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AVISO DE NOTIFICACION

CORREO CERTIFICADO

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Radicación	1-9823- -10-0 Fecha 2006-12-01 08:31 82
Trámite	2 PATENTES
Evento	1 REGDEPOSITO
Actuación	432 COMUNICACTOADM
Destinatario	GUSTAVO TAMAYO ARANGO Folios 1

Señor (a) (es)
GUSTAVO TAMAYO ARANGO
CALLE 72 # 5 - 83 PISO 5
BOGOTA D C

REF RESOLUCION 32789
FECHA 30/11/2006
Expediente 1-9823
Trámite 2 PATENTES DE INVENCION
Evento 1 REGISTRO/DEPOSITO/CONCESION/DEPOSITO
Actuación 432 COMUNICACION ACTO ADMINISTRATIVO

Comedidamente le solicito presentarse a este Despacho ubicado en la Carrera 13 No 27 - 00 Piso Quinto (5), de la ciudad de Bogotá D C , dentro del término de cinco (5) días hábiles contados a partir del envío de la presente citación, en horario de 8 00 a m a 4 30 p m jornada continua, con el fin de notificarle personalmente el contenido de la resolución de la referencia proferida dentro del expediente tramitado con el número de radicación citado en el asunto

De no hacerse presente en el término indicado anteriormente, la providencia en mención se notificará por edicto, el cual se fijará por el término de diez (10) días en el Centro de Documentación e Información

Para su comodidad el texto completo de la resolución se encontrará disponible en la página web de la Entidad desde el día hábil siguiente al de su notificación, la cual podrá ser consultada desde un computador con acceso a Internet, en la página www sic.gov co, con el numero de resolución a través de la opción servicios en línea - caracter general - consulta actos administrativos

Secretaría General

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

140

Industria y Comercio
SUPERINTENDENCIA

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCION 32789

Por la cual se niega una patente de invención

Rad. Nº 01-9823

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
en ejercicio de sus facultades legales, en especial de las que se confieren en el artículo 4, numeral 5 del decreto 2153 de 1992, y

CONSIDERANDO:

PRIMERO: Que mediante escrito radicado en esta Superintendencia el 09 de febrero del 2001, bajo el número 01009823 se presentó la solicitud de patente para la invención denominada "DERIVADOS DE PIRIMIDINA", contenida en el expediente de la referencia

SEGUNDO: Que efectuado el examen de forma en cuanto a los requisitos que debe llenar la solicitud y cumplidas las exigencias legales, se ordenó publicar el extracto sin que se hubieran presentado oposiciones por parte de terceros

TERCERO: Que el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina establece que. *"Si la oficina nacional competente encontrara que la invención no es patentable o que no cumple con alguno de los requisitos establecidos en esta Decisión para la concesión de la patente, lo notificará al solicitante Este deberá responder a la notificación dentro del plazo de sesenta días contados a partir de la fecha de la notificación Este plazo podrá ser prorrogado por una sola vez por un período de treinta días adicionales... si el solicitante no respondiera a la notificación dentro del plazo señalado, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, la oficina nacional competente denegará la patente".*

CUARTO: Que realizado el examen de fondo, se requirió al solicitante en los términos del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, para que presentara respuesta a las observaciones de carácter técnico visibles a folios 149 a 156 del cuaderno administrativo, relacionadas con la patentabilidad o cumplimiento de los requisitos establecidos por esta Decisión para la concesión de la patente Frente a dicho requerimiento no hubo pronunciamiento alguno por parte del mismo, motivo por el cual es procedente negar el privilegio de patente solicitado con fundamento en lo dispuesto en el artículo 45 de la Decisión 486.

RESUELVE

ARTICULO PRIMERO: Negar el privilegio de patente de invención para la solicitud correspondiente a "DERIVADOS DE PIRIMIDINA"

32789

Industria y Comercio
SUPERINTENDENCIA

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCION 32789

Por la cual se niega una patente de invención

Rad Nº 01-9823

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución al doctor Gustavo Tamayo Arango, o a quien haga sus veces, en su calidad de representante legal de Glaxo Group Limited , entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella

NOTIFÍQUESE Y CUMPLASE
Dada en Bogotá, D C , a los 30 NOV. 2006

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,

JAIRO RUBIO ESCOBAR

Doctor
GUSTAVO TAMAYO ARANGO
Calle 72 N° 5 – 83, Piso 5
Bogotá, D C.

2006-21

Glaxo Group L
01.009823

INVESTOR IN PEOPLE

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 R Mahoney

Dated 19 FEB 2001

Patents Form 1/77

Patents Act 1977
(Rule 16)

The Patent Office

1/77

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	GL/TC/PG3915
2	Patent application number *(The Patent office will fill in this part)*	0003224.3
3	Full name, address and postcode of the or of each applicant *(underline all surnames)*	GLAXO GROUP LIMITED GLAXO WELLCOME HOUSE BERKELEY AVENUE GREENFORD MIDDLESEX UB6 ONN GB
	Patents ADP number *(if you know it)*	07355870003
	If the applicant is a corporate body, give the country/state of its corporation	GB
4	Title of the invention	CHEMICAL COMPOUNDS
5	Name of your agent *(if you know one)*	GRAHAM LANE (SEE CONTINUATION SHEET)
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	GLAXO WELLCOME PLC 07164510001 GLAXO WELLCOME HOUSE, BERKELEY AVENUE GREENFORD, MIDDLESEX UB6 ONN, GB
	Patents ADP number *(if you know it)*	

		Country	Priority application number *(if you know it)*	Date of Filing (day / month / year)
6	If you are declaring priority from one or more earlier patent applications, give the country and date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number			

		Number of earlier application	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		

8	Is a statement of inventorship and of right to grant 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 not named as an applicant, or* *c) any named applicant is a corporate body* *See note (d))*	YES

Patents Form 1/77

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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	1
Description	22
Claim(s)	5
Abstract	1
Drawing(s)	-

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 7/77)*	
Request for preliminary examination and search *(Patent Form 9/77)*	
Request for substantive examination *(Patent Form 10/77)*	
Any other documents *(please specify)*	

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

Signature GRAHAM LANE 11 February 2000
AGENT FOR THE APPLICANTS

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

CATE WEST

0181-966 8685

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication of 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 patent Act 1977 stops you from applying for a patent abroad without first getting written permission form the Patent Office unless an application has been filed at least 6 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 received

a) *Notes*

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 the 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*

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d) *Once you have filled in the form you must remember to sign and date it*

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Additional Agents
(See Page 1 No. 5)

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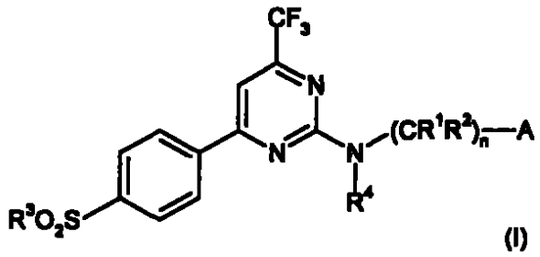
CHEMICAL COMPOUNDS

This invention relates to pyrimidine derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine

The enzyme cyclooxygenase (COX) has recently been discovered to exist in two isoforms, COX-1 and COX-2 COX-1 corresponds to the originally identified constitutive enzyme while COX-2 is rapidly and readily inducible by a number of agents including mitogens, endotoxin, hormones, cytokines and growth factors Prostaglandins generated by the action of COX have both physiological and pathological roles It is generally believed that COX-1 is responsible for the important physiological functions such as maintenance of gastrointestinal integrity and renal blood flow In contrast the inducible form, COX-2, is believed to be responsible for the pathological effects of prostaglandins where rapid induction of the enzyme occurs in response to such agents as inflammatory agents, hormones, growth factors and cytokines A selective inhibitor of COX-2 would therefore have anti-inflammatory, anti-pyretic and analgesic properties, without the potential side effects associated with inhibition of COX-1 We have now found a novel group of compounds which are both potent and selective inhibitors of COX-2

The invention thus provides the compounds of formula (I)



(I)

and pharmaceutically acceptable derivatives thereof, in which

R^1 and R^2 are independently selected from H, or C_{1-6}alkyl,
R^3 is C_{1-6}alkyl or NH_2,
R^4 is H or C_{1-6}alkyl,
A is a 5- or 6-membered aryl, or a 5- or 6-membered aryl substituted by one or more R^5,

R^5 is halogen, C_{1-6}alkyl, C_{1-6}alkyl substituted by one or more F, C_{1-6}alkoxy, C_{1-6}alkoxy substitued by one or more F, SO_2NH_2 or SO_2C_{1-6}alkyl, and
n is 1 to 4

By pharmaceutically acceptable derivative is meant any pharmaceutically acceptable salt, solvate, ester or amide, or salt or solvate of such ester or amide, of the compounds of formula (I), or any other compound which upon administration to the recipient is capable of providing (directly or indirectly) a compound of formula (I) or an active metabolite or residue thereof

It will be appreciated by those skilled in the art that the compounds of formula (I) may be modified to provide pharmaceutically acceptable derivatives thereof at any of the functional groups in the compounds Of particular interest as such derivatives are compounds modified at the benzenesulphonamide function to provide metabolically labile benzenesulphonamides Acylated benzenesulphonamide derivatives are of especial interest

It will be appreciated by those skilled in the art that the pharmaceutically acceptable derivatives of the compounds of formula (I) may be derivatised at more than one position

It will be further appreciated by those skilled in the art that benzenesulphonamide derivatives of formula (I) may be useful as intermediates in the preparation of compounds of formula (I), or as pharmaceutically acceptable derivatives of formula (I), or both

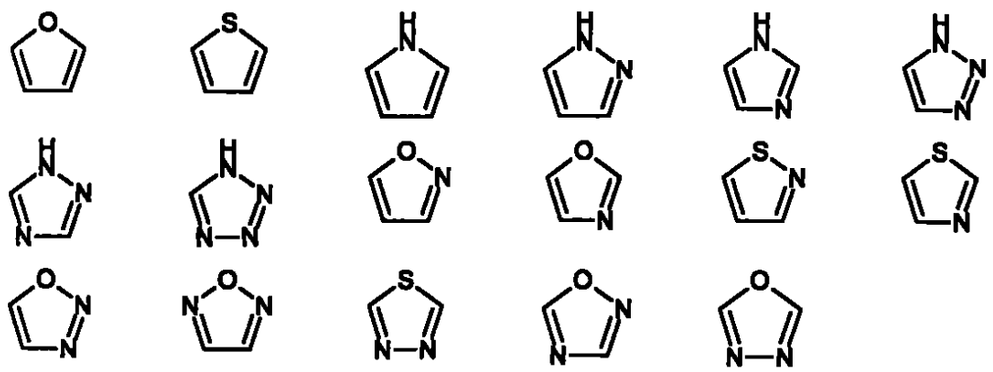
It will be appreciated that, for pharmaceutical use, the salts referred to above will be the physiologically acceptable salts, but other salts may find use, for example in the preparation of compounds of formula (I) and the physiologically acceptable salts thereof

Suitable pharmaceutically acceptable salts include acid addition salts formed with inorganic or organic acids, preferably inorganic acids, e g hydrochlorides, hydrobromides and sulphates, and alkali metal salts, formed from addition of alkali metal bases, such as alkali metal hydroxides, e g sodium salts

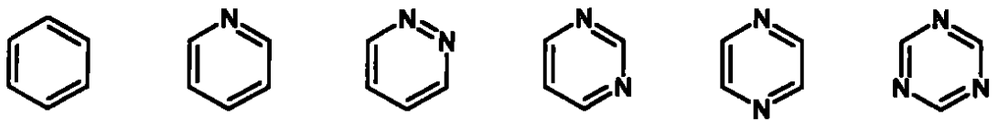
The term halogen is used to represent fluorine, chlorine, bromine or iodine

The term 'alkyl' as a group or part of a group means a straight or branched chain alkyl group, for example a methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl or t-butyl group

The term 5-membered aryl means an aryl selected from the following



The term 6- membered aryl means aryl selected from



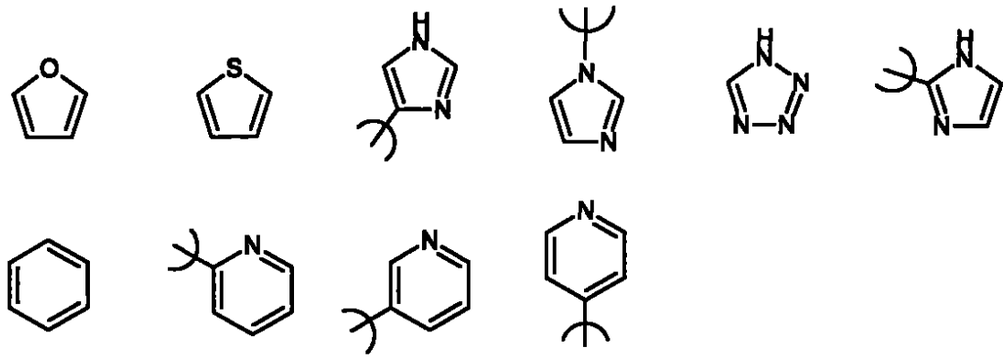
It is to be understood that the present invention encompasses all isomers of the compounds of formula (I) and their pharmaceutically acceptable derivatives, including all geometric, tautomeric and optical forms, and mixtures thereof (e g racemic mixtures)

In one aspect of the invention R^1 and R^2 are independently selected from H or methyl

In another aspect of the invention R^3 is C_{1-6}alkyl, such as C_{1-3}alkyl (e g methyl)

In another aspect of the invention, R^4 is H or C_{1-3}alkyl, such as methyl

In another aspect of the invention A is selected from

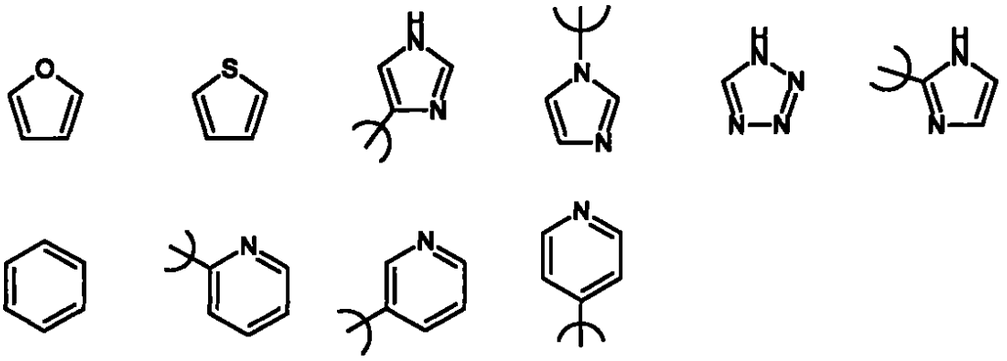


and A is unsubstituted or substituted by one or two R^5 (e g one R^5)

In another aspect of the invention R^5 is halogen (e g F), C_{1-3}alkyl (e g methyl), C_{1-3}alkyl substituted by one to three F (e g CF_3), C_{1-3}alkoxy (e g methoxy), C_{1-3}alkoxy substituted by one to three F (e g $OCHF_2$ or OCF_3), or $SONH_2$

In another aspect of the invention n is 1 to 3 (e g 1)

Within the invention there is provided one group of compounds of formula (I) (group A) wherein R^1 and R^2 are independently selected from H or methyl, R^3 is C_{1-6}alkyl, such as C_{1-3}alkyl (e g methyl), R^4 is H or C_{1-3}alkyl, such as methyl, A is selected from



and is unsubstituted or substituted by one or two R^5 (e g one R^5), R^5 is halogen (e g F), C_{1-3}alkyl (e g methyl), C_{1-3}alkyl substituted by one to three F (e g CF_3), C_{1-3}alkoxy (e g methoxy), C_{1-3}alkoxy substituted by one to three F (e g $OCHF_2$ or OCF_3), or $SONH_2$, and n is 1 to 3 (e g 1)

In another aspect the invention provides the following compounds
4-[4-(methylsulfonyl)phenyl]-N-(pyridin-4-ylmethyl)-6-(trifluoromethyl)pyrimidin-2-amine,
4-[4-(methylsulfonyl)phenyl]-N-(pyridin-3-ylmethyl)-6-(trifluoromethyl)pyrimidin-2-amine,
4-[4-(methylsulfonyl)phenyl]-N-(pyridin-2-ylmethyl)-6-(trifluoromethyl)pyrimidin-2-amine,
4-[4-(methylsulfonyl)phenyl]-N-(phenylmethyl)-6-(trifluoromethyl)-2-pyrimidinamine,
and pharmaceutically acceptable derivatives thereof

Compounds of the invention are potent and selective inhibitors of COX-2 This activity is illustrated by their ability to selectively inhibit COX-2 over COX-1

In view of their selective COX-2 inhibitory activity, the compounds of the present invention are of interest for use in human and veterinary medicine, particularly in the treatment of the pain (both chronic and acute), fever and inflammation of a variety of conditions and diseases mediated by selective inhibition of COX-2 Such conditions and diseases are well known in the art and include rheumatic fever; symptoms associated with influenza or other viral infections, such as the common cold, lower back and neck pain, headache, toothache, sprains and strains, myositis, neuropathic pain (e g neuralgia, such as post herpetic neuralgia, trigeminal neuralgia and sympathetically maintained pain), synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases, including osteoarthritis, gout and ankylosing spondylitis, tendinitis, bursitis, skin related conditions, such as psoriasis, eczema, burns and dermatitis, injuries, such as sports injuries and those arising from surgical and dental procedures

The compounds of the invention are also useful for the treatment of other conditions mediated by selective inhibition of COX-2

For example, the compounds of the invention inhibit cellular and neoplastic transformation and metastatic tumour growth and hence are useful in the treatment of certain cancerous diseases, such as colonic cancer

Compounds of the invention also prevent neuronal injury by inhibiting the generation of neuronal free radicals (and hence oxidative stress) and therefore

are of use in the treatment of stroke, epilepsy, and epileptic seizures (including grand mal, petit mal, myoclonic epilepsy and partial seizures)

Compounds of the invention also inhibit prostanoid-induced smooth muscle contraction and hence are of use in the treatment of dysmenorrhoea and premature labour

Compounds of the invention inhibit inflammatory processes and therefore are of use in the treatment of asthma, allergic rhinitis and respiratory distress syndrome, gastrointestinal conditions such as inflammatory bowel disease, Chron's disease, gastritis, irritable bowel syndrome and ulcerative colitis, and the inflammation in such diseases as vascular disease, migraine, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, type I diabetes, myasthenia gravis, multiple sclerosis, sorcoidosis, nephrotic syndrome, Bechet's syndrome, polymyositis, gingivitis, conjunctivitis and myocardial ischemia

Compounds of the invention are also useful in the treatment of ophthalmic diseases such as retinitis, retinopathies, uveitis and of acute injury to the eye tissue

Compounds of the invention are also useful for the treatment of cognitive disorders such as dementia, particularly degenerative dementia (including senile dementia, Alzheimer's disease, Pick's disease, Huntington's chorea, Parkinson's disease and Creutzfeldt-Jakob disease), and vascular dementia (including multi-infarct dementia), as well as dementia associated with intracranial space occupying lesions, trauma, infections and related conditions (including HIV infection), metabolism, toxins, anoxia and vitamin deficiency, and mild cognitive impairment associated with ageing, particularly Age Associated Memory Impairment

According to a further aspect of the invention, we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in human or veterinary medicine

According to another aspect of the invention, we provide a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in the treatment of a condition which is mediated by selective inhibition of COX-2

According to a further aspect of the invention, we provide a method of treating a human or animal subject suffering from a condition which is mediated by selective inhibition of COX-2 which comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative

According to a further aspect of the invention, we provide a method of treating a human or animal subject suffering from an inflammatory disorder, which method comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof

According to another aspect of the invention, we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a therapeutic agent for the treatment of a condition which is mediated by selective inhibition of COX-2

According to another aspect of the invention, we provide the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a therapeutic agent for the treatment of an inflammatory disorder

It is to be understood that reference to treatment includes both treatment of established symptoms and prophylactic treatment, unless explicitly stated otherwise

It will be appreciated that the compounds of the invention may advantageously be used in conjunction with one or more other therapeutic agents Examples of suitable agents for adjunctive therapy include pain relievers such as a glycine antagonist, a sodium channel inhibitor (e g lamotrigine), a substance P antagonist (e g an NK_1 antagonist), acetaminophen or phenacetin, a matrix metalloproteinase inhibitor; a nitric oxide synthase (NOS) inhibitor (e g an iNOS or an nNOS inhibitor), an inhibitor of the release, or action, of tumour necrosis factor α, an antibody therapy (e g a monoclonal antibody therapy), a stimulant, including caffeine, an H_2-antagonist, such as ranitidine, a proton pump inhibitor, such as omeprazole, an antacid, such as aluminium or magnesium hydroxide, an antiflatulent, such as simethicone, a decongestant, such as phenylephrine, phenylpropanolamine, pseudoephedrine, oxymetazoline, epinephrine,

naphazoline, xylometazoline, propylhexedrine, or levo-desoxyephedrine, an antitussive, such as codeine, hydrocodone, carmiphen, carbetapentane, or dextramethorphan, a diuretic, or a sedating or non-sedating antihistamine It is to be understood that the present invention covers the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof in combination with one or more other therapeutic agents

The compounds of formula (I) and their pharmaceutically acceptable derivatives are conveniently administered in the form of pharmaceutical compositions Thus, in another aspect of the invention, we provide a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof adapted for use in human or veterinary medicine Such compositions may conveniently be presented for use in conventional manner in admixture with one or more physiologically acceptable carriers or excipients

The compounds of formula (I) and their pharmaceutically acceptable derivatives may be formulated for administration in any suitable manner They may, for example, be formulated for topical administration or administration by inhalation or, more preferably, for oral, transdermal or parenteral administration The pharmaceutical composition may be in a form such that it can effect controlled release of the compounds of formula (I) and their pharmaceutically acceptable derivatives

For oral administration, the pharmaceutical composition may take the form of, for example, tablets (including sub-lingual tablets), capsules, powders, solutions, syrups or suspensions prepared by conventional means with acceptable excipients

For transdermal administration, the pharmaceutical composition may be given in the form of a transdermal patch, such as a transdermal iontophoretic patch

For parenteral administration, the pharmaceutical composition may be given as an injection or a continuous infusion (e g intravenously, intravascularly or subcutaneously) The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles and may contain formulatory agents such as suspending, stabilising and/or dispersing agents For

administration by injection these may take the form of a unit dose presentation or as a multidose presentation preferably with an added preservative

Alternatively for parenteral administration the active ingredient may be in powder form for reconstitution with a suitable vehicle

The compounds of the invention may also be formulated as a depot preparation Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt

As stated above, the compounds of the invention may also be used in combination with other therapeutic agents The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations

When a compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone Appropriate doses will be readily appreciated by those skilled in the art

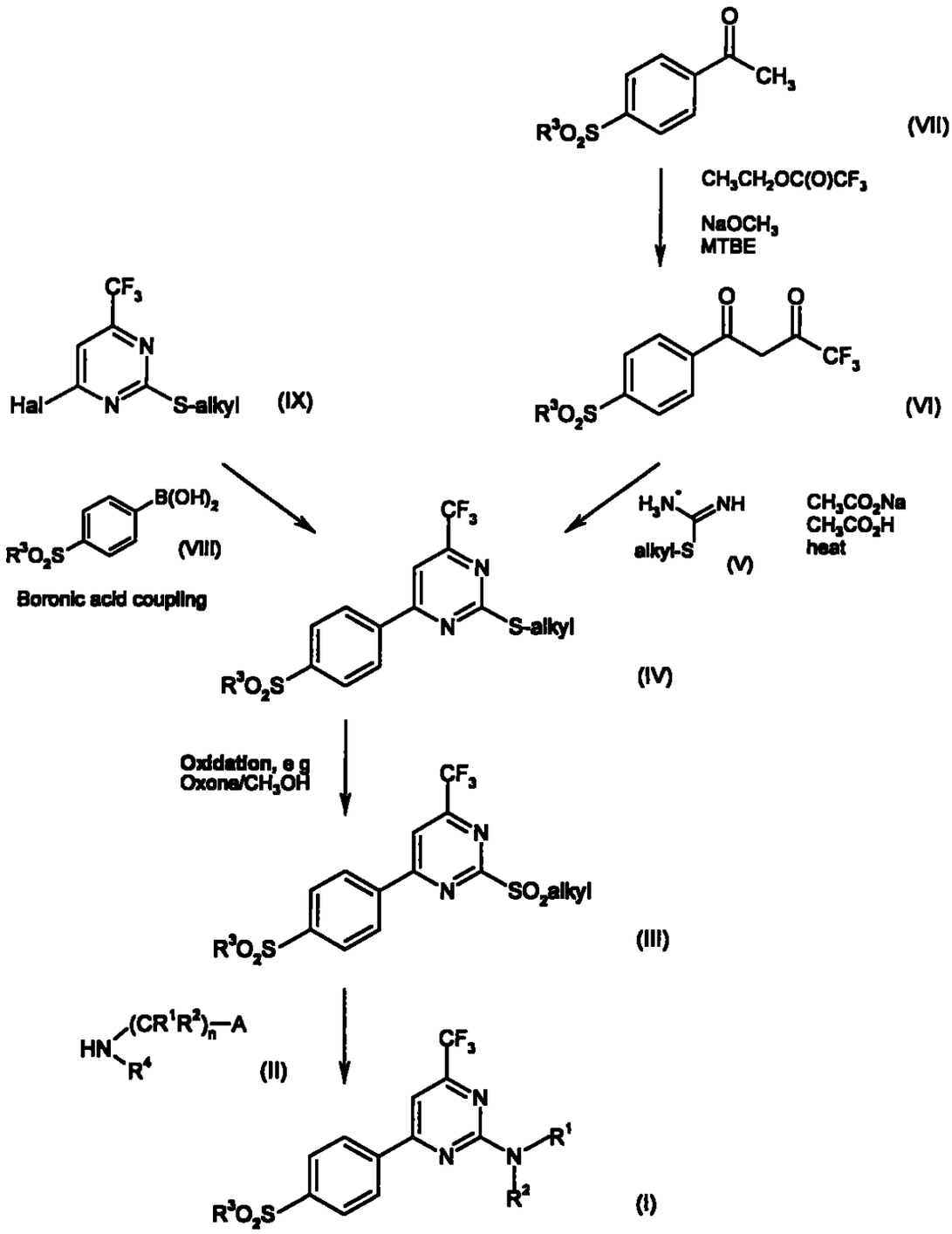
A proposed daily dosage of a compound of formula (I) for the treatment of man is 0 01mg/kg to 500mg/kg, such as 0 05mg/kg to 100mg/kg, e g 0 1mg/kg to 50mg/kg, which may be conveniently administered in 1 to 4 doses The precise dose employed will depend on the age and condition of the patient and on the

route of administration Thus, for example, a daily dose of 0 25mg/kg to 10mg/kg may be suitable for systemic administration

Compounds of formula (I) and pharmaceutically acceptable derivatives thereof may be prepared by any method known in the art for the preparation of compounds of analogous structure

Suitable methods for the preparation of compounds of formula (I) and pharmaceutically acceptable derivatives thereof follow In Scheme 1, R^1 to R^3 are as defined in formula (I) above unless otherwise stated, Hal is a halogen, such as Cl or Br, MTBE is methyl t-butyl ether, and alkyl is a straight or branched chain alkyl group, for example a methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl or t-butyl group

Scheme 1


(VII)
$CH_3CH_2OC(O)CF_3$
$NaOCH_3$
MTBE
(IX)
(VI)
(VIII)
Boronic acid coupling
(V)
CH_3CO_2Na
CH_3CO_2H
heat
(IV)
Oxidation, e g
Oxone/CH_3OH
(III)
(II)
(I)

Referring to Scheme 1, the treatment of compounds of formula (III) with an amine of formula (II) is conveniently carried out in a solvent, such as a nitrile (e g methylnitrile) and at elevated temperature (e g from about 50°C to reflux) An excess of the amine may be used in place of the solvent

Conveniently, the boronic acid coupling shown in Scheme 1 is carried out in a solvent, such as an ether (e g 1,2-dimethoxyethane), in the presence of a base, such as an inorganic base (e g sodium carbonate), and employing a palladium catalyst, such as tetrakis(triphenylphosphine)palladium(0)

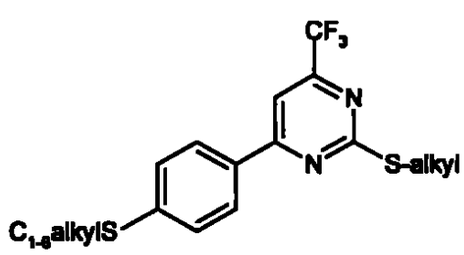
Conveniently the oxidation shown in Scheme 1 is effected using a monopersulfate compound, such as potassium peroxymonosulfate (known as Oxone™) and the reaction is carried out in a solvent, such as an aqueous alcohol, (e g aqueous methanol), and at between -78°C and ambient temperature

Referring to Scheme 1, the cyclisation of diones of formula (VI) to give the corresponding pyrimidines of formula (IV) is conveniently carried out employing a thioronium salt such as a 2-methyl-2-thiopseudourea sulfate and under reflux

It will be appreciated by those skilled in the art that certain of the procedures described in Scheme 1 for the preparation of compounds of formula (I) or intermediates thereto may not be applicable to some of the possible substituents

It will be further appreciated by those skilled in the art that it may be necessary or desirable to carry out the transformations described in Scheme 1 in a different order from that described, or to modify one or more of the transformations, to provide the desired compound of formula (I)

In one variation of Scheme 1, compounds of formula (III) wherein R^3 is C_{1-6}alkyl may be prepared by oxidising a disulphide of formula (IV)A



(IV)A

under oxidation conditions described hereinabove Disulphides of formula (IV)A may be prepared according to the general procedures of Scheme 1 by employing sulphide derivatives in place of the corresponding alkylsulphonyl compounds of formulae (VII) and (VIII)

It will be appreciated by those skilled in the art that compounds of formula (I) may be prepared by interconversion, utilising other compounds of formula (I) as precursors Suitable interconversions, such as alkylations, are well known to those skilled in the art and are described in many standard organic chemistry texts, such as 'Advanced Organic Chemistry' by Jerry March, fourth edition (Wiley, 1992), incorporated herein by reference For example, compounds of formula (I) wherein R^4 is C_{1-6}alkyl may be prepared by alkylating the corresponding compound of formula (I) wherein R^4 is H

Acylation of compounds of formula (I) wherein R^3 is NH_2 to provide corresponding acylated benzenesulphonamide derivatives may be carried out by conventional means, for example by employing conventional acylating agents such as those described in 'Advanced Organic Chemistry', pp 417-424

As will be appreciated by those skilled in the art it may be necessary or desirable at any stage in the synthesis of compounds of formula (I) to protect one or more sensitive groups in the molecule so as to prevent undesirable side reactions The protecting groups used in the preparation of compounds of formula (I) may be used in conventional manner See, for example, those described in 'Protective Groups in Organic Synthesis' by Theodora W Green and Peter G M Wuts, second edition, (John Wiley and Sons, 1991), incorporated herein by reference, which also describes methods for the removal of such groups

Amines of formula (II) are either known compounds or may be prepared by literature methods, such as those described in 'Comprehensive Organic Transformations a guide to functional group preparations' by Richard Larock (VCH, 1989), incorporated herein by reference

Thioronium salts of formula (V) are either known compounds or may be prepared by literature methods, such as those described in A H Owens *et al*, Eur J Med Chem, 1988, 23(3), 295-300, incorporated herein by reference

X00
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Acetophenones of formula (VII) are either known compounds or may be prepared by conventional chemistry

Boronic acids of formula (VIII) or derivatives thereof are either known compounds or may be prepared by literature methods, such as those described in EPA publication No 533268, or R Miyaura *et al*, J Org Chem, 1995, 60, 7508-7510, each incorporated herein by reference

4-Halo-6-trifluoromethylpyrimidines of formula (IX) are either known compounds or may be prepared by literature methods, such as those described in Japanese Patent no 42014952 (Chem Abs ref CAN 68 105224), incorporated herein by reference

Certain intermediates described above are novel compounds, and it is to be understood that all novel intermediates herein form further aspects of the present invention Compounds of formulae (III) and (IV) are key intermediates and represent a particular aspect of the present invention

Conveniently, compounds of the invention are isolated following work-up in the form of the free base Pharmaceutically acceptable acid addition salts of the compounds of the invention may be prepared using conventional means

Solvates (e g hydrates) of a compound of the invention may be formed during the work-up procedure of one of the aforementioned process steps

The Intermediates and Examples that follow illustrate the invention but do not limit the invention in any way All temperatures are in ^{0}C Flash column chromatography was carried out using Merck 9385 silica Solid Phase Extraction (SPE) chromatography was carried out using Varian Mega Bond Elut (Si) cartridges (Anachem) under 15mmHg vacuum with stepped gradient elution Thin layer chromatography (Tlc) was carried out on silica plates In addition to those already defined, the following abbreviations are used Me, methyl, Ac, acyl, DMSO, dimethylsulphoxide, TFA, trifluoroacetic acid, DME, dimethoxyethane, THF, tetrahydrofuran, DCM, dichloromethane, and MTBE, methyl t-butyl ether

Intermediate 1

4,4,4-Trifluoro-1-[4-(methylthio)phenyl]butane-1,3-dione

To a solution of ethyl trifluoroacetate (7 95ml, 1 1eq) in MTBE (125ml) was added dropwise 25% sodium methoxide in methanol (16ml, 1 2eq) 4-Methylthioacetophenone (Aldrich, 10g, 0 06mol) was added portionwise and the mixture stirred at ambient temperature overnight 2N Hydrochloric acid (40ml) was added cautiously and the organic phase separated, washed with brine and dried (Na_2SO_4) to give an orange solid The orange solid was recrystallised from hot isopropanol to give the title compound as a yellow crystalline solid (11 25g, 71%)

MH- 261

Intermediate 2

2-(Methylthio)-4-[4-(methylthio)phenyl]-6-(trifluoromethyl) pyrimidine

To a mixture of 4,4,4-trifluoro-1-[4-(methylthio)phenyl]butane-1,3-dione (5g) and 2-methyl-2-thiopseudourea sulfate (5 1g, 0 98eq) in acetic acid (100ml) was added sodium acetate (3g, 2eq) and heated under reflux for 8h The mixture was concentrated *in vacuo* and water (100ml) added to give a solid, which was isolated by filtration to give the title compound as a yellow solid (5 8g, quantitative)

MH+ 317

Intermediate 3

2-(Methylthio)-4-[4-(methylthio)phenyl]-6-(trifluoromethyl) pyrimidine

A mixture of 4-chloro-2-methylthio-6-(trifluoromethyl)pyrimidine (ButtPark Ltd, 2 86g, 14 55mmol), 4-(methylthio)phenylboronic acid (Aldrich, 2 83g, 1 1eq), tetrakistriphenylphosphine palladium (0) (0 2g) and sodium carbonate (4 04g, 2 6eq) in DME (200ml) and water (100ml) was heated under reflux with stirring under N_2 for 24h The reaction mixture was concentrated *in vacuo* and the resultant mixture partitioned between ethyl acetate and water The organic phase was separated, washed with water, dried (Na_2SO_4) and concentrated *in vacuo* to a purple solid Purification by flash column chromatography with cyclohexane ethyl acetate as (6 1) as eluant gave the title compound as a yellow crystalline solid (3 86g, 84%)

MH+ 317

Tlc SiO_2 cyclohexane ethyl acetate (3 1) Rf 0 75 uv_{254}

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Intermediate 4

2-(Methylsulfonyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine

To a solution of 2-(methylthio)-4-[4-(methylthio)phenyl]-6-(trifluoromethyl) pyrimidine (5 78g) in MeOH (500ml) was added a solution of OXONE™ (Aldrich, 56 23g, 5eq) in water (200ml) The mixture was stirred at ambient temperature overnight, concentrated *in vacuo* and the residue partitioned between water and ethyl acetate (2 x 100ml) The combined organic phases were dried and concentrated *in vacuo* to an off-white solid which was triturated with hot isopropanol to give the title compound as a white solid (5 6g, 80%)

MH+ 381

Tlc SiO_2 Ethyl acetate cyclohexane (1 1) Rf 0 45

Example 1

4-[4-(Methylsulfonyl)phenyl]-N-(pyridin-4-ylmethyl)-6-(trifluoromethyl)pyrimidin-2-amine

To a stirred solution of 2-(methylsulfonyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine (0 10g, 0 26mmol) in MeCN (4ml) was added 4-(aminomethyl)-pyridine (0 14ml, 5eq) and the resultant solution heated under reflux for 18h The cooled reaction mixture was concentrated *in vacuo* and purified by SPE chromatography using chloroform, diethyl ether, ethyl acetate, acetone and methanol as the eluotropic series of solvents Concentration *in vacuo* of the combined fractions containing pure product gave the title compound as a colourless solid (0 061g, 57%) MH+ 409

Example 2

4-[4-(Methylsulfonyl)phenyl]-N-(pyridin-3-ylmethyl)-6-(trifluoromethyl)pyrimidin-2-amine

To a stirred solution of 2-(methylsulfonyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine (0 10g, 0 26mmol) in MeCN (3ml) was added 3-(aminomethyl)-pyridine (169mg, 6eq) and the resultant solution heated under reflux for 3h The cooled reaction mixture was concentrated *in vacuo* and the resulting oil purified by SPE chromatography with chloroform then chloroform methanol (50 1) as eluant This gave the title compound as a yellow solid (100mg, 93%) MH+ 409.

Example 3

4-[4-(Methylsulfonyl)phenyl]-N-(pyridin-2-ylmethyl)-6-(trifluoromethyl)pyrimidin-2-amine

To a stirred solution of 2-(methylsulfonyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine (0 10g, 0 26mmol) in MeCN (4ml) was added 2-(aminomethyl)-pyridine (0 14, 5eq) and the resultant solution heated under reflux for 3h The cooled reaction mixture was concentrated *in vacuo* and purified by SPE chromatography using chloroform, diethyl ether, ethyl acetate, acetone and methanol as the eluotropic series of solvents Concentration *in vacuo* of the combined fractions containing pure product gave the title compound as a colourless solid (0 086g, 80%) MH+ 409

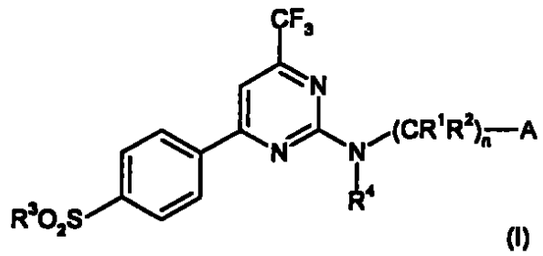
Example 4

4-[4-(Methylsulfonyl)phenyl]-N-(phenylmethyl)-6-(trifluoromethyl)-2-pyrimidinamine

To a stirred solution of 2-(Methylsulfonyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyrimidine (0 10g, 0 26mmol) in MeCN (4ml) was added benzylamine (5eq) and the resultant solution heated under reflux for 24h The cooled reaction mixture was concentrated *in vacuo* and purified by SPE chromatography with cyclohexane ethyl acetate (3 1) Concentration *in vacuo* of the combined fractions containing pure product gave the title compound as a white solid (0 090g, 80%) MH+ 407

The Examples of Table 1 were prepared in the manner described for Examples 1 to 4

Table 1

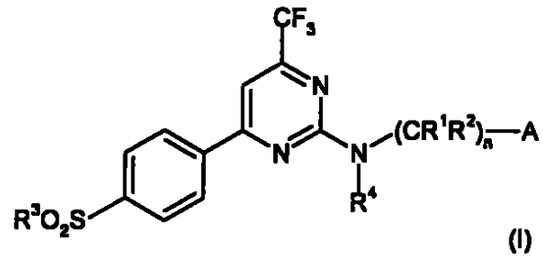


(I)

Ex	n	R^1	R^2	R^3	R^4	A	MS
5	1	(1*R*)-CH_3	H	CH_3	H	phenyl	MH+ 422
6	1	(1*S*)-CH_3	H	CH_3	H	phenyl	MH+ 422
7	1	CH_3	CH_3	CH_3	H	phenyl	MH+ 436
8	1	H	H	CH_3	H	3-methoxyphenyl	no ion
9	1	H	H	CH_3	H	4-methoxyphenyl	MH+ 438
10	1	H	H	CH_3	H	4-trifluoromethoxyphenyl	MH+ 492
11	1	H	H	CH_3	H	3,4-difluorophenyl	MH+ 444
12	1	H	H	CH_3	H	4-trifluoromethylphenyl	MH+ 476
13	1	H	H	CH_3	H	4-methylphenyl	MH+ 422
14	1	H	H	CH_3	H	3-fluorophenyl	MH+ 426
15	1	H	H	CH_3	H	4-fluorophenyl	MH+ 426
16	1	H	H	CH_3	H	3,5-difluorophenyl	MH+ 444
17	1	H	H	CH_3	H	2,5-difluorophenyl	MH+ 444
18	1	H	H	CH_3	H	2,6-difluorophenyl	MH+ 444
19	1	H	H	CH_3	H	2,4-difluorophenyl	MH+ 444
20	1	H	H	CH_3	H	4-difluoromethoxyphenyl	MH+ 474
21	1	H	H	CH_3	H	3-methylphenyl	MH+ 422

123
154

Table 1



(I)

Ex	n	R^1	R^2	R^3	R^4	A	MS
22	1	H	H	CH_3	H	2-fluorophenyl	MH+ 426
23	1	H	H	CH_3	H	3-chlorophenyl	MH+ 442
24	2	H	H	CH_3	H	2-pyridyl	MH+ 423
25	1	H	H	CH_3	H	2-furyl	MH+ 398
26	1	H	H	CH_3	CH_3	phenyl	MH+ 422
27	3	H	H	CH_3	H	phenyl	MH+ 426

Biological Data

Inhibitory activity against human COX-1 and COX-2 was assessed in COS cells which had been stably transfected with cDNA for human COX-1 and human COX-2 24 Hours prior to experiment, COS cells were transferred from the 175cm^2 flasks in which they were grown, onto 24-well cell culture plates using the following procedure The incubation medium (Dulbecco's modified eagles medium (DMEM) supplemented with heat-inactivated foetal calf serum (10%v/v), penicillin (100 IU/ml), streptomycin (100µg/ml) and geneticin (600µg/ml)) was removed from a flask of confluent cells (1 flask at confluency contains approximately 1x10^7 cells) 10ml of phosphate buffered saline (PBS) was added to the flask to wash the cells Having discarded the PBS, cells were then rinsed in 10ml trypsin for 20 seconds, after which the trypsin was removed and the flask placed in an incubator (37°) for 1-2 minutes until cells became detached from the flask The flask was then removed from the incubator and cells resuspended in 10ml of fresh incubation medium The contents of the flask was transferred to a 250ml sterile container and the volume of incubation medium subsequently made up to 100ml 1ml cell suspension was pipetted into each well of 4x24-well

cell culture plates The plates were then placed in an incubator (37°C, 95% air/5% CO_2) overnight If more than 1 flask of cells were required, the cells from the individual flasks were combined before being dispensed into the 24-well plates

Following the overnight incubation, the incubation medium was completely removed from the 24-well cell culture plates and replaced with 250µl fresh DMEM (37°C) The test compounds were made up to 250x the required test concentration in DMSO and were added to the wells in a volume of 1µl Plates were then mixed gently by swirling and then placed in an incubator for 1 hour (37°C, 95% air/5% CO_2) Following the incubation period, 10µl of arachidonic acid (750µM) was added to each well to give a final arachidonic acid concentration of 30µM Plates were then incubated for a further 15 minutes, after which the incubation medium was removed from each well of the plates and stored at -20°C, prior to determination of prostaglandin E_2 (PGE2) levels using enzyme immunoassay The inhibitory potency of the test compound was expressed as an IC_{50} value, which is defined as the concentration of the compound required to inhibit the PGE2 release from the cells by 50% The selectivity ratio of inhibition of COX-1 versus COX-2 was calculated by comparing respective IC_{50} values

The following IC_{50} values for inhibition of COX-2 and COX-1 were obtained for compounds of the invention

Example No.	COX-2: IC_{50}(nM)	COX-1: IC_{50}(nM)
1	1 3	>100,000
2	10 8	>100,000
3	2 5	>100,000
4	0 25	>100,000

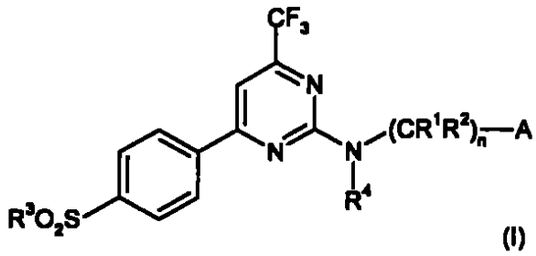
The application of which this description and these claims form a part may be used as a basis for priority in respect of any subsequent application The claims of such subsequent application may be directed to any novel feature or combination of features relating to the invention described herein They may

take the form of product, process or use claims and may include, by way of example and without limitation, the claims that follow

CLAIMS

Claim 1

Compounds of formula (I)



(I)

and pharmaceutically acceptable derivatives thereof, in which

R^1 and R^2 are independently selected from H, or C_{1-6}alkyl,
R^3 is C_{1-6}alkyl or NH_2,
R^4 is H or C_{1-6}alkyl,
A is a 5- or 6-membered aryl, or a 5- or 6-membered aryl substituted by one or more R^5,
R^5 is halogen, C_{1-6}alkyl, C_{1-6}alkyl substituted by one or more F, C_{1-6}alkoxy, C_{1-6}alkoxy substitued by one or more F, SO_2NH_2 or SO_2C_{1-6}alkyl, and
n is 1 to 4

Claim 2

Compounds as claimed in claim 1 wherein R^1 is H

Claim 3

Compounds as claimed in claim 1 or 2 wherein R^2 is H

Claim 4

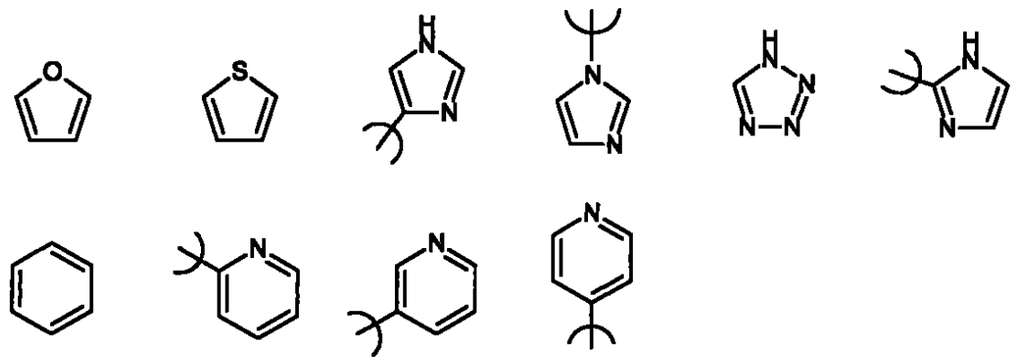
Compounds as claimed in any of claims 1 to 3 wherein R^3 is C_{1-6}alkyl, such as C_{1-3}alkyl (e g methyl)

Claim 5

Compounds as claimed in any of claims 1 to 4 wherein R^4 is H or C_{1-3}alkyl, such as methyl

Claim 6

Compounds as claimed in any of claims 1 to 5 wherein A is selected from



and A is unsubstituted or substituted by one or two R^5 (e g one R^5)

Claim 7

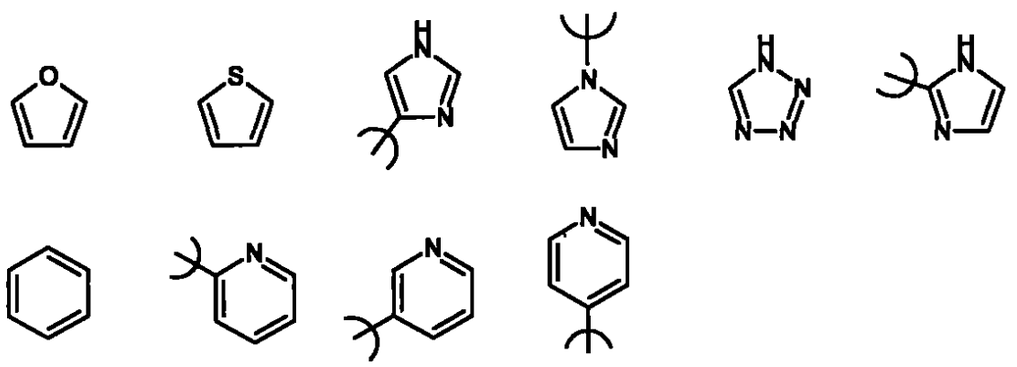
Compounds as claimed in any of claims 1 to 6 wherein R^5 is halogen (e g F), C_{1-3}alkyl (e g methyl), C_{1-3}alkyl substituted by one to three F (e g CF_3), C_{1-3}alkoxy (e g methoxy), C_{1-3}alkoxy substituted by one to three F (e g $OCHF_2$ or OCF_3), or $SONH_2$

Claim 8

Compounds as claimed in any of claims 1 to 7 wherein n is 1 to 3

Claim 9

Compounds as claimed in any of claims 1 to 8 wherein R^1 and R^2 are independently selected from H or methyl, R^3 is C_{1-6}alkyl, such as C_{1-3}alkyl (e g methyl), R^4 is H or C_{1-3}alkyl, such as methyl, A is selected from



and is unsubstituted or substituted by one or two R^5 (e g one R^5), R^5 is halogen (e g F), C_{1-3}alkyl (e g methyl), C_{1-3}alkyl substituted by one to three F (e g CF_3), C_{1-3}alkoxy (e g methoxy), C_{1-3}alkoxy substituted by one to three F (e g $OCHF_2$ or OCF_3), or $SONH_2$, and n is 1 to 3 (e g 1)

Claim 10

4-[4-(methylsulfonyl)phenyl]-N-(pyridin-4-ylmethyl)-6-(trifluoromethyl)pyrimidin-2-amine,

4-[4-(methylsulfonyl)phenyl]-N-(pyridin-3-ylmethyl)-6-(trifluoromethyl)pyrimidin-2-amine,

4-[4-(methylsulfonyl)phenyl]-N-(pyridin-2-ylmethyl)-6-(trifluoromethyl)pyrimidin-2-amine,

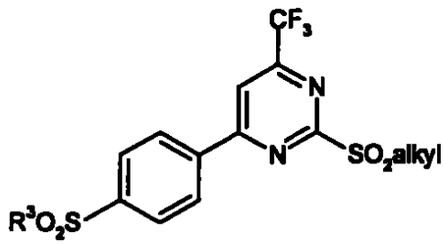
4-[4-(methylsulfonyl)phenyl]-N-(phenylmethyl)-6-(trifluoromethyl)-2-pyrimidinamine,

and pharmaceutically acceptable derivatives thereof

Claim 11

A process for the preparation of compounds of formula (I) and pharmaceutically acceptable derivatives thereof as defined in any one of claims 1 to 10, which comprises

(A), reacting an amine of formula (II) or a protected derivative thereof with a compound of formula (III)



(III)

or a protected derivative thereof, or

(B), interconversion of a compound of formula (I) into another compound of formula (I), or

(C), deprotecting a protected derivative of compound of formula (I), and

optionally converting compounds of formula (I) prepared by any one of processes (A) to (C) into pharmaceutically acceptable derivatives thereof

Claim 12

A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof as defined in any one of claims 1 to 10 in admixture with one or more physiologically acceptable carriers or excipients

Claim 13

A compound of formula (I) or a pharmaceutically acceptable derivative thereof as defined in any one of claims 1 to 10 for use in human or veterinary medicine

Claim 14

A method of treating a human or animal subject suffering from a condition which is mediated by selective inhibition of COX-2 which comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative as defined in any one of claims 1 to 10

Claim 15

A method of treating a human or animal subject suffering from an inflammatory disorder, which method comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof as defined in any one of claims 1 to 10

Claim 16

The use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof as defined in any one of claims 1 to 10 for the manufacture of a therapeutic agent for the treatment of a condition which is mediated by selective inhibition of COX-2

Claim 17

The use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof as defined in any one of claims 1 to 10 for the manufacture of a therapeutic agent for the treatment of an inflammatory disorder

Claim 18

A compound of formula (I) or a pharmaceutically acceptable derivative thereof as defined in any one of claims 1 to 10 for use in the treatment of a condition which is mediated by selective inhibition of COX-2.

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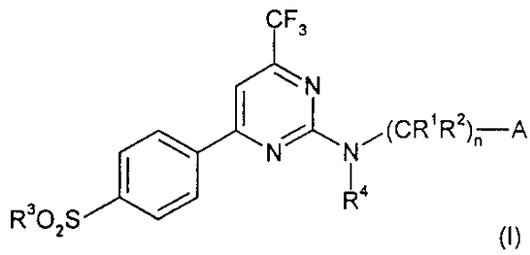
Abstract

The invention provides the compounds of formula (I)



(I)

and pharmaceutically acceptable derivatives thereof, in which:

R^1 and R^2 are independently selected from H, or C_{1-6}alkyl;
R^3 is C_{1-6}alkyl or NH_2;
R^4 is H or C_{1-6}alkyl;
A is a 5- or 6-membered aryl, or a 5- or 6-membered aryl substituted by one or more R^5;
R^5 is halogen, C_{1-6}alkyl, C_{1-6}alkyl substituted by one or more F, C_{1-6}alkoxy, C_{1-6}alkoxy substitued by one or more F, SO_2NH_2 or SO_2C_{1-6}alkyl; and
n is 1 to 4.

Compounds of formula (I) are potent and selective inhibitors of COX-2 and are of use in the treatment of the pain, fever, inflammation of a variety of conditions and diseases.

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EXAMEN TÉCNICO DE FONDO			
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Nº Prioridad	GB0003224 3	Fecha de Prioridad	11/02/2000

Palabras clave	PIRIMIDINA

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A61K31/505

DOCUMENTOS CORRESPONDIENTES EN OTROS PAÍSES		
Patente Original	WO0158881	EP1254119

BASES DE DATOS CONSULTADAS	
ESPACENET	EPOLINE

INFORMES DE EXÁMENES EN OTRAS OFICINAS		
Oficina	Fecha	Reivindicaciones
EPO		

ANTERIORIDADES ENCONTRADAS		
Documento	Relevancia	Reivindicaciones afectadas

LITERATURA NO PATENTES		
Documento no Patentes	Relevancia	Reiv. Afectadas

Observaciones	Unidad de invención

Fecha del examen	01/08/2006