

SEÑORES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISIÓN DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Ref.: Expediente N° 06-003.174

Solicitud de Patente de Invención Titulada: "NUEVOS COMPUESTOS DE INDOL, BENZOFURANO Y BENZOTIOFENO COMO AGENTES ACTIVADORES DE LOS CANALES DE POTASIO DE GRAN CONDUCTANCIA ACTIVADOS POR CALCIO".

Solicitante: SMITHKLINE BEECHAM CORPORATION

SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN
EL ARTÍCULO 44 DE LA DECISION 486, GACETA No. 577

J. IAN RAISBECK, mayor de edad y vecino de Bogotá, D.C., identificado tal como aparece al pie de mi firma, en mi condición de apoderado sustituto tal como 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 36155 de 28 de diciembre 2006.

Atentamente,



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

Anexo: Recibo por \$404.000 pesos
Sustitución

LMB/P2006/000005 70718 Sol exam

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Señores

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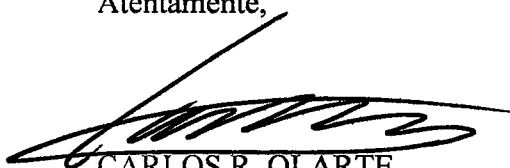
Solicitante: SMITHKLINE BEECHAM CORPORATION

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.

BICHROMOPHORIC BENZOXAZOLE ULTRAVIOLET STABILIZERS

This is a division of Application Ser. No. 615,033 filed Sept. 19, 1975, now U.S. Pat. No. 4,029,670.

This invention relates to bichromophoric heterocyclic ester ultraviolet stabilizers and their use in organic compositions. More particularly, the invention relates to bichromophoric heterocyclic ester compositions and the stabilization of ultraviolet degradable organic compositions against deterioration resulting from the exposure to such radiations with such bichromophoric heterocyclic ester compositions.

The degradative effects of ultraviolet light on various organic compositions is well known in the art. The photo-deterioration or degradation is of particular concern with organic photo-degradable compositions which are exposed to ultraviolet light, such as sunlight, for long periods of time. One group of such photo-degradable organic compositions are polymeric compositions such as polyolefins, polyesters and the like. On exposure to sunlight for extended periods of time, these polymeric compositions degrade and their physical properties are reduced to render the polymeric composition less useful for most applications. Therefore, considerable effort has been directed to providing a solution to the photo-degradation problem of polymeric compositions. As a result of this effort, there have been discovered many additives and stabilizers which improve the stability of polymeric compositions.

Moreover, various additives and stabilizers exhibit the power to absorb ultraviolet radiation within the band of 2900 to 4000 Å. and, when incorporated in various plastic materials such as transparent sheets, the resultant sheet acts as a filter for all the radiation passing through and will transmit only such radiations as are not absorbed by the sheet and/or the absorbing agent. It is thus possible to screen out undesirable radiations and utilize the resulting transparent sheet as a filter in many technical and commercial applications, such as wrappings for food products and the like.

While there are many additives, stabilizers and mixtures thereof which are known in the art to improve the ultraviolet light stability of organic compositions, there is a need in the art for more efficient and effective stabilizers to prevent the photo-degradation of organic compositions susceptible to photo-degradation. Therefore, to provide a more effective and efficient ultraviolet stabilizer for organic compositions susceptible to such degradation would be an advance in the state of the art.

It is, therefore, an object of the present invention to provide more effective and efficient ultraviolet light stabilizer compositions.

Another object of the present invention is to provide useful compositions characterized by improved resistance to ultraviolet degradation and deterioration.

It is still another object of the present invention to provide compositions containing bichromophoric compositions which are resistant to ultraviolet degradation.

It is a still further object of this invention to provide processes for improving the resistance of organic materials to deterioration and degradation by actinic radiation and especially ultraviolet radiation.

It is a still further object of this invention to provide compositions and processes for improving the resistance of organic materials to deterioration and degradation

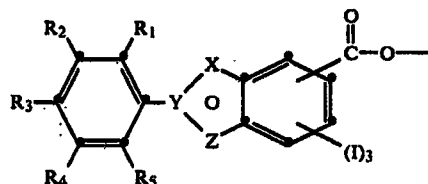
tion by actinic radiations, including short wave-length visible radiations.

Further objects and advantages of the invention will be apparent to those skilled in the art from the accompanying disclosure and claims.

In accordance with the present invention, bichromophoric heterocyclic ester compositions are provided which are useful as ultraviolet stabilizers or ultraviolet screening agents. These organic compositions contain at least one heterocyclic group containing composition connected through a carboxyl group to an aromatic ring which, upon exposure to ultraviolet light, may undergo the "photo-Fries" rearrangement. The polychromophoric compositions of the present invention have the following structure:

(A)—C

wherein A is a group having the structure:



wherein

X and Y are a carbon atom, a carbon atom containing an R group, or a nitrogen atom;

Z is an oxygen atom, a sulfur atom, a nitrogen atom, a nitrogen atom containing a hydrogen atom or a substituted or unsubstituted lower alkyl group having 1 to 12 carbon atoms;

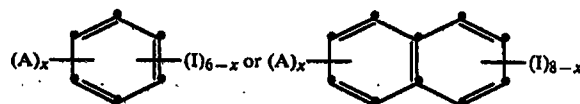
R, R₁, R₂, R₃, R₄ and R₅ are hydrogen, lower alkyl, substituted lower alkyl, cycloalkyl, substituted cycloalkyl, aryl, halogen, substituted aryl, lower alkylaryl, aryl-substituted-aryl, alkoxy, carboxy, nitrile carboalkoxy, and the substituents R₁ and R₂, R₂ and R₃, and R₃ and R₄, combined with the carbon atoms to which they are attached, are joined alkylene groups completing a carboxylic ring which can be substituted with any of the substituents listed above for R₁, R₂, R₃ and R₄.

I is a substituent listed above for R₁, R₂, R₃ and R₄ and is present on all positions of the benzenoid ring, except the carbon atom attached to the heterocyclic ring and the carbon atom attached to the carboxyl group connecting the heterocyclic aromatic A group with the aromatic C group. At least one I substituent on one of the carbon atoms adjacent to the carbon atom attached to the carbonyl group is hydrogen and the remaining I substituents can all be the same or different.

x is an integer of 1 to 4; and

C is:

(a) an aromatic group having the formula



where I is the same substituent as listed above and is present in all positions of the benzenoid ring except the carbon atom attached to the carbonyl group connecting the A and C moieties, and said I substituents can all be

The present invention relates to compounds of formula (I) which are non-peptide antagonists of GnRH which can be used to treat a variety of sex-hormone related conditions in men and women, to methods for their preparation, and to methods and pharmaceutical compositions containing said compounds for use in mammals.

- substituted aryl, aralkyl, substituted aralkyl, $R_{11}O(CH_2)_p$, $R_{11}C(O)O(CH_2)_p$, $R_{11}OC(O)(CH_2)_p$, $-(CH_2)_pS(O)_nR_{17}$, $-(CH_2)_pC(O)NR_{11}R_{12}$ or halogen; wherein R_{17} is hydrogen, C_1 - C_6 alkyl, C_1 - C_3 perfluoroalkyl, aryl or substituted aryl;
- 5 R_3 and R_4 taken together form a carbocyclic ring of 3-7 carbon atoms or a heterocyclic ring containing 1-3 heteroatoms selected from N, O and S;
- R_6 is hydrogen, C_1 - C_6 alkyl, substituted C_1 - C_6 alkyl, aryl, substituted aryl, C_1 - C_3 perfluoroalkyl, CN, NO_2 , halogen, $R_{11}O(CH_2)_p$, $NR_{21}C(O)R_{20}$, $NR_{21}C(O)NR_{20}R_{21}$ or SO_nR_{20} ;
- 10 R_7 is hydrogen, C_1 - C_6 alkyl, or substituted C_1 - C_6 alkyl, unless X is hydrogen or halogen, then R_7 is absent;
- R_8 is $C(O)OR_{20}$, $C(O)NR_{20}R_{21}$, $NR_{20}R_{21}$, $C(O)R_{20}$, $NR_{21}C(O)R_{20}$, $NR_{21}C(O)NR_{20}R_{21}$, $NR_{20}S(O)_2R_{21}$, $NR_{21}S(O)_2NR_{20}R_{21}$, $OC(O)R_{20}$, $OC(O)NR_{20}R_{21}$, OR_{20} , SO_nR_{20} , $S(O)_nNR_{20}R_{21}$, a
- 15 heterocyclic ring or bicyclic heterocyclic ring with from 1 to 4 heteroatoms selected from N, O or S which can be optionally substituted by R_3 , R_4 and R_5 , C_1 - C_6 alkyl or substituted C_1 - C_6 alkyl; or
- 20 R_7 and R_8 taken together form a heterocyclic ring containing one or more heteroatoms selected from N, O or S which can be optionally substituted by R_3 , R_4 and R_5 ;
- R_9 and R_{9a} are independently hydrogen, C_1 - C_6 alkyl, substituted C_1 - C_6 alkyl; aryl or substituted aryl, aralkyl or substituted aralkyl
- 25 when $m \neq 0$; or
- R_9 and R_{9a} taken together form a carbocyclic ring of 3-7 atoms or 
- when $m \neq 0$;
- R_9 and A taken together form a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms when $m \neq 0$; or
- 30 R_{10} and R_{10a} are independently hydrogen, C_1 - C_6 alkyl, substituted C_1 - C_6 alkyl, aryl, substituted aryl, aralkyl or substituted aralkyl; or

- R₁₀ and R_{10a} taken together form a carbocyclic ring of 3-7 atoms or  ;
 R₉ and R₁₀ taken together form a carbocyclic ring of 3-7 carbon atoms or
 a heterocyclic ring containing one or more heteroatoms
 when m≠0; or
- 5 R₉ and R₂ taken together form a heterocyclic ring containing 3-7 carbon
 atoms and one or more heteroatoms when m≠0; or
 R₁₀ and R₂ taken together form a heterocyclic ring containing 3-7 carbon
 atoms and one or more heteroatoms;
- 10 R₁₀ and A taken together form a heterocyclic ring containing 3-7 carbon
 atoms and one or more heteroatoms; or
 R₁₁ and R₁₂ are independently hydrogen, C₁-C₆ alkyl, substituted C₁-
 C₆ alkyl, aryl, substituted aryl, aralkyl, substituted aralkyl, a
 carbocyclic ring of 3-7 atoms or a substituted carbocyclic ring
 containing 3-7 atoms;
- 15 R₁₁ and R₁₂ taken together can form an optionally substituted ring of 3-7
 atoms;
- R₁₃ is hydrogen, OH, NR₇R₈, NR₁₁SO₂(C₁-C₆ alkyl),
 NR₁₁SO₂(substituted C₁-C₆ alkyl), NR₁₁SO₂(aryl),
 NR₁₁SO₂(substituted aryl), NR₁₁SO₂(C₁-C₃ perfluoroalkyl);
 20 SO₂NR₁₁(C₁-C₆ alkyl), SO₂NR₁₁(substituted C₁-C₆ alkyl),
 SO₂NR₁₁(aryl), SO₂NR₁₁(substituted aryl), SO₂NR₁₁(C₁-C₃
 perfluoroalkyl); SO₂NR₁₁(C(O)C₁-C₆ alkyl); SO₂NR₁₁(C(O)-
 substituted C₁-C₆ alkyl); SO₂NR₁₁(C(O)-aryl);
 SO₂NR₁₁(C(O)-substituted aryl); S(O)_n(C₁-C₆ alkyl); S(O)_n
 25 (substituted C₁-C₆ alkyl), S(O)_n(aryl), S(O)_n(substituted
 aryl), C₁-C₃ perfluoroalkyl, C₁-C₃ perfluoroalkoxy, C₁-C₆
 alkoxy, substituted C₁-C₆ alkoxy, COOH, halogen, NO₂ or
 CN;
- 30 R₁₄ and R₁₅ are independently hydrogen, C₁-C₆ alkyl, substituted C₁-C₆
 alkyl, C₂-C₆ alkenyl, substituted C₂-C₆ alkenyl, CN, nitro,
 C₁-C₃ perfluoroalkyl, C₁-C₃ perfluoroalkoxy, aryl,
 substituted aryl, aralkyl, substituted aralkyl, R₁₁O(CH₂)_p-,
 R₁₁C(O)O(CH₂)_p-, R₁₁OC(O)(CH₂)_p-, -(CH₂)_pS(O)_nR₁₇, -

FACTOR VIIA INHIBITORS

[0001] This application is based on and claims priority from U.S. Provisional application Ser. No. 60/224,713 filed on Aug. 11, 2000.

FIELD OF INVENTION

[0002] The present invention relates to compounds of Formula I which are useful as factor VIIA (fVIIa) inhibitors.

BACKGROUND OF THE INVENTION

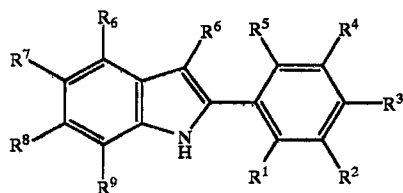
[0003] Factor VIIa (herein after "fVIIa"), the converting enzyme of factor X to factor Xa, has emerged as an alternative target to thrombin or factor Xa for the treatment of thromboembolic disorders. A variety of compounds have been developed as potential fVIIa inhibitors.

[0004] Kunitada and Nagahara in Current Pharmaceutical Design, 1996, Vol. 2, No.5, report amidinobenzyl compounds as fVIIa and thrombin inhibitors. Disclosed in U.S. Pat. No. 5,576,343 are aromatic amidine derivatives and salts thereof, as reversible inhibitors of fVIIa. These compounds comprise amidino substituted indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, naphthyl, tetrahydronaphthyl and indanyl groups, attached to a substituted phenyl ring by an alkylene group having from 1 to 4 carbon atoms.

[0005] In spite of the above discussed efforts, a desirable treatment for thromboembolic disorders based on fVIIa inhibition remains elusive. One of the hurdles that must be overcome to generate an effective therapeutic is the creation of fVIIa inhibitors with desirable pharmaceutical attributes. These attributes, (e.g. clearance, mean residence time in plasma, terminal phase half-life, bioavailability, and solubility) significantly affect the ultimate utility of a fVIIa inhibitors. Potent inhibitors, without drug-like properties are unsuitable as thromboembolic therapies. There is thus a need for novel compounds that will be not only effective in inhibiting blood-clotting enzymes such as fVIIa but will also perform as pharmaceutical agents. We have surprisingly found that compounds of the present invention have desirable clearance, mean residence time and increased terminal phase half-life.

SUMMARY OF THE INVENTION

[0006] The present invention provides compounds of Formula I:



Formula I

[0007] its prodrug forms or pharmaceutically acceptable salts of, wherein

[0008] R¹ represents OH;

[0009] R² represents phenyl or nitrophenyl;

[0010] R³ represents H;

[0011] R⁴ represents (CH₂)₀₋₂-tetrazolyl or (CH₂)₀₋₂-triazolyl;

[0012] R⁵ represents H;

[0013] R⁶ represents H or CH₂-phenyl;

[0014] R⁷ represents amino, amidino or guanidino;

[0015] R⁸ represents H; and

[0016] R⁹ represents H.

DETAILED DESCRIPTION

[0017] The present invention in its preferred embodiment provides a compound of Formula I selected from:

[0018] 2-[2-Hydroxy-5-(1H-tetrazol-5-yl)-biphenyl-3-yl]-1 H-indole-5-carboxamide;

[0019] 2-[2-Hydroxy-3'-nitro-5-(1H-tetrazol-5-yl)-biphenyl-3-yl]-1H-indole-5-carboxamide;

[0020] 2-[2-Hydroxy-3'-nitro-5-(1H-tetrazol-5-ylmethyl)-biphenyl-3-yl]-1H-indole-5-carboxamide;

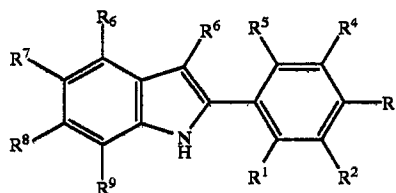
[0021] 2-[2-Hydroxy-5-(1H-tetrazol-5-ylmethyl)-biphenyl-3-yl]-1H-indole-5-carboxamide;

[0022] 2-[2-Hydroxy-5-(3H-[1,2,3]triazol-4-yl)-biphenyl-3-yl]-1H-indole-5-carboxamide; and

[0023] 2-(2-Hydroxy-5-tetrazol-1-yl-biphenyl-3-yl)-1H-indole-5-carboxamide.

[0024] Another preferred embodiment provides a compound of Formula I

Formula I



[0025] its prodrug forms or pharmaceutically acceptable salts of, wherein

[0026] R¹ represents OH;

[0027] R² represents phenyl;

[0028] R³ represents H;

[0029] R⁴ represents tetrazolyl;

[0030] R⁵ represents H;

[0031] R⁶ represents H or CH₂-phenyl;

[0032] R⁷ represents amino, amidino or guanidino;

[0033] R⁸ represents H; and

[0034] R⁹ represents H.

Problema Técnico Planteado: La necesidad de compuestos para el tratamiento de trastornos asociados con activación de los canales de potasio.

Solución: composiciones que contienen derivados de la fórmula (I)

IPC: A61K 31/404; A61K 31/343; A61P13-10

3. De la solicitud de Patente

a. Reivindicaciones (artículo 30 D 486)

La reivindicación 4 reclama una composición que comprende un compuesto de la reivindicación 1. Sin embargo la reivindicación 1 no se refiere a compuestos si no a un método para tratar o inhibir un trastorno, en consecuencia la reivindicación 4 no debe ser dependiente de la reivindicación 1.

Las reivindicaciones 5 y 6 carecen de concisión debido a que no existe una delimitación clara de los sustituyentes arilo y heterociclo de la fórmula (II).

Las reivindicaciones mencionadas no cumplen con el requisito de concisión de acuerdo al art. 30 de la Decisión 486.y/o art.22 Tratado PCT.

4. Excepción a la patentabilidad (artículo 20 D486 literal d)

Las reivindicaciones 1 a 3 reclaman un método para tratar o inhibir un trastorno. Estas reivindicaciones no son patentables.

5. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

Fecha de presentación de la solicitud prioritaria 15-07-2009

Teniendo en cuenta la fecha indicada se realizó la búsqueda en el estado de la técnica de documentos relacionados con la solicitud encontrándose los siguientes documentos más relevantes:

Nº	Documento	Título	Fecha de publicación*
D1	US 4.169.837	BICHROMOPHORIC BENZOXAZOLE ULTRAVIOLET STABILIZERS	2-10-1979
D2	WO 00/04013	ANTAGONISTS OF GONADOTROPIN RELEASING HORMONE	27-01-2000
D3	US 2002/0037912	FACTOR VIIA INHIBITORS	28-03-2002

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R1 = CO ₂ Ra, CONRaRb Ra, b = H, alquil C ₁₋₆ , alquil C ₁₋₆ -heterociclo X = NR _a , O, S B = arilo, heterociclo R ₂ = H, alquil, cicloalquil, heterociclo, CO ₂ Ra R ₃ = carboxi, SO ₃ H	(Col. 2 líneas 15-50)	
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En consecuencia el objeto de las reivindicaciones 4, 5, 6 y 8 no es nuevo a la luz de D1-D3

7. Conclusión

Los requisitos de Patentabilidad de la presente Solicitud se encuentran afectados así:

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	US 4.169.837	4,5,6 y 8	Novedad
D2	WO 00/04013	4,6 y 8	Novedad
D3	US 2002/0037912	4,6 y 8	Novedad

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

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

DORIS ELENA POLO CÓRDOBA
Jefe de División de Nuevas Creaciones (E)

El anterior requerimiento fue notificado por fijación en lista, de fecha 20 MAR. 2009

CONCEPTO TÉCNICO No. 387	EXAMINADOR TÉCNICO Código No. 202073
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