628060 COMMONWEALTH OF AUSTRALIA

Patents Act 1952

APPLICATION FOR A PATENT

We, **GLAXO GROUP LIMITED**, a British Company, of Clarges House, 6-12 Clarges Street, London W1Y 8DH, England, hereby apply for the grant of a Patent for an invention entitled: **"CEPHALOSPORIN ANTIBIOTICS"** which is described in the accompanying complete specification.

This application is a separate application made by virtue of sub-section (1) of Section 51 of the Patents Act 1952 in respect of an invention disclosed in the complete specification lodged in respect of Application No. 49305/85 in the name of **GLAXO GROUP LIMITED.**

Our address for service is: Care of Callinans, Patent and Trade Mark Attorneys, of 48 to 50 Bridge Road, Richmond, Victoria, 3121, Australia.

D A T E D this 28th day of June, 1989.

GLAXO GROUP LIMITED

By its Patent Attorneys:

CALLINANS

To: The Commissioner of Patents

M C10269 280689

COMMONWEALTH OF AUSTRALIA

The Patents Act 1952

DECLARATION IN SUPPORT

of the Application made by:

GLAXO GROUP LIMITED

(hereinafter termed "the applicant") for a patent for an invention entitled

"CEPHALOSPORIN ANTIBIOTICS"

I/~~We~~ Barry Anthony Newsam

of Glaxo Group Limited

do solemnly and sincerely declare as follows:

~~*I am/We are the applicant ,* or~~

I am/~~We are~~ authorised by the applicant to make this declaration on its/~~their~~ behalf.

RICHARD BELL, of 42c Edwards Avenue, South Ruislip, Middlesex, England; MICHAEL WALTER FOXTON, of The Finches, Mill Lane, Chalfont St. Giles, Buckinghamshire, England; and BRIAN EDGAR LOOKER, of 28 Middleton Avenue, Greenford, Middlesex, England

are the actual inventors of the invention and the facts upon which the applicant is entitled to make the application are as follows:

Glaxo Group Research Limited would, if a patent was to be granted upon an application made by the said actual inventors, be entitled to have the patent assigned to it; and the applicant is the assignee of rights to the invention from Glaxo Group Research Limited.

DECLARED at Greenford *this* 23rd *day of* September 1991 ~~1989~~.

Signed: _____

B.A. Newsam

(12) PATENT ABRIDGMENT (11) Document No. AU-B-37110/89
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 628060

(54) Title
CEPHALOSPORIN ANTIBIOTICS

International Patent Classification(s)
(51)[4] **C07D 277/42**

(21) Application No. : **37110/89** (22) Application Date : **28.06.89**

(30) Priority Data

(31) Number	(32) Date	(33) Country
8427807	02.11.84	GB UNITED KINGDOM
8427808	02.11.84	GB UNITED KINGDOM
8427809	02.11.84	GB UNITED KINGDOM
8521975	04.09.85	GB UNITED KINGDOM
8521976	04.09.85	GB UNITED KINGDOM

(43) Publication Date : **02.11.89**

(44) Publication Date of Accepted Application : **10.09.92**

(62) Related to Division(s) : **49305/85**

(71) Applicant(s)
GLAXO GROUP LIMITED

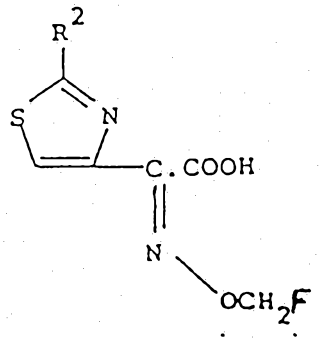
(72) Inventor(s)
RICHARD BELL; MICHAEL WALTER FOXTON; BRIAN EDGAR LOOKER

(74) Attorney or Agent
CALLINAN LAWRIE , Private Bag 7, KEW VIC 3101

(56) Prior Art Documents
GB 2039890
GB 2025933
GB 1600736

(57) Claim

1. Compounds of general formula (III)



(III)

(wherein R^2 is an amino, tritylamino, chloroacetylamino or formylamino group) and salts, acid halides, activated esters and symmetrical and mixed anhydrides thereof.

AUSTRALIA

Form 10

PATENTS ACT 1952

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE 628060

Short Title:

Int. Cl:

Application Number:
Lodged:

Complete Specification - Lodged:
Accepted:
Lapsed:
Published:

Priority:

Related Art:

TO BE COMPLETED BY APPLICANT

Name of Applicant: GLAXO GROUP LIMITED

Address of Applicant: Clarges House, 6-12 Clarges Street, London W1Y 8DH, England.

Actual Inventor: RICHARD BELL, MICHAEL WALTER FOXTON, BRIAN EDGAR LOOKER.

Address for Service: CALLINANS, Patent Attorneys, of 48-50 Bridge Road, Richmond, 3121, Victoria, Australia.

Complete Specification for the invention entitled:

"CEPHALOSPORIN ANTIBIOTICS"

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

"CEPHALOSPORIN ANTIBIOTICS"

This invention relates to improvements in -- relating to cephalosporins. More particularly it relates to intermediates for the production of new cephalosporin compounds having valuable antibiotic activity.

The cephalosporin compounds in this specification are named with reference to "cepham" after J.Amer.Chem. Soc., 1962, 84, 3400, the term "cephem" referring to the basic cepham structure with one double bond.

Cephalosporin antibiotics are widely used in the treatment of diseases caused by pathogenic bacteria in human beings and animals, and are especially useful in the treatment of diseases caused by bacteria which are resistant to other antibiotics such as penicillin compounds, and in the treatment of penicillin-sensitive patients. In many instances it is desirable to employ a cephalosporin antibiotic which exhibits activity against both Gram-positive and Gram-negative microorganisms, and a significant amount of research has been directed to the development of various types of broad spectrum cephalosporin antibiotics.

Thus, for example, in our British Patent Specification No. 1399086, we describe a novel class of cephalosporin antibiotics containing a 7β-(α-etherified oxyimino)-acylamido group, the oxyimino group having the syn configuration. This class of antibiotic compounds is characterised by high antibacterial activity against a range of Gram-positive and Gram-negative organisms coupled with particularly high stability to β-lactamases produced by various Gram-negative organisms.

The discovery of this class of compounds has stimulated further research in the same area in attempts to find compounds which have improved

properties, for example against particular classes of organisms, especially Gram-negative organisms. This interest is reflected in the very large numbers of patent applications which have been filed relating to cephalosporin antibiotics having particular oxyimino etherifying groups in combination with particular substituents both on the 7β-acylamido side chain and at the 3-position of the cephalosporin nucleus.

In British Patent Specification No. 1604971 a wide variety of cephalosporin antibiotics are generically disclosed in which the 7β-position side-chain may be selected from, inter alia, a 2-(2-aminothiazol-4-yl)-2-(etherified oxyimino)acetamido group, in which the etherifying group, amongst very many possible meanings, may be an alkyl group (e.g. methyl substituted by a halogen atom, although there is no specific exemplification of compounds having such a group and the preferred etherifying group is stated to be an unsubstituted methyl group. Preferred halogen atoms are stated to be chlorine and bromine atoms. The 3-position group may also be selected from a very large number of alternatives and possible 3-substituents include alkoxymethyl, optionally substituted pyridiniummethyl, optionally substituted carbamoyloxymethyl, hydroxymethyl, acetoxymethyl, halomethyl, alkoxymethyl and hydrogen. British Patent Specification No. 1604971 describes cephalosporins having sulphur at the 1-position while British Patent Specification No. 1603212 describes related sulphoxides.

British Patent Specification No. 1576625 contains a generic definition of cephalosporin compounds having a 7β-(α-etherified oxyimino)acetamido side chain wherein the etherifying group is an aliphatic hydrocarbon group which may have suitable substituent(s) (although the "suitable substituent(s)"

specifically mentioned for illustration do not include halogen atoms), which side chain is further α-substituted by a group which inter alia may be an aminothiazolyl group. The 3-position group may also be selected from a large number of alternatives and possible 3-substituents within the generic definition are hydroxymethyl, acetoxymethyl, halomethyl and optionally substituted carbamoyloxymethyl groups.

In British Patent Application No. 2039890A a wide variety of cephalosporin antibiotics are generically disclosed in which the 7β-position side chain is a 2-(2-aminothiazol-4-yl)-2-(etherified oxyimino)-acetamido group. One possible etherifying group recited is a halo-lower-alkyl group (with a fluoromethyl group being mentioned inter alia as an illustration). According to the generic definition, the 3-position of the cephalosporin nucleus may inter alia be a carbamoyloxymethyl group. However, in the compounds specifically exemplified, only 2-bromoethyl, 2-chloroethyl and 2,2,2-trifluoroethyl groups are found as examples of halo-lower-alkyl groups.

In British Patent Application No. 2017702A the corresponding oxyimino etherifying group, according to the generic definition, may inter alia be a straight-chain C_{1-4} alkyl group terminally monosubstituted e.g. by a halogen atom. The 3-position group of the cephalosporin nucleus may, according to the generic definition, inter alia be a carbamoyloxymethyl group. However, in the compounds specifically exemplified, only 2-bromoethyl and 2-iodoethyl groups are found as examples of haloalkyl groups.

European Patent Application No. 111935 generically defines cephalosporin compounds in which the 7β-position side chain may be selected from, inter alia, a 2-(2-aminothiazol-4-yl)-2-(etherified

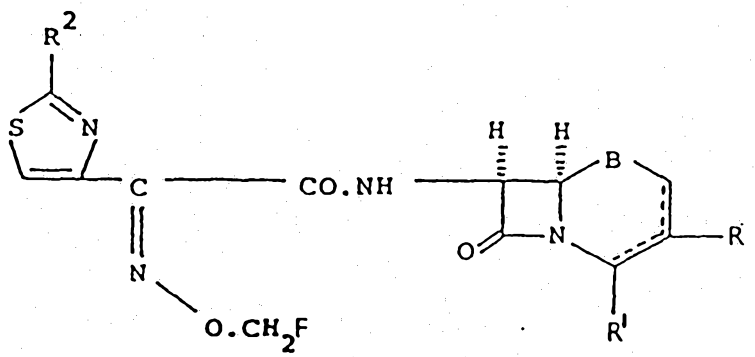
oxyimino)acetamido group in which the etherifying group may be chosen from a large number of possibilities, including alkyl groups which may carry, inter alia, one or more halogen atoms. According to the generic definition, the 3-position group of the cephalosporin nucleus may inter alia be a carbamoyloxymethyl, acetoxymethyl or halomethyl group. These compounds have no stated antibiotic utility, being solely for use as intermediates in the synthesis of the final products which are restricted to 3-quinoliniummethyl and 3-isoquinoliniummethyl compounds. However, in the compounds specifically exemplified, only difluoromethyl and 2,2,2-trifluoroethyl groups are found as examples of haloalkyl oxime groups, and these are only present in combination with isoquinoliniummethyl and 4-methylquinoliniummethyl groups at the 3-position in the final products of the processes, and not in the intermediate cephalosporin compounds.

British Patent Specification No. 1600735 also discloses a large number of cephalosporin antibiotics including within its generic disclosure compounds in which the 7-substituent is a 2-(2-aminothiazol-4-yl)-2-(etherified oxyimino)acetamido group, the oxime etherifying group being defined inter alia as an aliphatic hydrocarbon residue which may be substituted by halogen. Fluoromethyl is mentioned as an example of an etherifying group but the specific exemplification illustrates only chloroethyl and 2,2,2-trifluoroethyl groups. The 3-substituent may be inter alia hydrogen.

We have now discovered that by the selection of a (Z)-2-(2-aminothiazol-4-yl)-2-(etherified oxyimino)-acetamido group at the 7β-position in combination with hydrogen or certain specific groupings at the 3-position, and also by the selection of a monofluoromethoxyimino group as the etherified

oxyimino grouping, cephalosporin compounds having a particularly advantageous profile of activity (described in more detail below) against a wide range of commonly encountered pathogenic organisms may be obtained.

Our copending Application No. 49305/85 from which this application is divided provides compounds of the general formula (I)



(I)

(where R^1 is a carboxyl group, a group $COO^{\ominus}$ or a blocked carboxyl group;

R^2 is an amino or protected amino group;

R is hydrogen or a group of the formula CH_2X, where X represents a halogen atom, a hydroxyl group, an acetoxy group; a group of the formula $O.CO.NHR^3$, where R^3 is hydrogen, a C_{1-4} alkyl group optionally substituted by 1 to 3 halogen atoms or an N-protecting group; a group of the formula OR^4, where R^4 is a C_{1-4} alkyl group optionally substituted by halogen or a C_{1-4} alkoxy group; or a pyridinium, 3-carbamoyl-pyridinium or 4-carbamoyl-pyridinium group;

B is -S- or -SO-(α- or β-); and the dotted line bridging the 2-, 3- and 4- positions indicates that the compound is a ceph-2-em or ceph-3-em compound) and salts thereof, the compound of formula (I) being associated with an anion when X represents a pyridinium, 3-carbamoylpyridinium group or 4-carbamoyl-pyridinium group and R^1 is other than COO^-.

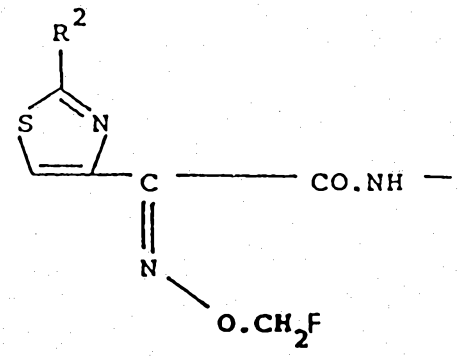
Where R^1 is a blocked carboxyl group the blocking group may, for example, be the residue of an ester-forming aliphatic or araliphatic alcohol or of an ester-forming phenol, silanol or stannanol (the said alochol, phenol, silanol or stannanol preferably containing from 1 to 20 carbon atoms)

Where R^2 is a protected amino group, the protecting group may be, for example, a trityl or acyl (for example chloroacetyl or formyl) group or the amino group may be protonated.

The compounds of formula (I) are syn isomers. The syn isomeric form is defined by the configuration of the

$$-O.CH_2F$$

group with respect to the carboxamido group. In this specification, the syn configuration is denoted structurally as



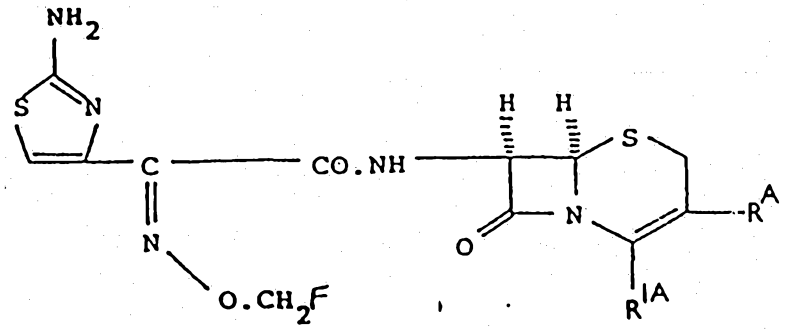
It will be understood that since the compounds of formula I are geometric isomers, some admixture

with the corresponding anti isomer may occur.

The compounds of formula (I) include both active antibiotics and intermediates for their preparation. This is set out in greater detail hereinafter.

It will be appreciated that salts of the compounds for use in medicine should be non-toxic. Similarly where R^1 is a carboxyl blocking group in compounds to be used in medicine, this should represent a metabolically labile non-toxic ester function.

Thus, antibiotically active compounds of formula I may be represented by the general formula (Ia)



(Ia)

(wherein R^A is hydrogen, an acetoxymethyl group, a group of formula $CH_2O.CO.NHR^{3A}$ where R^{3A} is hydrogen or a C_{1-4} alkyl group optionally substituted by 1 to 3 halogen atoms; a group of the formula CH_2OR^4, where R^4 is as defined above; or a pyridiniummethyl, 3-carbamoylpyridiniummethyl or 4-carbamoylpyridiniummethyl group, and R^{1A} is a carboxyl group or, when R^A is a pyridiniummethyl, 3-carbamoyl-pyridiniummethyl or 4-carbamoylpyridiniummethyl group, a group $COO^{\ominus}$, and the non-toxic salts and non-toxic metabolically labile esters thereof.

As indicated above certain of the compounds of formula I may be used as starting materials for the preparation of other cephalosporins having antibiotic activity. In particular, compounds

of formula (I) in which R is CH_2X where X is a leaving group such as a halogen atom or a hydroxy or acyloxy group may be used for preparing other cephalosporins possessing a syn 2-(2-aminothiazol-4-yl)-2-monofluoromethoxyiminoacetamido group at the 7β-position and a different substituent at the 3-position. This is set out in greater detail hereinafter.

The compounds of formula (Ia) and their non-toxic salts and metabolically labile esters exhibit broad spectrum antibiotic activity both in vitro and in vivo. They have high activity against both Gram-positive and Gram-negative organisms, including many β-lactamase producing strains. The compounds also possess high stability to β-lactamases produced by a range of Gram-negative and Gram-positive organisms.

Compounds of formula Ia have been found to exhibit high activity against strains (including penicillinase-producing strains) of Gram-positive bacteria such as Staphylococcus aureus, Staphylococcus epidermidis and Streptococcus species. This is coupled with high activity against various members of the Enterobacteriaceae (e.g. strains of Escherichia coli, Klebsiella pneumoniae, Citrobacter diversus, Enterobacter cloacae, Serratia marcescens, Proteus mirabilis and indole-positive Proteus organisms such as Proteus vulgaris, Proteus morganii and Providence species) and strains of Haemophilus influenzae and Acinetobacter calcoaceticus as well as good activity against Pseudomonas species. This combination of high activity against Gram-positive organisms with high activity against Gram-negative organisms possessed by the compounds of the invention is unusual and particularly advantageous.

Compounds of formula Ia is which R is a pyridinium-methyl group have shown especially high activity

against the above organisms, in particular against Enterobacter, Acinetobacter and Pseudomonas.

Non-toxic salt derivatives which may be formed by reaction of the carboxyl group present in the compounds of formula (I) include inorganic base salts such as alkali metal salts (e.g. sodium and potassium salts) and alkaline earth metal salts (e.g. calcium salts); amino acid salts (e.g. lysine and arginine salts); organic base salts (e.g. procaine, phenylethylbenzylamine, dibenzylethylenediamine, ethanolamine, diethanolamine and N-methylglucosamine salts). Other non-toxic salt derivatives include acid addition salts, e.g. formed with hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, formic and trifluoroacetic acids. The salts may also be in the form of resinates formed with, for example, a polystyrene resin or cross-linked polystyrene divinylbenzene copolymer resin containing amino or quaternary amino groups or sulphonic acid groups, or with a resin containing carboxyl groups, e.g. a polyacrylic acid resin. Soluble base salts (e.g. alkali metal salts such as the sodium salt) of the compounds of formula (I) may be used in therapeutic applications because of the rapid distribution of such salts in the body upon administration. Where, however, insoluble salts of compounds (I) are desired in a particular application, e.g. for use in depot preparations, such salts may be formed in conventional manner, for example with appropriate organic amines.

Non-toxic metabolically labile ester derivatives which may be formed by esterification of the carboxyl group in the parent compound of formula (I) include acyloxyalkyl esters, e.g. lower alkanoyloxy-methyl or -ethyl esters such as acetoxy-methyl or -ethyl or pivaloyloxymethyl esters. In addition to the above ester derivatives, the present invention

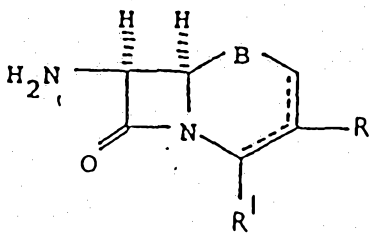
includes within its scope the compounds of formula (I) in the form of other physiologically acceptable equivalents, i.e. physiologically acceptable compounds which, like the metabolically labile esters, are converted in vivo into the parent antibiotic compound of formula (I).

These and other salt and ester derivatives such as the salts with toluene-p-sulphonic and methanesulphonic acids or the esters with t-butyl or diphenylmethyl esterifying groups may be employed as intermediates in the preparation and/or purification of the present compounds of formula (I), for example in the processes described below.

It will be appreciated that the compounds of formula (I) wherein R is a pyridiniummethyl group, a 3-carbamoylpyridiniummethyl group or a 4-carbamoylpyridinium methyl group and wherein R^1 is not a blocked carboxy group are usually present in the form of a betaine containing a positively-charged pyridinium group and a carboxylate group, and therefore esters and salts of compounds of formula (I) with bases will be associated with an anion to balance the positive charge on the pyridinium ring. Such an anion will also be non-toxic and may be derived from any of the acids described above which will form non-toxic salt derivatives.

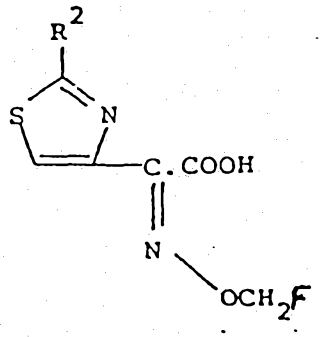
The compounds of formula (I) may be used for treating a variety of diseases caused by pathogenic bacteria in human beings and animals, such as septicaemia, respiratory tract infections, skin and soft tissue infections and urinary tract infections.

The parent application No. 49305/85 referred to above also provides a process for the preparation of compounds of general formula (I) as hereinbefore defined which comprises acylating a compound of the formula (II)



(II)

(wherein R, R^1, B and the dotted line are as defined above) which may be in the form of a salt, e.g. a betaine or an acid addition salt (the anion of which may be derived, for example, from a mineral acid such as hydrochloric, hydrobromic, sulphuric, nitric or phosphoric acid or an organic acid such as methanesulphonic or toluene-p-sulphonic acid) or an N-silyl derivative thereof, with an acid of formula (III)



(III)

(wherein R^2 is as defined above) or a salt thereof or with an acylating derivative thereof;

whereafter, if necessary and/or desired in each instance, any of the following reactions, in any appropriate sequence, are carried out:-

i) conversion of a Δ^2-isomer into the desired Δ^3-isomer,

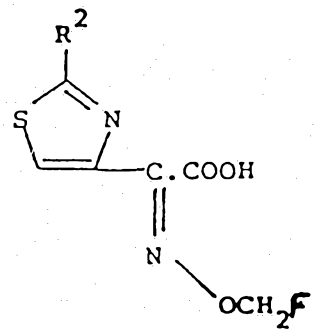
ii) reduction of a compound wherein B is -SO- to form a compound wherein B is -S-,

iii) conversion of a carboxyl group into a non-toxic metabolically labile ester function,

iv) formation of a non-toxic salt function, and

v) removal of any carboxyl blocking and/or N-protecting groups.

The present invention now provides compounds of general formula (III)



(wherein R^2 is an amino, tritylamino, chloroacetylamino or formylamino group) and salts thereof.

Acylating derivatives of formula III which may be employed in the preparation of compounds of formula (I) include acid halides, particularly acid chlorides or bromides. Such acylating agents may be prepared by reacting an acid (III) or a salt thereof with a halogenating agent e.g. phosphorus pentachloride, thionyl chloride or oxalyl chloride.

Acids of formula (III) may themselves be used as acylating agents in the preparation of compounds of formula (I). Acylations employing acids (III) are desirably conducted in the presence of a condensing agent, for example a carbodiimide such as N,N'-dicyclohexylcarbodiimide or N-ethyl-N'- -dimethylamino-propylcarbodiimide; a carbonyl compound such as

carbonyldiimidazole; an isoxazolium salt such as N-ethyl-5-phenylisoxazolium perchlorate; or N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline.

Acylation may also be effected with other amide-forming derivatives of acids of formula (III) such as, for example, an activated ester, a symmetrical anhydride or a mixed anhydride (e.g. formed with pivalic acid or with a haloformate, such as a lower alkylhaloformate). Mixed anhydrides may also be formed with phosphorus acids (for example phosphoric or phosphorous acids), sulphuric acid or aliphatic or aromatic sulphonic acids (for example toluene-p-sulphonic acid). An activated ester may conveniently be formed <u>in situ</u> using, for example, 1-hydroxybenzotriazole in the presence of a condensing agent as set out above. Alternatively, the activated ester may be preformed.

An alternative method of activation is, for example, by reacting an acid of formula (III) with a solution or suspension preformed by adding a carbonyl halide, in particular oxalyl chloride or phosgene, or a phosphoryl halide such as phosphorus oxychloride to a solvent such as a halogenated hydrocarbon, for example methylene chloride, containing a lower acyl tertiary amide such as N,N-dimethylformamide. The activated form of the the acid of formula (III) may then be reacted with a 7-amino compound of formula (II) in a suitable solvent or mixture of solvents for example an alcohol such as an alkanol, e.g. ethanol or methanol; halogenated hydrocarbons, e.g. dichloromethane; esters, e.g. ethyl acetate; ethers, e.g. dioxan or tetrahydrofuran; ketones, e.g. acetone; amides, e.g. dimethylacetamide; acetonitrile; water; and mixtures thereof. The acylation reaction may conveniently be effected at temperatures of from -50° to +50°C, preferably -40° to +30°C, if desired in the presence of an acid binding agent,

for example as described above (e.g. triethylamine, dimethylaniline or sodium bicarbonate).

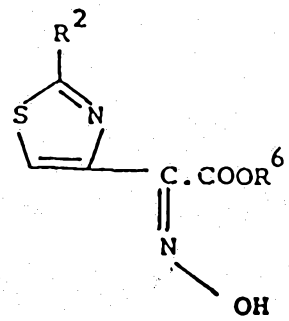
If desired, the above acylation reactions may be carried out in the presence of a catalyst such as 4-dimethylaminopyridine.

The acids of formula (III) and acylating agents corresponding thereto may, if desired, be prepared and employed in the form of their acid addition salts. Thus, for example, acid chlorides may conveniently be employed as their hydrochloride salts, and acid bromides as their hydrobromide salts.

In any of the foregoing reactions, the reaction product may be separated from the reaction mixture by a variety of processes including recrystallisation, ionophoresis, column chromatography and use of ion-exchangers (for example by chromatography on ion-exchange resins) or macroreticular resins.

The compounds of general formula (III) and acid halides and anhydrides corresponding thereto are preferably in their syn isomeric form or in the form of mixtures of the syn isomers and the corresponding anti isomers containing at least 90% of the syn isomer are preferably used.

Acids of formula (III) and their derivatives may be prepared by etherification of a compound of formula (VI)



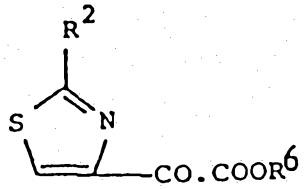
(VI)

(wherein R^2 is as hereinbefore defined and R^6 represents hydrogen or a carboxyl blocking group) or a salt thereof, by selective reaction with a compound of general formula (VII)

$$T.CH_2F \qquad (VII)$$

(wherein T is chloro, bromo or iodo), followed by removal of any carboxyl blocking group R^6. Separation of isomers may be effected either before or after such etherification. The etherification reaction is conveniently carried out in the presence of a base, e.g. potassium carbonate or sodium hydride, and is preferably conducted in an organic solvent, for example dimethylsulphoxide, a cyclic ether such as tetrahydro-furan or dioxan, or an N,N-disubstituted amide such as dimethylformamide. Under these conditions the configuration of the oxyimino group is substantially unchanged by the etherification reaction. When the compound of formula (VII) is employed in the form of a free acid or a salt with a base, the etherification reaction is generally carried out in the presence of a strong base, e.g., potassium t-butoxide, sufficient base being added to form a dianion. Furthermore, the reaction should be effected in the presence of a base if an acid addition salt of a compound of formula (VI) is used, the amount of base being sufficient to neutralise rapidly the acid in question.

Acids of formula (III) may also be prepared by reaction of a compound of formula (VIII)



(VIII)

(wherein R^2 and R^6 are as hereinbefore defined) with a compound of formula (IX)

$$H_2N.O.CH_2F \qquad (IX)$$

followed by removal of any carboxyl blocking group R^6, and where necessary the separation of syn and anti isomers.

The acids of formula (III) may be converted into the corresponding acid halides and anhydrides and acid addition salts by conventional methods, for example as described hereinabove.

It should be appreciated that in some of the above transformations it may be necessary to protect any sensitive groups in the molecule of the compound in question to avoid undesirable side reactions. Examples of suitable protecting groups are given in "Protective Groups in Organic Synthesis" by Theodora W. Greene (John Wiley and Sons, 1981). For example, during any of the reaction sequences referred to above it may be necessary to protect the NH_2 group of the aminothiazolyl moiety, for example by tritylation, acylation (e.g. chloroacetylation or formylation), protonation or other conventional method. The protecting group may thereafter be removed in any convenient way which does not cause breakdown of the desired compound, e.g. in the case of a trityl group by using an optionally halogenated carboxylic acid, e.g. acetic acid,

formic acid, chloroacetic acid or trifluoroacetic acid or using a mineral acid, e.g. hydrochloric acid or mixtures of such acids, preferably in the presence of a protic solvent such as water, or, in the case of a chloroacetyl group, by treatment with thiourea.

Carboxyl blocking groups used in the preparation of compounds of formula (III) or in the preparation of necessary starting materials are desirably groups which may readily be split off at a suitable stage in the reaction sequence, conveniently at the last stage. It may, however, be convenient in some instances to employ non-toxic metabolically labile carboxyl blocking groups such as acyloxy-methyl or -ethyl groups (e.g. acetoxy-methyl or-ethyl or pivaloyloxymethyl) and retain these in the final product to give an appropriate ester derivative of a compound of formula (I).

Suitable carboxyl blocking groups are well known in the art, a list of representative blocked carboxyl groups being included in British Patent No. 1399086. Preferred blocked carboxyl groups include aryl lower alkoxycarbonyl groups such as p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl and diphenylmethoxycarbonyl; lower alkoxycarbonyl groups such as t-butoxycarbonyl; and lower haloalkoxy-carbonyl groups such as 2,2,2-trichloroethoxycarbonyl. The carboxyl blocking group may subsequently be removed by any of the appropriate methods disclosed in the literature; thus, for example, acid catalysed hydrolysis or reduction is applicable in many cases, as is enzymically-catalysed hydrolysis.

The following Example illustrates the invention. All temperatures are in °C; DMSO is dimethylsulphoxide; EtOH is ethanol; Kieselgel 60 is silica gel manufactured by E. Merck and Co. of Darmstadt, West Germany. (Kieselgel is a registered Trade Mark).

Example

(a) Ethyl (Z)-2-fluoromethoxyimino-2-(2-triphenylmethylaminothiazol-4-yl)acetate

Ethyl (Z)-2-hydroxyimino-2-(2-triphenylmethylaminothiazol-4-yl)acetate, hydrochloride salt (8.7g) was stirred with potassium carbonate (15.35g) in dimethyl sulphoxide (30ml) under nitrogen at 21°. Bromofluoromethane (ca 3g) was added. The nitrogen flow was stopped and the stirring continued for two hours. The mixture was poured into an ice-water mixture with stirring and the solid was collected by filtration and washed with water. The solid was dissolved in methylene chloride and the organic layer was separated and dried with magnesium sulphate. Evaporation gave a foam. This was dissolved in methylene chloride and pre-absorbed onto Kieselgel 60 (50g). This was added to the top of a column of similar silica (125g) set up in 10% ethyl acetate in cyclohexane. The column was eluted successively with 10%, 20% and 33% ethyl acetate in cyclohexane. After combination of appropriate fractions, evaporation gave the title compound (8.06g) as a foam; λ_{max} (EtOH) 302nm ($E^{1\%}_{1cm}$ 92), λ_{infl} include 227.5nm ($E^{1\%}_{1cm}$ 546) and 259nm ($E^{1\%}_{1cm}$ 221), ν_{max} ($CHBr_3$) 3400 (NH), 1739 (ester) and 1533cm^{-1} (C=N).

(b) (Z)-2-Fluoromethoxyimino-2-(2-triphenylmethylaminothiazol-4-yl)acetic acid.

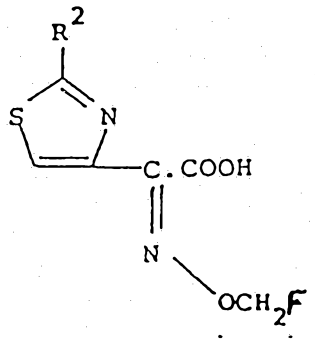
Intermediate 1 (7.8g) was stirred under reflux with sodium hydroxide (0.83g) in ethanol (50ml) and water (10ml) for 15 minutes. The mixture was cooled and the crystalline precipitate was collected by filtration and washed with ethanol and ether and dried. This solid was partitioned between methylene chloride (80ml) and water (40ml) with vigorous stirring and 88% orthophosphoric acid (2ml) was added. Solid remained and this was collected

by filtration. This solid was suspended in tetrahydrofuran (75ml) and 2M hydrochloric acid (8ml) was added when a solution formed. Evaporation reduced the volume of solution by one half and methylene chloride (50ml) was added. The aqueous layer was extracted with more methylene chloride and the combined organic layers were washed with water, dried with magnesium sulphate and evaporated to a solid, the title compound (4.82g); λ_{infl} include 224nm ($E^{1\%}_{1cm}$ 564), 254.5nm ($E^{1\%}_{1cm}$ 213) and 260nm ($E^{1\%}_{1cm}$ 205); τ (d_6DMSO) 1.02 (s; NH), 2.64 (s; phenyl protons) 2.91 (s; thiazole 5-H), and 4.29 (d, J 56Hz; CH_2F).

This Application is a divisional of the present applicant's Australian Patent Application No. 49305/85, and the disclosures therein are included herein by reference.

[redacted] The claims defining the invention are as follows:-

1. Compounds of general formula (III)

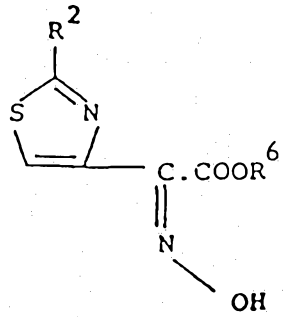


(III)

(wherein R^2 is an amino, tritylamino, chloroacetylamino or formylamino group) and salts, acid halides, activated esters and symmetrical and mixed anhydrides thereof.

2. A process for the preparation of compounds of general formula (III) as defined in claim 1 and salts, acid halides, activated esters and symmetrical and mixed anhydrides thereof which comprises

(a) etherification of a compound of formula (VI)



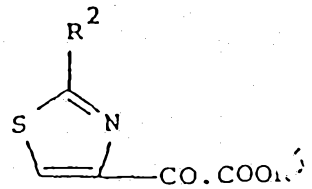
(VI)

(wherein R^2 is as defined in claim 1 and R^6 represents hydrogen or a carboxyl blocking group) or a salt thereof, by selective reaction with a compound of general formula (VII)

$T.CH_2F$ (VII)

(wherein T is chloro, bromo or iodo) followed by removal of any carboxyl blocking group R^6;

or (b) reacting a compound of formula (VIII)



(VIII)

(wherein R^2 and R^6 are as hereinbefore defined) with a compound of formula (IX)

$H_2N.O.CH_2F$ (IX)

followed by removal of any carboxyl blocking group R^6, and thereafter, if desired, separating into <u>syn</u> and <u>anti</u> isomers.

3. Compounds of formula (III) as claimed in claim 1 substantially as herein described.

DATED this 25 day of June 1992.

GLAXO GROUP LIMITED
By their Patent Attorneys:
CALLINAN LAWRIE

Michael J. Hourihan.