ANTIBACTERIAL PIPERIDINE DERIVATIVES

BACKGROUND OF THE INVENTION

The present invention relates to compounds which demonstrate antibacterial activity, processes for their preparation, pharmaceutical compositions containing them as the active ingredient, to their use as medicaments and to their use in the manufacture of medicaments for use in the treatment of bacterial infections in warm-blooded animals such as humans. In particular this invention relates to compounds useful for the treatment of bacterial infections in warm-blooded animals such as humans, more particularly to the use of these compounds in the manufacture of medicaments for use in the treatment of bacterial infections in warm-blooded animals such as humans.

The international microbiological community continues to express serious concern that the evolution of antibiotic resistance could result in strains against which currently available antibacterial agents will be ineffective. In general, bacterial pathogens may be classified as either Gram-positive or Gram-negative pathogens. Antibiotic compounds with effective activity against both Gram-positive and Gram-negative pathogens are generally regarded as having a broad spectrum of activity. The compounds of the present invention are regarded as effective against both Gram-positive and certain Gram-negative pathogens.

Gram-positive pathogens, for example Staphylococci, Enterococci, Streptococci and mycobacteria, are particularly important because of the development of resistant strains which are both difficult to treat and difficult to eradicate from the hospital environment once established. Examples of such strains are methicillin resistant *staphylococcus aureus* (MRSA), methicillin resistant coagulase negative staphylococci (MRCNS), penicillin resistant *Streptococcus pneumoniae* and multiple resistant *Enterococcus faecium*.

The preferred clinically effective antibiotic for treatment of last resort of such resistant Gram-positive pathogens is vancomycin. Vancomycin is a glycopeptide and is associated with various toxicities, including nephrotoxicity. Furthermore, and most importantly, antibacterial resistance to vancomycin and other glycopeptides is also appearing. This resistance is increasing at a steady rate rendering these agents less and less effective in the treatment of Gram-positive pathogens. There is also now increasing resistance appearing towards agents such as β-lactams, quinolones and macrolides used for the treatment of upper respiratory tract infections, also caused by certain Gram negative strains including *H.influenzae* and *M.catarrhalis*.

Consequently, in order to overcome the threat of widespread multi-drug resistant organisms, there is an on-going need to develop new antibiotics, particularly those with either a novel mechanism of action and/or containing new pharmacophoric groups.

Deoxyribonucleic acid (DNA) gyrase is a member of the type II family of topoisomerases that control the topological state of DNA in cells (Champoux, J. J.; 2001. Ann. Rev. Biochem. 70: 369-413). Type II topoisomerases use the free energy from adenosine triphosphate (ATP) hydrolysis to alter the topology of DNA by introducing transient double-stranded breaks in the DNA, catalyzing strand passage through the break and resealing the DNA. DNA gyrase is an essential and conserved enzyme in bacteria and is unique among topoisomerases in its ability to introduce negative supercoils into DNA. The enzyme consists of two subunits, encoded by *gyrA* and *gyrB*, forming an A_2B_2 tetrameric complex. The A subunit of gyrase (GyrA) is involved in DNA breakage and resealing and contains a conserved tyrosine residue that forms the transient covalent link to DNA during strand passage. The B subunit (GyrB) catalyzes the hydrolysis of ATP and interacts with the A subunit to translate the free energy from hydrolysis to the conformational change in the enzyme that enables strand-passage and DNA resealing.

Another conserved and essential type II topoisomerase in bacteria, called topoisomerase IV, is primarily responsible for separating the linked closed circular bacterial chromosomes produced in replication. This enzyme is closely related to DNA gyrase and has a similar tetrameric structure formed from subunits homologous to Gyr A and to Gyr B. The overall sequence identity between gyrase and topoisomerase IV in different bacterial species is high. Therefore, compounds that target bacterial type II topoisomerases have the potential to inhibit two targets in cells, DNA gyrase and topoisomerase IV; as is the case for existing quinolone antibacterials (Maxwell, A. 1997, Trends Microbiol. 5: 102-109).

DNA gyrase is a well-validated target of antibacterials, including the quinolones and the coumarins. The quinolones (*e.g.* ciprofloxacin) are broad-spectrum antibacterials that inhibit the DNA breakage and reunion activity of the enzyme and trap the GyrA subunit covalently complexed with DNA (Drlica, K., and X. Zhao, 1997, Microbiol. Molec. Biol. Rev. 61: 377-392). Members of this class of antibacterials also inhibit topoisomerase IV and as a result, the primary target of these compounds varies among species. Although the quinolones are successful antibacterials, resistance generated primarily by mutations in the target (DNA gyrase and topoisomerase IV) is becoming an increasing problem in several organisms, including *S. aureus* and *Streptococcus pneumoniae* (Hooper, D. C., 2002, The

Lancet Infectious Diseases 2: 530-538). In addition, quinolones, as a chemical class, suffer from toxic side effects, including arthropathy that prevents their use in children (Lipsky, B. A. and Baker, C. A., 1999, Clin. Infect. Dis. 28: 352-364). Furthermore, the potential for cardiotoxicity, as predicted by prolongation of the QT_c interval, has been cited as a toxicity concern for quinolones.

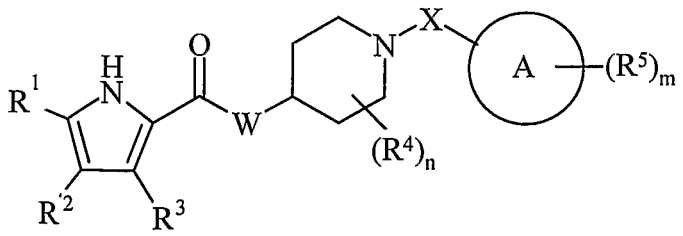
There are several known natural product inhibitors of DNA gyrase that compete with ATP for binding the GyrB subunit (Maxwell, A. and Lawson, D.M. 2003, Curr. Topics in Med. Chem. 3: 283-303). The coumarins are natural products isolated from *Streptomyces spp.*, examples of which are novobiocin, chlorobiocin and coumermycin A1. Although these compounds are potent inhibitors of DNA gyrase, their therapeutic utility is limited due to toxicity in eukaryotes and poor penetration in Gram-negative bacteria (Maxwell, A. 1997, Trends Microbiol. 5: 102-109). Another natural product class of compounds that targets the GyrB subunit is the cyclothialidines, which are isolated from *Streptomyces filipensis* (Watanabe, J. et al 1994, J. *Antibiot.* 47: 32-36). Despite potent activity against DNA gyrase, cyclothialidine is a poor antibacterial agent showing activity only against some eubacterial species (Nakada, N, 1993, *Antimicrob. Agents Chemother.* 37: 2656-2661).

Synthetic inhibitors that target the B subunit of DNA gyrase and topoisomeraseIV are known in the art. For example, coumarin-containing compounds are described in patent application number WO 99/35155, 5,6-bicyclic heteroaromatic compounds are described in patent application WO 02/060879, and pyrazole compounds are described in patent application WO 01/52845 (US patent US6,608,087).

We have discovered a new class of compounds which are useful for inhibiting DNA gyrase and topoisomerase IV.

SUMMARY OF THE INVENTION

Therefore the present invention provides a compound of formula **(I)**:



(I)

wherein:

R^1 is selected from hydrogen, nitro, hydroxy, halo, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkanoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2 and C_{3-6}cycloalkyl; wherein R^1 may be optionally substituted on carbon by one or more halo or cyclopropyl;

R^2 is selected from hydrogen, nitro, hydroxy, halo, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkanoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2 and C_{3-6}cycloalkyl; wherein R^2 may be optionally substituted on carbon by one or more halo or C_{3-6}cycloalkyl;

R^3 is selected from hydrogen, nitro, hydroxy, halo, cyano, -C=N-OR' wherein R' is H or C_{1-4}alkyl, C_{1-4}alkyl, C_{1-4}alkoxy, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkanoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2 and C_{3-6}cycloalkyl; wherein R^3 may be optionally substituted on carbon by one or more halo or C_{3-6}cycloalkyl;

W is -O-, -N(R^6)- or -C(R^7)(R^8)-;

X is a direct bond, -CH_2-, -C(O)- or S(O)$_q$- (wherein q is 1 or 2);

Ring A is carbocyclyl or heterocyclyl; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^9;

R^4 and **R^5** are substituents on carbon and are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, sulfo, formyl, ureido, hydroxyiminomethyl, C_{1-4}alkoxyiminomethyl, *N*-hydroxyformamido, C_{1-4}hydrazino, hydrazinocarbonyl, *N*-hydroxyethanimidoyl, amino(hydroxyimino)methyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, *N*-(C_{1-4}alkoxy)carbamoyl, *N'*-(C_{1-4}alkyl)ureido, *N',N'*-(C_{1-4}alkyl)$_2$ureido, *N*-(C_{1-4}alkyl)-*N*-(C_{1-4}alkoxy)carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, C_{1-4}alkoxycarbonylamino, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, C_{1-4}alkylsulphonylaminocarbonyl, *N'*-(C_{1-4}alkyl)hydrazinocarbonyl, *N',N'*-(C_{1-4}alkyl)$_2$hydrazinocarbonyl, carbocyclyl-R^{10}- or heterocyclyl-R^{11}—; wherein R^4 and R^5 independently of each other may be optionally substituted on carbon by one or more R^{12}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{13};

R^6, **R^7** and **R^8** are independently selected from hydrogen or C_{1-4}alkyl;

n is 1-4; wherein the values of R^4 may be the same or different;

m is 0-4; wherein the values of R^5 may be the same or different;

$\mathbf{R^{12}}$ is selected from azido, halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, N-(C_{1-4}alkyl)amino, N,N-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, N-(C_{1-4}alkyl)carbamoyl, N,N-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, N-(C_{1-4}alkyl)sulphamoyl, N,N-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, C_{1-4}alkoxycarbonylamino, carbocyclyl-R^{14}— or heterocyclyl-R^{15}—; wherein R^{12} independently of each other may be optionally substituted on carbon by one or more R^{16}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{17};

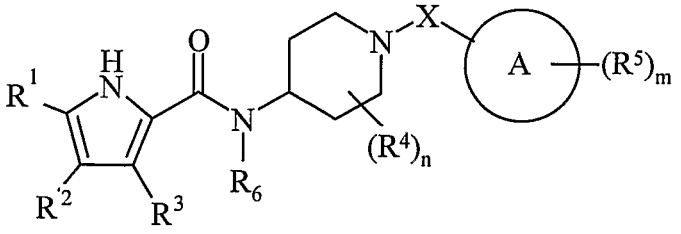
$\mathbf{R^9}$, $\mathbf{R^{13}}$ and $\mathbf{R^{17}}$ are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

$\mathbf{R^{10}}$, $\mathbf{R^{11}}$, $\mathbf{R^{14}}$ and $\mathbf{R^{15}}$ are independently selected from a direct bond, -O-, -N(R^{18})-, -C(O)-, -N(R^{19})C(O)-, -C(O)N(R^{20})-, -S(O)$_p$-, -SO_2N(R^{21})- or -N(R^{22})SO_2-; wherein R^{18}, R^{19}, R^{20}, R^{21} and R^{22} are independently selected from hydrogen or C_{1-4}alkyl and p is 0-2;

$\mathbf{R^{16}}$ is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, ethenyl, ethynyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

or a pharmaceutically acceptable salt thereof.

The present invention also provides a compound of formula **(IA)**:



(IA)

wherein:

R^1 is selected from hydrogen, nitro, hydroxy, halo, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkanoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2 and C_{3-6}cycloalkyl; wherein R^1 may be optionally substituted on carbon by one or more halo or cyclopropyl;

R^2 is selected from hydrogen, nitro, hydroxy, halo, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkanoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2 and C_{3-6}cycloalkyl; wherein R^2 may be optionally substituted on carbon by one or more halo or C_{3-6}cycloalkyl;

R^3 is selected from hydrogen, nitro, hydroxy, halo, cyano, -C=N-OR' wherein R' is H or C_{1-4}alkyl, C_{1-4}alkyl, C_{1-4}alkoxy, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkanoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2 and C_{3-6}cycloalkyl; wherein R^3 may be optionally substituted on carbon by one or more halo or C_{3-6}cycloalkyl; **X** is a direct bond, -CH_2-, -C(O)- or S(O)$_q$- (wherein q is 1 or 2);

Ring A is carbocyclyl or heterocyclyl; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^9;

R^4 and **R^5** are substituents on carbon and are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, sulfo, formyl, ureido, hydroxyiminomethyl, *N*-hydroxyformamido, hydrazinocarbonyl, *N*-hydroxyethanimidoyl, amino(hydroxyimino)methyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, *N*-(C_{1-4}alkoxy)carbamoyl, *N'*-(C_{1-4}alkyl)ureido, *N',N'*-(C_{1-4}alkyl)$_2$ureido, *N*-(C_{1-4}alkyl)-*N*-(C_{1-4}alkoxy)carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, C_{1-4}alkoxycarbonylamino, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, C_{1-4}alkylsulphonylaminocarbonyl, *N'*-(C_{1-4}alkyl)hydrazinocarbonyl, *N',N'*-(C_{1-4}alkyl)$_2$hydrazinocarbonyl, carbocyclyl-R^{10}- or heterocyclyl-R^{11}-; wherein R^4 and R^5 independently of each other may be optionally substituted on carbon by one or more R^{12}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{13};

R^6, **R^7** and **R^8** are independently selected from hydrogen or C_{1-4}alkyl;

n is 1-4; wherein the values of R^4 may be the same or different;

m is 0-4; wherein the values of R^5 may be the same or different;

R^{12} is selected from azido, halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy,

C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, N-(C_{1-4}alkyl)amino, N,N-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, N-(C_{1-4}alkyl)carbamoyl, N,N-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, N-(C_{1-4}alkyl)sulphamoyl, N,N-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, C_{1-4}alkoxycarbonylamino, carbocyclyl-R^{14}- or heterocyclyl-R^{15}-; wherein R^{12} independently of each other may be optionally substituted on carbon by one or more R^{16}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{17};

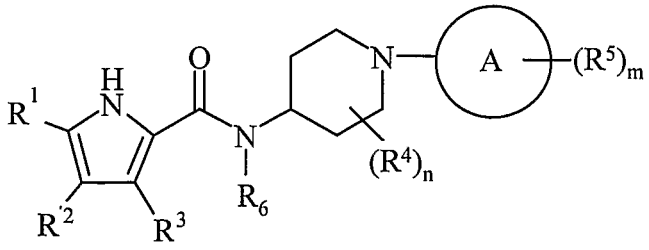
R^9, **R^{13}** and **R^{17}** are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

R^{10}, **R^{11}**, **R^{14}** and **R^{15}** are independently selected from a direct bond, -O-, -N(R^{18})-, -C(O)-, -N(R^{19})C(O)-, -C(O)N(R^{20})-, -S(O)$_p$-, -SO_2N(R^{21})- or -N(R^{22})SO_2-; wherein R^{18}, R^{19}, R^{20}, R^{21} and R^{22} are independently selected from hydrogen or C_{1-4}alkyl and p is 0-2;

R^{16} is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, ethenyl, ethynyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

or a pharmaceutically acceptable salt thereof.

The present invention also provides a compound of formula **(IB)**:



(IB)

wherein:

R^1 is selected from hydrogen, nitro, hydroxy, halo, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkanoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2 and C_{3-6}cycloalkyl; wherein R^1 may be optionally substituted on carbon by one or more halo or cyclopropyl;

R^2 is selected from hydrogen, nitro, hydroxy, halo, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkanoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2 and C_{3-6}cycloalkyl; wherein R^2 may be optionally substituted on carbon by one or more halo or C_{3-6}cycloalkyl;

R^3 is selected from hydrogen, nitro, hydroxy, halo, cyano, -C=N-OR' wherein R' is H or C_{1-4}alkyl, C_{1-4}alkyl, C_{1-4}alkoxy, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkanoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2 and C_{3-6}cycloalkyl; wherein R^3 may be optionally substituted on carbon by one or more halo or C_{3-6}cycloalkyl;

Ring A is carbocyclyl or heterocyclyl; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^9;

R^4 and **R^5** are substituents on carbon and are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, sulfo, formyl, ureido, hydroxyiminomethyl, *N*-hydroxyformamido, hydrazinocarbonyl, *N*-hydroxyethanimidoyl, amino(hydroxyimino)methyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, *N*-(C_{1-4}alkoxy)carbamoyl, *N'*-(C_{1-4}alkyl)ureido, *N',N'*-(C_{1-4}alkyl)$_2$ureido, *N*-(C_{1-4}alkyl)-*N*-(C_{1-4}alkoxy)carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, C_{1-4}alkoxycarbonylamino, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, C_{1-4}alkylsulphonylaminocarbonyl, *N'*-(C_{1-4}alkyl)hydrazinocarbonyl, *N',N'*-(C_{1-4}alkyl)$_2$hydrazinocarbonyl, carbocyclyl-R^{10}- or heterocyclyl-R^{11}-; wherein R^4 and R^5 independently of each other may be optionally substituted on carbon by one or more R^{12}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{13};

R^6, **R^7** and **R^8** are independently selected from hydrogen or C_{1-4}alkyl;

n is 1-4; wherein the values of R^4 may be the same or different;

m is 0-4; wherein the values of R^5 may be the same or different;

R^{12} is selected from azido, halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, N-(C_{1-4}alkyl)amino, N,N-(C_{1-4}alkyl)$_2$amino,

C_{1-4}alkanoylamino, N-(C_{1-4}alkyl)carbamoyl, N,N-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, N-(C_{1-4}alkyl)sulphamoyl, N,N-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, C_{1-4}alkoxycarbonylamino, carbocyclyl-R^{14}- or heterocyclyl-R^{15}-; wherein R^{12} independently of each other may be optionally substituted on carbon by one or more R^{16}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{17};

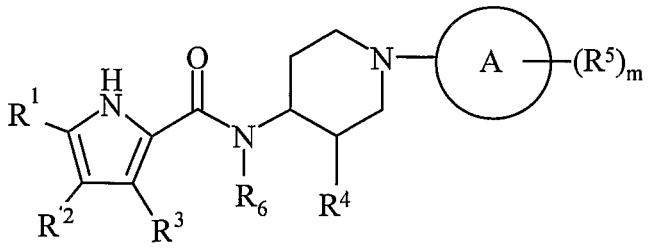
R^9, **R^{13}** and **R^{17}** are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

R^{10}, **R^{11}**, **R^{14}** and **R^{15}** are independently selected from a direct bond, -O-, -N(R^{18})-, -C(O)-, -N(R^{19})C(O)-, -C(O)N(R^{20})-, -S(O)$_p$-, -SO_2N(R^{21})- or -N(R^{22})SO_2-; wherein R^{18}, R^{19}, R^{20}, R^{21} and R^{22} are independently selected from hydrogen or C_{1-4}alkyl and p is 0-2;

R^{16} is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, ethenyl, ethynyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

or a pharmaceutically acceptable salt thereof.

The present invention also provides a compound of formula **(IC)**:



(IC)

wherein:

R^1 is selected from hydrogen, nitro, hydroxy, halo, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkanoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2 and C_{3-6}cycloalkyl; wherein R^1 may be optionally substituted on carbon by one or more halo or cyclopropyl;

R^2 is selected from hydrogen, nitro, hydroxy, halo, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkanoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2 and C_{3-6}cycloalkyl; wherein R^2 may be optionally substituted on carbon by one or more halo or C_{3-6}cycloalkyl;

R^3 is selected from hydrogen, nitro, hydroxy, halo, cyano, -C=N-OR' wherein R' is H or C_{1-4}alkyl, C_{1-4}alkyl, C_{1-4}alkoxy, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkanoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2 and C_{3-6}cycloalkyl; wherein R^3 may be optionally substituted on carbon by one or more halo or C_{3-6}cycloalkyl;

Ring A is carbocyclyl or heterocyclyl; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^9;

R^4 and **R^5** are substituents on carbon and are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, sulfo, formyl, ureido, hydroxyiminomethyl, *N*-hydroxyformamido, hydrazinocarbonyl, *N*-hydroxyethanimidoyl, amino(hydroxyimino)methyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, *N*-(C_{1-4}alkoxy)carbamoyl, *N'*-(C_{1-4}alkyl)ureido, *N',N'*-(C_{1-4}alkyl)$_2$ureido, *N*-(C_{1-4}alkyl)-*N*-(C_{1-4}alkoxy)carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, C_{1-4}alkoxycarbonylamino, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, C_{1-4}alkylsulphonylaminocarbonyl, *N'*-(C_{1-4}alkyl)hydrazinocarbonyl, *N',N'*-(C_{1-4}alkyl)$_2$hydrazinocarbonyl, carbocyclyl-R^{10}- or heterocyclyl-R^{11}-; wherein R^4 and R^5 independently of each other may be optionally substituted on carbon by one or more R^{12}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{13};

R^6, **R^7** and **R^8** are independently selected from hydrogen or C_{1-4}alkyl;

m is 0-4; wherein the values of R^5 may be the same or different;

R^{12} is selected from azido, halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, N-(C_{1-4}alkyl)amino, N,N-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, N-(C_{1-4}alkyl)carbamoyl, N,N-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, N-(C_{1-4}alkyl)sulphamoyl, N,N-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, C_{1-4}alkoxycarbonylamino, carbocyclyl-R^{14}- or heterocyclyl-R^{15}-; wherein R^{12} independently of each other may be

optionally substituted on carbon by one or more R^{16}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{17};

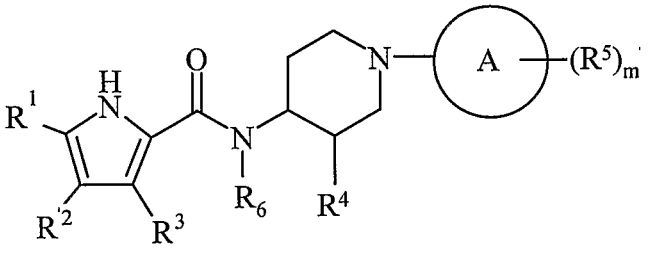
R^9, **R^{13}** and **R^{17}** are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

R^{10}, **R^{11}**, **R^{14}** and **R^{15}** are independently selected from a direct bond, -O-, -N(R^{18})-, -C(O)-, -N(R^{19})C(O)-, -C(O)N(R^{20})-, -S(O)$_p$-, -SO_2N(R^{21})- or -N(R^{22})SO_2-; wherein R^{18}, R^{19}, R^{20}, R^{21} and R^{22} are independently selected from hydrogen or C_{1-4}alkyl and p is 0-2;

R^{16} is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, ethenyl, ethynyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

or a pharmaceutically acceptable salt thereof.

The present invention also provides a compound of formula **(ID)**:



(ID)

wherein:

R^1 is selected from hydrogen, nitro, hydroxy, halo, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkanoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2 and C_{3-6}cycloalkyl; wherein R^1 may be optionally substituted on carbon by one or more halo or cyclopropyl;

R^2 is selected from hydrogen, nitro, hydroxy, halo, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkanoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2 and C_{3-6}cycloalkyl; wherein R^2 may be optionally substituted on carbon by one or more halo or C_{3-6}cycloalkyl;

R^3 is selected from hydrogen, nitro, hydroxy, halo, cyano, -C=N-OR' wherein R' is H or C_{1-4}alkyl, C_{1-4}alkyl, C_{1-4}alkoxy, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkanoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2 and C_{3-6}cycloalkyl; wherein R^3 may be optionally substituted on carbon by one or more halo or C_{3-6}cycloalkyl;

Ring A is heterocyclyl; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^9;

R^4 and **R^5** are substituents on carbon and are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, sulfo, formyl, ureido, hydroxyiminomethyl, *N*-hydroxyformamido, hydrazinocarbonyl, *N*-hydroxyethanimidoyl, amino(hydroxyimino)methyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, *N*-(C_{1-4}alkoxy)carbamoyl, *N'*-(C_{1-4}alkyl)ureido, *N',N'*-(C_{1-4}alkyl)$_2$ureido, *N*-(C_{1-4}alkyl)-*N*-(C_{1-4}alkoxy)carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, C_{1-4}alkoxycarbonylamino, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, C_{1-4}alkylsulphonylaminocarbonyl, *N'*-(C_{1-4}alkyl)hydrazinocarbonyl, *N',N'*-(C_{1-4}alkyl)$_2$hydrazinocarbonyl, carbocyclyl-R^{10}- or heterocyclyl-R^{11}-; wherein R^4 and R^5 independently of each other may be optionally substituted on carbon by one or more R^{12}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{13};

R^6, **R^7** and **R^8** are independently selected from hydrogen or C_{1-4}alkyl;

m is 0-4; wherein the values of R^5 may be the same or different;

R^{12} is selected from azido, halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, N-(C_{1-4}alkyl)amino, N,N-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, N-(C_{1-4}alkyl)carbamoyl, N,N-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, N-(C_{1-4}alkyl)sulphamoyl, N,N-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, C_{1-4}alkoxycarbonylamino, carbocyclyl-R^{14}- or heterocyclyl-R^{15}-; wherein R^{12} independently of each other may be optionally substituted on carbon by one or more R^{16}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{17};

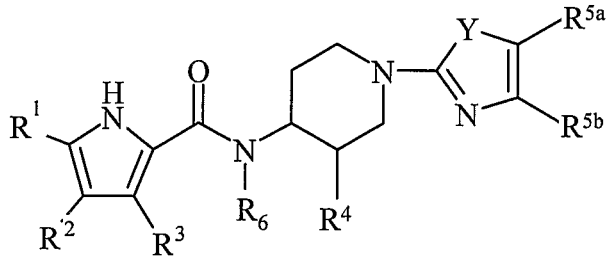
R^9, **R^{13}** and **R^{17}** are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

R^{10}, **R^{11}**, **R^{14}** and **R^{15}** are independently selected from a direct bond, -O-, -N(R^{18})-, -C(O)-, -N(R^{19})C(O)-, -C(O)N(R^{20})-, -S(O)$_p$-, -SO_2N(R^{21})- or -N(R^{22})SO_2-; wherein R^{18}, R^{19}, R^{20}, R^{21} and R^{22} are independently selected from hydrogen or C_{1-4}alkyl and p is 0-2;

R^{16} is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, ethenyl, ethynyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

or a pharmaceutically acceptable salt thereof.

The present invention also provides a compound of formula **(IE)**:



(IE)

wherein:Y is NH, N(C_{1-4}alkyl) or S;

R^1 is selected from hydrogen, nitro, hydroxy, halo, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkanoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2 and C_{3-6}cycloalkyl; wherein R^1 may be optionally substituted on carbon by one or more halo or cyclopropyl;

R^2 is selected from hydrogen, nitro, hydroxy, halo, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkanoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2 and C_{3-6}cycloalkyl; wherein R^2 may be optionally substituted on carbon by one or more halo or C_{3-6}cycloalkyl;

R^3 is selected from hydrogen, nitro, hydroxy, halo, cyano, -C=N-OR' wherein R' is H or C_{1-4}alkyl, C_{1-4}alkyl, C_{1-4}alkoxy, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkanoyl, C_{1-4}alkylS(O)$_a$

wherein a is 0 to 2 and C_{3-6}cycloalkyl; wherein R^3 may be optionally substituted on carbon by one or more halo or C_{3-6}cycloalkyl;

X is a direct bond, -CH_2-, -C(O)- or $S(O)_q$- (wherein q is 1 or 2);

Ring A is heterocyclyl; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^9;

R^4 is a substitutent on carbon selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, sulfo, formyl, ureido, hydroxyiminomethyl, *N*-hydroxyformamido, hydrazinocarbonyl, *N*-hydroxyethanimidoyl, amino(hydroxyimino)methyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, *N*-(C_{1-4}alkoxy)carbamoyl, *N'*-(C_{1-4}alkyl)ureido, *N',N'*-(C_{1-4}alkyl)$_2$ureido, *N*-(C_{1-4}alkyl)-*N*-(C_{1-4}alkoxy)carbamoyl, C_{1-4}alkyl$S(O)_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, C_{1-4}alkoxycarbonylamino, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, C_{1-4}alkylsulphonylaminocarbonyl, *N'*-(C_{1-4}alkyl)hydrazinocarbonyl, *N',N'*-(C_{1-4}alkyl)$_2$hydrazinocarbonyl, carbocyclyl-R^{10}— or heterocyclyl-R^{11}—; wherein R^4 and R^5 independently of each other may be optionally substituted on carbon by one or more R^{12}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{13};

R^{5a} and **R^{5b}** are substituents as defined for R^4 or taken together with the carbons to which they are attached form a 6-membered carbocyclyl ring substituted by one or two groups which may be the same or different and which are selected from R^{14};

R^6, **R^7** and **R^8** are independently selected from hydrogen or C_{1-4}alkyl;

R^{12} is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, N-(C_{1-4}alkyl)amino, N,N-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, N-(C_{1-4}alkyl)carbamoyl, N,N-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkyl$S(O)_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, N-(C_{1-4}alkyl)sulphamoyl, N,N-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, C_{1-4}alkoxycarbonylamino, carbocyclyl-R^{14}— or heterocyclyl-R^{15}—; wherein R^{12} independently of each other may be optionally substituted on carbon by one or more R^{16}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{17};

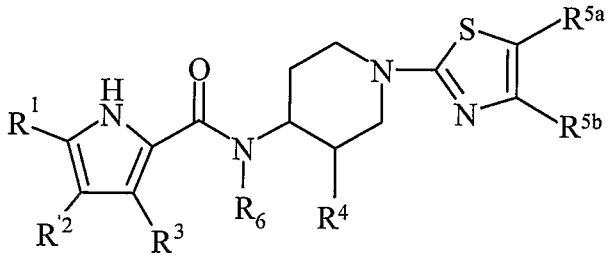
R^{9}, **R**^{13} and **R**^{17} are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

R^{10}, **R**^{11}, **R**^{14} and **R**^{15} are independently selected from a direct bond, -O-, -N(R^{18})-, -C(O)-, -N(R^{19})C(O)-, -C(O)N(R^{20})-, -S(O)$_p$-, -SO_2N(R^{21})- or -N(R^{22})SO_2-; wherein R^{18}, R^{19}, R^{20}, R^{21} and R^{22} are independently selected from hydrogen or C_{1-4}alkyl and p is 0-2;

R^{16} is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, ethenyl, ethynyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

or a pharmaceutically acceptable salt thereof.

The present invention also provides a compound of formula **(IF)**:



(IF)

wherein:

R^{1} is selected from hydrogen, nitro, hydroxy, halo, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkanoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2 and C_{3-6}cycloalkyl; wherein R^1 may be optionally substituted on carbon by one or more halo or cyclopropyl;

R^{2} is selected from hydrogen, nitro, hydroxy, halo, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkanoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2 and C_{3-6}cycloalkyl; wherein R^2 may be optionally substituted on carbon by one or more halo or C_{3-6}cycloalkyl;

R^{3} is selected from hydrogen, nitro, hydroxy, halo, cyano, -C=N-OR' wherein R' is H or C_{1-4}alkyl, C_{1-4}alkyl, C_{1-4}alkoxy, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkanoyl, C_{1-4}alkylS(O)$_a$

wherein a is 0 to 2 and C_{3-6}cycloalkyl; wherein R^3 may be optionally substituted on carbon by one or more halo or C_{3-6}cycloalkyl;

X is a direct bond, -CH_2-, -C(O)- or $S(O)_q$- (wherein q is 1 or 2);

$\mathbf{R^4}$ is a substitutent on carbon selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, sulfo, formyl, ureido, hydroxyiminomethyl, *N*-hydroxyformamido, hydrazinocarbonyl, *N*-hydroxyethanimidoyl, amino(hydroxyimino)methyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, *N*-(C_{1-4}alkoxy)carbamoyl, *N'*-(C_{1-4}alkyl)ureido, *N',N'*-(C_{1-4}alkyl)$_2$ureido, *N*-(C_{1-4}alkyl)-*N*-(C_{1-4}alkoxy)carbamoyl, C_{1-4}alkyl$S(O)_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, C_{1-4}alkoxycarbonylamino, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, C_{1-4}alkylsulphonylaminocarbonyl, *N'*-(C_{1-4}alkyl)hydrazinocarbonyl, *N',N'*-(C_{1-4}alkyl)$_2$hydrazinocarbonyl, carbocyclyl-R^{10}— or heterocyclyl-R^{11}—; wherein R^4 and R^5 independently of each other may be optionally substituted on carbon by one or more R^{12}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{13};

$\mathbf{R^{5a}}$ and $\mathbf{R^{5b}}$ are substituents as defined for R^4 or taken together with the carbons to which they are attached form a 6-membered carbocyclyl ring substituted by one or two groups which may be the same or different and which are selected from R^{14};

$\mathbf{R^6}$, $\mathbf{R^7}$ and $\mathbf{R^8}$ are independently selected from hydrogen or C_{1-4}alkyl;

$\mathbf{R^{12}}$ is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, N-(C_{1-4}alkyl)amino, N,N-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, N-(C_{1-4}alkyl)carbamoyl, N,N-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkyl$S(O)_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, N-(C_{1-4}alkyl)sulphamoyl, N,N-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, C_{1-4}alkoxycarbonylamino, carbocyclyl-R^{14}— or heterocyclyl-R^{15}—; wherein R^{12} independently of each other may be optionally substituted on carbon by one or more R^{16}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{17};

$\mathbf{R^9}$, $\mathbf{R^{13}}$ and $\mathbf{R^{17}}$ are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

$\mathbf{R^{10}}$, $\mathbf{R^{11}}$, $\mathbf{R^{14}}$ and $\mathbf{R^{15}}$ are independently selected from a direct bond, -O-, -N(R^{18})-, -C(O)-, -N(R^{19})C(O)-, -C(O)N(R^{20})-, -S(O)$_p$-, -SO_2N(R^{21})- or -N(R^{22})SO_2-; wherein R^{18}, R^{19}, R^{20}, R^{21} and R^{22} are independently selected from hydrogen or C_{1-4}alkyl and p is 0-2;

$\mathbf{R^{16}}$ is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, ethenyl, ethynyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

or a pharmaceutically acceptable salt thereof.

The invention also provides a compound which is

2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-5-carboxylic acid;

2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(2-methoxyethyl)amino]carbonyl}-1,3-thiazole-5-carboxylic acid;

2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[(1*S*)-2-methoxy-1-methylethyl]amino}carbonyl)-1,3-thiazole-5-carboxylic acid;

2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-[(methylamino)carbonyl]-1,3-thiazole-5-carboxylic acid;

2-((3*S*,4*R*)-4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid;

2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid;

4-acetyl-2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid;

2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[(1*R*)-2-methoxy-1-methylethyl]amino}carbonyl)-1,3-thiazole-5-carboxylic acid;

2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[(2*S*)-2-methoxypropyl]amino}carbonyl)-1,3-thiazole-5-carboxylic acid;

2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[(2*R*)-2-methoxypropyl]amino}carbonyl)-1,3-thiazole-5-carboxylic acid;

2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[(1*R*,2*S*)-2-fluorocyclopropyl]amino}carbonyl)-1,3-thiazole-5-carboxylic acid;

Cis(±)2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylic acid;

Cis(±)2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(methoxymethyl)-1,3-thiazole-5-carboxylic acid;

Cis(±)2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)isonicotinic acid;

2-((3*S*,4*R*)-4-{[(4-chloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylic acid;

Cis(±)-2-(3-chloro-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-4-(methoxymethyl)-1,3-thiazole-5-carboxylic acid;

2-((3*S*, 4*R*)-4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid;

Cis(±)-2-[4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(prop-2-yn-1-yloxy)piperidin-1-yl]-1,3-thiazole-5-carboxylic acid;

Cis(±)2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-4-carboxylic acid; or

2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[2-methoxy-1-(methoxymethyl)ethyl]amino}carbonyl)-1,3-thiazole-5-carboxylic acid;

or a pharmaceutically acceptable salt thereof.

The invention also provides a pharmaceutical composition that comprises a compound of formula I, IA, IB, IC, ID, or IE or a pharmaceutically-acceptable salt thereof, and a pharmaceutically-acceptable diluent or carrier.

The invention also provides a method of treating a bacterial infection in a warm-blooded animal, such as a human being, in need of such treatment, which comprises administering to said animal an effective amount of a compound of formula I, IA, IB, IC, ID, or IE, or a pharmaceutically-acceptable salt thereof.

The invention also provides a method for inhibiting bacterial DNA gyrase in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, IA, IB, IC, ID, or IE or a pharmaceutically acceptable salt.

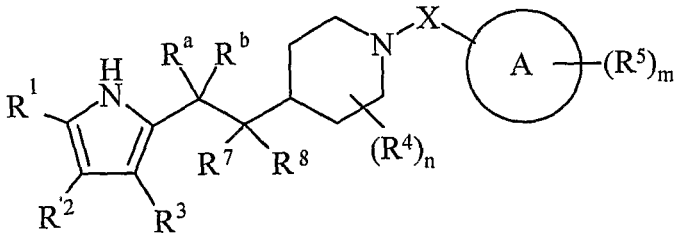
The invention also provides a compound of formula I, IA, IB, IC, ID, or IE and pharmaceutically acceptable salts thereof for use as a medicament.

Theinvention also provides the use of a compound of formula I, IA, IB, IC, ID, or IE, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the production of an anti-bacterial effect in a warm-blooded animal such as a human being.

The invention also provides the use of a compound of formula I, IA, IB, IC, ID, or IE, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of a bacterial infection in a warm-blooded animal such as a human being.

The present invention also provides a process for preparing compounds of formula **(I)** or pharmaceutically-acceptable salts thereof, comprising:

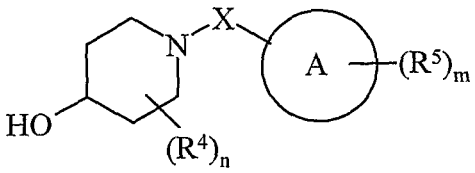
Process a) for compounds of formula **(I)** wherein W is $-C(R^7)(R^8)-$; converting a compound of formula **(II)**:



(II)

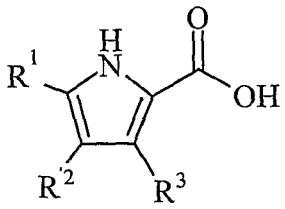
wherein R^a is cyano and R^b is dimethyamino or diethylamino; or R^a and R^b are independently selected from C_{1-4}alkylthio; or R^a and R^b together form 1,3-dithianyl or 1,3-dithiolanyl; into a compound of formula **(I)**;

Process b) for compounds of formula **(I)** wherein W is -O-; reacting a compound of formula **(III)**:



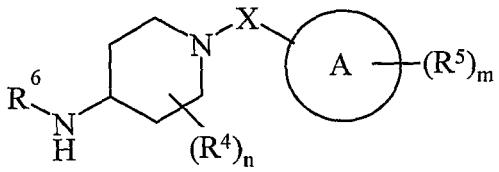
(III)

with a compound of formula **(IV)**:



(IV)

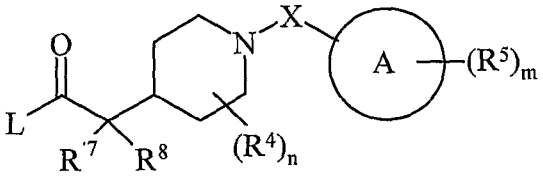
Process c) for compounds of formula **(I)** wherein W is -N(R^6)-; reacting a compound of formula **(V)**:



(V)

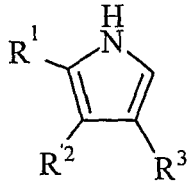
with a compound of formula **(IV)** or an activated acid derivative thereof;

Process d) for compounds of formula **(I)** wherein W is -C(R^7)(R^8)-; reacting a compound of formula **(VI)**:



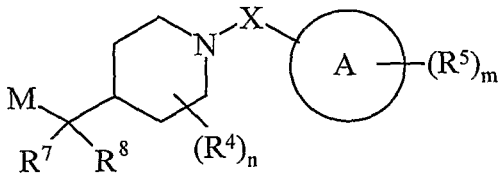
(VI)

wherein L is a displaceable group; with a compound of formula **(VII)**:



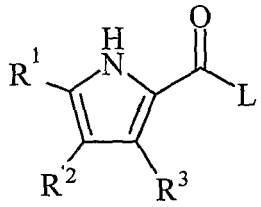
(VII)

Process e) for compounds of formula **(I)** wherein W is -C(R^7)(R^8)-; reacting a compound of formula **(VIII)**:



(VIII)

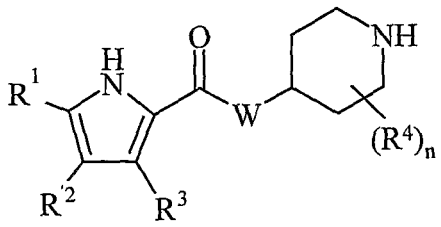
wherein M is an organometallic group; with a compound of formula **(IX)**:



(IX)

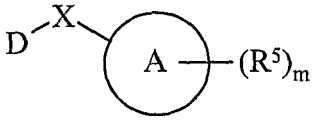
wherein L is a displaceable group;

Process f) reacting a compound of formula **(X)**:



(X)

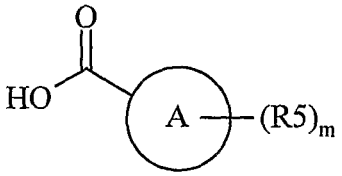
with a compound of formula **(XI)**:



(XI)

wherein D is a displaceable group;

Process g) for compounds of formula **(I)** wherein X is -C(O)-; reacting a compound of formula **(X)** with a compound of formula **(XII)**:



(XII)

and thereafter if necessary:

i) converting a compound of the formula **(I)** into another compound of the formula **(I)**;

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

In this specification the term alkyl includes both straight and branched chain alkyl groups. For example, "C_{1-4}alkyl" includes methyl, ethyl, propyl, isopropyl and *t*-butyl. However references to individual alkyl groups such as propyl are specific for the straight chain version only. An analogous convention applies to other generic terms.

Where optional substituents are chosen from one or more groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups.

A "heterocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 4-12 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)- and a ring nitrogen and / or a ring sulphur atom may be optionally oxidised to form the *N*- or S-oxide(s). In one aspect of the invention a "heterocyclyl" is a saturated, partially saturated or unsaturated, monocyclic ring containing 5 or 6 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, it may, unless otherwise specified, be carbon or nitrogen linked, a $-CH_2-$ group can optionally be replaced by a -C(O)-and a ring sulphur atom may be optionally oxidised to form the S-oxides. In a further aspect of the invention a "heterocyclyl" is an unsaturated, carbon-linked, monocyclic ring containing 5 or 6 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen. Examples and suitable values of the term "heterocyclyl" are morpholino, piperidyl, pyridyl, pyranyl, pyrrolyl, pyrazolyl, isothiazolyl, indolyl, quinolyl, thienyl, 1,3-benzodioxolyl, thiadiazolyl, piperazinyl, thiazolidinyl, pyrrolidinyl, thiomorpholino, pyrrolinyl, homopiperazinyl, 3,5-dioxapiperidinyl, tetrahydropyranyl, imidazolyl, pyrimidyl, pyrazinyl, pyridazinyl, isoxazolyl, *N*-methylpyrrolyl, 4-pyridone, 1-isoquinolone, 2-pyrrolidone, 4-thiazolidone, pyridine-*N*-oxide and quinoline-*N*-oxide. Further examples and

suitable values of the term "heterocyclyl" are thiazolyl, quinolinyl, benzothiazolyl, pyrimidinyl and pyridinyl.

A "carbocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic carbon ring that contains 3-12 atoms; wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-. Particularly "carbocyclyl" is a monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms. Suitable values for "carbocyclyl" include cyclopropyl, cyclobutyl, 1-oxocyclopentyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, phenyl, naphthyl, tetralinyl, indanyl or 1-oxoindanyl. A particular example of "carbocyclyl" is phenyl.

An example of "C_{1-4}alkanoyloxy" is acetoxy. Examples of "C_{1-4}alkoxycarbonyl" include methoxycarbonyl, ethoxycarbonyl, *n*- and *t*-butoxycarbonyl. Examples of "C_{1-4}alkoxycarbonylamino" include methoxycarbonylamino, ethoxycarbonylamino, *n*- and *t*-butoxycarbonylamino. Examples of "C_{1-4}alkoxy" include methoxy, ethoxy and propoxy. Examples of "C_{1-4}alkanoylamino" include formamido, acetamido and propionylamino. Examples of "C_{1-4}alkyl$S(O)_a$ wherein a is 0 to 2" include methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl and ethylsulphonyl. Examples of "C_{1-4}alkanoyl" include propionyl and acetyl. Examples of "*N*-(C_{1-4}alkyl)amino" include methylamino and ethylamino. Examples of "*N,N*-(C_{1-4}alkyl)$_2$amino" include di-*N*-methylamino, di-(*N*-ethyl)amino and *N*-ethyl-*N*-methylamino. Examples of "C_{2-4}alkenyl" are vinyl, allyl and 1-propenyl. Examples of "C_{2-4}alkynyl" are ethynyl, 1-propynyl and 2-propynyl. Examples of "*N*-(C_{1-4}alkyl)sulphamoyl" are *N*-(methyl)sulphamoyl and *N*-(ethyl)sulphamoyl. Examples of "*N,N*-(C_{1-4}alkyl)$_2$sulphamoyl" are *N,N*-(dimethyl)sulphamoyl and *N*-(methyl)-*N*-(ethyl)sulphamoyl. Examples of "*N*-(C_{1-4}alkyl)carbamoyl" are methylaminocarbonyl and ethylaminocarbonyl. Examples of "*N,N*-(C_{1-4}alkyl)$_2$carbamoyl" are dimethylaminocarbonyl and methylethylaminocarbonyl. Examples of "*N*-(C_{1-4}alkoxy)carbamoyl" are methoxyaminocarbonyl and isopropoxyaminocarbonyl. Examples of "*N*-(C_{1-4}alkyl)-*N*-(C_{1-4}alkoxy)carbamoyl" are *N*-methyl-*N*-methoxyaminocarbonyl and *N*-methyl-*N*-ethoxyaminocarbonyl. Examples of "C_{3-6}cycloalkyl" are cyclopropyl, cyclobutyl, cyclopropyl and cyclohexyl. Examples of "*N'*-(C_{1-4}alkyl)ureido" are *N'*-methylureido and *N'*-isopropylureido. Examples of "*N',N'*-(C_{1-4}alkyl)$_2$ureido" are *N'N'*-dimethylureido and *N'*-methyl-*N'*-isopropylureido. Examples of "*N'*-(C_{1-4}alkyl)hydrazinocarbonyl" are *N'*-methylhydrazinocarbonyl and *N'*-isopropylhydrazinocarbonyl. Examples of "*N',N'*-(C_{1-4}alkyl)$_2$hydrazinocarbonyl" are *N'N'*-dimethylhydrazinocarbonyl and *N'*-methyl-*N'*-isopropylhydrazinocarbonyl. Examples of

"C_{1-4}alkylsulphonylamino" include methylsulphonylamino, isopropylsulphonylamino and *t*-butylsulphonylamino. Examples of "C_{1-4}alkylsulphonylaminocarbonyl" include methylsulphonylaminocarbonyl, isopropylsulphonylaminocarbonyl and *t*-butylsulphonylaminocarbonyl. Examples of "C_{1-4}alkylsulphonyl" include methylsulphonyl, isopropylsulphonyl and *t*-butylsulphonyl.

A compound of formula **(I)** may form stable acid or basic salts, and in such cases administration of a compound as a salt may be appropriate, and pharmaceutically acceptable salts may be made by conventional methods such as those described following.

Suitable pharmaceutically-acceptable salts include acid addition salts such as methanesulfonate, tosylate, α-glycerophosphate, fumarate, hydrochloride, citrate, maleate, tartrate and (less preferably) hydrobromide. Also suitable are salts formed with phosphoric and sulfuric acid. In another aspect suitable salts are base salts such as an alkali metal salt for example sodium or potassium, an alkaline earth metal salt for example calcium or magnesium, an organic amine salt for example triethylamine, morpholine, *N*-methylpiperidine, *N*-ethylpiperidine, procaine, dibenzylamine, *N,N*-dibenzylethylamine, tris-(2-hydroxyethyl)amine, tromethamine, *N*-methyl d-glucamine and amino acids such as glycine or lysine. There may be more than one cation or anion depending on the number of charged functions and the valency of the cations or anions. A preferred pharmaceutically-acceptable salt is the sodium salt.

However, to facilitate isolation of the salt during preparation, salts which are less soluble in the chosen solvent may be preferred whether pharmaceutically-acceptable or not.

Within the present invention it is to be understood that a compound of the formula **(I)** or a salt thereof may exhibit the phenomenon of tautomerism and that the formulae drawings within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which inhibits DNA gyrase and/or topoisomeraseIV and is not to be limited merely to any one tautomeric form utilised within the formulae drawings. The formulae drawings within this specification can represent only one of the possible tautomeric forms and it is to be understood that the specification encompasses all possible tautomeric forms of the compounds drawn not just those forms which it has been possible to show graphically herein. The same applies to compound names. It will be appreciated by those skilled in the art that certain compounds of formula **(I)** contain an asymmetrically substituted carbon and/or sulphur atom, and accordingly may exist in, and be isolated in, optically-active and racemic forms. Some compounds may exhibit

polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic or stereoisomeric form, or mixtures thereof, which form possesses properties useful in the inhibition of DNA gyrase and/or topoisomeraseIV, it being well known in the art how to prepare optically-active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, by enzymatic resolution, by biotransformation, or by chromatographic separation using a chiral stationary phase) and how to determine efficacy for the inhibition of DNA gyrase and/or topoisomeraseIV by the standard tests described hereinafter.

It is also to be understood that certain compounds of the formula **(I)** and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which inhibit DNA gyrase and/or topoisomeraseIV.

Particular and suitable values for certain substituents and groups referred to in this specification are listed below. These values may be used where appropriate with any of the definitions and embodiments disclosed herein. Each stated species represents a particular and independent aspect of the invention.

Referring to a compound of formula I, R^1 is C_{1-4}alkyl. R^1 is methyl. R^1 is halo. R^1 is hydrogen.

R^2 is C_{1-4}alkyl. R^2 is methyl. R^2 is halo. R^2 is fluoro or chloro. R^2 is hydrogen. R^2 is chloro.

R^3 is C_{1-4}alkyl. R^3 is methyl. R^3 is halo. R^3 is fluoro or chloro. R^3 is hydrogen. R^3 is CN. R^3 is C=N-OH. R^3 is chloro.

W is -O-. W is $-N(R^6)-$. W is -NH-. W is $-C(R^7)(R^8)-$.

X is a direct bond. X is $-CH_2-$. X is -C(O)-. X is $S(O)_q-$ (wherein q is 1 or 2).

Ring A is carbocyclyl. Ring A is heterocyclyl; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^9.

Ring A is heterocyclyl. Ring A is thiazolyl, quinolinyl, benzothiazolyl, pyrimidinyl or pyridinyl. Ring A is thiazol-2-yl, quinolin-4-yl, benzothiazol-2-yl, pyrimidin-4-yl, pyridin-2-yl or pyridin-4-yl.

R^4 is a substituent on carbon and is selected from halo, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, *N*-(C_{1-4}alkyl)-*N*-(C_{1-4}alkoxy)carbamoyl, C_{1-4}alkoxycarbonyl or heterocyclyl-R^{11}-; wherein R^4 may be optionally substituted on carbon by one or more R^{12}. R^{12} is selected from hydroxy, C_{2-4}alkenyl, C_{1-4}alkoxy, N-(C_{1-4}alkyl)amino or N,N-(C_{1-4}alkyl)$_2$amino; and R^{11} is -C(O)-.

Alternatively, R^4 is a substituent on carbon and is selected from fluoro, hydroxy, carboxy, methyl, methoxy, propoxy, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N*-methyl-*N*-methoxycarbamoyl, methoxycarbonyl or morpholino-R^{11}-; wherein R^4 may be optionally substituted on carbon by one or more R^{12}. R^{12} is selected from hydroxy, ethenyl, methoxy, N-methylamino or N,N-dimethylamino; and R^{11} is -C(O)-.

Alternatively, R^4 is a substituent on carbon and is selected from methoxy, hydroxy, methoxycarbonyl, fluoro, allyloxy, propoxy, *N,N*-dimethylcarbamoyl, morpholinocarbonyl, *N*-ethylcarbamoyl, *N*-(2-hydroxyethyl)carbamoyl, dimethylaminomethyl, *N*-methyl-*N*-methoxycarbamoyl, methoxymethyl, methylaminomethyl and carboxy.

Alternatively, R^4 is a substituent on carbon and is selected from methoxy, hydroxy, methoxycarbonyl, fluoro, allyloxy, propoxy, *N,N*-dimethylcarbamoyl, morpholinocarbonyl, *N*-ethylcarbamoyl, *N*-(2-hydroxyethyl)carbamoyl, dimethylaminomethyl, *N*-methyl-*N*-methoxycarbamoyl, methoxymethyl, methylaminomethyl, carboxy, *N*-methyl-*N*-methoxyxcarbamoyl, N-hydroxyethylcarbamoyl, hydroxymethyl, (methylthio)methyl, (methylsulfinyl)methyl, (methylsulfonyl)methyl, benzyloxy, propynyloxy, methoxyethoxy, methoxypropoxy, chloro, methyl, cyclopropylmethoxy, thiazolylmethoxy, ethoxy, oxyacetic acid, ethylaminocarbonyloxy, allylaminocarbonyloxy, pyridinylmethoxy, hydroxypropoxy, methoxy(methyl)amino, and azido.

Alternatively R^4 is halo, particularly fluoro.

R^5 is a substituent on carbon and is selected from halo, carboxy, carbamoyl, C_{1-4}alkyl, C_{1-4}alkoxy, *N*-(C_{1-4}alkyl)carbamoyl, *N*-(C_{1-4}alkoxy)carbamoyl or C_{1-4}alkoxycarbonyl; wherein R^5 may be optionally substituted on carbon by one or more R^{12}. R^{12} is selected from C_{1-4}alkoxy or carbocyclyl-R^{14}-; and R^{14} is a direct bond.

Alternatively, R^5 is a substituent on carbon and is selected from chloro, carboxy, carbamoyl, methyl, methoxy, *N*-(isopropyl)carbamoyl, *N*-(methoxy)carbamoyl, methoxycarbonyl or ethoxycarbonyl; wherein R^5 may be optionally substituted on carbon by one or more R^{12}. R^{12} is selected from methoxy or phenyl-R^{14}-; and R^{14} is a direct bond.

Alternatively, R^5 is a substituent on carbon and is selected from chloro, carboxy, carbamoyl, methyl, methoxymethyl, methoxy, *N*-(1-methyl-1-phenylethyl)carbamoyl, *N*-(methoxy)carbamoyl, methoxycarbonyl or ethoxycarbonyl.

Alternatively, R^5 is a substituent on carbon and is selected from chloro, carboxy, carbamoyl, methyl, methoxymethyl, methoxy, *N*-(1-methyl-1-phenylethyl)carbamoyl, *N*-(methoxy)carbamoyl, methoxycarbonyl or ethoxycarbonyl, *N*-methoxycarbamoyl, formyl, (methoxyimino)methyl, isopropoxycarbonyl, ethoxy, morpholinocarbonyl, hydroxy-1-methylethyl, amino, methoxycarbonylamino, methylsulfonylamino, *N*-(1-methyl-1-phenylethyl)carbamoyl, *N*-2-morpholin-4-ylethylcarbamoyl, piperidinocarbonyl, N-methylcarbamoyl, *N*-2-hydroxyethylcarbamoyl, *N*-2-methoxyethylcarbamoyl, *N*-2-hydroxypropylcarbamoyl, *N*-2-hydroxy-1-methylethylcarbamoyl, *N*-isoxazolylcarbamoyl, *N*-2,2-difluoroethylcarbamoyl, *N*-tetrahydrofuran-3-ylcarbamoyl, *N*-cyclopropylcarbamoyl, *N*-1-cyanocyclopropylcarbamoyl, *N*-2-fluorocyclopropylcarbamoyl, *N*-2-hydroxy-1,1-dimethylethylcarbamoyl, *N*-1-cyano-1-methylethylcarbamoyl, *N*-1-(hydroxymethyl-2-methoxy-2-oxoethylcarbamoyl, *N*-1,3-dioxolan-2-ylmethylcarbamoyl, *N*-3-(2-oxopyrrolidin-1-ylpropylcarbamoyl, *N*-pyridin-2-ylmethylcarbamoyl, *N*-2-(methylthio)ethylcarbamoyl, *N*-1,3-oxazol-2-ylmethylcarbamoyl, *N*-2-fluoroethylcarbamoyl, *N*-(2-hydroxy-2-methylpropyl)carbamoyl, morpholin-4-ylmethyl, *tert*-butylaminomethyl, piperidine-1-ylmethyl, (3-hydroxypyrrolidin-1-yl)methyl, (hydroxyimino)methyl, 1,1-difluoromethyl, azidomethyl, cyano(morpholin-4-yl)methyl, *N*-2-(methylsulfonyl)ethylcarbamoyl, cyano, 1-hydroxy-1-methylethyl, cyclopropylmethyl, *N*-methylcarbamoyl, *N*-1-carboxycycloproylcarbamoyl, *N*-isoxazol-3-ylcarbamoyl, *N*-prop-2-yn-1ylcarbamoyl, *N*-1-carboxy-2-hydroxymethylcarbamoyl, *N*-[3-(2-oxopyrrolidin-1-yl)propyl]carbamoyl, *N*-(2-

hydroxy-2-methylpropyl)carbamoyl, *N*-methoxy-*N*-methylcarbamoyl, *N*-2-(methylsulfonyl)ethylcarbamoyl, *N*-methoxypropylcarbamoyl, and methoxymethyl)ethyl]amino}carbamoyl.

Alternatively R^5 is carboxy.

R^6 is hydrogen.

n is 1.

m is 1 or 2; wherein the values of R^5 may be the same or different. m is 1. m is 2.

In a further aspect of the invention there is provided a compound of formula **(I)** (as depicted above) wherein:

R^1 is selected from C_{1-4}alkyl;

R^2 is selected from halo.

R^3 is selected from hydrogen or halo;

W is -N(R^6)-;

X is a direct bond;

Ring A is heterocyclyl;

R^4 is a substituent on carbon and is selected from halo, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, *N*-(C_{1-4}alkyl)-*N*-(C_{1-4}alkoxy)carbamoyl, C_{1-4}alkoxycarbonyl or heterocyclyl-R^{11}-; wherein R^4 may be optionally substituted on carbon by one or more R^{12};

R^5 is a substituent on carbon and is selected from halo, carboxy, carbamoyl, C_{1-4}alkyl, C_{1-4}alkoxy, *N*-(C_{1-4}alkyl)carbamoyl, *N*-(C_{1-4}alkoxy)carbamoyl or C_{1-4}alkoxycarbonyl; wherein R^5 may be optionally substituted on carbon by one or more R^{12};

R^6 is hydrogen;

R^{11} is -C(O)-;

R^{12} is selected from hydroxy, C_{2-4}alkenyl, C_{1-4}alkoxy, N-(C_{1-4}alkyl)amino, N,N-(C_{1-4}alkyl)$_2$amino or carbocyclyl-R^{14}-;

R^{14} is a direct bond;

n is 1; and

m is 1 or 2; wherein the values of R^5 may be the same or different;

or a pharmaceutically acceptable salt thereof.

In a further aspect of the invention there is provided a compound of formula **(I)** (as depicted above) wherein:

R^1 is selected from methyl;

R^2 is fluoro or chloro;

R^3 is selected from hydrogen, fluoro or chloro;

W is -NH-;

X is a direct bond;

Ring A is thiazolyl, quinolinyl, benzothiazolyl, pyrimidinyl or pyridinyl;

R^4 is a substituent on carbon and is selected from methoxy, hydroxy, methoxycarbonyl, fluoro, allyloxy, propoxy, *N,N*-dimethylcarbamoyl, morpholinocarbonyl, *N*-ethylcarbamoyl, *N*-(2-hydroxyethyl)carbamoyl, dimethylaminomethyl, *N*-methyl-*N*-methoxycarbamoyl, methoxymethyl, methylaminomethyl and carboxy;

R^5 is a substituent on carbon and is selected from chloro, carboxy, carbamoyl, methyl, methoxymethyl, methoxy, *N*-(1-methyl-1-phenylethyl)carbamoyl, *N*-(methoxy)carbamoyl, methoxymethyl)ethyl]amino}carbamoyl, methoxycarbonyl or ethoxycarbonyl;

n is 1; and

m is 1 or 2; wherein the values of R^5 may be the same or different;

or a pharmaceutically acceptable salt thereof.

In a further aspect of the invention there is provided a compound of formula **(I)** (as depicted above) wherein:

R^1 is selected from hydrogen or methyl;

R^2 is hydrogen, bromo, fluoro, chloro, CN, or -C=NOMe;

R^3 is selected from hydrogen, fluoro or chloro;

W is -NH-;

X is a direct bond;

Ring A is thiazolyl, quinolinyl, benzothiazolyl, pyrimidinyl or pyridinyl;

R^4 is a substituent on carbon and is selected from methoxy, hydroxy, methoxycarbonyl, fluoro, allyloxy, propoxy, *N,N*-dimethylcarbamoyl, morpholinocarbonyl, *N*-ethylcarbamoyl, *N*-(2-hydroxyethyl)carbamoyl, dimethylaminomethyl,

N-methyl-*N*-methoxycarbamoyl, methoxymethyl, methylaminomethyl, carboxy, *N*-methyl-*N*-methoxyxcarbamoyl, N-hydroxyethylcarbamoyl, hydroxymethyl, (methylthio)methyl, (methylsulfinyl)methyl, (methylsulfonyl)methyl, benzyloxy, propynyloxy, methoxyethoxy, methoxypropoxy, chloro, methyl, cyclopropylmethoxy, thiazolylmethoxy, ethoxy, oxyacetic acid, ethylaminocarbonyloxy, allylaminocarbonyloxy, pyridinylmethoxy, hydroxypropoxy, methoxy(methyl)amino, and azido;

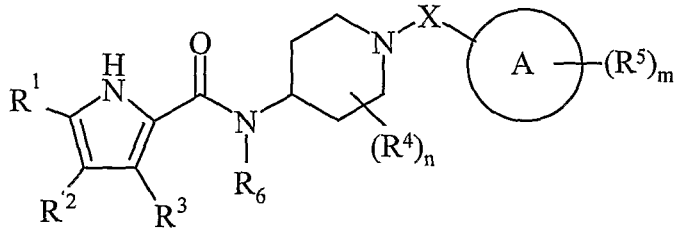
R^5 is a substituent on carbon and is selected from chloro, carboxy, carbamoyl, methyl, methoxymethyl, methoxy, *N*-(1-methyl-1-phenylethyl)carbamoyl, *N*-(methoxy)carbamoyl, methoxycarbonyl or ethoxycarbonyl, *N*-methoxycarbamoyl, formyl, (methoxyimino)methyl, isopropoxycarbonyl, ethoxy, morpholinocarbonyl, hydroxy-1-methylethyl, amino, methoxycarbonylamino, methylsulfonylamino, *N*-(1-methyl-1-phenylethyl)carbamoyl, *N*-2-morpholin-4-ylethylcarbamoyl, piperidinocarbonyl, N-methylcarbamoyl, *N*-2-hydroxyethylcarbamoyl, *N*-2-methoxyethylcarbamoyl, *N*-2-hydroxypropylcarbamoyl, *N*-2-hydroxy-1-methylethylcarbamoyl, *N*-isoxazolylcarbamoyl, *N*2,2-difluoroethylcarbamoyl, *N*-tetrahydrofuran-3-ylcarbamoyl, *N*-cyclopropylcarbamoyl, *N*-1-cyanocyclopropylcarbamoyl, *N*-2-fluorocyclopropylcarbamoyl, *N*-2-hydroxy-1,1-dimethylethylcarbamoyl, *N*-1-cyano-1-methylethylcarbamoyl, *N*-1-(hydroxymethyl-2-methoxy-2-oxoethylcarbamoyl, *N*-1,3-dioxolan-2-ylmethylcarbamoyl, *N*-3-(2-oxopyrrolidin-1-ylpropylcarbamoyl, *N*-pyridin-2-ylmethylcarbamoyl, *N*-2-(methylthio)ethylcarbamoyl, *N*-1,3-oxazol-2-ylmethylcarbamoyl, *N*-2-fluoroethylcarbamoyl, *N*-(2-hydroxy-2-methylpropyl)carbamoyl, morpholin-4-ylmethyl, *tert*-butylaminomethyl, piperidine-1-ylmethyl, (3-hydroxypyrrolidin-1-yl)methyl, (hydroxyimino)methyl, 1,1-difluoromethyl, azidomethyl, cyano(morpholin-4-yl)methyl, *N*-2-(methylsulfonyl)ethylcarbamoyl, cyano, 1-hydroxy-1-methylethyl, cyclopropylmethyl, *N*-methylcarbamoyl, *N*-1-carboxycycloproylcarbamoyl, *N*-isoxazol-3-ylcarbamoyl, *N*-prop-2-yn-1ylcarbamoyl, *N*-1-carboxy-2-hydroxymethylcarbamoyl, *N*-[3-(2-oxopyrrolidin-1-yl)propyl]carbamoyl, *N*-(2-hydroxy-2-methylpropyl)carbamoyl, *N*-methoxy-*N*-methylcarbamoyl, *N*-2-(methylsulfonyl)ethylcarbamoyl, *N*-methoxypropylcarbamoyl, and methoxymethyl)ethyl]amino}carbamoyl;

n is 1; and

m is 1 or 2; wherein the values of R^5 may be the same or different;

or a pharmaceutically acceptable salt thereof.

In a further aspect of the invention, there is provided a compound of the invention which is a compound of formula **(IA)**



(IA)

wherein:

R^1 is selected from hydrogen, halo, cyano, or C_{1-4}alkyl;

R^2 is selected from hydrogen, halo, cyano, or C_{1-4}alkyl;

R^3 is selected from hydrogen, halo, cyano, C_{1-4}alkyl, or -C=N-OH;

X is a direct bond, $-CH_2-$, -C(O)- or $S(O)_q$- (wherein q is 1 or 2);

Ring A is carbocyclyl or heterocyclyl; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^9;

R^4 and **R^5** are substituents on carbon and are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, sulfo, formyl, ureido, hydroxyiminomethyl, C_{1-4}alkoxyiminomethyl, *N*-hydroxyformamido, C_{1-4}hydrazino, hydrazinocarbonyl, *N*-hydroxyethanimidoyl, amino(hydroxyimino)methyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, *N*-(C_{1-4}alkoxy)carbamoyl, *N'*-(C_{1-4}alkyl)ureido, *N',N'*-(C_{1-4}alkyl)$_2$ureido, *N*-(C_{1-4}alkyl)-*N*-(C_{1-4}alkoxy)carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, C_{1-4}alkoxycarbonylamino, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, C_{1-4}alkylsulphonylaminocarbonyl, *N'*-(C_{1-4}alkyl)hydrazinocarbonyl, *N',N'*-(C_{1-4}alkyl)$_2$hydrazinocarbonyl, carbocyclyl-R^{10}- or heterocyclyl-R^{11}—; wherein R^4 and R^5 independently of each other may be optionally substituted on carbon by one or more R^{12}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{13};

R^6 is hydrogen or C_{1-4}alkyl;

n is 1-4; wherein the values of R^4 may be the same or different;

m is 0-4; wherein the values of R^5 may be the same or different;

R^{12} is selected from azido, halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy,

C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, N-(C_{1-4}alkyl)amino, N,N-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, N-(C_{1-4}alkyl)carbamoyl, N,N-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, N-(C_{1-4}alkyl)sulphamoyl, N,N-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, C_{1-4}alkoxycarbonylamino, carbocyclyl-R^{14}- or heterocyclyl-R^{15}-; wherein R^{12} independently of each other may be optionally substituted on carbon by one or more R^{16}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{17};

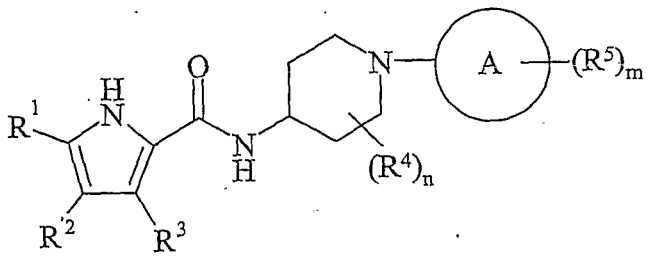
R^9, **R^{13}** and **R^{17}** are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

R^{10}, **R^{11}**, **R^{14}** and **R^{15}** are independently selected from a direct bond, -O-, -N(R^{18})-, -C(O)-, -N(R^{19})C(O)-, -C(O)N(R^{20})-, -S(O)$_p$-, -SO$_2$N(R^{21})- or -N(R^{22})SO$_2$-; wherein R^{18}, R^{19}, R^{20}, R^{21} and R^{22} are independently selected from hydrogen or C_{1-4}alkyl and p is 0-2;

R^{16} is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, ethenyl, ethynyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

or a pharmaceutically acceptable salt thereof.

In a further aspect of the invention, there is provided a compound of formula **(IA)** which is a compound of formula **(IB)**:



(IB)

wherein:

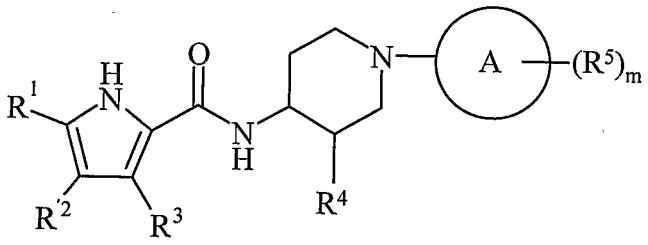
R^4 is a substituent on carbon and is selected from methoxy, hydroxy, methoxycarbonyl, fluoro, allyloxy, propoxy, *N,N*-dimethylcarbamoyl, morpholinocarbonyl, *N*-ethylcarbamoyl, *N*-(2-hydroxyethyl)carbamoyl, dimethylaminomethyl, *N*-methyl-*N*-methoxycarbamoyl, methoxymethyl, methylaminomethyl, carboxy, *N*-methyl-*N*-methoxyxcarbamoyl, N-hydroxyethylcarbamoyl, hydroxymethyl, (methylthio)methyl, (methylsulfinyl)methyl, (methylsulfonyl)methyl, benzyloxy, propynyloxy, methoxyethoxy, methoxypropoxy, chloro, methyl, cyclopropylmethoxy, thiazolylmethoxy, ethoxy, oxyacetic acid, ethylaminocarbonyloxy, allylaminocarbonyloxy, pyridinylmethoxy, hydroxypropoxy, methoxy(methyl)amino, and azido;

R^5 is a substituent on carbon and is selected from chloro, carboxy, carbamoyl, methyl, methoxymethyl, methoxy, *N*-(1-methyl-1-phenylethyl)carbamoyl, *N*-(methoxy)carbamoyl, methoxycarbonyl or ethoxycarbonyl, *N*-methoxycarbamoyl, formyl, (methoxyimino)methyl, isopropoxycarbonyl, ethoxy, morpholinocarbonyl, hydroxy-1-methylethyl, amino, methoxycarbonylamino, methylsulfonylamino, *N*-(1-methyl-1-phenylethyl)carbamoyl, *N*-2-morpholin-4-ylethylcarbamoyl, piperidinocarbonyl, N-methylcarbamoyl, *N*-2-hydroxyethylcarbamoyl, *N*-2-methoxyethylcarbamoyl, *N*-2-hydroxypropylcarbamoyl, *N*-2-hydroxy-1-methylethylcarbamoyl, *N*-isoxazolylcarbamoyl, *N*2,2-difluoroethylcarbamoyl, *N*-tetrahydrofuran-3-ylcarbamoyl, *N*-cyclopropylcarbamoyl, *N*-1-cyanocyclopropylcarbamoyl, *N*-2-fluorocyclopropylcarbamoyl, *N*-2-hydroxy-1,1-dimethylethylcarbamoyl, *N*-1-cyano-1-methylethylcarbamoyl, *N*-1-(hydroxymethyl-2-methoxy-2-oxoethylcarbamoyl, *N*-1,3-dioxolan-2-ylmethylcarbamoyl, *N*-3-(2-oxopyrrolidin-1-ylpropylcarbamoyl, *N*-pyridin-2-ylmethylcarbamoyl, *N*-2-(methylthio)ethylcarbamoyl, *N*-1,3-oxazol-2-ylmethylcarbamoyl, *N*-2-fluoroethylcarbamoyl, *N*-(2-hydroxy-2-methylpropyl)carbamoyl, morpholin-4-ylmethyl, *tert*-butylaminomethyl, piperidine-1-ylmethyl, (3-hydroxypyrrolidin-1-yl)methyl, (hydroxyimino)methyl, 1,1-difluoromethyl, azidomethyl, cyano(morpholin-4-yl)methyl, *N*-2-(methylsulfonyl)ethylcarbamoyl, cyano, 1-hydroxy-1-methylethyl, cyclopropylmethyl, *N*-methylcarbamoyl, *N*-1-carboxycycloproylcarbamoyl, *N*-isoxazol-3-ylcarbamoyl, *N*-prop-2-yn-1ylcarbamoyl, *N*-1-carboxy-2-hydroxymethylcarbamoyl, *N*-[3-(2-oxopyrrolidin-1-yl)propyl]carbamoyl, *N*-(2-hydroxy-2-methylpropyl)carbamoyl, *N*-methoxy-*N*-methylcarbamoyl, *N*-2-(methylsulfonyl)ethylcarbamoyl, *N*-methoxypropylcarbamoyl, and methoxymethyl)ethyl]amino}carbamoyl;

n is 1; wherein the values of R^4 may be the same or different; and

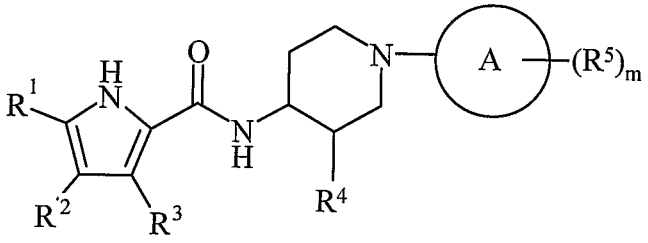
m is 1 or 2; wherein the values of R^5 may be the same or different.

In a further aspect of the invention, there is provided a compound of formula **(IB)** which is a compound of formula **(IC)**.



(IC)

In a further aspect of the invention, there is provided a compound of formula **(IC)** which is a compound of formula **(ID)**:

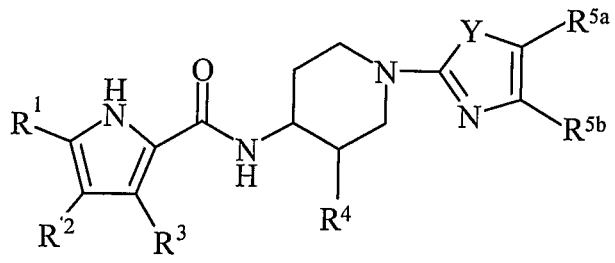


(ID)

wherein:

Ring A is heterocyclyl; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl.

In a further aspect of the invention, there is provided a compound of formula **(ID)** which is a compound of formula **(IE)**:



(IE)

wherein:

Y is N-H, N-C_{1-4}alkyl, S, or O;

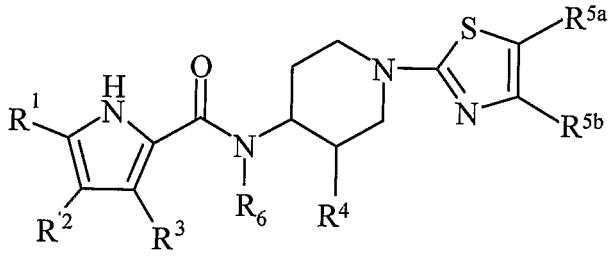
$\mathbf{R^{5a}}$ is H or as defined for R^5;

$\mathbf{R^{5b}}$ is H or as defined for R^5; or

$\mathbf{R^{5a}}$ and $\mathbf{R^{5b}}$ taken together with the carbons to which they are attached form a 6-membered carbocyclyl ring substituted by one or two groups selected from R^{14} which may be the same or different;

$\mathbf{R^{14}}$ is selected from a direct bond, -O-, -N(R^{18})-, -C(O)-, -N(R^{19})C(O)-, -C(O)N(R^{20})-, -$S(O)_p$-, -SO_2N(R^{21})- or -N(R^{22})SO_2-; wherein R^{18}, R^{19}, R^{20}, R^{21} and R^{22} are independently selected from hydrogen or C_{1-4}alkyl and p is 0-2.

In a further aspect of the invention, there is provided a compound of formula **(IE)** which is a compound of formula **(IF)**:



(IF)

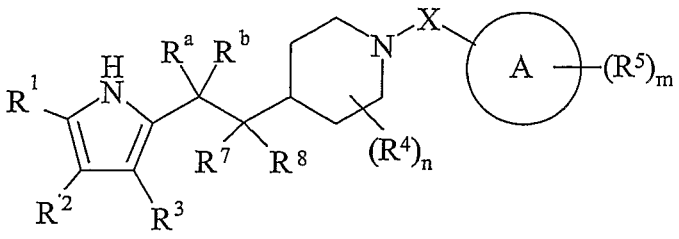
Particular compounds of the invention are the compounds of the Examples, each of which provides a further independent aspect of the invention. In further aspects, the present invention also comprises any two or more compounds of the Examples.

In one embodiment of the invention are provided compounds of formula **(I)**, in an alternative embodiment are provided pharmaceutically-acceptable salts of compounds of formula **(I)**.

In a further aspect the present invention provides a process for preparing a compound of formula **(I)** or a pharmaceutically-acceptable salt thereof.

Thus, the present invention also provides that the compounds of the formula **(I)** and pharmaceutically-acceptable salts thereof, can be prepared by a process as follows (wherein the variables are as defined above unless otherwise stated)

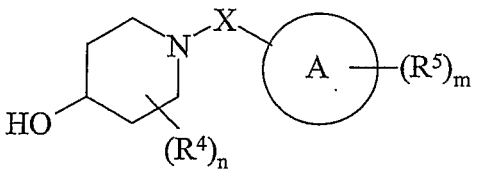
Process a) for compounds of formula **(I)** wherein W is -C(R^7)(R^8)-; converting a compound of formula **(II)**:



(II)

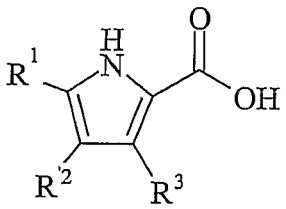
wherein R^a is cyano and R^b is dimethyamino or diethylamino; or R^a and R^b are independently selected from C_{1-4}alkylthio; or R^a and R^b together form 1,3-dithianyl or 1,3-dithiolanyl; into a compound of formula **(I)**;

Process b) for compounds of formula **(I)** wherein W is -O-; reacting a compound of formula **(III)**:



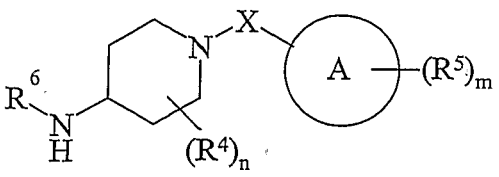
(III)

with a compound of formula **(IV)**:



(IV)

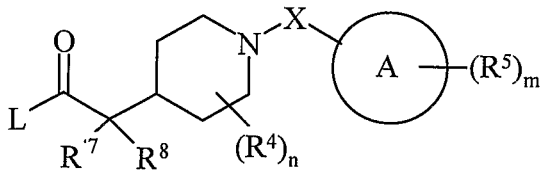
Process c) for compounds of formula **(I)** wherein W is -N(R^6)-; reacting a compound of formula **(V)**:



(V)

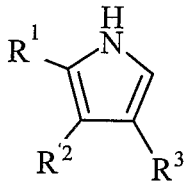
with a compound of formula **(IV)** or an activated acid derivative thereof;

Process d) for compounds of formula **(I)** wherein W is -C(R^7)(R^8)-; reacting a compound of formula **(VI)**:



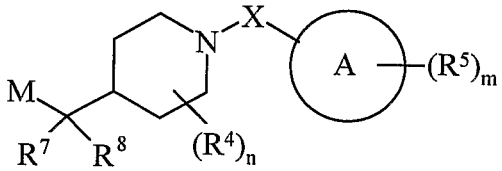
(VI)

wherein L is a displaceable group; with a compound of formula **(VII)**:



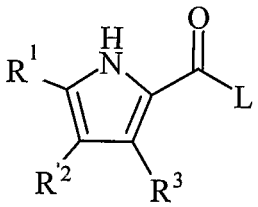
(VII)

Process e) for compounds of formula **(I)** wherein W is -C(R^7)(R^8)-; reacting a compound of formula **(VIII)**:



(VIII)

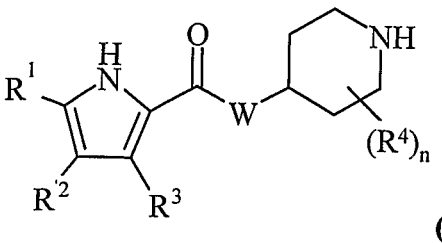
wherein M is an organometallic group; with a compound of formula **(IX)**:



(IX)

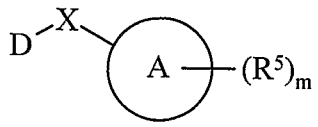
wherein L is a displaceable group;

Process f) reacting a compound of formula **(X)**:



(X)

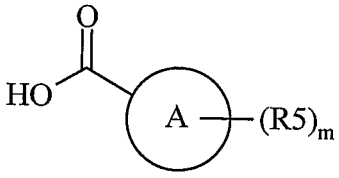
with a compound of formula **(XI)**:



(XI)

wherein D is a displaceable group;

Process g) for compounds of formula **(I)** wherein X is -C(O)-; reacting a compound of formula **(X)** with a compound of formula **(XII)**:



(XII)

and thereafter if necessary:

i) converting a compound of the formula **(I)** into another compound of the formula **(I)**;

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt.

L is a displaceable group. Suitable values for L include halo, for example chloro and bromo, pentafluorophenoxy and 2,5-oxopyrrolidin-1-yloxy.

D is a displaceable group. Suitable values for D include halo, for example chloro, bromo and iodo, tosylate and mesylate.

M is an organometallic group, suitable values for M include organocuprates, for example CuLi, organozincs, Zn, or a Grignard reagent for example MgG where G is halo for example chloro.

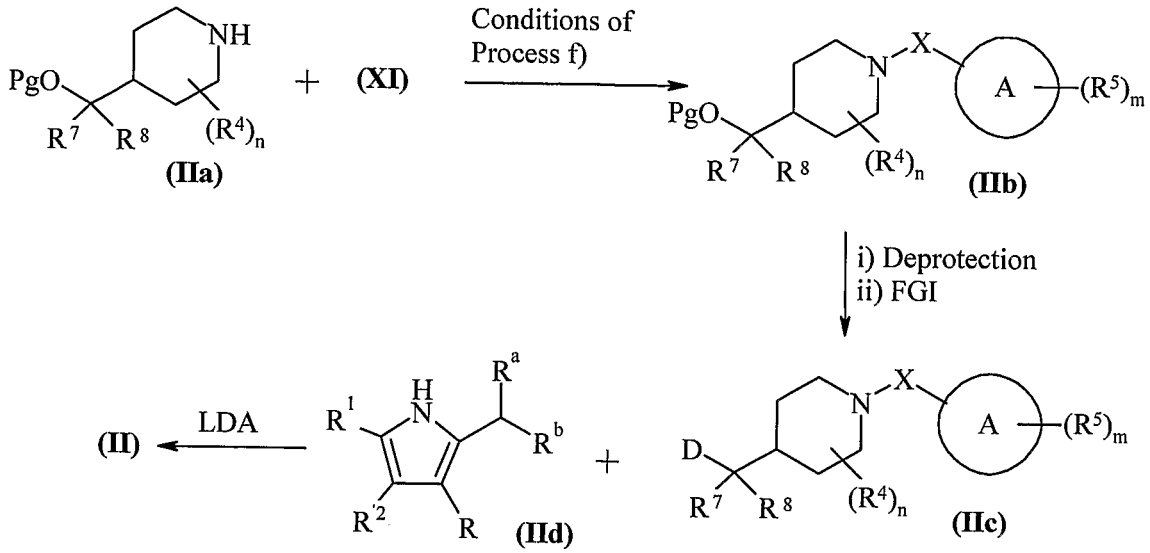
Specific reaction conditions for the above reaction are as follows.

Process a) Compounds of formula **(II)** may be converted into compounds of formula **(I)**:

(i) where R^a is cyano and R^b is dimethyamino or diethylamino; in the presence of a base for example sodium hydroxide, in a suitable solvent for example aqueous methanol at room temperature.

(ii) wherein or R^a and R^b are independently selected from C_{1-4}alkylthio; or R^a and R^b together form 1,3-dithianyl or 1,3-dithiolanyl; in the presence of a reagent such as a mercury, copper or silver salt for example $Hg(ClO_4)_2$, $CuCl_2$ or $AgNO_3/Ag_2O$ in the presence of a suitable solvent for example methanol, acetone or ethanol from a temperature ranging from room temperature to reflux.

Compounds of formula **(II)** may be prepared according to *Scheme 1*:



Scheme 1

wherein Pg is a hydroxy protecting group as defined hereinbelow; and D is a displaceable group as defined hereinabove.

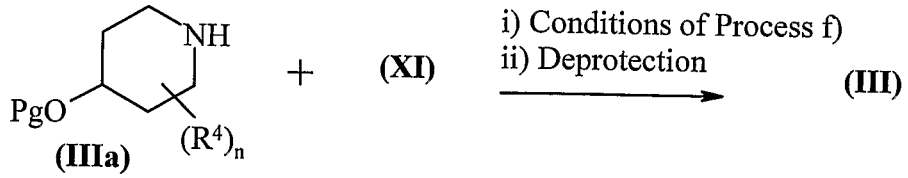
Deprotection of hydroxy protecting groups are well known in the art. Examples of such deprotections are given hereinbelow.

FGI stands for Functional Group Interconversion. In the above scheme such conversions between a hydroxy group and a D group are well known in the art and are well within the capabilities of a person skilled in the art.

Compounds of formula **(IIa)** and **(IId)** are known in the literature, or they are prepared by standard processes known in the art.

Process b) Compounds of formula **(III)** and **(IV)** may be reacted together may be reacted together in the presence of a coupling reagent, for example dicyclohexylcarbodiimide or EDC, in a suitable solvent, for example dichloromethane, THF or diethylether.

Compounds of formula **(III)** may be prepared according to *Scheme 2*:



Scheme 2

wherein Pg is a hydroxy protecting group as defined hereinbelow.

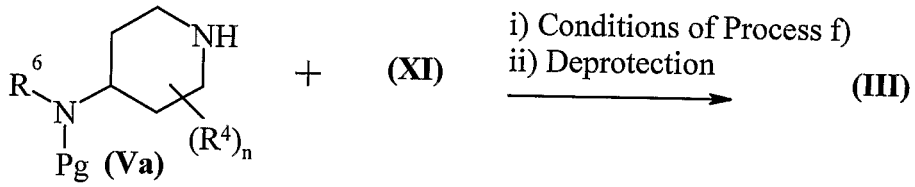
Deprotection of hydroxy protecting groups are well known in the art. Examples of such deprotections are given hereinbelow.

Compounds of formula **(IIIa)** and **(IV)** are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Process c) Compounds of formula **(V)** and **(IV)** may be coupled together in the presence of a suitable coupling reagent. Standard peptide coupling reagents known in the art can be employed as suitable coupling reagents, or for example carbonyldiimidazole and dicyclohexyl-carbodiimide, optionally in the presence of a catalyst such as dimethylaminopyridine or 4-pyrrolidinopyridine, optionally in the presence of a base for example triethylamine, pyridine, or 2,6-di-*alkyl*-pyridines such as 2,6-lutidine or 2,6-di-*tert*-butylpyridine. Suitable solvents include dimethylacetamide, dichloromethane, benzene, tetrahydrofuran and dimethylformamide. The coupling reaction may conveniently be performed at a temperature in the range of -40 to 40°C.

Suitable activated acid derivatives include acid halides, for example acid chlorides, and active esters, for example pentafluorophenyl esters. The reaction of these types of compounds with amines is well known in the art, for example they may be reacted in the presence of a base, such as those described above, and in a suitable solvent, such as those described above. The reaction may conveniently be performed at a temperature in the range of -40 to 40°C.

Compounds of formula **(V)** may be prepared according to *Scheme 3*:



Scheme 3

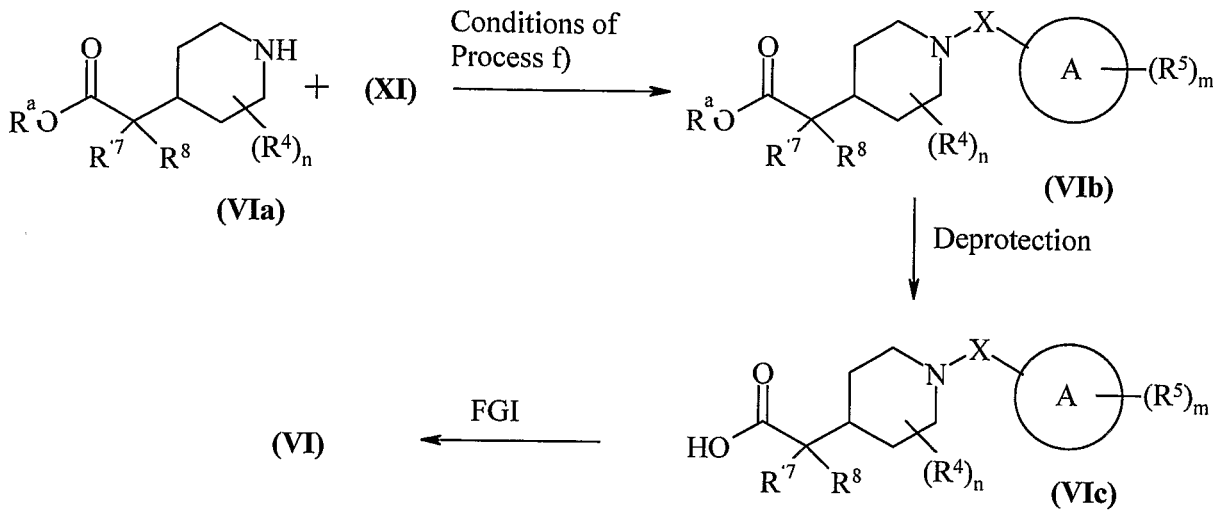
wherein Pg is a amino protecting group as defined hereinbelow. The skilled reader will appreciate that where R^6 is hydrogen, this hydrogen also needs protecting by way of a suitable protecting group.

Deprotection of amino protecting groups are well known in the art. Examples of such deprotections are given hereinbelow.

Compounds of formula **(Va)** are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Process d) Compounds of formula **(VI)** and **(VII)** may be reacted in a suitable solvent such a DCM or 1,2-dichloroethane, optionally in the presence of a Lewis acid, for example $AlCl_3$, from 0 °C to room temperature.

Compounds of formula **(VI)** may be prepared according to *Scheme 4*:



Scheme 4

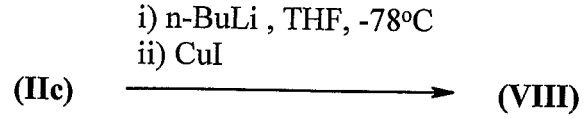
wherein $R^aOC(O)$ is an ester group.

Suitable values for R^a include C_{1-6}alkyl. Deprotection of the R^a carboxy protecting group may be achieved under standard conditions, for example acid or base hydrolysis, such as those conditions give hereinbelow.

FGI stands for Functional Group Interconversion. In the above scheme such conversions between an acid group and a -C(O)L group are well known in the art and are well within the capabilities of a person skilled in the art.

Compounds of formula **(VIa)** and **(VII)** are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art. *Process e)* Compounds of formula **(VIII)** and **(IX)** may be reacted in a suitable aprotic solvent such as THF or ether, at temperatures in the range of -78 °C to 0 °C.

Compounds of formula **(VIII)** may be prepared from compounds of formula **(IIc)** under standard conditions known in the art. For example where M is an organocuprous reagent such compounds could be prepared according to *Scheme 5*:

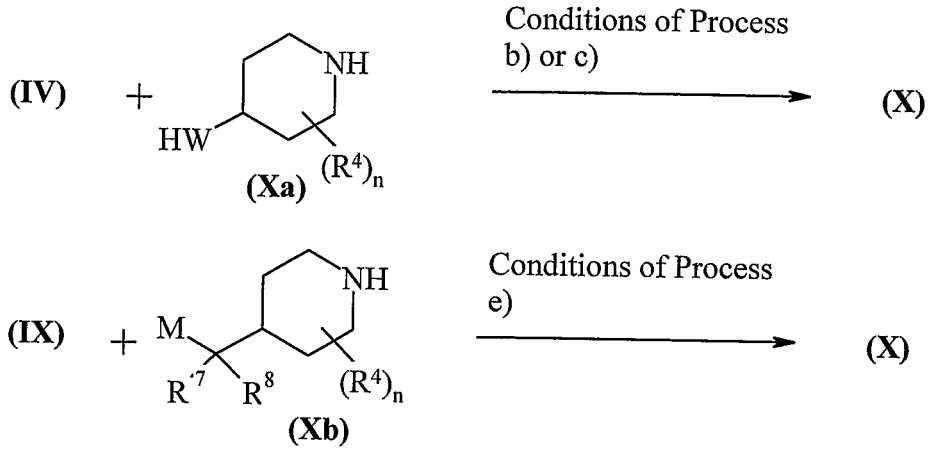


Scheme 5

Compounds of formula **(IX)** are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Process f) Compounds of formula **(X)** and **(XI)** may be reacted in a suitable solvent such as DMF, *N*-methylpyrrolidinone or dimethylacetamide in the presence of a base such as triethylamine or diisopropylethylamine under thermal conditions or a microwave reactor.

Compounds of formula **(X)** may be prepared according to *Scheme 6*:



Scheme 6

wherein M is an organometallic group as defined hereinabove.

Compounds of formula **(Xa)**, **(Xb)** and **(XI)** are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

Process g) Compounds of formula **(X)** and **(XII)** may be coupled together under the conditions outlined in *Process c)*.

Compounds of formula **(XII)** are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

The formation of a pharmaceutically-acceptable salt is within the skill of an ordinary organic chemist using standard techniques.

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. The reagents used to introduce such ring substituents are either commercially available or are made by processes known in the art.

Introduction of substituents into a ring may convert one compound of the formula **(I)** into another compound of the formula **(I)**. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents , oxidation of substituents, esterification of

substituents, amidation of substituents, formation of heteroaryl rings. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of alkoxides, diazotization reactions followed by introduction of thiol group, alcohol group, halogen group. Examples of modifications include; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

The skilled organic chemist will be able to use and adapt the information contained and referenced within the above references, and accompanying Examples therein and also the Examples herein, to obtain necessary starting materials, and products. If not commercially available, the necessary starting materials for the procedures such as those described above may be made by procedures which are selected from standard organic chemical techniques, techniques which are analogous to the synthesis of known, structurally similar compounds, or techniques which are analogous to the above described procedure or the procedures described in the examples. It is noted that many of the starting materials for synthetic methods as described above are commercially available and/or widely reported in the scientific literature, or could be made from commercially available compounds using adaptations of processes reported in the scientific literature. The reader is further referred to Advanced Organic Chemistry, 4th Edition, by Jerry March, published by John Wiley & Sons 1992, for general guidance on reaction conditions and reagents.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in compounds. The instances where protection is necessary or desirable are known to those skilled in the art, as are suitable methods for such protection. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Greene, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991).

Examples of a suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, a silyl group such as trimethylsilyl or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively a silyl group such as trimethylsilyl may be removed, for example, by fluoride or by aqueous acid; or an arylmethyl

group such as a benzyl group may be removed, for example, by hydrogenation in the presence of a catalyst such as palladium-on-carbon.

A suitable protecting group for an amino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine or 2-hydroxyethylamine, or with hydrazine.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art, or they may be removed during a later reaction step or work-up.

When an optically active form of a compound of the invention is required, it may be obtained by carrying out one of the above procedures using an optically active starting material (formed, for example, by asymmetric induction of a suitable reaction step), or by resolution of a racemic form of the compound or intermediate using a standard procedure, or by chromatographic separation of diastereoisomers (when produced). Enzymatic techniques may also be useful for the preparation of optically active compounds and/or intermediates.

Similarly, when a pure regioisomer of a compound of the invention is required, it may be obtained by carrying out one of the above procedures using a pure regioisomer as a starting material, or by resolution of a mixture of the regioisomers or intermediates using a standard procedure.

Enzyme Potency Testing Methods

Compounds were tested for inhibition of GyrB ATPase activity using an ammonium molybdate/malachite green-based phosphate detection assay (Lanzetta, P. A., L. J. Alvarez, P. S. Reinach, and O. A. Candia, 1979, 100: 95-97). Assays were performed in multiwell plates in 100µl reactions containing: 50 mM TRIS buffer pH 7.5, 75 mM ammonium acetate, 5.5 mM magnesium chloride, 0.5 mM ethylenediaminetetraacetic acid, 5% glycerol, 1 mM 1,4-Dithio-DL-threitol, 200 nM bovine serum albumin, 16 µg/ml sheared salmon sperm DNA, 4 nM *E. coli* GyrA, 4 nM *E. coli* GyrB, 250 µM ATP, and compound in dimethylsulfoxide. Reactions were quenched with 150 µl of ammonium molybdate/malachite green detection reagent containing 1.2 mM malachite green hydrochloride, 8.5 mM ammonium molybdate tetrahydrate, and 1 M hydrochloric acid. Plates were read in an absorbance plate reader at 625 nm and percent inhibition values were calculated using dimethylsulfoxide (2%)-containing reactions as 0% inhibition and novobiocin-containing (2 µM) reactions as 100% inhibition controls. Compounds were tested for inhibition of topoisomeraseIV ATPase activity as described above for GyrB except the 100µl reactions contained the following: 20 mM TRIS buffer pH 8, 50 mM ammonium acetate, 8 mM magnesium chloride, 5% glycerol, 5 mM 1,4-Dithio-DL-threitol, 0.005% Brij-35, 5 µg/ml sheared salmon sperm DNA, 10 nM *E. coli* GyrA, 10 nM *E. coli* GyrB, 160 µM ATP, and compound in dimethylsulfoxide. Compound potency was based on IC_{50} measurements determined from reactions performed in the presence of 10 different compound concentrations.

Compounds of the Examples generally have IC_{50} values of <20µg/ml.

Bacterial Susceptibility Testing Methods

Compounds were tested for antimicrobial activity by susceptibility testing in liquid media. Compounds were dissolved in dimethylsulfoxide and tested in 10 doubling dilutions in the susceptibility assays. The organisms used in the assay were grown overnight on suitable agar media and then suspended in a liquid medium appropriate for the growth of the

organism. The suspension was a 0.5 McFarland and a further 1 in 10 dilution was made into the same liquid medium to prepare the final organism suspension in 100 μL. Plates were incubated under appropriate conditions at 37 degrees C for 24 hrs prior to reading. The Minimum Inhibitory Concentration was determined as the lowest drug concentration able to reduce growth by 80% or more.

Example 48 had an MIC of 0.13μg/ml against *Streptococcus pneumoniae*. Other examples areprovided in the following table.

Example No.	MIC HIN446	MIC MCA445	MIC SPN548	MIC SAU516	MIC EFM073
333	4	0.13	0.063	2	0.5
60	4	0.25	2	2	8
315	2	0.13	0.5	4	4
345	0.25	0.031	0.03	0.5	0.13
294	0.031	0.001	0.0039	0.031	0.016

According to a further feature of the invention there is provided a compound of the formula **(I)**, or a pharmaceutically-acceptable salt thereof for use in a method of treatment of the human or animal body by therapy.

We have found that compounds of the present invention inhibit bacterial DNA gyrase and topoisomeraseIV and are therefore of interest for their antibacterial effects.

According to a further feature of the present invention there is provided a method for producing an antibacterial effect in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the present invention, or a pharmaceutically-acceptable salt thereof.

According to a further feature of the invention there is provided a method for inhibition of bacterial DNA gyrase and/or topoisomeraseIV in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula **(I)** or a pharmaceutically acceptable salt thereof as defined hereinbefore.

According to a further feature of the invention there is provided a method of treating a bacterial infection in a warm-blooded animal, such as a human being, in need of such

treatment which comprises administering to said animal an effective amount of a compound of formula **(I)** or a pharmaceutically acceptable salt thereof as defined hereinbefore.

A further feature of the present invention is a compound of formula **(I)** and pharmaceutically acceptable salts thereof for use as a medicament. Suitably the medicament is an antibacterial agent.

According to a further aspect of the invention there is provided the use of a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the production of an anti-bacterial effect in a warm-blooded animal such as a human being.

According to a further aspect of the invention there is provided the use of a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in inhibition of bacterial DNA gyrase and/or topoisomeraseIV in a warm-blooded animal such as a human being.

Thus according to a further aspect of the invention there is provided the use of a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of a bacterial infection in a warm-blooded animal such as a human being.

According to a further aspect of the invention there is provided a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof for use in the production of an anti-bacterial effect in a warm-blooded animal such as a human being.

According to a further aspect of the invention there is provided a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof for use in inhibition of bacterial DNA gyraseand/or topoisomeraseIV in a warm-blooded animal such as a human being.

Thus according to a further aspect of the invention there is provided a compound of formula **(I)**, or a pharmaceutically acceptable salt thereof for use in the treatment of a bacterial infection in a warm-blooded animal such as a human being.

In order to use a compound of the formula **(I)** or a pharmaceutically-acceptable salt thereof, (hereinafter in this section relating to pharmaceutical composition "a compound of this invention") for the therapeutic (including prophylactic) treatment of mammals including humans, in particular in treating infection, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Therefore in another aspect the present invention provides a pharmaceutical composition that comprises a compound of the formula **(I)** or a pharmaceutically-acceptable salt thereof, and a pharmaceutically-acceptable diluent or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition that comprises a compound of formula **(I)** as defined hereinbefore or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable excipient or carrier for use in producing an anti-bacterial effect in an warm-blooded animal, such as a human being.

According to a further aspect of the invention there is provided a pharmaceutical composition that comprises a compound of formula **(I)** as defined hereinbefore or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable excipient or carrier for use in inhibition of bacterial DNA gyrase and/or topoisomeraseIV in an warm-blooded animal, such as a human being.

According to a further aspect of the invention there is provided a pharmaceutical composition that comprises a compound of formula **(I)** as defined hereinbefore or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable excipient or carrier for use in the treatment of a bacterial infection in an warm-blooded animal, such as a human being.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for

example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions

may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

In addition to the compounds of the present invention the pharmaceutical composition of this invention may also contain or be co-administered (simultaneously, sequentially or separately) with one or more known drugs selected from other clinically useful antibacterial agents (for example, macrolides, quinolones, ß-lactams or aminoglycosides) and/or other anti-infective agents (for example, an antifungal triazole or amphotericin). These may include carbapenems, for example meropenem or imipenem, to broaden the therapeutic effectiveness. Compounds of this invention may also contain or be co-administered with bactericidal/permeability-increasing protein (BPI) products or efflux pump inhibitors to improve activity against gram negative bacteria and bacteria resistant to antimicrobial agents.

As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular disease state will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. Preferably a daily dose in the range of 1-50 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the

illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

In addition to its use in therapeutic medicine, compounds of formula **(I)** and their pharmaceutically acceptable salts are also useful as pharmacological tools in the development and standardisation of in-vitro and in-vi*vo* test systems for the evaluation of the effects of inhibitors of DNA gyrase in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

In the above other, pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and particular embodiments of the compounds of the invention described herein also apply.

Examples

The invention is now illustrated but not limited by the following Examples in which unless otherwise stated :-

(i) evaporations were carried out by rotary evaporation in-vacuo and work-up procedures were carried out after removal of residual solids by filtration;

(ii) operations were carried out at ambient temperature, that is typically in the range 18-26 °C and without exclusion of air unless otherwise stated, or unless the skilled person would otherwise work under an inert atmosphere;

(iii) column chromatography (by the flash procedure) was used to purify compounds and was performed on Merck Kieselgel silica (Art. 9385) unless otherwise stated;

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) the structure of the end-products of the invention were generally confirmed by NMR and mass spectral techniques [proton magnetic resonance spectra is quoted and was generally determined in DMSO-d_6 unless otherwise stated using a Bruker DRX-300 spectrometer operating at a field strength of 300 MHz. Chemical shifts are reported in parts per million downfield from tetramethysilane as an internal standard (δ scale) and peak multiplicities are shown thus: s, singlet; d, doublet; AB or dd, doublet of doublets; dt, doublet of triplets; dm, doublet of multiplets; t, triplet, m, multiplet; br, broad; fast-atom bombardment (FAB) mass spectral data were generally obtained using a Platform spectrometer (supplied by Micromass) run in electrospray and, where appropriate, either positive ion data or negative ion data were collected]or using Agilent 1100series LC/MSD equipped with Sedex 75ELSD, run in APCI mode and, where appropriate, either positive ion data or negative ion data were collected;

optical rotations were determined at 589 nm at 20 °C using a Perkin Elmer Polarimeter 341; reverse phase HPLC was carried out using YMC Pack ODS-AQ(100x20 mmID, S-5μ particle size, 12 nm pore size);

(vi) each intermediate was purified to the standard required for the subsequent stage and was characterised in sufficient detail to confirm that the assigned structure was correct; purity was assessed by HPLC, TLC, or NMR and identity was determined by infra-red spectroscopy (IR), mass spectroscopy or NMR spectroscopy as appropriate;

(vii) in which the following abbreviations may be used :-

DMF is N,N-dimethylformamide; DMA is N,N-dimethylacetamide; TLC is thin layer chromatography; HPLC is high pressure liquid chromatography; DMSO is dimethylsulfoxide; $CDCl_3$ is deuterated chloroform; MS is mass spectroscopy; APCI is atmospheric pressure chemical ionisation; EtOAc is ethyl acetate; MeOH is methanol; DIEA is diisopropylethlamine; TFA is trifluoroacetic acid; HATU is N-[(dimethylamino)-1H,2,3-triazolo[4,5-b-]pyridin-1-ylmethylene]-N-methylmethanaminium hexafluorophosphate N-oxide; HOAT is 1-hydroxy-7-azabenzotriazole; NMP is N-methylpyrrolidinone; THF is tetrahydrofuran; EtOH is ethanol; LCMS is liquid chromatography/mass spectrometry; DCM is dichloromethane;

(viii) temperatures are quoted as °C;

(ix) Smith Microwave Synthesizer refers to an equipment that uses microwave energy to heat organic reactions in a short period of time; it was used according to the manufacturers instruction and was obtained from Personal Chemistry Uppsala AB;

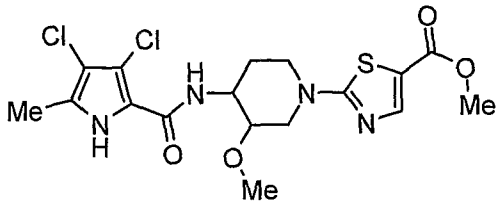
(x) Kugelrohr distillation refers to a piece of equipment that distils liquids and heats sensitive compounds using air-bath oven temperature; it was used according to the manufacturers instruction and was obtained from Buchi, Switzerland or Aldrich, Milwaukee, USA;

(xi) Where cis(±) or trans(±) is used it is to be understood that this refers to a racemic mixture of the cis or the trans isomers, (-) or (+) refers to the single enantiomer as does R,R or S,S where quoted. Rotations were measured for the first chiral compound in the synthetic scheme (see for example Intermediates 57 and 58) by measuring the rotation of the effluent from the chiral column, using a Perkin Elmer Polarimeter 341, at the point at which the enantiomer eluted, the nomenclature cis(-) or cis (+) was then continued for all the compounds in the synthesis (for example, Example 42 is the final compound in the synthesis which started from Intermediate 57); and

(xii) GCMS is Gas phase chromatography (model 6890N) with Mass Spectrometer(model 5973) manufactured by Agilent and was used according to manufacturers instructions.

Example 1

Cis(±)methyl 2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate



Method 1

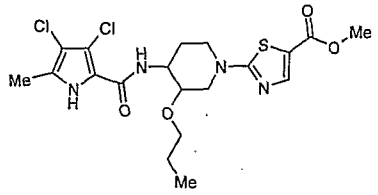
Cis(±)3,4-dichloro-N-(3-methoxypiperidin-4-yl)-5-methyl-1H-pyrrole-2-carboxamide (Intermediate 50; 380 mg), methyl 2-bromo-1,3-thiazole-5-carboxylate (276 mg), were dissolved in anhydrous DMA (5 ml). DIEA (216 µl) was added and the mixture was heated at 120 °C for 7 hours (h). The mixture was diluted with EtOAc, washed well with citrate buffer, water, brine, and dried over Na_2SO_4. The organic phase was concentrated in vacuo to give the title compound as a brown solid (337 mg).

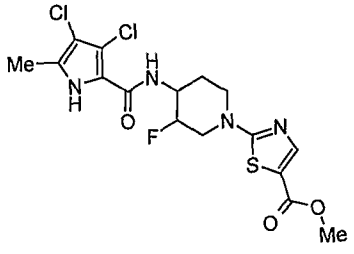
Method 2

Alternatively the title compounds were prepared using a Smith Microwave Synthesizer by subjecting the reaction mixture to single-mode microwave at 150 °C for 30 minutes (min.) or until the reaction is complete as judged by LCMS, using polar aprotic solvent such as DMA, NMP or 1-butyl-3-methyl imidazolium-tetrafluoroborate as reaction solvents. MS (ES) MH^+: 447 for $C_{17}H_{20}Cl_2N_4O_4S$; NMR: 1.65 (m, 2H), 2.09 (s, 3H), 3.07 (m, 3H), 3.48 (m, 1H), 3.63 (s, 3H), 3.86 (m, 1H), 4.15 (m, 2H), 6.91 (d, 1H), 7.45 (s, 1H), 11.19 (s, 1H).

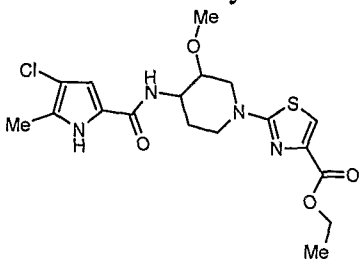
Examples 2-33

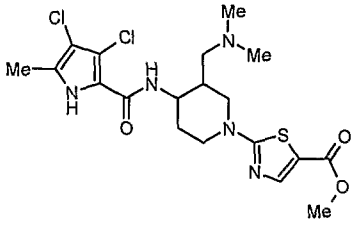
The following Examples were prepared by the procedure described in Example 1 from the starting materials (SM) indicated.

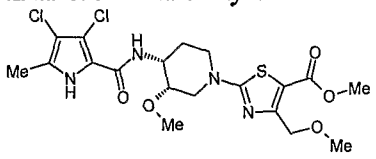
Ex	Compound	Data	SM
2	methyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+:447 for $C_{17}H_{20}Cl_2N_4O_4S$; NMR: 1.87 (m, 2H), 2.05 (m, 2H), 2.27 (s, 3H), 3.01 (m, 2H), 3.25 (s, 3H), 3.65 (m, 1H), 3.83 (s, 3H), 4.12 (m, 1H), 4.46 (m, 2H), 7.40 (d, 1H), 8.00 (s, 1H), 12.38 (s, 1H)	Intermediate 51 and methyl 2-bromo-1,3-thiazole-5-carboxylate
3	methyl 2-((3*R*,4*S*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5- carboxylate	MS (ES) MH^+:447 for $C_{17}H_{20}Cl_2N_4O_4S$; NMR:1.89 (m, 2H), 2.11 (m, 2H), 2.23 (s, 3H), 3.33 (m, 2H), 3.46 (s, 3H), 3.59 (m, 1H), 3.85 (s, 3H), 4.09 (m, 1H), 4.46 (m, 2H), 7.31 (d, 1H), 7.92 (s, 1H), 12.30 (s, 1H)	Intermediate 52 and methyl 2-bromo-1,3-thiazole-5-carboxylate
4	Cis(±)methyl 2-(4-{[(3,4-difluoro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+:414 for $C_{17}H_{20}F_2N_4O_4S$; NMR: 1.72 (m, 2H), 1.79 (s, 3H), 2.3 (m, 2H), 3.45 (s, 3H), 3.61 (s, 1H), 3.8 (s, 3H), 4.08 (m, 1H), 4.41 (m, 2H), 6.88 (d, 1H), 8.00 (s, 1H), 11.5 (brs, 1H)	Intermediate 56 and methyl 2-bromo-1,3-thiazole-5-carboxylate
5	Cis(±)methyl 2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-propoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate 	MS (ES) MH^+:475 for $C_{19}H_{24}Cl_2N_4O_4S$; NMR: 0.89 (m, 3H), 1.54 (m, 2H), 1.87 (m, 2H), 2.26 (s, 3H), 3.37 (m, 2H), 3.71 (m, 2H), 3.81 (s, 3H), 4.15 (m, 1H), 4.42 (m, 2H), 7.18 (d, 1H), 7.98 (s, 1H), 12.29 (s, 1H)	Intermediate 53 and methyl 2-bromo-1,3-thiazole-5-carboxylate

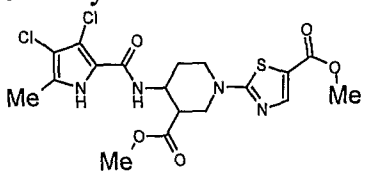
Ex	Compound	Data	SM
6	Cis(±)methyl 2-(3-(allyloxy)-4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+:473 for $C_{19}H_{22}Cl_2N_4O_4S$; NMR: 1.94 (m, 2H), 2.23 (s, 3H), 3.56 (m, 2H), 3.58 (m, 2H), 3.84 (s, 3H), 4.07 (m, 2H), 4.21 (m, 1H), 4.46 (m, 2H), 5.37 (m, 2H), 5.95 (m, 1H), 7.29 (d, 1H), 7.96 (s, 1H), 12.32 (s, 1H)	Intermediate 54 and methyl 2-bromo-1,3-thiazole-5-carboxylate
7	Cis(±)ethyl 4-(3-(allyloxy)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)quinoline-2-carboxylate	MS (ES) MH^+:531 for $C_{26}H_{28}Cl_2N_4O_4$	Intermediate 54 and Intermediate 10
8	Cis(±)ethyl 4-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-propoxypiperidin-1-yl)quinoline-2-carboxylate	MS (ES) MH^+:533 for $C_{26}H_{30}Cl_2N_4O_4$	Intermediate 53 and Intermediate 10
9	Cis(±)methyl-2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+:435, 437 for $C_{16}H_{17}Cl_2FN_4O_3S$; NMR: 1.77-1.79 (m, 2H), 2.12 (s, 3H), 3.25-3.27 (m, 2H), 3.49-3.62 (dd, 1H), 3.68 (s, 3H), 3.95 (m, 1H), 4.00-4.24 (m, 1H), 4.82-4.99 (m, 1H), 7.21 (d, 1H), 7.79 (s, 1H), 12.05 (brs, 1H)	Intermediate 32 and methyl 2-bromo-1,3-thiazole-5-carboxylate
10	Trans(±)methyl-2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-5-carboxylate 	MS (ES) MH^+:435, 437 for $C_{16}H_{17}Cl_2FN_4O_3S$	Intermediate 34 and methyl 2-bromo-1,3-thiazole-5-carboxylate

Ex	Compound	Data	SM
11	methyl 2-((3*R*,4*S*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+:435, 437 for $C_{16}H_{17}Cl_2FN_4O_3S$; NMR: 1.77-1.79 (m, 2H), 2.12 (s, 3H), 3.25-3.27 (m, 2H), 3.49-3.62 (dd, 1H), 3.68 (s, 3H), 3.95 (m, 1H), 4.00-4.24 (m, 1H), 4.82-4.99 (m, 1H), 7.21 (d, 1H), 7.79 (s, 1H), 12.05 (brs, 1H)	Intermediate 33 and methyl 2-bromo-1,3-thiazole-5-carboxylate
12	Cis(±)ethyl 2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-benzothiazole-7-carboxylate	MS (ES) MH^+:499, 501 for $C_{16}H_{17}Cl_2FN_4O_3S$	Intermediate 32 and ethyl 2-bromo-1,3-benzothiazole-7-carboxylate (US Pat 5770758)
13	Cis(±)Ethyl 2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylate	MS (ES) MH^+:511, 513 for $C_{22}H_{24}Cl_2N_4O_4S$; NMR: 1.45 (t, 3H), 1.87 (m, 2H), 3.44 (s, 3H), 3.46 (m, 2H), 3.67 (m, 1H), 4.23 (m, 1H), 4.28 (m, 1H), 4.36 (m, 1H), 4.47 (q, 2H), 7.27 (d, 1H), 7.50 (t, 1H), 7.77 (t, 1H0, 12.26 (s, 1H)	Intermediate 50 and ethyl 2-bromo-1,3-benzothiazole-7-carboxylate (US Pat 5770758)
14	Cis(±)Methyl 2-chloro-6-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)pyrimidine-4-carboxylate	MS (ES) MH^+:477, 479for $C_{18}H_{20}Cl_3N_5O_4$; NMR: 1.62 (m, 1H), 1.77 (m, 1H), 2.18 (s, 3H), 3.15 (m, 1H), 3.28 (s, 3H), 3.56 (m, 1H), 3.87 (s, 3H), 4.11 (m, 1H), 4.30 (m, 1H), 5.00 (m, 1H), 7.15 (m, 1H0, 7.36-7.48 (m, 1H), 12.16 (m, 1H)	Intermediate 50 and methyl 2,6-dichloropyrimidine-4-carboxylate

Ex	Compound	Data	SM
15	Cis(±)Ethyl 2-(4-{[(4-chloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-4-carboxylate 	MS (ES) MH^+:427, 429 for $C_{18}H_{23}ClN_4O_3$; NMR: 1.27 (t, 3H), 1.60 (m, 1H), 1.93 (m, 1H), 2.14 (s, 3H), 3.23 (m, 1H), 3.28 (s, 3H), 3.43 (m, 1H), 3.53 (m, 1H), 3.85 (m, 1H), 4.12 (m, 1H), 4.24 (m, 2H), 6.89 (s, 1H)	Intermediate 55 and ethyl 2-bromo-1,3-thiazole-4-carboxylate
16	Cis(±)ethyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-4-carboxylate	MS (ES) (M +H): 461, 463 for $C_{18}H_{22}Cl_2N_4O_4S$	Intermediate 50 and ethyl 2-bromo-1,3-thiazole-4-carboxylate
17	Cis(±)ethyl 4-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)pyridine-2-carboxylate	MS (ES) MH^+: 455 for $C_{20}H_{24}Cl_2N_4O_4$	Intermediate 50 and ethyl 4-chloropyridine-2-carboxylate (WO 2004007657)
18	Cis(±)methyl 2-[4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(methoxymethyl)piperidin-1-yl]-1,3-thiazole-5-carboxylate	MS (ES) MH^+:461 for $C_{18}H_{22}Cl_2N_4O_4S$	Intermediate 74 and methyl-2-bromothiazole-5-carboxylate
19	Cis(±)methyl-2-{4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-[(methylamino)methyl]piperidin-1-yl}-1,3-thiazole-5-carboxylate	MS (ES) MH^+:460 for $C_{18}H_{23}Cl_2N_5O_3S$	Intermediate 75 and methyl-2-bromothiazole-5-carboxylate

Ex	Compound	Data	SM
20	Cis(±)methyl 2-{4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-[(dimethylamino)methyl]piperidin-1-yl}-1,3-thiazole-5-carboxylate 	MS (ES) MH^+:474 for $C_{19}H_{25}Cl_2N_5O_3S$	Intermediate 76 and methyl-2-bromothiazole-5-carboxylate
21	Cis(±)methyl-2-(4-{[(4-chloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(1-methyl-1-phenylethyl)amino]carbonyl}-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 574 for $C_{27}H_{32}ClN_5O_5S$	Intermediate 16 and Intermediate 55
22	Cis(±)methyl-2-(4-{[(4-chloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 413 for $C_{17}H_{21}ClN_4O_4S$; NMR: 1.63 (s, 1H), 1.90 (s, 1H), 2.14 (s, 3H), 3.28 (s, 3H), 3.39 (s, 1H), 3.47 (s, 2H), 3.74 (s, 3H), 3.93 (s, 1H), 4.21 (s, 2H), 6.89 (d, *J*=2.64 Hz, 1H), 7.71 (d, *J*=7.91 Hz, 1H), 7.84 (s, 1H), 11.64 (s, 1H)	Intermediate 55 and methyl 2-bromo-1,3-thiazole-5-carboxylate
23	Cis(±)methyl-2-chloro-6-(4-{[(4-chloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)pyrimidine-4-carboxylate	MS (ES) MH^+: 442 for $C_{18}H_{21}Cl_2N_5O_4$; NMR: 1.63 (s, 1H), 1.79 (s, 1H), 2.09 - 2.20 (m, 3H), 3.08 (s, 1H), 3.17 (d, *J*=5.27 Hz, 1H), 3.25 (s, 3H), 3.30 - 3.81 - 3.89 (m, 3H), 4.22 (s, 2H), 4.91 (s, 1H), 6.87 (d, *J*=2.64 Hz, 1H), 7.37 (s, 1H), 7.67 (d, *J*=7.72 Hz, 1H), 11.62 (s, 1H)	Intermediate 55 and methyl 2,6-dichloropyrimidine-4-carboxylate

Ex	Compound	Data	SM
24	Cis(±)methyl-2-(4-{[(4-chloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(methoxymethyl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 457 for $C_{19}H_{25}ClN_4O_5S$; NMR: 1.63 (s, 1H), 1.84 - 1.99 (m, 1H), 2.12 - 2.19 (m, 3H), 3.33 (s, 3H), 3.35 - 3.38 (m, 1H), 3.52 - 3.57 (m, 1H), 3.72 (s, 3H), 3.97 (s, 1H), 4.15 - 4.29 (m, 3H), 4.52 - 4.61 (m, 2H), 6.89 (d, *J*=2.64 Hz, 1H), 7.70 (d, *J*=7.91 Hz, 1H), 11.63 (s, 1H)	Intermediate 55 and Intermediate 17
25	Cis(±)methyl-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(methoxymethyl)-1,3-thiazole-5-carboxylate 	MS (ES) MH^+: 491 for $C_{19}H_{24}Cl_2N_4O_5S$; NMR: 1.66 - 1.81 (m, 2H), 2.14 - 2.22 (m, 3H), 3.29 (s, 3H), 3.33 (s, 2H), 3.36 (s, 3H), 3.55 (s, 1H), 3.73 (s, 3H), 3.97 (s, 1H), 4.20 - 4.35 (m, 2H), 4.57 (d, *J*=1.32 Hz, 2H), 7.15 (d, *J*=8.29 Hz, 1H), 12.15 (s, 1H)	Intermediate 50 and Intermediate 17
26	Cis(±)ethyl 4-(4-{[(4-chloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)quinoline-2-carboxylate	MS (ES) MH^+: 471 for $C_{24}H_{27}ClN_4O_4$; NMR: 1.38 (t, *J*=7.06 Hz, 3H), 1.80 (s, 1H), 2.15 (s, 3H), 3.27 (s, 3H), 3.36 - 3.42 (m, 3H), 3.64 (s, 3H), 3.84 (s, 1H), 4.41 (q, *J*=7.10 Hz, 2H), 6.95 (d, *J*=2.64 Hz, 1H), 7.57 (s, 1H), 7.69 (d, *J*=7.16 Hz, 1H), 7.73 - 7.82 (m, 2H), 8.11 (dd, *J*=17.14, 8.29 Hz, 2H), 11.65 (s, 1H)	Intermediate 55 and Intermediate 10

Ex	Compound	Data	SM
27	Cis(±)ethyl-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)isonicotinate	MS (ES) MH^+: 455 for $C_{20}H_{24}Cl_2N_4O_4$; NMR: 1.32 (t, *J*=7.06 Hz, 3H), 1.72 (d, *J*=0.75 Hz, 2H), 2.18 (s, 3H), 3.13 (d, *J*=13.38 Hz, 2H), 3.29 - 3.31 (m, 3H), 3.50 (s, 1H), 4.23 (s, 2H), 4.32 (q, *J*=7.03 Hz, 2H), 4.67 (s, 1H), 6.97 (dd, *J*=5.09, 0.94 Hz, 1H), 7.14 (d, *J*=8.10 Hz, 1H), 7.23 (s, 1H), 8.24 (d, *J*=5.09 Hz, 1H), 12.15 (s, 1H)	Intermediate 50 and ethyl 2-fluoroisonicotinate (Konno, Akinori *J. Fluorine Chemistry* (1998), 87(2), 137-140)
28	Cis(±)ethyl-4-(4-{[(4-chloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)pyridine-2-carboxylate	MS (ES) MH^+: 421 for $C_{20}H_{25}ClN_4O_4$; NMR: 1.31 (t, *J*=7.06 Hz, 3H), 1.61 (s, 1H), 1.85 (s, 1H), 2.12 - 2.18 (m, 3H), 3.23 (s, 3H), 3.50 (s, 1H), 3.89 (s, 2H), 4.19 (s, 3H), 4.30 (q, *J*=7.16 Hz, 2H), 6.89 (d, *J*=2.83 Hz, 1H), 7.05 (dd, *J*=6.03, 2.64 Hz, 1H), 7.44 (d, *J*=2.64 Hz, 1H), 7.67 (d, *J*=8.10 Hz, 1H), 8.20 (d, *J*=5.84 Hz, 1H), 11.63 (s, 1H)	Intermediate 55 and ethyl 4-chloropyridine-2-carboxylate (WO 2004007657)
29	Cis(±)3,4-dicholoro-N-[3-methoxy-1-(2-methylquinolin-4-yl)piperidin-4-yl]-5-methyl-1H-pyrrole-2-carboxamide	MS (ES) MH^+: 447 for $C_{22}H_{24}Cl_2N_4O_2$	Intermediate 50 and 4-chloro-2-methylquinoline
30	Cis(±)Methyl 4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-1-[5-(methoxycarbonyl)-1,3-thiazol-2-yl]piperidine-3-carboxylate 	MS (ES) MH^+: 474 $C_{18}H_{22}ClN_5O_5S$; NMR: 1.98 (m, 2H), 2.23 (s, 3H), 3.08 (m, 1H), 3.24 (m, 1H), 3.55 (m, 1H), 3.66 (s, 3H), 3.79 (s, 3H), 3.97 (m, 1H), 4.23 (m, 1H), 4.63 (m, 1H), 7.64 (d, 1H), 7.95 (s, 1H), 12.01 (s, 1H)	Intermediate 35 and methyl 2-bromo-1,3-thiazole-5-carboxylate

Ex	Compound	Data	SM
31	Cis(±)ethyl 2-(4-{[(4-chloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylate	MS(ES) MH^+ : 477, 479 for $C_{22}H_{25}ClN_4O_4S$; NMR:1.33 (t, 3H), 1.76 (m, 1H), 1.83 (m, 1H), 2.10 (s, 3H), 3.37 (m, 2H), 3.45 (s, 3H), 3.54 (m, 1H), 4.21-4.29 (m, 3H), 4.36 (q, 2H), 6.86 (m, 1H), 7.38 (t, 1H), 7.62-7.69 (m, 3H), 11.60 (s, 1H)	Intermediate 55 and ethyl 2-bromo-1,3-benzothiazole-7-carboxylate (US Pat 5770758)
32	Cis(±)ethyl 4-(4-{[(3,4-difluoro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)quinoline-2-carboxylate	MS (ES) MH: 472 for for $C_{24}H_{26}F_2N_4O_4$	Intermediate 56 and Intermediate 10
33	methyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+:435,437 for $C_{16}H_{17}Cl_2FN_4O_3S$; NMR:1.77-1.79 (m, 2H), 2.12 (s, 3H), 3.25-3.27 (m, 2H), 3.49-3.62 (dd, 1H), 3.68 (s, 3H), 3.95 (m, 1H), 4.00-4.24 (m, 1H), 4.82-4.99 (m, 1H), 7.21 (d, 1H), 7.79 (s, 1H), 12.05 (br s, 1H)	Intermediate 36 and methyl 2-bromo-1,3-thiazole-5-carboxylate

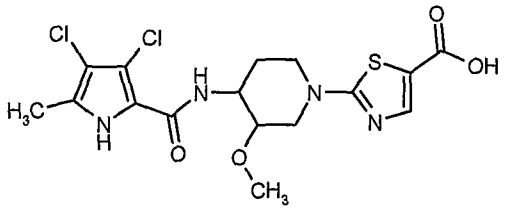
Example 34

Cis(±)methyl 4-(aminocarbonyl)-2-(4-{[(4-chloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate

Cis(±)methyl-2-(4-{[(4-chloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(1-methyl-1-phenylethyl)amino]carbonyl}-1,3-thiazole-5-carboxylate (Example 21; 0.058 g, 0.1 mmol) was dissolved in equal volumes of TFA and DCM. The reaction was heated in a sealed tube to an external temperature of 85 °C overnight. The reaction mixture was concentrated to remove the DCM and excess TFA. The residue was partitioned with EtOAc and $NaHCO_3$ and the organic extracts were dried with $MgSO_4$ and concentrated to a yellow solid (0.050 g, 100%). MS (ES) MH^+: 456 for $C_{18}H_{22}ClN_5O_5S$.

Example 35

Cis(±)2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid

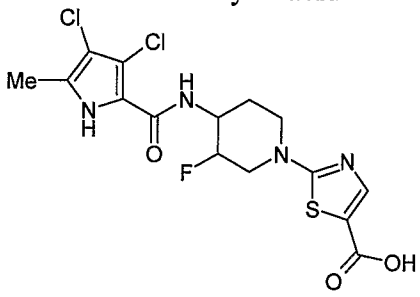


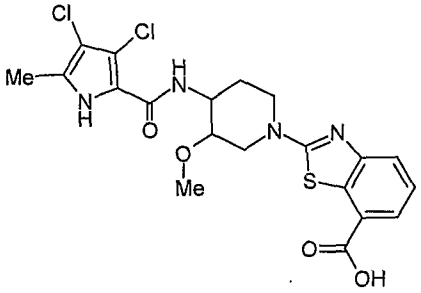
Cis(±)methyl 2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate (Example 1; 200 mg) was dissolved in THF (50 ml). 2N LiOH (100 ml) was added and the mixture was heated at 50 °C for 18 h. The reaction mixture was cooled to ambient and acidified with 20% aqueous citric acid. The aqueous phase was extracted with EtOAc and the organic phase was washed with water, brine, dried over Na_2SO_4. The organic phase was concentrated in vacuo and triturated with diethyl ether to give the title compound as an off white solid. (164 mg). MS (ES) MH^+: 433, 431 for $C_{16}H_{18}Cl_2N_4O_4S$; NMR: 1.87 (m, 2H), 2.28 (s, 3H), 3.32 (m, 6H), 3.63 (s, 1H), 3.87 (m, 1H), 4.45 (m, 2H), 7.04 (d, 1H), 7.90 (s, 1H), 11.97 (s, 1H), 12.30 (s, 1H).

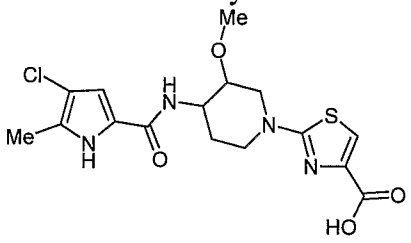
Examples 36-71

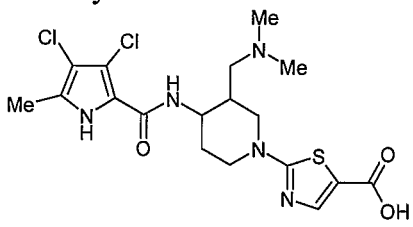
The following Examples were synthesized by an analogous method to Example 35 from the starting materials (SM) given in the table below.

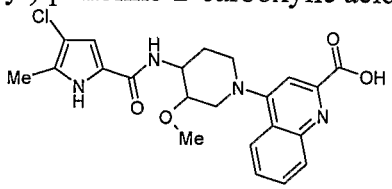
Ex	Compound	NMR	m/z	SM
36	Cis(±)2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-propoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid	0.87 (m, 3H), 1.57 (m, 2H), 1.93 (m, 2H), 2.24 (s, 3H), 2.6 (m, 2H), 3.45 (m, 2H), 3.69 (m, 2H), 4.36 (m, 2H), 7.23 (d, 1H), 7.87 (s, 1H), 12.34 (s, 1H)	461	Example 5
37	Cis(±)2-(3-(allyloxy)-4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylic acid	1.79 (m, 2H), 2.20 (s, 3H), 3.38 (m, 2H), 3.71 (s, 1H), 3.95 (m, 2H), 4.15 (m, 2H), 5.26 (m, 2H), 5.91 (m, 1H), 7.18 (d, 1H), 7.76 (s, 1H), 12.19 (s, 1H)	459	Example 6

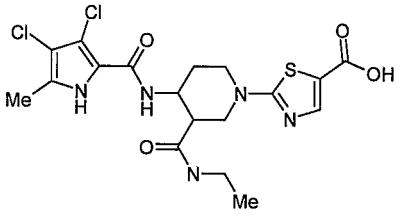
Ex	Compound	NMR	m/z	SM
38	Cis(±)4-(3-(allyloxy)-4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)quinoline-2-carboxylic acid	2.06 (m, 2H), 2.20 (s, 3H), 3.1-4.0 (m, 4H), 4.51 (m, 3H), 5.18 (m, 2H), 5.82 (m, 1H), 7.29 (d, 1H), 7.57 (s, 1H), 7.71 (m, 1H), 7.95 (m, 1H), 8.36 (m, 2H), 12.23 (s, 1H)	503	Example 7
39	Cis(±)4-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-propoxypiperidin-1-yl)quinoline-2-carboxylic acid	0.62 (t, 3H), 1.35 (m, 2H), 2.13 (s, 3H), 5.36 (m, 2H), 3.5-4.0 (m, 4H), 4.05 (m, 2H), 4.43 (m, 2H), 7.20 (d, 1H), 7.55 (s, 1H), 7.71 (m, 1H), 8.00 (m, 1H), 8.22 (m, 2H), 12.24 (s, 1H)	505	Example 8
40	Cis(±)2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-5-carboxylic acid 	1.75-1.79 (m, 2H), 2.13 (s, 3H), 3.39-3.57 (m, 2H), 3.93-3.96 (d, 1H), 4.25 (m, 2H), 4.81-4.97 (m, 1H), 7.28 (d, 1H), 7.63 (s, 1H), 12.12 (s, 1H)	421, 423	Example 9
41	Trans(±)2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-5-carboxylic acid	1.74-1.79 (m, 2H), 2.11 (s, 3H), 3.49-3.58 (m, 2H), 3.86-3.92 (d, 1H), 4.22 (m, 2H), 4.84-4.97 (m, 1H), 7.26 (d, 1H), 7.61 (s, 1H), 12.11 (s, 1H)	421, 423	Example 10
42	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-5-carboxylic acid	1.62-1.90 (m, 2H), 2.12 (s, 3H), 3.23 (m, 1H), 3.50 (dd, 1H), 3.83-4.03 (m, 1H), 4.12-4.43 (m, 2H), 4.90 (d, 1H), 7.21 (d, 1H), 7.69 (s, 1H), 12.04 (s, 1H), 12.61 (brs, 1H)	421, 423	Example 33

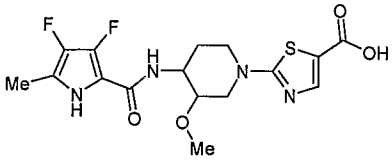
Ex	Compound	NMR	m/z	SM
43	2-((3*R*,4*S*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-5-carboxylic acid	1.63-1.92 (m, 2H), 2.13 (s, 3H), 3.21 (m, 1H), 3.50 (dd, 1H), 3.87-4.02 (m, 1H), 4.14-4.42 (m, 2H), 4.90 (d, 1H), 7.21 (d, 1H), 7.69 (s, 1H), 12.04 (s, 1H), 12.61 (brs, 1H)	421, 423	Example 11
44	Cis(±)2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-benzothiazole-7-carboxylic acid	1.82 (m, 2H), 2.13 (s, 3H), 3.48-3.67 (m, 2H), 4.12-4.41 (m, 3H), 4.92 (d, 1H), 7.22 (d, 1H), 7.34 (t, 1H), 7.62 (m, 1H), 12.06 (s, 1H), 13.45 (brs, 1H)	471, 473	Example 12
45	Cis(±)2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylic acid 	1.86 (m, 2H), 2.25 (s, 3H), 3.46 (s, 3H), 3.48 (m, 2H), 3.65 (m, 1H), 4.35 (m, 2H), 4.46 (m, 1H), 7.25 (d, 1H), 7.48 (t, 1H), 7.73 (t, 1H), 12.26 (s, 1H)	483, 485	Example 13
46	Cis(±)2-(4-{[(4-chloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylic acid	1.60 (m, 1H), 1.83 (m, 1H), 2.07 (s, 3H), 3.25 (s, 3H), 3.35 (m, 2H), 3.52 (m, 1H), 4.09-4.17 (m, 3H), 6.84 (d, 1H), 7.37 (t, 1H), 7.58-7.67 (m, 3H), 11.58 (s, 1H)	449, 451	Example 31
47	Cis(±)2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-4-carboxylic acid	1.74 (m, 2H), 2.17 (s, 3H), 3.26 (m, 2H), 3.35 (s, 3H), 3.52 (m, 1H), 3.84 (m, 1H), 4.21 (m, 2H), 7.13 (d, 1H), 7.57 (s, 1H), 12.15 (s, 1H), 12.61 (brs, 1H)	433, 435	Example 16

Ex	Compound	NMR	m/z	SM
48	Cis(±)2-Chloro-6-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)pyrimidine-4-carboxylic acid	1.59 (m, 1H), 1.77 (m, 1H), 2.18 (s, 3H), 3.16 (m, 1H), 3.17 (m, 1H), 3.56 (m, 1H), 4.11 (m, 1H), 4.30 (m, 1H), 4.55 (m, 1H), 4.98 (m, 1H), 7.15 (m, 1H), 7.38 (m, 1H), 12.10 (m, 1H)	463, 465	Example 14
49	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid	1.85 (m, 2H), 2.24 (s, 3H), 3.32 (s, 3H), 3.42 (m, 2H), 3.69 (s, 1H), 4.07 (m, 1H), 4.49 (m, 2H), 7.31 (d, 1H), 7.87 (s, 1H), 12.27 (s, 1H), 12.69 (s, 1H)	433	Example 2
50	Cis(±)2-(4-{[(4-chloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-4-carboxylic acid 	1.61 (m, 1H), 1.92 (m, 1H), 2.14 (s, 3H), 3.24 (m, 1H), 3.28 (s, 3H), 3.43 (m, 1H), 3.53 (m, 1H), 3.84 (m, 1H), 4.10 (m, 1H), 4.21 (m, 1H), 6.91 (s, 1H), 7.51 (s, 1H), 7.69 (m, 1H), 11.64 (s, 1H)	399, 401	Example 15
51	2-((3S,4S)-4-{[(3,4-Dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid	1.64 (m, 1H), 1.88 (m, 1H), 2.11 (s, 3H), 3.13-3.20 (m, 3H), 3.29 (s, 3H), 3.68 (m, 1H), 4.03 (m, 1H), 7.29 (d, 1H0, 7.71 (s, 1H), 11.95 (s, 1H), 12.63 (brs, 1H)	433, 435	Example 86
52	2-((3R,4R)-4-{[(3,4-Dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid	1.63 (m, 1H), 1.88 (m, 1H), 2.11 (s, 3H), 3.16-3.27 (m, 3H), 3.29 (s, 3H), 3.69 (m, 1H), 4.03-4.07 (m, 2H), 7.37 (d, 1H), 7.69 (s, 1H), 12.03 (s, 1H)	433, 435	Example 85
53	Cis(±)2-[4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-(methoxymethyl)piperidin-1-yl]-1,3-thiazole-5-carboxylic acid	1.62 (m, 1H), 2.03 (m, 1H), 2.16 (s, 3H), 2.98 (m, 1H), 3.21 (s, 3H), 3.25 (m, 3H), 3.41 (dd, 1H), 3.89 (m, 2H), 4.06 (dd, 1H), 7.51 (d, 1H), 7.63 (s, 1H)	447	Example 18

Ex	Compound	NMR	m/z	SM
54	Cis(±)2-{4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-[(methylamino)methyl]piperidin-1-yl}-1,3-thiazole-5-carboxylic acid	1.63 (m, 1H), 1.83 (m, 1H), 1.97 (m, 1H), 2.18 (s, 3H), 2.44 (s, 3H), 2.64 (m, 1H), 2.79 (m, 1H), 2.98 (m, 2H), 3.87 (m, 1H), 4.07 (m, 2H), 7.33 (s, 1H), 8.14 (d, 1H)	446	Example 19
55	Cis(±)2-{4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-[(dimethylamino)methyl]piperidin-1-yl}-1,3-thiazole-5-carboxylic acid 	1.66 (m, 1H), 1.88 (m, 1H0, 2.05 (m, 1H), 2.16 (s, 3H), 2.26 (s, 6H), 2.40 (m, 2H), 2.94 (t, 1H), 3.18 (t, 1H), 3.86 (m, 1H), 3.98 (dd, 2H), 7.63 (s, 1H), 7.67 (d, 1H), 12.3 (brs, 1H)	460	Example 20
56	Cis(±)2-(4-{[(4-chloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid	1.63 (d, J=3.39 Hz, 1H), 1.84 - 1.99 (m, 1H), 2.14 (s, 3H), 3.28 (s, 3H), 3.54 (s, 1H), 3.91 (s, 1H), 4.15 - 4.29 (m, 1H), 6.90 (d, J=2.83 Hz, 1H), 7.71 (d, J=8.10 Hz, 1H), 7.74 (s, 1H), 11.64 (d, J=1.70 Hz, 1H), 12.62 (s, 1H)	399	Example 22
57	Cis(±)2-chloro-6-{4-{[(4-chloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)pyrimidine-4-carboxylic acid	1.64 (s, 1H), 1.78 (s, 1H), 2.13 (s, 3H), 3.13 (s, 1H), 3.25 (s, 3H), 3.54 (s, 1H), 4.22 (s, 2H), 4.60 (s, 1H), 4.93 (s, 1H), 6.87 (d, J=2.45 Hz, 1H), 7.34 (s, 1H), 7.65 (s, 1H), 11.62 (s, 1H), 13.69 (s, 1H)	428	Example 23
58	Cis(±)2-(4-{[(4-chloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(methoxymethyl)-1,3-thiazole-5-carboxylic acid	1.62 (s, 1H), 1.93 (s, 1H), 2.14 (s, 3H), 3.28 (d, J=2.26 Hz, 3H), 3.36 (s, 3H), 3.54 (s, 2H), 3.91 (s, 1H), 4.19 (s, 2H), 4.56 (s, 2H), 6.89 (s, 1H), 7.69 (s, 1H), 11.63 (s, 1H)	443	Example 24

Ex	Compound	NMR	m/z	SM
59	Cis(±)2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(methoxymethyl)-1,3-thiazole-5-carboxylic acid	1.75 (s, 2H), 2.18 (s, 3H), 3.28 (s, 3H), 3.37 (s, 3H), 3.54 (s, 3H), 3.91 (s, 1H), 4.26 (s, 2H), 4.56 (s, 2H), 7.14 (s, 1H), 12.15 (s, 1H)	477	Example 25
60	Cis(±)4-(4-{[(4-chloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)quinoline-2-carboxylic acid 	1.80 (s, 1H), 2.15 (s, 3H), 3.15 (s, 3H), 3.64 (s, 3H), 3.80 (s, 2H), 4.09 (s, 1H), 4.30 (s, 1H), 6.93 (d, J=2.45 Hz, 1H), 7.57 (s, 1H), 7.68 (s, 1H), 7.85 (s, 2H), 8.19 (s, 2H), 11.65 (s, 1H)	443	Example 26
61	Cis(±)4-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)pyridine-2-carboxylic acid	1.67 (s, 1H), 1.81 (s, 1H), 2.18 (s, 3H), 3.28 (s, 3H), 3.59 (s, 2H), 4.20 (s, 2H), 4.32 (s, 1H), 4.55 (d, J=12.43 Hz, 1H), 7.14 (d, J=8.29 Hz, 1H), 7.18 (dd, J=7.06, 2.92 Hz, 1H), 7.44 (d, J=2.64 Hz, 1H), 7.97 (d, J=6.97 Hz, 1H), 12.18 (s, 1H)	393	Example 17
62	Cis(±)2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)isonicotinic acid	1.72 (s, 2H), 2.18 (s, 3H), 3.04 - 3.18 (m, 2H), 3.30 (s, 3H), 3.49 (s, 1H), 4.25 (s, 2H), 4.66 (s, 1H), 6.97 (d, J=4.71 Hz, 1H), 7.16 (s, 1H), 7.24 (s, 1H), 8.22 (d, J=4.90 Hz, 1H), 12.16 (s, 1H), 13.39 (s, 1H)	427	Example 27
63	Cis(±)2-[4-{[(3,4-Dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-(morpholin-4-ylcarbonyl)piperidin-1-yl]-1,3-thiazole-5-carboxylic acid	MS (ES^+): 516, 518 for $C_{20}H_{23}Cl_2N_4O_5S$; NMR: 1.82 (m, 2H), 2.15 (s, 3H), 3.32 (m, 6H), 3.61 (m, 5H), 3.99 (t, 2H), 4.40 (m, 1H), 7.18 (d, 1H), 7.78 (s, 1H), 12.03 (s, 1H), 12.8 (brs, 1H)		Example 78

Ex	Compound	NMR	m/z	SM
64	Cis(±)2-{4-{[(3,4-Dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-[(dimethylamino)carbonyl]piperidin-1-yl}-1,3-thiazole-5-carboxylic acid	1.75 (m, 1H), 1.89 (m, 1H), 2.14 (s, 3H), 2.87 (s, 3H), 3.09 (s, 3H), 3.36 (m [under water peak], 3H), 4.00 (m, 2H), 4.36 (m, 1H), 7.19 (d, 1H), 7.78 (s, 1H), 11.98 (s, 1H), 12.71 (brs, 1H)	474, 476	Example 79
65	Cis(±)2-{4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-[(ethylamino)carbonyl]piperidin-1-yl}-1,3-thiazole-5-carboxylic acid 	0.92 (t, 3H), 1.58 (m 1H), 1.99 (d, 1H), 2.15 (s, 3H), 2.62 (dd, 1H), 3.02 (m, 2H), 3.30 (q, 2H), 3.92 (d, 1H), 4.07 (d, 1H), 4.27 (m, 1H), 7.03 (d, 1H), 7.77 (s, 1H), 7.92 (t, 1H), 12.01 (s, 1H), 12.71 (brs, 1H)	474, 476	Example 80
66	Cis(±)2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-{[(2-hydroxyethyl)amino]carbonyl}piperidin-1-yl)-1,3-thiazole-5-carboxylic acid	1.50 (m, 1H), 1.96 (d, 1H), 2.41 (s, 3H), 2.61 (m, 1H), 3.07 (m, 2H), 3.26 (q, 2H), 3.32 (under water peak, 2H), 3.89 (d, 1H), 4.04 (d, 1H), 4.22 (m, 1H), 4.72 (brs, 1H), 7.39 (brs, 1H), 7.62 (s, 1H), 8.07 (t, 1H), 12.32 (brs, 1H)	490, 492	Example 81
67	Cis(±)2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-{[methoxy(methyl)amino]carbonyl}piperidin-1-yl)-1,3-thiazole-5-carboxylic acid	1.66 (m, 1H), 1.85 (m, 1H), 2.14 (s, 3H), 3.08 (m, 1H), 3.09 (s, 3H), 3.15 (m, 1H), 3.33 (under water peak, 1H), 3.74 (brs, 3H), 3.83 (m, 1H), 4.00 (m, 1H), 4.33 (m, 1H), 7.19 (s, 1H), 7.81 (brs, 1H), 12.98 (brs, 1H)	490, 492	Example 82
68	Cis(±)4-(aminocarbonyl)-2-(4-{[(4-chloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid	1.63 (s, 1H), 1.90 (s, 1H), 2.14 (s, 3H), 3.17 (s, 1H), 3.37 (s, 3H), 3.54 (s, 2H), 4.14 - 4.28 (m, 2H), 6.90 (s, 1H), 7.72 (s, 1H), 8.93 (s, 2H), 11.63 (s, 1H)	442	Example 34

Ex	Compound	NMR	m/z	SM
69	2-((3*R*,4*S*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid1,3-thiazole-5-carboxylic acid	1.89 (m, 2H), 2.11 (s, 3H), 2.23 (s, 3H), 3.33 (m, 2H), 3.46 (s, 3H), 3.59 (s, 1H), 4.09 (m, 1H), 4.46 (m, 2H), 7.31 (d, 1H), 7.92 (s, 1H), 12.28 (s, 1H), 12.67 (brs, 1H)	433	Example 3
70	Cis(±)2-(4-{[(3,4-difluoro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid 	1.75 (m, 2H), 2.13 (s, 3H), 3.33 (s, 3H), 3.36 (m, 2H), 3.54 (s, 1H), 3.89 (m, 1H), 3.94 (m, 2H), 6.73 (d, 1H), 7.90 (s, 1H), 11.40 (s, 1H)	441	Example 4
71	Cis(±)4-(4-{[(3,4-difluoro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)quinoline-2-carboxylic acid	1.69 (m, 2H), 2.01 (s, 3H), 3.16 (m, 1H), 3.16 (s, 3H), 3.8-4.02 (m, 2H), 4.18-4.38 (m, 2H), 6.57-6.84 (d, 1H), 7.44-7.56 (s, 1H), 7.56-7.72 (m, 1H), 7.78-7.94 (m, 1H), 8.04-8.27 (m, 2H), 11.23 (br, 1H)	444	Example 32

Example 72

Cis(±)2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-N-methoxy-1,3-thiazole-5-carboxamide

Cis(±)2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid (Example 35; 100 mg) was dissolved in anhydrous DMA (2 ml). HATU (97 mg), HOAT (31 mg), DIEA (41 µl) were added and the mixture was stirred for 30 min. *N*-Methoxyamine hydrochloride (19.3 mg) was added followed by DIEA (41 µl), and the mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with EtOAc, washed with H_2O, 20% citric acid solution, H_2O, sat. $NaHCO_3$, H_2O, brine and dried over Na_2SO_4. The organic phase was concentrated in vacuo to give the title compound as an off–white solid (82 mg). MS (ES)(MH^+): 462, 460 for $C_{17}H_{21}Cl_2N_5O_4S$; NMR: 1.64 (m, 2H), 1.85 (m, 1H), 2.05 (s, 3H), 2.83 (m, 1H), 3.33 (m, 5H), 3.73 (s, 3H), 4.07 (m, 1H), 4.38 (m, 2H), 7.24 (d, 1H), 7.74 (s, 1H), 11.39 (s, 1H), 12.05 (s, 1H).

Example 73

The following Example was prepared by the procedure described in Example 72 from the starting material (SM) indicated.

Ex	Compound	Data	SM
73	2-((3*R*,4*R*)-4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-*N*-methoxy-1,3-thiazole-5-carboxamide	MS (ES) (M +H): 462, 464 (M +H), for $C_{17}H_{21}Cl_2N_5O_4S$; NMR: 1.61 (m, 1H), 1.87 (m, 1H), 2.11 (s, 3H), 3.14 (m, 1H), 3.29 (s, 3H), 3.33 (m, 1H), 3.59 (s, 3H), 3.64 (m, 1H), 3.95-4.06 (m, 3H), 7.29 (d, 1H), 7.66 (s, 1H), 11.31 (brs, 1H), 11.95 (s, 1H)	Example 52

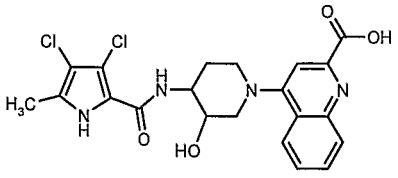
Example 74

Cis(±)2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-hydroxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid

Cis(±)2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid (Example 35; 100 mg) was suspended in anhydrous DCM. BBr_3/ DCM (15 ml) was added and the mixture was heated at 40 °C for 18 h. The reaction mixture was cooled to –50 °C and water was added. The mixture was extracted with EtOAc and the organic phase was washed with water, dried over Na_2SO_4. The organic phase was concentrated in vacuo to yield a pale brown solid which was dissolved in acetonitrile/water mixture and was lyophilized (46 mg). MS (ES) MH^+: 419 for $C_{15}H_{16}Cl_2N_4O_4S$; NMR: 1.87 (m, 2H), 2.20 (s, 3H), 3-4 (brm, 6H), 6.9 (d, 1H), 7.51 (s, 1H), 12.19 (s, 1H).

Example 75

The following Example was prepared by the procedure described in Example 74 from the starting material (SM) indicated.

Ex	Compound	Data	SM
75	Cis(±)4-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-hydroxypiperidin-1-yl)quinoline-2-carboxylic acid 	MS (ES) MH^+: 463 for $C_{21}H_{20}Cl_2N_4O_4$; NMR: 1.24 (m, 2H), 2.13 (m, 2H), 2.38 (s, 3H), 3.54 (m, 2H), 4.14 (m, 2H), 4.57 (m, 1H), 7.07 (s, 1H), 7.87 (m, 1H), 8.23 (m, 2H), 8.52 (m, 2H), 12.06 (s, 1H)	Example 76

Example 76

Cis(±)4-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)quinoline-2-carboxylic acid

Cis(±)3,4-dicholoro-N-[3-methoxy-1-(2-methylquinolin-4-yl)piperidin-4-yl]-5-methyl-1*H*-pyrrole-2-carboxamide (Example 29; 170 mg) was dissolved in pyridine (5 ml). Selenium dioxide (211 mg) was added and the mixture was heated at 130 °C for 3 h. The brown solution was cooled to room temperature, diluted with water and filtered through a bed of celite. The filtrate was extracted with EtOAc, washed with water and dried over Na_2SO_4, concentrated in vacuo. The brown solid that separated was triturated with Et_2O, filtered, washed well with n-hexanes and dried in vacuo to give the title compound as a brown solid (176 mg). MS (ES) MH^+: 477 for $C_{22}H_{22}Cl_2N_4O_4$; NMR: 1.34 (m, 1H), 2.01 (m, 1H), 2.28 (s, 3H), 3.10 (s, 3H), 3.42 (m, 3H), 3.72 (m, 2H), 4.23 (m, 1H), 7.36 (d, 1H), 7.63 (s, 1H), 7.78 (m, 1H), 7.92 (m, 1H), 8.30 (m, 2H), 12.30 (brs, 1H).

Example 77

Cis(±)4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-1-[5-(methoxycarbonyl)-1,3-thiazol-2-yl]piperidine-3-carboxylic acid

Cis(±)4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidine-3-carboxylic acid hydrochloride (Intermediate 79; 1.84 g) was dissolved in anhydrous DMF (20 ml) under an argon atmosphere in a 100-ml round bottom flask. Methyl 2-bromothiazole-5-carboxylate (1.43 g) was added followed by N,N-diisopropylethylamine (3.6 ml) at room temperature. The reaction was heated to 55 °C for 14 h cooled to room temperature. The reaction mixture was diluted with EtOAc (250 ml) and washed with a saturated aqueous

ammonium chloride solution (125 ml), followed by a saturated aqueous sodium chloride solution (100 ml). The EtOAc solution was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica gel chromatography using 0-10% CH_3OH in DCM. The recovered product was recrystallised from EtOAc to further enhance the diastereomeric excess, increasing it from a 90:10 cis:trans mixture to a 96:4 cis:trans mixture (by HPLC analysis). The recrystallised product was carried on to the next reaction (2 g). MS (ES – $(M+H)^+$): 461, 463 for $C_{17}H_{18}Cl_2N_4O_5S$; NMR: 1.71 (m, 1H), 1.91 (m, 1H), 2.16 (s, 3H), 2.81 (dt, 1H), 3.42 (m, 2H), 3.74 (s, 3H), 3.86 (m, 1H), 4.34 (m, 2H), 7.43 (d, 1H), 7.88 (s, 1H), 8.50 (brs, 1H), 12.06 (s, 1H).

Example 78

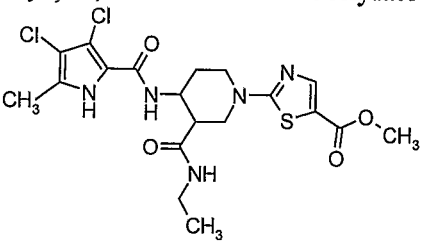
Cis(±)methyl 2-[4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(morpholin-4-ylcarbonyl)piperidin-1-yl]-1,3-thiazole-5-carboxylate

The title compound was prepared in a manner analogous to (Intermediate 37) starting from cis(±)4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-1-[5-(methoxycarbonyl)-1,3-thiazol-2-yl]piperidine-3-carboxylic acid (Example 77) and morpholine. MS (ES^+): 530, 532 for $C_{21}H_{25}Cl_2N_5O_5S$.

Examples 79-82

The following compounds were synthesized by an analogous method to Example 78 from Example 77 and the starting materials given in the table below.

Ex	Compound	m/z	SM
79	Cis(±)methyl 2-{4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-[(dimethylamino)carbonyl]piperidin-1-yl}-1,3-thiazole-5-carboxylate	M/z 488, 490	Dimethylamine (2 M in THF)

Ex	Compound	m/z	SM
80	Cis(±)methyl 2-{4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-[(ethylamino)carbonyl]piperidin-1-yl}-1,3-thiazole-5-carboxylate 	M/z 488, 490	Ethylamine (2 M in THF)
81	Cis(±)methyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-{[(2-hydroxyethyl)amino]carbonyl}piperidin-1-yl)-1,3-thiazole-5-carboxylate	M/z 504, 506	Ethanolamine
82	Cis(±)methyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-{[methoxy(methyl)amino]carbonyl}piperidin-1-yl)-1,3-thiazole-5-carboxylate	M/z 504, 506; NMR: 1.78 (m, 1H), 1.93 (m, 1H), 2.14 (s, 3H), 3.06 (brs, 3H), 3.24 (m, 1H), 3.32 (s, 1H), 3.38 (m, 1H), 3.72 (brs, 1H), 3.74 (s, 3H), 3.98 (m, 1H), 4.12 (m, 1H), 4.38 (m, 1H), 7.19 (d, 1H), 7.88 (s, 1H), 11.99 (s, 1H)	N,O-Dimethyl-hydroxylamine hydrochloride

Example 83

Cis(±)6-(4-{[(4-chloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-2-methoxypyrimidine-4-carboxylic acid

Cis(±)methyl 2-chloro-6-(4-{[(4-chloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)pyrimidine-4-carboxylate (Example 23; 0.12g, 0.27 mmol) was dissolved in 0.5 M sodium methoxide in MeOH (5.4 ml, 2.7 mmol) and heated in the microwave for 1.5 h at 85 °C. The reaction mixture was acidified with 1N HCl and the product was extracted with EtOAc, dried with $MgSO_4$ and concentrated to a solid which was purified by reverse phase chromatography (gradient elution from 20-50% CH_3CN in water with 0.5%TFA). Freeze drying yielded product as a white solid. MS (ES) MH^+: 424 for $C_{18}H_{22}ClN_5O_5$; NMR: 1.62 (s, 1H), 1.75 (s, 1H), 2.14 (s, 3H), 3.26 (s, 3H), 3.53 (m, 3H), 3.87 (s, 3H), 4.22 (s, 2H), 6.88 (d, *J*=2.64 Hz, 1H), 7.07 (s, 1H), 7.66 (d, *J*=7.91 Hz, 1H), 11.63 (s, 1H).

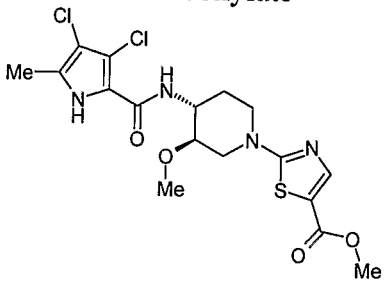
Example 84

The following compound was prepared by the procedure of Example 83 from the starting material (SM) indicated.

Ex	Compound	NMR	M/z	SM
84	Cis(±)6-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-2-methoxypyrimidine-4-carboxylic acid	1.61 (m, 1H), 1.74 (m, 1H), 2.18 (s, 3H), 3.21 (m, 1H), 3.33 (s, 3H), 3.51 (m, 1H), 3.53 (m, 1H), 3.85 (s, 3H), 4.28 (m, 2H), 5.10 (m, 1H), 7.03 (m, 1H), 7.12 (m, 1H), 12.15 (m, 1H)	458, 460	Example 14

Examples 85-86

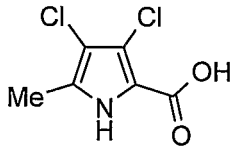
The following compounds were prepared by the procedure of Intermediate 37 using the starting materials (SM) indicated.

Ex	Compound	Data	SM
85	Methyl 2-((3R,4R)-4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate 	MS (ES) MH^+:447 for $C_{17}H_{20}ClN_4O_4S$; NMR: 1.71 (m, 1H), 1.93 (m, 1H), 2.18 (s, 3H), 3.24-3.28 (m, 2H), 3.31 (s, 3H), 3.75 (s, 3H), 3.79 (m, 1H), 4.02-4.11 (m, 2H), 7.35 (d, 1H), 7.88 (s, 1H0, 12.00 (s, 1H)	Intermediate 30 and Intermediate 1
86	Methyl 2-((3S,4S)-4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+:447 for $C_{17}H_{20}ClN_4O_4S$; NMR: 1.71 (m, 1H), 1.93 (m, 1H), 2.18 (s, 3H), 3.24-3.28 (m, 2H), 3.31 (s, 3H), 3.75 (s, 3H), 3.79 (m, 1H), 4.02-4.11 (m, 2H), 7.35 (d, 1H), 7.88 (s, 1H0, 12.00 (s, 1H)	Intermediate 31 and Intermediate 1

Preparation of starting materials for Examples 1-86

Intermediate 1

3,4-Dichloro-5-methyl-1*H*-pyrrole-2-carboxylic acid



Ethyl 3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxylate (Intermediate 2; 7.765 g, 0.03496 mol) was dissolved in MeOH (80 ml) and DCM (10 ml) and slowly added to a 70 °C solution of 2 N LiOH (105 ml, 0.21 mol). After 2 h, the reaction mixture was cooled to room temperature and then in an ice bath, followed by acidification with 2 N HCl. The mixture was stirred at 0 °C for 1 h, and a purple solid was filtered, washed with water and lyophilized overnight to give 4.314 g (0.0222 mol, 64% yield) of the desired product. MS (ES^-): 192.13, 194.13 for $C_6H_5Cl_2NO_2$; NMR: 2.17 (s, 3H).

Intermediate 2

Ethyl 3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxylate

Method 1

A solution of ethyl 5-methyl-1*H*-pyrrole-2-carboxylate (Intermediate 3; 7.00 g, 0.0457 mol) in tetrachloromethane (30 ml) was cooled to 0 °C under nitrogen. The rubber septum used in the apparatus was pierced with a needle, and SO_2Cl_2 (7.8 ml, 0.096 mol) was then added dropwise over 25 min. Within 1 h, the reaction mixture had formed a slurry. The solid was collected by suction filtration, washed with cold tetrachloromethane, and dried under vacuum overnight to give the title product as a peach coloured solid (7.84 g, 0.0353 mol, 77% yield). MS (ES^-): 222.00, 224.00 for $C_8H_9Cl_2NO_2$; NMR: 1.34-1.40 (t, 3H), 2.28 (s, 3H), 4.32-4.38 (m, 2H).

Method 2

A 4-neck 22L round bottom flask equipped with an overhead stirrer, reflux condenser, nitrogen inlet and an internal temperature probe was charged with (Intermediate 253, 1000 g, 3.9 mol), 1-methyl-2-pyrrolidinone (10 L) and sodium cyanoborohydride (382 g, 6.1 mol, 1.56 eq). The resulting solution was heated at 75–80 °C for 6 h and allowed to cool to ambient overnight. Reaction solution was poured into water (20 L) resulting in a light brown suspension and product was extracted with methyl *tert*-butyl ether (2 x 10 L). Organic layer

was dried with sodium sulfate and concentrated under reduced pressure to a thick slurry, which was filtered and solid dried in convection oven yielding **4** (518 g, 60 %) as a light brown solid.

Intermediate 3

Ethyl 5-methyl-1H-pyrrole-2-carboxylate

Sodium (2.79 g, 0.121 mmol) was dissolved in anhydrous EtOH (100 ml), then 2,2,2-trichloro-1-(5-methyl-1H-pyrrol-2-yl)ethanone (Intermediate 4; 22.5 g, 0.099 mmol) was added in small portions. The dark brown solution was stirred at room temperature for 30 min then concentrated under vacuum to a small volume. The mixture was cooled in an ice bath and 3 N HCl was added slowly then extracted with diethyl ether (3 x 100 ml). The ether extracts were washed with 10% $NaHCO_3$, water and brine, dried over Na_2SO_4 and concentrated in vacuo to give the title compound as a brown solid. (15.04 g). NMR: 1.32 (t, 3H), 2.1 (s, 3H), 4.371 (q, 2H), 5.96 (dd, 1H), 6.78 (dd, 1H), 11.67 (s, 1H).

Intermediate 4

2,2,2-Trichloro-1-(5-methyl-1H-pyrrol-2-yl)ethanone

2-Methyl-1H-pyrrole (Intermediate 5; 10 g, 0.123 mmol) in anhydrous diethyl ether (30 ml) was added dropwise over 1 h to a stirred solution of triacetyl chloride (29 g, 0.16 mmol) in anhydrous Et_2O (100 ml). The mixture was stirred for a further 1 h then K_2CO_3 (10 g/30 ml) was added slowly through a dropping funnel. The organic phase was dried over Na_2SO_4 and treated with decolourizing charcoal (3 g) for 30 min at room temperature. The resulting purple solution was concentrated and triturated with n-hexanes to give the title compound as a purple solid. (16.72 g). NMR ($CDCl_3$): 2.36 (s, 3H), 6.04 (dd, 1H), 7.45 (dd, 1H), 10.344 (s, 1H).

Intermediate 5

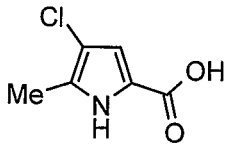
2-Methyl-1H-pyrrole

Potassium hydroxide (50 g, 0.89 mmol) was added to a solution of ethylene glycol (750 ml) and 1H-pyrrole-2-carbaldehyde (50 g,0.53 mmol). Hydrazine hydrate (37 ml, 0.745 mmol) was added slowly over 15 min. The reaction mixture was refluxed at 90 °C for 90 min. The mixture was cooled to room temperature and cold water (250 ml) was added. The aqueous mixture was extracted with DCM (250 ml). The organic phase was washed with

water (250 ml), dried over Na_2SO_4 and concentrated in vacuo. Kugelrohr distillation gave the title compound as a clear colourless liquid (29.75 g). NMR: 2.1 (s, 3H), 5.77 (s, 1H), 5.9 (dd, 1H), 6.25 (dd, 1H), 10.54 (s, 1H).

Intermediate 6

4-Chloro-5-methyl-1*H*-pyrrole-2-carboxylic acid



Lithium hydroxide (2 M, 4 ml) was warmed to 50 °C and a solution of ethyl 4-chloro-5-methyl-1*H*-pyrrole-2-carboxylate (Intermediate 7; 0.30 g, 1.60 mmol) in MeOH was added to it. The reaction was heated to 80 °C and stirred for two hours. The MeOH was removed and the aqueous solution was cooled to 0 °C and acidified with 30% HCl. The precipitated product (0.23 g, 92%) was filtered and dried. MS (ES): 160 (M+1) for $C_6H_6ClNO_2$; NMR ($CDCl_3$): 2.25 (s, 3H), 6.85 (s, 1H), 8.98 (brs, 1H).

Intermediate 7

Ethyl 4-chloro-5-methyl-1*H*-pyrrole-2-carboxylate

N-Chlorosuccinimide (0.67 g, 5.08 mmol) was added to a solution of ethyl 5-methyl-1*H*-pyrrole-2-carboxylate (Intermediate 3; 0.65 g, 4.23 mmol) in chloroform (20 ml). The reaction was warmed to 40 °C and stirred for 4 h, then poured to a beaker containing 2 N NaOH (20 ml) at 0 °C. The layers were separated and the aqueous layer was extracted with chloroform (x3). The combined organic extracts were dried over magnesium sulfate and concentrated. The resultant off-white solid was purified by flash chromatography (hexanes/EtOAc, 16:1) to give the title product as a white solid (0.3 g, 38%). MS (ES): 188 (M+1) for $C_8H_{10}ClNO_2$; NMR ($CDCl_3$): 1.34 (t, 3H), 2.27 (s, 3H), 4.30 (q, 2H), 6.76 (s, 1H), 9.07 (brs, 1H)

Intermediate 8

3,4-Difluoro-2-methyl-1*H*-pyrrole

BH_3THF (400 ml, 1M in THF) was added dropwise to a solution of 3,4-difluoro-1*H*-pyrrole-2-carbaldehyde (Intermediate 19; 3.82 g) in THF (50 ml) cooled in an ice-water bath under N_2. The reaction mixture was stirred at room temperature for 3 days. MeOH was added

slowly to quench excess of BH_3 and then the solvent was removed in vacuo at 0 °C. The resulting yellow oil was triturated with hexanes/DCM and the yellow precipitate was removed by filtration. The filtrate was washed with $NaHCO_3$, H_2O and brine, dried over Na_2SO_4, filtered and concentrated at 0 °C in vacuo to give a pale yellow oil (3.8 g). MS (ES) MH^+: 116 for $C_5H_5F_2N$; NMR ($CDCl_3$): 2.15 (s, 3H), 6.22 (m, 1H).

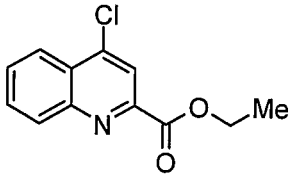
Intermediate 9

1-*tert*-Butyl-3-methyl-4-hydroxy-5,6-dihydropyridine-1,3-(2*H*)-dicarboxylate

Methyl-4-hydroxy-1,2,5,6-tetrahydropyridine-3-carboxylate-hydrochloride (25 g) was suspended in DCM (250 ml). DIEA (41.6 g) was added in a single portion and the resultant homogeneous solution was cooled to 0 °C. A DCM solution of di-tert-butyl dicarbonate (29.5 g, 1.05 moles) was added dropwise over a 1 h period. After the addition, the reaction was warmed to room temperature and stirred overnight. The reaction mixture was concentrated to one-half the volume and washed with water, brine, dried over Na_2SO_4, filtered and concentrated in vacuo to an oil. The crude product was purified by flash column chromatography eluting with (20% EtOAc / 80% hexanes) to give the title product (33 g). NMR ($CDCl_3$): 1.48 (s, 9H), 2.37 (m, 2H), 3.57 (t, 2H), 3.78 (s, 3H), 4.06 (brs, 2H), 11.9 (s, 1H).

Intermediate 10

Ethyl 4-chloroquinoline-2-carboxylate



Phosphorous oxychloride (5ml) was added to ethyl 4-hydroxyquinoline-2-carboxylate (1.01g). The reaction mixture was subjected to single-mode microwave at 100 °C for 30 min using a Smith Microwave Synthesizer. The solvent was removed in vacuo and recrystallized with acetone to gave the title compound as a white solid (1.90g). MS (ES) MH^+: 235, 237 for $C_{12}H_{10}ClNO_2$; NMR ($CDCl_3$): 1.44 (t, 3H, J = 7.16), 4.51 (q, 2H, J = 7.16), 7.19 (s, 1H), 7.71 (m, 1H), 7.81 (m, 1H), 8.22 (m, 1H), 8.36 (d, 1H, J = 8.29).

Intermediate 11

2-(Methylthio)-1,3-thiazole-4-carboxylic acid

Ethyl 2-(methylthio)-1,3-thiazole-4-carboxylate (5.0 g) (Sinha, Subhash C et al.*Tet.Lett.* 2000, 41 (43), 8243-8246) was dissolved in MeOH (50 ml) and 2N LiOH (74 ml) was added. After stirring at room temperature for five minutes the reaction mixture was concentrated to remove MeOH and the residue was suspended in water and acidified with conc. HCl to pH 3. The white precipitate was filtered and dried to yield the title compound (3.42 g). NMR: 2.72 (s, 3H), 8.35 (s, 1H).

Intermediate 12

2-(Methylthio)-4-thiazolecarbonyl chloride

2-(Methylthio)-1,3-thiazole-4-carboxylic acid (Intermediate 11; 1.0 g) in thionyl chloride (10 ml) was heated to reflux for 30 min. The solution was cooled to room temperature and concentrated in vacuo. The residue was washed with anhydrous THF and concentrated to yield a black solid which was dried and stored cold under nitrogen (1.2 g). NMR ($CDCl_3$): 2.76 (s, 3H), 8.32 (s, 1H).

Intermediate 13

N-(1-Methyl-1-phenylethyl)-2-(methylthio)-1,3-thiazole-4-carboxamide

Triethylamine (2.24 ml) was added to a solution of cumylamine (3.2 ml) in anhydrous THF (30 ml). After stirring for 15 min, a solution of 2-(methylthio)-4-thiazolecarbonyl chloride (Intermediate 12; 3.1 g) in anhydrous THF was added and the reaction mixture was concentrated in vacuo after 15 min. The residue was partitioned with EtOAc and water, dried with $MgSO_4$, and concentrated to an orange oil. Flash purification on silica gel with isocratic elution of DCM yielded the product as a yellow oil (3.7 g). MS (ES) MH^+: 293 for $C_{14}H_{16}N_2OS_2$; NMR: 1.68 (s, 6H), 2.76 (s, 3H), 7.20 (d, *J*=7.16 Hz, 1H), 7.29 (t, *J*=7.54 Hz, 2H), 7.36 - 7.41 (m, 2H), 8.04 (s, 1H), 8.08 (s, 1H).

Intermediate 14

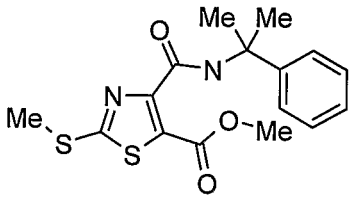
4-{[(1-Methyl-1-phenylethyl)amino]carbonyl}-2-(methylthio)-1,3-thiazole-5-carboxylic acid

Diisopropylamine (4.2 ml) was dissolve in anhydrous THF (100 ml) was cooled to -78°C and to this was added n-butyl lithium (12 ml) slowly. The solution was slowly warmed to 0 °C and then cooled back to -78°C. A solution of *N*-(1-methyl-1-phenylethyl)-2-

(methylthio)-1,3-thiazole-4-carboxamide (Intermediate 13; 2.8 g) in anhydrous THF was added slowly maintaining the temperature below -70°C. After stirring for 30 min, a solution of methyl cyano formate (1.6 ml) in anhydrous THF was added in one portion and the reaction was stirred at -78°C for 30 min followed by slow warming to room temperature. The reaction mixture was diluted with water and extracted with ether. The aqueous portion was acidified with conc. HCl, extracted with EtOAc, dried with $MgSO_4$ and concentrated to an orange solid (0.9 g). MS (ES) MH^+: 337 for $C_{15}H_{16}N_2O_3S_2$; NMR: 1.66 - 1.74 (m, 6H), 2.80 (s, 3H), 7.23 (d, *J*=7.16 Hz, 1H), 7.33 (t, *J*=7.54 Hz, 2H), 7.45 (s, 2H), 9.07 (s, 1H).

Intermediate 15

Methyl 4-{[(1-methyl-1-phenylethyl)amino]carbonyl}-2-(methylthio)-1,3-thiazole-5-carboxylate



Potassium carbonate (0.37 g) and iodomethane (0.17 ml) were added to a solution of 4-{[(1-methyl-1-phenylethyl)amino]carbonyl}-2-(methylthio)-1,3-thiazole-5-carboxylic acid (Intermediate 14; 0.9 g) in DMF (20 ml) and heated in a sealed tube at an external temperature of 85°C for 30 min. The reaction mixture was concentrated to remove DMF and partitioned with EtOAc and water. The combined organic extracts were washed with water, dried with $MgSO_4$, and concentrated to an orange solid (0.63 g). NMR: 1.60 - 1.65 (m, 6H), 2.76 (s, 3H), 3.78 - 3.83 (m, 3H), 7.22 (d, *J*=7.16 Hz, 1H), 7.33 (t, *J*=7.63 Hz, 2H), 7.46 (d, *J*=7.35 Hz, 2H), 8.75 (s, 1H).

Intermediate 16

Methyl 4-{[(1-methyl-1-phenylethyl)amino]carbonyl}-2-(methylsulfonyl)-1,3-thiazole-5-carboxylate

3-Chloroperbenzoic acid (0.89 g) was added to a solution of methyl 4-{[(1-methyl-1-phenylethyl)amino]carbonyl}-2-(methylthio)-1,3-thiazole-5-carboxylate (Intermediate 15; 0.63 g) in DCM (25 ml). After stirring overnight the reaction was complete. Aqueous sodium bisulfite was added to quench any unreacted peroxides and the solution was washed with sat. $NaHCO_3$. The organic portion was dried with $MgSO_4$ and concentrated to a yellow solid (0.6

g). NMR: 1.63 - 1.68 (m, 6H), 3.58 (s, 3H), 3.89 (s, 3H), 7.23 (d, *J*=7.16 Hz, 1H), 7.34 (t, *J*=7.63 Hz, 2H), 7.47 (d, *J*=7.54 Hz, 2H), 8.91 (s, 1H).

Intermediate 17

Methyl-2-chloro-4-(methoxymethyl)-1,3-thiazole-5-carboxylate

tert-Butyl nitrite (2.2 ml, 18.6 mmol) and cuprous chloride (1.5 g) were suspended in anhydrous CH_3CN (100 ml). Methyl 2-amino-4-(methoxymethyl)-1,3-thiazole-5-carboxylate (2.5 g) prepared as described in (Kennedy, Alan R. et al. *Acta Crystallographica, Section C: Crystal Structure Communications* (1999, C55 (7) 2) was added in one portion. The mixture was stirred at room temperature for 2 h and the temperature was raised to 70 °C for 1 h. The mixture was cooled to room temperature and filtered. The filtrate was poured into 6 N HCl, extracted with EtOAc, dried with $MgSO_4$ and concentrated to a black oil. Flash purification on silica gel with gradient elution (hexane to EtOAc) yielded product as a yellow liquid (0.82 g). NMR: 3.31 (s, 3H), 3.85 (s, 3H), 4.71 (s, 2H).

Intermediate 18

3,4-Difluoro-1*H*-pyrrole

3,4-Difluoro-1H-pyrrole was prepared as described in Eric K. Woller et al., *J. Org. Chem.*, 1998 *63(16),* 5706-5707) and references therein. Thus, to a solution of 3,3,4,4-tetrafluoro-pyrrolidine hydrochloride (30.2 g) in dry DMSO (250 ml) cooled in an ice-water bath, *t*-BuOK was added (100 g) under N_2. After the addition was complete (~0.5 h), the reaction mixture was stirred at room temperature for another 0.5 h. It was cooled to 0 °C and quenched with ice water (300 ml). After the solid dissolved, the mixture was diluted to ~1.5 l with water, neutralized to pH 7 with HCl, and extracted with DCM. The combined DCM extracts were washed with water, brine, dried over $MgSO_4$ and filtered. DCM was removed in vacuo at 0 °C, and the resulting orange oil was dissolved in pentane at room temperature, cooled to -20 °C overnight and filtered under N_2 to give the title compound as golden crystals (4.6 g). NMR ($CDCl_3$): 6.38 (d, 1H), 6.41 (d, 1H).

Intermediate 19

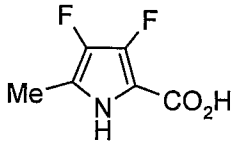
3,4-Difluoro-1*H*-pyrrole-2-carbaldehyde

DMF (4.3 ml) was cooled in ice-water bath under N_2 and $POCl_3$ (5.2 ml) was added dropwise. The mixture was stirred at room temperature for 10 min. The ice-water bath was

replaced, and the mixture was diluted with DCM (45 ml). A solution of 3,4-difluoro-1H-pyrrole (Intermediate 18; 4.57 g) in DCM (45 ml) was added dropwise. The mixture was refluxed for 30 min, cooled to room temperature and a solution of NaOAc (23 g) in water (60 ml) was added slowly. The resulting mixture was refluxed for 30 min, organic phase was separated and aqueous phase was extracted with DCM. The combined organic phase was washed with $NaHCO_3$, dried over Na_2SO_4, and concentrated in vacuo. The crude solid was triturated with DCM (20 ml)/pentane (100 ml), and then cooled to -20 °C to give the title compound as pale brown needles (4.73 g). NMR ($CDCl_3$): 6.87 (m, 1H), 9.6 (m, 1H).

Intermediate 20

3,4-Difluoro-5-methyl-1H-pyrrole-2-carboxylic acid



2,2,2-Trichloro-1-(3,4-difluoro-5-methyl-1*H*-pyrrol-2-yl)ethanone (Intermediate 80; 1.03 g) was added to an aqueous solution of NaOH (18 ml) at 0 °C under N_2. The mixture was stirred at room temperature for a further 2 h, cooled to 0 °C and acidified with HCl to ~pH 2. A brown precipitate of product was collected by filtration. The crude product was purified by column chromatography on silica gel elution with EtOAc/hexanes (1:1). Trituration with DCM (1 ml)/pentane (6 ml) gave the title compound as a pale brown solid (306 mg). M.p. 140 °C (dec.). MS (ES) MH^+: 160, 161 for $C_6H_5F_2NO_2$; NMR ($CDCl_3$): 2.15 (s, 3H), 11.5 (s, 1H), 12.8 (brs, 1H).

Intermediate 21

Cis(±)ethyl 4-amino-3-methoxypiperidine-1-carboxylate hydrochloride salt

The title compound can be prepared as described in Lee, C. et al. *Synth. Comm.* 2001, 31(7), 10881-10890 and / or WO 94/12494or from Intermediate 157 by the following procedure;

To a stirred solution of the benzylamine (36.45 g, 125 mmol) and 10% palladium on activated carbon (50% wet; approximately 4 g) in methanol (250 mL), at room temperature and under an atmosphere of N_2, was added ammonium formate (31.50 g, 500 mmol) as a solid. Temperature was increased to 70 °C; the reaction was stirred overnight at this temperature, under an atmosphere of N_2. Complete conversion was suggested by TLC (6%

methanol in ethyl acetate; Rf ~ 0.06 in a solution of 15 % methanol and 30% acetone in methylene chloride) in the morning. The reaction mixture was filtered through Celite and concentrated under vacuum. To the residue was added approximately 50 mL water; from this mixture was extracted the crude product with a solution of ~3% methanol in chloroform (4 X 300 mL). Organic layers were combined, dried over magnesium sulfate, and concentrated. Obtained 24.18 g (96%) of an off-white solid.

MS (ES) MH^+: 202 for $C_9H_{18}N_2O_3$.

Intermediate 22

Cis(±)ethyl 4-{[(benzyloxy)carbonyl]amino}-3-methoxypiperidine-1-carboxylate

Benzyl chloroformate (3.3 ml) was added dropwise to a cold solution of Cis(±)ethyl 4-amino-3-methoxypiperidine-1-carboxylate hydrochloride salt (Intermediate 21; 5 g) in saturated $NaHCO_3$. The mixture was stirred at room temperature for 14 h. The white precipitate was filtered, washed well with water, dried in vacuo to give the title compound as a white solid (6.66 g). MS (ES) MH^+: 336 for $C_{17}H_{24}N_2O_5$; NMR: 1.21 (t, 3H), 1.52-1.67 (m, 2H), 3.08 (m, 2H), 3.28 (s, 3H), 3.41 (s, 2H), 3.74-3.92 (m, 2H), 3.96 (m, 2H), 4.14 (m, 1H), 5.10 (s, 2H), 7.24 (d, 1H), 7.44 (m, 5H).

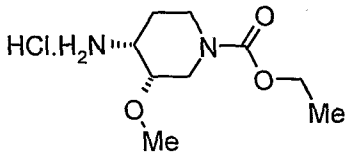
Intermediate 23 and Intermediate 24

ethyl (3*R*,4*S*)-4-{[(benzyloxy)carbonyl]amino}-3-methoxypiperidine-1-carboxylate and ethyl (3*S*,4*R*)-4-{[(benzyloxy)carbonyl]amino}-3-methoxypiperidine-1-carboxylate

Cis(±)ethyl 4-{[(benzyloxy)carbonyl]amino}-3-methoxypiperidine-1-carboxylate (Intermediate 22; 6.2 g) were separated into its enantiomers by chiral chromatography over a Chiralcel OJ column (eluant: hexanes/MeOH/EtOH;70/15/15;0.1% diethylamine). The fractions corresponding to the first chromatographic peak (Cis(-)isomer) were collected and evaporated yielding the title compound as a white solid (2.62 g). The fractions corresponding to the second chromatographic peak (Cis(+)isomer) were collected and evaporated yielding the title compound as a white solid (2.71 g). MS (ES) $(M+Na)^+$: 360 for $C_{17}H_{24}N_2O_5$; NMR: 1.21 (t, 3H), 1.52-1.67 (m, 2H), 3.08 (m, 2H), 3.28 (s, 3H), 3.41 (s, 2H), 3.74-3.92 (m, 2H), 3.96 (m, 2H), 4.14 (m, 1H), 5.10 (s, 2H), 7.24 (d, 1H), 7.44 (m, 5H).

Intermediate 25

ethyl (3*S*,4*R*)-4-amino-3-methoxypiperidine-1-carboxylate



Cis(+)ethyl 4-{[(benzyloxy)carbonyl]amino}-3-methoxypiperidine-1-carboxylate (Intermediate 24; 3.98 g) was dissolved in MeOH (100 ml) and 1N HCl (50 ml). 10% Pd-charcoal (600 mg) was added, degassed and hydrogenolysed under an atmosphere of H_2 gas at room temperature for 3 h. The catalyst was filtered through a bed of celite, concentrated in vacuo and lyophilized giving the title compound (2.8 g). MS (ES) MH^+: 202 for $C_9H_{18}N_2O_3$.

Intermediate 26

The title compound was prepared in a manner analogous to Intermediate 25 from the starting material indicated.

Int	Compound	MS	SM
26	ethyl (3*R*,4*S*)-4-amino-3-methoxypiperidine-1-carboxylate	MS (ES) MH^+: 202 for $C_9H_{18}N_2O_3$	Intermediate 23

Intermediate 27

Cis(±)ethyl-3-(allyloxy)-4-[(*tert*-butoxycarbonyl)amino]piperidine-1-carboxylate

A 50% aqueous solution of sodium hydroxide (3 ml) was added to a suspension of allyl bromide (693 mg, 5.70 mmol), cis(±)ethyl 4-[(tert-butoxycarbonyl)amino]-3-hydroxypiperidine-1-carboxylate (reference: C. H. Lee et al. *Syn. Commun.*, 2001, *31*, 1081.), (750 mg, 2.6 mmol), benzyltriethylammonium chloride (4 mg, cat.) and toluene (8 ml). The resultant mixture was stirred overnight at room temperature. The reaction mixture was diluted with EtOAc (150 ml) and water (35 ml). The organic phase was separated and the aqueous phase was back extracted with EtOAc (2 x 30 ml). The combined organic phase was washed with brine, dried over sodium sulfate, filtered and concentrated. The crude residue was purified by flash column chromatography (hexane/EtOAc, 3:2) to yield 734 mg of the title compound. MS (ES)(M+H): 329.for $C_{16}H_{28}N_2O_5$; NMR: 1.28 (t, 3H), 1.47 (s, 9H), 1.68 (m, 2H), 2.88 (brt, 2H), 3.50 (m, 1H), 3.68 (m, 1H), 3.90 (m, 1H), 4.00-4.45 (m, 3H), 4.10 (q, 2H), 4.92 (brs, 1H), 5.20 (m, 2H), 5.86 (m, 1H).

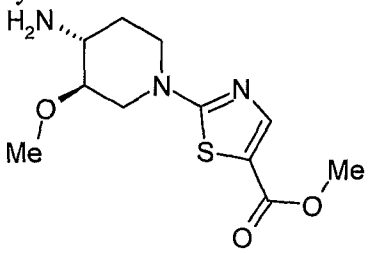
Intermediate 28

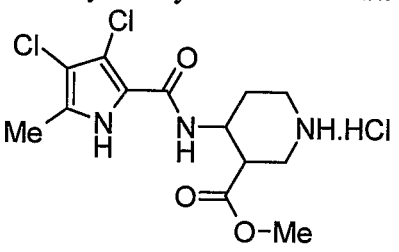
Cis(±)ethyl-3-(allyloxy)-4-amino]piperidine-1-carboxylate hydrochloride salt

4N HCl/dioxane (20 ml) was added to cis(±)ethyl-3-(allyloxy)-4-[(*tert*-butoxycarbonyl)amino]piperidine-1-carboxylate (Intermediate 27; 572 mg). The mixture was stirred at room temperature for 90 min. The solvent was removed in vacuo, dried in vacuo to give the title compound as an oily foam which was used without further purification (449 mg). MS (ES)(M+H): 228.for $C_{11}H_{20}N_2O_3$.

Intermediates 29-36

The following compounds were prepared in a manner analogous to Intermediate 28 from the starting material (SM) indicated.

Int	Compound	Data	SM
29	Cis(±)ethyl-4-amino-3-propyoxypiperidine-1-carboxylate hydrochloride salt	MS (ES)(M+H): 220 for $C_{11}H_{22}N_2O_3$	Intermediate 81
30	Methyl 2-[(3*R*,4*R*)-4-amino-3-methoxypiperidin-1-yl]-1,3-thiazole-5-carboxylate hydrochloride salt 	NMR: 1.63 (m, 1H), 2.08 (d, 1H), 2.97-3.01 (m, 1H), 3.21-3.24 (m, 2H), 3.25 (m, 2H), 3.40 (s, 3H), 3.73 (s, 3H), 3.88 (d, 1H), 4.34 (m, 1H), 7.87 (s, 1H), 8.28 (brs, 3H)	Intermediate 68
31	Methyl 2-[(3*S*,4*S*)-4-amino-3-methoxypiperidin-1-yl]-1,3-thiazole-5-carboxylate hydrochloride salt	NMR: 1.63 (m, 1H), 2.08 (d, 1H), 2.97-3.01 (m, 1H), 3.21-3.24 (m, 2H), 3.25 (m, 2H), 3.40 (s, 3H), 3.73 (s, 3H), 3.88 (d, 1H), 4.34 (m, 1H), 7.87 (s, 1H), 8.28 (brs, 3H)	Intermediate 69
32	Cis(±)3,4-dichloro-N-[3-fluoropiperidin-4-yl]-5-methyl-1H-pyrrole-2-carboxamide hydrochloride salt	NMR: 1.92-1.96 (m, 2H), 2.20 (s, 3H), 3.10 (m, 1H), 3.43-3.51 (m, 2H), 3.64 (m, 1H), 4.27-4.38 (m, 1H), 5.05 (d, 1H), 7.58 (d, 1H), 8.75 (brs, 1H), 9.43 (brs, 1H), 12.32 (s, 1H)	Intermediate 49

Int	Compound	Data	SM
33	3,4-dichloro-*N*-[(3*R*,4*S*)-3-fluoropiperidin-4-yl]-5-methyl-1*H*-pyrrole-2-carboxamide hydrochloride	MS (ES) (M+H): 294, 296 for $C_{11}H_{14}Cl_2FN_3O$	Intermediate 45
34	Trans(±)3,4-dichloro-N-[3-fluoropiperidin-4-yl]-5-methyl-1H-pyrrole-2-carboxamide hydrochloride	MS (ES)(M +H): 294, 296 for $C_{11}H_{14}Cl_2FN_3O$	Intermediate 44
35	Cis(±)methyl 4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidine-3-carboxylate hydrochloride salt 	MS (ES)(M +H): 332 for $C_{13}H_{17}Cl_2N_3O_3$	Intermediate 46
36	3,4-dichloro-*N*-[(3*S*,4*R*)-3-fluoropiperidin-4-yl]-5-methyl-1*H*-pyrrole-2-carboxamide hydrochloride	MS(ES)M+H): 294,296 for $C_{11}H_{14}Cl_2FN_3O$	Intermediate 48

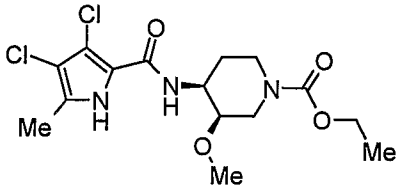
Intermediate 37

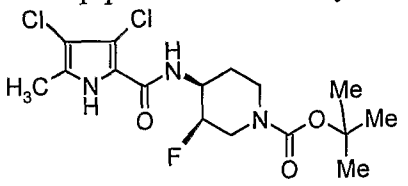
Cis(±)ethyl 4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate

3,4-Dichloro-5-methyl-1H-pyrrole-2-carboxylic acid (Intermediate 1; 304 mg) was dissolved in anhydrous DMF. HATU (596 mg), HOAT (213 mg) and DIEA (274 µl) were added and stirred at ambient for 15 min. Cis(±)ethyl 4-amino-3-methoxypiperidine-1-carboxylate (Intermediate 21; 317 mg) was added and the mixture was stirred at ambient for 18 h. The mixture was diluted with EtOAc and washed with water, 1N HCl, bicarbonate buffer, water, brine and dried over Na_2SO_4. The solution was concentrated in vacuo to give the title compound as a brown solid (503 mg). MS (ES) MH^+: 378, 380 for $C_{15}H_{21}Cl_2N_3O_4$; NMR: 1.29 (t, 3H), 1.79 (m, 2H), 2.27 (s, 3H), 3.12 (m, 2H), 3.30 (s, 3H), 3.37 (m, 1H), 3.83-4.16 (m, 5H), 7.25 (d, 1H), 12.23 (s, 1H).

Intermediates 38-49

The following compounds were prepared in a manner analogous to Intermediate 37 from the starting material (SM) indicated.

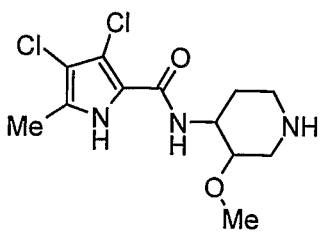
Int	Compound	Data	SM
38	Cis(±)ethyl-4-{[(3,4-difluoro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate	MS (ES) MH^+: 344 for $C_{15}H_{21}F_2N_3O_4$; NMR: 1.3 (t, 3H), 1.69 (m, 2H), 2.21 (s, 3H), 3.11 (m, 2H), 3.22 (s, 3H), 3.39 (m, 2H), 3.85 (q, 2H), 4.41 (m, 1H), 6.83 (d, 1H), 11.54 (s, 1H)	Intermediate 20 and Intermediate 21
39	ethyl (3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate	MS (ES) MH^+: 377 for $C_{15}H_{21}Cl_2N_3O_4$; NMR: 1.32 (t, 3H), 1.74 (m, 2H), 2.31 (s, 3H), 3.14 (m, 2H), 3.18-3.52 (s, 3H), 3.75-4.44 (m, 5H), 7.30 (d, 1H), 12.39 (s, 1H)	Intermediate 25 and Intermediate 1
40	ethyl (3*R*,4*S*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate 	MS (ES) MH^+: 377 for $C_{15}H_{21}Cl_2N_3O_4$; NMR: 1.32 (t, 3H), 1.74 (m, 2H), 2.31 (s, 3H), 3.14 (m, 2H), 3.18-3.52 (s, 3H), 3.75-4.44 (m, 5H), 7.30 (d, 1H), 12.39 (s, 1H)	Intermediate 26 and Intermediate 1
41	Ethyl 4-{[(4-chloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate	MS (ES) MH^+: for $C_{15}H_{22}ClN_3O_4$; NMR: 1.18 (t, *J*=7.06 Hz, 3H), 1.48 (d, *J*=3.58 Hz, 1H), 1.75 (td, *J*=12.29, 7.82 Hz, 1H), 2.10 - 2.18 (m, 3H), 2.95 (d, *J*=13.38 Hz, 2H), 3.20 - 3.27 (m, 3H), 3.27 - 3.35 (m, 2H), 3.38 (s, 1H), 3.97 - 4.09 (m, *J*=10.53, 7.08, 7.08, 3.39 Hz, 2H), 4.19 (s, 1H), 6.88 (d, *J*=2.64 Hz, 1H), 7.62 (d, *J*=7.91 Hz, 1H), 11.60 (s, 1H)	Intermediate 21 and Intermediate 6

Int	Compound	Data	SM
42	Cis(±)ethyl 3-(allyloxy)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidine-1-carboxylate	MS (ES) MH^+: 402, 404 for $C_{17}H_{23}Cl_2N_3O_4$	Intermediate 1 and Intermediate 28
43	Cis(±)ethyl 4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-propoxypiperidine-1-carboxylate	MS (ES) MH^+: 404, 406 for $C_{17}H_{25}Cl_2N_3O_4$	Intermediate 1 and Intermediate 29
44	Trans(±)*tert*-butyl-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidine-1-carboxylate	MS (ES) (M + Na): 416, 418 for $C_{16}H_{22}Cl_2FN_3O_3$	Intermediate 60 and Intermediate 1
45	*tert*-butyl (3*R*,4*S*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidine-1-carboxylate 	MS (ES) (M + Na): 416, 418 for $C_{16}H_{22}Cl_2FN_3O_3$	Intermediate 61 and Intermediate 1

Int	Compound	Data	SM
46, 47	1-*tert*-Butyl 3-methyl 4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidine-1,3-dicarboxylate **Note for Examples 46 and 47:** The resultant crude mixture dissolved in DCM, added to a silica gel column, and was purified using a gradient of 10-50% EtOAc in hexanes. The recovered mixture of diastereomers were taken up in EtOAc (200 ml), heated to 50°C, and filtered. The solid was washed with EtOAc and dried, to show a 90:10 cis:trans mixture of diastereomers (2.3 g, 30.6% yield) (Intermediate 46). The filtrate was then subjected to a recrystallisation using EtOAc and n-heptane, and a 90:10 trans:cis mixture (2.65 g, 35.3% yield) (Intermediate 47) was recovered.	46: MS (ES – $(M+H)^+$): 434, 436 for $C_{18}H_{25}Cl_2N_3O_5$; NMR 1.45 (s, 9H), 2.16 (m, 1H), 2.27 (s, 3H), 2.55 (dt, 1H), 2.93 (m, 1H), 3.09 (m, 2H), 3.66 (s, 3H), 4.08 (m, 1H), 4.29 (m, 2H), 6.68 (d, 1H), 9.66 (s, 1H) 47: MS (ES) $MH)^+$: 434, 436 for $C_{18}H_{25}Cl_2N_3O_5$; NMR: 1.44 (s, 9H), 1.75 (m, 1H), 2.09 (m, 1H), 2.26 (s, 3H), 2.86 (m, 1H), 2.98 (m, 1H), 3.17 (dd, 1H), 3.71 (s, 3H), 4.04 (m, 1H), 4.44 (m, 2H), 7.57 (d, 1H), 9.53 (s, 1H)	Intermediate 70 and Intermediate 1
48	*tert*-butyl (3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidine-1-carboxylate	MS (ES) (M + Na): 416, 418 for $C_{16}H_{22}Cl_2FN_3O_3$	Intermediate 64 and Intermediate 1
49	Cis(±)*tert*-butyl-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidine-1-carboxylate	NMR ($CDCl_3$): 1.47 (s, 9H), 1.84-1.88 (m, 2H), 2.28 (s, 3H), 2.76-3.02 (m, 2H), 4.11-4.26 (m, 2H), 4.43-4.51 (m, 1H), 4.77 (d, 1H)	Intermediate 59 and Intermediate 1

Intermediate 50

Cis(±)3,4-dichloro-N-(3-methoxypiperidin-4-yl)-5-methyl-1H-pyrrole-2-carboxamide



The title compound was prepared by the methods described below:

Method A

Cis(±)ethyl 4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate (Intermediate 37; 503 mg) was dissolved in MeOH (30 ml). 1 M NaOH was added and the mixture was heated at 100 °C for 12 h. The reaction mixture was cooled to ambient and extracted with EtOAc, washed with water, dried over Na_2SO_4 and concentrated in vacuo to give the title compound as a brown oily gum which was used without further purification (336 mg).

Method B

Cis(±)ethyl-4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate (Intermediate 37; 3.85 g) was suspended in anhydrous CH_3CN. Iodotrimethylsilane (2.2 ml) was added slowly. The reaction was heated to reflux for several hours until complete by LCMS. The crude reaction mixture was diluted with water and acidified with 1N HCl to pH 3. The solution was extracted with EtOAc. The aqueous layer was basified with 50% NaOH to pH 10. The aqueous layer as saturated with sodium chloride and extracted with THF, dried with $MgSO_4$ and concentrated to a tan solid (2.1 g). MH^+: 306 for $C_{12}H_{17}Cl_2N_3O_2$; NMR: 1.61 (d, *J*=3.77 Hz, 2H), 1.76 (dt, *J*=6.50, 3.16 Hz, 1H), 2.16 - 2.20 (m, 3H), 2.56 - 2.69 (m, 2H), 2.90 (d, *J*=13.19 Hz, 1H), 3.18 (dd, *J*=13.75, 3.01 Hz, 1H), 3.30 - 3.35 (m, 3H), 3.56 - 3.64 (m, 1H), 4.04 - 4.15 (m, *J*=8.10, 7.72, 7.72, 3.01 Hz, 1H), 7.14 (d, *J*=8.29 Hz, 1H).

Intermediates 51-56

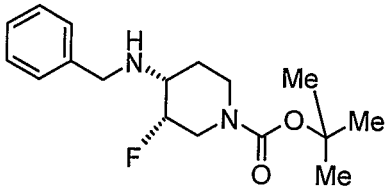
The following Intermediates were prepared as described by the general methods described in Intermediate 50 from the starting materials (SM) indicated.

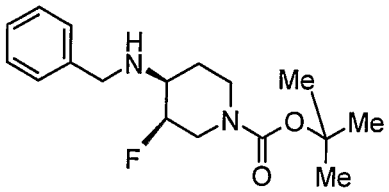
Int	Compound	Data	SM
51	3,4-dichloro-N-(3*S*, 4*R*)[3-methoxypiperidin-4-yl]-5-methyl-1H-pyrrole-2-carboxamide	M/z 306; 1.73 (m, 2H), 2.31 (s, 3H), 2.64 (m, 1H), 2.98 (m, 1H), 3.22 (m, 1H), 3.34 (m, 1H), 3.34 (s, 3H), 3.42 (m, 2H), 4.25 (m, 1H), 7.31 (d, 1H).	Intermediate 39
52	3,4-dichloro-N-(3*R*, 4*S*)[3-methoxypiperidin-4-yl]-5-methyl-1H-pyrrole-2-carboxamide	M/z 306; 1.73 (m, 2H), 2.31 (s, 3H), 2.64 (m, 1H), 2.98 (m, 1H), 3.22 (m, 1H), 3.34 (m, 1H), 3.34 (s, 3H), 3.42 (m, 2H), 4.25 (m, 1H), 7.31 (d, 1H).	Intermediate 40

Int	Compound	Data	SM
53	Cis(±)3,4-dichloro-5-methyl-N-(3-propoxypiperidin-4-yl)-1H-pyrrole-2-carboxamide	M/z 334	Intermediate 43
54	Cis(±)3,4-dichloro-5-methyl-N-(3-allyoxypiperidin-4-yl)-1H-pyrrole-2-carboxamide	M/z 332	Intermediate 42
55	Cis(±)4-chloro-N-(3-methoxypiperidin-4-yl)-5-methyl-1H-pyrrole-2-carboxamide	M/z 272; 1.41 (s, 1H), 1.67 (s, 1H), 2.13 (s, 3H), 2.47 (s, 1H), 2.55 (s, 1H), 2.86 (s, 1H), 3.08 (d, J=13.19 Hz, 1H), 3.25 (s, 3H), 3.31 (s, 1H), 6.89 (d, J=2.45 Hz, 1H), 7.52 (s, 1H), 11.59 (s, 1H)	Intermediate 41
56	Cis(±)3,4-difluoro-N-(3-methoxypiperidin-4-yl)-5-methyl-1H-pyrrole-2-carboxamide	M/z 273; 1.74 (m, 2H), 2.24 (s, 3H), 3.00 (m, 1H), 3.21 (m, 1H), 3.36 (s, 3H), 3.42 (m, 4H), 4.20 (brm, 1H), 6.74 (brm, 1H), 11.60 (brs, 1H).	Intermediate 38

Intermediate 57 and Intermediate 58

tert-Butyl-(3*S*,4*R*)-4-(benzylamino)-3-fluoropiperidine-1-carboxylate and *tert*-Butyl-(3*R*,4*S*)-4-(benzylamino)-3-fluoropiperidine-1-carboxylate





Cis(±)*tert*-butyl-4-(benzylamino)-3-fluoropiperidine-1-carboxylate (Intermediate 82; 2.2 g) was separated into the title compounds using chiral HPLC, in a manner analogous to Intermediate 23 and Intermediate 24 over a Chiralpak AD column (eluent: hexanes / MeOH / EtOH; 90 / 2.5 / 2.5; 0.1% diethylamine). The fractions corresponding to the first chromatographic peak (Cis(+) isomer; Intermediate 57) were collected and evaporated yielding the title compound as a white solid (942 mg). The fractions corresponding to the second chromatographic peak (Cis(-) isomer; Intermediate 58) were collected and evaporated yielding the title compound as a white solid (980 mg). NMR ($CDCl_3$): 1.40 (s, 9H), 1.88 (m, 2H), 3.01 (m, 2H), 3.55 (m, 2H), 3.77 (m, 1H), 4.66 (d, 1H).

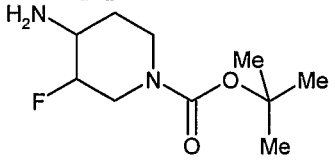
Intermediate 59

Cis(±)*tert*-butyl-4-amino-3-fluoropiperidine-1-carboxylate

Cis(±)*tert*-butyl-4-(benzylamino)-3-fluoropiperidine-1-carboxylate (Intermediate 82; 711 mg), ammonium formate (582 mg), and 10% Pd/C (200 mg) in MeOH (10 ml) was heated to 50 °C for 1 h. The reaction mixture was cooled to room temperature, filtered through diatomaceous earth and concentrated under reduced pressure to give the title compound (503 mg, quantitative). NMR ($CDCl_3$): 1.40 (s, 9H), 1.88 (m, 2H), 3.01 (m, 2H), 3.55 (m, 2H), 3.77 (m, 1H), 4.66 (d, 1H).

Intermediates 60-64

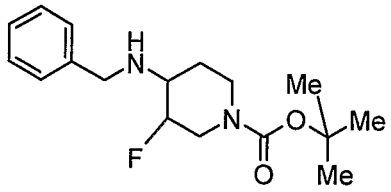
The following Intermediates were prepared by the procedure described in Intermediate 59 from the starting materials (SM) indicated.

Int	Compound	Data	SM
60	Trans(±)tert-butyl-4-amino-3-fluoropiperidine-1-carboxylate 	NMR ($CDCl_3$): 1.38 (s, 9H), 1.88 (m, 2H), 2.87 (m, 2H), 3.59 (m, 2H), 3.77 (m, 1H), 4.66 (d, 1H)	Intermediate 65
61	*tert*-butyl (3*R*,4*S*)-4-amino-3-fluoropiperidine-1-carboxylate	NMR ($CDCl_3$): 1.40 (s, 9H), 1.88 (m, 2H), 3.01 (m, 2H), 3.55 (m, 2H), 3.77 (m, 1H), 4.66 (d, 1H)	Intermediate 58
62	tert-Butyl [(3R,4R)-3-methoxypiperidin-4-yl]carbamate	NMR ($CDCl_3$): 1.45 (s, 9H), 2.43 (m, 1H), 2.50-2.57 (m, 1H), 2.59-2.66 (m, 1H), 2.89 (m, 1H), 3.01 (m, 1H), 3.24 (m, 1H), 3.41 (s, 3H), 3.67 (m, 1H), 4.71 (m, 1H)	Intermediate 66
63	tert-Butyl [(3S,4S)-3-methoxypiperidin-4-yl]carbamate	NMR ($CDCl_3$): 1.45 (s, 9H), 2.43 (m, 1H), 2.50-2.57 (m, 1H), 2.59-2.66 (m, 1H), 2.89 (m, 1H), 3.01 (m, 1H), 3.24 (m, 1H), 3.41 (s, 3H), 3.67 (m, 1H), 4.71 (m, 1H)	Intermediate 67

Int	Compound	Data	SM
64	*tert*-butyl (3*S*,4*R*)-4-amino-3-fluoropiperidine-1-carboxylate	NMR ($CDCl_3$): 1.40 (s, 9H), 1.88 (m, 2H), 3.01 (m, 2H), 3.55 (m, 2H), 3.77 (m, 1H), 4.66 (d, 1H)	Intermediate 57

Intermediate 65

Trans(±)*tert*-butyl 4-(benzylamino)-3-fluoropiperidine-1-carboxylate



The title compound was prepared as described in Monique B. van Neil et al. *J. Med. Chem.*, 1999, *42*, 2087-2104 and the references therein. NMR ($CDCl_3$): 1.40 (s, 9H), 1.88 (m, 2H), 3.01 (m, 2H), 3.55 (m, 2H), 3.77 (m, 1H), 4.66 (d, 1H).

Intermediate 66

tert-Butyl [(3R,4R)-1-benzyl-3-methoxypiperidin-4-yl]carbamate

The title compound (150 mg) was prepared from *tert*-butyl [(3*R*,4*R*)-1-benzyl-3-hydroxypiperidin-4-yl]carbamate by the procedure described (for similar compounds) in *Synth. Commun.*, 2001, *31*, 1081-1089. NMR ($CDCl_3$): 1.44 (s, 9H), 1.97-2.11 (m, 3H), 2.68 (d, 1H), 3.07-3.12 (m, 2H), 3.36 (s, 3H), 3.41 (m, 1H), 3.52 (m, 2H), 4.51 (m, 1H), 7.23-7.32 (m, 5H).

Intermediate 67

tert-Butyl [(3S,4S)-1-benzyl-3-methoxypiperidin-4-yl]carbamate

The title compound (426 mg) was prepared from *tert*-butyl [(3*S*,4*S*)-1-benzyl-3-hydroxypiperidin-4-yl]carbamate by the procedure described (for similar compounds) in *Synth. Commun.*, 2001, *31*, 1081-1089. NMR ($CDCl_3$): 1.44 (s, 9H), 1.97-2.11 (m, 3H), 2.68 (d, 1H), 3.07-3.12 (m, 2H), 3.36 (s, 3H), 3.41 (m, 1H), 3.52 (m, 2H), 4.51 (m, 1H), 7.23-7.32 (m, 5H).

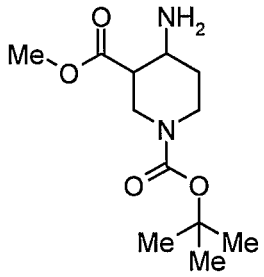
Intermediates 68-69

The following Intermediates were prepared by the procedure described in Example 1 from the starting materials (SM) indicated.

Int	Compound	Data	SM
68	2-{(3*R*,4*R*)-4-[(*tert*-Butoxycarbonyl)amino]-3-methoxypiperidin-1-yl}-1,3-thiazole-5-carboxylate	MS (ES) (M + Na): 394 for $C_{16}H_{25}N_3O_5S$; NMR ($CDCl_3$): 1.46 (s, 9H), 1.66 (m, 1H), 1.89 (m, 1H), 2.29 (m, 1H), 3.13-3.20 (m, 3H), 3.47 (s, 3H), 3.75 (m, 1H), 3.83 (s, 3H), 4.20 (m, 1H), 4.60 (brs, 1H), 7.85 (s, 1H)	Intermediate 62 and methyl 2-bromo-1,3-thiazole-5-carboxylate
69	2-{(3*S*,4*S*)-4-[(*tert*-Butoxycarbonyl)amino]-3-methoxypiperidin-1-yl}-1,3-thiazole-5-carboxylate	MS (ES) (M + Na): 394 for $C_{16}H_{25}N_3O_5S$; NMR ($CDCl_3$): 1.46 (s, 9H), 1.66 (m, 1H), 1.89 (m, 1H), 2.29 (m, 1H), 3.13-3.20 (m, 3H), 3.47 (s, 3H), 3.75 (m, 1H), 3.83 (s, 3H), 4.20 (m, 1H), 4.60 (brs, 1H), 7.85 (s, 1H)	Intermediate 63 and methyl 2-bromo-1,3-thiazole-5-carboxylate

Intermediate 70

1-*tert*-Butyl-3-methyl-4-aminopiperidine-1,3-dicarboxylate



The title compound was prepared according to (Cordero, F.M et al. *Gazz. Chim. Ital.* 1997, 127, 25-29). Thus, 1-*tert*-butyl-3-methyl-4-hydroxy-5,6-dihydropyridine-1,3-(2*H*)-dicarboxylate (Intermediate 9; 33 g) and NH_4OAc (100 g) were dissolved in dry MeOH (250 ml). $NaCNBH_3$ (8.1 g) was added in three equal portions at 1 h intervals. The reaction mixture was stirred at room temperature overnight. The reaction was monitored by GC/MS and additional NH_4OAc (2.5 equiv.) and $NaCNBH_3$ (0.25 equiv.) were added until reaction was completed. The reaction was cooled to –10 °C and acidified to pH = 2 with concentrated HCl and solvent was removed in vacuo. The solid residue was dissolved in water, and extracted with Et_2O. The pH of the aqueous phase was adjusted to 8-9 with solid KOH, solution

saturated with NaCl and extracted with EtOAc. The organic layer was dried over K_2CO_3, filtered and concentrate to an oil (25 g). GC/MS: 258 for $C_{12}H_{22}N_2O_4$.

Intermediate 71

Cis(±)*tert*-butyl-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(hydroxymethyl)piperidine-1-carboxylate

Cis(±)1-*tert*-butyl-3-methyl-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-piperidine-1,3-dicarboxylate (Intermediate 46; 4.26 g) and $LiBH_4$ (321 mg) were combined in dry THF (20 ml). MeOH (600 µl) was added in a single portion. The reaction was heated to reflux for 1 h. The mixture was cooled to room temperature, diluted with EtOAc and washed with 0.5% HCl. The organic layer was dried over Na_2SO_4, filtered and concentrated to a solid which was purified by flash column chromatography eluting with (60% EtOAc / 40% hexanes), to yield title compound (3.11 g). MS (ES) (MH^+): 406 for $C_{17}H_{25}Cl_2N_3O_4$; NMR ($CDCl_3$): 1.47 (s, 9H), 1.56 (m, 1H), 1.96 (m, 1H), 2.27 (s, 3H), 2.84 (m, 1H), 2.9 (m, 1H), 3.49 (m, 1H), 3.71 (m, 1H), 4.16 (m, 5H), 6.58 (d, 1H), 10.1 (brs, 1H).

Intermediate 72

Cis(±)*tert*-butyl-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-({[(4-methylphenyl)sulfonyl]oxy}methyl)piperidine-1-carboxylate.

Cis(±)*tert*-butyl-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(hydroxymethyl)piperidine-1-carboxylate (Intermediate 71; 1.46 g) was dissolved in dry pyridine (20 ml) and cooled to 0 °C. Tosylchloride (822 mg) was added in a single portion. The reaction was allowed to slowly warm to room temperature and stirred overnight. The mixture was diluted with EtOAc and washed with water, dried over Na_2SO_4, filtered and concentrated in vacuo. The foam was purified by flash column chromatography eluting with (40% EtOAc / 60% hexanes) to give title compound (1.58 g). MS (ES) (MH^+): 560 for $C_{24}H_{31}Cl_2N_3O_6S$; NMR ($CDCl_3$): 1.46 (brs, 11H), 1.89 (m, 1H), 1.98 (m, 1H), 2.31 (s, 3H), 2.35 (s, 3H), 2.8 (m, 2H), 3.96-4.23 (m, 4H), 6.4 (d, 1H), 7.19 (d, 2H), 7.68 (d, 2H), 10.3 (brs, 1H).

Intermediate 73

Cis(±)4-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)-amino]-3-methoxymethyl-piperidine-1-carboxylic acid tert-butyl ester.

Cis-*tert*-butyl-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-({[(4-methylphenyl)sulfonyl]oxy}methyl)piperidine-1-carboxylate (Intermediate 72; 325 mg) was dissolved in 5 ml of a 30wt% MeOH solution containing NaOMe and an additional 5 ml of dry MeOH. The homogeneous reaction was stirred at room temperature for 2 days. Upon reacting, solids began to precipitate from solution. The reaction was concentrated to a solid residue, re-dissolved in EtOAc and washed with saturated NH_4Cl (2x10 ml). The organic layer was dried over Na_2SO_4, filtered and concentrated. The residual material was purified by flash column chromatography eluting with (1:1 EtOAc / hexanes) to give the title compound (192 mg). MS (ES) (MH^+): 420 for $C_{19}H_{27}Cl_2N_3O_4$.

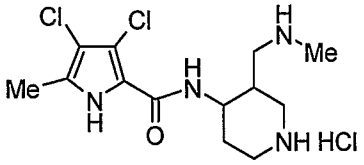
Intermediate 74

Cis(±)3,4-dichloro-*N*-[3-(methoxymethyl)piperidin-4-yl]-5-methyl-1*H*-pyrrole-2-carboxamide hydrochloride

Cis(±)*tert*-butyl4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(methoxymethyl)piperidine-1-carboxylate (Intermediate 73; 192 mg, 0.45 mmol) was dissolved in 4N HCl in dioxane (10 ml) and 10 ml of MeOH. The mixture was stirred at room temperature for 3 h, concentrated to dryness and azeotroped with MeOH to remove excess HCl (5 x 20 ml) to yield the title compound which was used without purification.(crude mixture 195 mg). MS (ES) (MH^+): 320 for $C_{13}H_{19}Cl_2N_3O_2$.

Intermediates 75-76

The following Intermediates were prepared by the procedure described in Intermediate 74 from the starting materials (SM) indicated.

Int	Compound	Data	SM
75	Cis(±)3,4-Dichloro-5-methyl-1H-pyrrole-2-carboxylic acid (3-methylaminomethyl-piperidin-4-yl)-amide hydrochloride 	MS (ES) MH^+: 319 for $C_{13}H_{20}Cl_2N_4O$	Intermediate 77
76	Cis-3,4-dichloro-5-methyl-1H-pyrrole-2-carboxylic acid (3-dimethylaminomethyl-piperidin-4-yl)-amide hydrochloride	MS (ES) MH^+: 333 for $C_{14}H_{22}Cl_2N_4O$	Intermediate 78

Intermediate 77

Cis(±)4-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)-amino]-3-methylaminomethyl-piperidine-1-carboxylic acid tert-butyl ester

Cis(±)*tert*-butyl-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-({[(4-methylphenyl)sulfonyl]oxy}methyl)-piperidine-1-carboxylate (Intermediate 72; 500 mg, 0.89 mmol) was dissolved in 5 ml of a 2.0 M THF solution containing $MeNH_2$. The reaction vessel was sealed and heated to 100 °C for 2 h. The mixture was cooled to room temperature and diluted with EtOAc, then washed with water. The organic layer was dried over Na_2SO_4, filtered and concentrated to a crude solid foam which was used without further purification. MS (ES)MH^+: 419 for $C_{18}H_{28}Cl_2N_4O_3$.

Intermediate 78

The title compound was prepared in a manner analogous to Intermediate 77 from the starting material indicated.

Int	Compound	MS	SM
78	Cis(±)4-[(3,4-Dichloro-5-methyl-1H-pyrrole-2-carbonyl)-amino]-3-dimethylaminomethyl-piperidine-1-carboxylic acid tert-butyl ester	MS (ES) MH^+: 433 for $C_{19}H_{30}Cl_2N_4O_3$	Intermediate 72 and dimethylamine

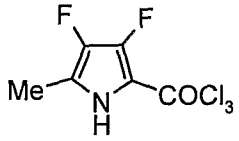
Intermediate 79

Cis(±)4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidine-3-carboxylic acid hydrochloride

THF (10 ml) and MeOH (8 ml) were added to cis(±)1-*tert*-butyl 3-methyl 4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidine-1,3-dicarboxylate (Intermediate 46; 2.24 g). The resultant mixture was cooled to 0°C, and a solution of lithium hydroxide (0.37 g) in water (5 ml) at 0°C was added dropwise via pipette, producing a clear, lightly yellow solution. The reaction was stirred at 0 °C for 2 h, stored overnight in a freezer without stirring, then stirred again at 0°C for six hours. The reaction was acidified to pH 3 with 2N HCl 9~7 ml), and was concentrated *in vacuo*. The resultant mixture was dissolved in EtOAc (125 ml) and a saturated aqueous sodium chloride solution (40 ml), followed by the addition of 2N HCl (~ 1 ml) to acidify the aqueous layer to pH 1. The phases were separated and the aqueous layer was washed with EtOAc (2 x 60 ml). The combined EtOAc layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The resultant white solid was suspended in anhydrous THF (35 ml) under an argon atmosphere, cooled to 0°C, followed by the addition of 4 M HCl in 1,4-dioxane (10 ml, 40 mmol). The reaction was warmed to room temperature, producing a clear orange-red solution. The reaction was stirred overnight at room temperature, followed by the addition of 5 ml of 4 M HCl in 1,4-dioxane. The reaction was stirred for two days at room temperature, then heated to 50°C for two hours, and allowed to slowly cool to room temperature overnight. The reaction was concentrated *in vacuo*, and carried on to the next reaction without further purification (5.16 mmol). MS (ES)$(M+H)^+$): 320, 322 for $C_{12}H_{15}Cl_2N_3O_3$.

Intermediate 80

2,2,2-Trichloro-1-(3,4-difluoro-5-methyl-1*H*-pyrrol-2-yl)ethanone



3,4-Difluoro-2-methyl-1*H*-pyrrole (Intermediate 8; 3.8 g) was dissolved in anhydrous diethyl ether (100 ml). Anhydrous K_2CO_3 (12.5 g) was added followed by trichloroacetyl chloride (10 ml). The mixture was stirred at room temperature under N_2 for 2 h, poured into a cold saturated solution of $NaHCO_3$, stirred for 10 min, and extracted with ether. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to give a red

brown oil. Trituration with pentane (50 ml)/DCM (2 ml), at –20 °C overnight to gave the title compound as a brown powder (1.3 g). MS (ES) MH^+: 262 for $C_7H_4Cl_3F_2NO$; NMR ($CDCl_3$): 2.35 (d, 3H), 9.0 (brs, 1H).

Intermediate 81

Cis(±)ethyl-4-[(*tert*-butoxycarbonyl)amino]-3-(propyoxypiperidine-1-carboxylate

Cis(±)ethyl-3-(allyloxy)-4-[(*tert*-butoxycarbonyl)amino]piperidine-1-carboxylate (Intermediate 27; 528 mg) was dissolved in MeOH (20 ml). 10% Pd-C (100 mg) was added and the mixture was evacuated and replaced with H_2 gas twice. The mixture was stirred under an atmosphere of H_2 gas for 12 h. The catalyst was removed over a bed of celite and solvent was removed in vacuo to give the title compound as an oil (445 mg). NMR: 0.94 (m, 3H), 1.25 (m, 3H), 1.43 (s, 9H), 1.53 (m, 2H), 1.71 (m, 1H), 3.04 (m, 2H), 3.37 (m, 2H), 3.50 (m, 2H), 3.69 (m, 1H), 3.89 (m, 1H), 4.15 (m, 2H), 6.5 (d, 1H).

Intermediate 82

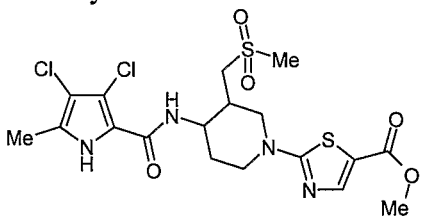
Cis(±)*tert*-butyl 4-(benzylamino)-3-fluoropiperidine-1-carboxylate

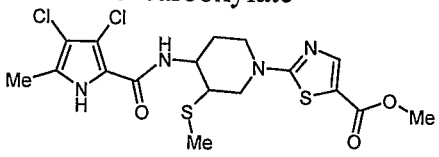
The title compound was prepared as described in Monique B. van Neil et al. *J. Med. Chem.*, 1999, *42*, 2087-2104 and the references therein. NMR ($CDCl_3$): 1.40 (s, 9H), 1.88 (m, 2H), 3.01 (m, 2H), 3.55 (m, 2H), 3.77 (m, 1H), 4.66 (d, 1H).

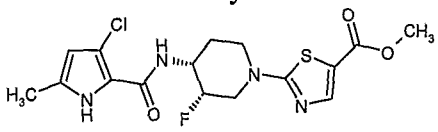
Examples 87-193

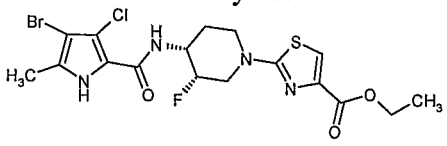
The following Examples were prepared by the procedure described in Example 1 from the starting materials (SM) indicated.

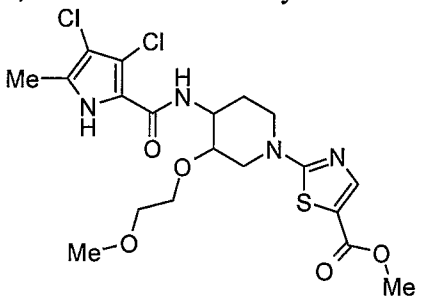
Ex	Compound	Data	SM
87	Cis(±)-methyl 2-[4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(hydroxymethyl)piperidin-1-yl]-1,3-thiazole-5-carboxylate.	MS (ES) MH^+:447, 449 for $C_{17}H_{20}Cl_2N_4O_4S$.	Intermediate115 and methyl 2-bromo-1,3-thiazole-5-carboxylate
88	Cis(±)-methyl 2-{4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-[(methylthio)methyl]piperidin-1-yl}-1,3-thiazole-5-carboxylate.	MS (ES) MH^+: 477, 479 for $C_{18}H_{22}Cl_2N_4O_3S_2$.	Intermediate116 and methyl 2-bromo-1,3-thiazole-5-carboxylate

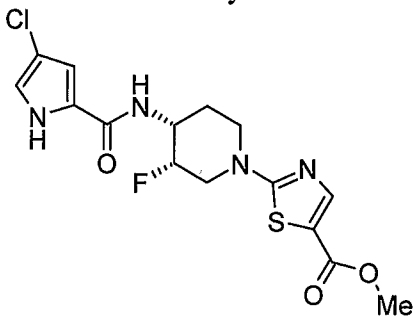
Ex	Compound	Data	SM
89	Cis(±)-methyl 2-{4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-[(methylsulfinyl)methyl]piperidin-1-yl}-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 493, 495 for $C_{18}H_{22}Cl_2N_4O_4S_2$.	Example 88 and methyl 2-bromo-1,3-thiazole-5-carboxylate
90	Cis(±)-methyl 2-{4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-[(methylsulfonyl)methyl]piperidin-1-yl}-1,3-thiazole-5-carboxylate 	MS (ES) MH^+: 509, 511 for $C_{18}H_{22}Cl_2N_4O_5S_2$.	Example 88 and methyl 2-bromo-1,3-thiazole-5-carboxylate
91	Ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-5-methyl-1,3-thiazole-4-carboxylate.	MS (ES) MH^+: 463, 465 for $C_{18}H_{21}Cl_2FN_4O_3S$.	Intermediate 36 and Intermediate179
92	Ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-methyl-1,3-thiazole-4-carboxylate	MS (ES) MH^+: 475, 477 for $C_{19}H_{24}Cl_2N_4O_4S$.	Intermediate 51 and Intermediate179
93	Ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-5-formyl-1,3-thiazole-4-carboxylate	MS (ES) MH^+: 477, 479 for $C_{18}H_{19}Cl_2FN_4O_4S$.	Intermediate 36 and Intermediate181
94	Ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-5-[(methoxyimino)methyl]-1,3-thiazole-4-carboxylate	MS (ES) MH^+: 506, 508 for $C_{19}H_{22}Cl_2FN_5O_4S$; ^1H NMR ($CDCl_3$): 1.41 (m, 6H), 2.0 (m, 4H), 2.3 (s,6H), 3.2 (m, 4H), 3.9 (s, 3H), 4.0 (s, 3H), 4.4 (m, 10H), 4.8 (s, 1H), 4.9 (s, 1H), 7.0 (s, 2H), 8.5 (s, 1H), 8.8 (s, 1H), 9.6 (s, 2H)	Intermediate93 and methoxyamine hydrochloride

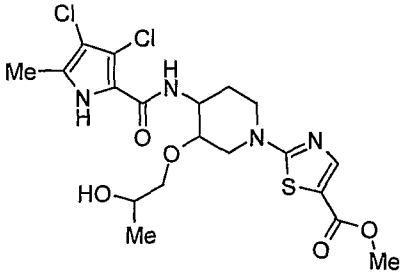
Ex	Compound	Data	SM
95	Cis(±)-methyl 2-[(-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(methylthio)piperidin-1-yl]-1,3-thiazole-5-carboxylate 	MS (ES) MH^+: 463.1 for $C_{17}H_{20}Cl_2N_4O_3S_2$; NMR: 1.90 (m, 2H); 2.14 (s, 3H); 2.28 (s, 3H); 3.28-3.45 (m, 2H); 3.74 (s, 3H); 3.77 (m, 1H); 3.95 (m, 2H); 4.44 (m, 1H); 7.25 (d, 1H); 7.85 (s, 1H); 12.14 (s, 1H)	Intermediate 117 and Intermediate 1
96	Cis(±)-methyl 2-[4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(methylsulfonyl)piperidin-1-yl]-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 495 for $C_{17}H_{20}Cl_2N_4O_5S_2$; NMR: 1.88 (m, 2H); 2.18 (s, 3H); 3.07 (s, 3H); 3.45 (t, 1H); 3.61 (t, 1H); 3.60-3.85 (m, 2H); 3.77 (s, 3H); 4.48 (m, 1H); 4.68 (m, 1H); 7.52 (d, 1H); 7.93 (s, 1H); 12.07 (s, 1H)	Intermediate95
97	Cis(±)methyl 2-(3-(benzyloxy)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 523 for $C_{23}H_{24}Cl_2N_4O_4S$; NMR: 1.73 (m, 2H); 2.12 (s, 3H); 3.36 (m, 2H); 3.68 (s, 3H); 3.71 (m, 2H); 3.90 (m, 1H); 4.25 (m, 1H); 4.40 (d, 1H); 4.65 (d, 1H); 7.02 (d, 1H); 7.19 (s, 5H); 7.79 (s, 1H); 12.06 (s, 1H)	Intermediate 118 and methyl 2-bromo-1,3-thiazole-5-carboxylate
98	Cis(±)-methyl 2-[4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(prop-2-yn-1-yloxy)piperidin-1-yl]-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 471 for $C_{19}H_{20}Cl_2N_4O_4S$; NMR: 1.76 (m, 2H); 2.18 (s, 3H); 3.36 (m, 2H); 3.44 (t, 1H); 3.74 (s, 3H); 3.87 (s, 1H); 3.98 (m, 1H); 4.22-4.36 (m, 4H); 7.15 (d, 1H); 7.83 (s, 1H); 12.15 (s, 1H)	Intermediate 119 and methyl-2-bromo-1,3-thiazole-5-carboxylate
99	Trans-(±)methyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-hydroxypiperidin-1-yl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 433 for $C_{16}H_{18}Cl_2N_4O_4S$; NMR: 1.62 (m, 1H), 2.02 (m, 1H), 2.18 (s, 3H), 3.12 (m, 1H), 3.63 (m, 1H), 3.75 (s, 3H), 3.87 (m, 2H), 4.02 (m, 1H), 5.37 (d, 1H), 5.76 (s, 1H), 7.19 (d, 1H), 7.87 (s, 1H), 11.99 (s, 1H)	Intermediate 120 and methyl 2-bromo-1,3-thiazole-5-carboxylate

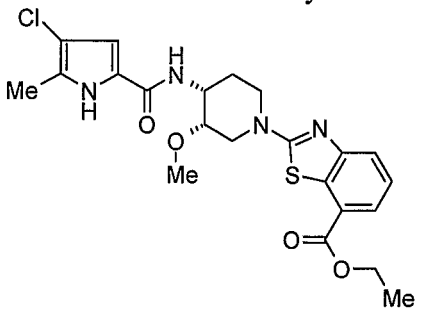
Ex	Compound	Data	SM
100	methyl 2-((3S,4R)-4-{[(3-chloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-5-carboxylate 	1.87 (m, 2H); 2.17 (s, 3H); 3.34 (m 1H); 3.60 (m 1H); 3.75 (s, 3H); 4.01 (m, 1H); 4.33 (m, 2H); 4.96 (d, br, 1H); 5.95 (s, 1H); 7.10 (d, 1H); 7.85 (s, 1H); 11.63 (s, 1H)	Intermediate 121 and methyl 2-bromo-1,3-thiazole-5-carboxylate
101	ethyl 2-((3S,4R)-4-{[(3-chloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-4-carboxylate	1.37 (t, 3H); 2.00 (m, 2H); 2.26 (s, 3H); 3.31 (m 2H); 4.21 (m, 1H); 4.34 (q, 2H); 4.45 (m, 2H); 4.90 (d, br, 1H); 5.93 (s, 1H); 6.97 (d, 1H); 7.46 (s, 1H); 8.98 (s, br, 1H)	Intermediate 121 and ethyl 2-bromo-1,3-thiazole-4-carboxylate
102	ethyl 2-((3S,4R)-4-{[(3-chloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-benzothiazole-7-carboxylate	MS (ES) MH^+: 465 for $C_{21}H_{22}ClFN_4O_3S$ NMR δ: 1.44 (t, 3H); 2.03 (m, 2H); 2.27 (s, 3H); 3.40 (m 2H); 4.36 (m, 2H); 4.44 (q, 2H); 4.67 (m, 1H); 4.90 (d, br, 1H); 5.93 (s, 1H); 7.05 (d, 1H); 7.37 (t, 1H); 7.71 (d, 1H); 7.79 (d, 1H); 9.89 (s, br, 1H)	Intermediate 121 and ethyl 2-bromo-1,3-benzothiazole-7-carboxylate
103	methyl 2-((3S,4R)-4-{[(4-bromo-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 446 for $C_{16}H_{18}BrFN_4O_3S$; NMR: 1.97 (m, 2H); 2.23 (s, 3H); 3.34 (m 2H); 3.80 (s, 3H); 4.26 (m, 2H); 4.55 (m, 1H); 4.86 (d, br, 1H); 6.0 (d, 1H); 6.53 (s, 1H); 7.82 (s, 1H); 9.83 (s, br, 1H)	Intermediate 122 and methyl 2-bromo-1,3-thiazole-5-carboxylate
104	methyl 2-((3S,4R)-4-{[(4-bromo-3-chloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 480 for $C_{16}H_{17}BrClFN_4O_3S$; NMR δ: 1.86 (m, 2H); 2.19 (s, 3H); 3.44 (m 1H); 3.60 (m 1H); 3.75 (s, 3H); 4.01 (m, 1H); 4.33 (m, 2H); 4.96 (d, br, 1H); 7.28 (d, 1H); 7.85 (s, 1H); 12.18 (s, 1H)	Intermediate 123 and methyl 2-bromo-1,3-thiazole-5-carboxylate

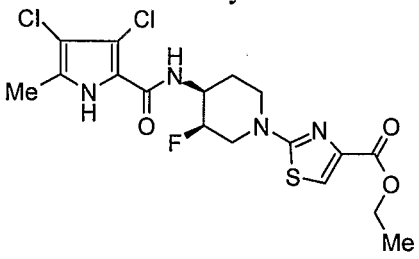
Ex	Compound	Data	SM
105	ethyl 2-((3S,4R)-4-{[(4-bromo-3-chloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-4-carboxylate 	MS (ES) MH^+: 494 for $C_{17}H_{19}BrClFN_4O_3S$; NMR δ: 1.22 (t, 3H); 1.81 (m, 2H); 2.15 (s, 3H); 3.41 (m 2H); 3.90 (m, 1H); 4.20 (q, 2H); 4.30 (m, 1H); 4.92 (d, br, 1H); 5.72 (s, 1H); 7.24 (d, 1H); 7.65 (s, 1H); 12.13 (s, 1H)	Intermediate 123 and ethyl 2-bromo-1,3-thiazole-4-carboxylate
106	isopropyl 2-((3S,4R)-4-{[(4-bromo-3-chloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)isonicotinate	1.32 (d, 6H); 1.80 (m, 2H); 2.19 (s, 3H); 3.07 (m 1H); 3.27 (m, 1H); 4.37 (m, 2H); 4.71 (m, 1H); 4.97 (d, br, 1H); 5.15 (m, 1H); 6.70 (d, 1H); 7.22 (d, 1H); 7.25 (s, 1H); 8.17 (d, 1H); 12.11 (s, br, 1H)	Intermediate 123 and isopropyl 2-bromo-isonicotinate
107	methyl 2-((3S,4R)-4-{[(4-bromo-3-chloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-4-(methoxymethyl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 524 for $C_{18}H_{21}BrClFN_4O_4S$; NMR δ: 1.86 (m, 2H); 2.19 (s, 3H); 3.29 (s, 2H); 3.60 (m 2H); 3.73 (s, 3H); 4.04 (m, 1H); 4.30 (m, 2H); 4.57 (s, 3H); 4.90 (d, br, 1H); 7.27 (d, 1H); 12.17 (s, 1H)	Intermediate 123 and Intermediate 17
108	ethyl 2-((3*S*,4*R*)-4-{[(3-chloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)isonicotinate	MS (ES) MH^+: 409 for $C_{19}H_{22}ClFN_4O_3$ NMR: 1.40 (t, 3H); 1.98 (m, 2H); 2.27 (s, 3H); 3.09 (m 2H); 4.38 (q, 2H); 4.47 (m, 2H); 4.84 (m, 1H); 4.90 (d, br, 1H); 5.92 (s, 1H); 7.03 (d, 1H); 7.15 (d, 1H); 7.30 (s, 1H); 8.27 (d, 1H); 9.88 (s, br, 1H)	Intermediate 121 and ethyl 2-bromo-isonicotinate

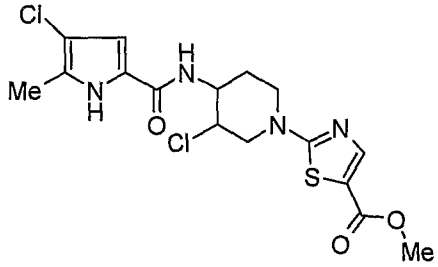
Ex	Compound	Data	SM
109	ethyl 2-((3*S*,4*R*)-4-{[(4-bromo-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)isonicotinate	MS (ES) MH^+: 409 for $C_{19}H_{22}BrFN_4O_3$ NMR: 1.40 (t, 3H); 1.98 (m, 2H); 2.27 (s, 3H); 3.09 (m 2H); 4.38 (q, 2H); 4.43 (m, 2H); 4.84 (m, 1H); 4.90 (d, br, 1H); 6.16 (d, 1H); 6.59 (s, 1H); 7.15 (d, 1H); 7.29 (s, 1H); 8.27 (d, 1H); 9.76 (s, br, 1H)	Intermediate 122 and ethyl 2-bromo-isonicotinate
110	Cis(±)-Methyl 2-[4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(2-methoxyethoxy)piperidin-1-yl]-1,3-thiazole-5-carboxylate 	MS (ES) MH^+: 491 for $C_{19}H_{24}Cl_2N_4O_5S$; NMR: 1.72-1.80 (m, 2H), 2.17 (s, 3H), 3.13 (s, 3H), 3.25-3.42 (m, 4H), 3.52-3.60 (m, 1H), 3.65-3.75 (m, 2H), 3.73 (s, 3H); 3.85-4.05 (m, 1H); 4.20-4.35 (m, 2H), 7.14 (d, 1H), 7.82 (s, 1H), 12.14 (brs, 1H)	Intermediate 124 and methyl 2-bromo-1,3-thiazole-5-carboxylate
111	Cis(±)-Ethyl 2{[-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(2-methoxyethoxy)piperidin-1-yl]-1,3-thiazole-4-carboxylate	MS (ES) MH^+: 505 for $C_{20}H_{26}Cl_2N_4O_5S$	Intermediate 124 and ethyl 2-bromo-1,3-thiazole-4-carboxylate
112	Cis(±)-Ethyl 2-[4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(2-methoxyethoxy)piperidin-1-yl]-4-methyl-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 519 for $C_{21}H_{28}Cl_2N_4O_5S$; NMR: 1.22 (t, 3H), 1.70-1.75 (m, 2H), 2.17 (s, 3H), 2.41 (s, 3H), 3.14 (s, 3H), 3.32-3.40 (m, buried under water peak), 3.45-3.62 (m, 1H), 3.67-3.73 (m, 2H), 3.86-3.98 (m, 1H), 4.16 (q, 2H), 4.19-4.30 (m, 2 H), 7.13 (d, 1H), 12.14 (s, 1H)	Intermediate 124 and ethyl 2-chloro-1,3-thiazole-5-carboxylate

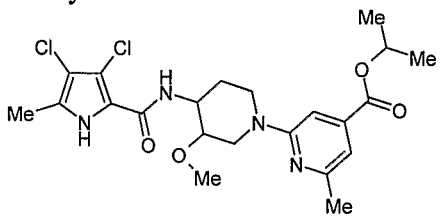
Ex	Compound	Data	SM
113	Cis(±)-Ethyl 2-[4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(2-methoxyethoxy)piperidin-1-yl]isonicotinate	MS (ES) MH^+: 499 for $C_{22}H_{28}Cl_2N_4O_5$	Intermediate 124 and ethyl 2-fluoroisonicotinate (Konno, Akinori *J. Fluorine Chemistry* (1998), 87(2), 137-140)
114	Cis(±)-Ethyl 2-[4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(2-methoxyethoxy)piperidin-1-yl]-1,3-benzothiazole-7-carboxylate	MS (ES) MH^+: 555 for $C_{24}H_{28}Cl_2N_4O_5S$	Intermediate 124 and ethyl 2-bromo-1,3-benzothiazole-7-carboxylate
115	Methyl 2-((3*S*,4*R*)-4-{[(4-chloro-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-5-carboxylate 	MS (ES) MH^+: 387 for $C_{15}H_{16}ClFN_4O_3S$; NMR: 1.55-1.76 (m, 1H), 1.85-2.00 (m, 1H), 3.36-3.45 (m, 1H), 3.50 (dd, 1H), 3.74 (s, 3H), 4.02-4.10 (m, 1H), 4.15-4.36 (m, 2H), 4.90 (d, 1H), 6.94-6.97 (m, 2H), 7.85 (s, 1H), 8.10 (d, 1H), 11.82 (s, 1H)	Intermediate 95 and methyl 2-bromo-1,3-thiazole-5-carboxylate
116	Ethyl 2-((3*S*,4*R*)-4-{[(4-chloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 429 for $C_{18}H_{22}ClFN_4O_3S$; NMR: 1.23 (t, 3H), 1.62-1.77 (m, 1H), 1.83-2.00 (m, 1H), 2.13 (s, 3H), 2.43 (s, 3H), 3.33-3.41(m, 1H), 3.50 (dd, 1H), 3.98-4.02 (m, 1H), 4.16 (q, 2H), 4.23-4.35 (m, 2H), 4.86 (d, 1H), 6.89 (d, 1H), 7.97 (d, 1H), 11.65 (s, 1H)	Intermediate 260 and ethyl 2-chloro-4-methyl-1,3-thiazole-5-carboxylate

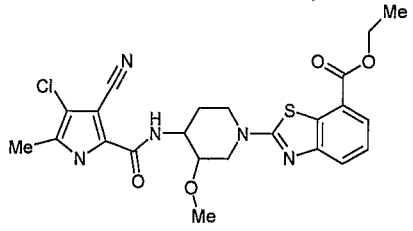
Ex	Compound	Data	SM
117	Ethyl 2-((3*S*,4*R*)-4-{[(4-chloro-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 415 for $C_{17}H_{20}ClFN_4O_3S$; NMR: 1.23 (t, 3H), 1.69-1.74 (m, 1H), 1.86-2.03 (m, 1H), 2.43 (s, 3H), 3.27-3.35 (m, 1H), 3.51 (dd, 1H), 3.98-4.05 (m, 1H), 4.16 (q, 2H), 4.23-4.33 (m, 2 H), 4.88 (d, 1H), 6.94-6.98 (m, 2H), 8.85 (d, 1H), 11.81 (s, 1H)	Intermediate 95 ethyl 2-chloro-4-methyl-1,3-thiazole-5-carboxylate
118	Ethyl 2-((3*S*,4*R*)-4-{[(4,5-dichloro-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 449 for $C_{17}H_{19}Cl_2FN_4O_3S$; NMR: 1.23 (t, 3H), 1.65-1.74 (m, 1H), 1.85-2.00 (m, 1H), 2.43(s, 3H), 3.30-3.40 (m, 1H), 3.51 (dd, 1H), 3.98-4.05 (m, 1H), 4.16 (q, 2H), 4.21-4.35 (m, 2H), 4.88 (d, 1H), 7.06 (d, 1H), 8.15 (d, 1H), 12.78 (s, 1H)	Intermediate 128 and ethyl 2-chloro-4-methyl-1,3-thiazole-5-carboxylate
119	Methyl 2-((3*S*,4*R*)-4-{[(4,5-dichloro-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 421 for $C_{15}H_{15}Cl_2FN_4O_3S$	Intermediate 128 and methyl 2-bromo-1,3-thiazole-5-carboxylate
120	Cis(±)-Methyl 2-{[4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(2-hydroxypropoxy)piperidin-1-yl]-1,3-thiazole-5-carboxylate 	MS (ES) MH^+: 491 for $C_{19}H_{24}Cl_2N_4O_5S$; NMR: 0.95 (d, 3H), 1.75-1.90 (m, 2H), 2.17 (s, 3H), 3.15-3.47 (peaks overlapping with H_2O signal), 3.55-3.68 (m, 2H), 3.73 (s, 3H), 3.94-3.97 (m, 1H), 4.23-4.35 (m, 2H), 7.17 (d, 1H), 7.82 (s, 1H), 12.11 (s, 1H)	Intermediate 126 and methyl 2-bromo-1,3-thiazole-5-carboxylate
121	Cis(±)-Methyl 2-[(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(2-methoxypropoxy)piperidin-1-yl]-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 505 for $C_{20}H_{26}Cl_2N_4O_5S$	Intermediate 125 and methyl 2-bromo-1,3-thiazole-5-carboxylate

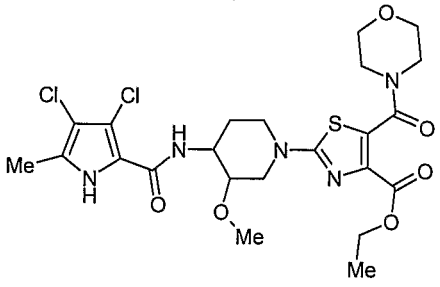
Ex	Compound	Data	SM
122	ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylate	MS (ES) MH^+: 511 for $C_{22}H_{24}Cl_2N_4O_4S$; NMR: 1.36 (t, 3H), 1.79 (m, 2H), 2.18 (s, 3H), 3.32-3.59 (m, 4H), 4.21 (m, 1H), 4.37 (m, 1H), 4.37 (q, 2H), 7.19 (d, 1H), 7.41 (t, 1H), 7.66 (m, 2H), 12.17 (s, 1H)	Intermediate 51 and 2-bromo-1,3-benzothiazole-7-carboxylate (US Pat 5770758)
123	ethyl 2-((3*R*,4*S*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylate	MS (ES) MH^+: 511 for $C_{22}H_{24}Cl_2N_4O_4S$; NMR: 1.36 (t, 3H), 1.79 (m, 2H), 2.18 (s, 3H), 3.32-3.59 (m, 4H), 4.21 (m, 1H), 4.37 (m, 1H), 4.37 (q, 2H), 7.19 (d, 1H), 7.41 (t, 1H), 7.66 (m, 2H), 12.17 (s, 1H)	Intermediate 52 and 2-bromo-1,3-benzothiazole-7-carboxylate (US Pat 5770758)
124	Cis (±)ethyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-4-carboxylate	MS (ES) MH^+: 448 for $C_{17}H_{19}Cl_2FN_4O_3S$	Intermediate 32 and ethyl 2-bromo-1,3-thiazole-4-carboxylate
125	ethyl 2-((3*S*,4*R*)-4-{[(4-chloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylate 	MS (ES) MH^+: 475 for $C_{22}H_{24}ClN_4O_4S$	Intermediate 129 and 2-bromo-1,3-benzothiazole-7-carboxylate (US Pat 5770758)
126	Cis(±)methyl 2-4-{[(4-chloro-3,5-dimethyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 427 for $C_{18}H_{23}ClN_4O_4S$	Intermediate 130 and methyl 2-bromo-1,3-thiazole-5-carboxylate

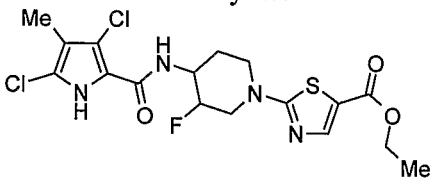
Ex	Compound	Data	SM
127	Cis(±)ethyl 2-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)[1,3]thiazolo[4,5-*b*]pyridine-7-carboxylate	MS (ES) MH^+: 513 for $C_{21}H_{23}Cl_2N_5O_4S$	Intermediate 51 and Intermediate204
128	ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-4-carboxylate	MS (ES) MH^+: 448 for $C_{17}H_{19}Cl_2FN_4O_3S$	Intermediate 31 and ethyl 2-bromo-1,3-thiazole-4-carboxylate
129	ethyl 2-((3*S*,4*R*)-4-{[(4-chloro-3,5-dimethyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-4-carboxylate	MS (ES) MH^+: 448 for $C_{18}H_{22}ClFN_4O_3S$	Intermediate 130 and ethyl 2-bromo-1,3-thiazole-4-carboxylate
130	ethyl 2-((3*R*,4*S*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-4-carboxylate 	MS (ES) MH^+: 448 for $C_{17}H_{19}Cl_2FN_4O_3S$	Intermediate 33 and ethyl 2-bromo-1,3-thiazole-4-carboxylate
131	Cis(±)methyl 2-3-chloro-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 451 for $C_{16}H_{17}Cl_3N_4O_3S$; NMR: 1.17 (t, 3H), 1.84 (m, 1H), 1.93 (m, 1H), 2.20 (s, 3H), 3.45 (m, 1H), 3.75 (s, 3H), 3.82 (d, 1H), 4.02 (m, 1H), 4.26 (m, 1H), 4.50 (m, 1H), 4.76 (s, 1H), 7.15 (d, 1H), 7.85 (s, 1H), 12.12 (s, 1H)	Intermediate 131 and 2-bromo-1,3-thiazole-5-carboxylate

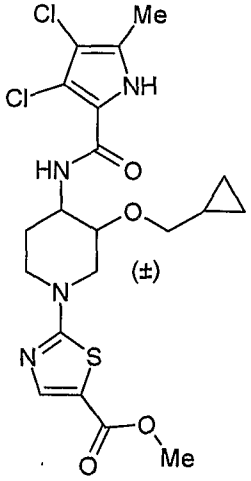
Ex	Compound	Data	SM
132	methyl 2-{(3*S*,4*R*)-4-[({4-chloro-3-[(*E*)-(methoxyimino)methyl]-5-methyl-1*H*-pyrrol-2-yl}carbonyl)amino]-3-fluoropiperidin-1-yl}-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 456 for $C_{18}H_{21}ClFN_5O_4S$;	Intermediate 132 and methyl-2-bromo-1,3-thiazole-5-carboxylate
133	Cis(±)-ethyl 2-3-chloro-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-benzothiazole-7-carboxylate	MS (ES) MH^+: 515 for $C_{21}H_{21}Cl_3N_4O_3S$	Intermediate 131 and 2-bromo-1,3-benzothiazole-7-carboxylate (US Pat 5770758)
134	Cis(±)-ethyl 2-(3-chloro-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-4-(hydroxymethyl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 495 for $C_{18}H_{21}Cl_3N_4O_4S$	Intermediate 131 and Intermediate 215
135	Cis(±)-methyl 2-(3-chloro-4-{[(4-chloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylate 	MS (ES) MH^+: 417 for $C_{16}H_{18}Cl_2N_4O_3S$	Intermediate 133 and methyl 2-bromo-1,3-thiazole-5-carboxylate
136	Cis(±)-methyl 2-(3-chloro-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-4-(methoxymethyl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 495 for $C_{18}H_{21}Cl_3N_4O_4S$	Intermediate 131 and Intermediate 17
137	Cis(±)-ethyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-nitroisonicotinate	MS (ES) MH^+: 500 for $C_{20}H_{23}Cl_2N_5O_6$; NMR: 1.3 (t, 3H), 1.65 (m, 1H), 1.8 (m, 1H), 2.2 (s, 3H), 3.2-3.3 (m 6H), 3.6 (m 1H), 4.3 (m, 3H), 7.1 (m, 2H), 8.9 (s, 1H), 12.1 (s, 1H)	Intermediate 226 and Intermediate 50

Ex	Compound	Data	SM
138	Cis(±)-methyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methylpiperidin-1-yl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 431 for $C_{17}H_{20}Cl_2N_4O_3S$; NMR: 0.9 (d, 3H), 1.8 (m, 2H), 2.2 (m, 4H), 3.2 (m 3H), 3.4-3.7 (m, 3H), 3.7 (s, 3H), 4.1 (m, 1H), 4.25 (m, 1H), 7.1 (d, 1H), 7.9 (s, 1H), 12.0 (s, 1H)	methyl 2-bromo-1,3-thiazole-5-carboxylate and Intermediate134
139	Cis(±)-methyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-2-methylpiperidin-1-yl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 431 for $C_{17}H_{20}Cl_2N_4O_3S$; NMR: 1.3 (d, 1H), 1.8-2.1 (m, 4H), 2.2 (s, 3H), 3.5 (m, 1H), 3.7 (m, 4H), 4.1 (m, 2H), 7.3 (s, 1H), 7.9 (s, 1H), 12.0 (s, 1H)	methyl 2-bromo-1,3-thiazole-5-carboxylate and Intermediate135
140	Cis(±)-isopropyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-6-methylisonicotinate 	MS (ES) MH^+: 483 for $C_{22}H_{28}Cl_2N_4O_4$; NMR: 0.9 (m, 1H),1.3 (d, 6H), 1.7, (m, 1H), 2.2 (s, 3H), 2.4 (s, 3H), 3.1 (m, 2H), 3.5 (m, 1H), 4.2 (m, 2H), 4.7 (d, 1H), 5.1 (m, 1H), 6.8 (s, 1H), 7.0 (s, 1H), 7.15 (s, 1H), 12.1 (s, 1H)	Intermediate 227 and Intermediate 50
141	Cis(±)-isopropyl 5-chloro-4-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)pyridine-2-carboxylate	MS (ES) MH^+: 503 for $C_{21}H_{25}Cl_3N_4O_4$	Intermediate 226 and Intermediate 50
142	ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-4-(hydroxymethyl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 479 for $C_{18}H_{21}Cl_2FN_4O_4S$; NMR: 1.2 (t, 3H), 1.9 (m, 2H), 2.2 (s, 3H), 3.6 (dd, 1H), 4.0-4.2 (m, 1H), 4.2 (q, 2H), 4.25-4.45 (m, 1H), 4.6 (s, 2H), 4.9 (m, 1H), 5.05 (m, 1H), 7.2 (d, 1H), 12.1 (s, 1H)	Intermediate 215 and Intermediate 36

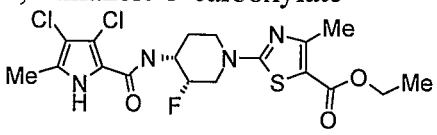
Ex	Compound	Data	SM
143	Cis(±)-ethyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(hydroxymethyl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 491 for $C_{19}H_{24}Cl_2N_4O_5S$; NMR: 1.2 (t, 3H), 1.7 (m, 2H), 2.2 (s, 3H), 3.4 (s, 3H), 3.55 (m, 1H), 4.0 (m, 1H), 4.1-4.4 (m, 4H), 4.6 (s, 2H), 7.1 (d, 1H), 12.1 (s, 1H)	Intermediate 215 and Intermediate 50
144	Cis(±)-ethyl 2-(4-{[(4-chloro-3-cyano-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 438 for $C_{18}H_{20}ClN_5O_4S$; NMR: 1.6-1.9 (m, 2H), 2.2 (s, 3H), 3.3 (s, 3H), 3.6 (m, 1H), 3.7 (s, 3H), 3.9 (m, 1H), 4.3 (m, 3H), 7.75 (d, 1H), 12.7 (s, 1H)	Intermediate 136 and methyl 2-bromo-1,3-thiazole-5-carboxylate
145	Cis(±)-ethyl 2-(4-{[(4-chloro-3-cyano-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylate 	MS (ES) MH^+: 502 for $C_{23}H_{24}ClN_5O_4S$; NMR: 1.35 (t, 3H), 1.6-2.0 (m, 2H), 2.2 (s, 3H), 3.3 (s, 3H), 3.4 (m, 1H), 3.6 (s, 3H), 4.1 (m, 1H), 4.3 (m, 1H), 4.4 (q, 2H), 7.7 (m, 2H), 7.8 (m, 1H), 7.9 (t, 1H), 12.7 (s, 1H)	Intermediate 136 and ethyl 2-bromo-1,3-benzothiazole-7-carboxylate (US Pat 5770758)
146	Cis(±)-ethyl 2-(4-{[(4-chloro-3-cyano-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 460 for $C_{22}H_{26}ClN_5O_4$ NMR: 1.3 (d, 6H), 1.7 (m, 2H), 2.2 (s, 3H), 3.1 (s, 2H), 3.3 (s, 3H), 3.5 (s, 3H), 4.2 (m, 1H), 4.6 (d, 1H), 5.1 (m, 1H), 7.0 (s, 1H), 7.2 (s, 1H), 7.7 (d, 1H), 8.2 (d, 1H), 12.7 (s, 1H)	Intermediate 136 and Intermediate 230
147	methyl 2-((3*S*,4*R*)-4-{[(4-chloro-3-cyano-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 426 for $C_{17}H_{17}ClFN_5O_3S$; NMR: 1.9 (m, 2H), 2.2 (s, 3H), 3.3 (s, 3H), 3.5 (dd, 1H), 3.75 (s, 3H), 4.0 (m, 1H), 4.2-4.5 (m, 2H), 5.0 (d, 1H), 7.9 (s, 1H), 8.15 (m, 1H), 12.6 (s, 1H)	Intermediate 137 and methyl 2-bromo-1,3-thiazole-5-carboxylate

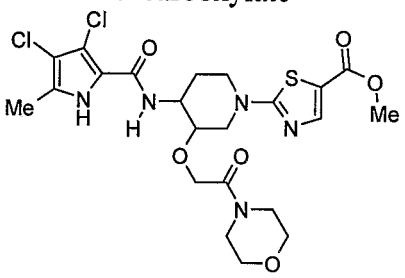
Ex	Compound	Data	SM
148	ethyl 2-((3*S*,4*R*)-4-{[(4-chloro-3-cyano-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-benzothiazole-7-carboxylate	MS (ES) MH^+: 490 for $C_{22}H_{21}ClFN_5O_3S$; NMR: 1.35 (t, 3H), 1.6-2.0 (m, 2H), 2.2 (s, 3H), 3.3 (m), 3.4 (m, 1H), 3.6 (s, 3H), 4.1 (m, 1H), 4.3 (m, 1H), 4.4 (q, 2H), 7.7 (m, 2H), 7.8 (m, 1H), 7.9 (t, 1H), 12.7 (s, 1H)	Intermediate 137 and ethyl 2-bromo-1,3-benzothiazole-7-carboxylate (US Pat 5770758)
149	isopropyl 2-((3*S*,4*R*)-4-{[(4-chloro-3-cyano-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)isonicotinate	MS (ES) MH^+: 460 for $C_{21}H_{23}ClFN_5O_3$ NMR: 1.3 (d, 6H), 1.8 (m, 2H), 2.2 (s, 3H), 3.0 (m, 2H), 3.3 (m), 4.1-4.2 (m, 1H), 4.45 (d, 1H), 4.9 (d, 1H), 5.0 (m, 1H), 5.1 (m, 1H), 7.0 (d, 1H), 7.3 (s, 1H), 8.1 (d, 1H), 8.3 (d, 1H), 12.6 (s, 1H)	Intermediated 137 and Intermediate 230
150	ethyl 2-((*cis*-3S,4R)-4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-(morpholin-4-ylcarbonyl)-1,3-thiazole-4-carboxylate 	MS (ES) MH^+: 579 for $C_{23}H_{29}Cl_2N_5O_6S$; NMR: 1.2 (m, 3H), 1.75 (m, 2H), 2.2 (s, 3H), 3.3 (s, 3H), 3.4 (m, 1H), 3.5-3.6 (m, 4H), 3.8 (m, 1H), 4.2 (m, 4H), 7.15 (d, 1H), 12.1 (s, 1H)	Intermediate 231 and Intermediate 50
151	Cis(±)-isopropyl 6-cyano-4-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)pyridine-2-carboxylate	MS (ES) MH^+: 494 for $C_{22}H_{25}Cl_2N_5O_4$; NMR: 1.3 (s, 6H), 1.8 (m, 2H), 2.25 (s, 3H), 3.4 (s, 3H), 3.6 (m, 1H), 4.1 (d, 1H), 4.3 (m, 1H), 4.5 (d, 1H), 5.2 (m, 1H), 7.2 (d, 1H), 7.65 (s, 1H), 7.8 (s, 1H), 12.2 (s, 1H)	Intermediate 231 and Intermediate 50.

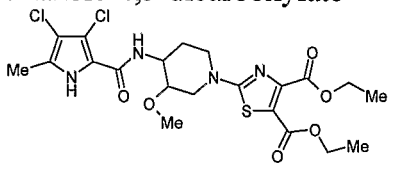
Ex	Compound	Data	SM
152	Cis(±)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-4,5-dicarboxamide	MS (ES) MH^+: 475 for $C_{17}H_{20}Cl_2N_6O_4S$; NMR: 1.7 (m, 2H), 2.2 (s, 3H), 3.3 (s, 3H), 3.5 (m, 1H), 4.0 (m, 1H), 4.2 (m, 1H), 4.4 (m, 1H), 7.1 (d, 1H), 7.6 (s, 1H), 8.1 (s, 1H), 8.2 (s, 1H), 10.4 (s, 1H), 12.1 (s, 1H)	2-chloro-1,3-thiazole-4,5-dicarboxamide (Robba, M.; Le Guen, Y. *Bulletin de la Societe Chimique de France* (1969), (6), 2152-7) and Intermediate 50.
153	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-4,5-dicarboxamide	MS (ES) MH^+: 463 for $C_{16}H_{17}Cl_2N_6O_3S$; NMR: 1.8-1.9 (m, 2H), 2.2 (s, 3H), 3.3 (s, 3H), 3.4 (dd, 1H), 4.1 (m, 1H), 4.4 (m, 2H), 4.95 (d, 1H), 7.3 (d, 1H), 7.6 (s, 1H), 8.1 (s, 1H), 8.2 (s, 1H), 10.4 (s, 1H), 12.1 (s, 1H)	2-chloro-1,3-thiazole-4,5-dicarboxamide (Robba, M.; Le Guen, Y. *Bulletin de la Societe Chimique de France* (1969), (6), 2152-7) and Intermediate 36.
154	Cis(±)-ethyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-formylisonicotinate	MS (ES) MH^+: 483 for $C_{21}H_{24}Cl_2N_4O_5$	Intermediate 202 and Intermediate 50
155	ethyl 2-((3*S*,4*R*)-4-{[(3,5-dichloro-4-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-5-carboxylate 	MS (ES) MH^+: 449 for $C_{17}H_{19}Cl_2FN_4O_3S$: NMR: 1.25 (m, 5H), 1.9 (s, 3H), 3.6 (dd, 1H), 3.9 (m, 1H), 4.3 (m, 2H), 5.0 (d, 1H), 7.3(d, 1H), 7.8 (s, 1H), 12.6 (s, 1H)	Intermediate 138 and ethyl 2-bromo-1,3-thiazole-5-carboxylate
156	2-((3*S*,4*R*)-4-{[(3,5-dichloro-4-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-5-(ethoxycarbonyl)-1,3-thiazole-4-carboxylic acid	MS (ES) MH^+: 465 for $C_{18}H_{19}Cl_2FN_4O_5S$; NMR: 1.25 (t, 3H), 1.8 (m, 2H), 1.9 (s, 3H), 3.5-3.8 (m, 2H), 3.9 (m, 1H), 4.2 (q, 2H),4.3 (m, 2H), 5.0 (d, 1H), 7.4(d, 1H), 12.6 (s, 1H), 13.6 (s, 1H)	Intermediate 138 and Intermediate 252

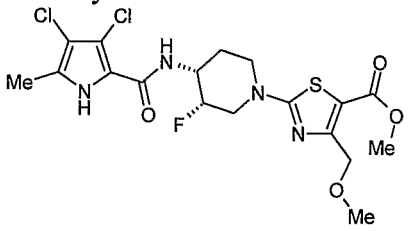
Ex	Compound	Data	SM
157	methyl 4-acetyl-2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 489 for $C_{19}H_{24}Cl_2N_4O_5S$; NMR: 1.75 (m, 2H), 2.2 (s, 3H), 2.45 (s, 3H), 3.2-3.4 (m), 3.9 (m, 1H), 4.3 (m, 2H), 7.15 (d, 1H), 12.15 (s, 1H)	Intermediate 212 and Intermediate 51
158	methyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(1-hydroxy-1-methylethyl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 505 for $C_{20}H_{26}Cl_2N_4O_5S$; NMR: 1.5 (s, 6H), 1.75 (m, 2H), 2.2 (s, 3H), 3.3 (s, 3H), 3.55 (m, 1H), 3.8 (s, 3H), 3.8-4.0 (m, 2H), 4.2 (m, 1H), 4.5 (m, 1H), 7.15 (d, 1H), 12.2 (s, 1H)	Intermediate 214 and Intermediate 51
159	methyl l 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)thieno[2,3-*d*][1,3]thiazole-6-carboxylate	MS (ES) MH^+: 503 for $C_{19}H_{20}Cl_2N_4O_4S_2$; NMR: 1.8 (m, 2H), 2.2 (s, 3H), 3.3 (m), 3.6 (m, 1H), 3.95 (m, 1H), 4.3 (m, 2H), 7.2 (d, 1H), 8.0 (s, 1H), 12.2 (s, 1H)	Intermediate 213 and Intermediate 51.
160	Cis(±)-methyl 2-(3-(cyclopropylmethoxy)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylate 	MS (ESI) M: 487 for $C_{20}H_{24}Cl_2N_4O_4S$; NMR 0.11 (m, 2H), 0.38 (m, 2H), 0.91 (m, 1H), 1.76 (m, 2H), 2.17 (s, 3H), 3.24-3.45 (m, 4H), 3.68 (bs, 1H), 3.73 (s, 3H), 3.94 (m, 1H), 4.25 (m, 2H), 7.14 (d, 1H), 7.82 (s, 1H), 12.16 (s, 1H)	Intermediate139 and methyl 2-bromo-1,3-thiazole-5-carboxylate

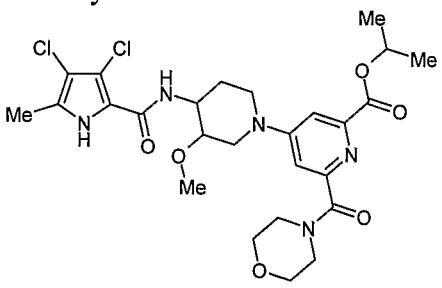
Ex	Compound	Data	SM
161	Cis(±)-methyl 2-[4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(1,3-thiazol-2-ylmethoxy)piperidin-1-yl]-1,3-thiazole-5-carboxylate	MS (ESI) M: 530 for $C_{20}H_{21}Cl_2N_5O_4S_2$; NMR 1.66 (s, 2H), 1.91 (m, 1H), 2.10 (qd, 1H), 2.27 (s, 3H), 3.20-3.37 (m, 2H), 3.82 (s, 3H), 3.96 (m, 2H), 4.40 (m, 1H), 4.64 (d, 1H), 4.96 (dd, 2H), 7.19 (d, 1H), 7.28 (d, 1H), 9.67 (bs, 1H)	Intermediate140 and methyl 2-bromo-1,3-thiazole-5-carboxylate
162	Cis(±)-Methyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 461, 463 for $C_{18}H_{22}Cl_2N_4O_4S$; ^{1}H-NMR: 1.04 (t, 3H); 1.75 (m, 2H); 2.17 (s, 3H); 3.35-3.45 (m, 3H); 3.63 (m, 2H); 3.73 (s, 3H); 3.96 (m, 1H); 4.25 (m, 2H); 7.11 (d, 1H); 7.82 (s, 1H); 12.12 (s, IH)	Intermediate 141 and methyl-2-bromo-1,3-thiazole-5 carboxylate
163	Cis(±)-Methyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-4-(methoxymethyl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 505, 507 for $C_{20}H_{26}Cl_2N_4O_5S$; ^{1}H-NMR: 1.05 (t, 3H); 1.74 (m, 2H); 2.17 (s, 3H); 3.27 (s, 3H); 3.39-3.47 (m, 3H); 3.63 (m, 2H); 3.71 (s, 3H); 3.96 (m, 1H); 4.23 (m, 2H); 4.55 (s, 2H); 7.12 (d, 1H); 12.16 (br s, 1H)	Intermediate 141 and Intermediate 17
164	Cis(±)-Ethyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 475, 477 for $C_{19}H_{24}Cl_2N_4O_4S$; ^{1}H-NMR: 1.22 (t, 3H); 1.72 (m, 2H); 2.17 (s, 3H); 2.42 (s, 3H); 3.31(m, 5H); 3.52 (m, 1H); 3.90 (m, 1H); 4.16 (q, 2H); 4.26 (m, 2H); 7.14 (d, 1H); 12.14 (br s, 1H)	Intermediate 50 and Intermediate 236

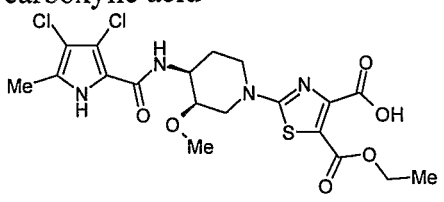
Ex	Compound	Data	SM
165	Ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate 	MS (ES) MH^+: 463 465 for $C_{18}H_{21}Cl_2FN_4O_3S$; NMR: 1.23 (t, 3H); 1.85 (m, 2H); 2.18 (s, 3H); 2.43 (s, 3H); 3.35 (m, 1H overlapping water) 3.53 (dd, 1H); 4.00 (m, 1H); 4.16 (q, 2H); 4.30 (m, 2H); 4.94 (d, 1H); 7.24 (d, 1H); 12.09 (s, 1H)	Intermediate 36 and Intermediate 236
166	Ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 475, 477 for $C_{19}H_{24}Cl_2N_4O_4S$; NMR: 1.22 (t, 3H); 1.72 (m, 2H); 2.17 (s, 3H); 2.42 (s, 3H); 3.31(m, 5H); 3.52 (m, 1H); 3.90 (m, 1H); 4.16 (q, 2H); 4.26 (m, 2H); 7.14 (d, 1H); 12.14 (br s, 1H)	Intermediate 51 and Intermediate 236
167	Trans(±)methyl 2-[4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(morpholin-4-ylcarbonyl)piperidin-1-yl]-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 530, 532 for $C_{21}H_{25}Cl_2N_5O_5S$; NMR: 1.89 (m, 1H), 2.14 (m, 1H), 2.17 (s, 3H), 3.73 (s, 3H), 3.23-3.79 (m, 12H), 3.93 (dd, 1H), 4.51 (m, 1H), 7.33 (d, 1H), 7.84 (s, 1H), 12.08 (s, 1H)	Intermediate142
168	Cis(±)methyl 2-[4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(morpholin-4-ylcarbonyl)piperidin-1-yl]-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 530, 532 for $C_{21}H_{25}Cl_2N_5O_5S$; NMR: 1.79 (dq, 1H), 1.90 (m, 1H), 2.15 (s, 3H), 3.22-3.42 (m, 6H), 3.51-3.71 (m, 5H), 3.74 (s, 3H), 3.96 (m, 1H), 4.02 (m, 1H), 4.40 (m, 1H), 7.17 (d, 1H), 7.88 (s, 1H), 12.02 (s, 1H)	Intermediate143

Ex	Compound	Data	SM
169	Cis(±)({4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-1-[5-(methoxycarbonyl)-1,3-thiazol-2-yl]piperidin-3-yl}oxy)acetic acid	MS (ES) MH^+: 491, 493 for $C_{18}H_{20}Cl_2N_4O_6S$; NMR: 1.61 (dq, 1H), 2.03 (m, 1H), 2.17 (s, 3H), 3.25 (dd, 1H), 3.35 (m, 1H), 3.63 (m, 1H), 3.74 (s, 3H), 3.88 (m, 1H), 4.06 (m, 1H), 4.17 (s, 2H), 4.23 (dd, 1H), 7.58 (d, 1H), 7.86 (s, 1H), 11.99 (s, 1H), 12.76 (s, 1H)	Intermediate 144
170	Cis(±)methyl 2-[(3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(2-morpholin-4-yl-2-oxoethoxy)piperidin-1-yl]-1,3-thiazole-5-carboxylate 	MS (ES) MH^+: 560, 562 for $C_{22}H_{27}Cl_2N_5O_6S$; NMR: 1.59 (dq, 1H), 2.07 (m, 1H), 2.17 (s, 3H), 3.24 (dd, 1H), 3.27-3.56 (m, 8H), 3.61 (m, 1H), 3.74 (s, 3H), 3.85 (m, 1H), 4.05 (m, 1H), 4.24 (dd, 2H), 4.35 (q, 2H), 7.78 (d, 1H), 7.86 (s, 1H), 11.95 (s, 1H)	Example 169
171	Methyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-hydroxypiperidin-1-yl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 433, 435 for $C_{16}H_{18}Cl_2N_4O_4S$	Intermediate 244
172	Methyl 2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-{[(ethylamino)carbonyl]oxy}piperidin-1-yl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 504, 506 for $C_{19}H_{23}Cl_2N_5O_5S$	Example 171
173	Methyl 2-(3-{[(allylamino)carbonyl]oxy}-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 516, 518 for $C_{20}H_{23}Cl_2N_5O_5S$	Example 171

Ex	Compound	Data	SM
174	ethyl 4-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)pyridine-2-carboxylate	MS (ES) MH^+: 443 for $C_{19}H_{21}Cl_2FN_4O_3$; NMR: 1.31 (t, 3 H) 1.81 (s, 2 H) 2.19 (s, 3 H) 2.69 (s, 1 H) 3.33 (s, 3 H) 4.05 (s, 1 H) 4.30 (q, 2 H) 4.40 (s, 1 H) 4.86 (d, 1 H) 7.07 (dd, 2.73 Hz, 1 H) 7.21 (d, 1 H) 7.46 (d, 1 H) 8.23 (d, 1 H) 12.09 (s, 1 H)	Intermediate 32 and ethyl 4-chloropyridine-2-carboxylate (WO 2004007657)
175	Cis(±)-diethyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-4,5-dicarboxylate 	MS (ES) MH^+: 533 for $C_{21}H_{26}Cl_2N_4O_6S$; NMR: 1.22 (t, 3 H) 1.28 (t, 3 H) 1.76 (d, 2 H) 2.15 - 2.21 (m, 3 H) 3.29 - 3.34 (m, 3 H) 3.36 (s, 3 H) 3.42 (s, 1 H) 3.56 (s, 1 H) 3.95 (s, 1 H) 4.19 (q, 2 H) 4.23 - 4.32 (m, 3 H) 7.19 (d, 1 H) 12.20 (s, 1 H)	Intermediate 50 and Intermediate 244
176	diethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-4,5-dicarboxylate	MS (ES) MH^+: 521 for $C_{20}H_{23}Cl_2FN_4O_5S$; NMR: 1.22 (t, 3 H) 1.28 (t, 3 H) 1.86 (d, 2 H) 2.19 (s, 3 H) 3.31 (s, 1 H) 3.41 (s, 2 H) 3.68-3.71 (dd, 1 H) 3.99 (s, 1 H) 4.20 (q, 2 H) 4.29 (q, 2 H) 4.89-5.05 (d, 1 H) 7.27 (d, 1 H) 12.09 (s, 1 H)	Intermediate 32 and Intermediate 247
177	Cis(±)-ethyl 4-(4-{[(4-chloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)pyridine-2-carboxylate	MS (ES) MH^+: 521 for $C_{20}H_{25}ClN_4O_4$ NMR: 1.31 (t, 3 H) 1.62 (s, 1 H) 1.79 - 1.95 (m, 1 H) 2.10 - 2.19 (m, 3 H) 3.07 - 3.19 (m, 2 H) 3.23 (s, 3 H) 3.45 - 3.54 (m, 1 H) 3.89 (s, 1 H) 4.18 (s, 1 H) 4.22 (d, 1 H) 4.30 (q, 2 H) 6.89 (d, 1 H) 7.04 (dd, 1 H) 7.44 (d, 1 H) 7.67 (d, 1 H) 8.20 (d, 1 H) 11.63 (s, 1 H)	Intermediate 55 and ethyl 4-chloropyridine-2-carboxylate (WO 2004007657)

Ex	Compound	Data	SM
178	Cis(±)-ethyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(1-methyl-1-phenylethyl)amino]carbonyl}-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 622 for $C_{28}H_{33}Cl_2N_5O_5S$	Intermediate 50 and Intermediate 55
179	ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)isonicotinate	MS (ES) MH^+: 443 for $C_{19}H_{21}Cl_2FN_4O_3$	Intermediate 32 and ethyl 2-fluoroisonicotinate (Konno, Akinori *J. Fluorine Chemistry* (1998), 87(2), 137-140)
180	methyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-4-(methoxymethyl)-1,3-thiazole-5-carboxylate 	MS (ES) MH^+: 479 for $C_{18}H_{21}Cl_2FN_4O_4S$ NMR: 1.86 (s, 2 H) 2.19 (s, 3 H) 3.25 - 3.31 (s, 3 H) 3.53-3.67 (dd, 1 H) 3.73 (s, 3 H) 4.00 (s, 2 H) 4.33 (s, 2 H) 4.57 (s, 2 H) 4.89-5.05 (d, 1 H) 7.27 (d, 1 H) 12.10 (s, 1 H)	Intermediate 32 and Intermediate 17
181	ethyl 4-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)quinoline-2-carboxylate	MS (ES) MH^+: 493 for $C_{23}H_{23}Cl_2FN_4O_3$	Intermediate 32 and Intermediate 10
182	ethyl 2-((3*S*,4*R*)-4-{[(4-chloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)isonicotinate	MS (ES) MH^+: 421 for $C_{20}H_{25}ClN_4O_4$ NMR: 1.32 (t, 3 H) 1.60 (d, 1 H) 1.84 (s, 1 H) 2.14 (s, 3 H) 3.13 (d, 2 H) 3.20 - 3.24 (m, 3 H) 3.49 (s, 1 H) 4.20 (d, 2 H) 4.33 (q, 2 H) 4.56 (s, 1 H) 6.89 (d, 1 H) 6.97 (d, 1 H) 7.23 (s, 1 H) 7.64 (d, 1 H) 8.24 (d, 1 H) 11.62 (s, 1 H)	Intermediate 55 and ethyl 2-fluoroisonicotinate (Konno, Akinori *J. Fluorine Chemistry* (1998), 87(2), 137-140)

Ex	Compound	Data	SM
183	methyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(methoxymethyl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+:491 for $C_{19}H_{24}Cl_2N_4O_5S$ NMR: 1.86 - 1.95 (m, 1 H) 1.97 - 2.04 (m, 1 H) 2.26 - 2.31 (m, 3 H) 3.16 - 3.31 (m, 2 H) 3.47 (s, 3 H) 3.48 (s, 2 H) 3.50 - 3.55 (m, 1 H) 3.82 (s, 3 H) 4.05 (d, 1 H) 4.25 - 4.37 (m, 1 H) 4.54 (s, 1 H) 4.69 - 4.81 (m, 2 H) 7.19 - 7.27 (m, 1 H) 9.54 (s, 1 H)	Intermediate 51 and Intermediate 17
184	methyl 2-((3*R*,4*S*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(methoxymethyl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+:491 for $C_{19}H_{24}Cl_2N_4O_5S$	Intermediate 52 and Intermediate 17
185	Cis(±)-isopropyl 4-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-6-(morpholin-4-ylcarbonyl)pyridine-2-carboxylate 	MS (ES) MH^+: 582 for $C_{26}H_{33}Cl_2N_5O_6$	Intermediate 50 and Intermediate 249
186	isopropyl 4-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-6-(morpholin-4-ylcarbonyl)pyridine-2-carboxylate	MS (ES) MH^+: 570 for $C_{25}H_{30}Cl_2FN_5O_5$ NMR: 1.32 (d, 6 H) 1.78 - 1.93 (m, 2 H) 2.19 (s, 3 H) 3.27 - 3.33 (m, 4 H) 3.39 (d, 2 H) 3.53 - 3.60 (m, 2 H) 3.65 (d, 4 H) 4.12 (s, 1 H) 4.39 (s, 1 H) 5.07 - 5.19 (m, 1 H) 7.16 - 7.26 (m, 2 H) 7.47 (d, 1 H) 12.08 (s, 1 H)	Intermediate 32 and Intermediate 249

Ex	Compound	Data	SM
187	isopropyl 4-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-6-[(dimethylamino)carbonyl]pyridine-2-carboxylate	MS (ES) MH^+: 528 for $C_{23}H_{28}Cl_2FN_5O_4$	Intermediate 32 and Intermediate 250
188	Cis(±)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-(ethoxycarbonyl)-1,3-thiazole-4-carboxylic acid	MS (ES) MH^+: 505 for $C_{19}H_{22}Cl_2N_4O_6S$ NMR: 1.24 (t, 3 H) 1.74 (s, 2 H) 2.18 (s, 3 H) 3.36 (s, 4 H) 3.56 (s, 1 H) 3.93 (s, 1 H) 4.19 (s, 3 H) 4.29 (s, 2 H) 7.13 (s, 1 H) 12.11 (s, 1 H) 13.51 (s, 1 H)	Intermediate 50 and Intermediate 252
189	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-5-(ethoxycarbonyl)-1,3-thiazole-4-carboxylic acid	MS (ES) MH^+: 493 for $C_{18}H_{19}Cl_2FN_4O_5S$ NMR: 1.19 - 1.27 (m, 3 H) 1.85 (d, 2 H) 2.18 (s, 3 H) 3.26 - 3.35 (m, 1 H) 3.53 (d, 1 H) 3.98 (s, 2 H) 4.18 (q, 1 H) 4.31 (s, 2 H) 4.88 -5.04 (s, 1 H) 7.26 (d, 1 H) 12.08 (s, 1 H) 13.55 (s, 1 H)	Intermediate 32 and Intermediate 252
190	2-((3*R*,4*S*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-(ethoxycarbonyl)-1,3-thiazole-4-carboxylic acid 	MS (ES) MH^+: 505 for $C_{19}H_{22}Cl_2N_4O_6S$ NMR: 1.16 (t, 3 H) 1.69 (s, 2 H) 2.12 (s, 2 H) 3.30 (s, 3 H) 3.50 (s, 2 H) 3.89 (s, 2 H) 4.13 (q, 2 H) 4.17 - 4.29 (m, 2 H) 7.10 (d, 1 H) 12.10 (s, 1 H) 13.50 (s, 1 H)	Intermediate 52 and Intermediate 252

Ex	Compound	Data	SM
191	ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(1-methyl-1-phenylethyl)amino]carbonyl}-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 505 for $C_{19}H_{22}Cl_2N_4O_6S$ NMR: 1.22 (t, 3 H) 1.75 (s, 2 H) 2.18 (s, 3 H) 3.31 (d, 1 H) 3.36 (s, 3 H) 3.42 (s, 1 H) 3.56 (s, 1 H) 3.95 (s, 1 H) 4.14 - 4.22 (m, 2 H) 4.29 (s, 1 H) 7.16 (d,1 H) 12.16 (s, 2 H) 13.56 (s, 1 H)	Intermediate 51 and Intermediate 252
192	ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-4-carboxylate	MS (ES) MH^+: 461 for $C_{18}H_{22}Cl_2N_4O_4S$	Intermediate 51 and ethyl 2-bromo-1,3-thiazole-4-carboxylate
193	ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)isonicotinate	MS (ES) MH^+: 455 for $C_{20}H_{24}Cl_2N_4O_4$ NMR: 1.32 (s, 3 H) 1.84 (s, 2 H) 2.22 (s, 3 H) 3.36 (s, 3 H) 3.45 (s, 1 H) 4.16 (s, 1 H) 4.25 (s, 1 H) 4.31 (s, 2 H) 4.81 (s, 1 H) 7.04 (s, 1 H) 7.26 (s, 1 H) 8.21 (s, 1 H) 10.53 (s, 1 H)	Intermediate 51 and ethyl 2-fluoroisonicotinate (Konno, Akinori *J. Fluorine Chemistry* (1998), 87(2), 137-140)

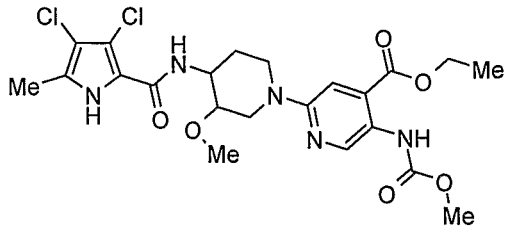
Example 194

Cis(±)-ethyl 5-amino-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)isonicotinate

A solution of $SnCl_2$ dihydrate (870 mg, 3.8 mmol) in 5 ml concentrated HCl was added to a solution of 436 mg (0.87 mmol) of Cis(±)-ethyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-nitroisonicotinate (Example 308) in 30 ml acetic acid. The mixture was stirred at room temperature overnight. Solvent was removed and the residue was partitioned between water and EtOAc. The EtOAc was separated and washed with brine. Drying ($MgSO_4$), removal of solvent and chromatography on silica gel (100% CH_2Cl_2 followed by gradient elution to 100% EtOAc and then to 10% MeOH in EtOAc) gave 230 mg of product. MS (ES) (MH^+): 470 for $C_{20}H_{25}Cl_2N_5O_4$; NMR ($CDCl_3$): 1.5 (t, 3H), 2.1 (m, 2H) 2.4 (s, 3H), 3.2 (m, 2H), 3.6 (s, 3H), 3.65 (m, 1H), 4.0 (m, 1H), 4.4 (m, 1H), 4.5 (q, 2H), 7.3 (s, 1H), 8.0 (s, 1H), 9.5 (s, 1H).

Example 195

Cis(±)-ethyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-[(methoxycarbonyl)amino]isonicotinate



Methylchlorofomate (15 µl, 0.19 mmol) was added to a solution of 60 mg (0.13 mmol) of Cis(±)-ethyl 5-amino-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)isonicotinate (Example 194) in 3 ml pyridine. After stirring at room temperature overnight, 7 µl more methylchloroformate was added. Solvent was removed and the residue was partitioned between EtOAc and $NaHCO_3$ (aqueous). The EtOAc was separated and washed with water and brine. Drying ($MgSO_4$) and removal of solvent gave 43 mg of product. NMR (d_6-DMSO): 1.3 (t, 3H), 1.7 (m, 2H) 2.2 (s, 3H), 3.1 (m, 2H), 3.3 (s, 3H), 3.5 (m, 1H), 3.6 (s, 3H), 4.0-4.3 (m, 4H), 4.6 (m, 1H), 7.05 (m, 1H), 7.15 (m, 1H), 8.2 (s, 1H), 9.1 (s, 1H), 12.2 (s, 1H).

Example 196

Cis(±)-ethyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-[(methylsulfonyl)amino]isonicotinate

Methanesulfonyl chloride (16 µl, 21 mmol) was added to 66 mg (0.14 mmol) of Cis(±)-ethyl 5-amino-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)isonicotinate (Example 194) in 3 ml pyridine. After stirring for 1 h, 5 µl more methanesulfonyl chloride was added. Stirred at room temperature overnight. Solvent was removed, and the residue was partitioned between EtOAc and Na_2CO_3 (aqueous). The EtOAc was separated and washed with water and brine. Drying ($MgSO_4$) and removal of solvent gave 63 mg of product. MS (ES) (MH^+): 534 for $C_{21}H_{27}Cl_2N_5O_6S$. NMR (d_6-DMSO): 1.4 (t, 3H), 1.8 (m, 2H) 2.2 (s, 3H), 2.9 (s, 3H), 3.1-3.2 (m, 2H), 3.3 –3.5 (m), 3.6 (m, 1H), 4.2-4.3 (m, 2H), 4.4 (q, 2H), 4.7 (m, 1H), 7.1 (s, 1H), 7.2 (d, 1H), 8.2 (s, 1H), 12.2 (s, 1H).

Example 197

Cis(±)-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(ethoxycarbonyl)nicotinic acid

A solution of 133 mg (0.84 mmol) $KMnO_4$ in 5 ml water was added to a solution of Cis(±)-ethyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-formylisonicotinate (Example 154) in 20 ml acetone, and the mixture was stirred at room temperature for 4 h. After quenching with aqueous $NaHSO_3$, the mixture was acidified to about pH = 4 with 1N HCl and extracted twice with EtOAc. The EtOAc extracts were washed with brine, dried ($MgSO_4$) and concentrated to give a solid that was triturated with MeOH to give 175 mg of product. MS (ES) MH^+: 499 for $C_{21}H_{24}Cl_2N_4O_6$; NMR: 1.25 (t, 3H), 1.5-1.8, (m, 3H), 2.1 (s, 3H), 3.1 (m, 3H), 3.3 (s, 3H), 3.5 (m, 1H), 4.2 (m, 2H), 4.4 (m, 1H), 4.9 (m, 1H), 6.9 (s, 1H), 7.1 (d, 1H), 8.6 (s, 1H), 12.1 (s, 1H), 13.3 (s, 1H).

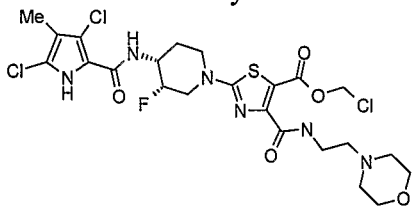
Example 198

Cis(±)-ethyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-{[(1-methyl-1-phenylethyl)amino]carbonyl}isonicotinate

HATU (87 mg, 24 mmol) was added to a solution of 118 mg (0.24 mmol) Cis(±)-6-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(ethoxycarbonyl)nicotinic acid (Example 197), 0.040 ml (28 mmol) Et_3N and 33 mg (0.24 mmol) cumylamine in 3 ml DMF. After stirring at room temperature overnight, the mixture was diluted with water and extracted with EtOAc. The EtOAc was washed 2 times with water and once with brine before being dried ($MgSO_4$) and concentrated to give 103 mg of a solid. MS (ES) MH^+: 616 for $C_{30}H_{35}Cl_2N_5O_5$.

Examples 199-200

The following Examples were prepared by the procedure described in Example 198 from the starting materials (SM) indicated.

Ex	Compound	Data	SM
199	ethyl 2-((3*S*,4*R*)-4-{[(3,5-dichloro-4-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-4-{[(1-methyl-1-phenylethyl)amino]carbonyl}-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 610 for $C_{27}H_{30}Cl_2FN_5O_4S$; NMR: 1.2 (t, 3H), 1.5 (s, 6H), 1.65 (m, 2H), 1.9 (s, 3H), 3.6 (m, 1H), 4.0 (m, 1H), 4.1-4.3 (m, 4H), 4.3 (dd, 1H), 4.95 (d, 1H), 7.0-7.5 (m, 5H), 8.6 (s, 1H), 12.6 (s, 1H)	Example 156 and cumylamine
200	ethyl 2-((3*S*,4*R*)-4-{[(3,5-dichloro-4-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-4-{[(2-morpholin-4-ylethyl)amino]carbonyl}-1,3-thiazole-5-carboxylate 	MS (ES) MH^+: 605 for $C_{24}H_{31}Cl_2FN_6O_6S$; NMR: 1.2 (t, 3H), 1.8 (m, 2H), 1.9 (s, 3H), 2.3 (m, 4H), 3.6 (m, 5H), 4.0 (m, 1H), 4.2 (q, 2H), 4.3 (m, 2H), 4.95 (d, 1H), 7.35 (d, 1H), 8.4 (t, 1H), 12.6 (s, 1H)	Example 156 and (2-morpholin-4-ylethyl)amine

Example 201

Cis(±)-ethyl 5-(aminocarbonyl)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)isonicotinate

A solution of 103 mg (0.17 mmol) of Cis(±)-ethyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-{[(1-methyl-1-phenylethyl)amino]carbonyl}isonicotinate (Example 198) in 10 ml TFA was heated at 40 °C overnight and at 50 °C for 6 h. Solvent was removed and the residue was triturated with MeOH to give 62 mg of a white solid. MS (ES) MH^+: 498 for $C_{21}H_{25}Cl_2N_5O_5$.

Example 202

The following Examples were prepared by the procedure described in Example 201 from the starting materials (SM) indicated.

Ex	Compound	Data	SM
202	5-thiazolecarboxylic acid, 4-(aminocarbonyl)-2-[(3*S*,4*R*)-4-[[(3,5-dichloro-4-methyl-1*H*-pyrrol-2-yl)carbonyl]amino]-3-fluoro-1-piperidinyl]-, ethyl ester	MS (ES) MH^+:492 for $C_{18}H_{20}Cl_2FN_5O_4SE$	Example 199

Example 203

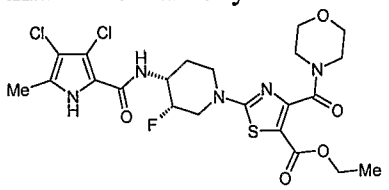
Cis(±)-ethyl 2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-[(dimethylamino)carbonyl]-1,3-thiazole-5-carboxylate

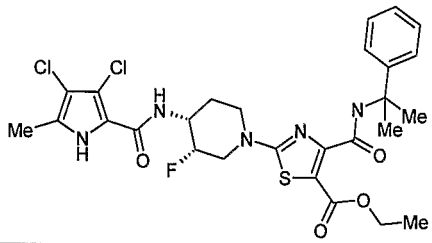
A solution of Cis(±)-2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-(ethoxycarbonyl)-1,3-thiazole-4-carboxylic acid (0.062g, 0.12mmol, Example 188), dimethylamine (0.06mL, 2M solution in THF, Aldrich), HATU (0.05g, 0.13mmol) and triethylamine (0.018mL, 0.13mmol) was stirred at room temperature until complete by LCMS (about 30 min). The crude reaction mixture was slowly poured into water and the resulting white precipitate was filtered, washed with water and dried under vacuum to yield pure product (0.028g). MS (ES) MH^+: 532 for $C_{21}H_{27}Cl_2N_5O_5S$; NMR: 1.20 (t, 3 H) 1.76 (s, 2 H) 2.18 (s, 3 H) 2.78 (s, 3 H) 2.93 (s, 3 H) 3.29 (d,1 H) 3.36 (s, 3 H) 3.39 - 3.43 (m, 1 H) 3.55 (s, 1 H) 3.91 (s, 1 H) 4.15 (q, 2 H) 4.29 (s, 2 H) 7.15 (d, 1 H) 12.14 (s, 1 H)

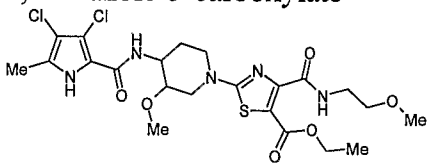
Examples 204-241

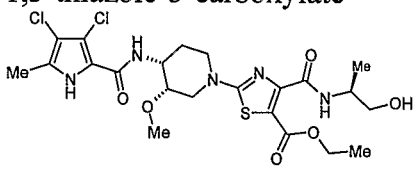
The following Examples were prepared by the procedure described in Example 203 from the starting materials (SM) indicated

Ex	Compound	Data	SM
204	Cis(±)-ethyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(morpholin-4-ylcarbonyl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 574 for $C_{23}H_{29}Cl_2N_5O_6S$; NMR: 1.21 (t, 3 H) 1.74 (s, 2 H) 2.17 (s, 3 H) 3.11 - 3.17 (m, 2 H) 3.34 (s, 3 H) 3.38 (s, 1 H) 3.47 - 3.59 (m, 5 H) 3.62 (s, 2 H) 3.87 (s, 1 H) 4.17 (q, 2 H) 4.29 (s, 2 H) 7.13 (d, 1 H) 12.13 (s, 1 H)	Example 188 and morpholine

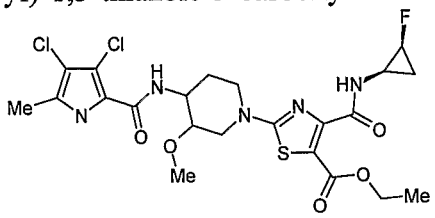
Ex	Compound	Data	SM
205	ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-4-(morpholin-4-ylcarbonyl)-1,3-thiazole-5-carboxylate 	MS (ES) MH^+: 562 for $C_{22}H_{26}Cl_2FN_5O_5S$; NMR: 1.16 (t, 3 H) 1.80 (s, 2 H) 2.12 (s, 3 H) 3.09 (d, 2 H) 3.45 (s, 2 H) 3.50 (s, 2 H) 3.57 (s, 2 H) 3.92 (s, 1 H) 4.12 (q, 2 H) 4.26 (s, 3 H) 4.82 (s, 1 H) 4.99 (s, 1 H) 7.19 (s, 1 H) 12.02 (s, 1 H)	Example 189 and morpholine
206	Cis(±)-ethyl-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-[(methoxyamino)carbonyl]-1,3-thiazole-5-carboxylate	MS (ES) MH^+:534 for $C_{20}H_{25}Cl_2N_5O_6S$; NMR: 1.18 - 1.25 (m, 3 H) 1.75 (s, 2 H) 2.17 (s, 3 H) 3.35 (s, 3 H) 3.54 (s, 2 H) 3.67 (s, 3 H) 3.95 (s, 2 H) 4.14 - 4.22 (m, 2 H) 4.28 (s, 2 H) 7.13 (d, 1 H) 11.48 (s, 1 H) 12.13 (s, 1 H)	Example 188 and methoxylamine hydrochloride
207	ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-4-[(methoxyamino)carbonyl]-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 522 for $C_{19}H_{22}Cl_2FN_5O_5S$; NMR: 1.16 (t, 3 H) 1.79 (s, 2 H) 2.12 (s, 3 H) 3.29 (s, 2 H) 3.62 (s, 3 H) 3.94 (s, 1 H) 4.12 (q, 2 H) 4.25 (s, 2 H) 4.82-4.98 (s, 1 H) 7.18 (d, 1 H) 11.44 (s, 1 H) 12.03 (s, 1 H)	Example 189 and methoxylamine hydrochloride
208	Cis(±)-ethyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(piperidin-1-ylcarbonyl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 572 for $C_{24}H_{31}Cl_2N_5O_5S$; NMR: 1.22 (s, 3 H) 1.43 (s, 2 H) 1.56 (s, 4 H) 1.74 (s, 2 H) 2.17 (s, 3 H) 3.12 (s, 2 H) 3.36 (s, 3 H) 3.52 (s, 3 H) 4.16 (s, 2 H) 4.27 (s, 2 H) 7.15 (s, 1 H) 12.18 (s, 1 H)	Example 188 and piperidine

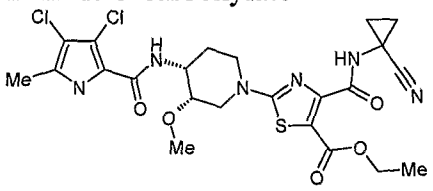
Ex	Compound	Data	SM
209	ethyl 2-((3*R*,4*S*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(1-methyl-1-phenylethyl)amino]carbonyl}-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 622 for $C_{28}H_{33}Cl_2N_5O_5S$; NMR: 1.18 (t, 3 H) 1.53 (s, 3 H) 1.56 (s, 3 H) 1.71 (s, 2 H) 2.13 (s, 3 H) 3.34 (s, 3 H) 3.51 (s, 2 H) 3.92 (s, 2 H) 4.15 (q, 2 H) 4.26 (s, 2 H) 7.12 (dd, 2 H) 7.23 (t,2 H) 7.40 (d, 2 H) 8.56 (s, 1 H) 12.11 (s, 1 H)	Example 190 and cumylamine
210	ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-4-{[(1-methyl-1-phenylethyl)amino]carbonyl}-1,3-thiazole-5-carboxylate 	MS (ES) MH^+: 610 for $C_{27}H_{30}Cl_2FN_5O_4S$; NMR: 1.23 (t, 3 H) 1.61 (s, 6 H) 1.86 (s, 2 H) 2.19 (s, 3 H) 3.31 (s, 3 H) 3.55 (s, 1 H) 4.04 (s, 1 H) 4.22 (q, 1 H) 4.32 (s, 2 H) 4.90-5.06 (d, 1H) 7.20 (d, 1 H) 7.31 (t, 3 H) 7.47 (d, 2 H) 8.63 (s, 1 H) 12.12 (s, 1H)	Example 189 and cumylamine
211	ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-4-[(methylamino)carbonyl]-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 506 for $C_{19}H_{22}Cl_2FN_5O_4S$; NMR: 1.14 (t, 3 H) 1.77 (s, 2 H) 2.12 (s, 3 H) 2.62 (d,3 H) 3.33 (s, 1 H) 3.43-3.63 (s, 1 H) 3.94 (s, 1 H) 4.09 (q, 2 H) 4.23 (s, 2 H) 4.82-4.98 (s, 1 H) 7.20 (d, 1 H) 8.27 (d, 1 H) 12.03 - 12.12 (m, 1 H)	Example 189 and methylamine
212	Cis(±)-ethyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(2-hydroxyethyl)amino]carbonyl}-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 548 for $C_{21}H_{27}Cl_2N_5O_6S$	Example 188 and 2-aminoethanol

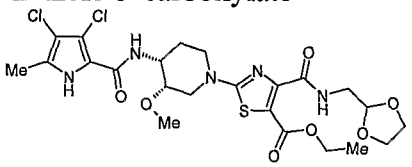
Ex	Compound	Data	SM
213	ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(1-methyl-1-phenylethyl)amino]carbonyl}-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 622 for $C_{28}H_{33}Cl_2N_5O_5S$; NMR: 1.23 (t, 3 H) 1.59 (s, 3 H) 1.62 (s, 3 H) 1.77 (s, 2 H) 2.19 (s, 3 H) 3.31 (s, 1 H) 3.36 (s, 1 H) 3.40 (s, 3 H) 3.57 (s, 1 H) 3.96 (s, 1 H) 4.21 (q, 2 H) 4.32 (s, 2 H) 7.12 - 7.22 (m, 2 H) 7.29 (t, 2 H) 7.46 (d, 2 H) 8.62 (s, 1 H)	Example 191 and cumylamine
214	Cis(±)-ethyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-[(methylamino)carbonyl]-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 518 for $C_{20}H_{25}Cl_2N_5O_5S$; NMR: 1.20 (s, 3 H) 1.74 (s, 2 H) 2.17 (s, 3 H) 2.68 (s, 3 H) 3.30 (s, 2 H) 3.36 (s, 3 H) 3.55 (s, 1 H) 3.99 (s, 1 H) 4.15 (s, 2 H) 4.26 (s, 2 H) 7.14 (s, 1 H) 8.32 (s, 1 H) 12.18 (s, 1 H)	Example 188 and methylamine
215	Cis(±)-ethyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(2-methoxyethyl)amino]carbonyl}-1,3-thiazole-5-carboxylate 	MS (ES) MH^+: 562 for $C_{22}H_{29}Cl_2N_5O_6S$; NMR: 1.15 - 1.25 (m, 3 H) 1.74 (s, 2 H) 2.18 (s, 3 H) 3.26 (s, 3 H) 3.30 (s, 1 H) 3.36 (s, 3 H) 3.41 (d, 3 H) 3.55 (s, 1 H) 4.00 (s, 1 H) 4.10 - 4.19 (m, 2 H) 4.26 (s, 2 H) 7.15 (d, 1 H) 8.44 - 8.56 (m, 1 H) 12.16 (s, 1 H)	Example 188 and (2-methoxyethyl)amine
216	Cis(±)-ethyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(2-hydroxy-1-methylethyl)amino]carbonyl}-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 562 for $C_{22}H_{29}Cl_2N_5O_6S$; NMR: 1.08 (d, 2H) 1.22 (t,3 H) 1.75 (s, 2 H) 2.18 (s, 3 H) 3.37 (s, 3 H) 3.47 (d, 1 H) 3.55 (s, 1 H) 3.81 - 3.92 (m, 1 H) 3.99 (s, 1 H) 4.17 (q, 2 H) 4.27 (s, 2 H) 4.62 (s, 2 H) 7.15 (d, 1 H) 8.20 (d, 1 H) 12.17 (s, 1 H)	Example 188 and 2-aminopropan-1-ol

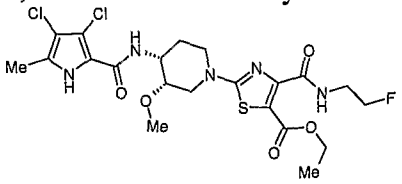
Ex	Compound	Data	SM
217	Cis(±)-ethyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(2-hydroxypropyl)amino]carbonyl}-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 562 for $C_{22}H_{29}Cl_2N_5O_6S$; NMR: 1.07 (d, 3 H) 1.21 (t, 3 H) 1.75 (s, 2 H) 2.18 (s, 3 H) 3.03 - 3.18 (m, 2 H) 3.36 (s, 3 H) 3.41 (s, 1 H) 3.55 (s, 1 H) 3.74 (s, 1 H) 3.98 (s, 1 H) 4.11 - 4.19 (m, 2 H) 4.19 (s, 1 H) 4.30 (s, 1 H) 4.61 (s, 1 H) 7.15 (d, 1 H) 8.33 - 8.43 (m, 1 H) 12.16 (s, 1 H)	Example 188 and 1-aminopropan-2-ol
218	ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-[(methylamino)carbonyl]-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 518 for $C_{20}H_{25}Cl_2N_5O_5S$; NMR: 1.21 (s, 3 H) 1.74 (s, 2 H) 2.18 (s, 3 H) 2.69 (s, 3 H) 3.17 (s, 2 H) 3.36 (s, 3 H) 3.55 (s, 1 H) 3.98 (s, 1 H) 4.14 (s, 2 H) 4.27 (s, 2 H) 7.13 (s, 1 H) 8.33 (s, 1 H) 12.17 (s, 1 H)	Example 191 and methylamine hydrochloride
219	ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(2-methoxyethyl)amino]carbonyl}-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 562 for $C_{22}H_{29}Cl_2N_5O_6S$	Example 191 and (2-methoxyethyl)amine
220	ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[(1*S*)-2-hydroxy-1-methylethyl]amino}carbonyl)-1,3-thiazole-5-carboxylate 	MS (ES) MH^+: 562 for $C_{22}H_{29}Cl_2N_5O_6S$	Example 191 and (2*S*)-2-aminopropan-1-ol

Ex	Compound	Data	SM
221	ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[(1*R*)-2-hydroxy-1-methylethyl]amino}carbonyl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 562 for $C_{22}H_{29}Cl_2N_5O_6S$	Example 191 and [(1*R*)-2-methoxy-1-methylethyl]amine
222	Cis(±)-ethyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(2,2-difluoroethyl)amino]carbonyl}-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 568 for $C_{21}H_{25}Cl_2F_2N_5O_5S$; NMR: 1.21 (t, 3 H) 1.75 (s, 2 H) 2.18 (s, 3 H) 3.36 (s, 3 H) 3.44 (s, 1 H) 3.55 (s, 3 H) 3.98 (s, 1 H) 4.16 (q, 2 H) 4.26 (s, 2 H) 5.88-6.26 (t, 1H) 7.15 (d,1 H) 8.88 (s, 1 H) 12.16 (s, 1 H)	Example 188 and difluoroethylamine
223	Cis(±)-ethyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-[(isoxazol-3-ylamino)carbonyl]-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 571 for $C_{22}H_{24}Cl_2N_6O_6S$; NMR: 1.12 (t, 3 H) 1.77 (d, 2 H) 2.18 (s, 3 H) 3.38 (s, 3 H) 3.56 (s, 2 H) 3.98 (s, 2 H) 4.14 (q, 2 H) 4.19 - 4.34 (m, 2 H) 6.99 (d, 1 H) 7.16 (d, 1 H) 8.86 (d, 1 H) 11.59 (s, 1 H) 12.17 (s, 1 H)	Example 188 and isoxazol-3-amine
224	Cis(±)-ethyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(3*R*)-tetrahydrofuran-3-ylamino]carbonyl}-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 574 for $C_{23}H_{29}Cl_2N_5O_6S$; NMR: 1.21 (t,3 H) 1.75 (d, 2 H) 1.87 (s, 1 H) 2.09 (s, 1 H) 2.18 (s, 3 H) 3.36 (s, 3 H) 3.42 (s, 1 H) 3.55 (s, 2 H) 3.69 (s, 1 H) 3.78 (s, 2 H) 4.01 (s, 1 H) 4.17 (d, 2 H) 4.28 (s, 3 H) 7.15 (d, 1 H) 8.67 (d, 1 H) 12.17 (s, 1 H)	Example 188 and (3*R*)-tetrahydrofuran-3-amine 4-methylbenzenesulfonate

Ex	Compound	Data	SM
225	Cis(±)-ethyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[(1*R*,2*S*)-2-fluorocyclopropyl]amino}carbonyl)-1,3-thiazole-5-carboxylate 	MS (ES) MH^+: 562 for $C_{22}H_{26}Cl_2FN_5O_5S$; NMR: 1.07 (s, 2 H) 1.21 (t, 3 H) 1.75 (s, 2 H) 2.18 (s, 3 H) 2.73 (s, 1 H) 3.36 (s, 3 H) 3.41 (s, 1 H) 3.55 (s, 1 H) 3.99 (s, 1 H) 4.17 (s, 2 H) 4.26 (s, 3 H) 4.62-4.84 (d, 1H) 7.16 (s, 1 H) 8.64 (s, 1 H) 12.17 (s, 1 H)	Example 188 and (1*R*,2*S*)-2-fluorocyclopropanamine 4-methylbenzenesulfonate
226	ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[(1*S*)-2-methoxy-1-methylethyl]amino}carbonyl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 576 for $C_{23}H_{31}Cl_2N_5O_6S$; NMR: 1.09 (d, 3 H) 1.22 (t, 3 H) 1.75 (s, 2 H) 2.18 (s, 3 H) 3.17 (s, 2 H) 3.26 (s, 3 H) 3.37 (s, 3 H) 3.55 (s, 1 H) 4.01 (d, 1 H) 4.17 (d, 2 H) 4.27 (s, 2 H) 7.16 (s, 1 H) 8.32 (d, 1 H) 12.16 (s, 1 H)	Example 191 and [(1*S*)-2-methoxy-1-methylethyl]amine
227	ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-[(prop-2-yn-1-ylamino)carbonyl]-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 542 for $C_{22}H_{25}Cl_2N_5O_5S$; NMR: 1.22 (s, 3 H) 1.74 (s, 2 H) 2.18 (s, 3 H) 3.16 (s, 1 H) 3.40 (m, 5 H) 3.55 (d, 1 H) 3.96 (s, 3 H) 4.17 (s, 2 H) 4.28 (s, 2 H) 7.14 (s, 1 H) 8.87 (s, 1 H) 12.16 (s, 1 H)	Example 191 and propargylamine
228	ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(2-hydroxy-1,1-dimethylethyl)amino]carbonyl}-1,3-thiazole-5-carboxylate	MS (ES) MH^+:576 for $C_{23}H_{31}Cl_2N_5O_6S$ NMR: 1.26 (s, 6 H) 1.75 (s, 2 H) 2.18 (s, 3 H) 3.37 (s, 3 H) 3.44 (s, 3 H) 3.56 (s, 1 H) 4.03 (s, 1 H) 4.19 (s, 2 H) 4.28 (s, 2 H) 4.67 (s, 1 H) 7.16 (s, 1 H) 7.87 (s, 1 H) 12.17 (s, 1 H)	Example 191 and 2-amino-2-methylpropan-1-ol

Ex	Compound	Data	SM
229	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(2-hydroxy-1,1-dimethylethyl)amino]carbonyl}-1,3-thiazole-5-carboxylic acid	MS (ES) MH^+: 562 for $C_{22}H_{26}Cl_2FN_5O_5S$; NMR: 1.08 (s, 3 H) 1.21 (t, 3 H) 1.76 (s, 2 H) 2.18 (s, 3H) 3.36 (s, 3 H) 3.41 (s, 1 H) 3.55 (s, 1 H) 3.97 (s, 1 H) 4.09 - 4.19 (m, 2 H) 4.27 (s, 2 H) 4.61-4.83 (s, 1 H) 7.15 (d, 1 H) 8.64 (s, 1 H) 12.16 (s, 1 H)	Example 191 and (1*R*,2*S*)-2-fluorocyclopropanamine 4-methylbenzenesulfonate
230	ethyl 4-{[(1-cyanocyclopropyl)amino]carbonyl}-2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate 	MS (ES) MH^+: 569 for $C_{23}H_{26}Cl_2N_6O_5S$; NMR: 1.21 (q, 5 H) 1.50 - 1.61 (m, 2 H) 1.75 (s, 2 H) 2.18 (s, 3 H) 3.36 (s, 3 H) 3.40 (s, 1 H) 3.55 (s, 1 H) 4.01 (s, 1 H) 4.13 - 4.22 (m, 2 H) 4.28 (s, 2 H) 7.14 (d, 1 H) 9.36 (s, 1 H) 12.17 (s, 1 H)	Example 191 and 1-aminocyclopropanecarbonitrile
231	ethyl 4-[(cyclopropylamino)carbonyl]-2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 544 for $C_{22}H_{27}Cl_2N_5O_5S$; NMR: 0.49 (s, 2 H) 0.66 (d, 2 H) 1.22 (s, 3 H) 1.75 (s, 2 H) 2.18 (s, 3 H) 2.72 (s, 1 H) 3.38 (m, 4 H) 3.55 (s, 1 H) 3.99 (s, 1 H) 4.17 (s, 2 H) 4.27 (s, 2 H) 7.16 (s, 1 H) 8.44 (s, 1 H) 12.17 (s, 1 H)	Example 191 and cyclopropylamine
232	ethyl 4-{[(1-cyano-1-methylethyl)amino]carbonyl}-2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 571 for $C_{23}H_{28}Cl_2N_6O_5S$; NMR: 1.23 (t, 3 H) 1.62 (s, 6 H) 1.76 (s, 2 H) 2.18 (s, 3 H) 3.37 (s, 3 H) 3.56 (s, 1 H) 4.04 (s, 1 H) 4.15 - 4.22 (m, 2 H) 4.23 (s, 2 H) 7.15 (d, 1 H) 9.07 (s, 1 H) 12.17 (s, 1 H)	Example 191 and 2-amino-2-methylpropanenitrile

Ex	Compound	Data	SM
233	ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[1-(hydroxymethyl)-2-methoxy-2-oxoethyl]amino}carbonyl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+:606 for $C_{23}H_{29}Cl_2N_5O_8S$ NMR: 1.21 (t, 3 H) 1.75 (s, 2 H) 2.18 (s, 3 H) 3.37 (s, 3 H) 3.56 (s, 1 H) 3.66 (s, 2 H) 3.69 - 3.75 (m, 1 H) 4.00 (s, 1 H) 4.16 (q, 2 H) 4.27 (s, 2 H) 4.42 - 4.54 (m, 1 H) 4.98 (s, 1 H) 7.16 (d, 1 H) 8.75 (dd, 1 H) 12.17 (s, 1 H)	Example 191 and methyl serinate
234	ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(2-morpholin-4-ylethyl)amino]carbonyl}-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 617 for $C_{25}H_{34}Cl_2N_6O_6S$; NMR: 1.22 (d, 3 H) 1.75 (s, 2 H) 2.18 (s, 3 H) 3.34 (m, 5H) 3.36 (s, 3 H) 3.55 (s, 1 H) 3.80 (s, 2 H) 3.91 (s, 2 H) 4.02 (s, 1 H) 4.16 (s, 2 H) 4.27 (s, 2 H) 4.94 (s, 1 H) 7.14 (s, 1 H) 8.59 (s, 1 H) 12.16 (s, 1 H)	Example 191 and (2-morpholin-4-ylethyl)amine
235	ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(1,3-dioxolan-2-ylmethyl)amino]carbonyl}-1,3-thiazole-5-carboxylate 	MS (ES) MH^+: 590 for $C_{23}H_{29}Cl_2N_5O_7S$ NMR: 1.22 (d, 3 H) 1.75 (s, 2 H) 2.18 (s, 3 H) 3.36 (s, 4 H) 3.55 (s, 1 H) 3.80 (s, 2 H) 3.91 (s, 2 H) 4.00 (s, 1 H) 4.16 (s, 3 H) 4.28 (s, 2 H) 4.94 (s, 1 H) 7.14 (s, 1 H) 8.59 (s, 1 H) 12.16 (s, 1 H)	Example 191 and (1,3-dioxolan-2-ylmethyl)amine
236	ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[3-(2-oxopyrrolidin-1-yl)propyl]amino}carbonyl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+:629 for $C_{26}H_{34}Cl_2N_6O_6S$	Example 191 and 1-(3-aminopropyl)pyrrolidin-2-one

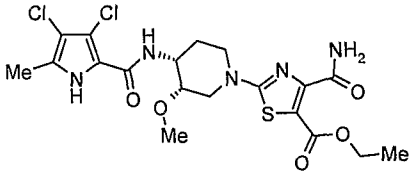
Ex	Compound	Data	SM
237	ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(pyridin-2-ylmethyl)amino]carbonyl}-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 595 for $C_{25}H_{28}Cl_2N_6O_5S$; NMR: 1.18 (t, 3 H) 1.76 (s, 2 H) 2.18 (s, 3 H) 3.46 (s, 2 H) 3.57 (s, 1 H) 3.99 (s, 1 H) 4.16 (q, 2 H) 4.28 (s, 2 H) 4.50 (d, 2 H) 7.16 (d, 1 H) 7.34 (s, 1 H) 7.53 (d, 1 H) 7.81 - 7.93 (m, 1 H) 8.53 (s, 1 H) 9.07 (t, 1 H) 12.17 (s, 1 H)	Example 191 and (pyridin-2-ylmethyl)amine
238	ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[2-(methylthio)ethyl]amino}carbonyl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 578 for $C_{22}H_{29}Cl_2N_5O_5S_2$	Example 191 and [2-(methylthio
239	ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(1,3-oxazol-2-ylmethyl)amino]carbonyl}-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 585 for $C_{23}H_{26}Cl_2N_6O_6S$; NMR: 1.17 (t, 3 H) 1.74 (s, 2 H) 2.18 (s, 3 H) 3.37 (s, 3 H) 3.55 (s, 1 H) 4.00 (s, 1 H) 4.13 (d, 2 H) 4.26 (s, 2 H) 4.49 (d, 2 H) 7.11 - 7.25 (m, 2 H) 8.08 (s, 1 H) 9.07 (s, 1 H) 12.16 (s, 1 H)	Example 191 and 1-(1,3-oxazol-2-yl)methanamine hydrochloride
240	ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(2-fluoroethyl)amino]carbonyl}-1,3-thiazole-5-carboxylate 	MS (ES) MH^+: 550 for $C_{21}H_{26}Cl_2FN_5O_5S$; NMR: 1.21 (t, 3 H) 1.74 (d, 2 H) 2.18 (s, 3 H) 3.40 (s, 3 H) 3.55 (s, 3 H) 3.99 (s, 1 H) 4.17 (d, 2 H) 4.27 (s, 2 H) 4.42 (s, 1 H) 4.58 (s, 1 H) 7.14 (s, 1 H) 8.70 (s, 1 H) 12.17 (s, 1 H)	Example 191 and 2-fluoroethanamine hydrochloride

Ex	Compound	Data	SM
241	ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(2-hydroxy-2-methylpropyl)amino]carbonyl}-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 576 for $C_{23}H_{31}Cl_2N_5O_6S$; NMR: 1.11 (s, 6 H) 1.22 (d, 3 H) 1.75 (s, 2 H) 2.18 (s, 3 H) 3.14 (s, 3 H) 3.38 (s, 3 H) 3.55 (s, 1 H) 3.95 (s, 1 H) 4.17 (s, 2 H) 4.27 (s, 2 H) 4.39 (s, 1 H) 7.14 (s, 1 H) 8.28 (s, 1 H) 12.17 (s, 1 H)	Example 191 and 1-amino-2-methylpropan-2-ol

Examples 242-245

The following Examples were prepared by the procedure described in Example 34 from the starting materials (SM) indicated.

Ex	Compound	Data	SM
242	Cis(±)-ethyl 4-(aminocarbonyl)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 504 for $C_{19}H_{23}Cl_2N_5O_5S$	Example 178
243	ethyl 4-(aminocarbonyl)-2-((3*R*,4*S*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 504 for $C_{19}H_{23}Cl_2N_5O_5S$	Example 209
244	ethyl 4-(aminocarbonyl)-2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 492 for $C_{18}H_{20}Cl_2FN_5O_4S$	Example 210

Ex	Compound	Data	SM
245	ethyl 4-(aminocarbonyl)-2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate 	MS (ES) MH^+: 504 for $C_{19}H_{23}Cl_2N_5O_5S$ NMR: 1.22 (t, 3H) 1.74 (d, 2 H) 2.18 (s, 3 H) 3.31 (s, 1 H) 3.37 (s, 3 H) 3.38 - 3.43 (m, 1 H) 3.55 (s, 1 H) 3.95 (s, 1 H) 4.17 (q, 2 H) 4.27 (s, 2 H) 7.15 (d, 1 H) 7.53 (s, 1 H) 7.82 (s, 1 H) 12.17 (s, 1 H)	Example 213

Example 246

Cis(±)-ethyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(morpholin-4-ylmethyl)-1,3-thiazole-5-carboxylate

To a solution of ethyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-formyl-1,3-thiazole-5-carboxylate (0.15g, 0.31mmol, Example 252) in methylene chloride (20mL) was added sodium triacetoxyborohydride (0.1g, 0.47mmol) and morpholine (0.03mL, 0.34mmol). Reaction was stirred at room temperature and monitored by LCMS. Upon completion, the reaction mixture was diluted with 1N HCl and then partitioned with EtOAc/sat. sodium bicarbonate. Washing with brine, drying with $MgSO_4$ and concentrating yielded a solid. Purification by silica gel flash column (gradient elution 70-100% EtOAc/CH_2Cl_2) afforded pure product (0.091g) MS (ES) $M+H^+$: 560 for $C_{23}H_{31}Cl_2N_5O_5S$; NMR: 1.24 (t, 3 H) 1.75 (s, 2 H) 2.18 (s, 3 H) 3.32 (s, 2 H) 3.36 (s, 3 H) 3.52 (s, 2 H) 3.54 (d, 4 H) 3.65 - 3.75 (m, 2 H) 3.76 - 3.86 (m, 2 H) 3.93 (s, 1 H) 4.18 (q, 2 H) 4.27 (s, 1 H) 7.16 (d, 1 H) 12.16 (s, 1 H)

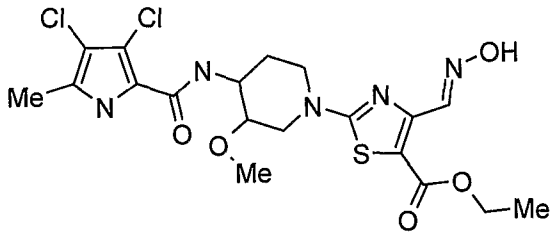
Examples 247-249

The following Intermediate was prepared by the procedure described in Example 246 from the starting materials (SM) indicated.

Ex	Compound	Data	SM
247	Cis(±)-ethyl 4-[(*tert*-butylamino)methyl]-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 546 for $C_{23}H_{33}Cl_2N_5O_4S$; NMR: 1.04 (s, 9 H) 1.22 (t, 3 H) 1.72 (d, 2 H) 2.17 (s, 3 H) 3.32 (s, 1 H) 3.35 (s, 3 H) 3.53 (s, 1 H) 3.78 - 3.92 (m, 2 H) 4.17 (q, 2 H) 4.23 (d, 2 H) 7.14 (d, 1 H)	Example 252 and *tert*-butylamine
248	Cis(±)-ethyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(piperidin-1-ylmethyl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 558 for $C_{24}H_{33}Cl_2N_5O_4S$	Example 252 and piperidine
249	ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-[(3-hydroxypyrrolidin-1-yl)methyl]-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 560 for $C_{23}H_{31}Cl_2N_5O_5S$	Example 252 and pyrrolidin-3-ol

Example 250

Cis(±)-ethyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-[(*E*)-(hydroxyimino)methyl]-1,3-thiazole-5-carboxylate



A solution of Cis(±)-ethyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-formyl-1,3-thiazole-5-carboxylate (0.10g, 0.2mmol, Example 252), sodium acetate (0.041g, 0.5mmol) and hydroxylamine hydrochloride (0.028g, 0.4mmol) were heated to reflux in absolute ethanol for 3 hours. After cooling to room temperature the ethanol was removed under reduced pressure followed by EtOAc/H_2O partitioning, drying with MgSO4 and concentrating to a yellow solid (0.081g) MS (ES): 504 NMR: 1.25 (t, 3H) 1.75 (s, 2 H) 2.18 (s, 3 H) 3.31 (s, 3 H) 3.36 (s, 3 H) 3.55 (s, 1 H) 3.95 (s, 1 H) 4.18 - 4.26 (m, 2 H) 4.26 (d, 2 H) 7.16 (d, 1 H) 8.61 (s, 1 H) 11.72 (s, 1 H) 12.16 (s, 1 H)

Examples 251

The following Intermediate was prepared by the procedure described in Example 250 from the starting materials (SM) indicated.

Ex	Compound	Data	SM
251	ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-[(*E*)-(methoxyimino)methyl]-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 518 for $C_{20}H_{25}Cl_2N_5O_5S$; NMR: 1.25 (t, 3 H) 1.76 (s, 2 H) 2.19 (s, 3 H) 3.30 - 3.32 (m, 2 H) 3.35 - 3.39 (m, 3 H) 3.57 (s, 1 H) 3.92 (s, 3 H) 4.04 (s, 1 H) 4.19 - 4.25 (m, 2 H) 4.25 - 4.33 (m, 2 H) 7.16 (d, 1 H) 8.66 (s, 1 H) 12.16 (s, 1 H)	Example 252 and methoxylamine hydrochloride

Example 252

Cis(±)-ethyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-formyl-1,3-thiazole-5-carboxylate

To a solution of Cis(±)-ethyl 2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(hydroxymethyl)-1,3-thiazole-5-carboxylate (0.63g, 1.3mmol, Example 143) in methylene chloride was added Dess-Martin periodinane (0.61g, 1.4mmol). After 1hr stirring at room temperature the reaction was complete. The crude reaction mixture was washed with water (x2) and brine, followed by drying with MgSO4 and concentrating to a minimal volume of methylene chloride after which it was directly deposited on a silica gel flash column (gradient elution to 1:1 EtOAc in CH2Cl2). Pure fractions concentrated to clean, yellow solid (0.56g). NMR: 1.29 (t, 3 H) 1.75 (s, 2 H) 2.18 (s, 3 H) 3.38 (s, 4 H) 3.44 (s, 1 H) 3.57 (s, 1 H) 4.03 (d, 1H) 4.22 - 4.35 (m, 4 H) 7.15 (d, 1 H) 10.31 (s, 1 H) 12.16 (s, 1 H).

Example 253

ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(difluoromethyl)-1,3-thiazole-5-carboxylate

Diethylaminosulfurtrifluoride (0.03mL, 0.22mmol) was added to a solution of ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-formyl-1,3-thiazole-5-carboxylate (0.10g, 0.2mmol, Example 252) in methylene chloride. The reaction was complete after heating at reflux overnight. Upon cooling to room temperature, the reaction was washed with water (x3) and brine (x1), dried with $MgSO_4$ and

concentrated to a yellow solid which, upon trituration, yielded a clean white solid (0.021g). MS (ES) M+H: 511 for $C_{19}H_{22}Cl_2F_2N_4O_4S$; NMR: 1.26 (t, 3 H) 1.75 (s, 2 H) 2.18 (s, 3 H) 3.37 (s, 3 H) 3.43 (s, 1 H) 3.56 (s, 1 H) 3.96 (s, 1 H) 4.25 (s, 1 H) 4.36 (s, 2 H) 7.16 (s, 1 H) 7.31 (s, 1 H) 12.17 (s, 1 H).

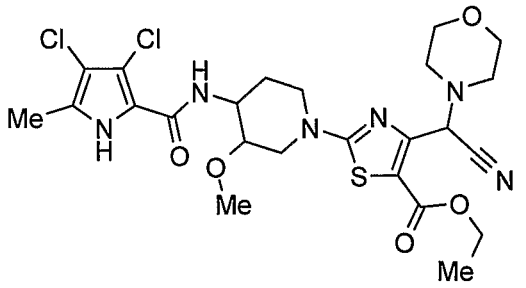
Example 254

ethyl 4-(azidomethyl)-2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate

To a suspension of ethyl 2-((3S,4R)-4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(hydroxymethyl)-1,3-thiazole-5-carboxylate (0.10g, 0.2mmol, Example 143) in anhydrous toluene was added diphenylphosphorylazide (0.053mL, 0.24mmol). The reaction was cooled to 0deg and DBU was added slowly. After stirring at 0deg for 30min the reaction was warmed to room temperature and stirred overnight. The biphasic reaction mixture was washed with water (x3), 1NHCl (x1), brine (x1), dried with MgSO4 and concentrated (0.048g). MS (ES) M+H: 516 for $C_{19}H_{23}Cl_2N_7O_4S$.

Example 255

Cis(±)-ethyl 4-[cyano(morpholin-4-yl)methyl]-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylate



A solution of sodium cyanide (0.011g, 0.22mmol) and morpholine (0.018mL, 0.21mmol) in water (5mL) was cooled to 0deg. 1N HCl (0.22mL, 0.22mmol) was added slowly. After warming to room temperature, a solution of Cis(±)-ethyl 2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-formyl-1,3-thiazole-5-carboxylate (0.10g, 0.2mmol, Example 252) in methanol (10mL) was added. After stirring at room temperature for six weeks the reaction was complete. The reaction mixture was concentrated to remove methanol and the residue was diluted with water and extracted with EtOAc (x3), washed with brine (x1), dried with $MgSO_4$ and concentrated to a pink solid (0.055g). MS (ES) M+H: 585 for $C_{24}H_{30}Cl_2N_6O_5S$.

Example 256

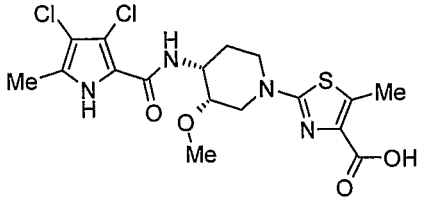
ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[2-(methylsulfonyl)ethyl]amino}carbonyl)-1,3-thiazole-5-carboxylate

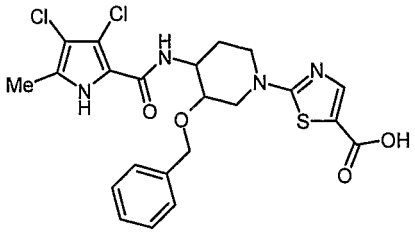
m-CPBA (0.091g, 0.37mmol) was added to a cold solution of ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[2-(methylthio)ethyl]amino}carbonyl)-1,3-thiazole-5-carboxylate (0.107g, 0.18mmol, Example 238) in methylene chloride. After stirring at room temperature for 2 hours, the reaction mixture was washed with sat. sodium bicarbonate (x3), dried with MgSO4, and concentrated to a white solid (0.092g). MS (ES) M+H: 610 for $C_{22}H_{29}Cl_2N_5O_7S_2$; NMR: 1.21 (q, 3 H) 1.66 - 1.80 (m, 2 H) 2.18 (s, 3 H) 3.04 (s, 3 H) 3.29 (s, 4 H) 3.36 (s, 3 H) 3.51 - 3.62 (m, 3 H) 3.99 (s, 1 H) 4.17 (q, 2 H) 4.28 (s, 2 H) 7.15 (d, 1 H) 8.72 (t, 1 H) 12.17 (s, 1 H).

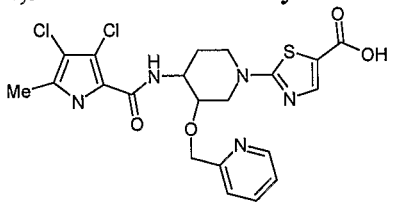
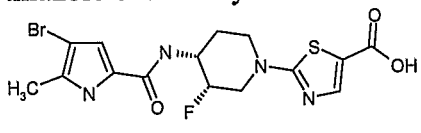
Examples 257-381

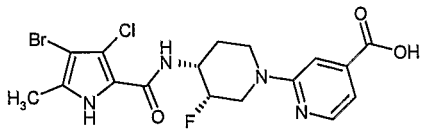
The following Examples were synthesized by an analogous method to Example 35 from the starting materials (SM) given in the table below.

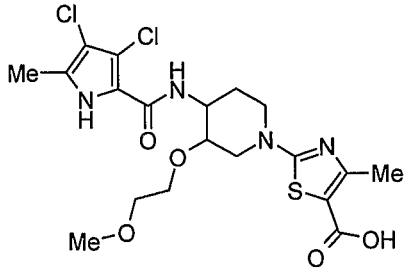
Ex	Compound	NMR	m/z	SM
257	Cis(±)-2-{4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-[(methylsulfinyl)methyl]piperidin-1-yl}-1,3-thiazole-5-carboxylic acid	1.85 (m, 2H), 2.16 (s, 3H), 2.2 (m, 1H), 2.5 (s, 3H), 2.6-2.9 (m, 2H), 3.0 (m, 1H), 3.2 (m, 1H), 3.9 (m, 2H), 4.17 (m, 1H), 7.4 (s, 1H), 7.7 (dd.1H), 7.9 (broad s, 1H).	479	Example 89
258	Cis(±)-2-{4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-[(methylsulfonyl)methyl]piperidin-1-yl}-1,3-thiazole-5-carboxylic acid	1.71 (m, 2H), 2.12 (s, 3H), 2.96 (s, 3H), 2.99 (m, 2H), 3.12 (m, 3H), 3.95 (m, 2H), 4.3 (m, 1H), 7.37 (d, 1H), 7.7 (s, 1H), 12 (broad s, 1H), 12.6 (broad s, 1H).	495	Example 90
259	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-5-methyl-1,3-thiazole-4-carboxylic acid	1.75 (m, 2H), 2.12 (s, 3H), 2.45 (s, 3H), 3.14 (m, 1H), 3.27 (dd, 1H), 3.8 (d, 1H), 4.0 (m, 2H), 4.78 (d, 1H), 5.9 (broad s, 1H), 7.16 (d, 1H), 12 (s, 1H).	435	Example 91

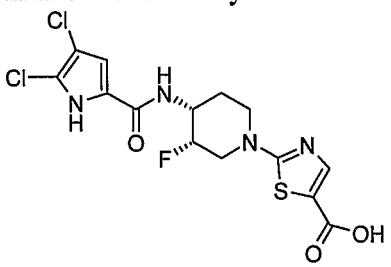
Ex	Compound	NMR	m/z	SM
260	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-methyl-1,3-thiazole-4-carboxylic acid 	1.67 (m, 2H), 2.1 (s, 3H), 2.45 (s,3H), 3.1 (m, 2H), 3.3 (s, 3H), 3.7 (d, 2H), 4.0 (dd, 2H), 4.4 (broad s, 1H), 7.0 (d, 1H), 12.1 (s, 1H).	447	Example 92
261	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-5-[(methoxyimino)methyl]-1,3-thiazole-4-carboxylic acid	1.86 (m, 4H), 2.2 (s, 6H), 3.4 (m, 4H), 3.8 (s, 3H), 3.9 (s, 3H), 4.0 (m, 2H), 4.3 (m, 4H), 4.9 (s, 1H), 5.0 (s, 1H), 7.2 (d, 2H), 8.4 (s, 1H), 8.7 (s, 1H), 12.1 (s, 2H), 13.2 (s, 2H).	478	Example 94
262	Cis(±)-2-[4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(morpholin-4-ylcarbonyl)piperidin-1-yl]-1,3-benzothiazole-7-carboxylic acid	1.93 (m, 2H), 2.16 (s, 3H), 3.3-3.8 (m, 11H), 4.0 (m, 2H), 4.4 (m, 1H), 7.2 (d, 1H), 7.4 (t, 1H), 7.6 (d, 1H), 7.7 (d, 1H), 9.8 (broad s, 1H), 12.0 (s, 1H).	566	Example 93
263	Cis(±)-2-[4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(methylthio)piperidin-1-yl]-1,3-thiazole-5-carboxylic acid	1.65-1.90 (m, 2H); 2.14 (s, 3H); 2.19 (s, 3H); 3.20-3.45 (m, 2H); 3.73 (d, 1H); 3.94 (d, 1H); 4.02 (dd, 1H); 4.43 (m, 1H); 7.24 (d, 1H); 7.75 (s, 1H); 12.13 (s, 1H); 12.66 (s, 1H).	449	Example 95
264	Cis(±)-2-[4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(methylsulfonyl)piperidin-1-yl]-1,3-thiazole-5-carboxylic acid	1.70 (m, 1H); 1.90 (m, 1H); 2.11 (s, 3H); 3.00 (s, 3H); 3.30-3.45 (m, 2H); 3.45 (m, 1H); 3.62 (m, 2H); 4.30 (bd, 1H); 7.39 (s, 1H); 8.20 (m, 1H); 12.10 (s, 1H); 12.60 (s, 1H).	481	Example 96

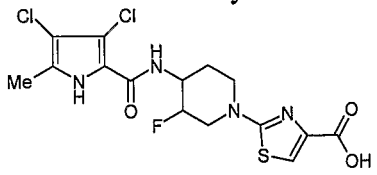
Ex	Compound	NMR	m/z	SM
265	Cis(±)2-(3-(benzyloxy)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylic acid 	1.79 (m, 2H); 2.18 (s, 3H); 3.35 (m, 2H); 3.81 (s, 1H); 3.95 (d, 1H); 4.29 (m, 1H); 4.46 (m, 2H); 4.71 (d, 1H); 7.09 (d, 1H); 7.25 (s, 5H); 7.75 (s, 1H); 12.12 (s, 1H); 12.63 (s, 1H).	509	Example 97
266	Cis(±)-2-[4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(prop-2-yn-1-yloxy)piperidin-1-yl]-1,3-thiazole-5-carboxylic acid	1.76 (m, 2H); 2.18 (s, 3H); 3.30 (m, 2H); 3.44 (t, 1H); 3.87 (s, 1H); 3.96 (m, 1H); 4.22-4.36 (m, 4H); 7.15 (d, 1H); 7.73 (s, 1H); 12.15 (s, 1H); 12.62 (s, 1H).	457	Example 98
267	Trans(±)2-(3-(benzyloxy)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylic acid	1.72 (m, 1H), 1.98 (m, 1H), 2.17 (s, 3H), 3.26 (m, 1H), 3.67 (m, 1H), 3.82 (m, 1H), 4.14 (m, 2H), 4.63 (dd, 2H), 7.28 (m, 5H), 7.34 (d, 2H), 7.76 (s, 1H), 12.00 (s, 1H), 12.66 (br s, 1H)	509	Example 99 and benzyl bromide
268	Trans(±)2-(3-(allyloxy)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylic acid	1.67 (m, 1H), 1.98 (m, 1H), 2.17 (s, 3H), 3.22 (m, 1H), 3.37 (m, 1H), 3.57 (m, 1H), 3.79 (m, 1H), 4.09 (m, 4H), 5.10 (d, 1H), 5.23 (dd, 1H), 5.85 (m, 1H), 7.31 (d, 2H), 7.76 (s, 1H), 11.99 (s, 1H)	459	Example 99 and allyl bromide
269	Trans(±)2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-hydroxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid	1.60 (m, 1H), 2.01 (m, 1H), 2.17 (s, 3H), 3.07 (m, 1H), 3.30 (m, 1H), 3.61 (m, 1H), 3.82 (m, 1H), 3.90 (m, 1H) 3.99 (m, 1H), 4.58 (m, 1H), 7.18 (d, 1H), 7.31 (m, 1H), 7.75 (s, 1H), 11.97 (s, 1H)	419	Example 99

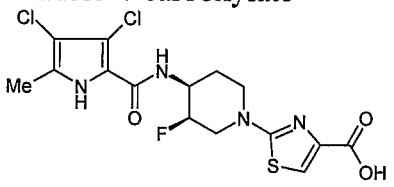
Ex	Compound	NMR	m/z	SM
270	Trans(±)2-[4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(pyridin-2-ylmethoxy)piperidin-1-yl]-1,3-thiazole-5-carboxylic acid 	1.74 (m, 1H), 2.00 (m, 1H), 2.16 (s, 3H), 3.36 (m, 2H), 3.79 (m, 2H), 4.18 (m, 2H), 4.80 (dd, 2H), 7.41 (brd, 1H), 7.46 (brt, 2H), 7.54 (brd, 1H), 7.76 (s, 1H), 7.94 (brt, 1H), 8.58 (brd, 1H), 11.99 (s, 1H)	510	Example 99 and 2-chloromethylpyridine
271	2-((3S,4R)-4-{[(3-chloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-5-carboxylic acid	1.85 (m, 2H); 2.17 (s, 3H); 3.48 (m 2H); 4.0 (m, 1H); 4.33 (m, 2H); 4.96 (d, br, 1H); 5.95 (s, 1H); 7.10 (d, 1H); 7.76 (s, 1H); 11.63 (s, 1H); 12.68 (s, br, 1H)	387	Example 100
272	2-((3S,4R)-4-{[(3-chloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-4-carboxylic acid	1.88 (m, 2H); 2.17 (s, 3H); 3.31 (m 2H); 3.94 (m, 1H); 4.23 (m, 2H); 4.90 (d, br, 1H); 5.93 (s, 1H); 7.10 (d, 1H); 7.62 (s, 1H); 11.62 (s, 1H)	387	Example 101
273	2-((3S,4R)-4-{[(3-chloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-benzothiazole-7-carboxylic acid	1.88 (m, 2H); 2.17 (s, 3H); 3.31 (m 2H); 4.19 (m, 1H); 4.46 (m, 2H); 4.97 (d, br, 1H); 5.93 (s, 1H); 7.10 (d, 1H); 7.41 (t, 1H); 7.68 (d, 1H); 7.69 (d, 1H); 11.62 (s, 1H)	437	Example 102
274	2-((3S,4R)-4-{[(3-chloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)isonicotinic acid	1.80 (m, 2H); 2.16 (s, 3H); 3.06 (m 2H); 4.40 (m, 2H); 4.71 (m, 1H); 4.90 (d, br, 1H); 5.94 (s, 1H); 7.03 (m, 2H); 7.26 (s, 1H); 8.22 (d, 1H); 11.61 (s, br, 1H)	381	Example 108
275	2-((3S,4R)-4-{[(4-bromo-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-5-carboxylic acid 	1.94 (m, 1H); 1.98 (m, 1H); 2.14 (s, 3H); 3.31 (m 2H); 4.01 (m, 1H); 4.28 (m, 2H); 4.86 (d, br, 1H); 6.94 (s, 1H); 7.75 (s, 1H); 8.02 (d, 1H); 11.73 (s, 1H).	432	Example 103

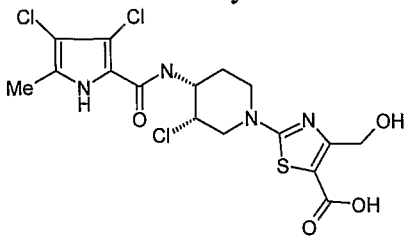
Ex	Compound	NMR	m/z	SM
276	2-((3S,4R)-4-{[(4-bromo-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)isonicotinic acid	1.72 (m, 1H); 1.92 (m, 1H); 2.15 (s, 3H); 3.10 (m, 1H); 3.30 (m, 1H); 4.24 (m, 1H); 4.44 (m, 1H); 4.69 (m, 1H); 4.86 (d, br, 1H); 6.96 (s, 1H); 7.05 (d, 1H); 7.33 (s, 1H); 7.95 (d, 1H); 8.24 (d, 1H); 11.74 (s, br, 1H).	426	Example 109
277	2-((3S,4R)-4-{[(4-bromo-3-chloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-5-carboxylic acid	1.86 (m, 2H); 2.19 (s, 3H); 3.48 (m 1H); 3.53 (m, 1H); 4.01 (m, 1H); 4.33 (m, 2H); 4.96 (d, br, 1H); 7.32 (d, 1H); 7.76 (s, 1H); 12.24 (s, 1H); 12.69 (br, 1H).	466	Example 104
278	2-((3S,4R)-4-{[(4-bromo-3-chloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-4-carboxylic acid	1.85 (m, 2H); 2.19 (s, 3H); 3.31 (m 2H); 3.95 (m, 1H); 4.23 (m, 2H); 4.90 (d, br, 1H); 7.45 (d, 1H); 7.63 (s, 1H); 12.39 (s, br, 1H).	466	Example 105
279	2-((3S,4R)-4-{[(4-bromo-3-chloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-4-(methoxymethyl)-1,3-thiazole-5-carboxylic acid	1.86 (m, 2H); 2.19 (s, 3H); 3.29 (s, 2H); 3.60 (m 2H); 4.04 (m, 1H); 4.30 (m, 2H); 4.57 (s, 3H); 4.90 (d, br, 1H); 7.32 (d, 1H); 12.25 (s, 1H); 12.78 (br, 1H)	510	Example 107
280	2-((3S,4R)-4-{[(4-bromo-3-chloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)isonicotinic acid 	1.86 (m, 2H); 2.19 (s, 3H); 3.07 (m, 1H); 4.04 (m, 1H); 4.28 (m, 2H); 4.69 (m, 1H); 4.90 (d, br, 1H); 7.01 (d, 1H); 7.27 (s, 1H); 7.82 (m, 1H); 8.02 (m, 1H); 13.38 (s, br, 1H)	460	Example 106
281	Cis(±)-2-[(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(2-methoxyethoxy)piperidin-1-yl]-1,3-thiazole-5-carboxylic acid	1.74-1.76 (m, 2H), 2.17 (s, 3H), 3.14 (s, 3H), 3.25-3.42 (m, 4H), 3.50-3.60 (m, 1H), 3.67-3.73 (m, 2H), 3.75- 4.00 (m, 2H), 4.20-4.35 (m, 2H), 7.14 (d, 1H), 7.72 (s, 1H), 12.14 (brs, 1H)	477	Example 110

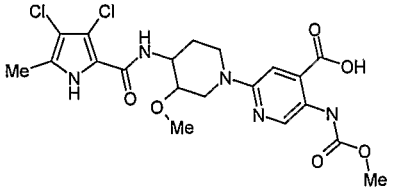
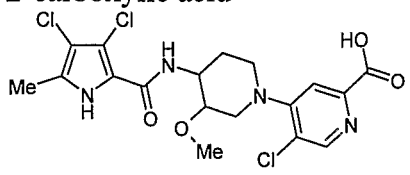
Ex	Compound	NMR	m/z	SM
282	Cis(±)-2-[(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(2-methoxyethoxy)piperidin-1-yl]-1,3-thiazole-4-carboxylic acid	1.74-1.80 (m, 2H), 2.17 (s, 3H), 3.14 (s, 3H), 3.25-3.42 (peaks overlapping with H_2O signal), 3.50-3.60 (m, 1H), 3.67-3.73 (m, 2H), 3.86- 3.90 (m, 1H), 4.12-4.35 (m, 2H), 7.15 (d, 1H), 7.57 (s, 1H), 12.13 (brs, 1H), 12.55 (brs, 1H)	477	Example 111
283	Cis(±)-2-[(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(2-methoxyethoxy)piperidin-1-yl]isonicotinic acid	1.70-1.75 (m, 2H), 2.17 (s, 3H), 3.05-3.20 (m, 2H), 3.09 (s, 3H), 3.25-3.35 (m, 2H), 3.45--3.73 (peaks overlapping with H_2O signal), 4.20-4.25 (m, 2H), 4.60-4.70 (m, 1H), 6.97 (d, 1H), 7.13 (d, 1H), 7.26 (s, 1H), 8.19 (d, 1H), 12.13 (s, 1H)	471	Example 113
284	Cis(±)-2-[(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(2-methoxyethoxy)piperidin-1-yl]-1,3-benzothiazole-7-carboxylic acid	1.79-1.75 (m, 2H), 2.19 (s, 3H), 3.12 (s, 3H), 3.27-3.45 (peaks overlapping with H_2O signal), 3.51-3.62 (m, 1H), 3.72-3.80 (m, 2H), 4.05-4.13 (m, 1H), 4.24-4.42 (m, 2H), 7.18 (d, 1H), 7.39 (t, 1H), 7.65 (t, 2H), 12.16 (s, 1H), 13.48 (brs, 1H)	527	Example 114
285	Cis(±)-2-[(4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(2-methoxyethoxy)piperidin-1-yl]-4-methyl-1,3-thiazole-5-carboxylic acid 	1.70-1.75 (m, 2H), 2.17 (s, 3H), 2.39(s, 3H), 3.15 (s, 3H), 3.32-3.40 (m, buried under water peak), 3.50-3.60 (m, 1H), 3.68-3.75 (m, 2H), 3.86-3.98 (m, 1H), 4.20-4.30 (m, 2 H), 7.14 (d, 1H), 12.14 (s, 1H), 12.38 (brs, 1H)	490	Example 112

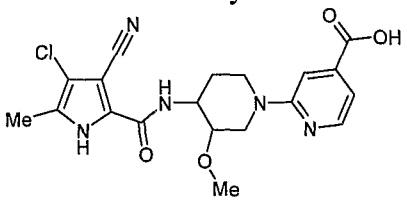
Ex	Compound	NMR	m/z	SM
286	2-((3*S*,4*R*)-4-{[(4-chloro-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-5-carboxylic acid	1.62-1.76 (m, 1H), 1.85-2.03 (m, 1H), 3.22 (s, 3H), 3.36-3.45 (m, 1H), 3.50 (dd, 1H), 3.75 (s, 1H), 4.02-4.10 (m, 1H), 4.15-4.36 (m, 2H), 4.90 (d, 1H), 6.94-6.97 (m, 2H), 7.85 (s, 1H), 8.10 (d, 1H), 11.82 (s, 1H)	373	Example 115
287	2-((3*S*,4*R*)-4-{[(4-chloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid	1.62-1.74 (m, 1H), 1.84-2.05 (m, 1H), 2.13 (s, 3H), 2.41 (s, 3H), 3.19-3.30 (m, 1H), 3.50 (dd, 1H), 3.96-4.02 (m, 1H), 4.20-4.31 (m, 2H), 4.87(d, 1H), 6.89 (d, 1H), 7.97 (d, 1H), 11.65 (s, 1H)	401	Example 116
288	2-((3*S*,4*R*)-4-{[(4-chloro-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid	1.68-1.74 (m, 1H), 1.85-2.00 (m, 1H), 2.39 (s, 3H), 3.30-3.54 (peaks buried under water peak), 3.94-4.00 (m, 1H), 4.10-4.32 (m, 2H), 4.82 (d, 1H), 6.94-6.97 (m, 2H), 8.11 (d, 1H), 11.84 (s, 1H)	387	Example 117
289	2-((3*S*,4*R*)-4-{[(4,5-dichloro-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid	1.69-1.74 (m, 1H), 1.86-2.00 (m, 1H), 2.40 (s, 3H), 3.25-3.35 (m, 1H, buried under water peak), 3.51 (dd, 1H), 3.96-4.00 (m, 1H), 4.16-4.31 (m, 2H), 4.87 (d, 1H), 7.06 (d, 1H), 8.15 (d, 1H), 12.48 (brs, 1H), 12.78 (s, 1H)	419	Example 118
290	2-((3*S*,4*R*)-4-{[(4,5-Dichloro-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-5-carboxylic acid 	1.64-1.74 (m, 1H), 1.85-2.00 (m, 1H), 3.30-3.40 (m, 1H, buried under water peak), 3.53 (dd, 1H), 4.00-4.08 (m, 1H), 4.12-4.40 (m, 2H), 4.89 (d, 1H), 7.06 (d, 1H), 7.75 (s, 1H), 8.16 (d, 1H), 12.78 (s, 1H)	405	Example 119

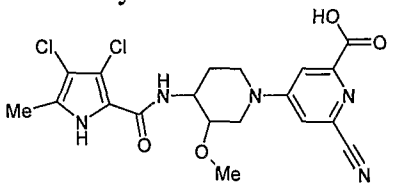
Ex	Compound	NMR	m/z	SM
291	Cis(±)-2-[4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(2-hydroxypropoxy)piperidin-1-yl]-1,3-thiazole-5-carboxylic acid	0.95 (d, 3H), 1.73-1.85 (m, 2H), 2.16 (s, 3H), 3.19-3.36 (m, 6 H, broad peaks), 3.61-3.67 (m, 3 H), 3.94-4.30 (m, difficult to integrate as the peaks are buried under water peak), 7.16 (d, 1H), 7.71 (s, 1H), 12.11 (s, 1H)	477	Example 120
292	Cis(±)-2-[4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(2-methoxypropoxy)piperidin-1-yl]-1,3-thiazole-5-carboxylic acid	0.96 (d, 3H), 1.73-1.76 (m, 2H), 2.17 (s, 3H), 3.14 (s, 1H), 3.28-3.67 (difficult to integrate as the peaks are buried under water peak), 3.89-3.92 (m, 1H), 4.20-4.45 (m, 2 H), 7.12(d, 1H), 7.72(s, 1H), 12.15 (s, 1H)	491	Example 121
293	2-((3*R*,4*S*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylic acid	1.85 (m, 2H), 2.25 (s, 3H), 3.41-3.48 (m, 6H), 4.16 (m, 1H), 5.35 (m, 1H), 4.41 (m, 1H), 7.26 (d, 1H), 7.49 (t, 1H), 7.72 (t, 2H0, 12.23 (s, 1H)	483	Example 123
294	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylic acid	1.85 (m, 2H), 2.25 (s, 3H), 3.41-3.48 (m, 6H), 4.16 (m, 1H), 5.35 (m, 1H), 4.41 (m, 1H), 7.26 (d, 1H), 7.49 (t, 1H), 7.72 (t, 2H), 12.23 (s, 1H)	483	Example 122
295	Cis(±)2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-4-carboxylic acid 	1.74 (m, 2H), 2.10 (s, 3H), 3.29 (m, 1H), 3.48 (d, 1H), 3.85 (d, 1H0, 4.14 (m, 1H), 4.29 (m, 1H), 4.83 (d, 1H), 7.18 (d, 1H), 7.53 (s, 1H), 12.03 (s, 1H)	421	Example 124
296	2-((3*S*,4*R*)-4-{[(4-chloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylic acid	1.85 (m, 1H), 2.14 (m, 1H), 2.23 (s, 3H), 3.33 (s, 3H), 3.62-3.81 (m, 2H), 4.29 (m, 1H), 4.43 (m, 1H), 4.51 (m, 1H). 7.09 (s, 1H), 7.59 (t, 1H), 7.82-7.90 (m, 2H), 11.84 (s, 1H)	449	Example 125

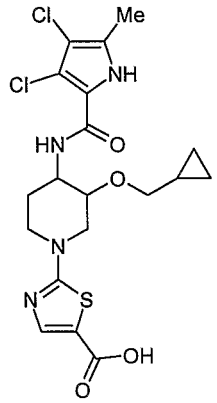
Ex	Compound	NMR	m/z	SM
297	Cis(±)2-4-{[(4-chloro-3,5-dimethyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid	1.47 (m, 1H), 1.62 (m, 1H), 1.95 (s, 3H0, 1.98 (s, 3H), 3.13 (m, 1H), 3.32 (m, 1H), 3.42 (s, 3H), 3.68 (m, 1H), 4.04 (m, 2H), 6.89 (d, 1H), 7.53 (s, 1H), 11.22 (s, 1H)	413	Example 126
299	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-4-carboxylate	1.74 (m, 2H), 2.10 (s, 3H), 3.29 (m, 1H), 3.48 (d, 1H), 3.85 (d, 1H0, 4.14 (m, 1H), 4.29 (m, 1H), 4.83 (d, 1H), 7.18 (d, 1H), 7.53 (s, 1H), 12.03 (s, 1H)	421	Example 128
300	2-((3*S*,4*R*)-4-{[(4-chloro-3,5-dimethyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-4-carboxylic acid	1.69 (m, 1H), 1.82 (m, 1H), 2.09 (s, 3H), 2.13 (s, 3H), 3.19-3.30 (m, 2H), 3.89 (m, 1H), 4.14 (m, 2H), 4.83 (d, 1H), 7.38 (d, 1H), 7.56 (s, 1H), 11.29 (s, 1H)	401	Example 129
301	2-((3*R*,4*S*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-4-carboxylate 	1.74 (m, 2H), 2.10 (s, 3H), 3.29 (m, 1H), 3.48 (d, 1H), 3.85 (d, 1H0, 4.14 (m, 1H), 4.29 (m, 1H), 4.83 (d, 1H), 7.18 (d, 1H), 7.53 (s, 1H), 12.03 (s, 1H)	421	Example 130
302	Cis(±)2-3-chloro-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylic acid	1.87 (m, 1H), 1.93 (m, 1H), 2.20 (s, 3H), 3.41 (m, 1H), 3.82 (d, 1H), 4.01 (d, 1H), 4.27 (d, 1H), 4.75 (s, 1H), 7.18 (d, 1H), 7.75 (s, 1H), 12.15 (s, 1H)	437	Example 131
303	2-{(3*S*,4*R*)-4-[({4-chloro-3-[(*E*)-(methoxyimino)methyl]-5-methyl-1*H*-pyrrol-2-yl}carbonyl)amino]-3-fluoropiperidin-1-yl}-1,3-thiazole-5-carboxylic acid	1.86 (m, 2H), 2.35 (s, 3H), 3.33 (m, 1H), 3.61 (dd, 1H), 3.82 (s, 3H), 4.00 (d, 1H), 4.34 (m, 2H), 4.93 (d, 1H), 7.28 (d, 1H), 7.76 (s, 1H), 8.02 (s, 1H), 12.14 (s, 1H), 12.66 (s, 1H)	444	Example 132
304	Cis(±)-2-(3-chloro)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)[1,3]thiazolo[4,5-*b*]pyridine-7-carboxylic acid	1.82(m, 2H), 2.25 (s, 3H), 3.41 (m, 1H), 3.42 (m, 2H), 4.19 (m, 1H), 5.35 (m, 1H), 4.41 (m, 1H), 7.28 (d, 1H), 7.43(t, 1H), 7.72 (t, 2H), 12.23 (s, 1H)	489	Example 133

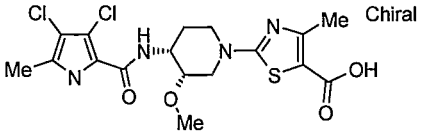
Ex	Compound	NMR	m/z	SM
305	Cis(±)-2-(3-chloro-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-4-(hydroxymethyl)-1,3-thiazole-5-carboxylic acid 	1.84 (m, 1H), 1.91 (m, 1H), 2.20 (s, 3H), 3.33 (m, 1H), 3.79 (m, 1H), 4.04 (m, 1H), 4.21 (m, 1H), 4.48 (m, 1H), 4.59 (m, 2H), 4.75 (s, 1H), 7.20 (d, 1H), 12.17 (s, 1H)	468	Example 134
306	Cis(±)-2-(3-chloro-4-{[(4-chloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylic acid	1.72 (m, 1H), 2.07 (m, 1H), 2.14 (s, 3H), 3.34 (t, 1H), 3.81 (d, 1H), 4.03 (d, 1H), 4.22 (d, 1H), 4.36 (m, 1H), 4.73 (s, 1H), 6.91 (s, 1H), 7.75 (s, 1H), 7.95 (d, 1H), 11.70 (s, 1H)	403	Example 135
307	Cis(±)-2-(3-chloro-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-4-(methoxymethyl)-1,3-thiazole-5-carboxylic acid	1.83 (m, 1H), 1.92 (m, 1H), 2.20 (s, 3H), 3.28 (s, 3H0, 3.35 (m, 1H), 3.80 (d, 1H), 4.01 (m, 1H), 4.22 (m, 1H), 4.43 (m, 1H), 4.56 (m, 2H), 4.75 (s, 1H), 7.18 (d, 1H), 12.15 (s, 1H)	481	Example 136
308	Cis(±)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-hydroxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylic acid	1.78 (m, 1H), 1.91 (m, 1H), 2.19 (s, 3H), 3.32 (m, 2H), 3.55 (d, 1H), 3.90 (s, 1H), 4.03 (m, 1H), 4.17 (m, 1H), 5.53 (d, 1H), 7.15 (d, 1H), 7.41 (t, 1H), 7.64 (t, 2H), 12.15 (s, 1H), 13.47 (s, 1H)	470	Intermediate 131 and 2-bromo-1,3-benzthiazole-7-carboxylate
309	Cis(±)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-nitroisonicotinic acid	1.65 (m, 1H), 1.8 (m, 1H), 2.2 (s, 3H), 3.3 (m), 3.55 (s, 1H), 4.3 (m, 1H), 7.1 (m 2H), 8.9 (s, 1H), 12.2 (s, 1H), 13.9 (s, 1H)	500	Example 137

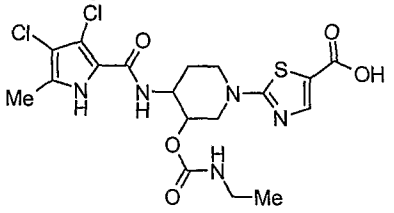
Ex	Compound	NMR	m/z	SM
310	Cis(±)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-[(methoxycarbonyl)amino]isonicotinic acid 	1.7 (m, 2H), 2.2 (s, 3H), 2.4-2.5 (m), 3.0-3.2 (m 2H), 3.3 (s, 3H), 3.5 (m 1H), 3.6 (s, 3H), 4.1 (m, 1H), 4.2 (m, 1H), 4.5 (m, 1H), 7.1 (m, 2H), 8.6 (s, 1H), 12.1 (s, 1H), 13.7 (s, 1H)	500	Example 195
311	Cis(±)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-[(methylsulfonyl)amino]isonicotinic acid	1.7 (m, 2H) 2.2 (s, 3H), 2.9 (s, 3H), 3.1 (m, 2H), 3.3 –3.5 (m), 3.5 (m, 1H), 4.2 (m, 2H), 4.6 (d, 1H), 7.1 (m, 2H), 8.1 (s, 1H), 12.1 (s, 1H).	506	Example 196
312	Cis(±)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methylpiperidin-1-yl)-1,3-thiazole-5-carboxylic acid	0.9 (d, 3H), 1.8 (m, 2H), 2.2 (m, 4H), 3.3-3.8 (m, 4H), 4.25 (m, 1H), 4.25 (m, 1H), 7.2 (d, 1H), 7.8 (s, 1H), 12.0 (s, 1H), 12.6 (s, 1H)	431	Example 138
313	Cis(±)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-2-methylpiperidin-1-yl)-1,3-thiazole-5-carboxylic acid	1.3 (d, 1H), 1.8-2.1 (m, 4H), 2.2 (s, 3H), 3.6 (m, 1H), 3.8 (m 1H), 4.1 (m, 2H), 7.3 (s, 1H), 7.8 (s, 1H), 12.1 (s, 1H)	417;	Example 139
314	Cis(±)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-6-methylisonicotinic acid	0.9 (m, 1H), 1.3 (d, 6H), 1.7, (m, 1H), 2.2 (s, 3H), 2.4 (s, 3H), 3.1 (m, 2H), 3.5 (m, 1H), 4.2 (m, 2H), 4.7 (d, 1H), 5.1 (m, 1H), 6.8 (s, 1H), 7.0 (s, 1H), 7.15 (s, 1H), 12.1 (s, 1H).	441	Example 140
315	Cis(±)-5-chloro-4-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)pyridine-2-carboxylic acid 	NMR: 1.8, (m, 3H), 2.2 (s, 3H), 3.3 (s, 3H), 3.6 (m, 2H), 4.0 (m, 1H), 4.2 (m, 1H), 7.2 (s, 1H), 7.7 (s, 1H), 8.5 (s, 1H), 12.1 (s, 1H), 12.4 (s, broad, 1H).	461	Example 141

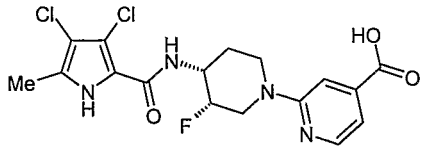
Ex	Compound	NMR	m/z	SM
316	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-4-(hydroxymethyl)-1,3-thiazole-5-carboxylic acid	NMR: 1.85 (m, 2H), 2.2 (s, 3H), 3.3-3.7 (m, 2H), 4.0 (m, 1H), 4.3 (m, 2H), 4.6 (s, 2H), 4.95 (d, 1H), 7.3 (d, 1H), 12.1 (s, 1H), 12.7 (s, 1H).	451	Example 142 and Intermediate 215
317	Cis(±)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(hydroxymethyl)-1,3-thiazole-5-carboxylic acid	NMR: 1.2 (t, 3H), 1.7 (m, 2H), 2.2 (s, 3H), 3.4 (s, 3H), 3.55 (m, 1H), 4.0 (m, 1H), 4.1-4.4 (m, 4H), 4.6 (s, 2H), 7.1 (d, 1H), 12.1 (s, 1H).	463	Example 143
318	Cis(±)-2-(4-{[(4-chloro-3-cyano-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylicacid	NMR: 1.6-1.9 (m, 2H), 2.2 (s, 3H), 3.3 (s, 3H), 3.6 (m, 1H), 3.7 (s, 3H), 3.9 (m, 1H), 4.3 (m, 2H), 7.75 (m, 2H), 12.6 (2s, 2H).	424	Example 144
319	Cis(±)-2-(4-{[(4-chloro-3-cyano-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylic acid	NMR: 1.6-2.0 (m, 2H), 2.2 (s, 3H), 3.3 (s, 3H), 3.4 (m, 1H), 3.6 (s, 3H), 4.1 (m, 1H), 4.2-4.4 (m, 2H), 7.4 (t, 1H), 7.65 (m, 2H), 7.8 (m, 1H), 12.6 (s, 1H), 13.5 (s, 1H).	479	Example 145
320	Cis(±)-2-(4-{[(4-chloro-3-cyano-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid 	NMR: 1.7 (m, 2H), 2.2 (s, 3H), 3.0-3.7 (m), 4.2 (m, 2H), 4.6 (m, 1H), 7.0 (s, 1H), 7.25 (s, 1H), 7.7 (s, 1H), 8.2 (s, 1H), 12.6 (s, 1H), 13.5 (s, 1H).	418	Example 146
322	2-((3*S*,4*R*)-4-{[(4-chloro-3-cyano-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-benzothiazole-7-carboxylic acid	NMR: 1.9 (m, 2H), 2.2 (s, 3H), 3.4 (m, 1H), 3.4 (m, 1H), 3.6 (s, 3H), 4.1 (m, 1H), 4.3 (m, 1H), 4.4 (q, 2H), 7.7 (m, 2H), 7.8 (m, 1H), 7.9 (t, 1H), 12.7 (s, 1H), 13.5 (s, 1H).	462	Example 148

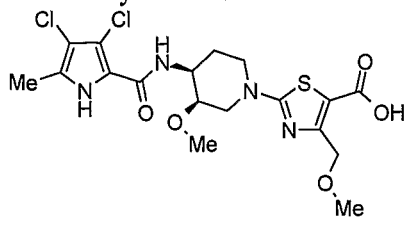
Ex	Compound	NMR	m/z	SM
323	2-((3*S*,4*R*)-4-{[(4-chloro-3-cyano-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)isonicotinic acid	NMR: 1.8 (m, 2H), 2.2 (s, 3H), 3.0 (m, 2H), 3.3 (m), 4.0-4.5 (m, 2H), 4.7 (m, 1H), 4.95 (d, 1H), 7.0 (d, 1H), 7.3 (s, 1H), 8.05 (m, 1H), 8.25 (d, 1H), 12.6 (s, 1H), 13.4 (s, 1H).	406	Example 149
324	Cis(±)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-(morpholin-4-ylcarbonyl)-1,3-thiazole-4-carboxylic acid	NMR: 1.7 (m, 2H), 2.2 (s, 3H), 3.3 (m), 3.4 (m, 4H), 3.5 (m, 4H), 3.8-3.9 (m, 1H), 4.0-4.2 (m, 4H), 7.3 (s, 1H), 12.3 (s, 1H), 12.9 (s, 1H).	546	Example 150
325	Cis(±)-6-cyano-4-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)pyridine-2-carboxylic acid 	NMR: 1.7 (m, 2H), 2.1 (s, 3H), 3.3 (s, 3H), 3.45 (m, 1H), 4.0 (d, 1H), 4.2 (m, 1H), 4.4 (d, 1H), 7.0 (d, 1H), 7.5 (s, 1H), 7.7 (s, 1H), 12.1 (s, 1H), 13.3 (s, 1H).	452	Example 151
326	2-((3*S*,4*R*)-4-{[(3,5-dichloro-4-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-5-carboxylic acid	NMR: 1.8 (m, 2H), 1.9 (s, 3H), 3.3 (m, 1H), 3.5 (dd, 1H), 4.0 (m, 1H), 4.3 (m, 2H), 5.0 (d, 1H), 7.35(d, 1H), 7.8 (s, 1H), 12.6 (s, 1H) 12.7 (s, 1H).	421	Example 155
327	4-acetyl-2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid	NMR: 1.7 (m, 2H), 2.2 (s, 3H), 3.3 (s, 3H), 3.9 (m, 2H), 4.3 (m, 2H), 7.15 (m, 1H), 12.2 (s, 1H), 13.2 (s, 1H).	475	Example 157
328	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(1-hydroxy-1-methylethyl)-1,3-thiazole-5-carboxylic acid	NMR: 1.5 (s, 6H), 1.7 (m, 2H), 2.2 (s, 3H), 3.3 (s, 3H), 3.5 (m, 1H), 3.8 (m, 2H), 4.3 (m, 1H), 4.4 (m, 1H), 7.15 (d, 1H), 12.2 (s, 1H).	491	Example 158

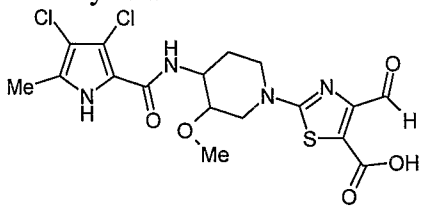
Ex	Compound	NMR	m/z	SM
329	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)thieno[2,3-*d*][1,3]thiazole-6-carboxylic acid	NMR: 1.8 (m, 2H), 2.2 (s, 3H), 3.3 (s, 3H), 3.6 (m, 1H), 4.0 (m, 1H), 4.3 (m, 2H), 7.2 (d, 1H), 7.9 (s, 1H), 12.2 (s, 1H), 13.1 (s, 1H).	489	Example 159
330	Cis(±)-2-(3-(cyclopropylmethoxy)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylic acid 	0.10 (m, 2H), 0.38 (m, 2H), 0.91 (m, 1H), 1.75 (m, 1H), 2.17 (s, 3H), 3.15-3.43 (m, 4H), 3.67 (m, 1H), 3.92 (m, 1H), 4.26 (m, 2H), 7.14 (d, 1H), 7.72 (s, 1H), 12.16 (s, 1H), 12.60 (bs, 1H).	473	Example 160
331	2-[4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(1,3-thiazol-2-ylmethoxy)piperidin-1-yl]-1,3-thiazole-5-carboxylic acid	1.80 (m, 2H), 2.16 (s, 3H), 3.40 (d, 2H), 3.94 (m, 2H), 4.33 (td, 1H), 4.46 (d, 1H), 4.81-4.99 (dd, 2H), 7.13 (d, 1H), 7.65 (d, 1H), 7.69 (s, 1H), 7.71 (d, 1H), 12.12 (s, 1H), 12.60 (bs, 1H).	515	Example 161
332	Cis(±)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid	1.05 (t, 3H); 1.74 (m, 2H); 2.17 (s, 3H); 3.35-3.45 (m, 3H); 3.63-3.73 (m, 2H); 3.97 (m, 1H); 4.25 (m, 2H); 7.12 (d, 1H); 7.72 (s, 1H); 12.16 (s, 1H); 12.55 (br s, 1H).	447, 449	Example 162
333	Cis(±)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-ethoxypiperidin-1-yl)-4-(methoxymethyl)-1,3-thiazole-5-carboxylic acid	1.06 (t, 3H); 1.74 (m, 2H); 2.17 (s, 3H); 3.27 (m, 4H); 3.42 (m, 1H); 3.62-3.71 (m, 2H); 3.82 (m, 1H); 4.08-4.21 (overlapping m, 3H); 4.55 (s, 2H); 6.64 (s, 1H); 7.11 (d, 1H); 12.16 (s, 1H).	435, 437	Example 163

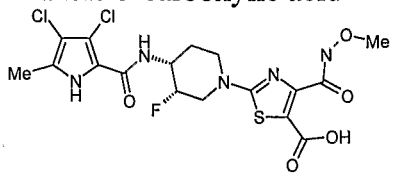
Ex	Compound	NMR	m/z	SM
334	2-((3*S*, 4*R*)-4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid	1.83 (m, 2H); 2.18 (s, 3H); 2.40 (s, 3H); 3.32 (m, overlapping water); 3.50 (dd, 1H); 3.97 (m, 1H); 4.21-4.31 (m, 2H); 4.93 (d, 1H); 7.26 (d, 1H); 12.11 (s, 1H); 12.44 br s, 1H).	435, 437	Example 165
335	2-((3*S*,4*R*)-4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid 	1.72 (m, 2H); 2.17 (s, 3H); 2.39 (s, 3H); 3.26-3.35 (m overlapping with water, 5H); 3.52 (m, 1H); 3.90 (m, 1H); 4.25 (m, 2H); 7.14 (d, 1H); 12.15 (s, 1H); 12.40 (s, 1H).	447, 449	Example 166
337	Trans(±)2-[4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(morpholin-4-ylcarbonyl)piperidin-1-yl]-1,3-thiazole-5-carboxylic acid	1.89 (m, 1H), 2.14 (m, 1H), 2.17 (s, 3H), 3.24-3.70 (m, 11H [under H_2O peak]), 3.74 (dd, 1H), 3.90 (dd, 1H), 4.51 (m, 1H), 7.33 (d, 1H), 7.74 (s, 1H), 12.09 (s, 1H), 12.64 (s, 1H)	516	Example 167
338	Cis(±)2-[4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(morpholin-4-ylcarbonyl)piperidin-1-yl]-1,3-thiazole-5-carboxylic acid	1.79 (dq, 1H), 1.89 (m, 1H), 2.15 (s, 3H), 3.21-3.42 (m, 6H), 3.49-3.72 (m, 5H), 3.95 (m, 1H), 4.02 (m, 1H), 4.40 (m, 1H), 7.17 (d, 1H), 7.78 (s, 1H), 12.02 (s, 1H), 12.69 (s, 1H)	516	Example 168
339	Cis(±)-2-[4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(2-morpholin-4-yl-2-oxoethoxy)piperidin-1-yl]-1,3-thiazole-5-carboxylic acid	1.51 (dq, 1H), 1.98 (m, 1H), 2.18 (s, 3H), 3.18 (m, 2H), 3.23-3.56 (m, 10H [under H_2O peak]), 3.77 (m, 1H), 4.04 (m, 2H), 4.32 (q, 2H), 7.36 (s, 1H), 8.26 (broad s, 2H)	546	Example 169

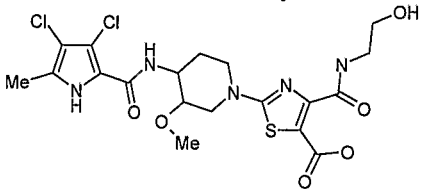
Ex	Compound	NMR	m/z	SM
340	2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-{[(ethylamino)carbonyl]oxy}piperidin-1-yl)-1,3-thiazole-5-carboxylic acid 	MS (ES) MH^+: 490, 492 for $C_{18}H_{21}Cl_2N_5O_5S$; NMR: 0.96 (t, 3H), 1.82 (m, 2H), 2.17 (s, 3H), 2.96 (m, 2H), 3.19-3.40 (m, 2H [under H_2O peak]), 3.47 (d, 1H), 3.95 (m, 1H), 4.08 (m, 1H), 4.33 (m, 1H), 4.83(m, 1H), 6.84 (broad s, 1H), 7.14 (d, 1H), 7.21 (t, 1H), 7.46 (s, 1H)	490	Example 172
341	2-(3-{[(allylamino)carbonyl]oxy}-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylic acid	NMR: 1.22 (s, 1H), 1.84 (m, 2H), 2.17 (s, 3H), 3.52 (m, 1H), 3.57, (m, 1H), 4.03 (m, 1H), 4.14 (m, 1H), 4.36 (m, 1H), 4.78-4.91 (m, 2H), 4.99 (dd, 1H), 5.07 (dd, 1H), 5.52 (broad s, 1H), 5.73 (m 1H), 7.00 (d, 1H), 7.10 (broad s, 1H), 7.44 (t, 1H), 7.62 (s, 1H)	502	Example 173
342	Cis(±)-4-(4-{[(4-chloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)pyridine-2-carboxylic acid	1.56 - 1.72 (m, 2 H) 2.08 - 2.20 (m, 3 H) 3.24 (s, 3 H) 3.55 (s, 2 H) 3.71 - 3.86 (m, 2 H) 4.16 (s, 2 H) 6.88 (d, 1 H) 7.44 (s, 1 H) 7.68 (s, 1 H) 7.97 (d, 1 H) 11.69 (s, 1 H)	393	Example 177
343	Cis(±)-4-(aminocarbonyl)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid	1.74 (s, 2 H) 2.19 (s, 3 H) 3.38 (s, 3 H) 3.55 (s, 2 H) 4.01 (s, 1 H) 4.25 (s, 3 H) 4.49 (s, 1 H) 7.16 (d, 1 H) 8.93 (s, 2 H) 12.16 (s, 1 H	476	Example 242
344	4-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)pyridine-2-carboxylic acid	1.81 - 1.95 (m, 2 H) 2.14 - 2.21 (m, 3 H) 3.73 (s, 2 H) 4.26 (t, 2 H) 4.62 (s, 1 H) 4.93 (s, 1 H) 7.22 (s, 1 H) 7.36 (s, 1 H) 7.49 (s, 1 H) 7.69 (s, 1 H) 8.04 (d, 1 H) 12.30 (s, 1 H)	415	Example 174

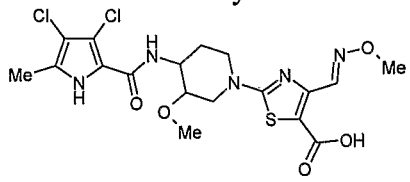
Ex	Compound	NMR	m/z	SM
345	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)isonicotinic acid 	1.80 (m, 2 H) 2.13 - 2.26 (s, 3 H) 4.14 (dd, 1 H) 4.27 (s, 1 H) 4.41 (s, 2 H) 4.72 (s, 1 H) 4.84-5.00 (d, 1 H) 7.02 (d, 1H) 7.17 - 7.32 (m, 1 H) 7.66 - 7.78 (m, 1 H) 8.24 (d, 1 H) 12.11 (s, 1 H)	415	Example 179
346	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-4-(methoxymethyl)-1,3-thiazole-5-carboxylic acid	1.85 (s, 2 H) 2.19 (s, 3 H) 3.28 (s, 3 H) 3.50-3.64 (dd, 1 H) 3.98 (s, 1 H) 4.32 (s, 2 H) 4.57 (s, 2 H) 4.88-5.04 (d, 1 H) 7.29 (d, 1 H) 12.12 (s, 1 H) 12.79 (s, 1 H)	465	Example 180
347	4-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)quinoline-2-carboxylic acid	2.00 (s, 2 H) 2.21 (s, 3 H) 3.33 (s, 1 H) 3.78 (d, 1 H) 4.08 (s, 2 H) 4.32- 4.42 (m, 1 H) 4.95-5.11 (d, 1 H) 7.34 (d, 1 H) 7.60 (s, 2 H) 7.69 (t, 1 H) 7.84 (t, 1H) 8.08 - 8.22 (m, 2 H) 12.15 (s, 1 H)	465	Example 181
348	Cis(±)-2-(4-{[(4-chloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)isonicotinic acid	1.57 (d, 1 H) 1.86 (d, 1 H) 2.14 (s, 3 H) 3.04 - 3.18 (m, 2 H) 3.19 - 3.25 (s, 3 H) 3.49 (s, 1 H) 4.19 (s, 1 H) 4.21 (d, 1 H) 4.55 (d, 1 H) 6.89 (d, 1 H) 6.96 (d, 1 H) 7.23 (s, 1 H) 7.64 (d, 1 H) 8.22 (d, 1 H) 11.62 (s, 1 H) 13.39 (s, 1 H)	393	Example 182
349	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(methoxymethyl)-1,3-thiazole-5-carboxylic acid	1.68 (s, 2 H) 2.12 (s, 3 H) 3.21 (s, 3 H) 3.33 (m, 5 H) 3.48 (s, 1 H) 3.85 (s, 1 H) 4.19 (s, 2 H) 4.49 (s, 2 H) 7.08 (s, 1 H) 12.09 (s, 1 H)	477	Example 183

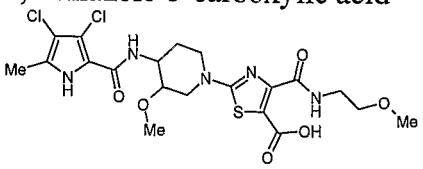
Ex	Compound	NMR	m/z	SM
350	2-((3*R*,4*S*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(methoxymethyl)-1,3-thiazole-5-carboxylic acid 	1.68 (s, 2 H) 2.12 (s, 3 H) 3.21 (s, 3 H) 3.25 (m, 2H) 3.30 (s, 3 H) 3.48 (s, 1 H) 3.84 (s, 1 H) 4.19 (s, 2 H) 4.49 (s, 2 H) 7.09 (d, 1 H) 12.09 (s, 1 H)	477	Example 184
351	Cis(±)-4-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)pyridine-2,6-dicarboxylic acid	1.68 (s, 1 H) 1.77 (s, 1 H) 2.18 (s, 3 H) 3.21 (s, 2 H) 3.31 (s, 3 H) 3.55 (s, 1 H) 4.02 (s, 1 H) 4.28 (s, 1 H) 4.41 (s, 1 H) 7.13 (s, 1 H) 7.61 (s, 2 H) 12.13 (s, 1 H)	471	Example 185
352	4-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-6-[(dimethylamino)carbonyl]pyridine-2-carboxylic acid	1.71 - 1.86 (m, 2 H) 2.22 (s, 3 H) 2.93 - 3.04 (m, 3 H) 3.04 - 3.15 (m, 3 H) 3.80 - 3.96 (m, 1 H) 4.08 (s, 1 H) 4.28 - 4.43 (m, 2 H) 4.77 (s, 1 H) 4.94 (s, 1 H) 6.87 (d,1 H) 7.10 (d, 1 H) 7.58 (d, 1 H) 9.33 (s, 2 H)	486	Example 187
353	Cis(±)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-4,5-dicarboxylic acid	1.75 (s, 2 H) 2.18 (s, 3 H) 3.33 (s, 2 H) 3.37 (s, 3 H) 3.55 (s, 1 H) 3.92 (s, 1 H) 4.26 (s, 2 H) 7.15 (d, 1 H) 12.14 (s, 1 H)	477	Example 175
354	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-4,5-dicarboxylic acid	1.85 (s, 2 H) 2.19 (s, 3 H) 3.33 (s, 1 H) 3.60 (s, 1 H) 3.99 (s, 1 H) 4.31 (s, 2 H) 4.88 -5.04 (s, 1 H) 7.28 (s, 1 H) 12.09 (s, 1 H)	465	Example 176

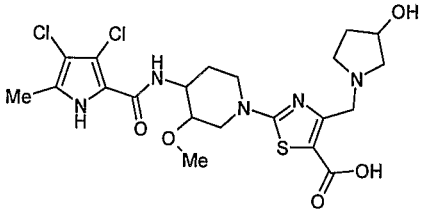
Ex	Compound	NMR	m/z	SM
355	Cis(±)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-formyl-1,3-thiazole-5-carboxylic acid 	1.75 (s, 2 H) 2.18 (s, 3 H) 3.17 (s, 1 H) 3.36 (s, 3 H) 3.56 (s, 1 H) 4.01 (s, 2 H) 4.25 (s, 2 H) 7.15 (d, 1 H) 10.35 (s, 1 H) 12.15 (s, 1 H)	461	Example 252
356	Cis(±)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-[(dimethylamino)carbonyl]-1,3-thiazole-5-carboxylic acid	1.69 (s, 2 H) 2.12 (s, 3 H) 2.72 (s, 3 H) 2.82 - 2.88 (m, 3 H) 3.22 (s, 1 H) 3.29 (s, 3 H) 3.32 (s, 1 H) 3.48 (d, 1 H) 3.81 (s, 1 H) 4.21 (s, 2 H) 7.09 (d, 1 H) 12.03 - 12.13 (m, 1 H) 12.68 (s, 1 H)	504	Example 203
357	Cis(±)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(morpholin-4-ylcarbonyl)-1,3-thiazole-5-carboxylic acid	1.75 (s, 2 H) 2.18 (s, 3 H) 3.12 - 3.22 (m, 2 H) 3.35 (s, 3 H) 3.53 (d, 6 H) 3.60 (d, 2 H) 3.85 (s, 2 H) 4.27 (s, 2 H) 7.14 (d, 1 H) 12.13 (s, 1 H) 12.81 (s, 1 H)	546	Example 204
358	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-4-(morpholin-4-ylcarbonyl)-1,3-thiazole-5-carboxylic acid	1.84 (s, 2 H) 2.18 (s, 3 H) 3.16 (s, 2 H) 3.51 (s, 2 H) 3.52 - 3.64 (m, 5 H) 3.96 (s, 1 H) 4.29 (s, 2 H) 4.37 (s, 1 H) 4.87-5.04 (d, 1 H) 7.26 (d, 1 H) 12.07 (s, 2 H)	534	Example 205
359	Cis(±)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-[(methoxyamino)carbonyl]-1,3-thiazole-5-carboxylic acid trifluoroacetate	1.79 (s, 2 H) 2.19 (s, 3 H) 3.38 (s, 3 H) 3.56 (s, 2 H) 3.64 (s, 1 H) 3.75 (s, 3 H) 4.03 (s, 1 H) 4.25 (s, 2 H) 7.16 (d, 1 H) 12.16 (s, 1 H)	506	Example 206

Ex	Compound	NMR	m/z	SM
360	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-4-[(methoxyamino)carbonyl]-1,3-thiazole-5-carboxylic acid 	1.83 - 1.92 (m, 2 H) 2.19 (s, 3 H) 3.50 -3.63 (dd, 1 H) 3.76 (s, 3 H) 4.11 (s, 1 H) 4.30 (s, 1 H) 4.42 (s, 2 H) 4.90-5.07 (s, 1 H) 7.29 (d, 1 H) 12.11 (s, 1 H) 12.39 (s, 1 H)	494	Example 207
361	Cis(±)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(piperidin-1-ylcarbonyl)-1,3-thiazole-5-carboxylic acid	1.51 (s, 3 H) 1.57 (s, 1 H) 1.75 (s, 2 H) 2.18 (s, 3 H) 3.07 - 3.17 (m, 2 H) 3.35 (s, 3 H) 3.54 (d, 2 H) 3.87 (s, 1 H) 4.27 (s, 2 H) 7.16 (d, 1 H) 12.16 (s, 1 H) 12.76 (s, 1 H)	544	Example 208
362	4-(aminocarbonyl)-2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid	1.74 (d, 2 H) 2.19 (s, 3 H) 3.32 (s, 2 H) 3.38 (s, 3 H) 3.55 (s, 1 H) 4.25 (s, 2 H) 4.49 (s, 1 H) 7.17 (d, 1 H) 8.87 (s, 1 H) 12.17 (s, 1 H)	476	Example 243
363	4-(aminocarbonyl)-2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-5-carboxylic acid	1.84 (s, 2 H) 2.19 (s, 3 H) 3.19 (s, 1 H) 3.95 (s, 2 H) 4.24 (s, 2 H) 4.86-5.02 (s, 1 H) 7.28 (s, 1 H) 12.12 (s, 1 H)	464	Example 244
364	Cis(±)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-{[(2-hydroxyethyl)amino]carbonyl}-1,3-thiazole-4-carboxylic acid trifluoroacetate (salt)	1.60 - 1.73 (m, 2 H) 2.12 (s, 3 H) 3.14 - 3.25 (m, 2 H) 3.30 (s, 3 H) 3.41 (t, 2 H) 3.86 (s, 2 H) 4.19 (s, 2 H) 7.09 (d,1 H) 9.66 (t, 1 H) 12.09 (s, 1 H)	520	Example 212

Ex	Compound	NMR	m/z	SM
365	Cis(±)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(2-hydroxyethyl)amino]carbonyl}-1,3-thiazole-5-carboxylic acid 	1.69 (s, 2 H) 2.12 (s, 3 H) 3.25 (s, 2 H) 3.31 (s, 3 H) 3.43 - 3.53 (m, 2 H) 4.03 (s, 1 H) 4.23 (s, 2 H) 4.80 (s, 1 H) 7.07 - 7.22 (m, 1 H) 9.23 (s, 1 H) 12.09 (s, 1 H)	520	Example 212
366	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-5-[(methylamino)carbonyl]-1,3-thiazole-4-carboxylic acid	1.84 (s, 2 H) 2.18 (s, 3 H) 2.76 (s, 3 H) 3.31 (s, 1 H) 3.40 (s, 1 H) 3.61 (s, 1 H) 3.98 (s, 1 H) 4.29 (s, 1 H) 4.87-5.03 (s, 1 H) 7.26 (s, 1 H) 9.43 (s, 1 H) 12.11 (s, 1 H)	478	Example 211
367	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-4-[(methylamino)carbonyl]-1,3-thiazole-5-carboxylic acid	1.87 (s, 2 H) 2.19 (s, 3 H) 2.87 (s, 3 H) 3.53 (s, 1 H) 4.13 (s, 1 H) 4.30 (s, 1 H) 4.43 (s, 2 H) 4.91-5.07 (d, 1 H) 7.31 (s, 1 H) 9.40 (s, 1 H) 12.11 (s, 1 H)	478	Example 211
368	Cis(±)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-[(hydroxyimino)methyl]-1,3-thiazole-5-carboxylic acid	1.76 (s, 2 H) 2.19 (s, 3 H) 2.91 (q, 1 H) 3.03 (d, 1 H) 3.35 - 3.38 (m, 3 H) 3.53 (s, 1 H) 3.93 (s, 1 H) 4.03 (d, 1 H) 4.23 (s, 1 H) 7.20 (d, 1 H) 7.54 (s, 1 H) 7.83 (s, 1 H) 8.76 (s, 1 H)	476	Example 355
369	Cis(±)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-[(methylamino)carbonyl]-1,3-thiazole-5-carboxylic acid	1.70 - 1.82 (m, 2 H) 2.19 (s, 3 H) 3.32 (s, 3H) 3.38 (s, 3 H) 3.41 (s, 1 H) 3.56 (s, 1 H) 4.09 (s, 1 H) 4.29 (d, 2 H) 4.46 (s, 1 H) 7.17 (d,1 H) 9.38 (s, 1 H) 12.17 (s, 1 H)	490	Example 214

Ex	Compound	NMR	m/z	SM
370	Cis(±)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-[(*E*)-(methoxyimino)methyl]-1,3-thiazole-5-carboxylic acid 	1.69 (s, 2 H) 2.12 (s, 3 H) 3.31 (s, 3 H) 3.49 (s, 2 H) 3.84 (s, 3 H) 3.96 (s, 2 H) 4.21 (s, 2 H) 7.10 (d, 1 H) 8.62 (s, 1 H) 12.10 (s, 1 H)	490	Example 251
371	Cis(±)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(morpholin-4-ylmethyl)-1,3-thiazole-5-carboxylic acid	1.61 - 1.71 (m, 2 H) 2.10 - 2.14 (m, 3 H) 2.68 (s, 3 H) 3.29 (s, 3 H) 3.47 (d, 1 H) 3.58 (s, 4 H) 3.67 - 3.80 (m, 2 H) 3.84 (d, 2 H) 4.19 (t, 2 H) 7.10 (d, 1 H) 12.12 (s, 1 H)	532	Example 246
372	Cis(±)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(difluoromethyl)-1,3-thiazole-5-carboxylic acid	1.60 - 1.74 (m, 2 H) 2.12 (s, 3 H) 3.27 (s, 1 H) 3.30 (s, 3 H) 3.34 (s, 1 H) 3.49 (s, 1 H) 3.87 (s, 1 H) 4.21 (s, 2 H) 7.10 (d, 1 H) 7.27 (s, 1 H) 12.10 (s, 1 H)	483	Example 253
373	Cis(±)-4-[(*tert*-butylamino)methyl]-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid	1.26 (s, 9 H) 1.72 (s, 2 H) 2.18 (s, 3 H) 3.32 (m, 3H) 3.36 (s, 3 H) 3.52 (s, 1 H) 3.95 (s, 2 H) 4.18 (s, 2 H) 7.15 (d, 1 H) 12.18 (s, 1 H)	518	Example 247
374	Cis(±)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(2-hydroxy-1-methylethyl)amino]carbonyl}-1,3-thiazole-5-carboxylic acid	1.11 - 1.20 (m, 3 H) 1.76 (s, 2 H) 2.19 (s, 3 H) 3.38 (s, 3 H) 3.48 (d, 3 H) 3.57 (s, 1 H) 4.04 (s, 1 H) 4.27 (s, 2 H) 4.91 (s, 2 H) 7.17 (d, 1 H) 8.83 (s, 1 H) 12.16 (s, 1 H)	534	Example 216

Ex	Compound	NMR	m/z	SM
375	Cis(±)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(2-methoxyethyl)amino]carbonyl}-1,3-thiazole-5-carboxylic acid 	1.79 (s, 3 H) 2.19 (s, 3 H) 3.23 - 3.28 (m, 3 H) 3.38 (s, 3 H) 3.42 (s, 2 H) 3.46 - 3.52 (m, 2 H) 3.57 (s, 1 H) 4.30 (d, 2 H) 7.17 (d, *J*=8.48 Hz, 1 H) 9.38 (s, 1 H) 12.16 (s, 1 H)	534	Example 215
376	Cis(±)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-{[(2-hydroxypropyl)amino]carbonyl }-1,3-thiazole-4-carboxylic acid	1.06 (d, 3 H) 1.69 - 1.79 (m, 3 H) 2.18 (s, 3 H) 3.37 (s, 3 H) 3.54 (s, 2 H) 3.71 (s, 1 H) 3.94 (s, 1 H) 4.25 (s, 3 H) 4.79 (s, 1 H) 6.55 (s, 1 H) 7.17 (s, 1 H) 9.78 (s, 1 H) 12.16 (s, 1 H)	534	Example 217
377	Cis(±)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(2-hydroxypropyl)amino]carbonyl }-1,3-thiazole-5-carboxylic acid	1.06 (dd, 3 H) 1.75 (s, 2 H) 2.19 (s, 3 H) 3.24 (s, 2 H) 3.38 (s, 3 H) 3.43 (s, 1 H) 3.56 (s, 1 H) 3.83 (s, 1 H) 4.05 (s, 1 H) 4.26 (s, 2 H) 4.90 (s, 1 H) 7.17 (d, 1 H) 9.21 (s, 1 H) 12.16 (s, 1 H)	534	Example 217
378	Cis(±)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(piperidin-1-ylmethyl)-1,3-thiazole-5-carboxylic acid	1.69 (s, 6 H) 2.18 (s, 3 H) 3.34 (s, 3 H) 3.40 (m, 3H) 3.54 (s, 5 H) 4.24 (s, 4 H) 7.14 (d, 1H) 12.16 (s, 1H)	530	Example 248
379	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-4-carboxylic acid	1.75 (s, 2 H) 2.19 (s, 3 H) 3.17 (d,1 H) 3.27 (s, 1 H) 3.36 (s, 3 H) 3.54 (s, 1 H) 3.85 (s, 1 H) 4.21 (d, 2 H) 7.16 (d, 1 H) 7.58 (s, 1 H) 12.16 (s, 1 H) 12.57 (s, 1 H)	433	Example 192

Ex	Compound	NMR	m/z	SM
380	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-[(3-hydroxypyrrolidin-1-yl)methyl]-1,3-thiazole-5-carboxylic acid 	1.73 (d, 3 H) 2.07 (s, 1 H) 2.18 (s, 3 H) 2.95 (s, 2 H) 3.26 (s, 2 H) 3.36 (s, 3 H) 3.53 (s, 1 H) 3.85 (s, 1 H) 4.15 (s, 4 H) 4.35 (s, 1 H) 5.20 (s, 1 H) 7.16 (d, 1 H) 12.16 (s, 1 H)	532	Example 249
381	4-{[(1-carboxycyclopropyl)amino]carbonyl}-2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid	1.25 (s, 2 H) 1.48 (s, 2 H) 1.75 (s, 2 H) 2.19 (s, 3 H) 3.39 (s, 4 H) 3.56 (s, 2 H) 4.26 (s, 2 H) 4.42 (s, 1 H) 7.15 (s, 1 H) 9.80 (s, 1 H) 12.15 (s, 1 H) 12.78 (s, 1 H) 16.05 (s, 1 H)	560	Example 402

Example 382

Cis(±)-5-(aminocarbonyl)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-4-carboxylic acid

A solution of 55 mg (23 mmol) of Cis(±)- 3,4-dichloro-*N*-[3-methoxypiperidin-4-yl]-5-methyl-1*H*-pyrrole-2-carboxamide (Intermediate 50), 55 mg (0.23 mmol) of ethyl 5-(aminocarbonyl)-2-chloro-1,3-thiazole-4-carboxylate (Intermediate 220) and 33 mg (0.23 mmol) K_2CO_3 in 3 ml NMP was heated at 150 °C for 1 h in a microwave reactor. Water (0.1 ml) was added and the mixture was heated at 150 °C for another hour. The solution was diluted with water and acidified with 1N HCl before being extracted 2 times with EtOAc. The EtOAc extracts were washed with brine, dried ($MgSO_4$) and concentrated to give a solid that was triturated with MeOH to give 41 mg of a white solid. MS (ES) MH^+: 479 for $C_{17}H_{19}Cl_2N_5O_5S$; NMR: 1.75 (m, 2H), 2.2 (s, 3H), 3.3 (s), 3.5 (s, 1H), 3.9 (m, 1H), 4.2 (m, 2H), 7.15 (d 1H), 7.8 (s, 1H), 8.9 (s, 1H), 12.2 (s, 1H).

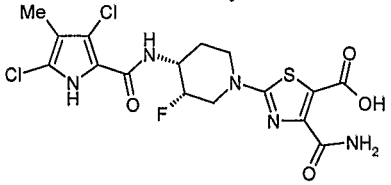
Example 383

Cis(±)-5-(aminocarbonyl)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)isonicotinic acid

A mixture of 85 mg (0.17 mmol) of Cis(±)-ethyl 5-(aminocarbonyl)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)isonicotinate (Example 198) and 86 mg (0.50 mmol) $Ba(OH)_2$ in 3 ml MeOH and 2 ml water was heated at 120 °C for 1 h. The mixture was acidified to about pH = 4 with 1N HCl and extracted 4 times with EtOAc. The EtOAc was concentrated and the residue was purified by reverse phase HPLC (20-40% CH_3CN gradient in water with 0.1% TFA) to afford 8 mg of product as a white solid. MS (ES) MH^+: 470 for $C_{19}H_{21}Cl_2N_5O_5$; NMR: 1.5-1.8, (m, 3H), 2.2 (s, 3H), 3.0-3.2 (m, 2H), 3.3 (s, 3H), 3.5 (m, 2H), 4.2-4.5 (m, 2H), 4.9 (d, 1H), 6.9 (s, 1H), 7.1-7.3 (m, 2H), 7.8 (s, 1H), 8.4 (s, 1H), 12.1 (s, 1H), 13.1 (s, 1H).

Examples 384-385

The following Examples were synthesized by an analogous method to Example 383 from the starting materials (SM) given in the table below.

Ex	Compound	NMR	m/z	SM
384	2-((3*S*,4*R*)-4-{[(3,5-dichloro-4-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-4-{[(2-morpholin-4-ylethyl)amino]carbonyl}-1,3-thiazole-5-carboxylic acid	NMR: 1.8 (m, 2H), 1.9 (s, 3H), 3.5-4.0 (m, 8H), 4.0-4.4 (m, 3H), 5.0 (d, 1H), 7.4 (d, 1H), 9.5 (s, 1H), 12.6 (s, 1H).	MS (ES) MH^+: 577 for $C_{22}H_{27}Cl_2FN_6O_5S$	Interme diate 138
385	4-(aminocarbonyl)-2-((3*S*,4*R*)-4-{[(3,5-dichloro-4-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-5-carboxylic acid 	NMR: 1.8 (m, 2H), 1.9 (s, 3H), 3.5-4.0 (m, 8H), 4.0-4.4 (m, 3H), 5.0 (d, 1H), 7.4 (d, 1H), 9.5 (s, 1H), 12.6 (s, 1H).	MS (ES) MH^+: 464 for $C_{16}H_{16}Cl_2FN_5O_4S$	Example 202

Example 386

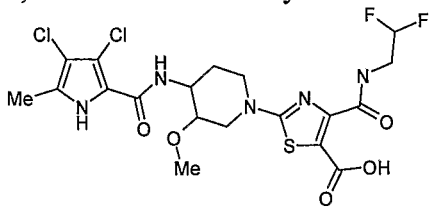
2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-[(methylamino)carbonyl]-1,3-thiazole-5-carboxylic acid

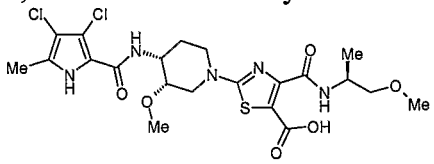
To a suspension/solution of ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-[(methylamino)carbonyl]-1,3-thiazole-5-carboxylate (0.078g, 0.15mmol, Example 218) in methanol (2mL) was added barium hydroxide (0.052g, 0.30mmol) and water (0.5mL). After stirring several hours the reaction was complete. The reaction was acidified with 1N HCl and then concentrated to remove methanol. The residue was extracted with EtOAc (x3), dried with $MgSO_4$ and concentrated to a white solid (0.059g). MS (ES) $M+H^+$: 490 for $C_{18}H_{21}Cl_2N_5O_5S$; NMR: 1.76 (s, 2 H) 2.18 (s, 3 H) 2.86 (s, 3 H) 3.38 (s, 3 H) 3.56 (s, 2 H) 4.02 (s, 1 H) 4.27 (s, 2 H) 4.40 (s, 1 H) 7.15 (s, 1 H) 9.38 (s, 1 H) 12.15 (s, 1 H)

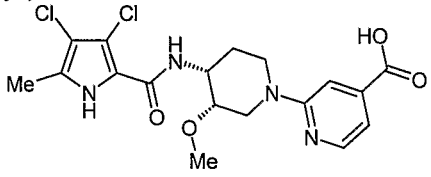
Examples 387-412

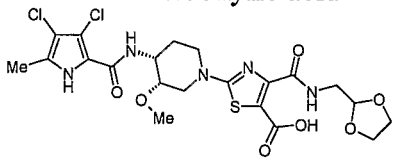
The following Intermediate was prepared by the procedure described in Example 386 from the starting materials (SM) indicated.

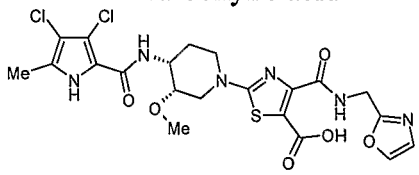
Ex	Compound	Data	SM
387	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(2-methoxyethyl)amino]carbonyl}-1,3-thiazole-5-carboxylic acid	MS (ES) MH^+: 534 for $C_{20}H_{25}Cl_2N_5O_6S$; NMR: 1.72 (s, 2 H) 2.18 (s, 3 H) 3.24 (s, 3 H) 3.36 (s, 3 H) 3.51 (s, 2 H) 3.84 (s, 2 H) 4.15 (s, 2 H) 7.15 (s, 1 H) 12.16 (s, 1 H) 13.18 (s, 1 H)	Example 219
388	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[(1*S*)-2-hydroxy-1-methylethyl]amino}carbonyl)-1,3-thiazole-5-carboxylic acid	MS (ES) MH^+: 534 for $C_{20}H_{25}Cl_2N_5O_6S$; NMR: 1.19 (s, 3 H) 1.77 (s, 2 H) 2.19 (s, 3 H) 3.38 (s, 3 H) 3.47 (s, 3 H) 3.58 (s, 1 H) 4.04 (s, 1 H) 4.29 (s, 2 H) 4.91 (s, 1 H) 7.18 (s, 1 H) 8.79 - 8.94 (m, 1 H) 12.16 (s, 1 H)	Example 220
389	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[(1*R*)-2-hydroxy-1-methylethyl]amino}carbonyl)-1,3-thiazole-5-carboxylic acid	MS (ES) MH^+: 534 for $C_{20}H_{25}Cl_2N_5O_6S$	Example 221

Ex	Compound	Data	SM
390	Cis(±)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(2,2-difluoroethyl)amino]carbonyl}-1,3-thiazole-5-carboxylic acid 	MS (ES) MH^+: 540 for $C_{19}H_{21}Cl_2F_2N_5O_5S$; NMR: 1.76 (s, 2 H) 2.19 (s, 3 H) 3.38 (s, 3 H) 3.44 (s, 1 H) 3.57 (s, 2 H) 3.73 (s, 3 H) 4.10 (s, 1 H) 4.27 (d, 2 H) 4.43 (s, 1 H) 7.17 (d, 1 H) 9.60 (s, 1 H) 12.16 (s, 1 H) 15.77 (s, 1 H)	Example 222
391	Cis(±)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-[(isoxazol-3-ylamino)carbonyl]-1,3-thiazole-5-carboxylic acid	MS (ES) MH^+: 543 for $C_{20}H_{20}Cl_2N_6O_6S$; NMR: 1.74 (s, 2 H) 2.19 (s, 3 H) 3.22 (s, 2 H) 3.38 (s, 3 H) 3.52 (s, 1 H) 3.88 (s, 1 H) 4.24 (s, 2 H) 6.99 (d, 1 H) 7.16 (s, 1 H) 8.75 (s, 1 H) 12.16 (s, 1 H)	Example 223
392	Cis(±)-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(3*R*)-tetrahydrofuran-3-ylamino]carbonyl}-1,3-thiazole-5-carboxylic acid	MS (ES) MH^+: 546 for $C_{21}H_{25}Cl_2N_5O_6S$; NMR: 1.76 (s, 3 H) 1.94 - 2.08 (m, 1 H) 2.19 (s, 3 H) 3.38 (s, 3 H) 3.44 (s, 1 H) 3.56 (s, 1 H) 3.63 - 3.76 (m, 2 H) 3.81 - 3.92 (m, 2 H) 4.12 (s, 1 H) 4.26 (s, 1 H) 4.51 (s, 1 H) 7.16 (d, 1 H) 9.17 (d, 1 H) 12.15 (s, 1 H) 15.97 (s, 1 H)	Example 224
393	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[(1*R*,2*S*)-2-fluorocyclopropyl]amino}carbonyl)-1,3-thiazole-5-carboxylic acid	MS (ES) MH^+: 534 for $C_{20}H_{22}Cl_2FN_5O_5S$; NMR: 1.23 (dd, 2 H) 1.75 (s, 2 H) 2.19 (s, 3 H) 2.87 (s, 1 H) 3.37 (d, 3 H) 3.42 (s, 1 H) 3.56 (s, 2 H) 4.10 (s, 1 H) 4.26 (s, 3 H) 4.45 (s, 1 H) 4.73 (d, 1 H) 4.96 (s, 1 H) 7.16 (d, 1 H) 9.29 (dd, 1 H) 12.15 (s, 2 H) 16.02 (d, 1 H)	Example 225

Ex	Compound	Data	SM
394	4-(azidomethyl)-2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid	MS (ES) MH^+: 488 for $C_{17}H_{19}Cl_2N_7O_4S$; NMR: 1.76 (s, 2 H) 2.18 (s, 3 H) 3.37 (s, 5 H) 3.56 (s, 1 H) 3.92 (s, 1 H) 4.28 (s, 2 H) 4.54 (d, 2 H) 7.18 (s, 1 H) 12.16 (s, 1 H) 12.97 (s, 1 H)	Example 254
395	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[(1*S*)-2-methoxy-1-methylethyl]amino}carbonyl)-1,3-thiazole-5-carboxylic acid 	MS (ES) MH^+: 548 for $C_{21}H_{27}Cl_2N_5O_6S$; NMR: 1.18 (d, 3 H) 1.76 (s, 2 H) 2.18 (s, 3 H) 3.24 (s, 3 H) 3.38 (s, 3 H) 3.49 (s, 2 H) 3.57 (s, 1 H) 4.06 (s, 1 H) 4.26 (s, 2 H) 7.15 (s, 1 H) 8.95 (s, 1 H) 12.16 (s, 1 H) 16.33 (s, 1H)	Example 226
396	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-[(prop-2-yn-1-ylamino)carbonyl]-1,3-thiazole-5-carboxylic acid	MS (ES) MH^+: 514 for $C_{20}H_{21}Cl_2N_5O_5S$; NMR: 1.76 (s, 2 H) 2.19 (s, 3 H) 3.26 (s, 2 H) 3.38 (s, 3 H) 3.57 (s, 2 H) 4.10 (d, 2 H) 4.27 (s, 2 H) 7.17 (d, 1 H) 9.78 (s, 1 H) 12.16 (s, 1 H) 15.96 (s, 1 H)	Example 227
397	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(2-hydroxy-1,1-dimethylethyl)amino]carbonyl}-1,3-thiazole-5-carboxylic acid	MS (ES) MH^+: 548 for $C_{21}H_{27}Cl_2N_5O_6S$; NMR: 1.29 (s, 6 H) 1.73 (s, 2 H) 2.17 (s, 3 H) 3.37 (m, 6 H) 3.46 (s, 2 H) 3.54 (s, 1 H) 3.91 (s, 1 H) 4.23 (s, 2 H) 7.16 (s, 1 H) 12.19 (s, 1 H)	Example 228
398	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(3*R*)-tetrahydrofuran-3-ylamino]carbonyl}-1,3-thiazole-5-carboxylic acid	MS (ES) MH^+: 546 for $C_{21}H_{25}Cl_2N_5O_6S$; NMR: 1.23 (s, 1 H) 1.76 (s, 2 H) 2.00 (d, 1 H) 2.19 (s, 3 H) 3.38 (s, 6 H) 3.43 (s, 1 H) 3.56 (s, 1 H) 3.64 - 3.77 (m, 2 H) 3.79 - 3.94 (m, 2 H) 4.26 (s, 1 H) 4.51 (s, 1 H) 7.16 (d, 1 H) 9.17 (s, 1 H) 12.16 (s, 1 H) 15.98 (s, 1 H)	Example 224

Ex	Compound	Data	SM
399	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[(1*R*,2*S*)-2-fluorocyclopropyl]amino}carbonyl)-1,3-thiazole-5-carboxylic acid	MS (ES) MH^+: 534 for $C_{20}H_{22}Cl_2FN_5O_5S$; NMR: 1.21 (d, 1 H) 1.40 (s, 1 H) 1.76 (s, 2 H) 2.19 (s, 3 H) 2.85 (s, 1 H) 3.38 (s, 3 H) 3.43 (s, 3 H) 3.56 (s, 1 H) 4.26 (s, 1 H) 4.74-4.97 (d, 1 H) 7.17 (d, 1 H) 9.27 (d, 1 H) 12.16 (s, 2 H) 16.01 (s, 2 H)	Example 229
400	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)isonicotinic acid 	MS (ES) MH^+: 427 for $C_{18}H_{20}Cl_2N_4O_4$ NMR: 1.72 (s, 2 H) 2.18 (s, 3 H) 3.13 (d, 2 H) 3.30 (s, 3 H) 3.49 (s, 1 H) 4.17 - 4.31 (m, 2 H) 4.68 (d, 1 H) 6.97 (d, 1 H) 7.15 (d, 1 H) 7.23 (s, 1 H) 8.22 (d, 1 H) 12.16 (s, 1 H) 13.39 (s, 1 H)	Example 193
401	4-[(cyclopropylamino)carbonyl]-2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid	MS (ES) MH^+: 516 for $C_{20}H_{23}Cl_2N_5O_5S$; NMR: 0.77 (d, 2 H) 0.80 (s, 2 H) 1.76 (s, 2 H) 2.19 (s, 3 H) 2.86 - 2.99 (m, 1 H) 3.30 (s, 1 H) 3.37 (s, 3 H) 3.56 (s, 1 H) 4.16 (s, 1 H) 4.26 (d, 2 H) 4.41 (s, 1 H) 7.16 (d, 1 H) 9.22 (d, 1 H) 12.15 (s, 1 H)	Example 231
402	1-({[2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-5-(methoxycarbonyl)-1,3-thiazol-4-yl]carbonyl}amino)cyclopropane carboxylic acid	MS (ES) MH^+: 574 for $C_{22}H_{25}Cl_2N_5O_7S$;	Example 230
403	4-{[(1-carboxy-2-hydroxyethyl)amino]carbonyl}-2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid	MS (ES) MH^+: 564 for $C_{20}H_{23}Cl_2N_5O_8S$; NMR: 1.78 (s, 2 H) 2.19 (s, 3 H) 3.39 (s, 3 H) 3.47 (s, 2 H) 3.59 (s, 1 H) 3.87 (s, 2 H) 4.30 (s, 2 H) 4.53 (s, 1 H) 7.16 (s, 1 H) 9.03 (s, 1 H) 12.16 (s, 1 H) 15.97 (s, 1 H)	Example 233

Ex	Compound	Data	SM
404	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(2-morpholin-4-ylethyl)amino]carbonyl}-1,3-thiazole-5-carboxylic acid	MS (ES) MH^+: 589 for $C_{23}H_{30}Cl_2N_6O_6S$; NMR: 1.76 (s, 2 H) 2.19 (s, 3 H) 3.14 (d, 2 H) 3.39 (s, 4 H) 3.57 (s, 3 H) 3.72 (s, 3 H) 3.78 (s, 1 H) 3.96 (s, 2 H) 4.27 (s, 2 H) 7.18 (d, 1 H) 9.59 (s, 1 H) 12.21 (s, 1 H)	Example 234
405	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(1,3-dioxolan-2-ylmethyl)amino]carbonyl}-1,3-thiazole-5-carboxylic acid 	MS (ES) MH^+: 562 for $C_{21}H_{25}Cl_2N_5O_7S$; NMR: 1.77 (s, 2 H) 2.19 (s, 3 H) 3.39 (s, 9 H) 3.44 - 3.52 (m, 2 H) 3.58 (s, 1 H) 3.79 - 3.87 (m, 2 H) 3.89 - 3.97 (m, 2 H) 4.27 (s, 2 H) 5.05 (t, 1 H) 7.17 (d, 1 H) 9.39 (t, 1 H) 12.16 (s, 1 H) 16.20 (s, 1 H)	Example 235
406	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(pyridin-2-ylmethyl)amino]carbonyl}-1,3-thiazole-5-carboxylic acid	MS (ES) MH^+: 567 for $C_{23}H_{24}Cl_2N_6O_5S$; NMR: 1.77 (s, 2 H) 2.19 (s, 3 H) 3.40 (s, 3 H) 3.58 (s, 2 H) 4.28 (s, 2 H) 4.67 (s, 2 H) 7.16 (s, 1 H) 7.31 - 7.45 (m, 2 H) 7.85 (s, 1 H) 8.56 (s, 1 H) 9.97 (s, 1 H) 12.17 (s, 1 H) 16.14 (s, 1 H)	Example 237
407	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[3-(2-oxopyrrolidin-1-yl)propyl]amino}carbonyl)-1,3-thiazole-5-carboxylic acid	MS (ES) MH^+: 601 for $C_{24}H_{30}Cl_2N_6O_6S$; NMR: 1.71 (s, 1 H) 1.74 (d, 3 H) 1.85 - 2.00 (m, 2 H) 2.19 (s, 3 H) 2.20 - 2.27 (m, 2 H) 3.19 - 3.35 (m, 11 H) 3.39 (s, 4 H) 3.56 (s, 1 H) 4.20 - 4.34 (m, 1 H) 7.17 (d, 1 H) 9.45 (t, 1 H) 12.16 (s, 1 H)	Example 236
408	Cis(±)-4-[cyano(morpholin-4-yl)methyl]-2-(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid	MS (ES) MH^+: 557 for $C_{22}H_{26}Cl_2N_6O_5S$; NMR: 1.75 (s, 2 H) 2.18 (s, 3 H) 2.71 (s, 3 H) 3.39 (s, 2 H) 3.43 (s, 5 H) 3.59 (s, 4 H) 3.80 (s, 2 H) 4.27 (s, 2 H) 4.44 (s, 1 H) 7.14 (s, 1 H) 12.15 (s, 1 H)	Example 255

Ex	Compound	Data	SM
409	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[2-(methylsulfonyl)ethyl]amino}carbonyl)-1,3-thiazole-5-carboxylic acid	MS (ES) MH^+: 582 for $C_{20}H_{25}Cl_2N_5O_7S_2$ NMR: 1.76 (s, 2 H) 2.19 (s, 3 H) 3.06 (s, 3 H) 3.38 (s, 5 H) 3.44 (t, 3 H) 3.57 (s, 1 H) 3.68 - 3.81 (m, 2 H) 4.26 (s, 2 H) 7.16 (d, 1 H) 9.45 - 9.56 (m, 1 H) 12.15 (s, 1 H)	Example 256
410	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(1,3-oxazol-2-ylmethyl)amino]carbonyl}-1,3-thiazole-5-carboxylic acid 	MS (ES) MH^+: 557 for $C_{21}H_{22}Cl_2N_6O_6S$; NMR: 1.76 (s, 2 H) 2.19 (s, 3 H) 3.38 (s, 3 H) 3.45 (s, 1 H) 3.57 (s, 1 H) 4.26 (d, 2 H) 4.65 (s, 2 H) 7.11 - 7.24 (m, 2 H) 8.09 (s, 1 H) 9.98 (s, 1 H) 12.16 (s, 1 H) 15.92 (s, 1 H)	Example 239
411	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(2-fluoroethyl)amino]carbonyl}-1,3-thiazole-5-carboxylic acid	MS (ES) MH^+: 522 for $C_{19}H_{22}Cl_2FN_5O_5S$; NMR: 1.76 (s, 2 H) 2.19 (s, 3 H) 3.38 (s, 4 H) 3.45 (s, 1 H) 3.58 (s, 2 H) 3.68 (s, 1 H) 4.14 (s, 1 H) 4.27 (s, 2 H) 4.47 - 4.54 (m, 1 H) 4.67 (t, 1 H) 7.26 (d, *J*=8.29 Hz, 1 H) 9.55 (s, 1 H) 12.29 (s, 1 H) 16.19 (s, 1 H)	Example 240
412	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(2-hydroxy-2-methylpropyl)amino]carbonyl}-1,3-thiazole-5-carboxylic acid	MS (ES) MH^+: 548 for $C_{21}H_{27}Cl_2N_5O_6S$; NMR: 1.11 (d, 6 H) 1.77 (s, 2 H) 2.18 (s, 3 H) 3.23 (s, 3 H) 3.38 (s, 3 H) 3.57 (s, 1 H) 4.29 (s, 1 H) 4.76 (s, 1 H) 7.18 (s, 1 H) 8.94 (s, 1 H) 12.16 (s, 1 H)	Example 241

Example 413

4-{[(1-cyanocyclopropyl)amino]carbonyl}-2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid

To a solution of ethyl 4-{[(1-cyanocyclopropyl)amino]carbonyl}-2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-

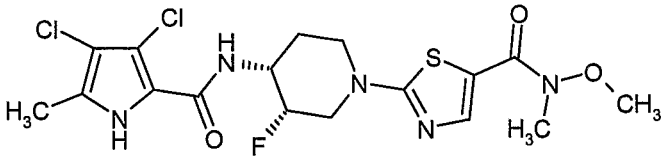
carboxylate (0.09g, 0.16mmol, Example 230) in methanol (2mL) was added potassium carbonate (0.022g, 0.16mmol) and water (0.5mL). After heating in the microwave for 30min at 80°, reaction was complete by LCMS analysis. The reaction mixture was diluted with water and acidified with1N HCl. After concentrating to remove methanol, the resulting white precipitate was filtered, washed with water and dried (0.071g). MS (ES) $M+H^+$: 541 for $C_{21}H_{22}Cl_2N_6O_5S$; NMR: 1.33 - 1.41 (m, 2 H) 1.64 (s, 2 H) 1.75 (s, 2 H) 2.19 (s, 3 H) 3.37 (s, 3H) 3.43 (s, 1 H) 3.57 (s, 1 H) 4.08 (s, 1 H) 4.27 (d, 2 H) 4.40 (s, 1 H) 7.16 (d, 1 H) 9.87 (s, 1 H) 12.17 (s, 1 H)

The following Intermediate was prepared by the procedure described in Example 413 from the starting materials (SM) indicated.

Ex	Compound	Data	SM
414	4-{[(1-cyano-1-methylethyl)amino]carbonyl}-2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid	MS (ES) MH^+: 543 for $C_{21}H_{24}Cl_2N_6O_5S$; NMR: 1.68 (s, 6 H) 1.76 (s, 2 H) 2.19 (s, 3 H) 3.38 (s, 4 H) 3.44 (s, 1 H) 3.56 (s, 1 H) 4.11 (s, 1 H) 4.25 (s, 2 H) 7.14 (s, 1 H) 9.10 (s, 1 H) 12.17 (s, 1 H)	Example 232

Example 415

2-((3S,4R)-4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-N-methoxy-N-methyl-1,3-thiazole-5-carboxamide



2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-5-carboxylic acid (10mg, 0.024mmol) was dissolved in dry DMF (10ml), HATU (9.1mg, 0.024mmol), triethylamine (7.27mg, 0.072mmol) and N,O-dimethylhydroxyamine (4.65mg, 0.048mmol) were added. The mixture was stirred at room temperature for 30 minutes, then was poured into cold water (30ml), the precipitate was filtered, washed with water and collected as the desired product (off white solid, 10mg).

MS (ESP): 465 (MH^+) for $C_{17}H_{20}Cl_2FN_5O_3S$

NMR ($CDCl_3$) δ: 1.87 (m, 2H); 2.19 (s, 3H); 3.07 (m, 2H); 3.21 (s, 3H); 3.72 (s, 3H); 4.01 (m, 1H); 4.30 (m, 2H); 4.96 (d, br, 1H); 7.28 (d, 1H); 7.85 (s, 1H); 12.09 (s, 1H).

The following compound was produced following the procedure described for Example 415 from Example 334 and N-methoxy amine hydrochloride.

Example 416

2-((3*S*,4*R*)-4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-*N*-methoxy-4-methyl-1,3-thiazole-5-carboxamide

MS (ES) MH^+: 476 for $C_{18}H_{23}Cl_2N_5O_4S$; NMR: 1.66-1.79 (m, 1H), 2.17(s, 3H), 2.37 (s, 3H), 3.20-3.35 (m, buried under water peak), 3.35 (s, 3H), 33.50-3.55 (m, 1H), 3.61 (s, 3H), 3.82-3.91 (m, 1H), 4.15-4.31 (m, 2H), 7.14 (d, 1H), 10.79 (s, 1H), 12.14 (s, 1H)

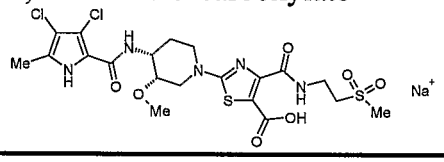
Example 417

sodium 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(2-methoxyethyl)amino]carbonyl}-1,3-thiazole-5-carboxylate

Sodium hydroxide (0.056mL, 0.056mmol, Acros 1N) was added to a suspension of 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(2-methoxyethyl)amino]carbonyl}-1,3-thiazole-5-carboxylic acid (0.03g, 0.056mmol, Example 387) in methanol (5mL). After stirring five minutes the reaction was homogeneous. The reaction mixture was concentrated and the resulting white solid was dried overnight (0.030g). MS (ES) MH^+: 534 for $C_{20}H_{24}Cl_2N_5O_6SNa$; NMR: 1.73 (s, 2 H) 2.19 (s, 3 H) 3.24 (s, 3 H) 3.32 (s, 2 H) 3.36 (s, 3 H) 3.51 (s, 1 H) 3.84 (s, 1 H) 4.22 (d, 2 H) 7.17 (d, 1 H) 12.17 (s, 1 H) 13.26 (s, 1 H)

Examples 419-423

The following Examples were prepared by the procedure described in Example 417 from the starting materials (SM) indicated.

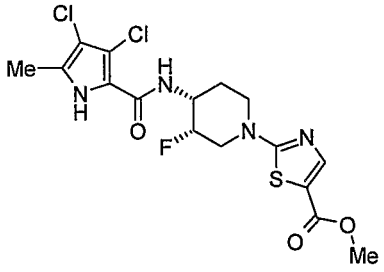
Ex	Compound	Data	SM
419	sodium 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[(1*S*)-2-methoxy-1-methylethyl]amino}carbonyl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 548 for $C_{21}H_{26}Cl_2N_5O_6SNa$ NMR: 1.04 - 1.15 (m, 3 H) 1.71 (s, 2 H) 2.18 (s, 3 H) 3.08 - 3.21 (m, 3 H) 3.25 (s, 3 H) 3.36 (s, 4 H) 3.50 (s, 1 H) 3.87 (d,1 H) 3.99 (dt, 1 H) 4.11 (s, 1 H) 4.22 (s, 1 H) 7.21 (d,1 H) 13.17 (d, 1 H)	Example 395
420	sodium 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[(1*S*)-2-methoxy-1-methylethyl]amino}carbonyl)-1,3-thiazole-5-carboxylate 	MS (ES) MH^+: 582 for $C_{20}H_{24}Cl_2N_5O_7S_2Na$ NMR: 1.67 - 1.78 (m, 2 H) 2.18 (s, 3 H) 3.00 (s, 3 H) 3.10 - 3.21 (m, 2 H) 3.24 - 3.31 (m, 3 H) 3.36 (s, 3 H) 3.47 - 3.60 (m, 3 H) 3.85 (s, 1 H) 4.10 (s, 1 H) 4.17 (s, 2 H) 7.17 (d, 1 H) 12.16 (s, 1 H) 13.71 (s, 1 H)	Example 409
421	sodium 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(1,3-oxazol-2-ylmethyl)amino]carbonyl}-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 556 for $C_{21}H_{21}Cl_2N_6O_6SNa$ NMR: 1.71 (d, 2 H) 2.15 (s, 3 H) 3.09 - 3.24 (m, 2 H) 3.35 (s, 3 H) 3.49 (s, 1 H) 3.84 (s, 1 H) 4.16 (s, 2 H) 4.48 (d, 2 H) 7.12 (s, 12 H) 7.18 (d, 1 H) 8.01 (s, 1 H) 12.17 (s, 1 H) 13.95 - 14.07 (m, 1 H)	Example 410
422	sodium 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[(1*R*,2*S*)-2-fluorocyclopropyl]amino}carbonyl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 534 for $C_{20}H_{21}Cl_2FN_5O_5SNa$	Example 399
423	Sodium-2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 435,437 for $C_{16}H_{17}Cl_2FN_4O_3S$; NMR: 1.77-1.79 (m, 1H), 1.99 (m, 1H), 2.24 (s, 3H), 3.25-3.27 (m, 1H), 3.74 (d, 1H), 4.16 (m, 1H), 4.22 (m, 1H), 4.38 (t, 1H), 4.83 (d, 1H), 7.19 (s, 1H), 8.13 (br d, 1H)	Example 42

Example 424

N-ethylethanaminium 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(2-methoxyethyl)amino]carbonyl}-1,3-thiazole-5-carboxylate

Diethylamine (0.0058mL, 0.056mmol, Aldrich) was added to a suspension of 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(2-methoxyethyl)amino]carbonyl}-1,3-thiazole-5-carboxylic acid (0.03g, 0.056mmol, Example 387) in methanol (5mL). After stirring five minutes, methylene chloride was added until solution was homogeneous. The reaction was concentrated and the resulting solid was dried overnight (0.024g). MS (ES) MH^+: 534 for $C_{24}H_{37}Cl_2N_6O_6S$; NMR: 1.16 (t, 3 H) 1.74 (s, 2 H) 2.19 (s, 3 H) 2.91 (q, 3 H) 3.25 (s, 3 H) 3.32 (s, 4 H) 3.37 (s, 3 H) 3.42 (d, 2 H) 3.53 (s, 1 H) 3.94 (s, 1 H) 4.22 (s, 2 H) 7.17 (d, 1 H)

The following compound was synthesized according to the procedure described for Example 424.

Ex	Compound	Data	SM
425	*N*-ethylethanaminium -2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-5-carboxylate 	MS (ES) MH^+: 435,437 for $C_{16}H_{17}Cl_2FN_4O_3S$; NMR: 1.14 (t, 3H), 1.81 (m, 2H), 2.21 (s, 3H), 2.84 (q, 2H), 3.34 (m, 2H), 3.86 (m, 1H), 4.30 (m, 1H), 4.89 (d, 1H), 7.32 (s, 1H), 7.61 (d, 1H)	Example 42

Example 426

Potassium 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-5-carboxylate

An aqueous solution of potassium hydroxide (0.1 M, 4.75 ml, 0.475 mmol) was added to a solution of 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-5-carboxylic acid (Example 42, 200 mg, 0.475 mmol) in methanol (35 ml). The mixture was stirred for 1 h and then concentrated under reduced

pressure to provide the crude salt (230 mg). The salt was dissolved in acetone/water (50 ml; 48:2) and acetone was added slowly to the stirred mixture until it became cloudy. Stirring was continued and more acetone was added very slowly over 20 min. The mixture was stored at 4 °C overnight. The solid was collected by filtration and air dried for 24 h to provide the salt (160 mg).

MS (ESP): 421 (M+H) for $C_{15}H_{15}Cl_2FN_4O_3S$

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.75 (d, 1H); 2.04 (m, 1H); 2.24 (s, 3H); 3.34 (m, 2H); 3.75 (d, 1H); 4.20 (m, 1H); 4.39 (t, 1H); 4.83 (d, 1H); 7.17 (s, 1H); 8.18 (s, 1H); 14.12 (s, 1H).

Example 427

1,3-Dihydroxy-2-(hydroxymethyl)propan-2-aminium 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-5-carboxylate

Tromethamine (43 mg, 0.36 mmol), 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-5-carboxylic acid (Example 42, 150 mg, 0.36 mmol), methanol (50 ml) and water (5 ml) were combined and stirred at 60 °C until the mixture was a homogeneous solution (30 min). The mixture was cooled to room temperature and concentrated under reduced pressure. The crude salt (80 mg) was dissolved in ethyl acetate/ methanol (8 ml; 50:50) and ethyl acetate was added slowly to the stirred solution until it became cloudy. Stirring was continued and additional ethyl acetate (~15 ml) was added slowly to the mixture. The mixture was stored at 4 °C overnight. The solid was collected by filtration and air dried for 24 h to provide the salt (64 mg).

MS (ESP): 421 (M+H) for $C_{15}H_{15}Cl_2FN_4O_3S$

^{1}H NMR (300 MHz, Methanol-d_4) δ: 2.00 (m, 2H); 2.25 (s, 3H); 3.33 (m, 2H); 3.30-3.55 (m, 2H); 3.67 (s, 6H); 4.10 (d, 1H); 4.35 (m, 2H); 4.90 (d, 1H); 7.57 (s, 1H).

The following Examples were prepared by the procedure described in Example 1 from the starting materials (SM) indicated in the table below.

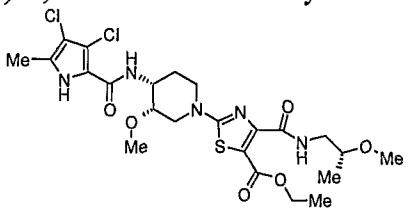
Ex	Compound	Data	SM
428	methyl 2-((3S,4R)-4-{[(4-chloro-3-fluoro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-5-carboxylate	MS (ESP): 419 (MH^+) for $C_{16}H_{17}ClF_2N_4O_3S$ ^{1}H-NMR ($CDCl_3$) δ: 1.96 (m, 2H); 2.25 (s, 3H); 3.37 (m 2H); 3.84 (s, 3H); 4.17 (m, 1H); 4.38 (m, 1H); 4.56 (m, 1H); 4.87 (d, br, 1H); 6.21 (m, 1H); 7.87 (s, 1H); 9.35 (s, br, 1H); ^{19}F-NMR ($CDCl_3$) δ: -158(s)	Intermediate 261

The following Examples were synthesized by an analogous method to Example 35 from the starting materials (SM) given in the table below.

Ex	Compound	NMR	m/z	SM
429	2-((3S,4R)-4-{[(4-chloro-3-fluoro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-5-carboxylic acid	1.85 (m, 2H); 2.15 (s, 3H); 3.31 (m 2H); 4.0 (m, 1H); 4.31 (m, 2H); 4.90 (d, br, 1H); 7.43 (d, 1H); 7.75 (s, 1H); 11.95 (s, br, 1H); ^{19}F-NMR ($CDCl_3$) δ: -158(s)ppm	405	Example 428

Example 430-433

The following Examples were prepared by the procedure described in Example 1 from the starting materials (SM) indicated in the table below.

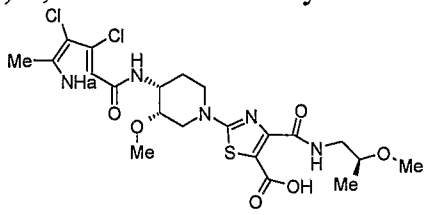
Ex	Compound	Data	SM
430	Ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[(2*R*)-2-methoxypropyl]amino}carbonyl)-1,3-thiazole-5-carboxylate 	MS (ES) MH: 575 for $C_{23}H_{31}Cl_2N_5O_6S$; NMR: 1.08 (d, 3H), 1.20 (t, 3H), 1.68-1.76 (m, 2H), 2.17 (s, 3H), 3.14- 3.19 (m, 1H), 3.25 (s, 3H), 3.35 (s, 3H), 3.54 (brs, 1H), 3.90-4.05 (m, 2H), 4.15 (q, 2H), 4.20-4.30 (m, 2H), 7.15 (d, 1H), 8.32 (d, 1H), 12.16 (s, 1H)	Example 191 and Intermediate 1725-162

Ex	Compound	Data	SM
431	Ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[(2*S*)-2-methoxypropyl]amino}carbonyl)-1,3-thiazole-5-carboxylate	MS (ES) MH: 575 for $C_{23}H_{31}Cl_2N_5O_6S$; NMR: 1.09 (d, 3H), 1.21 (t, 3H), 1.68-1.76 (m, 2H), 2.18 (s, 3H), 3.15- 3.21 (m, 1H), 3.26 (s, 3H), 3.36 (s, 3H), 3.54 (brs, 1H), 3.95-4.05 (m, 2H), 4.16 (q, 2H), 4.20-4.30 (m, 2H), 7.15 (d, 1H), 8.32 (d, 1H), 12.16 (s, 1H)	Example 191 and (2*S*)-2-methoxypropan-1-amine hydrochloride (1725-163)
432	Ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[(1*R*)-2-methoxy-1-methylethyl]amino}carbonyl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 576 for $C_{23}H_{31}Cl_2N_5O_6S$; NMR: 1.08 (d, 3H), 1.21 (t, 3H), 1.68-1.76 (m, 2H), 2.17 (s, 3H), 3.14- 3.20 (m, 1H), 3.25 (s, 3H), 3.35 (s, 3H), 3.54 (brs, 1H), 3.95-4.05 (m, 2H), 4.16 (q, 2H), 4.20-4.30 (m, 2H), 7.14 (d, 1H), 8.30 (d, 1H), 12.15 (s, 1H)	Example 191 and (2*R*)-1-methoxypropan-2-amine hydrochloride (1725-177)
433	Cis(±)-methyl 2-(3-azido-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylate	1.8 (m, 2H), 2.19 (s, 3H), 3.35 (m, 1H), 3.6 (d, 1H), 3.75 (s, 3H), 3.95 (d, 1H), 4.24 (m, 3H), 7.23 (d, 1H), 7.86 (s, 1H), 12.1 (s, 1H).	Intermediate 272 and methyl 2-bromo-1,3-thiazole-5-carboxylate

Examples 434-437

The following Examples were synthesized by an analogous method to Example 35 from the starting materials (SM) given in the table below.

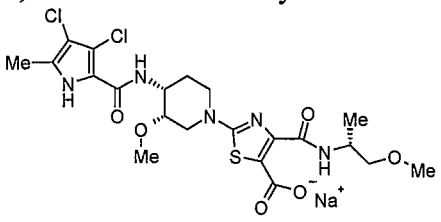
Ex	Compound	NMR	m/z	SM
434	2-((3*S*,4*R*)-4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[(2*R*)-2-methoxypropyl]amino}carbonyl)-1,3-thiazole-5-carboxylic acid	1.07 (d, 3H), 1.70-1.76 (m, 2H), 2.17 (s, 3H), 3.25 (s, 3H), 3.36 (s, 3H), 3.37-3.50 (m, 2H), 3.55 (brs, 1H), 4.20-4.30 (m, 2H), 4.45 (brs, 1H), 7.16 (d, 1H), 8.98 (d, 1H), 12.13 (s, 1H), 16.30 (s, 1H)	546	Example 430

Ex	Compound	NMR	m/z	SM
435	2-((3*S*,4*R*)-4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[(2*S*)-2-methoxypropyl]amino}carbonyl)-1,3-thiazole-5-carboxylic acid 	1.16 (d, 3H), 1.70-1.76 (m, 2H), 2.18 (s, 3H), 3.23 (s, 3H), 3.37 (s, 3H), 3.44-3.50 (m, 2H), 3.55 (brs, 1H), 4.20-4.30 (m, 2H), 4.45 (brs, 1H), 7.16 (d, 1H), 8.98 (d, 1H), 12.14 (s, 1H), 16.31 (s, 1H)	546	Example 431
436	2-((3*S*,4*R*)-4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[(1*R*)-2-methoxy-1-methylethyl]amino}carbonyl)-1,3-thiazole-5-carboxylic acid	1.16 (d, 3H), 1.70-1.76 (m, 2H), 2.17 (s, 3H), 3.26 (s, 3H), 3.38 (s, 3H), 3.46-3.52 (m, 2H), 3.55 (brs, 1H), 4.20-4.30 (m, 2H), 4.45 (brs, 1H), 7.16 (d, 1H), 8.96 (d, 1H), 12.14 (s, 1H), 16.31 (s, 1H)	547	Example 432
437	Cis(±)-2-(3-azido-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-1,3-thiazole-5-carboxylic acid	.8 (m, 2H), 2.2 (s, 3H), 3.3 (m, 1H), 3.6 (d, 1H), 3.9 (d, 1H), 4.24 (m, 3H), 7.23 (d, 1H), 7.7 (s, 1H), 12.1 (s, 1H), 12.7 (S, 1H)	444	Example 433

Examples 438-440

The following Examples were prepared by the procedure described in Example 417 from the starting materials (SM) indicated

Ex	Compound	Data	SM
438	sodium 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[(2*R*)-2-methoxypropyl]amino}carbonyl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 547 for $C_{21}H_{26}Cl_2N_5O_6S$; NMR: 1.07 (d, 3H), 1.60-1.75 (m, 2H), 2.14 (s, 3H), 3.10-3.19 (m, 3H), 3.24 (s, 3H), 3.34 (s, 3H), 3.47 (brs, 1H), 3.81-3.85 (m, 1H), 3.90-4.00 (m, 1H), 4.05-4.20 (m, 2H), 7.17 (d, 1H), 12.16 (brs, 1H), 13.22 (d, 1H)	Example 434

Ex	Compound	Data	SM
439	Sodium 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[(2*S*)-2-methoxypropyl]amino}carbonyl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+: 547 for $C_{21}H_{26}Cl_2N_5O_6S$; NMR: 1.07 (d, 3H), 1.60-1.75 (m, 2H), 2.17 (s, 3H), 3.10-3.22(m, 3H), 3.24 (s, 3H), 3.35 (s, 3H), 3.49 (brs, 1H), 3.81-3.85 (m, 1H), 3.90-4.00 (m, 1H), 4.05-4.20 (m, 2H), 7.15 (d, 1H), 12.15 (brs, 1H), 13.22 (d, 1H)	Example 435
440	Sodium 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[(1*R*)-2-methoxy-1-methylethyl]amino}carbonyl)-1,3-thiazole-5-carboxylate 	MS (ES) MH^+: 547 for $C_{21}H_{26}Cl_2N_5O_6S$; NMR: 1.07 (d, 3H), 1.65-1.73 (m, 2H), 2.17 (s, 3H), 3.10-3.22(m, 3H), 3.24 (s, 3H), 3.35 (s, 3H), 3.49 (brs, 1H), 3.81-3.85 (m, 1H), 3.90-4.00 (m, 1H), 4.05-4.20 (m, 2H), 7.17 (d, 1H), 12.18 (brs, 1H), 13.19 (d, 1H)	Example 436

Preparation of Starting Materials

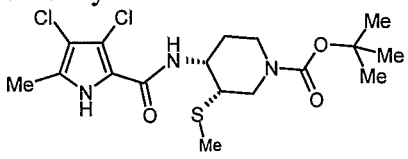
Intermediate 83

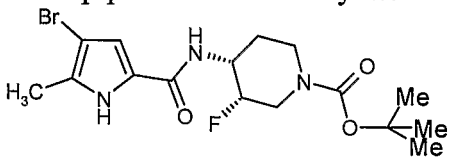
Cis(±)-ethyl (4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methylpiperidine-1-carboxylate

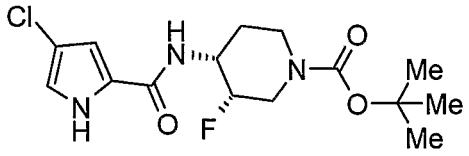
A solution of 167 mg (0.9 mmol) of Cis(±)-ethyl (4-amino-3-methylpiperidine-1-carboxylate (Intermediate 152), 235 µl (1.25 mmol) diisopropylethylamine and 280 mg (1.35) of 3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl chloride (Intermediate 202) was stirred at room temperature for 1 h. The mixture was diluted with EtOAc and washed with aqueous Na_2CO_3 and brine. Drying MgSO4 and removal of solvent gave an oil that was purified by chromatography (100% CH_2Cl_2 followed by gradient elution to 100% EtOAc) to afford 145 mg of product. MS (ES) (MH^+): 362 for $C_{15}H_{21}Cl_2N_3O_3$; NMR (d_6-DMSO): 0.8 (d, 3H), 1.2 (t, 3H), 1.65 (m, 2H), 1.9 (m, 1H), 2.2 (s, 3H), 3.5 (m, 1H), 4.0 (m, 2H), 4.1 (m, 1H), 7.1 (d, 1H), 12.0 (s, 1H).

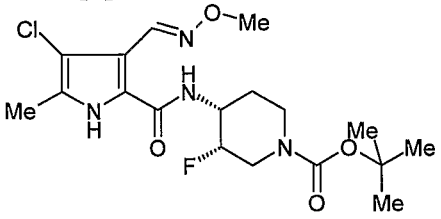
Intermediates 84-114

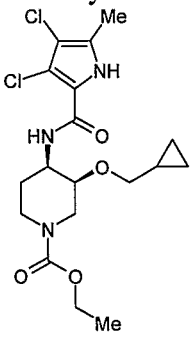
The following Intermediates were synthesized by an analogous method to Intermediate 37 or Intermediate 83 from the starting materials (SM) given in the table below.

Int	Compound	Data	SM
84	Cis(±)-*tert*-butyl 4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-[(methylthio)methyl]piperidine-1-carboxylate	N/A	Intermediate 72
85	Cis(±)-*tert*-butyl-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(methylthio)piperidine-1-carboxylate 	MS (ESP): 420.1 (M- H) for $C_{17}H_{25}Cl_2N_3O_3S$; NMR: 1.40 (s, 9H); 1.45-1.70 (m, 2H); 2.10 (s, 3H); 2.18 (s, 3H); 2.80-3.20 (m, 2H); 3.31 (m, 1H); 3.90 (m, 2H); 4.30 (m, 1H); 7.15 (d, 1H); 12.13 (s, 1H)	Intermediate 184 and Intermediate 1
86	Cis(±)-ethyl 3-(benzyloxy)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidine-1-carboxylate	MS (ESP): 454 (M+H) for $C_{21}H_{25}Cl_2N_3O_4$; NMR: 1.20 (q, 3H); 1.70 (m, 2H); 2.15 (s, 3H); 3.05 (m, 2H); 3.68 (s, 1H); 4.00 (m, 3H); 4.15 (m, 1H); 4.40 (m, 2H); 4.70 (d, 1H); 7.08 (d, 1H); 7.30 (m, 5H); 12.06 (s, 1H).	Intermediate 158 and Intermediate 1
87	Cis(±)-ethyl 4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(prop-2-yn-1-yloxy)piperidine-1-carboxylate	MS (ESP): 424 (M+Na) for $C_{17}H_{21}Cl_2N_3O_4$; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.27 (t, 3H); 1.79 (m, 2H); 2.27 (s, 3H); 2.40 (t, 1H); 2.90 (m, 2H); 3.85 (m, 1H); 4.10-4.55 (m, 7H); 7.25 (m, 1H); 9.53 (s, 1H).	Intermediate 256 and Intermediate 1

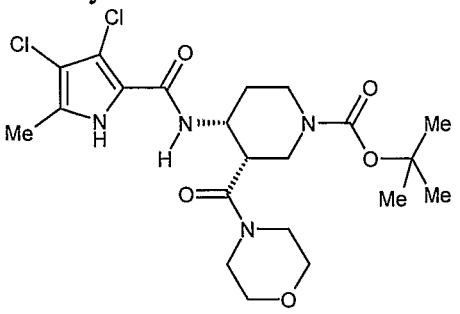
Int	Compound	Data	SM
88	Trans-(±)*tert*-butyl 4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2yl)carbonyl]amino}3-hydroxypiperidine-1-carboxylate	MS (ES) MH^+: 392 for $C_{16}H_{23}Cl_2N_3O_4$; NMR: 1.45 (s, 9H), 1.54 (m, 1H), 2.02 (m, 1H), 2.27 (s, 3H), 2.67 (dd, 1H), 2.84 (brt, 1H), 3.34 (m, 1H), 3.50 (m, 1H), 3.90 (m, 1H), 4.11 (m, 1H), 4.27 (m, 1H), 6.75 (brd, 1H), 10.06 (br s, 1H)	Intermediate185 and Intermediate 1
89	tert-butyl (3S,4R)-4-{[(3-chloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidine-1-carboxylate	MS (ES) MH^+: 360 for $C_{16}H_{23}ClFN_3O_3$	Intermediate 196 and Intermediate 64
90	tert-butyl (3S,4R)-4-{[(4-bromo-5-methyl-1H-pyrrol-2-yl) carbonyl]amino}-3-fluoropiperidine-1-carboxylate 	MS (ESN): 404 (M-1) for $C_{16}H_{23}BrN_3O_3$ NMR ($CDCl_3$) δ: 1.47 (t, 9H); 1.80 (m, 2H); 2.26 (s, 3H); 2.81 (s, 3H); 2.96 (m, 1H); 4.27 (m, 1H); 4.65 (d, br, 1H); 6.11 (d, 1H); 6.59 (s, 1H); 9.97 (s, br, 1H)	Intermediate 197 and Intermediate 64
91	tert-butyl (3S,4R)-4-{[(4-bromo-3-chloro-5-methyl-1H-pyrrol-2-yl) carbonyl]amino}-3-fluoropiperidine-1-carboxylate	MS (ES) MH^+: 440 for $C_{16}H_{22}BrClFN_3O_3$ NMR ($CDCl_3$) δ: 1.47 (s, 9H); 1.85 (m, 2H); 2.29 (s, 3H); 2.85 (m, 2H); 4.24 (m, 2H); 4.50 (m, 1H); 4.72 (d, br,1H); 6.96 (d, 1H); 9.30 (s, br, 1H)	Intermediate 198 and Intermediate 64
92	Cis(±)-Ethyl (4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(2-methoxyethoxy)piperidine-1-carboxylate	MS (ES) MH^-: 420 for $C_{17}H_{25}Cl_2N_4O_5$	Intermediate 159 and Intermediate 1

Int	Compound	Data	SM
93	Cis(±)-Ethyl 4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(2-methoxypropoxy)piperidine-1-carboxylate	MS (ES) MH^+: 436 for $C_{18}H_{27}Cl_2N_3O_5$	Intermediate 160 and Intermediate 1
94	Cis(±)-Ethyl 4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(2-hydroxypropoxy)piperidine-1-carboxylate	MS (ES) MH^+: 422 for $C_{17}H_{25}Cl_2N_3O_5$	Intermediate 161 and Intermediate 1
95	*tert*-Butyl (3*S*,4*R*)-4-{[(4-chloro-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidine-1-carboxylate 	$C_{15}H_{21}ClFN_3O_3$ NMR: 1.39 (s, 9H), 1.50-1.60 (m, 1H), 1.69-1.80 (m, 1H), 2.73-3.11 (m, 2H), 3.95-4.23 (m, 3H),4.71 (d, 1H), 6.94-6.96(m, 2H), 8.03 (d, 1H), 11.78 (s, 1H)	Intermediates 2,2,2-trichloro-1-(4-chloro-1*H*-pyrrol-2-yl)ethanone (*Tett lett. 27, 2505-2508*, **1979**) and Intermediate 64
96	*tert*-Butyl (3*S*,4*R*)-4-{[(4,5-dichloro-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidine-1-carboxylate	$C_{15}H_{21}ClFN_3O_3$ NMR: 1.39 (s, 9H), 1.50-1.60 (m, 1H), 1.69-1.80 (m, 1H), 2.73-3.11 (m, 2H), 3.95-4.23 (m, 3H), 4.71 (d, 1H), 6.94-6.96(m, 2H), 8.03 (d, 1H), 11.78 (s, 1H)	Intermediates 203 and Intermediate 64
97	Ethyl (3*S*,4*R*)-4-{[(4-chloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate	MS (ES) MH^+: for $C_{15}H_{22}ClN_3O_4$; NMR: 1.18 (t, *J*=7.06 Hz, 3H), 1.48 (d, *J*=3.58 Hz, 1H), 1.75 (td, *J*=12.29, 7.82 Hz, 1H), 2.10 - 2.18 (m, 3H), 2.95 (d, *J*=13.38 Hz, 2H), 3.20 - 3.27 (m, 3H), 3.27 - 3.35 (m, 2H), 3.38 (s, 1H), 3.97 - 4.09 (m, *J*=10.53, 7.08, 7.08, 3.39 Hz, 2H), 4.19 (s, 1H), 6.88 (d, *J*=2.64 Hz, 1H), 7.62 (d, *J*=7.91 Hz, 1H), 11.60 (s, 1H)	Intermediate 6 and Intermediate 25

Int	Compound	Data	SM
98	Cis(±)-ethyl-4-{[(4-chloro-3,5-dimethyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate	MS (ES) MH^+: 358 for $C_{16}H_{24}ClN_3O_4$.	Intermediate195 and Intermediate 26
99	*tert*-butyl (Cis(±)-3-chloro-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidine-1-carboxylate	1.40 (s, 9H), 1.67 (m, 2H), 2.19 (s, 3H), 2.68 (m, 1H), 3.43 (m, 1H), 4.02 (m, 1H), 4.17 (m, 1H), 4.36 (m, 1H), 4.58 (s, 1H), 7.05 (d, 1H), 12.12 (s, 1H)	Intermediate1 and Intermediate162
100	*tert*-butyl (3*S*,4*R*)-4-[({4-chloro-3-[(*E*)-(methoxyimino)methyl]-5-methyl-1*H*-pyrrol-2-yl}carbonyl)amino]-3-fluoropiperidine-1-carboxylate 	MS (ES) MH^+: 415 for $C_{18}H_{26}ClFN_4O_4$; NMR: 1.40 (s, 9H), 1.70 (m, 2H), 2.34 (s, 3H), 3.29 (m, 1H), 3.31 (s, 3H), 3.35 (m, 1H), 3.99 (m, 1H), 4.24 (m, 2H), 4.78 (d, 1H), 7.19 (d, 1H), 8.02 (s, 1H), 12.11 (s, 1H)	Intermediate199 and Intermediate 64
101	*tert*-butyl Cis(±)-3-chloro-4-{[(4-chloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidine-1-carboxylate	1.40 (s, 9H), 1.54 (m, 1H), 1.83 (m, 1H), 2.14 (s, 3H), 3.28 (m, 1H), 3.41 (m, 1H), 4.02-4.22 (m, 3H), 4.56 (s, 1H), 6.89 (s, 1H), 7.80 (d, 1H), 11.63 (s, 1H)	162 and Intermediate 6
102a	Cis(±)-ethyl (4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-2-methylpiperidine-1-carboxylate	MS (ES) (MH^+): 362 for $C_{15}H_{21}Cl_2N_3O_3$; NMR (d_6-DMSO): 0.8 (d, 3H), 1.2 (t, 3H), 1.65 (m, 2H), 1.9 (m, 1H), 2.2 (s, 3H), 3.5 (m, 1H), 4.0 (m, 2H), 4.1 (m, 1H), 7.1 (d, 1H), 12.0 (s, 1H)	Intermediate 202 and Intermediate 164

Int	Compound	Data	SM
102b	Cis(±)-ethyl (4-{[(4-chloro-3-cyano-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidine-1-carboxylate	MS (ES) (MH^+): 369 for $C_{16}H_{21}ClN_4O_4$; NMR (d_6-DMSO): 1.2 (t, 3H), 2.2 (s, 3H), 2.8-3.1 (m, 2H), 3.3 (s, 3H), 3.4 (m, 1H), 3.8-4.3 (m, 5H), 7.7 (d, 1H), 12.7 (s, 1H)	Intermediate 200 and Intermediate 21
103	*tert*-butyl (3*S*,4*R*)-4-{[(4-chloro-3-cyano-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidine-1-carboxylate	MS (ES) (MH^+): 383 for $C_{17}H_{22}ClFN_4O_3$; NMR (d_6-DMSO): 1.4 (s, 9H), 1.7 (m, 2H), 2.2 (s, 3H), 3.8-4.2 (m, 4H), 4.8 (d, 1H), 8.0 (d, 1H), 12.5 (s, 1H)	Intermediate200 and Intermediate 59
104	*tert*-butyl (3*S*,4*R*)-4-{[(3,5-dichloro-4-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidine-1-carboxylate	MS (ES) (MH^+): 394 for $C_{16}H_{22}Cl_2FN_3O_3$; NMR (d_6-DMSO): 1.4 (s, 9H), 1.6-1.8 (m, 2H), 1.9 (s, 3H), 2.9 (m, 2H), 4.0-4.3 (m, 3H), 4.8 (d, 1H), 7.3 (d, 1H), 12.5 (s, 1H)	Intermediate201 and Intermediate 59
105	Cis(±)-Ethyl3-(cyclopropylmethoxy)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidine-1-carboxylate 	MS (ESI) M: 418 for $C_{18}H_{25}Cl_2N_3O_4$; NMR: 0.22 (m, 2H), 0.50 (m, 2H), 1.04 (m, 1H), 1.24 (t, 3H), 1.69 (m, 2H), 2.24 (s, 3H), 2.87-3.09 (m, 2H), 3.28 (m, 1H), 3.59 (bs, 1H), 3.92-4.36 (m, 5H), 7.20 (m, 1H), 12.21 (bs, 1H)	Interemdiate165 and Intermediate 1

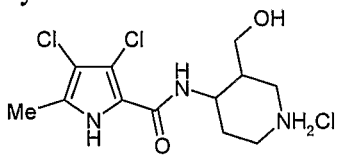
Int	Compound	Data	SM
106	Cis(±)-ethyl 4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(1,3-thiazol-2-ylmethoxy)piperidine-1-carboxylate	MS (ESI) M: 461 for $C_{18}H_{22}Cl_2N_4O_4S$; NMR (DMSO): 1.10 (m, 3H), 1.65 (m, 2H), 2.16 (s, 3H), 2.82-3.10 (m, 2H), 3.79 (bs, 1H), 3.97 (m, 3H), 4.21 (dt, 1H), 4.35 (t, 1H), 4.78 (d, 1H), 4.95 (d, 1H), 7.10 (d, 1H), 7.72 (dd, 2H), 12.12 (bs, 1H)	Intermediate166 and Intermediate 1
107	Cis(±)-Ethyl (rel 3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-ethoxypiperidine-1-carboxylate	MS (ES) MH^+: 392, 394 for $C_{16}H_{23}Cl_2N_3O_4$; NMR: 1.04-1.21 (m, 6H); 1.60 (m, 2H); 2.17 (s, 3H); 2.95 (m, 2H); 3.48 (br s, 1H); 3.65 (m, 1H); 3.92 (br s, 1H); 3.98-4.05 (m, 2H); 4.09-4.25 (m, 2H); 7.09 (d, 1H) 12.14 (s, 1H)	Intermediate257 and Intermediate 1
108	1-*tert*-butyl 3-methyl 4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidine-1,3-dicarboxylate	MS (ES) MH^+: 434, 436 for $C_{18}H_{25}Cl_2N_3O_5$; NMR ($CDCl_3$): 1.45 (s, 9H), 1.60 (m, 1H), 2.16 (m, 1H), 2.27 (s, 3H), 2.45 (dt, 1H), 2.93 (m, 1H), 3.10 (m, 1H), 3.66 (s, 3H), 4.05 (m, 1H), 4.29 (m, 2H), 6.68 (d, 1H), 9.66 (s, 1H)	Intermediate 167 and Intermediate 1
109	1-(*tert*-butoxycarbonyl)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidine-3-carboxylic acid	MS (ES) MH^+: 420, 422 for $C_{17}H_{23}Cl_2N_3O_5$.	Intermediate108 and Intermediate 1

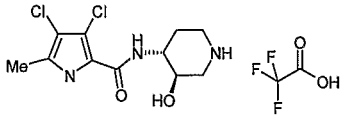
Int	Compound	Data	SM
110	Cis(±)*tert*-butyl 4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate 	MS (ES) MH^+: 489, 491 for $C_{21}H_{30}Cl_2N_4O_5$; NMR: 1.40 (s, 9H), 1.54 (m, 1H), 1.82 (m, 1H), 2.15 (s, 3H), 2.81 (broad s, 2H), 3.14 (dt, 1H), 3.24-3.40 (m, 2H [under H_2O peak]), 3.41-3.68 (m, 6H), 3.93 (m, 2H), 4.24 (m, 1H), 7.14 (d, 1H), 11.98 (s, 1H)	Intermediate 109 and Intermediate 1
111	Trans(±)*tert*-butyl 4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(morpholin-4-ylcarbonyl)piperidine-1-carboxylate	MS (ES) MH^+: 489, 491 for $C_{21}H_{30}Cl_2N_4O_5$; NMR: 1.37 (s, 9H), 1.64 (m, 1H), 2.11 (m, 1H), 2.16 (s, 3H), 3.14 (m, 1H), 3.18-3.68 (m, 11H [under H_2O peak]), 3.73 (dd, 1H), 4.37 (m, 1H), 7.24 (d, 1H), 12.08 (s, 1H)	Intermediate109 and Intermediate 1
112	Cis(±)ethyl 3-(2-*tert*-butoxy-2-oxoethoxy)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidine-1-carboxylate	MS (ES) MH^+: 478, 480 for $C_{20}H_{29}Cl_2N_3O_6$; NMR: 1.17 (t, 3H), 1.41 (s, 9H), 1.90 (m, 1H), 2.16 (s, 3H), 2.78-3.06 (m, 3H), 3.46 (m, 1H), 3.74 (m, 1H), 3.94 (m, 1H), 4.03 (q, 2H), 4.09 (s, 2H), 4.12 (m ,1H), 7.39 (d, 1H), 11.97 (s, 1H)	Intermediate 240 and Intermediate 1
113	Trans(±)ethyl 3-(2-*tert*-butoxy-2-oxoethoxy)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidine-1-carboxylate	NMR: 1.17 (t, 3H), 1.38 (s, 9H), 1.58 (m, 1H), 1.68 (m, 1H), 2.17 (s, 3H), 2.81-3.02 (m, 2H), 3.66 (m, 1H), 3.86-4.27 (m ,7H), 7.40 (d, 1H), 12.07 (s, 1H)	Intermediate 240 and Intermediate 1

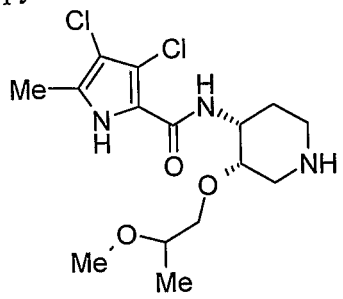
Int	Compound	Data	SM
114	Ethyl 3-{[*tert*-butyl(dimethyl)silyl]oxy}-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidine-1-carboxylate	MS (ES)MH^+: 478, 480 for $C_{20}H_{33}Cl_2N_3O_4Si$; NMR: -0.07 (s, 3H), 0.07 (s, 3H), 0.83 (s, 9H), 1.16 (t, 3H), 1.56 (m, 1H), 1.72 (m, 1H), 2.17 (s, 3H), 3.04 (m, 2H), 3.85-4.11 (m, 6H), 6.66 (m, 1H), 12.12 (s, 1H)	Intermediate 112 and Intermediate 1

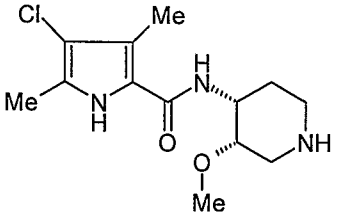
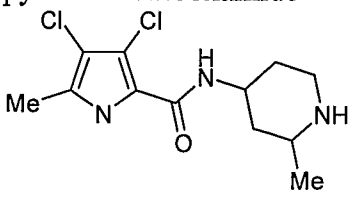
Intermediates 115-144

The following Intermediates were synthesized by an analogous method to Intermediate 50 or Intermediate 74 from the starting materials (SM) given in the table below.

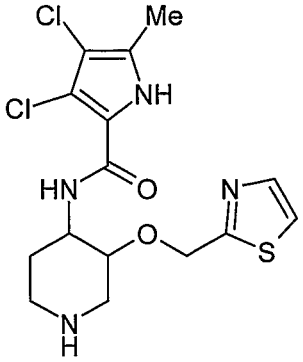
Int	Compound	Data	SM
115	Cis(±)-3,4-dichloro-*N*-[3-(hydroxymethyl)piperidin-4-yl]-5-methyl-1*H*-pyrrole-2-carboxamide hydrochloride 	MS (ES) MH^+: 306, 308 for $C_{12}H_{17}Cl_2N_3O_2$.	Intermediate 71
116	Cis(±)-3,4-dichloro-5-methyl-*N*-{3-[(methylthio)methyl]piperidin-4-yl}-1*H*-pyrrole-2-carboxamide hydrochloride	MS (ES) MH^+: 336, 338 for $C_{13}H_{19}Cl_2N_3OS$.	Intermediate84
117	Cis(±)-3,4-dichloro-5-methyl-*N*-[3-(methylthio)piperidin-4-yl]-1*H*-pyrrole-2-carboxamide	MS (ESP): 463.1 (M+ H) for $C_{17}H_{20}Cl_2N_4O_3S_2$; NMR: 1.90 (m, 2H); 2.14 (s, 3H); 2.28 (s, 3H); 3.28-3.45 (m, 2H); 3.74 (s, 3H); 3.77 (m, 1H); 3.95 (m, 2H); 4.44 (m, 1H); 7.25 (d, 1H); 7.85 (s, 1H); 12.14 (s, 1H)	Intermediate 85
118	Cis(±)-*N*-[3-(benzyloxy)piperidin-4-yl]-3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxamide	MS (ESP): 382 (M+H) for $C_{18}H_{21}Cl_2N_3O_2$	Intermediate 86

Int	Compound	Data	SM
119	Cis(±)-3,4-dichloro-5-methyl-*N*-[3-(prop-2-yn-1-yloxy)piperidin-4-yl]-1*H*-pyrrole-2-carboxamide	MS (ESP): 330 (M+H) for $C_{14}H_{17}Cl_2N_3O_2$	Intermediate 87
120	Trans-(±)3,4-dichloro-*N*-[3-hydroxypiperidin-4-yl]-5-methyl-1*H*-pyrrole-2-carboxamide trifluoroacetate 	MS (ES) MH^+: 292 for $C_{11}H_{15}Cl_2N_3O_2$	Intermediate 88
121	3-chloro-N-[(3S,4R)-3-fluoropiperidin-4-yl]-5-methyl-1H-pyrrole-2-carboxamide	MS (ES) MH^+: 260 for $C_{11}H_{15}ClFN_3O$; 1.91 (m, 2H); 2.17 (s, 3H); 3.13 (m, 1H); 3.35 (m, 2H); 3.57 (s, 1H); 4.35 (m, 1H); 5.05 (d, br, 1H); 5.96 (s, 1H); 7.26 (d, 1H); 8.67 (br, 1H); 9.16 (br, 1H); 11.70 (s, br, 1H)	Intermediate 89
122	4-bromo-N-[(3S,4R)-3-fluoropiperidin-4-yl]-5-methyl-1H-pyrrole-2-carboxamide	MS (ES) MH^+: 306 for $C_{11}H_{15}BrN_3O$	Intermediate 90
123	4-bromo-3-chloro-N-[(3S,4R)-3-fluoropiperidin-4-yl]-5-methyl-1H-pyrrole-2-carboxamide	MS (ES) MH^+: 340 for $C_{11}H_{14}BrN_3O$ NMR δ: 1.91 (m, 2H); 2.20 (s, 3H); 3.13 (m, 1H); 3.35 (m, 2H); 3.62 (m, 1H); 4.35 (m, 1H); 5.05 (d, br, 1H); 7.39 (d, 1H); 8.60 (s, br, 1H); 8.99 (s, br, 1H); 12.17 (s, br, 1H)	Intermediate 91
124	Cis(±)-3,4-dichloro-*N*-[(3-(2-methoxyethoxy)piperidin-4-yl]-5-methyl-1*H*-pyrrole-2-carboxamide	MS (ES) MH^+: 350 for $C_{14}H_{21}Cl_2N_3O_3$	Intermediate 92

Int	Compound	Data	SM
125	Cis(±)-3,4-Dichloro-*N*-[3-(2-methoxypropoxy)piperidin-4-yl]-5-methyl-1*H*-pyrrole-2-carboxamide 	MS (ES) MH^+: 364 for $C_{15}H_{23}Cl_2N_3O_3$	Intermediate 93
126	Cis(±)-3,4-Dichloro-*N*-3-(2-hydroxypropoxy)piperidin-4-yl]-5-methyl-1*H*-pyrrole-2-carboxamide	MS (ES) MH^+: 350 for $C_{14}H_{21}Cl_2N_3O_3$;	Intermediate 94
127	4-Chloro-*N*-[(3*S*,4*R*)-3-fluoropiperidin-4-yl]-1*H*-pyrrole-2-carboxamide hydrochloride	MS (ES) MH^+: 246 for $C_{10}H_{13}ClFN_3O$	Intermediate 95
128	4,5-dichloro-*N*-[(3*S*,4*R*)-3-fluoropiperidin-4-yl]-1*H*-pyrrole-2-carboxamide hydrochloride	MS (ES) MH^+: 280 for $C_{10}H_{12}Cl_2FN_3O$	Intermediate 96
129	4-chloro-N--[(3*S*,4*R*)-(3-methoxypiperidin-4-yl)]1-5-methyl-1H-pyrrole-2-carboxamide	1.41 (s, 1H), 1.67 (s, 1H), 2.13 (s, 3H), 2.47 (s, 1H), 2.55 (s, 1H), 2.86 (s, 1H), 3.08 (d, J=13.19 Hz, 1H), 3.25 (s, 3H), 3.31 (s, 1H), 6.89 (d, J=2.45 Hz, 1H), 7.52 (s, 1H), 11.59 (s, 1H)	Intermediate 97

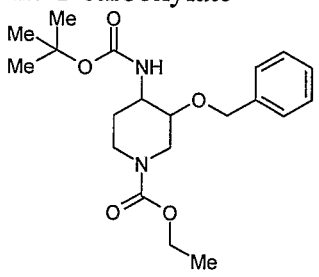
Int	Compound	Data	SM
130	Cis(±)-4-chloro-*N*-[(3*S*,4*R*)-3-methoxypiperidin-4-yl]-3,5-dimethyl-1*H*-pyrrole-2-carboxamide 	MS (ES) MH^+: 287 for $C_{13}H_{20}ClN_3O_2$.	Intermediate98
131	3,4-dichloro-*N*-[Cis(±)-3-chloropiperidin-4-yl]-5-methyl-1*H*-pyrrole-2-carboxamide hydrochloride	MS (ES) MH^+: 310 for $C_{11}H_{14}Cl_3N_3O$	Intermediate99
132	4-chloro-*N*-[(3*S*,4*R*)-3-fluoropiperidin-4-yl]-3-[(*E*)-(methoxyimino)methyl]-5-methyl-1*H*-pyrrole-2-carboxamide hydrochloride	MS (ES) MH^+: 317 for $C_{17}H_{18}ClFN_4O_2$	Intermediate 100
133	Cis(±)-3-chloro-*N*-[3-chloropiperidin-4-yl]-5-methyl-1*H*-pyrrole-2-carboxamide hydrochloride	MS (ES) MH^+: 276 for $C_{11}H_{15}Cl_2N_3O$	Intermediate101
134	Cis(±)-3,4-dichloro-5-methyl-*N*-[(3-methylpiperidin-4-yl]-1*H*-pyrrole-2-carboxamide	MS (ES) (MH^+): 290 for $C_{12}H_{17}Cl_2N_3O$.	Intermediate 83
135	Cis(±)-3,4-dichloro-5-methyl-*N*-[2-methylpiperidin-4-yl]-1*H*-pyrrole-2-carboxamide 	MS (ES) (MH^+): 290 for $C_{12}H_{17}Cl_2N_3O$. NMR: 1.0 (d, 3H), 1.2-1.4 (m, 1H), 1.7-1.9 (m, 1H), 2.2 (s, 3H), 2.5-2.7 (m, 2H), 3.0 (m, 1H), 3.3 (m, 1H), 3.7-3.8 (m, 1H), 7.1 (d, 1H)	Intermediate 101

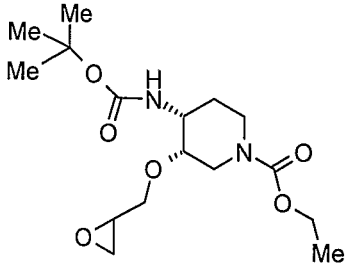
Int	Compound	Data	SM
136	Cis(±)-4-chloro-3-cyano-*N*-[(3-methoxypiperidin-4-yl]-5-methyl-1*H*-pyrrole-2-carboxamide	MS (ES) (MH^+): 297 for $C_{12}H_{17}Cl_2N_3O_2$. NMR: 1.6-1.9 (m, 2H), 2.2 (s, 3H), 2.8 (m, 2H), 3.0 (m, 1H), 3.3 (s, 3H), 3.5 (s, 1H), 4.15 (m, 1H), 7.7 (d, 1H), 8.7 (s, broad, 1H)	Intermediate 102
137	4-chloro-3-cyano-*N*-[(3*S*,4*R*)-3-fluoropiperidin-4-yl]-5-methyl-1*H*-pyrrole-2-carboxamide	MS (ES) (MH^+): 285 for $C_{11}H_{14}Cl_2FN_3O$. NMR: 1.6 (m, 2H), 2.2 (s, 3H), 2.3 (m, 1H), 2.3 (m, 1H), 2.5-3.0 (m, 2H), 3.1-3.3 (m, 1H), 3.5 (s, 1H), 4.0-4.2 (dd, 1H), 4.7 (d, 1H), 7.9 (d, 2H)	Intermediate 103
138	(3*S*,4*R*)-4-{[(3,5-dichloro-4-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidinium chloride	MS (ES) (MH^+): 294 for $C_{11}H_{14}Cl_2FN_3O$. NMR: 1.9 (s, 3H), 3.0-3.7 (m, 4H), 4.3 (m, 1H), 5.0 (d, 1H), 7.65 (d, 1H), 8.7 (s, broad, 1H), 9.4 (s, broad, 1H), 12.7 (s, 1H)	Intermediate 104
139	Cis(±)-3,4-dichloro-*N*-[3-(cyclopropylmethoxy)piperidin-4-yl]-5-methyl-1*H*-pyrrole-2-carboxamide	MS (ES) MH^+: 347 for $C_{15}H_{21}Cl_2N_3O_2$; NMR: 0.17 (m, 2H), 0.44 (m, 2H), 1.01 (m, 1H), 1.34 (s, 1H), 1.62 (m, 2H), 2.17 (s, 3H), 2.55-2.70 (m, 2H), 2.89 (m, 2H), 3.10-3.23 (m, 2H), 3.38-3.49 (m, 1H), 4.09 (m, 1H), 7.12 (d, 1H), 12.10 (bs, 1H).	Intermediate105

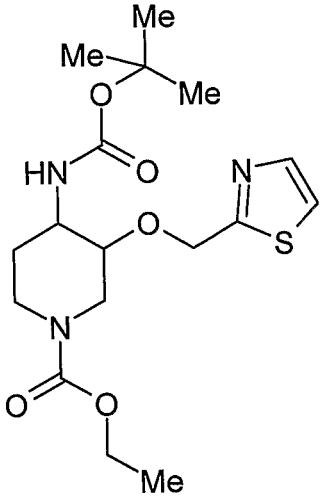
Int	Compound	Data	SM
140	Cis(±)-3,4-dichloro-5-methyl-*N*-[3-(1,3-thiazol-2-ylmethoxy)piperidin-4-yl]-1*H*-pyrrole-2-carboxamide 	MS (ESI) M: 389 for $C_{15}H_{18}Cl_2N_4O_2S$	Intermediate106
141	Cis(±)-3,4-Dichloro-*N*-[(rel 3*S*,4*R*)-3-ethoxypiperidin-4-yl]-5-methyl-1*H*-pyrrole-2-carboxamide	MS (ES) MH^+: 320 for $C_{13}H_{19}Cl_2N_3O_2$; NMR: 1.14 (t, 3H); 1.60 (br s, 2H); 2.17(s, 3H); 2.62 (m, 2H); 2.89 (m, 2H); 3.14 (m, 2H); 3.64 (m, 2H); 4.05 (m, 2H); 7.10 (d, 1H)	Intermediate107
142	Trans(±)3,4-dichloro-5-methyl-*N*-[3-(morpholin-4-ylcarbonyl)piperidin-4-yl]-1*H*-pyrrole-2-carboxamide hydrochloride	MS (ES) MH^+: 389, 391 for $C_{16}H_{22}Cl_2N_4O_3$	Intermediate111
143	Cis(±)3,4-dichloro-5-methyl-*N*-[3-(morpholin-4-ylcarbonyl)piperidin-4-yl]-1*H*-pyrrole-2-carboxamide hydrochloride	MS (ES) MH^+: 389, 391 for $C_{16}H_{22}Cl_2N_4O_3$	Intermediate110
144	Cis(±)[(4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-3-yl)oxy]acetic acid	MS (ES)[$(M+H)^+$]: 350, 352 for $C_{13}H_{17}Cl_2N_3O_4$	Intermediate 112

Intermediates 145-157

The following Intermediates were synthesized by an analogous method to Intermediate 59 from the starting materials (SM) given in the table below.

Int	Compound	Data	SM
145	Cis(±)-ethyl 3-(benzyloxy)-4-[(*tert*-butoxycarbonyl)amino]piperidine-1-carboxylate 	MS (ESP): 401 (M+Na) for $C_{20}H_{30}N_2O_5$; NMR ($CDCl_3$) δ: 1.25 (m, 3H); 1.43 (s, 9H); 1.65-1.85 (m, 2H); 2.81 (m, 2H); 3.58 (s, 1H); 3.71 (m, 1H); 4.05-4.30 (m, 3H); 4.30 (m, 2H); 4.76 (t, 1H); 4.94 (m, 1H); 7.26-7.38 (m, 5H)	cis(±)ethyl 4-[(tert-butoxycarbonyl)amino]-3-hydroxypiperidine-1-carboxylate (WO9412494) and Benzyl bromide
146	Cis(±)-ethyl 4-[(*tert*-butoxycarbonyl)amino]-3-(prop-2-yn-1-yloxy)piperidine-1-carboxylate	NMR: ($CDCl_3$) 1.26 (t, 3H); 1.45 (s, 9H); 1.67 (m, 2H); 2.43 (t, 1H); 2.79 (m, 2H); 3.74 (m, 2H); 4.00-4.45 (m, 6H); 5.00 (s, 1H)	cis(±)ethyl 4-[(tert-butoxycarbonyl)amino]-3-hydroxypiperidine-1-carboxylate (WO9412494) and Propargyl bromide
147	Cis(±)-Ethyl (4-benzylamino)-3-(2-methoxyethoxy)piperidine-1-carboxylate	MS (ES) MH^+: 337 for $C_{18}H_{28}N_2O_4$	Intermediate 169
148	Cis(±)-Ethyl 4-[(*tert*-butoxycarbonyl)amino]-3-(2-methoxypropoxy)piperidine-1-carboxylate	MS (ES) M+Na: 383 for $C_{17}H_{32}N_2O_6$	Intermediate 149 and methyl iodide
149	Cis(±)-Ethyl 4-[(*tert*-butoxycarbonyl)amino]-3-(2-hydroxypropoxy)piperidine-1-carboxylate	MS (ES) M + Na: 369 for $C_{16}H_{30}N_2O_6$	Intermediate 150 (*J.Org.Chem, 60, 4922-4924*, **1995**)

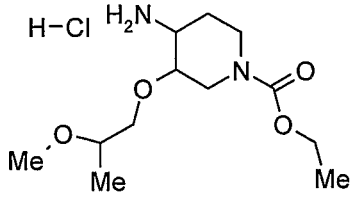
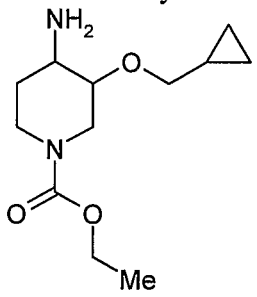
Int	Compound	Data	SM
150	Cis(±)-Ethyl 4-[(*tert*-butoxycarbonyl)amino]-3-(oxiran-2-ylmethoxy)piperidine-1-carboxylate 	MS (ES) M + Na: 367 for $C_{16}H_{28}N_2O_6$	Intermediate 27 and m-CPBA
151	*tert*-butyl (Cis(±)-4-(benzylamino)-3-chloropiperidine-1-carboxylate	1.39 (s, 9H), 1.54 (m, 2H), 1.93 (m, 1H), 2.80 (m, 2H), 3.20 (m, 1H), 3.75 (q, 2H), 4.06 (m, 1H), 4.57 (s, 1H), 7.22-7.36 (m, 5H).	Intermediate 170
152	Cis(±)-ethyl 4-(benzylamino)-3-methylpiperidine-1-carboxylate	NMR ($CDCl_3$): 0.9 (d, 3H), 1.2 (t, 3H), 1.6 (m, 2H), 2.0 (m, 1H), 2.8 (m, 1H), 2.9-3.2 (m, 2H), 3.7 (m, 1H), 3.8 (s, 2H), 4.1 (m, 2H), 7.2-7.4 (m, 5H).	ethyl 3-methyl-4-oxopiperidine-1-carboxylate (Ebnoether, A.; Niklaus, P.; Suess, R. *Helvetica Chimica Acta* (1969), 52(3), 629-38)
153	Cis(±)-ethyl (4-(benzylamino)-2-methylpiperidine-1-carboxylate	MS (ES) (MH^+): 277 for $C_{16}H_{24}N_2O_2$: NMR (d_6-DMSO): 1.25 (t, 3H), 1.3 (d, 3H), 1.3-1.5 (m, 2H), 1.65 (s, broad, 2H), 1.8-2.0 (m, 2H), 3.2-3.4 (m, 2H), 3.8 (m, 1H), 4.1 (3, 3H)	Intermediate 164
154	Cis(±)-Ethyl 4-(benzylamino)-3-(cyclopropylmethoxy)piperidine-1-carboxylate	MS (ES) MH^+: 333 for $C_{19}H_{28}N_2O_3$; NMR: 0.14 (m, 2H), 0.42 (m, 2H), 0.97 (m, 1H), 1.15 (t, 3H), 1.51 (m, 2H), 2.67 (m, 1H), 2.79-3.01 (m, 2H), 3.19 (m, 1H), 3.53 (m, 1H), 3.73 (m, 3H), 3.88-4.02 (m, 3H), 7.18-7.35 (m, 5H)	Intermediate171

Int	Compound	Data	SM
155	Cis(±)-ethyl 4-[(*tert*-butoxycarbonyl)amino]-3-(1,3-thiazol-2-ylmethoxy)piperidine-1-carboxylate 	MS (ES) MH^+: 386 for $C_{17}H_{27}N_3O_5S$; NMR ($CDCl_3$): 1.24 (t, 3H), 1.42 (s, 9H), 1.63 (s, 1H), 1.69-1.81 (m, 2H), 2.82 (m, 2H), 3.67 (m, 2H), 4.10 (q, 2H), 4.40-4.60 (m, 1H), 4.76 (d, 1H), 4.94-5.25 (m, 2H), 7.31 (d, 1H), 7.74 (d, 1H)	Intermediate235
156	Cis(±)-Ethyl (4-(benzylamino)-3-ethoxypiperidine-1-carboxylate	MS (ES) MH^+: 307 for $C_{17}H_{26}N_2O_3$; NMR: 1.08 (t, 3H); 1.15 (t, 3H); 1.50 (m, 2H); 1.75 (br s, 1H); 2.65 (br s, 1H); 2.92 (m, 2H); 3.47 (br s, 1H); 3.55 (m, 1H); 3.71 (m, 3H); 3.88 (br s, 1H); 3.98-4.05 (m, 2H); 7.18-7.34 (m 5H)	Intermediate172
157	Cis(±)-ethyl 4-(benzylamino)-3-methoxypiperidine-1-carboxylate	MS (ES) MH^+: 293 for $C_{16}H_{24}N_2O_3$. NMR: 1.16 (t, 3H), 1.50 (m, 2H), 1.89 (s, 2H), 2.66 (m, 1H), 2.89 (dd, 2H), 3.26 (s, 3H), 3.67-3.83 (m, 3H), 3.99 (m, 3H), 7.18-7.37 (m, 5H)	Intermediate168

Intermediates 158-167

The following Intermediates were synthesized by an analogous method to Intermediate 28 or Intermediate 59 from the starting materials (SM) given in the table below.

Int	Compound	Data	SM
158	Cis(±)-ethyl 4-amino-3-(benzyloxy)piperidine-1-carboxylate	MS (ESP): 279 (M+H) for $C_{15}H_{22}N_2O_3$	Intermediate 145

Int	Compound	Data	SM
160	Cis(±)-Ethyl 4-amino-3-(2-methoxypropoxy)piperidine-1-carboxylate hydrochloride 	MS (ES) MH^+: 261 for $C_{12}H_{24}N_2O_4$	Intermediate 148
161	Cis(±)-Ethyl 4-amino-3-(2-hydroxypropoxy)piperidine-1-carboxylate hydrochloride	MS (ES) MH^+: 247 for $C_{11}H_{22}N_2O_4$	Intermediate 149
162	*tert*-butyl Cis(±)-4-amino-3-chloropiperidine-1-carboxylate	1.39 (s, 9H), 1.45 (m, 1H), 1.58 (m, 2H), 2.95 (m, 1H), 3.31 (m, 1H), 3.82 (m, 1H), 4.03 (m, 1H), 4.26 (m, 1H)	Intermediate151
163	ethyl Cis(±)-4-amino-3-methylpiperidine-1-carboxylate	NMR ($CDCl_3$): 0.9 (d, 3H), 1.2 (t, 3H), 1.5 (m, 2H), 1.6 (m, 1H), 2.2 (s, broad, 2H), 3.0 (m, 1H), 3.2 (m, 2H), 3.4 (m, 1H), 4.0-4.2 (m, 2H)	Intermediate 152
164	Cis(±)-ethyl (4-amino-2-methylpiperidine-1-carboxylate	NMR: 1.25 (t, 3H), 1.3 (d, 3H), 1.3-1.5 (m, 2H), 1.65 (s, broad, 2H), 1.8-2.0 (m, 2H), 3.2-3.4 (m, 2H), 3.8 (m, 1H), 4.1 (3, 3H)	ethyl 2-methyl-4-oxopiperidine-1-carboxylate (EP 121972 A2)
165	Cis(±)-Ethyl 4-amino-3-(cyclopropylmethoxy)piperidine-1-carboxylate 	MS (ES) MH^+: 243 for $C_{12}H_{22}N_2O_3$; NMR ($CDCl_3$): 0.19 (m, 2H), 0.49 (m, 2H), 1.05 (m, 1H), 1.24 (t, 3H), 1.65-1.84 (m, 2H), 2.93 (d, 2H), 3.09 (m, 1H), 3.25-3.44 (m, 2H), 3.52 (bs, 1H), 3.85-4.21 (m, 6H)	Intermediate154

Int	Compound	Data	SM
166	Cis(±)-ethyl 4-amino-3-(1,3-thiazol-2-ylmethoxy)piperidine-1-carboxylate	MS (ES) MH^+: 286 for $C_{12}H_{19}N_3O_3S$; NMR (DMSO): 1.00 (t, 1.8H), 1.15 (t, 1.2H), 1.70 (m, 2H), 2.79-3.03 (m, 2H), 3.44 (m, 1H), 3.74-4.02 (m, 4H), 4.29 (m, 1H), 4.91 (t, 2H), 7.25 (bs, 1H), 7.77 (dd, 2H), 8.34 (s, 1H)	Intermediate155
167	1-*tert*-butyl 3-methyl 4-aminopiperidine-1,3-dicarboxylate	MS (GC-EI)[$(M)^+$]: 258 for $C_{12}H_{22}N_2O_4$	Intermediate237

Intermediate 168

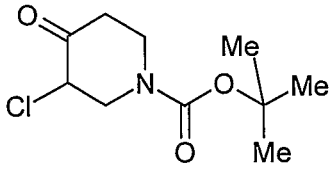
ethyl 3-methoxy-4-oxopiperidine-1-carboxylate

To a stirred solution of the methoxyketal (Intermediate 173, 55.15 g, 223 mmol, crude) in dry THF (30 mL), at room temperature and under ambient atmosphere, was added an aqueous solution of H_2SO_4 (5%, v/v, 190 mL). Temperature was increased to 60 °C; the reaction was stirred at this temperature. Complete conversion was suggested after 2 hours by TLC (50% ethyl acetate in hexanes; Hanessian's stain; Rf ~ 0.43). The reaction mixture was allowed to come to room temperature. THF was removed under vacuum. To the aqueous solution was added solid sodium bicarbonate until basic, and solid sodium chloride until saturated, with the addition of more water necessary. Crude product was extracted with methylene chloride (3 X 300 mL); the organic layers were combined, dried over magnesium sulfate, and concentrated. The crude material was used without further purification; yield was assumed quantitative.

MS (ESI) M: 201 for $C_9H_{15}NO_4$. ^1H NMR ($CDCl_3$): 1.28 (t, 3H), 2.38-2.60 (m, 2H), 3.30-3.41 (m, 2H), 3.45 (s, 3H), 3.69 (m, 1H), 4.05 (m, 2H), 4.17 (q, 2H).

Intermediates 169-172

The following Intermediates were synthesized by an analogous method to Intermediate 168 from the starting materials (SM) given in the table below.

Int	Compound	Data	SM
169	Ethyl 3-(2-methoxyethoxy)-4-oxopiperidine-1-carboxylate	MS (ES) MH^+: 246 for $C_{11}H_{19}NO_5$	Intermediate 174
170	*tert*-butyl 3-chloro-4-oxopiperidine-1-carboxylate 	1.30 (m, 1H), 1.34 (s, 9H), 2.45 (t, 2H), 3.34 (m, 1H), 3.17 (m, 1H), 4.10 (m, 1H), 4.66 (m, 1H)	*J. Org. Chem.*, **1994**, *59*, 6955-6964.
171	Ethyl 3-(cyclopropylmethoxy)-4-oxopiperidine-1-carboxylate	MS (ES) MH^+: 242 for $C_{12}H_{19}NO_4$; NMR ($CDCl_3$): 0.21 (m, 2H), 0.53 (m, 2H), 1.07 (m, 1H), 1.28 (t, 3H), 2.37-2.58 (m, 2H), 3.32-3.51 (m, 4H), 3.85 (bs, 1H), 4.04-4.41 (m, 4H)	Intermediate 255 and cyclopropylmethyl bromide
172	Ethyl 3-ethoxy-4-oxopiperidine-1-carboxylate	MS (ES) MNa^+: 238 for $C_{10}H_{17}NO_4$-Na adduct; NMR: 1.09 (t, 3H); 1.20 (t, 3H); 2.31 (m, 1H); 3.12 (br s, 1H); 3.45 (m, 1H); 3.59 (m, 1H); 3.94 (m, 2H); 4.03-4.11 (m, 4H).	Intermediate 175

Intermediate 173

ethyl 3,4,4-trimethoxypiperidine-1-carboxylate

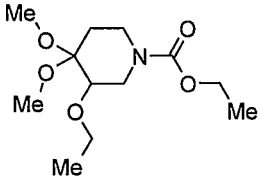
To a stirred solution of sodium hydride (6.96 g, 290 mmol) in dry THF (100 mL), at 0 °C and under an atmosphere of N_2, was added a solution of the hydroxyketal (Intermediate 255, 223 mmol) in THF (125 mL) over approximately 30 minutes, via addition funnel. The resulting solution was stirred at 0 °C under an atmosphere of N_2 for approximately 15 minutes; to it was then added methyl iodide (18.0 mL, 41.0 g, 290 mmol) portionwise, via syringe, over approximately 5 minutes. The reaction was stirred overnight under an atmosphere of N_2, gradually reaching room temperature. Complete conversion was suggested by TLC (50% ethyl acetate in hexanes; Hanessian's stain; Rf ~ 0.57) in the morning. The reaction was quenched with a small volume of water, then concentrated under vacuum. To the residue was added approximately 50 mL of water; from this mixture was extracted the crude product with ethyl acetate (3 X 150 mL). The organic layers were combined, dried over

magnesium sulfate, and concentrated. The crude material was used without further purification; yield was assumed quantitative.

MS (ESI) M: 247 for $C_{11}H_{21}NO_5$. ^1H NMR ($CDCl_3$): 1.24 (t, 3H), 1.72-1.83 (m, 2H), 2.82 (m, 2H), 2.98 (t, 1H), 3.20 (s, 3H), 3.21 (s, 3H), 3.41 (s, 3H), 4.10 (q, 2H), 4.20-4.37 (m, 2H).

Intermediates 174-175

The following Intermediates were synthesized by an analogous method to Intermediate 173 from the starting materials (SM) given in the table below.

Int	Compound	Data	SM
174	Ethyl 4,4-dimethoxy-3-(2-methoxyethoxy)piperidine-1-carboxylate	NMR ($CDCl_3$): 1.23 (t, 3H), 1.73-1.85 (m, 2H), 2.75-2.88 (m, 1H), 2.93-3.10 (m, 1H), 3.19 (s, 3H), 3.23 (s, 3H), 3.34 (s, 3H), 3.40-3.60 (m, 4H), 3.68-3.80 (m, 2H), 4.11 (q, 2H), 3.98-4.30 (m, 1 H)	Intermediate 255 and 1-bromo-2-methoxyethane
175	Ethyl 3-ethoxy-4,4-dimethoxypiperidine-1-carboxylate 	MS (ES) MNa^+: 284 for $C_{12}H_{23}NO_5$-Na adduct; NMR: 1.07 (t, 3H); 1.15 (t, 3H); 1.52 (m, 1H); 1.66 (m, 1H); 3.08 (s, 3H); 3.10 (s, 3H); 3.59 (m, 1H); 3.81 (m, 2H); 3.96-4.07 (m, 4H); 4.12 (m, 1H)	Intermediate 255 and ethyl iodide

Intermediate 176

Ethyl 2-oxobutanoate

Diethyl oxalate (10 g; 68 mmol) was dissolved in Et_2O (100 ml) and cooled to –78 C. Ethyl magnesium bromide (1.0 M in THF; 72 ml; 71.8 mmol; 1.05 equiv.) was added slowly via syringe. The dry ice / acetone bath was allowed to melt and warm to 10 C. Monitored the reaction by ^1H NMR. The reaction was cooled to 0 C and quenched with saturated NH_4Cl. Dilute with H_2O and separate phases. The organic layer was dried over Na_2SO_4, filtered and concentrated. Isolation gave 7.6 g of a crude yellow oil in 86% yield. No further purification.

Intermediate 177

Ethyl 3-bromo-2-oxobutanoate

$CuBr_2$ (39.3 g; 176 mmol; 3 equiv.) was suspended in EtOAc (160 ml). A $CHCl_3$ solution containing ethyl 2-oxobutanoate (Intermediate 176, 7.6 g; 58.7 mmol) was added

dropwise. The suspension was then heated to reflux for 6 hours and monitored by ^{1}H NMR. The solids were filtered through a pad of Celite and the mother liquor was concentrated. The crude oil was passed through a short plug of silica gel and eluted with a 1:1 mixture of EtOAc / hexanes. The yellow band was collected and concentrated to give 12.2 g of product. No further purification.

Intermediate 178

Ethyl 2-amino-5-methyl-1,3-thiazole-4-carboxylate

Ethyl 3-bromo-2-oxobutanoate (Intermediate 177, 12.2 g; 58.7 mmol) and thiourea (4.46 g; 76.1; 58.7 mmol) were combined and heated to reflux. The solution was allowed to cool to room temperature and stir for 12 hours. The reaction was monitored by LC/MS. The base was precipitated with 20% NH_4OH (10 ml) and then redissolved with 1N HCl (100 ml) and then finally reprecipitated with 20% NH_4OH. The precipitate was collected and washed with H_2O. The crude product was then crystallized from 9:1 ethanol / water to give 5.95 g of product in 55% yield. MS (ES) MH^+: 187 for $C_7H_{10}N_2O_2S$.

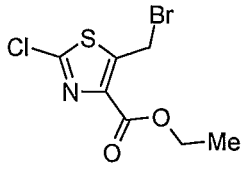
Intermediate 179

Ethyl 2-chloro-5-methyl-1,3-thiazole-4-carboxylate

Ethyl 2-amino-5-methyl-1,3-thiazole-4-carboxylate (Intermediate 178, 3 g; 16.1 mmol) and anhydrous $CuCl_2$ (3.25 g; 24.2 mmol; 1.5 equiv.) were combined in dry acetonitrile (28 ml). t-butyl nitrite (90% tech; 2.77 g; 24.2 mmol; 1.5 equiv.) was added dropwise. The suspension was stirered at room temperature for 12 hours and monitored by LC/MS. The acetonitrile was removed in vacou and the solid was redissolved in $CHCl_3$ and H_2O. The aqueous layer was acidified with 2N HCl and the phases were separated. Back extracted the aqueous with $CHCl_3$. The organic extracts were combined, dried over Na_2SO_4 and decolorizing carbon for 1 hour. Filtered through a pad of Celite and concentrated to an oil. Isolation gave 2.62 g of the title compound in 80% yield. The compound can be further purified via flash column chromatography and crystallization. MS (ES) MH^+: 206, 208 for $C_7H_8ClNO_2S$.

Intermediate 180

Ethyl 5-(bromomethyl)-2-chloro-1,3-thiazole-4-carboxylate



Ethyl 2-chloro-5-methyl-1,3-thiazole-4-carboxylate (Intermediate 179, 2.8 g; 13.6 mmol) was dissolved in CCl_4 (25 ml). NBS (2.3 g; 13 mmol) and AIBN (2.12 g; 13 mmol) were added in a single portion and the resultant reaction mixture was heated to reflux for 24 hours. Additional NBS (690 mg; 0.3 equiv.) and AIBN (636 mg; 0.3 mmol) were added to push the reaction to completion. Continued to heat for another 4 hours. Cooled to room temperature, filtered and concentrated the mother liquor. Redissolved in minimal DMSO (7 ml) and purified by Gilson HPLC (5-95% ACN / 0.1% TFA; run time = 35 min). Isolated 1.15 g of desired product in 29% yield MS (ES) MH^+: 284, 286, 288 for $C_7H_7BrClNO_2S$.

Intermediate 181

Ethyl 2-chloro-5-formyl-1,3-thiazole-4-carboxylate

Ethyl 5-(bromomethyl)-2-chloro-1,3-thiazole-4-carboxylate (Intermediate 180, 920 mg; 3.2 mmol) was dissolved in acetonitrile dried over moleculare sieves. The solution was cooled to 0 C and NMO (570 mg; 1.5 equiv.) was added in a single portion. The reaction was monitored by LC/MS. An additional 1.5 equivalents of NMO was added in two portions over two hours. The reaction was concentrated to a solid residue, redissolved in EtOAc and washed with H_2O. Dried the organic over Na_2SO_4, filtered and concentrated. No further purification. MS (ES) MH^+: 220,222 for $C_7H_6ClNO_3S$.

Intermediate 182

tert-Butyl 3-bromo-4-oxopiperidine-1-carboxylate

Chlorotrimethylsilane (5.6 ml, 44 mmol) was added slowly to a solution of *tert*-butyl 4-oxopiperidine-1-carboxylate (commercial, 8 g, 40 mmol), triethylamine (12.3 ml, 88 mmol) and DMF (40 ml) at room temperature. The resultant solution was heated to 75 °C and stirred overnight under nitrogen. The reaction mixture was cooled to room temperature and then in an ice bath. Cold hexane (250 ml) was added slowly to the reaction mixture followed by cold (saturated) aqueous sodium bicarbonate (50 ml). The organic phase was separated and washed with brine, dried over sodium sulfate, filtered and concentrated under reduced

pressure. The crude silyl enolether was dissolved in THF (15 ml) and cooled to 0 °C. N-Bromosuccinimide (7.1 g, 40 mmol) was dissolved in THF (120 ml) and added slowly (45 min.) to the reaction mixture. The resultant mixture was allowed to slowly warm to room temperature and stirred overnight. The reaction mixture was concentrated under reduced pressure. The crude residue was purified by flash chromatography (hexanes/ethyl acetate, 5:1) to provide the title compound as a white solid (11 g).

MS (ESP): 222.1 (M- tBu) for $C_{10}H_{16}BrNO_3$

^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.25 (s, 9H); 2.30 (m, 1H); 2.55 (m, 1H); 3.42-3.80 (m, 3H); 3.93 (m, 1H); 4.60 (m, 1H).

Intermediate 183

tert-Butyl 3-(methylthio)-4-oxopiperidine-1-carboxylate

Sodium thiomethoxide (805 mg, 11.5 mmol) was added to a solution of *tert*-butyl 3-bromo-4-oxopiperidine-1-carboxylate (Intermediate 182, 3.20 g, 11.5 mmol) and THF (15 ml) at 0 °C. The resultant mixture was allowed to slowly warm to room temperature and stirred overnight. The reaction was quenched with water (15 ml) and diluted with ethyl acetate (150 ml). The organic phase was separated and washed with brine. The combined aqueous phase was back extracted with ethyl acetate (50 ml). The combined organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (hexanes/ethyl acetate, 7:1) to provide the title compound (2.4 g).

MS (ESP): 190.2 (M- tBu) for $C_{11}H_{19}NO_3S$

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.43 (s, 9H); 2.02 (s, 3H); 2.23 (dt, 1H); 2.95 (m, 1H); 3.20-3.40 (m, 2H); 3.65 (m, 1H); 3.90-4.20 (m, 2H).

Intermediate 184

Cis(±)-*tert*-butyl-4-amino-3-(methylthio)piperidine-1-carboxylate

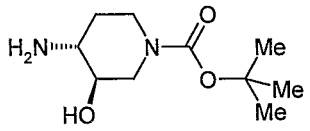
Sodium cyanoborohydride (344 mg, 5.48 mmol) was added to a solution of *tert*-butyl 3-(methylthio)-4-oxopiperidine-1-carboxylate (Intermediate 183, 1.07 g, 4.40 mmol), ammonium acetate (3.24 g, 42 mmol) and methanol (15 ml). The resultant mixture was stirred for 4 h. The reaction was quenched by addition of 1N HCl (3 ml). Aqueous sodium bicarbonate (saturated, 50 ml) was added slowly to the reaction mixture followed by

extraction with ethyl acetate (3 x 75 ml). The combined organic phase was dried over sodium sulfate, filtered and concentrated under reduced pressure to yield the crude amine.
MS (ESP): 247.3 (M+H) for $C_{11}H_{22}N_2O_2S$.

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Intermediate 185

Trans(±)*tert*-butyl 4-amino-3-hydroxypiperidine-1-carboxylate



The title compound was prepared as described in Marquis R.W. et al. *J. Med. Chem.* 1998, 41,3563-3567 and / or WO 9805336. MS (ES) MH^+:217 for $C_{10}H_{20}N_2O_3$; NMR: 1.45 (s, 9H), 1.80 (m, 1H), 1.95 (m, 1H), 2.21 (m, 1H), 2.62 (m, 1H), 2.75 (m, 1H), 3.28 (m, 1H), 3.47 (m, 1H), 3.81 (m, 1H), 4.11 (m, 1H), 4.28 (m, 1H), 8.20 (m, 1H)

Intermediate 186

Ethyl 3-chloro-5-methyl-1H-pyrrole-2-carboxylate

The compound was prepared by the procedure described for Intermediate 2.
MS (ESP): 188 (MH^+) for $C_8H_{10}ClNO_2$
^{1}H-NMR ($CDCl_3$) δ: 1.37 (t, 3H); 2.26 (s, 3H); 4.32 (q, 2H); 5.96 (s, 1H); 8.81 (br, 1H).

Intermediate 187

Ethyl 4-bromo-5-methyl-1H-pyrrole-2-carboxylate

The compound was prepared by the procedure described for Intermediate 2.

MS (ESP): 234 (MH^+) for $C_8H_{10}BrNO_2$

^{1}H-NMR δ: 1.27 (t, 3H); 2.17 (s, 3H); 4.22 (q, 2H); 6.74 (s, 1H); 12.10 (s, br, 1H).

Intermediate 188

4 Ethyl 4-bromo-3-chloro-5-methyl-1H-pyrrole-2-carboxylate

Ethyl 4-bromo-5-methyl-1H-pyrrole-2-carboxylate (Intermediate 187, 2.87g, 12.4mmol) was dissolved in dry DMF (30ml), N-chlorosuccinimide(1.66g, 12.4mmol) was added and resulting mixture was stirred at room temperature over night, more N-chlorosuccinimide (0.83g, 6.2mmol) was added and the reaction temperature was increased to

35oC, stirred for 4 hours. The mixture was poured into cold sodium hydroxide aqueous solution (2M) (50ml), extracted with diethyl ether (2x50ml). The organic phase was then washed with water (20ml) and brine (20ml), dried over anhydrous sodium sulfate and purified by column chromatography(hexanes/ethyl acetate, gradient) to give the desired product as a white crystal.(1.2g).

MS (ESP): 268 (MH^+) for $C_8H_9BrClNO_2$

^{1}H-NMR ($CDCl_3$) δ: 1.38 (t, 3H); 2.30 (s, 3H); 4.34 (q, 2H); 9.0 (br, 1H)

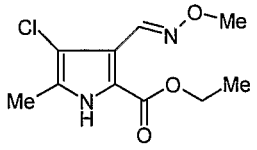
Intermediate 189

ethyl 4-chloro-3,5-dimethyl-1*H*-pyrrole-2-carboxylate

N-Chlorosuccinimide (1.77 g, 13.25 mmol) was added to a solution of ethyl 3,5-dimethyl-2-pyrrole carboxylate (2.11 g, 12.62 mmol) in chloroform (45 mL). The reaction mixture was stirred at room temperature for 24 h and then poured into 2 N NaOH. The organic layer was washed with water and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a crude solid. The crude solid was dissolved in hot MeOH, cooled to room temperature, and the precipitate was collected by filtration (493 mg, 19%). MS (ES) MH^+: 174 for $C_9H_{12}ClNO_2$.

Intermediate 190

ethyl 4-chloro-3-[(*E*)-(methoxyimino)methyl]-5-methyl-1*H*-pyrrole-2-carboxylate



A solution of Intermediate 191 (300 mg, 1.39 mmol) in MeOH (5 mL) and pyridine (1.5 mL) with methylamine hydrochloride (255 mg, 3.06 mmol) was heated to 60 °C overnight. The reaction was cooled to room temperature and then partitioned between methylene chloride and 10% HCl. The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure to give an off-white solid.

MS (ES) MH^+: 245 for $C_{10}H_{13}ClN_2O_3$;

NMR (DMSO-d_6): 1.29 (t, 3H), 2.36 (s, 3H), 3.83 (s, 3H), 4.27 (q, 2H), 8.03 (s, 1H), 12.31 (s, 1H).

Intermediate 191

ethyl 4-chloro-3-formyl-5-methyl-1*H*-pyrrole-2-carboxylate

$POCl_3$ in 1,2-dichloroethane (14 mL) was slowly added to a solution of DMF (4.37 mL, 59.79 mmol) in 1,2-dichloroethane (10 mL). The reaction mixture was stirred for 15 min and then Intermediate 7 (2.04 g, 10.87 mmol) was added. The reaction mixture was heated at reflux for 3 h and then cooled to room temperature. The reaction mixture was treated with sodium acetate (10 g) in water (25 mL) and stirred for 1 h. The mixture was extracted with methylene chloride, wshed with water, dried over sodium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 2:1 hexanes/ethyl acetate) gave the desired compound (720 mg).
MS (ES) MH^+: 216 for $C_9H_{10}ClNO_3$.

Intermediate 192

ethyl 3-bromo-4-chloro-5-methyl-1*H*-pyrrole-2-carboxylate

Bromine (0.56 ml, 11 mmol) was added to a solution of 1 g (5.3 mmol) of ethyl 4-chloro-5-methyl-1*H*-pyrrole-2-carboxylate (Intermediate 7) and 0.8 ml (5.7 mmol) Et_3N in CH_2Cl_2. After stirring at room temperature for 2 h, aqueous $NaHSO_3$ was added and the CH_2Cl_2 was removed and the aqueous residue was partitioned between water and EtOAc. The EtOAc was separated and washed with brine. Drying ($MgSO_4$) and removal of solvent gave 1.5 g of product as a solid. MS (ES) (MH^+): 240 for $C_8H_9BrClNO_2$; NMR (d_6-DMSO): 1.3 (t, 3H), 2.2 (s, 3H), 4.2 (q, 2H), 12.3 (s, 1H).

Intermediate 193

ethyl 4-chloro-3-cyano-5-methyl-1*H*-pyrrole-2-carboxylate

Nitrogen gas was bubbled through a mixture of 1.4 g (5.25 mmol) of ethyl 3-bromo-4-chloro-5-methyl-1*H*-pyrrole-2-carboxylate (Intermediate 192), 470 g (4 mol) $Zn(CN)_2$, 250 mg (0.26 mmol) $Pd_2(dba)_3$ and 302 mg (0.26 mmol) dppf in 15 ml DMF for 15 min. The mixture was heated at 130 °C for 1 h. Additional $Zn(CN)_2$ (1 g), $Pd_2(dba)_3$ (500 mg) and dppf (604 mg) were added. After bubbling through N_2 for 15 min and heating at 130 °C for 2 h, additional $Zn(CN)_2$ (0.5 g), $Pd_2(dba)_3$ (250 mg) and dppf (302 mg) were added. Heating was continued at 130 °C for 2h. Solvent was removed and the residue was partitioned between EtOAc and water. The EtOAc was separated and washed with brine. Combined aqueous layers were extracted again with EtOAc, which was washed with brine. Combined EtOAc

extracts were dried ($MgSO_4$) and concentrated. The residue was purified by silica gel chromatography (100% CH_2Cl_2 followed by gradient elution to 5% MeOH in CH_2Cl_2) to afford 750 mg of product as a solid. MS (ES) (MH^+): 213 for $C_9H_9ClN_2O_2$; NMR (d_6-DMSO): 1.3 (t, 3H), 2.2 (s, 3H), 4.3 (q, 2H), 13.1 (s, 1H).

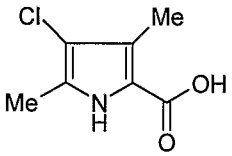
Intermediate 194

ethyl 3,5-dichloro-4-methyl-1*H*-pyrrole-2-carboxylate

Et_3N (5.5 ml, 39 mmol) was added slowly to a solution of 2.0 g (13 mmol) of ethyl 4-methyl-1*H*-pyrrole-2-carboxylate and 3.1 ml SO_2Cl_2 in 30 ml CH_2Cl_2 cooled in an ice water bath. The mixture was warmed to room temperature with stirring overnight. After treatment with aqueous $NaHSO_3$, the CH_2Cl_2 was removed and the aqueous residue was diluted with water and extracted twice with EtOAc. The EtOAc extracts were washed with brine, dried ($MgSO_4$) and concentrated. The solid residue was twice recrystallized from 50% aqueous EtOH to afford 1.38 g of product as a white solid. MS (ES) ($M-H^-$): 222 for $C_8H_9Cl_2NO_2$; NMR (d_6-DMSO): 1.3 (t, 3H), 1.9 (s, 3H), 4.25 (q, 2H), 12.8 (s, 1H).

Intermediate 195

4-chloro-3,5-dimethyl-1*H*-pyrrole-2-carboxylic acid



Prepared using the procedure described for Intermediate 1 using Intermediate 189 as the starting material.

MS (ES) MH^+: 174 for $C_7H_8ClNO_2$

Intermediate 196

3-chloro-5-methyl-1H-pyrrole-2-carboxylic acid

Prepared using the procedure described for Intermediate 1 using Intermediate 186 as the starting material.

MS (ESP): 160 (MH^+) for $C_6H_6ClNO_2$

^{1}H-NMR ($CDCl_3$) δ: 2.29 (s, 3H); 6.02 (s, 1H); 8.83 (br, 1H).

Intermediate 197

4-bromo-5-methyl-1H-pyrrole-2-carboxylic acid

Prepared by the procedure described for Intermediate 1 using Intermediate 187 as the starting material.

MS (ESP): 206 (MH^+) for $C_6H_6BrNO_2$

NMR ($CDCl_3$) δ: 2.31 (s, 3H); 6.97 (s, 1H); 9.08 (s, br, 1H).

Intermediate 198

4-bromo-3-chloro-5-methyl-1H-pyrrole-2-carboxylic acid

Prepared using the procedure described for Intermediate 1 and Intermediate 188. MS (ESP): 240 (MH^+) for $C_6H_5BrClNO_2$

Intermediate 199

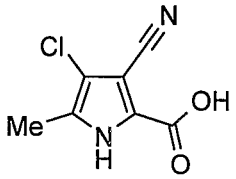
4-chloro-3-[(*E*)-(methoxyimino)methyl]-5-methyl-1*H*-pyrrole-2-carboxylic acid

Synthesized as described for Intermediate 1 from Intermediate 190.

MS (ES) MH^+: 217 for $C_9H_9ClN_2O_3$.

Intermediate 200

4-chloro-3-cyano-5-methyl-1*H*-pyrrole-2-carboxylic acid



A solution of 670 mg (3.2 mmol) of ethyl 4-chloro-3-cyano-5-methyl-1*H*-pyrrole-2-carboxylate (Intermediate 193) and 3.2 ml (3.2 mmol) 1N NaOH in 20 ml MeOH was heated at 100 °C in a microwave reactor for 2 h. The mixture was diluted with water and extracted with EtOAc. The EtOAc was washed with 1N NaOH. The combined aqueous layers were acidified with concentrated HCl and extracted 2 times with EtOAc, each extract being washed with brine. Drying ($MgSO_4$) and removal of solvent gave 535 mg of product as a solid. MS (ES) ($M-H^-$): 183 for $C_7H_5ClN_2O_2$; NMR (d_6-DMSO): 2.2 (s, 3H), 12.9 (s, 1H), 13.3 (s, 1H).

Intermediate 201

3,5-dichloro-4-methyl-1*H*-pyrrole-2-carboxylic acid

A solution of 1.1 gm (4.95 mmol) of ethyl 3,5-dichloro-4-methyl-1*H*-pyrrole-2-carboxylate (Intermediate 194) and 1.7 g (9.9 mmol) of $Ba(OH)_2$ in 50 ml 1:1 EtOH-H_2O was

heated at 85 °C for 9 h. The mixture was diluted with water, acidified with 20 ml 1N HCl and extracted 3 times with ether. The ether was washed with water, dried ($MgSO_4$) and concentrated to give 1.0 g of product as a solid. MS (ES) ($M-H^-$): 194 for $C_6H_5Cl_2NO_2$; NMR (d_6-DMSO): 1.9 (s, 3H), 12.7 (s, 1H), 12.8 (s, 1H).

Intermediate 202

3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl chloride

A solution of 10.4 g (54 mmol) of 3,4-Dichloro-5-methyl-1*H*-pyrrole-2-carboxylic acid (Intermediate 1) in 100 ml $SOCl_2$ was heated at reflux for 30 min. Solvent was removed to afford product. NMR ($CDCl_3$): 2.3 (s, 1H), 8.8 (s, 1H).

Intermediate 203

2,2,2-trichloro-1-(4,5-dichloro-1*H*-pyrrol-2-yl)ethanone

To a solution of 2,2,2-trichloro-1-(1*H*-pyrrol-2-yl)ethanone (1.00g, 47.06 mmol) in dichloromethane (8 mL), sulfuryl chloride (1.60 mL, 0.188 mol) was added slowly at room temperature. The reaction was stirred overnight and quenched with water and extracted with dichloromethane. The extract was washed with saturated sodium bicarbonate, water and brine. Then it was dried over magnesium sulfate and concentrated to give the desired product as a white solid (0.90 g).

MS (ES) M^-: 279 for $C_6H_2NCl_5O$

Intermediate 204

ethyl 2-bromo[1,3]thiazolo[4,5-*b*]pyridine-7-carboxylate

To a 0 °C mixture of $CuBr_2$ (229 mg, 1.02 mmol) in acetonitrile (3 mL) was slowly added t-Butyl nitrite (0.15 mL, 1.28 mmol). The reaction mixture was stirred for 15 min and then added Intermediate 205 (250 mg, 0.85 mmol). The reaction mixture was stirred for 2 h, partitioned between diethyl ether and water, and filtered through diatomaceous earth. The organic layer was washed with water and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:1 hexanes/ethyl acetate) gave the desired product (38 mg, 16%).

MS (ES) MH^+: 174 for $C_9H_7BrN_2O_2S$.

Intermediate 205

ethyl 2-amino[1,3]thiazolo[4,5-*b*]pyridine-7-carboxylate

To a solution of Intermediate 206 (944 mg, 4.20 mmol) in acetic acid (12 mL) was added benzyltrimethyl ammonium tribromide (1.67 g, 4.28 mmol). The reaction mixture was stirred at room temperature for 2 h and the solid that formed was collected by filtration to provide the desired compound as the acetic acid salt (1.20 g).

MS (ES) MH^+: 224 for $C_9H_9N_3O_2S$.

Intermediate 206

ethyl 2-[(aminocarbonothioyl)amino]isonicotinate

A solution of Intermediate 207 (2.10 g, 6.38 mmol) in ethanol (20 mL) and potassium carbonate (882 mg, 6.38 mmol) was heated to 80 °C for 2 h. The reaction mixture was cooled to room temperature and the solid that formed was collected by filtration to give the desired compound.

MS (ES) MH^+: 226 for $C_9H_{11}N_3O_2S$;

NMR (DMSO-d_6): 1.17 (t, 3H), 4.18 (q, 2H), 7.29 (m, 1H), 7.59 (s, 1H), 8.25 (m, 1H), 8.87 (s, 1H), 10.24 (s, 1H), 10.63 (s, 1H).

Intermediate 207

ethyl 2-{[(benzoylamino)carbonothioyl]amino}isonicotinate

To a 0 °C solution of benzyl isothiocyanate (1.25 mL, 9.27 mmol) in acetone (15 mL) was slowly added ethyl 2-aminoisonicotinate (1.4 g, 8.43 mmol). The reaction mixture was stirred for 1 h and then poured onto ice. The solid that formed was collected by filtration and washed with water to give the desired product (2.10 g).

MS (ES) MH^+: 330 for $C_{16}H_{15}N_3O_3S$.

Intermediate 208

2-chloro-5-nitroisonicotinic acid

A solution of 13.7 g (46 mmol) of $Na_2Cr_2O_3$ in 100 ml concentrated H_2SO_4 was added slowly to a solution of 3.0 g (17.4 mmol) of 2-chloro-4-methyl-5-nitropyridine dissolved in 100 ml concentrated H_2SO_4 while cooling in ice water. Allowed to warm to room temperature and stir overnight. The solution was poured onto 600 ml ice and extracted twice with EtOAc,

each extract being washed with brine. The combined organic extracts were dried ($MgSO_4$) and concentrated to afford product as a gummy oil. MS (ES) MH^+: 203 for $C_6H_3ClN_2O_4$.

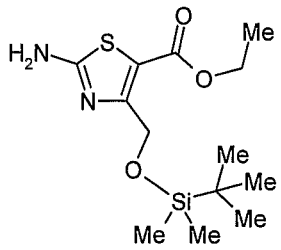
Intermediate 209

ethyl 2-amino-4-(hydroxymethyl)-1,3-thiazole-5-carboxylate

A solution of 5.0 g (37 mmol) of 3-chlorofuran-2,4(3*H*,5*H*)-dione and 3.3 g (43 mmol) of thiourea in 50 ml EtOH was heated at reflux for 4 h. Solvent was removed and the residue was dissolved in water with 1N HCl added. The aqueous solution was basified with aqueous Na_2CO_3. Thick solids that formed were filtered, rinsed with water and dried in vacuo. NMR: 1.2 (t, 3H), 4.2 (q, 2H), 4.6 (s, 2H), 4.9 (s, broad, 1H), 7.8 (s, 2H).

Intermediate 210

ethyl 2-amino-4-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-1,3-thiazole-5-carboxylate



To a solution of 2.0 g (9.8 mmol) of ethyl 2-amino-4-(hydroxymethyl)-1,3-thiazole-5-carboxylate (Intermediate 209) and 1.3 g (19.4 mmol) of imidazole in 20 ml DMF was added 1.6 g (10.6 mmol) of *t*-butyldimethylsilyl chloride. After stirring for 2 h, solvent was removed and the residue was taken up in water. Insoluble solids were collected, ground up, washed with water and dried in vacuo to afford 2.95 g of product. MS (ES) (MH^+): 317 for $C_{13}H_{24}N_2O_3SSi$; NMR (d_6-DMSO): 0.03 (s, 6H), 0.86 (s, 9H), 1.2 (t, 3H), 4.1 (q, 2H), 4.8 (s, 2H), 7.8 (s, 2H).

Intermediate 211

ethyl 4-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-2-chloro-1,3-thiazole-5-carboxylate

t-Butylnitrite (1.8 ml (14 mmol) was added slowly to a mixture of 2.9 g (9.2 mmol) of ethyl 2-amino-4-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-1,3-thiazole-5-carboxylate (Intermediate 210) and 1.95 g (14 mmol) $CuCl_2$ in CH_3CN. After stirring at room temperature for 2 h, solvent was removed and the residue was taken up in EtOAc, which was washed 2 times with 1NHCl and once with brine. Drying ($MgSO_4$) and removal of solvent gave 2.95 g

of product as an oil. NMR ($CDCl_3$): 0.1 (s, 6H), 0.9 (s, 9H), 1.35 (t, 3H), 4.3 (q, 2H), 5.0 (s, 2H).

Intermediates 212

The following Intermediates were synthesized by an analogous method to Intermediate 211 from the starting materials (SM) given in the table below

Int	Compound	Data	SM
212	ethyl 4-acetyl-2-chloro-1,3-thiazole-5-carboxylate	NMR ($CDCl_3$): 2.6 (s, 3H), 3.9 (s, 3H)	Intermediate 222

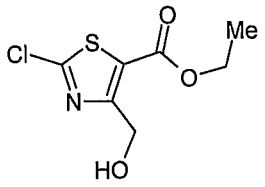
Intermediate 214

methyl 2-chloro-4-(1-hydroxy-1-methylethyl)-1,3-thiazole-5-carboxylate

A solution of 5.6 ml (11.2 mmol) 2N $AlMe_3$ in toluene was added to a dry ice-acetone bath of 1.14 g (5.2 mol) of methyl 4-acetyl-2-chloro-1,3-thiazole-5-carboxylate (Intermediate 212) in 20 ml dry CH_2Cl_2. The mixture was allowed to warm to room temperature slowly before being quenched with MeOH. After stirring at room temperature overnight, the mixture was diluted with 1N HCl and stirred 15 min before being diluted with water and extracted twice with EtOAc. The EtOAc was washed with brine, dried ($MgSO_4$) and concentrated to give an oil that was purified by chromatography (50% hexanes in CH_2Cl_2 with gradient elution to 100% CH_2Cl_2) affording 720 mg of product as an oil. NMR ($CDCl_3$): 1.5 (s, 6H), 3.8 (s, 3H), 5.7 (s, broad, 1H).

Intermediate 215

ethyl 2-chloro-4-(hydroxymethyl)-1,3-thiazole-5-carboxylate



A solution of 17.7 g (53 mmol) of ethyl 4-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-2-chloro-1,3-thiazole-5-carboxylate (Intermediate 211) and 53 ml (53 mmol) of 1N HCl in dioxane was stirred at room temperature for 1 h. The mixture was extracted 3 times with EtOAc, which was dried ($MgSO_4$) and concentrated to give 11.3 g of an orange oil.

Purification by silica gel chromatography affords a solid. NMR ($CDCl_3$): 1.2 (t, 3H), 3.1 (s, broad, 1H), 4.2 (q, 2H), 4.8 (s, 2H).

Intermediate 216

4-{[4-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-2-chloro-1,3-thiazol-5-yl]carbonyl}morpholine

A solution of 2N Me_3Al in hexanes (0.91 ml, 1.82 mmol) was added slowly to a solution of 0.16 ml (1.8 mmol) of morpholine in 4 ml CH_2Cl_2. After stirring for 15 min, a solution of 0.5 g (1.5 mmol) of ethyl 4-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-2-chloro-1,3-thiazole-5-carboxylate (Intermediate 218) in 4 ml CH_2Cl_2 was added. The solution was heated at 80 °C in a microwave reactor for 1 hour before pouring into dilute aqueous HCl. The mixture was extracted 3 times with CH_2Cl_2, which was washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by silica gel chromatography (100% CH_2Cl_2 followed by gradient elution to 30% EtOAc in CH_2Cl_2 to give 315 mg of product. MS (ES) (MH^+): 377 for $C_{15}H_{25}ClN_2O_3SSi$; NMR (d_6-DMSO): 0.1 (s, 6H), 0.9 (s, 9H), 3.6 (m, 4H), 3.7 (m, 4H), 4.1 (q, 2H), 4.75 (s, 2H).

The following Examples were synthesized by an analogous method to Intermediate 216 from the starting materials (SM) given in the table below.

Int	Compound	Data	SM
217	4-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-2-chloro-*N*-(1-methyl-1-phenylethyl)-1,3-thiazole-5-carboxamide	NMR (d_6-DMSO): 0.04 (s, 6H), 0.8 (s, 9H), 1.6 (s, 6H), 4.9 (s, 2H), 7.2 (7, 1H), 7.3 (t, 2H), 7.4 (d, 2H), 8.6 (s, 1H).	Intermediate 211 and cumylamine

Intermediate 218

2-chloro-5-(morpholin-4-ylcarbonyl)-1,3-thiazole-4-carboxylic acid

A solution of 173 mg (1.7 mmol) CrO_3 in 1 ml of 4:1 water/H_2SO_4 was added to as solution of 310 mg (0.82 mmol) of 4-{[4-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-2-chloro-1,3-thiazol-5-yl]carbonyl}morpholine (Intermediate 216) in 3 ml acetone cooled in an ice water bath. The mixture was stirred with warming room temperature over 90 min. A few drops of isopropanol were added, and the mixture was diluted with water and extracted 2 times with EtOAc. The EtOAc extracts were washed with brine, dried ($MgSO_4$) and

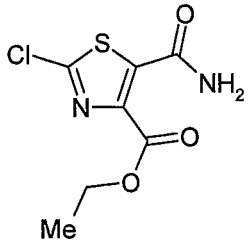
concentrated to give 190 mg of a white solid. MS (ES) (MH^+): 277 for $C_9H_9ClN_2O_4S$; NMR (d_6-DMSO): 3.3 (m, 4H), 3.6 (m, 4H), 13.7 (s, 1H).

The following Examples were synthesized by an analogous method to Intermediate 218 from the starting materials (SM) given in the table below.

Int	Compound	Data	SM
219	2-chloro-5-{[(1-methyl-1-phenylethyl)amino] carbonyl}-1,3-thiazole-4-carboxylic acid	MS (ES) ($M-H^-$): 323 for $C_{14}H_{13}ClN_2O_2S$	Intermediate 217

Intermediate 220

ethyl 5-(aminocarbonyl)-2-chloro-1,3-thiazole-4-carboxylate



A solution of 210 mg of ethyl 2-chloro-5-{[(1-methyl-1-phenylethyl)amino]carbonyl}-1,3-thiazole-4-carboxylate (Intermediate 233) in 5 ml TFA was stirred at room temperature overnight. Solvent was removed and the residue was dissolved in 5 ml MeOH. Solvent was again removed and the residue was triturated with ether to give 57 mg of a white solid. NMR (d_6-DMSO): 1.3 (t, 3H), 4.3 (q, 2H), 8.2 (s, 1H), 8.8 (s, 1H).

Intermediate 221

methyl 2-chloro-4,4-dimethoxy-3-oxopentanoate

SO_2Cl_2 (2.2 ml, 27 mmol) was added slowly to a solution of 5.0 g (26 mmol) of methyl 4,4-dimethoxy-3-oxopentanoate in 30 ml CH_2Cl_2 cooled in an ice water bath. The solution was warmed to room temperature and stirred for 1 h. Solvent was removed and the residue was taken up in EtOAc, which was washed with water and brine. Drying ($MgSO_4$) and removal of solvent gave 6.1 g of an oil. NMR: ($CDCl_3$): 1.5 (s, 3H), 3.25 (2s, 6H), 4.8 (s, 3H), 5.3 (s, 1H).

Intermediate 222

methyl 4-acetyl-2-amino-1,3-thiazole-5-carboxylate

A solution of 4.37 g (19 mmol) methyl 2-chloro-4,4-dimethoxy-3-oxopentanoate (Intermediate 221) and 1.8 g (24 mmol) thiourea in 50 ml EtOH was heated at reflux for 3 h. Solvent was removed and the residue was dissolved in 1:1 acetone-5N HCl and the solution was heated at reflux for 4 h. Acetone was removed and the aqueous residue was neutralized with 50% NaOH and then basified with aqueous Na_2CO_3. Precipitated solids were filtered, washed with water and dried in vacuo. NMR (d_6-DMSO): 2.4 (s, 3H), 3.7 (s, 3H), 8.0 (s, 2H).

Intermediate 223

isopropyl 4-chloropyridine-2-carboxylate 1-oxide

A solution of 2.55 g (14 mmol) of isopropyl 4-chloropyridine-2-carboxylate (Intermediate 232) and 1.4 g (26 mmol) of *m*-CPBA in 30 ml CH_2Cl_2 was stirred at room temperature for 2 d. The mixture was quenched with aqueous $NaHSO_3$ and CH_2Cl_2 was removed. The aqueous residue was basified with aqueous Na_2CO_3, saturated with NaCl and extracted repeatedly with EtOAc. The EtOAc was dried ($MgSO_4$) and concentrated. The residue was taken up in ether and insoluble material was filtered off. The filtrate was concentrated and the residue was chromatographed on silica gel (100% CH_2Cl_2 with gradient elution to 100% EtOAc) to afford 2.1 g of product as an oil. NMR (d_6-DMSO): 1.3 (d, 6H), 5.3 (septet, 1H), 7.25 (m, 1H), 7.5 (d, 1H), 8.1 (d, 1H).

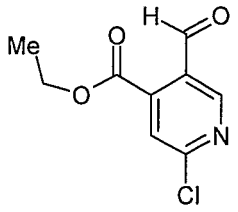
Intermediate 224

isopropyl 4-chloro-6-cyanopyridine-2-carboxylate

A solution of 200 mg (0.86 mmol) of isopropyl 4-chloropyridine-2-carboxylate 1-oxide (Intermediate 223), 0.14 ml (1 mmol) Et_3N and 0.36 ml (2.7 mmol) of trimethylsilylcyanide in 3 ml CH_3CN was heated at 90 °C overnight. The solution was diluted with EtOAc and washed with water and brine. Drying ($MgSO_4$) and removal of solvent gave an oil that was purified by chromatography on silica gel (100% CH_2Cl_2 followed by gradient elution to 10% EtOAc in CH_2Cl_2) to afford 130 mg of product as a white solid. MS (ES) (MH^+): 224 for $C_{19}H_9ClN_2O_2$; NMR (d_6-DMSO): 1.35 (d, 6H), 5.2 (septet, 1H), 8.4 (s, 1H), 8.6 (s, 1H).

Intermediate 225

ethyl 2-chloro-5-formylisonicotinate



A solution of 51 ml (128 mmol) of 2.5 N *n*-butyllithium in hexanes was added slowly to a THF solution of 16 ml (95 mmol) of tetramethylpiperidine cooled in a dry ice-acetone bath. The solution was warmed to –30 °C and cooled to –60 °C before 5.0 g (32 mmol) of 6-chloronicotinic acid was added portion wise. The mixture was warmed to –25 °C and stirred for 30 min. It was then cooled to –70 °C and 10 ml (129 mmol) DMF was added quickly. After quenching with 1N HCl, the solution was warmed to room temperature. The pH was brought to about 4 with additional 1N HCl and the solution was continuously extracted with EtOAc overnight. The EtOAc was dried ($MgSO_4$) and concentrated. The residue was dissolved in 100 ml EtOH and 2 ml concentrated H_2SO_4 was added. The solution was heated at reflux for 24 h. The mixture was brought to about pH = 4 with 50% NaOH and was extracted twice with ether. The ether was dried ($MgSO_4$) and concentrated to gave an oil that was chromatographed on silica gel (50% hexanes in CH_2Cl_2 with gradient elution to 100% CH_2Cl_2) to afford 1 g of product as an oil that slowly solidified. NMR ($CDCl_3$): 1.4 (t, 3H), 4.5 (q, 2H), 7.7 (s, 1H), 9.1 (s, 1H), 10.7 (s, 1H).

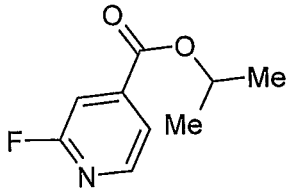
Intermediate 226

ethyl 2-chloro-5-nitroisonicotinate

A mixture of 2-chloro-5-nitroisonicotinic acid (Intermediate 208) and 16 ml triethylorthoacetate in 100 ml toluene was heated at reflux for 2 h. The mixture as stirred with 1N HCl for 30 min before being partitioned between EtOAc and water. The EtOAc was separated, washed with water and brine, dried ($MgSO_4$) and concentrated. Chromatographed on silica gel (100% hexanes with gradient elution to 100% CH_2Cl_2 to give product as an oil. MS (ES) (MH^+): 231 for $C_8H_7ClN_2O_4$; NMR (d_6-DMSO): 1.3 (t, 3H), 4.4 (m, 2H), 8.1 (s, 1H), 9.2 (s, 1H).

Intermediates 227-233

The following compounds were prepared in a manner analogous to Intermediate 226 from the starting material (SM) indicated.

Int	Compound	Data	SM
227	isopropyl 2-chloro-6-methylisonicotinate	MS (ES) (MH^+): 214 for $C_{10}H_{12}ClNO_2$; NMR (d_6-DMSO): 1.3 (d, 6H), 2.55 (s, 3H), 5.2 (septet, 1H), 7.65 (s, 1H), 7.7 (s, 1H)	2-chloro-6-methylisonicotinate and trisopropylorthoformate
228	isopropyl 4-chloropyridine-2-carboxylate	NMR ($CDCl_3$): 1.35 (d, 6H), 5.3 (septet, 1H), 7.4 (dd, 1H), 8.05 (d, 1H), 8.6 (d, 1H)	4-chloropyridine-2-carboxylate and trisopropylorthoformate
229	isopropyl 4,5-dichloropyridine-2-carboxylate	NMR ($CDCl_3$): 1.35 (d, 6H), 5.3 (septet, 1H), 8.1 (s, 1H), 8.7 (s, 1H)	4,5-dichloropyridine-2-carboxylate (Graf, R. *J. fuer Prakt. Chem. (Leipzig)* (1932), 133 36-50) and trisopropylorthoformate
230	isopropyl 2-fluoroisonicotinate 	NMR ($CDCl_3$): 1.4 (d, 6H), 5.3 (septet, 3H), 7.5 (m, 1H), 7.7 (m, 1H), 8.35 (d, 1H)	2-fluoroisonicotinic acid and trisopropylorthoformate
231	ethyl 2-chloro-5-(morpholin-4-ylcarbonyl)-1,3-thiazole-4-carboxylate	NMR: 1.3 (t, 3H), 3.3 (m, 2H), 3.5 (m, 2H), 3.6 (m, 2H), 3.65 (m 2H), 4.3 (q, 2H)	Intermediate 218 and triethylorthoacetate
232	isopropyl 4-chloropyridine-2-carboxylate	NMR ($CDCl_3$): 1.35 (d, 6H), 5.3 (septet, 1H), 7.4 (dd, 1H), 8.05 (d, 1H), 8.6 (d, 1H)	4-chloropyridine-2-carboxylic acid and trisopropylorthoformate
233	ethyl 2-chloro-5-{[(1-methyl-1-phenylethyl)amino]carbonyl}-1,3-thiazole-4-carboxylate	MS (ES) (MH^+): 353 for $C_{16}H_{17}ClN_2O_2S$	Intermediate 219 and triethylorthoacetate

Intermediate 234

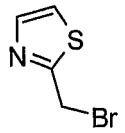
1,3-thiazol-2-ylmethanol

To a stirred solution of commercially available 1,3-thiazole-2-carbaldehyde (5.36 g, 47 mmol) in dry methanol (100 mL), at 0 °C and under an atmosphere of N_2, was added sodium borohydride (2.15 g, 57 mmol) as a solid over approximately 20 minutes. The reaction was stirred for an hour at ambient temperature, under an atmosphere of N_2. Complete conversion was suggested by TLC (50% ethyl acetate in hexanes; Rf ~ 0.23). The reaction was concentrated under vacuum. To the residue was added 15 mL of an aqueous solution of ammonium chloride, and 15 mL of an aqueous solution of sodium chloride; from this mixture was extracted the crude product with ethyl acetate (4 X 50 mL). The organic layers were combined, dried over magnesium sulfate, and concentrated. The crude material was used without further purification.

MS (ES) MH^+: 116 for C_4H_5NOS. ^1H NMR (DMSO): 4.72 (d, 2H), 6.03 (t, 1H), 7.61 (d, 1H), 7.71 (d, 1H).

Intermediate 235

2-(bromomethyl)-1,3-thiazole



This compound was synthesized from Intermediate 234 above, using the procedure described in Tetrahedron *61* (2005), p. 137. The crude material was purified by column chromatography (silica gel, 15% ethyl acetate in hexanes). A pale orange liquid (57% yield) was obtained; this material decomposed rapidly, and was used immediately in the next step. MS (ES) MH^+: 179 for C_4H_4BrNS. ^1H NMR ($CDCl_3$): 4.75 (s, 2H), 7.37 (d, 1H), 7.74 (d, 1H).

Intermediate 236

Ethyl 2-chloro-4-methyl-1,3-thiazole-5-carboxylate

Syntheisized according to the procedure described for Intermediate 17. MS (ES) MH^+: 206, 208 for $C_7H_8ClNO_2S$; ^1H-NMR (300 MHz; DMSO-d_6) δ: 1.28 (t, 3H); 2.60 (s, 3H); 4.28 (q, 2 H).

Intermediate 237

1-*tert*-butyl 3-methyl 4-hydroxy-5,6-dihydropyridine-1,3(2*H*)-dicarboxylate

Methyl 4-oxopiperidine-3-carboxylate hydrochloride (13.0 g) was suspended in anhydrous DCM (100 mL) under an argon atmosphere. DIEA (29.2 mL) was added slowly via syringe, producing a slightly cloudy solution. The reaction was cooled to 0°C, and di-*tert*-butyl dicarboxylate (16.1 g) was added, resulting in an exothermic reaction. The reaction mixture was left stirring overnight , slowly warming to room temperature. The reaction mixture was then concentrated *in vacuo* and partitioned between EtOAc (500 mL) and saturated aqueous NH_4Cl (350 mL). The EtOAc layer was washed with brine (125 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*, producing a yellow oil. The product was purified by silica gel chromatography (1-25% EtOAc in hexanes), producing the title compound as a clear, colourless oil (14.7 g, 85.1%). MS (ES)[$(M-H)^-$]: 256 for $C_{12}H_{19}NO_5$; NMR ($CDCl_3$): 1.46 (s, 9H), 2.36 (t, 2H), 3.55 (t, 2H), 3.76 (s, 3H) 4.04 (s, 2H), 11.97 (s, 1H).

Intermediate 238

Ethyl 4-azido-3-hydroxypiperidine-1-carboxylate

Ethyl 4-bromo-3-hydroxypiperidine-1-carboxylate (Preparation: Izamanishi, T. et al; 1982, Chem. Pharm. Bull., 30: 3617-3623) (5.1 g) was dissolved in anhydrous DMF (20 mL) under an argon atmosphere, followed by the addition of 18-crown-6 (0.27 g) and sodium azide (2.89 g). The reaction was heated at 90°C for twenty-three hours, then stirred overnight, slowly cooling to room temperature. The reaction was then added to deionised water (150 mL) to quench it, saturated with solid sodium chloride, and extracted with EtOAc (2 x 200 mL). The combined EtOAc layers were washed with brine (100 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*, yielding the title compound (4.3 g, 100%). MS (GC-EI)[$(M-N_2)^+$]: 186 for $C_8H_{14}BrN_4O_3$.

Intermediate 239

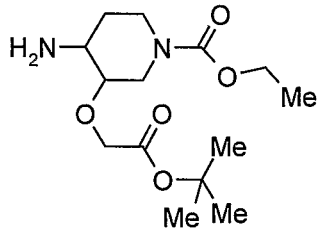
Ethyl 4-azido-3-(2-*tert*-butoxy-2-oxoethoxy)piperidine-1-carboxylate

Ethyl 4-azido-3-hydroxypiperidine-1-carboxylate (Intermediate 238, 1.71 g) was dissolved in anhydrous THF (15 mL) and cooled to 0°C. Sodium hydride (60% in mineral oil) (0.42 g) was added as a shot, stirred for twenty minutes at 0°C, followed by the slow addition of *tert*-butyl bromo acetate (0.86 mL) via syringe, and stirred for an additional two

hours at 0°C. The reaction was partitioned between EtOAc (250 mL) and saturated aqueous $NaHCO_3$ (200 mL), and the aqueous layer was washed with EtOAc (200 mL). The combined EtOAc layers were washed with brine (50 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*, yielding the title compound as a crude product (1.78 g, 103%). MS (GC-EI)[$(M-N_2)^+$]: 300 for $C_{14}H_{24}N_4O_5$.

Intermediate 240

Ethyl 4-amino-3-(2-*tert*-butoxy-2-oxoethoxy)piperidine-1-carboxylate



Ethyl 4-azido-3-(2-*tert*-butoxy-2-oxoethoxy)piperidine-1-carboxylate (Intermediate 239, 1.75 g) was dissolved in THF (60 mL), followed by the addition of deionised water (5 mL) and PS-triphenylphosphine resin (10.6 g), and stirred at room temperature over the week-end. The reaction mixture was filtered, and the resin was rinsed repeatedly with MeOH and a 1:5 MeOH:DCM mixture, and the filtrate was concentrated *in vacuo*, yielding the title compound (1.20 g, 75%). MS (GC-EI)[$(M)^+$]: 302 for $C_{14}H_{26}N_2O_5$.

Intermediate 241

Ethyl 4-bromo-3-{[*tert*-butyl(dimethyl)silyl]oxy}piperidine-1-carboxylate

Ethyl 4-bromo-3-hydroxypiperidine-1-carboxylate (Preparation: Izamanishi, T. et al; 1982, Chem. Pharm. Bull., 30: 3617-3623) (10.17 g) was dissolved in anhydrous DCM (100 mL) under an argon atmosphere and cooled to 0°C. *tert*-Butyldimethylsilyl trifluoromethylsulfonate (10.2 mL) was added dropwise via syringe, followed by 2,6-lutidine (4.7 mL), also added dropwise via syringe. The reaction was stirred overnight, slowly warming to room temperature, then diluted with DCM (200 mL) and washed with saturated aqueous $NaHCO_3$ (150 mL), saturated aqueous NH_4Cl ((150 mL), brine (100 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*, yielding the title compound as a crude product (15.1 g, 102%). MS (GC-EI)[$(M-C_4H_7)^+$]: 310, 312 for $C_{14}H_{28}BrNO_3Si$; NMR ($CDCl_3$): 0.10 (s, 3H), 0.12 (s, 3H), 0.88 (s, 9H), 1.24 (t, 3H), 1.87 (m, 1H), 2.34 (m, 1H), 2.84-3.40 (m, 2H), 3.69 (m, 2H), 3.93 (m, 2H), 4.13 (q, 2H).

Intermediate 242

Ethyl 4-azido-3-{[*tert*-butyl(dimethyl)silyl]oxy}piperidine-1-carboxylate

The title compound was prepared in a manner analogous to (Intermediate 238) starting with ethyl 4-bromo-3-{[*tert*-butyl(dimethyl)silyl]oxy}piperidine-1-carboxylate (Intermediate 241). MS (GC-EI)[$(M-N_2)^+$]: 300 for $C_{14}H_{28}N_4O_3Si$.

Intermediate 243

Ethyl 4-amino-3-{[*tert*-butyl(dimethyl)silyl]oxy}piperidine-1-carboxylate

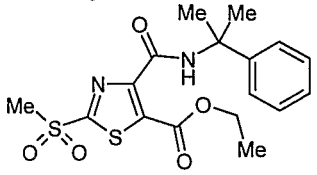
The title compound was prepared in a manner analogous to (Intermediate 240) starting with ethyl 4-azido-3-{[*tert*-butyl(dimethyl)silyl]oxy}piperidine-1-carboxylate (Intermediate 242). MS (GC-EI)[$(M)^+$]: 302 for $C_{14}H_{30}N_2O_3Si$.

Intermediate 244

3,4-dichloro-*N*-(3-hydroxypiperidin-4-yl)-5-methyl-1*H*-pyrrole-2-carboxamide

Ethyl 3-{[*tert*-butyl(dimethyl)silyl]oxy}-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidine-1-carboxylate (Intermediate 114, 0.805 g) was dissolved in a mixture of MeOH (10 mL) and 1,4-dioxane (15 mL), to which was added 1N NaOH (10 mL) and heated to reflux for twenty-four hours. An additional 5 mL of 1N NaOH was added, with 5 mL of 1,4-dioxane, and the reaction was heated for an additional forty-two hours, then cooled to 0°C and acidified to ~ pH 9 with 2N HCl (6 mL). The cold mixture was filtered and washed with deionised water, yielding the title compound as a crude product. MS (ES) MH^+: 292, 294 for $C_{11}H_{15}Cl_2N_3O_2$.

The following Intermediate was prepared by the procedure described in Intermediate 16 from the starting materials (SM) indicated.

Ex	Compound	Data	SM
245	ethyl 4-{[(1-methyl-1-phenylethyl)amino]carbonyl}-2-(methylsulfonyl)-1,3-thiazole-5-carboxylate 	MS (ES) MH^+:397 for $C_{17}H_{20}N_2O_5S_2$ NMR: 1.24 - 1.32 (m, 3 H) 1.66 (s, 6 H) 3.57 (s, 3 H) 4.36 (q, 2 H) 7.22 (t, 1 H) 7.34 (t, 2 H) 7.41 - 7.50 (m, 2 H) 8.91 (s, 1 H)	Intermediate 246

Intermediate 246

ethyl 4-{[(1-methyl-1-phenylethyl)amino]carbonyl}-2-(methylthio)-1,3-thiazole-5-carboxylate

Diisopropylamine (5.3 ml) was dissolve in anhydrous THF (100 ml) was cooled to -78°C and to this was added n-butyl lithium (15 ml) slowly. The solution was slowly warmed to 0 °C and then cooled back to -78°C. A solution of *N*-(1-methyl-1-phenylethyl)-2-(methylthio)-1,3-thiazole-4-carboxamide (Intermediate 13; 3.7 g) in anhydrous THF was added slowly maintaining the temperature below -70°C. After stirring for 30 min, a solution of ethyl cyano formate (2.5 ml) in anhydrous THF was added in one portion and the reaction was stirred at -78°C for 30 min followed by slow warming to room temperature. The reaction mixture was diluted with water and extracted with ethyl acetate (X3), dried with $MgSO_4$ and concentrated to a black oil (0.84g) NMR: 1.22 - 1.29 (m, 3 H) 1.63 (s, 6 H) 2.76 (s, 3 H) 4.28 (q, 2 H) 7.20 (t, 1 H) 7.32 (t,2 H) 7.46 (d, 2 H) 8.75 (s, 1 H)

Intermediate 247

diethyl 2-chloro-1,3-thiazole-4,5-dicarboxylate

To a solution of tert-butyl nitrite (3.4mL, 28 mmol) and copper (II) chloride (3.7g, 28mmol) in acetonitrile (50mL) was added diethyl 2-amino-1,3-thiazole-4,5-dicarboxylate (4.6g, 19mmol, Intermediate 248) all in one portion. Gas evolution was observed. After 45 min of stirring at room temperature LCMS indicated complete product formation. After concentrating to remove acetonitrile the residue was partitioned with chloroform and 1N HCl (Fisher), washed with chloroform, dried with $MgSO_4$ and concentrated to an orange oil. Purification by flash column yielded a pale yellow oil (4.2g, 85%). MS (ES): 264; NMR: 1.25 - 1.29 (t, 3 H) 1.29 - 1.33 (t, 3 H) 4.28 - 4.33 (q, 2 H) 4.33 - 4.39 (q, 2 H)

Intermediate 248

diethyl 2-amino-1,3-thiazole-4,5-dicarboxylate

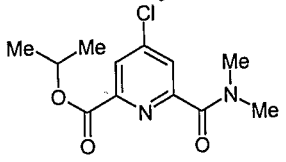
A solution of thiourea (1.7g, 22 mmol) and diethyl 2-chloro-3-oxosuccinate (5.0g, 22 mmol) in absolute ethanol (50mL) was heated at reflux for one hour. After cooling to room temperature the solvent was removed leaving a white solid. The solid was dissolved in water (100mL) and the resulting precipitate was filtered and dried (4.6g, 87%). MS (ES): 245; NMR: 1.21 (t, 3 H) 1.26 (t, 3 H) 4.16 (q, 2 H) 4.26 (q, 2 H) 8.04 (s, 2 H)

Intermediate 249

isopropyl 4-chloro-6-(morpholin-4-ylcarbonyl)pyridine-2-carboxylate

n-butyllithium (1.92mL, 2.5M in hexanes) was added dropwise to a –78°C solution of morpholine (0.42mL, 4.8mmol) in anhydrous THF followed by slow warming to room temperature. The solution was transferred to an addition funnel via cannulation and then added dropwise to a solution of dimethyl 4-chloropyridine-2,6-dicarboxylate (1.0g, 4.4mmol, Intermediate 251) in anhydrous THF. A slight precipitate was observed during the addition. After stirring two hrs at room temperature an additional 0.5 equivalence of the morpholino-lithium reagent was added to the reaction and after an additional two hrs of stirring another 0.5 equivalence was added followed by stirring one hour to reach completion. The solvent was removed under reduced pressure and the residue was suspended in methylene chloride and the product was extracted with a sat. sodium bicarbonate solution (x3). The sodium bicarbonate portion was acidified with conc. HCl to pH 3 and then extracted with EtOAc (x10), followed by drying with $MgSO_4$ and concentrating to a solid (0.8g, 70%). MS (ES) MH^+:271 for $C_{11}H_{11}ClN_2O_4$. The solid was suspended in anhydrous toluene (75mL) and to this was added triisopropylorthoformate (1.97mL, 8.9mmol) slowly followed by heating to reflux for 12 hours. After cooling to room temperature the solvent was removed under reduced pressure and the residue was suspended in 1N HCl. Basification to pH8 with saturated sodium bicarbonate followed by extraction with EtOAc (x3), drying with $MgSO_4$ and removal of solvent yielded a tan solid. Purification by silica gel flash column (gradient elution to 3:1 EtOAc:CH_2Cl_2) yielded a white solid (0.23g) MS (ES) MH^+:313 for $C_{14}H_{17}ClN_2O_4$; NMR: 1.33 (s, 3 H) 1.35 (s, 3 H) 3.41 (s, 2 H) 3.44 (d, 2 H) 3.58 (d, 2 H) 3.68 (s, 4 H) 5.17 (dt, 1 H) 8.01 (d, 1H) 8.13 (d,1 H).

The following Intermediate was prepared by the procedure described in Intermediate 249 from the starting materials (SM) indicated.

Ex	Compound	Data	SM
250	isopropyl 4-chloro-6-[(dimethylamino)carbonyl]pyridine-2-carboxylate 	MS (ES) MH^+: 271 for $C_{12}H_{15}ClN_2O_3$ NMR: 1.35 (d, 6 H) 2.93 (s, 3 H) 3.03 (s, 3 H) 5.18 (dt, 1 H) 7.96 (d, 1 H) 8.11 (d, 1 H)	Intermediate 251 and dimethylamine

Intermediate 251

dimethyl 4-chloropyridine-2,6-dicarboxylate

Phophorus pentachloride (45.5g, 218mmol) was weighed into a closed flask and suspended in chloroform. 4-hydroxypyridine-2,6-dicarboxylic acid (10.0g, 55 mmol) was added and after heating at a gentle reflux for 3 days the reaction was complete (60% conversion). After cooling to 0°C anhydrous methanol (150mL) was added dropwise. Once the exotherm subsided the solvent was removed under reduced pressureand the residue was partitioned with EtOAc and water and the insoluble material was filtered, washed with EtOAc and dried (6.7g). The EtOAc layer was washed with water, dried with $MgSO_4$ and concentrated. Recrystallization with methanol yielded additional pure product (0.64g). MS (ES) MH^+: 230 for $C_9H_8ClNO_4$; NMR: 3.94 (s, 3 H) 8.32 (s, 1 H).

Intermediate 252

2-chloro-5-(ethoxycarbonyl)-1,3-thiazole-4-carboxylic acid

To a solution of ethyl 2-chloro-4-(hydroxymethyl)-1,3-thiazole-5-carboxylate (2.5g, 11mmol, Intermediate 211) in acetone at 0°C was slowly added a solution of chromium trioxide (2.26g, 22mmol) in 20% conc. Sulfuric acid in water (20mL). After stirring at room temperature for 2 hrs, isopropanol (1mL) was added to quench unreacted chromium trioxide. The reaction was diluted with water and the acetone was removed. Partitioning with methylene chloride (x3), drying with MgSO4 and concentrating yielded a white solid (2.3g, 90%). MS (ES) MH^+: 236 for $C_7H_6ClNO_4S$; NMR: 1.26 (t, 3 H) 4.31 (q, 2 H) 13.99 - 14.15 (m, 1 H).

Intermediate 253

3,4-Dichloro-5-chloromethyl-1H-pyrrole-2-carboxylic acid ethyl ester

To a 4-neck 22L round bottom flask equipped with an overhead stirrer, liquid addition funnel, nitrogen inlet and an internal temperature probe was charged (Intermediate 254, 2000 g, 13.6 mol) and carbon tetrachloride (12 L). The reaction mixture was cooled to -5 °C and sulfuryl chloride was added at a rate that the temperature did not exceed 0 °C (1 h). Resulting reaction mixture became very thick (as precipitate becomes heavy, significant gas evolution was observed) and was allowed to stir at 0 °C for a total of 4 h after addition. Precipitate was filtered and solid azeotroped with toluene to remove excess sulfuryl chloride. The solid was and dried in convection oven at 50 °C yielding **3** (2077 g, 62 %) as a dark purple solid.

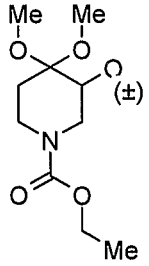
Intermediate 254

5-Methyl-1H-pyrrole-2-carboxylic acid ethyl ester

To a 4-neck 22L round bottom flask equipped with an overhead stirrer, liquid addition funnel, nitrogen inlet and an internal temperature probe was charged ethyl 3-oxobutanoate (1952 g, 15.0 mol) and glacial acetic acid (5 L). The resulting solution was cooled to 0 °C with an ice water bath and an aqueous solution of sodium nitrite (1242 g, 18.0 mol, 1.2 eq, in 1875 ml of water) was added slowly (4.5 h) not allowing the internal temperature above 10 °C. The homogeneous red solution was allowed to warm to ambient and stirred for 48 h. The solution color changed from light red to yellow. Reaction vessel was then placed in a heating mantle, fitted with a reflux condenser and acetylacetaldehyde dimethyl acetal (1982 g, 15.0 mol, 1 eq) was added in one portion (the top of the reflux condenser was left open to air to allow for the rapid gas evolution during the addition of the zinc). Zinc (dust, 2156 g, 33 mol, 2.2 eq) was added in portions (at a rate such that gas evolution was controlled) over 4 h. The addition of zinc brought the reaction to reflux and after addition the dark red solution was heated at reflux for an additional 1.5 h. Contents of the reaction were poured hot into a 50 L container with 20 kg of ice and allowed to stir for 16 h. Resulting suspension was filtered, dried in convection oven and recrystallized with hot heptane yielding a light yellow solid (312 g, 13.6% yield).

Intermediate 255

ethyl 3-hydroxy-4,4-dimethoxypiperidine-1-carboxylate



To a stirred solution of potassium hydroxide (42 g, 752 mmol) in dry methanol (100 mL), at 0 °C and under an atmosphere of N_2, was added a solution of ethyl 4-oxopiperidine-1-carboxylate (26.4 mL, 29.96 g, 175 mmol) in dry methanol (75 mL) via syringe. The resulting solution was stirred for an additional 30 minutes under an atmosphere of N_2 at 0 °C. To it, in small portions over approximately 90 minutes, was added iodobenzene diacetate (84.6 g, 262 mmol). Temperature was kept near 0 °C throughout this time. The reaction was stirred overnight under an atmosphere of N_2, gradually reaching room

temperature. Complete conversion was suggested by TLC (50% ethyl acetate in hexanes; Hanessian's stain; Rf ~ 0.25) in the morning. The reaction was concentrated under vacuum. To the residue was added approximately 50 mL water; from this mixture was extracted the crude product with ethyl acetate (3 X 200 mL). The organic layers were combined, dried over magnesium sulfate, and concentrated. The crude product was purified using column chromatography (silica gel; 10-65% ethyl acetate in hexanes), yielding 26.74 g (66%) of a pale yellow oil.

MS (ESI) M: 233 for $C_{10}H_{19}NO_5$. ^{1}H NMR ($CDCl_3$): 1.22 (t, 3H), 1.69-1.86 (m, 2H), 2.20 (m, 2H), 2.86 (t, 1H), 3.22 (s, 3H), 3.23 (s, 3H), 3.74 (m, 1H), 3.95 (m, 2H), 4.11 (q, 2H).

The following Intermediates were synthesized by an analogous method to Intermediate 28 or Intermediate 59 from the starting materials (SM) given in the table below.

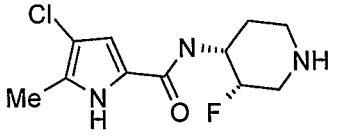
Int	Compound	Data	SM
256	Cis(±)-ethyl 4-amino-3-(prop-2-yn-1-yloxy)piperidine-1-carboxylate	MS (ESP): 227 (M+H) for $C_{11}H_{18}N_2O_3$	Intermediate 146
257	Cis(±)-Ethyl (4-amino-3-ethoxypiperidine-1-carboxylate	MS (ES) MH^+: 217 for $C_{10}H_{20}N_2O_3$	Intermediate156

The following Intermediates were synthesized by an analogous method to Intermediate 37 or Intermediate 83 from the starting materials (SM) given in the table below.

Int	Compound	Data	SM
258	*tert*-Butyl (3*S*,4*R*)-4-{[(4-chloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidine-1-carboxylate	MS (ES) MH^+: 360 for $C_{16}H_{23}ClFN_3O_3$;	Intermediate 64 and Intermediate 6

Int	Compound	Data	SM
259	*tert*-butyl (3*S*,4*R*)-4-{[(4-chloro-3-fluoro-5-methyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidine-1-carboxylate	MS (ESP): 530 (MNa^+) for $C_{22}H_{36}ClF_2N_3O_4Si$	Intermediate 263 and Intermediate 64

The following Intermediates were synthesized by an analogous method to Intermediate 50 or Intermediate 74 from the starting materials (SM) given in the table below.

Int	Compound	Data	SM
260	4-Chloro-*N*-[(3*S*,4*R*)-3-fluoroxypiperidin-4-yl]-5-methyl-1*H*-pyrrole-2-carboxamide 	MS (ES) MH^+: 260 for $C_{11}H_{15}ClFN_3O$	Intermediates 258
261	4-chloro-3-fluoro-N-[(3S,4R)-3-fluoropiperidin-4-yl]-5-methyl-1H-pyrrole-2-carboxamide	MS (ESP): 278 (MH^+) for $C_{11}H_{14}ClF_2N_3O$	Intermediate 262

Intermediate 262

tert-butyl (3*S*,4*R*)-4-{[(4-chloro-3-fluoro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidine-1-carboxylate

tert-butyl (3*S*,4*R*)-4-{[(4-chloro-3-fluoro-5-methyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidine-1-carboxylate (Intermediate 259, 80mg, 0.16mmol) was dissolved in anhydrous THF (6ml), followed by the addition of tetra-butyl ammonium fluoride (1ml, 1M in THF) and ethylene diamine (1mmol), the mixture was then stirred at 50oC over night. After cooling down to room temperature, the reaction mixture was diluted with ethyl acetate (20ml) and washed with saturated aqueous sodium bicarbonate (10ml) and brine (10ml), dried over anhydrous sodium sulfate, concentrated and purified by column chromatography (100%~70%hexanes/ethyl acetate) to give the desired product (55mg).

MS (ESP): 378 (MNa^+) for $C_{16}H_{22}ClF_2N_3O_3$

^{1}H-NMR ($CDCl_3$) δ: 1.46 (s, 9H); 1.84 (m, 2H); 2.24 (s, 3H); 2.89 (m, 2H); 4.28 (m, 2H); 4.50 (m, 1H); 4.70 (m, br, 1H); 6.32 (m, 1H); 9.36 (br, 1H).

Intermediate 263

4-chloro-3-fluoro-5-methyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-pyrrole-2-carboxylic acid

tert-butyl 4-chloro-3-fluoro-5-methyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-pyrrole-2-carboxylate (Intermediate 264, 100mg) was dissolved in N-methyl pyrolidinone (10ml), heated to 200°C for 30 minutes. The resulting solution was carried on to the next step without further purification.

MS (ESP): 307 (M^-) for $C_{12}H_{19}ClFNO_3Si$

Intermediate 264

tert-butyl 4-chloro-3-fluoro-5-methyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-pyrrole-2-carboxylate

tert-butyl 3-bromo-4-chloro-5-methyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-pyrrole-2-carboxylate (Intermediate 265, 480mg, 1.13mmol) was dissolved in dry THF(8ml), cooled down to -78°C, n-BuLi (2.5M in Hexane, 3.39mmol) was added dropwise into the mixture via syringe and the mixture was stirred at -78°C for 30min followed by a quick addition of N-Fluorobenzensulfonimide(1.25g, 3.96mmol in 5 ml of THF/Toluene 1:1), the resulting mixture was then stirred at -78°C for 30min and slowly warmed up to room temperature during a period of 12hrs. The reaction was quenched at 0°C with drops of saturated NH_4Cl solution and further diluted with EtOAc (50ml). The organic phase was washed with brine and dried over anhydrous $MgSO_4$, concentrated to an oil and purified by flash column chromatography eluted with 10% EtOAc in Hexanses. The desired product was obtained as an oil (125mg).

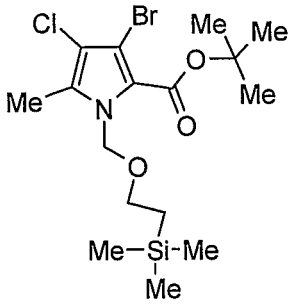
MS (ESP): 364 (MH^+) for $C_{16}H_{27}ClFNO_3Si$

^{1}H-NMR ($CDCl_3$) δ: 0.00 (s, 9H); 0.90 (t, 2H); 1.58 (s, 9H); 2.31 (s, 3H); 3.52 (t, 2H); 5.70 (s, 2H).

^{19}F-NMR ($CDCl_3$) δ: -148.85

Intermediate 265

tert-butyl 3-bromo-4-chloro-5-methyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-pyrrole-2-carboxylate



Ethyl 3-bromo-4-chloro-5-methyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-pyrrole-2-carboxylate (Intermediate 266, 564mg, 1.42mmol), t-Butylacetate (330mg, 2.84mmol) and potassium t-butoxide (0.14mmol) were mixed together and stirred at room temperature for 10 minutes, concentrated to an oil under vacuum. t-Butylacetate (330mg, 2.84mmol) and potassium t-butoxide (0.14mmol) were added again into the reaction mixture, repeated the same procedure again. The resulting reaction crude was filtered through a short pass silica gel, washed with ethyl acetate, the combined filtrate was concentrated to an oil and purified by column chromatography (2% ethyl acetate in hexanses) to give the desired product as an oil (485mg).

^{1}H-NMR ($CDCl_3$) δ: 0.00 (s, 9H); 0.90 (t, 2H); 1.58 (s, 9H); 2.33 (s, 3H); 3.52 (t, 2H); 5.75 (s, 2H)

Intermediate 266

Ethyl 3-bromo-4-chloro-5-methyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-pyrrole-2-carboxylate

To a suspension of sodium hydride (76mg, 3.16mmol) in dry DMF (5ml), solution of ethyl 3-bromo-4-chloro-5-methyl-1H-pyrrole-2-carboxylate (Intermediate 267, 420mg, 1.58mg) was added, the resulting mixture was stirred at 0°C for 30 minutes until gas evolution seized. Trimethylsilyl-ethoylmethyl chloride (315mg, 1.89mmol) was added drop wise and stirred over night while allowing the reaction mixture warmed up to room temperature slowly. The reaction was quenched with cold water, diluted with ether (20ml), washed with water and brine, the organic layer was dried over anhydrous sodium sulfate, concentrated and purified by column chromatography (95%hexanes in ethyl acetate) to give the desired product as an oil (624mg).

MS (ESP): 397 (MH^+) for $C_{14}H_{23}BrClNO_3Si$

^{1}H-NMR ($CDCl_3$) δ: 0.00 (s, 9H); 0.90 (t, 2H); 1.43 (t, 3H); 2.38 (s, 3H); 3.55 (t, 2H); 4.34 (q, 2H); 5.75 (s, 2H).

Intermediate 267

Ethyl 3-bromo-4-chloro-5-methyl-1H-pyrrole-2-carboxylate

Ethyl 4-chloro-5-methyl-1H-pyrrole-2-carboxylate (Intermediate 7, 300mg, 1.6mmol) was dissolved in dry dichloromethane (10ml), N-bromosuccinimide(285mg, 1.6mmol) was added at 0°C and resulting mixture was stirred at room temperature over night. The mixture was poured into cold sodium hydroxide aqueous solution (2M) (20ml), extracted with diethyl ether (2x20ml). The organic phase was then washed with water (20ml) and brine (20ml), dried over anhydrous sodium sulfate, concentrated and purified by column chromatography (hexanes/ethyl acetate, gradient) to give the desired product as a yellowish solid.(424mg).

MS (ESP): 266 (MH^+) for $C_8H_9BrClNO_2$

^{1}H-NMR ($CDCl_3$) δ: 1.39 (t, 3H); 2.32 (s, 3H); 4.34 (q, 2H); 9.04 (s, br, 1H).

Intermediate 268

Trans(±)-*tert*-butyl-4-[(diphenylmethylene)amino]-3-hydroxypiperidine-1-carboxylate

tert-butyl-4-amino-3-hydroxypiperidine-1-carboxylate (11.9 g; 55 mmol) and benzophenone imine (10g; 59 mmol; 1.05 eq.) were dissolved in anhydrous toluene and heated to reflux for 18 hrs. Monitored the reaction by TLC (30% EtOAc / hexanes with 0.1% triethylamine). The crude reaction was concentrated and purified by flash column chromatography. Isolation gave 18.4 g of the title compound in an 86% yield. LC/MS (ES^+)[$(M+H)^+$]: 381 for $C_{23}H_{28}N_2O_3$.

Intermediate 269

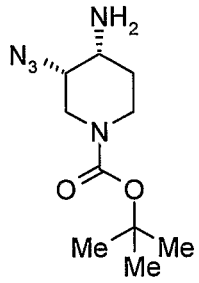
Cis(±)-*tert*-butyl-3-azido-4-[(diphenylmethylene)amino]piperidine-1-carboxylate

In a flame-dried flask triphenylphosphine (3.86 g; 14.7 mmol; 2 eq.) was dissolved in anhydrous THF (15 ml) and cooled to 0 C. DIAD (2.97 g; 14.7 mmol; 2 eq.) was slowly added dropwise. Upon addition a white precipitate formed. A THF solution containing *tert*-butyl-4-[(diphenylmethylene)amino]-3-hydroxypiperidine-1-carboxylate (Intermediate 268, 2.8 g; 7.36 mmol) was added (amount of THF added was such that the final concentration of alcohol was ca. 0.5 – 1M). The resultant reaction slurry was stirred at 0 C for 30 minutes.

$(PhO)_2PON_3$ (4.05 g; 14.7 mmol; 2eq.) was then added and the reaction was allowed to warm to RT and stirred for 12 hrs. Monitored by LC/MS. The reaction was concentrated and purified by flash column chromatography (0 - 30% EtOAc / hexanes with 0.1% triethylamine). Isolation gave 2.13 g of the title compound in 71% yield. LC/MS $(ES^+)[(M+H)^+]$: 406 for $C_{23}H_{27}N_5O_2$.

Intermediate 270

Cis(±)*tert*-butyl-4-amino-3-azidopiperidine-1-carboxylate



tert-butyl-3-azido-4-[(diphenylmethylene)amino]piperidine-1-carboxylate (Intermediate 269, 1.36 g; 3.3 mmol) was dissolved in 10 ml's of aqueous THF (5% H_2O). PPTS (850 mg; 3.4 mmol; 1.03 eq.) was added in a single portion. The initial cloudy solution became clear within minutes. Upon completion (as determined by LC/MS analysis) the reaction was concentrated and azeotropically dried with acetonitrile. No further purification. (LC/MS: see disappearance of starting material and formation of $Ph_2C{=}O$. Product is not observable due to lack of chromophore).

Intermediate 271

Cis(±)*tert*-butyl-3-azido-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidine-1-carboxylate

Crude *tert*-butyl-4-amino-3-azidopiperidine-1-carboxylate (Intermediate 270, 3.3 mmol) was dissolved in anhydrous CH_2Cl_2 (10 ml) and DIEA (1.27 g; 1.6 ml; 9.9 mmol; 3 eq.). The solution was cooled to 0 C and 3,4-dichloro-5-methyl-1*H*-pyrrole-2-carbonyl chloride (736 mg; 3.5 mmol; 1.05 eq.) was added. The reaction was complete within 30 minutes. Dilute with CH_2Cl_2 and wash with H_2O (x2), brine and dried over Na_2SO_4. Filter and concentrate. Purify by flash column chromatography (0 – 60% EtOAc / hexanes). Isolation gave 967 mg in 69% yield over the two-step sequence. LC/MS $(ES^-)[(M-H)^-]$: 415, 417 for $C_{16}H_{22}Cl_2N_6O_3$.

Intermediate 272

Cis(±)*N*-(-3-azidopiperidin-4-yl)-3,4-dichloro-5-methyl-1*H*-pyrrole-2-carboxamide hydrochloride.

tert-butyl-3-azido-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidine-1-carboxylate (Intermediate 271, 967 mg; 2.3 mmol) was dissolved in 4N HCl in dioxanes (20 ml) and methanol (10 ml). The solution was stirred for 2 hours and monitored by LC/MS. Upon completion the solvent was removed and the crude reaction mixture was azeotroped with methanol to remove excess HCl. No further purification. LC/MS (ES^+)[$(M+H)^+$]: 317, 319 for $C_{11}H_{14}Cl_2N_6O$.

Intermediate 273

(2*R*)-2-Methoxypropan-1-amine hydrochloride (1725-162)

tert-Butyl [(2*R*)-2-methoxypropyl]carbamate (Intermediate 277, 0.33 g, 1.74 mmol) and Hydrochloric acid (4 M, 1.5 mL) were combined and stirred at room temperature for two hours. Then it was concentrated and triturated with diethyl ether to give white crystalline solid (0.20 g) as the product.

NMR: 1.14 (d, 3H), 3.30 (s, 3H), 3.35- 3.45 (m, 2H), 7.99 (brs, 3H)

The following compounds were produced according to the procedure for Intermediate 273 or by hydrogenation using the starting materials listed.

Int	Compound	Data	SM
274	(2S)-2-methoxypropan-1-amine hydrochloride	NMR: 1.14 (d, 3H), 3.30 (s, 3H), 3.35- 3.45 (m, 2H), 7.99 (brs, 3H)	Intermediate 278
275	(2*R*)-1-Methoxypropan-2-amine hydrochloride	NMR: 1.14 (d, 3H), 3.29 (s, 3H), 8.07 (brs, 3H), rest of the peaks are buried under huge water peak	Intermediate 276

Intermediate 276

Benzyl [(1*R*)-2-methoxy-1-methylethyl]carbamate

To a solution of benzyl [(1*R*)-2-hydroxy-1-methylethyl]carbamate (0.5 g, 2.38 mmol) in acetonitrile (20 mL), silver oxide(3.8 g, 13.09 mmol) is added followed by the addition of methyl iodide (1.94 mL, 23.8 mmol). The resultant mixture was stirred overnight at room

temperature. The insoluble salt was filtered off and the filtrate was concentrated. The residue was flashed using silica and Ethyl acetate/hexanes system as eluent to give the desired product as clear oil (0.38 g).

MS (ES) MH+Na: 246 for $C_{12}H_{17}NO_3$;

NMR: 1.01 (d, 3H), 3.12- 3.17 (m, 1H), 3.22 (s, 3H), 3.25-3.26 (m, 1H), 3.60-3.75 (m, 1H), 5.00 (s, 2H), 7.16 (d, 1H), 7.29-7.36 (m, 5H)

Intermediate 277

tert-Butyl [(2*R*)-2-methoxypropyl]carbamate

To a solution of *tert*-butyl [(2*R*)-2-hydroxypropyl]carbamate (0.4 g, 2.28 mmol) in THF (5mL), sodium hydride (0.06 g, 2.51 mmol) was added at 0°C . The resulting solution was stirred for 30 minutes at that temperature and then methyl iodide (0.14 mL, 2.28 mmol) was added. The reaction was warmed to room temperature slowly and allowed to stir for an additional two hours. The reaction was quenched by adding water and extracted with ethyl acetate. The extract was washed with sodium bicarbonate solution, water and brine. It was dried over magnesium sulfate and concentrated. The desired product was obtained as clear oil (0.31 g) and it did not need any further purification.

NMR ($CDCl_3$): 1.15 (d, 3H), 1.43 (s, 9H), 3.31- 3.33 (m, 2H), 3.34 (s, 3H), 3.77-3.81 (m, 1H), 4.66 (brs, 1H)

Interemediate 278

tert-Butyl [(2*S*)-2-methoxypropyl]carbamate(1725-160)

The title compound was synthesized by using the method analogous to the synthesis of Intermediate 277 starting with *tert*-butyl [(2*S*)-2-hydroxypropyl]carbamate and alkylating it with methyl iodide.

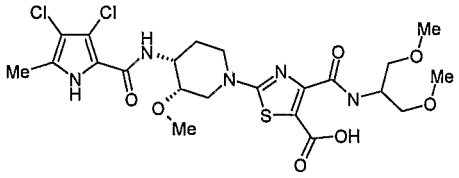
NMR ($CDCl_3$): 1.15 (d, 3H), 1.43 (s, 9H), 3.31- 3.33 (m, 2H), 3.34 (s, 3H), 3.77-3.81 (m, 1H), 4.66 (brs, 1H)

The following Intermediate was prepared by the procedure described in Example 203 from the starting materials (SM) indicated

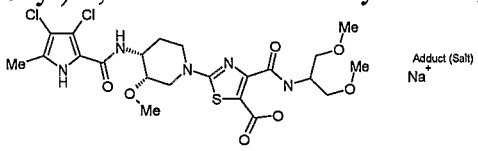
Ex	Compound	Data	SM
441	ethyl 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[2-methoxy-1-(methoxymethyl)ethyl]amino}carbonyl)-1,3-thiazole-5-carboxylate	MS (ES) MH^+:605 for $C_{24}H_{33}Cl_2N_5O_7S$;	Example 188 and [2-methoxy-1-(methoxymethyl)ethyl]amine (ChemPacific)

5

The following Intermediate was prepared by the procedure described in Example 383 from the starting materials (SM) indicated

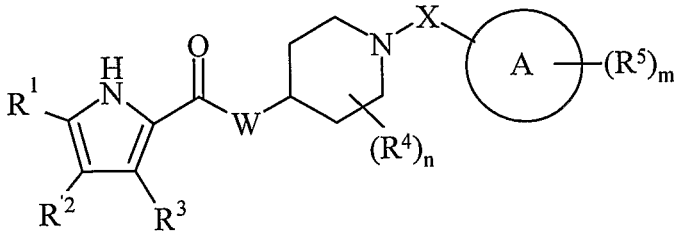
Ex	Compound	Data	SM
442	2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[2-methoxy-1-(methoxymethyl)ethyl]amino}carbonyl)-1,3-thiazole-5-carboxylic acid 	MS (ES) MH^+: 578 for $C_{22}H_{29}Cl_2N_5O_7S$ NMR: 1.77 (s, 2 H) 2.19 (s, 3 H) 3.24 (s, 3 H) 3.27 (s, 3 H) 3.38 (s, 5 H) 3.49 (s, 6 H) 4.32 (s, 2 H) 7.18 (s, 1 H) 8.93 (s, 1 H) 12.16 (s, 1 H) 16.17 (s, 1 H)	Example 441

The following Examples were prepared by the procedure described in Example 417 from the starting materials (SM) indicated

Ex	Compound	Data	SM
443	sodium 2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[2-methoxy-1-(methoxymethyl)ethyl]amino}carbonyl)-1,3-thiazole-5-carboxylate 	MS (ES) MH^+: 578 for $C_{22}H_{28}Cl_2N_5O_7SNa$ NMR: 1.70 (s, 2 H) 2.17 (s, 3 H) 3.21 - 3.26 (m, 6 H) 3.34 (s, 4 H) 3.35 - 3.38 (m, 6 H) 3.49 (s, 1 H) 3.86 (d, 1 H) 4.04 - 4.16 (m, 3 H) 4.22 (s, 1 H) 7.18 (d, 1 H) 12.17 (s, 1 H) 13.33 (d, 1 H)	Example 442

What is claimed is:

1. A compound of formula **(I)**:



(I)

wherein:

R^1 is selected from hydrogen, nitro, hydroxy, halo, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkanoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2 and C_{3-6}cycloalkyl; wherein R^1 may be optionally substituted on carbon by one or more halo or cyclopropyl;

R^2 is selected from hydrogen, nitro, hydroxy, halo, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkanoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2 and C_{3-6}cycloalkyl; wherein R^2 may be optionally substituted on carbon by one or more halo or C_{3-6}cycloalkyl;

R^3 is selected from hydrogen, nitro, hydroxy, halo, cyano, -C=N-OR' wherein R' is H or C_{1-4}alkyl, C_{1-4}alkyl, C_{1-4}alkoxy, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkanoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2 and C_{3-6}cycloalkyl; wherein R^3 may be optionally substituted on carbon by one or more halo or C_{3-6}cycloalkyl;

W is -O-, -N(R^6)- or -C(R^7)(R^8)-;

X is a direct bond, -CH_2-, -C(O)- or S(O)$_q$- (wherein q is 1 or 2);

Ring A is carbocyclyl or heterocyclyl; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^9;

R^4 and **R^5** are substituents on carbon and are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, sulfo, formyl, ureido, hydroxyiminomethyl, C_{1-4}alkoxyiminomethyl, *N*-hydroxyformamido, C_{1-4}hydrazino, hydrazinocarbonyl, *N*-hydroxyethanimidoyl, amino(hydroxyimino)methyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, *N*-(C_{1-4}alkyl)amino, *N,N*-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)$_2$carbamoyl, *N*-(C_{1-4}alkoxy)carbamoyl, *N'*-(C_{1-4}alkyl)ureido, *N',N'*-(C_{1-4}alkyl)$_2$ureido, *N*-(C_{1-4}alkyl)-*N*-(C_{1-4}alkoxy)carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, C_{1-4}alkoxycarbonylamino, *N*-(C_{1-4}alkyl)sulphamoyl, *N,N*-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, C_{1-4}alkylsulphonylaminocarbonyl,

N'-(C_{1-4}alkyl)hydrazinocarbonyl, *N',N'*-(C_{1-4}alkyl)$_2$hydrazinocarbonyl, carbocyclyl-R^{10}- or heterocyclyl-R^{11}—; wherein R^4 and R^5 independently of each other may be optionally substituted on carbon by one or more R^{12}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{13};

R^6, **R^7** and **R^8** are independently selected from hydrogen or C_{1-4}alkyl;

n is 1-4; wherein the values of R^4 may be the same or different;

m is 0-4; wherein the values of R^5 may be the same or different;

R^{12} is selected from azido, halo, nitro, cyano, hydroxy, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, N-(C_{1-4}alkyl)amino, N,N-(C_{1-4}alkyl)$_2$amino, C_{1-4}alkanoylamino, N-(C_{1-4}alkyl)carbamoyl, N,N-(C_{1-4}alkyl)$_2$carbamoyl, C_{1-4}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-4}alkoxycarbonyl, N-(C_{1-4}alkyl)sulphamoyl, N,N-(C_{1-4}alkyl)$_2$sulphamoyl, C_{1-4}alkylsulphonylamino, C_{1-4}alkoxycarbonylamino, carbocyclyl-R^{14}— or heterocyclyl-R^{15}—; wherein R^{12} independently of each other may be optionally substituted on carbon by one or more R^{16}; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R^{17};

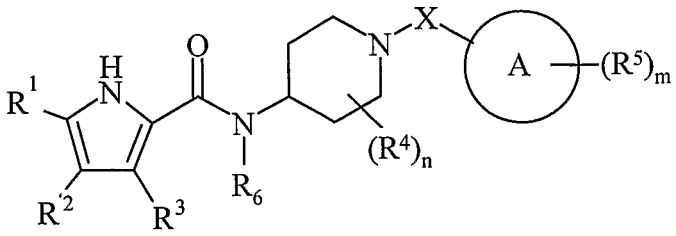
R^9, **R^{13}** and **R^{17}** are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

R^{10}, **R^{11}**, **R^{14}** and **R^{15}** are independently selected from a direct bond, -O-, -N(R^{18})-, -C(O)-, -N(R^{19})C(O)-, -C(O)N(R^{20})-, -S(O)$_p$-, -SO$_2$N(R^{21})- or -N(R^{22})SO$_2$-; wherein R^{18}, R^{19}, R^{20}, R^{21} and R^{22} are independently selected from hydrogen or C_{1-4}alkyl and p is 0-2;

R^{16} is selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, ethenyl, ethynyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

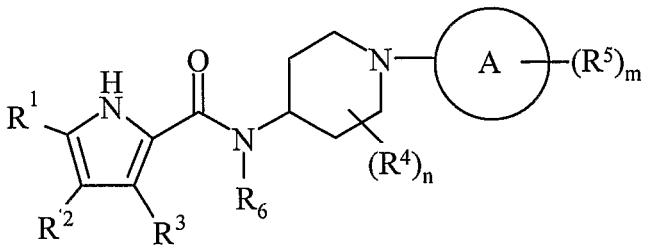
or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof which is a compound of formula **(IA)**.



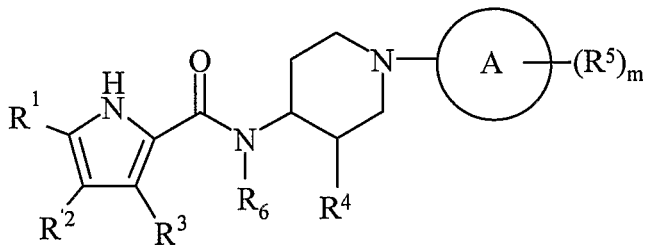
(IA)

3. The compound of claims 1-2, or a pharmaceutically acceptable salt thereof which is a compound of formula **(IB)**.



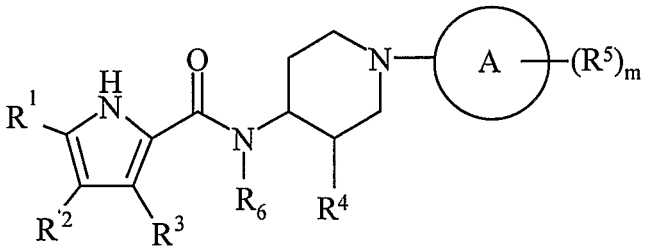
(IB)

4. The compound of claims 1-3, or a pharmaceutically acceptable salt thereof which is a compound of formula **(IC)**.



(IC)

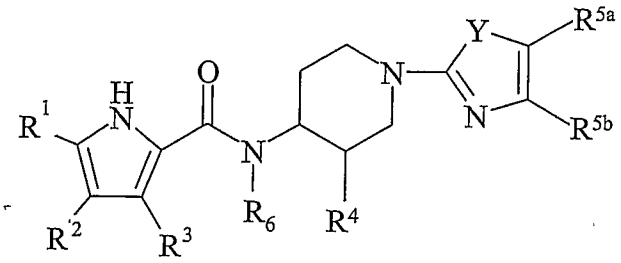
5. The compound of claims 1-4, or a pharmaceutically acceptable salt thereof which is a compound of formula **(ID)**:



(ID)

wherein **Ring A** is heterocyclyl; wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl.

6. The compound of claims 1-5, or a pharmaceutically acceptable salt thereof which is a compound of formula **(IE)**:



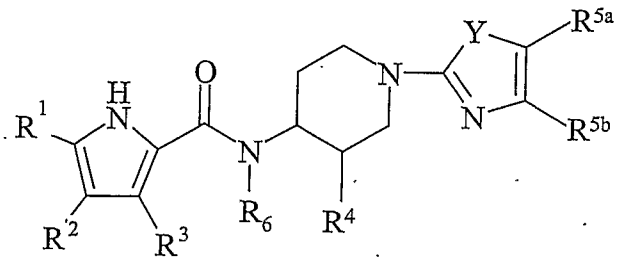
(IE)

wherein:

Y is NH, N(C_{1-4}alkyl) or S;

wherein R^{5a} and R^{5b} are substituents as defined for R^5 or taken together with the carbons to which they are attached form a 6-membered carbocyclyl ring substituted by one or two groups which may be the same or different and which are selected from R^{14};

7. The compound of claims 1-6, or a pharmaceutically acceptable salt thereof which is a compound of formula **(IF)**.



(IF)

8. A compound which is

2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-5-carboxylic acid;

2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-{[(2-methoxyethyl)amino]carbonyl}-1,3-thiazole-5-carboxylic acid;

2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[(1*S*)-2-methoxy-1-methylethyl]amino}carbonyl)-1,3-thiazole-5-carboxylic acid;

2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-[(methylamino)carbonyl]-1,3-thiazole-5-carboxylic acid;

2-((3*S*,4*R*)-4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid;

2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid;

4-acetyl-2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-thiazole-5-carboxylic acid;

2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[(1*R*)-2-methoxy-1-methylethyl]amino}carbonyl)-1,3-thiazole-5-carboxylic acid;

2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[(2*S*)-2-methoxypropyl]amino}carbonyl)-1,3-thiazole-5-carboxylic acid;

2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[(2*R*)-2-methoxypropyl]amino}carbonyl)-1,3-thiazole-5-carboxylic acid;

2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[(1*R*,2*S*)-2-fluorocyclopropyl]amino}carbonyl)-1,3-thiazole-5-carboxylic acid;

Cis(±)2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylic acid;

Cis(±)2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-(methoxymethyl)-1,3-thiazole-5-carboxylic acid;

Cis(±)2-(4-{[(3,4-dichloro-5-methyl-1H-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)isonicotinic acid;

2-((3*S*,4*R*)-4-{[(4-chloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-1,3-benzothiazole-7-carboxylic acid;

Cis(±)-2-(3-chloro-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}piperidin-1-yl)-4-(methoxymethyl)-1,3-thiazole-5-carboxylic acid;

2-((3*S*, 4*R*)-4-{[(3,4-Dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-4-methyl-1,3-thiazole-5-carboxylic acid;

Cis(±)-2-[4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-(prop-2-yn-1-yloxy)piperidin-1-yl]-1,3-thiazole-5-carboxylic acid;

Cis(±)2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-fluoropiperidin-1-yl)-1,3-thiazole-4-carboxylic acid; or

2-((3*S*,4*R*)-4-{[(3,4-dichloro-5-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-methoxypiperidin-1-yl)-4-({[2-methoxy-1-(methoxymethyl)ethyl]amino}carbonyl)-1,3-thiazole-5-carboxylic acid;

or a pharmaceutically acceptable salt thereof.

9. A pharmaceutical composition that comprises a compound of claims 1-8 or a pharmaceutically-acceptable salt thereof, and a pharmaceutically-acceptable diluent or carrier.

10. A method of treating a bacterial infection in a warm-blooded animal, such as a human being, in need of such treatment, which comprises administering to said animal an effective amount of a compound of claims 1-8, or a pharmaceutically-acceptable salt thereof.

11. A method for inhibiting bacterial DNA gyrase in a warm-blooded animal, such as a human being, in need of such treatment which comprises administering to said animal an effective amount of a compound of claims 1-8 or a pharmaceutically acceptable salt.

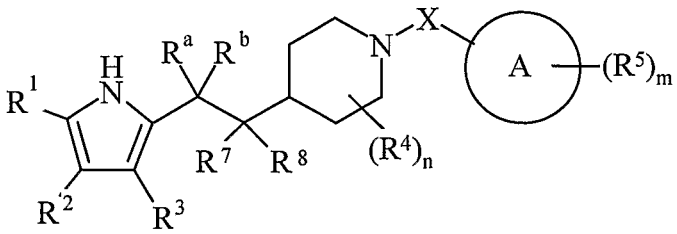
12. A compound of claims 1-8 and pharmaceutically acceptable salts thereof for use as a medicament.

13. The use of a compound of claims 1-8 formula **(I)**, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the production of an anti-bacterial effect in a warm-blooded animal such as a human being.

14. The use of a compound of claims 1-8 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of a bacterial infection in a warm-blooded animal such as a human being.

15. A process for preparing compounds of formula **(I)** or pharmaceutically-acceptable salts thereof, comprising:

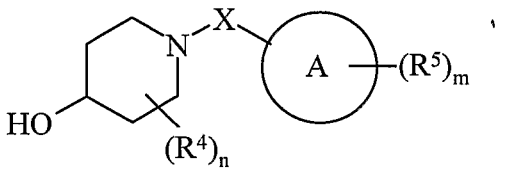
Process a) for compounds of formula **(I)** wherein W is -C(R^7)(R^8)-; converting a compound of formula **(II)**:



(II)

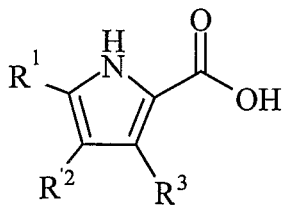
wherein R^a is cyano and R^b is dimethyamino or diethylamino; or R^a and R^b are independently selected from C_{1-4}alkylthio; or R^a and R^b together form 1,3-dithianyl or 1,3-dithiolanyl; into a compound of formula **(I)**;

Process b) for compounds of formula **(I)** wherein W is -O-; reacting a compound of formula **(III)**:



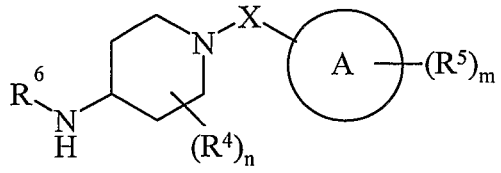
(III)

with a compound of formula **(IV)**:



(IV)

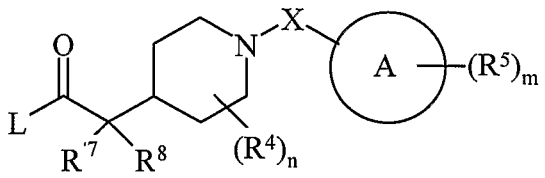
Process c) for compounds of formula **(I)** wherein W is -N(R^6)-; reacting a compound of formula **(V)**:



(V)

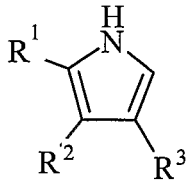
with a compound of formula **(IV)** or an activated acid derivative thereof;

Process d) for compounds of formula **(I)** wherein W is -C(R^7)(R^8)-; reacting a compound of formula **(VI)**:



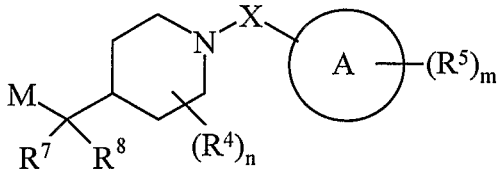
(VI)

wherein L is a displaceable group; with a compound of formula **(VII)**:



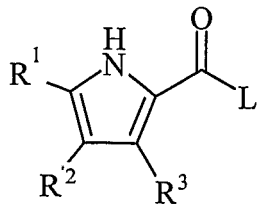
(VII)

Process e) for compounds of formula **(I)** wherein W is -C(R^7)(R^8)-; reacting a compound of formula **(VIII)**:



(VIII)

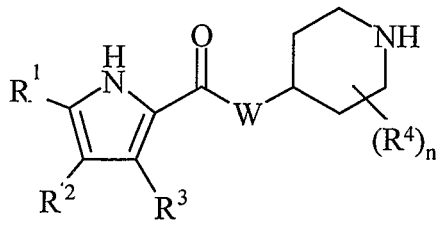
wherein M is an organometallic group; with a compound of formula **(IX)**:



(IX)

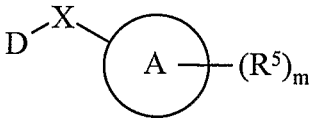
wherein L is a displaceable group;

Process f) reacting a compound of formula **(X)**:



(X)

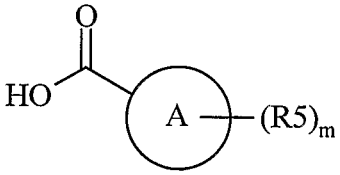
with a compound of formula **(XI)**:



(XI)

wherein D is a displaceable group;

Process g) for compounds of formula **(I)** wherein X is -C(O)-; reacting a compound of formula **(X)** with a compound of formula **(XII)**:



(XII)

and thereafter if necessary:

i) converting a compound of the formula **(I)** into another compound of the formula **(I)**;

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt.