (2*R/S*, 3*R*)-(3-amino-2-hydroxybutyl)phosphonous acid.

In a preferred embodiment

R_1 represents hydrogen;

R_2 represents fluoro, hydroxy or an oxo group;

R_3 represents hydrogen; and

R_4 represents hydrogen;

with the exception of the racemate of (3-amino-2-hydroxypropyl)phosphonous acid.

Most preferred compounds are (3-amino-2-fluoropropyl)phosphonous acid, (3-amino-2-oxopropyl)phosphonous acid and (*S*)-(3-amino-2-hydroxypropyl)phosphonous acid.

Within the scope of the invention, it is to be understood that when R_2 is an oxo group the bond between R_2 and the carbon is a double bond.

Within the scope of the invention, it is to be understood by "lower" radicals and compounds, for example, those having up to and including 7, especially up to and including 4, carbon atoms. Also the general terms have the following meanings:

Lower alkyl is, for example, C_1-C_4 alkyl, such as methyl, ethyl, n-propyl or n-butyl, also isopropyl, isobutyl, secondary butyl or tertiary butyl, but may also be a C_5-C_7 alkyl group such as a pentyl, hexyl or heptyl group.

Lower alkoxy is, for example, C_1-C_4 alkoxy, such as methoxy, ethoxy, n-propoxy or n-butoxy, also isopropoxy, isobutoxy, secondary butoxy or tertiary butoxy, but may also be a C_5-C_7 alkoxy group, such as a pentoxy, hexoxy or heptoxy group.

Lower thioalkoxy is, for example, C_1-C_4 thioalkoxy, such as thiomethoxy, thioethoxy, n-thiopropoxy or n-thiobutoxy, also thioisopropoxy, thioisobutoxy, secondary thiobutoxy or

tertiary thiobutoxy, but may also be a C_5-C_7 thioalkoxy group, such as a thiopentoxy, thiohexoxy or thioheptoxy group.

Halogen is, for example, halogen of an atomic number up to and including 35, such as flourine or chlorine, less prefered, bromine.

The compounds according to formula I of the invention are of amphoteric nature and may be presented in the form of internal salts. They can also form acid addition salts and salts with bases. Such salts are particularly pharmaceutically acceptable acid addition salts, as well as pharmaceutically acceptable salts formed with bases. Suitable acids for the formation of such salts include, for example, mineral acids such as hydrochloric, hydrobromic, sulfuric, or phosphoric acid or organic acids such as sulfonic acids and carboxylic acids. Salts with bases are, for example, alkali metal salts, e.g. sodium or potassium salts, or alkaline earth metal salts, e.g. calcium or magnesium salts, as well as ammonium salts, such as those with ammonia or organic amines.

When one or more stereocentre is present in the molecule, the compounds according to formula I can be in the form of a stereoisomeric mixture, i.e. a mixture of diastereomers and/or racemates, or in the form of the single stereoisomers, i.e. the single enantiomer and/or diastereomer.

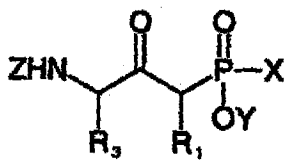
The novel compounds according to the invention can be used for the inhibition of TLOSR, and thus for the treatment of gastro-oesophageal reflux disease. The said inhibition of TLOSR also implies that the said compounds can be used for the treatment of regurgitation in infants. Effective management of regurgitation in infants would be an important way of managing failure to thrive due to excessive loss of ingested nutrient. Furthermore the novel compounds can be used for the treatment of GORD-related or non-GORD related asthma, belching, coughing, pain, cocaine addition, hiccups, IBS, dyspepsia, emesis and nociception.

As opposed to what is stated in prior art, (*J.Med.Chem. (1995) 3297-3312* and *The GABA Receptors; Second Edition, Edited by S.J. Enna and Norman Bowery, Humana Press (1997) especially p. 281-282)*, the compounds according to the invention have surprisingly high metabolic stability in spite of the presence of a P-H bond. The compounds also possess a surprisingly high therapeutic index.

Preparation

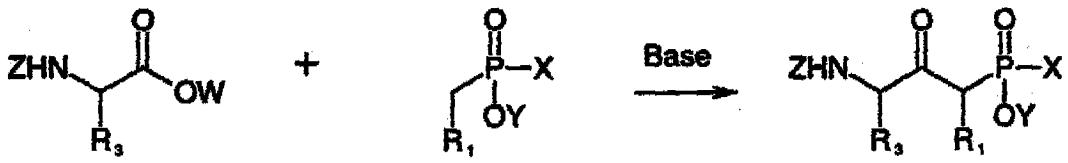
The compounds according to formula I of the present invention may be prepared by one of the following methods.

a) A compound of formula II



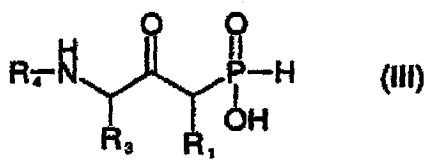
(II)

in which R_1 and R_3 are as defined above in formula I, X is hydrogen or a protecting group such as $-CCH_3(OCH_2CH_3)_2$, Z is a protecting group such as t-butyloxycarbonyl and Y is hydrogen or a protecting group such as lower alkyl, which compound of formula II may have been synthesized by a condensation reaction according to Scheme 1 employing an appropriate N-protected amino acid ester in which R_3 is as defined above, W is a protecting group such as lower alkyl and Z is as defined in formula II, and a suitable protected phosphinic acid derivative in which R_1 is as defined above in formula I, X and Y are as defined in formula II, and a base such as lithium diisopropylamide,



Scheme 1

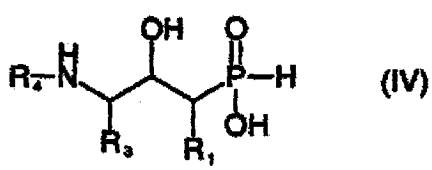
is optionally converted by an N-alkylation reaction in order to introduce R_4 if R_4 is desired to be not equal to hydrogen, and thereafter a hydrolytic reaction to obtain a compound of formula III



(III)

wherein R_1, R_3 and R_4 are as defined above in formula I, and if desired, a resulting compound is converted into another compound of the formula III, a resulting mixture of isomers is separated into the individual isomers and/or a resulting salt obtained in this process is converted into the free compound of the formula III or into another salt and/or, if desired, a resulting free compound of the formula III is converted into a salt to correspond to the above definition;

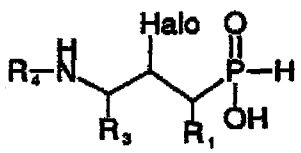
or a compound of formula II is converted by a reductive reaction, optionally an N-alkylation reaction if R_4 is desired to be not equal to hydrogen, and finally a hydrolytic reaction to obtain a compound of formula IV



(IV)

wherein R_1, R_3 and R_4 are as defined above in formula I, and if desired, a resulting compound is converted into another compound of the formula IV, a resulting mixture of isomers is separated into the individual isomers and/or a resulting salt obtained in this process is converted into the free compound of the formula IV or into another salt and/or, if desired, a resulting free compound of the formula IV is converted into a salt to correspond to the above definition;

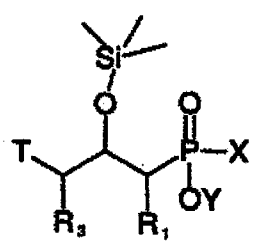
or a compound of formula II is converted by a reductive reaction followed by a deoxohalogenation reaction, optionally an N-alkylation reaction in order to introduce R_4 if R_4 is desired to be not equal to hydrogen, and finally a hydrolytic reaction to obtain a compound of formula V



(V)

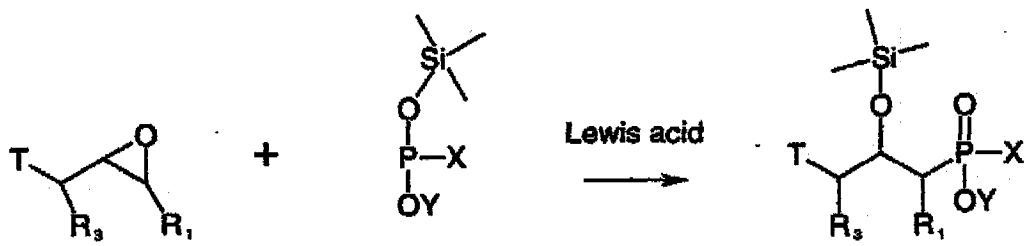
wherein R_1, R_3 and R_4 are as defined above in formula I and Halo is a halogen atom, and if desired, a resulting compound is converted into another compound of the formula V, a resulting mixture of isomers is separated into the individual isomers and/or a resulting salt obtained in this process is converted into the free compound of the formula V or into another salt and/or, if desired, a resulting free compound of the formula V is converted into a salt to correspond to the above definition;

or b) a compound of formula VI



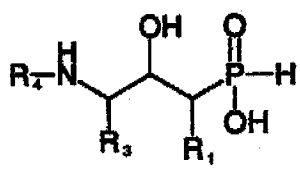
(VI)

in which R_1, and R_3 are as defined above in formula I, X is hydrogen or a protecting group such as $-CCH_3(OCH_2CH_3)_2$, T is a group that can be converted to a-NH_2 group, and Y is hydrogen or a protecting group such as lower alkyl, which compound of formula VI may have been synthesized by a condensation reaction according to Scheme 2 employing an 2,3-epoxypropyl derivative, such as an appropriate N-protected 2,3-epoxypropylamine derivative or an epichlorohydrin derivative, in which R_1 and R_3 is as defined above in formula I, and a suitable protected phosphinic acid derivative activated by O-silylation, in which X and Y are as defined in formula VI, and a Lewis acid such as anhydrous $ZnCl_2$,



Scheme 2

is converted by a reaction where the trimethylsilyl group is replaced by a hydrogen atom, a reaction where the T group as defined in formula VI is converted to $-NHR_4$ wherein R_4 is as defined above in formula I, and finally a hydrolytic reaction to obtain a compound of formula VII

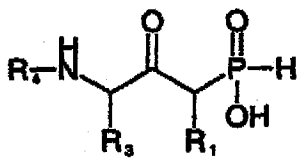


(VII)

wherein R_1, R_3 and R_4 are as defined above in formula I, and if desired, a resulting compound is converted into another compound of the formula VII, a resulting mixture of

isomers is separated into the individual isomers and/or a resulting salt obtained in this process is converted into the free compound of the formula VII or into another salt and/or, if desired, a resulting free compound of the formula VII is converted into a salt to correspond to the above definition;

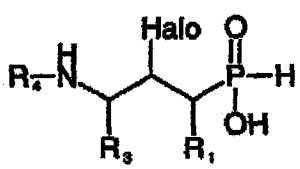
or compound of formula VI is converted by a reaction where the trimethylsilyl group is replaced by hydrogen, an oxidative reaction, a reaction where the T group as defined in formula VI is converted to -NHR_4 wherein R_4 is as defined above in formula I, and finally a hydrolytic reaction to obtain a compound of formula VIII



(VIII)

wherein R_1, R_3 and R_4 are as defined above in formula I, and if desired, a resulting compound is converted into another compound of the formula VIII, a resulting mixture of isomers is separated into the individual isomers and/or a resulting salt obtained in this process is converted into the free compound of the formula VIII or into another salt and/or, if desired, a resulting free compound of the formula VIII is converted into a salt to correspond to the above definition;

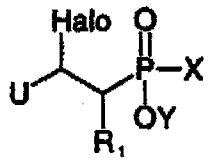
or a compound of formula VI is converted by a reaction where the trimethylsilyl group is replaced by hydrogen, a deoxohalogenation reaction, a reaction where the T group as defined in formula VI is converted to -NHR_4 wherein R_4 is as defined above in formula I, and finally a hydrolytic reaction to obtain a compound of formula IX



(IX)

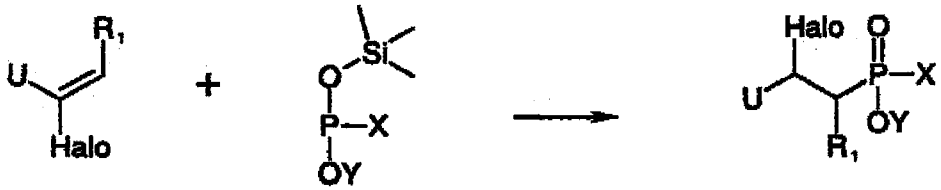
wherein R_1, R_3 and R_4 are as defined above in formula I, and Halo is a halogen atom, and if desired, a resulting compound is converted into another compound of the formula IX, a resulting mixture of isomers is separated into the individual isomers and/or a resulting salt obtained in this process is converted into the free compound of the formula IX or into another salt and/or, if desired, a resulting free compound of the formula IX is converted into a salt to correspond to the above definition;

or c) a compound of formula XI



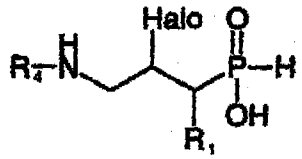
(XI)

in which R_1 is as defined above in formula I, X is hydrogen or a protecting group such as $-CCH_3(OCH_2CH_3)_2$, U is an electron-withdrawing group, such as for instance –CN or $-CO_2Et$ which can be converted to a $-CH_2NH_2$ group, and Y is hydrogen or a protecting group such as lower alkyl, and Halo is a halogen atom, which compound of formula XI may have been synthesized by an addition reaction according to Scheme 3 employing an unsaturated compound in which R_1 is as defined above in formula I, U and halo are as defined in formula XI, and a suitable protected phosphinic acid derivative activated by O-silylation, in which X and Y are as defined in formula XI,



Scheme 3

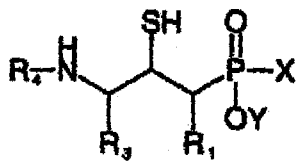
is converted by a reaction where the U group is being converted to -NHR_4 wherein R_4 is as defined above in formula I, and a hydrolytic reaction to obtain a compound of formula XII



(XII)

wherein R_1 and R_4 are as defined above in formula I and Halo is a halogen atom, and if desired, a resulting compound is converted into another compound of the formula XII, a resulting mixture of isomers is separated into the individual isomers and/or a resulting salt obtained in this process is converted into the free compound of the formula XII or into another salt and/or, if desired, a resulting free compound of the formula XII is converted into a salt to correspond to the above definition;

or d) a compound of formula XIII

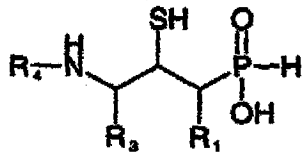


(XIII)

in which R_1, R_3 and R_4 are as defined above in formula I, X is hydrogen or a protecting group such as -$CCH_3(OCH_2CH_3)_2$, and Y is hydrogen or a protecting group such as lower alkyl, which compound of formula XIII may have been synthesized by an addition reaction according to Scheme 4 treating an unsaturated phosphinic acid derivative, in which R_1, R_3 and R_4 are as defined in above in formula I, with H_2S, a mercaptide ion (HS^-) or a protected mercapto compound such as benzyl thiol in which case the protective group thereafter is removed

Scheme 4

is converted by a hydrolytic reaction to obtain a compound of formula XIV,



(XIV)

in which R_1, R_3 and R_4 are as defined above in formula I, and if desired, a resulting compound is converted into another compound of the formula XIV, a resulting mixture of isomers is separated into the individual isomers and/or a resulting salt obtained in this process is converted into the free compound of the formula XIV or into another salt and/or, if desired, a resulting free compound of the formula XIV is converted into a salt to correspond to the above definition.

Examples

Example 1. (3-Amino-2-fluoropropyl)phosphonous acid

To an ice bath cooled solution of ethyl (3-amino-2-fluoro-3-oxopropyl)(diethoxymethyl)phosphinate in THF (tetrahydrofuran) was added 1 M BH_3-THF while under an argon atmosphere. After 10 minutes, the solution was heated to reflux for 2.5 h. The solution was cooled to room temperature and 6 N HCl (200 mL) was added. The THF was removed by rotoevaporation and the aqueous layer refluxed for 2.5 h. The solution was cooled and evaporated. The residue was purified by ion exchange column chromatography (DOWEX® 50WX-8-200, H^+ form, 3.5 x 4.0 cm). The ion exchange resin

was pre-washed with 2:1 methanol/water (400 mL). The crude product dissolved in 1:1 methanol/water was loaded onto the column and washed with 1:1 methanol/water (400 mL). The eluent was changed to 3:1 methanol/concentrated ammonium hydroxyde. Two fractions (150 mL totally) were combined and evaporated to give 645 mg (34%) of (3-amino-2-fluoropropyl)phosphonous acid as a white solid. Data: mp 203-207 °C; $R_f = 0.35$ (60:40:1 methanol, methylene chloride, concentrated ammonium hydroxide); ^{1}H NMR (300 MHz, D_2O) δ 7.11 (d, $J = 528$ Hz, 1H), 5.18 (dm, $J = 54$ Hz, 1H), 3.28-3.45 (m, 2H), 1.65-2.23 (m, 2H); ^{13}C NMR (125 MHz, D_2O + Dioxane) δ 87.8 (d, $J = 170$ Hz), 44.3 (dd, $J = 12.6, 21.6$ Hz), 35.6 (dd, $J = 20.2, 86.5$ Hz); APIMS: $m/z = 142$ $(M+H)^+$.

Example 2. (*S*)-(3-Amino-2-hydroxypropyl)phosphonous acid

A mixture of ethyl (*S*)-(3-amino-2-hydroxypropyl)(1,1-diethoxyethyl)phosphinate (1.0 g, 3.5 mmol) and concentrated HCl (50 mL) was heated to reflux for 2 h. The solution was cooled to room temperature and evaporated. The residue was dissolved in methanol (100 ml) and treated with propylene oxide (2 ml) at room temperature. After the mixture was stirred for 5 hours, the precipitated solid was collected by decanting off the solvent. The solid was dried with a stream of argon to give 220 mg (45%) of (*S*)-(3-amino-2-hydroxypropyl)phosphonous acid as a white solid. Data: ^{1}H NMR (300 MHz, D_2O) δ 7.1 (d, $J = 540$ Hz, 1H), 4.2 (m, 1H), 2.9-3.2 (m, 2H), 1.7-2.0 (m, 2H); ^{31}P NMR (121 MHz, D_2O) δ 24.2 (d, $J = 522$ Hz); FABMS: $m/z = 140$ $(M+H)^+$; $[\alpha]_D$ at 20 °C = +8 ° (0.5% in 0.1M HCl).

Example 3. (*R*)-(3-Amino-2-hydroxypropyl)phosphonous acid

A mixture of ethyl (*R*)-(3-amino-2-hydroxypropyl)(1,1-diethoxyethyl)phosphinate (0.9 g, 3.2 mmol) and concentrated HCl (50 mL) was heated to reflux for 2 h. The solution was cooled to room temperature and evaporated. The residue was dissolved in methanol (50 ml) and treated with propylene oxide (3 ml) at room temperature. After the mixture was stirred for 5 hours, the precipitated solid was collected by decanting off the solvent. The solid was dried with a stream of argon to give 260 mg (59%) of (*R*)-(3-amino-2-hydroxypropyl)phosphonous acid as a white solid. Data: ^{1}H NMR (300 MHz, D_2O) δ 7.1

(d, J = 540 Hz, 1H), 4.2 (m, 1H), 2.9-3.2 (m, 2H), 1.7-2.0 (m, 2H); ^{31}P NMR (121 MHz, D_2O) δ 23.9 (d, J = 525 Hz); FABMS: m/z = 140 $(M+H)^+$; $[\alpha]_D$ at 20 °C = -8 ° (0.5% in 0.1M HCl).

Example 4. (3-Amino-2-oxopropyl)phosphinic acid

A sample of ethyl(3-amino-2-oxopropyl)(1,1-diethoxyethyl)phosphinate (8.11 g, 21.0 mmol) was dissolved in 3 N HCl (400 mL) which was previously deoxygenated by bubbling N_2 through the solution. The mixture was stirred for 14 h at room temperature and then concentrated. The residue was coevaporated with methanol. The residue was then dissolved in methanol (10 mL) and propylene oxide was added (10 mL). The mixture was stirred for 6 h and the resulting precipitate isolated by filtration. The solid was washed with cold methanol and dried under vacuum at 50 °C to give 2.1 g (73%) of (3-amino-2-oxopropyl)phosphinic acid as an off-white solid. Data: mp 126-127 °C; R_f = 0.64 (85:15 methanol, water); ^{1}H NMR (300 MHz, D_2O) δ 7.13 (d, J = 551 Hz, 1H), 4.14 (s, 2H), 3.14 (d, J = 18 Hz, 2 H); ^{13}C NMR (75 MHz, D_2O + Dioxane) δ 199.5, 49.2, 47.3 (d, J = 69 Hz); FABMS: m/z = 138 $(M+H)^+$.

The following intermediates were used in the preparation of compounds of the invention.

Intermediates

Example I1. Ethyl 3-[(diethoxymethyl)(ethoxy)phosphoryl]-2-fluoropropanoate (intermediate to the compound according to Example 1)

A mixture of ethyl (diethoxymethyl)phosphinate (26.0 g, 133 mmol) and 1,1,1,3,3,3-hexamethyldisilazane (28 mL, 133 mmol) was heated to reflux for 2 h under an argon atmosphere. The mixture was cooled to room temperature and fluoroacrylate (10.5 g, 89.0 mmol) was added. The reagents were heated to 60 °C for three days under an argon atmosphere. The mixture was cooled to room temperature, diluted with ethyl acetate (300 mL), washed with 1 N HCl (2 x 150 mL) and saturated sodium chloride (100 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated to give 32.0 g of a yellow

oil. The residue was purified by coloumn chromatography on a wet-packed silica gel column (6 x 30 cm) eluting with 97:3 methylene chloride/methanol. The appropriate fractions were combined and evaporated to give 16.0 g (57%) of ethyl 3-[(diethoxymethyl)(ethoxy)phosphoryl]-2-fluoropropanoate as a clear oil. Data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.32 (dm, 1H), 4.67-4.77 (m, 1H), 4.18-4.32 (m, 2H), 3.58-3.91 (m, 4H), 2.30-2.62 (m, 2H), 1.20-1.41 (m, 9H).

Example I2. Ethyl (3-amino-2-fluoro-3-oxopropyl)(diethoxymethyl)phosphinate (intermediate to compound according to example 1)

To a solution of ethyl 3-[(diethoxymethyl)(ethoxy)phosphoryl]-2-fluoropropanoate (16.0 g, 51.1 mmol) in ethanol (22 mL) was added concentrated ammonium hydroxyde (14.8 N, 3.5 mL, 51.1 mmol). The solution was stirred for 16 h and evaporated. The residue was purified by chromatography on a wet-packed silica gel column (7 x 37 cm) eluting with 96.5:3.5 methylene chloride/methanol. The appropriate fractions were combined and evaporated to give 3.43 g (27%) of ethyl (3-amino-2-fluoro-3-oxopropyl)(diethoxymethyl)phosphinate as a clear oil. Data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.43 (s, 1H), 5.70 (s, 1H), 5.21-5.49 (dm, 1H), 4.7 (dd, 1H), 4.18-4.31 (m, 2H), 3.65-3.91 (m, 4H), 2.21-2.81 (m, 2H), 1.30-1.40 (m, 3H), 1.20-1.28 (m, 6H).

Example I3. Ethyl (*R*)-(3-chloro-2-hydroxypropyl)(1,1-diethoxyethyl)phosphinate (intermediate to the compound according to Example 2)

After a mixture of ethyl (diethoxyethyl)phosphinate (15.0 g, 71 mmol) and toluene was evaporated to dryness, the residue and 1,1,1,3,3,3-hexamethyldisilazane (13.2 g, 82 mmol) was heated to reflux for 3 h under an argon atmosphere. The mixture was cooled to room temperature and evaporated. (*R*)-Epichlorohydrin (6.6 g, 71 mmol) and anhydrous zinc chloride (2.5 g, 18 mmol) were added and the reagents were heated to 60 °C over night under an argon atmosphere. The mixture was cooled to room temperature, diluted with methylene chloride and water. The organic layer was washed with water, dried over $MgSO_4$, filtered, and evaporated to give 20.7 g of a yellow oil. The residue was dissolved in methanol (150 mL) containing 1% acetic acid and the solution was stirred over night.

The solvent was removed to give 17.7 g (82%) of ethyl (*R*)-(3-chloro-2-hydroxypropyl)(1,1-diethoxyethyl)phosphinate as a clear oil. Data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.3-4.4 (m, 1H), 4.1-4.3 (m, 2H), 3.5-3.8 (m, 4H), 1.9-2.4 (m, 2H), 1.5 (dd, J = 2.3, 11.4 Hz, 3H), 1.32-1.37 (m, 3H), 1.18-1.24 (m, 6H).

Example I4. Ethyl (*S*)-(3-amino-2-hydroxypropyl)(1,1-diethoxyethyl)phosphinate (intermediate to the compound according to Example 2)

A solution of (*R*)-(3-chloro-2-hydroxypropyl)(1,1-diethoxyethyl)phosphinate (5.0 g, 17 mmol) in ethanol containing 9% of ammonia was stirred in an autoclave at room temperature for 4 days and at 60 °C for one further day. The solution was evaporated and the residue was purified by chromatography on a wet-packed silica gel column eluting with methylene chloride/methanol (5-8% MeOH) containing 5% triethylamine. The appropriate fractions were combined, evaporated and diluted with methylene chloride and water. The aqueous layer was pH adjusted by the addition of a few mL of 10% aqueous Na_2CO_3 and repeatedly extracted with methylene chloride. The combined organic layers were dried over Na_2SO_4 and evaporated to give 1.2 g (26%) of ethyl (*S*)-(3-amino-2-hydroxypropyl)(1,1-diethoxyethyl)phosphinate as a clear oil. Data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.40-4.55 (b, 1H), 4.10-4.30 (m, 2H), 3.55-3.80 (m, 4H), 3.20-3.30 (m, 1H), 3.00-3.10 (m, 1H), 2.00-2.40 (m, 2H), 1.45-1.53 (dd, J = 3.4, 11.7 Hz, 3H), 1.30-1.40 (m, 3H), 1.15-1.25 (m, 6H).

Example I5. Ethyl (*S*)-(3-chloro-2-hydroxypropyl)(1,1-diethoxyethyl)phosphinate (intermediate to the compound according to Example 3)

After a mixture of ethyl (diethoxyethyl)phosphinate (15.0 g, 71 mmol) and toluene was evaporated to dryness, the residue and 1,1,1,3,3,3-hexamethyldisilazane (13.2 g, 82 mmol) was heated to reflux for 3 h under an argon atmosphere. The mixture was cooled to room temperature and evaporated. (*S*)-Epichlorohydrin (6.6 g, 71 mmol) and anhydrous zinc chloride (2.5 g, 18 mmol) were added and the reagents were heated to 60 °C over night under an argon atmosphere. The mixture was cooled to room temperature, diluted with methylene chloride and water. The organic layer was washed with water, dried over

$MgSO_4$, filtered, and evaporated to give 20.7 g of a yellow oil. The residue was dissolved in methanol (150 mL) containing 1% acetic acid and the solution was stirred over night. The solvent was removed to give 16.8 g (79%) of ethyl (*S*)-(3-chloro-2-hydroxypropyl)(1,1-diethoxyethyl)phosphinate as a clear oil. Data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.4 (m, 1H), 4.2-4.3 (m, 2H), 3.6-3.8 (m, 4H), 1.9-2.4 (m, 2H), 1.5 (dd, J = 2.3, 11.4 Hz, 3H), 1.32-1.37 (m, 3H), 1.18-1.24 (m, 6H).

Example I6. Ethyl (*R*)-(3-amino-2-hydroxypropyl)(1,1-diethoxyethyl)phosphinate (intermediate to the compound according to Example 3)

A solution of (*S*)-(3-chloro-2-hydroxypropyl)(1,1-diethoxyethyl)phosphinate (5.0 g, 17 mmol) in ethanol containing 9% of ammonia was stirred in an autoclave at room temperature for 6 days and at 55 °C for one further day. The solution was evaporated and the residue was purified by chromatography on a wet-packed silica gel column eluting with methylene chloride/methanol (5-8% MeOH) containing 5% triethylamine. The appropriate fractions were combined, evaporated and diluted with methylene chloride and water. The aqueous layer was pH adjusted by the addition of a few mL of 10% aqueous Na_2CO_3 and repeatedly extracted with methylene chloride. The combined organic layers were dried over Na_2SO_4 and evaporated to give 0.9 g (19%) of ethyl (*R*)-(3-amino-2-hydroxypropyl)(1,1-diethoxyethyl)phosphinate as a clear oil. Data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.1-4.3 (m, 2H), 4.05 (b, 1H), 3.60-3.80 (m, 4H), 2.4-2.9 (m, 2H), 1.7-2.1 (m, 2H), 1.4-1. 5 (dd,3H), 1.3-1.4 (m, 3H), 1.2 (m, 6H).

Example I7. (3-Amino-2-oxopropyl)(1,1-diethoxyethyl)phosphinate (intermediate to the compound according to the Example 4)

To a solution of diisopropylamine (3.0 mL, 21 mmol) in THF (5 mL) at –10 °C was added dropwise *n*-BuLi (2.5 M in hexanes, 8.6 mL, 21 mmol). After 10 minutes, the reaction was cooled to –78 °C and a solution ethyl (1,1-diethoxyethyl)(methyl)phosphinate (4.80 g, 21.0 mmol) in THF (5 mL) was added dropwise. After the addition, the solution was stirred at –78 °C for 1h. A solution of *N*-Boc-glycine methyl ester (810 mg, 4.3 mmol) in THF (15 mL) was added dropwise. After the addition was complete, the reaction mixture was

stirred for 45 minutes. Acetic acid (1.2 mL, 21 mmol) was added and the reaction mixture was warmed to room temperature. The reaction mixture was partitioned between methylene chloride and water and the layers were separated. The aqueous layer was extracted once with methylene chloride. The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated to give 4.89 g of an oil. The residue was purified by chromatography on 100 g of silica gel eluting with ethyl acetate. The appropriate fractions were collected to give 1.2 g (74%) of (3-amino-2-oxopropyl)(1,1-diethoxyethyl)phosphinate as an oil. Data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.48 (s, 1H), 4.10-4.30 (m, 2H), 4.17 (d, 2H), 3.60-3.80 (m, 4H), 3.01-3.30 (m, 2H), 1.52 (d, 3H), 1.43 (s, 9H), 1.32 (t, 3H), 1.19 (t, 6H).

Pharmaceutical preparations

The compound according to formula I of the present invention can be used as an active ingredient in a pharmaceutical preparation for oral, rectal, epidural, intravenous, intramuscular, subcutanous, nasal administration and administration by infusion or for any other suitable route of administration. Preferably the way of administration is oral or by injection/infusion.

The pharmaceutical preparations contain a compound of the present invention in combination with one or more pharmaceutically acceptable ingredients. The finished dosage forms are manufactured by known pharmaceutical processes. Usually the amount of active compounds is between 0.1-95% by weight of the preparation, preferably between 0.2-20% by weight in preparations for parenteral use and preferably between 1-50% by weight in preparations for oral administration.

In the preparation of pharmaceutical preparations containing a compound of the present invention in the form of solid dosage units for oral administration, the compound selected may be mixed with solid pharmaceutically acceptable ingredients (among these for instance disintegrating agents and lubricating agents). The mixture is then processed into granules, tablets, capsules or sachets.

Dosage units for rectal administration may be prepared in the form of suppositories; in the form of a gelatine rectal capsule; in the form of a ready-made micro enema; or in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

Liquid preparations for oral administration may be prepared in the form of syrups or suspensions, or in the form of a dry mixture to be reconstituted with a suitable solvent prior to use.

Solutions for parenteral administration may be prepared as a solution of a compound of the invention in a pharmaceutically acceptable solvent and are dispensed into ampoules or vials. They may also be prepared as a dry preparation to by reconstituted with a suitable solvent extemporaneously before use.

The typical daily dose of the active compound will depend on various factors such as for example the individal requirement of each patient, the route of administration and the disease. In general, dosages will be in the range of 1 µg to 100 mg per day and kg body weight, preferably 10 µg to 20 mg per day and kg body weight.

Biological studies

[^{3}H]GABA radioligand binding assay

Rat synaptic membranes were prepared from the whole brain of Sprague Dawley male rats essentially as described previously (Zukin, et al. (1974) Proc. Natl. Acad. USA 71, 4802-4807). The [^{3}H]GABA competition assay, modified from Olpe et al ((1990) Eur. J. Pharmacol. 187, 27-38), was performed in 200 µl TCI (Tris Calcium Isoguvacine) buffer (50 mM Tris (tri(hydroxymethyl)aminomethane), pH 7.4, 2.5 mM $CaCl_2$ and 40 µM isoguvacine) containing 20 nM [^{3}H]GABA (specific activity: 3 Tera Becquerel (TBq)/mmol), test compound or solvent and 80 µg synaptic membrane protein using 96-

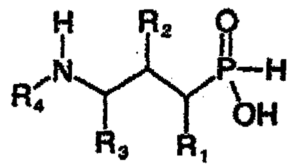
well plates. After incubation for 12-20 min at room temperature, incubations were terminated by rapid filtration through a glass fiber filter (Printed filtermat B filters, Wallac), which had been pretreated with 0.3% polyethyleneimine, using a 96-well plate cell harvester (Skatron or Tomtec). The filters were washed with buffer containing 50 mM Tris (tris(hydroxymethyl)aminomethane) and 2.5 mM $CaCl_2$, pH 7.4, at 4 °C and then dried at 55° C. MeltiLex B/HS scintillator sheet (Wallac) was melted onto the filter, and radioactivity was determined in a Microbeta scintillation counter (Wallac).

Results and discussion

The compounds of the present invention were found to have high affinity and potency for the $GABA_B$ receptor as revealed by low IC_{50} and EC_{50} in the binding and ileum assays, respectively. The compounds have also been found to reduce TLOSR when administered i.v. as well as p.o. in animal models. Contrary to what has been claimed in the literature for 3-aminopropyl phosphonous acid derivatives, we have found that the compounds of the present invention have high metabolic stability in animal models. Moreover, CNS side-effects (as measured by reduction in body temperature in the mouse) were not observable or only seen at very high doses. Therefore, the difference between therapeutic dose (inhibition of TLOSR in the dog model) and dose causing side-effects (in the mouse model) was unexpectedly high.

CLAIMS

1. A compound according to the formula I



(I)

wherein

R_1 represents hydrogen, hydroxy, lower alkyl, lower alkoxy or halogen;

R_2 represents hydroxy, mercapto, halogen, or an oxo group;

R_3 represents hydrogen, lower alkyl (optionally substituted with hydroxy, mercapto, lower alkoxy, lower thioalkoxy or aryl);

R_4 represents hydrogen, lower alkyl (optionally substituted with aryl) or aryl;

and pharmaceutically acceptable salts and the stereoisomers thereof,

with the exceptions of:

i) the racemate of (3-amino-2-hydroxypropyl)phosphonous acid, and

ii) (2*R/S*, 3*R*)-(3-amino-2-hydroxybutyl)phosphonous acid.

2. A compound according to claim 1 wherein

R_1 represents hydrogen;

R_2 represents fluoro, hydroxy or an oxo group;

R_3 represents hydrogen; and

R_4 represents hydrogen,

with the exception of the racemate of (3-amino-2-hydroxypropyl)phosphonous acid.

3. (3-Amino-2-flouropropyl)phosphonous acid or a pharmaceutically acceptable salt or the stereoisomers thereof.

4. (3-Amino-2-oxopropyl)phosphonous acid or a pharmaceutically acceptable salt or the stereoisomers thereof.

5. (*S*)-(3-Amino-2-hydroxypropyl)phosphonous acid or a pharmaceutically acceptable salt thereof.

6. A compound according to claim 1, for use in theraphy.

7. Use of a compound according to any one of claims1-5 for the manufacture of a medicament for the inhibition of transient lower oesophageal sphincter relaxations.

8. Use of a compound according to any one of claims 1-5 for the manufacture of a medicament for the treatment of gastro-oesophageal reflux disease.

9. Use according to any one of claims 1-5 for the manufacture of a medicament for the [illegible] of regurgitation in infants.

10. Use of a compound according to any one of claims 1-5 for the manufacture of a medicament for GORD-related or non-GORD related asthma, belching, coughing, pain, cocaine addition, hiccups, IBS, dyspepsia, emesis or nociception.

11. A method for the treatment of transient lower oesophageal sphincter relaxations which method comprises treating a subject suffering from said condition with a pharmaceutical preparation comprising a compound of formula I.

12. A method for the treatment of gastro-oesophaegeal reflux disease which method comprises treating a subject suffering from said condition with a pharmaceutical preparation comprising a compound of formula I.

13. A method for the treatment of regurgitation in infants which method comprises treating a subject suffering from said condition with a pharmaceutical preparation comprising a compound of formula I.

14. A method for the treatment of GORD-related or non-GORD related asthma, belching, coughing, pain, cocaine addition, hiccups, IBS, dyspepsia, emesis or nociception which method comprises treating a subject suffering from said condition with a pharmaceutical preparation comprising a compound of formula I.

15. A pharmaceutical formulation comprising as active ingredient a therapeutically acceptable amount of the compound of any one of claims 1-5 optionally in association with diluents, excipients or inert carriers.

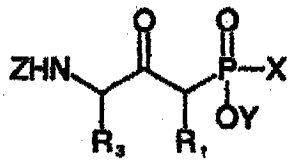
16. A pharmaceutical formulation according to claim 15 for use in the inhibition of transient lower oesophageal sphincter relaxations.

17. A pharmaceutical formulation according to claim 14 for use in the treatment of gastro-oesophageal reflux disease.

18. A pharmaceutical formulation according to claim 14 for use in the treatment of regurgitation in infants.

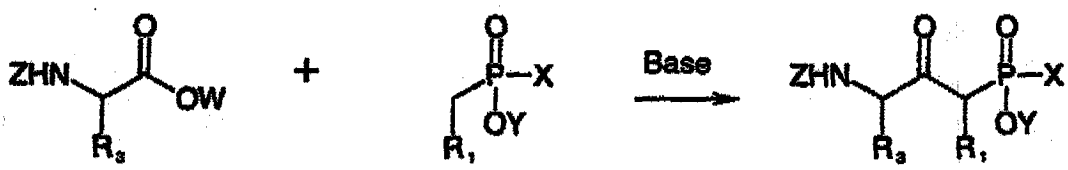
19. A process for the preparation of a compound of the formula I according to claim 1, wherein

a) a compound of formula II



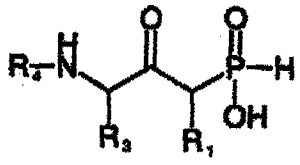
(II)

in which R_1 and R_3 are as defined above in formula I, X is hydrogen or a protecting group such as $-CCH_3(OCH_2CH_3)_2$, Z is a protecting group such as t-butyloxycarbonyl and Y is hydrogen or a protecting group such as lower alkyl, which compound of formula II may have been synthesized by a condensation reaction according to Scheme 1 employing an appropriate N-protected amino acid ester in which R_3 is as defined above, W is a protecting group such as lower alkyl and Z is as defined in formula II, and a suitable protected phosphinic acid derivative in which R_1 is as defined above in formula I, X and Y are as defined in formula II, and a base such as lithium diisopropylamide,



Scheme 1

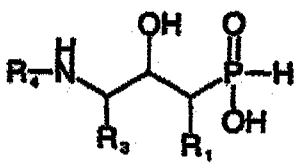
is converted optionally by an N-alkylation reaction in order to introduce R_4 if R_4 is desired to be not equal to hydrogen, and thereafter a hydrolytic reaction to obtain a compound of formula III



(III)

wherein R_1, R_3 and R_4 are as defined above in formula I, and if desired, a resulting compound is converted into another compound of the formula III, a resulting mixture of isomers is separated into the individual isomers and/or a resulting salt obtained in this process is converted into the free compound of the formula III or into another salt and/or, if desired, a resulting free compound of the formula III is converted into a salt to correspond to the above definition;

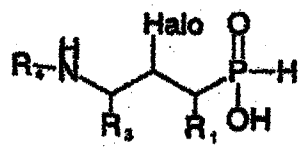
or a compound of formula II is converted by a reductive reaction, optionally an N-alkylation reaction if R_4 is desired to be not equal to hydrogen, and finally a hydrolytic reaction to obtain a compound of formula IV



(IV)

wherein R_1, R_3 and R_4 are as defined above in formula I, and if desired, a resulting compound is converted into another compound of the formula IV, a resulting mixture of isomers is separated into the individual isomers and/or a resulting salt obtained in this process is converted into the free compound of the formula IV or into another salt and/or, if desired, a resulting free compound of the formula IV is converted into a salt to correspond to the above definition;

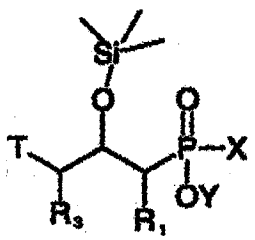
or a compound of formula II is converted by a reductive reaction followed by a deoxohalogenation reaction, optionally an N-alkylation reaction in order to introduce R_4 if R_4 is desired to be not equal to hydrogen, and finally a hydrolytic reaction to obtain a compound of formula V



(V)

wherein R_1, R_3 and R_4 are as defined above in formula I and Halo is a halogen atom, and if desired, a resulting compound is converted into another compound of the formula V, a resulting mixture of isomers is separated into the individual isomers and/or a resulting salt obtained in this process is converted into the free compound of the formula V or into another salt and/or, if desired, a resulting free compound of the formula V is converted into a salt to correspond to the above definition;

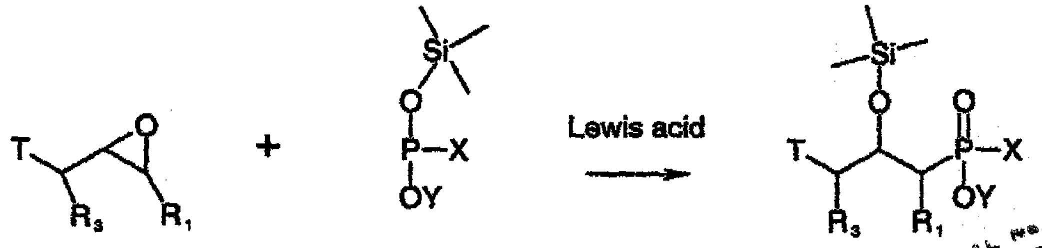
or b) a compound of formula VI



(VI)

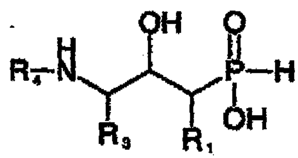
in which R_1, and R_3 are as defined above in formula I, X is hydrogen or a protecting group such as $-CCH_3(OCH_2CH_3)_2$, T is a group that can be converted to a-NH_2 group, and Y is hydrogen or a protecting group such as lower alkyl, which compound of formula VI may have been synthesized by a condensation reaction according to Scheme 2 employing an 2,3-epoxypropyl derivative, such as an appropriate N-protected 2,3-epoxypropylamine derivative or an epichlorohydrin derivative, in which R_1 and R_3 is as defined above in

formula I, and a suitable protected phosphinic acid derivative activated by O-silylation, in which X and Y are as defined in formula VI, and a Lewis acid such as anhydrous $ZnCl_2$,



Scheme 2

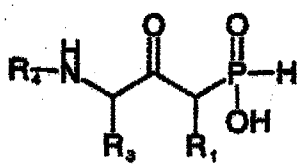
is converted by a reaction where the trimethylsilyl group is replaced by a hydrogen atom, a reaction where the T group as defined in formula VI is converted to -NHR_4 wherein R_4 is as defined above in formula I, and finally a hydrolytic reaction to obtain a compound of formula VII

 (VII)

wherein R_1, R_3 and R_4 are as defined above in formula I, and if desired, a resulting compound is converted into another compound of the formula VII, a resulting mixture of isomers is separated into the individual isomers and/or a resulting salt obtained in this process is converted into the free compound of the formula VII or into another salt and/or, if desired, a resulting free compound of the formula VII is converted into a salt to correspond to the above definition;

or a compound of formula VI is converted by a reaction where the trimethylsilyl group is replaced by hydrogen, an oxidative reaction, a reaction where the T group as defined in

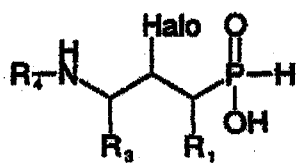
formula VI is converted to -NHR_4 wherein R_4 is as defined above in formula I, and finally a hydrolytic reaction to obtain a compound of formula VIII



(VIII)

wherein R_1, R_3 and R_4 are as defined above in formula I, and if desired, a resulting compound is converted into another compound of the formula VIII, a resulting mixture of isomers is separated into the individual isomers and/or a resulting salt obtained in this process is converted into the free compound of the formula VIII or into another salt and/or, if desired, a resulting free compound of the formula VIII is converted into a salt to correspond to the above definition;

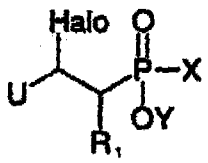
or a compound of formula VI is converted by a reaction where the trimethylsilyl group is replaced by hydrogen, a deoxohalogenation reaction, a reaction where the T group as defined in formula VI is converted to -NHR_4 wherein R_4 is as defined above in formula I, and finally a hydrolytic reaction to obtain a compound of formula IX



(IX)

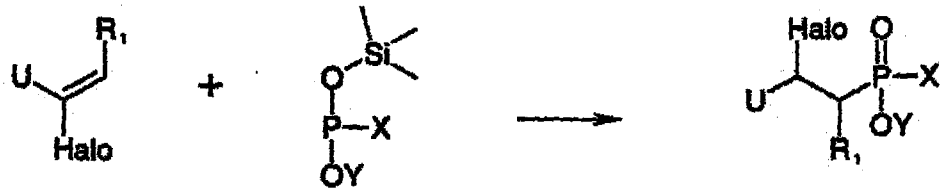
wherein R_1, R_3 and R_4 are as defined above in formula I, and Halo is a halogen atom, and if desired, a resulting compound is converted into another compound of the formula IX, a resulting mixture of isomers is separated into the individual isomers and/or a resulting salt obtained in this process is converted into the free compound of the formula IX or into another salt and/or, if desired, a resulting free compound of the formula IX is converted into a salt to correspond to the above definition;

or c) a compound of formula XI



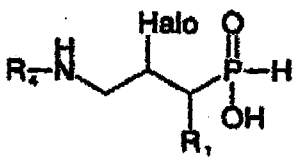
(XI)

in which R_1 is as defined above in formula I, X is hydrogen or a protecting group such as $-CCH_3(OCH_2CH_3)_2$, U is an electron-withdrawing group, such as for instance –CN or $–CO_2Et$ which can be converted to a $-CH_2NH_2$ group, and Y is hydrogen or a protecting group such as lower alkyl, and Halo is a halogen atom, which compound XI may have been synthesized by an addition reaction according to Scheme 3 employing an unsaturated compound in which R_1 is as defined above in formula I, U and halo are as defined in formula XI, and a suitable protected phosphinic acid derivative activated by O-silylation, in which X and Y are as defined in formula XI,



Scheme 3

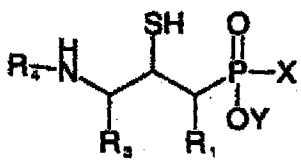
is converted by a reaction where the U group is being converted to $-NHR_4$ wherein R_4 is as defined above in formula I, and a hydrolytic reaction to obtain a compound of formula XII



(XII)

wherein R_1 and R_4 are as defined above in formula I and Halo is a halogen atom, and if desired, a resulting compound is converted into another compound of the formula XII, a resulting mixture of isomers is separated into the individual isomers and/or a resulting salt obtained in this process is converted into the free compound of the formula XII or into another salt and/or, if desired, a resulting free compound of the formula XII is converted into a salt to correspond to the above definition;

or d) a compound of formula XIII

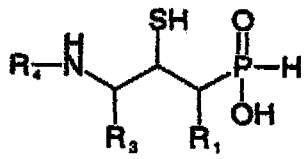


(XIII)

in which R_1, R_3 and R_4 are as defined above in formula I, X is hydrogen or a protecting group such as $-CCH_3(OCH_2CH_3)_2$, and Y is hydrogen or a protecting group such as lower alkyl, which compound of formula XIII may have been synthesized by an addition reaction according to Scheme 4 treating an unsaturated phosphinic acid derivative, in which R_1, R_3 and R_4 are as defined in above in formula I, with H_2S, a mercaptide ion (HS^-) or a protected mercapto compound such as benzyl thiol in which case the protective group thereafter is removed

Scheme 4

is converted by a hydrolytic reaction to obtain a compound of formula XIV,



(XIV)

in which R_1, R_3 and R_4 are as defined above in formula I, and if desired, a resulting compound is converted into another compound of the formula XIV, a resulting mixture of isomers is separated into the individual isomers and/or a resulting salt obtained in this process is converted into the free compound of the formula XIV or into another salt and/or, if desired, a resulting free compound of the formula XIV is converted into a salt to correspond to the above definition.

20. Ethyl 3-[(diethoxymethyl)(ethoxy)phosphoryl]-2-fluoropropanoate.

21. Ethyl (3-amino-2-fluoro-3-oxopropyl)(diethoxymethyl)phosphinate.

22. Ethyl (*R*)-(3-chloro-2-hydroxypropyl)(1,1-diethoxyethyl)phosphinate.

23. Ethyl (*S*)-(3-amino-2-hydroxypropyl)(1,1-diethoxyethyl)phosphinate.

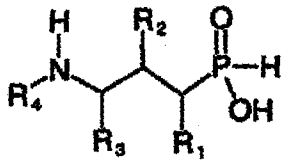
24. Ethyl (*S*)-(3-chloro-2-hydroxypropyl)(1,1-diethoxyethyl)phosphinate.

25. Ethyl (*R*)-(3-amino-2-hydroxypropyl)(1,1-diethoxyethyl)phosphinate.

26. (3-Amino-2-oxopropyl)(1,1-diethoxyethyl)phosphinate.

ABSTRACT

Novel compounds of formula I having affinity to one or more $GABA_B$ receptors, their pharmaceutically acceptable salts and stereoisomers, as well as processes for their preparation, pharmaceutical compositions containing said therapeutically active compounds and the use of said active compounds in therapy.



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PRV

DIRECCION NACIONAL DE PATENTES Y REGISTRO

TRADUCCION OFICIAL No. 5.787
María Luisa Bellard de Restrepo
Intérprete Oficial

Certificado

Por el presente se certifica que la anexa es una copia fiel de los documentos registrados originalmente ante la Oficina de Patentes y Registro en relación con la siguiente solicitud de patente.

La solicitud fue registrada originalmente en inglés.

(71) Solicitante(s) Astra AB, Södertälje SE

(21) Solicitud de patente número 0003640-0

(86) Fecha de registro 9-10-2000

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120

Estocolmo, 25-10-2000

Por la Oficina de Patentes y Registro

(Firma)

Therese Friberger

Derechos 170:-

TRADUCCION OFICIAL No. 5.787
María Luisa Brigard de Restrepo
Intérprete Oficial

EN ESPAÑOL, las autenticaciones de la firma anterior hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 392392 de fecha 23 de noviembre del 2.000

MINISTERIO DE RELACIONES EXTERIORES
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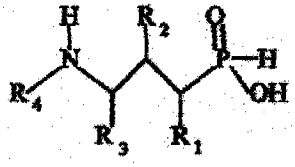
COTA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

REIVINDICACIONES

1. Un compuesto acorde con la fórmula I



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en donde

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R_1 representa hidrógeno, hidroxi, alquilo inferior, alcoxi inferior o halógeno;

R_2 representa hidroxi, mercapto, halógeno o un grupo oxo;

R_3 representa hidrógeno, alquilo inferior (opcionalmente sustituído con hidroxi, mercapto, alcoxi inferior, tioalcoxi inferior o arilo);

R_4 representa hidrógeno, alquilo inferior (opcionalmente sustituído con arilo), o arilo;

y sales farmaceuticamente aceptables y los esteroisómeros del mismo,

con la excepción de:

i) el racemato de ácido (3-amino-2-hidroxipropil)fosfínico, y

ii) ácido (*2R/S, 3R*)-(3-amino-2-hidroxibutil)fosfínico.

2. Un compuesto acorde con la reivindicación 1 en el que

R_1 representa hidrógeno;

R_2 representa flúor, hidroxi o un grupo oxo;

R_3 representa hidrógeno; y

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R_4 representa hidrógeno;

con la excepción del racemato de ácido (3-amino-2-hidroxipropil)fosfínico.

3. Acido (3-amino-2-fluoropropil)fosfínico o una sal farmaceuticamente aceptable o los esteroisómeros del mismo.

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María Luisa Brigard de Restrepo
Intérprete Oficial

4. Acido (2*R*)(3-amino-2-fluoropropil)fosfínico o una sal farmaceuticamente aceptable o los esteroisómeros del mismo.

5. Acido (3-amino-2-oxopropil)fosfínico o una sal farmaceuticamente aceptable o los esteroisómeros del mismo.

6. Acido (*S*)(3-amino-2-hidroxipropil)fosfínico o una sal farmaceuticamente aceptable o los esteroisómeros del mismo.

7. Un compuesto acorde con la reivindicación 1 para usarlo en terapia.

8. Uso de un compuesto acorde con cualquiera de las reivindicaciones 1 a 6 para la fabricación de un medicamento para la inhibición de relajaciones transitorias del esfínter esofágeo inferior.

9. Uso de un compuesto acorde con cualquiera de las reivindicaciones 1 a 6 para la fabricación de un medicamento para el tratamiento de enfermedad de reflujo gastro-

esofágeo.

10. Uso de un compuesto acorde con cualquiera de las reivindicaciones 1 a 6 para la fabricación de un medicamento para el tratamiento de regurgitación en infantes.

11. Uso de un compuesto acorde con cualquiera de las reivindicaciones 1 a 6 para la fabricación de un medicamento para asma relacionada o no con GORD, eructos, tos, dolor, adicción a la cocaína, hipo, IBS, dispepsia, emesis o nocicepción.

12. Un método para el tratamiento de relajaciones transitorias del esfínter esofágeo inferior que consiste en tratar a un paciente que sufre de dicho estado con una preparación farmacéutica que comprende un compuesto de la fórmula I.

13. Un método para el tratamiento de enfermedad de reflujo gastro-esofágeo que consiste en tratar a un paciente que sufre de dicho estado con una preparación farmacéutica que comprende un compuesto de la fórmula I.

14. Un método para el tratamiento de regurgitación en infantes que consiste en tratar a un paciente que sufre de dicho estado con una preparación farmacéutica que comprende un compuesto de la fórmula I.

15. Un método para el tratamiento de asma relacionada o no con GORD, eructos, tos, dolor, adicción a la cocaína, hipo, IBS, dispepsia, emesis o nocicepción. que consiste en tratar a un paciente que sufre de dicho estado con una preparación farmacéutica que

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comprende un compuesto de la fórmula I.

16. Una preparación farmacéutica que comprende como ingrediente activo una cantidad terapeuticamente aceptable del compuesto de cualquiera de las reivindicaciones 1 a 6, opcionalmente en asociación con diluentes, excipientes o portadores inertes.

17. Una preparación farmacéutica acorde con la reivindicación 16 para usarla en la inhibición de relajaciones transitorias del esfínter esofágeo inferior.

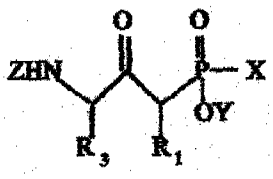
18. Una preparación farmacéutica acorde con la reivindicación 16 para usarla en el tratamiento de enfermedad de reflujo gastro-esofágeo.

19. Una preparación farmacéutica acorde con la reivindicación 16 para usarla en el tratamiento de regurgitación en infantes.

20. Un procedimiento para la preparación de un compuesto de la fórmula I acorde con la reivindicación 1,

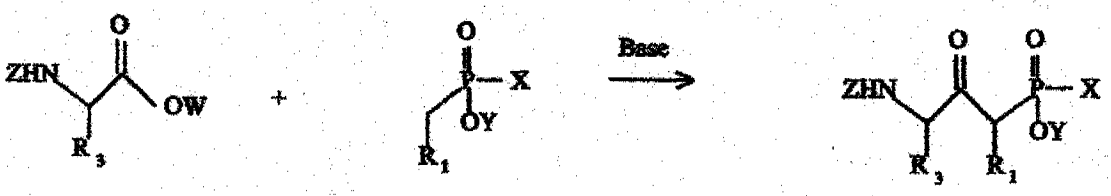
en el que

a) un compuesto de la fórmula II



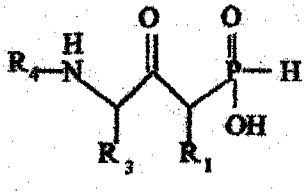
(II)

en donde R_1 y R_3 corresponden a las definiciones dadas arriba en la fórmula I, X es hidrógeno o un grupo protector tal como $-CCH_3(OCH_2CH_3)_2$, Z es un grupo protector tal como t-butiloxicarbonilo y Y es hidrógeno o un grupo protector tal como alquilo inferior. y ese compuesto de la fórmula II puede haber sido sintetizado mediante reacción de condensación de acuerdo con el Esquema 1 empleando un éster de aminoácido N-protegido en el que R_3 corresponde a la definición dada arriba, W es un grupo protector tal como alquilo inferior y Z corresponde a la definición dada en la fórmula II, y un derivado de ácido fosfínico protegido en el que R_1 corresponde a la definición dada arriba en la fórmula I, X y Y corresponden a las definiciones dadas en la fórmula II, y una base tal como diisopropilamida de litio,



Esquema 1

se convierte opcionalmente mediante una reacción de N-alquilación con el fin de introducir R_4, si se desea que R_4 no sea igual a hidrógeno, y luego una reacción hidrolítica para obtener un compuesto de la fórmula III



(III)

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en donde R_1, R_3 y R_4 corresponden a las definiciones dadas arriba en la fórmula I, y, si se desea, un compuesto resultante se convierte en otro compuesto de la fórmula III, una mezcla resultante de isómeros se separa en los isómeros individuales y/o una sal resultante obtenida en este proceso se convierte en el compuesto libre de la fórmula III o en otra sal y/o, si se desea, un compuesto libre resultante de la fórmula III se convierte en una sal que corresponda a la definición anterior;

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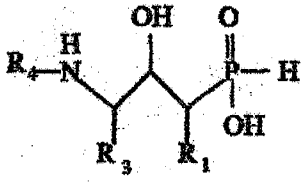
o un compuesto de la fórmula II se convierte, mediante una reacción reductora, opcionalmente una reacción de N-alquilación si se desea que R_4 no sea igual a hidrógeno, y finalmente una reacción hidrolítica para obtener un compuesto de la fórmula IV

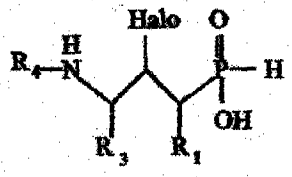


(IV)

en donde R_1, R_3 y R_4 corresponden a las definiciones dadas arriba en la fórmula I, y, si se desea, un compuesto resultante se convierte en otro compuesto de la fórmula IV, una mezcla resultante de isómeros se separa en los isómeros individuales y/o una sal resultante obtenida en este proceso se convierte en el compuesto libre de la fórmula IV o en otra sal y/o, si se desea, un compuesto libre resultante de la fórmula IV se convierte en una sal que corresponda a la definición anterior;

o un compuesto de la fórmula II se convierte, mediante una reacción reductora seguida por una reacción de desoxohalogenación, opcionalmente una reacción de N-alquilación, para

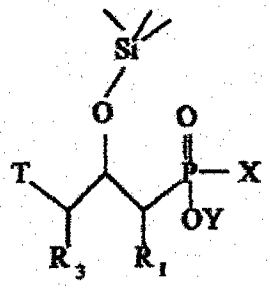
introducir R_4 si se desea que R_4 no sea igual a hidrógeno, y finalmente una reacción hidrolítica para obtener un compuesto de la fórmula V



(V)

en donde R_1, R_3 y R_4 corresponden a las definiciones dadas arriba en la fórmula I y Halo es un átomo de halógeno, y, si se desea, un compuesto resultante se convierte en otro compuesto de la fórmula V, una mezcla resultante de isómeros se separa en los isómeros individuales y/o una sal resultante obtenida en este proceso se convierte en el compuesto libre de la fórmula V o en otra sal y/o, si se desea, un compuesto libre resultante de la fórmula V se convierte en una sal que corresponda a la definición anterior;

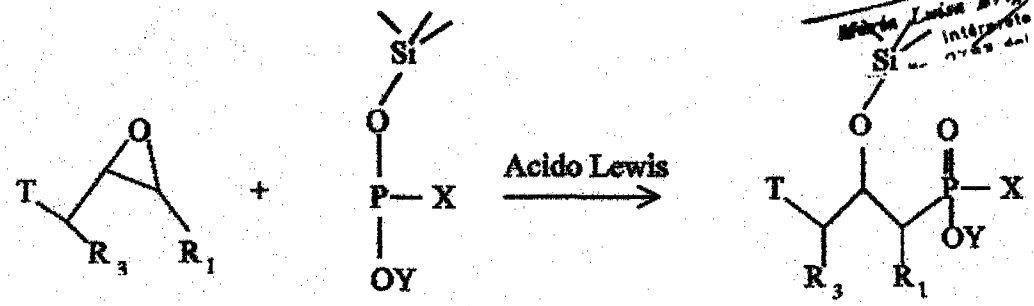
o b) un compuesto de la fórmula VI



(VI)

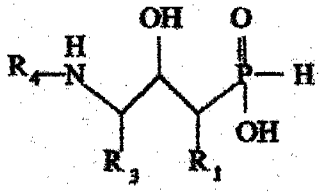
en donde R_1 y R_3 corresponden a las definiciones dadas arriba en la fórmula I, X es hidrógeno o un grupo protector tal como $-CCH_3(OCH_2CH_3)_2$, T es un grupo que puede convertirse en un grupo $-NH_2$, y Y es hidrógeno o un grupo protector tal como alquilo

inferior, y ese compuesto de la fórmula VI puede haber sido sintetizado mediante una reacción de condensación de acuerdo con el Esquema 2 empleando un derivado de 2,3-epoxipropilo, tal como un derivado de 2,3-epoxipropilamina o un derivado de epiclorohidrina N-protegido adecuado, en el que R_1 y R_3 corresponden a las definiciones dadas arriba en la fórmula I, y un derivado de ácido fosfínico protegido adecuado activado mediante O-sililación, en donde X y Y corresponden a las definiciones dadas en la fórmula VI, y un ácido Lewis tal como $ZnCl_2$ anhidro,



Esquema 2

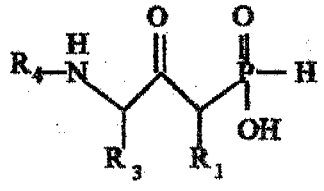
se convierte mediante una reacción en la que el grupo trimetilsililo es reemplazado por un grupo hidrógeno, una reacción en la que el grupo T definido en la fórmula VI se convierte en $-NHR_4$ en donde R_4 corresponde a la definición dada en la fórmula I, y finalmente una reacción hidrolítica para obtener un compuesto de la fórmula IV



(IV)

en donde R_1, R_3 y R_4 corresponden a las definiciones dadas arriba en la fórmula I, y si se desea, un compuesto resultante se convierte en otro compuesto de la fórmula IV, una mezcla resultante de isómeros se separa en los isómeros individuales y/o una sal resultante obtenida en este proceso se convierte en el compuesto libre de la fórmula IV o en otra sal y/o, si se desea, un compuesto libre resultante de la fórmula IV se convierte en una sal que corresponda a la definición anterior;

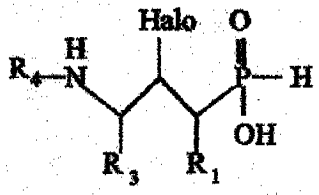
o un compuesto de la fórmula VI se convierte, mediante una reacción en la que el grupo trimetilsililo es reemplazado por hidrógeno, una reacción de oxidación, una reacción en la que el grupo T definido en la fórmula VI se convierte en $-NHR_4$, en donde R_4 corresponde a la definición dada en la fórmula I, y finalmente una reacción hidrolítica para obtener un compuesto de la fórmula III



(III)

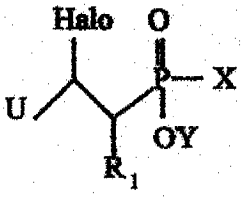
en donde R_1, R_3 y R_4 corresponden a las definiciones dadas arriba en la fórmula I, y si se desea, un compuesto resultante se convierte en otro compuesto de la fórmula III, una mezcla resultante de isómeros se separa en los isómeros individuales y/o una sal resultante obtenida en este proceso se convierte en el compuesto libre de la fórmula III o en otra sal y/o, si se desea, un compuesto libre resultante de la fórmula III se convierte en una sal que corresponda a la definición anterior;

o un compuesto de la fórmula VI se convierte, mediante una reacción en la que el grupo trimetilsililo es reemplazado por hidrógeno, una reacción de oxohalogenación, una reacción en la que el grupo T definido en la fórmula VI se convierte en $-NHR_4$ en donde R_4 corresponde a la definición dada en la fórmula I, y finalmente una reacción hidrolítica para obtener un compuesto de la fórmula V



en donde R_1, R_3 y R_4 corresponden a las definiciones dadas arriba en la fórmula I, y Halo es un átomo de halógeno, y si se desea, un compuesto resultante se convierte en otro compuesto de la fórmula V, una mezcla resultante de isómeros se separa en los isómeros individuales y/o una sal resultante obtenida en este proceso se convierte en el compuesto libre de la fórmula V o en otra sal y/o, si se desea, un compuesto libre resultante de la fórmula V se convierte en una sal que corresponda a la definición anterior;

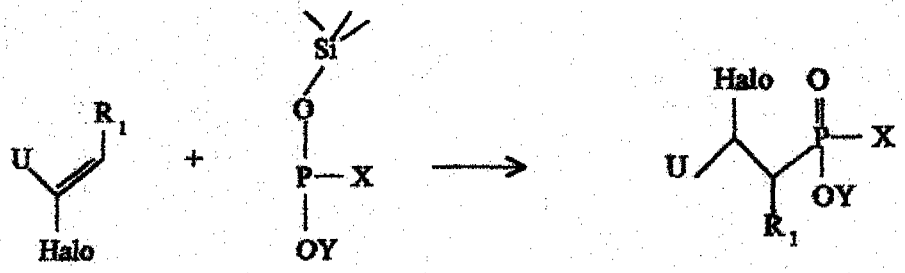
o c) un compuesto de la fórmula VII



(VII)

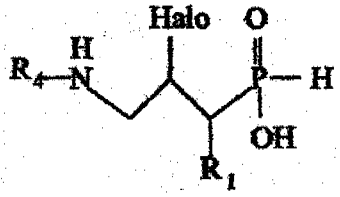
en donde R_1 corresponde a la definición dada arriba en la fórmula I, X es hidrógeno o un

grupo protector tal como $-CCH_3(OCH_2CH_3)_2$, U es un grupo que retira electrones, tal como -CN o CO_2Et que puede convertirse en un grupo $-CH_2NH_2$, y Y es hidrógeno o un grupo protector tal como alquilo inferior y Halo es un átomo de halógeno, y ese compuesto de la fórmula VII puede haber sido sintetizado mediante una reacción de adición de acuerdo con el Esquema 3 empleando un compuesto insaturado en el que R_1 corresponde a la definición dada arriba en la fórmula I, U y halo corresponden a las definiciones dadas en la fórmula VII, y un derivado de ácido fosfínico protegido adecuado activado mediante O-sililación, en donde X y Y corresponden a las definiciones dadas en la fórmula VII,



Esquema 3

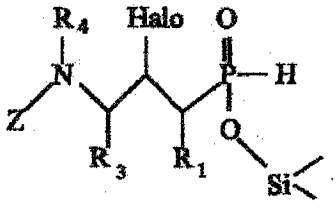
se convierte, mediante una reacción en la que el grupo U se convierte en $-NHR_4$ en donde R_4 corresponde a la definición dada arriba en la fórmula I, y una reacción hidrolítica para obtener un compuesto de la fórmula VIII



(VIII)

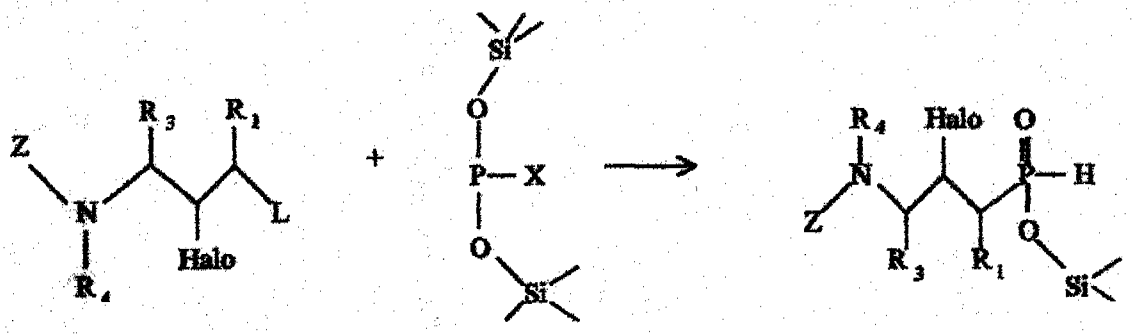
en donde R_1 y R_4 corresponden a las definiciones dadas arriba en la fórmula I, y Halo es un átomo de halógeno, y si se desea, un compuesto resultante se convierte en otro compuesto de la fórmula VIII, una mezcla resultante de isómeros se separa en los isómeros individuales y/o una sal resultante obtenida en este proceso se convierte en el compuesto libre de la fórmula VIII o en otra sal y/o, si se desea, un compuesto libre resultante de la fórmula VIII se convierte en una sal que corresponda a la definición anterior;

o d) un compuesto de la fórmula IX opcionalmente como un estereoisómero individual



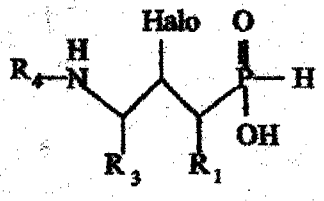
(IX)

donde R_1, R_3 y R_4 corresponden a las definiciones dadas arriba en la fórmula I, Z es un grupo protector tal como t-butiloxicarbonilo y Halo es un átomo de halógeno, y ese compuesto de la fórmula IX puede haber sido sintetizado mediante una reacción de sustitución de acuerdo con el Esquema 4 empleando un compuesto electrofílico en el que R_1 R_3 y R_4 corresponden a las definiciones dadas arriba en la fórmula I, L es un grupo saliente tal como yodo, X y Halo corresponden a las definiciones dadas arriba, y ácido fosfínico activado mediante O-sililación,



Esquema 4

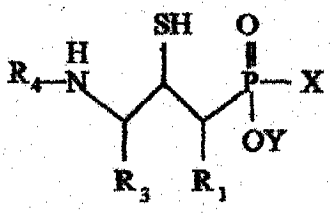
se convierte mediante reacción hidrolítica en un compuesto de la fórmula V



(V)

en donde R_1, R_3 y R_4 corresponden a las definiciones dadas arriba en la fórmula I, y si se desea, un compuesto resultante se convierte en otro compuesto de la fórmula V, si se desea, una mezcla resultante de isómeros se separa en los isómeros individuales y/o una sal resultante obtenida en este proceso se convierte en el compuesto libre de la fórmula V o en otra sal y/o, si se desea, un compuesto libre resultante de la fórmula V se convierte en una sal que corresponda a la definición anterior;

o e) un compuesto de la fórmula XI

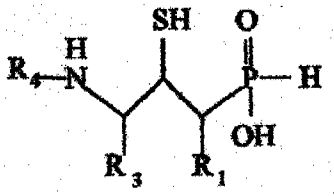


(XI)

en donde R_1, R_3 y R_4 corresponden a las definiciones dadas arriba en la fórmula I, X es hidrógeno o un grupo protector tal como $-CCH_3(OCH_2CH_3)_2$, y Y es hidrógeno o un grupo protector tal como alquilo inferior, y ese compuesto de la fórmula XI puede haber sido sintetizado mediante una reacción de adición de acuerdo con el Esquema 4 tratando un derivado de ácido fosfínico insaturado en el que R_1, R_3 y R_4 corresponden a las definiciones dadas arriba en la fórmula I, con H_2S, un ion de mercaptido (HS) o un compuesto de mercapto protegido tal como bencilotiol caso en el cual el grupo protector se remueve luego

Esquema 5

se convierte mediante una reacción hidrolítica para obtener un compuesto de la fórmula XII,



(XII)

en donde R_1, R_3 y R_4 corresponden a las definiciones dadas arriba en la fórmula I, y si se desea, un compuesto resultante se convierte en otro compuesto de la fórmula XII, una mezcla resultante de isómeros se separa en los isómeros individuales y/o una sal resultante obtenida en este proceso se convierte en el compuesto libre de la fórmula XII o en otra sal y/o, si se desea, un compuesto libre resultante de la fórmula XII se convierte en una sal que corresponda a la definición anterior.

21. 3-[(dietoximetil)(etoxi)fosforil]-2-fluoropropanoato de etilo.

22. (3-amino-2-fluoro-3-oxopropil)(dietoximetil)fosfinato de etilo.

23. (*R*)-(3-cloro-2-hidroxipropil)(1,1-dietoxietil)fosfinato de etilo.

24. (*S*)-(3-amino-2-hidroxipropil)(1,1-dietoxietil)fosfinato de etilo.

25. (*S*)-(3-cloro-2-hidroxipropil)(1,1-dietoxietil)fosfinato de etilo.

26. (*R*)-(3-amino-2-hidroxipropil)(1,1-dietoxietil)fosfinato de etilo.

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27. (3-amino-2-oxopropil)(1,1-dietoxietil)fosfinato.

28. (2*R*)-3-(dibencilamino)-2-fluoro-1-propanol

29. (2*R*)-3-amino-2-fluoro-1-propanol

30. *terc*-butil(2*R*)-2-fluoro-3-hidroxipropilcarbamato.

31. *terc*-butil(2*R*)-2-fluoro-3-yodopropilcarbamato.

ES TRADUCCION FIEL Y COMPLETA, de la cual queda copia en los archivos de esta oficina de traducciones, para su confrontación y a la que me remito.

Derechos de Traducción: $162.000,oo

BOGOTA, 25 DE NOVIEMBRE DEL 2000.

TRADUCTOR OFICIAL No. 5.787

María Luisa Brigard de Restrepo

Intérprete Oficial

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The application was originally filed in English.

5.787

TRADUCCION OFICIAL No. 5.787
María Luisa Bustard de Restrepo
Intérprete Oficial
Cons. No 07252 del Min. de Justicia

(71) *Sökande* / *Applicant (s)* AstraZeneca AB, Södertälje SE

(21) *Patentansökningsnummer* / *Patent application number* 0003640-0

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Stockholm, 2000-10-25

För Patent- och registreringsverket
For the Patent- and Registration Office

Therese Friberger

Therese Friberger

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Fee 170:-

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Encargada de las Funciones Consulares

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DEL OFICIAL DE 5.787

Anne-Marie Borde, Notario P
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otorgado y firmado el documento que

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De

NEW COMPOUNDS

Field of the invention

The present invention is related to novel compounds having affinity to one or more $GABA_B$ receptors, as well as to their pharmaceutically acceptable salts and stereoisomers. The invention is also related to processes for their preparation, pharmaceutical compositions containing said therapeutically active compounds and to the use of said active compounds in therapy.

Background and prior art

Reflux

Gastro-oesophageal reflux disease (GORD) is the most prevalent upper gastrointestinal tract disease. Current therapy has aimed at reducing gastric acid secretion, or at reducing oesophageal acid exposure by enhancing oesophageal clearance, lower oesophageal sphincter tone and gastric emptying. The major mechanism behind reflux has earlier been considered to depend on a hypotonic lower oesophageal sphincter. However recent research (e.g. *Holloway & Dent (1990) Gastroenterol. Clin. N. Amer. 19, 517-535*) has shown that most reflux episodes occur during transient lower oesophageal sphincter relaxations, hereinafter referred to as TLOSR, i.e. relaxations not triggered by swallows. It has also been shown that gastric acid secretion usually is normal in patients with GORD.

Consequently, there is a need for compounds which reduce the incidence of TLOSR and thereby prevent reflux.

Pharmaceutical compositions comprising a local anaesthetic, adapted to inhibit relaxation of the lower oesophageal sphicter are disclosed in WO 87/04077 and in US 5,036,057. Recently $GABA_B$-receptor agonists have been shown to inhibit TLOSR which is disclosed in WO 98/11885.

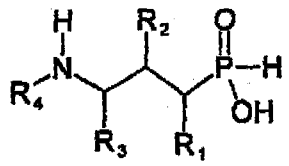
$GABA_B$ receptor agonists

GABA (4-aminobutanoic acid) is an endogenous neurotransmitter in the central and peripheral nervous systems. Receptors for GABA have traditionally been divided into $GABA_A$ and $GABA_B$ receptor subtypes. $GABA_B$ receptors belong to the superfamily of G-protein coupled receptors. $GABA_B$ receptor agonists are being described as being of use in the treatment of CNS disorders, such as muscle relaxation in spinal spasticity, cardiovascular disorders, asthma, gut motility disorders such as irritable bowel syndrome (IBS) and as prokinetic and anti-tussive agents. $GABA_B$ receptor agonists have also been disclosed as useful in the treatment of emesis (WO 96/11680) and recently, as mentioned above, in the inhibition of TLOSR (WO 98/11885).

The most studied $GABA_B$ receptor agonist is baclofen (4-amino-3-(chlorophenyl)butanoic acid) disclosed in the Swiss patent No. CH 449, 046. Baclofen has for several years been used as an antispastic agent. EP 0356128 describes the use of the specific compound (3-aminopropyl)methyl phosphinic acid, as a potent $GABA_B$ receptor agonist, in therapy. EP 0181833 discloses substituted 3-aminopropyl phosphinic acids (or more correctly 3-aminopropyl phosphinic acids) which are found to have very strong affinities towards $GABA_B$ receptor sites. In analogy to baclofen, the compounds can be used as for instance muscle relaxants. EP 0399949 discloses derivatives of (3-aminopropyl)methyl phosphinic acid which are described as potent $GABA_B$ receptor agonists. These compounds are stated to be useful as muscle relaxants. EP 0463969 and FR 2722192 are both applications related to 4-aminobutanoic acid derivatives having different heterocyclic substituents at the β-carbon of the butyl chain. Structure-activity relationships of several phosphinic acid analogues with respect to their affinities to the $GABA_B$ receptor as well as their muscle relaxant effect are discussed in *J. Med. Chem.* (1995), 38, 3297-3312. The conclusion in said article is that considerably stronger muscle relaxation could be achieved with the (S)-enantiomer of (3-amino-2-hydroxypropyl)methyl phosphinic acid than with baclofen without the occurrence of unwanted CNS effects.

Outline of the invention

The present invention provides novel compounds of the formula I



(I)

wherein

R_1 represents hydrogen, hydroxy, lower alkyl, lower alkoxy or halogen;

R_2 represents hydroxy, mercapto, halogen, or an oxo group;

R_3 represents hydrogen, lower alkyl (optionally substituted with hydroxy, mercapto, lower alkoxy, lower thioalkoxy or aryl);

R_4 represents hydrogen, lower alkyl (optionally substituted with aryl), or aryl;

and pharmaceutically acceptable salts and the stereoisomers thereof,

with the exceptions of:

i) the racemate of (3-amino-2-hydroxypropyl)phosphinic acid, and

ii) (2*R/S*, 3*R*)-(3-amino-2-hydroxybutyl)phosphinic acid.

In a preferred embodiment

R_1 represents hydrogen;

R_2 represents fluoro, hydroxy or an oxo group;

R_3 represents hydrogen; and

R_4 represents hydrogen;

with the exception of the racemate of (3-amino-2-hydroxypropyl)phosphinic acid.

Even more preferred compounds are (3-amino-2-fluoropropyl)phosphinic acid, (2*R*)-(3-amino-2-fluoropropyl)phosphinic acid, (3-amino-2-oxopropyl)phosphinic acid and (*S*)-(3-amino-2-hydroxypropyl)phosphinic acid.

Most preferred the compound is (2*R*)-(3-amino-2-fluoropropyl)phosphinic acid.

Within the scope of the invention, it is to be understood that when R_2 is an oxo group the bond between R_2 and the carbon is a double bond.

Within the scope of the invention, it is to be understood by "lower" radicals and compounds, for example, those having up to and including 7, especially up to and including 4, carbon atoms. Also the general terms have the following meanings:

Lower alkyl is, for example, C_1-C_4 alkyl, such as methyl, ethyl, n-propyl or n-butyl, also isopropyl, isobutyl, secondary butyl or tertiary butyl, but may also be a C_5-C_7 alkyl group such as a pentyl, hexyl or heptyl group.

Lower alkoxy is, for example, C_1-C_4 alkoxy, such as methoxy, ethoxy, n-propoxy or n-butoxy, also isopropoxy, isobutoxy, secondary butoxy or tertiary butoxy, but may also be a C_5-C_7 alkoxy group, such as a pentoxy, hexoxy or heptoxy group.

Lower thioalkoxy is, for example, C_1-C_4 thioalkoxy, such as thiomethoxy, thioethoxy, n-thiopropoxy or n-thiobutoxy, also thioisopropoxy, thioisobutoxy, secondary thiobutoxy or tertiary thiobutoxy, but may also be a C_5-C_7 thioalkoxy group, such as a thiopentoxy, thiohexoxy or thioheptoxy group.

Halogen is, for example, halogen of an atomic number up to and including 35, such as flourine or chlorine, less prefered, bromine.

The compounds according to formula I of the invention are of amphoteric nature and may be presented in the form of internal salts. They can also form acid addition salts and salts with bases. Such salts are particularly pharmaceutically acceptable acid addition salts, as well as pharmaceutically acceptable salts formed with bases. Suitable acids for the formation of such salts include, for example, mineral acids such as hydrochloric, hydrobromic, sulfuric, or phosphoric acid or organic acids such as sulfonic acids and carboxylic acids. Salts with bases are, for example, alkali metal salts, e.g. sodium or potassium salts, or alkaline earth metal salts, e.g. calcium or magnesium salts, as well as ammonium salts, such as those with ammonia or organic amines.

When one or more stereocentre is present in the molecule, the compounds according to formula I can be in the form of a stereoisomeric mixture, i.e. a mixture of diastereomers and/or racemates, or in the form of the single stereoisomers, i.e. the single enantiomer and/or diastereomer.

The novel compounds according to the invention can be used for the inhibition of TLOSR, and thus for the treatment of gastro-oesophageal reflux disease. The said inhibition of TLOSR also implies that the said compounds can be used for the treatment of regurgitation in infants. Effective management of regurgitation in infants would be an important way of managing failure to thrive due to excessive loss of ingested nutrient. Furthermore the novel compounds can be used for the treatment of GORD-related or non-GORD related asthma,

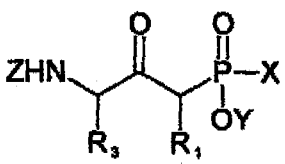
belching, coughing, pain, cocaine addition, hiccups, IBS, dyspepsia, emesis and nociception.

As opposed to what is stated in prior art, (*J.Med.Chem. (1995) 3297-3312* and *The GABA Receptors; Second Edition, Edited by S.J. Enna and Norman Bowery, Humana Press (1997) especially p. 281-282)*, the compounds according to the invention have surprisingly high metabolic stability in spite of the presence of a P-H bond. The compounds also possess a surprisingly high therapeutic index.

Preparation

The compounds according to formula I of the present invention may be prepared by one of the following methods.

a) A compound of formula II



(II)

in which R_1 and R_3 are as defined above in formula I, X is hydrogen or a protecting group such as $-CCH_3(OCH_2CH_3)_2$, Z is a protecting group such as t-butyloxycarbonyl and Y is hydrogen or a protecting group such as lower alkyl, which compound of formula II may have been synthesized by a condensation reaction according to Scheme 1 employing an appropriate N-protected amino acid ester in which R_3 is as defined above, W is a protecting group such as lower alkyl and Z is as defined in formula II, and a suitable protected phosphinic acid derivative in which R_1 is as defined above in formula I, X and Y are as defined in formula II, and a base such as lithium diisopropylamide,

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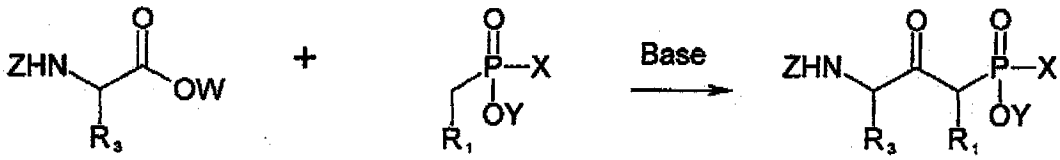
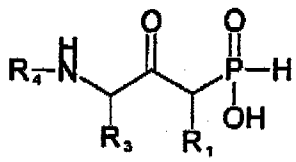


Scheme 1

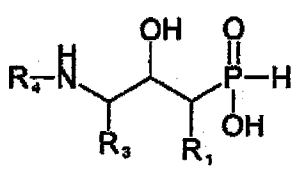
is optionally converted by an N-alkylation reaction in order to introduce R_4 if R_4 is desired to be not equal to hydrogen, and thereafter a hydrolytic reaction to obtain a compound of formula III



(III)

wherein R_1, R_3 and R_4 are as defined above in formula I, and if desired, a resulting compound is converted into another compound of the formula III, a resulting mixture of isomers is separated into the individual isomers and/or a resulting salt obtained in this process is converted into the free compound of the formula III or into another salt and/or, if desired, a resulting free compound of the formula III is converted into a salt to correspond to the above definition;

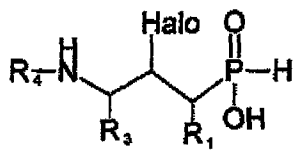
or a compound of formula II is converted by a reductive reaction, optionally an N-alkylation reaction if R_4 is desired to be not equal to hydrogen, and finally a hydrolytic reaction to obtain a compound of formula IV



(IV)

wherein R_1, R_3 and R_4 are as defined above in formula I, and if desired, a resulting compound is converted into another compound of the formula IV, a resulting mixture of isomers is separated into the individual isomers and/or a resulting salt obtained in this process is converted into the free compound of the formula IV or into another salt and/or, if desired, a resulting free compound of the formula IV is converted into a salt to correspond to the above definition;

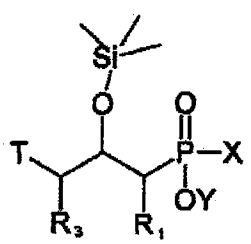
or a compound of formula II is converted by a reductive reaction followed by a deoxohalogenation reaction, optionally an N-alkylation reaction in order to introduce R_4 if R_4 is desired to be not equal to hydrogen, and finally a hydrolytic reaction to obtain a compound of formula V



(V)

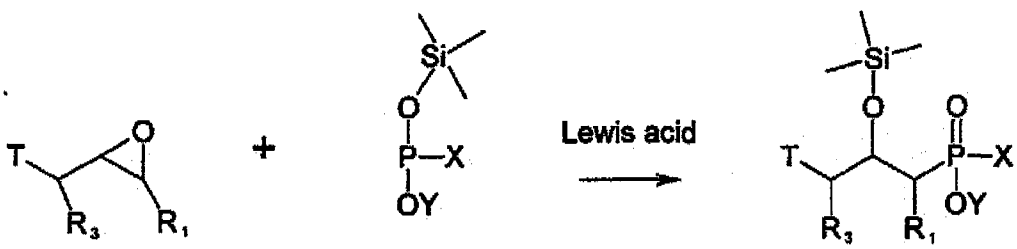
wherein R_1, R_3 and R_4 are as defined above in formula I and Halo is a halogen atom, and if desired, a resulting compound is converted into another compound of the formula V, a resulting mixture of isomers is separated into the individual isomers and/or a resulting salt obtained in this process is converted into the free compound of the formula V or into another salt and/or, if desired, a resulting free compound of the formula V is converted into a salt to correspond to the above definition;

or b) a compound of formula VI



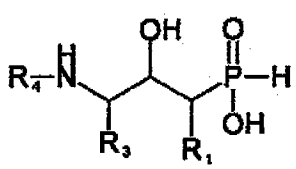
(VI)

in which R_1, and R_3 are as defined above in formula I, X is hydrogen or a protecting group such as $-CCH_3(OCH_2CH_3)_2$, T is a group that can be converted to a-NH_2 group, and Y is hydrogen or a protecting group such as lower alkyl, which compound of formula VI may have been synthesized by a condensation reaction according to Scheme 2 employing an 2,3-epoxypropyl derivative, such as an appropriate N-protected 2,3-epoxypropylamine derivative or an epichlorohydrin derivative, in which R_1 and R_3 is as defined above in formula I, and a suitable protected phosphinic acid derivative activated by O-silylation, in which X and Y are as defined in formula VI, and a Lewis acid such as anhydrous $ZnCl_2$,



Scheme 2

is converted by a reaction where the trimethylsilyl group is replaced by a hydrogen atom, a reaction where the T group as defined in formula VI is converted to $-NHR_4$ wherein R_4 is as defined above in formula I, and finally a hydrolytic reaction to obtain a compound of formula IV

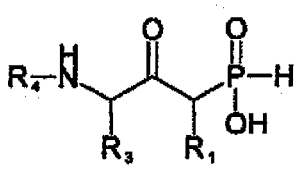


(IV)

wherein R_1, R_3 and R_4 are as defined above in formula I, and if desired, a resulting compound is converted into another compound of the formula IV, a resulting mixture of

isomers is separated into the individual isomers and/or a resulting salt obtained in this process is converted into the free compound of the formula IV or into another salt and/or, if desired, a resulting free compound of the formula IV is converted into a salt to correspond to the above definition;

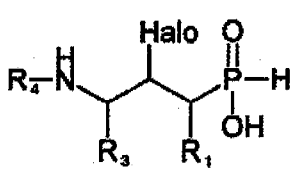
or compound of formula VI is converted by a reaction where the trimethylsilyl group is replaced by hydrogen, an oxidative reaction, a reaction where the T group as defined in formula VI is converted to -NHR_4 wherein R_4 is as defined above in formula I, and finally a hydrolytic reaction to obtain a compound of formula III



(III)

wherein R_1, R_3 and R_4 are as defined above in formula I, and if desired, a resulting compound is converted into another compound of the formula III, a resulting mixture of isomers is separated into the individual isomers and/or a resulting salt obtained in this process is converted into the free compound of the formula III or into another salt and/or, if desired, a resulting free compound of the formula III is converted into a salt to correspond to the above definition;

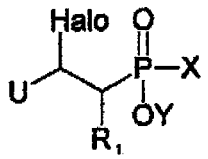
or a compound of formula VI is converted by a reaction where the trimethylsilyl group is replaced by hydrogen, a deoxohalogenation reaction, a reaction where the T group as defined in formula VI is converted to -NHR_4 wherein R_4 is as defined above in formula I, and finally a hydrolytic reaction to obtain a compound of formula V



(V)

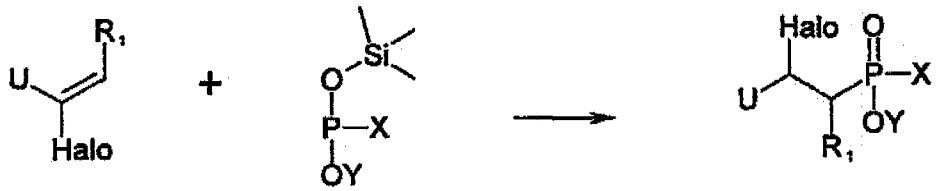
wherein R_1, R_3 and R_4 are as defined above in formula I, and Halo is a halogen atom, and if desired, a resulting compound is converted into another compound of the formula V, a resulting mixture of isomers is separated into the individual isomers and/or a resulting salt obtained in this process is converted into the free compound of the formula V or into another salt and/or, if desired, a resulting free compound of the formula V is converted into a salt to correspond to the above definition;

or c) a compound of formula VII



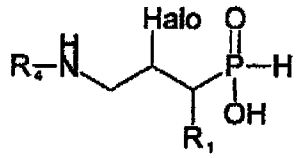
(VII)

in which R_1 is as defined above in formula I, X is hydrogen or a protecting group such as $-CCH_3(OCH_2CH_3)_2$, U is an electron-withdrawing group, such as for instance –CN or $-CO_2Et$ which can be converted to a $-CH_2NH_2$ group, and Y is hydrogen or a protecting group such as lower alkyl, and Halo is a halogen atom, which compound of formula VII may have been synthesized by an addition reaction according to Scheme 3 employing an unsaturated compound in which R_1 is as defined above in formula I, U and halo are as defined in formula VII, and a suitable protected phosphinic acid derivative activated by O-silylation, in which X and Y are as defined in formula VII,



Scheme 3

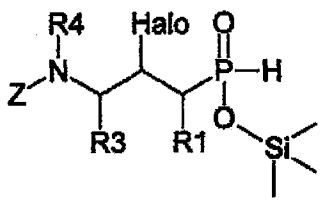
is converted by a reaction where the U group is being converted to -NHR_4 wherein R_4 is as defined above in formula I, and a hydrolytic reaction to obtain a compound of formula VIII



(VIII)

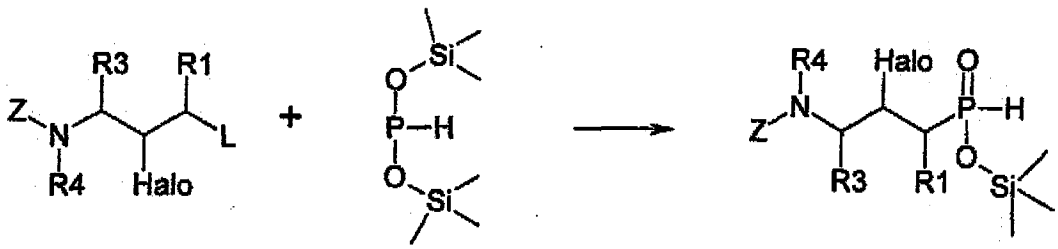
wherein R_1 and R_4 are as defined above in formula I and Halo is a halogen atom, and if desired, a resulting compound is converted into another compound of the formula VIII, a resulting mixture of isomers is separated into the individual isomers and/or a resulting salt obtained in this process is converted into the free compound of the formula VIII or into another salt and/or, if desired, a resulting free compound of the formula VIII is converted into a salt to correspond to the above definition;

or d) a compound of formula IX optionally as an individual stereo isomer



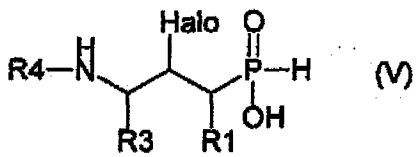
(IX)

in which R_1, R_3 and R_4 are as defined in formula I, Z is a protecting group such as t-butyloxycarbonyl and Halo is a halogen atom, which compound of formula IX may have been synthesized by a substitution reaction according to Scheme 4 employing an electrophilic compound in which R_1, R_3 and R_4 are as defined above, L is a leaving group such as iodo, Z and Halo are as defined above, and phosphinic acid activated by O-silylation,



Scheme 4

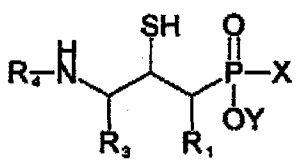
is converted by a hydrolytic reaction to a compound of formula V



(V)

wherein R_1, R_3 and R_4 are as defined above in formula I, and if desired, a resulting compound is converted into another compound of the formula V, if desired a resulting mixture of isomers is separated into the individual isomers and/or a resulting salt obtained in this process is converted into the free compound of the formula V or into another salt and/or, if desired, a resulting free compound of the formula V is converted into a salt to correspond to the above definition;

or e) a compound of formula XI



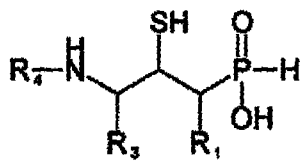
(XI)

in which R_1, R_3 and R_4 are as defined above in formula I, X is hydrogen or a protecting group such as $-CCH_3(OCH_2CH_3)_2$, and Y is hydrogen or a protecting group such as lower alkyl, which compound of formula XI may have been synthesized by an addition reaction according to Scheme 4 treating an unsaturated phosphinic acid derivative, in which R_1, R_3

and R_4 are as defined in above in formula I, with H_2S, a mercaptide ion (HS^-) or a protected mercapto compound such as benzyl thiol in which case the protective group thereafter is removed

Scheme 5

is converted by a hydrolytic reaction to obtain a compound of formula XII,



(XII)

in which R_1, R_3 and R_4 are as defined above in formula I, and if desired, a resulting compound is converted into another compound of the formula XII, a resulting mixture of isomers is separated into the individual isomers and/or a resulting salt obtained in this process is converted into the free compound of the formula XII or into another salt and/or, if desired, a resulting free compound of the formula XII is converted into a salt to correspond to the above definition.

Examples

Example 1. (3-Amino-2-fluoropropyl)phosphinic acid

To an ice bath cooled solution of ethyl (3-amino-2-fluoro-3-

oxopropyl)(diethoxymethyl)phosphinate in THF (tetrahydrofuran) was added 1 M BH_3-THF while under an argon atmosphere. After 10 minutes, the solution was heated to reflux for 2.5 h. The solution was cooled to room temperature and 6 N HCl (200 mL) was added. The THF was removed by rotoevaporation and the aqueous layer refluxed for 2.5 h. The solution was cooled and evaporated. The residue was purified by ion exchange column chromatography (DOWEX® 50WX-8-200, H^+ form, 3.5 x 4.0 cm). The ion exchange resin was pre-washed with 2:1 methanol/water (400 mL). The crude product dissolved in 1:1 methanol/water was loaded onto the column and washed with 1:1 methanol/water (400 mL). The eluent was changed to 3:1 methanol/concentrated ammonium hydroxyde. Two fractions (150 mL totally) were combined and evaporated to give 645 mg (34%) of (3-amino-2-fluoropropyl)phosphinic acid as a white solid. Data: mp 203-207 °C; R_f = 0.35 (60:40:1 methanol, methylene chloride, concentrated ammonium hydroxide); ^{1}H NMR (300 MHz, D_2O) δ 7.11 (d, J = 528 Hz, 1H), 5.18 (dm, J = 54 Hz, 1H), 3.28-3.45 (m, 2H), 1.65-2.23 (m, 2H); ^{13}C NMR (125 MHz, D_2O + Dioxane) δ 87.8 (d, J = 170 Hz), 44.3 (dd, J = 12.6, 21.6 Hz), 35.6 (dd, J = 20.2, 86.5 Hz); APIMS: m/z = 142 $(M+H)^+$.

Example 2. (*S*)-(3-Amino-2-hydroxypropyl)phosphinic acid

A mixture of ethyl (*S*)-(3-amino-2-hydroxypropyl)(1,1-diethoxyethyl)phosphinate (1.0 g, 3.5 mmol) and concentrated HCl (50 mL) was heated to reflux for 2 h. The solution was cooled to room temperature and evaporated. The residue was dissolved in methanol (100 ml) and treated with propylene oxide (2 ml) at room temperature. After the mixture was stirred for 5 hours, the precipitated solid was collected by decanting off the solvent. The solid was dried with a stream of argon to give 220 mg (45%) of (*S*)-(3-amino-2-hydroxypropyl)phosphinic acid as a white solid. Data: ^{1}H NMR (300 MHz, D_2O) δ 7.1 (d, J = 540 Hz, 1H), 4.2 (m, 1H), 2.9-3.2 (m, 2H), 1.7-2.0 (m, 2H); ^{31}P NMR (121 MHz, D_2O) δ 24.2 (d, J = 522 Hz); FABMS: m/z = 140 $(M+H)^+$; $[\alpha]_D$ at 20 °C = +8 ° (0.5% in 0.1M HCl).

Example 3. (*R*)-(3-Amino-2-hydroxypropyl)phosphinic acid

A mixture of ethyl (*R*)-(3-amino-2-hydroxypropyl)(1,1-diethoxyethyl)phosphinate (0.9 g, 3.2 mmol) and concentrated HCl (50 mL) was heated to reflux for 2 h. The solution was cooled to room temperature and evaporated. The residue was dissolved in methanol (50 ml) and treated with propylene oxide (3 ml) at room temperature. After the mixture was stirred for 5 hours, the precipitated solid was collected by decanting off the solvent. The solid was dried with a stream of argon to give 260 mg (59%) of (*R*)-(3-amino-2-hydroxypropyl)phosphinic acid as a white solid. Data: ^{1}H NMR (300 MHz, D_2O) δ 7.1 (d, J = 540 Hz, 1H), 4.2 (m, 1H), 2.9-3.2 (m, 2H), 1.7-2.0 (m, 2H); ^{31}P NMR (121 MHz, D_2O) δ 23.9 (d, J = 525 Hz); FABMS: m/z = 140 $(M+H)^+$; $[\alpha]_D$ at 20 °C = -8 ° (0.5% in 0.1M HCl).

Example 4. (3-Amino-2-oxopropyl)phosphinic acid

A sample of ethyl(3-amino-2-oxopropyl)(1,1-diethoxyethyl)phosphinate (8.11 g, 21.0 mmol) was dissolved in 3 N HCl (400 mL) which was previously deoxygenated by bubbling N_2 through the solution. The mixture was stirred for 14 h at room temperature and then concentrated. The residue was coevaporated with methanol. The residue was then dissolved in methanol (10 mL) and propylene oxide was added (10 mL). The mixture was stirred for 6 h and the resulting precipitate isolated by filtration. The solid was washed with cold methanol and dried under vacuum at 50 °C to give 2.1 g (73%) of (3-amino-2-oxopropyl)phosphinic acid as an off-white solid. Data: mp 126-127 °C; R_f = 0.64 (85:15 methanol, water); ^{1}H NMR (300 MHz, D_2O) δ 7.13 (d, J = 551 Hz, 1H), 4.14 (s, 2H), 3.14 (d, J = 18 Hz, 2 H); ^{13}C NMR (75 MHz, D_2O + Dioxane) δ 199.5, 49.2, 47.3 (d, J = 69 Hz); FABMS: m/z = 138 $(M+H)^+$.

Example 5. (2*R*)-(3-Amino-2-fluoropropyl)phosphinic acid

Ammonium hypophosphite (73.8 g, 0.89 mol) was added to 3 necked 2-L flask equipped with a mechanical stirrer, thermometer, addition funnel and an argon bubbler. The flask was placed in a water bath at room temperature and N,O-*Bis*-(trimethylsilyl)acetamide

(215 mL, 0.87 mol -BSA) was added at such a rate that the internal temperature was maintained below 38 °C (30 minutes approx.) using ice cooling. Upon completing the addition of BSA, the reaction mixture was heated to 45-48 °C and maintained at this temperature for 1 h. The reaction was cooled to room temperature and a solution of *tert*-butyl (2*R*)-2-fluoro-3-iodopropylcarbamate (27.3 g, 0.09 mol) in methylene chloride (300 mL) was added to the reaction mixture. The reaction was then allowed to stir at room temperature for 18 h. The reaction mixture was cooled to 0 °C and was cautiously quenched with methanol (275 mL) and then with water (32 mL). The reaction mixture was stirred for 30 min after which the reaction was filtered and the solids were washed with methanol. The filtrate was concentrated and the residue placed under high vacuum (0.1 mm Hg) overnight. The crude residue was triturated with methylene chloride, methanol, concentrated ammonium hydroxide solution (80:20:1) and was filtered. The filtrate was concentrated under reduced pressure and the trituration was repeated. The crude concentrate was transferred to a 2-L flask, dissolved in methanol (375 mL) and placed in a water bath at room temperature. A saturated solution of hydrogen chloride gas in ethyl acetate (500 mL) was added and the mixture stirred for 3 h. The reaction mixture was filtered and the solids were washed with a mixture of methanol and ethyl acetate (90:10). The filtrate was concentrated under reduced pressure and the crude product was passed through a Dowex® 50WX8-200 mesh H^+ form (500 g, 8x15 cm) column eluting with 1:1 methanol/water until no further material was detected by TLC analysis. The requisite crude product was then eluted with 1:3 concentrated ammonium hydroxide solution/methanol. The product was further purified by column chromatography eluting with chloroform, methanol, concentrated ammonium hydroxide solution (6:3:1) to afford (2*R*)-3-Amino-2-fluoropropylphosphinic acid as a white solid (3.12 g, 24%).

^{1}H NMR (300 MHz, D_2O) δ 7.90 (s, 0.5 H), 6.15 (s, 0.5 H), 5.12-5.29 (m, 0.5 H), 4.92-5.10 (m, 0.5 H), 3.12-3.42 (m, 2H), 1.74-2.26 (m, 2H).

The following intermediates were used in the preparation of compounds of the invention.

Intermediates

Example I1. Ethyl 3-[(diethoxymethyl)(ethoxy)phosphoryl]-2-fluoropropanoate (intermediate to the compound according to Example 1)

A mixture of ethyl (diethoxymethyl)phosphinate (26.0 g, 133 mmol) and 1,1,1,3,3,3-hexamethyldisilazane (28 mL, 133 mmol) was heated to reflux for 2 h under an argon atmosphere. The mixture was cooled to room temperature and fluoroacrylate (10.5 g, 89.0 mmol) was added. The reagents were heated to 60 °C for three days under an argon atmosphere. The mixture was cooled to room temperature, diluted with ethyl acetate (300 mL), washed with 1 N HCl (2 x 150 mL) and saturated sodium chloride (100 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated to give 32.0 g of a yellow oil. The residue was purified by coloumn chromatography on a wet-packed silica gel column (6 x 30 cm) eluting with 97:3 methylene chloride/methanol. The appropriate fractions were combined and evaporated to give 16.0 g (57%) of ethyl 3-[(diethoxymethyl)(ethoxy)phosphoryl]-2-fluoropropanoate as a clear oil. Data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.32 (dm, 1H), 4.67-4.77 (m, 1H), 4.18-4.32 (m, 2H), 3.58-3.91 (m, 4H), 2.30-2.62 (m, 2H), 1.20-1.41 (m, 9H).

Example I2. Ethyl (3-amino-2-fluoro-3-oxopropyl)(diethoxymethyl)phosphinate (intermediate to compound according to example 1)

To a solution of ethyl 3-[(diethoxymethyl)(ethoxy)phosphoryl]-2-fluoropropanoate (16.0 g, 51.1 mmol) in ethanol (22 mL) was added concentrated ammonium hydroxyde (14.8 N, 3.5 mL, 51.1 mmol). The solution was stirred for 16 h and evaporated. The residue was purified by chromatography on a wet-packed silica gel column (7 x 37 cm) eluting with 96.5:3.5 methylene chloride/methanol. The appropriate fractions were combined and evaporated to give 3.43 g (27%) of ethyl (3-amino-2-fluoro-3-oxopropyl)(diethoxymethyl)phosphinate as a clear oil. Data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.43 (s, 1H), 5.70 (s, 1H), 5.21-5.49 (dm, 1H), 4.7 (dd, 1H), 4.18-4.31 (m, 2H), 3.65-3.91 (m, 4H), 2.21-2.81 (m, 2H), 1.30-1.40 (m, 3H), 1.20-1.28 (m, 6H).

Example I3. Ethyl (*R*)-(3-chloro-2-hydroxypropyl)(1,1-diethoxyethyl)phosphinate (intermediate to the compound according to Example 2)

After a mixture of ethyl (diethoxyethyl)phosphinate (15.0 g, 71 mmol) and toluene was evaporated to dryness, the residue and 1,1,1,3,3,3-hexamethyldisilazane (13.2 g, 82 mmol) was heated to reflux for 3 h under an argon atmosphere. The mixture was cooled to room temperature and evaporated. (*R*)-Epichlorohydrin (6.6 g, 71 mmol) and anhydrous zinc chloride (2.5 g, 18 mmol) were added and the reagents were heated to 60 °C over night under an argon atmosphere. The mixture was cooled to room temperature, diluted with methylene chloride and water. The organic layer was washed with water, dried over $MgSO_4$, filtered, and evaporated to give 20.7 g of a yellow oil. The residue was dissolved in methanol (150 mL) containing 1% acetic acid and the solution was stirred over night. The solvent was removed to give 17.7 g (82%) of ethyl (*R*)-(3-chloro-2-hydroxypropyl)(1,1-diethoxyethyl)phosphinate as a clear oil. Data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.3-4.4 (m, 1H), 4.1-4.3 (m, 2H), 3.5-3.8 (m, 4H), 1.9-2.4 (m, 2H), 1.5 (dd, J = 2.3, 11.4 Hz, 3H), 1.32-1.37 (m, 3H), 1.18-1.24 (m, 6H).

Example I4. Ethyl (*S*)-(3-amino-2-hydroxypropyl)(1,1-diethoxyethyl)phosphinate (intermediate to the compound according to Example 2)

A solution of (*R*)-(3-chloro-2-hydroxypropyl)(1,1-diethoxyethyl)phosphinate (5.0 g, 17 mmol) in ethanol containing 9% of ammonia was stirred in an autoclave at room temperature for 4 days and at 60 °C for one further day. The solution was evaporated and the residue was purified by chromatography on a wet-packed silica gel column eluting with methylene chloride/methanol (5-8% MeOH) containing 5% triethylamine. The appropriate fractions were combined, evaporated and diluted with methylene chloride and water. The aqueous layer was pH adjusted by the addition of a few mL of 10% aqueous Na_2CO_3 and repeatedly extracted with methylene chloride. The combined organic layers were dried over Na_2SO_4 and evaporated to give 1.2 g (26%) of ethyl (*S*)-(3-amino-2-hydroxypropyl)(1,1-diethoxyethyl)phosphinate as a clear oil. Data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.40-4.55 (b, 1H), 4.10-4.30 (m, 2H), 3.55-3.80 (m, 4H), 3.20-3.30 (m, 1H),

3.00-3.10 (m, 1H), 2.00-2.40 (m, 2H), 1.45-1.53 (dd, J = 3.4, 11.7 Hz, 3H), 1.30-1.40 (m, 3H), 1.15-1.25 (m, 6H).

Example I5. Ethyl (*S*)-(3-chloro-2-hydroxypropyl)(1,1-diethoxyethyl)phosphinate (intermediate to the compound according to Example 3)

After a mixture of ethyl (diethoxyethyl)phosphinate (15.0 g, 71 mmol) and toluene was evaporated to dryness, the residue and 1,1,1,3,3,3-hexamethyldisilazane (13.2 g, 82 mmol) was heated to reflux for 3 h under an argon atmosphere. The mixture was cooled to room temperature and evaporated. (*S*)-Epichlorohydrin (6.6 g, 71 mmol) and anhydrous zinc chloride (2.5 g, 18 mmol) were added and the reagents were heated to 60 °C over night under an argon atmosphere. The mixture was cooled to room temperature, diluted with methylene chloride and water. The organic layer was washed with water, dried over $MgSO_4$, filtered, and evaporated to give 20.7 g of a yellow oil. The residue was dissolved in methanol (150 mL) containing 1% acetic acid and the solution was stirred over night. The solvent was removed to give 16.8 g (79%) of ethyl (*S*)-(3-chloro-2-hydroxypropyl)(1,1-diethoxyethyl)phosphinate as a clear oil. Data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.4 (m, 1H), 4.2-4.3 (m, 2H), 3.6-3.8 (m, 4H), 1.9-2.4 (m, 2H), 1.5 (dd, J = 2.3, 11.4 Hz, 3H), 1.32-1.37 (m, 3H), 1.18-1.24 (m, 6H).

Example I6. Ethyl (*R*)-(3-amino-2-hydroxypropyl)(1,1-diethoxyethyl)phosphinate (intermediate to the compound according to Example 3)

A solution of (*S*)-(3-chloro-2-hydroxypropyl)(1,1-diethoxyethyl)phosphinate (5.0 g, 17 mmol) in ethanol containing 9% of ammonia was stirred in an autoclave at room temperature for 6 days and at 55 °C for one further day. The solution was evaporated and the residue was purified by chromatography on a wet-packed silica gel column eluting with methylene chloride/methanol (5-8% MeOH) containing 5% triethylamine. The appropriate fractions were combined, evaporated and diluted with methylene chloride and water. The aqueous layer was pH adjusted by the addition of a few mL of 10% aqueous Na_2CO_3 and repeatedly extracted with methylene chloride. The combined organic layers were dried over Na_2SO_4 and evaporated to give 0.9 g (19%) of ethyl (*R*)-(3-amino-2-

hydroxypropyl)(1,1-diethoxyethyl)phosphinate as a clear oil. Data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.1-4.3 (m, 2H), 4.05 (b, 1H), 3.60-3.80 (m, 4H), 2.4-2.9 (m, 2H), 1.7-2.1 (m, 2H), 1.4-1. 5 (dd,3H), 1.3-1.4 (m, 3H), 1.2 (m, 6H).

Example I7. (3-Amino-2-oxopropyl)(1,1-diethoxyethyl)phosphinate (intermediate to the compound according to the Example 4)

To a solution of diisopropylamine (3.0 mL, 21 mmol) in THF (5 mL) at –10 °C was added dropwise *n*-BuLi (2.5 M in hexanes, 8.6 mL, 21 mmol). After 10 minutes, the reaction was cooled to –78 °C and a solution ethyl (1,1-diethoxyethyl)(methyl)phosphinate (4.80 g, 21.0 mmol) in THF (5 mL) was added dropwise. After the addition, the solution was stirred at –78 °C for 1h. A solution of *N*-Boc-glycine methyl ester (810 mg, 4.3 mmol) in THF (15 mL) was added dropwise. After the addition was complete, the reaction mixture was stirred for 45 minutes. Acetic acid (1.2 mL, 21 mmol) was added and the reaction mixture was warmed to room temperature. The reaction mixture was partitioned between methylene chloride and water and the layers were separated. The aqueous layer was extracted once with methylene chloride. The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated to give 4.89 g of an oil. The residue was purified by chromatography on 100 g of silica gel eluting with ethyl acetate. The appropriate fractions were collected to give 1.2 g (74%) of (3-amino-2-oxopropyl)(1,1-diethoxyethyl)phosphinate as an oil. Data: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.48 (s, 1H), 4.10-4.30 (m, 2H), 4.17 (d, 2H), 3.60-3.80 (m, 4H), 3.01-3.30 (m, 2H), 1.52 (d, 3H), 1.43 (s, 9H), 1.32 (t, 3H), 1.19 (t, 6H).

Example I8. (2*R*)-3-(dibenzylamino)-2-fluoro-1-propanol (intermediate to the compound according to the Example 5)

Lithium borohydride (5.3 g, 0.24 mol) was suspended in THF (200 mL) under a nitrogen atmosphere and cooled to –15 °C with stirring. Methyl (2*R*)-3-(dibenzylamino)-2-fluoropropanoate (56.6 g, 0.19 mol) was suspended in THF (250 mL) and added dropwise to the mixture over 1 h; the internal temperature was maintained below –10 °C during the addition. On completion of addition, the reaction mixture was allowed to warm to room

temperature and stirred at this temperature for 17 h. The reaction mixture was cooled to 0 °C and cautiously quenched with a saturated aqueous solution of ammonium chloride (300 mL). The reaction mixture was extracted with ethyl acetate (2 x 200 mL) and the organic phase was concentrated under reduced pressure. The crude residue was dissolved in 2 N hydrochloric acid (200 mL, pH=2 approx.) and the aqueous phase was washed with ether (2 x 200 mL). The aqueous phase was basified (pH=10 approx.) with 80% ammonium hydroxide in brine, extracted with ethyl acetate (3 x 200 mL), dried over anhydrous sodium sulfate (10 g), filtered and concentrated under reduced pressure to afford (2*R*)-3-(dibenzylamino)-2-fluoro-1-propanol (48 g, 93%) as a yellow oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15-7.38 (m, 10H), 4.65-4.78 (m, 0.5H), 4.48-4.58 (m, 0.5H), 3.50-3.82 (m, 6H), 2.70-2.88 (m, 2H).

Example I9. (2*R*)-3-amino-2-fluoro-1-propanol (intermediate to the compound according to the Example 5)

(2*R*)-3-(dibenzylamino)-2-fluoro-1-propanol (29.2 g, 0.11 mol) was dissolved in ethanol (300 mL). 10 wt.% Palladium (II) hydroxide on carbon (5.0 g) was added and the mixture placed on a Parr® shaker and shaken under a hydrogen atmosphere (55 psi) for 6 h. When no further hydrogen uptake was observed, the mixture was filtered through a pad of Celite® (20 g). A fresh batch of palladium (II) hydroxide (5 g) was added to the ethanol mixture and re-subjected to the hydrogenation conditions described above for 17 h. The crude reaction mixture was filtered through Celite® and concentrated under reduced pressure to afford (2*R*)-3-amino-2-fluoro-1-propanol as a pale yellow oil (9.6 g, 96%).
^{1}H NMR (300 MHz, CD_3OD) δ 4.78–5.00 (br s, 3H), 4.49–4.62 (m, 0.5H), 4.32-4.46 (m, 0.5H), 3.54-3.70 (m, 2H), 2.70-2.96 (m, 2H).

Example I10. *tert*-butyl (2*R*)-2-fluoro-3-hydroxypropylcarbamate (intermediate to the compound according to the Example 5)

(2*R*)-3-amino-2-fluoro-1-propanol (4.6 g, 49 mmol) was dissolved in 25% aqueous dioxane (160 mL), potassium carbonate (7.1 g, 51 mmol) was added and the mixture cooled to 0 °C. Di-*tert*-butyl dicarbonate (11.6 g, 53 mmol) was added in two portions.

The mixture was then allowed to warm to room temperature overnight. The crude reaction mixture was concentrated to dryness, water (150 mL) was added followed by saturated aqueous potassium hydrogen sulfate (until pH=3 approx.). The organic material was extracted with methylene chloride (2 x 150 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to afford *tert*-butyl (2*R*)-2-fluoro-3-hydroxypropylcarbamate (9.5 g, 100%) as a colorless oil.
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.82-5.04 (br s, 1H), 4.62-4.72 (m, 0.5H), 4.48-4.58 (m, 0.5H), 3.62-3.72 (m, 2H), 3.32-3.62 (m, 2H), 3.20-3.44 (br s, 1H), 1.48 (s, 9H).

Example I11. *tert*-butyl (2*R*)-2-fluoro-3-iodopropylcarbamate (intermediate to the compound according to the Example 5)

Imidazole (26.6 g, 0.39 mol) was dissolved in methylene chloride (400 mL) at room temperature. Iodine (102.5 g, 0.39 mol) was added and the reaction mixture was stirred for 10 min at room temperature and then cooled to 0 °C. Triphenylphosphine (102.5 g, 0.39 mol) was added portionwise over 10 min such that the internal temperature remained below 10 °C. A solution of *tert*-butyl (2*R*)-2-fluoro-3-hydroxypropylcarbamate (60.4 g, 0.31 mol) in methylene chloride (100 mL) was added dropwise. On completion of addition of *tert*-butyl (2*R*)-2-fluoro-3-hydroxypropylcarbamate, additional methylene chloride (200 mL) was added. The reaction mixture was allowed to warm to room temperature and stirring was continued for 17 h. The reaction mixture was filtered through a pad of Celite® (50 g) and washed with additional methylene chloride. The filtrate was concentrated under reduced pressure and purified by silica gel column chromatography eluting with methylene chloride. This procedure afforded *tert*-butyl (2*R*)-2-fluoro-3-iodopropylcarbamate as a white solid (64.7 g, 68%).
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.80–5.10 (br s, 1H), 4.58-4.72 (m, 0.5H), 4.42-4.56 (m, 0.5 H), 3.48-3.70 (m, 1H), 3.20-3.46 (m, 3H), 1.48 (s, 9H).

Pharmaceutical preparations

The compound according to formula I of the present invention can be used as an active ingredient in a pharmaceutical preparation for oral, rectal, epidural, intravenous, intramuscular, subcutanous, nasal administration and administration by infusion or for any other suitable route of administration. Preferably the way of administration is oral or by injection/infusion.

The pharmaceutical preparations contain a compound of the present invention in combination with one or more pharmaceutically acceptable ingredients. The finished dosage forms are manufactured by known pharmaceutical processes. Usually the amount of active compounds is between 0.1-95% by weight of the preparation, preferably between 0.2-20% by weight in preparations for parenteral use and preferably between 1-50% by weight in preparations for oral administration.

In the preparation of pharmaceutical preparations containing a compound of the present invention in the form of solid dosage units for oral administration, the compound selected may be mixed with solid pharmaceutically acceptable ingredients (among these for instance disintegrating agents and lubricating agents). The mixture is then processed into granules, tablets, capsules or sachets.

Dosage units for rectal administration may be prepared in the form of suppositories; in the form of a gelatine rectal capsule; in the form of a ready-made micro enema; or in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

Liquid preparations for oral administration may be prepared in the form of syrups or suspensions, or in the form of a dry mixture to be reconstituted with a suitable solvent prior to use.

Solutions for parenteral administration may be prepared as a solution of a compound of the invention in a pharmaceutically acceptable solvent and are dispensed into ampoules or vials. They may also be prepared as a dry preparation to by reconstituted with a suitable solvent extemporaneously before use.

The typical daily dose of the active compound will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, dosages will be in the range of 1 µg to 100 mg per day and kg body weight, preferably 10 µg to 20 mg per day and kg body weight.

Biological studies

[^{3}H]GABA radioligand binding assay

Rat synaptic membranes were prepared from the whole brain of Sprague Dawley male rats essentially as described previously (Zukin, et al. (1974) Proc. Natl. Acad. USA 71, 4802-4807). The [^{3}H]GABA competition assay, modified from Olpe et al ((1990) Eur. J. Pharmacol. 187, 27-38), was performed in 200 µl TCI (Tris Calcium Isoguvacine) buffer (50 mM Tris (tri(hydroxymethyl)aminomethane), pH 7.4, 2.5 mM $CaCl_2$ and 40 µM isoguvacine) containing 20 nM [^{3}H]GABA (specific activity: 3 Tera Becquerel (TBq)/mmol), test compound or solvent and 80 µg synaptic membrane protein using 96-well plates. After incubation for 12-20 min at room temperature, incubations were terminated by rapid filtration through a glass fiber filter (Printed filtermat B filters, Wallac), which had been pretreated with 0.3% polyethyleneimine, using a 96-well plate cell harvester (Skatron or Tomtec). The filters were washed with buffer containing 50 mM Tris (tris(hydroxymethyl)aminomethane) and 2.5 mM $CaCl_2$, pH 7.4, at 4 °C and then dried at 55° C. MeltiLex B/HS scintillator sheet (Wallac) was melted onto the filter, and radioactivity was determined in a Microbeta scintillation counter (Wallac).

Results and discussion

The compounds of the present invention were found to have high affinity and potency for the $GABA_B$ receptor as revealed by low IC_{50} and EC_{50} in the binding and ileum assays, respectively. The compounds have also been found to reduce TLOSR when administered i.v. as well as p.o. in animal models. Contrary to what has been claimed in the literature for 3-aminopropyl phosphinic acid derivatives, we have found that the compounds of the present invention have high metabolic stability in animal models. Moreover, CNS side-effects (as measured by reduction in body temperature in the mouse) were not observable or only seen at very high doses. Therefore, the difference between therapeutic dose (inhibition of TLOSR in the dog model) and dose causing side-effects (in the mouse model) was unexpectedly high.

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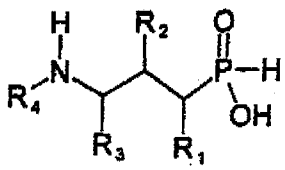
CLAIMS

1. A compound according to the formula I



(I)

wherein

R_1 represents hydrogen, hydroxy, lower alkyl, lower alkoxy or halogen;

R_2 represents hydroxy, mercapto, halogen, or an oxo group;

R_3 represents hydrogen, lower alkyl (optionally substituted with hydroxy, mercapto, lower alkoxy, lower thioalkoxy or aryl);

R_4 represents hydrogen, lower alkyl (optionally substituted with aryl) or aryl;

and pharmaceutically acceptable salts and the stereoisomers thereof,

with the exceptions of:

i) the racemate of (3-amino-2-hydroxypropyl)phosphinic acid, and

ii) (2*R/S*, 3*R*)-(3-amino-2-hydroxybutyl)phosphinic acid.

2. A compound according to claim 1 wherein

R_1 represents hydrogen;

R_2 represents fluoro, hydroxy or an oxo group;

R_3 represents hydrogen; and

R_4 represents hydrogen,

with the exception of the racemate of (3-amino-2-hydroxypropyl)phosphinic acid.

3. (3-Amino-2-flouropropyl)phosphinic acid or a pharmaceutically acceptable salt or the stereoisomers thereof.

4. (2*R*)-(3-Amino-2-fluoropropyl)phosphinic acid or a pharmaceutically acceptable salt thereof.

5. (3-Amino-2-oxopropyl)phosphinic acid or a pharmaceutically acceptable salt or the stereoisomers thereof.

6. (*S*)-(3-Amino-2-hydroxypropyl)phosphinic acid or a pharmaceutically acceptable salt thereof.

7. A compound according to claim 1, for use in theraphy.

8. Use of a compound according to any one of claims1-6 for the manufacture of a medicament for the inhibition of transient lower oesophageal sphincter relaxations.

9. Use of a compound according to any one of claims 1-6 for the manufacture of a medicament for the treatment of gastro-oesophageal reflux disease.

10. Use according to any one of claims 1-6 for the manufacture of a medicament for the treatment of regurgitation in infants.

11. Use of a compound according to any one of claims 1-6 for the manufacture of a medicament for GORD-related or non-GORD related asthma, belching, coughing, pain, cocaine addition, hiccups, IBS, dyspepsia, emesis or nociception.

12. A method for the treatment of transient lower oesophageal sphincter relaxations which method comprises treating a subject suffering from said condition with a pharmaceutical preparation comprising a compound of formula I.

13. A method for the treatment of gastro-oesophaegeal reflux disease which method comprises treating a subject suffering from said condition with a pharmaceutical preparation comprising a compound of formula I.

14. A method for the treatment of regurgitation in infants which method comprises treating a subject suffering from said condition with a pharmaceutical preparation comprising a compound of formula I.

15. A method for the treatment of GORD-related or non-GORD related asthma, belching, coughing, pain, cocaine addition, hiccups, IBS, dyspepsia, emesis or nociception which method comprises treating a subject suffering from said condition with a pharmaceutical preparation comprising a compound of formula I.

16. A pharmaceutical formulation comprising as active ingredient a therapeutically acceptable amount of the compound of any one of claims 1-6 optionally in association with diluents, excipients or inert carriers.

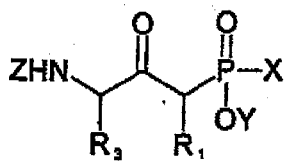
17. A pharmaceutical formulation according to claim 16 for use in the inhibition of transient lower oesophageal sphincter relaxations.

18. A pharmaceutical formulation according to claim 16 for use in the treatment of gastro-oesophageal reflux disease.

19. A pharmaceutical formulation according to claim 16 for use in the treatment of regurgitation in infants.

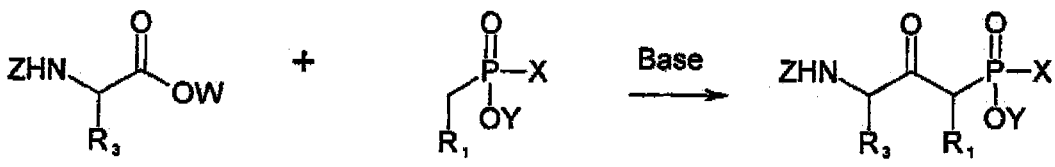
20. A process for the preparation of a compound of the formula I according to claim 1, wherein

a) a compound of formula II



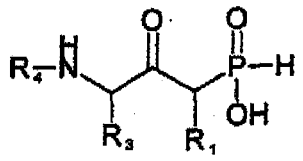
(II)

in which R_1 and R_3 are as defined above in formula I, X is hydrogen or a protecting group such as $-CCH_3(OCH_2CH_3)_2$, Z is a protecting group such as t-butyloxycarbonyl and Y is hydrogen or a protecting group such as lower alkyl, which compound of formula II may have been synthesized by a condensation reaction according to Scheme 1 employing an appropriate N-protected amino acid ester in which R_3 is as defined above, W is a protecting group such as lower alkyl and Z is as defined in formula II, and a suitable protected phosphinic acid derivative in which R_1 is as defined above in formula I, X and Y are as defined in formula II, and a base such as lithium diisopropylamide,



Scheme 1

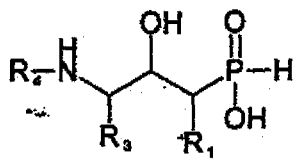
is optionally converted by an N-alkylation reaction in order to introduce R_4 if R_4 is desired to be not equal to hydrogen, and thereafter a hydrolytic reaction to obtain a compound of formula III



(III)

wherein R_1, R_3 and R_4 are as defined above in formula I, and if desired, a resulting compound is converted into another compound of the formula III, a resulting mixture of isomers is separated into the individual isomers and/or a resulting salt obtained in this process is converted into the free compound of the formula III or into another salt and/or, if desired, a resulting free compound of the formula III is converted into a salt to correspond to the above definition;

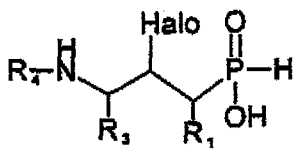
or a compound of formula II is converted by a reductive reaction, optionally an N-alkylation reaction if R_4 is desired to be not equal to hydrogen, and finally a hydrolytic reaction to obtain a compound of formula IV



(IV)

wherein R_1, R_3 and R_4 are as defined above in formula I, and if desired, a resulting compound is converted into another compound of the formula IV, a resulting mixture of isomers is separated into the individual isomers and/or a resulting salt obtained in this process is converted into the free compound of the formula IV or into another salt and/or, if desired, a resulting free compound of the formula IV is converted into a salt to correspond to the above definition;

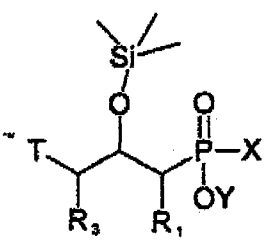
or a compound of formula II is converted by a reductive reaction followed by a deoxohalogenation reaction, optionally an N-alkylation reaction in order to introduce R_4 if R_4 is desired to be not equal to hydrogen, and finally a hydrolytic reaction to obtain a compound of formula V



(V)

wherein R_1, R_3 and R_4 are as defined above in formula I and Halo is a halogen atom, and if desired, a resulting compound is converted into another compound of the formula V, a resulting mixture of isomers is separated into the individual isomers and/or a resulting salt obtained in this process is converted into the free compound of the formula V or into another salt and/or, if desired, a resulting free compound of the formula V is converted into a salt to correspond to the above definition;

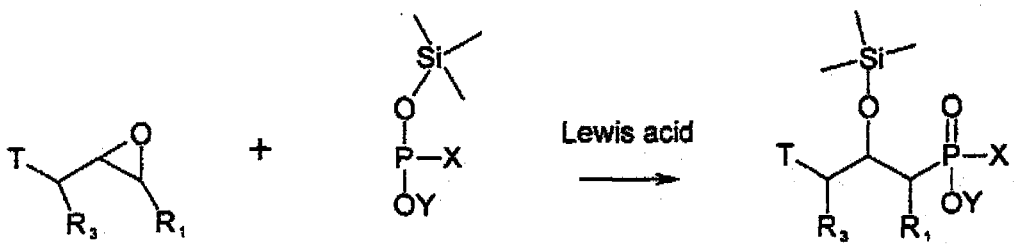
or b) a compound of formula VI



(VI)

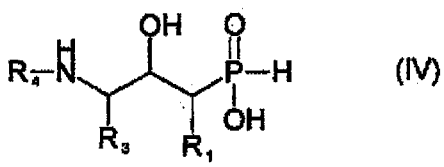
in which R_1, and R_3 are as defined above in formula I, X is hydrogen or a protecting group such as $-CCH_3(OCH_2CH_3)_2$, T is a group that can be converted to a-NH_2 group, and Y is hydrogen or a protecting group such as lower alkyl, which compound of formula VI may have been synthesized by a condensation reaction according to Scheme 2 employing an 2,3-epoxypropyl derivative, such as an appropriate N-protected 2,3-epoxypropylamine

derivative or an epichlorohydrin derivative, in which R_1 and R_3 is as defined above in formula I, and a suitable protected phosphinic acid derivative activated by O-silylation, in which X and Y are as defined in formula VI, and a Lewis acid such as anhydrous $ZnCl_2$,



Scheme 2

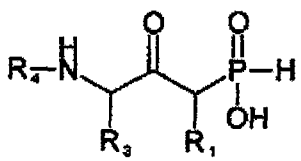
is converted by a reaction where the trimethylsilyl group is replaced by a hydrogen atom, a reaction where the T group as defined in formula VI is converted to -NHR_4 wherein R_4 is as defined above in formula I, and finally a hydrolytic reaction to obtain a compound of formula IV



(IV)

wherein R_1, R_3 and R_4 are as defined above in formula I, and if desired, a resulting compound is converted into another compound of the formula IV, a resulting mixture of isomers is separated into the individual isomers and/or a resulting salt obtained in this process is converted into the free compound of the formula IV or into another salt and/or, if desired, a resulting free compound of the formula IV is converted into a salt to correspond to the above definition;

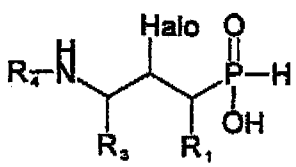
or compound of formula VI is converted by a reaction where the trimethylsilyl group is replaced by hydrogen, an oxidative reaction, a reaction where the T group as defined in formula VI is converted to -NHR_4 wherein R_4 is as defined above in formula I, and finally a hydrolytic reaction to obtain a compound of formula III



(III)

wherein R_1, R_3 and R_4 are as defined above in formula I, and if desired, a resulting compound is converted into another compound of the formula III, a resulting mixture of isomers is separated into the individual isomers and/or a resulting salt obtained in this process is converted into the free compound of the formula III or into another salt and/or, if desired, a resulting free compound of the formula III is converted into a salt to correspond to the above definition;

or a compound of formula VI is converted by a reaction where the trimethylsilyl group is replaced by hydrogen, a deoxohalogenation reaction, a reaction where the T group as defined in formula VI is converted to -NHR_4 wherein R_4 is as defined above in formula I, and finally a hydrolytic reaction to obtain a compound of formula V

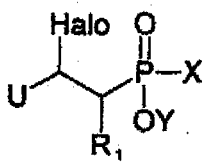


(V)

wherein R_1, R_3 and R_4 are as defined above in formula I, and Halo is a halogen atom, and if desired, a resulting compound is converted into another compound of the formula V, a resulting mixture of isomers is separated into the individual isomers and/or a resulting salt obtained in this process is converted into the free compound of the formula V or into

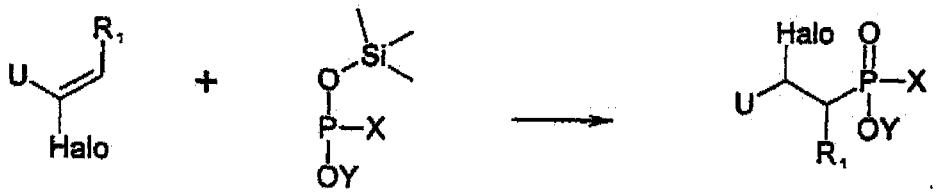
another salt and/or, if desired, a resulting free compound of the formula V is converted into a salt to correspond to the above definition;

or c) a compound of formula VII



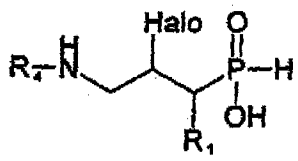
(VII)

in which R_1 is as defined above in formula I, X is hydrogen or a protecting group such as $-CCH_3(OCH_2CH_3)_2$, U is an electron-withdrawing group, such as for instance –CN or $–CO_2Et$ which can be converted to a $-CH_2NH_2$ group, and Y is hydrogen or a protecting group such as lower alkyl, and Halo is a halogen atom, which compound of formula VII may have been synthesized by an addition reaction according to Scheme 3 employing an unsaturated compound in which R_1 is as defined above in formula I, U and halo are as defined in formula VII, and a suitable protected phosphinic acid derivative activated by O-silylation, in which X and Y are as defined in formula VII,



Scheme 3

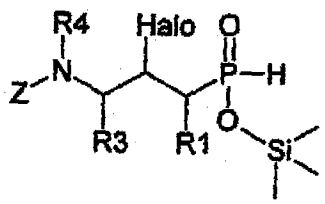
is converted by a reaction where the U group is being converted to $-NHR_4$ wherein R_4 is as defined above in formula I, and a hydrolytic reaction to obtain a compound of formula VIII



(VIII)

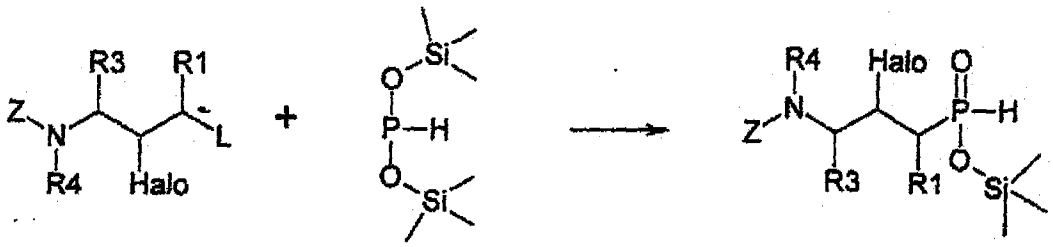
wherein R_1 and R_4 are as defined above in formula I and Halo is a halogen atom, and if desired, a resulting compound is converted into another compound of the formula VIII, a resulting mixture of isomers is separated into the individual isomers and/or a resulting salt obtained in this process is converted into the free compound of the formula VIII or into another salt and/or, if desired, a resulting free compound of the formula VIII is converted into a salt to correspond to the above definition;

or d) a compound of formula IX optionally as an individual stereo isomer



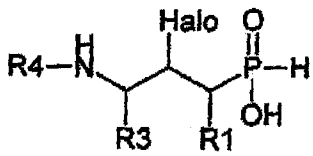
(IX)

in which R_1, R_3 and R_4 are as defined in formula I, Z is a protecting group such as t-butyloxycarbonyl and Halo is a halogen atom, which compound of formula IX may have been synthesized by a substitution reaction according to Scheme 4 employing an electrophilic compound in which R_1, R_3 and R_4 are as defined above, L is a leaving group such as iodo, Z and Halo are as defined above, and phosphinic acid activated by O-silylation,



Scheme 4

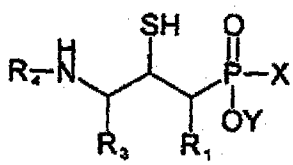
is converted by a hydrolytic reaction to a compound of formula V



(V)

wherein R_1, R_3 and R_4 are as defined above in formula I, and if desired, a resulting compound is converted into another compound of the formula V, if desired a resulting mixture of isomers is separated into the individual isomers and/or a resulting salt obtained in this process is converted into the free compound of the formula V or into another salt and/or, if desired, a resulting free compound of the formula V is converted into a salt to correspond to the above definition;

or e) a compound of formula XI



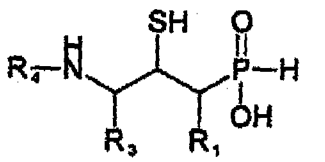
(XI)

in which R_1, R_3 and R_4 are as defined above in formula I, X is hydrogen or a protecting group such as $-CCH_3(OCH_2CH_3)_2$, and Y is hydrogen or a protecting group such as lower alkyl, which compound of formula XI may have been synthesized by an addition reaction according to Scheme 4 treating an unsaturated phosphinic acid derivative, in which R_1, R_3

and R_4 are as defined in above in formula I, with H_2S, a mercaptide ion (HS^-) or a protected mercapto compound such as benzyl thiol in which case the protective group thereafter is removed

Scheme 5

is converted by a hydrolytic reaction to obtain a compound of formula XII,



(XII)

in which R_1, R_3 and R_4 are as defined above in formula I, and if desired, a resulting compound is converted into another compound of the formula XII, a resulting mixture of isomers is separated into the individual isomers and/or a resulting salt obtained in this process is converted into the free compound of the formula XII or into another salt and/or, if desired, a resulting free compound of the formula XII is converted into a salt to correspond to the above definition.

21. Ethyl 3-[(diethoxymethyl)(ethoxy)phosphoryl]-2-fluoropropanoate.

22. Ethyl (3-amino-2-fluoro-3-oxopropyl)(diethoxymethyl)phosphinate.

23. Ethyl (*R*)-(3-chloro-2-hydroxypropyl)(1,1-diethoxyethyl)phosphinate.

24. Ethyl (*S*)-(3-amino-2-hydroxypropyl)(1,1-diethoxyethyl)phosphinate.

25. Ethyl (*S*)-(3-chloro-2-hydroxypropyl)(1,1-diethoxyethyl)phosphinate.

26. Ethyl (*R*)-(3-amino-2-hydroxypropyl)(1,1-diethoxyethyl)phosphinate.

27. (3-Amino-2-oxopropyl)(1,1-diethoxyethyl)phosphinate.

28. (2*R*)-3-(dibenzylamino)-2-fluoro-1-propanol.

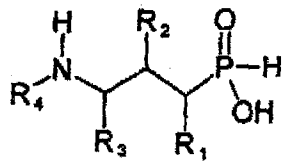
29. (2*R*)-3-amino-2-fluoro-1-propanol.

30. *tert*-butyl (2*R*)-2-fluoro-3-hydroxypropylcarbamate.

31. *tert*-butyl (2*R*)-2-fluoro-3-iodopropylcarbamate.

ABSTRACT

Novel compounds of formula I having affinity to one or more $GABA_B$ receptors, their pharmaceutically acceptable salts and stereoisomers, as well as processes for their preparation, pharmaceutical compositions containing said therapeutically active compounds and the use of said active compounds in therapy.



(I)

Traducción No. 365/12-00

El presente documento lleva dos sellos redondos en tintilla azul y otro sobrepuesto en papel dorado que dicen en idioma sueco:

ANNE-MARIE BONDE * NOTARIO PUBLICO EN ESTOCOLMO

Lleva el sello No. 003858 del Consulado de Colombia en Estocolmo, de fecha 2000-11-15, firmado por Maria Smith Rueda, Encargada de las Funciones Consulares.

Lleva el sello No. 490025 del Ministerio de Relaciones Exteriores, de fecha 2000-12-12, firmado por el Jefe de Legalizaciones.

Certifico que esta traducción es correcta y fiel a su original.

SUZANNE NORRTHON MARIOTTE
Traductora Oficial Jurada
Resolución No. 1022 del
Ministerio de Justicia de Mayo 11/87

Astrazeneca
A-1919-1 CO

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ASSIGNMENT

The undersigned,

Thomas Elebring, Anders Holmén, Marianne Swanson,
Thomas Olsson and Sverker Von Unge
All Swedish citizens

domiciled in
AstraZeneca R&D Mölndal
S-431 83 Mölndal
Sweden
and
Peter Guzzo
an American citizen
domiciled in
Albany Molecular Research Inc.
21 Corporate Circle
Albany, New York 12212-5098
USA

hereby state under oath to be the sole and true inventor of

NEW AMINOPROPYLPHOSPHINIC ACIDS

We state as well that we assign, without reservations or limitation, in favor of

AstraZeneca AB

a corporation organized and existing under the laws of

Sweden
domiciled in
S-151 85 Södertälje, Sweden

all rights inherent to said invention, and that the above mentioned corporation hereby is enabled to apply, in its name, for the corresponding patent in the Republic of Colombia.

Thomas Elebring
Thomas Elebring

Anders Holmén
Anders Holmén

Thomas Olsson
Thomas Olsson

TRASPASO

abajo firmado

Thomas Elebring, Anders Holmén, Marianne Swanson,
Thomas Olsson y Sverker Von Unge
Todos Ciudadanos Suecos

domiciliado en
AstraZeneca R&D Mölndal
S-431 83 Mölndal
Suecia
y
Peter Guzzo
un ciudadano Americano
domiciliado en
Albany Molecular Research Inc.
21 Corporate Circle
Albany, New York 12212-5098
Estados Unidos de América

declaramos bajo juramento ser únicos y verdaderos inventores de.

NUEVOS ACIDOS AMINOPROPILFOSFINICOS

Declaramos asimismo que cedemos y transferimos sin reserva ni limitación, a favor de la sociedad

AstraZeneca AB

organizada y existente de conformidad con la leves de

Suecia
domiciliada en
S-151 85 Södertälje, Suecia

Todos los derechos inherentes a dicha invención y que la citada sociedad queda facultada para solicitar en su nombre la patente correspondiente en la República de Colombia.

Peter Guzzo

Marianne Swanson

Sverker Von Unge

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

114

CERTIFICADO NOTARIAL (INDIVIDUO)

A los 13 días del mes de Noviembre 2000 , compareci personalmente ante mi, Notario Publico,

THOMAS E L E B R I N G,
ANDERS H O L M É N,
THOMAS O L S S O N,
MARIANNE S W A N S O N y
SVERKER V O N U N G E

a quienes doy fé de conocer y me consta que las personas descritas y firmantes del documento que precede, declarado ante mí que otorgan el mismo para los fines y propósitos que en él se expresan.

NOTARY PUBLIC (Notario Público)
Anne-Marie Bonde

NOTARIAL CERTIFICATE (INDIVIDUAL)

On this 13 day of Noviembre 2000 personally appeared before me, a Notary Public,

THOMAS E L E B R I N G,
ANDERS H O L M E N,
THOMAS O L S S O N,
MARIANNE S W A N S O N y
SVERKER V O N U N G E

to me known and known to me to be the person described in and who executed the foregoing document, and duly acknowledged to me that executed the same for the uses and purposes therein expressed.

NOTARIUS PUBLICUS I STOCKHOLM
ANNE-MARIE BONDE

CERTIFICADO NOTARIAL (INDIVIDUO)

A los días del mes de 19 , compareci personalmente ante mi, Notario Publico,

a quien doy fé de conocer y me consta que la persona descrita y firmante del documento que precede, declarado ante mí que otorga el mismo para los fines y propósitos que en él se expresan.

NOTARIAL CERTIFICATE (INDIVIDUAL)

On this day of 19 personally appeared before me, a Notary Public,

to me known and known to me to be the person described in and who executed the foregoing document, and duly acknowledged to me that executed the same for the uses and purposes therein expressed.

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EL CONSULADO DE COLOMBIA EN
ESTOCOLMO, SUECIA

Fecha 2000 -11- 15 No: 003858

Previa la confrontación correspondiente DA FE de que la firma que aparece en este documento es similar a la REGISTRADA aquí por:

Anna-Maria Bouvin, Notario Publico, Estocolmo, Suecia

MARIA SMITH RUEDA
Encargada de las Funciones Consulares

PAGADO
Impuesto de Timbre Siete dólares US$ 7
Derechos Consulares Quince dólares US$ 15

CONSULADO DE COLOMBIA
ESTOCOLMO

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TRADUCCION OFICIAL NO. 8185

De un documento escrito en inglés.

= = = = = = =

Legalizaciones de un traspaso de patente a AstraZeneca AB escrito simultáneamente en inglés y en español, firmado por Peter Guzzo el 31-10-00.

Expediente # A-1919 – ICO.

El certificado notarial está firmado por Katrina L. Arnold y tiene los siguientes sellos:

De caucho: KATRINA ARNOLD – Notario Público, Estado de Nueva York –

No. 01AR6037001 – Calificado en el Condado de Rensselaer – La Comisión Expira en Febrero 14 de 2002

Sello en relieve: KATRINA ARNOLD – NOTARIO PÚBLICO – ESTADO DE NUEVA YORK

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ESTADO DE NUEVA YORK } 0841

} SS

CIUDAD DE TROY, DESPACHO DEL ESCRIBANO, CONDADO DE RENSSELAER }

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FRANK J. MEROLA, Escribano del Condado y de las Cortes Suprema y del Condado en y para el Condado de Rensselaer, las cuales son Tribunales de Registro que tienen sello por ley, por el presente certifico que

Katrina Arnold

cuyo nombre está suscrito a la declaración bajo juramento, certificado de reconocimiento o prueba del instrumento adjunto, era en el momento de tomar el mismo un NOTARIO PUBLICO en y para el Estado de Nueva York, debidamente comisionado, juramentado y calificado para actuar como tal en todo el Estado de Nueva York; que de acuerdo con la ley se ha registrado en mi despacho una comisión o un certificado de su nombramiento y capacidades y su firma autógrafa; que en su condición de Notario estaba debidamente autorizado por las leyes del Estado de Nueva York para administrar juramentos y declaraciones, para recibir y certificar el reconocimiento o prueba de escrituras, hipotecas, poderes, para terrenos, viviendas, y lo que pueda heredarse para leer como evidencia o registrar en este Estado, protestar pagarés y tomar y certificar testimonios y declaraciones bajo juramento, y que conozco bien la escritura manuscrita de dicho NOTARIO PUBLICO o he comparado la firma puesta en el instrumento adjunto con su firma autógrafa depositada en mi oficina y creo que dicha firma es auténtica

PARA CONSTANCIA DE ELLO, he puesto mi firma en el presente y estampado mi sello oficial a los 20 días de noviembre de 2000.

Firmado con facsímil: F. J. Merola

TRADUCTOR OFICIAL
Ref. 6987 Ministerio de Justicia

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Escribano del Condado y de los Tribunales Superior y del Condado, Condado de Rensselaer, Nueva York.

Sello en relieve ilegible

= = = = = =

Es traducción fiel y completa, de la cual queda copia en el archivo de esta Oficina de traducciones para su confrontación, a la cual me remito.

El documento fué legalizado en el Ministerio de Relaciones Exteriores bajo el No. 490020 de Diciembre 12 de 2000.

Derechos de traducción: $20.000.00

Bogotá, .D.C. 13 de diciembre de 2000

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MINISTERIO DE RELACIONES EXTERIORES
94068
ESTA FIRMA APARECE EN EL DOCUMENTO QUE PRECEDE
LAS FUNCIONES INDICADAS

NO SE AUTORIZA RESPONSABILIDAD DEL TEXTO

1999 DIC 15 A 11:14

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

Astra Zeneca
A1910-1CO
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CONSULADO GENERAL DE COLOMBIA
10 EAST 46TH STREET, NUEVA YORK, N.Y. 10017
TEL. (212) 370-0004 FAX (212) 972-1725

LA SUSCRITA CONSUL DE COLOMBIA

VISTOS LOS DOCUMENTOS PRESENTADOS POR LOS INTERESADOS

CERTIFICA

Que el (la) señor(a) **FRANK J. MEROLA** , County Clerk de la Corte del Estado de **NUEVA YORK,** Estados Unidos de América, verifica la firma y sellos de el documento certificado por el señor(a) **KATRINA ARNOLD,** Notaria Pública del estado de Pennsylvania, Estados Unidos de América, quien ejercía en la fecha las funciones allí señaladas y que la firma y sello que se estampan en el documento son suyos y los que usa y acostumbra en sus actos oficiales ;

Que quien firma el documento anexo es el señor(a) **PETER R. GUZZO** en su calidad de Representante de la compañia **ALBANY MOLECULAR RESEARCH INC.,** que existe y esta legalmente organizada bajo las leyes de los Estados Unidos de América.

Que ha tenido a la vista los documentos probatorios de los hechos citados y constatados por la Notaria Pública, los cuales forman parte integral del presente documento.

Se expide la presente certificación en cumplimiento de los artículos 259 del Código de Procedimiento Civil y 480 del Código de Comercio y a solicitud del interesado a los 29 días del mes de Noviembre del 2000.

NO SE ASUME RESPONSABILIDAD POR EL CONTENIDO DEL DOCUMENTO ADJUNTO.

PAGADO IMPUESTO DE TIMBRE Y DERECHOS CONSULARES
VALOR CINCUENTA Y SIETE DOLARES US$57.00 RECIBO No. 263555

CONSULADO GENERAL DE COLOMBIA NUEVA YORK

JOHANNA M. WARTICOVSCHI
Cónsul de Colombia

MINISTERIO DE RELACIONES EXTERIORES

490020

CUYA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

NO SE ASUME RESPONSABILIDAD POR EL CONTENIDO

2000 DIC 12 A 10:13

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

CONSULADO GENERAL DE COLOMBIA

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STATE OF NEW YORK
CITY OF TROY, RENSSELAER COUNTY CLERK'S OFFICE } SS:

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FRANK J. MEROLA, County Clerk of the Supreme and County Courts in and for Rensselaer County, being Courts of Record, having by law a seal, DO HEREBY CERTIFY that

Katrina Arnold

whose name is subscribed to the deposition, certificate of acknowledgment or proof of the annexed instrument, was at the time of taking the same a NOTARY PUBLIC in and for the State of New York, duly commissioned and sworn and qualified to act as such throughout the State of New York; that pursuant to law a commission, or a certificate of his appointment and qualifications and his autograph signature, have been filed in my office, that as such Notary he was duly qualified by the laws of the State of New York to administer oaths and affirmations, to receive and certify the acknowledgments or proof of Deeds, Mortgages, Powers of attorney and other written instrument for lands, tenements, and hereditaments to be read in evidence or recorded in this State, to protest notes and to take and certify affidavits and depositions; and that I am well acquainted with the handwriting of such NOTARY PUBLIC, or have compared the signature on the annexed instrument with his autograph signature in my office, and believe that the signature is genuine.

IN WITNESS WHEREOF I have hereunto set my hand and affixed my official seal this 20 day of Nov, 19 2000

County Clerk and Clerk of the Supreme
and County Courts, Rensselaer County, New York

CERTIFICADO NOTARIAL (INDIVIDUO)

A los 31 días del mes de Octubre 2000 ~~19~~, comparecio personalmente ante mi, Notario Publico,
Peter R. Guzzo

a quien doy fé de conocer y me consta que él es la persona descrita y firmante del documento que precede, declarado ante mí que otorga el mismo para los fines y propósitos que en él se expresan.

NOTARY PUBLIC (Notario Público)

NOTARIAL CERTIFICATE (INDIVIDUAL)

On this 31 day of October, 2000 ~~19~~ personally appeared before me, a Notary Public,
Peter R. Guzzo

to me known and known to me to be the person described in and who executed the foregoing document, and he duly acknowledged to me that he executed the same for the uses and purposes therein expressed.

KATRINA ARNOLD
Notary Public, State of New York
No. 01AR6037001
Qualified in Rensselaer County
Commission Expires February 14, 2002

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186

CERTIFICADO NOTARIAL (INDIVIDUO)

A los días del mes de 19 , compareci personalmente ante mi, Notario Publico,

a quien doy fé de conocer y me consta que la persona descrita y firmante del documento que precede, declarado ante mí que otorga el mismo para los fines y propósitos

NOTARIAL CERTIFICATE (INDIVIDUAL)

On this day of 19 personally appeared before me, a Notary Public,

to me known and known to me to be the person described in and who executed the foregoing document, and duly acknowledged to me that

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ASSIGNMENT

The undersigned,

Thomas Elebring, Anders Holmén, Marianne Swanson,
Thomas Olsson and Sverker Von Unge
All Swedish citizens

domiciled in
AstraZeneca R&D Mölndal
S-431 83 Mölndal
Sweden
and
Peter Guzzo
an American citizen
domiciled in
Albany Molecular Research Inc.
21 Corporate Circle
Albany, New York 12212-5098
USA

hereby state under oath to be the sole and true inventor of

NEW AMINOPROPYLPHOSPHINIC ACIDS

We state as well that we assign, without reservations or limitation, in favor of

AstraZeneca AB

a corporation organized and existing under the laws of

Sweden
domiciled in
S-151 85 Södertälje, Sweden

all rights inherent to said invention, and that the above mentioned corporation hereby is enabled to apply, in its name, for the corresponding patent in the Republic of Colombia.

.....
Thomas Elebring

.....
Anders Holmén

.....
Thomas Olsson

TRASPASO

abajo firmado

domiciliado en

declara bajo juramento ser único y verdadero inventor de.

Declara asimismo que cede y transfiere sin reserva ni limitación, a favor de la sociedad

organizada y existente de conformidad con la leves de

domiciliada en

Todos los derechos inherentes a dicha invención y que la citada sociedad queda facultada para solicitar en su nombre la patente correspondiente en la República de Colombia.

Peter J. Guzzo 10/31/00
Peter Guzzo

.....
Marianne Swanson

.....
Sverker Von Unge

SUPERINDUSTRIA Y COMERCIO
Radicacion : 00093167 00000000
Fecha (AMD): 2001-03-14 15:14:54 Folios: 3
Tramite : 002 PATENTES D 1 REGISTRO/ 339 COMPLEMEN
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

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Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

Re: P1.-**ASTRAZENECA AB**- Solicitud de Patente de Invención para **"NUEVOS ACIDOS AMINOPROPILFOSFINICOS".-** Expediente número 00-093.167.-

1. Me refiero a mi memorial de fecha 21 de Febrero de 2001.

2. Anexo me permito presentar a ese Despacho recibos número 16.762 Y 16.763, expedidos por la Superintendencia de Industria y Comercio, que acredita el pago de la tasa de invocación de prioridad en el presente caso.

3. Ruego a usted tomar atenta nota de lo anterior y proceder de conformidad.

Señor Superintendente,

JOSE ANTONIO LLOREDA
T.P. 10.784
Código 231