598654

COMMONWEALTH of AUSTRALIA

PATENTS ACT 1952

APPLICATION FOR A STANDARD PATENT

I
We SMITH KLINE & FRENCH LABORATORIES LIMITED.
of Mundells, Welwyn Garden City,
Hertfordshire AL7 IEY.
England

hereby apply for the grant of a Standard Patent for an invention entitled:

"BIOLOGICALLY ACTIVE COMPOUNDS"

which is described in the accompanying ~~provisional~~ complete specification.

Details of basic application(s):—

Number	Convention Country	Date
GB 8708233	United Kingdom	7th April 1987

The address for service is care of DAVIES & COLLISON, Patent Attorneys, of 1 Little Collins Street, Melbourne, in the State of Victoria, Commonwealth of Australia.

Dated this 31st day of March 1988

To: THE COMMISSIONER OF PATENTS

H. M. Rimington
.....
(a member of the firm of DAVIES & COLLISON for and on behalf of the Applicant).

AU/1

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

DECLARATION IN SUPPORT OF CONVENTION OR NON-CONVENTION APPLICATION FOR A PATENT

1936

In support of the Application made for a patent for an invention

Insert title of invention.

entitled:

BIOLOGICALLY ACTIVE COMPOUNDS

Insert full name(s) and address(es) of declarant(s) being the applicant(s) or person(s) authorized to sign on behalf of an applicant company.

I
~~We~~
David Martin Waters
of Patents Department,
SMITH KLINE & FRENCH LABORATORIES LIMITED
Mundells, Welwyn Garden City, Hertfordshire AL7, 1EY,
England

do solemnly and sincerely declare as follows:-

Cross out whichever of paragraphs 1(a) or 1(b) does not apply
1(a) relates to application made by individual(s)
1(b) relates to application made by company; insert name of applicant company.

1. (a) ~~I am / We are the applicant..... for the patent~~

or (b) I am authorized by
SMITH KLINE & FRENCH LABORATORIES LIMITED

the applicant~~s~~..... for the patent to make this declaration on ~~its~~ their behalf.

Cross out whichever of paragraphs 2(a) or 2(b) does not apply
2(a) relates to application made by inventor(s)
2(b) relates to application made by company(s) or person(s) who are not inventor(s); insert full name(s) and address(es) of inventors

2. (a) ~~I am / We are the actual inventor..... of the invention~~

or (b)
DAVID GWYN COOPER 59 Penn Way, Lordship Estate, Letchworth, Hertfordshire SG62SH, England

APPLICATION ACCEPTED AND AMENDMENTS ALLOWED 9-4-90

~~is~~ / ~~are~~ the actual inventor..... of the invention and the facts upon which the applicant~~s~~..... ~~is~~ / ~~are~~ entitled to make the application are as follows:-

State manner in which applicant(s) derive title from inventor(s)

By virtue of an Acknowledgement and General Assignment dated: 22 June 1987 whereby the applicant would if a patent were granted on an application made by the said inventor be entitled to have the patent assigned to it.

Cross out paragraphs 3 and 4 for non-convention applications. For convention applications, insert basic country(s) followed by date(s) and basic applicant(s).

3. The basic application..... as defined by Section 141 of the Act ~~was~~ made

in		on the
by	Great Britain	7 April 1987
	SMITH KLINE & FRENCH LABORATORIES LIMITED	
in		on the
by		
in		on the
by		

4. The basic application..... referred to in paragraph 3 of this Declaration ~~was~~ the first application..... made in a Convention country in respect of the invention the subject of the application.

Insert place and date of signature.

Declared at Welwyn Garden City, this 8th day of February 1988
England

Signature of declarant(s) (no attestation required)

For SMITH KLINE & FRENCH LABORATORIES LIMITED

D.M. Waters -Authorised Official

Note: Initial all alterations.

DAVIES & COLLISON, MELBOURNE and CANBERRA.

(12) PATENT ABRIDGMENT (11) Document No. AU-B-14068/88
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 598654

(54) Title
PYRIDYLALKANOIC ACID THROMBOXANE A2-ANTAGONISTS

International Patent Classification(s)
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(71) Applicant(s)
SMITH KLINE & FRENCH LABORATORIES LIMITED

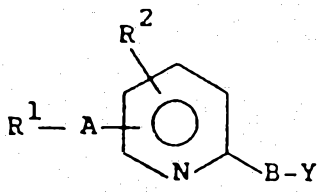
(72) Inventor(s)
DAVID GWYN COOPER

(74) Attorney or Agent
DAVIES & COLLISON, MELBOURNE

(57) USEFUL IN TREATING CIRCULATORY SHOCK AND MYOCARDIAL ISCHAEMIA.

CLAIM

1. A compound of the formula (I):



(I)

and salts thereof; wherein
A is a group NR^3SO_2 or SO_2NR^3; B is C_{1-6}alkylene;
Y is:
C_{1-4}alkoxycarbonyl, carbamoyl, monoC_{1-6}alkylcarbamoyl or diC_{1-6}alkylcarbamoyl ;

R^1 is phenyl optionally substituted by one or more substituents chosen from the group consisting of halogen, C_{1-4}alkyl, C_{1-6}acyl, C_{1-4}alkoxy, nitro and trifluoromethyl, provided that when R^1 is phenyl substituted by two or more substituents, no more than one substituent can be meta-trifluoromethyl;
R^2 is hydrogen or one or more C_{1-4}alkyl substituents;
and R^3 is hydrogen or C_{1-6}alkyl.

COMMONWEALTH OF AUSTRALIA

PATENT ACT 1952

598654

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE

CLASS INT. CLASS

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority:

Related Art:

This document contains the amendments made under Section 49 and is correct for printing.

NAME OF APPLICANT: SMITH KLINE & FRENCH LABORATORIES LIMITED.

ADDRESS OF APPLICANT: Mundells, Welwyn Garden City,
Hertfordshire AL7 IEY.
England.

NAME(S) OF INVENTOR(S) David Gwynn COOPER

ADDRESS FOR SERVICE: DAVIES & COLLISON, Patent Attorneys
1 Little Collins Street, Melbourne, 3000.

COMPLETE SPECIFICATION FOR THE INVENTION ENTITLED:

"BIOLOGICALLY ACTIVE COMPOUNDS"

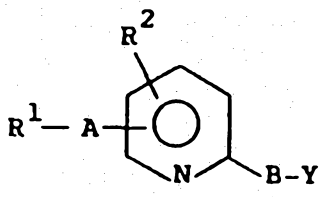
The following statement is a full description of this invention, including the best method of performing it known to us :-

The present invention relates to a class of pyridylalkanoic acid compounds containing a sulphonamido group which have activity as thromboxane A_2 antagonists, to the use of the compounds in medicine, to pharmaceutical compositions containing them and to methods for their preparation.

Thromboxane A_2 (TXA_2) is a potent vasoconstricting and platelet aggregating agent which is formed in platelets and other tissues as a product of the "arachidonic acid cascade". TXA_2 is produced by the thromboxane synthetase catalysed conversion of prostaglandin H_2 (PGH_2) which in turn is produced, via the intermediacy of prostaglandin G_2 (PGG_2), by the action of cyclooxygenase on arachidonic acid. The potency of TXA_2 is such that very small amounts can trigger serious biological consequences and it has been implicated in mediating pathophysiological actions in severe disorders such as circulatory shock and myocardial ischaemia.

One method of inhibiting the effects of thromboxane A_2 is through the selective antagonism of TXA_2/PGH_2 at the receptor level and various compounds have been reported as TXA_2 receptor antagonists, see for example U.S. 4,536,510 and U.S. 4,443,477.

It has now been discovered that a class of sulphonamide-substituted pyridylalkanoic acids has biological activity indicative of an ability to antagonise the action of TXA_2 at TXA_2 receptors. Accordingly, in a first aspect, the present invention provides compounds of the formula (I):



(I)

and salts thereof; wherein

A is a group NR^3SO_2 or SO_2NR^3; B is C_{1-6}alkylene;

Y is CO_2H or a group hydrolysable to CO_2H and in particular: C_{1-4}alkoxycarbonyl, carbamoyl, monoC_{1-6}alkylcarbamoyl or diC_{1-6}alkylcarbamoyl ;

R^1 is phenyl optionally substituted by one or more substituents chosen from the group comprising halogen, C_{1-4}alkyl, C_{1-6}acyl, C_{1-4}alkoxy, nitro and trifluoromethyl, provided that when R^1 is phenyl substituted by two or more substituents, no more than one substituent can be meta-trifluoromethyl;

R^2 is hydrogen or one or more C_{1-4}alkyl substituents;

and R^3 is hydrogen or C_{1-6}alkyl.

The group R^1-A can be ortho, meta or para with respect to the nitrogen atom of the pyridine ring. Preferably it is meta to the pyridine nitrogen atom, and particularly preferably it is also para to the group B-Y.

The group Y hydrolysable to CO_2H suitably is a nitrile, amide or ester, for example a C_{1-4}alkoxy-carbonyl group such as ethoxycarbonyl or methoxycarbonyl, or a carbamoyl, mono-C_{1-6}alkylcarbamoyl or di-C_{1-6}alkyl-carbamoyl group such as N-methylaminocarbonyl and N,N-dimethylaminocarbonyl.

In particular R^1 represents an unsubstituted phenyl group or a phenyl group having one or two substituents, preferably in the 3- and/or 4-positions of the phenyl ring.

Examples of C_{1-6}acyl substituents for R^1 are C_{1-6}alkanoyl, C_{1-6}alkoxycarbonyl and carbamoyl.

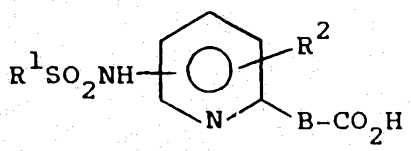
Preferred examples of the group R^1 are unsubstituted phenyl or mono-substituted phenyl wherein the substituent is an atom or group in the 3- or 4-position, preferably the 4-position, selected from chloro, bromo, methyl, trifluoromethyl and methoxy, a most preferred example being phenyl substituted with 4-chloro or 4-bromo.

Examples of the group R^2 are hydrogen, methyl and ethyl, particularly hydrogen.

Suitably R^3 is hydrogen or methyl, particularly hydrogen.

The group B can be a straight chain or branched chain alkylene group but preferably it is a straight chain alkylene group having from two to five carbon atoms, particularly three or four carbon atoms. Examples of straight chain groups are ethane-1,2-diyl, propane-1,3-diyl, butane-1,4-diyl and pentane-1,5-diyl. Examples of branched chain alkylene groups are 2-methylbutane-2,4-diyl and 2-methylpentane-2,5-diyl, the point of attachment of the group Y being at the 2-position. Preferred alkylene groups are propane-1,3-diyl and butane-1,4-diyl, a particularly preferred group being propane-1,3-diyl.

One particular group of compounds of the present invention is represented by the general formula (II):



(II)

and salts thereof, wherein R^1, R^2 and B are as defined above.

Particular and preferred groups B, R^1 and R^2 for compounds of the formula (II) are as defined above in respect of compounds of the formula (I).

Preferably the group R^1SO_2NH is meta to the pyridine ring nitrogen, and particularly preferably it is also para to the group $B\text{-}CO_2H$.

Particular compounds of the present invention are

4-(5-benzenesulphonamidopyrid-2-yl)butanoic acid,
4-[5-(4-chlorobenzenesulphonamido)pyrid-2-yl]butanoic acid,
4-(5-benzenesulphonamido-3-methylpyrid-2-yl)butanoic acid,
5-[5-(4-chlorobenzenesulphonamido)pyrid-2-yl]pentanoic acid,
4-[5-(3-chlorobenzenesulphonamido)pyrid-2-yl]butanoic acid.
4-[5-(3,4-dichlorobenzenesulphonamido)pyrid-2-yl]butanoic acid,
4-[5-(4-bromobenzenesulphonamido)pyrid-2-yl]butanoic acid, and
4-[5-(4-methylbenzenesulphonamido)pyrid-2-yl]butanoic acid.

Compounds of the formula (I) can form several different types of salt, for example acid addition salts, formed by interaction of the nitrogen atom of the pyridine ring with an appropriate proton acid, and salts formed by interaction of the carboxylic acid group and/or the sulphonamido group with an appropriate base. Where compounds of the formula (I) exist in zwitterionic form, such forms are also within the scope of this invention.

Examples of acid addition salts are those formed by interaction of a compound of the formula (I) with an acid selected from hydrochloric, sulphuric, phosphoric, acetic, methanesulphonic, ethanesulphonic, isethionic, glucuronic, lactobionic, toluenesulphonic, benzenesulphonic, naphthalenesulphonic, hydrobromic, tartaric, citric, maleic, lactic, and camphorsulphonic acids.

Examples of carboxylate salts are alkali metal, alkaline earth metal and ammonium salts. Alkali and alkaline earth metal salts typically are formed by interaction of a carboxylic acid with a metal alkoxide or

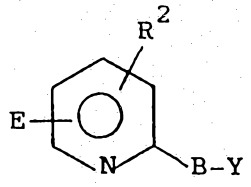
hydroxide whereas ammonium salts typically are formed by interaction of the carboxylic acid with the appropriate amine or the appropriate ammonium hydroxide.

It is preferred that the salts are pharmaceutically acceptable, although non-pharmaceutical salts are also within the scope of the invention. Such salts can be converted into pharmaceutically acceptable salts or into the corresponding free base or free acid.

Where the compounds of formula (I) exist as solvates, for example hydrates and alcoholates, such forms are also within the scope of the invention.

Compounds of the formula (I) wherein Y is CO_2H have activity as thromboxane A_2 receptor antagonists. Compounds of the formula (I) wherein Y is a group hydrolysable to CO_2H are primarily useful as chemical intermediates, unless they are metabolised by mammals to compounds wherein Y is CO_2H in which case they can function as pro-drugs.

Compounds of the formula (I) can be prepared by the reaction of a compound of the formula (III):



(III)

wherein E is amino or a group SO_2L;

R^2 is as defined above; and

L is a leaving group displaceable by amino;

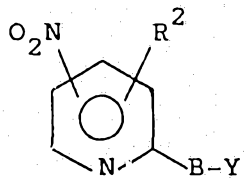
with a compound of the formula R^1M wherein M is amino or a group SO_2L, provided that one of E and M is SO_2L and the other is amino; and thereafter, where necessary, hydrolysing Y to give CO_2H.

Examples of leaving groups L are the halogens, particularly chlorine.

The reaction of compounds of the formula (III) with compounds of the formula R^1M can be conducted under conditions known for the preparation of analogous sulphonamides. Thus, for example, the reaction can be conducted in a solvent, for example benzene, toluene or a polar solvent such as acetone, acetonitrile, a halogenated hydrocarbon such as dichloromethane or a basic solvent such as pyridine, with heating where required, for example at the reflux temperature of the solvent. Where the solvent is non-basic the reaction typically is conducted in the presence of a base such as pyridine or a trialkylamine such as triethylamine.

Alternatively, the reaction can be conducted under Schotten-Baumann conditions, i.e. the reactants are stirred or shaken together in the presence of an aqueous alkali such as dilute sodium hydroxide.

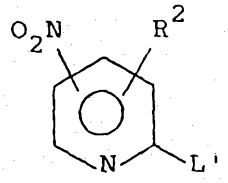
Compounds of the formula (III) wherein E is amino can be prepared from a compound of the formula (IV):



(IV)

by treatment with an appropriate reducing agent, for example by hydrogenating over a transition metal catalyst such as palladium on charcoal, or by treatment with hydrazine in the presence of palladium on charcoal. Suitable solvents for use in such reactions are C_{1-4}alkanols such as methanol and ethanol and typically the reaction is conducted at approximately ambient temperature.

Compounds of the formula (IV) can be prepared by the reaction of a compound of the formula (V):



(V)

wherein L' is a leaving group, with a metal derivative of a compound $H-B^1-Y$ wherein B^1 is a group B optionally substituted by one or more anion-stabilising groups, and thereafter removing any anion-stabilising groups. Suitable leaving groups L' will be apparent to those skilled in the art and include, for example, a halogen, e.g. chlorine.

By anion-stabilising group is meant a removable group adjacent to the terminal carbon atom of the group H-B-Y which increases the acidity of the group and which subsequently exerts a stabilising influence on an anion $^{\ominus}B^1-Y$. Examples of such removable groups are alkoxycarbonyl groups such as ethoxycarbonyl.

Examples of compounds of the formula $H-B^1-Y$ containing anion-stabilising groups are compounds of the formula $HC(X)(X)-B^2-Y$ wherein X is cyano or C_{1-4}alkoxycarbonyl and B^2 is a bond or a C_{1-5}alkylene group. A particular example of such a group is $HC(CO_2Et)_2B^2-Y$. The metal typically is an alkaline metal such as lithium, sodium or potassium and usually it is sodium.

The reaction of a compound of the formula (V) with the metal derivative of the compound $H-B^1-Y$ can be carried out in a polar solvent, for example, ethers such

as diethyl ether and tetrahydrofuran, or dimethylsulphoxide, with heating where necessary; for example to the reflux temperature of the solvent. Metal derivatives of compounds of the formula $H\text{-}B^1\text{-}Y$ can be formed according to conventional methods, for example by reacting the compound with elemental metal, or a strong base containing the metal, such as the metal hydride.

Compounds of the formula (III) wherein E is a group SO_2Cl can be prepared by diazotisation of the corresponding compound wherein E is NH_2 with sodium nitrite and hydrochloric acid followed by treatment with sulphur dioxide in acetic acid in the presence of a copper catalyst such as Cu(I)Cl or $Cu(II)Cl_2$ - see for example E.E. Gilbert, Synthesis. 1969, 6.

When the group Y is a group hydrolysable to CO_2H, the hydrolysis conditions employed will depend upon the precise nature of the group, but generally the hydrolysis is achieved by treating with either an aqueous mineral acid such as hydrochloric or sulphuric acids or an alkali such as sodium hydroxide, with heating as required.

Compounds of the formula (I) are useful in the treatment of diseases in which TXA_2 is a factor. Thus they would be useful in the treatment of disorders in which aggregation of blood platelets and vasoconstriction play a part.

Particular clinical indications in which the present compounds would be of interest include the treatment or management of post myocardial infarction, coronary thromboses (e.g. in combination with tissue plasminogen activator and other thrombolytics), unstable angina, transient ischaemia, coronary artery bypass grafts, cardiac valve replacement and peripheral and vascular grafts including for example renal transplants.

The compounds of the formula (I) can be administered as the pure compound but it is more usual to administer them as part of a pharmaceutical composition in association with a carrier and one or more excipients. In a further aspect, therefore, the present invention provides a pharmaceutical composition comprising a compound of the formula (I) and a pharmaceutically acceptable carrier.

The compositions can be administered in standard manner, for example orally, parenterally, transdermally, rectally, via inhalation or via buccal administration.

Compounds of formula (I) and their pharmaceutically acceptable salts which are active when given orally or via buccal administration can be formulated as syrups, tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, glycerine or water with a flavouring or colouring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of the compound or salt in a sterile aqueous

or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil, or sesame oil. Such compositions can be administered, for example, by bolus injection or by infusion.

A typical suppository formulation comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats.

Typical transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer to himself a single dose.

Each such dosage unit suitably contains from 1 mg to 1 g, preferably from 5 mg to 500 mg, e.g. 100 mg or 200 mg, of a compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the compound itself.

A typical daily dosage regimen is 10 mg to 1 g for an average human weighing approximately 70 kg, administered in 1 to 4 dosage units, preferably 1 or 2.

The compositions of this invention, in addition to containing a compound of the formula (I) can also contain other agents; for example one or more agents chosen from phosphodiesterase inhibitors, hypolipidemic agents, platelet aggregation inhibitors, vasodilators, ß-adrenergic receptor blockers, ACE inhibitors, tissue plasminogen activator and other thrombolytics, and antiarrhythmics.

The compositions of the present invention are prepared by bringing the active constituent into association with a pharmaceutically acceptable carrier and optionally other excipients and ingredients as defined above.

As indicated above, compounds of the formula (I) have biological activity that is indicative of an ability to antagonise TXA_2 receptors. The TXA_2 activity has been demonstrated in the human platelet binding assay.

The platelet binding assay used was essentially the method described by Mais et al, J. Pharm. Exp. Ther., 1985, 235(3), 729-734 where [^{125}I]PTA-OH was used as the receptor ligand.

The IC_{50} values represent the concentration which produces a 50% inhibition of specific [^{125}I]PTA-OH binding.

The following Examples are illustrative of the invention.

In the Examples, all temperatures are in °C. Melting points are uncorrected and were obtained in an open capillary tube using a Büchi 510 Melting Point Apparatus.

Example 1

(a) Diethyl 2-(2-cyanoethyl)-2-(5-nitropyrid-2-yl)malonate

Sodium hydride (53% dispersion in oil) (30.71g, 0.66mole) was washed by decantation with xylene (2 x 150ml), ether (150ml), tetrahydrofuran (THF) (150ml) and finally suspended in THF (245ml). Diethyl 2-(2-cyanoethyl) malonate (156g, 0.73mole) in THF (80ml) was added dropwise over 1hr keeping the internal temperature at 18°C to 22°C (with ice bath cooling). The resulting suspension cleared over 15 minutes when 2-chloro-5-nitropyridine (88.3g, 0.55mole) was added to give a deep magenta solution. The resulting solution was refluxed for 1hr and the solvent was removed on the rotary evaporator. The resulting oil was partitioned between water (500ml) and chloroform (800ml), the pH was adjusted to ~7 (concentrated hydrochloric acid), and the chloroform was run off. The aqueous layer was extracted with a further (2 x 250ml) chloroform, the extracts were combined, dried over magnesium sulphate and the solvent was removed to give an amber oil (~245g). Ether (150ml) was added and the solution was allowed to crystallise to give the title compound (121.98g, 65%), m.p. 59.5-61°C.
(Found C, 53.7; H, 5.05; N, 12.35%. $C_{15}H_{17}N_3O_6$ requires C, 53.75; H, 5.1; N, 12.55%) NMR ($CDCl_3$, 60 MHz); δ 1.37 (6H, t); 2.65 (4H, m); 4.26 (4H, q); 7.84 (1H, dd); 8.49 (1H, dd); 9.32 (1H, dd).

(b) 4-(5-nitropyrid-2-yl)butanoic acid

A solution of diethyl 2-(2-cyanoethyl)-2-(5-nitropyrid-2-yl)malonate (50g, 0.15mole) in 48% w/v hydrobromic acid (200 ml) was refluxed for 2 hours. The pH of the solution

was adjusted to pH = 2 with 40% w/v sodium hydroxide solution. The resulting solution was extracted with chloroform (3 x 200ml). The combined chloroform extracts were dried over magnesium sulphate, evaporated to dryness and the residue was treated with charcoal in ethanol and recrystallised from ethanol to give the title compound (24.94g) as white needles. m.p. 108-110°C.

(c) Methyl 4-(5-aminopyrid-2-yl)butanoate

Hydrazine hydrate (10ml) in ethanol (20ml) was added over 30 minutes to a stirred suspension of 4-(5-nitropyrid-2-yl)butanoic acid (7.5g, 0.036mole) and 10% palladium on carbon (1g) in ethanol (100ml). The solution was stirred for 1 hour, filtered through hyflo and the filtrate was evaporated to dryness. The residue was dissolved in methanol (250ml) containing concentrated sulphuric acid (20ml) and the resulting solution was refluxed for 4 hours, cooled and the solvent was removed under reduced pressure. The residue was dissolved in water (100ml), basified and extracted with chloroform (3 x 100ml). The chloroform extracts were combined, dried over magnesium sulphate, and evaporated to dryness. The residue was distilled in a kugelrohr apparatus (oven temp. 145°C at 0.05mmHg) to give the title compound 3.84g as a straw coloured oil.

(d) Methyl 4-(5-Benzenesulphonamidopyrid-2-yl)butanoate

Triethylamine (1ml) in chloroform (10ml) was added over 10 minutes to a solution of methyl 4-(5-aminopyrid-2-yl)-butanoate (1.5g, 8.3mmole) and benzene sulphonyl chloride (2.2g, 12mmole) in chloroform (20ml). The solution was stirred for 4 hours. Chromatography on silica gel eluted with 5% v/v methanol in chloroform gave the title compound (1.46g) as a straw coloured oil.

(e) 4-(5-Benzenesulphonamidopyrid-2-yl)butanoic acid

A solution of methyl 4-(5-benzenesulphonamidopyrid-2-yl)-butanoate (1.3g, 4.2mmole) in ethanol (25ml) and 10% w/v sodium hydroxide solution (10ml) was stirred for 1 hour. The solution was treated with hydrochloric acid and the precipitate was collected by filtration. Recrystallisation from ethanol gave the title compound (0.94g) as white needles. m.p. 181-182°C. (Found: C, 56.18; H, 5.05; N, 8.74; S, 10.13%, $C_{15}H_{16}N_2O_4S$ requires C, 56.23; H, 5.03; N, 8.74; S, 10.0%).

Example 2

(a) 4-(5-Aminopyrid-2-yl)butanoic acid

A mixture of 4-(nitropyrid-2-yl)butanoic acid (15g) and 10% palladium on carbon (1.5g) in methanol (250ml) was shaken under an atmosphere of hydrogen at 50 p.s.i. until uptake of hydrogen was complete. The catalyst was removed by filtration and filtrate was evaporated to dryness. The residue was recrystallised from acetonitrile to give the title compound as cream coloured needles (11.27g). m.p. 101-102°C.

(b) 4-[5-(4-Chlorobenzenesulphonamido)pyrid-2-yl]-butanoic acid

4-Chlorobenzenesulphonyl chloride (1.17g) was added portionwise to a solution of 4-(5-aminopyrid-2-yl)butanoic acid (1g) in pyridine (15ml). The resulting solution was allowed to stand at room temperature overnight when the solvent was removed under reduced pressure. The residue was dissolved in dilute sodium hydroxide solution (50ml) and extracted with chloroform (4 x 50ml) and the

chloroform extracts were discarded. The aqueous layer was adjusted to pH=4 and was extracted with chloroform (3 x 100ml). The chloroform extracts were dried over magnesium sulphate, the solvent was removed and residue was recrystallised from acetonitrile/water 1:1 to give the title compound (0.7g) as white plates.

m.p. 178-180°C.

Anal.

Found: C = 50.97, H = 4.32, N = 7.82, Cl = 9.99, S = 8.76%

$C_{15}H_{15}ClN_2O_4S$ requires:

C = 50.78, H = 4.26, N = 7.90, Cl = 9.99, S = 8.76%

NMR (250 MHz) (d^6-dimethylsulphoxide)

δ(ppm) 1.82 (2H, m), 2.19 (2H, m), 2.62 (2H, m)
7.15 (1H, d), 7.40 (1H, dd), 7.63 (1H, m), 7.66 (1H, m),
8.16 (1H, m)

Infra Red (nujol mull) ν (cm^{-1}) 3088, 2430, 1669, 1608.

Example 3

(a) 5-Benzenesulphonamido-2-(3-cyanopropyl)-3-methylpyridine

A solution of 5-amino-2-(3-cyanopropyl)-3-methylpyridine* (5g) in chloroform (50ml) was treated with benzenesulphonyl chloride (7.35ml) and triethylamine (3ml) for 96 hours. The chloroform layer was extracted with dilute sodium hydroxide solution (2x50ml). The chloroform layer was discarded and the combined aqueous extracts were adjusted to pH=5 and extracted with chloroform (3x50ml). The combined extracts were dried over magnesium sulphate, the solvent was removed and the residue was chromatographed on silica gel eluted with 2% v/v methanol in chloroform to give the title compound (3.28g) as white prisms. m.p. 119-120°C.

*see Example 1 of U.S. 4,486,434.

(b) 4-(5-Benzenesulphonamido-3-methylpyrid-2-yl)-butanoic acid

A solution of 5-benzenesulphonamido-2-(3-cyano-propyl)-3-methylpyridine (1.5g) in ethanol (100ml) and 15% w/v sodium hydroxide solution (20ml) was refluxed for 8 hours. The ethanol was removed under reduced pressure and the pH of the remaining aqueous was adjusted to pH 4 when a white solid crystallised. The solid was collected and recrystallised from methanol to give the title compound (0.7g) as white needles. m.p. 169-179°C.

Example 4

(a) 3-Benzenesulphonamido-2-(3-cyanopropyl)pyridine

A solution of 3-amino-2-(3-cyanopropyl)pyridine* (5g, 0.031mole) in acetonitrile (50ml) was treated with benzenesulphonyl chloride (4ml) and pyridine (6ml). The solution was allowed to stand at room temperature overnight when the solvent was removed in vacuo. The residue was dissolved in dilute sodium hydroxide (100ml) and was extracted with chloroform (4x100ml) the chloroform extracts being discarded. The aqueous layer was adjusted to pH=4 and extracted with chloroform (3x100ml). The combined chloroform extracts were dried over magnesium sulphate, the solvent was removed to give the title compound (7.12g) as a cream coloured solid. m.p. 80-81°C.

*see Example 13 of U.S. 4,154,834

(b) 4-(3-Benzenesulphonamidopyrid-2-yl)butanoic acid

A solution of 3-benzenesulphonamido-2-(3-cyano-propyl)pyridine (5.22g) in ethanol (100ml) and 15% w/v sodium hydroxide solution (50ml) was refluxed for 6 hours.

The pH of the solution was adjusted to pH=4 when a white solid precipitated from the solution. The solid was collected by filtration and recrystallised from ethanol to give the title compound (3.34g) as white needles. m.p. 156-157°C.

Example 5

4-[5-(3-Chlorobenzenesulphonamido)pyrid-2-yl]butanoic acid

A solution of 3-chlorobenzenesulphonyl chloride (1.17g), dissolved in 5ml pyridine, was added dropwise to a solution of 4-(5-aminopyrid-2-yl)butanoic acid (1g) in pyridine (10ml). The resulting solution was allowed to stand at room temperature overnight when the solvent was removed under reduced pressure. The residue was taken up in dilute sodium hydroxide solution (40ml) and extracted with chloroform (4x50ml); the chloroform extracts were discarded. The aqueous layer was adjusted to pH4 with hydrochloric acid, extracted with chloroform (3x100ml) and then ethyl acetate (2x100ml). Chloroform and ethyl acetate extracts were dried over magnesium sulphate, solvents removed and residue recrystallised from acetonitrile/water to give the title compound (1.29g) as a white solid. m.p. 141°-142°C.

Example 6

(a) Diethyl 2-(3-cyanopropyl)-2-(5-nitropyrid-2-yl)malonate

Sodium hydride (50% dispersion in oil) (5.85g, 0.12mole) was washed by decantation with hexane (2 x 150ml), tetrahydrofuran (THF) (100ml) and was finally suspended in THF (160ml). Diethyl 2-(3-cyanopropyl) malonate (30g, 0.13mole) in THF (20ml) was added dropwise over 45

minutes keeping the internal temperature at 18°C to 22°C (with ice bath cooling). The resulting suspension cleared over 30 min when 2-chloro-5-nitropyridine (16.1g, 0.1mole) was added to give a deep magenta solution. The resulting solution was refluxed for 1hr and the solvent was removed on the rotary evaporator. The resulting oil was partitioned between water (100ml) and chloroform (200ml), the pH was adjusted to ~7 (concentrated hydrochloric acid), and the chloroform was run off. The aqueous layer was extracted with a further (2 x 250ml) chloroform, the extracts were combined, dried over magnesium sulphate and the solvent was removed to give the title compound as an amber oil (42.53g) which was used without further purification.

(b) 5-(5-Nitropyrid-2-yl)pentanoic acid

A solution of diethyl 2-(3-cyanopropyl)-2-(5-nitropyrid-2-yl)malonate (42.53g, 0.1mole) in 48% w/v hydrobromic acid (165ml) was refluxed for 3 hours. The pH of the solution was adjusted to pH = 3 with 40% w/v sodium hydroxide solution. The resulting solution was extracted with chloroform (3 x 200ml). The combined chloroform extracts were dried over magnesium sulphate, evaporated to dryness and the residue was treated with charcoal in ethanol and recrystallised from ethanol to give the title compound (12.12g) as white needles. m.p. 105-107°C.

(c) 5-(5-Aminopyrid-2-yl)pentanoic acid

A solution of 5-(5-nitropyrid-2-yl)pentanoic acid (6.0g) in ethanol (140ml) containing 10% palladium on carbon (0.6g) was shaken under an atmosphere of hydrogen at 3.4 atmospheres pressure for 1 hour. The catalyst was removed by filtration, the filtrate was evaporated to dryness and the residue was recrystallised from

acetonitrile to give the title compound as a cream coloured solid (4.04g). m.p. 80-82°C.

(d) 5-[5-(4-Chlorobenzenesulphonamido)pyrid-2-yl]-pentanoic acid

4-Chlorobenzenesulphonyl chloride (1.09g, 5.15mmole) was added portionwise over 10 minutes to a solution of 5-(5-aminopyrid-2-yl)pentanoic acid (1.00g, 5.15 mmole) in pyridine (15ml). The resulting solution was stirred for 18 hours when the solvent was removed and the residue was dissolved in dilute sodium hydroxide solution (30ml). This solution was extracted with ethyl acetate (4 x 50ml) the extracts being discarded. The aqueous layer was acidified (pH 3) and extracted with ethyl acetate (4 x 100ml). The combined ethyl acetate extracts were dried over magnesium sulphate, evaporated to dryness and the residue was recrystallised from acetonitrile to give the title compound (1.21g) as a pale yellow solid. m.p. 145-147°C.

Example 7

5-[5-(Benzenesulphonamido)pyrid-2-yl]pentanoic acid

Substituting benzenesulphonyl chloride (0.91g, 5.15mmole) for 4-chlorobenzenesulphonyl chloride in the method described in Example 6 gave the title compound (0.99g). m.p. 136-138°C.

Example 8

(a) Diethyl 2-(cyanomethyl)-2-(5-nitropyrid-2-yl)malonate

Sodium hydride (53% dispersion in oil) (5.17g, 0.1mole)

was washed by decantation with hexane (2 x 150ml), tetrahydrofuran (THF) (150ml) and was finally suspended in THF (150ml). Diethyl 2-(cyanomethyl)malonate (26.4g, 0.11mole) in THF (20ml) was added dropwise over 45 minutes keeping the internal temperature at 18°C to 22°C (with ice bath cooling). The resulting suspension cleared over 15 minutes when 2-chloro-5-nitropyridine (14.22g, 0.09mole) was added to give a deep magenta solution. The resulting solution was refluxed for 3 hours and the solvent was removed on the rotary evaporator. The resulting oil was partitioned between water (200ml) and chloroform (200ml), the pH was adjusted to ~7 (concentrated hydrochloric acid), and the chloroform was run off. The aqueous layer was extracted with a further (2 x 250ml) chloroform, the extracts were combined, dried over magnesium sulphate and the solvent was removed to give the title compound as an amber oil. Ether (25ml) was added and the solution was allowed to crystallise to give the title compound (18.48g).
m.p. 66-68°C.

(b) 3-(5-Nitropyrid-2-yl)propionic acid

A solution of diethyl 2-(cyanomethyl)-2-(5-nitropyrid-2-yl)malonate (18.44g, 0.057mole) in 48% w/v hydrobromic acid (100ml) was refluxed for 3.5 hours. The pH of the solution was adjusted to pH = 3 with 40% w/v sodium hydroxide solution. The resulting solution was extracted with chloroform (3 x 200ml). The combined chloroform extracts were dried over magnesium sulphate, evaporated to dryness and the residue was recrystallised from ethanol to give the title compound (8.24g).
m.p. 126-128°C.

(c) 3-(5-Aminopyrid-2-yl)propionic acid

A solution of 3-(5-nitropyrid-2-yl)propionic acid (4.50g) in ethanol (140ml) containing 10% palladium on carbon (0.45g) was shaken under an atmosphere of hydrogen at 3.4 atmospheres pressure for 1.5 hours. The catalyst was removed by filtration and the filtrate was evaporated to dryness. The residue was recrystallised from acetonitrile to give the title compound (3.43g) m.p. 118-120°C.

(d) 3-[5-(4-Chlorobenzenesulphonamido)pyrid-2-yl]propionic acid

A solution of 3-(5-aminopyrid-2-yl)propionic acid (1.00g) and 4-chlorobenzenesulphonyl chloride (1.27g) in pyridine (15ml) was stirred at room temperature overnight. The solvent was removed and the residue was dissolved in dilute sodium hydroxide (30ml) and extracted with chloroform (4 x 50ml). The aqueous layer was acidified with dilute hydrochloric acid (pH 3) and extracted with ethyl acetate (4 x 100ml). The ethyl acetate extracts were combined, dried over magnesium sulphate, the solvent was removed and the residue was recrystallised from acetonitrile to give the title compound (1.30g). m.p. 144-146°C.

Example 9

(a) Methyl 4-(5-chlorosulphonylpyrid-2-yl)butanoate

Sodium nitrite (6.08g) in water (12ml) was added over 20 minutes to a solution of methyl 4-(5-aminopyrid-2-yl)-butanoate (7.48g, 0.04 mole) in glacial acetic acid (20ml) and concentrated hydrochloric acid (32ml) stirred at -10°C. The solution was stirred for 15 minutes then

added over 15 minutes to a solution of cuprous chloride (2g) in glacial acetic acid saturated with sulphur dioxide at 10°C. The resulting solution was stirred at room temperature for 1 hour then poured into ice water (250ml) and extracted with chloroform (3 x 200ml). The chloroform extracts were dried over magnesium sulphate and the solvent was removed to give the title compound as a pale green oil which was used without further purification.

(b) Methyl 4-[5-(4-chlorophenylsulphamoyl)-pyrid-2-yl]butanoate

A mixture of methyl 4-(5-chlorosulphonylpyrid-2-yl) butanoate (2.5g), 4-chloroaniline (1.9g) and pyridine (10ml) was allowed to stand at room temperature overnight. The solvent was removed in vacuo and the residue was dissolved in water, acidified (pH 3) and extracted with chloroform (3 x 25ml). The chloroform extracts were dried over magnesium sulphate, the solvent was removed and the residue was chromatographed on silica gel, eluting with chloroform, and recrystallised from chloroform/hexane to give the title compound (1.26g) as white needles. m.p. 80-81°C.

(c) 4-[5-(4-Chlorophenylsulphamoyl)pyrid-2-yl]-butanoic acid

A solution of methyl 4-[5-(4-chlorophenylsulphamoyl)pyrid-2-yl]butanoate (0.8g), 10% w/v sodium hydroxide solution (5ml) in ethanol (15ml) was stirred for 1 hour. The solution was acidified with dilute hydrochloric acid (pH 3) and cooled to 5°C. The white precipitate was collected and recrystallised from ethanol to give the title compound (0.504g) as prisms. m.p. 150-152°C.

Anal.

Found, C = 50.78, H = 4.31, N = 7.88, Cl = 10.09,
S = 8.85%

$C_{15}H_{15}ClN_2O_4S$ requires C = 50.78, H = 4.26, N = 7.90,
Cl = 9.99, S = 9.04%.

Example 10

(a) Methyl 4-[5-(phenylsulphamoyl)pyrid-2-yl]butanoate

Substituting aniline (1.4g) in the previous example gave the title compound (1.17g) as needles from chloroform/hexane. m.p. 79-80°C.

(b) 4-[5-(Phenylsulphamoyl)pyrid-2-yl)]butanoic acid

A solution of methyl 4-[5-(phenylsulphamoyl)pyrid-2-yl]butanoate (0.7g), 10% w/v sodium hydroxide solution (5ml) in ethanol (10ml) was stirred for 1 hour. The solution was acidified with dilute hydrochloric acid (pH = 3) and cooled. The precipitate was collected and recrystallised from ethanol to give the title compound as prisms (0.56g). m.p. 158-159°C.

Anal.

Found C = 56.02, H = 5.08, N = 8.67, S = 10.14%

$C_{15}H_{16}N_2O_4S$ requires C = 56.24, H = 5.03, N = 8.74,
S = 10.01%

Example 11

4-[5-(4-Methoxybenzenesulphonamido)pyrid-2-yl]-butanoic acid

A solution of 4-methoxybenzenesulphonyl chloride (2.06g) and 4-(5-aminopyrid-2-yl)butanoic acid (1.8g) in pyridine (15ml) was allowed to stand at room temperature for 18

hours. The solvent was removed and the residue was dissolved in water and treated with dilute hydrochloric acid to give a solution at pH 4.5. The resulting precipitate was collected and recrystallised from ethanol to give the title compound (1.96g) as prisms.
m.p. 129-130°C.
Anal.
Found: C = 55.06, H = 5.15, N = 8.06, S = 9.01%
$C_{16}H_{18}N_2O_5S$ requires:
C = 54.84, H = 5.18, N = 8.00, S = 9.15%

Example 12

4-[5-(3-Trifluoromethylbenzenesulphonamido)-pyrid-2-yl]butanoic acid

Substituting 3-trifluoromethylbenzenesulphonyl chloride (2.44g) in Example 11 gave the title compound (2.37g) as prisms from ethanol-water. m.p. 157-159°C.
Anal.
Found: C = 49.59, H = 3.95, N = 7.22, S = 8.33%
$C_{16}H_{15}F_3N_2O_4S$ requires:
C = 49.48, H = 3.89, N = 7.21, S = 8.25%

Example 13

4-[5-(4-Bromobenzenesulphonamido)pyrid-2-yl]butanoic acid

Substituting 4-bromobenzenesulphonyl chloride (2.55g) in Example 11 gave the title compound (2.27g) as prisms from ethanol. m.p. 188-190°C.
Anal.
Found: C = 45.17, H = 3.89, N = 6.86, Br = 19.96, S = 7.78%
$C_{15}H_{15}N_2BrO_4S$ requires:
C = 45.12, H = 3.79, N = 7.02, Br = 20.01, S = 8.03%

Example 14

4-[5-(4-Methylbenzenesulphonamido)pyrid-2-yl]butanoic acid

Substituting 4-toluenesulphonyl chloride (1.90g) in Example 11 gave the title compound (2.57g) as prisms from ethanol. m.p. 154-155°C.

Anal.

Found: C = 57.34, H = 5.42, N = 8.29, S = 9.43%

$C_{16}H_{18}N_2O_4S$ requires:

C = 57.47, H = 5.43, N = 8.38, S = 9.59%

Example 15

4-[5-(3,4-Dichlorobenzenesulphonamido)-pyrid-2-yl]butanoic acid

Substituting 3,4-dichlorobenzenesulphonyl chloride (1.47g) in Example 11 gave the title compound (1.80g) as prisms. m.p. 193-194°C.

Anal.

Found: C = 46.21, H = 3.58, N = 6.97, Cl = 18.09, S = 7.78%

$C_{15}H_{14}N_2ClO_4S$ requires:

C = 46.28, H = 3.60, N = 7.19, Cl = 18.22, S = 8.23%

Example 16

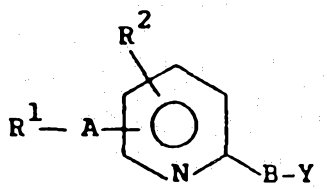
Biological Activity

The compounds of Examples 1 and 5 were tested in the human platelet binding assay. The results obtained are shown in the Table below :

Compound of Example No.	Human Platelet Binding IC_{50}(μm)
1	1.3
2	0.36
3	2.6
4	102.0
5	1.2
6	1.0
7	4.0
8	251.0
9	21.0
10	28.0
11	5.2
12	16.0
13	0.2
14	0.6
15	2.1

The claims defining the invention are as follows:

1. A compound of the formula (I):



(I)

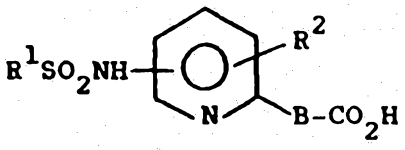
and salts thereof; wherein
A is a group NR^3SO_2 or SO_2NR^3; B is C_{1-6}alkylene;
Y is:
C_{1-4}alkoxycarbonyl, carbamoyl, monoC_{1-6}alkylcarbamoyl or diC_{1-6}alkylcarbamoyl ;

R^1 is phenyl optionally substituted by one or more substituents chosen from the group consisting of halogen, C_{1-4}alkyl, C_{1-6}acyl, C_{1-4}alkoxy, nitro and trifluoromethyl, provided that when R^1 is phenyl substituted by two or more substituents, no more than one substituent can be meta-trifluoromethyl;
R^2 is hydrogen or one or more C_{1-4}alkyl substituents;
and R^3 is hydrogen or C_{1-6}alkyl.

2. A compound according to claim 1 wherein Y is CO_2H.

3. A compound according to either of claims 1 or 2 wherein R^3 is hydrogen or methyl.

4. A compound according to claim 1 having the general formula (II):



(II)

and salts thereof; wherein R^1, R^2 and B are as defined in claim 1.

5. A compound according to any one of claims 1 to 4 wherein R^1 is chosen from unsubstituted phenyl or mono-substituted phenyl, wherein the substituent is attached to the 3- or 4-position of the phenyl ring and is chosen from chloro, bromo, methyl, trifluoromethyl and methoxy.

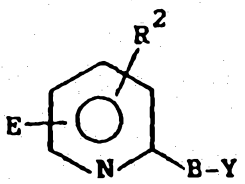
6. A compound according to any one of claims 1 to 5 wherein B is selected from propane-1, 3-diyl and butane-1, 4-diyl.

7. A compound according to claim 6 wherein B is propane-1,3-diyl.

8. A compound according to claim 1 which is
4-(5-benzenesulphonamidopyrid-2-yl)butanoic acid,
4-[5-(4-chlorobenzenesulphonamido)pyrid-2-yl]butanoic acid,
4-(5-benzenesulphonamido-3-methylpyrid-2-yl)butanoic acid,
5-[5-(4-chlorobenzenesulphonamido)pyrid-2-yl]pentanoic acid,
4-[5-(3-chlorobenzenesulphonamido)pyrid-2-yl]butanoic acid.
4-[5-(3,4-dichlorobenzenesulphonamido)pyrid-2-yl]butanoic acid,
4-[5-(4-bromobenzenesulphonamido)pyrid-2-yl]butanoic acid,
or
4-[5-(4-methylbenzenesulphonamido)pyrid-2-yl]butanoic acid.

9. A pharmaceutical composition comprising a compound as defined in any one of claims 2 to 8 and a pharmaceutically acceptable carrier.

10. A process for the preparation of a compound as defined in any one of claims 1 to 8 which process comprises reaction of a compound of the formula (III):



(III)

wherein E is amino or a group SO_2L;

R^2 is as defined above; and

L is a leaving group displaceable by amino;

with a compound of the formula R^1M wherein M is amino or a group SO_2L, provided that one of E and M is SO_2L and the other is amino; and thereafter, where necessary, hydrolysing Y to give CO_2H.

11. A compound according to any one of claims 1 to 9 substantially as described herein with reference to the Examples.

12. A compound of the formula (I) substantially as described herein with reference to the Examples.

13. A process according to claim 10 substantially as described herein with reference to the Examples.

Dated this 3rd day of April, 1990
SMITHKLINE & FRENCH LABORATORIES LIMITED
By its Patent Attorneys
DAVIES & COLLISON