(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 April 2004 (15.04.2004)

PCT

(10) International Publication Number
WO 2004/031194 A1

(51) International Patent Classification[7]: C07D 495/04, 333/36 // (C07D 495/04, 333:00, 209:00)

(21) International Application Number: PCT/GB2003/004217

(22) International Filing Date: 29 September 2003 (29.09.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0222912.8 3 October 2002 (03.10.2002) GB

(71) Applicant *(for AE, AG, AL, AM, AT, AU, AZ, BA, BB, BE, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CY, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, FR, GB, GD, GE, GH, GM, GR, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, SZ, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW only)*: **ASTRAZENECA AB** [SE/SE]; Sodertalje, S-151 85 (SE).

(71) Applicant *(for MG only)*: **ASTRAZENECA UK LIMITED** [GB/GB]; 15 Stanhope Gate, London, Greater London W1K 1LN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **MURRAY, Paul, Michael** [IE/GB]; AstraZeneca, Avlon Works, Severn Road, Hallen, Bristol, Avon BS10 7ZE (GB). **PARKER, Jeremy, Stephen** [GB/GB]; AstraZeneca, Avlon Works, Severn Road, Hallen, Bristol, Avon BS10 7ZE (GB). **SCHOFIELD, Paul** [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB). **STOCKER, Andrew** [GB/GB]; AstraZeneca R & D Alderley, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).

(74) Agent: **ASTRAZENECA**; Global Intellectual Property, P O Box 272, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4GR (GB).

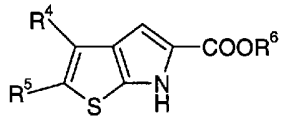
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

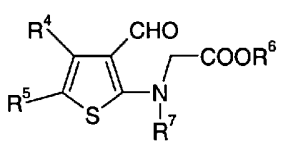
**Published:**
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: PROCESS AND INTERMEDIATES FOR THE PREPARATION OF THE THIENOPYRROLE DERIVATIVES




(I)




(II)

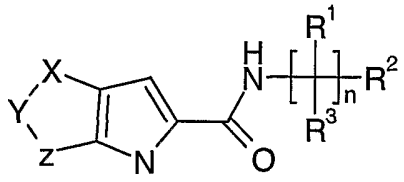
(57) Abstract: A process for preparing a compound of formula (I) where $R^4$ and $R^5$are as defined in the specification; and $R^6$ is hydrogen or a protecting group, which process comprises cyclisation of a compound of formula (II) where $R^4$, $R^5$and $R^6$ are as defined in relation to formula (I) and $R^7$is a nitrogen-protecting group, and removing protecting group $R^7$-, and thereafter if desired or necessary, removing any protecting group $R^6$ to obtain the corresponding carboxylic acid. Novel intermediates and the use of the products in the preparation of pharmaceutical compounds is also described and claimed.

WO 2004/031194 A1

# PROCESS AND INTERMEDIATES FOR THE PREPARATION OF THIENOPYRROLE DERIVATIVES

The present invention relates to a novel process for preparing intermediates for therapeutically effective compounds, together with novel intermediates for use in the process.

Compounds with glycogen phosphorylase activity are described in WO 02/20530. These compounds have a general formula which may be represented as formula (A)

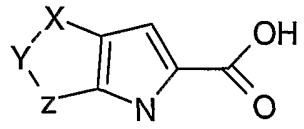


(A)

where X, Y and Z is selected from *inter alia* $-CR^4=CR^5-S-$, $R^4$ and $R^5$ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, $C_{1-6}$alkanoyloxy, *N*-($C_{1-6}$alkyl)amino, *N,N*-($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, *N*-($C_{1-6}$alkyl)carbamoyl, *N,N*-($C_{1-6}$alkyl)$_2$carbamoyl, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-6}$alkoxycarbonyl, $C_{1-6}$alkoxycarbonylamino, *N*-($C_{1-6}$alkyl)sulphamoyl, *N,N*,-($C_{1-6}$alkyl)$_2$sulphamoyl, $C_{1-6}$alkylsulphonylamino and $C_{1-6}$alkylsulphonyl-*N*-($C_{1-6}$alkyl)amino;

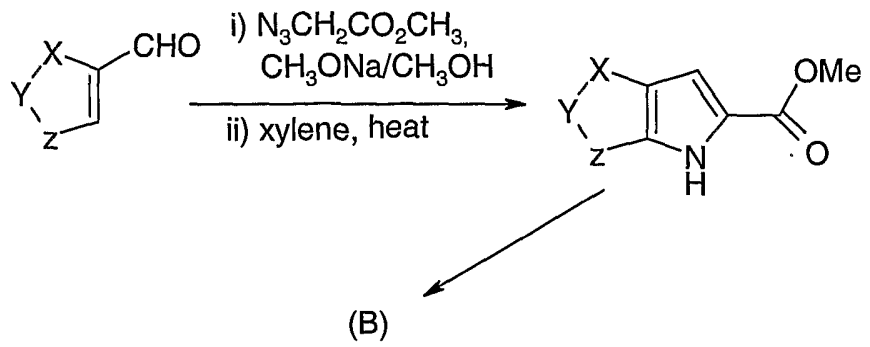
n is 0-4, and $R^1$, $R^2$ and $R^3$ are various specified organic groups.

These compounds are generally prepared by a reacting an acid of formula (B)



(B)

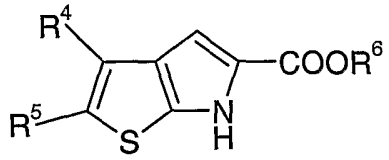
with an appropriate amine. Acids of formula (B) are prepared according to the following scheme:




However, this process is difficult to effect as it may proceed explosively.

The applicants have found an improved process for the production of certain intermediates.

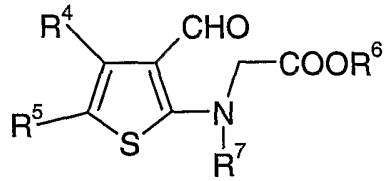
The present invention provides a process for preparing a compound of formula (I)




(I)

where $R^4$ and $R^5$ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, $C_{1-6}$alkanoyloxy, *N*-($C_{1-6}$alkyl)amino, *N,N*-($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, *N*-($C_{1-6}$alkyl)carbamoyl, *N,N*-($C_{1-6}$alkyl)$_2$carbamoyl, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-6}$alkoxycarbonyl, $C_{1-6}$alkoxycarbonylamino, *N*-($C_{1-6}$alkyl)sulphamoyl, *N,N*,-($C_{1-6}$alkyl)$_2$sulphamoyl, $C_{1-6}$alkylsulphonylamino and $C_{1-6}$alkylsulphonyl-N-($C_{1-6}$alkyl)amino; and $R^6$ is hydrogen or a protecting group,

which process comprises cyclisation of a compound of formula (II)




(II)

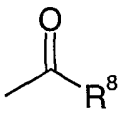
where $R^4$, $R^5$ and $R^6$ are as defined in relation to formula (I) and $R^7$ is a nitrogen-protecting group, and removing protecting group $R^7$, and thereafter if desired or necessary, removing any protecting group $R^6$ to obtain the corresponding carboxylic acid.

Cyclisation is suitably effected in an organic solvent such as methanol or dimethylformamide (DMF) in the presence of a base. Suitable bases include particularly strong bases such as an alkali metal alkoxide, for instance sodium methoxide, but also weaker bases such as alkali metal carbonates like potassium carbonate. The reaction is suitably carried out at a broad range of temperatures, for example of from ambient temperature to 70°C, and conveniently at the reflux temperature of the solvent. Under these conditions, $R^7$ is generally removed in the same reaction step. Depending upon the nature of the group employed however, it might be necessary to remove $R^7$ in a subsequent step, for example by acid or base hydrolysis reactions.

Acid hydrolysis reactions may be carried out using conventional methods, and in particular using acids such as trifluoromethanesulphonic acid, acetic acid or hydrochloric acid. Base hydrolysis reactions are suitably effected in the presence of bases, such as alkali metal hydroxides, and in particular sodium or potassium hydroxide.

Suitable example of protecting groups $R^7$ are listed in T.W. Green, Protecting Groups in Organic Synthesis, J. Wiley and Sons, 1991 and in particular are those designated as nitrogen-protection groups.

Particular examples of protecting groups $R^7$ are groups of sub-formula (i)



(i)

where $R^8$ is a hydrocarbyl or heterocyclic group, either of which may be optionally substituted.

As used herein, the expression "hydrocarbyl" includes any structure comprising carbon and hydrogen atoms. For example, these may be alkyl, alkenyl, alkynyl, aryl such as phenyl or napthyl, arylalkyl such as benzyl, or cycloalkyl, cycloalkenyl or cycloalkynyl. Suitably hydrocarbyl groups contain up to 20 and preferably up to 10 carbon atoms.

The term "aryl" refers to aromatic rings such as phenyl or naphthyl.

The term "heterocyclic" includes aromatic or non-aromatic rings, for example containing from 4 to 20, suitably from 5 to 8 ring atoms, at least one of which, and suitably from 1 to 4 of which is a heteroatom such as oxygen, sulphur or nitrogen. They may be monocyclic or have fused rings, such a bicyclic or tricyclic ring systems. Examples of such groups include furyl, thienyl, pyrrolyl, pyrrolidinyl, imidazolyl, triazolyl, thiazolyl, tetrazolyl, oxazolyl, isoxazolyl, piperidinyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl,

triazinyl, quinolinyl, isoquinolinyl, quinoxalinyl, benzothiazolyl, benzoxazolyl, benzothienyl or benzofuryl.

The term "heteroaryl" refers to heterocyclic groups which are aromatic in nature. Thus these may comprises cyclic aromatic hydrocarbons in which one or more carbon atoms have been replaced with a heteroatom. If the heteroaryl group contains more than one heteroatom, the heteroatoms may be the same or different. Examples of heteroaryl groups include pyridyl, pyrimidinyl, imidazolyl, thienyl, furyl, pyrazinyl, pyrrolyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, indolyl, isoindolyl, indolizinyl, triazolyl, pyridazinyl, indazolyl, purinyl, quniolizinyl, isoquinolyl, quinolyl phthalazinyl, naphthyridinyl, quinoxalinyl, isothiazolyl and benzo[b]thienyl. Preferred heteroaryl groups are five or six membered rings and contain from one to three heteroatoms.

Suitable optional substituents for heterocyclic and hydrocarbyl groups $R^8$ include nitro, cyano, halo, oxo, $=CR^{13}R^{14}$, $C(O)_xR^{12}$, $OR^{12}$, $S(O)_yR^{12}$, $NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, $OC(O)NR^{13}R^{14}$, $=NOR^{12}$, $-NR^{12}C(O)_xR^{13}$, $-NR^{12}CONR^{13}R^{14}$, $-N=CR^{13}R^{14}$, $S(O)_yNR^{13}R^{14}$ or $-NR^{12}S(O)_yR^{13}$ where $R^{12}$, $R^{13}$ and $R^{14}$ are independently selected from hydrogen or optionally substituted hydrocarbyl, or $R^{13}$ and $R^{14}$ together form an optionally substituted ring which optionally contains further heteroatoms such as $S(O)_y$ oxygen and nitrogen, x is an integer of 1 or 2, y is 0 or an integer of 1-3. Hydrocarbyl groups $R^8$ may also include heterocyclic substituents, which may themselves be optionally substituted by one or more of the optional substituents listed above. Heterocyclic groups may also be substituted with hydrocarbyl groups which may also be optionally substituted by any of the groups listed above.

Preferably $R^8$ is a hydrocarbyl group such as alkyl, aryl or arylalkyl. Most preferably $R^8$ is a straight chain alkyl group of from 1 to 6 carbon atoms, and particularly is a straight chain $C_{1-4}$alkyl group, such as methyl.

Particular examples of groups $R^4$ and $R^5$ are hydrogen, halo, nitro, cyano, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, sulphamoyl, ureido, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl and $C_{1-6}$alkanoyloxy.

Suitably $R^4$ and $R^5$ are independently selected from hydrogen, halo, nitro, cyano, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, sulphamoyl, $C_{1-4}$alkyl, $C_{2-4}$alkenyl, $C_{2-4}$alkynyl, $C_{1-4}$alkoxy, $C_{1-4}$alkanoyl, and $C_{1-4}$alkanoyloxy.

Preferably $R^4$ and $R^5$ are independently selected from hydrogen and halogen such as chlorine, fluorine and bromine, and in particular chlorine.

Most preferably $R^4$ is hydrogen and $R^5$ is halogen such as chlorine.

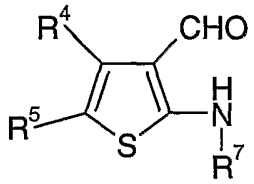
Particular examples of protecting groups $R^6$ are any organic groups which can be removed by hydrogenation or hydrolysis. These include optionally substituted hydrocarbyl or optionally substituted heterocyclic groups. Such groups may be similar to those listed above in relation to $R^7$.

Suitable example of protecting groups $R^6$ are also listed in T.W. Green, Protecting Groups in Organic Synthesis, J. Wiley and Sons, 1991 and in particular are those designated as acid protecting groups.

In particular $R^6$ is a hydrocarbyl group such as $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, aryl such as phenyl, or arylalkyl such as benzyl.

Conversion of a protecting group $R^6$ to hydrogen is suitably effected using conventional methods, for example as described in WO 02/20530. In particular, the compound is reacted with a base such as lithium hydroxide, in an organic solvent such as methanol, at temperatures of from 20-80°C, and conveniently at the reflux temperature of the solvent.

Compounds of formula (II) are suitably prepared by reacting a compound of formula (III)



(III)

where $R^4$ and $R^5$ are as defined in relation to formula (I), and $R^6$ and $R^7$ are as defined in relation to formula (II), with a compound of formula (IV):

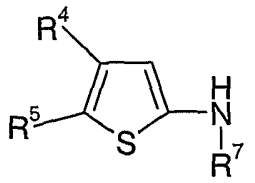
$$LCH_2COOR^6$$

(IV)

where L is a leaving group such as halogen and in particular bromine. The reaction is suitably effected in the presence of a base in an organic solvent such as dimethylformamide, N-methylpyrrolidone (NMP) or acetone. Suitable bases include alkali metal carbonates, bicarbonates, hydroxides, or methoxides, but are preferably weak bases such as alkali metal carbonates or bicarbonates, for instance potassium bicarbonate. The reaction may be

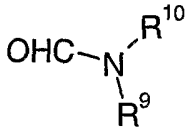
conducted at elevated temperatures, for example of from 30 to 100°C depending on the solvent used. For example when dimethylformamide is the solvent, the reaction is preferably carried out from 50 to 70°C and most preferably at about 60°C. When NMP is the solvent, the reaction may be carried out from 30 to 50°C, preferably at about 40°C.

Compounds of formula (III) are suitably prepared by formylation of a compound of formula (V)



(V)

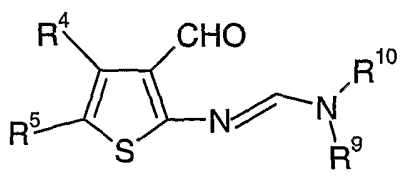
where $R^4$ and $R^5$ are as defined above in relation to formula (I) and $R^7$ is as defined above in relation to formula (II). This can be carried out using conventional methods such as the Vilsmeier-Haack reaction. In this reaction, the compound of formula (V) is reacted with a formyl containing reagent such as a compound of formula (VI)



(VI)

where $R^9$ and $R^{10}$ are independently selected from phenyl and alkyl groups (in particular lower alkyl groups of 1 to 4 carbon atoms, such as methyl) in the presence of phosphorus oxychloride. The reaction is suitably effected at moderate temperatures and conveniently at room temperature. The compound of formula (VI) may act as a solvent also, where it is for example, DMF, alternatively a different organic solvent may be used, such as dichloromethane.

The applicants have found however that under some conditions this reaction produces a significant proportion of an amidine of formula (VII)



(VII)

where $R^4$ and $R^5$ are as defined in relation to formula (I) and $R^9$ and $R^{10}$ are as defined in relation to formula (VI). A compound of formula (VII) may be converted to a compound of formula (III) by reaction with a compound of formula (VIII)

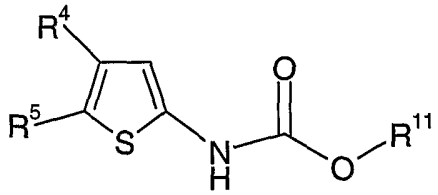
$(R^7)_2O$

(VIII)

where $R^7$ are as defined in relation to formula (II), under acidic conditions, for example in a solvent comprising an organic acid, such as acetic acid. Elevated temperatures for example of from 80-150°C and preferably from 110-130°C are employed. Conveniently the reaction may be effected at the reflux temperature of the solvent. Particular examples of compounds of formula (VIII) are those where groups $R^7$ are groups of sub-formula (i) as defined above, and in particular where $R^8$ is methyl, so that the compound of formula (VIII) is acetic anhydride.

Generally, where the compound of the formula (V) is reacted with the formyl containing compound of the formula (VI) using a solvent such as dichloromethane, an amidine of formula (VII) is not formed in significant quantities, and the desired compound of the formula (III) is instead obtained in good yield.

Compounds of formula (V) are suitably prepared by reacting a compound of formula (IX)

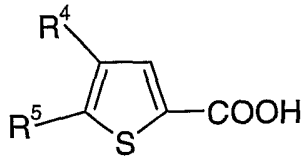



(IX)

where $R^4$ and $R^5$ are as defined above in relation to formula (I), and $R^{11}O(C=O)$ is a labile nitrogen-protecting group, with a compound of formula (VIII) as defined above, under acidic conditions, for example in a solvent comprising an organic acid, such as acetic acid. Elevated temperatures for example of from 80-150°C and preferably from 110-130°C are employed. Conveniently the reaction may be effected at the reflux temperature of the solvent.

Suitable labile nitrogen protecting groups for $R^{11}O(C=O)$ include tertiary-butoxy carbonyl groups, or benzyloxycarbonyl groups.

Compounds of formula (IX) are either known (see for example Binder et al., Synthesis, (1977, (4) 255-6) or can be prepared from known compounds. In particular, compounds of formula (IX) are suitably prepared by subjecting a compound of formula (X)



(X)

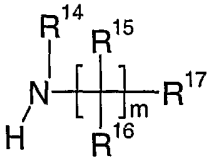
where $R^4$ and $R^5$ are as defined in relation to formula (I), to a Curtius rearrangement reaction, in the presence of an alcohol of formula $R^{11}OH$. In this reaction, the compound of formula (X) is reacted with an diphenylphosphorylazide, to convert the acid group to a carbonyl azide, which is thermally decomposed to the amide via an isocyanate. Suitable reaction conditions are illustrated hereinafter.

Compounds of formula (II), (III) and (VII) are novel and form further aspects of the invention.

Compounds of formula (IV), (V), (VI), (VIII), (IX) and (X) are known compounds or they can be prepared from known compounds by conventional methods.

Compounds of formula (I) are suitably used in the production of pharmaceutical compounds and in particular, compounds with glycogen phosphorylase activity as described in WO 02/20530 and EP-A-1088824.

Thus in a further aspect, the invention provides a method as described above, for the production of a compound of formula (I) where $R^6$ is hydrogen, and further comprising reacting the compound of formula (I) obtained with an amine of formula (XI),



(XI)

where $R^{14}$ is selected from hydrogen or $C_{1-8}$alkyl,

m is an integer of from 0 to 4,

each $R^{15}$ is the same or different and is selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, $C_{1-6}$alkanoyloxy, *N*-($C_{1-6}$alkyl)amino, *N,N*-($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, *N*-($C_{1-6}$alkyl)carbamoyl, *N,N*-($C_{1-4}$alkyl)$_2$carbamoyl, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-6}$alkoxycarbonyl, $C_{1-6}$alkoxycarbonylamino, *N*-($C_{1-6}$alkyl)sulphamoyl, *N,N*-($C_{1-6}$alkyl)$_2$sulphamoyl, $C_{1-6}$alkylsulphonylamino, $C_{1-6}$alkylsulphonyl-*N*-($C_{1-6}$alkyl)amino, $C_{3-8}$cycloalkyl, $C_{3-8}$cycloalkyl$C_{1-6}$alkyl, aryl, aryl$C_{1-6}$alkyl, heterocyclic group and (heterocyclic group)$C_{1-6}$alkyl; wherein $R^{15}$ may be

optionally substituted on carbon by one or more groups selected from P and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R;

each $R^{16}$ is the same or different and is selected from hydrogen and $C_{1-6}$alkyl;

$R^{17}$ is selected from hydrogen, halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, $C_{1-6}$alkanoyloxy, *N*-($C_{1-6}$alkyl)amino, *N,N*-($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, *N*-($C_{1-6}$alkyl)carbamoyl, *N,N*-($C_{1-4}$alkyl)$_2$carbamoyl, *N*-($C_{1-6}$alkyl)-*N*-($C_{1-6}$alkoxy)carbamoyl, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-6}$alkoxycarbonyl, $C_{1-6}$alkoxycarbonylamino, *N*-($C_{1-6}$alkyl)sulphamoyl, *N,N*-($C_{1-6}$alkyl)$_2$sulphamoyl, sulphamoylamino, *N*-($C_{1-6}$alkyl)sulphamoylamino, *N,N*-($C_{1-6}$alkyl)$_2$sulphamoylamino, $C_{1-6}$alkylsulphonylamino, $C_{1-6}$alkylsulphonylaminocarbonyl, $C_{1-6}$alkylsulphonyl-*N*-($C_{1-6}$alkyl)amino and a group -E-F-G-H;

wherein E and G are independently selected from a direct bond, -O-, -S-, -SO-, -$SO_2$-, -OC(O)-, -C(O)O-, -C(O)-, -$NR^a$-, -$NR^a$C(O)-, -C(O)$NR^a$-, -$SO_2NR^a$-, -$NR^aSO_2$-, -$NR^a$C(O)$NR^b$-, -OC(O)$NR^a$-, -$NR^a$C(O)O-, -$NR^aSO_2NR^b$-, -$SO_2NR^a$C(O)- and -C(O)$NR^aSO_2$-; wherein $R^a$ and $R^b$ are independently selected from hydrogen and $C_{1-6}$alkyl which is optionally substituted by a group V ;

F is $C_{1-6}$alkylene optionally substituted by one or more Q or a direct bond;

H is selected from aryl, $C_{3-8}$cycloalkyl and heterocyclic group; wherein H may be optionally substituted on carbon by one or more groups selected from S and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from T;

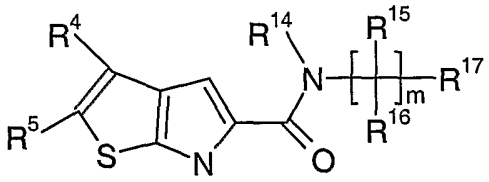
P, S and Q are independently selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, $C_{1-6}$alkanoyloxy, *N*-($C_{1-6}$alkyl)amino, *N,N*-($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, *N*-($C_{1-6}$alkyl)carbamoyl, *N,N*-($C_{1-6}$alkyl)$_2$carbamoyl, *N*-($C_{1-6}$alkyl)-*N*-($C_{1-6}$alkoxy)carbamoyl, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-6}$alkoxycarbonyl, $C_{1-6}$alkoxycarbonylamino, *N*-($C_{1-6}$alkyl)sulphamoyl, *N,N*-($C_{1-6}$alkyl)$_2$sulphamoyl, $C_{1-6}$alkylsulphonylamino, $C_{1-6}$alkylsulphonyl-*N*-($C_{1-6}$alkyl)amino, $C_{3-8}$cycloalkyl, aryl and heterocyclic group; wherein P, S and Q may be optionally and independently substituted on carbon by one or more groups

selected from V and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from U;

V is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl, *N*-methyl-*N*-ethylsulphamoyl, morpholino, morpholinocarbonyl, *N*- benzylcarbamoyl, and 4-hydroxypiperidinocarbonyl;

R, T and U are independently selected from $C_{1-4}$alkyl, $C_{1-4}$alkanoyl, $C_{1-4}$alkylsulphonyl, $C_{1-4}$alkoxycarbonyl, carbamoyl, *N*-($C_{1-4}$alkyl)carbamoyl, *N,N*-($C_{1-4}$alkyl)carbamoyl, phenyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl wherein R, T and U may be optionally and independently substituted on carbon by one or more groups selected from V;

to produce a compound of formula (XII)



(XII)

where $R^4$, $R^5$, $R^{15}$, $R^{16}$, $R^{17}$ and m are as defined above, or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

Particular examples of compounds of formula (XII) are compounds where $R^{14}$ is hydrogen, as described in WO 02/20530. For instance, suitable compounds of formula (XII) are compounds where $R^4$ and $R^5$ are as defined above, $R^{14}$ is hydrogen, m is 0 and $R^{17}$ is a group -E-F-G-H;

wherein E, F and G are each a direct bond;

H is a $C_{3-12}$cycloalkyl which is optionally fused to a benz ring wherein H may be optionally substituted on carbon by one or more groups S which are independently selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy,

$C_{1-6}$alkanoyl, $C_{1-6}$alkanoyloxy, *N*-($C_{1-6}$alkyl)amino, *N,N*-($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, *N*-($C_{1-6}$alkyl)carbamoyl, *N,N*-($C_{1-6}$alkyl)$_2$carbamoyl, *N*-($C_{1-6}$alkyl)-*N*-($C_{1-6}$alkoxy)carbamoyl, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-6}$alkoxycarbonyl, $C_{1-6}$alkoxycarbonylamino, *N*-($C_{1-6}$alkyl)sulphamoyl, *N,N*-($C_{1-6}$alkyl)$_2$sulphamoyl, $C_{1-6}$alkylsulphonylamino, $C_{1-6}$alkylsulphonyl-*N*-($C_{1-6}$alkyl)amino, $C_{3-8}$cycloalkyl, aryl and heterocyclic groups; wherein S may be optionally substituted on carbon by one or more groups selected from V;

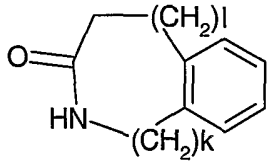
V is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl, *N*-methyl-*N*-ethylsulphamoyl, morpholino , morpholinocarbonyl , *N*- benzylcarbamoyl, and 4-hydroxypiperidinocarbonyl ;

or a pharmaceutically acceptable salt thereof.

Other suitable compounds of formula (XII) are compounds where $R^4$ and $R^5$ are as defined above, $R^{14}$ is hydrogen, m is 0, and $R^{17}$ is a group -E-F-G-H;

wherein E, F and G are each a direct bond; and

H is a cyclic amide of formula




in which the point of attachment is the carbon atom adjacent to the carbonyl group, k is 0, 1 or 2 and l is 0, 1 or 2 such that the sum of (k + l) is1, 2 or 3 and wherein one of the carbon atoms governed by k or l may be replaced by sulphur and wherein H is optionally substituted on the carbon atom adjacent to the aromatic ring by a group selected from S and may be independently optionally substituted on nitrogen by a group selected from T;

S is selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, $C_{1-6}$alkanoyloxy, *N*-($C_{1-6}$alkyl)amino, *N,N*-($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, *N*-($C_{1-6}$alkyl)carbamoyl, *N,N*-($C_{1-6}$alkyl)$_2$carbamoyl,

*N*-($C_{1-6}$alkyl)-*N*-($C_{1-6}$alkoxy)carbamoyl, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-6}$alkoxycarbonyl, $C_{1-6}$alkoxycarbonylamino, *N*-($C_{1-6}$alkyl)sulphamoyl, *N,N*-($C_{1-6}$alkyl)$_2$sulphamoyl, $C_{1-6}$alkylsulphonylamino, $C_{1-6}$alkylsulphonyl-*N*-($C_{1-6}$alkyl)amino, $C_{3-8}$cycloalkyl, aryl and heterocyclic group; wherein S may be optionally and independently substituted on carbon by one or more groups selected from V and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from U;

T and U are independently selected from $C_{1-4}$alkyl, $C_{1-4}$alkanoyl, $C_{1-4}$alkylsulphonyl, $C_{1-4}$alkoxycarbonyl, carbamoyl, *N*-($C_{1-4}$alkyl)carbamoyl, *N,N*-($C_{1-4}$alkyl)carbamoyl, phenyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl wherein R, T and U may be optionally and independently substituted on carbon by one or more groups selected from V;

V is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl, *N*-methyl-*N*-ethylsulphamoyl, morpholino, morpholinocarbonyl, *N*- benzylcarbamoyl and 4-hydroxypiperidinocarbonyl ;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

Yet further examples of compounds of formula (XII) are compounds where $R^{14}$ is hydrogen, and wherein $R^4$ and $R^5$ are independently selected from hydrogen, halo or $C_{1-6}$alkyl,

m is 1; $R^{15}$ is hydrogen or aryl$C_{1-6}$alkyl, $R^{16}$ is hydrogen or $C_{1-6}$alkyl, and $R^{17}$ is selected from a group -E-F-G-H; wherein E, F and G are each a direct bond;

H is an unsaturated five membered heterocyclic group containing at least one nitrogen atom and one or two ring atoms selected from oxygen and sulphur and wherein H may be optionally substituted on carbon by one or more groups S which are independently selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, $C_{1-6}$alkanoyloxy, *N*-($C_{1-6}$alkyl)amino, *N,N*-($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, *N*-($C_{1-6}$alkyl)carbamoyl, *N,N*-($C_{1-6}$alkyl)$_2$carbamoyl,

*N*-($C_{1-6}$alkyl)-*N*-($C_{1-6}$alkoxy)carbamoyl, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-6}$alkoxycarbonyl, $C_{1-6}$alkoxycarbonylamino, *N*-($C_{1-6}$alkyl)sulphamoyl, *N,N*-($C_{1-6}$alkyl)$_2$sulphamoyl, $C_{1-6}$alkylsulphonylamino, $C_{1-6}$alkylsulphonyl-*N*-($C_{1-6}$alkyl)amino, $C_{3-8}$cycloalkyl and aryl groups; or a pharmaceutically acceptable salt thereof.

Other particular examples include compounds of formula (XII) where $R^{14}$ is hydrogen, $R^4$ and $R^5$ are independently selected from hydrogen, halo or $C_{1-6}$alkyl.

m is 0; and $R^{17}$ is a group -E-F-G-H;

wherein E is a direct bond;

F is methylene;

wherein G is -C(O)NR$^a$-, wherein $R^a$ is selected from hydrogen or $C_{1-6}$alkyl which is optionally substituted by a group V;

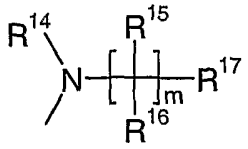
H is aryl which may be optionally substituted on carbon by one or more groups selected from S;

S is selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, $C_{1-6}$alkanoyloxy, *N*-($C_{1-6}$alkyl)amino, *N,N*-($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, *N*-($C_{1-6}$alkyl)carbamoyl, *N,N*-($C_{1-6}$alkyl)$_2$carbamoyl, *N*-($C_{1-6}$alkyl)-*N*-($C_{1-6}$alkoxy)carbamoyl, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-6}$alkoxycarbonyl, $C_{1-6}$alkoxycarbonylamino, *N*-($C_{1-6}$alkyl)sulphamoyl, *N,N*-($C_{1-6}$alkyl)$_2$sulphamoyl, $C_{1-6}$alkylsulphonylamino, $C_{1-6}$alkylsulphonyl-*N*-($C_{1-6}$alkyl)amino, $C_{3-8}$cycloalkyl, aryl and heterocyclic group; wherein S may be optionally and independently substituted on carbon by one or more groups selected from V ;

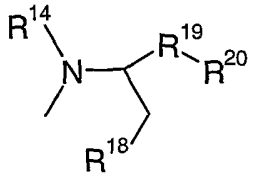
V is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl, *N*-methyl-*N*-ethylsulphamoyl, morpholino, morpholinocarbonyl, *N*- benzylcarbamoyl, and 4-hydroxypiperidinocarbonyl;

or a pharmaceutically acceptable salt thereof.

Other particular compounds of formula (XII) are compounds where the group

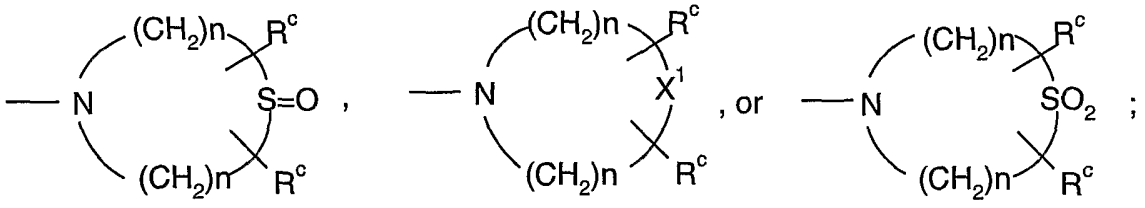


is a group of sub-formula (ii)



(ii)

where $R^{14}$ is as defined above, $R^{18}$ is aryl, substituted aryl, heteroaryl, or substituted heteroaryl, $R^{19}$ is a bond or a group –CH(OH)-, and $R^{20}$ is a group –C(=O)-A or a group –CH(OH)–C(=O)-A in which A is $NR^dR^d$, $-NR^aCH_2CH_2OR^a$, or



each $R^a$ and $R^b$ is independently hydrogen or $-C_1$-$C_8$alkyl;

each $R^d$ is independently hydrogen, $C_1$-$C_8$alkyl, $C_1$-$C_8$alkoxy, aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

each $R^c$ is independently hydrogen, $-C(=O)OR^a$, $-OR^a$, $-SR^a$, or $-NR^aR^a$; and each n is independently 1-3, and

$X^1$ is $NR^a$, $-CH_2-$, O or S.

Examples of substituents for aryl and heteroaryl groups Q and $R^d$ include halogen, $C_{1-8}$alkoxy, $C_{1-8}$alkyl, trifluoromethyl, amino, mono or di-($C_{1-8}$alkyl)amino, nitro, cyano, carboxy or $C_{1-8}$alkyl esters thereof.

The invention will now be particularly described by way of example, in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C and under an atmosphere of an inert gas such as argon;

(ii) organic solutions were dried over anhydrous magnesium sulphate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30 mmHg) with a bath temperature of up to 60°C;

(iii) chromatography means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates;

(iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

(v) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vi) where given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz using perdeuterio dimethyl sulphoxide (DMSO-$d_6$) as solvent or other solvents (where indicated in the text) including deuterated chloroform $CDCl_3$;

(vii) chemical symbols have their usual meanings; SI units and symbols are used;

(viii) reduced pressures are given as absolute pressures in Pascals (Pa); elevated pressures are given as gauge pressures in bars;

(ix) solvent ratios are given in volume : volume (v/v) terms;

(x) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (CI) mode using a direct exposure probe; where indicated ionisation was effected by electron impact (EI), fast atom bombardment (FAB) or electrospray (ESP); values for m/z are given; generally, only ions which indicate the parent mass are reported and unless otherwise stated the value quoted is $(M-H)^-$;

The following abbreviations are used:

DMSO = dimethylsulfoxide

DCM = dichloromethane

THF is tetrahydrofuran

HPLC is high performance liquid chromatography

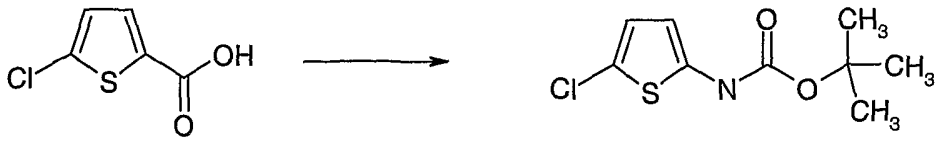
DMF is dimethylformamide

THF is tetrahydrofuran

LCMS is liquid chromatography/mass spectrometry

**Example 1**

Step 1



Under argon, 5-chlorothiophene-2-carboxylic acid (5.48 g) was dissolved in warm dry tertiary butanol (34 ml) and triethylamine (4.7 ml) added followed by diphenylphosphorylazide (DPPA) (7.26 ml). The mixture was then heated slowly to reflux and refluxed for about 12 hours.

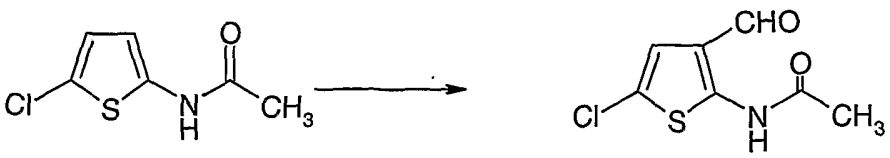
The reaction mixture was then cooled and poured into $H_2O$ (~180 ml). The resultant dark suspension was filtered, and the solid was washed with $H_2O$ then dried under suction to a brown powder. This was dissolved in diethyl ether and the solution dried over $MgSO_4$, filtered and evaporated to the desired product, *tert*-butyl (5-chloro-2-thienyl)carbamate, as a dark brown solid (Yield = 6.75 g).

$^1$H NMR (400 MHz, d$^6$-DMSO) 6.82 (d, 1H), 6.34 (d, 1H), 1.50 (s, 9H)

Step 2

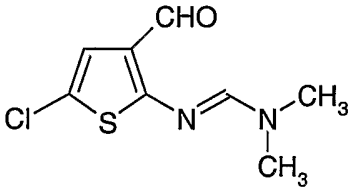
A mixture of acetic anhydride (6.42 ml) in acetic acid (60ml) was added to the product from step 1 (7.48 g) and the resultant mixture heated at 120°C for 4 hours. On cooling the reaction mixture was poured into water and extracted with EtOAc. The EtOAc layer was washed with saturated aqueous $K_2CO_3$, dried over $Na_2SO_4$, filtered and evaporated under reduced pressure to give a black solid. Chromatography through silica using an eluent of $CH_2Cl_2$ to $Et_2O$ gave *N*-(5-chloro-2-thienyl)acetamide (4.63g, 83%) as a pale brown solid. $^1$H NMR (400 MHz, d$^6$-DMSO) 11.33 (br s, 1H), 6.82 (d, 1H), 6.40 (d, 1H), 2.05 (s, 3H); ESP$^-$ 174.29

Step 3



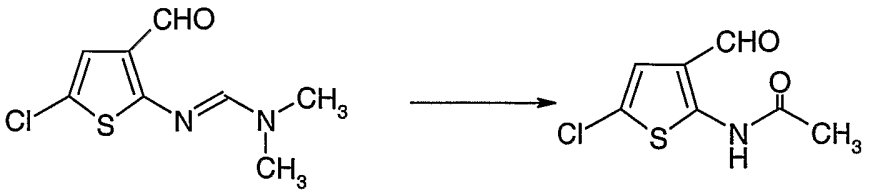
The product from step 2 (1.09 g) was dissolved in dimethyl formamide (DMF) (3 ml) and cooled in an ice bath. $POCl_3$ (0.58 ml) was added dropwise and the dark mixture stirred at 0°C for 30 minutes then allowed to warm to room temperature, and stirred at room temperature for 64 hours.

The reaction mixture was poured into ice water and the aqueous phase was extracted into dichloromethane. The dichloromethane layer was dried over $MgSO_4$, filtered and evaporated to a black gum. Purification was effected by suction column chromatography though silica using hexane as initial eluent and $CH_2Cl_2$ to apply the material to the top of the column. The concentration of diethyl ether was slowly increased (10% jumps) to neat diethyl ether. Several fractions were analysed by LCMS. The 2 fractions which had (MH)+ at 217 and $(MH)^-$ at 202 were combined. They were evaporated to give a yellow solid (0.53 g). Spectral analysis both by LCMS and $^1H$ NMR showed that this was a mixture of the desired *N*-(5-chloro-3-formyl-2-thienyl)acetamide (87%) and *N'*-(5-chloro-3-formyl-2-thienyl)-*N,N*-dimethylimidoformamide (13%).




$^1H$ NMR *N*-(5-chloro-3-formyl-2-thienyl)acetamide (300 MHz, $d^6$-DMSO) 11.65 (br s, 1H), 9.93 (s, 1H), 7.22 (s, 1H), 2.25 (s, 3H); $ESP^-$ 202.21;
*N'*-(5-chloro-3-formyl-2-thienyl)-*N,N*-dimethylimidoformamide (300 MHz, $d^6$-DMSO) 9.90 (s, 1H), 7.97 (s, 1H), 6.93 (s, 1H), 3.13 (s, 3H), 3.02 (s, 3H); $ESP^+$ 217.22

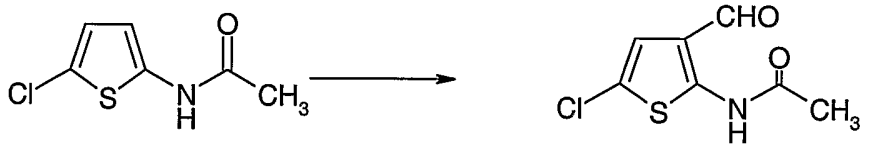
Step 4




The mixture from Step 3 (0.53 g) was dissolved in acetic acid (5 ml) and to this was added acetic anhydride (0.5 ml) followed by $H_2O$ (0.25 ml). The mixture was heated to reflux for approximately 1 hour whereupon tlc analysis indicated that none of the dimethyl amidine derivative remained.

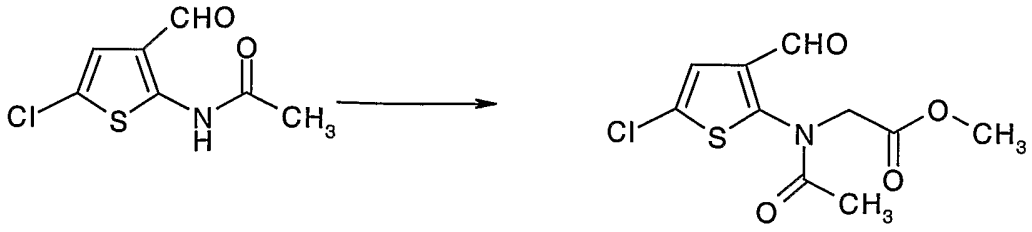
The reaction mixture was poured into $H_2O$ and the precipitate filtered. The aqueous phase was extracted into a mixture of dichloromethane and methanol in a ratio of 19:1 and the precipitate was dissolved in a similar mixture. The combined organic solutions were washed with dilute aqueous potassium carbonate, ensuring that the pH remained at about 12, then dried over $MgSO_4$. Filtration and evaporation under reduced pressure gave the desired product, *N*-(5-chloro-3-formyl-2-thienyl)acetamide, as a yellow, orange solid (Yield = 0.53g). $^1$H NMR (300 MHz, d$^6$-DMSO) 11.65 (br s, 1H), 9.93 (s, 1H), 7.22 (s, 1H), 2.25 (s, 3H); ESP$^-$ 202.21

Alternative Step 3 (removing need for Step 4)



Dichloromethane (7 ml), $POCl_3$ (2.24 ml) and DMF (3.10 ml) were stirred at room temperature for 15 minutes to form a clear solution. The product from step 2 (3.50g) was dissolved in dichloromethane (70 ml) and added via syringe pump to the $POCl_3$/DMF solution over a period of 1.5 hours to form a dark solution. The reaction was stirred at room temperature for 23 hours. Saturated sodium bicarbonate (200 ml) was added gradually to the reaction mixture, until pH 8 was obtained. The organic phase was separated and sodium hydroxide (1M, 150 ml and 2M, 100 ml) was added slowly to the solution in an ice bath, until pH 14 was obtained. The aqueous layers were combined and hydrochloric acid (2M, 150 ml) was added until pH 3 was obtained. The product was extracted into ethyl acetate (150 ml) and washed with brine (25 ml). The solvent was evaporated to give *N*-(5-chloro-3-formyl-2-thienyl)acetamide (2.09 g, 52%) as a dark grey solid.
$^1$H NMR (400 MHz, $CDCl_3$) 11.37 (br s, 1H), 9.69 (s, 1H), 7.01 (s, 1H), 2.31 (s, 1H)

Step 5



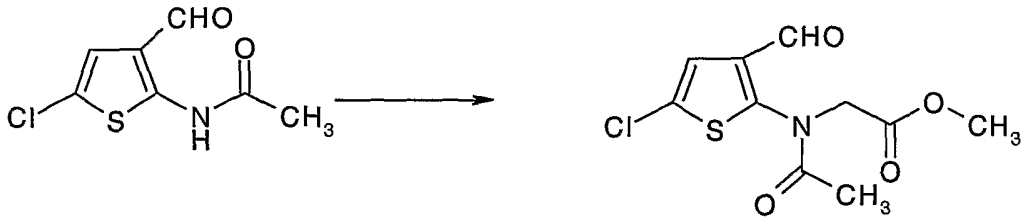
The product from Step 4 (460mg) was placed under argon, in dry glassware, and dissolved in dry DMF (2 ml). Potassium bicarbonate (567mg) was added to the solution

followed by methylbromoacetate (0.54 ml). The mixture was heated to 40°C for 150 mins, and then at 60°C for a further 120 mins. The reaction was stirred at room temperature overnight at again heated at 60°C for 270 minutes on the next day.

The product was partitioned between dichloromethane and water and the dichloromethane layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure to give a dark oil. This was purified by suction column chromatography through silica using hexane as initial eluent and $CH_2Cl_2$ to apply the material to the top of the column. The concentration of $CH_2Cl_2$ was increased (10% increments, 50 ml fractions) to 100% $CH_2Cl_2$, held at $CH_2Cl_2$ for a few fractions then the concentration of $Et_2O$ increases (1% increments) until the spots were removed from the column. The spot corresponding to the desired methyl *N*-acetyl-*N*-(5-chloro-3-formyl-2-thienyl)glycinate (identified using LCMS) was collected for use in the subsequent step.

$^1$H NMR (300 MHz, d$^6$-DMSO) 9.93 (s, 1H), 7.20 (s, 1H), 4.40 (br s, 2H), 3.77 (s, 3H), 2.06 (s, 3H).

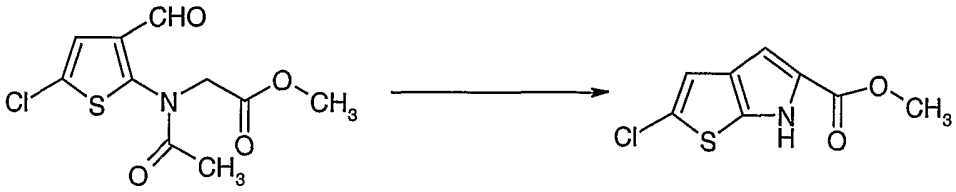
Alternative Step 5




The product from Step 4 (1.50g) was placed under argon, in dry glassware, and dissolved in dry NMP (10ml). Potassium bicarbonate (2.96g) was added to the solution followed by NMP (5ml), methyl-bromoacetate (2.79ml) and *tert*-butyl methyl ether (0.5ml). The mixture was heated to 40°C for 23 hours. The product was partitioned between EtOAc and water and the EtOAc layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure to give an orange oil. This was purified by suction column chromatography through silica using $CH_2Cl_2$ as initial eluent and to apply the material to the top of the column. The concentration of $Et_2O$ increased (0.25% increments) to give after evaporation the product methyl *N*-acetyl-*N*-(5-chloro-3-formyl-2-thienyl)glycinate (1.20g, 59%) as a clear, yellow gum.

$^1$H NMR (300 MHz, d$^6$-DMSO) 9.93 (s, 1H), 7.20 (s, 1H), 4.40 (br s, 2H), 3.77 (s, 3H), 2.06 (s, 3H)

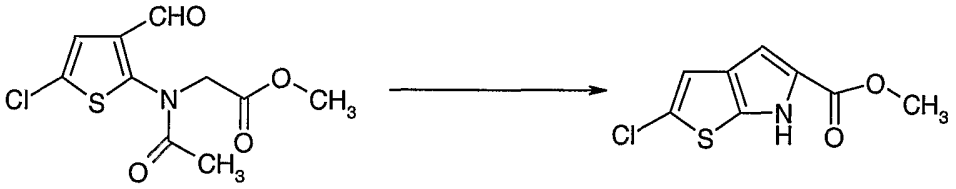
Step 6



The product from Step 5 (170mg) was dissolved in MeOH under an argon atmosphere, and a solution of sodium methoxide in methanol (0.62ml of 25% solution) added causing a slight darkening to a brown, clear solution. The mixture was refluxed for about 1 hour.

The reaction mixture was partitioned between dichloromethane and water, and the dichloromethane layer was dried over $MgSO_4$, filtered and evaporated under reduced pressure to give the desired product, methyl 2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxylate as a yellow solid (Yield = 97mgs (93%). The structure was confirmed by LCMS and $^1$HNMR spectroscopy. $^1$H NMR (300 MHz, d$^6$-DMSO) 9.40 (br s, 1H), 6.91 (s, 1H), 6.82 (s, 1H), 3.82 (s, 3H); ESP$^-$ 214.16

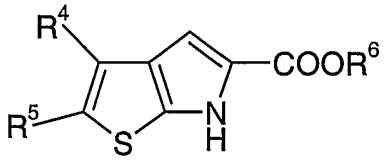
Alternative Step 6



The product from Step 5 (1.20 g) was dissolved in DMF (15ml), $K_2CO_3$ (631 mg) added and the mixture heated to 60°C for 90 minutes. On cooling to room temperature the mixture was poured into water (30 ml) and the white solid filtered off and washed with water to give the desired product, methyl 2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxylate (741mg, 79%) as an off white solid. $^1$H NMR (300 MHz, d$^6$-DMSO) 9.40 (br s, 1H), 6.91 (s, 1H), 6.82 (s, 1H), 3.82 (s, 3H); ESP$^-$ 214.16

## Claims

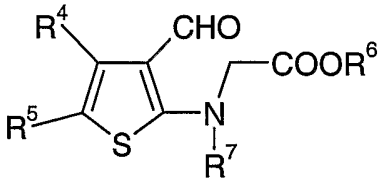
1. A process for preparing a compound of formula (I)



(I)

where $R^4$ and $R^5$ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, $C_{1-6}$alkanoyloxy, *N*-($C_{1-6}$alkyl)amino, *N,N*-($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, *N*-($C_{1-6}$alkyl)carbamoyl, *N,N*-($C_{1-6}$alkyl)$_2$carbamoyl, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-6}$alkoxycarbonyl, $C_{1-6}$alkoxycarbonylamino, *N*-($C_{1-6}$alkyl)sulphamoyl, *N,N*,-($C_{1-6}$alkyl)$_2$sulphamoyl, $C_{1-6}$alkylsulphonylamino and $C_{1-6}$alkylsulphonyl-*N*-($C_{1-6}$alkyl)amino; and $R^6$ is hydrogen or a protecting group,

which process comprises cyclisation of a compound of formula (II)

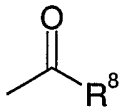


(II)

where $R^4$, $R^5$ and $R^6$ are as defined in relation to formula (I) and $R^7$ is a nitrogen protecting group, and removing protecting group $R^7$, and thereafter if desired or necessary, removing any protecting group $R^6$ to obtain the corresponding carboxylic acid.

2. A process according to claim 1 wherein the protecting group $R^7$ is removed during the same reaction step as the cyclisation.

3. A process according to claim 1 or claim 2 wherein in structure of formula (II), $R^7$ is a groups of sub-formula (i)



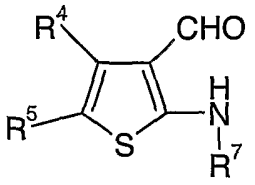
(i)

where $R^8$ is a straight chain alkyl group of from 1 to 6 carbon atoms.

4. A process according to any one of the preceding claims wherein $R^4$ and $R^5$ are independently selected from hydrogen, halo, nitro, cyano, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, sulphamoyl, $C_{1-4}$alkyl, $C_{2-4}$alkenyl, $C_{2-4}$alkynyl, $C_{1-4}$alkoxy, $C_{1-4}$alkanoyl, and $C_{1-4}$alkanoyloxy.

5. A compound of formula (II) as defined in claim 1.

6. A process for preparing a compound according to claim 5 which comprises reacting a compound of formula (III)



(III)

where $R^4$, $R^5$ are as defined in claim 1, $R^6$ and $R^7$ are as defined in claim 1, with a compound of formula (IV)

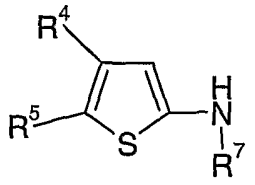
$$LCH_2COOR^6$$

(IV)

where L is a leaving group.

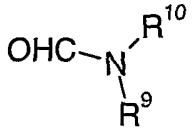
7. A compound of formula (III) as defined in claim 6.

8. A process for preparing a compound according to claim 7 which comprises reacting a compound of formula (V)



(V)

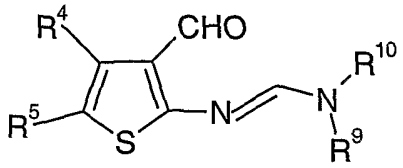
where $R^4$, $R^5$ and $R^7$ are as defined in claim 1, with a compound of formula (VI)



(VI)

where $R^9$ and $R^{10}$ are alkyl groups in the presence of phosphorus oxychloride.

9. A process for preparing a compound of formula (III) as defined in claim 6 by reacting a compound of formula (VII)



(VII)

where $R^4$ and $R^5$ are as in claim 1 and $R^9$ and $R^{10}$ are as defined in claim 8, with a compound of formula (VIII)

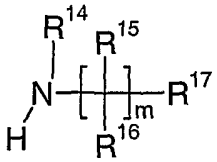
$(R^7)_2O$

(VIII)

where $R^7$ are as defined in claim 1.

10. A compound of formula (VII) as defined in claim 9.

11. A method according to claim 1 for the production of a compound of formula (I) where $R^6$ is hydrogen, and further comprising reacting the compound of formula (I) obtained with an amine of formula (XI),



(XI)

where $R^{14}$ is selected from hydrogen and $C_{1-8}$alkyl,

m is an integer of from 0 to 4,

each $R^{15}$ is the same or different and is selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl,

$C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, $C_{1-6}$alkanoyloxy, *N*-($C_{1-6}$alkyl)amino, *N,N*-($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, *N*-($C_{1-6}$alkyl)carbamoyl, *N,N*-($C_{1-4}$alkyl)$_2$carbamoyl, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-6}$alkoxycarbonyl, $C_{1-6}$alkoxycarbonylamino, *N*-($C_{1-6}$alkyl)sulphamoyl, *N,N*-($C_{1-6}$alkyl)$_2$sulphamoyl, $C_{1-6}$alkylsulphonylamino, $C_{1-6}$alkylsulphonyl-*N*-($C_{1-6}$alkyl)amino, $C_{3-8}$cycloalkyl, $C_{3-8}$cycloalkyl$C_{1-6}$alkyl, aryl, aryl$C_{1-6}$alkyl, heterocyclic group and (heterocyclic group)$C_{1-6}$alkyl; wherein $R^{15}$ may be optionally substituted on carbon by one or more groups selected from P and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R;

each $R^{16}$ is the same or different and is selected from hydrogen and $C_{1-6}$alkyl;

$R^{17}$ is selected from hydrogen, halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, $C_{1-6}$alkanoyloxy, *N*-($C_{1-6}$alkyl)amino, *N,N*-($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, *N*-($C_{1-6}$alkyl)carbamoyl, *N,N*-($C_{1-4}$alkyl)$_2$carbamoyl, *N*-($C_{1-6}$alkyl)-*N*-($C_{1-6}$alkoxy)carbamoyl, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-6}$alkoxycarbonyl, $C_{1-6}$alkoxycarbonylamino, *N*-($C_{1-6}$alkyl)sulphamoyl, *N,N*-($C_{1-6}$alkyl)$_2$sulphamoyl, sulphamoylamino, *N*-($C_{1-6}$alkyl)sulphamoylamino, *N,N*-($C_{1-6}$alkyl)$_2$sulphamoylamino, $C_{1-6}$alkylsulphonylamino, $C_{1-6}$alkylsulphonylaminocarbonyl, $C_{1-6}$alkylsulphonyl-*N*-($C_{1-6}$alkyl)amino and a group -E-F-G-H;

wherein E and G are independently selected from a direct bond, -O-, -S-, -SO-, -$SO_2$-, -OC(O)-, -C(O)O-, -C(O)-, -$NR^a$-, -$NR^a$C(O)-, -C(O)$NR^a$-, -$SO_2NR^a$-, -$NR^aSO_2$-, -$NR^a$C(O)$NR^b$-, -OC(O)$NR^a$-, -$NR^a$C(O)O-, -$NR^aSO_2NR^b$-, -$SO_2NR^a$C(O)- and -C(O)$NR^aSO_2$-; wherein $R^a$ and $R^b$ are independently selected from hydrogen or $C_{1-6}$alkyl which is optionally substituted by a group V ;

F is $C_{1-6}$alkylene optionally substituted by one or more Q or a direct bond;

H is selected from aryl, $C_{3-8}$cycloalkyl and heterocyclic group; wherein H may be optionally substituted on carbon by one or more groups selected from S and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from T;

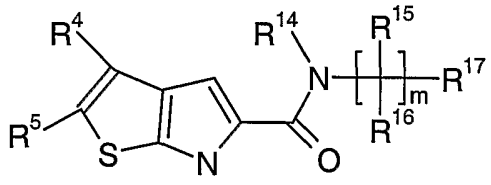
P, S and Q are independently selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, ureido, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, $C_{1-6}$alkanoyloxy,

*N*-($C_{1-6}$alkyl)amino, *N,N*-($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, *N*-($C_{1-6}$alkyl)carbamoyl, *N,N*-($C_{1-6}$alkyl)$_2$carbamoyl, *N*-($C_{1-6}$alkyl)-*N*-($C_{1-6}$alkoxy)carbamoyl, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-6}$alkoxycarbonyl, $C_{1-6}$alkoxycarbonylamino, *N*-($C_{1-6}$alkyl)sulphamoyl, *N,N*-($C_{1-6}$alkyl)$_2$sulphamoyl, $C_{1-6}$alkylsulphonylamino, $C_{1-6}$alkylsulphonyl-*N*-($C_{1-6}$alkyl)amino, $C_{3-8}$cycloalkyl, aryl and heterocyclic group; wherein P, S and Q may be optionally and independently substituted on carbon by one or more groups selected from V and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from U;

V is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl, *N*-methyl-*N*-ethylsulphamoyl, morpholino, morpholinocarbonyl, *N*- benzylcarbamoyl, and 4-hydroxypiperidinocarbonyl;

R, T and U are independently selected from $C_{1-4}$alkyl, $C_{1-4}$alkanoyl, $C_{1-4}$alkylsulphonyl, $C_{1-4}$alkoxycarbonyl, carbamoyl, *N*-($C_{1-4}$alkyl)carbamoyl, *N,N*-($C_{1-4}$alkyl)carbamoyl, phenyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl wherein R, T and U may be optionally and independently substituted on carbon by one or more groups selected from V;

to produce a compound of formula (XII)




(XII)

where $R^4$, $R^5$, $R^{15}$, $R^{16}$, $R^{17}$ and m are as defined above, or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

# INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/GB 03/04217

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D495/04 C07D333/36 //(C07D495/04,333:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BEILSTEIN Data, CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | YOSHINORI NAKAMURA: "Construction of heterocyclic compounds by use of alpha-diazaphosphonates: new one-pot syntheses of indoles and isocoumarines" ORGANIC LETTERS., vol. 4, no. 14, 2002, pages 2317-20, XP002266825 ACS, WASHINGTON, DC., US ISSN: 1523-7060 table 1 ---<br>-/-- | 1 |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 20 January 2004 | 13/02/2004 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31–70) 340–2040, Tx. 31 651 epo nl,<br>Fax: (+31–70) 340–3016 | Alfaro Faus, I |

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication,where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SHVEDOV, V. I. ET AL: "2-Aminothieno'2,3-b!pyridine derivatives" retrieved from STN Database accession no. 78:159580 XP002266826 compound with RN = 41405-96-3 & SU 364 613 T (ORDZHONIKIDZE, S., ALL-UNION SCIENTIFIC-RESEARCH CHEMICAL-PHARMACEUTIC) 28 December 1972 (1972-12-28) --- | 7 |
| X | WO 01 28993 A (MERCK & CO INC) 26 April 2001 (2001-04-26) page 75 (10-3) --- | 7 |
| X | SUGIYAMA, MITSUO ET AL: "Condensed thienopyrimidines. IV. Synthesis and gastric antisecretory activity of 2,3-dihydro-5H-oxazolothienopyrimidine derivatives" CHEMICAL & PHARMACEUTICAL BULLETIN (1989), 37(10), 2717-22 , XP002267346 table III, compounds 4a-4d --- | 7 |
| X | SUGIYAMA, MITSUO ET AL: "Condensed thienopyrimidines. 5. Studies on the thermal cyclization of various ortho-formylthiophenecarbamates with ethanolamine" HETEROCYCLES (1989), 29(7), 1317-23 , XP008026471 table 1, compounds 1i,1j --- | 7 |
| X | METH-COHN, OTTO ET AL: "The preparation and formylation of 2-acetamidothiophenes" SYNTHESIS (1980), (2), 133-5 , XP002267347 table 2, compounds 3b,3f ----- | 7 |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No
PCT/GB 03/04217

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| SU 364613 T | | NONE | |
| WO 0128993 A | 26-04-2001 | AU 1091301 A | 30-04-2001 |
| | | CA 2387840 A1 | 26-04-2001 |
| | | EP 1226119 A2 | 31-07-2002 |
| | | JP 2003512353 T | 02-04-2003 |
| | | WO 0128993 A2 | 26-04-2001 |
| | | US 6479512 B1 | 12-11-2002 |