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Ciudad

02-01-09

Re.: Expediente No. 00 - 30.779

Solicitud de Patente

Debidamente traducidas, adjunto acompaño las copias oficiales de las solicitudes básicas de patente Inglesas No. GB 9910048.9 y No. GB 0002096.6, las cuales le solicito agregar a este expediente para los efectos legales respectivos.-

De Ud. atentamente,

GERMAN CASTILLO GRAU

T.P. 2978



The
Patent
Office



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

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

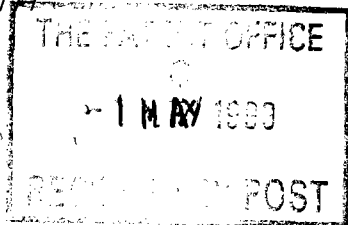
Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed

Andrew Gurney

Dated

14.12.2000



04MAY99 E444100-1 D02029
P01/7700 0.00 - 9910048.9

Request for grant of a patent

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

01 MAY 1999

The Patent Office
Cardiff Road
Newport
Gwent NP9 1RH

1. Your reference ACC/JR/P32296

2. Patent application number

(The Patent Office will fill in his part)

9910048.9

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

SmithKline Beecham plc
New Horizons Court, Brentford, Middx TW8 9EP,
Great Britain

Patents ADP number (if you know it)

If the applicant is a corporate body, give the country/state of its incorporation

577 6299002

4. Title of the invention

Novel Compounds

5. Name of your agent (if you have one)

CORPORATE INTELLECTUAL PROPERTY

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

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

Patents ADP number (if you know it)

5800 974002.

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

Country	Priority application number (if you know it)	Date of filing (day / month / year)
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7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing (day / month / year)
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8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer yes if:

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

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

Continuation sheets of this form	
Description	61
Claim(s)	4
Abstract	
Drawings	



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

Priority Documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (Patents Form 1/77)

Request for preliminary examination and search (Patents Form 9/77)

Request for substantive examination (Patents Form 10/77)

Any other documents (please specify)

11.

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

Signature A C Connell Date 30-Apr-99

A C Connell

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

A C Connell 01279 644395

Warning

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

Notes

- a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505
- b) Write your answers in capital letters using black ink or you may type them.
- c) If there is not enough space for all relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.
- d) If you have answered 'Yes' Patents Form 7/77 will need to be filed.
- f) For details of the fee and ways to pay please contact the Patent Office.

Novel Compounds

The present invention relates to certain novel pyrimidinone compounds, processes for their preparation, intermediates useful in their preparation, pharmaceutical compositions containing them and their use in therapy, in particular in the treatment of atherosclerosis.

WO 95/00649 (SmithKline Beecham plc) describe the phospholipase A2 enzyme Lipoprotein Associated Phospholipase A₂ (Lp-PLA₂), the sequence, isolation and purification thereof, isolated nucleic acids encoding the enzyme, and recombinant host cells transformed with DNA encoding the enzyme. Suggested therapeutic uses for inhibitors of the enzyme included atherosclerosis, diabetes, rheumatoid arthritis, stroke, myocardial infarction, reperfusion injury and acute and chronic inflammation. A subsequent publication from the same group further describes this enzyme (Tew D *et al*, *Arterioscler Thromb Vas Biol* 1996;16:591-9) wherein it is referred to as LDL-PLA₂. A later patent application (WO 95/09921, Icos Corporation) and a related publication in *Nature* (Tjoelker *et al*, vol 374, 6 April 1995, 549) describe the enzyme PAF-AH which has essentially the same sequence as Lp-PLA₂ and suggest that it may have potential as a therapeutic protein for regulating pathological inflammatory events.

It has been shown that Lp-PLA₂ is responsible for the conversion of phosphatidylcholine to lysophosphatidylcholine, during the conversion of low density lipoprotein (LDL) to its oxidised form. The enzyme is known to hydrolyse the sn-2 ester of the oxidised phosphatidylcholine to give lysophosphatidylcholine and an oxidatively modified fatty acid. Both products of Lp-PLA₂ action are biologically active with lysophosphatidylcholine, a component of oxidised LDL, known to be a potent chemoattractant for circulating monocytes. As such, lysophosphatidylcholine is thought play a significant role in atherosclerosis by being responsible for the accumulation of cells loaded with cholesterol ester in the arteries. Inhibition of the Lp-PLA₂ enzyme would therefore be expected to stop the build up of these macrophage enriched lesions (by inhibition of the formation of lysophosphatidylcholine and oxidised free fatty acids) and so be useful in the treatment of atherosclerosis.

The increased lysophosphatidylcholine content of oxidatively modified LDL is also thought to be responsible for the endothelial dysfunction observed in patients with atherosclerosis. Inhibitors of Lp-PLA₂ could therefore prove beneficial in the treatment of this phenomenon. An Lp-PLA₂ inhibitor could also find utility in other disease states that exhibit endothelial dysfunction including diabetes, hypertension, angina pectoris and after ischaemia and reperfusion.

In addition, Lp-PLA₂ inhibitors may also have a general application in any disorder that involves activated monocytes, macrophages or lymphocytes, as all of these cell types express Lp-PLA₂. Examples of such disorders include psoriasis.

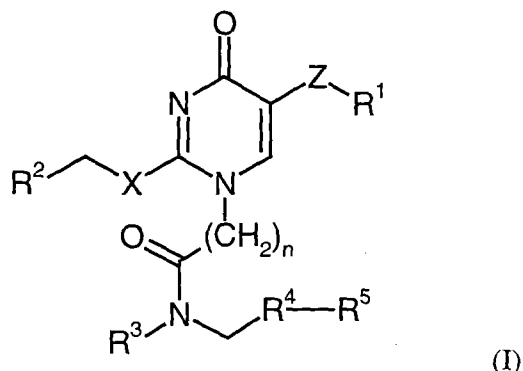
Furthermore, Lp-PLA₂ inhibitors may also have a general application in any disorder that involves lipid peroxidation in conjunction with Lp-PLA₂ activity to produce the two injurious products, lysophosphatidylcholine and oxidatively modified fatty acids. Such conditions include the aforementioned conditions atherosclerosis, diabetes, rheumatoid arthritis, stroke, myocardial infarction,

reperfusion injury and acute and chronic inflammation. Further such conditions include various neuropsychiatric disorders such as schizophrenia (see *Psychopharmacology Bulletin*, 31, 159-165, 1995).

Patent applications WO 96/12963, WO 96/13484, WO96/19451, WO 97/02242, WO97/217675, WO97/217676, WO 96/41098, and WO97/41099 (SmithKline Beecham plc) disclose *inter alia* various series of 4-thionyl/sulfinyl/sulfonyl azetidinone compounds which are inhibitors of the enzyme Lp-PLA₂. These are irreversible, acylating inhibitors (Tew *et al*, *Biochemistry*, 37, 10087, 1998).

A new class of compounds has now been identified which are inhibitors of the enzyme Lp-PLA₂.

Accordingly, the present invention provides a compound of formula (I):



in which:

R^1 is an aryl or heteroaryl group, optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from $C_{(1-18)}$ alkyl, $C_{(1-18)}$ alkoxy, $C_{(1-18)}$ alkylthio, aryl $C_{(1-18)}$ alkoxy, hydroxy, halogen, CN, COR⁶, carboxy, COOR⁶, CONR⁶R⁷, NR⁶COR⁷, SO₂NR⁶R⁷, NR⁶SO₂R⁷, NR⁶R⁷, mono to perfluoro- $C_{(1-4)}$ alkyl and mono to perfluoro- $C_{(1-4)}$ alkoxy, or, as a single substituent, optionally in combination with a further substituent as hereinbefore defined, CH₂COOH or a salt thereof, CH₂COOR⁸, CH₂CONR⁹R¹⁰, CH₂CN, (CH₂)_mNR⁹R¹⁰, (CH₂)_mOH or (CH₂)_mOR⁸ where m is an integer from 1 to 3;

R^2 is an aryl or heteroaryl group, optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from $C_{(1-18)}$ alkyl, $C_{(1-18)}$ alkoxy, $C_{(1-18)}$ alkylthio, aryl $C_{(1-18)}$ alkoxy, hydroxy, halogen, CN, COR⁶, carboxy, COOR⁶, CONR⁹R¹⁰, NR⁶COR⁷, SO₂NR⁹R¹⁰, NR⁶SO₂R⁷, NR⁹R¹⁰, mono to perfluoro- $C_{(1-4)}$ alkyl, mono to perfluoro- $C_{(1-4)}$ alkoxyaryl, and aryl $C_{(1-4)}$ alkyl;

R^3 is hydrogen or $C_{(1-4)}$ alkyl optionally substituted by hydroxy, OR⁶, COR⁶, carboxy, COOR⁶, CONR⁹R¹⁰, NR⁹R¹⁰;

R^4 is an aryl or a heteroaryl ring optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from $C_{(1-18)}$ alkyl, $C_{(1-18)}$ alkoxy, $C_{(1-18)}$ alkylthio, aryl $C_{(1-18)}$ alkoxy, hydroxy, halogen, CN, COR⁶, carboxy, COOR⁶, CONR⁹R¹⁰, NR⁶COR⁷, SO₂NR⁹R¹⁰, NR⁶SO₂R⁷, NR⁹R¹⁰, mono to perfluoro- $C_{(1-4)}$ alkyl and mono to perfluoro- $C_{(1-4)}$ alkoxy;

R^5 is an aryl ring which is further optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from $C_{(1-18)}$ alkyl, $C_{(1-18)}$ alkoxy, $C_{(1-18)}$ alkylthio, aryl $C_{(1-18)}$ alkoxy, hydroxy, halogen, CN, COR⁶, carboxy, COOR⁶, CONR⁹R¹⁰, NR⁶COR⁷, SO₂NR⁹R¹⁰, NR⁶SO₂R⁷, NR⁹R¹⁰, mono to perfluoro- $C_{(1-4)}$ alkyl and mono to perfluoro- $C_{(1-4)}$ alkoxy;

R^6 and R^7 are independently hydrogen or $C_{(1-20)}$ alkyl, for instance $C_{(1-4)}$ alkyl (e.g. methyl or ethyl);

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R^8 is $C_{(1-4)}$ alkyl or a pharmaceutically acceptable *in vivo* hydrolysable ester group;

R^9 and R^{10} which may be the same or different is each selected from hydrogen, $C_{(1-12)}$ alkyl, CH_2R^{11} , $CHR^{12}CO_2H$ or a salt thereof, or R^9 and R^{10} together with the nitrogen to which they are attached form a 5- to 7 membered ring optionally containing one or more further heteroatoms selected from oxygen, nitrogen and sulphur, and optionally substituted by one or two substituents selected from hydroxy, oxo, $C_{(1-4)}$ alkyl, $C_{(1-4)}$ alkylCO, aryl, e.g. phenyl, or aralkyl, e.g. benzyl, for instance morpholine or piperazine;

R^{11} is COOH or a salt thereof, $COOR^8$, $CONR^6R^7$, CN, CH_2OH or CH_2OR^6 ;

R^{12} is an amino acid side chain such as CH_2OH from serine;

n is an integer from 1 to 4, preferably 1 or 3;

X is O or S; and

Z is $CR^{13}R^{14}$ where R^{13} and R^{14} are each hydrogen or $C_{(1-4)}$ alkyl, or R^{13} and R^{14} together with the intervening carbon atom form a $C_{(3-6)}$ cycloalkyl ring.

Preferably, Z is CH_2 .

Representative examples of R^1 when an aryl group include phenyl and naphthyl.

Representative examples of R^1 when a heteroaryl group include a 5- or 6- membered, monocyclic heteroaryl group containing 1 or 2 nitrogen heteroatoms.

Preferably R^1 is pyrimidyl optionally substituted by 1 or 2 substituents preferably selected from oxo, aryl $C_{(1-4)}$ alkyl (e.g. benzyl), $C_{(1-6)}$ alkyl (e.g. methyl or ethyl), $C_{(3-6)}$ cycloalkyl, hydroxy, $C_{(1-4)}$ alkoxy (e.g. methoxy), carboxy $C_{(1-6)}$ alkyl, $C_{(1-6)}$ alkylcarboxy $C_{(1-6)}$ alkyl, di- $C_{(1-6)}$ alkylamino, and morpholino; or pyrazolyl optionally substituted by $C_{(1-6)}$ alkyl (e.g. methyl or ethyl).

Preferably, ZR^1 is pyrimid-5-ylmethyl optionally substituted by 2-methoxy, 2-trifluoromethyl, 2-(1-morpholino) or 2-dimethylamino, 2-oxo-pyrimid-5-ylmethyl in which the 2-oxo-pyrimid-5-yl moiety is as herein before defined or 1-methylpyrazolyl-5-ylmethyl.

Preferably X is S.

Representative examples of R^2 when an aryl group include phenyl and naphthyl. Representative examples of R^2 when a heteroaryl group include pyridyl, pyrimidinyl, pyrazolyl, furanyl, thienyl, thiazolyl, quinolyl, benzothiazolyl, pyridazolyl and pyrazinyl. Preferably, R^2 is phenyl optionally substituted by halogen.

Representative examples of R^2CH_2X include 4-fluorobenzylthio.

Representative examples of R^3 include hydrogen, methyl and 2-(dimethylamino)ethyl.

Representative examples of R^4 include phenyl, thiophene and pyridine.

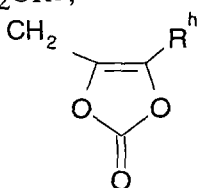
Representative examples of R^5 include phenyl optionally substituted by halogen, or trifluoromethyl, preferably at the 4-position.

Preferably, R⁴ and R⁵ together form a 4-(phenyl)phenyl substituent in which the remote phenyl ring may be optionally substituted by halogen or trifluoromethyl, preferably at the 4-position.

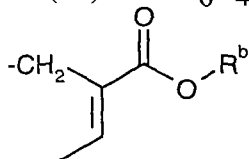
- 5 Pharmaceutically acceptable *in vivo* hydrolysable ester groups for R⁸ include those which break down readily in the human body to leave the parent acid or its salt.

Representative examples of values of pharmaceutically acceptable *in vivo* hydrolysable ester groups for R⁸ include:

- 10 -CH(R^a)O.CO.R^b;
 -CH(R^a)O.CO.OR^c;
 -CH(R^a)CO.NR^eR^f
 -R^dNR^eR^f;
 -CH₂OR^g;



- 15 CH(R^a)O.CO.C₆H₄Y¹COCH(Rⁱ)NH₂; and



in which:

- 20 R^a is hydrogen, (C₁-6)alkyl, in particular methyl, (C₃-7)cycloalkyl, or phenyl, each of which may be optionally substituted;
 R^b is (C₁-6)alkyl, (C₁-6)alkoxy(C₁-6)alkyl, phenyl, benzyl, (C₃-7)cycloalkyl, (C₁-6)alkyl(C₃-7)cycloalkyl, 1-amino(C₁-6)alkyl, or 1-(C₁-6)alkylamino(C₁-6)alkyl, each of which may be optionally substituted; or
 R^a and R^b together form a 1,2-phenylene group optionally substituted by one or two methoxy groups;
 25 R^c is (C₁-6)alkyl, (C₃-7)cycloalkyl, (C₁-6)alkyl(C₃-7)cycloalkyl;
 R^d is (C₁-6)alkylene optionally substituted with a methyl or ethyl group;
 R^e and R^f which may be the same or different is each (C₁-6)alkyl; or aryl(C₁-4) alkyl, optionally substituted with e.g. hydroxy;
 R^g is (C₁-6)alkyl;
 30 R^h is hydrogen, (C₁-6)alkyl or phenyl;
 Rⁱ is hydrogen or phenyl optionally substituted by up to three groups selected from halogen, (C₁-6)-alkyl, or (C₁-6)alkoxy;
 and
 Y¹ is oxygen or NH;
 35 for instance:

(a) acyloxyalkyl groups such as acetoxymethyl, isobutyryloxymethyl, pivaloyloxymethyl, benzoyloxymethyl, α-acetoxyethyl, α-pivaloyloxyethyl, 1-(cyclohexylcarbonyloxy)ethyl, (1-aminoethyl)carbonyloxymethyl, 2-methoxyprop-2-ylcarbonyloxymethyl, phenylcarbonyloxymethyl and 4-methoxyphenyl-carbonyloxymethyl;

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- (b) alkoxy/cycloalkoxycarbonyloxyalkyl groups, such as ethoxycarbonyloxymethyl, t-butylloxycarbonyloxymethyl, cyclohexyloxycarbonyloxymethyl, 1-methylcyclohexyloxycarbonyloxymethyl and α -ethoxycarbonyloxyethyl;
- (c) dialkylaminoalkyl, especially di-loweralkylamino alkyl groups such as dimethylaminomethyl, dimethylaminoethyl, diethylaminomethyl or diethylaminoethyl;
- (d) acetamido groups such as N,N-dimethylaminocarbonylmethyl, N,N-(2-hydroxyethyl)aminocarbonylmethyl;
- (e) lactone groups such as phthalidyl and dimethoxyphthalidyl;
- (f) (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl; and
- (g) (2-methoxycarbonyl-*E*-but-2-en-yl)methyl.

Representative examples of pharmaceutically acceptable *in vivo* hydrolysable ester groups for R⁸ include:

- (2-methoxycarbonyl-*E*-but-2-en-yl)methyl, isobutyryloxymethyl, 2-methoxyprop-2-ylcarbonyloxymethyl, phenylcarbonyloxymethyl, 4-methoxyphenyl-carbonyloxymethyl, t-butylloxycarbonyloxymethyl, cyclohexyloxy-carbonyloxymethyl, 1-methylcyclohexyloxycarbonyloxymethyl, N,N-dimethylaminocarbonylmethyl, and (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl.

- It will be appreciated that in some instances, compounds of the present invention may include a carboxy group as a substituent. Such carboxy groups may be used to form salts, in particular pharmaceutically acceptable salts. Pharmaceutically acceptable salts include those described by Berge, Bighley, and Monkhouse, *J. Pharm. Sci.*, 1977, **66**, 1-19. Preferred salts include alkali metal salts such as the sodium and potassium salts.

- When used herein, the term "alkyl" and similar terms such as "alkoxy" includes all straight chain and branched isomers. Representative examples thereof include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *t*-butyl, *n*-pentyl and *n*-hexyl.

- When used herein, the term "aryl" refers to, unless otherwise defined, a mono- or bicyclic aromatic ring system containing up to 10 carbon atoms in the ring system, for instance phenyl or naphthyl.

- When used herein, the term "heteroaryl" refers to a mono- or bicyclic heteroaromatic ring system comprising up to four, preferably 1 or 2, heteroatoms each selected from oxygen, nitrogen and sulphur. Each ring may have from 4 to 7, preferably 5 or 6, ring atoms. A bicyclic heteroaromatic ring system may include a carbocyclic ring.

- When used herein, the terms "halogen" and "halo" include fluorine, chlorine, bromine and iodine and fluoro, chloro, bromo and iodo, respectively.

- Particularly preferred compounds of formula (I) are
- 1-(N-Methyl-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one;
- 1-(N-(Dimethylaminocarbonylmethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one;

1-(N-(2-Methoxyethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one;

1-(N-(2-Dimethylaminoethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one hydrochloride; and

5 1-(N-(3-Dimethylaminopropyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one hydrochloride.

Since the compounds of the present invention, in particular compounds of formula (I), are intended for use in pharmaceutical compositions, it will be understood that they are each provided in substantially pure form, for example at least 50% pure, more suitably at least 75% pure and preferably at least 95% pure (% are on a wt/wt basis). Impure preparations of the compounds of formula (I) may be used for
10 preparing the more pure forms used in the pharmaceutical compositions. Although the purity of intermediate compounds of the present invention is less critical, it will be readily understood that the substantially pure form is preferred as for the compounds of formula (I). Preferably, whenever possible, the compounds of the present invention are obtained in crystalline form.

15 When some of the compounds of this invention are allowed to crystallise or are recrystallised from organic solvents, solvent of crystallisation may be present in the crystalline product. This invention includes within its scope such solvates. Similarly, some of the compounds of this invention may be crystallised or recrystallised from solvents containing water. In such cases water of hydration may be
20 formed. This invention includes within its scope stoichiometric hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation. In addition, different crystallisation conditions may lead to the formation of different polymorphic forms of crystalline products. This invention includes within its scope all polymorphic forms of the compounds of formula (I).

25 Compounds of the present invention are inhibitors of the enzyme lipoprotein associated phospholipase A₂ (Lp-PLA₂) and as such are expected to be of use in therapy, in particular in the treatment of atherosclerosis. In a further aspect therefore the present invention provides a compound of formula (I) for use in therapy.

30 The compounds of formula (I) are inhibitors of lysophosphatidylcholine production by Lp-PLA₂ and may therefore also have a general application in any disorder that involves endothelial dysfunction, for example atherosclerosis, diabetes, hypertension, angina pectoris and after ischaemia and reperfusion. In addition, compounds of formula (I) may have a general application in any disorder that involves lipid
35 peroxidation in conjunction with enzyme activity, for example in addition to conditions such as atherosclerosis and diabetes, other conditions such as rheumatoid arthritis, stroke, inflammatory conditions of the brain such as Alzheimer's Disease, myocardial infarction, reperfusion injury, sepsis, and acute and chronic inflammation. Further such conditions include various neuropsychiatric disorders such as schizophrenia (see Psychopharmacology Bulletin, 31, 159-165, 1995).

40 Further applications include any disorder that involves activated monocytes, macrophages or lymphocytes, as all of these cell types express Lp-PLA₂. Examples of such disorders include psoriasis.

Accordingly, in a further aspect, the present invention provides for a method of treating a disease state
45 associated with activity of the enzyme Lp-PLA₂, which method involves treating a patient in need thereof

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with a therapeutically effective amount of an inhibitor of the enzyme. The disease state may be associated with the increased involvement of monocytes, macrophages or lymphocytes; with the formation of lysophosphatidylcholine and oxidised free fatty acids; with lipid peroxidation in conjunction with Lp PLA2 activity; or with endothelial dysfunction.

Compounds of the present invention may also be of use in treating the above mentioned disease states in combination with anti-hyperlipidaemic or anti-atherosclerotic or anti-diabetic or anti-anginal or anti-inflammatory or anti-hypertension agents. Examples of the above include cholesterol synthesis inhibitors such as statins, anti-oxidants such as probucol, insulin sensitisers, calcium channel antagonists, and anti-inflammatory drugs such as NSAIDs.

In therapeutic use, the compounds of the present invention are usually administered in a standard pharmaceutical composition. The present invention therefore provides, in a further aspect, a pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable carrier.

Suitable pharmaceutical compositions include those which are adapted for oral or parenteral administration or as a suppository.

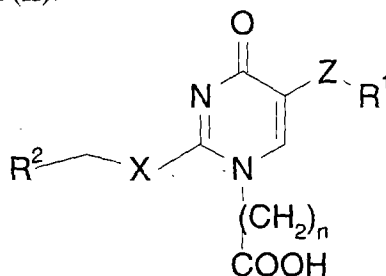
Suitable pharmaceutical compositions include those which are adapted for oral or parenteral administration or as a suppository. Compounds of formula (I) which are active when given orally can be formulated as liquids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges. A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s) for example, ethanol, glycerine, non-aqueous solvent, for example polyethylene glycol, oils, or water with a suspending agent, preservative, flavouring or colouring agent. A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose. A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule. Typical parenteral compositions consist of a solution or suspension of the compound of formula (I) in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration. A typical suppository formulation comprises a compound of formula (I) which is active when administered in this way, with a binding and/or lubricating agent such as polymeric glycols, gelatins or cocoa butter or other low melting vegetable or synthetic waxes or fats.

Preferably the composition is in unit dose form such as a tablet or capsule. Each dosage unit for oral administration contains preferably from 1 to 500 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a compound of the formula (I). The daily dosage regimen for an adult patient may be, for example, an oral dose of between 1 mg and 1000 mg, preferably between 1 mg and 500 mg, or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg,

preferably between 0.1 mg and 25 mg, of the compound of the formula (I), the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

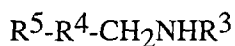
5 A compound of formula (I) may be prepared by a number of processes which include:

(a) reacting a compound of formula (II):



(II)

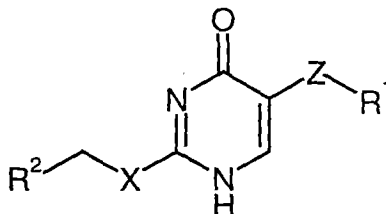
10 in which X, Y, Z, R¹ and R² are as hereinbefore defined,
with a compound of formula (III):



(III)

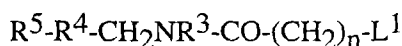
15 in which R³, R⁴ and R⁵ are as hereinbefore defined; under amide forming conditions;

(b) reacting a compound of formula (IV):



(IV)

20 in which X, Z, R¹ and R² are as hereinbefore defined,
with a compound of formula (V):

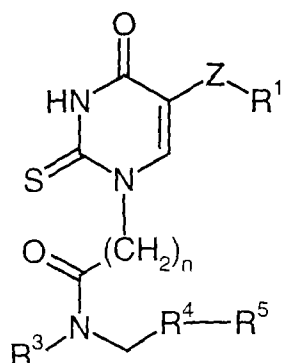


(V)

25 in which n, R³, R⁴ and R⁵ are as hereinbefore defined, and L¹ is a leaving group such as halogen, for instance bromo or iodo,

in the presence of a base such as a secondary or tertiary amine, for instance di-isopropylethylamine, in an inert solvent such as dichloromethene;

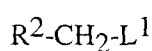
30 (c) when X is S, reacting a compound of formula (VI):

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(VI)

in which n , Z , R^1 , R^3 , R^4 and R^5 are as hereinbefore defined,
with a compound of formula (VII):

5



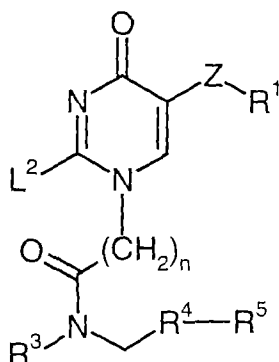
(VII)

in which R^2 and L^1 are as hereinbefore defined,

in the presence of a base such as a secondary or tertiary amine, for instance di-isopropylethylamine, in an
inert solvent such as dichloromethene; or

10

(d) when X is O , reacting a compound of formula (VIII):

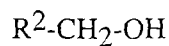


(VIII)

in which n , Z , R^1 , R^3 , R^4 and R^5 are as hereinbefore defined, and L^2 is a leaving group such as halogen
or alkylthio, for instance methylthio,
with a compound of formula (IX):

15

20



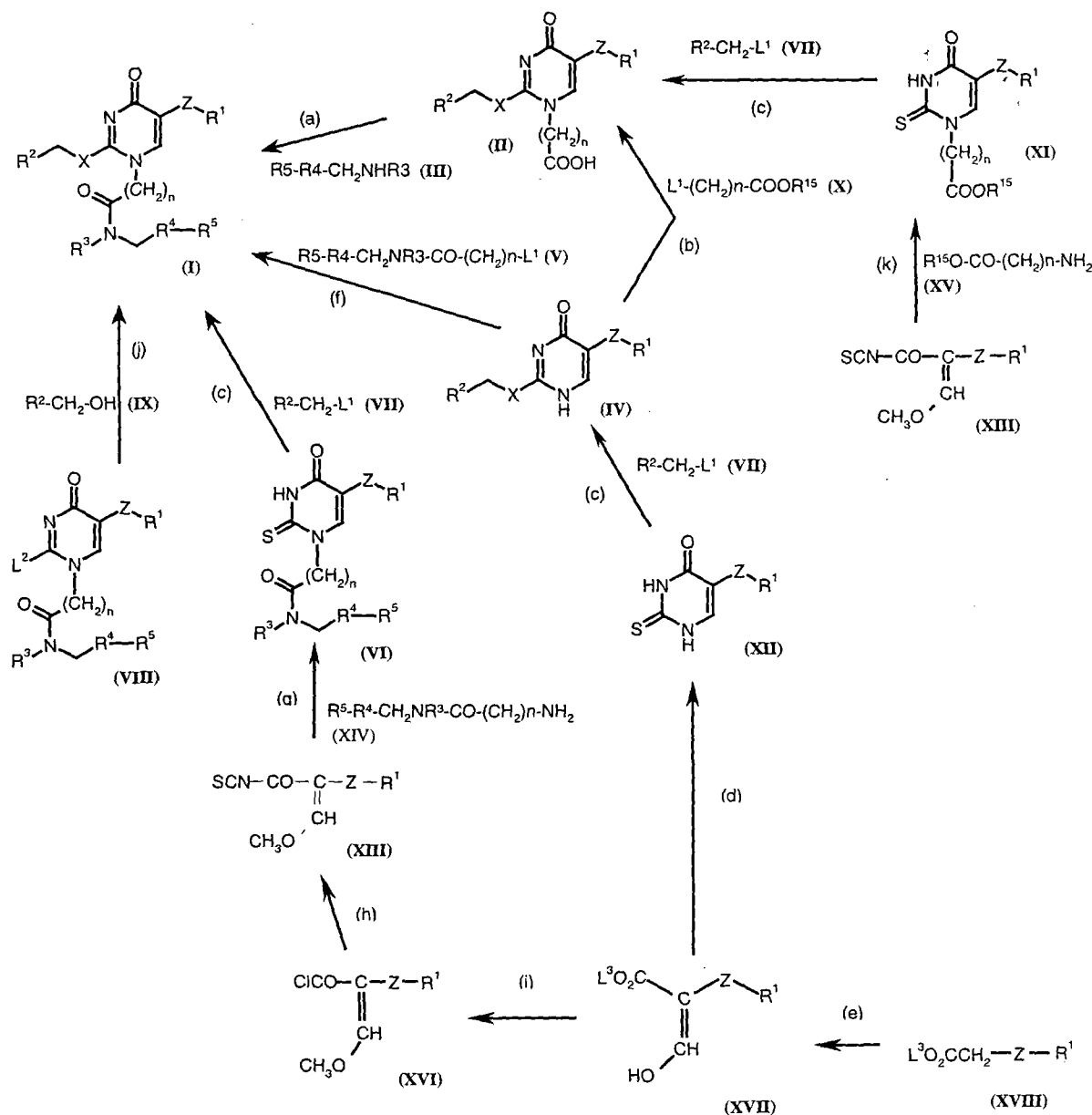
(IX)

in which R^2 is as hereinbefore defined,

in the presence of a base such as 4-dimethylaminopyridine, in an inert solvent such as pyridine.

Compounds of formulae (II), (IV), (VI) and (VIII) for use in the above processes may be prepared by
processes illustrated in the following scheme I:

25



Scheme I

in which:

L^3 is a C(1-6)alkyl group, for instance methyl;

5 R^{15} is a C(1-6)alkyl group, for instance ethyl and

$L^1, L^2, R^1, R^2, R^3, R^4, R^5, n, X$ and Z are as hereinbefore defined.

With reference to Scheme I:

10 Amide forming conditions for step (a) are well known in the art. Preferably, the acid of formula (II) is reacted with the amine of formula (III) in an inert solvent, such as dichloromethane, at ambient temperature and in the presence of an activating agent such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide plus hydroxybenzotriazole.

15 Alkylation conditions for step (b) include reaction in the presence of a base such as a secondary or tertiary amine, for instance di-isopropylethylamine, in an inert solvent such as dichloromethane, forming

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A

an intermediate ester which is then converted to the acid of formula (II) by hydrolysis, for instance using aqueous sodium hydroxide in a solvent such as dioxan.

5 Conditions for step (c) include under thioether forming conditions. Advantageously, the reaction is carried out in the presence of a base such as sodium ethoxide or potassium carbonate, preferably in a solvent such as ethanol or dimethyl formamide, or a secondary or tertiary amine base such as di-isopropylethyl amine, in solvent such as dichloromethane.

10 In step (d), a compound of formula (XVII) is reacted with thiourea, in the presence of sodium ethoxide (preferably generated *in situ* from sodium and ethanol).

In step (e), a compound of formula (XVIII) is reacted with ethyl formate in the presence of a base such as sodium hydride or potassium isopropoxide.

15 In step (f), a compound of formula (VI) is reacted with a compound of formula (V) in the presence of a base such as a secondary or tertiary amine, for instance di-isopropylethylamine, in an inert solvent such as dichloromethane

20 In step (g), a compound of formula (XIII) is reacted with a compound of formula (XIV) in a solvent such as dimethylformamide to form an intermediate thiourea, which is then treated with a base such as sodium methoxide.

25 In step (h), a compound of formula (XVI) is reacted with a metal thiocyanate, for example potassium thiocyanate, in a solvent such as acetonitrile.

30 In step (i), a compound of formula (XVII) is reacted with a methylating agent such as dimethyl sulphate in the presence of a base such as potassium carbonate, followed by hydrolysis of the intermediate ester in conventional manner e.g. by basic hydrolysis using sodium hydroxide to give the corresponding carboxylic acid which may then be converted into the acyl chloride, for instance by treatment with oxalyl chloride.

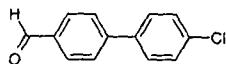
In step (j), a catalyst such as 4-dimethylaminopyridine, and in a solvent such as pyridine are used.

35 In step (k), a compound of formula (XIII) is reacted with a compound of formula (XV) in a solvent such as dimethylformamide to form an intermediate thiourea, which is then treated with a base such as sodium methoxide.

The present invention will now be illustrated by the following examples.

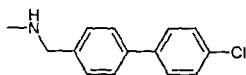
Examples

Intermediate A1 — 4-(4-Chlorophenyl)benzaldehyde



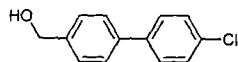
- 5 (a) A mixture of 4-formylbenzeneboronic acid (2.50g, 2 equiv), 4-chloriodobenzene (1.98g, 1 equiv), tetrakis(triphenylphosphine)palladium(0) (0.50g, 0.05 equiv), aqueous sodium carbonate (18ml, 2M solution, 2 equiv) and dimethoxyethane (50ml) was stirred at reflux under argon overnight, then cooled and diluted with ethyl acetate. The mixture was filtered as necessary to remove inorganic residues, then the organic layer was washed successively with aqueous citric acid and brine, dried and evaporated. The
- 10 crude product was purified by chromatography (silica, 5% ethyl acetate in hexane); product fractions were evaporated to a white solid (1.32g, 72%).
- (b) A mixture of 4-chlorobenzeneboronic acid (19.4g, 1 equiv), 4-bromobenzaldehyde (22.9g, 1 equiv), palladium(II) acetate (1.4g, 0.05 equiv) aqueous sodium carbonate (30.3 g in 144ml solution, 2 equiv) and dimethoxyethane (500ml) was stirred at reflux under argon for 2.5h, then evaporated to low volume
- 15 and diluted with dichloromethane. Workup continued as in (a) above to give identical material (25.2g, 94%). ¹H-NMR (CDCl₃) δ 10.05 (1H, s), 7.96 (2H, d), 7.73 (2H,d), 7.57 (2H, d), 7.46 (2H, d); MS (AP+) found (M+1) = 217, C₁₃H₉³⁵ClO requires 216.

Intermediate A2 — N-Methyl-4-(4-chlorophenyl)benzylamine



- 20 A mixture of Intermediate A1 (3.5g, 1 equiv), methylamine (32.3ml of a 2M solution in THF, 4 equiv) and anhydrous magnesium sulphate (4.47g, 2 equiv) was stirred at room temperature for 16h, then filtered, the solid washed thoroughly with ethyl acetate, and the combined filtrates evaporated to a white solid (3.7g). This imine intermediate was suspended in ethanol (100ml), cooled in ice and sodium borohydride (0.61g, 1 equiv) added portionwise. The ice bath was removed, and the mixture stirred for 45min at
- 25 room temperature then at 50°C for 1h. The solvent was removed in vacuo, water was added to the residue, and the product extracted into dichloromethane. Drying and evaporation of the solvent gave a white solid (3.56g). ¹H-NMR (CDCl₃) δ 7.51 (4H, d), 7.40 (4H, d), 3.79 (2H, s), 2.48 (3H, s); MS (APCI+) found (M+1) = 232, C₁₄H₁₄³⁵ClN requires 231.

Intermediate A3 — 4-(4-Chlorophenyl)benzyl alcohol



- 30 A mixture of Intermediate A1 (1.73g, 1 equiv), sodium borohydride (0.3g, 1 equiv) and ethanol (20ml) was stirred until a clear solution was obtained; a gentle exotherm was observed. The temperature was raised to 50°C and stirring continued for 2h, then the solvent was removed in vacuo, water added to the residue, and the product extracted into dichloromethane. Drying and evaporation of the solvent gave a
- 35 white solid (1.67g).

108-106

LEGALIZACIONES

OFICINA DE PATENTES

Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

El suscrito, un funcionario debidamente autorizado conforme a los Artículos 74(1) y (4) de la Ley de Desreglamentación y Contratación de 1994 para firmar y expedir certificados en nombre del Contralor General, certifico que la copia adjunta es una copia correcta de los documentos archivados originalmente con respecto a la solicitud de patente que allí se identifica.

De acuerdo con las Reglamentaciones de Patentes de 1982 (Re-registro de Compañías), si una compañía nombrada en este certificado y en los documentos adjuntos se ha vuelto a registrar según la Ley de Compañías de 1980 con el mismo nombre con el que fue registrada inmediatamente antes del re-registro, salvo la sustitución o inclusión como la última parte del nombre de las palabras “sociedad anónima” o su equivalente en galés, las referencias al nombre de la compañía y sus documentos adjuntos serán tratadas como referencias al nombre con el cual fue re-registrada.

De acuerdo con las reglas, las palabras “sociedad anónima” (o en inglés *public limited company*) pueden ser reemplazadas por las letras p.l.c, plc. P.L.C ó PLC.

El re-registro bajo la Ley de Compañías no constituye una nueva entidad legal sino simplemente somete a la compañía a ciertas normas de ley adicionales.

(FIRMA) ANDREW CRESSEY

FECHA: 14 de marzo de 2000

(SELLO DE LACRE)

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OFICINA DE PATENTES

SOLICITUD DE PATENTE

1. Su referencia: **ACC/JR/P32296**

2. Solicitud No. **9910048.9** 01 de mayo de 1999

3. Nombre completo y código postal de cada solicitante:

Dirección: SMITHKLINE BEECHAM plc.
New Horizons Court,
Brentford, Mddlesex TW8 9EP

No. APD 5776299002

Si el solicitante es una entidad, indique el país/estado de constitución:

REINO UNIDO

4. TITULO DEL INVENTO:

COMPUESTOS NOVEDOSOS

5. NOMBRE DE SU AGENTE:

Nombre del Agente: CORPORATE INTELLECTUAL PROPERTY

Dirección para notificaciones: SMITHKLINE BEECHAM PLC
TWO NEW HORIZONS COURT
BRENTFORD
MIDDLESEX TW8 9EP

NO. ADP Patentes 5800974003

6. N/A

7. N/A

8. SI

110 108 20

9. Número de hojas radicadas (En inglés). Descripción: 61 Reivindicaciones: 4

Resumen : - Dibujos: -

10. Solicitud de examen preliminar y búsqueda:

11. Solicitamos se nos adjudique una patente con base en esta solicitud.

A C CONNELL

30 de abril de 1999

12. Nombre y teléfono del contacto en el Reino Unido Nombre y teléfono del contacto en el

Reino Unido (FIRMA) A C CONNELL

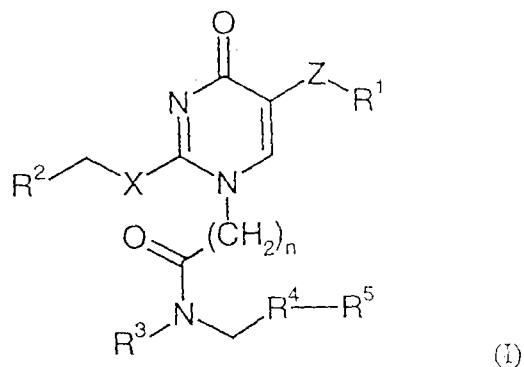
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COMPUESTOS NOVEDOSOS

REIVINDICACIONES:

1. Un compuesto de la fórmula (I):



en la cual:

R^1 es un grupo aril o heteroaril, sustituido opcionalmente por 1, 2, 3 o 4 sustituyentes que pueden ser el mismo o diferente, seleccionados de alquil $C_{(1-18)}$, alcoxi $C_{(1-18)}$, alquiltio $C_{(1-18)}$, aril alcoxi $C_{(1-18)}$, hidroxil, halógeno, CN, COR^6 , carboxi, $COOR^6$, $CONR^6R^7$, NR^6COR^7 , $SO_2NR^6R^7$, $NR^6SO_2R^7$, NR^6R^7 , mono a perfluoro-alquil $C_{(1-4)}$ y mono a perfluoro-alcoxi $C_{(1-4)}$, o como un solo sustituyente, opcionalmente en combinación con otro sustituyente según se describe arriba, CH_2COH o una sal de lo mismo, CH_2COOR^8 , $CH_2CONR^9R^{10}$, CH_2CN , $(CH_2)_mNR^9R^{10}$, $(CH_2)_mOH$ o $(CH_2)_mOR^8$, donde m es un entero de 1 a 3;

R^2 es un grupo aril o heteroaril, sustituido opcionalmente por 1, 2, 3 o 4 sustituyentes que pueden ser el mismo o diferente seleccionados de alquil $C_{(1-18)}$, alcoxi $C_{(1-18)}$, alquiltio $C_{(1-18)}$, aril alcoxi $C_{(1-18)}$, hidroxil, halógeno, CN, COR^6 , carboxi, $COOR^6$, $CONR^9R^{10}$, NR^6COR^7 , $SO_2NR^9R^{10}$, $NR^6SO_2R^7$, NR^9R^{10} , mono a perfluoro-alquil $C_{(1-4)}$, mono a perfluoro-alcoxilaril $C_{(1-4)}$ y aril-alquil $C_{(1-4)}$;

112-110

R^3 es hidrógeno o alquil $C_{(1-4)}$ sustituido opcionalmente por hidroxilo, OR^6 , COR^6 , carboxi, $COOR^6$, $CONR^9R^{10}$, NR^9R^{10} ;

R^4 es un anillo aril o heteroaril sustituido opcionalmente por 1, 2, 3 o 4 sustituyentes que pueden ser los mismos o diferentes seleccionados de alquil $C_{(1-18)}$, alcoxi $C_{(1-18)}$, alquiltio $C_{(1-18)}$, aril alcoxi $C_{(1-18)}$, hidroxilo, halógeno, CN, COR^6 , carboxi, $COOR^6$, $CONR^9R^{10}$, NR^6COR^7 , $SO_2NR^9R^{10}$, $NR^6SO_2R^7$, NR^9R^{10} , mono a perfluoro-alquil $C_{(1-4)}$ y mono a perfluoro-alcoxi $C_{(1-4)}$;

R^5 es un anillo aril que es además sustituido por 1, 2, 3 o 4 sustituyentes que pueden ser los mismos o diferentes seleccionados de alquil $C_{(1-18)}$, alcoxi $C_{(1-18)}$, alquiltio $C_{(1-18)}$, aril alcoxi $C_{(1-18)}$, hidroxilo, halógeno, CN, COR^6 , carboxi, $COOR^6$, $CONR^9R^{10}$, NR^6COR^7 , $SO_2NR^9R^{10}$, $NR^6SO_2R^7$, NR^9R^{10} , mono a perfluoro-alquil $C_{(1-4)}$ y mono a perfluoro-alcoxi $C_{(1-4)}$;

R^6 y R^7 son independientemente hidrógeno o alquil $C_{(1-20)}$, por ejemplo alquil $C_{(1-4)}$ (por ej. metil o etil);

R^8 es alquil $C_{(1-4)}$ o un grupo éster hidrolizable *in vivo* farmacéuticamente aceptable;

R^9 y R^{10} que pueden ser los mismos o diferentes es cada uno seleccionado de hidrógeno, alquil $C_{(1-2)}$, CH_2R^{11} , $CHR^{12}CO_2H$ o una sal de lo mismo, o R^9 y R^{10} junto con el nitrógeno al que están fijos forman un anillo de 5 a 7 miembros que contiene opcionalmente uno o más heteroátomos seleccionados de oxígeno, nitrógeno y azufre, y sustituidos opcionalmente por uno o dos sustituyentes seleccionados de hidroxilo, oxo alquil $C_{(1-4)}$, alquil $C_{(1-4)}CO$, aril, por ej. fenil o aralquil, por ej. bencil, por ejemplo, morfolina o piperazina;

R^{11} es $COOH$ o una sal de lo mismo, $COOR^8$, $CONR^6R^7$, CN, CH_2OH o CH_2OR^6 ;

#3 III K

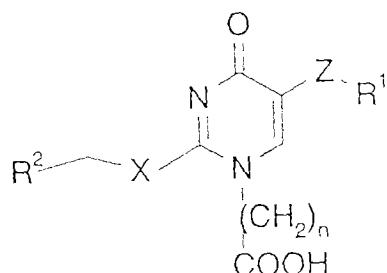
R^{12} es una cadena lateral amino ácida tal como CH_2OH de serina;

n es un entero de 1 a 4, preferiblemente, 1 ó 3;

X es O o S; y

Z es $CR^{13}R^{14}$, donde R^{13} y R^{14} son cada uno hidrógeno o alquil $C_{(1-4)}$, o R^{13} y R^{14} junto con el átomo de carbono que interviene forma un anillo cicloalquil $C_{(3-6)}$.

2. Una composición farmacéutica que comprende un compuesto de la fórmula (I) según la reivindicación 1, y un vehículo farmacéuticamente aceptable.
3. Un compuesto de la fórmula (I) según la reivindicación 1, para uso en terapia.
4. El uso de un compuesto de la fórmula (I) según la reivindicación 1 para la manufactura de un medicamento para el tratamiento de aterosclerosis.
5. Un método de tratamiento de un estado de enfermedad asociado con la actividad de la enzima Lp-PLA, cuyo método implica tratar a un paciente que lo requiera con una cantidad terapéuticamente efectiva de un compuesto de la fórmula(I) según la reivindicación 1.
6. Un proceso para preparar un compuesto de la fórmula (I) según se define en la reivindicación 1, dicho proceso consiste en:
 - a) hacer reaccionar un compuesto de la fórmula (II):



#41120

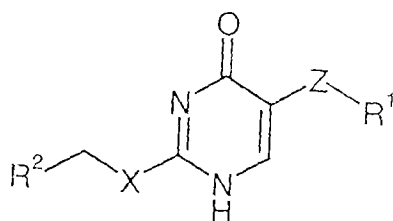
en el cual X, Y, Z, R¹ y R² son según se define arriba,

con un compuesto de la fórmula (III):



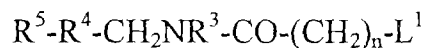
en la cual R³, R⁴ y R⁵ son según se define antes; bajo condiciones de formado de amida;

b) hacer reaccionar un compuesto de la fórmula (IV):



en la cual X, Z, R¹ y R² son según se define arriba,

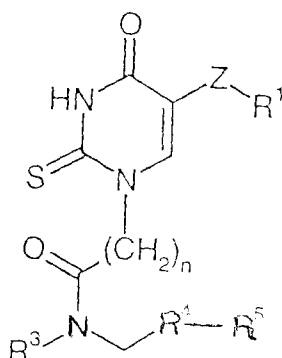
con un compuesto de la fórmula (V):



en la cual n, R³, R⁴ y R⁵ son según se define arriba, y L¹ es un grupo saliente tal como halógeno, por ejemplo bromo o yodo,

en la presencia de una base tal como una amina secundaria o terciaria, por ejemplo di-isopropiletilamina, en un solvente inerte tal como diclorometano;

c) cuando X es X, hacer reaccionar un compuesto de la fórmula (VI):



#51139

en la cual n , R^1 , R^3 , R^4 y R^5 son según se define arriba,

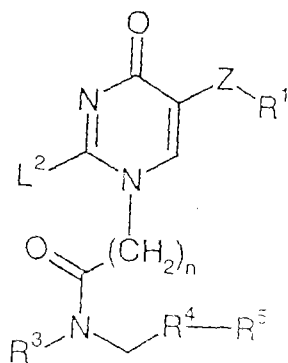
con un compuesto de la fórmula (VII):



en la cual R^2 y L^1 son según se define arriba,

en la presencia de una base tal como una amina secundaria o terciaria, por ejemplo di-isopropiletilamina, en un solvente inerte tal como diclorometano; o

d) cuando X es O, hacer reaccionar un compuesto de la fórmula (VIII):



en la cual n , R^1 , R^3 , R^4 , y R^5 son según se define arriba, y L^2 es un grupo saliente tal como halógeno o alquiltio, por ejemplo, metiltio,

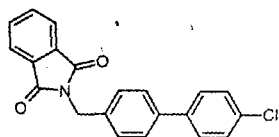
con un compuesto de la fórmula (IX):



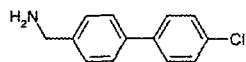
en la cual R^2 es según se describe arriba,

en la presencia de una base tal como 4-dimetilaminopiridina, en un solvente inerte, tal como piridina.

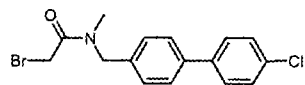
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Intermediate A4 — N-(4-(4-Chlorophenyl)benzyl)phthalimide

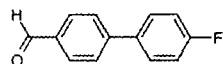
Intermediate A3 (1.62g, 1 equiv), phthalimide (1.42g, 1.3 equiv) and triphenylphosphine (2.53g, 1.3 equiv) were dissolved in dry THF (50ml), the solution was cooled in ice, and DEAD (1.52ml, 1.3 equiv) was added slowly with stirring. The yellow solution was stirred for 16h at room temperature, then the solvent was evaporated. Chromatography (silica, 1:1 dichloromethane/pet. ether) and trituration with ether gave the desired product (2.03g, 79%). $^1\text{H-NMR}$ (CDCl_3) δ 4.89 (2H, s), 7.36-7.50 (8H, m), 7.69-7.74 (2H, m), 7.82-7.89 (2H, m).

Intermediate A5 — 4-(4-Chlorophenyl)benzylamine

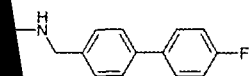
A mixture of Intermediate A4 (1.98g, 1 equiv) and hydrazine hydrate (0.55ml, 2 equiv) in ethanol (40ml) was heated at reflux for 2h, then the solvent was evaporated. The residue was shaken with dichloromethane and 0.5M aqueous sodium hydroxide, the aqueous layer re-extracted with dichloromethane, and the combined organic extracts purified by chromatography (silica, 1-3% methanolic ammonia in dichloromethane). Product fractions were evaporated to a white solid (0.53g, 43%). $^1\text{H-NMR}$ (CDCl_3) δ 3.92 (2H, s), 7.28-7.41 (4H, m), 7.49-7.54 (4H, m).

Intermediate A6 — N-Methyl-N-(4-(4-chlorophenyl)benzyl)bromoacetamide

Bromoacetyl bromide (0.123ml, 1.1 equiv) was added to a well-stirred mixture of Intermediate A2 (0.3g, 1 equiv), sodium hydroxide (0.06g, 1.2 equiv), water and dichloromethane. Stirring was continued for 3h at room temperature, then the phases were separated and the organic layer dried and evaporated. Chromatography (silica, 3:1 hexane/ethyl acetate) gave the desired product as an oil (0.37g). $^1\text{H-NMR}$ (CDCl_3) δ 7.38-7.68 (8H, m), 4.77 (2H, s), 4.07 (2H, s), 3.24 (3H, s); MS (APCI+) found $(\text{M}+1) = 352$, $\text{C}_{16}\text{H}_{15}^{79}\text{Br}^{35}\text{ClNO}$ requires 351.

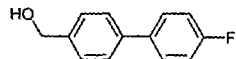
Intermediate A7 — 4-(4-Fluorophenyl)benzaldehyde

Prepared from 4-formylboronic acid and 4-fluoroiodobenzene by the method of Example A1 (a). $^1\text{H-NMR}$ (CDCl_3) δ 10.06 (1H, s), 7.95 (2H, d), 7.71 (2H, d), 7.63-7.58 (2H, m), 7.17 (2H, t); MS (APCI-) found $(\text{M}-1) = 201$, $\text{C}_{13}\text{H}_9\text{FO}$ requires 202.

Intermediate A8 — N-Methyl-4-(4-fluorophenyl)benzylamine

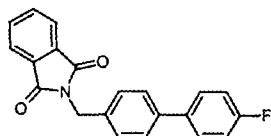
Prepared from Intermediate A7 by the method of Example A2. $^1\text{H-NMR}$ (CDCl_3) δ 7.56-7.49 (4H, m), 7.38 (2H, d), 7.11 (2H, t), 3.79 (2H, s), 2.48 (3H, s); MS (APCI+) found $(\text{M}+1) = 216$, $\text{C}_{14}\text{H}_{14}\text{FN}$ requires 215.

Intermediate A9 — 4-(4-Fluorophenyl)benzyl alcohol



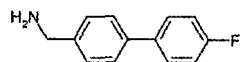
Prepared from Intermediate A7 by the method of Example A3. $^1\text{H-NMR}$ (CDCl_3) δ 7.56-7.52 (4H, m), 7.43 (2H, d), 7.12 (2H, t), 4.74 (2H, d), 1.70 (1H, t); MS (APCI+) found $(\text{M}+1-\text{H}_2\text{O}) = 185$, $\text{C}_{13}\text{H}_{11}\text{FO}$ requires 202.

Intermediate A10 — N-(4-(4-Fluorophenyl)benzyl)phthalimide



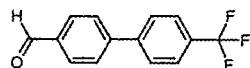
Prepared from Intermediate A9 by the method of Example A4. $^1\text{H-NMR}$ (CDCl_3) δ 4.88 (2H, s), 7.10 (2H, m), 7.49 (6H, m), 7.71 (2H, m), 7.86 (2H, m).

Intermediate A11 — 4-(4-Fluorophenyl)benzylamine



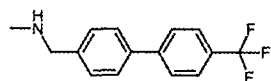
Prepared from Intermediate A10 by the method of Example A5. $^1\text{H-NMR}$ (CDCl_3) δ 3.91 (2H, s), 7.12 (2H, m), 7.38 (2H, m), 7.53 (4H, m).

Intermediate A12 — 4-(4-Trifluoromethylphenyl)benzaldehyde



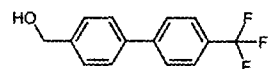
Prepared from 4-bromobenzaldehyde and 4-trifluoromethylbenzeneboronic acid by the method of Example A1 (b). $^1\text{H-NMR}$ (CDCl_3) δ 7.77-8.03 (8H, m), 10.09 (1H, s).

Intermediate A13 — N-Methyl-4-(4-trifluoromethylphenyl)benzylamine

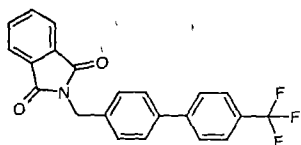


Prepared from Intermediate A12 by the method of Example A2. $^1\text{H-NMR}$ (CDCl_3) δ 7.68 (4H, m), 7.56-7.58 (2H, m), 7.43-7.45 (2H, m), 3.83 (2H, s), 2.50 (3H, s); MS (APCI+) found $(\text{M}+1) = 266$, $\text{C}_{15}\text{H}_{14}\text{F}_3\text{N}$ requires 265.

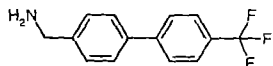
Intermediate A14 — 4-(4-Trifluoromethylphenyl)benzyl alcohol



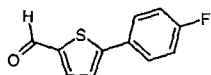
Prepared from Intermediate A12 by the method of Example A3. $^1\text{H-NMR}$ (CDCl_3) δ 7.39-7.63 (8H, m), 4.70 (2H, d), 1.63 (1H, t).

H7 115
KX**Intermediate A15 — N-(4-(4-Trifluoromethylphenyl)benzyl)phthalimide**

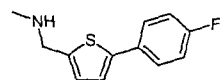
Prepared from Intermediate A14 by the method of Example A4. $^1\text{H-NMR}$ (CDCl_3) δ 7.86 (2H,m), 7.72 (2H,m), 7.65 (4H,m), 7.54 (4H,s), 4.90 (2H,s); MS(APCI+) found (M+1)=382, $\text{C}_{22}\text{H}_{14}\text{F}_3\text{NO}_2$ requires 381.

Intermediate A16 — 4-(4-Trifluoromethylphenyl)benzylamine

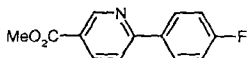
Prepared from Intermediate A15 by the method of Example A5. $^1\text{H-NMR}$ (CDCl_3) δ 7.69 (4H,s), 7.58 (2H,d), 7.43 (2H,d), 3.94 (2H,s); MS(APCI+) found (M-NH₃+1)=235, $\text{C}_{14}\text{H}_{12}\text{F}_3\text{N}$ requires 251.

10 Intermediate A17 — 5-(4-Fluorophenyl)-2-thiophene carboxaldehyde

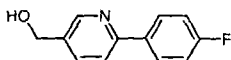
Prepared from 2-bromothiophene-5-carboxaldehyde and 4-fluorobenzeneboronic acid by the method of Example A1 (a). $^1\text{H-NMR}$ (CDCl_3) δ 9.89 (1H, s), 7.72-7.73 (1H, d), 7.63-7.66 (2H, m), 7.33-7.34 (1H, d), 7.11-7.15 (2H, t); MS(APCI+) found (M+1)=208, $\text{C}_{11}\text{H}_7\text{FOS}$ requires 207.

15 Intermediate A18 — 2-Methylaminomethyl-5-(4-fluorophenyl)thiophene

Prepared from Intermediate A17 by the method of Example A2. $^1\text{H-NMR}$ (CDCl_3) δ 7.50-7.54 (2H, m), 7.02-7.09 (3H, m), 6.87-6.88 (1H,d), 3.94 (2H, s), 2.50 (3H, s); MS(APCI+) found (M+1-CH₃NH₂)=191, $\text{C}_{11}\text{H}_7\text{FS}$ requires 190.

20 Intermediate A19 — Methyl 6-(4-fluorophenyl)nicotinate

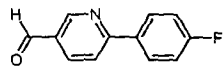
Prepared from methyl 6-chloronicotinate and 4-fluorobenzeneboronic acid by the method of Example A1 (a). $^1\text{H-NMR}$ (CDCl_3) δ 9.26 (1H, d), 8.34 (1H, dd), 8.056 (2H, m), 7.77 (1H, d), 7.18 (2H, t), 3.98 (3H, s); MS(APCI+) found (M+1)=232 $\text{C}_{13}\text{H}_{10}\text{FNO}_2$ requires 231.

25 Intermediate A20 — 5-Hydroxymethyl-2-(4-fluorophenyl)pyridine

A solution of Intermediate A19 (4.63g) in dry dichloromethane (100ml) was cooled to -78°C under argon, then DIBAL-H (26.7ml, 1.5M solution in toluene) was added dropwise over 20min. Stirring was continued for 40min at -78°C , then 2M hydrochloric acid (52ml) was added dropwise over 15min. The solution was allowed to warm slowly to room temperature, then the organic layer was separated, washed with water, dried and evaporated. Chromatography (silica, 1:1 ethyl acetate/hexane) gave the product as

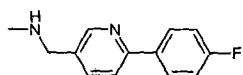
a white solid (3.03g, 75%). $^1\text{H-NMR}$ (CDCl_3) δ 9.65 (1H, d), 7.98 (2H, m), 7.77 (1H, m), 7.68 (1H, d), 7.15 (2H, t), 4.77 (2H, d), 1.802 (1H, t); MS(APCI+) found $(\text{M}+1)=204$, $\text{C}_{12}\text{H}_{10}\text{FNO}$ requires 203.

Intermediate A21 — 5-Formyl-2-(4-fluorophenyl)pyridine



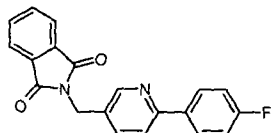
- 5 Activated manganese dioxide (3.19g) was added to a solution of Intermediate A20 (0.75g) in dichloromethane (50ml) and stirred at room temperature for 16h. The solids were filtered off and the filtrate evaporated to a pale yellow solid (0.57g). $^1\text{H-NMR}$ (CDCl_3) δ 10.15 (1H, s), 9.11 (1H, s), 8.22 (1H, dd), 8.10 (2H, m), 7.87 (1H, d), 7.20 (2H, t); MS(APCI+) found $(\text{M}+1)=202$, $\text{C}_{12}\text{H}_8\text{FNO}$ requires 201.

10 Intermediate A22 — 5-Methylaminomethyl-2-(4-fluorophenyl)pyridine



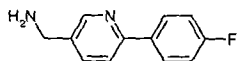
Prepared from Intermediate A21 by the method of Intermediate A2. $^1\text{H-NMR}$ (CDCl_3) δ 8.60 (1H, s), 7.97 (2H, m), 7.74 (1H, m), 7.65 (1H, d), 7.15 (2H, t), 3.80 (2H, s), 2.49 (3H, s); MS(APCI+) found $(\text{M}+1)=217$, $\text{C}_{13}\text{H}_{13}\text{FN}_2$ requires 216.

15 Intermediate A23 — N-(5-(4-Fluorophenyl)pyrid-2-ylmethyl)phthalimide



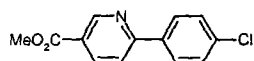
Prepared from Intermediate A20 by the method of Intermediate A4. $^1\text{H-NMR}$ (CDCl_3) δ 8.78 (1H, m), 7.64-7.98 (8H, m), 7.15 (2H, m), 4.91 (2H, s); MS (APCI+) found $(\text{M}+1) = 333$, $\text{C}_{20}\text{H}_{13}\text{FN}_2\text{O}_2$ requires 332.

20 Intermediate A24 — 5-Aminomethyl-2-(4-fluorophenyl)pyridine



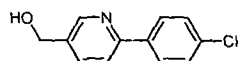
Prepared from Intermediate A23 by the method of Intermediate A5. $^1\text{H-NMR}$ (CDCl_3) δ 8.84 (1H, s), 8.20 (2H, m), 7.86 (2H, m), 7.37 (2H, m), 4.16 (2H, s); MS (APCI+) found $(\text{M}+1) = 203$, $\text{C}_{12}\text{H}_{11}\text{FN}_2$ requires 202.

25 Intermediate A25 — Methyl-6-(4-chlorophenyl)nicotinate



Prepared from methyl 6-chloronicotinate and 4-chlorobenzeneboronic acid by the method of Intermediate A1 (a). $^1\text{H-NMR}$ (CDCl_3) δ 3.98 (3H, s), 7.47 (2H, d), 7.79 (1H, d), 8.01 (2H, d), 8.35 (1H, d), 9.27 (1H, s); MS (APCI+) found $(\text{M}+1)=248$, $\text{C}_{13}\text{H}_{10}\text{ClNO}_2$ requires 247.

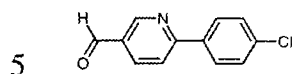
30 Intermediate A26 — 5-Hydroxymethyl-2-(4-chlorophenyl)pyridine



H9114

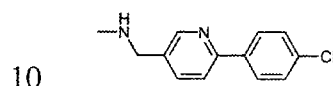
Prepared from Intermediate A25 by the method of Intermediate A20. $^1\text{H-NMR}$ (CDCl_3) δ 1.87 (1H, t), 4.77 (2H, d), 7.44 (2H, m), 7.70 (1H, d), 7.77 (1H, m), 7.94 (2H, m), 8.67 (1H, m); MS (APCI+) found (M+1)=220/222, $\text{C}_{12}\text{H}_{10}\text{ClNO}$ requires 219/221.

Intermediate A27 — 5-Formyl-2-(4-chlorophenyl)pyridine



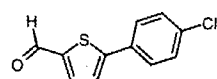
Prepared from Intermediate A26 by the method of Intermediate A21. $^1\text{H-NMR}$ (CDCl_3) δ 7.49 (2H, m), 7.88 (1H, d), 8.05 (2H, m), 8.23 (1H, m), 9.12 (1H, m), 10.14 (1H, s); MS (APCI+) found (M+1)=218/220, $\text{C}_{12}\text{H}_8\text{ClNO}$ requires 217/219.

Intermediate A28 — 5-Methylaminomethyl-2-(4-chlorophenyl)pyridine



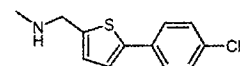
Prepared from Intermediate A27 by the method of Intermediate A22. $^1\text{H-NMR}$ (CDCl_3) δ 2.49 (3H, s), 3.81 (2H, s), 7.43 (2H, m), 7.67 (1H, m), 7.74 (1H, m), 7.93 (2H, m), 8.61 (1H, m).

Intermediate A29 — 5-(4-Chlorophenyl)-2-thiophene carboxaldehyde



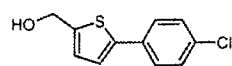
Prepared from 2-bromothiophene-5-carboxaldehyde and 4-chlorobenzeneboronic acid by the method of Intermediate A1 (a). $^1\text{H-NMR}$ (CDCl_3) δ 9.70 (1H, s), 7.53 (1H, d), 7.39 (2H, m), 7.22 (3H, m); MS (APCI+) found (M+1) = 223, $\text{C}_{11}\text{H}_7^{35}\text{ClOS}$ requires 222.

Intermediate A30 — 2-Methylaminomethyl-5-(4-chlorophenyl)thiophene



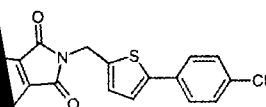
Prepared from Intermediate A29 by the method of Intermediate A2. $^1\text{H-NMR}$ (CDCl_3) δ 7.67 (2H, m), 7.22 (3H, m), 7.03 (1H, d), 4.00 (2H, s), 2.65 (3H, s).

Intermediate A31 — 5-Hydroxymethyl-2-(4-chlorophenyl)thiophene

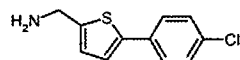


Prepared from Intermediate A29 by the method of Intermediate A3. $^1\text{H-NMR}$ (CDCl_3) δ 7.30 (2H, d), 7.13 (2H, d), 6.95 (1H, d), 6.79 (1H, d), 4.63 (2H, d), 1.59 (1H, t); MS (APCI+) found (M-H₂O+1) 207, $\text{C}_{11}\text{H}_9^{35}\text{ClOS}$ requires 224.

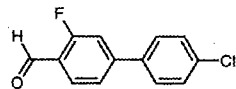
Intermediate A32 — N-(5-(4-Chlorophenyl)thien-2-ylmethyl)phthalimide



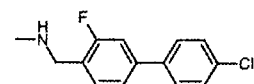
Prepared from Intermediate A31 by the method of Intermediate A4. $^1\text{H-NMR}$ (CDCl_3) δ 7.94 (2H, m), 7.74 (2H, m), 7.53 (2H, m), 7.37 (2H, m), 7.18 (1H, s), 5.08 (2H, s).

Intermediate A33 — 5-Aminomethyl-2-(4-chlorophenyl)thiophene

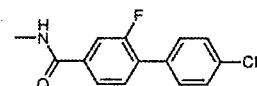
Prepared from Intermediate A32 by the method of Intermediate A5. Yellow solid. $^1\text{H-NMR}$ (CDCl_3) δ 4.05 (2H, s), 6.82-6.92 (1H, d), 7.06-7.17 (1H, d), 7.29-7.39 (2H, m), 7.42-7.55 (2H, m). No molecular ion seen.

Intermediate A34 — 4-(4-Chlorophenyl)-2-fluorobenzaldehyde

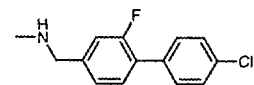
Prepared from 4-bromo-2-fluorobenzaldehyde and 4-chlorobenzeneboronic acid by the method of Intermediate A1 (b). $^1\text{H-NMR}$ (CDCl_3) δ 7.36 (1H, m), 7.44-7.57 (5H, m), 7.94 (1H, m), 10.38 (1H, s); MS (APCI+) found ($M+1$) = 235/237, $\text{C}_{13}\text{H}_8\text{FClO}$ requires 234/236

Intermediate A35 — N-Methyl-4-(4-chlorophenyl)-2-fluorobenzylamine

Prepared from Intermediate A34 by the method of Intermediate A2. $^1\text{H-NMR}$ (CDCl_3) δ 2.48 (3H, s), 3.84 (2H, s), 7.2-7.5 (7H, m); MS (APCI+) found ($M+1$) = 250/252, $\text{C}_{14}\text{H}_{13}\text{FCIN}$ requires 249/251

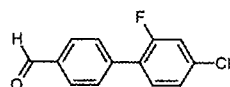
Intermediate A36 — N-Methyl-4-(4-chlorophenyl)-3-fluorobenzamide

Prepared from N-methyl-4-bromo-3-fluorobenzamide and 4-chlorobenzeneboronic acid by the method of Intermediate A1 (b). $^1\text{H-NMR}$ (CDCl_3) δ 3.05 (3H, d), 6.19 (1H, br. s), 7.42-7.50 (5H, m), 7.57-7.60 (2H, m); MS (APCI+) found ($M+1$) = 264, $\text{C}_{14}\text{H}_{11}\text{ClFNO}$ requires 263.

Intermediate A37 — N-Methyl-4-(4-chlorophenyl)-3-fluorobenzylamine

Borane (1M solution in THF, 2 equiv) was stirred under argon with ice cooling, and a suspension of Intermediate A36 (1 equiv) in dry THF was added gradually over a few minutes. After 5 mins the ice bath was removed and the mixture heated to reflux for 1h, then cooled to room temperature. 5M

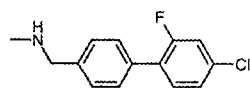
Hydrochloric acid was added dropwise, and the THF was removed from the resulting suspension by distillation. The residue was diluted with water and made strongly basic with sodium hydroxide, then product was extracted into ether. Drying and evaporation of the organic solution, followed by chromatography gave the title compound as an oil (88%). $^1\text{H-NMR}$ (CDCl_3) δ 2.48 (3H, s), 3.79 (2H, s), 7.12-7.18 (2H, m), 7.33-7.50 (5H, m); MS (APCI+) found ($M+1$) = 250; $\text{C}_{14}\text{H}_{13}\text{ClFN}$ requires 249

Intermediate A38 — 4-(4-Chloro-2-fluorophenyl)benzaldehyde

114
117M

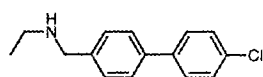
Prepared from 4-formylbenzeneboronic acid and 4-chloro-2-fluoriodobenzene by the method of Intermediate A1 (b). $^1\text{H-NMR}$ (CDCl_3) δ 7.21-7.28 (2H, m), 7.38-7.45 (1H, m), 7.67-7.71 (2H, m), 7.95-7.98 (2H, m), 10.06 (1H, s).

Intermediate A39 — N-Methyl-4-(4-chloro-2-fluorophenyl)benzylamine



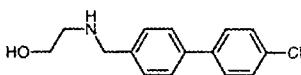
Prepared from Intermediate A38 by the method of Intermediate A2. $^1\text{H-NMR}$ (CDCl_3) δ 2.49 (3H, s), 3.80 (2H, s), 7.17-7.26 (2H, m), 7.35-7.41 (3H, m), 7.46-7.49 (2H, m); MS (APCI+) found (M+1) = 250; $\text{C}_{14}\text{H}_{13}\text{ClFN}$ requires 249.

Intermediate A40 — N-Ethyl-4-(4-chlorophenyl)benzylamine



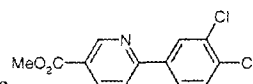
Prepared from Intermediate A1 and ethylamine by the method of Intermediate A2. $^1\text{H-NMR}$ (CDCl_3) δ 1.15 (3H, t), 2.71 (2H, q), 3.84 (2H, s), 7.4 (4H, m), 7.5 (4H, m); MS (APCI+) found (M+1) = 246/248; $\text{C}_{15}\text{H}_{16}\text{ClN}$ requires 245/247.

Intermediate A41 — N-(2-Hydroxyethyl)-4-(4-chlorophenyl)benzylamine



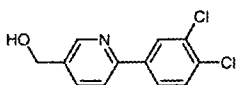
Prepared from Intermediate A1 and ethanolamine by the method of Intermediate A2, except that imine formation was carried out in the presence of powdered molecular sieve in place of magnesium sulfate. $^1\text{H-NMR}$ (CDCl_3) δ 2.84 (2H, t), 3.68 (2H, t), 3.85 (2H, s), 7.4 (4H, m), 7.5 (4H, m); MS (APCI+) found (M+1) = 262/264; $\text{C}_{15}\text{H}_{16}\text{ClNO}$ requires 261/263.

Intermediate A42 — Methyl-6-(3,4-dichlorophenyl)nicotinate



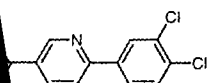
Prepared from methyl 6-chloronicotinate and 3,4-dichlorobenzeneboronic acid by the method of Intermediate A1 (a). $^1\text{H-NMR}$ (CDCl_3) δ 3.98 (3H, s), 7.57 (1H, d), 7.79 (1H, d), 7.9 (1H, m), 8.2 (1H, dd), 8.36 (1H, m), 9.27 (1H, dd); MS (APCI+) found (M+1) = 282; $\text{C}_{13}\text{H}_9\text{Cl}_2\text{NO}_2$ requires 281.

Intermediate A43 — 5-Hydroxymethyl-2-(3,4-dichlorophenyl)pyridine



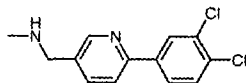
Prepared from Intermediate A42 by the method of Intermediate A20. $^1\text{H-NMR}$ (CDCl_3 / DMSO-d_6) δ 4.67 (2H, d), 5.14 (1H, t), 7.56 (1H, d), 7.7-7.95 (3H, m), 8.18 (1H, m), 8.64 (1H, m); MS (APCI+) found (M+1) = 254; $\text{C}_{12}\text{H}_9\text{Cl}_2\text{NO}$ requires 253.

Intermediate A44 — 5-Formyl-2-(3,4-dichlorophenyl)pyridine



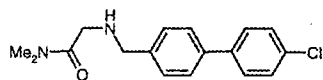
Prepared from Intermediate A43 by the method of Intermediate A21. $^1\text{H-NMR}$ (CDCl_3) δ 7.59 (1H,d), 7.89 (1H,d), 7.93 (1H,m), 8.2-8.3 (2H,m), 9.13 (1H,m), 10.17 (1H,s), MS (APCI+) found $(M+1) = 252$; $\text{C}_{12}\text{H}_7\text{Cl}_2\text{NO}$ requires 253.

Intermediate A45 — 5-Methylaminomethyl-2-(3,4-dichlorophenyl)pyridine



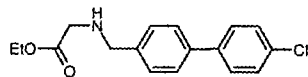
Prepared from Intermediate A44 by the method of Intermediate A22. $^1\text{H-NMR}$ (CDCl_3) δ 2.48 (3H,s), 3.82 (2H,s), 7.53 (1H,d), 7.67 (1H,d), 7.7-7.85 (2H,m), 8.13 (2H,dd), 8.63 (1H,dd), MS (APCI+) found $(M+1) = 267$; $\text{C}_{13}\text{H}_{12}\text{Cl}_2\text{N}_2$ requires 266.

Intermediate A46 — N-(Dimethylaminocarbonylmethyl)-4-(4-chlorophenyl)benzylamine



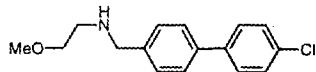
Prepared from Intermediate A1 and N,N-dimethylglycine by the method of Intermediate A2. Light green solid. $^1\text{H-NMR}$ (CDCl_3) δ 2.92 (3H, s), 2.99 (3H, s), 3.42 (2H, s), 3.86 (2H, s), 7.34-7.58 (8H, m); MS (APCI+) found $(M+1) = 303$; $\text{C}_{17}\text{H}_{19}\text{ClNO}_2$ requires 302.

Intermediate A47 — N-(Ethoxycarbonylmethyl)-4-(4-chlorophenyl)benzylamine



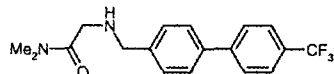
A mixture of Intermediate A1 (0.5 g, 1 equiv), glycine ethyl ester hydrochloride (0.32 g, 1 equiv), diisopropylethylamine (0.4 ml, 1 equiv) and 1,2-dichloroethane (10 ml) was stirred at room temperature, sodium triacetoxymethylborohydride (0.73 g, 1.5 equiv) was added, and stirring continued overnight. After diluting with dichloromethane, the solution was washed with water and dried over potassium carbonate. Evaporation of the solvent yielded the title compound (0.57 g) as a white waxy solid. $^1\text{H-NMR}$ (CDCl_3) δ 1.22-1.37 (3H, t), 3.44 (2H, s), 3.85 (2H, s), 4.15-4.32 (2H, q), 7.35-7.62 (8H, m); MS (APCI+) found $(M+1) = 304$; $\text{C}_{17}\text{H}_{18}\text{ClNO}_2$ requires 303.

Intermediate A48 — N-(2-Methoxyethyl)-4-(4-chlorophenyl)benzylamine

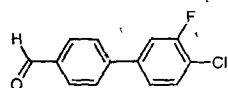


Prepared from Intermediate A1 and 2-methoxyethylamine by the method of Intermediate A2. Solid. $^1\text{H-NMR}$ (CDCl_3) δ 2.77-2.89 (2H, t), 3.37 (3H, s), 3.50-3.59 (2H, t), 3.85 (2H, s), 7.34-7.55 (8H, m); MS (APCI+) found $(M+1) = 276$; $\text{C}_{16}\text{H}_{18}\text{ClNO}$ requires 275.

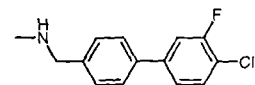
Intermediate A49 — N-(Dimethylaminocarbonylmethyl)-4-(4-trifluoromethylphenyl)benzylamine



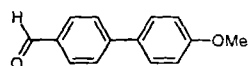
Prepared from Intermediate A12 and N,N-dimethylglycine by the method of Intermediate A2. Pale green solid. $^1\text{H-NMR}$ (CDCl_3) δ 2.88 (3H, s), 2.99 (3H, s), 3.44 (2H, s), 3.88 (2H, s), 7.42-7.78 (8H, m); MS (APCI+) found $(M+1) = 337$; $\text{C}_{18}\text{H}_{19}\text{FN}_2\text{O}$ requires 336.

120
118**Intermediate A50 — 4-(4-Chloro-3-fluorophenyl)benzaldehyde**

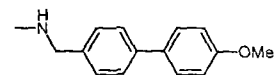
Prepared from 4-formylbenzeneboronic acid and 3-chloro-4-fluoroiodobenzene by the method of Intermediate A1(b), and used immediately in the subsequent step without purification or analysis.

5 Intermediate A51 — N-Methyl-4-(4-chloro-3-fluorophenyl)benzylamine

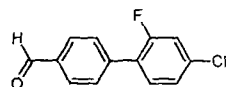
Prepared from Intermediate A50 by the method of Intermediate A2. $^1\text{H-NMR}$ (CDCl_3) δ 2.48 (3H,s), 3.79 (2H,d), 7.2-7.6 (7H,m); MS (APCI+) found ($M+1$) = 250; $\text{C}_{14}\text{H}_{13}\text{ClFN}$ requires 249.

10 Intermediate A52 — 4-(4-Methoxyphenyl)benzaldehyde

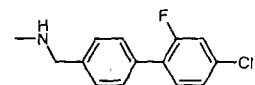
Prepared from 4-methoxybenzeneboronic acid and 4-bromobenzaldehyde by the method of Intermediate A1(b). $^1\text{H-NMR}$ (CDCl_3) δ 3.87 (3H,s), 7.01 (2H,d), 7.59 (2H,d), 7.71 (2H,d), 7.93 (2H,d), 10.05 (1H,s); MS (APCI+) found ($M+1$) = 213; $\text{C}_{14}\text{H}_{12}\text{O}_2$ requires 212.

15 Intermediate A53 — N-Methyl-4-(4-methoxyphenyl)benzylamine

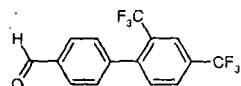
Prepared from Intermediate A52 by the method of Intermediate A2. $^1\text{H-NMR}$ (CDCl_3) δ 2.48 (3H,s), 3.78 (2H,s), 3.85 (3H,s), 6.96(2H,m), 7.36 (2H,d), 7.5 (4H,m).

20 Intermediate A54 — 4-(2-Fluoro-4-chlorophenyl)benzaldehyde

Prepared from 4-formylbenzeneboronic acid and 4-chloro-2-fluoroiodobenzene by the method of Intermediate A1(b). $^1\text{H-NMR}$ (CDCl_3) δ 7.21-7.28 (2H, m), 7.38-7.45(1H, m), 7.67-7.71 (2H, m), 7.95-7.98 (2H, m), 10.06 (1H, s).

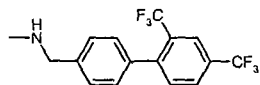
25 Intermediate A55 — N-Methyl-4-(2-fluoro-4-chlorophenyl)benzylamine

Prepared from Intermediate A54 by the method of Intermediate A2. $^1\text{H-NMR}$ (CDCl_3) δ 2.49 (3H, s), 3.80 (2H, s), 7.17-7.21 (2H, m), 7.35-7.41 (3H, m), 7.47-7.49 (2H, m).

Intermediate A56 — 4-(2,4-bis(trifluoromethyl)phenyl)benzaldehyde

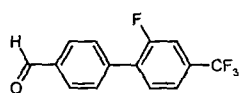
Prepared from 4-formylbenzeneboronic acid and 2,4-bis(trifluoromethyl)bromobenzene by the method of Intermediate A1(b). $^1\text{H-NMR}$ (CDCl_3) δ 7.50 (3H,m), 7.87 (1H,m), 7.96 (2H,m), 8.04 (1H,s), 10.12 (1H,s); MS (APCI+) found ($M+1$) = 319; $\text{C}_{15}\text{H}_8\text{F}_6\text{O}$ requires 318.

Intermediate A57 — N-Methyl-4-(2,4-bis(trifluoromethyl)phenyl)benzylamine



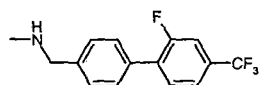
5 Prepared from Intermediate A56 by the method of Intermediate A2. $^1\text{H-NMR}$ (CDCl_3) δ 2.50 (3H,s), 3.82 (2H,s), 7.27 (2H,m), 7.38 (2H,m), 7.48 (1H,m), 7.81 (1H,m), 8.00 (1H,s); MS (APCI+) found ($M+1$) = 334; $\text{C}_{16}\text{H}_{13}\text{F}_6\text{N}$ requires 333.

Intermediate A58 — 4-(2-Fluoro-4-trifluoromethylphenyl)benzaldehyde



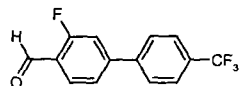
10 Prepared from 4-formylbenzeneboronic acid and 4-bromo-3-fluorobenzotrifluoride by the method of Intermediate A1(b). $^1\text{H-NMR}$ (CDCl_3) δ 7.40-7.75 (5H, m), 7.93-8.00 (2H, m), 10.10 (1H, s).

Intermediate A59 — N-Methyl-4-(2-fluoro-4-trifluoromethylphenyl)benzylamine



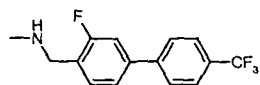
15 Prepared from Intermediate A58 by the method of Intermediate A2. $^1\text{H-NMR}$ (CDCl_3) δ 2.50 (3H, s), 3.82 (2H, s), 7.38-7.61 (7H, m).

Intermediate A60 — 2-Fluoro-4-(4-trifluoromethylphenyl)benzaldehyde



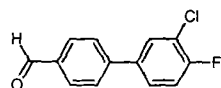
20 Prepared from 4-bromo-2-fluorobenzaldehyde and 4-trifluoromethylbenzeneboronic acid by the method of Intermediate A1(b). White solid. $^1\text{H-NMR}$ (CDCl_3) δ 7.35-7.55 (2H, m), 7.67-7.83 (4H, m), 7.92-8.05 (1H, t), 10.41 (1H, s); MS (APCI+) found ($M+1$) = 269; $\text{C}_{14}\text{H}_8\text{F}_4\text{O}$ requires 268.

Intermediate A61 — N-Methyl-2-fluoro-4-(4-trifluoromethylphenyl)benzylamine



25 Prepared from Intermediate A60 by the method of Intermediate A2. Oil. $^1\text{H-NMR}$ (CDCl_3) δ 2.49 (3H, s), 3.86 (2H, s), 7.29-7.49 (3H, m), 7.62-7.77 (4H, m); MS (APCI+) found ($M+1$) = 284; $\text{C}_{15}\text{H}_{13}\text{F}_4\text{N}$ requires 283.

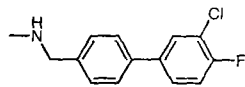
Intermediate A62 — 4-(3-Chloro-4-fluorophenyl)benzaldehyde



127
119 21

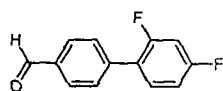
Prepared from 3-chloro-4-fluorobenzeneboronic acid and 4-bromobenzaldehyde by the method of Intermediate A1(b). $^1\text{H-NMR}$ (CDCl_3) δ 7.27 (1H,m), 7.45-7.55 (1H,m), 7.65-7.71 (3H,m), 7.96 (2H,m), 10.09 (1H,s); MS (APCI+) found (M+1) = 235/237; $\text{C}_{13}\text{H}_8\text{ClFO}$ requires 234/236.

Intermediate A63 — N-Methyl-4-(3-chloro-4-fluorophenyl)benzylamine



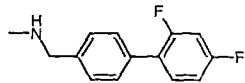
Prepared from Intermediate A62 by the method of Intermediate A2. $^1\text{H-NMR}$ (CDCl_3) δ 2.48 (3H,s), 3.79 (2H,s), 7.18 (1H,m), 7.39 (2H,d), 7.45 (1H,m), 7.49 (2H,d), 7.60 (1H,m); MS (APCI+) found (M+1) = 250/252; $\text{C}_{14}\text{H}_{13}\text{ClFN}$ requires 249/251.

Intermediate A64 — 4-(2,4-Difluorophenyl)benzaldehyde



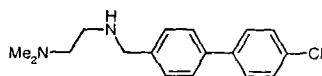
Prepared from 4-formylbenzeneboronic acid and 2,4-difluoroiodobenzene by the method of Intermediate A1(b). $^1\text{H-NMR}$ (CDCl_3) δ 6.9-7.0 (2H,m), 7.45 (1H,m), 7.68 (2H,m), 7.96 (2H,m), 10.09 (1H,s); MS (APCI+) found (M+1) = 219; $\text{C}_{13}\text{H}_8\text{F}_2\text{O}$ requires 218.

Intermediate A65 — N-Methyl-4-(2,4-difluorophenyl)benzylamine



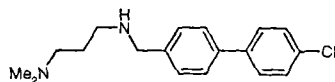
Prepared from Intermediate A64 by the method of Intermediate A2. $^1\text{H-NMR}$ (CDCl_3) δ 2.49 (3H,s), 3.79 (2H,s), 6.8-7.0 (2H,m), 7.3-7.5 (5H,m); MS (APCI+) found (M+1) = 234; $\text{C}_{14}\text{H}_{13}\text{F}_2\text{N}$ requires 233.

Intermediate A66 — N-(2-Dimethylaminoethyl)-4-(4-chlorophenyl)benzylamine

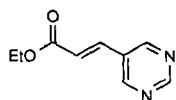


Prepared from Intermediate A1 and 2-(dimethylamino)ethylamine by the method of Intermediate A2. $^1\text{H-NMR}$ (CDCl_3) δ 2.21 (6H, s), 2.44 (2H, t), 2.71 (2H, t), 3.85 (2H, s), 7.37-7.43 (4H, m), 7.52-7.56 (4H, m).

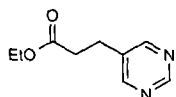
Intermediate A67 — N-(3-Dimethylaminopropyl)-4-(4-chlorophenyl)benzylamine



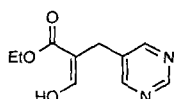
Prepared from Intermediate A1 and 3-(dimethylamino)propylamine by the method of Intermediate A2. $^1\text{H-NMR}$ (CDCl_3) δ 1.70 (2H, t), 2.22 (6H, s), 2.33 (2H, t), 2.69 (2H, br. m), 3.83 (2H, s), 7.37-7.43 (4H, m), 7.52-7.56 (4H, m).

Intermediate B1 – Ethyl 3-(5-pyrimidinyl)acrylate

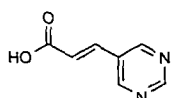
A mixture of 5-bromopyrimidine (5.93g), ethyl acrylate (5.08g), palladium acetate (0.112g), triphenyl phosphine (0.23g) and triethylamine (4.5g) was stirred at 150°C in a pressure vessel for 6 hours. After cooling overnight, water (50ml) was added to the dark residue, and the product was extracted into toluene. Drying, charcoaling and evaporation gave a pale oil, which was triturated with pet. ether to obtain ethyl 3-(5-pyrimidinyl)acrylate (4.78g). ¹H-NMR (CDCl₃) δ 1.36 (3H,t), 4.27 (2H,q), 6.59 (1H,d), 7.62 (1H,d), 8.88 (2H,s), 9.20 (1H,s).

Intermediate B2 – Ethyl 3-(5-pyrimidinyl)propionate

To a solution of ethyl 3-(5-pyrimidinyl)acrylate (4.75g) in ethanol (90ml) was added 5% palladium on charcoal (0.2g). The mixture was hydrogenated at an initial pressure of 50 psi, then filtered to remove catalyst and the solvent evaporated. Water was added, and the product extracted into ether. Drying, charcoaling and evaporation gave ethyl 3-(5-pyrimidinyl)propionate (2.3g) as a yellow oil. ¹H-NMR (CDCl₃) δ 1.23 (3H,t), 2.69 (2H,t), 2.96 (2H,t), 4.14 (2H,q), 8.635 (2H,s) and 9.09 (1H,s).

Intermediate B3 – Ethyl 2-formyl-3-(5-pyrimidinyl)propionate

A mixture of ethyl 3-(5-pyrimidinyl)propionate (2.28g) and ethyl formate (1.41ml) dissolved in dry dimethoxyethane (5ml) was added dropwise over 30 min to a suspension of sodium hydride (60%, 4.0g) in DME (5 ml) under nitrogen, keeping the temperature below 0°C. Stirring was continued for a further 24h, then the mixture was poured onto ice and washed with ether. The aqueous layer was adjusted to pH 7, then evaporated and the residue extracted with acetone. Filtration and evaporation gave crude product, which was taken up in ethyl acetate, charcoaled, dried and evaporated to give ethyl 2-formyl-3-(5-pyrimidinyl)propionate. Like other compounds of this type, this proved difficult to characterise and was used without further purification.

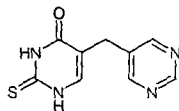
Intermediate B4 – 3-(5-Pyrimidinyl)acrylic acid

A mixture of 5-bromopyrimidine (100g), acrylic acid (48g), triphenylphosphine (2.5g) and palladium II acetate (0.1g) was refluxed in tri-n-butylamine (260ml) with overhead stirring for 4.5h at 145-160°C. The mixture was cooled and a 10% solution of potassium carbonate (2L) added followed by dichloromethane (500mL). The organic layer was separated and the aqueous phase extracted with diethyl ether (3 x 300ml). The aqueous layer was brought to pH 3 with concentrated hydrochloric acid

122
1208

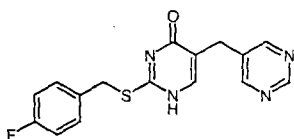
(ice-cooling) and the solid so formed was filtered and dried *in vacuo* to give 3-(5-pyrimidyl)acrylic acid (35g). $^1\text{H-NMR}$ ($\text{d}_6\text{-DMSO}$) δ 6.82(1H,d), 7.60(1H,d) and 9.15(3H, 2xs)

Intermediate B5 – 5-(Pyrimid-5-ylmethyl)-2-thiouracil



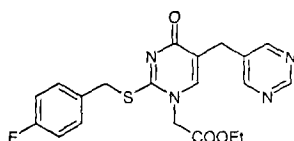
- 5 Sodium (0.25 g) was dissolved in ethanol (5 ml), thiourea (0.77 g) added, and the mixture stirred under reflux for 1 hour. A solution of ethyl 2-formyl-3-(5-pyrimidyl)propionate (1.99 g) in ethanol (5 ml) was added slowly, and reflux continued for 18 hours. The solvent was evaporated, and the residue taken up in water and washed with dichloromethane. The aqueous solution was acidified to pH 5, and the precipitate filtered off, washed with water and dried to obtain 5-(pyrimid-5-ylmethyl)-2-thiouracil (0.71 g). $^1\text{H-NMR}$ ($\text{d}_6\text{-DMSO}$) δ 3.58 (2H,s), 7.54 (1H,s), 8.70 (2H,s) and 9.02 (1H,s). MPt 265-6°C

Intermediate B6 – 2-(4-Fluorobenzylthio)-5-((pyrimid-5-yl)methyl)pyrimidin-4-one



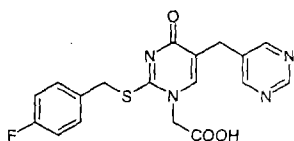
- 15 A mixture of intermediate B5 (0.90g), 4-fluorobenzyl bromide (0.51ml), potassium carbonate (1.41g) and dry DMF (11 ml) was stirred at 70°C under argon for 5h. The DMF was evaporated, water added, and the mixture acidified to pH 4 with acetic acid. The precipitate was filtered off and purified by chromatography (silica, 15-20% methanol in ethyl acetate) to give the product as an off-white solid (0.13g). $^1\text{H-NMR}$ ($\text{d}_6\text{-DMSO}$) δ 3.65 (2H,s), 4.38 (2H,s), 7.05-7.2 (2H,m), 7.35-7.5 (2H,m), 7.94 (1H,bs), 8.71 (2H,s), 9.06 (1H,s); MS (APCI-) found (M-1) = 327; $\text{C}_{16}\text{H}_{13}\text{FN}_4\text{OS}$ requires 328.

Intermediate B7 – 1-Ethoxycarbonylmethyl-2-(4-fluorobenzyl)thio-5-(pyrimid-5-ylmethyl)pyrimidin-4-one



- 25 A mixture of intermediate B6 (10g), ethyl bromoacetate (3.38ml), diisopropylethylamine (5.84ml) and dichloromethane (50ml) was stirred overnight, then the solution was washed sequentially with aqueous ammonium chloride and aqueous sodium bicarbonate. Chromatography (silica, 5-10% methanol in ethyl acetate) and trituration with ether gave the desired product (7.02g). $^1\text{H-NMR}$ (CDCl_3) δ 1.26 (3H, t), 3.71 (2H, s), 4.26 (2H, q), 4.46 (2H, s), 4.48 (2H, s), 6.91 (1H, s), 6.98 (2H, m), 7.35 (2H, m), 8.70 (2H, s), 9.09 (1H, s); MS(APCI⁺) M+1=415, $\text{C}_{20}\text{H}_{19}\text{FN}_4\text{O}_3\text{S}$ requires 414. MPt 145.1°C.

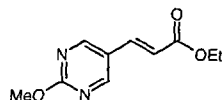
Intermediate B8 – 1-Carboxymethyl-2-(4-fluorobenzyl)thio-5-(pyrimid-5-ylmethyl)pyrimidin-4-one



30

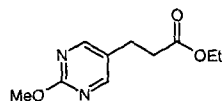
0.5M aqueous sodium hydroxide (33.8ml) was added slowly to a solution of Intermediate B7 (7.01g) in dioxan (150ml). The mixture was stirred for 2.5h at room temperature, then the dioxan was evaporated, water added, and the mixture acidified with aqueous sodium bisulfate. The precipitate was filtered off, washed with water and dried to obtain the desired product (6.31g). ¹H-NMR (d₆-DMSO) δ 3.59 (2H, s), 4.41 (2H, s), 4.67 (2H, s), 7.11 (2H, m), 7.45 (2H, m), 7.72 (1H, s), 8.70 (2H, s), 9.03 (1H, s), 13.55 (1H, bs); MS (APCI-) M-1=385, C₁₈H₁₅FN₄O₃S requires 386. MPt 206-207°C.

Intermediate B9 – Ethyl 3-(2-methoxypyrimidin-5-yl)acrylate



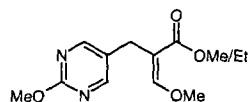
A mixture of 2-methoxy-5-bromopyrimidine (75.43 g, 0.399 mol), ethyl acrylate (47.5 ml, 0.439 mol), palladium (II) acetate (1.07 g, 0.0048 mol), tri-*o*-tolylphosphine (2.92 g, 0.0096 mol) and triethylamine (84 ml) were heated at 135°C with stirring under argon for 12 h. After allowing to cool the solid mass was dissolved in water and ethyl acetate, filtered, and the aqueous phase separated and further extracted with ethyl acetate. The combined extracts were washed with saturated aqueous ammonium chloride, dried (MgSO₄) and evaporated. The solid thus obtained was triturated with ether/light petrol (1:3, 350 ml), filtered, washed and dried, yield 52.41 g (63%). ¹H-NMR (CDCl₃) δ 1.33 (3H, t), 4.06 (3H, s), 4.28 (2H, q), 6.45 (1H, d), 7.58 (1H, d), 8.67 (2H, s); MS (APCI+) found (M+H) = 209; C₁₀H₁₂N₂O₃ requires 208.

Intermediate B10 – Ethyl 3-(2-methoxypyrimidin-5-yl)propanoate



A suspension of ethyl 3-(2-methoxypyrimidin-5-yl)acrylate (52.4 g, 0.252 mol) in ethanol (400 ml) and triethylamine (50 ml) was treated with 10% palladium on carbon (3 g) and hydrogenated at 50 psi for 1.75 h. The catalyst was filtered off through hyflo and the filtrate evaporated. The residue was dissolved in dichloromethane, washed twice with saturated aqueous ammonium chloride, dried (MgSO₄) and evaporated to an oil, yield 41.2 g (78%). ¹H-NMR (CDCl₃) δ 1.23 (3H, t), 2.61 (2H, t), 2.87 (2H, t), 3.99 (3H, s), 4.13 (2H, q), 8.39 (2H, s); MS (APCI+) found (M+H) = 211; C₁₀H₁₄N₂O₃ requires 210.

Intermediate B11 – 2-(Methoxymethylene)-3-(2-methoxypyrimidin-5-yl)propionic acid, mixed methyl/ethyl esters

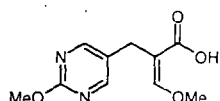


To a stirring suspension of sodium hydride (0.83 g of a 60% dispersion in oil) in anhydrous 1, 2-dimethoxyethane (6 ml) was added dropwise a solution of methyl formate (1.54 ml) and ethyl 3-(2-methoxypyrimidin-5-yl)propanoate (3.5 g) in anhydrous 1,2-dimethoxyethane (6 ml) at such a rate as to maintain the reaction temperature at 25-30°C. After 1 h, ether was added and the precipitated oil allowed to settle. The solution was decanted off and replaced with fresh ether, and the oil slowly solidified. The solid 2-(hydroxymethylene) derivative was filtered, washed and dried, yield 3.8 g. A 1.33 g portion was suspended in dimethyl formamide (10 ml) together with anhydrous potassium carbonate (1.15 g), and a solution of dimethyl sulphate (0.48 ml) in dimethylformamide (10 ml) was added dropwise with stirring

123
12/1/18

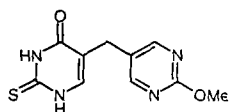
over 30 min. After 16 h the solvent was evaporated and the residue treated with water and extracted with ethyl acetate. The extracts were washed with water, dried (MgSO_4) and evaporated to give the product as an oil, yield 0.91 g. $^1\text{H-NMR}$ (CDCl_3) δ 1.23 (3H, t), 3.46 (2H, s), 3.69 (3H, s, methyl ester), 3.88 (3H, s), 3.97 (3H, s), 4.16 (2H, q), 7.39 (1H, s), 8.40 (2H, s). 3:2 ratio of methyl:ethyl esters. MS (APCI+) found ($M+1$) = 253, 239 (ethyl and methyl esters); $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_4$ requires 252, $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_4$ requires 238.

Intermediate B12 – 2-(Methoxymethylene)-3-(2-methoxypyrimidin-5-yl)propionic acid



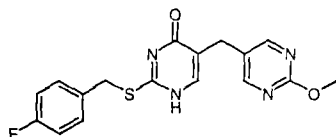
A suspension of the mixed esters of Intermediate B11 (0.9 g) in 2M aqueous sodium hydroxide (3.6 ml) was stirred at ambient temperature for 16 h to give a clear solution. This was diluted with water, extracted with dichloromethane and evaporated to about half volume, then acidified to pH 3-4 (2M hydrochloric acid) when the product crystallised out. The white solid was filtered, washed with ice-cold water and dried, yield 0.46 g. $^1\text{H-NMR}$ (CDCl_3) δ 3.43 (2H, s), 3.91 (3H, s), 3.99 (3H, s), 7.49 (1H, s), 8.42 (2H, s); MS (APCI+) found ($M+1$) = 225, $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_4$ requires 224.

Intermediate B13 – 5-(2-Methoxypyrimidin-5-ylmethyl)-2-thiouracil

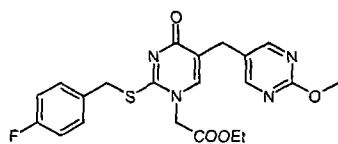


To an ice cooled solution of potassium t-butoxide (7.83 g, 0.07 mol) in anhydrous THF (60 ml) was added dropwise with stirring under argon over 1 hour to a solution of ethyl 3-(2-methoxypyrimidin-5-yl)propionate (5.87 g, 0.028 mol) and methyl formate (3.6 ml, 0.059 mol) in anhydrous ether (70 ml). After stirring for 16 h, the solvents were evaporated, thiourea (4.25 g, 0.056 mol) and propan-2-ol (80 ml) added and the mixture refluxed for 5 h. The solvent was evaporated and the residue dissolved in water, extracted twice with ether and acidified to pH 4.5 with acetic acid. The solid which precipitated was filtered, washed well with water and dried, yield 5.57 g (80%). $^1\text{H-NMR}$ (d_6 -DMSO) δ 3.47 (2H, s), 3.85 (3H, s), 7.43 (1H, s), 8.48 (2H, s), 12.25 (1H, br s), 12.46 (1H, br s); MS (APCI+) found ($M+H$) = 251; $\text{C}_{10}\text{H}_{10}\text{N}_4\text{O}_2\text{S}$ requires 250.

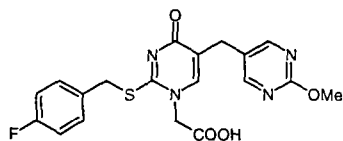
Intermediate B14 – 2-(4-Fluorobenzylthio)-5-((2-methoxypyrimidin-5-yl)methyl)pyrimidin-4-one



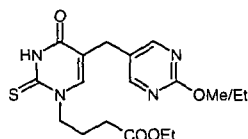
Prepared from Intermediate B13 by the method of Intermediate B6. $^1\text{H-NMR}$ (d_6 DMSO) δ 3.55 (2H, s), 3.85 (3H, s), 4.36 (2H, s), 7.0-7.2 (2H, m), 7.35-7.5 (2H, m), 7.86 (1H, bs), 8.48 (2H, s), 12.81 (1H, b); MS (APCI+) found ($M+1$) = 359; $\text{C}_{17}\text{H}_{15}\text{FN}_4\text{O}_2\text{S}$ requires 358.

Intermediate B15 – 1-(Ethoxycarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxypyrimid-5-ylmethyl)pyrimidin-4-one

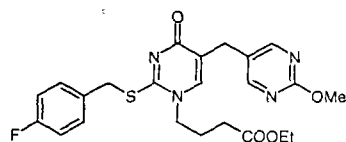
- Prepared from Intermediate B14 by the method of Intermediate B7. ¹H-NMR (CDCl₃) δ 1.25 (3H, t), 3.65 (2H, s), 3.97 (3H, s), 4.23 (2H, q), 4.47 (2H, s), 4.51 (2H, s), 6.94-7.01 (3H, m), 7.35 (2H, m), 8.42 (2H, s); MS (APCI+) found (M+1) = 445; C₂₁H₂₁FN₄O₄S requires 444.

Intermediate B16 — 1-Carboxymethyl-2-(4-Fluorobenzylthio)-5-(2-methoxypyrimid-5-ylmethyl)-pyrimidin-4-one

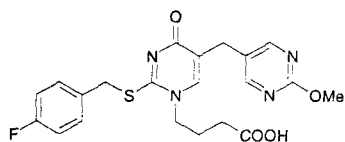
- Prepared from Intermediate B15 by the method of Intermediate B8. ¹H-NMR (d₆-DMSO) δ 3.51 (2H, s), 3.88 (3H, s), 4.41 (2H, s), 4.63 (2H, s), 7.12 (2H, m), 7.45 (2H, m), 7.62 (1H, s), 8.48 (2H, s); MS (APCI+) found (M+1) = 417; C₁₉H₁₇FN₄O₄S requires 416.

Intermediate B17 – 1-(3-Ethoxycarbonylprop-1-yl)-5-(2-methoxypyrimid-5-ylmethyl)-2-thiouracil

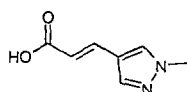
- Oxalyl chloride (3.94ml, 2 equiv) was added over 5min to a solution of Intermediate B12 (5.0g, 1 equiv) and DMF (1 drop) in dry dichloromethane (50ml), then the mixture was stirred under argon for 4h. The solvent was evaporated, and the residue twice taken up in dichloromethane and re-evaporated to remove volatile impurities. The acid chloride was dissolved in acetonitrile (100ml) and treated with dry, powdered potassium thiocyanate (3.2g, 1.5 equiv). The resulting suspension was stirred under argon for 24h, then evaporated to dryness. The residue was suspended in dry DMF (100ml), cooled to 10°C, ethyl 4-aminobutyrate hydrochloride (4.60g, 1.25 equiv) and triethylamine (7.34ml, 2.4 equiv) added, and the mixture stirred at room temperature for 20h to form the intermediate thiourea. Sodium methoxide solution (prepared by dissolving sodium (1.26g, 2.5 equiv) in methanol (25ml)) was added to the DMF solution, and the mixture heated to 110°C for 2h. The solvent was evaporated, water was added, and acidified to pH 5 with acetic acid, then the product extracted into ethyl acetate. Drying, evaporation, and trituration with ether gave a pale brown solid (4.55g). Some ether/ester exchange took place during the reaction, and the title compound was obtained mixed with ca 30% of the corresponding 2-ethoxypyrimidine. ¹H-NMR (DMSO-d₆) δ 1.17 (3H, t), 1.31 (t, ethoxy), 1.97 (2H, t), 2.36 (2H, t), 3.49 (s, ethoxy), 3.51 (s, methoxy), 3.88 (s, methoxy), 4.04 (2H, q), 4.16 (2H, t), 4.31 (q, ethoxy), 7.81 (1H, s), 8.48 (s, ethoxy), 8.50 (s, methoxy), 12.50 (bs, NH) (light brown solid).

124
122
X**Intermediate B18 – 1-(3-Ethoxycarbonylprop-1-yl)-2-(4-fluorobenzyl)thio-5-(2-methoxypyrimidin-5-ylmethyl)pyrimidin-4-one**

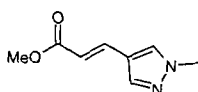
- Intermediate B17 (1.0g, 1 equiv) in dichloromethane (60ml) was treated with diisopropylethylamine (0.63ml, 1.3 equiv) followed by 4-fluorobenzyl bromide (0.38ml, 1.1 equiv), giving an orange solution which was stirred under argon for 4h, then washed with water, dried and evaporated. Chromatography (silica, 5% ethanol in ethyl acetate) eluted first the 2-ethoxypyrimidine impurity, followed by the title compound (0.35g). ¹H-NMR (CDCl₃) δ 1.25 (3H, t), 2.03 (2H, m), 2.33 (2H, t), 3.64 (2H, s), 3.83 (2H, m), 3.99 (3H, s), 4.12 (2H, q), 4.47 (2H, s), 6.98 (3H, m), 7.37 (2H, m), 8.46 (2H, s); MS (APCI+) M+1=473; C₂₃H₂₅FN₄O₄S requires 472 (pale waxy solid).

Intermediate B19 – 1-(3-Carboxyprop-1-yl)-2-(4-fluorobenzyl)thio-5-(2-methoxypyrimidin-5-ylmethyl)pyrimidin-4-one

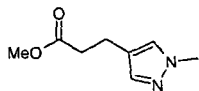
- Prepared from Intermediate B18 by the method of Intermediate B8. ¹H-NMR (DMSO-d₆) δ 1.89 (2H, m), 2.28 (2H, t), 3.50 (2H, s), 3.86 (5H, m), 4.40 (2H, sm), 7.13 (2H, m), 7.47 (2H, m), 7.72 (1H, s), 8.50 (2H, s); MS (APCI+) M+1=445; C₂₁H₂₁FN₄O₄S requires 444 (colourless solid).

Intermediate B20 – 3-(1-Methylpyrazol-4-yl)acrylic acid

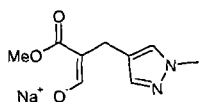
- A mixture of 1-methylpyrazole-4-carboxaldehyde (18.1 g), malonic acid (17.1 g), pyridine (15 ml) and piperidine (0.2 ml) was heated to 100°C for 1 hour. After cooling, water was added, followed by aqueous ammonia to obtain a clear solution, which was acidified to pH5 with hydrochloric acid. The resulting solid was filtered off, washed with water and dried to obtain 3-(1-methylpyrazol-4-yl)acrylic acid (18.9 g). ¹H-NMR (d₆-DMSO) δ 3.83 (3H,s), 6.18 (1H,d), 7.44 (1H,d), 7.83 (1H,s), 8.07 (1H,s). (APCI) found (M+H)=153. C₇H₈N₂O₂ requires 152.

Intermediate B21 – Methyl 3-(1-methylpyrazol-4-yl)acrylate

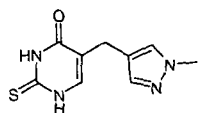
- 3-(1-Methylpyrazol-4-yl)acrylic acid (18.86 g) was added to a solution of sulphuric acid (15 ml) in methanol (150 ml), and the mixture refluxed for 2 hours, cooled, and poured onto ice. The acid was neutralised with solid sodium carbonate and the product extracted into dichloromethane, which was dried and evaporated. Crystallisation from ether/petrol gave methyl 3-(1-methylpyrazol-4-yl)acrylate (16.0 g). ¹H-NMR (d₆-DMSO) δ 3.77 (3H,s), 3.91 (3H,s), 6.16 (1H,d), 7.54 (1H,s), 7.56 (1H,d), 7.69 (1H,s). (APCI) found (M+H)=167. C₈H₁₀N₂O₂ requires 166.

Intermediate B22 – Methyl 3-(1-methylpyrazol-4-yl)propionate

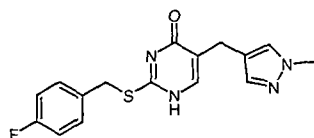
Prepared from Intermediate B21 by the method of Intermediate B2, except that the reaction was run at 50°C. ¹H-NMR (d₆-DMSO) δ 2.56 (2H,t), 2.79 (2H,t), 3.67 (3H,s), 3.85 (3H,s), 7.17 (1H,s), 7.31 (3H,s). (APCI) M+H=169. C₈H₁₂N₂O₂ requires 168.

Intermediate B23 – Methyl 2-formyl-3-(1-methylpyrazol-4-yl)propionate, sodium salt

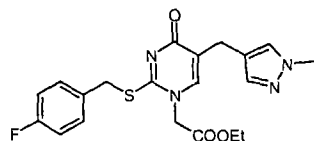
Sodium hydride (2.62 g, 60% in oil) was washed with petrol and suspended in dry dimethoxyethane (20 ml). Methyl 3-(1-methylpyrazol-4-yl)propionate (8.8 g) and methyl formate (4.87 ml) were dissolved in DME (20 ml), and a few drops of the mixture added to the sodium hydride suspension, which was warmed briefly to initiate the reaction before continuing dropwise addition at a rate which sustained controlled evolution of hydrogen. The mixture was stirred for a further 16 hours at room temperature, then diluted with ether. The solid was filtered off, washed with ether and immediately dried, and was used promptly without further purification.

Intermediate B24 – 5-((1-Methylpyrazol-4-yl)methyl)-2-thiouracil

Prepared from Intermediate B23 analogously to Intermediate B5, except using the preformed sodium salt instead of adding sodium ethoxide. ¹H-NMR (d₆-DMSO) δ 3.33 (3H,s), 3.75 (3H,s), 7.15 (1H,s), 7.23 (1H,s), 7.46 (1H,s), 12.2 (1H,br s), 12.4 (1H,br s). (APCI) M+H=223. C₉H₁₀N₄OS requires 222.

Intermediate B25 – 2-(4-Fluorobenzylthio)-5-((1-methylpyrazol-4-yl)methyl)pyrimidin-4-one

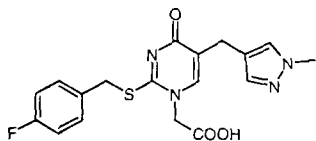
Prepared from Intermediate B24 by the method of Intermediate B6. ¹H-NMR (d₆-DMSO) δ 3.47 (2H, s), 3.81 (3H, s), 4.41 (2H, s), 7.19 (2H, s), 7.29 (1H, s), 7.48 (3H, m), 7.84 (1H, s), 12.74 (1H, br.s); MS (APCI+) found (M+1) = 331; C₁₆H₁₅FN₄OS requires 330.

Intermediate B26 – 1-(Ethoxycarbonylmethyl)-2-(4-fluorobenzylthio)-5-((1-methylpyrazol-4-yl)methyl)pyrimidin-4-one

1233

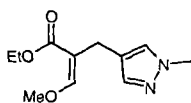
Prepared from Intermediate B25 by the method of Intermediate B7. $^1\text{H-NMR}$ (CDCl_3) δ 1.22 (3H, s), 3.60 (2H, s), 3.87 (3H, s), 4.23 (2H, q), 4.42 (2H, s), 4.50 (2H, s), 6.77 (1H, s), 6.96 (2H, m), 7.25-7.39 (4H, m); MS (APCI+) found $(\text{M}+1) = 417$; $\text{C}_{20}\text{H}_{21}\text{FN}_4\text{O}_3\text{S}$ requires 416.

5 **Intermediate B27 – 1-(Carboxymethyl)-2-(4-fluorobenzylthio)-5-((1-methylpyrazol-4-yl)methyl)pyrimidin-4-one**



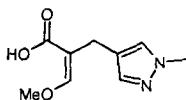
Prepared from Intermediate B26 by the method of Intermediate B8. $^1\text{H-NMR}$ ($d_6\text{-DMSO}$) δ 3.36 (2H, s), 3.76 (3H, s), 4.41 (2H, s), 4.67 (2H, s), 7.14 (2H, m), 7.23 (1H, s), 7.43-7.49 (4H, m); MS (APCI+) found $(\text{M}+1) = 389$; $\text{C}_{18}\text{H}_{17}\text{FN}_4\text{O}_3\text{S}$ requires 388.

10 **Intermediate B28 – Ethyl 2-(methoxymethylene)-3-(1-methylpyrazol-4-yl)propionate**



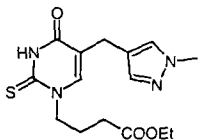
Prepared from Intermediate B23 by the method of Intermediate B11. $^1\text{H-NMR}$ (CDCl_3) *inter alia* 3.37 (2H, s), 3.70 (3H, s), 3.81 (3H, s), 3.85 (3H, s), 7.17 (1H, s), 7.30 (1H, s) and 7.31 (1H, s). MS(APCI+) $\text{MH}^+ 211$; $\text{C}_{10}\text{H}_{14}\text{N}_2\text{O}_3$ requires $\text{M}^+ 210$.

15 **Intermediate B29 – 2-(Methoxymethylene)-3-(1-methylpyrazol-4-yl)propionic acid**



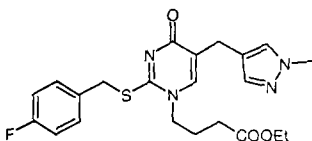
Prepared from Intermediate B28 by the method of Intermediate B12. $^1\text{HNMR}$ (CDCl_3) 3.36 (2H, s), 3.82 (3H, s), 3.88 (3H, s), 7.18 (1H, s), 7.33 (1H, s) and 7.40 (1H, s). MS(APCI+) $\text{MH}^+ 197$; $\text{C}_9\text{H}_{12}\text{N}_2\text{O}_3$ requires $\text{M}^+ 196$.

20 **Intermediate B30 – 1-(3-Ethoxycarbonylprop-1-yl)-5-(1-methylpyrazol-4-ylmethyl)-2-thiouracil**



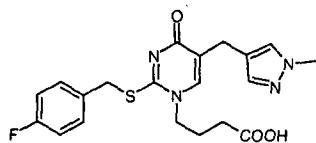
Prepared from Intermediate B29 by the method of Intermediate B17. $^1\text{HNMR}$ (CDCl_3) 1.27 (3H, t, J 7.1 Hz), 2.07 (2H, m), 2.38 (2H, t, J 6.9 Hz), 3.52 (2H, s), 3.88 (3H, s), 4.15 (4H, m), 7.05 (1H, s), 7.30 (1H, s) and 7.35 (1H, s). MS(APCI+) $\text{MH}^+ 337$; $\text{C}_{15}\text{H}_{20}\text{N}_4\text{O}_3\text{S}$ requires $\text{M}^+ 336$.

25 **Intermediate B31 – 1-(3-Ethoxycarbonylprop-1-yl)-2-(4-fluorobenzylthio)-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one**



Prepared from Intermediate B30 by the method of Intermediate B18. $^1\text{H-NMR}$ (CDCl_3) 1.24 (3H,t, $J=7.2\text{Hz}$), 2.00 (2H,m), 2.32 (2H,t,6.8Hz), 3.58 (2H,s), 3.79 (2H,t, $J=7.4\text{Hz}$), 3.87 (3H,s), 4.12 (2H,q,7.2Hz), 4.49 (2H,s), 6.89 (1H,s), 7.00 (2H,m) and 7.37 (4H,m). MS(APCI+) MH^+ 445; $\text{C}_{22}\text{H}_{25}\text{FN}_4\text{O}_3\text{S}$ requires M^+ 444.

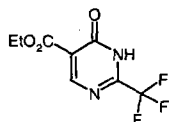
5 **Intermediate B32 – 1-(3-Carboxyprop-1-yl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one**



Prepared from Intermediate B31 by the method of Intermediate B8. $^1\text{H-NMR}$ (CDCl_3) 2.02 (2H,m), 2.35 (2H,t, $J=6.5\text{Hz}$), 3.57 (2H,s), 3.84 and 3.85 (5H,m and s), 4.46 (2H,s), 6.98 (3H,m) and 7.35 (4H,m).

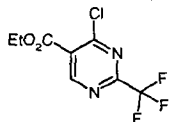
10 MS(APCI+) MH^+ 417; $\text{C}_{20}\text{H}_{21}\text{FN}_4\text{O}_3\text{S}$ requires M^+ 416.

Intermediate B33 — Ethyl 2-trifluoromethyl-4-oxypyrimidine-5-carboxylate

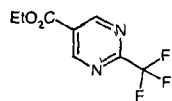


15 To a solution of trifluoroacetamide (36.5 g) and diethyl ethoxymalonate (71 g) in ethanol (300 ml) was added a solution of sodium ethoxide in ethanol (21 wt %, 109.5 ml) over 5 min. The mixture was heated at reflux for 6 h, then cooled, concentrated and water (200 ml) added. The resulting solid was collected by filtration, washed with cold water (50 ml) and diethyl ether (2 x 100 ml) and then suspended in water (400 ml). Dichloromethane (300 ml) was added and the mixture acidified with dilute HCl (2.5 M, 125 ml). The organic extract was washed with water, dried (MgSO_4) and evaporated to give the title compound as a buff solid (53 g, 68%). $^1\text{H-NMR}$ (CDCl_3) δ 12.00 (1H, br s), 9.18 (1H, s), 4.57 (2H, q), 1.49 (3H, t); $^{13}\text{C-NMR}$ (CDCl_3) δ 171.4, 167.3, 160.4, 160.2 (q, $J = 38\text{ Hz}$), 118.8 (q, $J = 276\text{ Hz}$), 109.2, 63.8, 14.0; MS (APCI+) found ($\text{M}+1$) = 237, $\text{C}_8\text{H}_7\text{F}_3\text{N}_2\text{O}_3$ requires 236.

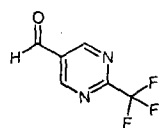
Intermediate B34 — Ethyl 2-trifluoromethyl-4-chloropyrimidine-5-carboxylate



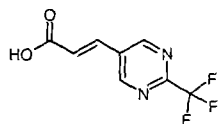
25 To a solution of ethyl 4-hydroxy-2-trifluoromethylpyrimidine-5-carboxylate (51.8 g) in dichloromethane (600 ml) cooled in an ice bath was added oxalyl chloride (57.4 ml) followed by dimethylformamide (0.2 ml). The mixture was stirred at room temperature for 16 h and then evaporated. Toluene was added and evaporated. The residue was dissolved in dichloromethane, washed with water, dried (MgSO_4) and evaporated to give the title compound as an orange oil (55.7 g, 100%). $^1\text{H-NMR}$ (CDCl_3) δ 9.25 (1H, s), 4.51 (2H, q), 1.46 (3H, t); $^{13}\text{C-NMR}$ (CDCl_3) δ 162.0 (2C), 161.1, 158.1 (q, $J = 39\text{ Hz}$), 127.0, 118.9 (q, $J = 276\text{ Hz}$), 63.5, 14.4.

126
124
20**Intermediate B35 — Ethyl 2-trifluoromethylpyrimidine-5-carboxylate**

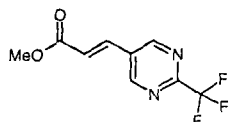
A mixture of ethyl 4-chloro-2-trifluoromethylpyrimidine-5-carboxylate (55.7 g), 10% palladium on carbon (0.3 g), ethanol (1000 ml) and *N,N*-diisopropylethylamine (90 ml) was shaken under hydrogen pressure maintained at 1 atmosphere for 2 h. The catalyst was then filtered off and the solvents evaporated. The residue was dissolved in dichloromethane, washed with ammonium chloride solution, then water, dried (MgSO₄) and evaporated to give the title compound as a buff solid (48 g, 100%). ¹H-NMR (CDCl₃) δ 9.42 (2H, s), 4.51 (2H, q), 1.45 (3H, t); ¹³C-NMR (CDCl₃) δ 162.7, 159.4 (2C), 159.3 (q, *J* = 37 Hz), 126.3, 119.6 (q, *J* = 275 Hz), 62.9, 14.4.

Intermediate B36 — 2-Trifluoromethyl-5-formylpyrimidine

To a solution of ethyl 2-trifluoromethylpyrimidine-5-carboxylate (5.17 g) in toluene (120 ml) cooled in dry ice/acetone was added a solution of diisobutylaluminium hydride (25 wt %, 31 ml) over 15 min. The mixture was stirred at -78°C for 45 min, then dilute HCl (2M, 120 ml) was added cautiously. After allowing the mixture to warm to room temperature diethyl ether was added. The organic phase was separated, washed with water, then brine, dried (MgSO₄) and evaporated to give the title compound as a colourless solid (3.46 g, 84%). ¹H-NMR (CDCl₃) δ 10.29 (1H, s), 9.37 (2H, s); ¹³C-NMR (CDCl₃) δ 187.7, 159.6 (q, *J* = 38 Hz), 159.1 (2C), 129.6, 119.2 (q, *J* = 276 Hz).

Intermediate B37 — 3-(2-Trifluoromethylpyrimidin-5-yl)acrylic acid

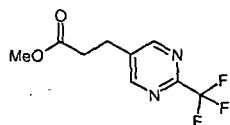
A mixture of 5-formyl-2-trifluoromethylpyrimidine (13.15 g), malonic acid (7.77 g), pyridine (45 ml) and piperidine (0.1 ml) were heated at 110°C for 2 h. After cooling, the solvent was evaporated and the residue was suspended in water. Ammonium hydroxide was added to effect solution, then the mixture was acidified with HCl. The resulting solid was collected by filtration, washed with water and dried under vacuum to give the title compound as a buff solid (12.7 g, 78%). ¹H-NMR (DMSO-d₆) δ 12.8 (1H, br s), 9.40 (2H, s), 7.70 (2H, d), 6.71 (2H, d); ¹³C-NMR (DMSO-d₆) δ 167.0, 157.7 (2C), 155.1 (q, *J* = 36 Hz), 136.5, 131.1, 126.0, 119.9 (q, *J* = 275 Hz); MS (APCI-) found (*M*-1) = 217, C₈H₅F₃N₂O₂ requires 218.

Intermediate B38 — Methyl 3-(2-trifluoromethylpyrimidin-5-yl)acrylate

A mixture of (*E*)-3-(2-trifluoromethylpyrimidin-5-yl)propenoic acid (12.7 g), methanol (80 ml) and concentrated sulphuric acid (4 ml) was heated under reflux for 4 h. After cooling, the solvent was evaporated and the residue partitioned between dichloromethane and water. The organic phase was

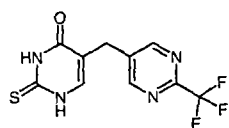
separated, washed with sodium bicarbonate solution, dried (MgSO_4) and evaporated to give the title compound as an off-white solid (10.12 g, 75%). $^1\text{H-NMR}$ (CDCl_3) δ 9.04 (2H, s), 7.69 (2H, d), 6.71 (2H, d), 3.87 (3H, s); $^{13}\text{C-NMR}$ (CDCl_3) δ 165.9, 157.2 (q, $J = 37$ Hz), 156.8 (2C), 136.1, 130.5, 124.7, 120.6, (q, $J = 275$ Hz), 52.6; MS (APCI+) found $(M+1) = 233$, $\text{C}_9\text{H}_7\text{F}_3\text{N}_2\text{O}_2$ requires 232.

5 **Intermediate B39 – Methyl 3-(2-trifluoromethylpyrimidin-5-yl)propanoate**



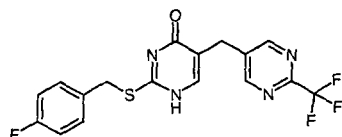
Prepared from Intermediate B38 by the method of Intermediate B10. $^1\text{H-NMR}$ (CDCl_3) δ 9.23 (2H, s), 3.78 (3H, s), 3.14 (2H, t), 2.81 (2H, t); MS (APCI+) found $(M+1) = 235$, $\text{C}_9\text{H}_9\text{F}_3\text{N}_2\text{O}_2$ requires 234.

Intermediate B40 – 5-(2-Trifluoromethylpyrimidin-5-ylmethyl)-2-thiouracil



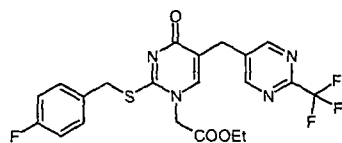
10 Prepared from Intermediate B39 by the method of Intermediate B13. $^1\text{H-NMR}$ (DMSO-d_6) δ 12.41 (1H br s), 8.96 (2H, s), 7.58 (1H, s), 3.70 (2H, s); MS (APCI-) found $(M-1) = 287$, $\text{C}_{10}\text{H}_7\text{F}_3\text{N}_4\text{OS}$ requires 288.

15 **Intermediate B41 – 2-(4-Fluorobenzylthio)-5-((2-trifluoromethylpyrimidin-5-yl)methyl)pyrimidin-4-one**

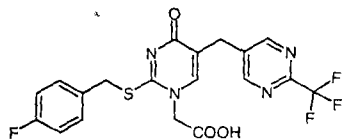


Prepared from Intermediate B40 by the method of Intermediate B6. $^1\text{H-NMR}$ (CDCl_3) δ 8.91 (2H, s), 7.95 (1H, s), 7.45-7.40 (2H, m), 7.05 (2H, t), 4.44 (2H, s), 3.82 (2H, s); MS (APCI+) found $(M+1) = 397$, $\text{C}_{17}\text{H}_{12}\text{F}_4\text{N}_4\text{OS}$ requires 396.

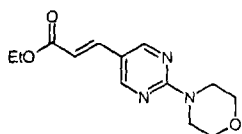
20 **Intermediate B42 – 1-((Ethoxycarbonylmethyl)-2-(4-fluorobenzylthio)-5-((2-trifluoromethylpyrimidin-5-yl)methyl)pyrimidin-4-one**



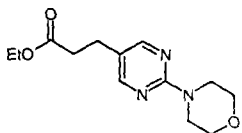
25 Prepared from Intermediate B41 by the method of Intermediate B7. Foam. $^1\text{H-NMR}$ (CDCl_3) δ 1.18-1.38 (3H, t), 3.79 (2H, s), 4.19-4.34 (2H, q), 4.46 (2H, s), 4.52 (2H, s), 6.91-7.11 (3H, m), 7.30-7.42 (2H, m), 8.88 (2H, s). No molecular ion seen.

127
125**Intermediate B43 — 1-((Ethoxycarbonylmethyl)-2-(4-fluorobenzylthio)-5-((2-trifluoromethylpyrimid-5-yl)methyl)pyrimidin-4-one**

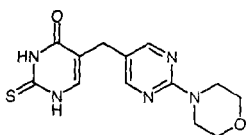
5 Prepared from Intermediate B42 by the method of Intermediate B8. White solid. $^1\text{H-NMR}$ (DMSO) δ 3.72 (2H, s), 4.41 (2H, s), 4.65 (2H, s), 7.04-7.21 (2H, t), 7.38-7.53 (2H, m), 7.73 (1H, s), 8.96 (2H, s). No molecular ion seen.

Intermediate B44 — Ethyl 3-[2-(1-morpholino)-5-pyrimidyl]acrylate

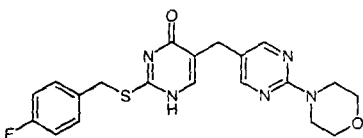
10 Prepared from 2-(1-morpholino)-5-bromopyrimidine by the method of Intermediate B9. $^1\text{H-NMR}$ (CDCl_3) δ 1.33 (t, 3H), 3.78 (m, 4H), 3.88 (m, 4H), 4.25 (q, 2H), 6.3 (d, 1H), 7.5 (d, 1H), 8.50 (s, 2H). MS (APCI+) Found (M+1) = 264; $\text{C}_{13}\text{H}_{17}\text{N}_3\text{O}_3$ requires 263.

Intermediate B45 — Ethyl 3-[2-(1-morpholino)-5-pyrimidyl]propionate

15 Prepared from Intermediate B44 by the method of Intermediate B10. $^1\text{H-NMR}$ (CDCl_3) δ 1.26 (t, 3H), 2.55 (t, 2H), 2.77 (t, 2H), 3.76 (s, 8H), 4.13 (q, 2H), 8.20 (s, 2H). MS (APCI+) Found (M+1) = 266; $\text{C}_{13}\text{H}_{19}\text{N}_3\text{O}_3$ requires 265.

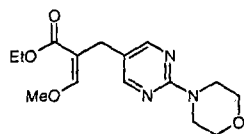
Intermediate B46 — 5-(2-(1-Morpholino)pyrimid-5-ylmethyl)-2-thiouracil

20 Prepared from Intermediate B45 by the method of Intermediate B13. $^1\text{H-NMR}$ (DMSO-d_6) δ 3.36 (s, 2H), 3.63 (s, 8H), 7.37 (s, 1H), 8.28 (s, 2H), 12.25 (br s, 2H). MS (ES+) Found (M+1) = 306; $\text{C}_{13}\text{H}_{15}\text{N}_5\text{O}_2\text{S}$ requires 305.

Intermediate B47 — 2-(4-Fluorobenzylthio)-5-(2-(1-morpholino)pyrimid-5-ylmethyl)pyrimidin-4-one

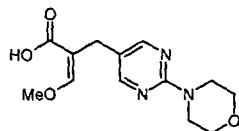
Prepared from Intermediate B46 by the method of Intermediate B6. $^1\text{H-NMR}$ (DMSO-d_6) δ 3.44 (s, 2H), 3.63 (s, 8H), 4.37 (s, 2H), 7.13 (t, 2H), 7.43 (m, 2H), 7.80 (br s, 1H), 8.30 (s, 2H), 12.75 (br s, 1H). MS (ES+) Found $(\text{M}+1) = 414$; $\text{C}_{20}\text{H}_{20}\text{FN}_5\text{O}_2\text{S}$ requires 413.

5 **Intermediate B48 – 2-(Methoxymethylene)-3-(2-(1-morpholino)pyrimidin-5-yl)propionic acid ethyl ester**



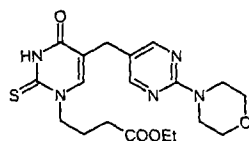
Prepared from Intermediate B47 by the method of Intermediate B11. $^1\text{H-NMR}$ (CDCl_3) (1.26 (3H, t), 3.36 (2H, s), 3.76 (8H, m), 3.86 (2H, s), 4.14 (2H, q), 7.35 (1H, s), 8.24 (2H, s). MS (AP+) Found $\text{M}+1 = 308$; $\text{C}_{15}\text{H}_{21}\text{N}_3\text{O}_4$ requires 307 (Colourless solid)

10 **Intermediate B49 – 2-(Methoxymethylene)-3-(2-(1-morpholino)pyrimidin-5-yl)propionic acid**



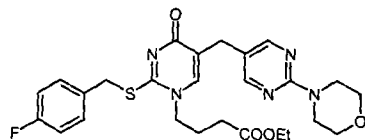
Prepared from Intermediate B48 by the method of Intermediate B12. $^1\text{H-NMR}$ (DMSO-d_6) (3.25 (2H, s), 3.64 (8H, m), 3.87 (3H, s), 7.43 (1H, s), 8.18 (2H, s). MS (AP+) Found $\text{M}+1 = 280$; $\text{C}_{13}\text{H}_{17}\text{N}_3\text{O}_4$ requires 279 (Colourless solid)

15 **Intermediate B50 – 1-(3-Ethoxycarbonylprop-1-yl)-5-(2-(1-morpholino)pyrimidin-5-ylmethyl)-2-thiouracil**



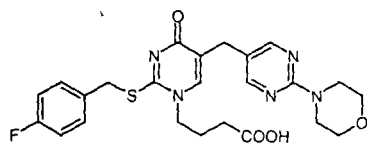
Prepared from Intermediate B49 by the method of Intermediate B17. $^1\text{H-NMR}$ (CDCl_3) (1.27 (3H, t), 2.09 (2H, m), 2.39 (2H, t), 3.48 (2H, s), 3.77 (8H, m), 4.16 (4H, m), 7.10 (1H, s), 8.24 (2H, s), 9.40 (1H, bs). MS (AP+) Found $\text{M}+1 = 420$; $\text{C}_{19}\text{H}_{25}\text{N}_5\text{O}_4\text{S}$ requires 419 (Cream coloured solid)

20 **Intermediate B51 – 1-(3-Ethoxycarbonylprop-1-yl)-2-(4-fluorobenzyl)thio-5-(2-(1-morpholino)pyrimidin-5-ylmethyl)pyrimidin-4-one**

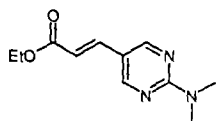


Prepared from Intermediate B50 by the method of Intermediate B18. $^1\text{H-NMR}$ (CDCl_3) (1.24 (3H, t), 2.01 (2H, m), 2.33 (2H, t), 3.55 (2H, s), 3.79 (10H, m), 4.12 (2H, q), 4.47 (2H, s), 6.88 (1H, s), 7.00 (2H, m), 7.37 (2H, m), 8.26 (2H, s). MS (AP+) Found $\text{M}+1 = 528$; $\text{C}_{26}\text{H}_{30}\text{FN}_5\text{O}_4\text{S}$ requires 527 (Colourless foam)

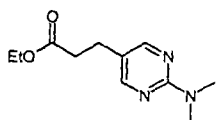
126 126

Intermediate B52 – 1-(3-Carboxyprop-1-yl)-2-(4-fluorobenzyl)thio-5-(2-(1-morpholino)pyrimid-5-ylmethyl)pyrimidin-4-one

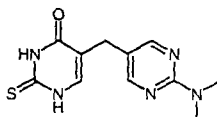
5 Prepared from Intermediate B51 by the method of Intermediate B8. $^1\text{H-NMR}$ (DMSO- d_6) δ : 1.87 (2H, m), 2.27 (2H, t), 3.39 (2H, s), 3.65 (8H, s), 3.86 (2H, t), 4.12 (2H, s), 7.15 (2H, m), 7.49 (2H, m), 7.70 (1H, s), 8.32 (2H, s). MS (AP-) Found 498; $\text{C}_{24}\text{H}_{26}\text{FN}_5\text{O}_4\text{S}$ requires 499 (Colourless solid)

Intermediate B53 — Ethyl 3-(2-dimethylamino-5-pyrimidyl)acrylate

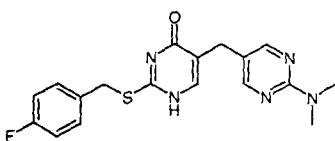
10 Prepared from 2-dimethylamino-5-bromopyrimidine by the method of Intermediate B9. $^1\text{H-NMR}$ (CDCl_3) δ : 1.33 (t, 3H), 3.24 (s, 6H), 4.25 (q, 2H), 6.3 (d, 1H), 7.5 (d, 1H), 8.49 (s, 2H). MS (APCI+) Found (M+1) = 222; $\text{C}_{11}\text{H}_{15}\text{N}_3\text{O}_2$ requires 221.

Intermediate B54 — Ethyl 3-(2-dimethylamino-5-pyrimidyl)propionate

15 Prepared from Intermediate B53 by the method of Intermediate B10. $^1\text{H-NMR}$ (CDCl_3) δ : 1.24 (t, 3H), 2.53 (t, 2H), 2.75 (t, 2H), 3.16 (s, 6H), 4.13 (q, 2H), 8.27 (s, 2H). MS (APCI+) Found (M+1) = 224; $\text{C}_{11}\text{H}_{17}\text{N}_3\text{O}_2$ requires 223.

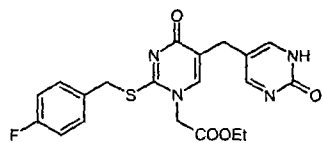
Intermediate B55 — 5-(2-Dimethylaminopyrimid-5-ylmethyl)-2-thiouracil

20 Prepared from Intermediate B54 by the method of Intermediate B13. $^1\text{H-NMR}$ (DMSO- d_6) δ : 3.07 (s, 6H), 3.34 (s, 2H), 7.33 (s, 1H), 8.23 (s, 2H), 12.25 (br s, 2H). MS (ES+) Found (M+1) = 264; $\text{C}_{11}\text{H}_{13}\text{N}_5\text{OS}$ requires 263.

Intermediate B56 — 2-(4-Fluorobenzyl)thio-5-(2-dimethylaminopyrimid-5-ylmethyl)pyrimidin-4-one

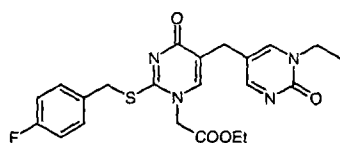
25 Prepared from Intermediate B55 by the method of Intermediate B6. $^1\text{H-NMR}$ (CDCl_3) δ : 3.15 (s, 6H), 3.51 (s, 2H), 4.36 (s, 2H), 7.0 (m, 2H), 7.35 (m, 2H), 7.66 (br s, 1H), 8.23 (s, 2H). MS (ES+) Found (M+1) = 372; $\text{C}_{18}\text{H}_{18}\text{FN}_5\text{OS}$ requires 371.

Intermediate B57 — 1-Ethoxycarbonylmethyl-2-(4-fluorobenzyl)thio-5-(2-oxopyrimidin-5-ylmethyl)pyrimidin-4-one



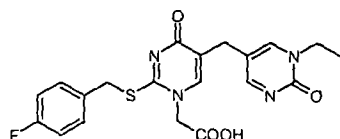
- 5 Prepared from Intermediate B15 by the method of Example 18, except using only 2 equivalents of B-bromocatecholborane. ¹H-NMR (d6-DMSO) δ 1.28 (3H, t), 4.26 (4H, q), 4.53 (2H, s), 4.90 (2H, s), 7.26 (2H, m), 7.57 (2H, m), 7.69 (1H, s), 8.25 (2H, br. s); MS (APCI+) found (M+1) = 431; C₂₀H₁₉FN₄O₄S requires 430.

Intermediate B58 — 1-Ethoxycarbonylmethyl-2-(4-fluorobenzyl)thio-5-(1-ethyl-2-oxopyrimidin-5-ylmethyl)pyrimidin-4-one



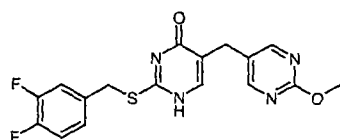
- 10 To a solution of Intermediate B57 (3.1g) in dry dimethylformamide (40ml) under argon was added ethyl iodide (1.4g) and anhydrous potassium carbonate (2.5g). The mixture was stirred at room temperature for 20h and the solvent removed *in vacuo*. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine and added in equal portions to three 10g silica cartridges.
- 15 Elution of each column with EtOAc to 18% MeOH:EtOAc and combining appropriate fractions gave the title compound (1.5g). ¹H-NMR (CDCl₃) δ 1.27 (3H,t), 1.39 (3H,t), 3.46 (2H,s), 3.94 (2H,q), 4.25 (2H,q), 4.48 (2H,s), 4.57 (2H,s), 6.9-7.15 (2H,m), 7.21 (1H,s), 7.3-7.4 (2H,m), 7.9 (1H,m), 8.4 (1H,m), MS (APCI+) found (M+1) = 459; C₂₂H₂₃FN₄O₄S requires 458.

Intermediate B59 — 1-Carboxymethyl-2-(4-fluorobenzyl)thio-5-(1-ethyl-2-oxopyrimidin-5-ylmethyl)pyrimidin-4-one



- 20 Prepared from Intermediate B58 by the method of Intermediate B8. ¹H-NMR (DMSO-d₆) δ 1.23 (3H,t), 3.34 (2H,s), 3.84 (2H,q), 4.42 (2H,s), 4.67 (2H,s), 7.05-7.2 (2H,m), 7.4-7.55 (2H,m), 7.60 (1H,s), 8.1 (1H,m), 8.5 (1H,m), No molecular ion found.

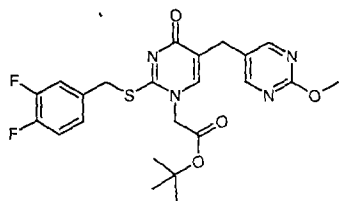
Intermediate B60 — 2-(3,4-Difluorobenzylthio)-5-((2-methoxypyrimidin-5-yl)methyl)pyrimidin-4-one



- 25 Prepared from intermediate B13 by the method of Intermediate B6. ¹H-NMR (d6-DMSO) δ 3.57 (2H, s), 3.87 (3H, s), 4.37 (2H, s), 7.24-7.53 (3H, m), 7.88 (1H, br.s), 8.49 (2H, s), 12.88 (1H, br s); MS (APCI+) found (M+1) = 377; C₁₇H₂₀F₂N₄O₂S requires 376.
- 30

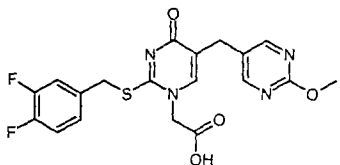
129 127

Intermediate B61 — 1-(*Tert*-butoxycarbonylmethyl)-2-(3,4-difluorobenzyl)thio-5-(2-methoxypyrimid-5-ylmethyl)pyrimidin-4-one



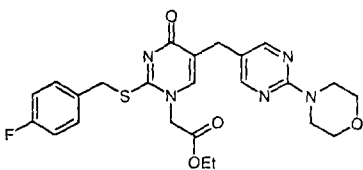
- 5 A mixture of Intermediate B60 (1.04g, 2.77mmol), *tert*-butylbromoacetate (408ul, 2.77mmol) and di-*iso*-propylethylamine (530ul, 3.04mmol) in dichloromethane (15ml) was stirred at room temperature under an atmosphere of argon for 16h. The mixture was diluted with saturated aqueous sodium bicarbonate, the phases separated and the aqueous phase extracted with dichloromethane (2×). The combined organic phase was dried (MgSO₄) and the solvent removed under reduced pressure to give a crude oil which was chromatographed (Silica, 2%MeOH / EtOAc) to afford a colourless solid (553mg, 40%). ¹H-NMR (CDCl₃) δ 8.46 (2H, s), 7.05-7.23 (3H, m), 6.81 (1H, s), 4.50 (2H, s), 4.34 (2H, s), 4.02 (3H, s), 3.70 (2H, s), 1.44 (9H, s); MS(APCI+) found (M+1) = 491, C₂₃H₂₄F₂N₄O₄S requires 490.
- 10

Intermediate B62 — 1-(Carboxymethyl)-2-(3,4-difluorobenzyl)thio-5-(2-methoxypyrimid-5-ylmethyl)pyrimidin-4-one



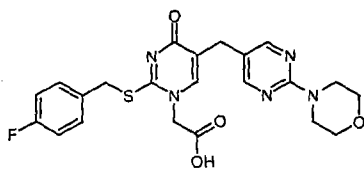
- 15 Trifluoroacetic acid (2ml) was added to a mixture of Intermediate B61 (490mg, 1mmol) in dichloromethane (4ml) and the reaction stirred at room temperature for 48h. The solvent was removed under reduced pressure and the resultant oil triturated with ether to afford a colourless solid (395mg, 91%). ¹H-NMR (CDCl₃) δ 8.49 (2H, s), 7.61 (1H, s), 7.28-7.50 (3H, m), 4.66 (2H, s), 4.41 (2H, s), 3.88 (3H, s), 3.51 (2H, s).

20 **Intermediate B63 — 1-(Ethoxycarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-(1-morpholino)-pyrimid-5-ylmethyl)pyrimidin-4-one**



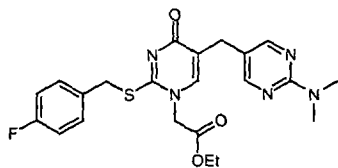
- Prepared from Intermediate B47 by the method of Intermediate B7. ¹H NMR (DMSO-d₆) δ: 1.18 (t, 3H), 3.40 (s, 2H), 3.64 (s, 8H), 4.15 (q, 2H), 4.41 (s, 2H), 4.81 (d, 2H), 7.14 (t, 2H), 7.45 (m, 2H), 7.59 (s, 1H), 8.29 (m, 2H). MS (APCI+) Found (M+1) = 500; C₂₄H₂₆FN₅O₄S requires 499.
- 25

Intermediate B64 — 1-(Carboxymethyl)-2-(4-fluorobenzyl)thio-5-(2-(1-morpholino)pyrimid-5-ylmethyl)pyrimidin-4-one



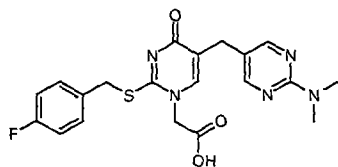
- 5 Prepared from Intermediate B63 by the method of Intermediate B8. ^1H NMR (DMSO- d_6) δ : 3.37 (s, 2H), 3.63 (s, 8H), 4.02 (s, 2H), 4.33 (s, 2H), 7.12 (t, 2H), 7.45 (m, 2H), 7.51 (s, 1H), 8.29 (s, 2H). MS (ES+) Found (M+1) = 472; $\text{C}_{22}\text{H}_{22}\text{FN}_5\text{O}_4\text{S}$ requires 471.

Intermediate B65 — 1-(Ethoxycarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-dimethylamino-pyrimid-5-ylmethyl)pyrimidin-4-one



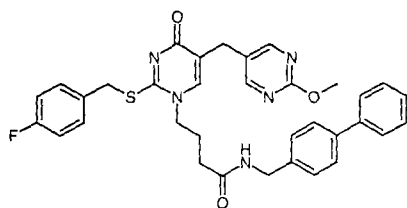
- 10 Prepared from Intermediate B56 by the method of Intermediate B7. ^1H NMR (DMSO- d_6) δ : 1.16 (t, 3H), 3.08 (s, 6H), 3.38 (s, 2H), 4.15 (q, 2H), 4.41 (s, 2H), 4.81 (d, 2H), 7.15 (t, 2H), 7.45 (m, 2H), 7.56 (s, 1H), 8.22 (m, 2H). MS (APCI+) Found (M+1) = 458; $\text{C}_{22}\text{H}_{24}\text{FN}_5\text{O}_3\text{S}$ requires 457.

Intermediate B66 — 1-(Carboxymethyl)-2-(4-fluorobenzyl)thio-5-(2-dimethylaminopyrimid-5-ylmethyl)pyrimidin-4-one



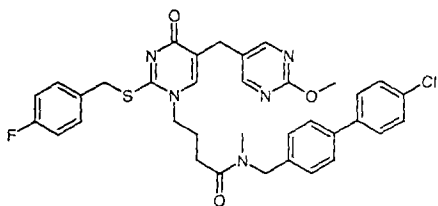
- 15 Prepared from Intermediate B65 by the method of Intermediate B8. ^1H NMR (DMSO- d_6) δ : 3.08 (s, 6H), 3.37 (s, 2H), 4.41 (s, 2H), 4.64 (s, 2H), 7.13 (t, 2H), 7.45 (m, 2H), 7.57 (s, 1H), 8.23 (m, 2H). MS (ES+) Found (M+1) = 430; $\text{C}_{20}\text{H}_{20}\text{FN}_5\text{O}_3\text{S}$ requires 429.

130 128 11

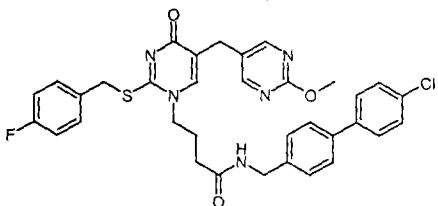
Example 1 — 1-(3-(4-Phenylbenzylaminocarbonyl)prop-1-yl)-2-(4-fluorobenzyl)thio-5-(2-methoxypyrimid-5-ylmethyl)pyrimidin-4-one

A mixture of Intermediate B19 (0.3g, 1 equiv), 4-(aminomethyl)biphenyl (0.12g, 1 equiv)

- 5 hydroxybenzotriazole (0.010g, 0.1 equiv), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (0.135g, 1.03 equiv) and dichloromethane (12ml) was stirred at room temperature overnight, then diluted with dichloromethane and washed with aqueous sodium bicarbonate. The organic layer was applied directly to a 10g silica cartridge, which was eluted with 0-12% methanol in dichloromethane. Product fractions were evaporated to a white solid (0.34g). ¹H-NMR (CDCl₃) δ 1.95-2.17 (2H, m), 2.19-2.31 (2H, m), 3.60 (2H, s), 3.84-43.96 (2H, t), 3.98 (3H, s), 4.40-4.50 (4H, d), 5.80-5.94 (1H, t), 6.90-7.05 (2H, t), 7.12 (1H, s), 7.30-7.53 (11H, m), 8.47 (2H, s); MS (APCI+) found (M+1) = 610; C₃₄H₃₂FN₅O₃S requires 609.
- 10

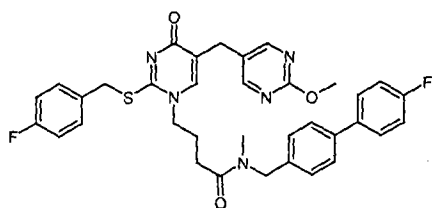
Example 2 — 1-(3-(N-Methyl-N-(4-(4-chlorophenyl)benzyl)aminocarbonyl)prop-1-yl)-2-(4-fluorobenzyl)thio-5-(2-methoxypyrimid-5-ylmethyl)pyrimidin-4-one

- 15 Prepared from Intermediates A2 and B19 by the method of Example 1. ¹H-NMR (CDCl₃, 400 MHz): δ 2.05-2.10 (2H, m); 2.37-2.40 (2H, t); 2.89 (2H, s); 2.99 (1H, s); 3.60 (2H, s); 3.88-3.96 (2H, m); 3.98 (3H, s); 4.45 (2H, s); 6.97 (2H, m); 7.19 (2H, m); 7.27 (1H, m); 7.29-7.40 (4H, m); 7.48-8.44 (4H, m); 8.45 (2H, s).

Example 3 — 1-(3-(4-(4-Chlorophenyl)benzylaminocarbonyl)prop-1-yl)-2-(4-fluorobenzyl)thio-5-(2-methoxypyrimid-5-ylmethyl)pyrimidin-4-one

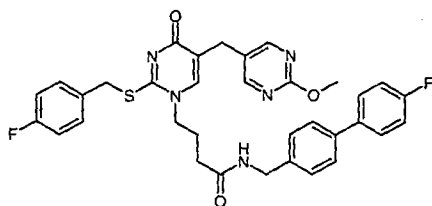
- 20 Prepared from Intermediates A5 and B19 by the method of Example 1. ¹H-NMR (CDCl₃, 400 MHz): δ 2.05-2.09 (2H, m); 2.22-2.26 (2H, t); 3.60 (2H, s); 3.91 (2H, t); 3.98 (3H, s); 4.45 (2H, s); 5.84 (1H, t); 6.97 (2H, t); 7.11 (1H, s); 7.32-7.41 (6H, m); 7.46-7.52 (4H, m); 8.45 (2H, s).
- 25

Example 4 — 1-(3-(N-Methyl-N-(4-(4-fluorophenyl)benzyl)aminocarbonyl)prop-1-yl)-2-(4-fluorobenzyl)thio-5-(2-methoxypyrimid-5-ylmethyl)pyrimidin-4-one



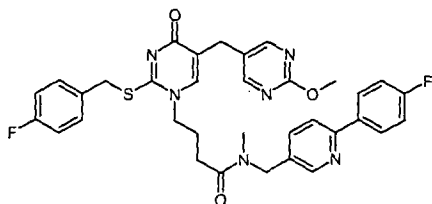
Prepared from Intermediates A8 and B19 by the method of Example 1. ¹H-NMR (CDCl₃, 400 MHz): δ 2.05-2.10 (2H, m); 2.37-2.40 (2H, t); 2.89 (2H, s); 2.99 (1H, s); 3.60 (2H, s); 3.92-3.97 (2H, m); 3.99 (3H, s); 4.45 (2H, s); 6.97 (2H, m); 7.13 (3H, m); 7.27 (2H, m); 7.35 (2H, m); 7.48-8.44 (4H, m); 8.45 (2H, s).

Example 5 — 1-(3-(4-(4-Fluorophenyl)benzylaminocarbonyl)prop-1-yl)-2-(4-fluorobenzyl)thio-5-(2-methoxypyrimid-5-ylmethyl)pyrimidin-4-one



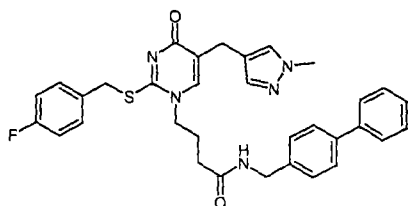
Prepared from Intermediates A11 and B19 by the method of Example 1. ¹H-NMR (CDCl₃, 400 MHz): δ 2.05-2.09 (2H, m); 2.22-2.26 (2H, t); 3.60 (2H, s); 3.91 (2H, t); 3.98 (3H, s); 4.45 (2H, s); 5.83 (1H, t); 6.99 (2H, t); 7.14 (3H, m); 7.34 (4H, m); 7.51 (4H, m); 8.45 (2H, s).

Example 6 — 1-(3-(N-Methyl-N-(2-(4-fluorophenyl)pyrid-5-ylmethyl)aminocarbonyl)prop-1-yl)-2-(4-fluorobenzyl)thio-5-(2-methoxypyrimid-5-ylmethyl)pyrimidin-4-one



Prepared from Intermediates A22 and B19 by the method of Example 1. ¹H-NMR (CDCl₃) δ 2.08 (2H, m), 2.38 (2H, m), 2.91, 2.99 (3H, 2xs), 3.62 (2H, s), 3.92 (2H, m), 3.98 (3H, s), 4.46 (2H, m), 4.51 (2H, 2xs), 7.00 (2H, m), 7.13 (3H, m), 7.35 – 8.55 (9H, m); MS (APCI+) M+1=643; C₃₄H₃₂F₂N₆O₃S requires 642 (colourless foam).

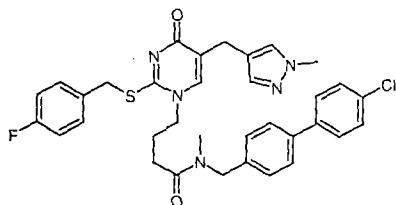
Example 7 — 1-(3-(N-Methyl-N-(4-phenylbenzyl)aminocarbonyl)prop-1-yl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one



131 129 M

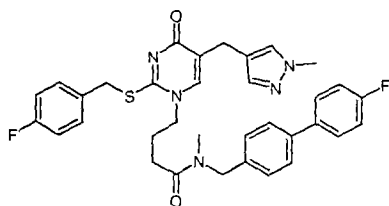
Prepared from 4-(aminomethyl)biphenyl and Intermediate B32 by the method of Example 1. $^1\text{H-NMR}$ (CDCl_3) δ 1.95-2.15 (2H,m), 2.23 (2H,t), 3.54 (2H,s), 3.8-3.95 (5H,m), 4.4-4.5 (4H,m), 5.91 (1H,t), 6.9-7.05 (3H,m), 7.25-7.4 (7H,m), 7.4-7.5 (2H,m), 7.5-7.6 (4H,m) MS (APCI+) found ($M+1$) = 582; $\text{C}_{33}\text{H}_{32}\text{FN}_5\text{O}_2\text{S}$ requires 581.

5 **Example 8 — 1-(3-(N-Methyl-N-(4-(4-chlorophenyl)benzyl)aminocarbonyl)prop-1-yl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one**



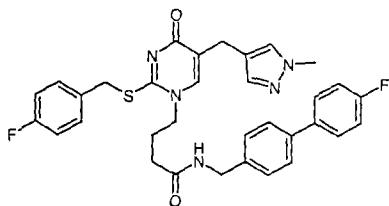
Prepared from Intermediates A2 and B32 by the method of Example 1. $^1\text{H-NMR}$ (CDCl_3) δ 1.95-2.15 (2H,m), 2.37 (2H,t), 2.88 and 2.94 (3H,2xs), 3.56 (2H,s), 3.75-3.95 (5H,m), 4.4-4.65 (4H,m), 6.9-7.05 (3H,m), 7.1-7.6 (12H,m), MS (APCI+) found ($M+1$) = 630; $\text{C}_{34}\text{H}_{33}\text{ClFN}_5\text{O}_2\text{S}$ requires 629.

10 **Example 9 — 1-(3-(N-Methyl-N-(4-(4-fluorophenyl)benzyl)aminocarbonyl)prop-1-yl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one**



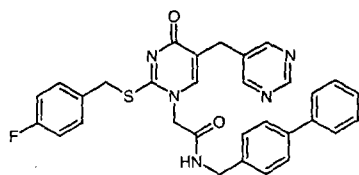
Prepared from Intermediates A8 and B32 by the method of Example 1. White solid. $^1\text{H-NMR}$ (CDCl_3) δ 1.95-2.18 (2H, m), 2.30-2.46 (2H, t), 2.82-3.03 (3H, 2xs), 3.57 (2H, s), 3.75-3.98 (5H, m), 4.42-4.63 (4H, m), 6.90-7.60 (15H, m); MS (APCI+) found ($M+1$) = 614; $\text{C}_{34}\text{H}_{33}\text{N}_5\text{O}_2\text{SF}_2$ requires 613.

15 **Example 10 — 1-(3-(4-(4-Fluorophenyl)benzylaminocarbonyl)prop-1-yl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one**



20 Prepared from Intermediates A11 and B32 by the method of Example 1. White solid. $^1\text{H-NMR}$ (CDCl_3) δ 1.95-2.14 (2H, m), 2.17-2.29 (2H, t), 3.54 (2H, s), 3.78-3.93 (5H, m), 4.38-4.53 (4H, m), 5.72-5.85 (1H, br.t), 6.90-7.03 (3H, m), 7.05-7.20 (2H, m), 7.21-7.58 (10H, m); MS (APCI+) found ($M+1$) = 600; $\text{C}_{33}\text{H}_{31}\text{N}_5\text{O}_2\text{SF}_2$ requires 599.

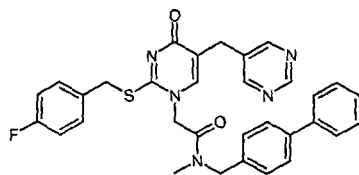
Example 11 — 1-(4-Phenylbenzylaminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(pyrimid-5-ylmethyl)pyrimidin-4-one



Prepared from Intermediate B8 and 4-(aminomethyl)biphenyl by the method of Example 1. Cream solid.

- 5 $^1\text{H-NMR}$ (CDCl_3) δ 3.61 (2H, s), 4.32-4.39 (2H, d), 4.43 (2H, s), 4.68 (2H, s), 7.05-7.19 (2H, t), 7.28-7.79 (11H, m), 8.73 (2H, s), 8.82-8.92 (1H, br.t), 9.05 (1H, s); No molecular ion seen.

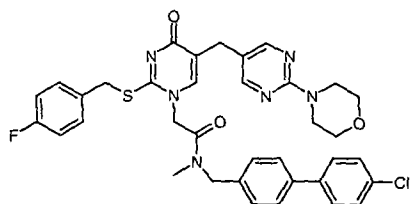
Example 12 — 1-(N-Methyl-N-(4-phenylbenzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(pyrimid-5-ylmethyl)pyrimidin-4-one



- 10 Prepared from Intermediate B8 and 4-(methylaminomethyl)biphenyl by the method of Example 1. $^1\text{H-NMR}$ ($\text{d}_6\text{-DMSO}$) δ 3.02 and 3.10 (3H, 2Xs), 3.75 (2H, m), 4.51 and 4.56 (2H, 2Xs), 4.70 and 4.78 (2H, 2Xs), 5.10 (2H, m), 7.20-7.31 (2H, m), 7.43-7.80 (12H, m), 8.85 (2H, s), 9.18 (1H, s); MS (APCI+) found $(\text{M}+1) = 566$; $\text{C}_{32}\text{H}_{28}\text{FN}_5\text{O}_2\text{S}$ requires 565.

Example 13 — 1-(N-Methyl-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-(1-morpholino)pyrimid-5-ylmethyl)pyrimidin-4-one

- 15

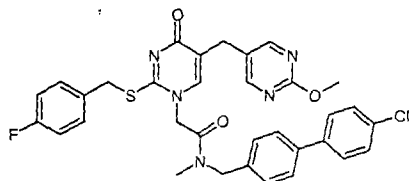


A solution of Intermediate A6 (0.23g, 1 equiv), Intermediate B47 (0.27g, 1 equiv) and diisopropylethylamine (0.10g, 1.2 equiv) in dry dichloromethane (6ml) was stirred at room temperature under argon for 20h, then diluted with more dichloromethane and washed successively with water and aqueous ammonium chloride. Drying and evaporation of the organic phase, followed by chromatography (silica, 0-5% methanol in ethyl acetate) gave the desired product as a pale solid (0.19g). $^1\text{H-NMR}$ (DMSO-d_6) δ : 2.95 (d, 3H), 3.42 (d, 2H), 3.64 (s, 8H), 4.40 (d, 2H), 4.60 (d, 2H), 4.95 (d, 2H), 7.1 (m, 2H), 7.30 (d, 2H), 7.35-7.6 (m, 6H), 7.65 (m, 3H), 8.30 (s, 2H). MS (APCI+) Found $(\text{M}+1) = 685/687$; $\text{C}_{36}\text{H}_{34}\text{ClFN}_6\text{O}_3\text{S}$ requires 685.

- 20

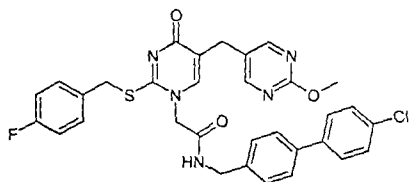
32130
M

Example 14 — 1-(N-Methyl-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxypyrimid-5-ylmethyl)pyrimidin-4-one



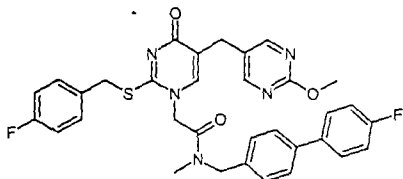
Prepared from Intermediates A2 and B16 by the method of Example 1. White solid. $^1\text{H-NMR}$ (CDCl_3) δ 2.97, 3.10 (3H, 2xs), 3.62-3.73 (2H, m), 4.00 (3H, s), 4.46 (1H, s), 4.50-4.66 (5H, m), 6.74-6.87 (1H, m), 6.90-7.05 (2H, m), 7.20-7.55 (10H, m), 8.40-8.50 (2H, d); MS (APCI+) found (M+1) = 630; $\text{C}_{33}\text{H}_{29}\text{N}_5\text{O}_3\text{SFCl}$ requires 629.

Example 15 — 1-(4-(4-Chlorophenyl)benzylaminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxypyrimid-5-ylmethyl)pyrimidin-4-one



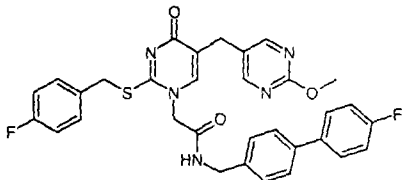
Prepared from Intermediates A5 and B16 by the method of Example 1. $^1\text{H-NMR}$ ($\text{d}_6\text{-DMSO}$) δ 3.52 (2H, s), 3.88 (3H, s), 4.35 (2H, m), 4.41 (2H, s), 4.65 (2H, s), 7.13 (2H, m), 7.34 (2H, m), 7.44-7.68 (9H, m), 8.49 (2H, s), 8.85 (1H, br.s); MS (APCI+) found (M+1) = 616; $\text{C}_{32}\text{H}_{27}\text{ClFN}_5\text{O}_3\text{S}$ requires 615.

Example 16 — 1-(N-Methyl-N-(4-(4-fluorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxypyrimid-5-ylmethyl)pyrimidin-4-one



Prepared from Intermediates A8 and B16 by the method of Example 1. $^1\text{H-NMR}$ ($\text{d}_6\text{-DMSO}$) δ 2.87 and 2.95 (3H, 2xs), 3.54 (2H, s), 3.88 (3H, s), 4.37 and 4.43 (2H, 2xs), 4.55 and 4.63 (2H, 2xs), 4.95 (2H, m), 7.11-7.26 (2H, m), 7.27-7.70 (11H, m), 8.49 (2H, s); MS (APCI+) found (M+1) = 614; $\text{C}_{33}\text{H}_{29}\text{F}_2\text{N}_5\text{O}_3\text{S}$ requires 613.

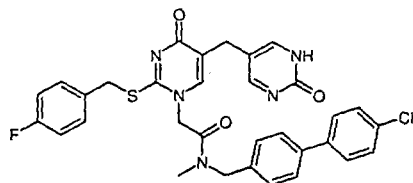
Example 17 — 1-(4-(4-Fluorophenyl)benzylaminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxypyrimid-5-ylmethyl)pyrimidin-4-one



Prepared from Intermediates A11 and B16 by the method of Example 1. $^1\text{H-NMR}$ ($\text{d}_6\text{-DMSO}$) δ 3.52 (2H, s), 3.88 (3H, s), 4.34 (2H, m), 4.41 (2H, s), 4.65 (2H, s), 7.09-7.16 (2H, m), 7.30-7.34 (4H, m),

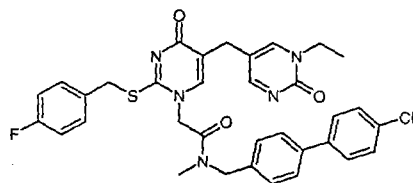
7.44-7.56 (4H, m), 7.64-7.70 (3H, m), 8.49 (2H, s), 8.85 (1H, br.t); MS (APCI+) found (M+1) = 600; $C_{32}H_{27}F_2N_5O_3S$ requires 599.

Example 18 — 1-(N-Methyl-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-oxopyrimid-5-ylmethyl)pyrimidin-4-one



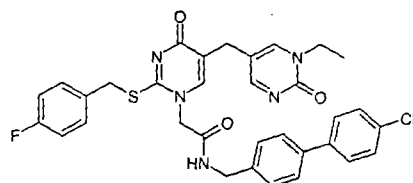
A mixture of Example 14 (0.73g, 1.2mmol), B-bromocatecholborane (1.01g, 5.1mmol) and dry dichloromethane (20ml) was stirred under argon at room temperature overnight, giving a clear orange solution. water was added and stirring continued for 30min, then the organic layer was separated and applied directly to a 10g silica cartridge, which was eluted with 0-14% methanol in dichloromethane. Product fractions were evaporated to obtain a pale yellow solid (0.36g). 1H -NMR (DMSO) δ 2.80-3.06 (3H, 2xs), 3.37 (2H, s), 4.33-4.49 (2H, 2xs), 4.50-4.72 (2H, 2xs), 4.87-5.06 (2H, m), 7.04-7.75 (13H, m), 8.19 (2H, s); MS (APCI-) found (M-1) = 614; $C_{32}H_{27}N_5O_3SFCl$ requires 615.

Example 19 — 1-(N-Methyl-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-ethyl-2-oxopyrimid-5-ylmethyl)pyrimidin-4-one



Prepared from Intermediates A2 and B59 by the method of Example 1. White solid. 1H -NMR ($CDCl_3$) δ 1.33-1.47 (3H, t), 2.92-3.13 (3H, 2xs), 3.39-3.53 (2H, d), 3.84-4.02 (2H, q), 4.39-4.79 (6H, m), 6.88-7.05 (2H, m), 7.10-7.54 (11H, m), 7.88-7.98 (1H, m), 8.37-8.46 (1H, m); MS (APCI+) found (M+1) = 644; $C_{34}H_{31}N_5O_3SFCl$ requires 643.

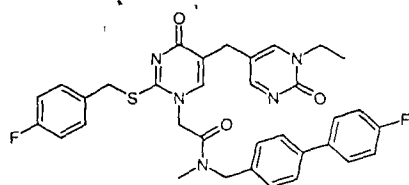
Example 20 — 1-(4-(4-Chlorophenyl)benzylaminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-ethyl-2-oxopyrimid-5-ylmethyl)pyrimidin-4-one



Prepared from Intermediates A5 and B59 by the method of Example 1. 1H -NMR (d_6 -DMSO) δ 1.22 (3H,t), 3.35 (2H,s), 3.83 (2H,q), 4.33 (2H,m), 4.42 (2H,s), 4.65 (2H,s), 7.12 (2H,t), 7.25-7.4 (2H,m), 7.4-7.75 (9H,m), 8.07 (1H,bd), 8.46 (1H,bd), 8.85 (1H,t).

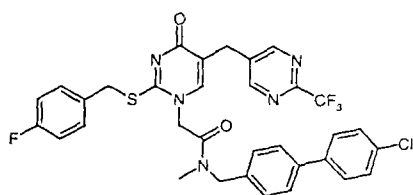
133
13/1/14

Example 21 — 1-(N-Methyl-N-(4-(4-fluorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-ethyl-2-oxopyrimid-5-ylmethyl)pyrimidin-4-one



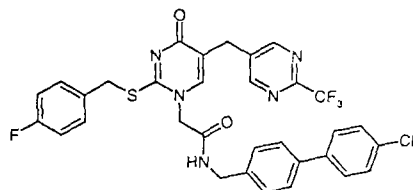
Prepared from Intermediates A8 and B59 by the method of Example 1. $^1\text{H-NMR}$ ($\text{d}_6\text{-DMSO}$) δ 1.23 (3H,t), 2.87 and 2.96 (3H,2xs), 3.3-3.45 (2H,m), 3.84 (2H,q), 4.38, 4.43, 4.55 and 4.63 (4H,4xs), 4.94 and 4.97 (2H,2xs), 7.05-7.2 (2H,m), 7.2-7.75 (11H,m), 8.05-8.15 (1H,m), 8.47 (1H,m), MS (APCI+) found $(\text{M}+1) = 628$; $\text{C}_{34}\text{H}_{31}\text{F}_2\text{N}_5\text{O}_3\text{S}$ requires 627.

Example 22 — 1-(N-Methyl-N-(4-(4-fluorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-trifluoromethylpyrimid-5-ylmethyl)pyrimidin-4-one



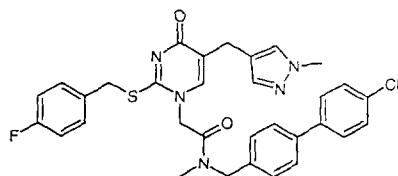
Prepared from Intermediates A2 and B43 by the method of Example 1. $^1\text{H-NMR}$ (CDCl_3) δ 8.85 & 8.82 (2H, s+s), 7.46-7.22 (10H, m), 7.02-6.90 (3H, m), 4.59-4.40 (6H, m), 3.78 & 3.75 (2H, s+s), 3.08 & 2.96 (3H, s+s); MS (APCI+) found $(\text{M}+1) = 668$, $\text{C}_{33}\text{H}_{26}^{35}\text{ClF}_4\text{N}_5\text{O}_2\text{S}$ requires 667.

Example 23 — 1-(4-(4-Fluorophenyl)benzylaminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-trifluoromethylpyrimid-5-ylmethyl)pyrimidin-4-one



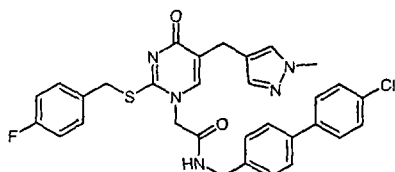
Prepared from Intermediates A5 and B43 by the method of Example 1. White solid. $^1\text{H-NMR}$ (DMSO) δ 3.73 (2H, s), 4.30-4.39 (2H, d), 4.41 (2H, s), 4.66 (2H, s), 7.05-7.20 (2H, t), 7.30-7.39 (2H, d), 7.40-7.60 (6H, m), 7.61-7.72 (2H, d), 7.79 (1H, s), 8.80-8.91 (1H, t), 8.97 (2H, s); MS (ES+) found $(\text{M}+1) = 654$; $\text{C}_{32}\text{H}_{24}\text{N}_5\text{O}_2\text{SF}_4\text{Cl}$ requires 653.

Example 24 — 1-(N-Methyl-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one



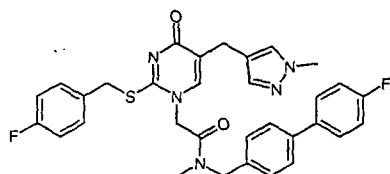
Prepared from Intermediates A2 and B27 by the method of Example 1. $^1\text{H-NMR}$ ($\text{d}_6\text{-DMSO}$) δ 2.95 and 3.08 (3H, 2Xs), 3.61 (2H, m), 3.86 (3H, m), 4.46-4.61 (6H, m), 6.74 and 6.80 (1H, 2Xs), 6.91-6.99 (2H, m), 7.21-7.49 (12H, m); MS (APCI+) found $(\text{M}+1) = 602$; $\text{C}_{32}\text{H}_{29}\text{ClFN}_5\text{O}_2\text{S}$ requires 601.

Example 25 — 1-(4-(4-Chlorophenyl)benzylaminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one



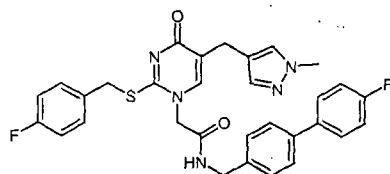
Prepared from Intermediates A5 and B27 by the method of Example 1. $^1\text{H-NMR}$ ($\text{d}_6\text{-DMSO}$) δ 3.37 (2H, s), 3.76 (3H, s), 4.33 (2H, m), 4.42 (2H, s), 4.65 (2H, s), 7.13 (2H, m), 7.25 (1H, s), 7.33 (2H, d), 7.45-7.56 (8H, m) 7.66 (2H, d), 8.84 (1H, br. m); MS (APCI+) found $(\text{M}+1) = 588$; $\text{C}_{31}\text{H}_{27}\text{ClFN}_5\text{O}_2\text{S}$ requires 587.

Example 26 — 1-(N-Methyl-N-(4-(4-fluorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one



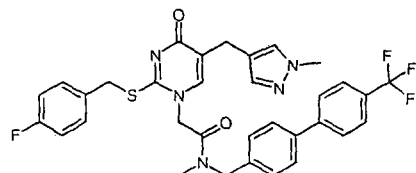
Prepared from Intermediates A8 and B27 by the method of Example 1. $^1\text{H-NMR}$ (CDCl_3) δ 2.88-3.14 (3H, 2xs), 3.54-3.70 (2H, m), 3.86 (3H, s), 4.60-4.69 (6H, m), 6.65-7.60 (15H, m); MS (APCI+) found $(\text{M}+1) = 586$; $\text{C}_{32}\text{H}_{29}\text{N}_5\text{O}_2\text{SF}_2$ requires 585.

Example 27 — 1-(4-(4-Fluorophenyl)benzylaminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one



Prepared from Intermediates A11 and B27 by the method of Example 1. White solid. $^1\text{H-NMR}$ (DMSO) δ 3.28-3.42 (2H, m), 3.76 (3H, s), 4.28-4.47 (4H, m), 4.65 (2H, s), 7.05-7.19 (2H, t), 7.21-7.73 (13H, m), 8.77-8.89 (1H, br.t).

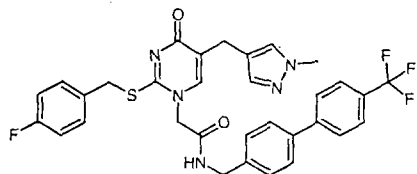
Example 28 — 1-(N-Methyl-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one



13A
132/4

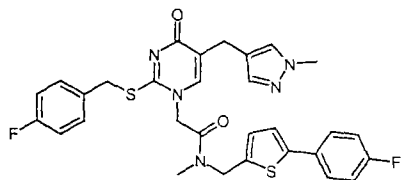
Prepared from Intermediates A13 and B27 by the method of Example 1. $^1\text{H-NMR}$ (DMSO) δ 2.96 (3H,s), 3.39 (2H,m), 3.77 (3H,s), 4.43 (2H, s), 4.57 (2H,s), 4.97 (2H,s), 7.12 (3H,m), 7.25 (1H,s), 7.34-7.48 (6H, m), 7.62-6.70 (2H,m), 8.84 (4H,m).; MS (APCI+) found (M+1) = 636; $\text{C}_{33}\text{H}_{29}\text{F}_4\text{N}_5\text{O}_2\text{S}$ requires 635.

5 **Example 29 — 1-(4-(4-Fluorophenyl)benzylaminocarbonylmethyl)-2-(4-trifluoromethylbenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one**



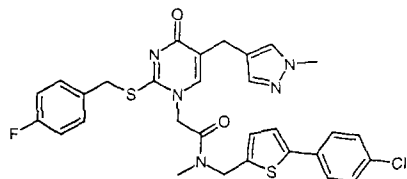
Prepared from Intermediates A16 and B27 by the method of Example 1. $^1\text{H-NMR}$ (DMSO) δ 3.38 (2H, m), 3.76 (3H, s), 4.36 (2H,d), 4.42 (2H,s), 4.65 (2H,s), 7.13 (2H,t), 7.25 (1H,s), 7.37 (2H, m), 7.47 (4H,m), 7.62 (2H,m), 7.83 (4H,m), 9.85 (1H,br t); MS (APCI+) found (M+1) = 622; $\text{C}_{32}\text{H}_{27}\text{F}_4\text{N}_5\text{O}_2\text{S}$ requires 621.

10 **Example 30 — 1-(N-Methyl-N-(5-(4-fluorophenyl)thien-2-ylmethyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one**



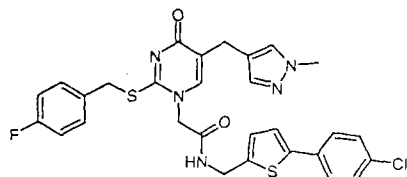
15 Prepared from Intermediates A18 and B27 by the method of Example 1. $^1\text{H-NMR}$ (CDCl_3) δ 2.95-3.16 (3H, 2xs), 3.60 (2H, s), 3.82 (3H, s), 4.40-4.75 (6H, m), 6.69-7.60 (13H, m); MS (APCI+) found (M+1) = 592; $\text{C}_{30}\text{H}_{27}\text{N}_5\text{O}_2\text{S}_2\text{F}_2$ requires 591.

20 **Example 31 — 1-(N-Methyl-N-(5-(4-chlorophenyl)thien-2-ylmethyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one**



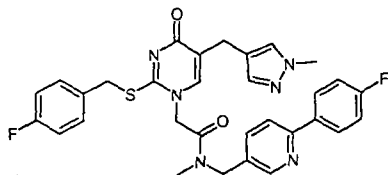
Prepared from Intermediates A30 and B27 by the method of Example 1. White foam. $^1\text{H-NMR}$ (CDCl_3) δ 2.95-3.15 (3H, 2xs), 3.61 (2H, s), 3.84 (3H, s), 4.44-4.74 (6H, m), 6.73-7.58 (13H, m). No molecular ion seen.

25 **Example 32 — 1-(5-(4-Chlorophenyl)thien-2-ylmethylaminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one**



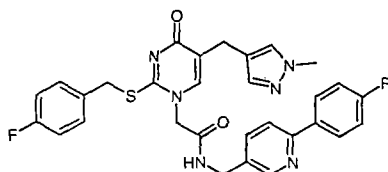
Prepared from Intermediates A33 and B27 by the method of Example 1. Pale yellow solid. $^1\text{H-NMR}$ (CDCl_3) δ 3.50 (2H, s), 3.79 (3H, s), 4.36 (2H, s), 4.41 (2H, s), 4.54-4.67 (2H, d), 6.78-7.48 (13H, m). No molecular ion seen.

Example 33 — 1-(N-Methyl-N-(2-(4-fluorophenyl)pyrid-5-ylmethyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one



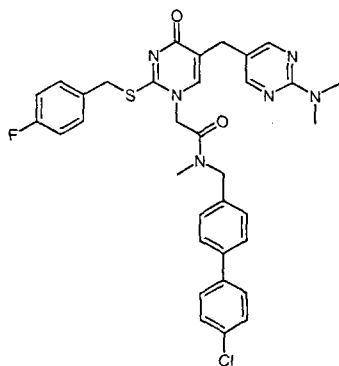
Prepared from Intermediates A22 and B27 by the method of Example 1. $^1\text{H-NMR}$ (CDCl_3) δ 2.90-3.10 (3H, m), 3.62 (2H, s), 3.85 (3H, s), 4.42-4.68 (6H, m), 6.70-6.82 (1H, m), 6.90-7.08 (2H, m), 7.08-7.43 (6H, m), 7.50-7.70 (2H, m), 7.86-8.02 (2H, m), 8.52 (1H, s); MS (APCI+) found (M+1) = 587; $\text{C}_{31}\text{H}_{28}\text{N}_6\text{O}_2\text{SF}_2$ requires 586

Example 34 — 1-(2-(4-Fluorophenyl)pyrid-5-ylmethylaminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one



Prepared from Intermediates A24 and B27 by the method of Example 1. $^1\text{H-NMR}$ (DMSO) δ 8.86 (1H, t), 8.55 (1H, s), 8.11 (2H, m), 7.84 (1H, d), 7.73 (1H, m), 7.46 (4H, m), 7.33 (2H, t), 7.24 (1H, s), 7.11 (2H, t), 4.64 (2H, s), 4.40 (2H, s), 4.36 (2H, d), 3.76 (3H, s), 3.37 (2H, s); MS(APCI+) found (M+1) = 573, $\text{C}_{30}\text{H}_{26}\text{F}_2\text{N}_6\text{O}_2\text{S}$ requires 572.

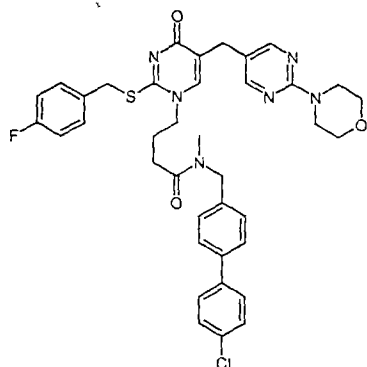
Example 35 — 1-(N-Methyl-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-dimethylaminopyrimid-5-ylmethyl)pyrimidin-4-one



Prepared from Intermediates A6 and B56 by the method of Example 13. $^1\text{H NMR}$ (DMSO-d_6) δ : 2.95 (d, 3H), 3.08 (s, 6H), 3.39 (d, 2H), 4.40 (d, 2H), 4.59 (d, 2H), 4.95 (d, 2H), 7.1 (m, 2H), 7.30 (d, 2H), 7.35-7.6 (m, 6H), 7.65 (m, 3H), 8.24 (s, 2H). MS (APCI+) Found (M+1) = 643/645; $\text{C}_{34}\text{H}_{32}\text{ClFN}_6\text{O}_2\text{S}$ requires 643.

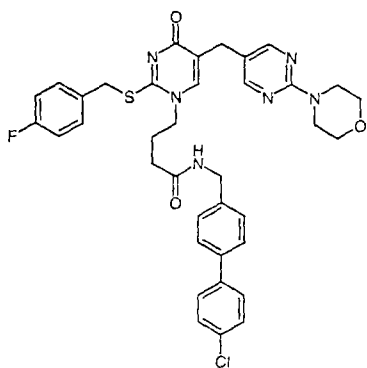
135 133
M

Example 36 — 1-(3-(N-Methyl-N-(4-(4-chlorophenyl)benzyl)aminocarbonyl)prop-1-yl)-2-(4-fluorobenzyl)thio-5-(2-(1-morpholino)pyrimid-5-ylmethyl)pyrimidin-4-one



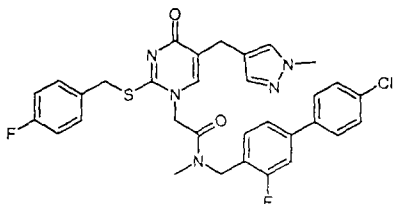
Prepared from Intermediates A2 and B52 by the method of Example 1. $^1\text{H-NMR}$ (CDCl_3) δ 2.08 (2H, m), 2.38 (2H, m), 2.89, 2.99 (3H, 2xs), 3.53 (2H, s), 3.75 (8H, bs), 3.89 (2H, m), 4.45 (2H, m), 4.49, 4.58 (2H, 2xs), 6.97-7.51 (13H, m), 8.26 (2H, m). MS (AP+) Found $M+1 = 713$; $\text{C}_{38}\text{H}_{38}\text{ClFN}_6\text{O}_3\text{S}$ requires 712 (Colourless solid)

Example 37 — 1-(3-(4-(4-Chlorophenyl)benzylaminocarbonyl)prop-1-yl)-2-(4-fluorobenzyl)thio-5-(2-(1-morpholino)pyrimid-5-ylmethyl)pyrimidin-4-one



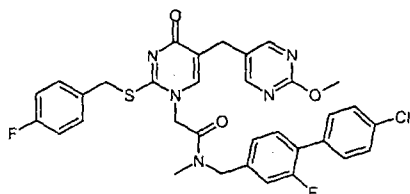
Prepared from Intermediates A5 and B52 by the method of Example 1. $^1\text{H-NMR}$ (CDCl_3) δ 2.06 (2H, m), 2.23 (2H, t), 3.52 (2H, s), 3.75 (8H, m), 3.88 (2H, t), 4.46 (4H, m), 5.75 (1H, bt), 6.98 (3H, m), 7.31-7.53 (10H, m), 8.26 (2H, m). MS (AP+) Found $M+1 = 699$; $\text{C}_{37}\text{H}_{36}\text{ClFN}_6\text{O}_3\text{S}$ requires 698 (Colourless solid).

Example 38 — 1-(N-Methyl-N-(4-(4-chlorophenyl)-2-fluorobenzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one



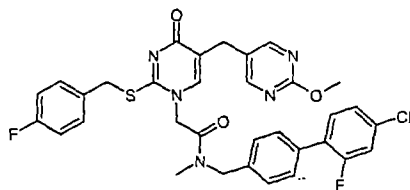
Prepared from Intermediates A34 and B27 by the method of Example 1. $^1\text{H-NMR}$ (CDCl_3) δ 3.02 (3H, s), 3.61 (2H, s), 3.86 (3H, s), 4.44-4.66 (6H, m), 6.77 (1H, m), 6.9 (2H, m), 7.1-7.5 (11H, m); MS (APCI+) found $(M+1) = 620/622$; $\text{C}_{32}\text{H}_{28}\text{ClF}_2\text{N}_5\text{O}_2\text{S}$ requires 619/621.

Example 39 — 1-(N-Methyl-N-(4-(4-chlorophenyl)-3-fluorobenzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxypyrimid-5-ylmethyl)pyrimidin-4-one



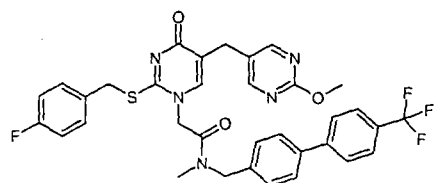
Prepared from Intermediates A37 and B16 by the method of Example 1. $^1\text{H-NMR}$ ($\text{d}_6\text{-DMSO}$) δ 2.88 and 2.99 (3H, 2xs), 3.54 (2H, s), 3.88 (3H, s), 4.38 and 4.41 (2H, 2xs), 4.57 and 4.65 (2H, 2xs), 4.94 and 4.99 (2H, 2xs), 7.07-7.26 (4H, m), 7.41-7.55 (8H, m), 8.50 (2H, s); MS (APCI+) found $(\text{M}+1) = 648$; $\text{C}_{33}\text{H}_{28}\text{F}_2\text{ClN}_5\text{O}_3\text{S}$ requires 647.

Example 40 — 1-(N-Methyl-N-(4-(2-fluoro-4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxypyrimid-5-ylmethyl)pyrimidin-4-one



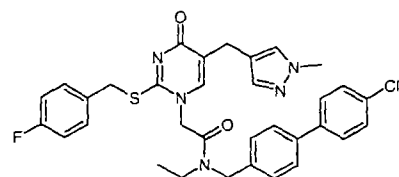
Prepared from Intermediates A39 and B16 by the method of Example 1. $^1\text{H-NMR}$ ($\text{d}_6\text{-DMSO}$) δ 2.87 and 2.97 (3H, 2xs), 3.54 (2H, s), 3.88 (3H, s), 4.37 and 4.42 (2H, 2xs), 4.57 and 4.65 (2H, 2xs), 4.96 (2H, m), 7.06-7.16 (2H, m), 7.30-7.59 (10H, m), 8.49 (2H, s); MS (APCI+) found $(\text{M}+1) = 648$; $\text{C}_{33}\text{H}_{28}\text{F}_2\text{ClN}_5\text{O}_3\text{S}$ requires 647.

Example 41 — 1-(N-Methyl-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxypyrimid-5-ylmethyl)pyrimidin-4-one



Prepared from Intermediates A13 and B16 by the method of Example 1. White solid. $^1\text{H-NMR}$ (CDCl_3) δ 2.94-3.15 (3H, 2xs), 3.62-3.73 (2H, 2xs), 3.95-4.04 (3H, 2xs), 4.43-4.72 (6H, m), 6.73-6.87 (1H, 2xs), 6.88-7.05 (2H, m), 7.22-7.78 (10H, m), 8.40-8.50 (2H, d); MS (APCI+) found $(\text{M}+1) = 664$; $\text{C}_{34}\text{H}_{29}\text{N}_5\text{O}_3\text{SF}_4$ requires 663.

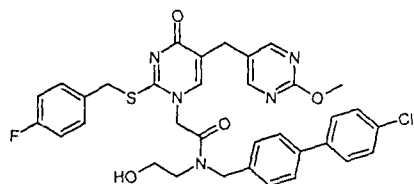
Example 42 — 1-(N-Ethyl-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one



136, 34

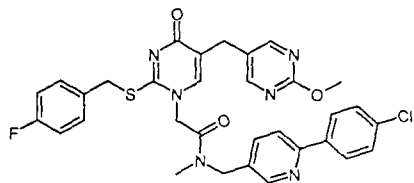
Prepared from Intermediates A40 and B27 by the method of Example 1. Solid. $^1\text{H-NMR}$ (CDCl_3) δ 1.12-1.30 (3H, t), 3.20-3.68 (4H, m), 3.82-3.92 (3H, d), 4.37-4.67 (6H, m), 6.70-7.04 (3H, m), 7.19-7.58 (12, m); MS (APCI+) found $(\text{M}+1) = 616$; $\text{C}_{33}\text{H}_{31}\text{N}_5\text{O}_2\text{SFCl}$ requires 615.

Example 43 — 1-(N-(2-Hydroxyethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxypyrimid-5-ylmethyl)pyrimidin-4-one



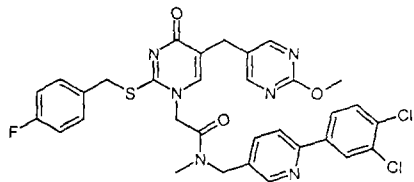
Prepared from Intermediates A41 and B16 by the method of Example 1. Solid. $^1\text{H-NMR}$ (CDCl_3) δ 3.32-3.43 (2H, br.t), 3.60 (2H, s), 3.71-3.87 (2H, br.t), 3.94 (3H, s), 4.37-4.70 (4H, m), 4.87 (2H, s), 6.83-7.03 (3H, m), 7.19-7.52 (10H, m), 8.37-8.48 (2H, d); MS (APCI+) found $(\text{M}+1) = 660$; $\text{C}_{34}\text{H}_{31}\text{ClFN}_5\text{O}_4\text{S}$ requires 659.

Example 44 — 1-(N-Methyl-N-(2-(4-chlorophenyl)pyrid-5-methyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxypyrimid-5-ylmethyl)pyrimidin-4-one



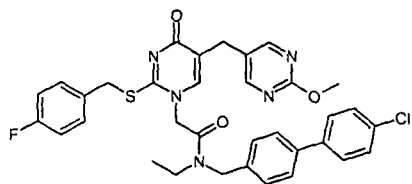
Prepared from Intermediates A28 and B16 by the method of Example 1. $^1\text{H-NMR}$ (CDCl_3) δ 3.00 (3H, s), 3.68 (2H, s), 3.99 (3H, s), 4.52 (2H, s), 4.57 (2H, s), 4.62 (2H, s), 6.80 (1H, s), 6.99 (2H, m), 7.36 (2H, m), 7.46 (2H, m), 7.61 (2H, m), 7.91 (2H, m), 8.47 (2H, m), 8.55 (1H, m); MS (APCI+) found $(\text{M}+1) = 631/633$; $\text{C}_{32}\text{H}_{28}\text{ClFN}_6\text{O}_3\text{S}$ requires 630/632.

Example 45 — 1-(N-Methyl-N-(2-(3,4-dichlorophenyl)pyrid-5-methyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxypyrimid-5-ylmethyl)pyrimidin-4-one



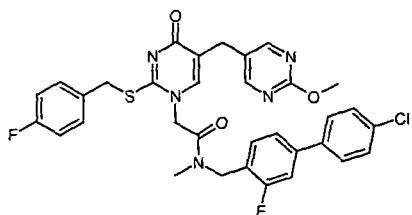
Prepared from Intermediates A45 and B16 by the method of Example 1. $^1\text{H-NMR}$ (CDCl_3) δ 2.9-3.15 (3H, bm), 3.55-3.75 (2H, bm), 3.99 (3H, s), 4.35-4.7 (6H, m), 6.82 (1H, bs), 6.9-7.05 (2H, m), 7.25-7.45 (2H, m), 7.5-7.72 (3H, m), 7.72-7.9 (1H, m), 8.05-8.2 (1H, m), 8.4-8.5 (2H, m), 8.5-8.6 (1H, m), MS (APCI+) found $(\text{M}+1) = 665$; $\text{C}_{32}\text{H}_{27}\text{Cl}_2\text{FN}_6\text{O}_3\text{S}$ requires 664.

Example 46 — 1-(N-Ethyl-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxypyrimid-5-ylmethyl)pyrimidin-4-one



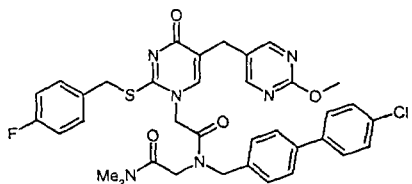
Prepared from Intermediates A40 and B16 by the method of Example 1. Solid. $^1\text{H-NMR}$ (CDCl_3) δ 1.15-1.31 (3H, t), 3.20-3.62 (2H, 2xq), 3.63-3.73 (2H, d), 3.94-4.04 (3H, s), 4.38-4.69 (6H, m), 6.75-7.08 (3H, m), 7.20-7.55 (10H, m), 8.39-8.50 (2H, d); MS (APCI+) found (M+1) = 644; $\text{C}_{34}\text{H}_{31}\text{ClFN}_5\text{O}_3\text{S}$ requires 643.

Example 47 — 1-(N-Methyl-N-(4-(4-chlorophenyl)-2-fluorobenzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxypyrimid-5-ylmethyl)pyrimidin-4-one



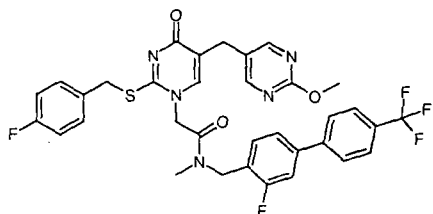
Prepared from Intermediates A35 and B16 by the method of Example 1. White solid. $^1\text{H-NMR}$ (CDCl_3) δ 3.03 (3H, s), 3.67 (2H, s), 4.00 (3H, s), 4.42-4.74 (6H, m), 6.81 (1H, s), 6.89-7.05 (2H, m), 7.16-7.54 (9H, m), 8.45 (2H, s); MS (APCI+) found (M+1) = 648; $\text{C}_{33}\text{H}_{28}\text{ClF}_2\text{N}_5\text{O}_3\text{S}$ requires 647.

Example 48 — 1-(N-(Dimethylaminocarbonylmethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxypyrimid-5-ylmethyl)pyrimidin-4-one



Prepared from Intermediates A46 and B16 by the method of Example 1. White solid. $^1\text{H-NMR}$ (CDCl_3) δ 2.85-3.04 (6H, m), 3.58-3.72 (2H, 2xs), 4.0 (3H, s), 4.17-4.75 (8H, m), 6.85-7.07 (3H, m), 7.21-7.57 (10H, m), 8.40-8.51 (2H, m); MS (APCI+) found (M+1) = 701; $\text{C}_{36}\text{H}_{34}\text{ClFN}_6\text{O}_4\text{S}$ requires 700.

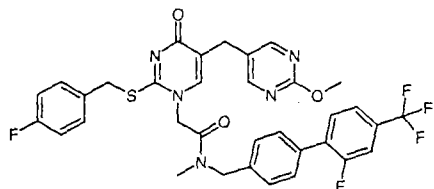
Example 49 — 1-(N-Methyl-N-(4-(4-trifluoromethylphenyl)-2-fluorobenzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxypyrimid-5-ylmethyl)pyrimidin-4-one



1375

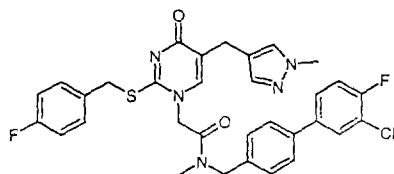
Prepared from Intermediates A61 and B16 by the method of Example 1. White solid. $^1\text{H-NMR}$ (CDCl_3) δ 3.03 (3H, s), 3.66 (2H, s), 3.96 (3H, s), 4.42-4.75 (6H, m), 6.80-7.03 (3H, m), 7.21-7.45 (5H, m), 7.56-7.79 (4H, m), 8.44 (2H, s); MS (APCI+) found $(\text{M}+1) = 682$; $\text{C}_{34}\text{H}_{28}\text{F}_5\text{N}_5\text{O}_3\text{S}$ requires 681.

Example 50 — 1-(N-Methyl-N-(4-(2-fluoro-4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxypyrimidin-5-ylmethyl)pyrimidin-4-one



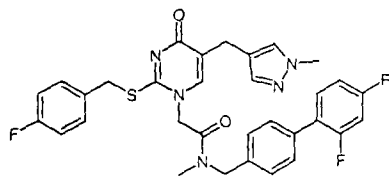
Prepared from Intermediates A59 and B16 by the method of Example 1. $^1\text{H-NMR}$ ($\text{d}_6\text{-DMSO}$) δ 2.89 and 2.99 (3H, 2xs), 3.53 and 3.54 (2H, 2xs), 3.88 (3H, s), 4.37 and 4.42 (2H, 2xs), 4.59 and 4.67 (2H, 2xs), 4.94 and 4.98 (2H, 2xs), 7.10-7.14 (2H, m), 7.35-7.56 (7H, m), 7.69-7.82 (3H, m), 8.50 (2H, s); MS (APCI+) found $(\text{M}+1) = 682$; $\text{C}_{34}\text{H}_{28}\text{F}_5\text{N}_5\text{O}_3\text{S}$ requires 681.

Example 51 — 1-(N-Methyl-N-(4-(3-chloro-4-fluorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one



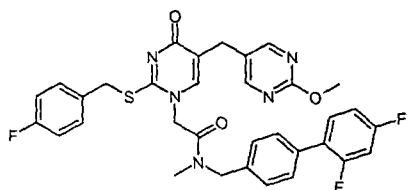
Prepared from Intermediates A63 and B27 by the method of Example 1. $^1\text{H-NMR}$ (CDCl_3) δ 2.95 and 3.08 (3H, 2xs), 3.60 and 3.62 (2H, 2xs), 3.85 and 3.87 (3H, 2xs), 4.47-4.61 (6H, m), 6.74 and 6.81 (1H, 2xs), 6.98 (2H, m), 7.2-7.5 (10H, m), 7.55-7.6 (1H, m); MS (APCI+) found $(\text{M}+1) = 620/622$; $\text{C}_{32}\text{H}_{28}\text{ClF}_2\text{N}_5\text{O}_2\text{S}$ requires 619/621.

Example 52 — 1-(N-Methyl-N-(4-(2,4-difluorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one



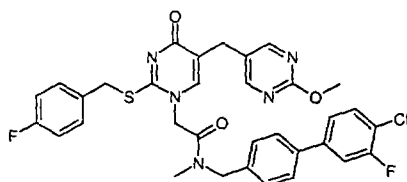
Prepared from Intermediates A65 and B27 by the method of Example 1. $^1\text{H-NMR}$ (CDCl_3) δ 2.96 and 3.09 (3H, 2xs), 3.60 and 3.62 (2H, 2xs), 3.85 and 3.86 (3H, 2xs), 4.45-4.62 (6H, m), 6.75 and 6.81 (1H, 2xs), 6.9-7.0 (4H, m), 7.20-7.45 (8H, m); MS (APCI+) found $(\text{M}+1) = 604$; $\text{C}_{32}\text{H}_{28}\text{F}_3\text{N}_5\text{O}_2\text{S}$ requires 603.

Example 53 — 1-(N-Methyl-N-(4-(2,4-difluorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxypyrimid-5-ylmethyl)pyrimidin-4-one



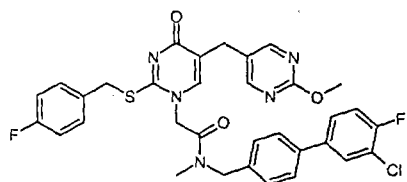
Prepared from Intermediates A65 and B16 by the method of Example 1. ¹H-NMR (CDCl₃) δ 2.98 and 3.10 (3H,2xs), 3.6-3.7 (2H,m), 3.98 and 3.99 (3H,2xs), 4.45-4.62 (6H,m), 6.75-7.0 (5H,m), 7.25-7.45 (6H,m), 8.45 and 8.47 (2H,2xs); MS (APCI+) found (M+1) = 632; C₃₃H₂₈F₃N₅O₃S requires 631.

Example 54 — 1-(N-Methyl-N-(4-(4-chloro-3-fluorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxypyrimid-5-ylmethyl)pyrimidin-4-one



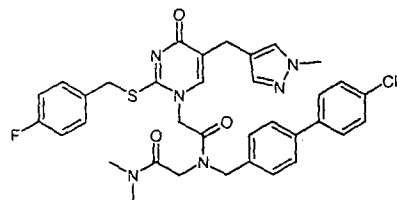
Prepared from Intermediates A51 and B16 by the method of Example 1. ¹H-NMR (CDCl₃) δ 2.96 and 3.09 (3H,2xs), 3.65 and 3.68 (2H,2xs), 3.98 and 3.99 (3H,2xs), 4.45-4.61 (6H,m), 6.79 and 6.85 (1H,2xs), 6.93-7.01 (2H,m), 7.2-7.45 (8H,m), 7.55-7.6 (1H,m), 8.44 and 8.46 (2H,2xs), MS (APCI+) found (M+1) = 648; C₃₃H₂₈ClF₂N₅O₃S requires 647.

Example 55 — 1-(N-Methyl-N-(4-(3-chloro-4-fluorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxypyrimid-5-ylmethyl)pyrimidin-4-one



Prepared from Intermediates A63 and B16 by the method of Example 1. ¹H-NMR (CDCl₃) δ 2.97 and 3.09 (3H,2xs), 3.6-3.7 (2H,m), 3.98 and 3.99 (3H,2xs), 4.45-4.62 (6H,m), 6.74 and 6.81 (1H,2xs), 6.98 (2H,m), 7.2-7.5 (10H,m), 7.55-7.6 (1H,m); MS (APCI+) found (M+1) = 604; C₃₂H₂₈F₃N₅O₂S requires 603.

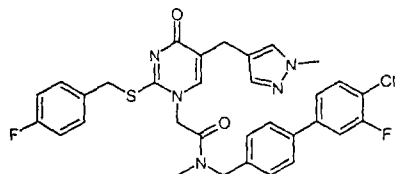
Example 56 — 1-(N-(Dimethylaminocarbonylmethyl)l-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one



136

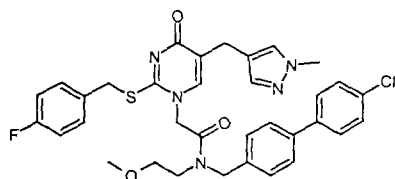
Prepared from Intermediates A46 and B27 by the method of Example 1. Pale green solid. $^1\text{H-NMR}$ (CDCl_3) δ 2.85-3.06 (6H, 2xs), 3.53-4.73 (13H, m), 6.80-7.05 (3H, m), 7.20-7.53 (12H, m); MS (APCI+) found $(\text{M}+1) = 673$; $\text{C}_{35}\text{H}_{34}\text{ClFN}_6\text{O}_3\text{S}$ requires 672.

5 **Example 57 — 1-(N-Methyl-N-(4-(4-chloro-3-fluorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one**



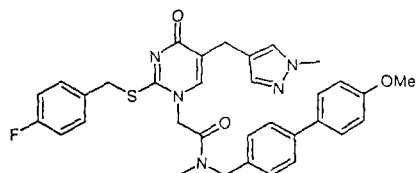
Prepared from Intermediates A51 and B27 by the method of Example 1. $^1\text{H-NMR}$ (CDCl_3) δ 2.96 and 3.08 (3H, 2xs), 3.55-3.65 (2H, m), 3.85 and 3.86 (3H, 2xs), 4.45-4.62 (6H, m), 6.7-7.05 (3H, m), 7.15-7.55 (11H, m), MS (APCI+) found $(\text{M}+1) = 620$; $\text{C}_{32}\text{H}_{28}\text{ClF}_2\text{N}_5\text{O}_2\text{S}$ requires 619.

10 **Example 58 — 1-(N-(2-Methoxyethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one**



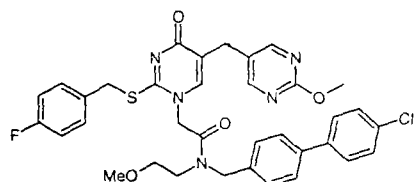
15 Prepared from Intermediates A48 and B27 by the method of Example 1. White solid. $^1\text{H-NMR}$ (CDCl_3) δ 3.19-3.37 (3H, 2xs), 3.43 (3H, s), 3.55-3.64 (2H, m), 3.86 (3H, s), 4.40-4.59 (3H, 2xs), 4.65 (2H, s), 4.77 (2H, s), 6.70-7.07 (3H, m), 7.20-7.55 (12H, m); MS (APCI+) found $(\text{M}+1) = 646$; $\text{C}_{34}\text{H}_{33}\text{ClFN}_5\text{O}_3\text{S}$ requires 645.

Example 59 — 1-(N-Methyl-N-(4-(4-methoxyphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one



20 Prepared from Intermediates A53 and B27 by the method of Example 1. $^1\text{H-NMR}$ (CDCl_3) δ 7.00-7.49 (10H, m), 6.98 (4H, m), 6.80 (1H, s), 4.46-4.60 (6H, m), 3.86 (6H, m), 3.59 (2H, s), 2.94 (2H, s); MS(APCI+) found $(\text{M}+1) = 598$, $\text{C}_{33}\text{H}_{32}\text{FN}_5\text{O}_3\text{S}$ requires 597; Mpt: 177°C.

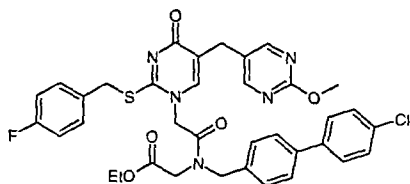
Example 60 — 1-(N-(2-Methoxyethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxypyrimid-5-ylmethyl)pyrimidin-4-one



25

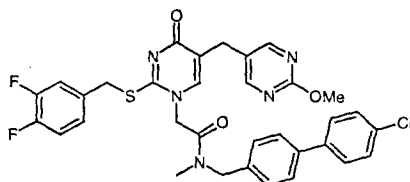
Prepared from Intermediates A48 and B16 by the method of Example 1. White solid. $^1\text{H-NMR}$ (CDCl_3) δ 3.20-3.73 (8H, m), 3.98 (3H, s), 4.41-4.55 (3H, m), 4.64-4.85 (4H, 2xs), 6.75-6.85 (1H, 2xs), 6.87-7.06 (2H, m), 7.20-7.53 (10H, m), 8.40-8.50 (2H, m); MS (APCI+) found (M+1) = 674; $\text{C}_{35}\text{H}_{33}\text{ClFN}_5\text{O}_4\text{S}$ requires 673.

5 **Example 61** — 1-(N-(Ethoxycarbonylmethyl)-N-(4-(4-chlorophenyl)benzyl)amino-carbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxypyrimid-5-ylmethyl)pyrimidin-4-one



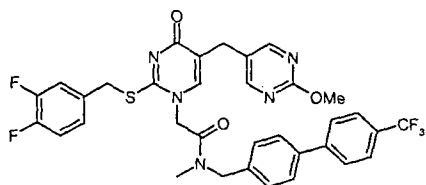
10 Prepared from Intermediates A47 and B16 by the method of Example 1. Pale green solid. $^1\text{H-NMR}$ (CDCl_3) δ 1.16-1.30 (3H, t), 3.60-3.70 (2H, 2xs), 3.91-4.30 (7H, m), 4.40-4.72 (6H, m), 6.85-7.05 (3H, m), 7.20-7.53 (10H, m), 8.42-8.50 (2H, 2xs); MS (APCI+) found (M+1) = 702; $\text{C}_{36}\text{H}_{33}\text{ClFN}_5\text{O}_5\text{S}$ requires 701.

Example 62 — 1-(N-Methyl-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(3,4-difluorobenzyl)thio-5-(2-methoxypyrimid-5-ylmethyl)pyrimidin-4-one



15 Prepared from Intermediates A2 and B62 by the method of Example 1. $^1\text{H-NMR}$ (CDCl_3) δ 8.46 (2H, s), 7.00-7.51 (11H, m), 6.82 (2H, s), 4.42-4.62 (6H, m), 3.98 (3H, s), 3.68 (2H, s), 2.98 (3H, s); MS (APCI+) found (M+1) = 648, $\text{C}_{33}\text{H}_{28}^{35}\text{ClF}_2\text{N}_5\text{O}_3\text{S}$ requires 647; Mpt: 188°C.

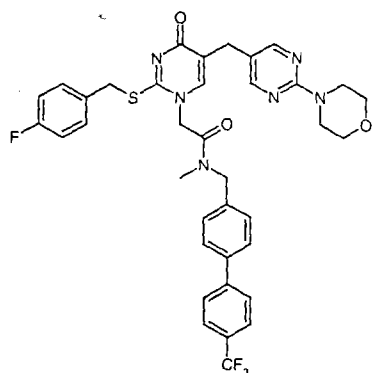
Example 63 — 1-(N-Methyl-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(3,4-difluorobenzyl)thio-5-(2-methoxypyrimid-5-ylmethyl)pyrimidin-4-one



20 Prepared from Intermediates A13 and B62 by the method of Example 1. $^1\text{H-NMR}$ (CDCl_3) δ 8.46 (2H, s), 7.06-7.71 (11H, m), 8.83 (1H, s), 4.43-4.63 (6H, m), 3.98 (3H, s), 3.68 (2H, s), 2.99 (3H, s); MS (APCI+) found (M+1) = 682, $\text{C}_{34}\text{H}_{28}\text{F}_5\text{N}_5\text{O}_3\text{S}$ requires 681; Mpt: 210°C.

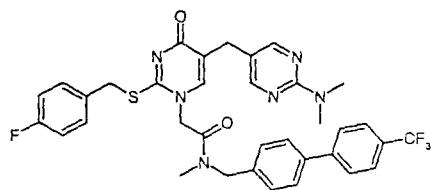
137

Example 64 — 1-(N-Methyl-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-(1-morpholino)pyrimid-5-ylmethyl)pyrimidin-4-one



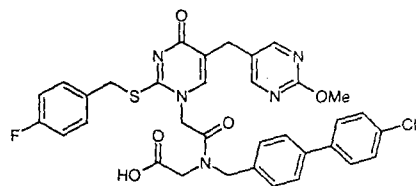
Prepared from Intermediates A13 and B64 by the method of Example 1. ¹H NMR (DMSO-d₆) δ: 2.93 (d, 3H), 3.42 (s, 2H), 3.64 (s, 8H), 4.40 (d, 2H), 4.61 (d, 2H), 4.96 (d, 2H), 7.14 (m, 2H), 7.36 (d, 1H), 7.4 (m, 1H), 7.5 (m, 1H), 7.53 (s, 1H), 7.63 (d, 2H), 7.69 (d, 1H), 7.85 (m, 4H), 8.30 (s, 2H). MS (ES+) Found (M+1) = 719; C₃₇H₃₄F₄N₆O₃S requires 718.

Example 65 — 1-(N-Methyl-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-dimethylaminopyrimid-5-ylmethyl)pyrimidin-4-one



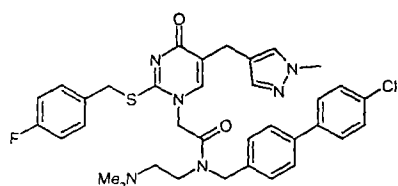
Prepared from Intermediates A13 and B66 by the method of Example 1. ¹H NMR (DMSO-d₆) δ: 2.93 (d, 3H), 3.08 (s, 6H), 3.40 (s, 2H), 4.40 (d, 2H), 4.61 (d, 2H), 4.95 (d, 2H), 7.14 (m, 2H), 7.35-7.55 (m, 6H), 7.6-7.75 (m, 2H), 7.84 (m, 3H), 8.24 (s, 2H). MS (ES+) Found (M+1) = 677; C₃₅H₃₂F₄N₆O₂S requires 676.

Example 66 — 1-(N-(Carboxymethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxypyrimid-5-ylmethyl)pyrimidin-4-one, sodium salt



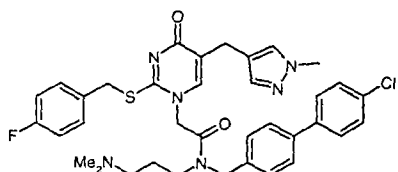
A solution of Example 61 (290 mg) in dioxan (2 ml) was treated with sodium hydroxide (16 mg) in water (1.6 ml) and the mixture was stirred overnight. After evaporation of the dioxan, the residue was taken up in water and washed with ethyl acetate. The aqueous layer was acidified to pH 3 with sodium bisulfate, and the precipitated acid filtered off, washed with water and dried (120 mg). This material was dissolved in aqueous sodium bicarbonate (1 equiv) with stirring and gently warming. Filtration and lyophilisation yielded the sodium salt as a white solid (86 mg). ¹H-NMR (DMSO) δ 3.47-3.58 (4H, 2xs), 3.89 (3H, s), 4.32-4.53 (4H, m), 4.85 (2H, s), 7.08-7.20 (2H, t), 7.25-7.73 (11H, m), 8.45-8.52 (2H, 2xs); MS (APCI+) found (M+1) = 673; C₃₄H₂₈ClFN₅NaO₅SF requires 672.

Example 67 — 1-(N-(2-Dimethylaminoethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one hydrochloride



Prepared from Intermediates A66 and B27 by the method of Example 1. $^1\text{H-NMR}$ (CDCl_3) δ 2.95 (3H, s), 2.96 (3H, s), 3.19 (2H, m), 3.58 (2H, s), 3.87 (3H, s), 3.91 (2H, m), 4.42 (2H, s), 4.68 (2H, s), 4.99 (2H, s), 6.88-6.93 (2H, m), 7.25-7.29 (6H, m), 7.36-7.45 (6H, m) 7.62 (1H, s); MS (APCI+) found (M+1) = 659; $\text{C}_{35}\text{H}_{36}\text{ClFN}_6\text{O}_2\text{S}$ requires 658.

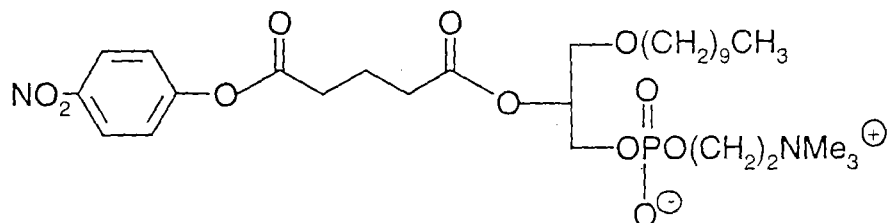
Example 68 — 1-(N-(3-Dimethylaminopropyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one hydrochloride



Prepared from Intermediates A67 and B27 by the method of Example 1. $^1\text{H-NMR}$ (CDCl_3) δ 2.13 and 2.25 (2H, 2xbr. m), 2.76 (3H, s), 2.77 (3H, s), 3.07 and 3.21 (2H, 2xbr. m), 3.49-3.96 (7H, m), 4.44 and 4.47 (2H, 2xs), 4.65 and 4.69 (2H, 2xs), 4.87 (2H, s), 6.90-6.94 (2H, m), 7.26-7.32 (6H, m), 7.42-7.63 (7H, m); MS (APCI+) found (M+1) = 673; $\text{C}_{36}\text{H}_{38}\text{ClFN}_6\text{O}_2\text{S}$ requires 672.

Biological Data**1. Screen for Lp-PLA₂ inhibition.**

- 5 Enzyme activity was determined by measuring the rate of turnover of the artificial substrate (A) at 37 °C in 50mM HEPES (N-2-hydroxyethylpiperazine-N'-2-ethanesulphonic acid) buffer containing 150mM NaCl, pH 7.4.



(A)

Assays were performed in 96 well titre plates.

- 15 Recombinant LpPLA₂ was purified to homogeneity from baculovirus infected Sf9 cells, using a zinc chelating column, blue sepharose affinity chromatography and an anion exchange column. Following purification and ultrafiltration, the enzyme was stored at 6mg/ml at 4°C. Assay plates of compound or vehicle plus buffer were set up using automated robotics to a volume of 170µl. The reaction was initiated by the addition of 20µl of 10x substrate (A) to give a final substrate concentration of 20µM and 10 µl of diluted enzyme to a final 0.2nM LpPLA₂.

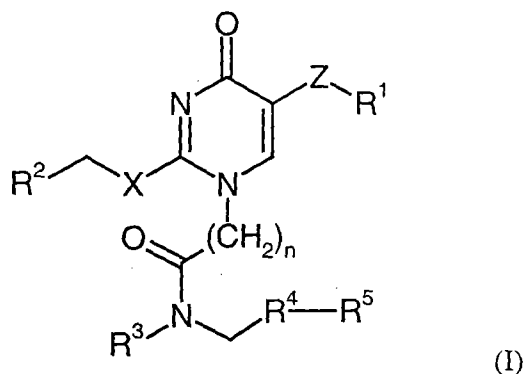
- 20 The reaction was followed at 405 nm and 37 °C for 20 minutes using a plate reader with automatic mixing. The rate of reaction was measured as the rate of change of absorbance.

Results

- 25 The compounds described in Examples 28, 56, 58, 67 and 68 were tested as described above and had respective IC₅₀ values of 0.7, 0.2, 4.5, 0.6 and 0.5 nM.

Claims

1. A compound of formula (I):



in which:

R¹ is an aryl or heteroaryl group, optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from C₍₁₋₁₈₎alkyl, C₍₁₋₁₈₎alkoxy, C₍₁₋₁₈₎alkylthio, arylC₍₁₋₁₈₎alkoxy, hydroxy, halogen, CN, COR⁶, carboxy, COOR⁶, CONR⁶R⁷, NR⁶COR⁷, SO₂NR⁶R⁷, NR⁶SO₂R⁷, NR⁶R⁷, mono to perfluoro-C₍₁₋₄₎alkyl and mono to perfluoro-C₍₁₋₄₎alkoxy, or, as a single substituent, optionally in combination with a further substituent as hereinbefore defined, CH₂COOH or a salt thereof, CH₂COOR⁸, CH₂CONR⁹R¹⁰, CH₂CN, (CH₂)_mNR⁹R¹⁰, (CH₂)_mOH or (CH₂)_mOR⁸ where m is an integer from 1 to 3;

R² is an aryl or heteroaryl group, optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from C₍₁₋₁₈₎alkyl, C₍₁₋₁₈₎alkoxy, C₍₁₋₁₈₎alkylthio, arylC₍₁₋₁₈₎alkoxy, hydroxy, halogen, CN, COR⁶, carboxy, COOR⁶, CONR⁹R¹⁰, NR⁶COR⁷, SO₂NR⁹R¹⁰, NR⁶SO₂R⁷, NR⁹R¹⁰, mono to perfluoro-C₍₁₋₄₎alkyl, mono to perfluoro-C₍₁₋₄₎alkoxyaryl, and arylC₍₁₋₄₎alkyl;

R³ is hydrogen or C₍₁₋₄₎alkyl optionally substituted by hydroxy, OR⁶, COR⁶, carboxy, COOR⁶, CONR⁹R¹⁰, NR⁹R¹⁰;

R⁴ is an aryl or a heteroaryl ring optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from C₍₁₋₁₈₎alkyl, C₍₁₋₁₈₎alkoxy, C₍₁₋₁₈₎alkylthio, arylC₍₁₋₁₈₎alkoxy, hydroxy, halogen, CN, COR⁶, carboxy, COOR⁶, CONR⁹R¹⁰, NR⁶COR⁷, SO₂NR⁹R¹⁰, NR⁶SO₂R⁷, NR⁹R¹⁰, mono to perfluoro-C₍₁₋₄₎alkyl and mono to perfluoro-C₍₁₋₄₎alkoxy;

R⁵ is an aryl ring which is further optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from C₍₁₋₁₈₎alkyl, C₍₁₋₁₈₎alkoxy, C₍₁₋₁₈₎alkylthio, arylC₍₁₋₁₈₎alkoxy, hydroxy, halogen, CN, COR⁶, carboxy, COOR⁶, CONR⁹R¹⁰, NR⁶COR⁷, SO₂NR⁹R¹⁰, NR⁶SO₂R⁷, NR⁹R¹⁰, mono to perfluoro-C₍₁₋₄₎alkyl and mono to perfluoro-C₍₁₋₄₎alkoxy;

R⁶ and R⁷ are independently hydrogen or C₍₁₋₂₀₎alkyl, for instance C₍₁₋₄₎alkyl (e.g. methyl or ethyl);

R⁸ is C₍₁₋₄₎alkyl or a pharmaceutically acceptable *in vivo* hydrolysable ester group;

R⁹ and R¹⁰ which may be the same or different is each selected from hydrogen, C₍₁₋₁₂₎alkyl, CH₂R¹¹, CHR¹²CO₂H or a salt thereof, or R⁹ and R¹⁰ together with the nitrogen to which they are attached form a 5- to 7 membered ring optionally containing one or more further heteroatoms selected from oxygen, nitrogen and sulphur, and optionally substituted by one or two substituents selected from hydroxy, oxo, C₍₁₋₄₎alkyl, C₍₁₋₄₎alkylCO, aryl, e.g. phenyl, or aralkyl, e.g. benzyl, for instance morpholine or piperazine;

R¹¹ is COOH or a salt thereof, COOR⁸, CONR⁶R⁷, CN, CH₂OH or CH₂OR⁶;

1419
131

R^{12} is an amino acid side chain such as CH_2OH from serine;

n is an integer from 1 to 4, preferably 1 or 3;

X is O or S; and

Z is $CR^{13}R^{14}$ where R^{13} and R^{14} are each hydrogen or $C_{(1-4)}$ alkyl, or R^{13} and R^{14} together

5 with the intervening carbon atom form a $C_{(3-6)}$ cycloalkyl ring.

2. A pharmaceutical composition comprising a compound of formula (I) as claimed in claim 1 and a pharmaceutically acceptable carrier.

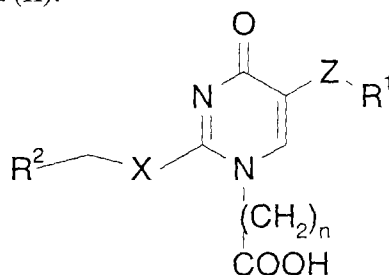
10 3. A compound of formula (I) as claimed in claim 1 for use in therapy.

4. The use of a compound of formula (I) as claimed in claim 1 for the manufacture of a medicament for treating atherosclerosis.

15 5. A method of treating a disease state associated with activity of the enzyme $Lp-PLA_2$ which method involves treating a patient in need thereof with a therapeutically effective amount of a compound of formula (I) as claimed in claim 1.

20 6. A process for preparing a compound of formula (I) as defined in claim 1 which process comprises:

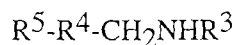
(a) reacting a compound of formula (II):



(II)

in which X , Y , Z , R^1 and R^2 are as hereinbefore defined,

25 with a compound of formula (III):

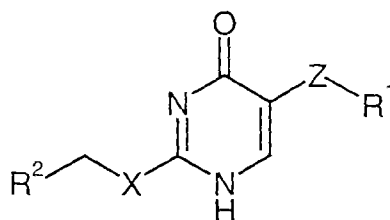


(III)

in which R^3 , R^4 and R^5 are as hereinbefore defined; under amide forming conditions;

30

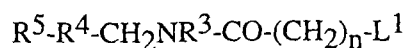
(b) reacting a compound of formula (IV):



(IV)

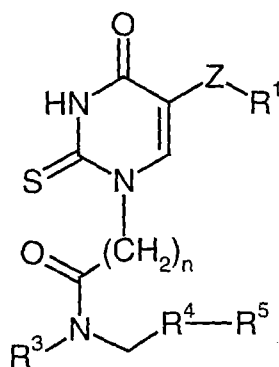
35 in which X , Z , R^1 and R^2 are as hereinbefore defined,

with a compound of formula (V):



(V)

- 5 in which n , R^3 , R^4 and R^5 are as hereinbefore defined, and L^1 is a leaving group such as halogen, for instance bromo or iodo,
in the presence of a base such as a secondary or tertiary amine, for instance di-isopropylethylamine, in an inert solvent such as dichloromethene;
- 10 (c) when X is S, reacting a compound of formula (VI):



(VI)

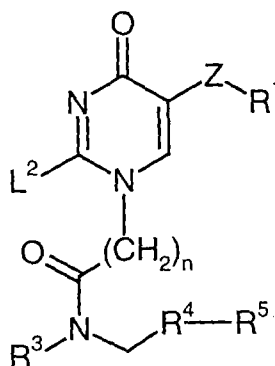
- 15 in which n , Z , R^1 , R^3 , R^4 and R^5 are as hereinbefore defined,
with a compound of formula (VII):



(VII)

- 20 in which R^2 and L^1 are as hereinbefore defined,
in the presence of a base such as a secondary or tertiary amine, for instance di-isopropylethylamine, in an inert solvent such as dichloromethene; or

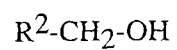
(d) when X is O, reacting a compound of formula (VIII):



(VIII)

- 25 in which n , Z , R^1 , R^3 , R^4 and R^5 are as hereinbefore defined, and L^2 is a leaving group such as halogen or alkylthio, for instance methylthio,
with a compound of formula (IX):

142 405
1 \$



(IX)

in which R^2 is as hereinbefore defined,

- 5 in the presence of a base such as 4-dimethylaminopyridine, in an inert solvent such as pyridine.



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ACC/JR/P32505 31 JAN 00 E509207-1 002029
501/7700 0.02 002029

2. Patent application number

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0002096.6

28 JAN 2000

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

SmithKline Beecham plc
New Horizons Court, Brentford, Middx TW8 9EP.
Great Britain

Patents ADP number (*if you know it*)

7605058001

If the applicant is a corporate body, give the country/state of its incorporation

United Kingdom

4. Title of the invention

Novel Compounds

5. Name of your agent (*if you have one*)

CORPORATE INTELLECTUAL PROPERTY

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

4471231005

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

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

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

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- See note (d)

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Continuation sheets of this form

Description

61

Claim(s)

4

Abstract

Drawings

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Translations of priority documents

Statement of inventorship and right to grant of a patent (*Patents Form 1/77*)

Request for preliminary examination and search (*Patents Form 9/77*)

Request for substantive examination (*Patents Form 10/77*)

Any other documents
(please specify)

11. We request the grant of a patent on the basis of this application
Signature A C Connell Date 27-Jan-00
A C Connell

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A C Connell 01279 644395

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145
143 71

Novel Compounds

The present invention relates to certain novel pyrimidinone compounds, processes for their preparation, intermediates useful in their preparation, pharmaceutical compositions containing them and their use in therapy, in particular in the treatment of atherosclerosis.

WO 95/00649 (SmithKline Beecham plc) describe the phospholipase A₂ enzyme Lipoprotein Associated Phospholipase A₂ (Lp-PLA₂), the sequence, isolation and purification thereof, isolated nucleic acids encoding the enzyme, and recombinant host cells transformed with DNA encoding the enzyme. Suggested therapeutic uses for inhibitors of the enzyme included atherosclerosis, diabetes, rheumatoid arthritis, stroke, myocardial infarction, reperfusion injury and acute and chronic inflammation. A subsequent publication from the same group further describes this enzyme (Tew D *et al*, *Arterioscler Thromb Vas Biol* 1996;16:591-9) wherein it is referred to as LDL-PLA₂. A later patent application (WO 95/09921, Icos Corporation) and a related publication in *Nature* (Tjoelker *et al*, vol 374, 6 April 1995, 549) describe the enzyme PAF-AH which has essentially the same sequence as Lp-PLA₂ and suggest that it may have potential as a therapeutic protein for regulating pathological inflammatory events.

It has been shown that Lp-PLA₂ is responsible for the conversion of phosphatidylcholine to lysophosphatidylcholine, during the conversion of low density lipoprotein (LDL) to its oxidised form. The enzyme is known to hydrolyse the sn-2 ester of the oxidised phosphatidylcholine to give lysophosphatidylcholine and an oxidatively modified fatty acid. Both products of Lp-PLA₂ action are biologically active with lysophosphatidylcholine, a component of oxidised LDL, known to be a potent chemoattractant for circulating monocytes. As such, lysophosphatidylcholine is thought play a significant role in atherosclerosis by being responsible for the accumulation of cells loaded with cholesterol ester in the arteries. Inhibition of the Lp-PLA₂ enzyme would therefore be expected to stop the build up of these macrophage enriched lesions (by inhibition of the formation of lysophosphatidylcholine and oxidised free fatty acids) and so be useful in the treatment of atherosclerosis.

The increased lysophosphatidylcholine content of oxidatively modified LDL is also thought to be responsible for the endothelial dysfunction observed in patients with atherosclerosis. Inhibitors of Lp-PLA₂ could therefore prove beneficial in the treatment of this phenomenon. An Lp-PLA₂ inhibitor could also find utility in other disease states that exhibit endothelial dysfunction including diabetes, hypertension, angina pectoris and after ischaemia and reperfusion.

In addition, Lp-PLA₂ inhibitors may also have a general application in any disorder that involves activated monocytes, macrophages or lymphocytes, as all of these cell types express Lp-PLA₂. Examples of such disorders include psoriasis.

Furthermore, Lp-PLA₂ inhibitors may also have a general application in any disorder that involves lipid peroxidation in conjunction with Lp-PLA₂ activity to produce the two injurious products, lysophosphatidylcholine and oxidatively modified fatty acids. Such conditions include the aforementioned conditions atherosclerosis, diabetes, rheumatoid arthritis, stroke, myocardial infarction.

reperfusion injury and acute and chronic inflammation. Further such conditions include various neuropsychiatric disorders such as schizophrenia (see Psychopharmacology Bulletin, 31, 159-165, 1995).

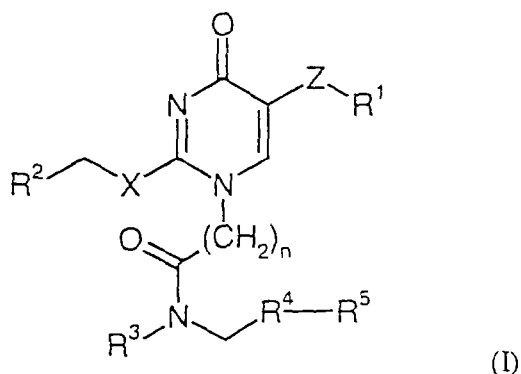
Patent applications WO 96/12963, WO 96/13484, WO96/19451, WO 97/02242, WO97/217675,

5 WO97/217676, WO 96/41098, and WO97/41099 (SmithKline Beecham plc) disclose *inter alia* various series of 4-thionyl/sulfinyl/sulfonyl azetidinone compounds which are inhibitors of the enzyme Lp-PLA₂. These are irreversible, acylating inhibitors (Tew *et al*, Biochemistry, 37, 10087, 1998).

A new class of compounds has now been identified which are inhibitors of the enzyme Lp-PLA₂.

10

Accordingly, the present invention provides a compound of formula (I):



in which:

15 R^1 is an aryl or heteroaryl group, optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from C₍₁₋₁₈₎alkyl, C₍₁₋₁₈₎alkoxy, C₍₁₋₁₈₎alkylthio, arylC₍₁₋₁₈₎alkoxy, hydroxy, halogen, CN, COR⁶, carboxy, COOR⁶, CONR⁹R¹⁰, NR⁶COR⁷, SO₂NR⁹R¹⁰, NR⁶SO₂R⁷, NR⁹R¹⁰, mono to perfluoro-C₍₁₋₄₎alkyl and mono to perfluoro-C₍₁₋₄₎alkoxy, or, as a single substituent, optionally in combination with a further substituent as hereinbefore defined, CH₂COOH or a salt thereof,
20 CH₂COOR⁸, CH₂CONR⁹R¹⁰, CH₂CN, (CH₂)_mNR⁹R¹⁰, (CH₂)_mOH or (CH₂)_mOR⁶ where m is an integer from 1 to 3;

R^2 is an aryl or heteroaryl group, optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from C₍₁₋₁₈₎alkyl, C₍₁₋₁₈₎alkoxy, C₍₁₋₁₈₎alkylthio, arylC₍₁₋₁₈₎alkoxy, hydroxy, halogen, CN, COR⁶, carboxy, COOR⁶, CONR⁹R¹⁰, NR⁶COR⁷, SO₂NR⁹R¹⁰, NR⁶SO₂R⁷,
25 NR⁹R¹⁰, mono to perfluoro-C₍₁₋₄₎alkyl, mono to perfluoro-C₍₁₋₄₎alkoxyaryl, and arylC₍₁₋₄₎alkyl;

R^3 is hydrogen or C₍₁₋₄₎alkyl which may be unsubstituted or substituted by hydroxy, OR⁶, COR⁶, carboxy, COOR⁶, CONR⁹R¹⁰, NR⁹R¹⁰, mono- or di-(hydroxyC₍₁₋₆₎alkyl)amino or N-hydroxyC₍₁₋₆₎alkyl-N-C₍₁₋₆₎alkyl amino;

R^4 is an aryl or a heteroaryl ring optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from C₍₁₋₁₈₎alkyl, C₍₁₋₁₈₎alkoxy, C₍₁₋₁₈₎alkylthio, arylC₍₁₋₁₈₎alkoxy, hydroxy, halogen, CN, COR⁶, carboxy, COOR⁶, CONR⁹R¹⁰, NR⁶COR⁷, SO₂NR⁹R¹⁰, NR⁶SO₂R⁷,
30 NR⁹R¹⁰, mono to perfluoro-C₍₁₋₄₎alkyl and mono to perfluoro-C₍₁₋₄₎alkoxy;

R^5 is an aryl ring which is further optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from C₍₁₋₁₈₎alkyl, C₍₁₋₁₈₎alkoxy, C₍₁₋₁₈₎alkylthio, arylC₍₁₋₁₈₎alkoxy, hydroxy, halogen, CN, COR⁶, carboxy, COOR⁶, CONR⁹R¹⁰, NR⁶COR⁷, SO₂NR⁹R¹⁰, NR⁶SO₂R⁷,
35 NR⁹R¹⁰, mono to perfluoro-C₍₁₋₄₎alkyl and mono to perfluoro-C₍₁₋₄₎alkoxy;

248
214

R^6 and R^7 are independently hydrogen or $C_{(1-20)}$ alkyl, for instance $C_{(1-4)}$ alkyl (e.g. methyl or ethyl);

R^8 is $C_{(1-4)}$ alkyl or a pharmaceutically acceptable *in vivo* hydrolysable ester group;

R^9 and R^{10} which may be the same or different is each selected from hydrogen, $C_{(1-12)}$ alkyl,

- 5 CH_2R^{11} , $CHR^{12}CO_2H$ or a salt thereof, or R^9 and R^{10} together with the nitrogen to which they are attached form a 4- to 7-, preferably 5- to 7-, membered ring optionally containing one or more further heteroatoms selected from oxygen, nitrogen and sulphur, and optionally substituted by one or two substituents selected from hydroxy, oxo, $C_{(1-4)}$ alkyl, $C_{(1-4)}$ alkylCO, aryl, e.g. phenyl, or aralkyl, e.g. benzyl, for instance morpholine or piperazine;

- 10 R^{11} is $COOH$ or a salt thereof, $COOR^8$, $CONR^6R^7$, CN , CH_2OH or CH_2OR^6 ;

R^{12} is an amino acid side chain such as CH_2OH from serine;

n is an integer from 1 to 4, preferably 1 or 3;

X is O or S; and

- 15 Z is $CR^{13}R^{14}$ where R^{13} and R^{14} are each hydrogen or $C_{(1-4)}$ alkyl, or R^{13} and R^{14} together with the intervening carbon atom form a $C_{(3-6)}$ cycloalkyl ring.

Preferably, Z is CH_2 .

Representative examples of R^1 when an aryl group include phenyl and naphthyl.

- 20 Representative examples of R^1 when a heteroaryl group include a 5- or 6- membered, monocyclic heteroaryl group containing 1 or 2 nitrogen heteroatoms.

- 25 Preferably R^1 is pyrimidyl optionally substituted by 1 or 2 substituents preferably selected from oxo, aryl $C_{(1-4)}$ alkyl (e.g. benzyl), $C_{(1-6)}$ alkyl (e.g. methyl or ethyl), $C_{(3-6)}$ cycloalkyl, hydroxy, $C_{(1-4)}$ alkoxy (e.g. methoxy), carboxy $C_{(1-6)}$ alkyl, $C_{(1-6)}$ alkylcarboxy $C_{(1-6)}$ alkyl, di- $C_{(1-6)}$ alkylamino, and morpholino; or pyrazolyl optionally substituted by $C_{(1-6)}$ alkyl (e.g. methyl or ethyl).

- 30 Preferably, ZR^1 is pyrimid-5-ylmethyl optionally substituted by 2-methoxy, 2-trifluoromethyl, 2-(4-morpholino) or 2-dimethylamino, 2-oxo-pyrimid-5-ylmethyl in which the 2-oxo-pyrimid-5-yl moiety is as herein before defined or 1-methyl-4-pyrazolylmethyl.

Preferably X is S.

- 35 Representative examples of R^2 when an aryl group include phenyl and naphthyl. Representative examples of R^2 when a heteroaryl group include pyridyl, pyrimidinyl, pyrazolyl, furanyl, thienyl, thiazolyl, quinolyl, benzothiazolyl, pyridazolyl and pyrazinyl. Preferably, R^2 is phenyl optionally substituted by halogen.

- 40 Representative examples of R^2CH_2X include 4-fluorobenzylthio.

- 45 Representative examples of R^3 include hydrogen, methyl, ethyl and propyl, optionally substituted by amino, alkyl amino, dialkyl amino, hydroxyalkylamino, hydroxy, alkoxy, carboxy, alkylcarboxy, and heterocycyl such as piperidine, piperazine, pyrrolidone and morpholine, wherein the alkyl moiety, if present, is $C_{(1-3)}$ alkyl, preferably methyl, or ethyl.

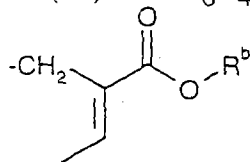
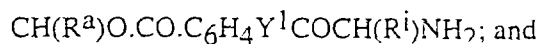
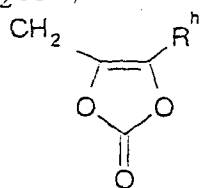
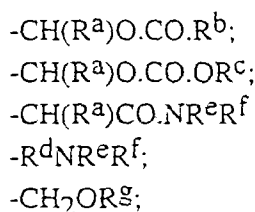
Representative examples of R^4 include phenyl optionally substituted by halogen; thiophene; pyridine; and pyrimidine.

- 5 Representative examples of R^5 include phenyl optionally substituted by halogen, trifluoromethyl, or trifluoromethoxy, preferably at the 4-position.

Preferably, R^4 and R^5 together form a 4-(phenyl)phenyl substituent in which the remote phenyl ring may be optionally substituted by halogen or trifluoromethyl, preferably at the 4-position.

- 10 Pharmaceutically acceptable *in vivo* hydrolysable ester groups for R^8 include those which break down readily in the human body to leave the parent acid or its salt.

- 15 Representative examples of values of pharmaceutically acceptable *in vivo* hydrolysable ester groups for R^8 include:



in which:

- 25 R^a is hydrogen, (C₁-6)alkyl, in particular methyl, (C₃-7)cycloalkyl, or phenyl, each of which may be optionally substituted;
 R^b is (C₁-6)alkyl, (C₁-6)alkoxy(C₁-6)alkyl, phenyl, benzyl, (C₃-7)cycloalkyl, (C₁-6)alkyl(C₃-7)cycloalkyl, 1-amino(C₁-6)alkyl, or 1-(C₁-6alkyl)amino(C₁-6)alkyl, each of which may be optionally substituted; or
 30 R^a and R^b together form a 1,2-phenylene group optionally substituted by one or two methoxy groups;
 R^c is (C₁-6)alkyl, (C₃-7)cycloalkyl, (C₁-6)alkyl(C₃-7)cycloalkyl;
 R^d is (C₁-6)alkylene optionally substituted with a methyl or ethyl group;
 R^e and R^f which may be the same or different is each (C₁-6)alkyl; or aryl(C₁-4) alkyl, optionally substituted with e.g. hydroxy;
 35 R^g is (C₁-6)alkyl;
 R^h is hydrogen, (C₁-6)alkyl or phenyl;
 R^i is hydrogen or phenyl optionally substituted by up to three groups selected from halogen, (C₁-6)-alkyl, or (C₁-6)alkoxy;
 and

147
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Y¹ is oxygen or NH;

for instance:

- (a) acyloxyalkyl groups such as acetoxymethyl, isobutyryloxymethyl, pivaloyloxymethyl, benzoyloxymethyl, α -acetoxylethyl, α -pivaloyloxyethyl, 1-(cyclohexylcarbonyloxy)ethyl.
- 5 (1-aminoethyl)carbonyloxymethyl, 2-methoxyprop-2-ylcarbonyloxymethyl, phenylcarbonyloxymethyl and 4-methoxyphenyl-carbonyloxymethyl;
- (b) alkoxy/cycloalkoxycarbonyloxyalkyl groups, such as ethoxycarbonyloxymethyl, t-butyloxycarbonyloxymethyl, cyclohexyloxycarbonyloxymethyl, 1-methylcyclohexyloxycarbonyloxymethyl and α -ethoxycarbonyloxyethyl;
- 10 (c) dialkylaminoalkyl, especially di-loweralkylamino alkyl groups such as dimethylaminomethyl, dimethylaminoethyl, diethylaminomethyl or diethylaminoethyl;
- (d) acetamido groups such as N,N-dimethylaminocarbonylmethyl, N,N-(2-hydroxyethyl)aminocarbonylmethyl;
- (e) lactone groups such as phthalidyl and dimethoxyphthalidyl;
- 15 (f) (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl; and
- (g) (2-methoxycarbonyl-E-but-2-en-yl)methyl.

Representative examples of pharmaceutically acceptable *in vivo* hydrolysable ester groups for R⁸ include:

- 20 (2-methoxycarbonyl-E-but-2-en-yl)methyl, isobutyryloxymethyl, 2-methoxyprop-2-ylcarbonyloxymethyl, phenylcarbonyloxymethyl, 4-methoxyphenyl-carbonyloxymethyl, t-butyloxycarbonyloxymethyl, cyclohexyloxy-carbonyloxymethyl, 1-methylcyclohexyloxycarbonyloxymethyl, N,N-dimethylaminocarbonylmethyl, and (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl.
- 25 It will be appreciated that in some instances, compounds of the present invention may include a basic function such as an amino group as a substituent. Such basic functions may be used to form acid addition salts, in particular pharmaceutically acceptable salts. Pharmaceutically acceptable salts include those described by Berge, Bighley, and Monkhouse, *J. Pharm. Sci.*, 1977, 66, 1-19. Such salts may be formed from inorganic and organic acids. Representative examples thereof include maleic, fumaric,
- 30 benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methanesulfonic, p-toluenesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, taurocholic acid, benzenesulfonic, hydrochloric, hydrobromic, sulfuric, cyclohexylsulfamic, phosphoric and nitric acids.

- 35 It will be appreciated that in some instances, compounds of the present invention may include a carboxy group as a substituent. Such carboxy groups may be used to form salts, in particular pharmaceutically acceptable salts. Pharmaceutically acceptable salts include those described by Berge, Bighley, and Monkhouse, *J. Pharm. Sci.*, 1977, 66, 1-19. Preferred salts include alkali metal salts such as the sodium and potassium salts.

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When used herein, the term "alkyl" and similar terms such as "alkoxy" includes all straight chain and branched isomers. Representative examples thereof include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *t*-butyl, *n*-pentyl and *n*-hexyl.

When used herein, the term "aryl" refers to, unless otherwise defined, a mono- or bicyclic aromatic ring system containing up to 10 carbon atoms in the ring system, for instance phenyl or naphthyl.

When used herein, the term "heteroaryl" refers to a mono- or bicyclic heteroaromatic ring system comprising up to four, preferably 1 or 2, heteroatoms each selected from oxygen, nitrogen and sulphur. Each ring may have from 4 to 7, preferably 5 or 6, ring atoms. A bicyclic heteroaromatic ring system may include a carbocyclic ring.

When used herein, the terms "halogen" and "halo" include fluorine, chlorine, bromine and iodine and fluoro, chloro, bromo and iodo, respectively.

Particularly preferred compounds of formula (I) are:

- 1-(N-Methyl-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one;
- 15 1-(N-Methyl-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one;
- 1-(N-(2-Dimethylaminoethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one;
- 1-(N-Methyl-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-(4-morpholino)pyrimidin-5-ylmethyl)pyrimidin-4-one;
- 20 1-(N-(2-(dimethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one;
- 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one;
- 25 1-(N-(2-(diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyridin-5-ylmethyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one;
- 1-(N-(2-(1-Piperidino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one bitartrate;
- 1-(N-(Carboxymethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one sodium salt; and
- 30 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one or a pharmaceutically acceptable salt thereof, including the hydrochloride, bitartrate, citrate and tosylate salts.

35 Since the compounds of the present invention, in particular compounds of formula (I), are intended for use in pharmaceutical compositions, it will be understood that they are each provided in substantially pure form, for example at least 50% pure, more suitably at least 75% pure and preferably at least 95% pure (% are on a wt/wt basis). Impure preparations of the compounds of formula (I) may be used for preparing the more pure forms used in the pharmaceutical compositions. Although the purity of intermediate compounds of the present invention is less critical, it will be readily understood that the substantially pure form is preferred as for the compounds of formula (I). Preferably, whenever possible, the compounds of the present invention are obtained in crystalline form.

45 When some of the compounds of this invention are allowed to crystallise or are recrystallised from organic solvents, solvent of crystallisation may be present in the crystalline product. This invention

148
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includes within its scope such solvates. Similarly, some of the compounds of this invention may be crystallised or recrystallised from solvents containing water. In such cases water of hydration may be formed. This invention includes within its scope stoichiometric hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation. In addition, different crystallisation conditions may lead to the formation of different polymorphic forms of crystalline products. This invention includes within its scope all polymorphic forms of the compounds of formula (I).

Compounds of the present invention are inhibitors of the enzyme lipoprotein associated phospholipase A₂ (Lp-PLA₂) and as such are expected to be of use in therapy, in particular in the treatment of atherosclerosis. In a further aspect therefore the present invention provides a compound of formula (I) for use in therapy.

The compounds of formula (I) are inhibitors of lysophosphatidylcholine production by Lp-PLA₂ and may therefore also have a general application in any disorder that involves endothelial dysfunction, for example atherosclerosis, diabetes, hypertension, angina pectoris and after ischaemia and reperfusion. In addition, compounds of formula (I) may have a general application in any disorder that involves lipid peroxidation in conjunction with enzyme activity, for example in addition to conditions such as atherosclerosis and diabetes, other conditions such as rheumatoid arthritis, stroke, inflammatory conditions of the brain such as Alzheimer's Disease, myocardial infarction, reperfusion injury, sepsis, and acute and chronic inflammation. Further such conditions include various neuropsychiatric disorders such as schizophrenia (see Psychopharmacology Bulletin, 31, 159-165, 1995).

Further applications include any disorder that involves activated monocytes, macrophages or lymphocytes, as all of these cell types express Lp-PLA₂. Examples of such disorders include psoriasis.

Accordingly, in a further aspect, the present invention provides for a method of treating a disease state associated with activity of the enzyme Lp-PLA₂ which method involves treating a patient in need thereof with a therapeutically effective amount of an inhibitor of the enzyme. The disease state may be associated with the increased involvement of monocytes, macrophages or lymphocytes; with the formation of lysophosphatidylcholine and oxidised free fatty acids; with lipid peroxidation in conjunction with Lp PLA₂ activity; or with endothelial dysfunction.

Compounds of the present invention may also be of use in treating the above mentioned disease states in combination with an anti-hyperlipidaemic, anti-atherosclerotic, anti-diabetic, anti-anginal, anti-inflammatory, or anti-hypertension agent or an agent for lowering Lp(a). Examples of the above include cholesterol synthesis inhibitors such as statins, anti-oxidants such as probucol, insulin sensitisers, calcium channel antagonists, and anti-inflammatory drugs such as NSAIDs. Examples of agents for lowering Lp(a) include the aminophosphonates described in WO 97/02037, WO 98/28310, WO 98/28311 and WO 98/28312 (Symphar SA and SmithKline Beecham).

In therapeutic use, the compounds of the present invention are usually administered in a standard pharmaceutical composition. The present invention therefore provides, in a further aspect, a pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable carrier.

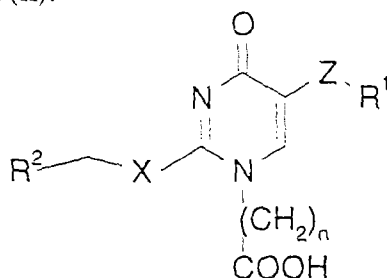
Suitable pharmaceutical compositions include those which are adapted for oral or parenteral administration or as a suppository.

- 5 Suitable pharmaceutical compositions include those which are adapted for oral or parenteral administration or as a suppository. Compounds of formula (I) which are active when given orally can be formulated as liquids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges. A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s) for example, ethanol, glycerine, non-
 10 aqueous solvent, for example polyethylene glycol, oils, or water with a suspending agent, preservative, flavouring or colouring agent. A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose. A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the
 15 active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule. Typical parenteral compositions consist of a solution or suspension of the compound of formula (I) in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol,
 20 polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration. A typical suppository formulation comprises a compound of formula (I) which is active when administered in this way, with a binding and/or lubricating agent such as polymeric glycols, gelatins or cocoa butter or other low melting vegetable or synthetic waxes or fats.

- 25 Preferably the composition is in unit dose form such as a tablet or capsule. Each dosage unit for oral administration contains preferably from 1 to 500 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a compound of the formula (I). The daily dosage regimen for an adult patient may be, for example, an oral dose of between 1 mg and 1000 mg, preferably between 1 mg and
 30 500 mg, or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 25 mg, of the compound of the formula (I), the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

- 35 A compound of formula (I) may be prepared by a number of processes which include:

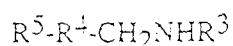
(a) reacting a compound of formula (II):



(II)

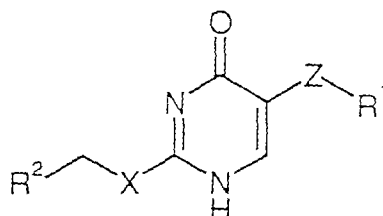
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in which X, Y, Z, R¹ and R² are as hereinbefore defined,
with a compound of formula (III):



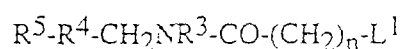
in which R³, R⁴ and R⁵ are as hereinbefore defined; under amide forming conditions:

(b) reacting a compound of formula (IV):



(IV)

in which X, Z, R¹ and R² are as hereinbefore defined,
with a compound of formula (V):

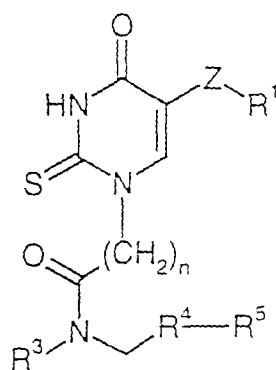


(V)

in which n, R³, R⁴ and R⁵ are as hereinbefore defined, and L¹ is a leaving group such as halogen, for instance bromo or iodo,

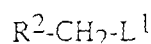
in the presence of a base such as a secondary or tertiary amine, for instance di-isopropylethylamine, in an inert solvent such as dichloromethane;

(c) when X is S, reacting a compound of formula (VI):



(VI)

in which n, Z, R¹, R³, R⁴ and R⁵ are as hereinbefore defined,
with a compound of formula (VII):

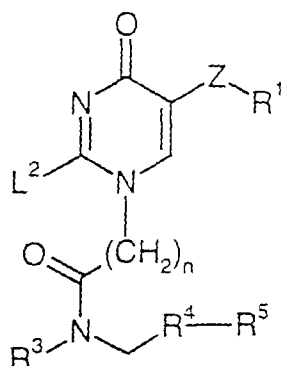


(VII)

in which R² and L¹ are as hereinbefore defined,

in the presence of a base such as a secondary or tertiary amine, for instance di-isopropylethylamine, in an inert solvent such as dichloromethane; or

(d) when X is O, reacting a compound of formula (VIII):

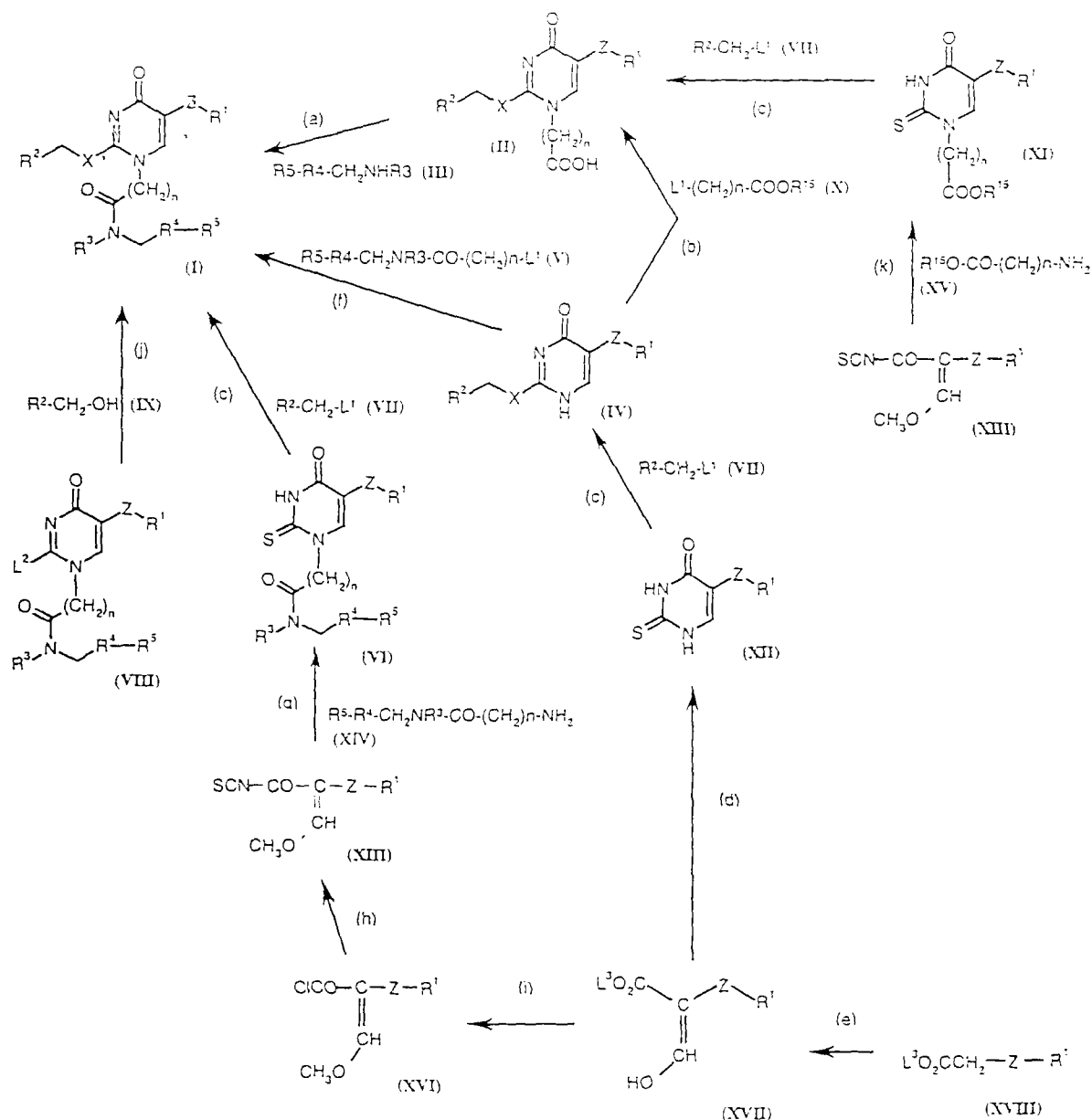


5 (VIII)
in which n, Z, R¹, R³, R⁴ and R⁵ are as hereinbefore defined, and L² is a leaving group such as halogen or alkylthio, for instance methylthio,
with a compound of formula (IX):

10 R^2-CH_2-OH (IX)

in which R² is as hereinbefore defined,
in the presence of a base such as 4-dimethylaminopyridine, in an inert solvent such as pyridine.

15 Compounds of formulae (II), (IV), (VI) and (VIII) for use in the above processes may be prepared by processes illustrated in the following scheme I:

150
1418

Scheme I

in which:

L^3 is a C(1-6)alkyl group, for instance methyl;

5 R^{15} is a C(1-6)alkyl group, for instance ethyl and

L^1 , L^2 , R^1 , R^2 , R^3 , R^4 , R^5 , n , X and Z are as hereinbefore defined.

With reference to Scheme I:

10 Amide forming conditions for step (a) are well known in the art. Preferably, the acid of formula (II) is reacted with the amine of formula (III) in an inert solvent, such as dichloromethane, at ambient temperature and in the presence of an activating agent such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide plus hydroxybenzotriazole.

15 Alkylation conditions for step (b) include reaction in the presence of a base such as a secondary or tertiary amine, for instance di-isopropylethylamine, in an inert solvent such as dichloromethane, forming

an intermediate ester which is then converted to the acid of formula (II) by hydrolysis, for instance using aqueous sodium hydroxide in a solvent such as dioxan.

5 Conditions for step (c) include under thioether forming conditions. Advantageously, the reaction is carried out in the presence of a base such as sodium ethoxide or potassium carbonate, preferably in a solvent such as ethanol or dimethyl formamide, or a secondary or tertiary amine base such as di-isopropylethyl amine, in solvent such as dichloromethane.

10 In step (d), a compound of formula (XVII) is reacted with thiourea, in the presence of sodium ethoxide (preferably generated *in situ* from sodium and ethanol).

In step (e), a compound of formula (XVIII) is reacted with ethyl formate in the presence of a base such as sodium hydride or potassium isopropoxide.

15 In step (f), a compound of formula (VI) is reacted with a compound of formula (V) in the presence of a base such as a secondary or tertiary amine, for instance di-isopropylethylamine, in an inert solvent such as dichloromethane

20 In step (g), a compound of formula (XIII) is reacted with a compound of formula (XIV) in a solvent such as dimethylformamide to form an intermediate thiourea, which is then treated with a base such as sodium methoxide.

25 In step (h), a compound of formula (XVI) is reacted with a metal thiocyanate, for example potassium thiocyanate, in a solvent such as acetonitrile.

30 In step (i), a compound of formula (XVII) is reacted with a methylating agent such as dimethyl sulphate in the presence of a base such as potassium carbonate, followed by hydrolysis of the intermediate ester in conventional manner e.g. by basic hydrolysis using sodium hydroxide to give the corresponding carboxylic acid which may then be converted into the acyl chloride, for instance by treatment with oxalyl chloride.

In step (j), a catalyst such as 4-dimethylaminopyridine, and in a solvent such as pyridine are used.

35 In step (k), a compound of formula (XIII) is reacted with a compound of formula (XV) in a solvent such as dimethylformamide to form an intermediate thiourea, which is then treated with a base such as sodium methoxide.

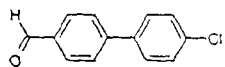
The present invention will now be illustrated by the following examples.

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119

Examples

The structure and purity of the intermediates and examples was confirmed by ¹H-NMR and (in nearly all cases) mass spectroscopy, even where not explicitly indicated below.

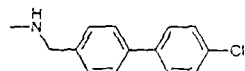
5 Intermediate A1 — 4-(4-Chlorophenyl)benzaldehyde



(a) A mixture of 4-formylbenzeneboronic acid (2.50g, 2 equiv), 4-chloriodobenzene (1.98g, 1 equiv), tetrakis(triphenylphosphine)palladium(0) (0.50g, 0.05 equiv), aqueous sodium carbonate (18ml, 2M solution, 2 equiv) and dimethoxyethane (50ml) was stirred at reflux under argon overnight, then cooled and diluted with ethyl acetate. The mixture was filtered as necessary to remove inorganic residues, then the organic layer was washed successively with aqueous citric acid and brine, dried and evaporated. The crude product was purified by chromatography (silica, 5% ethyl acetate in hexane); product fractions were evaporated to a white solid (1.32g, 72%).

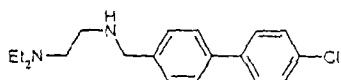
(b) A mixture of 4-chlorobenzeneboronic acid (19.4g, 1 equiv), 4-bromobenzaldehyde (22.9g, 1 equiv), palladium(II) acetate (1.4g, 0.05 equiv) aqueous sodium carbonate (30.3 g in 144ml solution, 2 equiv) and dimethoxyethane (500ml) was stirred at reflux under argon for 2.5h, then evaporated to low volume and diluted with dichloromethane. Workup continued as in (a) above to give identical material (25.2g, 94%). ¹H-NMR (CDCl₃) δ 10.05 (1H, s), 7.96 (2H, d), 7.73 (2H, d), 7.57 (2H, d), 7.46 (2H, d); MS (AP+) found (M+1) = 217, C₁₃H₉³⁵ClO requires 216.

20 Intermediate A2 — N-Methyl-4-(4-chlorophenyl)benzylamine



A mixture of Intermediate A1 (3.5g, 1 equiv), methylamine (32.3ml of a 2M solution in THF, 4 equiv) and anhydrous magnesium sulphate (4.47g, 2 equiv) was stirred at room temperature for 16h, then filtered. the solid washed thoroughly with ethyl acetate, and the combined filtrates evaporated to a white solid (3.7g). This imine intermediate was suspended in ethanol (100ml), cooled in ice and sodium borohydride (0.61g, 1 equiv) added portionwise. The ice bath was removed, and the mixture stirred for 45min at room temperature then at 50°C for 1h. The solvent was removed in vacuo, water was added to the residue, and the product extracted into dichloromethane. Drying and evaporation of the solvent gave a white solid (3.56g). ¹H-NMR (CDCl₃) δ 7.51 (4H, d), 7.40 (4H, d), 3.79 (2H, s), 2.48 (3H, s); MS (APCI+) found (M+1) = 232, C₁₄H₁₄³⁵ClN requires 231.

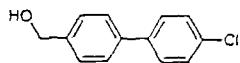
Intermediate A3 — N-(2-Diethylaminoethyl)-4-(4-chlorophenyl)benzylamine



A mixture of Intermediate A1 (55.0g), N,N-diethylethylenediamine (35.6ml), 4A molecular sieve (37g), and dichloromethane (1100ml) was reacted at room temperature under argon for 16h, with occasional agitation. The solid was filtered off and washed with dichloromethane, and the combined filtrates evaporated to a yellow foam (72.4g). This intermediate imine was reduced with sodium borohydride (8.7g) in ethanol (850ml) as described for Intermediate A2, yielding the title compound as a yellow oil

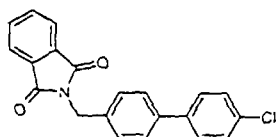
(72.7g). $^1\text{H-NMR}$ (CDCl_3) δ 1.70 (2H, t), 2.22 (6H, s), 2.33 (2H, t), 2.69 (2H, br. m), 3.83 (2H, s), 7.37-7.43 (4H, m), 7.52-7.56 (4H, m).

Intermediate A4 — 4-(4-Chlorophenyl)benzyl alcohol



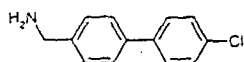
- 5 A mixture of Intermediate A1 (1.73g, 1 equiv), sodium borohydride (0.3g, 1 equiv) and ethanol (20ml) was stirred until a clear solution was obtained; a gentle exotherm was observed. The temperature was raised to 50°C and stirring continued for 2h, then the solvent was removed in vacuo, water added to the residue, and the product extracted into dichloromethane. Drying and evaporation of the solvent gave a white solid (1.67g). $^1\text{H-NMR}$ (CDCl_3) δ 1.73 (1H, t), 4.74 (2H, d), 7.2-7.6 (8H, m).

10 **Intermediate A5 — N-(4-(4-Chlorophenyl)benzyl)phthalimide**



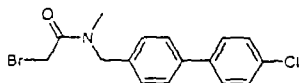
- 15 Intermediate A4 (1.62g, 1 equiv), phthalimide (1.42g, 1.3 equiv) and triphenylphosphine (2.53g, 1.3 equiv) were dissolved in dry THF (50ml), the solution was cooled in ice, and diethyl azodicarboxylate (1.52ml, 1.3 equiv) was added slowly with stirring. The yellow solution was stirred for 16h at room temperature, then the solvent was evaporated. Chromatography (silica, 1:1 dichloromethane/pet. ether) and trituration with ether gave the desired product (2.03g, 79%). $^1\text{H-NMR}$ (CDCl_3) δ 4.89 (2H, s), 7.36-7.50 (8H, m), 7.69-7.74 (2H, m), 7.82-7.89 (2H, m).

Intermediate A6 — 4-(4-Chlorophenyl)benzylamine

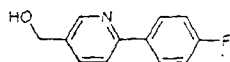


- 20 A mixture of Intermediate A5 (1.98g, 1 equiv) and hydrazine hydrate (0.55ml, 2 equiv) in ethanol (40ml) was heated at reflux for 2h, then the solvent was evaporated. The residue was shaken with dichloromethane and 0.5M aqueous sodium hydroxide, the aqueous layer re-extracted with dichloromethane, and the combined organic extracts purified by chromatography (silica, 1-3% methanolic ammonia in dichloromethane). Product fractions were evaporated to a white solid (0.53g, 43%). $^1\text{H-NMR}$ (CDCl_3) δ 3.92 (2H, s), 7.28-7.41 (4H, m), 7.49-7.54 (4H, m).

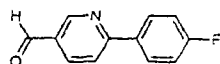
Intermediate A7 — N-Methyl-N-(4-(4-chlorophenyl)benzyl)bromoacetamide



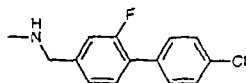
- 30 Bromoacetyl bromide (0.123ml, 1.1 equiv) was added to a well-stirred mixture of Intermediate A2 (0.3g, 1 equiv), sodium hydroxide (0.06g, 1.2 equiv), water and dichloromethane. Stirring was continued for 3h at room temperature, then the phases were separated and the organic layer dried and evaporated. Chromatography (silica, 3:1 hexane/ethyl acetate) gave the desired product as an oil (0.37g). $^1\text{H-NMR}$ (CDCl_3) δ 7.38-7.68 (8H, m), 4.77 (2H, s), 4.07 (2H, s), 3.24 (3H, s); MS (APCI+) found ($M+1$) = 352. $\text{C}_{16}\text{H}_{15}^{79}\text{Br}^{35}\text{ClNO}$ requires 351.

152
150/5**Intermediate A8 — 5-Hydroxymethyl-2-(4-fluorophenyl)pyridine**

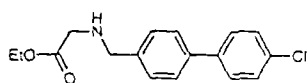
A solution of Intermediate A23 (4.63g) in dry dichloromethane (100ml) was cooled to -78°C under argon, then DIBAL-H (26.7ml, 1.5M solution in toluene) was added dropwise over 20min. Stirring was continued for 40min at -78°C, then 2M hydrochloric acid (52ml) was added dropwise over 15min. The solution was allowed to warm slowly to room temperature, then the organic layer was separated, washed with water, dried and evaporated. Chromatography (silica, 1:1 ethyl acetate/hexane) gave the product as a white solid (3.03g, 75%). ¹H-NMR (CDCl₃) δ (1H, d), 7.98 (2H, m), 7.77 (1H, m), 7.68 (1H, d), 7.15 (2H, t), 4.77 (2H, d), 1.802 (1H, t); MS(APCI+) found (M+1)=204, C₁₂H₁₀FNO requires 203.

Intermediate A9 — 5-Formyl-2-(4-fluorophenyl)pyridine

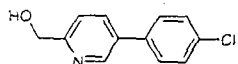
Activated manganese dioxide (3.19g) was added to a solution of Intermediate A8 (0.75g) in dichloromethane (50ml) and stirred at room temperature for 16h. The solids were filtered off and the filtrate evaporated to a pale yellow solid (0.57g). ¹H-NMR (CDCl₃) δ 10.15 (1H, s), 9.11 (1H, s), 8.22 (1H, dd), 8.10 (2H, m), 7.87 (1H, d), 7.20 (2H, t); MS(APCI+) found (M+1)=202, C₁₂H₈FNO requires 201.

Intermediate A10 — N-Methyl-4-(4-chlorophenyl)-3-fluorobenzylamine

Borane (1M solution in THF, 2 equiv) was stirred under argon with ice cooling, and a suspension of Intermediate A39 (1 equiv) in dry THF was added gradually over a few minutes. After 5 mins the ice bath was removed and the mixture heated to reflux for 1h, then cooled to room temperature. 5M Hydrochloric acid was added dropwise, and the THF was removed from the resulting suspension by distillation. The residue was diluted with water and made strongly basic with sodium hydroxide, then the product was extracted into ether. Drying and evaporation of the organic solution, followed by chromatography gave the title compound as an oil (88%). ¹H-NMR (CDCl₃) δ 2.48 (3H, s), 3.79 (2H, s), 7.12-7.18 (2H, m), 7.33-7.50 (5H, m); MS (APCI+) found (M+1) = 250; C₁₄H₁₃ClFN requires 249.

Intermediate A11 — N-(Ethoxycarbonylmethyl)-4-(4-chlorophenyl)benzylamine

A mixture of Intermediate A1 (0.5 g, 1 equiv), glycine ethyl ester hydrochloride (0.32 g, 1 equiv), diisopropylethylamine (0.4 ml, 1 equiv) and 1,2-dichloroethane (10 ml) was stirred at room temperature. sodium triacetoxyborohydride (0.73 g, 1.5 equiv) was added, and stirring continued overnight. After diluting with dichloromethane, the solution was washed with water and dried over potassium carbonate. Evaporation of the solvent yielded the title compound (0.57 g) as a white waxy solid. ¹H-NMR (CDCl₃) δ 1.22-1.37 (3H, t), 3.44 (2H, s), 3.85 (2H, s), 4.15-4.32 (2H, q), 7.35-7.62 (8H, m); MS (APCI+) found (M+1) = 304; C₁₇H₁₈ClNO₂ requires 303.

Intermediate A12 — 2-Hydroxymethyl-5-(4-chlorophenyl)pyridine

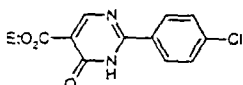
m-Chloroperbenzoic acid (0.93 g) was added portionwise over 30 min to a solution of Intermediate A11 (0.77 g) in dichloromethane (10 ml), then the mixture was stirred at room temperature for a further hour.

diluted with dichloromethane, washed with aq. sodium bicarbonate, dried and evaporated.

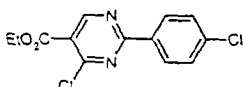
Chromatography (silica, 5% methanol in dichloromethane) gave 2-methyl-5-(4-chlorophenyl)pyridine-*N*-oxide (0.79 g) as a white solid. This material was dissolved in dichloromethane (15 ml), trifluoroacetic anhydride (1.9 ml) added, and the mixture stirred for 1 hour at room temperature followed by 1 hour at reflux. Volatile components were removed in vacuo, then the residue was redissolved in

dichloromethane (5 ml), 2M aq. sodium carbonate (14 ml) was added, and stirred vigorously for 2 hours. The mixture was diluted with dichloromethane and water, and the organic layer was washed with water, dried and evaporated. Chromatography (silica, 5% methanol in dichloromethane) gave the title

compound (0.67 g) as an off-white solid. ¹H-NMR (CDCl₃) δ 3.61 (1H,t), 4.82 (2H,d), 7.33 (1H,d), 7.45 (2H,m), 7.51 (2H,m), 7.85 (1H,dd), 7.78 (1H,d); MS (APCI+) found (M+1) = 220/222; C₁₂H₁₀ClNO requires 219/221.

Intermediate A13 — Ethyl 2-(4-chlorophenyl)-4-oxopyrimidine-5-carboxylate

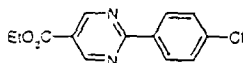
Sodium ethoxide (11.12 ml, 2 equiv) as a 21% w/v solution in ethanol was added dropwise to a suspension of diethyl ethoxymalonate (3.03 ml, 1 equiv) and 4-chlorobenzamidine hydrochloride (4.23 g, 1 equiv) in ethanol (30 ml), then the mixture was heated to reflux for 4 hours. After cooling, the solvent was removed in vacuo and the residue was triturated with ether. The solid was filtered off, then resuspended in water and acidified to pH 2. The product was filtered off, washed with water and dried: yield 2.94 g. ¹H-NMR (d₆-DMSO) δ 1.29 (3H,t), 4.26 (2H,q), 7.65 (2H,m), 8.18 (2H,m), 8.65 (1H,s); MS (APCI-) found (M-1) = 277/279; C₁₃H₁₁ClN₂O₃ requires 278/280.

Intermediate A14 — Ethyl 2-(4-chlorophenyl)-4-chloropyrimidine-5-carboxylate

Oxalyl chloride (0.31 ml, 2 equiv) was added to Intermediate A13 (0.49 g) in dichloromethane (20 ml) with ice cooling, then the mixture was stirred for 3 hours with warming to room temperature.

Evaporation of the volatile components gave the product as a white solid (2.94 g). ¹H-NMR (CDCl₃) δ 1.44 (3H,t), 4.48 (2H,q), 7.50 (2H,m), 8.45 (2H,m), 9.17 (1H,s); MS (APCI+) found (M+1) = 297;

C₁₃H₁₀Cl₂N₂O₂ requires 296.

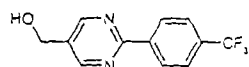
Intermediate A15 — Ethyl 2-(4-chlorophenyl)pyrimidine-5-carboxylate

A mixture of Intermediate A14 (6.8 g, 1 equiv), zinc powder (1.79 g, 1.2 equiv), acetic acid (1.57 ml, 1.2 equiv) and THF (100 ml) was stirred at 60°C under argon for 18 hours, then a further portion of acetic acid (1 ml) and zinc (1.0 g) was added, and the reaction allowed to continue for a further 24 hours. The solvent was removed in vacuo, the residue was taken up in a mixture of dichloromethane and methanol.

153
151

and undissolved zinc powder was removed by filtration. After evaporation of the solvent, the product crystallised from ethanol; yield 2.02 g. $^1\text{H-NMR}$ (CDCl_3) δ 1.44 (3H,t), 4.46 (2H,q), 7.48 (2H,m), 8.48 (2H,m), 9.30 (2H,s); MS (APCI+) found ($M+1$) = 263; $\text{C}_{13}\text{H}_{11}\text{ClN}_2\text{O}_2$ requires 262.

Intermediate A16 — 5-Hydroxymethyl-2-(4-trifluoromethylphenyl)pyrimidine



Intermediate A129 (0.96g) was hydrogenated over 10% palladium on charcoal (96 mg) in a mixture of triethylamine (2 ml) and ethanol (20 ml) for 90 mins at 1 atmosphere pressure. The catalyst was removed by filtration, the solvent was evaporated, and the residue was taken up in ethyl acetate and washed successively with aq. ammonium chloride and aq. sodium bicarbonate. Drying and evaporation gave the title compound (2.02 g). $^1\text{H-NMR}$ (CDCl_3) δ 4.82 (2H,s), 7.75 (2H,m), 8.57 (2H,m), 8.85 (2H,s); MS (APCI+) found ($M+1$) = 255; $\text{C}_{11}\text{H}_9\text{ClN}_2\text{O}$ requires 254.

The following intermediates were made by the method of Intermediate A1:

No.	Precursors	Structure	Name
A20	4-formylboronic acid, 4-fluoriodobenzene		4-(4-Fluorophenyl)benzaldehyde
A21	2-bromothiophene-5-carboxaldehyde, 4-fluorobenzeneboronic acid		5-(4-Fluorophenyl)-2-thiophene carboxaldehyde
A22	2-bromothiophene-5-carboxaldehyde, 4-chlorobenzeneboronic acid		5-(4-Chlorophenyl)-2-thiophene carboxaldehyde
A23	methyl 6-chloronicotinate, 4-fluorobenzeneboronic acid		Methyl 6-(4-fluorophenyl)-nicotinate
A24	methyl 6-chloronicotinate, 4-chlorobenzeneboronic acid		Methyl-6-(4-chlorophenyl)-nicotinate
A25	methyl 6-chloronicotinate, 3,4-dichlorobenzeneboronic acid		Methyl-6-(3,4-dichlorophenyl)-nicotinate
A26	4-bromobenzaldehyde, 4-trifluoromethylbenzeneboronic acid		4-(4-Trifluoromethylphenyl)-benzaldehyde
A27	4-bromo-2-fluorobenzaldehyde, 4-chlorobenzeneboronic acid		4-(4-Chlorophenyl)-2-fluorobenzaldehyde
A28	4-formylbenzeneboronic acid, 4-chloro-2-fluoriodobenzene		4-(4-Chloro-2-fluorophenyl)-benzaldehyde
A29	4-formylbenzeneboronic acid, 4-chloro-3-fluoriodobenzene		4-(4-Chloro-3-fluorophenyl)-benzaldehyde
A30	4-methoxybenzeneboronic acid, 4-bromobenzaldehyde		4-(4-Methoxyphenyl)-benzaldehyde

A31	4-formylbenzeneboronic acid, 4-chloro-2-fluoriodobenzene		4-(2-Fluoro-4-chlorophenyl)- benzaldehyde
A32	4-formylbenzeneboronic acid, 2,4-bis(trifluoromethyl)- bromobenzene		4-(2,4-bis(trifluoromethyl)phenyl)- benzaldehyde
A33	4-formylbenzeneboronic acid, 4-bromo-3-fluorobenzotrifluoride		4-(2-Fluoro-4-trifluoromethyl- phenyl)benzaldehyde
A34	4-bromo-2-fluorobenzaldehyde, 4-trifluoromethylbenzeneboronic acid		2-Fluoro-4-(4-trifluoromethyl- phenyl)benzaldehyde
A35	3-chloro-4-fluorobenzeneboronic acid, 4-bromobenzaldehyde		4-(3-Chloro-4-fluorophenyl)- benzaldehyde
A36	4-formylbenzeneboronic acid, 2,4-difluoriodobenzene		4-(2,4-Difluorophenyl)- benzaldehyde
A37	4-formylbenzeneboronic acid, 4-trifluoromethoxyiodobenzene		4-(4-Trifluoromethoxyphenyl)- benzaldehyde
A38	4-formylbenzeneboronic acid, 4-difluoromethoxyiodobenzene		4-(4-Difluoromethoxyphenyl)- benzaldehyde
A39	N-methyl-4-bromo-3- fluorobenzamide, 4-chlorobenzeneboronic acid		N-Methyl-4-(4-chlorophenyl)-3- fluorobenzamide
A40	methyl 6-chloronicotinate, 4-trifluoromethylbenzeneboronic acid		Methyl 6-(4-trifluoromethyl- phenyl)nicotinate
A41	2-methyl-5-bromopyridine, 4-chlorobenzeneboronic acid		2-methyl-5-(4-trifluoromethyl- phenyl)pyridine
A42	2-methyl-5-triflylpyridine, 4-trifluoromethylbenzeneboronic acid		2-methyl-5-(4-trifluoromethyl- phenyl)pyridine
A43	2-methyl-5-triflylpyridine, 4-trifluoromethoxybenzene- boronic acid		2-methyl-5-(4-trifluoromethoxy- phenyl)pyridine

The following intermediates were made by the method of Intermediate A2, using an appropriate amine in place of methylamine as necessary:

No.	Precursor	Structure	Name
A44	Int. A20		N-Methyl-4-(4-fluorophenyl)benzylamine
A45	Int. A26		N-Methyl-4-(4-trifluoromethylphenyl)benzylamine
A46	Int. A27		N-Methyl-4-(4-chlorophenyl)-2-fluorobenzylamine

154
152 80

A47	Int. A28		N-Methyl-4-(4-chloro-2-fluorophenyl)benzylamine
A48	Int. A1		N-Ethyl-4-(4-chlorophenyl)benzylamine
A49	Int. A131		5-Methylaminomethyl-2-(3,4-dichlorophenyl)-pyridine
A50	Int. A1		N-(Dimethylaminocarbonylmethyl)-4-(4-chlorophenyl)benzylamine
A51	Int. A1		N-(2-Methoxyethyl)-4-(4-chlorophenyl)-benzylamine
A52	Int. A26		N-(Dimethylaminocarbonylmethyl)-4-(4-trifluoromethylphenyl)benzylamine
A53	Int. A29		N-Methyl-4-(4-chloro-3-fluorophenyl)benzylamine
A54	Int. A30		N-Methyl-4-(4-methoxyphenyl)benzylamine
A55	Int. A31		N-Methyl-4-(2-fluoro-4-chlorophenyl)benzylamine
A56	Int. A32		N-Methyl-4-(2,4-bis(trifluoromethyl)phenyl)-benzylamine
A57	Int. A33		N-Methyl-4-(2-fluoro-4-trifluoromethylphenyl)-benzylamine
A58	Int. A34		N-Methyl-2-fluoro-4-(4-trifluoromethylphenyl)benzylamine
A59	Int. A35		N-Methyl-4-(3-chloro-4-fluorophenyl)benzylamine
A60	Int. A36		N-Methyl-4-(2,4-difluorophenyl)benzylamine
A61	Int. A1		N-(2-Dimethylaminoethyl)-4-(4-chlorophenyl)-benzylamine
A62	Int. A1		N-(3-Dimethylaminopropyl)-4-(4-chlorophenyl)-benzylamine
A63	Int. A21		2-Methylaminomethyl-5-(4-fluorophenyl)-thiophene
A64	Int. A9		5-Methylaminomethyl-2-(4-fluorophenyl)pyridine
A65	Int. A130		5-Methylaminomethyl-2-(4-chlorophenyl)pyridine
A66	Int. A22		2-Methylaminomethyl-5-(4-chlorophenyl)-thiophene

A67: N-Methyl-4-phenylbenzylamine was made from commercially available 4-biphenylcarboxaldehyde.

The following intermediates were made by the method of Intermediate A3:

No.	Precursor	Structure	Name
A70	Int. A1		N-(2-Hydroxyethyl)-4-(4-chlorophenyl)-benzylamine
A71	Int. A26		N-(2-Hydroxyethyl)-4-(4-trifluoromethylphenyl)benzylamine
A72	Int. A26		N-(2-(dimethylamino)ethyl)-4-(4-trifluoromethylphenyl)benzylamine
A73	Int. A26		N-(2-(diethylamino)ethyl)-4-(4-trifluoromethylphenyl)benzylamine
A74	Int. A1		N-(2-(diisopropylamino)ethyl)-4-(4-chlorophenyl)benzylamine
A75	Int. A1		N-(2-(1-pyrrolidino)ethyl)-4-(4-chlorophenyl)benzylamine
A76	Int. A1		N-(2-(4-morpholino)ethyl)-4-(4-chlorophenyl)benzylamine
A77	Int. A1		N-(2-(4-methyl-1-piperazino)ethyl)-4-(4-chlorophenyl)benzylamine
A78	Int. A26		N-(3-(dimethylamino)propyl)-4-(4-trifluoromethylphenyl)benzylamine
A79	Int. A1		N-(3-(diethylamino)propyl)-4-(4-chlorophenyl)benzylamine
A80	Int. A1		N-(3-(1-pyrrolidino)propyl)-4-(4-chlorophenyl)benzylamine
A81	Int. A1		N-(3-(1-piperidino)propyl)-4-(4-chlorophenyl)benzylamine
A82	Int. A1		N-(3-(4-morpholino)propyl)-4-(4-chlorophenyl)benzylamine
A83	Int. A1		N-(3-(4-methyl-1-piperazino)propyl)-4-(4-chlorophenyl)benzylamine
A84	Int. A1		N-(2-(t-butoxycarbonylamino)ethyl)-4-(4-chlorophenyl)benzylamine
A85	Int. A1		N-(N'-(2-(t-butoxycarbonyl)-N'-methylamino)ethyl)-4-(4-chlorophenyl)benzylamine
A86	Int. A1		N-(N'-(2-(t-butoxycarbonyl)-N'-ethylamino)ethyl)-4-(4-chlorophenyl)benzylamine

1537

A87	Int. A26		N-(N'-(2-(t-butoxycarbonyl)-N'-ethylamino)ethyl)-4-(4-(trifluoromethyl)phenyl)benzylamine
A88	Int. A1		N-(3-(t-butoxycarbonylamino)propyl)-4-(4-chlorophenyl)benzylamine
A89	Int. A1		N-(N'-(3-(t-butoxycarbonyl)-N'-methylamino)propyl)-4-(4-(trifluoromethyl)phenyl)benzylamine
A90	Int. A1		N-(2-(4-t-butoxycarbonyl-1-piperazino)ethyl)-4-(4-chlorophenyl)benzylamine
A91	Int. A1		N-(2-(2-oxo-4-t-butoxycarbonyl-1-piperazino)ethyl)-4-(4-chlorophenyl)benzylamine
A92	Int. A37		N-(2-(diethylamino)ethyl)-4-(4-(trifluoromethoxy)phenyl)benzylamine
A93	Int. A38		N-(2-(diethylamino)ethyl)-4-(4-(difluoromethoxy)phenyl)benzylamine
A94	Int. A1		N-(2-(N'-(2-hydroxyethyl)-N'-ethylamino)ethyl)-4-(4-chlorophenyl)benzylamine
A95	Int. A1		N-(2-(bis-(2-hydroxyethyl)amino)ethyl)-4-(4-chlorophenyl)benzylamine
A96	Int. A26		N-((4-morpholino)carbonylmethyl)-4-(4-(trifluoromethyl)phenyl)benzylamine
A97	Int. A26		N-((4-methyl-1-piperazino)carbonylmethyl)-4-(4-(trifluoromethyl)phenyl)benzylamine
A98	Int. A133		N-(2-(diethylamino)ethyl)-5-(4-chlorophenyl)pyrid-2-ylmethylamine
A99	Int. A134		N-(2-(diethylamino)ethyl)-5-(4-(trifluoromethyl)phenyl)pyrid-2-ylmethylamine
A100	Int. A132		N-(2-(dimethylamino)ethyl)-2-(4-(trifluoromethyl)phenyl)pyrid-5-ylmethylamine
A101	Int. A130		N-(2-(diethylamino)ethyl)-2-(4-chlorophenyl)pyrid-5-ylmethylamine
A102	Int. A135		N-methyl-5-(4-(trifluoromethoxy)phenyl)pyrid-2-ylmethylamine
A103	Int. A130		N-(2-hydroxyethyl)-2-(4-chlorophenyl)pyrid-5-ylmethylamine
A104	Int. A136		N-(2-(diethylamino)ethyl)-2-(4-chlorophenyl)pyrimid-5-ylmethylamine

A105	Int. A137		N-(2-(diethylamino)ethyl)-2-(4-(trifluoromethyl)phenyl)pyrimidin-5-ylmethylamine
A106	Int. A132		N-(2-(diethylamino)ethyl)-2-(4-(trifluoromethyl)phenyl)pyridin-5-ylmethylamine
A107	Int. A1		N-(2-(1-piperidino)ethyl)-4-(4-chlorophenyl)benzylamine
A108	Int. A26		N-(2-(1-piperidino)ethyl)-4-(4-(trifluoromethyl)phenyl)benzylamine

The following intermediates were made by the method of Intermediate A4:

No.	Precursor	Structure	Name
A110	Int. A20		4-(4-Fluorophenyl)benzyl alcohol
A111	Int. A26		4-(4-Trifluoromethylphenyl)benzyl alcohol
A112	Int. A22		5-Hydroxymethyl-2-(4-chlorophenyl)thiophene

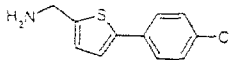
The following intermediates were made by the method of Intermediate A5:

No.	Precursor	Structure	Name
A115	Int. A110		N-(4-(4-Fluorophenyl)benzyl)phthalimide
A116	Int. A111		N-(4-(4-Trifluoromethylphenyl)benzyl)phthalimide
A117	Int. A8		N-(2-(4-Fluorophenyl)pyridin-5-ylmethyl)phthalimide
A118	Int. A112		N-(5-(4-Chlorophenyl)thien-2-ylmethyl)phthalimide

The following intermediates were made by the method of Intermediate A6:

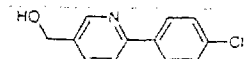
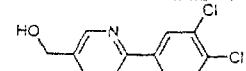
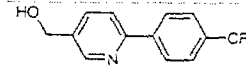
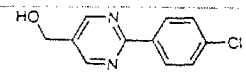
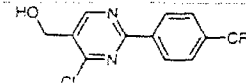
No.	Precursor	Structure	Name
A120	Int. A115		4-(4-Fluorophenyl)benzylamine
A121	Int. A116		4-(4-Trifluoromethylphenyl)benzylamine
A122	Int. A117		5-Aminomethyl-2-(4-fluorophenyl)pyridine

156/19
124/5

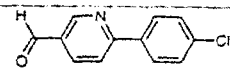
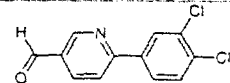
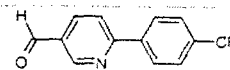
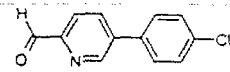
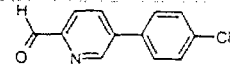
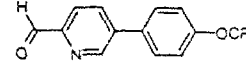
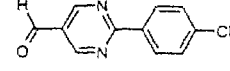
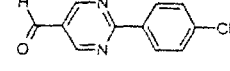
A123 Int. A118  5-Aminomethyl-2-(4-chlorophenyl)thiophene

A124: 4-Phenylbenzylamine is commercially available.

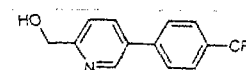
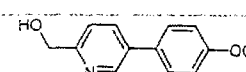
The following intermediates were made by the method of Intermediate A8:

No.	Precursor	Structure	Name
A125	Int. A24		5-Hydroxymethyl-2-(4-chlorophenyl)pyridine
A126	Int. A25		5-Hydroxymethyl-2-(3,4-dichlorophenyl)pyridine
A127	Int. A40		5-Hydroxymethyl-2-(4-trifluoromethylphenyl)-pyridine
A128	Int. A15		5-Hydroxymethyl-2-(4-chlorophenyl)pyrimidine
A129	Int. A150		4-chloro-5-hydroxymethyl-2-(4-trifluoromethylphenyl)pyrimidine

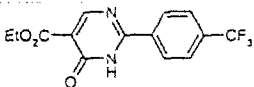
The following intermediates were made by the method of Intermediate A9:

No.	Precursor	Structure	Name
A130	Int. A125		5-Formyl-2-(4-chlorophenyl)pyridine
A131	Int. A126		5-Formyl-2-(3,4-dichlorophenyl)pyridine
A132	Int. A127		5-Formyl-2-(4-trifluoromethylphenyl)pyridine
A133	Int. A12		2-Formyl-5-(4-chlorophenyl)pyridine
A134	Int. A140		2-Formyl-5-(4-trifluoromethylphenyl)pyridine
A135	Int. A141		2-Formyl-5-(4-trifluoromethoxyphenyl)pyridine
A136	Int. A128		5-Formyl-2-(4-chlorophenyl)pyrimidine
A137	Int. A16		5-Formyl-2-(4-trifluoromethylphenyl)pyrimidine

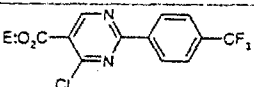
The following intermediates were made by the method of Intermediate A12:

Precursor	Structure	Name
Int. A134		2-hydroxymethyl-5-(4-trifluoromethylphenyl)-pyridine
Int. A135		2-hydroxymethyl-5-(4-trifluoromethoxyphenyl)-pyridine

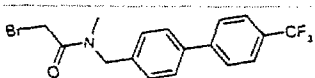
The following intermediate was made by the method of Intermediate A13:

No.	Precursors	Structure	Name
A145	diethyl ethoxymalonate, 4-trifluoromethyl- benzamidinium.HCl		Ethyl 2-(4-trifluoromethylphenyl)-4-oxopyrimidine-5-carboxylate

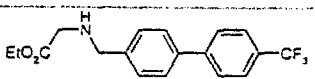
The following intermediate was made by the method of Intermediate A14:

No.	Precursor	Structure	Name
A150	Int. A145		Ethyl 2-(4-trifluoromethylphenyl)-4-chloro-pyrimidine-5-carboxylate

The following intermediate was made by the method of Intermediate A7:

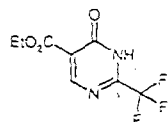
No.	Precursor	Structure	Name
A155	Int. A45		N-Methyl-N-(4-(4-trifluoromethylphenyl)benzyl)-bromoacetamide

The following intermediate was made by the method of Intermediate A11:

No.	Precursor	Structure	Name
A160	Int. A26		N-(Ethoxycarbonylmethyl)-4-(4-trifluoromethylphenyl)benzylamine

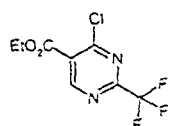
157
155

Intermediate B1 — Ethyl 2-trifluoromethyl-4-oxypyrimidine-5-carboxylate



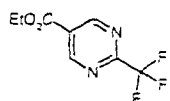
To a solution of trifluoroacetamide (36.5 g) and diethyl ethoxymalonate (71 g) in ethanol (300 ml) was added a solution of sodium ethoxide in ethanol (21 wt %, 109.5 ml) over 5 min. The mixture was heated at reflux for 6 h, then cooled, concentrated and water (200 ml) added. The resulting solid was collected by filtration, washed with cold water (50 ml) and diethyl ether (2 x 100 ml) and then suspended in water (400 ml). Dichloromethane (300 ml) was added and the mixture acidified with dilute HCl (2.5 M, 125 ml). The organic extract was washed with water, dried (MgSO₄) and evaporated to give the title compound as a buff solid (53 g, 68%). ¹H-NMR (CDCl₃) δ 12.00 (1H, br s), 9.18 (1H, s), 4.57 (2H, q), 1.49 (3H, t); ¹³C-NMR (CDCl₃) δ 171.4, 167.3, 160.4, 160.2 (q, *J* = 38 Hz), 118.8 (q, *J* = 276 Hz), 109.2, 63.8, 14.0; MS (APCI+) found (*M*+1) = 237, C₈H₇F₃N₂O₃ requires 236.

Intermediate B2 — Ethyl 2-trifluoromethyl-4-chloropyrimidine-5-carboxylate



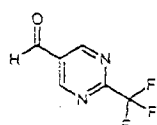
To a solution of ethyl 4-hydroxy-2-trifluoromethylpyrimidine-5-carboxylate (51.8 g) in dichloromethane (600 ml) cooled in an ice bath was added oxalyl chloride (57.4 ml) followed by dimethylformamide (0.2 ml). The mixture was stirred at room temperature for 16 h and then evaporated. Toluene was added and evaporated. The residue was dissolved in dichloromethane, washed with water, dried (MgSO₄) and evaporated to give the title compound as an orange oil (55.7 g, 100%). ¹H-NMR (CDCl₃) δ 9.25 (1H, s), 4.51 (2H, q), 1.46 (3H, t); ¹³C-NMR (CDCl₃) δ 162.0 (2C), 161.1, 158.1 (q, *J* = 39 Hz), 127.0, 118.9 (q, *J* = 276 Hz), 63.5, 14.4.

Intermediate B3 — Ethyl 2-trifluoromethylpyrimidine-5-carboxylate



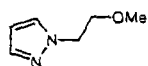
A mixture of ethyl 4-chloro-2-trifluoromethylpyrimidine-5-carboxylate (55.7 g), 10% palladium on carbon (0.3 g), ethanol (1000 ml) and *N,N*-diisopropylethylamine (90 ml) was shaken under hydrogen pressure maintained at 1 atmosphere for 2 h. The catalyst was then filtered off and the solvents evaporated. The residue was dissolved in dichloromethane, washed with ammonium chloride solution, then water, dried (MgSO₄) and evaporated to give the title compound as a buff solid (48 g, 100%). ¹H-NMR (CDCl₃) δ 9.42 (2H, s), 4.51 (2H, q), 1.45 (3H, t); ¹³C-NMR (CDCl₃) δ 162.7, 159.4 (2C), 159.3 (q, *J* = 37 Hz), 126.3, 119.6 (q, *J* = 275 Hz), 62.9, 14.4.

Intermediate B4 — 2-Trifluoromethyl-5-formylpyrimidine



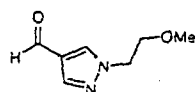
To a solution of ethyl 2-trifluoromethylpyrimidine-5-carboxylate (5.17 g) in toluene (120 ml) cooled in dry ice/acetone was added a solution of diisobutylaluminium hydride (25 wt %, 31 ml) over 15 min. The mixture was stirred at -78°C for 45 min, then dilute HCl (2M, 120 ml) was added cautiously. After allowing the mixture to warm to room temperature diethyl ether was added. The organic phase was separated, washed with water, then brine, dried (MgSO₄) and evaporated to give the title compound as a colourless solid (3.46 g, 84%). ¹H-NMR (CDCl₃) δ 10.29 (1H, s), 9.37 (2H, s); ¹³C-NMR (CDCl₃) δ 187.7, 159.6 (q, J = 38 Hz), 159.1 (2C), 129.6, 119.2 (q, J = 276 Hz).

Intermediate B5 – 1-(2-Methoxyethyl)pyrazole



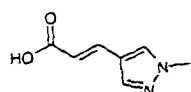
- 2-Bromomethyl methyl ether (10.22 g) was added dropwise with stirring to a mixture of pyrazole (5.0 g), finely powdered potassium hydroxide (8.25 g) and tetrabutylammonium bromide (1.19 g) with occasional ice cooling to keep the temperature below 10°C. The mixture was allowed to stand at room temperature for 48 hours, then columned on silica and eluted with ether. Product fractions were evaporated to a pale green oil (7.27 g). ¹H-NMR (CDCl₃) δ 3.33 (3H, s), 3.75 (2H, t), 4.30 (2H, t), 6.25 (1H, s), 7.47 (1H, d), 7.52 (1H, d); MS (APCI+) found (M+H) = 127; C₆H₁₀N₂O requires 126.

Intermediate B6 – 1-(2-Methoxyethyl)pyrazole-4-carboxaldehyde



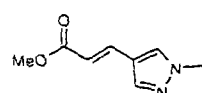
- A solution of 1-(2-methoxyethyl)pyrazole (7.27 g) in dry DMF (11.4 ml) was heated to 90°C, then phosphorus oxychloride (5.4 ml) was added dropwise over 1 hour, maintaining the temperature between 95-100°C. After heating for a further 2 hours, the mixture was cooled and poured onto ice. Sodium hydroxide was added to adjust the mixture to pH 4, then the product was extracted into dichloromethane. Drying and evaporation of the organic extracts yielded a brown oil (7.19 g). ¹H-NMR (CDCl₃) δ 3.34 (3H, s), 3.75 (2H, m), 4.32 (2H, m), 7.98 (1H, s), 8.02 (1H, s), 9.85 (1H, s).

Intermediate B10 – 3-(1-Methylpyrazol-4-yl)acrylic acid



- A mixture of 1-methylpyrazole-4-carboxaldehyde (85.55 g), malonic acid (80.85 g), pyridine (69.2 ml) and piperidine (1.5 ml) was heated to 110°C under argon for 4 hours. After cooling, water (100 ml) was added, followed by aqueous ammonia (75 ml) to obtain a clear solution, which was acidified to pH 1 with hydrochloric acid. The resulting solid was filtered off, washed with water and dried to obtain the title compound (93.5 g). ¹H-NMR (d₆-DMSO) δ 3.83 (3H, s), 6.18 (1H, d), 7.44 (1H, d), 7.83 (1H, s), 8.07 (1H, s). (APCI) found (M+H)=153. C₇H₈N₂O₂ requires 152.

Intermediate B11 – Methyl 3-(1-methylpyrazol-4-yl)acrylate

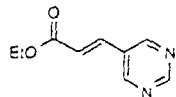


- 3-(1-Methylpyrazol-4-yl)acrylic acid (86.8 g) was added to a solution of sulphuric acid (20 ml) in methanol (690 ml), and the mixture refluxed for 2.5 hours, cooled, then poured onto ice. The acid was

158
156

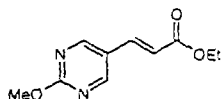
neutralised with aqueous sodium hydroxide and the product extracted into dichloromethane, which was dried and evaporated. Crystallisation from ether/petrol gave methyl 3-(1-methylpyrazol-4-yl)acrylate (89.0 g). $^1\text{H-NMR}$ ($\text{d}_6\text{-DMSO}$) δ 3.77 (3H,s), 3.91 (3H,s), 6.16 (1H,d), 7.54 (1H,s), 7.56 (1H,d), 7.69 (1H,s). (APCI) found (M+H)=167. $\text{C}_8\text{H}_{10}\text{N}_2\text{O}_2$ requires 166.

5 Intermediate B12 – Ethyl 3-(5-pyrimidinyl)acrylate



A mixture of 5-bromopyrimidine (5.93g), ethyl acrylate (5.08g), palladium acetate (0.112g), triphenyl phosphine (0.23g) and triethylamine (4.5g) was stirred at 150°C in a pressure vessel for 6 hours. After cooling overnight, water (50ml) was added to the dark residue, and the product was extracted into toluene. Drying, charcoaling and evaporation gave a pale oil, which was triturated with pet. ether to obtain ethyl 3-(5-pyrimidinyl)acrylate (4.78g). $^1\text{H-NMR}$ (CDCl_3) δ 1.36 (3H,t), 4.27 (2H,q), 6.59 (1H,d), 7.62 (1H,d), 8.88 (2H,s), 9.20 (1H,s).

Intermediate B13 – Ethyl 3-(2-methoxypyrimidin-5-yl)acrylate



A mixture of 2-methoxy-5-bromopyrimidine (75.43 g, 0.399 mol), ethyl acrylate (47.5 ml, 0.439 mol), palladium (II) acetate (1.07 g, 0.0048 mol), tri-*o*-tolylphosphine (2.92 g, 0.0096 mol) and triethylamine (84 ml) were heated at 135°C (oil bath temperature) with stirring under argon for 12 h. After allowing to cool the solid mass was dissolved in water and ethyl acetate, filtered, and the aqueous phase separated and further extracted with ethyl acetate. The combined extracts were washed with saturated aqueous ammonium chloride, dried (MgSO_4) and evaporated. The solid thus obtained was triturated with ether/light petrol (1:3, 350 ml), filtered, washed and dried, yield 52.41 g (63%). $^1\text{H-NMR}$ (CDCl_3) δ 1.33 (3H, t), 4.06 (3H, s), 4.28 (2H, q), 6.45 (1H, d), 7.58 (1H, d), 8.67 (2H, s); MS (APCI+) found (M+H) = 209; $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_3$ requires 208.

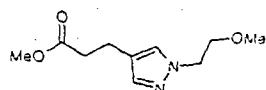
The following intermediates were prepared by the method of intermediate B10 (Knoevenagel):

No.	Precursors	Structure	Name
B14	Int. B4		3-(2-Trifluoromethylpyrimidin-5-yl)acrylic acid
B15	Int. B6		3-(1-(2-Methoxyethyl)pyrazol-4-yl)acrylic acid

The following intermediates were prepared by the method of intermediate B11 (esterification):

No.	Precursors	Structure	Name
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B23 Int. B17

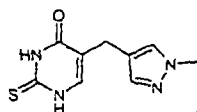


Methyl 3-(1-(2-methoxyethyl)pyrazol-4-yl)propionate

The following intermediates were made by the method of Intermediate B21 (ethyl esters in ethanol solvent, methyl esters in methanol):

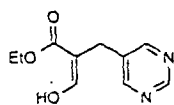
No.	Precursors	Structure	Name
B24	Int. B16		Methyl 3-(2-trifluoromethylpyrimidin-5-yl)propanoate
B25	Int. B18		Ethyl 3-(2-dimethylamino-5-pyrimidyl)propionate
B26	Int. B19		Ethyl 3-[2-(4-morpholino)-5-pyrimidyl]propionate

Intermediate B30 – 5-((1-Methylpyrazol-4-yl)methyl)-2-thiouracil



- 5 A solution of methyl 3-(1-methylpyrazol-4-yl)propionate (170 g) and methyl formate (131 ml) in dry diethyl ether (2000 ml) was added dropwise over 2 hours to a stirred, ice-cooled solution of potassium tert-butoxide (284g) in dry THF (1800 ml) under argon. The mixture was then allowed to warm to room temperature and stirring continued for 16 hours. The solvents were evaporated in vacuo to a pale solid.
- 10 Methanol (2500 ml) and thiourea (154 g) were added, and the mixture was heated to 50°C for 16 hours with vigorous stirring. The solvent was evaporated, and the pale brown solid residue was taken up in water (750 ml). The ice-cooled solution was adjusted to pH3 with hydrochloric acid, stirred for 2 hours in the ice bath, then the precipitate was filtered off and washed with water and ether to obtain the title compound (120 g). ¹H-NMR (d₆-DMSO) δ 3.33 (3H,s), 3.75 (3H,s), 7.15 (1H,s), 7.23 (1H,s), 7.46 (1H,s), 12.2 (1H,br s), 12.4 (1H,br s). (APCI) M+H=223. C₉H₁₀N₄OS requires 222.

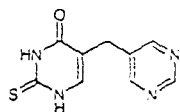
15 Intermediate B31 – Ethyl 2-formyl-3-(5-pyrimidyl)propionate



- A mixture of ethyl 3-(5-pyrimidyl)propionate (2.28g) and ethyl formate (1.41ml) dissolved in dry dimethoxyethane (5ml) was added dropwise over 30 min to a suspension of sodium hydride (60%, 4.0g) in DME (5 ml) under nitrogen, keeping the temperature below 0°C. Stirring was continued for a further
- 20 24h, then the mixture was poured onto ice and washed with ether. The aqueous layer was adjusted to pH 7, then evaporated and the residue extracted with acetone. Filtration and evaporation gave crude product, which was taken up in ethyl acetate, charcoaled, dried and evaporated to give ethyl 2-formyl-3-(5-

pyrimidyl)propionate. Like other compounds of this type, this proved difficult to characterise and was used without further purification.

Intermediate B32 – 5-(Pyrimid-5-ylmethyl)-2-thiouracil

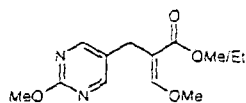


- 5 Sodium (0.25 g) was dissolved in ethanol (5 ml), thiourea (0.77 g) added, and the mixture stirred under reflux for 1 hour. A solution of ethyl 2-formyl-3-(5-pyrimidyl)propionate (1.99 g) in ethanol (5 ml) was added slowly, and reflux continued for 18 hours. The solvent was evaporated, and the residue taken up in water and washed with dichloromethane. The aqueous solution was acidified to pH 5, and the precipitate filtered off, washed with water and dried to obtain 5-(pyrimid-5-ylmethyl)-2-thiouracil (0.71 g). ¹H-NMR (d₆-DMSO) δ 3.58 (2H,s), 7.54 (1H,s), 8.70 (2H,s) and 9.02 (1H,s). MPt 265-6°C
- 10

The following intermediates were made by the method of Intermediate B30 (thiouracils):

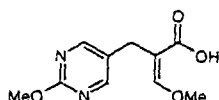
No.	Precursors	Structure	Name
B33	Int. B21		5-(2-Methoxypyrimidin-5-ylmethyl)-2-thiouracil
B34	Int. B24		5-(2-Trifluoromethylpyrimidin-5-ylmethyl)-2-thiouracil
B35	Int. B26		5-(2-(4-Morpholino)pyrimidin-5-ylmethyl)-2-thiouracil
B36	Int. B25		5-(2-Dimethylaminopyrimidin-5-ylmethyl)-2-thiouracil
B37	Int. B23		5-((1-(2-Methoxyethyl)pyrazol-4-yl)methyl)-2-thiouracil
B38	ethyl 3-phenyl-propionate		5-Benzyl-2-thiouracil
B39	ethyl 3-(4-chlorophenyl)-propionate		5-(4-Chlorobenzyl)-2-thiouracil

Intermediate B40 – 2-(Methoxymethylene)-3-(2-methoxypyrimidin-5-yl)propionic acid, mixed methyl/ethyl esters



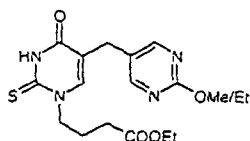
To a stirring suspension of sodium hydride (0.83 g of a 60% dispersion in oil) in anhydrous 1,2-dimethoxyethane (6 ml) was added dropwise a solution of methyl formate (1.54 ml) and ethyl 3-(2-methoxypyrimidin-5-yl)propionate (3.5 g) in anhydrous 1,2-dimethoxyethane (6 ml) at such a rate as to maintain the reaction temperature at 25-30°C. After 1 h, ether was added and the precipitated oil allowed to settle. The solution was decanted off and replaced with fresh ether, and the oil slowly solidified. The solid 2-(hydroxymethylene) derivative was filtered, washed with ether and dried, yield 3.8 g. A 1.33 g portion was suspended in dimethyl formamide (10 ml) together with anhydrous potassium carbonate (1.15 g), and a solution of dimethyl sulphate (0.48 ml) in dimethylformamide (10 ml) was added dropwise with stirring over 30 min. After 16 h the solvent was evaporated and the residue treated with water and extracted with ethyl acetate. The extracts were washed with water, dried (MgSO₄) and evaporated to give the product as an oil, yield 0.91 g. ¹H-NMR (CDCl₃) δ 1.23 (3H, t), 3.46 (2H, s), 3.69 (3H, s, methyl ester), 3.88 (3H, s), 3.97 (3H, s), 4.16 (2H, q), 7.39 (1H, s), 8.40 (2H, s). 3:2 ratio of methyl:ethyl esters. MS (APCI+) found (M+1) = 253, 239 (ethyl and methyl esters); C₁₂H₁₆N₂O₄ requires 252, C₁₁H₁₄N₂O₄ requires 238.

15 **Intermediate B41 – 2-(Methoxymethylene)-3-(2-methoxypyrimidin-5-yl)propionic acid**



A suspension of the mixed esters of Intermediate B40 (0.9 g) in 2M aqueous sodium hydroxide (3.6 ml) was stirred at ambient temperature for 16 h to give a clear solution. This was diluted with water, extracted with dichloromethane and evaporated to about half volume, then acidified to pH 3-4 (2M hydrochloric acid) when the product crystallised out. The white solid was filtered, washed with ice-cold water and dried, yield 0.46 g. ¹H-NMR (CDCl₃) δ 3.43 (2H, s), 3.91 (3H, s), 3.99 (3H, s), 7.49 (1H, s), 8.42 (2H, s); MS (APCI+) found (M+1) = 225, C₁₀H₁₂N₂O₄ requires 224.

Intermediate B42 – 1-(3-Ethoxycarbonylprop-1-yl)-5-(2-methoxypyrimidin-5-ylmethyl)-2-thiouracil



Oxalyl chloride (3.94ml, 2 equiv) was added over 5min to a solution of Intermediate B41 (5.0g, 1 equiv) and DMF (1 drop) in dry dichloromethane (50ml), then the mixture was stirred under argon for 4h. The solvent was evaporated, and the residue twice taken up in dichloromethane and re-evaporated to remove volatile impurities. The acid chloride was dissolved in acetonitrile (100ml) and treated with dry, powdered potassium thiocyanate (3.2g, 1.5 equiv). The resulting suspension was stirred under argon for 24h, then evaporated to dryness. The residue was suspended in dry DMF (100ml), cooled to 10°C, ethyl 4-aminobutyrate hydrochloride (4.60g, 1.25 equiv) and triethylamine (7.34ml, 2.4 equiv) added, and the mixture stirred at room temperature for 20h. Sodium methoxide solution (prepared by dissolving sodium (1.26g, 2.5 equiv) in methanol (25ml)) was added to the DMF solution, and the mixture heated to 110°C for 2h. The solvent was evaporated, water was added, and acidified to pH 5 with acetic acid, then the product extracted into ethyl acetate. Drying, evaporation, and trituration with ether gave a pale brown solid (4.55g). Some ether/ester exchange took place during the reaction, and the title compound was obtained mixed with ca 30% of the corresponding 2-ethoxypyrimidine. ¹H-NMR (DMSO-d₆) δ 1.17 (3H, t), 1.31 (t, ethoxy), 1.97 (2H, t), 2.36 (2H, t), 3.49 (s, ethoxy), 3.51 (s, methoxy), 3.88 (s, methoxy),

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15062

OFICINA DE PATENTES

SOLICITUD DE PATENTE

1. Su referencia: **ACC/JR/P32505**

2. Solicitud No. **0002096.6** 28 de enero de 2000

3. Nombre completo y código postal de cada solicitante:

Dirección: SMITHKLINE BEECHAM plc.
New Horizons Court,
Brentford, Mddlesex TW8 9EP

No. APD 7605058001

Si el solicitante es una entidad, indique el país/estado de constitución:

REINO UNIDO

4. TITULO DEL INVENTO:

COMPUESTOS NOVEDOSOS

5. NOMBRE DE SU AGENTE:

Nombre del Agente: **CORPORATE INTELLECTUAL PROPERTY**

Dirección para notificaciones: **SMITHKLINE BEECHAM PLC
TWO NEW HORIZONS COURT
BRENTFORD
MIDDLESEX TW8 9EP**

NO. ADP Patentes 4471231005

6. N/A

7. N/A

8. SI

164
159 57

9. Número de hojas radicadas (En inglés). Descripción: 61 Reivindicaciones: 4

Resumen : - Dibujos: -

10. Solicitud de examen preliminar y búsqueda:

11. Solicitamos se nos adjudique una patente con base en esta solicitud.

A C CONNELL

27 de enero de 2000

12. Nombre y teléfono del contacto en el Reino Unido Nombre y teléfono del contacto en el
Reino Unido (FIRMA) A C CONNELL 01279 644395

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LEGALIZACIONES

OFICINA DE PATENTES

Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

El suscrito, un funcionario debidamente autorizado conforme a los Artículos 74(1) y (4) de la Ley de Desreglamentación y Contratación de 1994 para firmar y expedir certificados en nombre del Contralor General, certifico que la copia adjunta es una copia correcta de los documentos archivados originalmente con respecto a la solicitud de patente que allí se identifica.

De acuerdo con las Reglamentaciones de Patentes de 1982 (Re-registro de Compañías), si una compañía nombrada en este certificado y en los documentos adjuntos se ha vuelto a registrar según la Ley de Compañías de 1980 con el mismo nombre con el que fue registrada inmediatamente antes del re-registro, salvo la sustitución o inclusión como la última parte del nombre de las palabras “sociedad anónima” o su equivalente en galés, las referencias al nombre de la compañía y sus documentos adjuntos serán tratadas como referencias al nombre con el cual fue re-registrada.

De acuerdo con las reglas, las palabras “sociedad anónima” (o en inglés *public limited company*) pueden ser reemplazadas por las letras p.l.c, plc. P.L.C ó PLC.

El re-registro bajo la Ley de Compañías no constituye una nueva entidad legal sino simplemente somete a la compañía a ciertas normas de ley adicionales.

(FIRMA) ANDREW BREWER

FECHA: 15 de marzo de 2000

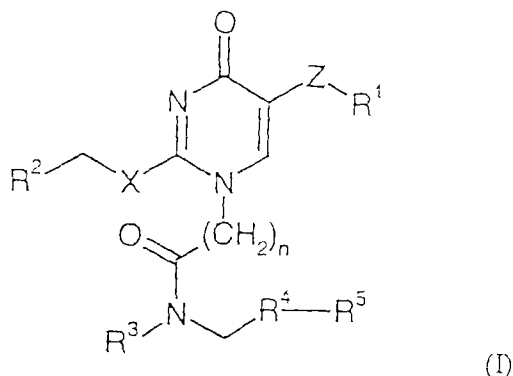
(SELLO DE LACRE)

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COMPUESTOS NOVEDOSOS

REIVINDICACIONES:

1. Un compuesto de la fórmula (I):



en la cual:

R^1 es un grupo aril o heteroaril, sustituido opcionalmente por 1, 2, 3 o 4 sustituyentes que pueden ser el mismo o diferente, seleccionados de alquil $C_{(1-18)}$, alcoxi $C_{(1-18)}$, alquiltio $C_{(1-18)}$, aril alcoxi $C_{(1-18)}$, hidroxil, halógeno, CN, COR^6 , carboxi, $COOR^6$, $CONR^6R^7$, NR^6COR^7 , $SO_2NR^6R^7$, $NR^6SO_2R^7$, NR^9R^{10} , mono a perfluoro-alquil $C_{(1-4)}$ y mono a perfluoro-alcoxi $C_{(1-4)}$, o como un solo sustituyente, opcionalmente en combinación con otro sustituyente según se describe arriba, CH_2COH o una sal de lo mismo, CH_2COOR^8 , $CH_2CONR^9R^{10}$, CH_2CN , $(CH_2)_mNR^9R^{10}$, $(CH_2)_mOH$ o $(CH_2)_mOR^6$, donde m es un entero de 1 a 3;

R^2 es un grupo aril o heteroaril, sustituido opcionalmente por 1, 2, 3 o 4 sustituyentes que pueden ser el mismo o diferente seleccionados de alquil $C_{(1-18)}$, alcoxi $C_{(1-18)}$, alquiltio $C_{(1-18)}$, aril alcoxi $C_{(1-18)}$, hidroxil, halógeno, CN, COR^6 , carboxi, $COOR^6$, $CONR^9R^{10}$, NR^6COR^7 , $SO_2NR^9R^{10}$, $NR^6SO_2R^7$, NR^9R^{10} , mono a perfluoro-alquil $C_{(1-4)}$, mono a perfluoro-alcoxiaril $C_{(1-4)}$ y aril-alquil $C_{(1-4)}$;

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R^3 es hidrógeno o alquil $C_{(1-4)}$ que puede ser insitituido o sustituido por hidroxi, OR^6 , COR^6 , carboxi, $COOR^6$, $CONR^9R^{10}$, NR^9R^{10} , mono o di-(hidroxi-alquil $C_{(1-6)}$ amino o N-hidroxi alquil $C_{(1-6)}$ -N-alquil $C_{(1-6)}$ amino;

R^4 es un anillo aril o heteroaril sustituido opcionalmente por 1, 2, 3 o 4 sustituyentes que pueden ser los mismos o diferentes seleccionados de alquil $C_{(1-18)}$, alcoxi $C_{(1-18)}$, alquiltio $C_{(1-18)}$, aril alcoxi $C_{(1-18)}$, hidroxi, halógeno, CN, COR^6 , carboxi, $COOR^6$, $CONR^9R^{10}$, NR^6COR^7 , $SO_2NR^9R^{10}$, $NR^6SO_2R^7$, NR^9R^{10} , mono a perfluoro-alquil $C_{(1-4)}$ y mono a perfluoro-alcoxi $C_{(1-4)}$;

R^5 es un anillo aril que es además sustituido por 1, 2, 3 o 4 sustituyentes que pueden ser los mismos o diferentes seleccionados de alquil $C_{(1-18)}$, alcoxi $C_{(1-18)}$, alquiltio $C_{(1-18)}$, aril alcoxi $C_{(1-18)}$, hidroxi, halógeno, CN, COR^6 , carboxi, $COOR^6$, $CONR^9R^{10}$, NR^6COR^7 , $SO_2NR^9R^{10}$, $NR^6SO_2R^7$, NR^9R^{10} , mono a perfluoro-alquil $C_{(1-4)}$ y mono a perfluoro-alcoxi $C_{(1-4)}$;

R^6 y R^7 son independientemente hidrógeno o alquil $C_{(1-20)}$, por ejemplo alquil $C_{(1-4)}$ (por ej: metil o etil);

R^8 es alquil $C_{(1-4)}$ o un grupo éster hidrolizable *in vivo* farmacéuticamente aceptable;

R^9 y R^{10} que pueden ser los mismos o diferentes es cada uno seleccionado de hidrógeno, alquil $C_{(1-2)}$, CH_2R^{11} , $CHR^{12}CO_2H$ o una sal de lo mismo, o R^9 y R^{10} junto con el nitrógeno al que están fijos forman un anillo de 4- a 7-, preferiblemente de 5- a 7- miembros que contiene opcionalmente uno o más heteroátomos seleccionados de oxígeno, nitrógeno y azufre, y sustituidos opcionalmente por uno o dos sustituyentes seleccionados de hidroxi, oxo alquil $C_{(1-4)}$, alquil $C_{(1-4)}CO$, aril, por ej: fenil o aralquil, por ej: bencil, por ejemplo, morfolina o piperazina;

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R^{11} es COOH o una sal de lo mismo, COOR^8 , CONR^6R^7 , CN , CH_2OH o CH_2OR^6 ;

R^{12} es una cadena lateral amino ácida tal como CH_2OH de serina;

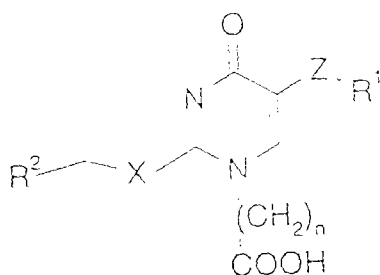
n es un entero de 1 a 4, preferiblemente, 1 ó 3;

X es O o S ; y

Z es $\text{CR}^{13}\text{R}^{14}$, donde R^{13} y R^{14} son cada uno hidrógeno o alquil $\text{C}_{(1-4)}$, o R^{13} y R^{14} junto con el átomo de carbono que interviene forma un anillo cicloalquil $\text{C}_{(3-6)}$.

2. Una composición farmacéutica que comprende un compuesto de la fórmula (I) según la reivindicación 1, y un vehículo farmacéuticamente aceptable.
3. Un compuesto de la fórmula (I) según la reivindicación 1, para uso en terapia.
4. El uso de un compuesto de la fórmula (I) según la reivindicación 1 para la manufactura de un medicamento para el tratamiento de aterosclerosis.
5. Un método de tratamiento de un estado de enfermedad asociado con la actividad de la enzima Lp-PLA_2 , cuyo método implica tratar a un paciente que lo requiera con una cantidad terapéuticamente efectiva de un compuesto de la fórmula(I) según la reivindicación 1.
6. Un proceso para preparar un compuesto de la fórmula (I) según se define en la reivindicación 1, dicho proceso consiste en:
 - a) hacer reaccionar un compuesto de la fórmula (II):

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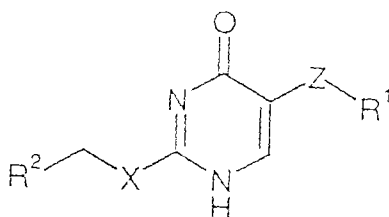
en el cual X, Y, Z, R¹ y R² son según se define arriba,

con un compuesto de la fórmula (III):



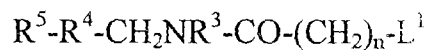
en la cual R³, R⁴ y R⁵ son según se define antes; bajo condiciones de formado de amida;

b) hacer reaccionar un compuesto de la fórmula (IV):



en la cual X, Z, R¹ y R² son según se define arriba,

con un compuesto de la fórmula (V):

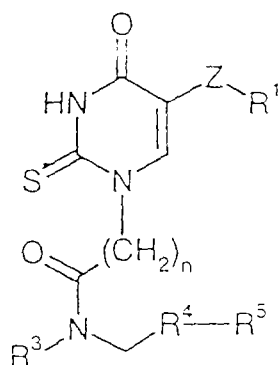


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en la cual n , R^3 , R^4 y R^5 son según se define arriba, y L^1 es un grupo saliente tal como halógeno, por ejemplo bromo o yodo,

en la presencia de una base tal como una amina secundaria o terciaria, por ejemplo di-isopropiletilamina, en un solvente inerte tal como diclorometano;

c) cuando X es S, hacer reaccionar un compuesto de la fórmula (VI):



en la cual n , R^3 , R^4 y R^5 son según se define arriba,

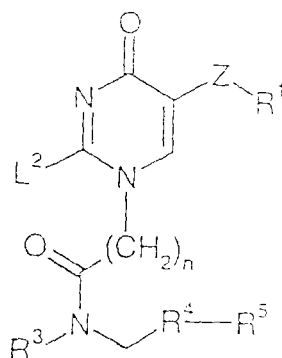
con un compuesto de la fórmula (VII):



en la cual R^2 y L^1 son según se define arriba,

en la presencia de una base tal como una amina secundaria o terciaria, por ejemplo di-isopropiletilamina, en un solvente inerte tal como diclorometano; o

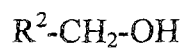
d) cuando X es O, hacer reaccionar un compuesto de la fórmula (VIII):



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en la cual n , R^1 , R^3 , R^4 , y R^5 son según se define arriba, y L^2 es un grupo saliente tal como halógeno o alquiltio, por ejemplo, metiltio,

con un compuesto de la fórmula (IX):



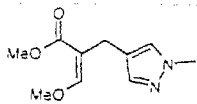
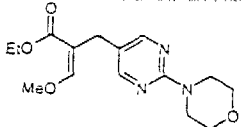
en la cual R^2 es según se describe arriba,

en la presencia de una base tal como 4-dimetilaminopiridina, en un solvente inerte, tal como piridina.

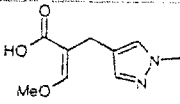
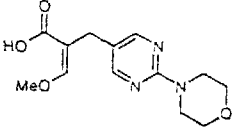
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4.04 (2H, q), 4.16 (2H, t), 4.31 (q, ethoxy), 7.81 (1H, s), 8.48 (s, ethoxy), 8.50 (s, methoxy), 12.50 (bs, NH) (light brown solid).

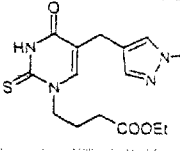
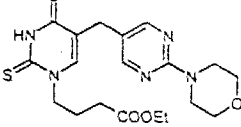
The following intermediates were prepared by the method of intermediate B40:

No.	Precursors	Structure	Name
B43	Int. B20		Methyl 2-(methoxymethylene)-3-(1-methylpyrazol-4-yl)propionate
B44	Int. B26		Ethyl 2-(methoxymethylene)-3-(2-(4-morpholino)pyrimidin-5-yl)propionate

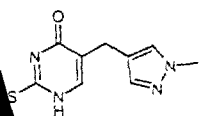
The following intermediates were prepared by the method of intermediate B41:

No.	Precursors	Structure	Name
B45	Int. B43		2-(Methoxymethylene)-3-(1-methylpyrazol-4-yl)propionic acid
B46	Int. B44		2-(Methoxymethylene)-3-(2-(4-morpholino)pyrimidin-5-yl)propionic acid

The following intermediates were prepared by the method of intermediate B42:

No.	Precursors	Structure	Name
B47	Int. B45		1-(3-Ethoxycarbonylprop-1-yl)-5-(1-methylpyrazol-4-ylmethyl)-2-thiouracil
B48	Int. B46		1-(3-Ethoxycarbonylprop-1-yl)-5-(2-(4-morpholino)pyrimidin-5-ylmethyl)-2-thiouracil

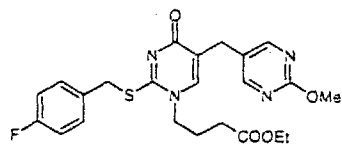
Intermediate B50 – 2-(4-Fluorobenzylthio)-5-((1-methylpyrazol-4-yl)methyl)pyrimidin-4-one



of 5-((1-methylpyrazol-4-yl)methyl)-2-thiouracil (118 g), 4-fluorobenzyl chloride (76.8 g), carbonate (183.5 g), and dry DMF (100 ml) was stirred under argon at 80°C for 16 hours, then evaporated. The solid residue was suspended in water (1500 ml) with vigorous stirring, then with hydrochloric acid and stirred for a further hour. The white solid was filtered off with water and ether to obtain the title compound (168 g). ¹H-NMR (d6-DMSO) δ 3.47 (2H,

s), 3.81 (3H, s), 4.41 (2H, s), 7.19 (2H, s), 7.29 (1H, s), 7.48 (3H, m), 7.84 (1H, s), 12.74 (1H, br.s); MS (APCI+) found (M+1) = 331; C₁₆H₁₅FN₄OS requires 330.

Intermediate B51 – 1-(3-Ethoxycarbonylprop-1-yl)-2-(4-fluorobenzyl)thio-5-(2-methoxypyrimid-5-ylmethyl)pyrimidin-4-one



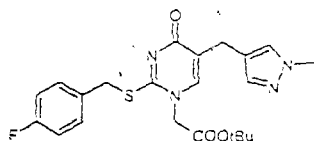
Intermediate B24 (1.0g, 1 equiv) in dichloromethane (60ml) was treated with diisopropylethylamine (0.63ml, 1.3 equiv) followed by 4-fluorobenzyl bromide (0.38ml, 1.1 equiv), giving an orange solution which was stirred under argon for 4h, then washed with water, dried and evaporated. Chromatography (silica, 5% ethanol in ethyl acetate) eluted first the 2-ethoxypyrimidine impurity, followed by the title compound (0.35g). ¹H-NMR (CDCl₃) δ 1.25 (3H, t), 2.03 (2H, m), 2.33 (2H, t), 3.64 (2H, s), 3.83 (2H, m), 3.99 (3H, s), 4.12 (2H, q), 4.47 (2H, s), 6.98 (3H, m), 7.37 (2H, m), 8.46 (2H, s); MS (APCI+) M+1=473; C₂₃H₂₅FN₄O₄S requires 472 (pale waxy solid).

The following intermediates were prepared by the method of intermediate B50:

No.	Precursors	Structure	Name
B52	Int. B32		2-(4-Fluorobenzylthio)-5-((pyrimid-5-yl)-methyl)pyrimidin-4-one
B53	Int. B33		2-(4-Fluorobenzylthio)-5-((2-methoxypyrimid-5-yl)methyl)pyrimidin-4-one
B54	Int. B34		2-(4-Fluorobenzylthio)-5-((2-trifluoromethylpyrimid-5-yl)methyl)pyrimidin-4-one
B55	Int. B35		2-(4-Fluorobenzylthio)-5-(2-(4-morpholinyl)pyrimid-5-ylmethyl)pyrimidin-4-one
B56	Int. B36		2-(4-Fluorobenzylthio)-5-((2-methylpyrimid-5-yl)methyl)pyrimidin-4-one
B57	Int. B33 + 3,4-difluorobenzyl chloride		2-(3,4-Difluorobenzylthio)-5-((2-methoxypyrimid-5-yl)methyl)pyrimidin-4-one
B58	Int. B37		2-(4-Fluorobenzylthio)-5-((2-ethoxypyrimid-5-yl)methyl)pyrimidin-4-one

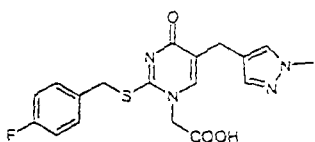
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Intermediate B70 – 1-(tert-Butoxycarbonylmethyl)-2-(4-fluorobenzylthio)-5-((1-methylpyrazol-4-yl)methyl)pyrimidin-4-one



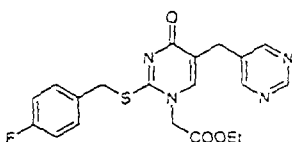
A mixture of 2-(4-fluorobenzylthio)-5-((1-methylpyrazol-4-yl)methyl)pyrimidin-4-one (175 g), tert-butyl iodoacetate (128.3 g), diisopropylethylamine (101.5 ml) and dichloromethane (200 ml) was stirred at room temperature under argon for 48 hours. The solution was washed with aq. sodium bicarbonate then with aq. ammonium chloride, dried and evaporated to a pale viscous oil. Ethyl acetate (300 ml) was added, the precipitate was filtered off and discarded, and the solution was chromatographed (silica, 2.5%-10% methanol + 0.5% aq. ammonia in dichloromethane). Product fractions were evaporated to an orange solid which solidified on standing (140 g). $^1\text{H-NMR}$ (d_6 -DMSO) δ 1.36 (9H,s), 3.37 (2H,s), 3.76 (3H,s), 4.42 (2H,s), 4.65 (2H,s), 7.13 (2H,m), 7.23 (1H,m), 7.45 (4H,m); MS (APCI+) found ($M+1$) = 445; $\text{C}_{22}\text{H}_{25}\text{FN}_4\text{O}_3\text{S}$ requires 444.

Intermediate B71 – 1-(Carboxymethyl)-2-(4-fluorobenzylthio)-5-((1-methylpyrazol-4-yl)methyl)-pyrimidin-4-one



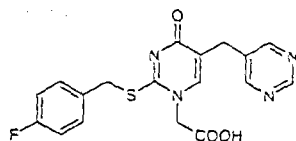
1-(tert-Butoxycarbonylmethyl)-2-(4-fluorobenzylthio)-5-((1-methylpyrazol-4-yl)methyl)pyrimidin-4-one (96.8 g) was dissolved in dichloromethane (195 ml), cooled in ice/water, and trifluoroacetic acid (130 ml) added slowly with rapid stirring. After a further 36 hours stirring, the solvent was evaporated and the glassy residue triturated with ether; yield 78.6g. $^1\text{H-NMR}$ (d_6 -DMSO) δ 3.36 (2H, s), 3.76 (3H, s), 4.41 (2H, s), 4.67 (2H, s), 7.14 (2H, m), 7.23 (1H, s), 7.43-7.49 (4H, m); MS (APCI+) found ($M+1$) = 389; $\text{C}_{18}\text{H}_{17}\text{FN}_4\text{O}_3\text{S}$ requires 388.

Intermediate B72 – 1-Ethoxycarbonylmethyl-2-(4-fluorobenzylthio)-5-(pyrimid-5-ylmethyl)-pyrimidin-4-one



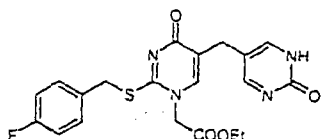
A mixture of intermediate B52 (10g), ethyl bromoacetate (3.38ml), diisopropylethylamine (5.84ml) and dichloromethane (50ml) was stirred overnight, then the solution was washed sequentially with aqueous ammonium chloride and aqueous sodium bicarbonate. Chromatography (silica, 5-10% methanol in ethyl acetate) and trituration with ether gave the desired product (7.02g). $^1\text{H-NMR}$ (CDCl_3) δ 1.26 (3H, t), 3.71 (2H, s), 4.26 (2H, q), 4.46 (2H, s), 4.48 (2H, s), 6.91 (1H, s), 6.98 (2H, m), 7.35 (2H, m), 8.70 (2H, s), 9.09 (1H, s); MS (APCI+) $M+1=415$, $\text{C}_{20}\text{H}_{19}\text{FN}_4\text{O}_3\text{S}$ requires 414. MPt 145.1°C.

Intermediate B73 – 1-Carboxymethyl-2-(4-fluorobenzyl)thio-5-(pyrimid-5-ylmethyl)pyrimidin-4-one



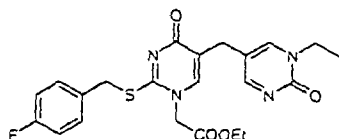
0.5M aqueous sodium hydroxide (33.8ml) was added slowly to a solution of Intermediate B72 (7.01g) in dioxan (150ml). The mixture was stirred for 2.5h at room temperature, then the dioxan was evaporated. water added, and the mixture acidified with aqueous sodium bisulfate. The precipitate was filtered off, washed with water and dried to obtain the desired product (6.31g). ¹H-NMR (d₆-DMSO) δ 3.59 (2H, s), 4.41 (2H, s), 4.67 (2H, s), 7.11 (2H, m), 7.45 (2H, m), 7.72 (1H, s), 8.70 (2H, s), 9.03 (1H, s), 13.55 (1H, bs); MS (APCI-) M-1=385, C₁₈H₁₅FN₄O₃S requires 386. MPt 206-207°C.

Intermediate B74 — 1-Ethoxycarbonylmethyl-2-(4-fluorobenzyl)thio-5-(2-oxopyrimid-5-ylmethyl)pyrimidin-4-one



Prepared from Intermediate B86 by the method of Example 21, except using only 2 equivalents of B-bromocatecholborane. ¹H-NMR (d₆-DMSO) δ 1.28 (3H, t), 4.26 (4H, q), 4.53 (2H, s), 4.90 (2H, s), 7.26 (2H, m), 7.57 (2H, m), 7.69 (1H, s), 8.25 (2H, br. s); MS (APCI+) found (M+1) = 431; C₂₀H₁₉FN₄O₄S requires 430.

Intermediate B75 — 1-Ethoxycarbonylmethyl-2-(4-fluorobenzyl)thio-5-(1-ethyl-2-oxopyrimid-5-ylmethyl)pyrimidin-4-one



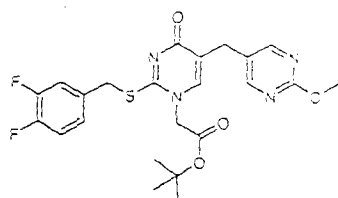
To a solution of Intermediate B74 (3.1g) in dry dimethylformamide (40ml) under argon was added ethyl iodide (1.4g) and anhydrous potassium carbonate (2.5g). The mixture was stirred at room temperature for 20h and the solvent removed *in vacuo*. The residue was partitioned between ethyl acetate and water. The organic layer was washed with brine and added in equal portions to three 10g silica cartridges. Elution of each column with EtOAc to 18% MeOH:EtOAc and combining appropriate fractions gave the title compound (1.5g). ¹H-NMR (CDCl₃) δ 1.27t1.39t, 3.46 (2H,s), 3.94 (2H,q), 4.25 (2H,q), 4.48 (2H,s), 4.57 (2H,s), 6.9-7.15 (2H,m), 7.21 (1H,s), 7.3-7.4 (2H,m), 7.9 (1H,m), 8.4 (1H,m), MS (APCI+) found (M+1) = 459; C₂₂H₂₃FN₄O₄S requires 458.

The following intermediates were prepared by the method of intermediate B70:

No.	Precursors	Structure	Name
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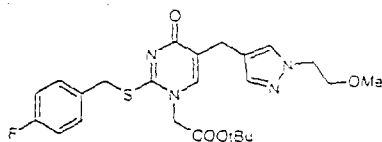
171
169/27

B76 Int. B57



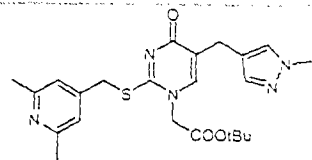
1-(tert-Butoxycarbonylmethyl)-2-(3,4-difluorobenzylthio)-5-(2-methoxypyrimidin-5-ylmethyl)pyrimidin-4-one

B77 Int. B58



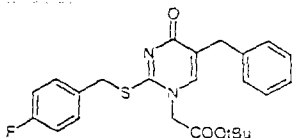
1-(tert-Butoxycarbonylmethyl)-2-(4-fluorobenzylthio)-5-((1-(2-methoxyethyl)pyrazol-4-yl)methyl)pyrimidin-4-one

B78 Int. B60



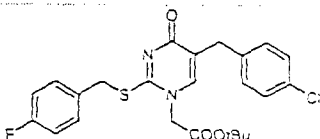
1-(tert-Butoxycarbonylmethyl)-2-(2,6-dimethylpyridin-4-ylmethylthio)-5-((1-methylpyrazol-4-yl)methyl)pyrimidin-4-one

B79 Int. B64



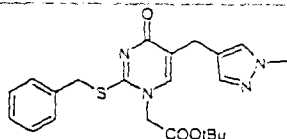
1-(tert-Butoxycarbonylmethyl)-2-(4-fluorobenzylthio)-5-benzylpyrimidin-4-one

B80 Int. B65



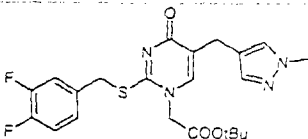
1-(tert-Butoxycarbonylmethyl)-2-(4-fluorobenzylthio)-5-(4-chlorobenzyl)pyrimidin-4-one

B81 Int. B59



1-(tert-Butoxycarbonylmethyl)-2-benzylthio-5-((1-methylpyrazol-4-yl)methyl)pyrimidin-4-one

B82 Int. B66



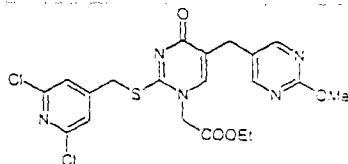
1-(tert-Butoxycarbonylmethyl)-2-(3,4-difluorobenzylthio)-5-((1-methylpyrazol-4-yl)methyl)pyrimidin-4-one

The following intermediates were prepared by the method of intermediate B72:

No. Precursors Structure

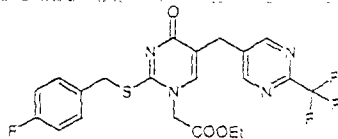
Name

B84 Int. B61



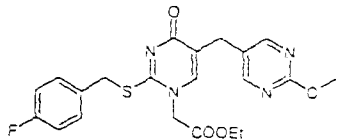
1-(Ethoxycarbonylmethyl)-2-(2,6-dichloropyridin-4-ylmethylthio)-5-(2-methoxypyrimidin-5-ylmethyl)pyrimidin-4-one

B85 Int. B54



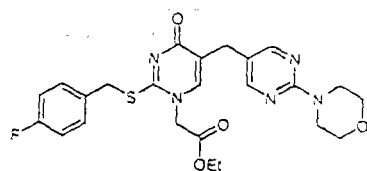
1-((Ethoxycarbonylmethyl)-2-(4-fluorobenzylthio)-5-(2-trifluoromethylpyrimidin-5-ylmethyl)pyrimidin-4-one

B86 Int. B53



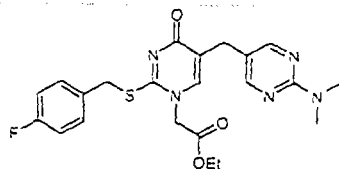
1-(Ethoxycarbonylmethyl)-2-(4-fluorobenzylthio)-5-(2-methoxypyrimidin-5-ylmethyl)pyrimidin-4-one

B87 Int. B55



1-(Ethoxycarbonylmethyl)-2-(4-fluorobenzylthio)-5-(2-(4-morpholino)pyrimidin-5-ylmethyl)pyrimidin-4-one

B88 Int. B56



1-(Ethoxycarbonylmethyl)-2-(4-fluorobenzylthio)-5-(2-dimethylaminopyrimidin-5-ylmethyl)pyrimidin-4-one

The following intermediates were prepared by the method of intermediate B71:

No.	Precursors	Structure	Name
B89	Int. B81		1-(Carboxymethyl)-2-benzylthio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one
B90	Int. B76		1-(Carboxymethyl)-2-(3,4-difluorobenzylthio)-5-(2-methoxypyrimidin-5-ylmethyl)pyrimidin-4-one
B91	Int. B82		1-(Carboxymethyl)-2-(3,4-difluorobenzylthio)-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one
B92	Int. B78		1-(Carboxymethyl)-2-(2,6-dimethylpyridin-4-ylmethylthio)-5-((1-methylpyrazol-4-yl)methyl)pyrimidin-4-one
B93	Int. B79		1-Carboxymethyl-2-(4-fluorobenzylthio)-5-benzylpyrimidin-4-one
B94	Int. B80		1-Carboxymethyl-2-(4-fluorobenzylthio)-5-(4-chlorobenzyl)pyrimidin-4-one
B10 4	Int. B77		1-(Carboxymethyl)-2-(4-fluorobenzylthio)-5-((1-(2-methoxyethyl)pyrazol-4-yl)methyl)pyrimidin-4-one

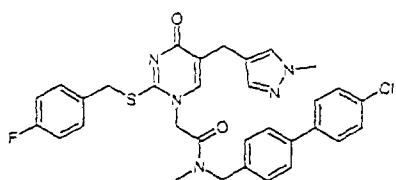
The following intermediates were prepared by the method of intermediate B73:

No.	Precursors	Structure	Name
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122
170
7

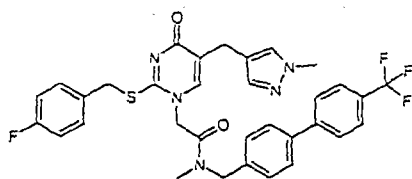
B96	Int. B51		1-(3-Carboxyprop-1-yl)-2-(4-fluorobenzyl)-thio-5-(2-methoxypyrimid-5-ylmethyl)-pyrimidin-4-one
B97	Int. B67		1-(3-Carboxyprop-1-yl)-2-(4-fluorobenzyl)-thio-5-(1-methylpyrazol-4-ylmethyl)-pyrimidin-4-one
B98	Int. B85		1-Carboxymethyl-2-(4-fluorobenzylthio)-5-((2-trifluoromethylpyrimid-5-yl)methyl)pyrimidin-4-one
B99	Int. B68		1-(3-Carboxyprop-1-yl)-2-(4-fluorobenzyl)-thio-5-(2-(4-morpholino)pyrimid-5-ylmethyl)-pyrimidin-4-one
B100	Int. B75		1-Carboxymethyl-2-(4-fluorobenzylthio)-5-(1-ethyl-2-oxopyrimid-5-ylmethyl)pyrimidin-4-one
B101	Int. B87		1-(Carboxymethyl)-2-(4-fluorobenzylthio)-5-(2-(4-morpholino)pyrimid-5-ylmethyl)pyrimidin-4-one
B102	Int. B88		1-(Carboxymethyl)-2-(4-fluorobenzylthio)-5-(2-dimethylaminopyrimid-5-ylmethyl)pyrimidin-4-one
B103	Int. B84		1-(Carboxymethyl)-2-(2,6-dichloropyrid-4-ylmethylthio)-5-(2-methoxypyrimid-5-ylmethyl)pyrimidin-4-one
B104	Int. B86		1-Carboxymethyl-2-(4-Fluorobenzylthio)-5-(2-methoxypyrimid-5-ylmethyl)pyrimidin-4-one

Example 1 — 1-(N-Methyl-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one



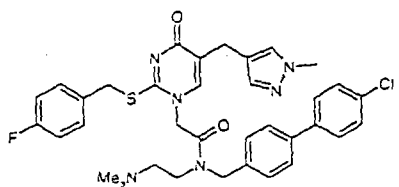
A mixture of Intermediate A2 (0.27g, 1 equiv), Intermediate B71 (0.45g, 1 equiv), hydroxybenzotriazole (0.018g, 0.1 equiv), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (0.25g, 1.1 equiv) and dichloromethane (15ml) was stirred at room temperature overnight, then diluted with dichloromethane and washed with aqueous sodium bicarbonate. The organic layer was applied directly to a 10g silica cartridge, which was eluted with 0-10% methanol in ethyl acetate. Product fractions were evaporated to an oil, which was triturated with ether to obtain a white solid (0.39g). $^1\text{H-NMR}$ (d_6 -DMSO) δ 2.95 and 3.08 (3H, 2Xs), 3.61 (2H, m), 3.86 (3H, m), 4.46-4.61 (6H, m), 6.74 and 6.80 (1H, 2Xs), 6.91-6.99 (2H, m), 7.21-7.49 (12H, m); MS (APCI+) found $(M+1) = 602$; $\text{C}_{32}\text{H}_{29}\text{ClFN}_5\text{O}_2\text{S}$ requires 601.

Example 2 — 1-(N-Methyl-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one



Prepared from Intermediates A45 and B71 by the method of Example 1. $^1\text{H-NMR}$ (DMSO) δ 2.96 (3H,s), 3.39 (2H,m), 3.77 (3H,s), 4.43 (2H, s), 4.57 (2H,s), 4.97 (2H,s), 7.12 (3H,m), 7.25 (1H,s), 7.34-7.48 (6H, m), 7.62-6.70 (2H,m), 8.84 (4H,m).; MS (APCI+) found $(M+1) = 636$; $\text{C}_{33}\text{H}_{29}\text{F}_4\text{N}_5\text{O}_2\text{S}$ requires 635.

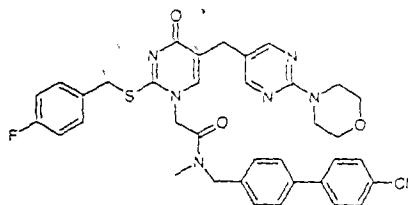
Example 3 — 1-(N-(2-Dimethylaminoethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methylpyrazol-4-ylmethyl)pyrimidin-4-one hydrochloride



Prepared from Intermediates A61 and B71 by the method of Example 1. $^1\text{H-NMR}$ (CDCl_3) δ 2.95 (3H, s), 2.96 (3H, s), 3.19 (2H, m), 3.58 (2H, s), 3.87 (3H, s), 3.91 (2H, m), 4.42 (2H, s), 4.68 (2H, s), 4.99 (2H, s), 6.88-6.93 (2H, m), 7.25-7.29 (6H, m), 7.36-7.45 (6H, m) 7.62 (1H, s); MS (APCI+) found $(M+1) = 659$; $\text{C}_{35}\text{H}_{36}\text{ClFN}_6\text{O}_2\text{S}$ requires 658.

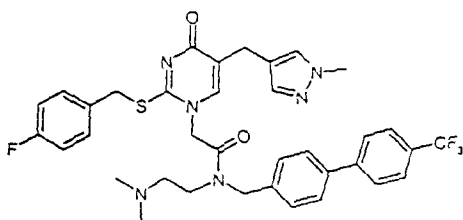
173
1714

Example 4 — 1-(N-Methyl-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-(4-morpholino)pyrimidin-5-ylmethyl)pyrimidin-4-one



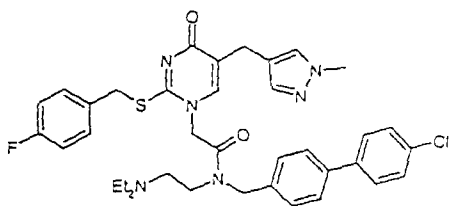
A solution of Intermediate A7 (0.23g, 1 equiv), Intermediate B55 (0.27g, 1 equiv) and diisopropylethylamine (0.10g, 1.2 equiv) in dry dichloromethane (6ml) was stirred at room temperature under argon for 20h, then diluted with more dichloromethane and washed successively with water and aqueous ammonium chloride. Drying and evaporation of the organic phase, followed by chromatography (silica, 0-5% methanol in ethyl acetate) gave the desired product as a pale solid (0.19g). ¹H-NMR (DMSO-d₆) δ: 2.95 (d, 3H), 3.42 (d, 2H), 3.64 (s, 8H), 4.40 (d, 2H), 4.60 (d, 2H), 4.95 (d, 2H), 7.1 (m, 2H), 7.30 (d, 2H), 7.35-7.6 (m, 6H), 7.65 (m, 3H), 8.30 (s, 2H). MS (APCI+) Found (M+1) = 685/687; C₃₆H₃₄ClFN₆O₃S requires 685.

Example 5 — 1-(N-(2-(dimethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one hydrochloride



Prepared from Intermediates A72 and B71 by the method of Example 1. ¹H-NMR (CDCl₃) δ 2.93 (3H,s), 2.99 (3H,s), 3.20 (2H,m), 3.60 (2H,s), 3.93 (5H,m), 4.42 (3H,s), 4.69(2H,s), 5.00 (2H,s), 6.39 (2H,m), 7.2-7.3 (4H,m), 7.47 (4H, m), 7.55 (2H,d), 7.70 (3H,m), 11.7 (1H, br s); MS (APCI+) found (M+1) = 693; C₃₆H₃₆F₄N₆O₂S requires 692.

Example 6 — 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one



A mixture of Intermediate A3 (82.7g, 1 equiv), B71 (101.3g, 1 equiv), hydroxybenzotriazole (39.9g, 1 equiv), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (100.0g, 2 equiv) and dichloromethane (1200ml) was stirred under argon at room temperature overnight, then aqueous sodium bicarbonate was added slowly with stirring. The organic layer was separated, the aqueous layer extracted twice more with dichloromethane, and the combined organic extracts dried over potassium carbonate and evaporated to a brown oil. Trituration with ether gave a solid, which was filtered off and purified by chromatography on silica, eluting with methanol/dichloromethane then with methanolic ammonia/dichloromethane. Product fractions were evaporated to a yellow foam (98g). ¹H-NMR (CDCl₃, rotamer mixture) δ 0.9-1.0 (6H,m)

δ 2.4-2.6 (6H,m), 3.23/3.52 (4H,2x t), 3.58/3.61 (4H, 2x s), 3.85 (3H,s), 4.46/4.53/4.64/4.82 (6H,4x s), 6.75/6.79 (1H,2x s), 6.9 (2H,m), 7.2-7.5 (12H,m); MS (APCI+) found (M+1) = 687/689; $C_{37}H_{40}ClFN_6O_2S$ requires 686/688.

5 **Example 7 — 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one hydrochloride**

The free base from Example 6 (8.7g, 1 equiv) was dissolved in dichloromethane (50ml) and 1M hydrogen chloride in ether (1 equiv) was added dropwise under argon. The mixture was evaporated to ca. half volume and sonicated to obtain a clear solution, which was transferred to a syringe and added dropwise to ether (200ml) with vigorous stirring. The white solid was filtered off, washed with ether and dried in vacuo; yield 8.55g. 1H -NMR (DMSO, ca. 2:1 rotamer mixture) δ 1.14-1.24 (6H,m), 3.1 (6H, m), 3.6 (2H,m), 3.76 (3H,s), 4.38/4.45 (2H,2x s), 4.61/4.70 (2H,2x s), 4.98/5.11 (2H,2x s), 6.75/6.79 (1H,2x s), 7.1-7.7 (15H,m), 10.15/10.75 (1H,2x br s); MS (APCI+) found (M+1) = 687/689; $C_{37}H_{40}ClFN_6O_2S$ requires 686/688.

15 **Example 8 — 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one bitartrate**

A solution of L-tartaric acid (0.75g, 1 equiv) in 2-propanol (12ml) was added to a solution of the free base from Example 6 (3.43g, 1 equiv) in 2-propanol (25ml) with stirring. The mixture was evaporated to ca. one third volume, diluted with ether, then the solid was filtered off, washed with ether and dried in vacuo; yield 3.87g. 1H -NMR (DMSO, ca. 60:40 rotamer mixture) δ 0.9-1.1 (6H,m), 2.5-2.8 (4H,m), 3.2-3.4 (6H,m), 3.76 (3H,s), 4.20 (2H,s), 4.39/4.43 (2H,2x s), 4.60/4.67 (2H,2x s), 4.92/5.08 (2H,2x s), 7.1-7.7 (15H,m); MS (APCI+) found (M+1) = 687/689; $C_{37}H_{40}ClFN_6O_2S$ requires 686/688.

Example 9 — 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one maleate

25 A solution of maleic acid (0.58g, 1 equiv) in methanol (10ml) was added to a solution of the free base from Example 6 (3.43g, 1 equiv) in methanol (10ml) with stirring. The mixture was evaporated to ca. half volume, diluted with ether, then the supernatant decanted off. The oil was triturated with ether to obtain a solid, which was filtered off, washed with ether and dried in vacuo; yield 3.69g. 1H -NMR (DMSO, ca. 3:1 rotamer mixture) essentially similar to Example 7, plus δ 2.33 (3H,s); MS (APCI+) found (M+1) = 687/689; $C_{37}H_{40}ClFN_6O_2S$ requires 686/688.

30 **Example 10 — 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one mesylate**

Prepared by the method of example 9, using methanesulfonic acid (0.32ml, 1 equiv) in place of maleic acid; yield 3.59g. 1H -NMR (DMSO, ca. 3:1 rotamer mixture) essentially similar to Example 7, plus δ 6.03 (2H,s); MS (APCI+) found (M+1) = 687/689; $C_{37}H_{40}ClFN_6O_2S$ requires 686/688.

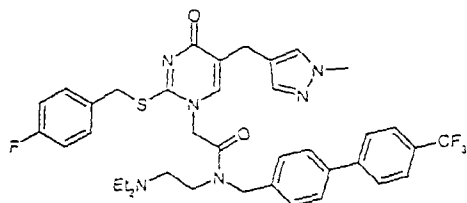
35 **Example 11 — 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one taurocholate**

Prepared by the method of example 9, using taurocholic acid (2.57g, 1 equiv) in place of maleic acid; yield 5.56g. 1H -NMR (DMSO, ca. 3:1 rotamer mixture) essentially similar to Example 7, plus (*inter*

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alia) δ 0.58 (3H,s), 0.81 (3H,s), 0.91 (3H,d), 1.14 (3H,s); MS (APCI+) found (M+1) = 687/689; $C_{37}H_{40}ClFN_6O_2S$ requires 686/688.

Example 12 — 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one



Prepared from Intermediates A73 and B71 by the method of Example 1. 1H -NMR ($CDCl_3$, rotamer mixture) δ 0.9-1.0 (6H,m), δ 2.4-2.6 (6H,m), 3.24/3.4-3.6 (4H,2x m), 3.85 (3H,s), 4.46/4.53/4.66/4.83 (6H,4x s), 6.75/6.8 (1H,2x s), 6.9-7.0 (2H,m), 7.3-7.7 (12H,m); MS (APCI+) found (M+1) = 721; $C_{38}H_{40}F_4N_6O_2S$ requires 720.

Example 13 — 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one hydrochloride

The free base from Example 12 (0.75g, 1 equiv) was dissolved in dichloromethane (5 ml) and 1M hydrogen chloride in ether (1 equiv) was added dropwise under argon, then excess ether was added with vigorous stirring. The white solid was filtered off, washed with ether and dried in vacuo; yield 0.73g.

1H -NMR (DMSO, ca. 3:1 rotamer mixture) δ 1.1-1.2 (6H,m), 3.1 (6H, m), 3.37 (2H+ H_2O ,m), 3.66 (2H,m), 3.76 (3H,s), 4.37/4.45 (2H,2x s), 4.63/4.72 (2H,2x s), 4.97/5.12 (2H,2x s), 7.1 (2H,m), 7.24/7.26 (1H,2x s), 7.4-7.5 (6H,m), 6.62/6.71 (2H, 2x d), 7.84 (4H,m), 10.1/10.65 (1H,2x br s); MS (APCI+) found (M+1) = 721; $C_{38}H_{40}F_4N_6O_2S$ requires 720.

Example 14 — 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one bitartrate

Prepared from the free base of Example 12 by the method of Example 8. 1H -NMR (DMSO, ca. 60:40 rotamer mixture) δ 0.9-1.0 (6H,m), 2.5-2.8 (4H,m), 3.2-3.5 (6H,m), 3.76 (3H,s), 4.19 (2H,s), 4.38/4.43 (2H,2x s), 4.62/4.69 (2H,2x s), 4.92/5.10 (2H,2x s), 7.0-7.5 (12H,m), 7.6/7.7 (1H, 2x d), 7.84 (2H,m); MS (APCI+) found (M+1) = 721; $C_{38}H_{40}F_4N_6O_2S$ requires 720.

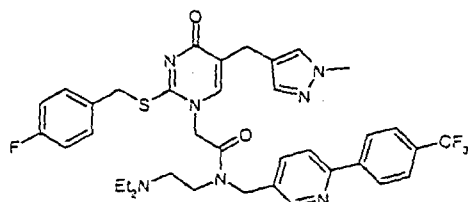
Example 15 — 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one citrate

Free base from Example 12 (0.69g, 1equiv) was added to acetone (10ml) followed by citric acid (0.20g, 1equiv). The mixture was warmed to dissolve the solids then allowed to cool, whereupon the solids were filtered off and dried in vacuo; yield 0.80g, 90%, m.p. 130-133°C. 1H -NMR (d_6 -DMSO, ca. 1:1 rotamer mixture) essentially similar to Example 14, plus δ 2.61 (2H,d); MS (APCI+) found (M+1) = 721; $C_{38}H_{40}F_4N_6O_2S$ requires 720.

Example 16 — 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one tosylate

Free base from Example 12 (1.0 g, 1 equiv) and tosic acid (0.26 g, 1 equiv) were dissolved in acetone (20 ml) at room temperature, then isopropyl acetate (60 ml) was added with stirring. After stirring for a further 2 hours, the mixture was allowed to stand overnight then the solid was filtered off, washed with 3:1 isopropyl acetate/acetone, and dried in vacuo; yield 0.87 g, m.p. 147°C. ¹H-NMR (d6-DMSO, ca. 3:1 rotamer mixture) essentially similar to Example 13, plus (inter alia) δ 2.28 (3H,s); MS (APCI+) found (M+1) = 721; C₃₈H₄₀F₄N₆O₂S requires 720

Example 17 — 1-(N-(2-(diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrid-5-ylmethyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one



A mixture of Intermediate A106 (0.523g, 1 equiv), Intermediate B71 (0.473g, 1 equiv), HATU (0.55g, 1.2 equiv), diisopropylethylamine (0.622ml, 2.4 equiv) and dichloromethane (20ml) was stirred under argon at room temperature overnight, then washed with aqueous ammonium chloride and aqueous sodium bicarbonate. The organic layer was dried and evaporated, and the free-base product isolated by chromatography (silica, 3-8% methanol in dichloromethane) as a pale foam (0.39g). ¹H-NMR (CDCl₃, major rotamer) δ 0.94 (6H,t), 2.47 (4H,q), 2.58 (2H,m), 3.26 (2H,m), 3.61 (2H,s), 3.85 (3H,s), 4.52 (2H,s), 4.66 (2H,s), 4.82 (2H,s), 6.78 (1H,s), 6.98 (2H,m), 7.3-7.4 (4H,m), 7.6-7.8 (2H,m), 8.08 (2H,m), 8.57 (1H,m); MS (APCI+) found (M+1) = 722; C₃₇H₃₉F₄N₇O₂S requires 721.

Example 18 — 1-(N-(2-(Diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrid-5-ylmethyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one hydrochloride

The free base from Example 17 (0.373g, 1 equiv) was dissolved in dichloromethane (10ml), and a solution of hydrogen chloride in ether (0.517ml, 1.0M solution, 1 equiv) was added dropwise with stirring. The solvent was removed in vacuo, and the residue triturated with ether to obtain a white solid (0.362g). ¹H-NMR (DMSO, ca. 60:40 rotamer mixture) δ 1.1-1.3 (6H,m), 3.77 (3H,s), 4.38/4.43 (2H,s), 4.65/4.76 (2H,s), 5.00/5.08 (2H,s), 7.10 (2H,m), 7.25 (1H,m), 7.3-7.5 (4H,m), 7.78 (1H,m), 7.87 (2H,d), 7.97/8.06 (1H,d), 8.28 (2H,d), 8.61/8.70 (1H,m); MS (APCI+) found (M+1) = 722; C₃₇H₃₉F₄N₇O₂S requires 721.

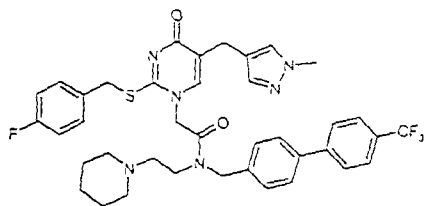
Example 19 — 1-(N-(2-(Diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrid-5-ylmethyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one bitartrate

Prepared from the free base of Example 17 by the method of Example 8. ¹H-NMR (DMSO, ca. 60:40 rotamer mixture) δ 0.88-1.05 (6H,m), 3.76 (3H,s), 4.39/4.42 (2H,s), 4.65/4.74 (2H,s), 4.97/5.10 (2H,s),

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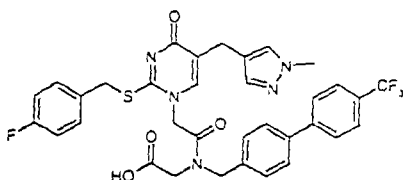
7.11 (2H,m), 7.25 (1H,m), 7.3-7.5 (4H,m), 7.78 (1H,m), 7.87 (2H,m), 7.98/8.07 (1H,d), 8.28 (2H,d), 8.61/8.70 (1H,m); MS (APCI+) found (M+1) = 722; C₃₇H₃₉F₄N₇O₂S requires 721.

Example 20 — 1-(N-(2-(1-Piperidino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)amino-carbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one bitartrate



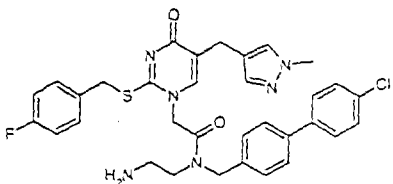
The free base was prepared from Intermediates A108 and B71 by the method of Example 1, then converted to bitartrate salt by the method of Example 8. ¹H-NMR (DMSO, ca. 60:40 rotamer mixture) δ 1.3-1.6 (6H,m) δ 2.3-2.7 (6H,m), 3.3-3.6 (4H,m), 3.77 (3H,s), 4.22 (2H,s), 4.37/4.44 (2H,2x s), 4.62/4.69 (2H,2x s), 4.88/5.08 (2H,2x s), 7.1-7.5 (12H,m), 7.6/7.7 (1H, 2x d), 7.83 (2H,m); MS (APCI+) found (M+1) = 733; C₃₉H₄₀F₄N₆O₂S requires 732.

Example 21 — 1-(N-(Carboxymethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one sodium salt



Example 102 (130 mg) was added to a solution of sodium bicarbonate (16 mg) in water (4 ml) and stirred for 1 hour at room temperature. A small proportion of methanol was added to obtain a clear solution on warming and sonication. Filtration and lyophilisation gave the desired sodium salt as a white solid. ¹H-NMR (DMSO) δ 3.49 (2H,s), 3.76 (3H,s), 4.42 (2H,s), 4.85 (2H,s), 7.14 (2H,m), 7.26 (1H,s), 7.36 (3H,m), 7.49 (3H,m), 7.60 (2H,m), 7.84 (4H,m); MS (APCI-) found (M+1) = 678; C₃₄H₂₉F₄N₅O₄S requires 679.

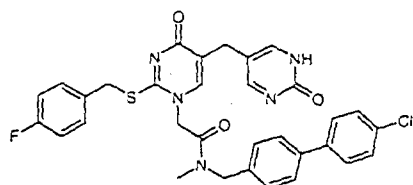
Example 22 — 1-(N-(2-aminoethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one hydrochloride



The Boc-protected product was prepared from Intermediates A84 and B71 by the method of Example 1, then deprotected by suspending in dioxan and treating with excess hydrogen chloride (4M solution in dioxan). After stirring for 1 hour, excess ether was added and stirring continued until a fine white solid was obtained. This was filtered off, washed with ether and dried to obtain the crude product, which was purified by chromatography (silica, 10-20% methanol in dichloromethane). ¹H-NMR (DMSO, ca. 60:40 rotamer mixture) δ 2.97/3.04 (2H,m) δ 3.37 (2H,m), 3.55 (2H,m), 3.77 (3H,s), 4.36/4.45 (2H,2x s),

4.604.67 (2H, 2x s), 4.93/5.09 (2H, 2x s), 7.0-7.7 (15H, m), 8.05/8.20 (2H, 2x br s); MS (APCI+) found (M+1) = 733; C₃₉H₄₀F₄N₆O₂S requires 732.

Example 23 — 1-(N-Methyl-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-oxypyrimidin-5-ylmethyl)pyrimidin-4-one



A mixture of Example 121 (0.73g, 1.2mmol), B-bromocatecholborane (1.01g, 5.1mmol) and dry dichloromethane (20ml) was stirred under argon at room temperature overnight, giving a clear orange solution. Water was added and stirring continued for 30min, then the organic layer was separated and applied directly to a 10g silica cartridge, which was eluted with 0-14% methanol in dichloromethane.

Product fractions were evaporated to obtain a pale yellow solid (0.36g). ¹H-NMR (DMSO) δ 2.80-3.06 (3H, 2xs), 3.37 (2H, s), 4.33-4.49 (2H, 2xs), 4.50-4.72 (2H, 2xs), 4.87-5.06 (2H, m), 7.04-7.75 (13H, m), 8.19 (2H, s); MS (APCI-) found (M-1) = 614; C₃₂H₂₇N₅O₃SFCl requires 615.

The following Examples were made either by the method of Example 1 (EDC coupling) or Example 15 (HATU coupling); where indicated, the salts were subsequently prepared by the methods of Examples 7-8 as appropriate:

Ex. No.	Precursors	Structure	Name
30	Int. A2 Int. B97		1-(3-(N-methyl-N-(4-(4-chlorophenyl)benzyl)aminocarbonyl)prop-1-yl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one
31	Int. A120 Int. B97		1-(3-(4-(4-fluorophenyl)benzylamino)carbonyl)prop-1-yl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one
32	Int. A44 Int. B97		1-(3-(N-methyl-N-(4-(4-fluorophenyl)benzyl)aminocarbonyl)prop-1-yl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one
33	Int. A124 Int. B97		1-(3-(4-phenylbenzylamino)carbonyl)prop-1-yl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one

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34	Int. A6 Int. B99		1-(3-(4-(4-chlorophenyl)benzylamino-carbonyl)prop-1-yl)-2-(4-fluorobenzyl)-thio-5-(2-(4-morpholino)-5-pyrimidylmethyl)pyrimidin-4-one
35	Int. A2 Int. B99		1-(3-(N-methyl-N-(4-(4-chlorophenyl)-benzyl)aminocarbonyl)prop-1-yl)-2-(4-fluorobenzyl)thio-5-(2-(4-morpholino)-5-pyrimidylmethyl)pyrimidin-4-one
36	Int. A6 Int. B96		1-(3-(4-(4-chlorophenyl)benzylamino-carbonyl)prop-1-yl)-2-(4-fluorobenzyl)-thio-5-(2-methoxy-5-pyrimidylmethyl)-pyrimidin-4-one
37	Int. A2 Int. B96		1-(3-(N-methyl-N-(4-(4-chlorophenyl)-benzyl)aminocarbonyl)prop-1-yl)-2-(4-fluorobenzyl)thio-5-(2-methoxy-5-pyrimidylmethyl)pyrimidin-4-one
38	Int. A120 Int. B96		1-(3-(4-(4-fluorophenyl)benzylamino-carbonyl)prop-1-yl)-2-(4-fluorobenzyl)-thio-5-(2-methoxy-5-pyrimidylmethyl)-pyrimidin-4-one
39	Int. A44 Int. B96		1-(3-(N-methyl-N-(4-(4-fluorophenyl)-benzyl)aminocarbonyl)prop-1-yl)-2-(4-fluorobenzyl)thio-5-(2-methoxy-5-pyrimidylmethyl)pyrimidin-4-one
40	Int. A124 Int. B96		1-(3-(4-phenylbenzylaminocarbonyl)prop-1-yl)-2-(4-fluorobenzyl)thio-5-(2-methoxy-5-pyrimidylmethyl)pyrimidin-4-one
41	Int. A64 Int. B96		1-(3-(N-methyl-N-(2-(4-fluorophenyl)-pyrid-5-ylmethyl)aminocarbonyl)prop-1-yl)-2-(4-fluorobenzyl)thio-5-(2-methoxy-5-pyrimidylmethyl)pyrimidin-4-one
42	Int. A3 Int. B104		1-(N-(2-(diethylamino)ethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonyl-methyl)-2-(4-fluorobenzyl)thio-5-(1-(2-methoxyethyl)-4-pyrazolylmethyl)-pyrimidin-4-one bitartrate

43	Int. A73 Int. B104		1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-(2-methoxyethyl)-4-pyrazolylmethyl)pyrimidin-4-one bitartrate
44	Int. A6 Int. B100		1-(4-(4-chlorophenyl)benzylamino-carbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-ethyl-2-oxo-5-pyrimidylmethyl)-pyrimidin-4-one
45	Int. A2 Int. B100		1-(N-methyl-N-(4-(4-chlorophenyl)-benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-ethyl-2-oxo-5-pyrimidylmethyl)pyrimidin-4-one
46	Int. A44 Int. B100		1-(N-methyl-N-(4-(4-fluorophenyl)-benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-ethyl-2-oxo-5-pyrimidylmethyl)pyrimidin-4-one
47	Int. A2 Int. B92		1-(N-methyl-N-(4-(4-chlorophenyl)-benzyl)aminocarbonylmethyl)-2-(2,6-dimethylpyrid-4-yl)methylthio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one
48	Int. A3 Int. B90		1-(N-(2-(diethylamino)ethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonyl-methyl)-2-(3,4-difluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one hydrochloride
49	Int. A45 Int. B90		1-(N-methyl-N-(4-(4-trifluoromethyl-phenyl)benzyl)aminocarbonylmethyl)-2-(3,4-difluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one
50	Int. A46 Int. B71		1-(N-methyl-N-(4-(4-chlorophenyl)-2-fluorobenzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolyl-methyl)pyrimidin-4-one
51	Int. A56 Int. B71		1-(N-methyl-N-(4-(2,4-bis(trifluoro-methyl)phenyl)benzyl)aminocarbonyl-methyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one

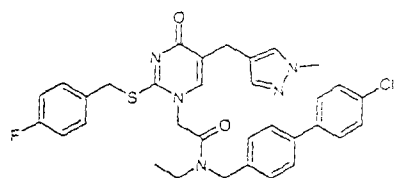
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52	Int. A60 Int. B71		1-(N-methyl-N-(4-(2,4-difluorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one
53	Int. A59 Int. B71		1-(N-methyl-N-(4-(3-chloro-4-fluorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one
54	Int. A53 Int. B71		1-(N-methyl-N-(4-(3-fluoro-4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one
55	Int. A107 Int. B71		1-(N-(2-(1-piperidino)ethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one hydrochloride
56	Int. A75 Int. B71		1-(N-(2-(1-pyrrolidino)ethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one hydrochloride
57	Int. A76 Int. B71		1-(N-(2-(4-morpholino)ethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one hydrochloride
58	Int. A95 Int. B71		1-(N-(2-(bis(2-hydroxyethyl)amino)ethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one
59	Int. A74 Int. B71		1-(N-(2-(di-isopropylamino)ethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one hydrochloride
60	Int. A94 Int. B71		1-(N-(2-(N-(2-hydroxyethyl)-N-ethylamino)ethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one bitartrate

61	Int. A70 Int. B71		1-(N-(2-hydroxyethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one
62	Int. A51 Int. B71		1-(N-(2-methoxyethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one
63	Int. A80 Int. B71		1-(N-(3-(1-pyrrolidino)propyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one hydrochloride
64	Int. A83 Int. B71		1-(N-(3-(4-methyl-1-piperazino)propyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one hydrochloride
65	Int. A82 Int. B71		1-(N-(3-(4-morpholino)propyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one hydrochloride
66	Int. A79 Int. B71		1-(N-(3-(diethylamino)propyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one
67	Int. A62 Int. B71		1-(N-(3-(dimethylamino)propyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one hydrochloride
68	Int. A50 Int. B71		1-(N-(dimethylaminocarbonylmethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one

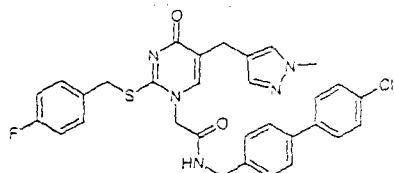
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69 Int. A48
Int. B71



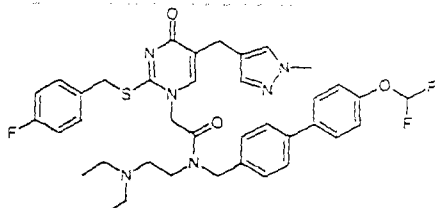
1-(N-ethyl-N-(4-(4-chlorophenyl)-benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one

70 Int. A6
Int. B71



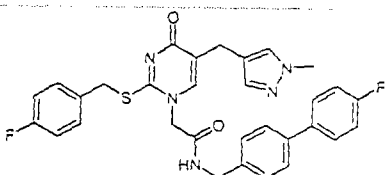
1-(4-(4-chlorophenyl)benzylamino-carbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one

71 Int. A93
Int. B71



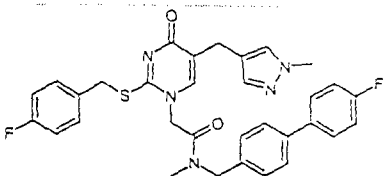
1-(N-(2-(diethylamino)ethyl)-N-(4-(4-difluoromethoxyphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one hydrochloride

72 Int. A120
Int. B71



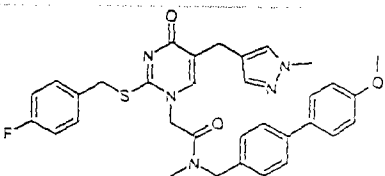
1-(4-(4-fluorophenyl)benzylamino-carbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one

73 Int. A44
Int. B71



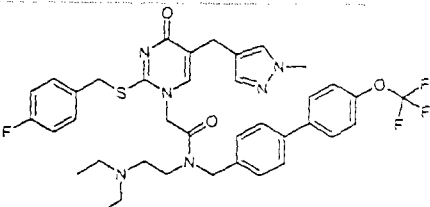
1-(N-methyl-N-(4-(4-fluorophenyl)-benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one

74 Int. A54
Int. B71



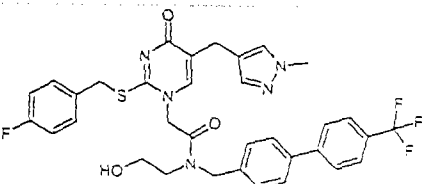
1-(N-methyl-N-(4-(4-methoxyphenyl)-benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one

75 Int. A92
Int. B71



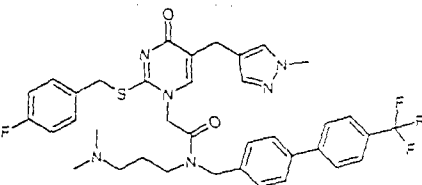
1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethoxyphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one hydrochloride

76 Int. A71
Int. B71



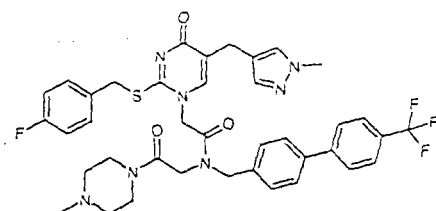
1-(N-(2-hydroxyethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one

77 Int. A78
Int. B71



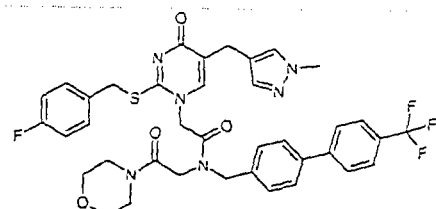
1-(N-(3-(dimethylamino)propyl)-N-(4-(4-trifluoromethylphenyl)benzyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one hydrochloride

78 Int. A97
Int. B71



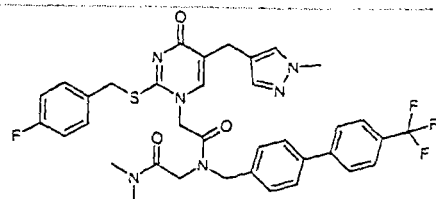
1-(N-(4-methyl-1-piperazinocarbonylmethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one hydrochloride

79 Int. A96
Int. B71



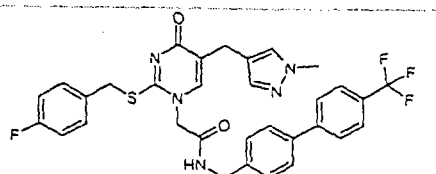
1-(N-(4-morpholinocarbonylmethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one

80 Int. A52
Int. B71



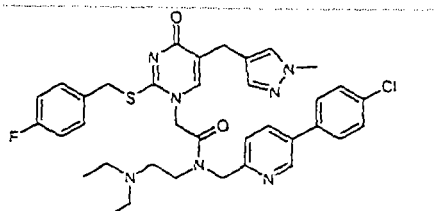
1-(N-(dimethylaminocarbonylmethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one

81 Int. A121
Int. B71



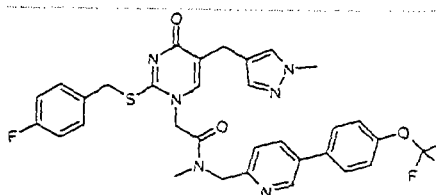
1-(4-(4-trifluoromethylphenyl)benzylaminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one

82 Int. A98
Int. B71



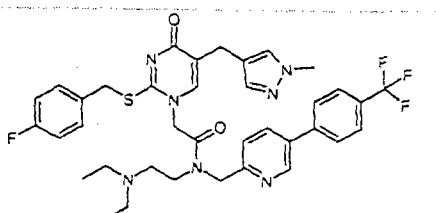
1-(N-(2-(diethylamino)ethyl)-N-(5-(4-chlorophenyl)pyrid-2-ylmethyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one hydrochloride

83 Int. A102
Int. B71



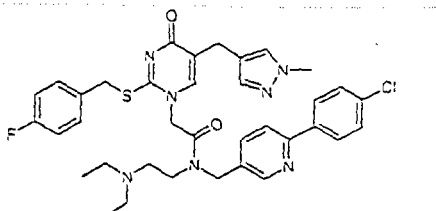
1-(N-(2-(dimethylamino)ethyl)-N-(5-(4-trifluoromethoxyphenyl)pyrid-2-ylmethyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one

84 Int. A99
Int. B71



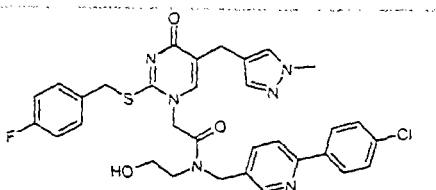
1-(N-(2-(diethylamino)ethyl)-N-(5-(4-trifluoromethylphenyl)pyrid-2-ylmethyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one hydrochloride

85 Int. A101
Int. B71



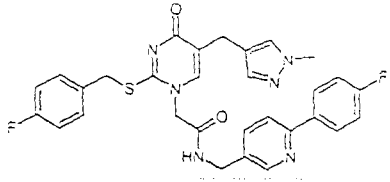
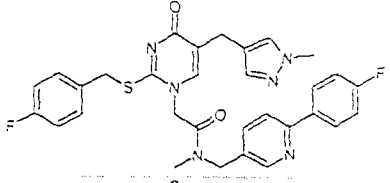
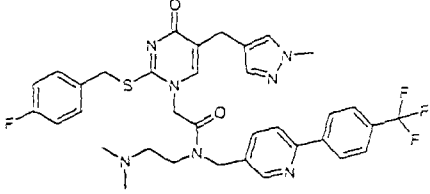
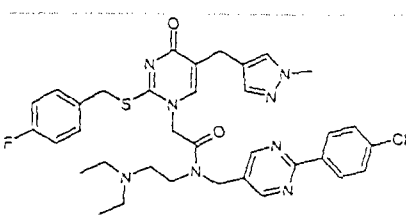
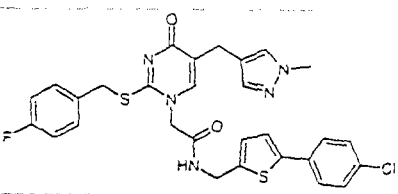
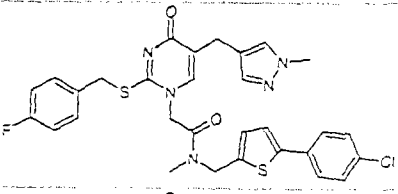
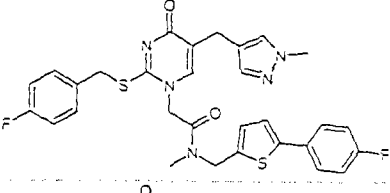
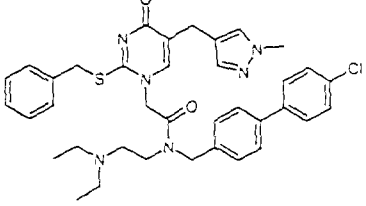
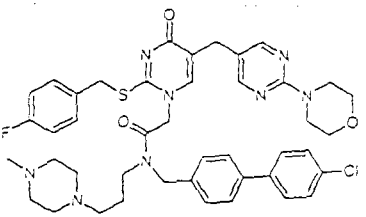
1-(N-(2-(diethylamino)ethyl)-N-(2-(4-chlorophenyl)pyrid-5-ylmethyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one hydrochloride

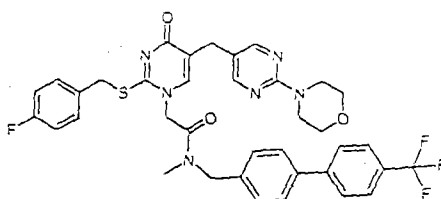
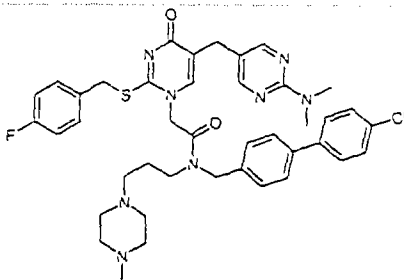
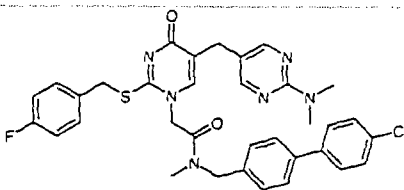
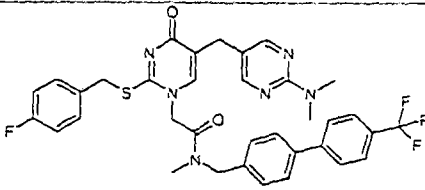
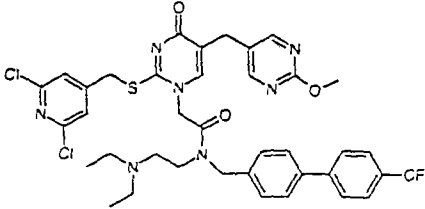
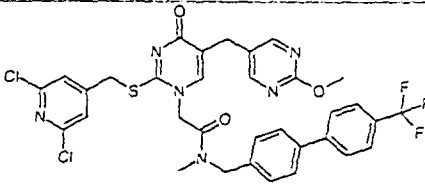
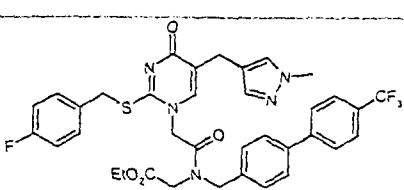
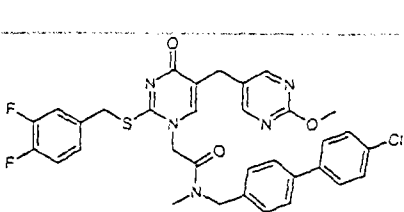
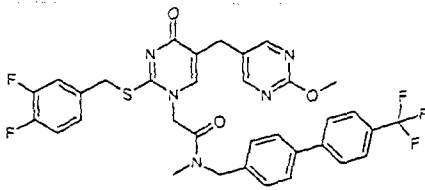
86 Int. A103
Int. B71



1-(N-(2-hydroxyethyl)-N-(2-(4-chlorophenyl)pyrid-5-ylmethyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one

179
1728

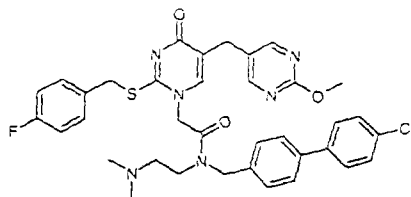
87	Int. A122 Int. B71		1-(2-(4-fluorophenyl)pyrid-5-ylmethyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)-thio-5-(1-methyl-4-pyrazolyl-methyl)pyrimidin-4-one
88	Int. A64 Int. B71		1-(N-methyl-N-(2-(4-fluorophenyl)pyrid-5-ylmethyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolyl-methyl)pyrimidin-4-one
89	Int. A100 Int. B71		1-(N-(2-(dimethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrid-5-ylmethyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolyl-methyl)pyrimidin-4-one hydrochloride
90	Int. A104 Int. B71		1-(N-(2-(diethylamino)ethyl)-N-(2-(4-chlorophenyl)pyrimid-5-ylmethyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolyl-methyl)pyrimidin-4-one bitartrate
91	Int. A123 Int. B71		1-(5-(4-chlorophenyl)thien-2-ylmethyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)-thio-5-(1-methyl-4-pyrazolyl-methyl)pyrimidin-4-one
92	Int. A66 Int. B71		1-(N-methyl-N-(5-(4-chlorophenyl)thien-2-ylmethyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolyl-methyl)pyrimidin-4-one
93	Int. A63 Int. B71		1-(N-methyl-N-(5-(4-fluorophenyl)thien-2-ylmethyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolyl-methyl)pyrimidin-4-one
94	Int. A3 Int. B89		1-(N-(2-(diethylamino)ethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-benzylthio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one hydrochloride
95	Int. A83 Int. B101		1-(N-(3-(4-methyl-1-piperazino)propyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-(4-morpholino)-5-pyrimidylmethyl)-pyrimidin-4-one bitartrate

96	Int. A45 Int. B101		1-(N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-(4-morpholino)-5-pyrimidylmethyl)pyrimidin-4-one
97	Int. A83 Int. B102		1-(N-(3-(4-methyl-1-piperazino)propyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-dimethylamino-5-pyrimidylmethyl)pyrimidin-4-one bitartrate
98	Int. A2 Int. B102		1-(N-methyl-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-dimethylamino-5-pyrimidylmethyl)pyrimidin-4-one
99	Int. A45 Int. B102		1-(N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-dimethylamino-5-pyrimidylmethyl)pyrimidin-4-one
100	Int. A73 Int. B103		1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(2,6-dichloropyrid-4-yl)methylthio-5-(2-methoxy-5-pyrimidylmethyl)pyrimidin-4-one bitartrate
101	Int. A45 Int. B103		1-(N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(2,6-dichloropyrid-4-yl)methylthio-5-(2-methoxy-5-pyrimidylmethyl)pyrimidin-4-one
102	Int. A160 Int. B71		1-(N-(Ethoxycarbonylmethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one
103	Int. A2 Int. B90		1-(N-methyl-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(3,4-difluorobenzyl)thio-5-(2-methoxy-5-pyrimidylmethyl)pyrimidin-4-one
104	Int. A45 Int. B90		1-(N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(3,4-difluorobenzyl)thio-5-(2-methoxy-5-pyrimidylmethyl)pyrimidin-4-one

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178 2

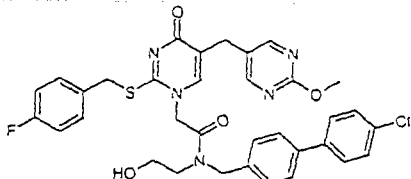
105	Int. A46 Int. B104		1-(N-methyl-N-(4-(4-chlorophenyl)-2-fluorobenzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxy-5-pyrimidylmethyl)pyrimidin-4-one
106	Int. A58 Int. B104		1-(N-methyl-N-(4-(4-trifluoromethylphenyl)-2-fluorobenzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxy-5-pyrimidylmethyl)pyrimidin-4-one
107	Int. A10 Int. B104		1-(N-methyl-N-(4-(4-chlorophenyl)-3-fluorobenzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxy-5-pyrimidylmethyl)pyrimidin-4-one
108	Int. A57 Int. B104		1-(N-methyl-N-(4-(2-fluoro-4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxy-5-pyrimidylmethyl)pyrimidin-4-one
109	Int. A60 Int. B104		1-(N-methyl-N-(4-(2,4-difluorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxy-5-pyrimidylmethyl)pyrimidin-4-one
110	Int. A55 Int. B104		1-(N-methyl-N-(4-(2-fluoro-4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxy-5-pyrimidylmethyl)pyrimidin-4-one
111	Int. A59 Int. B104		1-(N-methyl-N-(4-(3-chloro-4-fluorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxy-5-pyrimidylmethyl)pyrimidin-4-one
112	Int. A53 Int. B104		1-(N-methyl-N-(4-(3-fluoro-4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxy-5-pyrimidylmethyl)pyrimidin-4-one
113	Int. A3 Int. B104		1-(N-(2-(diethylamino)ethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxy-5-pyrimidylmethyl)pyrimidin-4-one hydrochloride

114 Int. A61
Int. B104



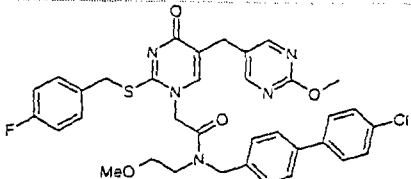
1-(N-(2-(dimethylamino)ethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxy-5-pyrimidylmethyl)pyrimidin-4-one hydrochloride

115 Int. A70
Int. B104



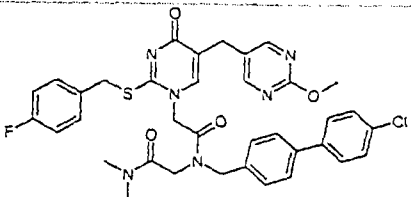
1-(N-(2-hydroxyethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxy-5-pyrimidylmethyl)pyrimidin-4-one

116 Int. A51
Int. B104



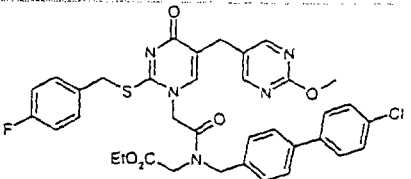
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117 Int. A50
Int. B104



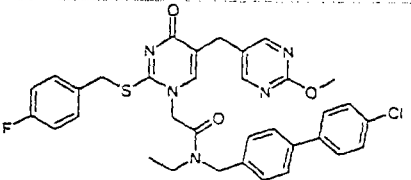
1-(N-(dimethylaminocarbonylmethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxy-5-pyrimidylmethyl)pyrimidin-4-one

118 Int. A11
Int. B104



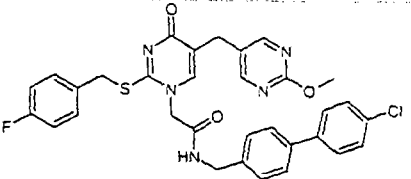
1-(N-(ethoxycarbonylmethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxy-5-pyrimidylmethyl)pyrimidin-4-one

119 Int. A48
Int. B104



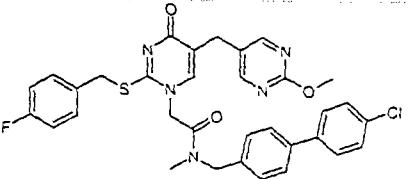
1-(N-ethyl-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxy-5-pyrimidylmethyl)pyrimidin-4-one

120 Int. A6
Int. B104



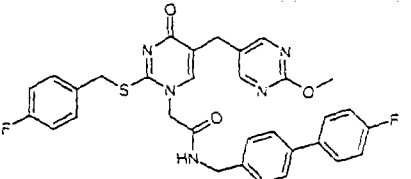
1-(4-(4-chlorophenyl)benzylaminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxy-5-pyrimidylmethyl)pyrimidin-4-one

121 Int. A2
Int. B104



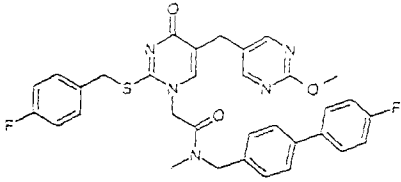
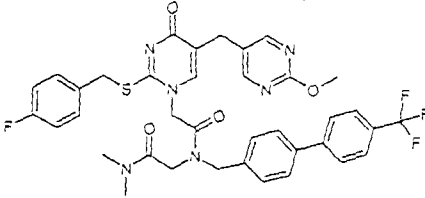
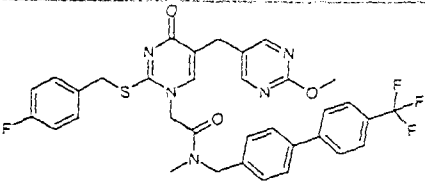
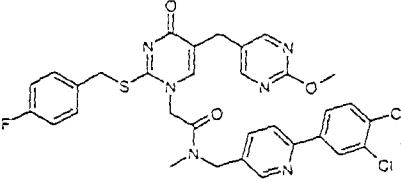
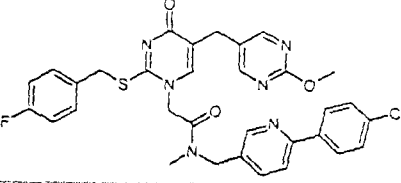
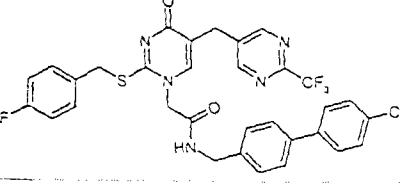
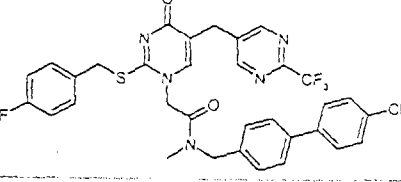
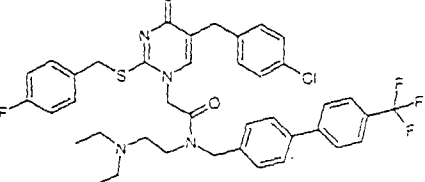
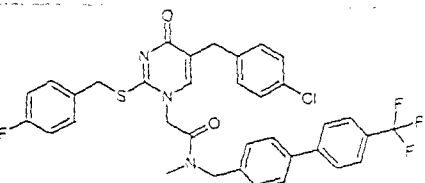
1-(N-methyl-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxy-5-pyrimidylmethyl)pyrimidin-4-one

122 Int. A120
Int. B104



1-(4-(4-fluorophenyl)benzylaminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxy-5-pyrimidylmethyl)pyrimidin-4-one

181
179/8

123	Int. A44 Int. B104		1-(N-methyl-N-(4-(4-fluorophenyl)-benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxy-5-pyrimidylmethyl)pyrimidin-4-one
125	Int. A52 Int. B104		1-(N-(dimethylaminocarbonylmethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)-thio-5-(2-methoxy-5-pyrimidyl-methyl)pyrimidin-4-one
126	Int. A45 Int. B104		1-(N-methyl-N-(4-(4-trifluoromethyl-phenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxy-5-pyrimidylmethyl)pyrimidin-4-one
127	Int. A49 Int. B104		1-(N-methyl-N-(2-(3,4-dichlorophenyl)-pyrid-5-ylmethyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxy-5-pyrimidylmethyl)pyrimidin-4-one
128	Int. A65 Int. B104		1-(2-(4-chlorophenyl)pyrid-5-ylmethyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)-thio-5-(2-methoxy-5-pyrimidyl-methyl)pyrimidin-4-one
130	Int. A6 Int. B98		1-(4-(4-chlorophenyl)benzylamino-carbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-trifluoromethyl-5-pyrimidylmethyl)-pyrimidin-4-one
131	Int. A2 Int. B98		1-(N-methyl-N-(4-(4-chlorophenyl)-benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-trifluoromethyl-5-pyrimidylmethyl)pyrimidin-4-one
132	Int. A73 Int. B94		1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)amino-carbonylmethyl)-2-(4-fluorobenzyl)thio-5-(4-chlorophenylmethyl)pyrimidin-4-one bitartrate
133	Int. A45 Int. B94		1-(N-methyl-N-(4-(4-trifluoromethyl-phenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(4-chlorophenyl-methyl)pyrimidin-4-one

134	Int. A124 Int. B73		1-(4-phenylbenzylaminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(5-pyrimidylmethyl)pyrimidin-4-one
135	Int. A67 Int. B73		1-(N-methyl-N-(4-phenylbenzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(5-pyrimidylmethyl)pyrimidin-4-one
136	Int. A73 Int. B93		1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(phenylmethyl)pyrimidin-4-one bitartrate
137	Int. A45 Int. B93		1-(N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(phenylmethyl)pyrimidin-4-one
138	Int. A73 Int. B101		1-(N-(2-(diethylamino)ethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-(4-morpholino)pyrimidin-5-ylmethyl)pyrimidin-4-one

The following Examples were made by the method of Example 4; the salts were subsequently prepared by the methods of Examples 7-8 as appropriate:

Ex. No.	Precursors	Structure	Name
140	Int. A155 Int. B63		1-(N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(2-methylthiazol-4-yl)methylthio-5-(2-methoxy-5-pyrimidylmethyl)pyrimidin-4-one
141	Int. A155 Int. B62		1-(N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(pyridin-3-yl)methylthio-5-(2-methoxy-5-pyrimidylmethyl)pyrimidin-4-one

The following Examples were made by the method of Example 22; the salts were subsequently prepared by the methods of Examples 7-8 as appropriate:

Ex. No.	Precursors	Structure	Name
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102
180/8

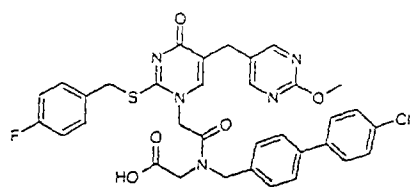
150	Int. A90 Int. B71		1-(N-(2-(1-piperazino)ethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one hydrochloride
151	Int. A86 Int. B71		1-(N-(2-(ethylamino)ethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one hydrochloride
152	Int. A85 Int. B71		1-(N-(2-(methylamino)ethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one hydrochloride
153	Int. A91 Int. B71		1-(N-(3-(2-oxo-1-piperazino)propyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one hydrochloride
154	Int. A89 Int. B71		1-(N-(3-(methylamino)propyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one hydrochloride
155	Int. A88 Int. B71		1-(N-(3-aminopropyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one hydrochloride
156	Int. A87 Int. B71		1-(N-(2-(ethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(1-methyl-4-pyrazolylmethyl)pyrimidin-4-one bitartrate

The following Example was made by the method of Example 21:

Ex. No. Precursor Structure Name

157

Ex. 118



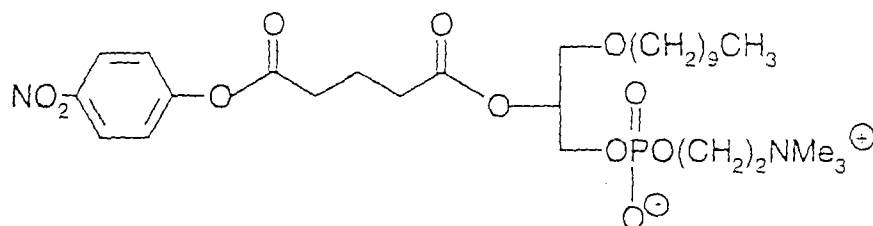
1-(N-(carboxymethyl)-N-(4-(4-chloro-phenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methoxy-5-pyrimidylmethyl)pyrimidin-4-one, sodium salt

103
101/85

Biological Data

1. Screen for Lp-PLA₂ inhibition.

- 5 Enzyme activity was determined by measuring the rate of turnover of the artificial substrate (A) at 37 °C in 50mM HEPES (N-2-hydroxyethylpiperazine-N'-2-ethanesulphonic acid) buffer containing 150mM NaCl, pH 7.4.



(A)

Assays were performed in 96 well titre plates.

Recombinant LpPLA₂ was purified to homogeneity from baculovirus infected Sf9 cells, using a zinc chelating column, blue sepharose affinity chromatography and an anion exchange column. Following purification and ultrafiltration, the enzyme was stored at 6mg/ml at 4°C. Assay plates of compound or vehicle plus buffer were set up using automated robotics to a volume of 170µl. The reaction was initiated by the addition of 20µl of 10x substrate (A) to give a final substrate concentration of 20µM and 10µl of diluted enzyme to a final 0.2nM LpPLA₂.

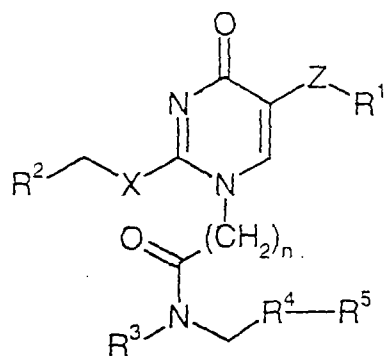
The reaction was followed at 405 nm and 37 °C for 20 minutes using a plate reader with automatic mixing. The rate of reaction was measured as the rate of change of absorbance.

Results

The compounds described in the Examples were tested as described above and had IC₅₀ values in the range 0.001 to 0.00005 µM.

Claims

1. A compound of formula (I):



(I)

in which:

in which:

R^1 is an aryl or heteroaryl group, optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from $C_{(1-18)}$ alkyl, $C_{(1-18)}$ alkoxy, $C_{(1-18)}$ alkylthio, aryl $C_{(1-18)}$ alkoxy, hydroxy, halogen, CN, COR^6 , carboxy, $COOR^6$, $CONR^9R^{10}$, NR^6COR^7 , $SO_2NR^9R^{10}$, $NR^6SO_2R^7$, NR^9R^{10} , mono to perfluoro- $C_{(1-4)}$ alkyl and mono to perfluoro- $C_{(1-4)}$ alkoxy, or, as a single substituent, optionally in combination with a further substituent as hereinbefore defined, CH_2COOH or a salt thereof, CH_2COOR^8 , $CH_2CONR^9R^{10}$, CH_2CN , $(CH_2)_mNR^9R^{10}$, $(CH_2)_mOH$ or $(CH_2)_mOR^6$ where m is an integer from 1 to 3;

R^2 is an aryl or heteroaryl group, optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from $C_{(1-18)}$ alkyl, $C_{(1-18)}$ alkoxy, $C_{(1-18)}$ alkylthio, aryl $C_{(1-18)}$ alkoxy, hydroxy, halogen, CN, COR^6 , carboxy, $COOR^6$, $CONR^9R^{10}$, NR^6COR^7 , $SO_2NR^9R^{10}$, $NR^6SO_2R^7$, NR^9R^{10} , mono to perfluoro- $C_{(1-4)}$ alkyl, mono to perfluoro- $C_{(1-4)}$ alkoxyaryl, and aryl $C_{(1-4)}$ alkyl;

R^3 is hydrogen or $C_{(1-4)}$ alkyl which may be unsubstituted or substituted by hydroxy, OR^6 , COR^6 , carboxy, $COOR^6$, $CONR^9R^{10}$, NR^9R^{10} , mono- or di-(hydroxy $C_{(1-6)}$ alkyl)amino or N-hydroxy $C_{(1-6)}$ alkyl-N- $C_{(1-6)}$ alkyl amino;

R^4 is an aryl or a heteroaryl ring optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from $C_{(1-18)}$ alkyl, $C_{(1-18)}$ alkoxy, $C_{(1-18)}$ alkylthio, aryl $C_{(1-18)}$ alkoxy, hydroxy, halogen, CN, COR^6 , carboxy, $COOR^6$, $CONR^9R^{10}$, NR^6COR^7 , $SO_2NR^9R^{10}$, $NR^6SO_2R^7$, NR^9R^{10} , mono to perfluoro- $C_{(1-4)}$ alkyl and mono to perfluoro- $C_{(1-4)}$ alkoxy;

R^5 is an aryl ring which is further optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from $C_{(1-18)}$ alkyl, $C_{(1-18)}$ alkoxy, $C_{(1-18)}$ alkylthio, aryl $C_{(1-18)}$ alkoxy, hydroxy, halogen, CN, COR^6 , carboxy, $COOR^6$, $CONR^9R^{10}$, NR^6COR^7 , $SO_2NR^9R^{10}$, $NR^6SO_2R^7$, NR^9R^{10} , mono to perfluoro- $C_{(1-4)}$ alkyl and mono to perfluoro- $C_{(1-4)}$ alkoxy;

R^6 and R^7 are independently hydrogen or $C_{(1-20)}$ alkyl, for instance $C_{(1-4)}$ alkyl (e.g. methyl or ethyl);

R^8 is $C_{(1-4)}$ alkyl or a pharmaceutically acceptable *in vivo* hydrolysable ester group;

R^9 and R^{10} which may be the same or different is each selected from hydrogen, $C_{(1-12)}$ alkyl, CH_2R^{11} , $CHR^{12}CO_2H$ or a salt thereof, or R^9 and R^{10} together with the nitrogen to which they are attached form a 4- to 7-, preferably 5- to 7-, membered ring optionally containing one or more further heteroatoms selected from oxygen, nitrogen and sulphur, and optionally substituted by one or two

184
102

substituents selected from hydroxy, oxo, C₍₁₋₄₎alkyl, C₍₁₋₄₎alkylCO, aryl, e.g. phenyl, or aralkyl, e.g. benzyl, for instance morpholine or piperazine;

R¹¹ is COOH or a salt thereof, COOR⁸, CONR⁶R⁷, CN, CH₂OH or CH₂OR⁶;

R¹² is an amino acid side chain such as CH₂OH from serine;

5 n is an integer from 1 to 4, preferably 1 or 3;

X is O or S; and

Z is CR¹³R¹⁴ where R¹³ and R¹⁴ are each hydrogen or C₍₁₋₄₎alkyl, or R¹³ and R¹⁴ together with the intervening carbon atom form a C₍₃₋₆₎cycloalkyl ring.

10 2. A pharmaceutical composition comprising a compound of formula (I) as claimed in claim 1 and a pharmaceutically acceptable carrier.

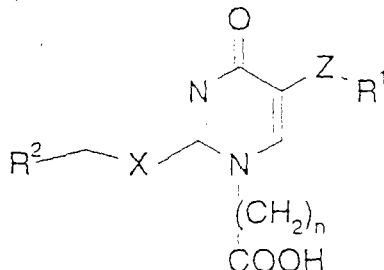
3. A compound of formula (I) as claimed in claim 1 for use in therapy.

15 4. The use of a compound of formula (I) as claimed in claim 1 for the manufacture of a medicament for treating atherosclerosis.

20 5. A method of treating a disease state associated with activity of the enzyme Lp-PLA₂ which method involves treating a patient in need thereof with a therapeutically effective amount of a compound of formula (I) as claimed in claim 1.

6. A process for preparing a compound of formula (I) as defined in claim 1 which process comprises:

(a) reacting a compound of formula (II):



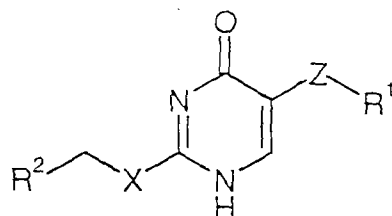
25 (II)

in which X, Y, Z, R¹ and R² are as hereinbefore defined,
with a compound of formula (III):

30
$$\text{R}^5\text{-R}^4\text{-CH}_2\text{NHR}^3$$
 (III)

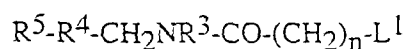
in which R³, R⁴ and R⁵ are as hereinbefore defined; under amide forming conditions:

35 (b) reacting a compound of formula (IV):



(IV)

in which X, Z, R¹ and R² are as hereinbefore defined,
with a compound of formula (V):

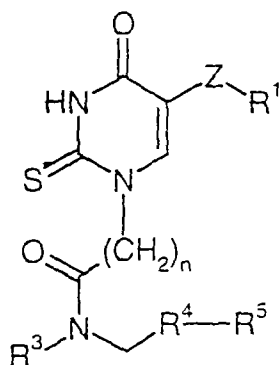


(V)

in which n, R³, R⁴ and R⁵ are as hereinbefore defined, and L¹ is a leaving group such as halogen, for instance bromo or iodo,

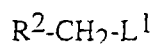
in the presence of a base such as a secondary or tertiary amine, for instance di-isopropylethylamine, in an inert solvent such as dichloromethane;

(c) when X is S, reacting a compound of formula (VI):



(VI)

in which n, Z, R¹, R³, R⁴ and R⁵ are as hereinbefore defined,
with a compound of formula (VII):

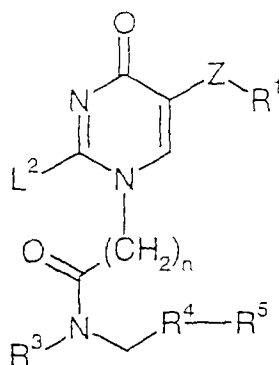


(VII)

in which R² and L¹ are as hereinbefore defined,

in the presence of a base such as a secondary or tertiary amine, for instance di-isopropylethylamine, in an inert solvent such as dichloromethane; or

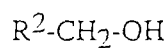
(d) when X is O, reacting a compound of formula (VIII):



(VIII)

in which n , Z , R^1 , R^3 , R^4 and R^5 are as hereinbefore defined, and L^2 is a leaving group such as halogen or alkylthio, for instance methylthio,

5 with a compound of formula (IX):



(IX)

in which R^2 is as hereinbefore defined,

10 in the presence of a base such as 4-dimethylaminopyridine, in an inert solvent such as pyridine.