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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 December 2003 (24.12.2003)

PCT

(10) International Publication Number
WO 03/106420 A1

(51) International Patent Classification[7]: C07D 213/74, 221/22, 227/40, 401/06, 405/06, 409/06, A61K 31/44, 31/439, 31/427, A61P 7/02

(21) International Application Number: PCT/SE03/00970

(22) International Filing Date: 10 June 2003 (10.06.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0201837-2 14 June 2002 (14.06.2002) SE

(71) Applicant *(for all designated States except US)*: **ASTRAZENECA AB** [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **POLLA, Magnus** [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE).

(74) Agent: **GLOBAL INTELLECTUAL PROPERTY**; AstraZeneca AB, S-151 85 Södertälje (SE).

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

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

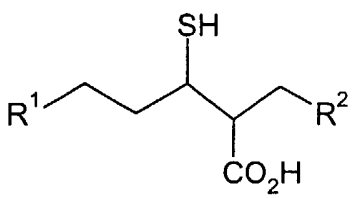
Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *with international search report*

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

WO 03/106420 A1

(54) Title: 2,5-DISUBSTITUTED 3-MERCAPTOPENTANOIC ACID



(I)

(57) Abstract: The present invention concerns compounds of formula (I), and pharmaceutically acceptable salts or solvates thereof, or solvates of such salts, which compounds inhibit carboxypeptidase U and thus can be used in the prevention and treatment of diseases where inhibition of carboxypeptidase U is beneficial. In further aspects, the invention relates to compounds of the invention for use in therapy; to processes for preparation of such new compounds; to pharmaceutical compositions containing at least one compound of the invention, or a pharmaceutically acceptable salt or solvate thereof, as active ingredient; and to the use of the active compounds in the manufacture of medicaments for the medical use indicated above.

2,5-disubstituted 3-mercaptopentanoic acid

The present invention relates to novel compounds, and pharmaceutically acceptable salts thereof, which inhibit basic carboxypeptidases, more specifically carboxypeptidase U, and thus can be used in the prevention and treatment of diseases wherein inhibition of carboxypeptidase U is beneficial, such as thrombosis and hypercoagulability in blood and tissue, atherosclerosis, adhesions, dermal scarring, cancer, fibrotic conditions, inflammatory diseases and those conditions which benefit from maintaining or enhancing bradykinin levels in the body. In further aspects, the invention relates to compounds of the invention for use in therapy; to processes for preparation of such new compounds; to pharmaceutical compositions containing at least one compound of the invention, or a pharmaceutically acceptable salt thereof, as active ingredient; and to the use of the active compounds in the manufacture of medicaments for the medical use indicated above.

Fibrinolysis is the result of a series of enzymatic reactions resulting in the degradation of fibrin by plasmin. The activation of plasminogen is the central process in fibrinolysis. The cleavage of plasminogen to produce plasmin is accomplished by the plasminogen activators, tissue-type plasminogen activator (t-PA) or urokinase-type plasminogen activator (u-PA). Initial plasmin degradation of fibrin generates carboxy-terminal lysine residues that serve as high affinity binding sites for plasminogen. Since plasminogen bound to fibrin is much more readily activated to plasmin than free plasminogen this mechanism provides a positive feedback regulation of fibrinolysis.

One of the endogenous inhibitors to fibrinolysis is carboxypeptidase U (CPU). CPU is also known as plasma carboxypeptidase B, active thrombin activatable fibrinolysis inhibitor (TAFIa), carboxypeptidase R and inducible carboxypeptidase activity. CPU is formed during coagulation and fibrinolysis from its precursor proCPU by the action of proteolytic enzymes, such as thrombin, thrombin-thrombomodulin complex or plasmin. CPU cleaves basic amino acids at the carboxy-terminal of fibrin fragments. The loss of carboxy-terminal lysines and thereby of lysine binding sites for plasminogen then serves to inhibit fibrinolysis. By inhibiting the loss of lysine binding sites for plasminogen and thus increase the rate of plasmin formation, effective inhibitors of carboxypeptidase U are expected to facilitate fibrinolysis.

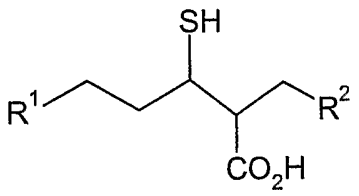
2-Mercaptomethyl-3-guanidinoethylthiopropanoic acid is reported as a carboxypeptidase N inhibitor. More recently, this compound has been shown to inhibit CPU, Hendriks, D. *et al.*, Biochimica et Biophysica Acta, 1034 (1990) 86-92.

Guanidinoethylmercaptosuccinic acid is reported as a carboxypeptidase N inhibitor. More recently, this compound has been shown to inhibit CPU, Eaton, D. L., *et al.*, The Journal of Biological Chemistry, 266 (1991) 21833-21838.

CPU inhibitors are disclosed in WO 00/66550, WO 00/66557, WO 03/013526 and WO 03/027128 and a pharmaceutical formulation containing a CPU inhibitor and a thrombin inhibitor is disclosed in WO 00/66152. Inhibitors of plasma carboxypeptidase B are disclosed in WO 01/19836. Inhibitors of TAFIa are disclosed in WO 02/14285.

It has now been found that compounds of formula (I) are particularly effective as inhibitors of carboxypeptidase U and are thereby useful as medicaments for the treatment or prophylaxis of conditions wherein inhibition of carboxypeptidase U is beneficial.

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



(I)

wherein:

R^1 is phenyl {optionally substituted by halogen, hydroxy, cyano, C_{1-4} alkyl (itself optionally mono-substituted by cyano, hydroxy or phenyl), C_{1-4} alkoxy (itself optionally substituted by tetrahydrofuranyl), CF_3, OCF_3, methylenedioxy, $C(O)R^3$, $S(O)_2R^4$, phenyl (itself optionally substituted by halogen), phenoxy (itself optionally substituted by halogen) or tetrahydrofuranyloxy}, naphthyl, pyridinyl, 1,2,3,4-tetrahydropyrimidin-2,4-dione-yl (optionally substituted by C_{1-4} alkyl) or tetrahydrothienyl;

R^2 is aminopyridinyl, aminothiazolyl or 3-azabicyclo[3.2.1]octyl;

R^3 is hydroxy, C_{1-4} alkoxy (itself optionally substituted by phenyl (itself optionally substituted by halogen) or pyridinyl), NR^5R^6 or an N-linked 5- or 6-membered heterocyclic ring {unsubstituted or mono-substituted by hydroxy, oxo, C_{1-4} alkyl (itself optionally substituted by hydroxy or NHphenyl), $CO_2(C_{1-4}$ alkyl) or phenyl (itself optionally substituted by halogen)};

R^4 is NR^7R^8 or an N-linked 5- or 6-membered heterocyclic ring {unsubstituted; mono-substituted by hydroxy, oxo, C_{1-4} alkyl (itself optionally substituted by hydroxy or NHphenyl), $CO_2(C_{1-4}$ alkyl) or phenyl (itself optionally substituted by halogen); or fused to a benzene ring which is optionally substituted by C_{1-4} alkoxy};

R^5, R^6, R^7 and R^8 are, independently, hydrogen, C_{1-4} alkyl {optionally substituted by halogen, cyano, hydroxy, phenyl (itself optionally substituted by halogen or methylenedioxy), pyridinyl, CO_2H or $CO_2(C_{1-4}$ alkyl)} or C_{2-4} alkenyl;

provided that when R^1 is 6-aminopyridin-3-yl then R^2 is substituted phenyl, naphthyl, pyridinyl, 1,2,3,4-tetrahydropyrimidin-2,4-dione-yl (optionally substituted by C_{1-4} alkyl) or tetrahydrothienyl;

or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

The compounds of formula (I) exist in isomeric forms and the present invention covers all such forms and mixtures thereof in all proportions. Both the pure enantiomers, racemic mixtures and equal and unequal mixtures of two enantiomers are within the scope of the present invention. It should also be understood that all the diastereomeric forms possible are within the scope of the invention.

The term C_{1-4} alkyl denotes a straight or branched alkyl group having 1 to 4 carbon atoms in the chain. Examples of alkyl include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl and tert-butyl.

The term C_{1-4} alkoxy denotes an alkyl-O-group, where alkyl is straight or branched chain and examples include methoxy and ethoxy.

Halogen includes fluoro, chloro, bromo and iodo (but is, for example, fluoro or chloro).

An N-linked 5- or 6-membered heterocyclic ring is, for example, a pyrrolidinyl, piperidinyl or piperazinyl ring.

In one particular aspect the present invention provides a compound of formula (I) wherein R^1 is phenyl {optionally substituted by halogen, hydroxy, cyano, C_{1-4} alkyl (itself optionally mono-substituted by cyano or hydroxy), C_{1-4} alkoxy, CF_3, OCF_3, methylenedioxy, $C(O)NH_2$, $S(O)_2NH_2$ or phenyl (itself optionally substituted by halogen)}, pyridinyl or tetrahydrothienyl; R^2 is aminopyridinyl, aminothiazolyl or 3-azabicyclo[3.2.1]octyl; provided that when R^2 is 6-aminopyridin-3-yl then R^1 is substituted

phenyl, pyridinyl or tetrahydrothienyl; or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

In another aspect the invention provides a compound of formula (I) wherein R^1 is phenyl {optionally substituted (for example carrying 1 or 2 substituents) by halogen, hydroxy, cyano, C_{1-4} alkyl (itself optionally mono-substituted by cyano, hydroxy or phenyl), C_{1-4} alkoxy, CF_3, OCF_3, methylenedioxy, phenoxy (itself optionally substituted by halogen), tetrahydrofuranyloxy or tetrahydrofuranylmethoxy}, naphthyl, pyridinyl or tetrahydrothienyl.

In yet another aspect the present invention provides a compound of formula (I) wherein R^1 is phenyl {substituted (for example mono-substituted) by halogen, hydroxy, cyano, C_{1-4} alkyl (itself optionally mono-substituted by cyano or hydroxy), C_{1-4} alkoxy (for example methoxy), CF_3 or methylenedioxy} or tetrahydrothienyl.

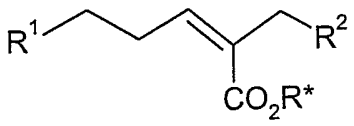
In a still further aspect the present invention provides a compound of formula (I) wherein R^1 is phenyl {mono-substituted by halogen (for example chloro or fluoro), hydroxy, cyano, C_{1-4} alkyl (mono-substituted by cyano), CF_3 or methylenedioxy} or tetrahydrothienyl.

Aminopyridinyl is, for example, 6-aminopyridin-3-yl. Aminothiazolyl is, for example, 2-aminothiazol-5-yl. 3-Azabicyclo[3.2.1]octyl is, for example, 3-azabicyclo[3.2.1]oct-8-yl.

In a further aspect the present invention provides a compound of formula (I) wherein R^2 is aminopyridine (for example 6-aminopyridin-3-yl).

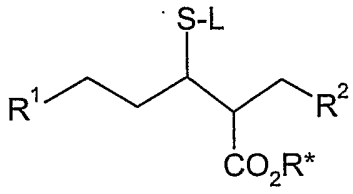
The compounds of the present invention can be prepared by adaptation of methods described in the literature (for example WO 00/66557), or by using or adapting the methods of Examples 1, 26 or 51 below. It will be appreciated that when adapting methods of the literature or Examples 1, 26 or 51 functional groups of intermediate compounds may need to be protected by protecting groups. The preparations of certain intermediates are presented in Schemes 1 and 2.

For example a compound of formula (I) can be prepared by reacting a compound of formula (II):



(II)

wherein R^1 is as defined above or includes a group that can be subsequently reacted to form the group R^1, R* is a suitable protecting group (such as a C_{1-6} alkyl group (for example tert-butyl)) and R^2 is as defined above or the amine function of R^2 can be protected (for example by a tert-butoxycarbonyl group), with a thiol of formula L-SH, wherein L is a suitable protecting group (for example 4-methoxybenzyl), in the presence of a suitable catalyst (for example sodium hydride) and in a suitable solvent (for example N,N-dimethyl formamide) to form a compound of formula (III):



(III)

and, optionally reacting the functional group on R^1 (for example R^1 might include an acid group that can be coupled with an amino function to form an amide in the presence of a catalyst (such as HATU)), and subsequently removing the protecting groups as necessary.

Functional groups which it is desirable to protect include hydroxy, carboxylate and amino groups. Suitable protecting groups for hydroxy include trialkylsilyl or diarylalkylsilyl (for example tert-butyldimethylsilyl, tert-butyldiphenylsilyl or trimethylsilyl), tetrahydropyranyl, methoxymethyl, benzyloxymethyl and 4-methoxybenzyl. Suitable protecting groups for carboxylate include ethyl, tert-butyl and benzyl esters. Suitable protecting groups for amino include tert-butyloxycarbonyl, 2,4,6-trimethoxybenzyl and benzyloxycarbonyl. The use of protecting groups is described in 'Protective Groups in Organic Synthesis', third edition, T.W. Greene & P.G.M. Wutz, Wiley-Interscience (1999). The protective group may also be a polymer resin such as Wang resin or a 2-chorotrityl chloride resin.

The compounds of the invention are inhibitors of carboxypeptidase U and are thus expected to be useful in those conditions where inhibition of carboxypeptidase U is beneficial, such as in the treatment or prophylaxis of thrombosis and hypercoagulability in blood and tissues, atherosclerosis, adhesions, dermal scarring, cancer, fibrotic conditions, inflammatory diseases and those conditions which benefit from maintaining or enhancing bradykinin levels in the body of mammals, such as man.

In a further aspect of the invention a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, is used in the

in the treatment or prophylaxis of thrombosis. In another aspect of the invention a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, is used in method of manufacturing a medicament for the treatment or prophylaxis of thrombosis.

It is known that hypercoagulability may lead to thrombo-embolic diseases. Conditions associated with hypercoagulability and thrombo-embolic diseases which may be mentioned include protein C resistance and inherited or aquired deficiences in antithrombin III, protein C, protein S and heparin cofactor II. Other conditions known to be associated with hypercoagulability and thrombo-embolic disease include circulatory and septic shock, circulating antiphospholipid antibodies, hyperhomocysteinemia, heparin induced thrombocytopenia and defects in fibrinolysis. The compounds of the invention are thus indicated both in the therapeutic and/or prophylactic treatment of these conditions.

Other disease states which may be mentioned include the therapeutic and/or prophylactic treatment of venous thrombosis and pulmonary embolism, arterial thrombosis (for example in myocardial infarction, unstable angina, thrombosis-based stroke and peripheral arterial thrombosis) and systemic embolism usually from the atrium during atrial fibrillation or from the left ventricle after transmural myocardial infarction.

The compounds of the invention are further indicated in the treatment of conditions where there is an undesirable excess of proCPU/CPU.

Moreover, the compounds of the invention are expected to have utility in prophylaxis of re-occlusion and restenosis (that is, thrombosis) after thrombolysis, percutaneous trans-luminal intervention (PTI) and coronary bypass operations; the prevention of re-thrombosis after microsurgery and vascular surgery in general.

Further indications include the therapeutic and/or prophylactic treatment of disseminated intravascular coagulation caused by bacteria, multiple trauma, intoxication or any other mechanism, fibrinolytic treatment when blood is in contact with foreign surfaces in the body, such as vascular grafts, vascular stents, vascular catheters, mechanical and biological prosthetic valves or any other medical device, and fibrinolytic treatment when blood is in contact with medical devices outside the body, such as during cardiovascular surgery using a heart-lung machine or in haemodialysis.

Furthermore, the compounds of the invention are expected to have utility in prophylaxis of atherosclerotic progression and transplant rejection in patients subject to organ transplantation, for example renal transplantation.

The compounds of the invention are also expected to have utility in inhibiting tumor maturation and progression.

Moreover, the compounds of the invention are expected to have utility in treatment of any condition in which fibrosis is a contributing factor. Such fibrotic conditions include cystic fibrosis, pulmonary fibrotic disease eg chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), fibromuscular dysplasia, fibrotic lung disease and fibrin deposits in the eye during opthalmic surgery.

The compounds of the invention are also expected to have utility in treatment of inflammation. In particular the invention may be used for the treatment or prevention of inflammatory diseases such as asthma, arthritis, endometriosis, inflammatory bowel diseases, psoriasis and atopic dermatitis.

The compounds of the invention are also expected to have utility in treatment of neurodegenerative diseases such as Alzheimers and Parkinsons.

The compounds of the invention are also expected to have utility in treatment of conditions known to benefit from maintaining or enhancing bradykinin levels. Such conditions include hypertension, angina, heart failure, pulmonary hypertension, renal failure and organ failure.

The compounds of the invention may also be combined and/or co-administered with any antithrombotic agent with a different mechanism of action, such as an anticoagulant (for example a vitamin K antagonist, an unfractionated or low molecular weight heparin, a synthetic heparin fragment such as fondaparinux, a thrombin inhibitor, a factor Xa inhibitor or other coagulation factor/enzyme inhibitor, a recombinant coagulation factor such as a recombinant human activated protein C) or an antiplatelet agent (such as acetylsalicylic acid, dipyridamole, ticlopidine, clopidogrel or other ADP-receptor [such as a P2Y12 or P2Y1] antagonist, a thromboxane receptor and/or synthetase inhibitor, a fibrinogen receptor antagonist, a prostacyclin mimetic or a phosphodiesterase inhibitor). The compounds of the invention may further be combined and/or coadministered with thrombolytics such as tissue plasminogen activator (natural, recombinant or modified), streptokinase, urokinase, prourokinase, anisoylated plasminogen-streptokinase activator

complex (APSAC), animal salivary gland plasminogen activators, and the like, in the treatment of thrombotic diseases, in particular myocardial infarction, ischaemic stroke and massive pulmonary embolism.

The compounds of the invention should have a selectivity for carboxypeptidase U over carboxypeptidase N of >100:1, for example >1000:1, using the assay described below.

The inhibiting effect of the compounds of the present invention was estimated using the assay described in: Dirk Hendriks, Simon Scharpé and Marc van Sande, Clinical Chemistry, 31, 1936-1939 (1985); and Wei Wang, Dirk F. Hendriks, Simon S. Scharpé, The Journal of Biological Chemistry, 269, 15937-15944 (1994).

Thus, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present invention, the term "therapy" includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be understood accordingly.

The invention also provides a method of treating a condition where inhibition of carboxypeptidase U is beneficial in a mammal suffering from, or at risk of, said condition, which comprises administering to the mammal a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

The compounds of formula (I) and pharmaceutically acceptable salts, solvates or solvates of salts thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound, salt, solvate or solvate of salt (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical

composition will, for example, comprise from 0.05 to 99 %w (per cent by weight), such as from 0.05 to 80 %w, for example from 0.10 to 70 %w, such as from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The present invention thus also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, as hereinbefore defined, with a pharmaceutically acceptable adjuvant, diluent or carrier.

Also included in the invention are derivatives of compounds of formula (I) which have the biological function of compounds of formula (I), such as prodrugs. Prodrugs are, for example, (pivaloyloxy)methyl esters and [(ethoxycarbonyl)oxy]methyl esters of carboxylic acids.

The following Examples illustrate the invention.

EXAMPLES

General Experimental Procedures

Mass spectra were recorded on a VG Platform II or a Micromass ZQ mass spectrometer equipped with an electrospray interface (LC-MS). High resolution mass spectra were recorded on a Micromass LCT mass spectrometer equipped with an electrospray interface (LC-HRMS). ^{1}H NMR measurements were performed on Varian UNITY plus 400, 500 and 600 spectrometers, operating at ^{1}H frequencies of 400, 500 and 600 MHz respectively. NMR spectra were recorded in DMSO, D_2O, CD_3CN or mixtures thereof. Chemical shifts are given in ppm with the solvent as internal standard. Chromatography separations were performed using Merck Silica gel 60 (0.063-0.200 mm). The compounds named below were named using ACD/Name version 6.06/ 11 June 2002 available from advanced chemistry development inc., Canada.

EXAMPLE 1

This Example illustrates the preparation of 2-[(6-aminopyridin-3-yl)methyl]-5-(1,1'-biphenyl-3-yl)-3-mercaptopentanoic acid

(a) 3-(1,1'-Biphenyl-3-yl)propanal

To a solution of 3-iodo-1,1'-biphenyl (0.964 g, 3.44 mmol) and tetrabutylammonium chloride (0.956g, 3.44 mmol) in dry DMF (3 mL) was added allyl alcohol (0.351 mL, 5.16 mmol), sodium hydrogencarbonate (0.723 g, 8.60 mmol), and palladium(II) acetate (31 mg, 0.14 mmol), and the mixture was stirred at room temperature for 18 h. The reaction mixture was then diluted with EtOAc and the solid material filtered off (Celite). The filtrate was washed with water three times, dried (Na_2SO_4) and concentrated. Flash chromatography (heptan/*tert*-butyl methyl ether, 4:1) of the residue gave 3-(1,1'-biphenyl-3-yl)propanal (0.601 g, 83%).

(b) *tert*-Butyl 5-(1,1'-biphenyl-3-yl)-2-({6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}methyl)pent-2-enoate

A solution of *tert*-butyl 3-{6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}-2-(diethoxyphosphoryl)propanoate (1.058 g, 2.31 mmol) in dry THF (4 mL) was added to a solution of sodium hydride (0.111 g, 60% in mineral oil, 2.77 mmol) in dry THF (3 mL) at 0 °C and the mixture was stirred at 0 °C for 60 min. To this mixture a solution of 3-(1,1'-biphenyl-3-yl)propanal (0.582 g, 2.77 mmol) in dry THF (3 mL) was added, and the reaction mixture was allowed to attain room temperature over 22 h. EtOAc was then added, and the organic phase was washed with saturated aqueous NH_4Cl and water, dried (Na_2SO_4) and concentrated. Flash chromatography (toluene/EtOAc, 15:1) of the residue gave *tert*-butyl 5-(1,1'-biphenyl-3-yl)-2-({6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}methyl)pent-2-enoate (1.105 g, 93%) as a mixture of E/Z-isomers.

(c) *tert*-Butyl 5-(1,1'-biphenyl-3-yl)-2-({6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}methyl)-3-[(4-methoxybenzyl)thio]pentanoate

A solution of 4-methoxy-α-toluenethiol (0.58 mL, 4.17 mmol) in dry, degassed DMF (2 mL) was treated at room temperature with a catalytic amount of sodium hydride

(60% in mineral oil), followed by a solution of *tert*-butyl 5-(1,1'-biphenyl-3-yl)-2-({6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}methyl)pent-2-enoate (1.073 g, 2.08 mmol) in dry, degassed DMF (5 mL). After 20 h at room temperature the reaction mixture was diluted with EtOAc and washed with water three times. The organic layer was dried (Na_2SO_4), concentrated, and subjected to flash chromatography (heptan/EtOAc, 3:1 and toluene/EtOAc 12:1) to give *tert*-butyl 5-(1,1'-biphenyl-3-yl)-2-({6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}methyl)-3-[(4-methoxybenzyl)thio]pentanoate (1.251 g, 90%)

(d) 2-[(6-Aminopyridin-3-yl)methyl]-5-(1,1'-biphenyl-3-yl)-3-mercaptopentanoic acid

tert-Butyl 5-(1,1'-biphenyl-3-yl)-2-({6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}methyl)-3-[(4-methoxybenzyl)thio]pentanoate (0.669 g, 1.00 mmol) was dissolved in triethylsilane (0.75 mL) and trifluoroacetic acid (6.0 mL). The solution was heated to 60 °C for 3h and then concentrated. Purification of the residue by reversed-phase HPLC (C-8 column, linear gradient 40%→100% of MeCN in 5% aqueous MeCN containing 0.15% trifluoroacetic acid) gave the title diastereomeric compound as the trifluoroacetic salt (0.342g, 68%) after freeze-drying.

^{1}H NMR (400 MHz, CD_3CN/D_2O): δ 7.70 (dd, J = 2.1, 9.2 Hz, 0.5H), 7.66 (dd, J = 2.1, 9.2 Hz, 0.5 Hz), 7.61-7.58 (m, 2H), 7.53-7.51 (m, 1H), 7.46-7.41 (m, 4H), 7.38-7.32 (m, 2H), 7.22-7.16 (m, 1H), 6.88 (d, J = 9.1 Hz, 0.5H), 6.84 (d, J = 9.1 Hz, 0.5H), 3.10-2.74 (m, 6H) ,2.17-2.04 (m, 1H),1.91-1.78 (m, 1H). ^{13}C NMR (101 MHz, CD_3CN/D_2O): δ 175.3, 174.9, 153.0, 146.0, 145.8, 142.3, 141.1,140.9, 134.0, 133.9, 129.4, 129.2, 127.9, 127.9, 127.8, 127.3, 127.2, 127.1, 124.9, 124.8, 124.4, 124.1, 113.9, 113.8, 53.6, 53.0, 41.3, 40.5, 37.9, 33.1, 33.0, 31.2, 30.3. HRMS (ESI) calculated for $C_{23}H_{25}N_2O_2S$ 393.1637 $(M+H)^+$, found 393.1650.

EXAMPLE 2

2-[(6-Aminopyridin-3-yl)methyl]-3-mercapto-5-(1-naphthyl)pentanoic acid was synthesised according to the procedure for Example 1.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14-8.10 (d, 1H), 7.93-7.89 (d, 1H), 7.80-7.54 (m, 1H), 7.67-7.35 (m, 6H), 6.83-6.77 (m, 1H), 3.52-3.35(m, 1H), 3.22-3.12 (m, 2H), 2.90-2.80 (m,

3H),2.25-2.13 (m, 1H), 2.05-1.87 (m, 1H). HRMS (ESI) calculated for $C_{21}H_{23}N_2O_2S$ 367.1480 $(M+H)^+$, found 367.1497.

EXAMPLE 3

2-[(6-Aminopyridin-3-yl)methyl]-5-(3-cyanophenyl)-3-mercaptopentanoic acid was synthesised according to the procedure for Example 1.

^1H NMR (400 MHz, CD_3CN/D_2O): δ 7.73 (dd, *J*= 2.2, 9.3 Hz, 0.5H), 7.70 (dd, *J*= 2.2, 9.3 Hz, 0.5H), 7.58-7.40 (m, 5H), 6.90 (d, *J* = 9.1 Hz, 0.5H), 6.88 (d, *J* = 9.3 Hz, 0.5H), 2.99-2.88 (m, 2H), 2.82-2.71 (m, 4H), 2.12-2.00 (m, 1H), 1.88-1.74 (m, 1H).

^{13}C NMR (101 MHz, CD_3CN/D_2O): δ 175.5, 174.9, 153.0, 146.0, 145.8, 143.1, 133.9, 132.4, 132.3, 130.3, 130.3, 129.8, 124.3, 124.0, 119.4, 113.9, 113.9, 111.6, 53.8, 52.8, 41.1, 40.2, 37.4, 32.5, 32.5, 31.1, 30.5. HRMS (ESI) calcd for $C_{18}H_{20}N_3O_2S$ 342.1276 $(M+H)^+$, found 342.1277

EXAMPLE 4

5-[3-(Aminocarbonyl)phenyl]-2-[(6-aminopyridin-3-yl)methyl]-3-mercaptopentanoic acid was synthesised according to the procedure for Example 1, starting from 3-iodo-*N*-(2,4,6-trimethoxybenzyl)benzamide. 3-iodo-*N*-(2,4,6-trimethoxybenzyl)benzamide was synthesised from 3-iodobenzoic acid using standard procedures.

^1H NMR (400 MHz, CD_3CN/D_2O): δ 7.72-7.67 (m, 1H), 7.65-7.61 (m, 2H), 7.52-7.49 (m, 1H), 7.42-7.35 (m, 2H), 6.89 (d, *J* = 9.3 Hz, 0.7H), 6.85 (d, *J* = 9.1 Hz, 0.3H), 3.00-2.87 (m, 2H), 2.81-2.72 (m, 4H), 2.13-2.00 (m, 1H), 1.90-1.86 (m, 1H).

^{13}C NMR (101 MHz, CD_3CN/D_2O): δ 175.7, 175.1, 171.5, 161.7, 161.4, 153.0, 146.0, 145.8, 142.1, 142.0, 133.9, 133.4, 132.7, 129.1, 127.8, 127.7, 125.5, 124.3, 124.0, 114.0, 113.9, 53.7, 52.6, 41.0, 39.9, 37.7, 37.6, 32.8, 32.7, 31.0, 30.4. HRMS (ESI) calcd for $C_{18}H_{22}N_3O_3S$ 360.1382 $(M+H)^+$, found 360.1378.

EXAMPLE 5

2-[(6-Aminopyridin-3-yl)methyl]-5-[2-fluoro-4-(trifluoromethyl)phenyl]-3-mercaptopentanoic acid was synthesised according to the procedure for Example 1.

^{1}H NMR (400 MHz, CD_3CN/D_2O): δ 7.75-7.71 (m, 1H), 7.56 (d, J = 1.6H, 1H), 7.47-7.35 (m, 3H), 6.91 (d, J = 9.3 Hz, 1 H), 3.04-2.91 (m, 1H), 2.88-2.74 (m, 4H).

^{13}C NMR (101 MHz, CD_3CN/D_2O): δ 175.4, 174.9, 162.0, 161.4, 159.6, 153.0, 146.0, 145.9, 134.0, 133.2, 133.0, 129.9, 124.2, 124.0, 121.4, 114.0, 113.9, 112.8, 112.6, 53.8, 53.0, 41.5, 40.8, 36.3, 36.2, 31.2, 30.6, 26.5. HRMS (ESI) calcd for $C_{18}H_{19}F_4N_2O_2S$ 403.1103 $(M+H)^+$, found 403.1137.

EXAMPLE 6

2-[(6-Aminopyridin-3-yl)methyl]-5-(3-chlorophenyl)-3-mercaptopentanoic acid was synthesised according to the procedure for Example 1.

^{1}H NMR (500 MHz, CD_3CN/D_2O): δ 7.75 (dd, 0.5H), 7.72 (dd, 0.5 H), 7.56 (d, 0.5H), 7.54 (d, 0.5 H), 7.30-7.10 (m, 4H), 6.92 (d, 0.5H), 6.91 (d, 0.5H), 3.02-2.65 (m, 6H), 2.10-2.00 (m, 1H), 1.88-1.74 (m, 1H). MS (ESI) 351.1 $(M+H)^+$.

EXAMPLE 7

2-[(6-Aminopyridin-3-yl)methyl]-5-(1,3-benzodioxol-5-yl)-3-mercaptopentanoic acid was synthesised according to the procedure for Example 1.

^{1}H NMR (400 MHz, CD_3CN/D_2O): δ 7.72(dd, 1H), 7.69 (d, 0.5H), 7.55 (s, 0.5H), 7.53 (s, 0.5H), 6.89 (m, 1H), 6.77-6.60 (m, 3H), 5.88(s, 2H), 3.0-2.70 (m, 5H), 2.58-2.68 (m, 1H), 1.92-2.08 (m, 1H), 1.69-1.81(m, 1H). HRMS (ESI) calculated for $C_{18}H_{20}N_2O_4S$ 361.1222 $(M+H)^+$, found 361.1236.

EXAMPLE 8

2-[(6-Aminopyridin-3-yl)methyl]-3-mercapto-5-pyridin-2-ylpentanoic acid was synthesised according to the procedure for Example 1, starting from 3-pyridin-2-ylpropanal.

^{1}H NMR (600 MHz, D_2O) δ ppm 1.90-2.37 (m, 2 H), 2.70-2.98 (m, 3 H), 3.05-3.11 (m, 1 H), 3.12-3.24 (m, 1 H), 3.32-3.41 (m, 1 H), 6.89 (d, 1 H), 7.57 (s, 1 H), 7.75 (dd, 1 H), 7.80-7.85 (m, 1 H), 7.88 (d, 1 H), 8.39-8.46 (m, 1 H), 8.54-8.60 (m, 1 H).

MS (ESI) 318.2 $(M+H)^+$.

EXAMPLE 9

2-[(6-Aminopyridin-3-yl)methyl]-3-mercapto-5-(3,4,5-trimethoxyphenyl)pentanoic acid was synthesised according to the procedure for Example 1.

^{1}H NMR (600 MHz, , CD_3CN/D_2O) δ ppm 1.71-1.87 (m, 1H), 1.98-2.10 (m, 1H), 2.58-2.70 (m, 1H), 2.73-2.87 (m, 4H), 2.90 (d, 0.5H), 2.88-3.02 (m, 0.5H), 3.65 (s, 3H), 3.75 (s, 3H), 3.75 (s, 3H), 6.48 (s, 1H), 6.49 (s, 1H), 6.88 (d, 0.5H), 6.89 (d, 0.5H), 7.52 (d, 1H), 7.67-7.72 (m, 1H). MS (ESI) 407.2 $(M+H)^+$.

EXAMPLE 10

2-[(6-Aminopyridin-3-yl)methyl]-3-mercapto-5-pyridin-3-ylpentanoic acid was synthesised according to the procedure for Example 1, starting from 3-pyridin-3-ylpropanal.

^{1}H NMR (600 MHz, CD_3CN/D_2O) δ ppm 1.78-1.90 (m, 1H), 2.03-2.19 (m, 1H), 2.71-2.78 (m, 1H), 2.78-3.02 (m, 4H), 3.07-3.18 (m, 1H), 6.90 (d, 1H), 7.56 (s, 1H), 7.73-7.76 (m, 1H), 7.91-7.95 (m, 1H), 8.40-8.44 (m, 1H), 8.55-8.59 (m, 2H).

MS (ESI) 318.2 $(M+H)^+$.

EXAMPLE 11

2-[(6-Aminopyridin-3-yl)methyl]-5-[4-(cyanomethyl)phenyl]-3-mercaptopentanoic acid was synthesised according to the procedure for Example 1.

^{1}H NMR (500 MHz, CD_3CN/D_2O): δ 7.99(dd, 0.5H), 7.96 (dd, 0.5H), 7.81 (d, 0.5H), 7.80 (d, 0.5H), 7.56-7.46 (m, 4H), 7.17 (d, 0.5H), 7.15 (d, 0.5H), 4.11 (s, 2H), 3.26-2.97 (m, 6H), 2.40-2.25 (m, 1H), 2.17-2.02 (m, 1H). MS (ESI) 356.2 $(M+H)^+$.

EXAMPLE 12

2-[(6-Aminopyridin-3-yl)methyl]-5-(2-hydroxyphenyl)-3-mercaptopentanoic acid was synthesised according to the procedure for Example 1, starting from 1-iodo-2-[(4-methoxybenzyl)oxy]benzene. 1-iodo-2-[(4-methoxybenzyl)oxy]benzene was synthesised from 2-iodophenol using standard procedures.

^{1}H NMR (500 MHz, 90% CD_3CN/D_2O) δ ppm 1.72-1.87 (m, 1 H), 2.00-2.15 (m, 1 H), 2.60-2.75 (m, 1 H), 2.77-2.94 (m, 4.6 H), 3.06-3.11 (m, 0.4 H), 6.75-6.81 (m, 2 H), 6.90-

6.94 (m, 1H), 7.02-7.13 (m, 2 H), 7.56 (d, 0.6 H), 7.57 (d, 0.4 H), 7.75 (dd, 0.6 H), 7.77 (dd, 0.4 H). MS (ESI) 333.2 $(M+H)^+$.

EXAMPLE 13

2-[(6-Aminopyridin-3-yl)methyl]-5-[4-(aminosulfonyl)phenyl]-3-mercaptopentanoic acid was synthesised according to the procedure for Example 1, starting from 4-iodo-*N*-(2,4,6-trimethoxybenzyl)benzenesulfonamide. 4-iodo-*N*-(2,4,6-trimethoxybenzyl)benzenesulfonamide was synthesised from 4-iodobenzenesulfonyl chloride using standard procedures.

^{1}H NMR (500 MHz, 75% CD_3CN/D_2O) δ ppm 1.79-1.92 (m, 1 H), 2.04-2.18 (m, 1 H), 2.76-2.88 (m, 4 H), 2.90-3.07 (m, 2 H), 6.92 (d, 0.5 H), 6.93 (d, 0.5 H), 7.40 (d, 1 H), 7.42 (d, 1 H), 7.57 (d, 0.5 H), 7.58 (d, 0.5 H), 7.72-7.81 (m, 3 H). MS (ESI) 396.1 $(M+H)^+$.

EXAMPLE 14

2-[(6-Aminopyridin-3-yl)methyl]-3-mercapto-5-(4-methoxyphenyl)pentanoic acid was synthesised according to the procedure for Example 1.

^{1}H NMR (500 MHz, 75% CD_3CN/D_2O) δ ppm 1.73-1.85 (m, 1 H), 1.99-2.11 (m, 1 H), 2.61-2.72 (m, 1 H), 2.75-2.95 (m, 4.5 H), 2.98-3.04 (m, 0.5 H), 3.75 (s, 1.5 H), 3.76 (s, 1.5 H), 6.82-6.88 (m, 2 H), 6.92 (d, 0.5 H), 6.93 (d, 0.5 H), 7.12 (d, 0.5 H), 7.15 (d, 0.5 H), 7.56 (s, 0.5 H), 7.58 (s, 0.5), 7.72-7.78 (m, 1 H). MS (ESI) 347.2 $(M+H)^+$.

EXAMPLE 15

2-[(6-Aminopyridin-3-yl)methyl]-5-(4-hydroxyphenyl)-3-mercaptopentanoic acid was synthesized from 2-[(6-aminopyridin-3-yl)methyl]-3-mercapto-5-(4-methoxyphenyl)pentanoic acid using standard conditions for the methoxy group hydrolysis (concentrated aqueous hydrochloric acid at reflux under argon for 24 h).

1H NMR (500 MHz, 25% CD_3CN in D_2O) δ ppm 1.73-1.85 (m, 1 H), 1.94-2.09 (m, 1 H), 2.59-2.68 (m, 1 H), 2.75-2.87 (m, 4 H), 2.90 (d, 0.5 H), 2.98-3.03 (m, 0.5 H), 6.71-6.76 (m, 2 H), 6.90-6.95 (m, 1 H), 7.00-7.07 (m, 2 H), 7.54-7.57 (m, 1 H), 7.71-7.76 (m, 1 H). MS (ESI) 333.2 $(M+H)^+$.

EXAMPLE 16

2-[(6-Aminopyridin-3-yl)methyl]-3-mercapto-5-[4-(trifluoromethoxy)phenyl]-pentanoic acid was synthesised according to the procedure for Example 1.

^{1}H NMR (500 MHz, CD_3CN/D_2O) δ ppm 1.76-1.88 (m, 1 H), 2.01-2.14 (m, 1 H), 2.66-3.07 (m, 6 H), 6.94 (d, 1 H), 7.16-7.25 (m, 2 H), 7.26-7.34 (m, 2 H), 7.59 (d, 1 H), 7.78 (dd, 1 H). MS (ESI) 401.3 $(M+H)^+$.

EXAMPLE 17

2-[(6-Aminopyridin-3-yl)methyl]-5-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-3-mercaptopentanoic acid was synthesised according to the procedure for Example 1.

^{1}H NMR (500 MHz, CD_3CN/D_2O) δ ppm 1.57-1.76 (m, 1 H), 1.92-2.06 (m, 1 H), 2.31-2.45 (m, 1 H), 2.53-2.63 (m, 1 H), 2.75-3.07 (m, 4 H), 3.22 (s, 1.5 H), 3.23 (s, 1.5 H) 3.30 (s, 1.5 H), 3.30 (s, 1.5 H), 6.94 (d, 1 H), 7.30 (s, 0.5 H), 7.32 (s, 0.5 H), 7.59-7.64 (m, 1 H), 7.80 (dd, 1 H). MS (ESI) 379.2 $(M+H)^+$.

EXAMPLE 18

2-[(6-Aminopyridin-3-yl)methyl]-3-mercapto-5-(tetrahydro-2-thienyl)pentanoic acid was synthesised according to the procedure for Example 1, starting from 3-thien-2-ylpropanal.

1H NMR (500 MHz, , 90%CD_3CN/D_2O) δ ppm 1.48-1.60 (m, 3 H), 1.70-1.90 (m, 3 H), 2.00-2.10 (m, 2 H), 2.70-3.10 (m, 6 H), 3.25-3.33 (m, 1 H), 6.92 (d, 1 H), 7.59 (s, 1 H), 7.78 (dd, 1 H). MS (ESI) 327.3 $(M+H)^+$.

EXAMPLE 19

2-[(6-Aminopyridin-3-yl)methyl]-5-[3-(hydroxymethyl)phenyl]-3-mercaptopentanoic acid was synthesised according to the procedure for Example 1, starting from 1-iodo-3-{[(4-methoxybenzyl)oxy]methyl}benzene. 1-iodo-3-{[(4-methoxybenzyl)oxy]methyl}benzene was synthesized from (3-iodophenyl)methanol using standard procedures.

^{1}H NMR (500 MHz, CD_3CN/D_2O) δ ppm 1.94-2.10 (m, 1 H), 2.21-2.37 (m, 1 H), 2.78-3.24 (m, 6 H), 4.77 (s, 1 H), 4.78 (s, 1 H), 7.09 (d, 0.5 H), 7.12 (d, 0.5 H), 7.34-7.44 (m, 3

H), 7.48-7.54 (m, 1 H), 7.73 (d, 0.5H), 7.74 (d, 0.5H), 7.91 (dd, 0.5H), 7.96 (dd, 0.5H). MS (ESI) 347.3 $(M+H)^+$.

EXAMPLE 20

2-[(6-Aminopyridin-3-yl)methyl]-5-[2-(2,4-dichlorophenoxy)phenyl]-3-mercaptopentanoic acid was synthesised according to the procedure for Example 1.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, 1H), 7.51 (d, 1 H), 7.40 (d, 1H), 7.27 (m, 1H), 7.18-7.04 (m, 3H), 7.78-7.69 (m, 3H), 3.15-2.92(m, 2H), 2.87-2.65 (m, 4H) ,2.21-2.08 (m, 1H),1.89-1.75 (m, 1H). HRMS (ESI) calculated for $C_{23}H_{22}Cl_2N_2O_3S$ 477.0806 $(M+H)^+$, found 477.0170..

EXAMPLE 21

2-[(6-Aminopyridin-3-yl)methyl]-5-(3,5-dimethylphenyl)-3-mercaptopentanoic acid was synthesised according to the procedure for Example 1.
^{1}H NMR (500 MHz, CD_3CN/D_2O) δ ppm 1.72-1.85 (m, 1 H), 1.97-2.11(m, 1 H), 2.23 (s, 3 H), 2.24 (s, 3 H), 2.57-2.66 (m, 1 H), 2.75-2.87 (m, 4 H), 2.90 (d, 0.5 H), 2.99-3.05 (m, 0.5 H), 6.78-6.85 (m, 3 H), 6.88-6.94 (m, 1 H), 7.54 (d, 0.5 H), 7.56 (d, 0.5 H), 7.71 (dd, 0.5 H), 7.73 (d, 0.5 H). MS (ESI) 345.2 $(M+H)^+$.

EXAMPLE 22

2-[(6-Aminopyridin-3-yl)methyl]-3-mercapto-5-(4-propylphenyl)pentanoic acid was synthesised according to the procedure for Example 1.
^{1}H NMR (500 MHz, CD_3CN/D_2O) δ ppm 0.84 (t, 3 H), 1.49-1.58 (m, 2 H), 1.70-1.81 (m, 1 H), 1.96-2.04 (m, 1 H), 2.50 (t, 2 H), 2.60-2.70 (m, 1 H), 2.71-2.93 (m, 4 H), 2.93-3.01 (m, 1 H), 6.88 (d, 1 H), 7.07-7.10 (m, 4 H), 7.54 (d, 1 H), 7.71 (dd, 1 H). MS (ESI) 359.2 $(M+H)^+$.

EXAMPLE 23

2-[(6-Aminopyridin-3-yl)methyl]-5-(4-benzylphenyl)-3-mercaptopentanoic acid was synthesised according to the procedure for Example 1 starting from (4-iodophenyl)(phenyl)methanone.

^{1}H NMR (500 MHz, 80% CD_3CN/D_2O) δ ppm 1.72-1.82 (m, 1 H), 2.00-2.10 (m, 1 H), 2.72-2.62 (m, 1 H), 2.78-3.04 (m, 5H), 3.9 (s, 2 H), 6.90 (d, H), 7.08-7.29 (m, 9H), 7.55 (d, 1 H), 7.73 (dd, 1 H). HRMS (ESI) calculated for $C_{24}H_{27}N_2O_2S$ 407.1793 $(M+H)^+$, found 407.1804.

EXAMPLE 24

2-[(2-Amino-1,3-thiazol-5-yl)methyl]-3-mercapto-5-phenylpentanoic acid was synthesised according to the procedure for Example 1 starting from *tert*-butyl 3-{2-[(*tert*-butoxycarbonyl)amino]-1,3-thiazol-5-yl}-2-(diethoxyphosphoryl)propanoate. *Tert*-butyl 3-{2-[(*tert*-butoxycarbonyl)amino]-1,3-thiazol-5-yl}-2-(diethoxyphosphoryl)propanoate was synthesised as shown in Scheme 1.

^{1}H NMR (500 MHz, 90% CD_3CN/D_2O) δ ppm 1.78-1.90 (m, 1H), 2.00-2.11 (m, 1H), 2.68-2.77 (m, 1H), 2.78-3.2 (m, 4.5H), 3.05-3.11 (m, 0.5H), 6.85-6.88 (m, 1H), 7.16-7.33 (m, 5H). MS (ESI) 323.2 $(M+H)^+$.

EXAMPLE 25

2-(3-Azabicyclo[3.2.1]oct-8-ylmethyl)-3-mercapto-5-phenylpentanoic acid was synthesised according to the procedure for Example 1 starting from *tert*-butyl 8-[3-*tert*-butoxy-2-(diethoxyphosphoryl)-3-oxopropyl]-3-azabicyclo[3.2.1]octane-3-carboxylate. *Tert*-butyl 8-[3-*tert*-butoxy-2-(diethoxyphosphoryl)-3-oxopropyl]-3-azabicyclo[3.2.1]octane-3-carboxylate was synthesised as shown in Scheme 2.

^{1}H NMR (400 MHz, CD_3CN/D_2O): δ 7.90-7.80 (m, 2H), 7.80-7.70 (m, 3H), 3.80-3.60 (m, 2H), 3.60-3.35 (m, 4H), 3.35-3.18 (m, 1H), 3.18-3.00 (m, 1H), 2.90-1.80 (m, 11H). MS (ESI) 333.5 $(M+H)^+$.

EXAMPLE 26

This Example illustrates the preparation of 2-[(6-aminopyridin-3-yl)methyl]-3-mercapto-5-(3-{[methyl(2-phenylethyl)amino]carbonyl}phenyl)pentanoic acid.

(a) 3-{5-*tert*-butoxy-4-({6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}methyl)-3-[(4-methoxybenzyl)thio]-5-oxopentyl}benzoic acid

KOH (5 mL of a 1M solution in ethanol) was added to a solution of ethyl 3-{5-*tert*-butoxy-4-({6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}methyl)-3-[(4-methoxybenzyl)thio]-5-oxopentyl}benzoate (0.27 g, 0.406 mmol, synthesised according to the procedure for Example 1) in ethanol (2 mL), and the mixture was stirred at room temperature for 2 h and then at 50 °C for 2 h. The reaction mixture was then diluted with diethyl ether and water. The organic phase was extracted with 0.1M aqueous KOH and the combined aqueous phase was acidified (pH 5) using 3M aqueous HCl. The aqueous phase was then extracted with diethyl ether and the organic phase was washed with brine, dried and concentrated. Purification of the residue by reversed-phase HPLC (C-8 column, linear gradient 40%→100% of MeCN in 5% aqueous MeCN containing 0.1 M ammonium acetate) gave a residue that was dissolved in toluene and water and concentrated to give 3-{5-*tert*-butoxy-4-({6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}methyl)-3-[(4-methoxybenzyl)thio]-5-oxopentyl}benzoic acid (0.12 g, 54%).

(b) *tert*-butyl 2-({6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}methyl)-3-[(4-methoxybenzyl)thio]-5-(3-{[methyl(2-phenylethyl)amino]carbonyl}phenyl)pentanoate

N-methylphenethylamine (20 µL, 0.14 mmoL), HATU (55 mg, 0.15 mmoL) and iPr_2EtN (46 µL, 0.26 mmoL) was added to a solution of 3-{5-*tert*-butoxy-4-({6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}methyl)-3-[(4-methoxybenzyl)thio]-5-oxopentyl}benzoic acid (84 mg, 0.132 mmol) in DMF (2 mL) under argon at 0 °C. The reaction mixture was stirred for 2 h and was then quenched with ice. Diethylether and water was added and the aqueous phase was extracted diethyl ether. The combined organic phase was dried and concentrated. Flash chromatography (heptan/EtOAc, 3:1) gave *tert*-butyl 2-({6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}methyl)-3-[(4-methoxybenzyl)thio]-5-(3-{[methyl(2-phenylethyl)amino]carbonyl}phenyl)pentanoate (81 mg , 81.4 %).

(c) 2-[(6-aminopyridin-3-yl)methyl]-3-mercapto-5-(3-{[methyl(2-phenylethyl)amino]carbonyl}phenyl)pentanoic acid

tert-butyl 2-({6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}methyl)-3-[(4-methoxybenzyl)thio]-5-(3-{[methyl(2-phenylethyl)amino]carbonyl}phenyl)pentanoate (80 mg, 0.106 mmol) was dissolved in triethylsilane (0.4 mL) and trifluoroacetic acid (3.0 mL). The solution was heated to 60 °C for 1 h and was then concentrated. Purification of

the residue by reversed-phase HPLC (C-8 column, linear gradient 20%→100% of MeCN in 5% aqueous MeCN containing 0.15% trifluoroacetic acid) gave the title diastereomeric compound as the trifluoroacetic salt (64 mg, 100 %) after freeze-drying.

^{1}H NMR (400 MHz, CD_3CN/D_2O): δ 7.76-6.63 (m, 12 H), 3.71 (m, 1H), 3.40 (m, 1H), 3.21-2.54 (m, 11H), 2.12-1.63 (m, 2H). HRMS (ESI) calcd for $C_{27}H_{31}N_3O_3S$ 478.2164 $(M+H)^+$, found 478.2133.

EXAMPLE 27

3-[5-(6-Aminopyridin-3-yl)-4-carboxy-3-mercaptopentyl]benzoic acid was synthesised according to the procedure for Example 26 starting from 3-{5-*tert*-butoxy-4-({6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}methyl)-3-[(4-methoxybenzyl)thio]-5-oxopentyl}benzoic acid.

^{1}H NMR (400 MHz, D_2O): δ 8.05-8.01 (dd, 1H), 8.01-7.99 (s,1 H), 7.90-7.86 (dd, 1H), 7.73-7.70 (s, 1H), 7.68-7.58 (m, 2H), 7.08-7.04 (d, 1H), 3.18-3.08 (m, 1H), 3.06-2.90 (m, 5H), 2.36-2.26 (m, 1H), 2.14-2.04 (m, 1H). HRMS (ESI) calculated for $C_{18}H_{20}N_2O_4S$ 361.1222 $(M+H)^+$, found 361.1212.

EXAMPLE 28

2-[(6-Aminopyridin-3-yl)methyl]-5-[3-(3,4-dihydroisoquinolin-2(1*H*)-ylcarbonyl)phenyl]-3-mercaptopentanoic acid was synthesised according to the procedure for Example 26.

^{1}H NMR (500 MHz, CD_3CN/D_2O): δ 7.73 (m, 1H), 7.52 (s, 1H), 7.44-7.11 (m, 8H), 6.90 (m, 1H), 4.81 (s, 1H), 4.54 (s, 1H), 3.89 (br, 1H), 3.57 (br, 1H), 2.99-2.65 (m, 8H), 2.09 (m, 1H), 1.85 (m, 1H). HRMS (ESI) calcd for $C_{27}H_{29}N_3O_3S$ 476.2008 $(M+H)^+$, found 476.2002.

EXAMPLE 29

2-[(6-Aminopyridin-3-yl)methyl]-5-{3-[(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)carbonyl]phenyl}-3-mercaptopentanoic acid was synthesised according to the procedure for Example 26.

^{1}H NMR (400 MHz, CD_3CN/D_2O): δ 7.68 (m, 1H), 7.49 (s, 1H), 7.38-7.22 (m, 4H), 6.90-6.72 (m, 2.5H), 6.47 (s, 0.5H), 4.69 (s, 1H), 4.44 (s, 1H), 3.96-3.46 (m, 8H), 3.01-2.59 (m,

8H), 2.17-1.67 (m, 2H). HRMS (ESI) calcd for $C_{29}H_{33}N_3O_5S$ 536.2219 $(M+H)^+$, found 536.2248.

EXAMPLE 30

2-[(6-Aminopyridin-3-yl)methyl]-3-mercapto-5-{3-[(2-pyridin-2-ylethoxy)carbonyl]phenyl}pentanoic acid was synthesised according to the procedure for Example 26.

^{1}H NMR (400 MHz, CD_3CN/D_2O): δ 8.64 (d, 1H), 8.46 (dd, 1H), 7.98 (d, 1H), 7.88 (dd, 1H), 7.77-7.64 (m, 3H), 7.58-7-31 (m, 3H), 6.89 (dd, 1H), 4.65 (t, 2H), 3.50 (t, 2H), 2.99-2.62 (m, 6H), 2.03 (m, 1H), 1.79 (m, 1H). HRMS (ESI) calcd for $C_{25}H_{27}N_3O_4S$ 466.1803 $(M+H)^+$, found 466.1813.

EXAMPLE 31

2-[(6-Aminopyridin-3-yl)methyl]-5-(3-{[2-(2,6-dichlorophenyl)ethoxy]carbonyl}phenyl)-3-mercaptopentanoic acid was synthesised according to the procedure for Example 26.

^{1}H NMR (400 MHz, CD_3CN/D_2O): δ 7.69 (m, 3H), 7.51 (s, 1H), 7.38-7.28 (m, 4H), 7.12 (m, 1H), 6.84 (m, 1H), 4.48 (m, 2H), 3.62 (m, 0.5H), 3.31 (m, 2H), 3.10 (m, 0.5H), 2.98-2.53 (m, 5H), 2.0 (m, 1H), 1.75 (m, 1H). HRMS (ESI) calcd for $C_{26}H_{26}Cl_2N_2O_4S$ 533.1069 $(M+H)^+$, found 533.1071.

EXAMPLE 32

2-[(6-Aminopyridin-3-yl)methyl]-5-[3-(ethoxycarbonyl)phenyl]-3-mercaptopentanoic acid was synthesised according to the procedure for Example 26 starting from ethyl 3-{5-*tert*-butoxy-4-({6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}methyl)-3-[(4-methoxybenzyl)thio]-5-oxopentyl}benzoate.

^{1}H NMR (500 MHz, CD_3CN/D_2O): δ 7.90(d, 1H), 7.87 (s, 1H), 7.74 (d, 1H), 7.58 (s, 1H), 7.53 (d, 1H), 7.48 (t, 1H), 6.91 (d, 1H), 4.41 (q, 2H), 2.95-3.03 (m, 1H), 2.95-2.82 (m, 4H), 2.75-2.80 (m, 1H), 2.14-2.23 (m, 1H), 1.95-2.03 (m, 1H), 1.41 (t, 3H). HRMS (ESI) calculated for $C_{20}H_{25}N_2O_4S$ 389.1535 $(M+H)^+$, found 389.1555.

EXAMPLE 33

2-[(6-Aminopyridin-3-yl)methyl]-5-(3-{[(2-fluoroethyl)amino]carbonyl}phenyl)-3-mercaptopentanoic acid was synthesised according to the procedure for Example 26.

^{1}H NMR (500 MHz, 10%CD_3CN in D_2O): δ 7.95 (dd, 0.5H), 7.90 (dd, 0.5 H), 7.86-7.81 (m, 2H), 7.75 (dd, 0.5H), 7.73 (dd, 0.5H), 7.70-7.60 (m, 2H), 7.13 (d, 0.5H), 7.07 (d, 0.5H), 4.89-4.86 (m, 1H), 4.8-4.76 (m, 1H), 3.91-3.94 (m, 1H), 3.85-3.89 (m, 1H), 3.25-3.12 (m, 2.5H), 3.11-2.98 (m, 3H), 2.92-2.97 (m, 0.5H), 2.41-2.24 (m, 1H), 2.21-2.01 (m, 1H). HRMS (ESI) calculated for $C_{20}H_{25}FN_3O_3S$ 406.1600 $(M+H)^+$, found 406.1560.

EXAMPLE 34

2-[(6-Aminopyridin-3-yl)methyl]-5-{3-[(dimethylamino)carbonyl]phenyl}-3-mercaptopentanoic acid was synthesised according to the procedure for Example 26.

^{1}H NMR (500 MHz, 5%CD_3CN/D_2O): δ 7.77(dd, 0.5H), 7.72 (dd, 0.5H), 7.52-7.54 (m, 1H), 7.45-7.32 (m, 2H), 7.25-7.29 (m, 2H), 6.91 (d, 0.5H), 6.93 (d, 0.5H), 3.07 (s, 3H), 2.95 (two s, 3H), 3.05-2.71 (m, 6H), 2.19-2.0 (m, 1H), 1.99-1.82 (m, 1H). HRMS (ESI) calculated for $C_{20}H_{26}N_3O_3S$ 388.1695 $(M+H)^+$, found 388.1683.

EXAMPLE 35

2-[(6-Aminopyridin-3-yl)methyl]-3-mercapto-5-{3-[(vinylamino)carbonyl]phenyl}pentanoic acid was synthesised according to the procedure for Example 26.

^{1}H NMR (500 MHz, 10% CD_3CN/D_2O): δ 7.71(two dd, 1H), 7.53 (two dd, 0.5H), 6.89 (m, 1H), 6.77-6.60 (m, 3H), 5.88(s, 2H), 3.0-2.70 (m, 5H), 2.62 (m, 1H), 2.00 (m, 1H), 1.75(m, 1H). HRMS (ESI) calculated for $C_{20}H_{24}N_3O_3S$ 386.1538 $(M+H)^+$, found 386.1470.

EXAMPLE 36

2-[(6-Aminopyridin-3-yl)methyl]-5-[3-({[2-(1,3-benzodioxol-5-yl)ethyl]amino}carbonyl)phenyl]-3-mercaptopentanoic acid was synthesised according to the procedure for Example 26.

^{1}H NMR (500 MHz, 20% CD_3CN/D_2O) δ ppm 1.88-2.06 (m, 1 H), 2.10-2.27 (m, 1 H), 2.79-3.11 (m, 8 H), 3.68 (t, 2 H), 6.00 (s, 2 H), 6.85 (m, 1 H), 6.90 (m, 2 H), 6.96 (d, 0.7 H), 7.01 (d, 0.3 H), 7.47 (m, 1.2H), 7.51 (m, 0.6 H), 7.56 (s, 0.7 H), 7.58 (s, 0.3 H), 7.62 (s,

2 H), 7.76 (d, 0.7 H), 7.81 (d, 0.3 H). HRMS (ESI) calculated for $C_{27}H_{29}N_3O_5S$ 508.1906 $(M+H)^+$, found 508.1935.

EXAMPLE 37

2-[(6-Aminopyridin-3-yl)methyl]-5-{3-[(dibenzylamino)carbonyl]phenyl}-3-mercaptopentanoic acid was synthesised according to the procedure for Example 26.

^1H NMR (500 MHz, , 50% CD_3CN/D_2O) δ ppm 2.28-2.40 (m, 1 H), 2.52-2.63 (m, 1 H), 3.25-3.53 (m, 6 H), 4.99 (s, 2 H), 5.23 (s, 2 H), 7.46 (d, 0.4 H), 7.48 (d, 0.6 H), 7.71 (d, 2 H), 7.83-8.00 (m, 12 H), 8.08 (s, 1 H), 8.25 (dd, 0.4 H), 8.28 (dd, 0.6 H).

HRMS (ESI) calculated for $C_{32}H_{33}N_3O_3S$ 540.2321 $(M+H)^+$, found 540.2340.

EXAMPLE 38

2-[(6-Aminopyridin-3-yl)methyl]-5-(3-{[(2-hydroxyethyl)(methyl)amino]carbonyl}phenyl)-3-mercaptopentanoic acid was synthesised according to the procedure for Example 26.

^1H NMR (500 MHz, 50% CD_3CN/D_2O) δ ppm 1.71-2.11 (m, 2 H), 2.67-2.96 (m, 6 H), 2.89 (s, 1.5 H), 3.01 (s, 1.5 H), 3.34 (q, 1 H), 3.52-3.57 (m, 1 H), 3.59 (t, 1 H), 3.77 (t, 1 H), 6.74-6.86 (m, 1 H), 7.12-7.41 (m, 4 H), 7.45 (s, 1 H) 7.58-7.63 (m, 0.5 H), 7.65-7.69 (m, 0.5 H). HRMS (ESI) calculated for $C_{21}H_{28}N_3O_4S$ 418.1800 $(M+H)^+$, found 418.1752.

EXAMPLE 39

2-[(6-Aminopyridin-3-yl)methyl]-5-{3-[(3-hydroxypyrrolidin-1-yl)carbonyl]phenyl}-3-mercaptopentanoic acid was synthesised according to the procedure for Example 26.

^1H NMR (400 MHz, CD_3CN/D_2O): δ 8.35-8.15 (m, 1H), 8.05 (br s, 1H), 8.00-7.75 (m, 4H), 7.50-7.35 (m, 1H), 6.16 (br m, 0.5H), 6.02 (br m, 0.5H), 5.02 (br m, 0.5H), 4.88 (br m, 0.5H), 4.50-3.60 (m, 4H), 3.55-3.20 (m, 7H), 3.0-2.2 (m, 4H). HRMS (ESI) calculated for $C_{22}H_{28}N_3O_4S$ 430.1829 $(M+H)^+$, found 430.1801.

EXAMPLE 40

2-[(6-Aminopyridin-3-yl)methyl]-5-(3-{[4-(4-chlorophenyl)piperazin-1-yl]carbonyl}phenyl)-3-mercaptopentanoic acid was synthesised according to the procedure for Example 26.

^{1}H NMR (400 MHz, CD_3CN): δ 7.75-7.67 (m, 1H), 7.52-7.47 (dd, 1 H), 7.40-7.28(m, 5H), 7.12-7.07 (m, 3H), 6.90-6.84 (m, 1H), 4.00-3.50 (m, 4H), 3.40-3.20 (m, 4H), 3.03 –2.90 (m, 1H), 2.87-2.70 (m, 5H), 2.17-2.03 (m, 1H) ,1.97-1.89 (m, 1H). HRMS (ESI) calculated for $C_{28}H_{31}ClN_4O_3S$ 539.1884 $(M+H)^+$, found 539.1868.

EXAMPLE 41

2-[(6-Aminopyridin-3-yl)methyl]-5-(3-{[benzyl(methyl)amino]carbonyl}phenyl)-3-mercaptopentanoic acid was synthesised according to the procedure for Example 26.

^{1}H NMR (400 MHz, CD_3CN): δ 7.75-7.18 (m, 11H), 6.88-6.80 (d, 1 H), 4.80-4.70 (s, 1H), 4.53-4.45 (s, 1H), 3.00-2.95 (m, 1H), 2.93-2.90 (s, 3H), 2.88-2.78 (m, 5H), 2.05-2.00 (m, 1H), 1.99-1.94 (m, 1H). HRMS (ESI) calculated for $C_{26}H_{29}N_3O_3S$ 464.2008 $(M+H)^+$, found 464.1972.

EXAMPLE 42

2-[(6-Aminopyridin-3-yl)methyl]-3-mercapto-5-[3-(pyrrolidin-1-ylcarbonyl)phenyl]pentanoic acid was synthesised according to the procedure for Example 26.

^{1}H NMR (500 MHz, 95% CD_3CN in D_2O): δ 7.75 (dd, 0.5H), 7.69 (dd, 0.5 H), 7.51-7.54 (m, 1H), 7.44-7.30 (m, 4H), 6.91 (d, 0.5H), 6.87 (d, 0.5H), 3.53 (t, 2H), 3.30-3.40 (m, 2H), 3.00-2.79 (m, 5.5H), 2.67-2.74 (m, 0.5H), 2.18-1.8 (m, 6H). HRMS (ESI) calculated for $C_{22}H_{28}N_3O_3S$ 414.1851 $(M+H)^+$, found 414.1837.

EXAMPLE 43

2-[(6-Aminopyridin-3-yl)methyl]-5-(3-{[4-(ethoxycarbonyl)piperidin-1-yl]carbonyl}phenyl)-3-mercaptopentanoic acid was synthesised according to the procedure for Example 26.

^{1}H NMR (500 MHz, CD_3CN/D_2O): δ 1.28 (t, 3H), 1.59-1.79 (m, 2H),1.86-1.96 (m, 2H), 2.0-2.22 (m, 2H), 2.68-2.75 (m, 1H), 2.80-3.12 (m, 7H), 3.13-3.25 (m, 1H), 3.65 (d, 1H),

4.18 (q, 2H), 4.40-4.48 (m, 1H), 6.95-7.00 (m, 1H), 7.27-7.31 (m, 2H), 7.36-7.48 (m, 2H), 7.60 (s, 1H), 7.78 (dd, 0.5H), 7.82 (dd, 0.5H). HRMS (ESI) calculated for $C_{26}H_{34}N_3O_5S$ 500.2219 $(M+H)^+$, found 500.2233.

EXAMPLE 44

2-[(6-Aminopyridin-3-yl)methyl]-5-(3-{[4-(hydroxymethyl)piperidin-1-yl]carbonyl}phenyl)-3-mercaptopentanoic acid was synthesised according to the procedure for Example 26.

^1H NMR (400MHz, CD_3CN): δ 7.65-7.71 (dd, 1H), 7.49-7.52 (d, 1H), 7.18-7.36 (m, 4H), 6.82-6.85 (dd, 1H), 3.41-3.47 (m, 4H), 2.77-3.10 (m, 7H), 2.0-2.1 (m, 2H), 1.68-1.92 (m, 5H). HRMS(ESI) calculated for $C_{24}H_{32}N_3O_4S$ 458.2114 $(M+H)^+$, found 458.2097.

EXAMPLE 45

2-[(6-Aminopyridin-3-yl)methyl]-3-mercapto-5-{3-[(3-oxopiperazin-1-yl)carbonyl]phenyl}pentanoic acid was synthesised according to the procedure for Example 26.

^1H NMR (500 MHz, CD_3CN/D_2O) δ ppm 1.77-1.90 (m, 1H), 1.99-2.12 (m, 1H), 2.75-3.0 (m, 6H), 3.25-3.58 (m, 4H), 3.80-4.10 (m, 1H), 4.2 (s, 1H), 6.89 (d, 0.5H), 6.91 (d, 0.5H), 7.24-7.29 (m, 2H), 7.31-7.42 (m, 2H), 7.52 (s, 1H), 7.71 (dd, 0.4H), 7.74 (dd, 0.6H). HRMS (ESI) calculated for $C_{22}H_{27}N_4O_4S$ 443.1753 $(M+H)^+$, found 443.1766.

EXAMPLE 46

2-[(6-Aminopyridin-3-yl)methyl]-5-(3-{[benzyl(3-ethoxy-3-oxopropyl)amino]carbonyl}phenyl)-3-mercaptopentanoic acid was synthesised according to the procedure for Example 26.

^1H NMR (500 MHz, CD_3CN/D_2O) δ ppm 1.06 (t, 1H), 1.19 (t, 2H), 1.67-1.88 (m, 1H), 1.90-2.15 (m, 1H), 2.40-3.0 (m, 8H), 3.40-3.58 (m, 0.7H), 3.58-3.66 (m, 1.3H), 3.91 (q, 0.7H), 4.07 (q, 1.3H), 4.47 (s, 1.3H), 4.69 (s, 0.7H), 6.80-6.92 (m, 1H), 7.1-7.4 (m, 9H), 7.46 (s, 0.7H), 7.50 (s, 0.3H), 7.60-7.74 (m, 1H). HRMS (ESI) calculated for $C_{30}H_{36}N_3O_5S$ 550.2376 $(M+H)^+$, found 550.2361.

EXAMPLE 47

2-[(6-Aminopyridin-3-yl)methyl]-5-(3-{[(cyanomethyl)(methyl)amino]-sulfonyl}phenyl)-3-mercaptopentanoic acid was synthesised according to the procedure for Example 1, starting from *N*-(cyanomethyl)-3-iodo-*N*-methylbenzenesulfonamide. *N*-(cyanomethyl)-3-iodo-*N*-methylbenzenesulfonamide was synthesised from 3-iodobenzenesulfonyl chloride using standard procedures.

^{1}H NMR (500 MHz, CD_3CN/D_2O): δ 7.79 (dd, 0.5H), 7.76 (dd, 0.5H), 7.74-7.69 (m, 2H), 7.64-7.54 (m, 3H), 6.95 (d, 0.5H), 6.94 (d, 0.5H), 4.29 (s, 2H), 3.11-3.00 (m, 2H), 2.86 (s, 3H), 2.98-2.78 (m, 4H), 2.20-2.09 (m, 1H), 1.95-1.83 (m, 1H). HRMS (ESI) calculated for $C_{20}H_{25}N_2O_4S_2$ 449.1317 $(M+H)^+$, found 449.1329.

EXAMPLE 48

2-[(6-Aminopyridin-3-yl)methyl]-5-(3-{[(2*S*)-2-(anilinomethyl)pyrrolidin-1-yl]sulfonyl}phenyl)-3-mercaptopentanoic acid was synthesised according to the procedure for Example 1, starting from *N*-({(2*S*)-1-[(3-iodophenyl)sulfonyl]pyrrolidin-2-yl}methyl)aniline. *N*-({(2*S*)-1-[(3-iodophenyl)sulfonyl]pyrrolidin-2-yl}methyl)aniline was synthesised from 3-iodobenzenesulfonyl chloride using standard procedures.

^{1}H NMR (500 MHz, CD_3OD): δ 7.71 (dd, J = 2.1, 9.1 Hz, 1H), 7.59-7.45 (m, 7H), 7.31-7.29 (m, 3H), 6.89 (d, J = 9.3 Hz, 1H), 3.83-3.75 (m, 1H), 3.53 (ddd, J = 3.1, 6.0, 13.0 Hz, 1H), 3.44-3.36 (m, 2H), 3.26-3.18 (m, 1H), 3.00-2.70 (m, 6H), 2.05-1.97 (m, 1H), 1.82-1.65 (m, 3H), 1.57-1.50 (m, 1H), 1.42-1.32 (m, 1H). HRMS (ESI) calculated for $C_{28}H_{34}N_4O_4S_2$ 555.2100 $(M+H)^+$, found 555.2032.

EXAMPLE 49

2-[(6-Aminopyridin-3-yl)methyl]-3-mercapto-5-{3-[(methylamino)sulfonyl]-phenyl}pentanoic acid was synthesised according to the procedure for Example 1, starting from *N*-(2-furylmethyl)-3-iodo-*N*-methylbenzenesulfonamide. *N*-(2-furylmethyl)-3-iodo-*N*-methylbenzenesulfonamide was synthesised from 3-iodobenzenesulfonyl chloride using standard procedures.

^{1}H NMR (500 MHz, CD_3OD): δ 7.85 (dd, J = 2.1, 9.1 Hz, 1H), 7.69-7.65 (m, 3H), 7.51-7.50 (m, 2H), 6.94 (dd, J = 0.5, 9.1 Hz, 1H), 3.12-3.07 (m, 2H), 3.00-2.96 (m, 1H), 2.93-

2.77 (m, 3H), 2.51(s, 3H), 2.16-2.10 (m, 1H), 1.91-1.83 (m, 1H). HRMS (ESI) calculated for $C_{18}H_{23}N_3O_4S_2$ 410.1208 $(M+H)^+$, found 410.1207.

EXAMPLE 50

2-[(6-Aminopyridin-3-yl)methyl]-3-mercapto-5-(3-{[methyl(2-phenylethyl)amino]sulfonyl}phenyl)pentanoic acid was synthesised according to the procedure for Example 1, starting from 3-iodo-*N*-methyl-*N*-(2-phenylethyl)benzenesulfonamide. 3-iodo-*N*-methyl-*N*-(2-phenylethyl)benzenesulfonamide was synthesised from 3-iodobenzenesulfonyl chloride using standard procedures. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (s, 1H), 7.54-7.57 (d, 3H), 7.39-7.40 (d, 3H), 7.24-7.27 (t, 3H), 7.14-7.20 (m, 3H), 6.75 (s, 2H), 3.23-3.27 (t, 2H), 2.96-3.03 (m, 3H), 2.80-2.84 (t, 3H), 2.72 (s, 3H), 2.07 (s, 1H), 1.69-1.80 (dd, 1H), 1.53-1.55 (d, 1H). MS (ESI) 514.3 $(M+H)^+$.

EXAMPLE 51

This Example illustrates the preparation of 2-[(6-aminopyridin-3-yl)methyl]-3-mercapto-5-[3-(tetrahydrofuran-3-yloxy)phenyl]pentanoic acid.

(a) *tert*-butyl(3-iodophenoxy)dimethylsilane

Imidazole (7.8 g, 115 mmol) was added to a solution of 3-iodophenol (12.7 g, 58 mmol) and *tert*-butyl(chloro)dimethylsilane (9.9 g, 65 mmol) in dichloromethane (80 mL) at 0 °C. The reaction mixture was stirred at rt overnight. The suspension was washed three times with water and once with brine, dried and concentrated to give crude *tert*-butyl(3-iodophenoxy)dimethylsilane (20 g, 93%).

(b) *tert*-butyl 2-({6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}methyl)-5-(3-hydroxyphenyl)-3-[(4-methoxybenzyl)thio]pentanoate

Glacial acetic acid (190 µL, 3.3 mmoL) was added to a solution of *tert*-butyl 2-({6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}methyl)-5-(3-{[*tert*-butyl(dimethyl)silyl]oxy}phenyl)-3-[(4-methoxybenzyl)thio]pentanoate (800 mg, 0.89 mmol, synthesised according to the procedure for Example 1, starting from *tert*-butyl(3-iodophenoxy)dimethylsilane) in dry THF (10 mL). Tetrabutylammonium fluoride

trihydrate (489 mg, 1.5 mmol) was added and the mixture was stirred for 12 h at room temperature. EtOAc (150 mL) was added and the solution was washed with saturated aqueous $NaHCO_3$, water and brine, dried and concentrated. Flash chromatography (CH_2Cl_2/EtOAc, 10:1) gave *tert*-butyl 2-({6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}methyl)-5-(3-hydroxyphenyl)-3-[(4-methoxybenzyl)thio]pentanoate (660 mg, 98 %).

(c) *tert*-butyl 2-({6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}methyl)-3-[(4-methoxybenzyl)thio]-5-[3-(tetrahydrofuran-3-yloxy)phenyl]pentanoate

1,1'-azobis(*N,N*-dimethylformamide) (134 mg, 0.78 mmol) was added to a solution of tri-n-butylphosphine (221 µL, 0.89 mmol) in toluene (2 mL). Tetrahydrofuran-3-ol (36 µL, 44 mmol) and *tert*-butyl 2-({6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}methyl)-5-(3-hydroxyphenyl)-3-[(4-methoxybenzyl)thio]pentanoate (154 mg, 0.25 mmol) was added sequentially. The reaction mixture was stirred for 12 h at 80 °C. Toluene (100 mL) was added and the mixture was washed with brine, dried and concentrated. Flash chromatography (toluene/EtOAc, 100:0 to 70:30) gave *tert*-butyl 2-({6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}methyl)-3-[(4-methoxybenzyl)thio]-5-[3-(tetrahydrofuran-3-yloxy)phenyl]pentanoate (75 mg, 35 %).

(d) 2-[(6-aminopyridin-3-yl)methyl]-3-mercapto-5-[3-(tetrahydrofuran-3-yloxy)phenyl]pentanoic acid

2-[(6-aminopyridin-3-yl)methyl]-3-mercapto-5-[3-(tetrahydrofuran-3-yloxy)phenyl]pentanoic acid was synthesised according to the procedure for Example 1, starting from *tert*-butyl 2-({6-[(*tert*-butoxycarbonyl)amino]pyridin-3-yl}methyl)-3-[(4-methoxybenzyl)thio]-5-[3-(tetrahydrofuran-3-yloxy)phenyl]pentanoate.

^{1}H NMR (500 MHz, CD_3CN/D_2O (1:1): δ 7.72 (dd, 1H), 7.53 (d, 1H), 7.22 (dd, 1H), 6.90 (d, 1H), 6.83 (d, 1H), 6.76-6.72 (m, 2H), 4.98 (m, 1H), 3.93-3.79 (m, 4H), 2.99-2.84 (m, 3H), 2.83-2.66 (m, 3H), 2.27-2.18 (m, 1H), 2.07-1.96 (m, 2H), 1.83-1.73 (m, 1H). HRMS (ESI) calculated for $C_{21}H_{27}N_2O_4S$ 403.1692 $(M+H)^+$, found 403.1698.

EXAMPLE 52

2-[(6-Aminopyridin-3-yl)methyl]-3-mercapto-5-[3-(tetrahydrofuran-3-ylmethoxy)-phenyl]pentanoic acid was synthesised according to the procedure for Example 51.

^{1}H NMR (400 MHz, CD_3CN): δ 7.75-7.69 (d, 1H), 7.58-7.56 (s, 1 H), 7.25-7.18 (m, 1H), 6.88-6.75 (m, 4H), 3.98-3.58 (m, 6H), 3.10-3.00 (m, 1H), 2.95-2.82 (m, 3H), 2.74-2.65 (m, 2H), 2.13-2.03 (m, 1H), 1.98-1.66 (m, 4H). MS (ESI) 417.9 $(M+H)^+$.

EXAMPLE 53

The activities of certain Examples in the assay described in: Dirk Hendriks, Simon Scharpé and Marc van Sande, Clinical Chemistry, 31, 1936-1939 (1985) are presented in Table I below.

TABLE I

Example No.	IC_{50}
6	0.8 μM
7	0.8 μM
11	0.8 μM
18	1.0 μM
24	6.3 μM
25	4.0 μM
28	0.8 μM

Example No.	IC_{50}
31	0.6 μM
33	0.6 μM
41	0.6 μM
42	0.6 μM
43	2.0 μM
47	1.0 μM

Abbreviations

HOAc = acetic acid

MeOH = methanol

min = minutes

rt = room temperature

DMF = dimethylformamide

DMSO = dimethyl sulfoxide

EtOAc = ethyl acetate

DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene

HOAc = acetic acid

MeOH = methanol

min = minutes

rt = room temperature

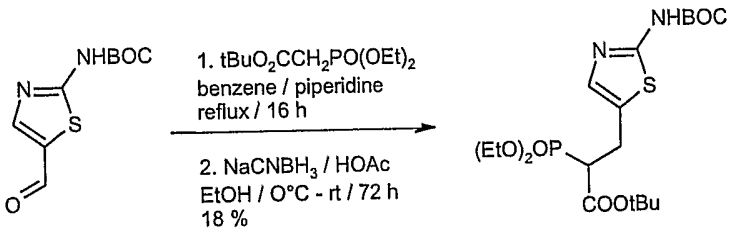
TFA = trifluoroacetic acid

THF = tetrahydrofuran

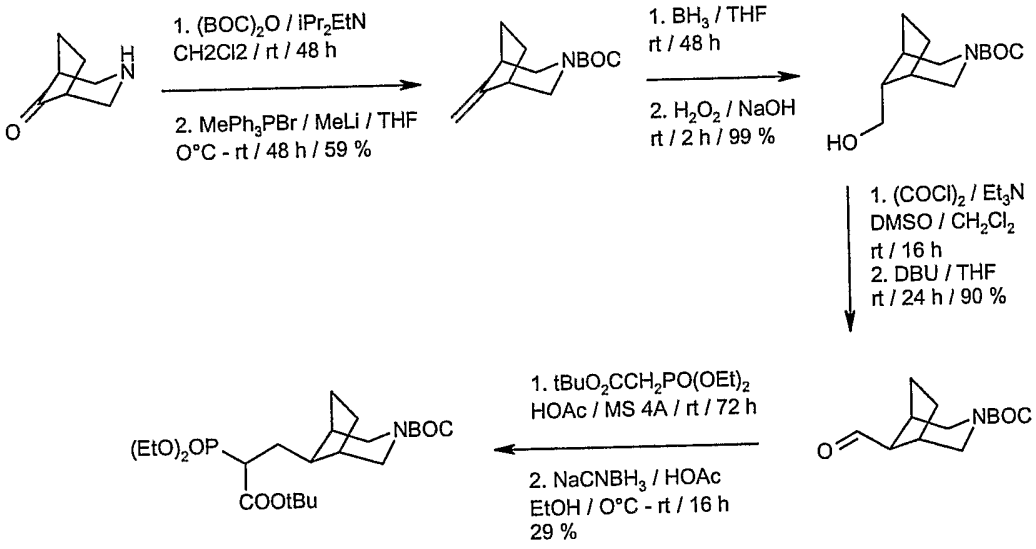
h = hour

HATU = O-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate

SCHEME 1

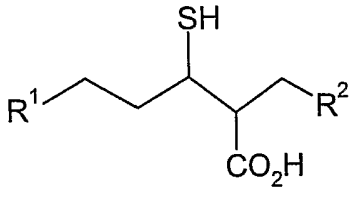


SCHEME 2



CLAIMS

1. A compound of formula (I):



(I)

wherein:

R^1 is phenyl {optionally substituted by halogen, hydroxy, cyano, C_{1-4} alkyl (itself optionally mono-substituted by cyano, hydroxy or phenyl), C_{1-4} alkoxy (itself optionally substituted by tetrahydrofuranyl), CF_3, OCF_3, methylenedioxy, $C(O)R^3$, $S(O)_2R^4$, phenyl (itself optionally substituted by halogen), phenoxy (itself optionally substituted by halogen) or tetrahydrofuranyloxy}, naphthyl, pyridinyl, 1,2,3,4-tetrahydropyrimidin-2,4-dione-yl (optionally substituted by C_{1-4} alkyl) or tetrahydrothienyl;

R^2 is aminopyridinyl, aminothiazolyl or 3-azabicyclo[3.2.1]octyl;

R^3 is hydroxy, C_{1-4} alkoxy (itself optionally substituted by phenyl (itself optionally substituted by halogen) or pyridinyl), NR^5R^6 or an N-linked 5- or 6-membered heterocyclic ring {unsubstituted or mono-substituted by hydroxy, oxo, C_{1-4} alkyl (itself optionally substituted by hydroxy or NHphenyl), $CO_2(C_{1-4}$ alkyl) or phenyl (itself optionally substituted by halogen)};

R^4 is NR^7R^8 or an N-linked 5- or 6-membered heterocyclic ring {unsubstituted; mono-substituted by hydroxy, oxo, C_{1-4} alkyl (itself optionally substituted by hydroxy or NHphenyl), $CO_2(C_{1-4}$ alkyl) or phenyl (itself optionally substituted by halogen); or fused to a benzene ring which is optionally substituted by C_{1-4} alkoxy};

R^5, R^6, R^7 and R^8 are, independently, hydrogen, C_{1-4} alkyl {optionally substituted by halogen, cyano, hydroxy, phenyl (itself optionally substituted by halogen or methylenedioxy), pyridinyl, CO_2H or $CO_2(C_{1-4}$ alkyl)} or C_{2-4} alkenyl;

provided that when R^1 is 6-aminopyridin-3-yl then R^2 is substituted phenyl, naphthyl, pyridinyl, 1,2,3,4-tetrahydropyrimidin-2,4-dione-yl (optionally substituted by C_{1-4} alkyl) or tetrahydrothienyl;

or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt.

2. A compound of formula (I) as claimed in claim 1 wherein R^1 is phenyl {optionally substituted by halogen, hydroxy, cyano, C_{1-4} alkyl (itself optionally mono-substituted by cyano or hydroxy), C_{1-4} alkoxy, CF_3, OCF_3, methylenedioxy, $C(O)NH_2$, $S(O)_2NH_2$ or phenyl (itself optionally substituted by halogen)}, pyridinyl or tetrahydrothienyl.

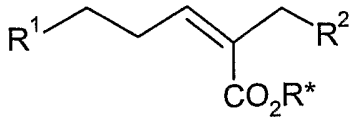
3. A compound of formula (I) as claimed in claim 1 wherein R^1 is phenyl {optionally substituted by halogen, hydroxy, cyano, C_{1-4} alkyl (itself optionally mono-substituted by cyano, hydroxy or phenyl), C_{1-4} alkoxy, CF_3, OCF_3, methylenedioxy, phenoxy (itself optionally substituted by halogen), tetrahydrofuranyloxy or tetrahydrofuranylmethoxy}, naphthyl, pyridinyl or tetrahydrothienyl.

4. A compound of formula (I) as claimed in claim 1 wherein R^1 is phenyl {substituted by halogen, hydroxy, cyano, C_{1-4} alkyl (itself optionally mono-substituted by cyano or hydroxy), C_{1-4} alkoxy, CF_3 or methylenedioxy} or tetrahydrothiophenyl.

5. A compound of formula (I) as claimed in claim 1, 2, 3 or 4 wherein R^2 is 6-aminopyridin-3-yl, 2-aminothiazol-5-yl or 3-azabicyclo[3.2.1]oct-8-yl.

6. A compound of formula (I) as claimed in claim 1, 2, 3 or 4 wherein R^2 is 6-aminopyridin-3-yl.

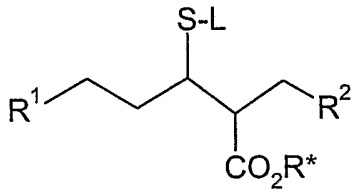
7. A process for preparing a compound of formula (I) comprising reacting a compound of formula (II):



(II)

wherein R^1 is as defined in claim 1 or includes a group that can be subsequently reacted to form the group R^1, R* is a suitable protecting group and R^2 is as defined in claim 1 or the amine function of R^2 can be protected, with a thiol of formula L-

SH, wherein L is a suitable protecting group, in the presence of a suitable catalyst and in a suitable solvent, to form a compound of formula (III):



(III)

and, optionally reacting the functional group on R^1, and subsequently removing the protecting groups as necessary.

8. A pharmaceutical formulation containing a compound according to any one of claims 1 to 6 as active ingredient in combination with a pharmaceutically acceptable adjuvant, diluent or carrier.

9. The use of a compound as claimed in claim 1 in therapy.

10. The use of a compound as claimed in claim 1 for the manufacture of a medicament for the inhibition of carboxypeptidase U.

11. A method for treatment or prophylaxis of conditions where inhibition of carboxypeptidase U is beneficial, comprising administering to a mammal, including man, in need of such treatment an effective amount of a compound as claimed in claim 1.

12. A pharmaceutical formulation for use in the treatment or prophylaxis of conditions where inhibition of carboxypeptidase U is beneficial, comprising a compound as claimed in claim 1 in combination with a pharmaceutically acceptable adjuvant, diluent or carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 03/00970

A. CLASSIFICATION OF SUBJECT MATTER
IPC7: C07D 213/74, 221/22, 227/40, 401/06, 405/06, 409/06, A61K 31/44, 31/439, 31/427, A61P 7/02
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

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

SE,DK,FI,NO classes as above

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 0066557 A1 (ASTRAZENECA AB), 9 November 2000 (09.11.00), see esp. example31 and claims 1 1-13	1-12

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 Sept 2003	16 -09- 2003
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Solveig Gustavsson/EÖ Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE03/00970

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **9**
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Claim 9 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT
Information on patent family members

26/07/03

International application No.
PCT/SE 03/00970

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0066557 A1	09/11/00	AU 4447200 A	17/11/00
		AU 4790200 A	17/11/00
		AU 6377099 A	03/04/00
		BR 0010255 A	13/02/02
		BR 0010257 A	13/02/02
		BR 9913560 A	05/06/01
		CA 2371213 A	09/11/00
		CA 2371217 A	02/11/00
		CN 1350463 T	22/05/02
		CN 1358174 T	10/07/02
		CZ 20013930 A	16/10/02
		CZ 20013932 A	17/04/02
		EE 200100574 A	17/02/03
		EE 200100578 A	17/02/03
		EP 1112644 A	04/07/01
		EP 1180098 A	20/02/02
		EP 1181048 A	27/02/02
		HU 0201615 A	28/09/02
		HU 0202876 A	28/01/03
		JP 2002525915 T	13/08/02
		JP 2002543148 T	17/12/02
		JP 2002543184 T	17/12/02
		NO 20015308 A	03/12/01
		NO 20015383 A	21/12/01
		SE 9901573 D	00/00/00
		SK 15462001 A	06/11/02
		SK 15652001 A	02/07/02
		TR 200103151 T	00/00/00
		TR 200103153 T	00/00/00
		WO 0066152 A	09/11/00