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Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Ref.: Expediente No. 06-018.321

Solicitud de Patente de Invención titulada: "FORMULACION FARMACEUTICA QUE
COMPRENDE UN DERIVADO PIRIMIDINA-A-ONA Y UNA CUBIERTA QUE
COMPRENDE UN POLIMERO ENTERICO".

Solicitante: GLAXO GROUP LIMITED

SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN
EL ARTÍCULO 44 DE LA DECISION 486, GACETA No. 579

J. IAN RAISBECK, mayor de edad y vecino de Bogotá, D.C., identificado tal como aparece al pie de mi firma, en mi carácter de apoderado sustituto de la sociedad solicitante, 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 de Naciones. Adjunto recibo por el monto de \$404.000 pesos para cubrir la tasa correspondiente, según la Resolución No. 36155 del año 2006.

Atentamente,

J. IAN RAISBECK
C.C. 79.376.996 de Bogotá
T.P. 135.799

Anexo: Recibo por \$404.000 pesos
Sustitución

LMB/P2006/000026 070921 Sol Exam

DILIGENCIA DE PRESENTACION PERSONAL Y RECONOCIMIENTO DE CONVENIO Y FIRMA.
NOTARIA EL ANTERIOR ESCRITO OTORGADO A:
27
FUE PRESENTADO CONFORMANTE
ANTE MI
D. [illegible]
EL OTORGANTE:
[Firma]
HOY: 27 SEP 2007



EL ASESORADO DE LA DECISION NO GACETA No. 570
SOLO EN DE PATENTABILIDAD SEGUN

La Ley 1712 de 2003, mayor de edad y varón de Bogotá D.C., identificado tal como aparece en
el documento en mi carácter de abogado sustituto de la sociedad solicitante, según consta en
la certificación adjunta, respectivamente no permite solicitar que se examine si la invención
de los dispositivos de patentabilidad previstos en la misma, dando cumplimiento a lo establecido en el
artículo 41 de la Decisión 486 de la Comisión de la Comunidad Andina de Naciones. Adjunto
recibo por el monto de \$404.000 pesos para cubrir la tasa correspondiente, según la resolución
No. 00153 del año 2006.

Atentamente,
[Firma]
J. J. ARTERABECK
C.E. 70320 WVA de Bogotá
T.P. 133 700

Recibo por \$404.000 pesos
[Firma]
[Firma]

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77

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Ref.: Expediente No. 06-018.321

Solicitud de Patente de Invención titulada: "FORMULACION FARMACEUTICA QUE COMPRENDE UN DERIVADO PIRIMIDINA-A-ONA Y UNA CUBIERTA QUE COMPRENDE UN POLIMERO ENTERICO".

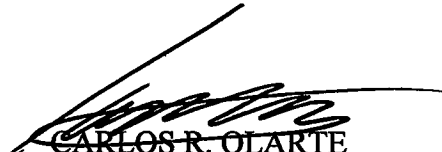
Solicitante: GLAXO GROUP LIMITED

SUSTITUCIÓN DE PODER

CARLOS R. OLARTE, 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 J. IAN RAISBECK LLINAS, mayor de edad, domiciliado en Bogotá D.C., identificado con la Cédula de Ciudadanía No. 79.376.996 de Bogotá y portador de la Tarjeta Profesional No. 135.799 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,


CARLOS R. OLARTE
C.C. No. 79.782.747 de Bogotá
T.P. 74.295 del C. S. de la J.

GOBIERNO DE COLOMBIA
MINISTERIO DE JUSTICIA Y COMERCIO
DIVISION DE NOTARIAS PUBLICAS

DILIGENCIA DE PRESENTACION PERSONAL Y RECONOCIMIENTO DE CONTENIDO Y FIRMA.

NOTARIA EL ANTERIOR ESCRITO DIRIGIDO A:

27 FUE PRESENTADO PERSONALMENTE ANTE EL SUSCRITO NOTARIO VEINTISIETE DE SANATE DE BOGOTA POR

EL PRESENTANTE

HOY: 28 AGO 2007

MARIA EUGENIA RUJAS DE URUETA
NOTARIA VEINTISIETE
REPUBLICA DE COLOMBIA

HUELLA

REPUBLICA DE COLOMBIA

MARIA EUGENIA RUJAS DE URUETA
NOTARIA

Notaria 27 Bogotá D C

(43) Pub. Date: Aug. 1, 2002

(52) U.S. CI. 514/249; 514/258; 514/259;
514/211.15; 514/217.06; 514/227.8;
514/235.8; 544/314; 544/287;
544/253; 544/123; 544/60;
540/600; 540/544

(57) **ABSTRACT**

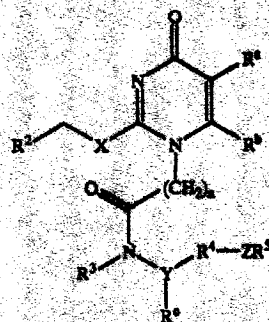
Pyrimidone compounds of formula (I):

(30) Foreign Application Priority Data

Feb. 16, 2000 (GB) 0003636.8
Jan. 19, 2001 (GB) 0101437.2

Publication Classification

(51) Int. Cl. A61K 31/513; A61K 31/517;
A61K 31/5377; A61K 31/541;
A61K 31/554; A61K 31/553;
A61K 31/55; C07D 239/32;
C07D 239/88; C07D 417/02;
C07D 413/02



are inhibitors of the enzyme Lp-PLA₂ and are of use in treating atherosclerosis.

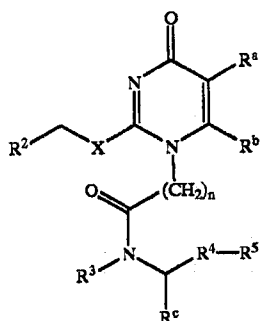
prising N and in which N may be substituted by C₍₁₋₆₎alkyl. More preferably, R³ is 2-(diethylamino)ethyl.

[0045] Representative examples of R⁴ include phenyl, pyridine and pyrimidine. Preferably, R⁴ is phenyl.

[0046] Representative examples of R⁵ include phenyl or thienyl, optionally substituted by halogen or trifluoromethyl, preferably at the 4-position. Preferably, R⁵ is phenyl substituted by trifluoromethyl, preferably at the 4-position.

[0047] Preferably, R⁴ and R⁵ together form a 4-(phenyl)phenyl, 2-(phenyl)pyrimidinyl or a 2-(phenyl)pyridinyl substituent in which the remote phenyl ring may be optionally substituted by halogen or trifluoromethyl, preferably at the 4-position. More preferably, R⁴ and R⁵ together form a 4-(4-trifluoromethylphenyl)phenyl moiety.

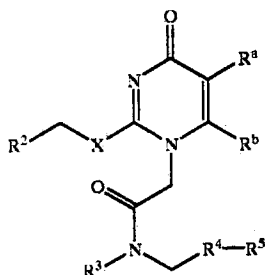
[0048] It will be appreciated that within the compounds of formula (I) there is a sub-group of compounds which has the formula (IA):



[0049] in which:

[0050] R^a, R^b, R^c, n, R², R³, R⁴, R⁵, and X are as hereinbefore defined; and

[0051] a further sub-group of compounds which has the formula (IB):



[0052] in which:

[0053] R^a, R^b, R², R³, R⁴, R⁵, and X are as hereinbefore defined, in particular:

[0054] R^a and R^b together with the pyrimidine ring carbon atoms to which they are attached form a fused 5-membered carbocyclic ring;

[0055] R²CH₂X is 4-fluorobenzylthio;

[0056] R³ is C₍₁₋₃₎alkyl substituted by NR⁸R⁹; or

[0057] R³ is Het-C₍₀₋₂₎alkyl in which Het is a 5- to 7-membered heterocyclyl ring containing N and in which N may be substituted by C₍₁₋₆₎alkyl;

[0058] R⁴ and R⁵ form a 4-(4-trifluoromethylphenyl)phenyl moiety;

[0059] R⁸ and R⁹ which may be the same or different is each selected from hydrogen, or C₍₁₋₆₎alkyl; and

[0060] X is S.

[0061] Pharmaceutically acceptable in vivo hydrolysable ester groups for R¹² include those which break down readily in the human body to leave the parent acid or its salt. Pharmaceutically acceptable in vivo hydrolysable ester groups are well known in the art and examples of such for use in R¹² are described in WO 00/68208 (SmithKline Beecham).

[0062] It will be appreciated that when R^c is C₍₁₋₃₎alkyl, the carbon to which it is attached will be a chiral centre so that diastereoisomers may be formed. In the absence of further chiral centres, these will be enantiomers. The present invention covers all such diastereoisomers and enantiomers, including mixtures thereof.

[0063] It will be appreciated that in some instances, compounds of the present invention may include a basic function such as an amino group as a substituent. Such basic functions may be used to form acid addition salts, in particular pharmaceutically acceptable salts. Pharmaceutically acceptable salts include those described by Berge, Bighley, and Monkhouse, *J. Pharm. Sci.*, 1977, 66, 1-19. Such salts may be formed from inorganic and organic acids. Representative examples thereof include maleic, fumaric, benzoic, ascorbic, pantoic, succinic, bismethylenesalicylic, methanesulfonic, ethanedithiolsulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, taurocholic, benzenesulfonic, p-toluenesulfonic, hydrochloric, hydrobromic, sulfuric, cyclohexylsulfamic, phosphoric and nitric acids.

[0064] It will be appreciated that in some instances, compounds of the present invention may include a carboxy group as a substituent. Such carboxy groups may be used to form salts, in particular pharmaceutically acceptable salts. Pharmaceutically acceptable salts include those described by Berge, Bighley, and Monkhouse, *J. Pharm. Sci.*, 1977, 66, 1-19. Preferred salts include alkali metal salts such as the sodium and potassium salts.

[0065] When used herein, the term "alkyl" and similar terms such as "alkoxy" includes all straight chain and branched isomers. Representative examples thereof include methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, t-butyl, n-pentyl and n-hexyl.

[0066] When used herein, the term "aryl" refers to, unless otherwise defined, a mono- or bicyclic aromatic ring system containing up to 10 carbon atoms in the ring system, for instance phenyl or naphthyl.

[0067] When used herein, the term "heteroaryl" refers to a mono- or bicyclic heteroaromatic ring system comprising up to four, preferably 1 or 2, heteroatoms each selected from oxygen, nitrogen and sulphur. Each ring may have from 4 to 7, preferably 5 or 6, ring atoms. A bicyclic heteroaromatic ring system may include a carbocyclic ring.

present invention include the PPARgamma activators, for instance GI262570 (Glaxo Wellcome) and the glitazone class of compounds such as rosiglitazone (Avandia, Smith-Kline Beecham), troglitazone and pioglitazone.

[0088] Preferred indications include primary and secondary prevention of acute coronary events, for instance those caused by atherosclerosis, including peripheral vascular atherosclerosis and cerebrovascular atherosclerosis; adjunctive therapy in prevention of restenosis, and delaying the progression of diabetic/hypertensive renal insufficiency.

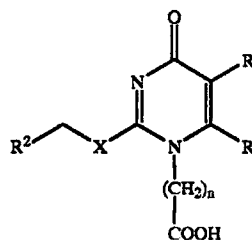
[0089] In therapeutic use, the compounds of the present invention are usually administered in a standard pharmaceutical composition. The present invention therefore provides, in a further aspect, a pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable carrier.

[0090] Suitable pharmaceutical compositions include those which are adapted for oral or parenteral administration or as a suppository. Compounds of formula (I) which are active when given orally can be formulated as liquids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges. A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s) for example, ethanol, glycerine, non-aqueous solvent, for example polyethylene glycol, oils, or water with a suspending agent, preservative, flavouring or colouring agent. A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose. A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule. Typical parenteral compositions consist of a solution or suspension of the compound of formula (I) in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration. A typical suppository formulation comprises a compound of formula (I) which is active when administered in this way, with a binding and/or lubricating agent such as polymeric glycols, gelatins or cocoa butter or other low melting vegetable or synthetic waxes or fats.

[0091] Preferably the composition is in unit dose form such as a tablet or capsule. Each dosage unit for oral administration contains preferably from 1 to 500 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a compound of the formula (I). The daily dosage regimen for an adult patient may be, for example, an oral dose of between 1 mg and 1000 mg, preferably between 1

mg and 500 mg, or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 25 mg, of the compound of the formula (I), the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

[0092] A compound of formula (I) may be prepared by reacting a compound of formula (II):



[0093] in which X, n, R^a, R^b and R² are as hereinbefore defined, with a compound of formula (III):

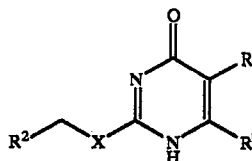


[0094] in which R^c, R³, R⁴, R⁵, Y and Z are as hereinbefore defined; under amide forming conditions.

[0095] Amide forming conditions are well known in the art, see for instance Comprehensive Organic Synthesis 6, 382-399, and include reacting the acid compound of formula (II) and the amine compound of formula (III) in an inert solvent such as dichloromethane, at ambient temperature, in the presence of a coupling agent. Preferred coupling agents include those developed for use in peptide chemistry, such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride ("EDC"), preferably in the presence of an additive such as 1-hydroxybenzotriazole, or O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate ("HATU"), preferably in the presence of di-isopropylethylamine.

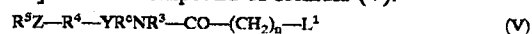
[0096] Compounds of formula (I) may also be prepared by a number of other processes, for instance:

[0097] (a) reacting a compound of formula (IV):



[0098] in which X, R^a, R^b and R² are as hereinbefore defined,

[0099] with a compound of formula (V):



[0100] in which n, R³, R⁴, R⁵, R⁶, Y and Z are as hereinbefore defined, and L¹ is a leaving group such as halogen, for instance bromo iodo, or triflate;

[0101] in the presence of a base such as a secondary or tertiary amine, for instance di-isopropylethylamine, in an inert solvent such as dichloromethane;

R^3 is hydrogen, $C_{(1-6)}$ alkyl which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from the group consisting of hydroxy, halogen, OR^6 , COR^6 , carboxy, $COOR^6$, $CONR^6R^9$, NR^6R^9 , NR^6COR^6 , mono- or di-(hydroxy $C_{(1-6)}$ alkyl)amino and N-hydroxy $C_{(1-6)}$ alkyl-N- $C_{(1-6)}$ alkylamino; or

R^3 is Het- $C_{(0-4)}$ alkyl in which Het is a 5- to 7- membered heterocyclyl ring comprising N and optionally O or S, bonded through a carbon atom and in which N is unsubstituted or substituted by COR^6 , $COOR^6$, $CONR^6R^9$; or $C_{(1-6)}$ alkyl unsubstituted or substituted by 1, 2 or 3 substituents selected from the group consisting of hydroxy, halogen, OR^6 , COR^6 , carboxy, $COOR^6$, $CONR^6R^9$ and NR^6R^9 ;

R^4 is an aryl or a heteroaryl ring optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from the group consisting of $C_{(1-18)}$ alkyl, $C_{(1-18)}$ alkoxy, $C_{(1-18)}$ alkylthio, aryl $C_{(1-18)}$ alkoxy, hydroxy, halogen, CN, COR^6 , carboxy, $COOR^6$, NR^6COR^7 , $CONR^6R^9$, $SO_2NR^6R^9$, $NR^6SO_2R^7$, NR^6R^9 , mono to perfluoro- $C_{(1-4)}$ alkyl and mono to perfluoro- $C_{(1-4)}$ alkoxy;

R^5 is an aryl or heteroaryl ring which is unsubstituted or substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from the group consisting of $C_{(1-18)}$ alkyl, $C_{(1-18)}$ alkoxy, $C_{(1-18)}$ alkylthio, aryl $C_{(1-18)}$ alkoxy, hydroxy, halogen, CN, COR^6 , carboxy, $COOR^6$, $CONR^6R^9$, NR^6COR^7 , $SO_2NR^6R^9$, $NR^6SO_2R^7$, NR^6R^9 , mono to perfluoro- $C_{(1-4)}$ alkyl and mono to perfluoro- $C_{(1-4)}$ alkoxy;

R^6 and R^7 are independently hydrogen or $C_{(1-20)}$ alkyl;

R^8 and R^9 may be the same or different and are selected from the group consisting of hydrogen and $C_{(1-12)}$ alkyl; or

R^8 and R^9 together with the nitrogen to which they are attached form a 5- to 7 membered ring optionally containing one or more further heteroatoms which are oxygen, nitrogen or sulphur, and is unsubstituted or substituted by one or two substituents selected from the group consisting of hydroxy, oxo, $C_{(1-4)}$ alkyl, $C_{(1-4)}$ alkylCO, aryl, and aralkyl; or

R^8 and R^9 may be the same or different and are selected from the group consisting of CH_2R^{10} and $CHR^{11}CO_2H$, or a salt thereof;

R^{10} is COOH or a salt thereof, $COOR^{12}$, $CONR^6R^7$, CN, CH_2OH or CH_2OR^6 ;

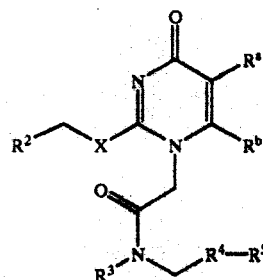
R^{11} is an amino acid side chain;

R^{12} is $C_{(1-4)}$ alkyl or a pharmaceutically acceptable in vivo hydrolysable ester group;

n is 1 to 4; and

X is O or S.

18. A compound of the formula (IB):



(IB)

in which:

R^a and R^b together with the pyrimidine ring carbon atoms to which they are attached form a fused 5-membered carbocyclic ring;

R^2CH_2X is 4-fluorobenzylthio;

R^3 is $C_{(1-3)}$ alkyl substituted by NR^6R^9 ; or

R^3 is Het- $C_{(0-2)}$ alkyl in which Het is a 5- to 7- membered heterocyclyl ring comprising N and in which N is unsubstituted or substituted by $C_{(1-6)}$ alkyl;

R^4 and R^5 form a 4-(4-trifluoromethylphenyl)phenyl moiety;

R^8 and R^9 which may be the same or different are selected from the group consisting of hydrogen, or $C_{(1-6)}$ alkyl; and

X is S.

19. A compound as claimed in claim 1 which is:

1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)amino-carbonylmethyl)-2-(4-fluorobenzyl)thio-5-ethylpyrimidin-4-one;

1-(N-(2-(diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrid-5-yl-methyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-ethylpyrimidin-4-one; 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5,6-trimethylenepyrimidin-4-one; 1-(N-(2-(diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrid-5-yl-methyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5,6-trimethylenepyrimidin-4-one;

1-(N-(2-(diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrimid-5-yl-methyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5,6-trimethylenepyrimidin-4-one;

1-(N-methyl-N-(2-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-aminoethyl)pyrimidin-4-one;

1-(N-(2-(diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrid-5-ylmethyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-ethylpyrimidin-4-one;

1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5,6-trimethylenepyrimidin-4-one;

1-(N-(2-(diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrid-5-yl-methyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5,6-trimethylenepyrimidin-4-one; or

1-(N-(2-(diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrimid-5-ylmethyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5,6-trimethylenepyrimidin-4-one;

or a pharmaceutically acceptable salt thereof.

21. A compound as claimed in claim 1 which is 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5,6-trimethylenepyrimidin-4-one, or a pharmaceutically acceptable salt thereof.

22. A pharmaceutical composition comprising a compound of formula (I) as claimed in claim 1 and a pharmaceutically acceptable carrier.

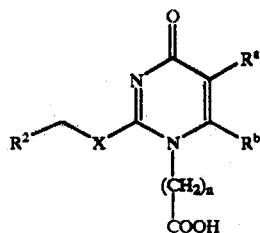
23. A method for the primary and secondary prevention of acute coronary events which method comprises administering a therapeutically effective amount of a compound of formula (I) as claimed in claim 1 to a patient in need thereof.

24. The method as claimed in claim 23 wherein the coronary event is caused by atherosclerosis.

25. A method of treating a disease state associated with activity of the enzyme Lp-PLA₂ which method involves treating a patient in need thereof with a therapeutically effective amount of a compound of formula (I) as claimed in claim 1.

26. A process for preparing a compound of formula (I) which process comprises:

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



in which

R^a is hydrogen, halogen, C₍₁₋₃₎alkyl, C₍₁₋₃₎alkoxy, hydroxyC₍₁₋₃₎alkyl, C₍₁₋₃₎alkylthio, C₍₁₋₃₎alkylsulphonyl, aminoC₍₁₋₃₎alkyl, mono- or di-C₍₁₋₃₎alkylaminoC₍₁₋₃₎alkyl, C₍₁₋₃₎alkylcarbonylaminoC₍₁₋₃₎alkyl, C₍₁₋₃₎alkoxyC₍₁₋₃₎alkylcarbonylaminoC₍₁₋₃₎alkyl, C₍₁₋₃₎alkylsulphonylaminoC₍₁₋₃₎alkyl, C₍₁₋₃₎alkylcarboxy, or C₍₁₋₃₎alkylcarboxyC₍₁₋₃₎alkyl;

R^b is hydrogen, halogen, C₍₁₋₃₎alkyl, or hydroxyC₍₁₋₃₎alkyl, with the proviso that R^a and R^b are not simultaneously each hydrogen; or

R^a and R^b together are (CH₂)_n where n is 3 or 4, to form, with the pyrimidine ring carbon atoms to which they are attached a fused 5- or 6-membered carbocyclic ring; or

R^a and R^b together with the pyrimidine ring carbon atoms to which they are attached form a fused benzo or heteroaryl ring unsubstituted or substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from the group consisting of halogen, C₍₁₋₄₎alkyl, cyano, C₍₁₋₄₎alkoxy or C₍₁₋₄₎alkylthio, and mono to perfluoro-C₍₁₋₄₎alkyl);

R² is an aryl or heteroaryl group unsubstituted or substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from the group consisting of C₍₁₋₁₈₎alkyl, C₍₁₋₁₈₎alkoxy, C₍₁₋₁₈₎alkylthio, arylC₍₁₋₁₈₎alkoxy, hydroxy, halogen, CN, COR⁶, carboxy, COOR⁶, NR⁶COR⁷, CONR⁶R⁹, SO₂NR⁶R⁹, NR⁶SO₂R⁷, NR⁶R⁹, mono to perfluoro-C₍₁₋₄₎alkyl, mono to perfluoro-C₍₁₋₄₎alkoxyaryl, and arylC₍₁₋₄₎alkyl;

R⁶ and R⁷ are independently hydrogen or C₍₁₋₂₀₎alkyl;

R⁸ and R⁹ may be the same or different and are selected from the group consisting of hydrogen and C₍₁₋₁₂₎alkyl; or

R⁸ and R⁹ together with the nitrogen to which they are attached form a 5- to 7 membered ring optionally containing one or more further heteroatoms selected from the group consisting of oxygen, nitrogen and sulphur, and is unsubstituted or substituted by one or two substituents selected from the group consisting of hydroxy, oxo, C₍₁₋₄₎alkyl, C₍₁₋₄₎alkylCO, aryl, or aralkyl; or

R⁸ and R⁹ may be the same or different and are selected from the group consisting of CH₂R¹⁰ and CHR¹¹CO₂H or a salt thereof;

R¹⁰ is COOH or a salt thereof, COOR¹², CONR⁶R⁷, CN, CH₂OH or CH₂OR⁶;

R¹¹ is an amino acid side chain;

n is 1 to 4; and

X is O or S;

with a compound of formula (III):



in which R⁰, R³, R⁴, R⁵, are as hereinbefore defined;

Y is (CH₂)_p(O)_q in which p is 1, 2 or 3 and q is 0 or p is 2 or 3 and q is 1; and

Z is O or a bond;

under amide forming conditions;

(12) **United States Patent**
Odidi et al.

(10) **Patent No.:** US 6,296,876 B1
(45) **Date of Patent:** Oct. 2, 2001

(54) **PHARMACEUTICAL FORMULATIONS FOR ACID LABILE SUBSTANCES**

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(*) **Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) **Appl. No.:** 09/166,274

(22) **Filed:** Oct. 5, 1998

Related U.S. Application Data

(60) **Provisional application No.** 60/061,211, filed on Oct. 6, 1997, and **provisional application No.** 60/068,517, filed on Dec. 22, 1997.

(51) **Int. Cl.⁷** A61K 9/32; A61K 9/34; A61K 9/36

(52) **U.S. Cl.** 424/480; 424/481; 424/482; 424/494; 424/495; 424/496; 424/497; 514/770; 514/772.3; 514/778; 514/781

(58) **Field of Search** 424/474, 475, 424/480, 481, 482, 490, 497, 496, 495, 494

(56) **References Cited**

U.S. PATENT DOCUMENTS

2,540,979 2/1951 Clymer et al. 167/82
4,786,505 * 11/1988 Lovgren et al. 424/468
4,853,230 * 8/1989 Lovgren et al. 424/468

FOREIGN PATENT DOCUMENTS

1 204 363 4/1965 (DE) .
0 005129 B1 4/1981 (EP) .
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Primary Examiner—James M. Spear

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(57) **ABSTRACT**

This invention in general relates to novel pharmaceutical compositions for acid labile substances as well as for methods of making such. Specifically, the invention provides a pharmaceutical composition comprising about 1 to 75% by weight acid labile compound, up to about 5% by weight disintegrant, at least one protector coat layer used to separate and protect the acid labile substance from acid reacting groups and gastric juice, and at least one enteric coat layer which surrounds the protector coating layer and ensures delivery of over 80% the acid labile substance to the small intestine.

15 Claims, No Drawings

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PHARMACEUTICAL FORMULATIONS FOR ACID LABILE SUBSTANCES

This application claims benefit of provisional No. 60/061,211 filed Oct. 6, 1997 and No. 60/068,517 filed Dec. 22, 1997.

FIELD OF THE INVENTION

This invention in general relates to novel pharmaceutical compositions for acid labile substances as well as for methods of making such.

BACKGROUND OF THE INVENTION

Substituted benzimidazoles are substituted sulfoxides which are potent inhibitors of gastric acid secretion. Such substituted sulfoxides are described for example in EP 0005129. These compounds are susceptible to degradation and/or transformation in both acid and neutral media. The acidic decomposition of these acid labile compounds is due to an acid catalyzed reaction described by G. Rackur et al., in *Biochem. Biophys. Res. Commun.* 1985: 128(1). P477-484.

In order to provide a pharmaceutical composition containing such acid labile substances which is not degraded in the gastrointestinal tract, the acid labile substances must be enteric coated. However, pharmaceutically acceptable enteric coating materials are acidic in nature or contain acid reacting groups. Therefore, if the acid labile substances are directly covered by these enteric coating materials, the acid labile substance rapidly degrades.

U.S. Pat. Nos. 4,853,230 and 4,786,505 describe enteric coated pharmaceutical formulations of acid labile substances for oral use, where the cores contain acid labile drugs mixed with alkaline reacting substances. This is then coated with a first separating layer which is rapidly disintegrated in gastric fluid and a final enteric layer. However, the alkaline reacting substances in the core do not completely protect the acid labile substances from degradation and thus additional pH buffering substances are required. These formulations may also contain aluminium, potassium, sodium, calcium and magnesium which compounds or composites may be of concern for oral ingestion in humans.

U.S. Pat. No. 2,540,979 describes an enteric coated pharmaceutical in an oral dosage form, where the enteric coating is combined with a second and/or first coating of a water insoluble "wax" layer. This coating is not suitable as direct contact with acid labile substances as it will result in degradation of the acid labile active.

WO No. 85/03436 discloses a pharmaceutical preparation in which the core contains active drugs mixed with buffering compounds such as sodium dihydrogenphosphate which maintains a constant pH. A coating material is used to provide a constant rate of diffusion of the pharmaceutical active. However, this formulation is not suitable for acid labile compounds where a rapid release in the small intestine is required. The direct application of an enteric coating onto the pharmaceutical active would adversely influence the storage stability of the acid labile compounds contained therein.

DE-A1-1 204 363 describes a three layer coating method for pharmaceuticals. The first coating layer is a surface membrane soluble in gastric but insoluble in intestinal juice. The second coating layer is soluble at all physiological pHs and the third coating layer is an enteric coating. This method is complicated and is also not suitable for acid labile

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compounds such as substituted benzimidazoles where rapid release of the drug in the small intestine is required, as it results in a dosage form which is not dissolved in gastric juice and dissolves slowly in the small intestine.

There was therefore a need to develop a pharmaceutical composition for acid labile substances that adequately protected the acid labile active prior to its being release in the small intestine. Accordingly, a novel pharmaceutical composition was developed for the delivery of acid labile substances to the gut which differs from known compositions and delivery mechanisms in the type of stabilizer(s) utilized, the mechanism(s) of stabilization used in the core containing the acid labile compound(s), by the type of protector coat applied to the core(s), the mechanism(s) by which the protector coat elicits it's protective action and the type of enteric coating compound(s) used in the composition. These lead to a different mechanism by which the acid labile drug is released in the small intestine to provide a stabilized acid labile compound composition.

SUMMARY OF THE INVENTION

The present invention provides an enteric coated dosage form of a selected acid labile compound, in particular proton pump inhibitor compounds which decrease production of acid in the gut. Such compounds include but are not limited to as omeprazole, 5-methoxy-2-(4-methoxy-3,5 dimethyl-2-pyridinyl methyl sulfinyl-1H-benzimidazole, lansoprazole, 2-(2-diethylaminobenzyl)sulfinyl-benzimidazole and their related compounds such as their salts which rapidly disintegrate in the small intestine.

The novel pharmaceutical composition comprises an acid labile compound or an alkaline salt of the acid labile compound. The composition optionally comprises acid sequestering compound(s), and further comprises disintegrants and at least one coating layer which is swellable and/or permeable at physiological pH (preferably >5.0). This first coating layer separates and protects the core containing the acid labile active from the outer enteric coating layers.

According to an object of the present invention there is provided a pharmaceutical composition comprising:

- about 1 to 75% by weight acid labile compound;
- up to about 5% by weight disintegrant;

- at least one protector coat layer used to separate and protect the acid labile substance from acid reacting groups and gastric juice; and

- at least one enteric coat layer which surrounds the protector coating layer and ensures delivery of over 80% the acid labile substance to the small intestine.

Optionally, the composition may additionally comprise not less than about 0.1% acid sequestering compound.

According to another object of the present invention is a method for preparing the novel pharmaceutical composition of the present invention.

The novel formulation of the present invention demonstrates excellent resistance to dissolution in acid media and dissolves rapidly in neutral to alkaline media. The novel acid labile substance formulation has a good stability during long term storage.

The novel pharmaceutical composition is well suited for oral administration in a dosage unit form.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

The present invention provides an enteric coated dosage form of a selected active acid labile compound, in particular

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or hard gelatin capsules are stored together with a desiccant in order to maintain a low moisture content during long term storage. The final composition of the present invention provides that not more than 10% of the acid labile substance is released in acid media in about 2 hours and more than about 80% of the acid labile substance is released in 24 hours in alkaline media using USP dissolution apparatus I, II, III or IV.

EXAMPLES

The examples are described for the purposes of illustration and are not intended to limit the scope of the invention.

Methods of synthetic chemistry, pharmacy and pharmacology referred to but not explicitly described in this disclosure and examples are reported in the scientific literature and are well known to those skilled in the art.

Example 1

1. Composition of tablets	
Omeprazole	20 mg
Eudragit E	20 mg
Lactose	80 mg
Calcium sulfate dihydrate	20 mg
Carboxymethylcellulose sodium	20 mg
Microcrystalline cellulose	20 mg
Sodium lauryl sulfate	20 mg
PVP XL 10	2 mg
Talc	10 mg

Lactose, microcrystalline cellulose, sodium lauryl sulfate, carboxymethylcellulose sodium, and calcium sulfate dihydrate were blended in a planetary mixer. The blend was granulated with alcoholic solution of Eudragit E and dried in a tray dryer to an LOD of 1%. The dried granules are blended with omeprazole, talc and PVP XL 10 and pressed into tables.

II. Composition of protector coated tablets	
Tablets from 1	3.00 kg
Eudragit E	0.300 kg
Kaolin	0.100 kg
Talc	0.050 kg
Acetone	0.234 kg
Isopropyl alcohol	0.281 kg
Ethylcellulose 1% soln	0.300 kg

Finely disperse kaolin and Talc in the Eudragit E solvent mixture using a propeller mixer. Apply the protector coat solution unto the tablets in a perforated coating pan. Apply a 1-3% solution of ethylcellulose to the protector coated tablets in a perforated coating pan.

III. Composition of enteric coated tablets	
Protector coated tablets from II	3.450 kg
Shellac*	0.052 kg
Talc	0.004 kg

*in specially denatured alcohol 45/200 proof

Apply the enteric coating solution unto the protector coated tablets in a perforated coating pan and dry in a tray dryer if necessary. One or more of the enteric coated tablets are filled into hard gelatin capsules.

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Temperature and relative humidity of the manufacturing area should be no greater than 35° C. and 50%.

Example 2

I. Composition of tablets	
Omeprazole	20 mg
Eudragit E	20 mg
Lactose	90 mg
Calcium sulfate dihydrate	20 mg
Sodium lauryl sulfate	20 mg
Microcrystalline cellulose	20 mg
Sodium starch glycolate	5 mg
Talc	15 mg

Lactose, microcrystalline cellulose, calcium sulfate and sodium lauryl sulphate were blended in a planetary mixer. The blend was granulated with alcoholic solution of Eudragit E and dried in a tray dryer to an LOD of 1%. The dried granules are blended with omeprazole, talc sodium starch glycolate and pressed into tablets.

II. Composition of protector coated tablet	
Tablets from I	3.0 kg
Eudragit E	0.3 kg
Kaolin	0.10 kg
Talc	0.05 kg
Acetone	0.234 kg
Isopropyl alcohol	0.281 kg

Finely dispersed kaolin and Talc in the Eudragit E solvent mixture using a propeller mixer. Apply the protector coat solution unto the tablets in a perforated coating pan.

III. Composition of enteric coated tablets	
Protector coated tablets from II	3.450 kg
Hydroxypropyl methylcellulose acetate succinate**	0.345 kg
**from the following coating solution shown below for 3 kg batch	
Polymer solution	
Hydroxypropyl methylcellulose acetate succinate	0.345 kg
Triethyl citrate	0.041 kg
Ethanol/water (80:20)	0.807 kg
Pigment suspension	
Opadry	0.034 kg
Talc	0.034 kg
PEG 6000	0.015 kg
Water	0.053 kg

Add the homogenized pigment and talc suspension to the polymer solution to form the enteric coating solution. Apply the enteric coating solution unto the protector coated tablets in perforated coating pan and dry in a tray dryer if necessary. One or more of the enteric coated tablets are filled into hard gelatin capsules.

Temperature and relative humidity of the manufacturing area should be no greater than 35° C. and 50%.

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5. The composition of claim 3, wherein said enteric coating layer comprises a compound selected from the group consisting of shellac, its constituent aliphatic polyhydroxy acids and their derivatives.

6. A pharmaceutical composition comprising:

about 1 to 75% by weight proton pump inhibitor compound;

up to about 5% by weight disintegrant;

at least one protector coat layer used to separate and protect the proton pump inhibitor compound from acid reacting groups and gastric juice, wherein said protector coat layer comprises an aminoalkyl methacrylate copolymer; and

at least one enteric coat layer which surrounds the protector coating layer and ensures delivery of over 80% of the proton pump inhibitor compound to the small intestine.

7. The composition of claim 1, wherein said protector coat additionally comprises one or more of plasticizers, pigments, kaolin, bentonite and talc.

8. The composition of claim 6, wherein said enteric coating layer comprises a compound selected from the group consisting of shellac, its constituent aliphatic polyhydroxy acids and its derivatives.

9. The composition of claim 8, wherein said enteric coating layer additionally comprises plasticizers, pigments, colorants, kaolin, bentonite and talc.

10. The composition of claim 1, wherein the enteric coating layer comprises hydroxypropylmethylcellulose

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phthalate or hydroxypropyl methylcellulose acetate succinate having free succinic acid not more than 10% and a weight-average molecular weight of 4.5 to 12×10^4 as measured by gel permeation chromatography.

11. The composition of claim 6, wherein said enteric coating layer comprises polymers based on methacrylic acid and methacrylic acid esters consisting of methacrylic acid copolymer type A or type B or type C or any combination thereof.

12. The composition of claim 1, wherein said disintegrant is selected from the group consisting of sodium starch glycolate, crospovidone, pregelatinized starch, cross-linked carboxymethylcellulose, cross-linked starch, cross-linked polyvinyl pyrrolidone, methacrylic acid DVP and croscarmellose sodium.

13. The composition of claim 12, wherein said disintegrant is mixed with an inert pharmaceutical filler.

14. The composition of claim 13, wherein said inert pharmaceutical filler is selected from the group consisting of lactose, starch, and microcrystalline cellulose.

15. The composition of claim 3, wherein said disintegrant is selected from the group consisting of sodium starch glycolate, crospovidone, pregelatinized starch, cross-linked carboxymethyl cellulose, cross-linked polyvinyl pyrrolidone, methacrylic acid DVP and croscarmellose sodium.

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

2020
Bogotá, D.C.,

Abogado
J IAN RAISBECK LLINÁS
Apoderado

ASUNTO

Radicación 06-018321
Trámite 002
Evento 001
Actuación 430
Oficio 11128
Folios 13

Patente de Invención ☒ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

Vía PCT (fase nacional) ☒ Cap. I ☒ Cap. II ☐

No. Sol. Internacional PCT/EP2004/009726

Fecha de Presentación Internal. 06 de Agosto de 2004

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

1. Documentos estudiados

Descripción: Folios: 29 a 48 y 51 como se radicó inicialmente

Reivindicaciones: Folios 49 a 50 como se radicó inicialmente

Prioridad: Folios: 1
02 de Septiembre de 2003, GB, 032050522.6

2. Análisis de la Prioridad

La fecha de prioridad del 02 de Septiembre de 2003 y su correspondiente documento, son aceptados para el estudio de patentabilidad.

3. Objeto de la Invención

Título de la solicitud: formulación farmacéutica que comprende un derivado pirimidina-A-ona y una cubierta que comprende un polímero entérico

El objeto de la presente solicitud de patente de invención consiste obtener una composición farmacéutica de un derivado pirimidina-A-ona y una cubierta que comprende un polímero entérico

El problema planteado en esta solicitud es proveer una formulación farmacéutica de pirimidina-A-ona en tableta cubierta entérica.