



No. 07-062887- -00003-0000

Fecha: 2008-04-24 16:18:59 Dep. 2020 NUECREACIONE
Tra. 11 PATENTE Y II Eve: 378 FASE NACIONAL I
Act. 538 PETICION Folios: 3

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Ref.: Expediente No. 07.062.887

Solicitud de Patente de Invención titulada: "COMPUESTOS DE PIRIDINA PARA EL TRATAMIENTO DE ENFERMEDADES RELACIONADAS CON LAS PROSTAGLANDINAS".

Solicitante: GLAXO GROUP LIMITED

Nuestra Ref.: P2007/000095

SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN
EL ARTÍCULO 44 DE LA DECISION 486, GACETA No. 590

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, D.C., identificado tal como aparece al pie de mi firma, en mi condición de apoderado sustituto, según consta en la sustitución adjunta, respetuosamente me permito solicitar que se examine si la invención reúne los requisitos de patentabilidad previstos en la misma, dando cumplimiento a lo establecido en el artículo 44 de la Decisión 486 de la comisión de la Comunidad Andina. Adjunto recibo por el monto de \$420.000 pesos para cubrir la tasa correspondiente, según la Resolución 44372 del año 2007.

Atentamente,

CARLOS R. OLARTE
C.C. 79.782.747 de Bogotá
T.P. 74.295

Anexo: Recibo por \$420.000 pesos
Sustitución

LMB/P2007/000095/08/04/04

Industria y Comercio
Carlos Clor

79742747 gk dp 74295024

15 ABR 2008

REPUBLICA DE COLOMBIA
MINISTERIO DE INDUSTRIA Y COMERCIO
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SUSTITUCIÓN DE PODER

J. IAN RAISBECK LLINAS, mayor de edad y vecino de Bogotá D.C., identificado como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad de la referencia, respetuosamente me permito manifestar que **SUSTITUYO** el poder a mi conferido por la mencionada sociedad, en el doctor **CARLOS R. OLARTE**, mayor de edad, domiciliado en Bogotá D.C., identificado con la Cédula de Ciudadanía No. 79.782.747 de Bogotá y portador de la Tarjeta Profesional No. 74.295 del Consejo Superior de la Judicatura, para que sea él quien en adelante asuma el trámite de la presente acción.

El apoderado sustituto conserva las mismas facultades del principal.

Atentamente,

J. IAN RAISBECK

C.C. No. 79.376.996 de Bogotá

T.P. 135.799 del C. S. de la J.

...INDIA DE PRESENTACION PERSONAL Y
RECONOCIMIENTO DE CONTENIDO Y FIRMA
NOTARIA EL NOTARIO ESCOLAR ORDENADO A.

Industria y Comercio

Juan Zarabeg
29376.996 \$to DP1357993

Alm. Kimbela

02 ABR 2008



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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 900176089-2

RECIBO OFICIAL DE CAJA : 08 - 33,074
FECHA : ABRIL 24 DE 2008

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	598751	23/04/2008	5,130,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	85 EXAMEN DE PATENTABILIDAD DE INVEN
			TOTAL : \$ 420,000.00

EN: CUATROCIENTOS VEINTE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

185

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 07-62887

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **590** DE

FECHA **31 DE MARZO DE 2008** EL TÉRMINO HÁBIL SEÑALADO POR LA LEY

EXPIRA EL **27 DE JUNIO DE 2008**

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

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO X

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

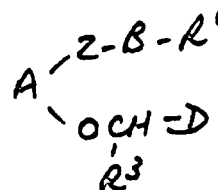
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07C 65/24, A61K 31/19, C07C 65/40, C07D 257/00, C07C 205/06, 321/24		A1	(11) International Publication Number: WO 96/11902
			(43) International Publication Date: 25 April 1996 (25.04.96)
(21) International Application Number: PCT/GB95/02417 (22) International Filing Date: 12 October 1995 (12.10.95) (30) Priority Data: 9420557.2 12 October 1994 (12.10.94) GB (71) Applicant (for all designated States except US): ZENECA LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): BREAUT, Gloria, Ann [US/GB]; 17 Blackfirs Lane, Congleton, Cheshire CW12 4QG (GB). OLDFIELD, John [GB/GB]; 68 Hallwood Road, Handforth, Wilmslow, Cheshire SK9 3BJ (GB). TUCKER, Howard [GB/GB]; 32 Millers Meadow, Rainow, Macclesfield, Cheshire SK10 5UE (GB). WARNER, Peter [GB/GB]; 25 Barnside Way, Tytherington, Macclesfield, Cheshire SK10 2TZ (GB). (74) Agent: DENERLEY, Paul, Millington; Zeneca Pharmaceuticals, Intellectual Property Group, Intellectual Property Dept., Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).		(81) Designated States: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG). Published With international search report.	

(54) Title: PHARMACEUTICALLY ACTIVE SUBSTITUTED AROMATIC COMPOUNDS

(57) Abstract

The present invention relates to compounds of formula (I), wherein: A, B and D are various ring systems as defined in the description, R¹ is one of a variety of groups as defined in the description, R³ is hydrogen or C₁₋₄ alkyl and Z is of the formula -(CH(R⁵))_m, -(CHR⁵)_pCR⁵=CR⁵(CHR⁵)_q, -(CHR⁵)_rC(=O)CR⁵(CHR⁵)_s or -(CHR⁵)_tC(=O)(CHR⁵)_u, wherein m is 2, 3 or 4, p and q are independently 0, 1 or 2 providing p+q is not greater than 2, one of r and s is 0 and the other is 1 and t and u are independently 0, 1, 2 or 3 providing t + u is not less than 1 or greater than 3; and R⁵ is hydrogen, methyl, ethyl, hydroxy, methoxy or ethoxy; and N-oxides where chemically possible; and S-oxides where chemically possible; and pharmaceutically acceptable salt and *in vivo* hydrolysable ester amide thereof. Processes for their preparation, their use as therapeutic agents and pharmaceutical compositions containing them.



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PHARMACEUTICALLY ACTIVE SUBSTITUTED AROMATIC COMPOUNDS

This invention relates to novel, aromatic compounds and pharmaceutically-acceptable salts thereof which possess useful pharmacological properties. More particularly the compounds of the invention are antagonists of the pain enhancing effects of E-type prostaglandins. The invention also relates to processes for the manufacture of the aromatic compounds and pharmaceutically-acceptable salts thereof; to novel pharmaceutical compositions containing them; and to use of the compounds in pain relief.

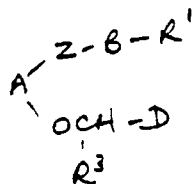
The compounds of the invention are useful in the treatment of pain such as the pain associated with joint conditions (such as rheumatoid arthritis and osteoarthritis), postoperative pain, post-partum pain, the pain associated with dental conditions (such as dental caries and gingivitis), the pain associated with burns (including sunburn), the treatment of bone disorders (such as osteoporosis, hypercalcaemia of malignancy and Paget's disease), the pain associated with sports injuries and sprains and all other painful conditions in which E-type prostaglandins wholly or in part play a pathophysiological role.

Non-steroidal anti-inflammatory drugs (NSAIDS) and opiates are the main classes of drugs in pain relief. However both possess undesirable side effects. NSAIDS are known to cause gastrointestinal irritation and opiates are known to be addictive.

We have now found a class of compounds structurally different to NSAIDS and opiates, and useful in the relief of pain.

The compounds of the invention may also possess anti-inflammatory, anti-pyretic and anti-diarrhoeal properties and be effective in other conditions in which prostaglandin E_2 (PGE_2) wholly or in part plays a pathophysiological role.

According to the invention there is provided a compound of the formula I;



(I)

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membered heteroarylC₁₋₆alkyl or 5- or 6-membered heteroaryliumC₁₋₄alkyl

Particular acylhydrazides are, for example of the formula -CONR⁶N(R¹⁶)R¹⁷ wherein R⁶ is as hereinabove defined, R¹⁶ is hydrogen or C₁₋₆alkyl and R¹⁷ is hydrogen, hydroxy or optionally substituted: C₁₋₁₀alkyl, C₂₋₁₀alkenyl, C₂₋₁₀alkynyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₆alkyl, C₃₋₇cycloalkylC₂₋₆alkenyl, C₃₋₇cycloalkylC₂₋₆alkynyl, C₅₋₇cycloalkenyl, C₅₋₇cycloalkenylC₁₋₆alkyl, C₅₋₇cycloalkenylC₂₋₆alkenyl, C₅₋₇cycloalkenylC₂₋₆alkynyl, 5- or 6-membered heteroaryl, 5- or 6-membered heteroarylC₁₋₆alkyl, 5- or 6-membered saturated or partially saturated heterocyclyl, 5- or 6-membered saturated or partially saturated heterocyclylC₁₋₆alkyl, or R¹⁶ and R¹⁷, together with the nitrogen atom to which they are attached, form a 4 to 8-membered saturated or partially saturated heterocyclic ring or form an amino acid residue or ester thereof.

A 5- or 6-membered heteroaryl ring system is a monocyclic aryl ring system having 5 or 6 ring atoms wherein 1, 2 or 3 ring atoms are selected from nitrogen, oxygen and sulphur.

A 5- or 6-membered saturated or partially saturated heterocyclyl is a ring system having 5 or 6 ring atoms wherein 1, 2 or 3 of the ring atoms are selected from nitrogen, oxygen and sulphur.

A 4 to 8-membered saturated or partially saturated heterocyclic ring is a ring system having 4 to 8 ring atoms wherein 1, 2 or 3 of the ring atoms are selected from nitrogen, oxygen and sulphur.

Particular 5- or 6-membered heteroaryl rings include pyrrolyl, imidazolyl, pyrazolyl, isothiazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, thiazolyl, thiadiazolyl, thienyl, furyl and oxazolyl.

Particular 5- or 6-membered saturated or partially saturated heterocyclic ring systems include pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, piperidyl, piperazinyl and morpholinyl.

An 8-10 bicyclic heteroaryl is a bicyclic aryl ring system having 8 to 10 ring atoms wherein 1, 2, 3 or 4 ring atoms are selected from nitrogen, oxygen and sulphur.

Examples of suitable optional substituents for C₁₋₆alkyl in amides, reverse amides, acylsulphonamides and acylhydrazides are

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hydroxy, amino, C_{1-4} alkoxy, halo, C_{1-4} alkoxycarbonyl, C_{1-4} alkylS(O)_p - (p is 0, 1 or 2), cyano, carboxy, C_{1-4} alkanoyl, C_{1-4} alkanoylamino, trifluoromethyl, pentafluoroethyl, nitro, C_{3-7} cycloalkyl, phenyl, 5- or 6-membered monocyclic heteroaryl, tetrazolyl, a 5- or 6-membered saturated or partially saturated heterocyclic ring and 5- or 6-membered monocyclic heteroarylium.

Particular substituents for ring systems in amides and reverse amides include, halo, trifluoromethyl, nitro, hydroxy, amino, cyano, C_{1-4} alkylS(O)_p - (p is 0, 1 or 2), carbamoyl, C_{1-4} alkanoylamino, C_{1-4} alkanesulphonamido and, when the ring system contains a saturated ring carbon (-CH₂-), oxo, hydroxyimino and C_{1-4} alkoxyimino.

Suitable ring systems of the formula (IIA), (IIB) or (IIC) include 5-oxo-4,5-dihydro-1,2,4-oxadiazole-3-yl, 3-oxo-2,3-dihydro-1,2,4-oxadiazole-5-yl, 3-thioxo-2,3-dihydro-1,2,4-oxadiazole-5-yl, 5-oxo-4,5-dihydro-1,3,4-oxadiazole-2-yl, 5-oxo-4,5-dihydro-1,2,4-triazole-3-yl, 3-oxo-2,3-dihydroisoxazole-5-yl, 5-oxo-1,5-dihydroisoxazole-3-yl and 5-oxo-2,3-dihydropyrazol-3-yl.

Amino acid residues formed from R⁶ and R⁷ or R¹⁶ and R¹⁷ together with the amide nitrogen to which they are attached and esters thereof include for example radicals of the formula -NH-CH(R^c)-COOR^d wherein R^c is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, phenyl, phenyl C_{1-3} alkyl, 5- or 6-membered heteroaryl or 5- or 6-membered heteroaryl C_{1-3} alkyl and R^d is hydrogen or C_{1-6} alkyl, wherein alkyl, alkenyl, alkynyl, phenyl and heteroaryl groups are optionally substituted. Examples of substituents include those mentioned above for ring A. In particular hydroxy.

Particular substituents for ring carbon atoms in A, include halo, trifluoromethyl, nitro, hydroxy, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, cyano, C_{1-6} alkoxy, carboxy, allyloxy, C_{1-6} alkylS(O)_p - (p is 0, 1 or 2), phenylS(O)_p - (p is 0, 1 or 2), trifluoromethyl S(O)_p - (p is 0, 1 or 2) C_{1-6} alkyl (optionally substituted by hydroxy, C_{1-4} alkoxy, amino, halo, nitro, C_{1-4} alkylS(O)_p - (p is 0, 1 or 2), phenylS(O)_p - (p is 0, 1 or 2) or cyano), carbamoyl, C_{1-4} alkylcarbamoyl, di(C_{1-4} alkyl)carbamoyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-3} alkyl, C_{3-7} cycloalkyl C_{2-3} alkenyl, C_{5-7} cycloalkenyl.

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C_{5-7} cycloalkenyl C_{2-3} alkenyl, benzyl, benzoyl, benzyloxy,
 C_{1-4} alkoxy carbonylamino, C_{1-4} alkanoylamino, (wherein the alkanoyl group
 is optionally substituted by hydroxy), C_{1-4} alkanoyl (N- C_{1-4} alkyl) amino
 (wherein the alkanoyl group is optionally substituted by hydroxy),
 C_{1-4} alkanesulphonamido, benzenesulphonamido, aminosulphonyl,
 C_{1-4} alkylaminosulphonyl, di(C_{1-4} alkyl)aminosulphonyl,
 C_{1-4} alkoxy carbonyl, C_{2-4} alkanoyloxy, C_{1-6} alkanoyl, formyl C_{1-4} alkyl,
 trifluoro C_{1-3} alkylsulphonyl, 1-(hydroxyimino)-1-(phenyl)methyl,
 1-(C_{1-4} alkoxyimino)-1-(phenyl)methyl, hydroxyimino C_{1-6} alkyl,
 C_{1-4} alkoxyimino C_{1-6} alkyl, C_{1-6} alkylcarbamoylamino, C_{2-6} alkenyl
 (substituted by halo), N-(amino)imino C_{1-4} alkyl,
 N-(C_{1-4} alkylamino)imino C_{1-4} alkyl, N-[di(C_{1-4} alkyl)amino]imino C_{1-4} alkyl,
 N-(phenyl)aminoimino C_{1-4} alkyl and 5-membered heteroaryl containing 1 or
 2 heteroatoms selected from nitrogen, oxygen and sulphur and, when A is
 phenyl or a 6-membered heteroaryl ring having ring carbon atoms in the
 4-position in relation to the $-O-CH(R^4)-$ substituent and in the
 4-position in relation to the $-Z-B-R^1$ substituent, suitable
 substituents include tetramethylene and diradicals of the formula
 $-(CH_2)_3CO-$, $-(CH_2)_3C(=N-OH)-$ and $-(CH_2)_3C(=N-OC_{1-4}alkyl)-$, wherein the
 left hand side of the diradical is attached to the a carbon atom in the
 4-position in relation to the $-O-CH(R^4)-$ substituent and the right
 hand side of the diradical is attached to a carbon atom in the
 4-position in relation to the $-Z-B-R^1$ substituent.

Particular substituents for ring carbon atoms in B include
 halo, trifluoromethyl, nitro, hydroxy, C_{1-6} alkoxy, C_{1-6} alkyl, amino,
 C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, cyano, $-S(O)_pC_{1-6}alkyl$ (p is 0, 1
 or 2), C_{1-4} alkanoylamino, benzenesulphonamido, C_{1-4} alkanesulphonamido,
 C_{1-6} alkoxy carbonylamino, carbamoyl, C_{1-4} alkylcarbamoyl and
 di(C_{1-4} alkyl)carbamoyl.

Particular optional substituents for D are halo,
 trifluoromethyl, nitro, hydroxy, amino, C_{1-4} alkylamino,
 di(C_{1-4} alkyl)amino, C_{1-4} alkanoylamino, cyano, C_{1-6} alkoxy, allyloxy,
 $-S(O)_pC_{1-4}alkyl$ (p is 0, 1 or 2), C_{1-4} alkanoyl or C_{1-4} alkyl optionally
 substituted by hydroxy, halo, nitro, cyano and amino.

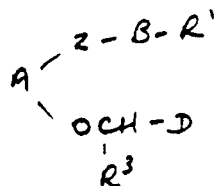
Particular substituents for tetrazole groups include C_{2-6}
 alkanoyloxy and C_{1-6} alkyl.

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CLAIMS

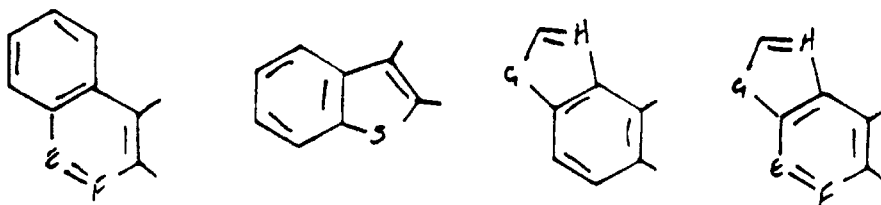
1. A compound of the formula (I):



wherein:

A is optionally substituted:

phenyl, naphthyl or a 5- or 6-membered heteroaryl ring system containing no more than two ring nitrogen atoms or thiadiazolyl or a bicyclic ring system of the formula:

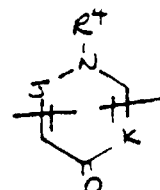
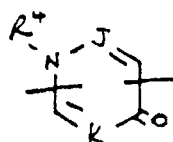
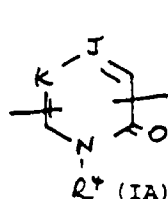


wherein E is nitrogen or CH, F is nitrogen or CH, G is sulphur or oxygen and H is nitrogen or CH;

wherein the -Z- and -OCH(R³)- groups are positioned in a 1,2 relationship to one another on ring carbon atoms;

and provided that the ring atom in the 2-position relative to the ring carbon atom bearing the -OCH(R³)- group and in the 3-position relative to the ring carbon atom bearing the -Z-B-R¹ group is unsubstituted and, when A is naphthyl, either the -Z-B-R¹ group is in the 1-position and the -OCH(R³)- group is in the 2-position of the naphthyl group and the ring atom in the 3-position is not substituted, or the -Z-B-R¹ group is in the 2-position and the -OCH(R³)- group is in the 3-position of the naphthyl group and the ring atom in the 4-position is not substituted (according to the IUPAC system);

B is an optionally substituted 5- or 6-membered heteroaryl ring system, optionally substituted phenyl or an optionally substituted ring system of the formula:

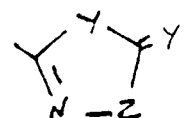
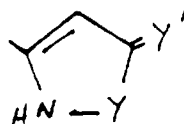
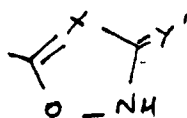


wherein 0 or 1 of J and K are ring nitrogen atoms and the remainder are ring carbon atoms and R^4 is C_{1-6} alkyl;

wherein the -Z-A and $-R^1$ groups are positioned in either a 1,3 or a 1,4 relationship to one another on ring carbon atoms in B in 6 membered rings and in a 1,3 relationship to one another on ring carbon atoms in B in 5-membered rings;

D is optionally substituted: phenyl or a 5- or 6- membered heteroaryl ring system;

R^1 is carboxy, optionally substituted tetrazolyl, carboxy C_{1-4} alkyl, optionally substituted tetrazolyl C_{1-4} alkyl, hydroxamic acid, sulphonic acid, tetronic acid or a pharmaceutically acceptable amide (-CONR-), reverse amide (-NRCO-), acylsulphonamide (-CONRSO₂-), acylhydrazide (-CON(R)N) or C_{1-4} alkyl substituted by a pharmaceutically-acceptable amide, reverse amide, acylsulphonamide or acylhydrazide or R^1 is of the formula (IIA), (IIB) or (IIC):



wherein X is CH or nitrogen, Y is oxygen or NH, Z is CH₂, NH or oxygen and Y¹ is oxygen or sulphur provided that there is no more than one ring oxygen and there are at least two ring heteroatoms;

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R^3 is hydrogen or C_{1-4} alkyl;

Z is of the formula $-(CH(R^5))_m-$, $-(CH(R^5))_rC(=O)CR^5=CR^5(CH(R^5))_s-$ or $-(CH(R^5))_tC(=O)(CH(R^5))_u-$, wherein m is 2, 3 or 4, p and q are independently 0, 1 or 2 providing p+q is not greater than 2, one of r and s is 0 and the other is 1 and t and u are independently 0, 1, 2 or 3 providing t + u is not less than 1 or greater than 3;

or R^5 is hydrogen, methyl, ethyl, hydroxy, methoxy or ethoxy;

or N-oxides where chemically possible;

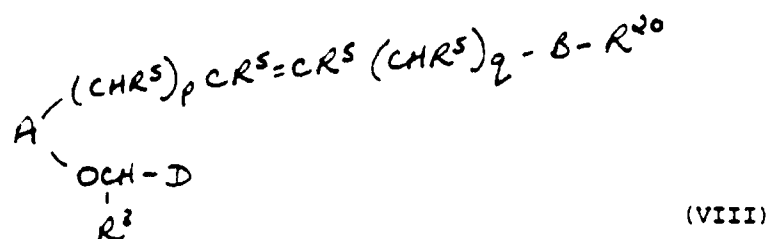
or S-oxides where chemically possible;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester or amide thereof.

2. A compound of the formula (I) according to claim 1 wherein R^1 is carboxy, optionally substituted tetrazolyl, carboxy C_{1-4} alkyl, optionally substituted tetrazolyl C_{1-4} alkyl, hydroxamic acid, sulphonic acid, tetronic acid, of the formula $-CONR^6R^7$ wherein R^6 is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-3} alkyl, C_{5-7} cycloalkenyl or C_{5-7} cycloalkenyl C_{1-3} alkyl and R^7 is hydrogen, C_{1-6} alkoxycarbonyl, hydroxy or optionally substituted: C_{1-10} alkyl, C_{1-10} alkenyl, C_{1-10} alkynyl, C_{3-7} cycloalkyl, C_{3-7} cycloalkyl C_{1-6} alkyl, C_{3-7} cycloalkyl C_{2-6} alkenyl, C_{3-7} cycloalkyl C_{2-6} alkynyl, C_{5-7} cycloalkenyl, C_{3-7} cycloalkenyl C_{1-6} alkyl, C_{5-7} cycloalkenyl C_{2-6} alkenyl, C_{5-7} cycloalkenyl C_{2-6} alkynyl, 5- or 6-membered heteroaryl, 5- or 6-membered heteroaryl C_{1-6} alkyl, 5- or 6-membered saturated or partially saturated heterocyclyl, 5- or 6-membered saturated or partially saturated heterocyclyl C_{1-6} alkyl, 5- or 6-membered heteroarylium or 5- or 6-membered heteroarylium C_{1-6} alkyl; or wherein R^6 and R^7 together with the amide nitrogen to which they are attached (NR^6R^7) form an amino acid residue or ester thereof, or R^1 is of the formula $-NR^6COR^8$ wherein R^6 is as hereinabove defined and R^8 is of the formula OR^9 wherein R^9 is hydrogen, optionally substituted C_{1-6} alkyl, 5- or 6-membered monocyclic heteroaryl or a 5- or 6-membered monocyclic saturated or partially saturated heterocyclyl, or R^8 is of formula $NR^{10}R^{11}$ wherein

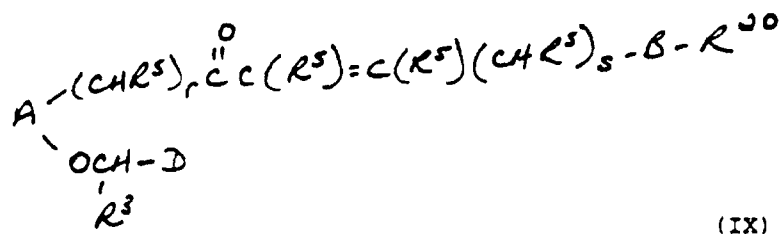
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- b) when Z is $-(CH(R^5))_m-$ by reducing a compound of the formula (VIII):



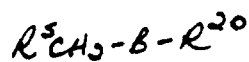
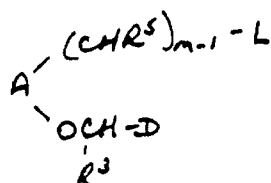
wherein A, B, D, R^3 , R^5 , R^{20} , n, p and q are as hereinabove defined;

- c) when Z is $-(CHR^5)_tC(=O)(CHR^5)_u-$ or $-(CH(R^5))_m-$ and m is 3 or 4, by reducing a compound of the formula (IX):



wherein A, B, D, R^3 , R^5 , R^{20} , and n are as hereinabove defined and one of r and s is 0 and the other is 1;

- d) when B is an activated heterocycle and Z is $-(CH(R^5))_m-$, by reacting a compound of the formula (X) with a compound of the formula (XI):



(X)

(XI)