AP 47

Castillo Grau & Asociados
ABOGADOS

Señores

DIVISIÓN DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá, D.C.

SUPERINDUSTRIA Y COMERCIO
Radicacion : 01024184 00000002
Fecha (AMD): 2001-07-04 14:54:18 Folios: 22
Tramite : 002 PATENTES D 1 REGISTRO/ 444 REPUESTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Re.: Código 02-01-444
Expediente No. 01-24.184
Solicitud de Patente
SMITHKLINE BEECHAM CORPORATION

En relación con el expediente de la referencia y dando cumplimiento a la última providencia recaída sobre este asunto por medio del presente escrito me permito manifestarles lo siguiente:

1. Siguiendo precisas instrucciones de mis clientes modifico el título de esta solicitud como sigue:

TRIARILIMIDAZOLES SUSTITUIDOS CON PIRIDILO, METODO PARA SU PREPRACION Y SU USO EN MEDICINA

2. Acompaño el documento que acredita la cesión de los inventores a la sociedad solicitante.

3. La dirección completa de la sociedad solicitante es One Franklin Plaza, Filadelfia, Estado de Pennsylvania, Estados Unidos de América.

4. Adjunto la copias certificada de la solicitud de patente de la cual se reclama prioridad.

5. Acompaño el arte final por triplicado.

6. Igualmente acompaño, debidamente corregidas, la carátula, la hoja de presentación, el extracto y las tarjetas de propietario y archivo temático.

7. Por concepto de exceso de palabras en el extracto adjunto el recibo de pago No. 40.304, y por concepto de modificación de la solicitud acompaño el recibo de pago No. 01/40.294 -

Renuncio al término faltante de traslado, y les solicito ordenar la publicación del extracto.

De Ustedes Atentamente,

GERMAN CASTILLO GRAU

T.P. No. 2978 del C.S.J.

49

Industria y Comercio

SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO
Radicacion : 01024184 00000002 Folios: 22
Fecha (AMD): 2001-07-04 14:54:18
Tramite : 002 PATENTES D 1 REGISTRO/ 444 REPUESTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 01 - 40,301
FECHA : JULIO 4 DE 2001

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CASTILLO GRAU Y ASOCIADOSCONSIGNACION		BANCO POPULAR	050-00110-6	4103879	04/07/2001	1,898,860.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
150	50005-01-01 SOLICITUDES	9 POR PALABRA ADICIONAL (A PARTIR D	81,000.00
		TOTAL : $	81,000.00

SON: OCHENTA Y UNO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Carrera 13 No. 27-00 Pisos 5, 7 y 10
Conmutador 382 0840
Fax 350 5220
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

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Industria y Comercio

SUPERINTENDENCIA

NIT : 800176089-2

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Radicacion : 01024184 00000002 Folios: 22
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Tramite : 002 PATENTES D 1 REGISTRO/ 444 REPUESTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

RECIBO OFICIAL DE CAJA : 01 - 40,294
FECHA : JULIO 4 DE 2001

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CASTILLO GRAU Y ASOCIADOSCONSIGNACION	BANCO POPULAR	050-00110-6	4103879	04/07/2001	1,898,880.00	

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-03 CAMBIO DE MODALIDAD Y MODIFICA	12 MARCAS Y LEMAS COMERCIALES		73,440.00
		TOTAL :	$	73,440.00

SON: SETENTA Y TRES MIL CUATROCIENTOS CUARENTA PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Carrera 13 No. 27-00 Pisos 5, 7 y 10
Conmutador 382 0840
Fax 350 5220
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

Y , el infrascrito, **JOHN DAVID WOODWARD**, Notario Público de la Ciudad de Londres, Inglaterra, por la Autoridad Real debidamente admitido y juramentado,

C E R T I F I C O:

QUE son auténticas las firmas "John David Harling" y "Laramie Mary Gaster" suscritas al pie de la adjunta Cesión, por haberlas puesto los Señores Don **JOHN DAVID HARLING** y Don **LARAMIE MARY GASTER**, cuyas identidades me constan.

Y PARA QUE CONSTE donde y como convenga y fuere necesario, expido la presente que firmo y sello en dicha Ciudad de Londres, el día de hoy veintinueve de mayo del año dos mil uno.

SCRIVENER NOTARIES

APOSTILLE

(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

1. Country: United Kingdom of Great Britain and Northern Ireland
   Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

   This public document / Le présent acte public

2. Has been signed by — John David Woodward
   a été signé par

3. Acting in the capacity of — Notary Public
   agissant en qualité de

4. Bears the seal/stamp of — The Said Notary Public
   est revêtu du sceau/timbre de

Certified/Attesté

5. at London/à Londres

6. the/le 30 May 2001

7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
   par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

8. Number/sous No G899141

9. Stamp: timbre:

10. Signature: A. Beckwith

For the Secretary of State / Pour le Secrétaire d'Etat

P32548

Castillo Grau & Associates
Law Offices
P Box 251473
Bogota
Colombia

ASSIGNMENT

The undersigned, John David HARLING and Laramie Mary GASTER, of GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW, United Kingdom hereby appoint DR GERMAN CASTILLO GRAU and/or Dr ADRIANA CASTILLO GIBSONE and/or Dr LUIS FELIPE CASTILLO GISBONE, domiciled in Bogotá, Colombia, with offices at Carrera 13 No. 37-43, 12th Floor in Bogotá, as attorney with ample and sufficient power, including that of receiving notifications and appointing judicial and extra-judicial attorneys, to apply for and obtain from the Colombian offices and authorities Patent of Invention for 'COMPOUNDS' to be issued in the name of SmithKline Corporation, domiciled in Philadelphia, Pennsylvania, USA, to whom assignment has been made of all rights and titles on said invention without any restrction whatsoever.

Given and signed at *(place)* HARLOW, U.K

Date: 17th May 2001

John David Harling
John David HARLING

Laramie Mary Gaster
Laramie Mary GASTER

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed P. Mahoney

Dated 15 May 2001

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Patents Form 1/77

Patents Act 1977
(Rule 16)

THE PATENT OFFICE
D
27 MAR 2000
LONDON

The Patent Office

1/77

28MAR00 E524512-2 D02029
P01/7700 0.00-0007405.4

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office
Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference — AJB/PMS/P32548

2. Patent application number
(The Patent Office will fill in his part) — **0007405.4** — 27 MAR 2000

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

SmithKline Beecham Corporation
One Franklin Plaza, P.O. Box 7929, Philadelphia, Pennsylvania 19103, USA

Patents ADP number *(if you know it)* 5949417001

If the applicant is a corporate body, give the country/state of its incorporation — United States of America

4. Title of the invention — Compounds

5. Name of your agent *(if you have one)* — CORPORATE INTELLECTUAL PROPERTY

"Address for service" in the United Kingdom to which all correspondence should be sent
(including the postcode)

SMITHKLINE BEECHAM PLC
TWO NEW HORIZONS COURT
BRENTFORD
MIDDLESEX TW8 9EP

Patents ADP number *(if you know it)* 5800974004

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is named as an applicant, or
c) any named applicant is a corporate body
See note (d)

R

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	0
Description	16
Claim(s)	3
Abstract	1
Drawings	0

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10. If you are also filing any of the following, state how many against each item.

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 1/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

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11. We request the grant of a patent on the basis of this application

Signature Alison Blakey Date 27-Mar-00

A J Blakey

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12. Name and daytime telephone number of person to contact in the United Kingdom

A J Blakey 01279 644355

Warning

After an application for a Patent has beeen filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission unless an application has been filed at least six weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505

b) Write your answers in capital letters using black ink or you may type them.

c) If there is not enough space for all relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.

d) If you have answered 'Yes' Patents Form 7/77 will need to be filed.

f) For details of the fee and ways to pay please contact the Patent Office.

57

56

COMPOUNDS

This invention relates to pyridyl substituted triarylimidazoles which are inhibitors of the transforming growth factor, ("TGF")-ß signaling pathway, in particular, the phosphorylation of smad2 or smad3 by the TGF-β type I or activin-like kinase ("ALK")-5 receptor, methods for their preparation and their use in medicine, specifically in the treatment and prevention of a disease state mediated by this pathway.

TGF-β1 is the prototypic member of a family of cytokines including the TGF-ßs, activins, inhibins, bone morphogenetic proteins and Müllerian-inhibiting substance, that signal through a family of single transmembrane serine/threonine kinase receptors. These receptors can be divided in two classes, the type I or activin like kinase (ALK) receptors and type II receptors. The ALK receptors are distinguished from the type II receptors in that the ALK receptors (a) lack the serine/threonine rich intracellular tail, (b) possess serine/threonine kinase domains that are very homologous between type I receptors, and (c) share a common sequence motif called the GS domain, consisting of a region rich in glycine and serine residues. The GS domain is at the amino terminal end of the intracellular kinase domain and is critical for activation by the type II receptor. Several studies have shown that TGF-β signaling requires both the ALK and type II receptors. Specifically, the type II receptor phosphorylates the GS domain of the type I receptor for TGF-β, ALK5, in the presence of TGF-β. The ALK5, in turn, phosphorylates the cytoplasmic proteins smad2 and smad3 at two carboxy terminal serines. Generally it is believed that in many species, the type II receptors regulate cell proliferation and the type I receptors regulate matrix production. Therefore, preferred compounds of this invention are selective in that they inhibit the type I receptor and thus matrix production, and not the type II receptor mediated proliferation.

Activation of the TGF-β1 axis and expansion of extracellular matrix are early and persistent contributors to the development and progression of chronic renal disease and vascular disease. Border W.A., Noble N.A., *N. Engl. J. Med.*, Nov. 10, 1994; 331(19):1286-92. Further, TGF-β1 plays a role in the formation of fibronectin and plasminogen activator inhibitor-1, components of sclerotic deposits, through the action of smad3 phosphorylation by the TGF-β1 receptor ALK5. Zhang Y., Feng X.H., Derynck R., *Nature*, Aug. 27, 1998; 394(6696):909-13; Usui T., Takase M., Kaji Y., Suzuki K., Ishida K., Tsuru T., Miyata K., Kawabata M., Yamashita H., *Invest. Ophthalmol. Vis. Sci.*, Oct. 1998; 39(11):1981-9.

Progressive fibrosis in the kidney and cardiovascular system is a major cause of suffering and death and an important contributor to the cost of health care. TGF-β1 has been implicated in many renal fibrotic disorders. Border W.A., Noble N.A., *N. Engl. J. Med.*, Nov 10, 1994; 331(19):1286-92. TGF-β1 is elevated in acute and chronic glomerulonephritis, Yoshioka K., Takemura T., Murakami K., Okada M., Hino S., Miyamoto H., Maki S., *Lab. Invest.*, Feb. 1993; 68(2):154-63, diabetic nephropathy, Yamamoto, T., Nakamura, T., Noble, N.A., Ruoslahti, E., Border, W.A., (1993) *PNAS* 90:1814-1818, allograft rejection, HIV nephropathy and angiotensin-induced nephropathy, Border W.A., Noble N.A., *N. Engl. J. Med.*, Nov. 10, 1994; 331(19):1286-92. In these diseases the levels of TGF-β1 expression coincide with the production of extracellular matrix. Three lines of evidence suggest a causal relationship between TGF-β1 and the production of matrix. First, normal glomeruli, mesangial cells and non-renal cells can be induced to produce extracellular-matrix protein and inhibit protease activity by

9

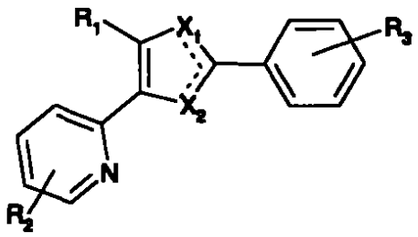
exogenous TGF-β1 in vitro. Second, neutralizing anti-bodies against TGF-β1 can prevent the accumulation of extracellular matrix in nephritic rats. Third, TGF-β1 transgenic mice or in vivo transfection of the TGF-β1 gene into normal rat kidneys resulted in the rapid development of glomerulosclerosis. Kopp J.B., Factor V.M., Mozes M., Nagy P., Sanderson N., Bottinger E.P., Klotman P.E., Thorgeirsson S.S., *Lab Invest*, June 1996; 74(6):991-1003. Thus, inhibition of TGF-β1 activity is indicated as a therapeutic intervention in chronic renal disease.

TGF-β1 and its receptors are increased in injured blood vessels and are indicated in neointima formation following balloon angioplasty, Saltis J., Agrotis A., Bobik A., *Clin Exp Pharmacol Physiol*, Mar. 1996; 23(3):193-200. In addition TGF-β1 is a potent stimulator of smooth muscle cell ("SMC") migration in vitro and migration of SMC in the arterial wall is a contributing factor in the pathogenesis of atherosclerosis and restenosis. Moreover, in multivariate analysis of the endothelial cell products against total cholesterol, TGF-β receptor ALK5 correlated with total cholesterol ($P < 0.001$) Blann A.D., Wang J.M., Wilson P.B., Kumar S., *Atherosclerosis*, Feb. 1996; 120(1-2):221-6. Furthermore, SMC derived from human atherosclerotic lesions have an increased ALK5/TGF-β type II receptor ratio. Because TGF-β1 is over-expressed in fibroproliferative vascular lesions, receptor-variant cells would be allowed to grow in a slow, but uncontrolled fashion, while overproducing extracellular matrix components McCaffrey T.A., Consigli S., Du B., Falcone D.J., Sanborn T.A., Spokojny A.M., Bush H.L., Jr., *J Clin Invest*, Dec. 1995; 96(6):2667-75. TGF-β1 was immunolocalized to non-foamy macrophages in atherosclerotic lesions where active matrix synthesis occurs, suggesting that non-foamy macrophages may participate in modulating matrix gene expression in atherosclerotic remodeling via a TGF-β-dependent mechanism. Therefore, inhibiting the action of TGF-β1 on ALK5 is also indicated in atherosclerosis and restenosis.

TGF-β is also implicated in peritoneal adhesions Saed G.M., Zhang W., Chegini N., Holmdahl L., and Diamond MP., *Wound Repair Regeneration. 7(6):504-510, 1999 Nov-Dec.* Therefore, inhibitors of ALK5 would be beneficial in preventing peritoneal and sub-dermal fibrotic adhesions following surgical procedures.

Surprisingly, it has now been discovered that a class of 2-pyridyl substituted triarylimidazoles of formula (I), function as potent and selective non-peptide inhibitors of ALK5 kinase and therefore, have utility in the treatment and prevention of various disease states mediated by ALK5 kinase mechanisms, such as chronic renal disease, acute renal disease, wound healing, arthritis, osteoporosis, kidney disease, congestive heart failure, ulcers, occular disorders, corneal wounds, diabetic nephropathy, impaired neurological function, Alzheimer's disease, trophic conditions, atherosclerosis, peritoneal and sub-dermal adhesion, any disease wherein fibrosis is a major component, including, but not limited to lung fibrosis and liver fibrosis, and restenosis.

According to the invention there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein R_1 is naphthyl or phenyl optionally substituted with one or more substituents selected from the group consisting of halo, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, C_{1-6}alkyl, C_{1-6}haloalkyl, -O-$(CH_2)_n$-Ph, -S-$(CH_2)_n$-Ph, cyano, phenyl, and CO_2R, wherein R is hydrogen or C_{1-6}alkyl, and n is 0, 1, 2 or 3; or R_1 is phenyl fused with an aromatic or non-aromatic cyclic ring of 5-7 members wherein said cyclic ring optionally contains up to three heteroatoms, independently selected from N, O and S;

R_2 is H, C_{1-6}alkyl, C_{1-6}alkoxy, phenyl, $NH(CH_2)_n$-Ph, NH-C_{1-6}alkyl, halo, or alkoxy;

R_3 is COOH, tetrazole, CN, NO_2, OH, -S-C_{1-6}alkyl, -SO-C_{1-6}alkyl, -O-C_{1-6}alkyl, $SONH_2$, CHO, CH_2OH, $(CH_2)_nNH_2$, CONHOR', $O(CH_2)_nCO_2R'$, $O(CH_2)_nCONHR'$, CONHR', $(CH_2)_nCO_2R'$, or $(CH_2)_nCONHR'$ wherein R' is hydrogen or C_{1-6}alkyl, and n is 0, 1, 2 or 3; and

one of X_1 and X_2 is N or CR", and the other is NR" or CHR" wherein R" is hydrogen, C_{1-6}alkyl, or C_{3-7}cycloalkyl; or when one of X_1 and X_2 is N or CR" then the other may be S or O;

provided that the compound is not one in which R_1 is naphthyl or phenyl optionally substituted with one or more substituents selected from the group consisting of halo, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, C_{1-6}alkyl, -O-$(CH_2)_n$-Ph, -S-$(CH_2)_n$-Ph, cyano, phenyl, and CO_2R, wherein R is hydrogen or C_{1-6}alkyl and n is 0, 1, 2 or 3; or R_1 is phenyl fused with an aromatic or non-aromatic cyclic ring of 5-7 members wherein said cyclic ring optionally contains up to two heteroatoms, independently selected from N, O and S;

and R_2 is H, $NH(CH_2)_n$-Ph or NH-C_{1-6}alkyl;

and R_3 is CO_2H, $CONH_2$, CN, NO_2, C_{1-6}alkylthio, SO_2-C_{1-6}alkyl, C_{1-6}alkoxy, $SONH_2$, CONHOH, NH_2, CHO, CH_2OH, CH_2NH_2, or CO_2R, wherein R is hydrogen or C_{1-6}alkyl.

As used herein, the double bond indicated by the dotted lines of formula (I), represent the possible tautomeric ring forms of the compounds falling within the scope of this invention. It will be understood that when either X_1 or X_2 are carbon, then the double bond could be either to the carbon or the heteroatom. When X_1 and X_2 are both carbon, then the double bond could be to either X_1 or X_2. When X_1 and X_2 are both heteroatoms, then the double bond is to the unsubstituted heteroatom.

Preferably R_1 is optionally substituted naphthyl or phenyl. More preferably R_1 is phenyl optionally substituted with one or more substituents selected from the group consisting of halo, C_{1-6}alkoxy, C_{1-6}alkylthio, and phenyl; or R_1 is phenyl fused with an aromatic or non-aromatic cyclic ring of 5-7 members wherein said cyclic ring optionally contains up to two heteroatoms, independently selected from N, O and S, for example R_1 represents benzo[1,3]dioxolyl, 2,3-dihydrobenzo[1,4]dioxinyl, benzoxazolyl, benzothiazolyl, benzo[1,2,5]oxadiazolyl, benzo[1,2,5]thiadiazolyl, quinoxalinyl, or dihydrobenzofuranyl.

Preferably, R_2 is positioned ortho to the nitrogen of the pyridyl ring.

Preferably R_3 is CO_2H, $CONH_2$, CONHOH, CH_2OH, CN or tetrazole.

Preferably one of X_1 and X_2 is N or CR", and the other is NR" or CHR' wherein R" is hydrogen, C_{1-6}alkyl, or C_{3-7}cycloalkyl, provided that at least one of X_1 and X_2 is N or NR"; or one of one of X_1 and X_2 is N and the other is O. More preferably one of X_1 and X_2 is N and the other is NR".

Preferably each R" is hydrogen.

Specific compounds of the invention which may be mentioned includethe following and pharmaceutically acceptable salts thereof:

4-(4-Benzo[1,3]dioxol-5-yl-5-pyridin-2-yl-1*H*-imidazol-2-yl)phenol;

4-(4-Benzo[1,3]dioxol-5-yl-5-pyridin-2-yl-1*H*-imidazol-2-yl)-N-methyl-benzamide;

4-(4-Benzo[1,3]dioxol-5-yl-5-pyridin-2-yl-1*H*-imidazol-2-yl)-N-methoxy-benzamide;

2-{4-Benzo[1,3]dioxol-5-yl-2-[4-(2-*H*-tetrazol-5-yl)-phenyl]-1*H*-imidazol-5-yl}-pyridine;

[4-(4-Benzo[1,3]dioxol-5-yl-5-pyridin-2-yl-1*H*-imidazol-2-yl)-phenoxy]-acetic acid;

4-[4-(4-Fluoro-3-methoxyphenyl)-5-(6-methylpyridin-2-yl)-1-*H*-imidazol-2-yl]-benzonitrile;

4-[4-(4-Fluoro-3-methoxyphenyl)-5-(6-methylpyridin-2-yl)-1-*H*-imidazol-2-yl]-benzamide;

4-[4-(3-Fluoro-4-methoxyphenyl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl]benzonitrile;

4-[4-(3-Fluoro-4-methoxyphenyl)-5-(6-methylpyridin-2-yl)-1H-imidazol-2-yl]benzamide;

4-[4-Benzo[1,2,5]oxadiazol-5-yl-5-(6-methyl-pyridin-2-yl)-1H-imidazol-2-yl]benzonitrile;

4-[4-Benzo[1,2,5]oxadiazol-5-yl-5-(6-methylpyridin-2-yl)-1H-imidazol-2-yl]benzamide;

4-[4-(6-Methoxynaphthalen-2-yl)-5-(6-methylpyridin-2-yl)-1H-imidazol-2-yl]benzonitrile;

4-[4-(6-Methoxynaphthalen-2-yl)-5-(6-methylpyridin-2-yl)-1H-imidazol-2-yl]benzamide;

4-[4-Benzo[1,2,5]thiadiazol-5-yl-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl]benzonitrile;

4-[4-Benzo[1,2,5]thiadiazol-5-yl-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl]benzamide;

4-[4-Benzo[1,3]dioxol-5-yl-5-(6-methylpyridin-2-yl-1*H*-imidazol-2-yl] benzonitrile; and

4-[4-Benzo[1,3]dioxol-5-yl-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl]benzamide;

and pharmaceutically acceptable salts thereof.

Suitable, pharmaceutically acceptable salts of the compounds of formula (I) include, but are not limited to, salts with inorganic acids such as hydrochloride, sulfate, phosphate, diphosphate, hydrobromide, and nitrate, or salts with an organic acid such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methanesulfonate, p-toluenesulfonate, palmitate, salicylate, and stearate.

Some of the compounds of this invention may be crystallised or recrystallised from solvents such as aqueous and organic solvents. In such cases solvates may be formed. This invention includes within its scope stoichiometric solvates including hydrates as well as

compounds containing variable amounts of water that may be produced by processes such as lyophilisation.

Certain of the compounds of formula (I) may exist in the form of optical isomers, e.g. diastereoisomers and mixtures of isomers in all ratios, e.g. racemic mixtures. The invention includes all such forms, in particular the pure isomeric forms. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions; these less pure preparations of the compounds should contain at least 1%, more suitably at least 5% and preferably from 10 to 59% of a compound of the formula (I) or pharmaceutically acceptable derivative thereof.

The term "C_{1-6}alkyl" as used herein whether on its own or as part of a larger group e.g. C_{1-6}alkoxy, means a straight or branched chain radical of 1 to 6 carbon atoms, unless the chain length is limited thereto, including, but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl and tert-butyl.

C_{1-6} haloalkyl groups may contain one or more halo atoms, a particular C_{1-6} haloalkyl group that may be mentioned in CF_3.

The terms "halo" or "halogen" are used interchangeably herein to mean radicals derived from the elements chlorine, fluorine, iodine and bromine.

The term "cycloalkyl" is used herein at all occurrences to mean cyclic radicals, preferably of 3 to 7 carbons, including but not limited to cyclopropyl, cyclopentyl and cyclohexyl.

The term "aryl" is used herein at all occurrences to mean 5- to 14-membered substituted or unsubstituted aromatic ring(s) or ring systems which may include bi- or tri-cyclic systems, including, but not limited to phenyl, naphthyl.

The term "ALK5 inhibitor" is used herein at all occurrences to mean a compound, other than inhibitory smads, e.g. smad6 and smad7, which selectively inhibits the ALK5 receptor preferentially over p38 or type II receptors.

The term "ALK5 mediated disease state" is used herein at all occurrences to mean any disease state which is mediated (or modulated) by ALK5, for example a disease which is modulated by the inhibition of the phosphorylation of smad 2/3 in the TGF-1ß signaling pathway.

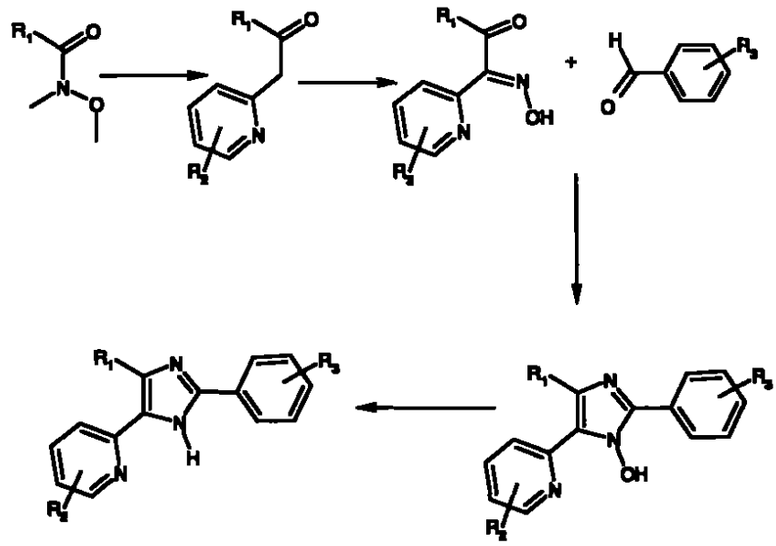
The term "ulcers" is used herein at all occurrences to include, but not to be limited to, diabetic ulcers, chronic ulcers, gastric ulcers, and duodenal ulcers.

The compounds of formula (I) can be prepared by art-recognized procedures from known or commercially available starting materials. If the starting materials are unavailable from a commercial source, their synthesis is described herein, or they can be prepared by procedures known in the art.

Specifically, compounds of formula (I) wherein one of X_1 and X_2 is N and the other is NH may be prepared as illustrated in Scheme 1 for compounds wherein X_1 is N and X_2 is NH.

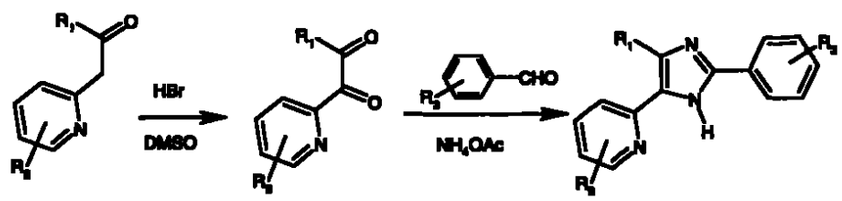
Using the method detailed in US 3,940,486, N-methoxy-N-methylaryl amide is alkylated with the anion generated from a 2(6)-methylpyridine to give a ketone. The ketone is treated with sodium nitrite to form the oxime which is condensed with an aldehyde and NH_4OAc to give a hydroxy imidazole. The hydroxy imidazole may then be reduced with triphenylphosphite by the method described in US 5,656,644 to give the corresponding imidazole. The hydroxy imidazoles used as intermediates in this reaction are also novel and as such form part of the present invention.

Scheme 1



Alternatively, the ketone may be oxidised to a diketone with HBr in DMSO. This diketone can then be condensed with a suitably substituted benzaldeyde and ammonium acetate to give the imidazole according to the method outlined in WO 98/56788 and as illustrated in Scheme 2 for compounds wherein X_1 is N and X_2 is NH.

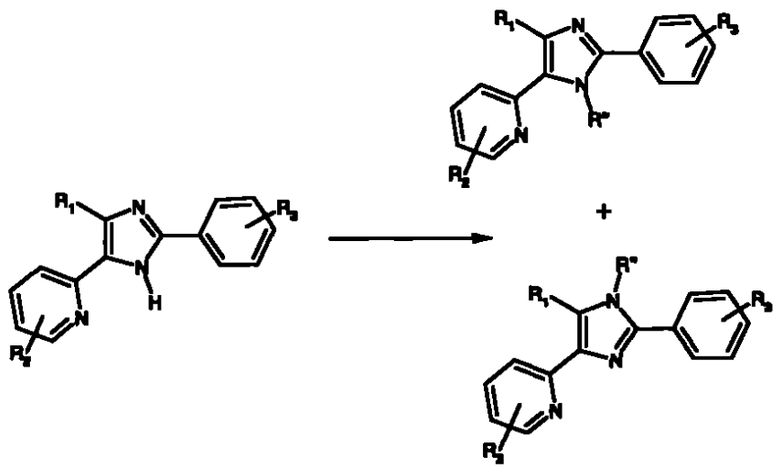
Scheme 2



Non-selective alkylation of the imidazole nitrogen (using one of the procedures outlined in N. J. Liverton et al; *J. Med. Chem.*, 1999, 42, 2180-2190) with a compound of formula L-R" wherein L is a leaving group, e.g. halo, sulfonate or triflate, will yield both isomers of the compounds where one of X_1 or X_2 is NR" wherein R" is C_{1-6}alkyl, or C_{3-7}cycloalkyl, as illustrated in Scheme 3, the isomers can be separated by chromatographic methods.

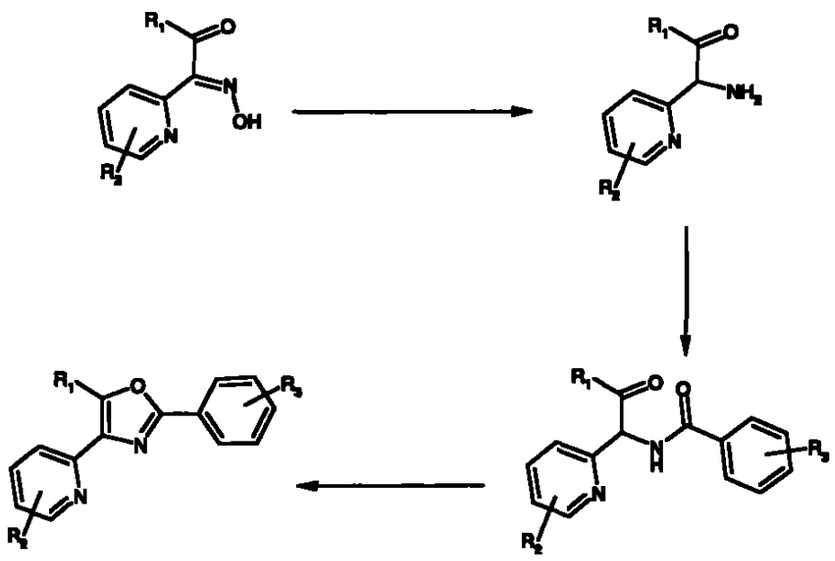
12

Scheme 3



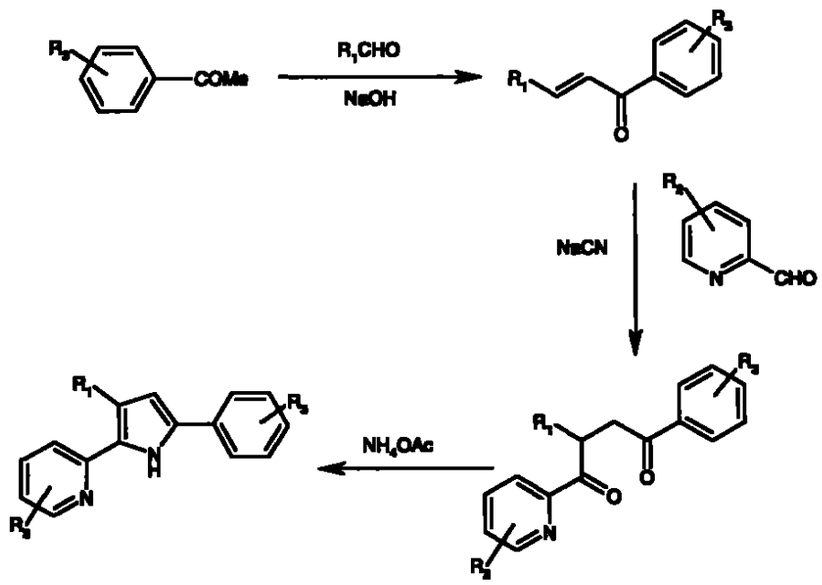
Compounds of formula (I) wherein one of X_1 and X_2 is N and the other is O may be prepared according to Scheme 4. The oximino ketone may be reduced via catalytic hydrogen to afford the amino ketone which can be further reacted with an appropriately substituted benzoyl chloride compound. Reaction of the amide product with thionyl chloride affords the oxazole product.

Scheme 4



Compounds of formula (I) where one of X_1 and X_2 is CH or CHR" may be prepared according to Scheme 5. A suitably substituted acetophenone and a benzaldehyde are condensed under basic conditions to afford the enone aldol product. This enone is then reacted with a pyridine-2-carboxaldehyde under sodium cyanide catalysis to afford the 1,4-diketone which is condensed with ammonium acetate to afford the pyrrole.

Scheme 5



During the synthesis of the compounds of formula (I) labile functional groups in the intermediate compounds, e.g. hydroxy, carboxy and amino groups, may be protected. A comprehensive discussion of the ways in which various labile functional groups groups may be protected and methods for cleaving the resulting protected derivatives is given in for example *Protective Groups in Organic Chemistry,* T.W. Greene and P.G.M. Wuts, (Wiley-Interscience, New York, 2nd edition, 1991).

Further details for the preparation of compounds of formula (I) are found in the examples.

The compounds of formula (I) may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000 compounds, and more preferably 10 to 100 compounds of formula (I). Libraries of compounds of formula (I) may be prepared by a combinatorial 'split and mix' approach or by multiple parallel synthesis using either solution phase or solid phase chemistry, by procedures known to those skilled in the art.

Thus according to a further aspect of the invention there is provided a compound library comprising at least 2 compounds of formula (I) or pharmaceutically acceptable salts thereof.

According to a further aspect of the present invention there is provided the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease mediated by the ALK5 receptor in mammals.

ALK5-mediated disease states, include, but are not limited to, chronic renal disease, acute renal disease, wound healing, arthritis, osteoporosis, kidney disease, congestive heart failure, ulcers, ocular disorders, corneal wounds, diabetic nephropathy, impaired neurological function, Alzheimer's disease, trophic conditions, atherosclerosis, any disease wherein fibrosis is a major component, including, but not limited to peritoneal and sub-dermal adhesion, lung fibrosis and liver fibrosis, and restenosis.

By the term "treating" is meant either prophylactic or therapeutic therapy.

According to a further aspect of the present invention there is provided a method of inhibiting the TGF-ß signaling pathway in mammals, for example, inhibiting the phosphorylation of smad2 or smad3 by the type I or activin-like kinase ALK5 receptor.

According to a further aspect of the present invention there is provided a method of inhibiting matrix formation in mammals by inhibiting the TGF-β signalling pathway, for example, inhibiting the phosphorylation of smad2 or smad3 by the type I or activin-like kinase ALK5 receptor.

The pharmaceutically effective compounds of formula (I) and pharmaceutically acceptable salts thereof, may be administered in conventional dosage forms prepared by combining a compound of formula (I) ("active ingredient") with standard pharmaceutical carriers or diluents according to conventional procedures well known in the art. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

According to a further aspect of the present invention there is provided a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

The pharmaceutical compositions of the invention may be formulated for administration by any route, and include those in a form adapted for oral, topical or parenteral administration to mammals including humans.

The compositions may be formulated for administration by any route. The compositions may be in the form of tablets, capsules, powders, granules, lozenges, creams or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

The topical formulations of the present invention may be presented as, for instance, ointments, creams or lotions, eye ointments and eye or ear drops, impregnated dressings and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams.

The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from about 1% up to about 98% of the formulation. More usually they will form up to about 80% of the formulation.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils),

for example almond oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxybenzoate or sorbic acid, and, if desired, conventional flavouring or colouring agents.

Suppositories will contain conventional suppository bases, e.g. cocoa-butter or other glyceride.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing.

Advantageously, agents such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain from 0.1% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration. Where the compositions comprise dosage units, each unit will preferably contain from 50-500 mg of the active ingredient. The dosage as employed for adult human treatment will preferably range from 100 to 3000 mg per day, for instance 1500 mg per day depending on the route and frequency of administration. Such a dosage corresponds to 1.5 to 50 mg/kg per day. Suitably the dosage is from 5 to 20 mg/kg per day.

It will be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a formula (I) compound will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular mammal being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of the formula (I) compound given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

No toxicological effects are indicated when a compound of formula (I) or a pharmaceutically acceptable derivative thereof is administered in the above-mentioned dosage range.

All publications, including, but not limited to, patents and patent applications cited in this specification, are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following examples are to be construed as merely illustrative and not a limitation on the scope of the invention in any way. In the Examples, mass spectra were performed using an

Hitachi Perkin-Elmer RMU-6E with chemical ionization technique (CI) or a Micromass Platform II instrument with electrospray (ES) ionization technique.

EXAMPLES

Example 1: 4-(4-Benzo[1,3]dioxol-5-yl-5-pyridin-2-yl-1*H*-imidazol-2-yl)phenol

The title compound was prepared from 4-Benzo[1,3]dioxol-5-yl-2-(4-hydroxyphenyl-5-pyridin-2-ylimidazol-1-ol using the procedure in U.S. Patent 5,656,644 (Example 1) to prepare 2-(4-cyanophenyl)-4-(4-fluorophenyl)-5-(4-pyridyl)-1*H*-imidazole. ^{1}H NMR (250 MHz; CD_3OD) δ: 5.92 (2H, s), 6.83 - 6.98 (5H, m), 7.35 - 7.45 (2H, m), 7.74 - 7.82 (3H, m), 8.59 (1H, d): m/z [ESMS]: 358.1 $[M+H]^{\oplus}$.

Example 2: 4-(4-Benzo[1,3]dioxol-5-yl-5-pyridin-2-yl-1*H*-imidazol-2-yl)-N-methyl-benzamide

4-(4-Benzo[1,3]dioxol-5-yl-5-pyridin-2-yl-1*H*-imidazol-2-yl)benzoyl chloride hydrochloride (100 mg; 0.23 mmol) was suspended in tetrahydrofuran (5 ml) and treated with a solution of methylamine in water (40% w/v; ml) and the resulting mixture stirred at ambient temperature for 18 h. The title compound (55 mg; 60%) was obtained as a brown powder by filtration, washing with water and drying at 40°C under reduced pressure. ^{1}H NMR (250 MHz; CD_3OD) δ: 2.84 (3H, s), 5.89 (2H, s), 6.76 (1H, d), 6.85 - 7.80 (5H, m), 7.82 (2H, d), 8.00 (2H, d), 8.49 (1H, br); m/z (ESMS): 399 $[M+H]^{\oplus}$

Example 3: 4-(4-Benzo[1,3]dioxol-5-yl-5-pyridin-2-yl-1*H*-imidazol-2-yl)-N-methoxy-benzamide

4-(4-Benzo[1,3]dioxol-5-yl-5-pyridin-2-yl-1H-imidazol-2-yl)benzoyl chloride hydrochloride (100 mg; 0.23 mmol) was suspended in dichloromethane (10 ml), N,O-dimethyl hydroxylamine hydrochloride (38 mg; 0.45 mmol) added followed by triethylamine (0.16 ml; 1.1 mmol). The resulting mixture was stirred at ambient temperature for 18 h. The mixture was evaporated to dryness under reduced pressure and the residue partitioned between ethyl acetate and water. The organic phase was washed with water, saturated brine, dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The title compound (4 mg; 4%) was obtained by high performance liquid chromatography. ^{1}H NMR (250 MHz; CD_3OD) δ: 3.74 (3H, s), 6.00 (2H, s), 6.94 (1H, d,), 7.04 - 7.08 (2H, m), 7.50 - 7.70 (2H, m), 7.85 (2H, d), 8.00 - 8.20 (3H, m), 8.59 (1H, d); m/z (ESMS): 415.1 $[M+H]^{\oplus}$

Example 4: 2-[4-Benzo[1,3]dioxol-5-yl-2-[4-(2-*H*-tetrazol-5-yl)-phenyl]-1*H*-imidazol-5-yl]-pyridine

Prepared according to the method of Example 1 from 2-[4-benzo[1,3]dioxol-5-yl-5-pyridin-2-yl-2-[4-(1*H*-tetrazol-5-yl)-phenyl]imidazol-1-ol (19%). ^{1}H NMR (250 MHz; CD_3OD) δ: 6.03 (2H, s), 6.96 - 7.12 (3H, m), 7.59 - 7.74 (2H, m), 8.10 - 8.25 (5H, m), 8.61 - 8.63 (1H, m); m/z [ESMS]: 382.0 $[M+H-N_2]^{\oplus}$

Example 5: [4-(4-Benzo[1,3]dioxol-5-yl-5-pyridin-2-yl-1*H*-imidazol-2-yl)-phenoxy]-acetic acid

4-(4-Benzo[1,3]dioxol-5-yl-5-pyridin-2-yl-1H-imidazol-2-yl)-phenol (357 mg; 1 mmol) was dissolved in tetrahydrofuran (20 ml) under argon and treated portionwise with sodium hydride (60% dispersion in oil; 60 mg; 1.5 mmol). When effervescence had ceased, bromoacetonitrile (178.5 mg; 103.5 µl; 1.5 mmol) was added and the mixture was stirred at ambient temperature for 18h. Saturated aqueous ammonium chloride solution was added and the nitrile extracted into ethyl acetate. The organic extracts were combined, washed with water, saturated brine, dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The residue was purified by chromatography through SiO_2, eluting with ethyl acetate in 60 - 80° petroleum ether (50 → 100% ethyl acetate gradient), to give [4-(4-benzo[1,3]dioxol-5-yl-5-pyridin-2-yl-1H-imidazol-2-yl)-phenoxy]-acetonitrile (120 mg; 30 %). This nitrile (120 mg; 0.31 mmol) was treated with ethanol (30 ml) and 2M aq. sodium hydroxide solution and the resulting mixture heated at reflux for 3h. Cooled and evaporated to dryness under reduced pressure. The residue was treated with water and acidified to pH4 - 5 with 5M hydrochloric acid. The yellow precipitate was collected by filtration, washed with water and dried at 40°C under reduced pressure (92mg; 73%). ^1H NMR (250 MHz; CD_3OD) δ: 4.77 (2H, s), 6.12 (2H, s), 7.02 (1H, d), 7.12 - 7.14 (2H, m), 7.18 (2H, d), 7.44 - 7.49 (1H, m), 7.60 (1H, d), 7.86 - 7.92 (1H, m), 8.05 (2H, d), 8.72 (1H, d); m/z (API): 416.3 $[M+H]^{\oplus}$

Example 6: 4-[4-(4-Fluoro-3-methoxyphenyl)-5-(6-methylpyridin-2-yl)-1-*H*-imidazol-2-yl]-benzonitrile

Prepared according to the method of Example 1 from 4-[4-(fluoro-3-methoxyphenyl)-1-hydroxy-5-(6-methylpyridin-2-yl)-1-*H*-imidazol-2-yl]-benzonitrile. ^1H NMR ($CDCl_3$) δ: 2.51 (3H, s), 3.91 (3H, s), 7.02-7.16 (3H, m), 7.33 (2H, d), 7.50 (1H, t), 7.69 (2H, d), 8.06 (2H, d, 8Hz); m/z (API) 385 ($M+H^+$)

Example 7: 4-[4-(4-Fluoro-3-methoxyphenyl)-5-(6-methylpyridin-2-yl)-1-*H*-imidazol-2-yl]-benzamide

4-[4-(Fluoro-3-methoxyphenyl)-5-(6-methylpyridin-2-yl)-1-*H*-imidazol-2-yl]-benzonitrile (1g, 2.6mmol) (prepared according to the method of Example 1) and potassium hydroxide (0.53g) were added to tert-butanol (50ml) and heated overnight at reflux. On cooling, the solid mixture was diluted with ethyl acetate and evaporate *in vacuo*. The residue was then partitioned between dichloromethane and water. The organic phase was dried over sodium sulfate and concentrated *in vacuo* to afford the title compound. ^1H NMR($CDCl_3$) δ: 2.57 (3H, s), 3.91 (3H, s), 7.01 (1H, d), 7.09-7.21 (2H, m), 7.33 (2H, d), 7.46 (1H, t), 7.90 (2H, d), 8.06 (2H, d); m/z (API) 403 ($M+H^+$).

Example 8: 4-[4-(3-Fluoro-4-methoxyphenyl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl]benzonitrile

Prepared according to the method of Example 1 from 4-[4-(3-Fluoro-4-methoxyphenyl)-1-hydroxy-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl]benzonitrile. ^1H NMR ($CDCl_3$) δ: (2.48 (3H, s), 3.96 (3H, s), 7.00-7.08 (2H, m), 7.30-7.57 (4H, m), 7.67 (2H, d), 8.03 (2H, d); m/z (API) 405 ($M+H^+$, 100%).

Example 9: 4-[4-(3-Fluoro-4-methoxy-phenyl)-5-(6-methyl-pyridin-2-yl)-1H-imidazol-2-yl]benzamide

Prepared according to the method of Example 7 from 4-[4-(3-fluoro-4-methoxy-phenyl)-5-(6-methyl-pyridin-2-yl)-1H-imidazol-2-yl]benzonitrile. ^{1}H NMR ($CDCl_3$) δ: 2.57 (3H, s), 3.96 (3H, s), 7.00-7.09 (2H, m), 7.32 (1H, d), 7.39-7.50 (3H, m), 7.89 (2H, d), 8.05 (2H, d); $^m/_z$(API) 403 ($M+H^+$, 100%).

Example 10: 4-[4-Benzo[1,2,5]oxadiazol-5-yl-5-(6-methyl-pyridin-2-yl)-1H-imidazol-2-yl]benzonitrile

Prepared according to the method of Example 1 from 4-[4-benzo[1,2,5]oxadiazol-5-yl-1-hydroxy-5-(6-methyl-pyridin-2-yl)-1H-imidazol-2-yl]benzonitrile. ^{1}H NMR ($CDCl_3$) δ: 2.66 (3H, s), 6.85-6.97 (1H, m), 7.39 (1H, d), 7.52-7.76 (1H, m), 7.75 (3H, t), 7.87 (1H, d), 7.92-7.98 (1H, m), 8.12 (2H, d); $^m/_z$(API) 379 ($M+H^+$,100%).

Example 11: 4-[4-Benzo[1,2,5]oxadiazol-5-yl-5-(6-methyl-pyridin-2-yl)-1H-imidazol-2-yl]benzamide

Prepared according to the mehod of Example 7 from 4-[4-benzo[1,2,5] oxadiazol-5-yl-5-(6-methyl-pyridin-2-yl)-1H-imidazol-2-yl]benzonitrile; $^m/_z$ (API) 397.

Example 12: 4-[4-(6-Methoxynaphthalen-2-yl)-5-(6-methylpyridin-2-yl)-1H-imidazol-2-yl]benzonitrile

Prepared according to the method of Example 1 from 4-[4-(6-methoxynaphthalen-2-yl)-1-hydroxy-5-(6-methylpyridin-2-yl)-1H-imidazol-2-yl]benzonitrile. ^{1}H NMR ($CDCl_3$) δ: 2.79 (3H, s), 3.92 (3H, s), 7.27 (1H, d), 7.45 (1H, s), 7.45 (1H, s), 7.54 (1H, d), 7.68 (2H, d), 7.88-7.98 (2H, m), 8.07 (2H, d), 8.17 (2H, t), 8.25 (1H, s), 8.45 (2H, d); $^m/_z$(API) 417 ($M+H^+$,100%)

Example 13: 4-[4-(6-Methoxynaphthalen-2-yl)-5-(6-methylpyridin-2-yl)-1H-imidazol-2-yl]benzamide

Prepared according to the method of Example 7 from 4-[4-(6-methoxynaphthalen-2-yl)-5-(6-methylpyridin-2-yl)-1H-imidazol-2-yl]benzonitrile. ^{1}H NMR ($CDCl_3$) δ: 2.75 (1H, s), 3.92 (1H, s), 7.27 (1H, d), 7.43-7.71 (4H, m), 7.88-7.97 (2H, m), 8.10 (2H, d), 8.17-8.24 (2H,m), 8.26 (1H,s), 8.36 (2H, d); $^m/_z$(API) 435 ($M+H^+$,100%)

Example 14: 4-[4-Benzo[1,2,5]thiadizol-5-yl-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl]benzonitrile

1-Benzo[1,2,5]thiadiazol-5-y1-2-(6-methyl-pyridin-2-y1)-ethane-1,2-dione (5.2g, 18.4mmol) was dissolved in *tert*-butyl methyl ether (100ml) and treated with 4-cyanobenzaldehyde (2.4g). Ammonium acetate (14.2g) in methanol (20 ml) was added and the reaction was heated at reflux temperature for 3 hours. The reaction mixture was partitioned between dichloromethane and water then, dichloromethane and brine. The dichloromethane layer was separated, dried ($MgSO_4$) and evaporated to dryness under reduce pressure. The title compound was isolated by silica gel column chromatography using a 1:1 ethyl acetate: petroleum spirit solution as eluent (

400mg, 5.5%). ^{1}H NMR ($CDCl_3$) δ: 2.60 (3H, s), 7.08 (2H, d), 7.47-7.53 (2H,m), 7.77 (2H, d), 7.95-8.17 (4H, m), 8.38 (1H, s); m/z (API) 395 ($M+H^+$,100%)

Example 15: 4-[4-Benzo[1,2,5]thiadizol-5-yl-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl]benzamide

Prepared according to the method of Example 7 from 4-[4-benzo [1,2,5]thiadizol-5-yl-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl]benzonitrile. ^{1}H NMR ($CDCl_3$) δ: 2.44 (3H, s), 6.94 (2H, d), 7.12 (1H, s), 7.58 (1H, t), 7.81 (2H, d), 8.13 (1H, d), 8.32 (1H, s), 8.57-8.64 (1H, m), 8.95 (1H, s); m/z (API) 413 ($M+H^+$, 100%).

Example 16: 4-[4-Benzo[1,3]dioxol-5-yl-5-(6-methylpyridin-2-yl-1*H*-imidazol-2-yl] benzonitrile

Prepared according to the method of Example 1 from 4-[4-benzo[1,3]dioxol-5-yl-1-hydroxy-5-(6-methylpyridin-2-yl-1*H*-imidazol-2-yl] benzonitrile. ^{1}H NMR ($CDCl_3$) δ: 2.48 (3H, s), 6.03 (2H, d), 6.88 (1H, d), 7.00 (2H, d), 7.14 (1H, s), 7.17 (1H, d), 7.37 (1H, d), 7.49 (1H, t), 7.68 (2H, d), 8.02 (2H, d); m\z (API) 381 ($M+H^+$).

Example 17: 4-[4-Benzo[1,3]dioxol-5-yl-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl]benzamide

Prepared according to the method of Example 7 from 4-[4-benzo[1,3]dioxol-5-yl-5-(6-methylpyridin-2-yl-1*H*-imidazol-2-yl] benzonitrile. ^{1}H NMR ($CDCl_3$) δ: 2.48 (3H, s), 5.66 (1H, br. s), 6.01 (2H, d), 6.01 (1H, brs), 6.86 (1H, d), 6.98 (2H, d), 7.14 (2H, m), 7.33 (1H, d), 7.46 (1H, t), 7.77 (2H, d), 7.94 (2H, d); m\z (API) 399 ($M+H^+$).

INTERMEDIATES

Preparation 1: 4-(4-Benzo[1,3]dioxol-5-yl-5-pyridin-2-yl-1*H*-imidazol-2-yl)benzoyl chloride

4-(4-Benzo[1,3]dioxol-5-yl-5-pyridin-2-yl-1*H*-imidazol-2-yl)benzoic acid (prepared according to the method of Example 1) (379mg; 0.98mmol) was suspended in dry dichloromethane (20ml) and treated with oxalyl chloride (2ml) and N,N-dimethylformamide (1 drop). This mixture was stirred at ambient temperature for 5h then evaporated to dryness under reduced pressure to give the title compound as a yellow powder.

Preparation 2: 1-Benzo[1,2,5]thiadiazol-5-y1-2-(6-methyl-pyridin-2-y1)-ethane-1,2-dione

1-Benzo[1,2,5]thiadiazol-5-y1-2-(6-methyl-pyridin-2-y1)-ethanone (5.88g, 21.8mmol) was dissolved in dimethyl sulfoxide (50 ml) heated to 60 °C. Hydrogen bromide (7.1ml of a 48% solution in water) was added dropwise and the reaction stirred for 3 hours at 60 °C. The cooled reaction was poured into water (100 ml) and the pH adjusted to pH 8 with saturated sodium bicarbonate solution. The organic product was extracted into ethyl acetate (3 x 100 ml), dried over anhydrous magnesium sulfate and evaporated to dryness under reduced pressure (5.19g, 84%); ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.47 (3H, s), 7.40 (1H, d), 7.85 (1H, t), 8.06 (1H, d), 8.15 (1H, d), 8.28 (1H, d), 8.45 (1H, s); m/z (API) 284 ($M+H^+$,100%)

Biological Data

The biological activity of the compounds of the invention may be assessed using the following assays:

Method for evaluating ALK5 kinase phosphorylation of smad3

Basic Flash-Plates (NEN Life Sciences) were coated by pipetting 100 micro liter of 0.1 molar sodium bicarbonate (pH 7.6), containing 150 nanograms of the fusion protein glutathion-S-transferase-smad3/100 micro liter of coating buffer. Plates were covered and incubated at room temperature for 10-24 hours. Then the plates were washed 2 times with 200 micro liter of coating buffer (0.1 molar sodium bicarbonate) and allowed to air dry for 2-4 hours.

For the phosphorylation reaction each well received 90 microliter containing 50 millimolar HEPES buffer (pH 7.4); 5 millimolar $MgCl_2$; 1 millimolar $CaCl_2$; 1 millimolar dithiothreitol; 100 micromolar guanosine triphosphate; 0.5 micro Ci/well gamma^{33}P-adenosine triphosphate (NEN Life Sciences) and 400 nanograms of a fusion protein of glutathion –S-transferase at the N-terminal end of the kinase domain of ALK5 (GST-ALK5). Background counts were measured by not adding any GST-ALK5. Inhibitors of ALK5 were evaluated by determining the activity of the enzyme in the presence of various compounds. Plates were incubated for 3 hours at 30°C. After incubation the assay buffer was removed by aspiration and the wells were washed 3 times with 200 microliter cold 10 millimolar sodium pyrophosphate in phosphate buffered saline. The last wash was aspirated and blotted plate dry. Plate was then counted on a Packard TopCount.

Inhibition of Matrix Markers: Western Blot Protocol

Data confirming activity in the enzyme assay was obtained as follows.

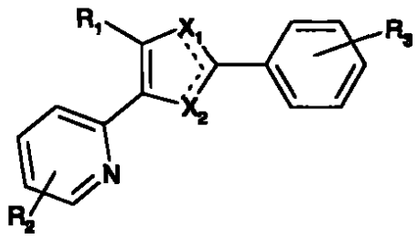
Cells were grown to near confluence in flasks, starved overnight and treated with TGF-beta and compounds. Cells were washed at 24 or 48 hours after treatment with ice cold phosphate buffered saline, then 500 microliter of 2X loading buffer was added to plate and cells were scraped and collected in microcentrifuge tube. (2X loading buffer: 100 mM Tris-Cl, pH6.8, 4% sodium dodecyl sulfate, 0.2% bromophenol blue, 20% glycerol, 5% beta-mercapto-ethanol). Cells were lysed in tube and vortexed. Sample was boiled for 10 minutes. 20 microliters of sample was loaded on 7.5% polyacrylamide gel (BioRad) and electrophoresed.

Size fractionated proteins in gel were transferred to nitrocellulose membrane by semidry blotting. Membrane was blocked overnight with 5% powdered milk in phosphate buffer saline (PBS) and 0.05% Tween-20 at 4 degrees C. After 3 washes with PBS/Tween membranes were incubated with primary antibody for 4 hours at room temperature. After three washes with PBS/Tween membrane was incubated with secondary antibody for 1 hour at room temperature. Finally, a signal was visualized with ECL detection kit from Amersham.

The compounds of this invention generally show ALK5 receptor modulator activity having IC_{50} values in the range of 0.0001 to 10 μM.

Claims:

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein R_1 is naphthyl, or phenyl optionally substituted with one or more substituents selected from the group consisting of halo, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, C_{1-6}alkyl, C_{1-4}haloalkyl, -O-$(CH_2)_n$-Ph, -S-$(CH_2)_n$-Ph, cyano, phenyl, and CO_2R, wherein R is hydrogen or C_{1-6}alkyl, and n is 0, 1, 2 or 3; or R_1 is phenyl fused with an aromatic or non-aromatic cyclic ring of 5-7 members wherein said cyclic ring optionally contains up to three heteroatoms, independently selected from N, O and S;

R_2 is H, C_{1-6}alkyl, C_{1-6}alkoxy, phenyl, $NH(CH_2)_n$-Ph, NH-C_{1-6}alkyl, halo or alkoxy;

R_3 is COOH, tetrazole, CN, NO_2, OH, -S-C_{1-6}alkyl, -SO-C_{1-6}alkyl, -O-C_{1-6}alkyl, $SONH_2$, CHO, CH_2OH, $(CH_2)_nNH_2$, CONHOR', $O(CH_2)_nCO_2R'$, $O(CH_2)_nCONHR'$, CONHR', $(CH_2)_nCO_2R'$, or $(CH_2)_nCONHR'$ wherein R' is hydrogen or C_{1-6}alkyl, and n is 0, 1, 2 or 3; and

one of X_1 and X_2 is N or CR", and the other is NR" or CHR" wherein R" is hydrogen, C_{1-6}alkyl, or C_{3-7}cycloalkyl; or when one of X_1 and X_2 is N or CR" then the other may be S or O;

provided that the compound is not one in which R_1 is naphthyl, or phenyl optionally substituted with one or more substituents selected from the group consisting of halo, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, C_{1-6}alkyl, -O-$(CH_2)_n$-Ph, -S-$(CH_2)_n$-Ph, cyano, phenyl, and CO_2R, wherein R is hydrogen or C_{1-6}alkyl and n is 0, 1, 2 or 3; or R_1 is phenyl fused with an aromatic or non-aromatic cyclic ring of 5-7 members wherein said cyclic ring optionally contains up to two heteroatoms, independently selected from N, O and S;

and R_2 is H, $NH(CH_2)_n$-Ph or NH-C_{1-6}alkyl; and

and R_3 is CO_2H, $CONH_2$, CN, NO_2, C_{1-6}alkylthio, SO_2-C_{1-6}alkyl, C_{1-6}alkoxy, $SONH_2$, CONHOH, NH_2, CHO, CH_2OH, CH_2NH_2, or CO_2R, wherein R is hydrogen or C_{1-6}alkyl.

2. A compound according to claim 1 wherein R_1 is phenyl optionally substituted with one or more substituents selected from the group consisting of halo, C_{1-6}alkoxy, C_{1-6}alkylthio, and phenyl; or R_1 is phenyl fused with an aromatic or non-aromatic cyclic ring of 5-7 members wherein said cyclic ring optionally contains up to two heteroatoms, independently selected from N, O and S.

3. A compound according to claim 1 or 2 wherein R_2 is positioned ortho to the nitrogen of the pyridyl ring.

4. A compound according to any one of the preceding claims wherein R_3 is CO_2H, $CONH_2$, CONHOH, CH_2OH, CN or tetrazole.

5. A compound according to any one of the preceding claims wherein one of X_1 and X_2 is N or CR", and the other is NR" or CHR" wherein R" is hydrogen, C_{1-6}alkyl, or C_{3-7}cycloalkyl, provided that at least one of X_1 and X_2 is N or NR"; or one of one of X_1 and X_2 is N and the other is O.

6. A compound according to claim 5 wherein one of X_1 and X_2 is N and the other is NR".

7. A compound according to any one of the preceding claims wherein each R' is hydrogen.

8. A compound according to claim 1 selected from:
4-(4-Benzo[1,3]dioxol-5-yl-5-pyridin-2-yl-1*H*-imidazol-2-yl)phenol;
4-(4-Benzo[1,3]dioxol-5-yl-5-pyridin-2-yl-1*H*-imidazol-2-yl)-N-methyl-benzamide;
4-(4-Benzo[1,3]dioxol-5-yl-5-pyridin-2-yl-1*H*-imidazol-2-yl)-N-methoxy-benzamide;
2-{4-Benzo[1,3]dioxol-5-yl-2-[4-(2-*H*-tetrazol-5-yl)-phenyl]-1*H*-imidazol-5-yl}-pyridine;
[4-(4-Benzo[1,3]dioxol-5-yl-5-pyridin-2-yl-1*H*-imidazol-2-yl)-phenoxy]-acetic acid;
4-[4-(4-Fluoro-3-methoxyphenyl)-5-(6-methylpyridin-2-yl)-1-*H*-imidazol-2-yl]-benzonitrile;
4-[4-(4-Fluoro-3-methoxyphenyl)-5-(6-methylpyridin-2-yl)-1-*H*-imidazol-2-yl]-benzamide;
4-[4-(3-Fluoro-4-methoxyphenyl)-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl]benzonitrile;
4-[4-(3-Fluoro-4-methoxyphenyl)-5-(6-methylpyridin-2-yl)-1H-imidazol-2-yl]benzamide;
4-[4-Benzo[1,2,5]oxadiazol-5-yl-5-(6-methyl-pyridin-2-yl)-1H-imidazol-2-yl]benzonitrile;
4-[4-Benzo[1,2,5]oxadiazol-5-yl-5-(6-methylpyridin-2-yl)-1H-imidazol-2-yl]benzamide;
4-[4-(6-Methoxynaphthalen-2-yl)-5-(6-methylpyridin-2-yl)-1H-imidazol-2-yl]benzonitrile;
4-[4-(6-Methoxynaphthalen-2-yl)-5-(6-methylpyridin-2-yl)-1H-imidazol-2-yl]benzamide;
4-[4-Benzo[1,2,5]thiadiazol-5-yl-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl]benzonitrile;
4-[4-Benzo[1,2,5]thiadiazol-5-yl-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl]benzamide;
4-[4-Benzo[1,3]dioxol-5-yl-5-(6-methylpyridin-2-yl-1*H*-imidazol-2-yl] benzonitrile; and
4-[4-Benzo[1,3]dioxol-5-yl-5-(6-methylpyridin-2-yl)-1*H*-imidazol-2-yl]benzamide;
and pharmacutically acceptable salts thereof.

9. A pharmaceutical composition comprising a compound according to any one of the claims 1 to 8, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

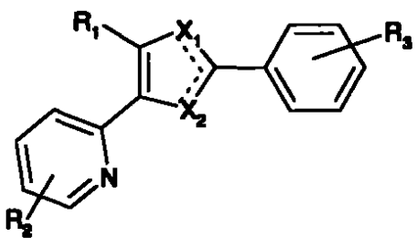
10. A method of inhibiting the TGF-8 signaling pathway in mammals, comprising administering to a mammal, comprising administering to a mammal in need of such treatment, a therapeutically effective amount of a compound according to any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof.

11. A method for treating a disease selected from chronic renal disease, acute renal disease, wound healing, arthritis, osteoporosis, kidney disease, congestive heart failure, ulcers, ocular disorders, corneal wounds, diabetic nephropathy, impaired neurological function, Alzheimer's disease, trophic conditions, atherosclerosis, peritoneal and sub-dermal adhesion, any disease wherein fibrosis is a major component, and restenosis, comprising administering to a mammal in need of such treatment, a therapeutically effective amount of a compound according to any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof.

12. A method for inhibiting matrix formation in mammals, comprising administering to a mammal, a therapeutically effective amount of a compound according to any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof.

ABSTRACT
TRIARYLIMIDAZOLES

Compounds of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein R_1, R_2 and R_3 are various substituent groups; and

one of X_1 and X_2 is N or CR", and the other is NR" or CHR" wherein R" is hydrogen, OH, C_{1-4}alkyl, or C_{3-7}cycloalkyl; or when one of X_1 and X_2 is N or CR" then the other may be S or O;

and their use as pharmaceuticals.

Se extraen folios 72 y 73 correspondientes a tarjetas

Angelly 11-DIC/02

Se extraen folios 70 y 71 correspondiente a extracto de publicacion

[redacted]

FORMATO DE DIGITALIZACION
RELACION DE ANEXOS

Reynl Technologies S.A.

67

Item	Expediente No	01024184 No de unidades	No de Folio
1	CD		
2	DVD		
3	REVISTA		
4	LIBRO		
5	PERIODICO		
6	DISQUETES		
7	SOBRE DE MANILA		
8	SOBRE BLANCO TAMAÑO CARTA		
9	SOBRE BLANCO TAMAÑO OFICIO X	1	✓
10	OTROS:		

Observaciones: un sobre 9 contiene arte final

Industria y Comercio
SUPERINTENDENCIA

2do. EXAMEN DE FORMA PATENTE DE INVENCION

Folio 74

Radicación no 01 24184

Concepto Técnico no 1859
Clasificación Internacional de Patentes: A61K 31/435 // 31/41

Practicado el examen de acuerdo a lo establecido en el Art. 38 de la Decisión 486 se determinó que esta solicitud de Patente de Invención:

SI [✔] NO [ ] Contiene un resumen de la invención (Art.26-e).

SI [✔] NO [ ] Contiene el título o nombre de la invención (Art.27-d).

SI [✔] NO [ ] Contiene la descripción de la invención (Art.26-b).

SI [✔] NO [ ] NO ES APLICABLE [ ] Contiene los dibujos necesarios para comprender la invención (Art.26-d)

SI [✔] NO [ ] Contiene una o más reivindicaciones. (Art.26-c).

SI [ ] NO [ ] NO ES APLICABLE [✔] Han sido desarrollados los productos y/o procedimientos a partir de recursos genéticos o de sus productos derivados de los que cualquiera de los Países Miembros es país de origen. (Art. 26- h).

SI [ ] NO [ ] NO ES APLICABLE [✔]Los productos y/o procedimientos han sido obtenidos o desarrollados a partir de los conocimientos tradicionales de las comunidades indígenas, afroamericanas, o locales de los países miembros, de acuerdo a lo establecido en la Decisión 391 y sus modificaciones y reglamentaciones vigentes.(Art.26-I).

SI [ ] NO [✔] La invención se refiere a un producto relativo a un material biológico. (Art.26-J).

SI [✔] NO [ ] La prioridad coincide con la materia reivindicada.

SI [✔] NO [ ] CUMPLE LOS REQUISITOS TÉCNICOS

OBSERVACIONES Y OTROS: SI [ ] NO [✔] ver hoja(s) anexa(s)

EXAMINADOR TÉCNICO
202048

Bogotá D. C., . enero 15 del 2002

Carrera 13 No. 27-00 Piso 5 y 10
Conmutador: 334 12 21-2-3-4
Fax: 281 31 25 e-mail: info@sic.gov.co
Santa Fe de Bogotá D.C. - Colombia

Industria y Comercio
SUPERINTENDENCIA

Folio: 75

2020
Bogotá DC

Doctor(a)
GERMAN CASTILLO GRAU
Apoderado(a)

REFERENCIA:	Radicación No.	01-24184
	Trámite	002
	Evento	001
	Actuación	416
	Oficio No.	2353
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en los artículos 26 y 27 de la Decisión 486 de la Comisión de la Comunidad Andina, y en las demás disposiciones vigentes sobre la materia, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial, conforme lo establece el artículo 40 de la misma Decisión.

Cúmplase
Dado en Bogotá DC, a los 30 ENE 2003

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

202048

528.

Carrera 13 No. 27-00 Piso 5 y 10
Conmutador: 334 12 21-2-3-4
Fax: 281 31 28 e-mail: info@sic.gov.co
Santa Fe de Bogotá D.C. - Colombia