HU000033281T2

(19) **HU**

(11) Lajstromszám: **E 033 281**

(13) **T2**

MAGYARORSZÁG
Szellemi Tulajdon Nemzeti Hivatala

EURÓPAI SZABADALOM
SZÖVEGÉNEK FORDÍTÁSA

(21) Magyar ügyszám: **E 07 732629**
(22) A bejelentés napja: **2007. 05. 01.**

(96) Az európai bejelentés bejelentési száma:
EP 20070732629
(97) Az európai bejelentés közzétételi adatai:
EP 2013175 A1 **2007. 11. 15.**
(97) Az európai szabadalom megadásának meghirdetési adatai:
EP 2013175 B1 **2016. 11. 09.**

(51) Int. Cl.: ***C07D213/73*** *(2006.01)*
A61P 1/00 *(2006.01)*
A61P 37/00 *(2006.01)*
A61K 31/44 *(2006.01)*
A61P 29/00 *(2006.01)*

(86) A nemzetközi (PCT) bejelentési szám:
PCT/GB 07/001596
(87) A nemzetközi közzétételi szám:
WO 07129040

(30) Elsőbbségi adatok:
0608855 **2006. 05. 04.** **GB**
0613914 **2006. 07. 13.** **GB**

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(54) **p38 mitogén-aktivált protein (MAP) kináz inhibitorok**

Az európai szabadalom ellen, megadásának az Európai Szabadalmi Közlönyben való meghirdetésétől számított kilenc hónapon belül, felszólalást lehet benyújtani az Európai Szabadalmi Hivatalnál. (Európai Szabadalmi Egyezmény 99. cikk(1))

A fordítást a szabadalmas az 1995. évi XXXIII. törvény 84/H. §-a szerint nyújtotta be. A fordítás tartalmi helyességét a Szellemi Tulajdon Nemzeti Hivatala nem vizsgálta.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 2 013 175 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
09.11.2016 Bulletin 2016/45

(21) Application number: **07732629.6**

(22) Date of filing: **01.05.2007**

(51) Int Cl.:
C07D 213/73 *(2006.01)* ***A61K 31/44*** *(2006.01)*
A61P 1/00 *(2006.01)* ***A61P 29/00*** *(2006.01)*
A61P 37/00 *(2006.01)*

(86) International application number:
PCT/GB2007/001596

(87) International publication number:
WO 2007/129040 (15.11.2007 Gazette 2007/46)

(54) p38 MAP KINASE INHIBITORS

P38-MAP-KINASE-INHIBITOREN

INHIBITEURS DE PROTÉINE-KINASE ASSOCIÉE AUX MEMBRANES p38

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU LV MC MT NL PL PT RO SE SI SK TR

(30) Priority: **04.05.2006 GB 0608855**
13.07.2006 GB 0613914

(43) Date of publication of application:
14.01.2009 Bulletin 2009/03

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WO-A-03/076405 **WO-A1-2009/106844**

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Description

[0001] This invention relates to a series of amino acid and amino acid ester compounds, to compositions containing them, to processes for their preparation and to their use in medicine as p38 MAP kinase inhibitors for the treatment of autoimmune and inflammatory diseases, including rheumatoid arthritis, psoriasis, inflammatory bowel disease, Crohns disease, ulcerative colitis, chronic obstructive pulmonary disease, asthma, multiple sclerosis, diabetes, atopic dermatitis, graft versus host disease, systemic lupus erythematosus and others.

Background of the Invention

[0002] Inappropriate activation of leukocytes including monocytes, macrophages and neutrophils leading to the production of elevated levels cytokines such as TNF-α, IL1-β and IL-8, is a feature of the pathogenesis of several inflammatory diseases including rheumatoid arthritis, ulcerative colitis, Crohn's disease, chronic obstructive pulmonary disease (COPD), asthma and psoriasis. The production of cytokines by inflammatory cells is a result of response to a variety of external stimuli, leading to the activation of a number of intracellular signalling mechanisms. Prominent amongst these is the mitogen-activated protein kinase (MAPK) superfamily consisting of highly conserved signalling kinases that regulate cell growth, differentiation and stress responses. Mammalian cells contain at least three families of MAPKs: the p42/44 extracellular signal-regulated kinase (ERK) MAPKs, c-Jun NH2-terminal kinases (JNKs) and p38 MAPK (also termed p38a/Mpk2/RK/SAPK2a/CSBP1/2). p38 MAPK was first cloned following its identification as a kinase that is tyrosine phosphorylated after stimulation of monocytes by lipopolysaccharide (LPS) [Han et al, Science 1994,265,808]. Additional homologues of mammalian p38 have been described and include p38β [Jiang et al, J.Biol.Chem, 1996, 271, 17920], p38γ [Li et al, Biochem. Biophys. Res. Commun., 1996, 228, 334] and p38δ [Jiang et al, J.Biol.Chem. 1997, 272, 30122]. While p38α and p38β are ubiquitously expressed, p38γ is restricted primarily to skeletal muscle and p38δ is predominantly expressed in lung and kidney.

[0003] The release of cytokines by host defence cells and the response of leukocytes to cytokines and other pro-inflammatory stresses are to varying extent regulated by p38 MAPK [Cuenda et al, FEBS Lett, 1995, 364, 229-233]. In other cell types, p38 MAPK controls stress responses such as the production of IL-8 by bronchial epithelial cells stimulated by TNF-α, and the up-regulation of the cell adhesion molecule ICAM-1 in LPS-stimulated endothelial cells. Upon activation, via dual phosphorylation of a TGY motif by the dual specificity kinases MKK3 and MKK6, p38 MAPK exerts its effects through phosphorylation of transcription factors and other kinases. MAP kinase-activated protein kinase-2 (MAPKAPK-2) has been identified as a target for p38 phosphorylation. It has been demonstrated that mice [Kotlyarov et al, Nat. Cell Biol. 1999, 1, 94-97] lacking MAPKAP-K2 release reduced levels of TNF-α, IL-1β, IL-6, IL-10 and IFN-γ in response to LPS/galactosamine mediated endotoxic shock. The regulation of the levels of these cytokines as well as COX-2 is at the mRNA level. TNF-α levels are regulated through translational control via AU-rich elements of the 3'-UTR of TNF-α mRNA, with MAPKAP-K2 signalling increasing TNF-α mRNA translation. MAPKAP-K2 signalling leads to increased mRNA stability for COX-2, IL-6 and macrophage inflammatory protein. MAPKAP K2 determines the cellular location of p38 MAPK as well as transducing p38 MAPK signalling, possessing a nuclear localisation signal at its carboxyl terminus and a nuclear export signal as part of its autoinhibitory domain [Engel et al, EMBO J. 1998, 17, 3363-3371]. In stressed cells, MAPKAP-K2 and p38 MAPK migrate to the cytoplasm from the nucleus, this migration only occurring when p38 MAPK is catalytically active. It is believed that this event is driven by the exposure of the MAPKAP-K2 nuclear export signal, as a result of phosphorylation by p38 MAPK [Meng et al, J. Biol. Chem. 2002, 277, 37401-37405]. Additionally p38 MAPK either directly or indirectly leads to the phosphorylation of several transcription factors believed to mediate inflammation, including ATF1/2 (activating transcription factors 1/2), CHOP-10/GADD-153 (growth arrest and DNA damage inducible gene 153), SAP-1 (serum response factor accessory protein-1) and MEF2C (myocyte enhancer factor-2) [Foster et al, Drug News Perspect. 2000, 13, 488-497].

[0004] It has been demonstrated in several instances that the inhibition of p38 MAPK activity by small molecules, is useful for the treatment of several disease states mediated by inappropriate cytokine production including rheumatoid arthritis, COPD, asthma and cerebral ischemia. This modality has been the subject of several reviews [Salituro et al, Current Medicinal Chemistry, 1999, 6, 807-823 and Kumar et al, Nature Reviews Drug Discovery 2003, 2, 717-726].

[0005] Inhibitors of p38 MAPK have been shown to be efficacious in animal models of rheumatoid arthritis, such as collagen-induced arthritis in rat [Revesz et al, Biorg. Med. Chem. Lett., 2000, 10, 1261-1364] and adjuvant-induced arthritis in rat [Wadsworth et al, J. Pharmacol. Exp. Ther., 1999, 291, 1685-1691 In murine models of pancreatitis-induced lung injury, pretreatment with a p38 MAPK inhibitor reduced TNF-α release in the airways and pulmonary edema [Denham et al, Crit. Care Med., 2000, 29, 628 and Yang et al, Surgery, 1999, 126, 216]. Inhibition of p38 MAPK before ovalbumin (OVA) challenge in OVA-sensitized mice decreased cytokine and inflammatory cell accumulation in the airways in an allergic airway model of inflammation, [Underwood et al, J. Pharmacol. Exp. Ther., 2000,293, 281]. Increased activity of p38 MAP kinase has been observed in patients suffering from inflammatory bowel disease [Waetzig et al, J. Immunol, 2002,168, 5432-5351]. p38 MAPK inhibitors have been shown to be efficacious in rat models of cardiac hypertrophy

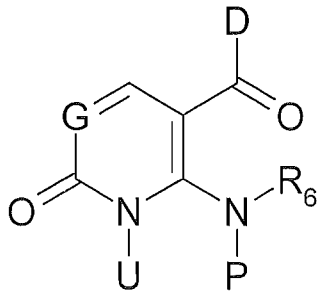
[Behr et al, Circulation, 2001, 104, 1292-1298] and cerebral focal ischemia [Barone et al, J. Pharmacol. Exp. Ther., 2001, 296, 312-321].

[0006] We have now discovered a group of compounds which are potent and selective inhibitors of p38 MAPK (p38α,β,γ and δ) and the isoforms and splice variants thereof especially p38α, p38β and p38β2. The compounds are thus of use in medicine, for example in the treatment and prophylaxis of immune and inflammatory disorders described herein. The compounds are characterised by the presence in the molecule of an amino acid motif or an amino acid ester motif which is hydrolysable by an intracellular carboxylesterase. Compounds of the invention having the lipophilic amino acid ester motif cross the cell membrane, and are hydrolysed to the acid by the intracellular carboxylesterases. The polar hydrolysis product accumulates in the cell since it does not readily cross the cell membrane. Hence the p38 MAP kinase activity of the compound is prolonged and enhanced within the cell. The compounds of the invention are related to the p38 MAP kinase inhibitors encompassed by the disclosures in International Patent Application WO03076405 but differ therefrom in that the present compounds have the amino acid ester motif referred to above.

[0007] WO 2003/076905 discusses monocyclic aroylpyridines, processes for their production and their use as medicaments, especially in the treatment of COPD.

Detailed Description of the Invention

[0008] According to the invention there is provided a compound of formula (I):



(I)

wherein:

G is -CH=

D is an optionally substituted phenyl ring;

$\mathbf{R_6}$ is hydrogen;

P represents hydrogen and U represents a radical of formula (IA); or U represents hydrogen and P represents a radical of formula (IA);

$$-A-(CH_2)_z-X^1-L^1-Y-NH-CHR_1R_2 \qquad (IA)$$

wherein

A represents an optionally substituted phenyl or cyclohexyl ring;

z is 0 or 1;

Y is a bond, -C(=O)-, $-S(=O)_2-$, $-C(=O)NR_3-$, $-C(=S)-NR_3$, $-C(=NH)NR_3$ or $-S(=O)_2NR_3-$ wherein R_3 is hydrogen or optionally substituted C_1-C_6 alkyl;

$\mathbf{L^1}$ is a divalent radical of formula $-(Alk^1)_m(Q)_n(Alk^2)_p-$ wherein

m, n and p are independently 0 or 1,

Q is (i) an optionally substituted divalent mono- or bicyclic carbocyclic or heterocyclic radical having 5 - 13 ring members, or (ii), in the case where both m and p are 0, a divalent radical of formula $-X^2-Q^1-$ or $-Q^1-X^2-$ wherein X^2 is -O-, S- or NR^A- wherein R^A is hydrogen or optionally substituted C_1-C_3 alkyl, and Q^1 is an optionally substituted divalent mono- or bicyclic carbocyclic or heterocyclic radical having 5 - 13 ring members,

$\mathbf{Alk^1}$ and $\mathbf{Alk^2}$ independently represent optionally substituted divalent C_3-C_7 cycloalkyl radicals, or optionally substituted straight or branched, C_1-C_6 alkylene, C_2-C_6 alkenylene ,or C_2-C_6 alkynylene radicals which may optionally contain or terminate in an ether (-O-), thioether (-S-) or amino ($-NR^A-$) link wherein R^A is hydrogen or optionally substituted C_1-C_3 alkyl; and

X^1 represents a bond; -C(=O); or -$S(=O)_2$-; -$NR_4C(=O)$-, -$C(=O)NR_4$-,-$NR_4C(=O)NR_5$-,-$NR_4S(=O)_2$-, or -$S(=O)_2NR_4$- wherein R_4 and R_5 are independently hydrogen or optionally substituted C_1-C_6 alkyl.

R_1 is an ester group which is hydrolysable by one or more intracellular carboxylesterase enzymes to a carboxylic acid group; and

$\mathbf{R}_2$ is selected from:

(i) C_1-C_6 alkyl, phenyl, 2,- 3-, or 4-hydroxyphenyl, 2,- 3-, or 4-methoxyphenyl, 2,-3-, or 4-pyridylmethyl, benzyl, phenylethyl, 2-, 3-, or 4-hydroxybenzyl, 2,- 3-, or 4-benzyloxybenzyl, 2,- 3-, or 4- C_1-C_6 alkoxybenzyl, and benzyloxy(C_1-C_6alkyl)-groups;

(ii) the characterising group of a natural α amino acid, in which any functional group may be protected;

(iii) groups -$[Alk]_nR_6$ where Alk is a (C_1-C_6)alkyl or (C_2-C_6)alkenyl group optionally interrupted by one or more -O-, or -S- atoms or -$N(R_7)$- groups [where R_7 is a hydrogen; atom or a (C_1-C_6)alkyl group], n is 0 or 1, and R_6 is an optionally substituted cycloalkyl or cycloalkenyl group;

(iv) a benzyl group substituted in the phenyl ring by a group of formula -OCH_2COR_{15} where R_{15} is hydroxyl, amino, (C_1-C_6)alkoxy, phenyl(C_1-C_6)alkoxy, (C_1-C_6)alkylamino, di((C_1-C_6)alkyl)amino, phenyl(C_1-C_6)alkylamino, the residue of an amino acid or acid halide, ester or amide derivative thereof, said residue being linked via an amide bond, said amino acid being selected from glycine, α or β alanine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan, serine, threonine, cysteine, methionine, asparagine, glutamine, lysine, histidine, arginine, glutamic acid, and aspartic acid;

(v) a heterocyclic(C_1-C_6)alkyl group, either being unsubstituted or mono- or di-substituted in the heterocyclic ring with halo, nitro, carboxy, (C_1-C_6)alkoxy, cyano, (C_1-C_6)alkanoyl, trifluoromethyl (C_1-C_6)alkyl, hydroxy, formyl, amino, (C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, mercapto, (C_1-C_6)alkylthio, hydroxy(C_1-C_6)alkyl, mercapto(C_1-C_6)alkyl or (C_1-C_6)alkylphenylmethyl; and

(vi) a group -$CR_aR_bR_c$ in which:

each of R_a, R_b and R_c is independently hydrogen, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, phenyl(C_1-C_6)alkyl, (C_3-C_8)cycloalkyl; or

R_c is hydrogen and R_a and R_b are independently phenyl or heteroaryl such as pyridyl; or

R_c is hydrogen, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, phenyl(C_1-C_6)alkyl, or (C_3-C_8)cycloalkyl, and R_a and R_b together with the carbon atom to which they are attached form a 3 to 8 membered cycloalkyl or a 5- to 6-membered heterocyclic ring; or

R_a, R_b and R_c together with the carbon atom to which they are attached form a tricyclic ring (for example adamantyl); or

R_a and R_b are each independently (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, phenyl(C_1-C_6)alkyl, or a group as defined for R_c below other than hydrogen, or R_a and R_b together with the carbon atom to which they are attached form a cycloalkyl or heterocyclic ring, and R_c is hydrogen, -OH, -SH, halogen, -CN,-CO_2H, (C_1-C_4)perfluoroalkyl, -CH_2OH, -CO_2(C_1-C_6)alkyl, -O(C_1-C_6)alkyl, -O(C_2-C_6)alkenyl, -S(C_1-C_6)alkyl, -SO(C_1-C_6)alkyl, -SO_2(C_1-C_6) alkyl, -S(C_2-C_6)alkenyl,-SO(C_2-C_6)alkenyl, -SO_2(C_2-C_6)alkenyl or a group -Q^2-W wherein Q^2 represents a bond or -O-, -S-, -SO- or -SO_2- and W represents a phenyl, phenylalkyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkylalkyl, (C_4-C_8)cycloalkenyl, (C_4-C_8)cycloalkenylalkyl, heteroaryl or heteroarylalkyl group, which group W may optionally be substituted by one or more substituents independently selected from, hydroxyl, halogen, -CN, -CO_2H, -CO_2(C_1-C_6)alkyl, -$CONH_2$, -CONH(C_1-C_6)alkyl, -CONH(C_1-C_6alkyl)$_2$, -CHO, -CH_2OH, (C_1-C_4)perfluoroalkyl, -O(C_1-C_6)alkyl, -S(C_1-C_6)alkyl, -SO(C_1-C_6)alkyl, -SO_2(C_1-C_6)alkyl, -NO_2, -NH_2, -NH(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, -NHCO(C_1-C_6)alkyl, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_8)cycloalkyl, (C_4-C_8)cycloalkenyl, phenyl or benzyl;

unless otherwise specified in the context in which it occurs, the term "substituted" as applied to any moiety herein means substituted with up to four compatible substituents, each of which independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxy, hydroxy(C_1-C_6)alkyl, mercapto, mercapto(C_1-C_6)alkyl, (C_1-C_6)alkylthio, phenyl, halo includ-

ing fluoro, bromo and chloro, trifluoromethyl, trifluoromethoxy, nitro, nitrile (-CN), oxo, -COOH, -$COOR^A$, -COR^A, -SO_2R^A, -$CONH_2$, -SO_2NH_2, -$CONHR^A$, -SO_2NHR^A,-$CONR^AR^B$, -$SO_2NR^AR^B$, -NH_2, -NHR^A, -NR^AR^B, -$OCONH_2$, -$OCONHR^A$, -$OCONR^AR^B$,-$NHCOR^A$, -$NHCOOR^A$, -NR^BCOOR^A, -$NHSO_2OR^A$, -NR^BSO_2OH, -$NR^BSO_2OR^A$,-$NHCONH_2$, -NR^ACONH_2, -$NHCONHR^B$, -NR^ACONHR^B, -$NHCONR^AR^B$, or -$NR^ACONR^AR^B$ wherein R^A and R^B are independently a (C_1-C_6)alkyl, (C_3-C_6) cycloalkyl, phenyl or monocyclic heteroaryl having 5 or 6 ring atoms.

[0009] Compounds of formula (I) above may be prepared in the form of salts, especially pharmaceutically acceptable salts, N-oxides, hydrates, and solvates thereof. Any claim to a compound herein, or reference herein to "compounds of the invention", "compounds with which the invention is concerned", "compounds of formula (I)" and the like, includes salts, N-oxides, hydrates, and solvates of such compounds.

[0010] Although the above definition potentially includes molecules of high molecular weight, it is preferable, in line with general principles of medicinal chemistry practice, that the compounds with which this invention is concerned should have molecular weights of no more than 600.

[0011] The present invention also provides a pharmaceutical composition comprising a compounds defined above together with a pharmaceutically acceptable carrier.

[0012] The compounds with which the invention is concerned may be used for the inhibition of p38 MAP kinase enzyme activity *in vitro* or *in vivo.*

[0013] In one aspect of the invention, the invention provides a compound as defined above for the treatment of autoimmune or inflammatory disease, particularly those mentioned above in which p38 MAP kinase activity plays a role.

Terminology

[0014] The term "ester" or "esterified carboxyl group" means a group $R^XO(C=O)$- in which R^X is the group characterising the ester, notionally derived from the alcohol R^XOH.

[0015] As used herein, the term "(C_a-C_b)alkyl" wherein a and b are integers refers to a straight or branched chain alkyl radical having from a to b carbon atoms. Thus when a is 1 and b is 6, for example, the term includes methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl and n-hexyl.

[0016] As used herein the term "divalent (C_a-C_b)alkylene radical" wherein a and b are integers refers to a saturated hydrocarbon chain having from a to b carbon atoms and two unsatisfied valences.

[0017] As used herein the term "(C_a-C_b)alkenyl" wherein a and b are integers refers to a straight or branched chain alkenyl moiety having from a to b carbon atoms having at least one double bond of either E or Z stereochemistry where applicable. The term includes, for example, vinyl, allyl, 1- and 2-butenyl and 2-methyl-2-propenyl.

[0018] As used herein the term "divalent (C_a-C_b)alkenylene radical" means a hydrocarbon chain having from a to b carbon atoms, at least one double bond, and two unsatisfied valences.

[0019] As used herein the term "C_a-C_b alkynyl" wherein a and b are integers refers to straight chain or branched chain hydrocarbon groups having from a to b carbon atoms and having in addition one triple bond. This term would include for example, ethynyl, 1-propynyl, 1- and 2-butynyl, 2-methyl-2-propynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl.

[0020] As used herein the term "divalent (C_a-C_b)alkynylene radical" wherein a and b are integers refers to a divalent hydrocarbon chain having from a to b carbon atoms, and at least one triple bond.

[0021] As used herein the term "carbocyclic" refers to a mono-, bi- or tricyclic radical having up to 16 ring atoms, all of which are carbon, and includes aryl and cycloalkyl.

[0022] As used herein the term "cycloalkyl" refers to a monocyclic saturated carbocyclic radical having from 3-8 carbon atoms and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

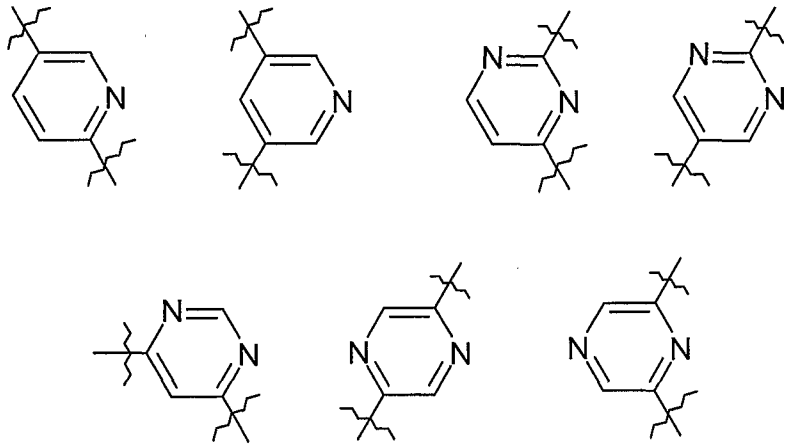
[0023] As used herein the unqualified term "aryl" refers to a mono-, bi- or tri-cyclic carbocyclic aromatic radical, and includes radicals having two monocyclic carbocyclic aromatic rings which are directly linked by a covalent bond. Illustrative of such radicals are phenyl, biphenyl and napthyl.

[0024] As used herein the unqualified term "heteroaryl" refers to a mono-, bi- or tri-cyclic aromatic radical containing one or more heteroatoms selected from S, N and O, and includes radicals having two such monocyclic rings, or one such monocyclic ring and one monocyclic aryl ring, which are directly linked by a covalent bond. Illustrative of such radicals are thienyl, benzthienyl, furyl, benzfuryl, pyrrolyl, imidazolyl, benzimidazolyl, thiazolyl, benzthiazolyl, isothiazolyl, benzisothiazolyl, pyrazolyl, oxazolyl, benzoxazolyl, isoxazolyl, benzisoxazolyl, isothiazolyl, triazolyl, benztriazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, indolyl and indazolyl.

[0025] As used herein the unqualified term "heterocyclyl" or "heterocyclic" includes "heteroaryl" as defined above, and in its non-aromatic meaning relates to a mono-, bi- or tri-cyclic non-aromatic radical containing one or more heteroatoms selected from S, N and O, and to groups consisting of a monocyclic non-aromatic radical containing one or more such heteroatoms which is covalently linked to another such radical or to a monocyclic carbocyclic radical. Illustrative of such

radicals are pyrrolyl, furanyl, thienyl, piperidinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrimidinyl, piperazinyl, indolyl, morpholinyl, benzfuranyl, pyranyl, isoxazolyl, benzimidazolyl, methylenedioxyphenyl, ethylenedioxyphenyl, maleimido and succinimido groups.

[0026] A "divalent phenylene, pyridinylene, pyrimidinylene, or pyrazinylene radical" is a benzene, pyridine, pyrimidine or pyrazine ring, with two unsatisfied valencies, and includes 1,3-phenylene, 1,4-phenylene, and the following:



[0027] Unless otherwise specified in the context in which it occurs, the term "substituted" as applied to any moiety herein means substituted with up to four compatible substituents, each of which independently may be, for example, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, hydroxy, hydroxy$(C_1\text{-}C_6)$alkyl, mercapto, mercapto$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylthio, phenyl, halo (including fluoro, bromo and chloro), trifluoromethyl, trifluoromethoxy, nitro, nitrile (-CN), oxo, -COOH, $-COOR^A$, $-COR^A$, $-SO_2R^A$, $-CONH_2$, $-SO_2NH_2$, $-CONHR^A$, $-SO_2NHR^A$, $-CONR^AR^B$, $-SO_2NR^AR^B$, $-NH_2$, $-NHR^A$, $-NR^AR^B$, $-OCONH_2$, $-OCONHR^A$, $-OCONR^AR^B$, $-NHCOR^A$, $-NHCOOR^A$, $-NR^BCOOR^A$, $-NHSO_2OR^A$, $-NR^BSO_2OH$, $-NR^BSO_2OR^A$, $-NHCONH_2$, $-NR^ACONH_2$, $-NHCONHR^B$, $-NR^ACONHR^B$, $-NHCONR^AR^B$, or $-NR^ACONR^AR^B$ wherein R^A and R^B are independently a $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$ cycloalkyl , phenyl or monocyclic heteroaryl having 5 or 6 ring atoms. An "optional substituent" may be one of the foregoing substituent groups.

[0028] The term "side chain of a natural or non-natural alpha-amino acid" refers to the group R^Y in a natural or non-natural amino acid of formula $NH_2\text{-}CH(R^Y)\text{-}COOH$.

[0029] Examples of side chains of natural alpha amino acids include those of alanine, arginine, asparagine, aspartic acid, cysteine, cystine, glutamic acid, histidine, 5-hydroxylysine, 4-hydroxyproline, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, α-aminoadipic acid, α-amino-n-butyric acid, 3,4-dihydroxyphenylalanine, homoserine, α-methylserine, ornithine, pipecolic acid, and thyroxine.

[0030] Natural alpha-amino acids which contain functional substituents, for example amino, carboxyl, hydroxy, mercapto, guanidyl, imidazolyl, or indolyl groups in their characteristic side chains include arginine, lysine, glutamic acid, aspartic acid, tryptophan, histidine, serine, threonine, tyrosine, and cysteine. When R_2 in the compounds of the invention is one of those side chains, the functional substituent may optionally be protected.

[0031] The term "protected" when used in relation to a functional substituent in a side chain of a natural alpha-amino acid means a derivative of such a substituent which is substantially non-functional. For example, carboxyl groups may be esterified (for example as a $C_1\text{-}C_6$ alkyl ester), amino groups may be converted to amides (for example as a $NHCOC_1\text{-}C_6$ alkyl amide) or carbamates (for example as an $NHC(=O)OC_1\text{-}C_6$ alkyl or $NHC(=O)OCH_2Ph$ carbamate), hydroxyl groups may be converted to ethers (for example an $OC_1\text{-}C_6$ alkyl or a $O(C_1\text{-}C_6$ alkyl)phenyl ether) or esters (for example a $OC(=O)C_1\text{-}C_6$ alkyl ester) and thiol groups may be converted to thioethers (for example a tert-butyl or benzyl thioether) or thioesters (for example a $SC(=O)C_1\text{-}C_6$ alkyl thioester). Examples of side chains of non-natural alpha amino acids include those referred to below in the discussion of suitable R_2 groups for use in compounds of the present invention.

[0032] As used herein the term "salt" includes base addition, acid addition and quaternary salts. Compounds of the invention which are acidic can form salts, including pharmaceutically acceptable salts, with bases such as alkali metal hydroxides, e.g. sodium and potassium hydroxides; alkaline earth metal hydroxides e.g. calcium, barium and magnesium hydroxides; with organic bases e.g. N-methyl-D-glucamine, choline tris(hydroxymethyl)amino-methane, L-arginine, L-lysine, N-ethyl piperidine, dibenzylamine and the like. Those compounds (I) which are basic can form salts, including pharmaceutically acceptable salts with inorganic acids, e.g. with hydrohalic acids such as hydrochloric or hydrobromic acids, sulphuric acid, nitric acid or phosphoric acid and the like, and with organic acids e.g. with acetic, tartaric, succinic, fumaric, maleic, malic, salicylic, citric, methanesulphonic, p-toluenesulphonic, benzoic, benzenesulphonic, glutamic, lactic, and mandelic acids and the like. For a review on suitable salts, see Handbook of Pharmaceutical Salts: Properties,

Selection, and Use by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

[0033] The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and a stoichiometric amount of one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

[0034] Compounds of the invention which contain one or more actual or potential chiral centres, because of the presence of asymmetric carbon atoms, can exist as enantiomers or as a number of diastereoisomers with R or S stereochemistry at each chiral centre. The invention includes all such enantiomers and diastereoisomers and mixtures thereof.

[0035] As mentioned, the esters of the invention are converted by intracellular esterases to the carboxylic acids. Both the esters and carboxylic acids may have p38 MAP kinase inhibitory activity in their own right.

[0036] In the compounds with which the invention is concerned:

The group D

D is an optionally substituted phenyl ring.

The substituent $\mathbf{R_6}$

R_6 is hydrogen.

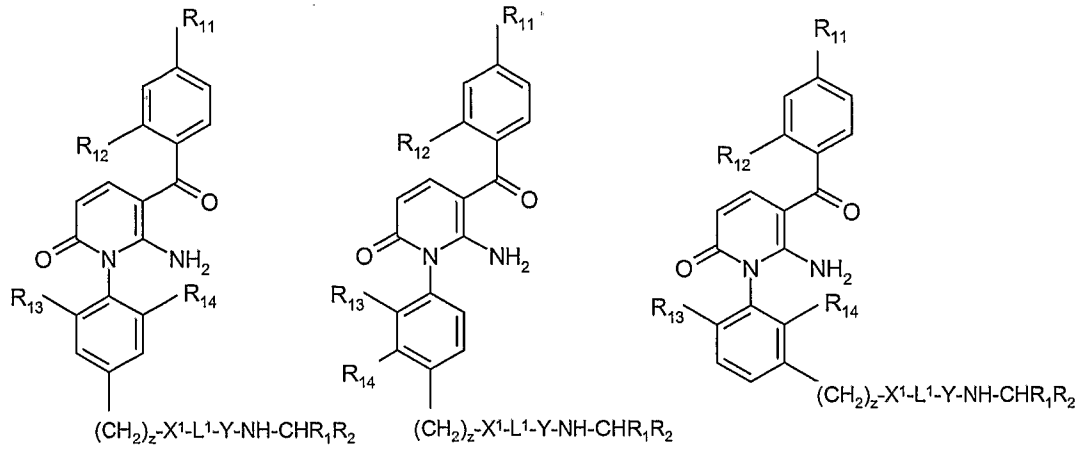
P/U regioisomers

Presently it is preferred that P be hydrogen and U be a radical of formula (IA) as defined above.

The radical A

In the radical of formula (IA), it is currently preferred that A be optionally substituted 1,4 phenylene. In that case preferred optional substituents include fluoro and chloro. A may also be a cyclohexyl ring, which is optionally substituted.

[0037] A particularly preferred sub-group of compounds of the invention consists of those of formula (IIA), (IIB) and (IIC):



(IIA) (IIB) (IIC)

wherein R_{11} = F, R_{12} = H, R_{13} = H and R_{14} = H; or
R_{11} = F, R_{12} = F, R_{13} = H and R_{14} = H; or
R_{11} = F, R_{12} = H, R_{13} = F and R_{14} = F; or
R_{11} = F, R_{12} = F, R_{13} = F and R_{14} = F; or
R_{11} = F, R_{12} = F, R_{13} = F and R_{14} = H

and wherein z, X^1, L^1, Y, R^1 and R^2 are as defined above with reference to formula (I), and as further discussed below.

The radical -Y-L^1-X^1-$[CH_2]_z$-

[0038] This radical (or bond) arises from the particular chemistry strategy chosen to link the amino acid ester motif $R_1CH(R_2)NH$- to the ring system A. Clearly the chemistry strategy for that coupling may vary widely, and thus many combinations of the variables Y, L^1, X^1 and z are possible. The precise combination of variables making up the linking chemistry between the amino acid ester motif and the ring system A will often be irrelevant to the primary binding mode of the compound as a whole. On the other hand, that linkage chemistry will in some cases pick up additional binding

interactions with the enzyme. It should also be noted that the benefits of the amino acid ester motif (facile entry into the cell, esterase hydrolysis within the cell, and accumulation within the cell of active carboxylic acid hydrolysis product) are best achieved when the linkage between the amino acid ester motif and the ring system A is not a substrate for peptidase activity within the cell, which might result in cleavage of the amino acid from the molecule. Of course, stability to intracellular peptidases is easily tested by incubating the compound with disrupted cell contents, and analysing for any such cleavage.

[0039] With the foregoing general observations in mind, taking the variables making up the radical-Y-L^1-X^1-$[CH_2]_z$- in turn:

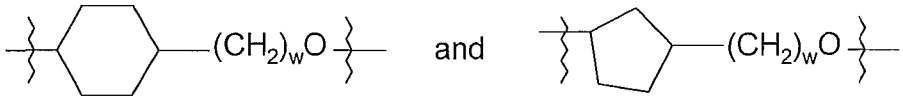
z may be 0 or 1, so that a methylene radical linked to the ring system A is optional;

specific preferred examples of Y when macrophage selectivity is not required include-(C=O)- and -(C=O)NH-; Where macrophage selectivity is required any of the other options for Y, including the case where Y is a bond, are appropriate. In the radical L^1, examples of Alk^1 and Alk^2 radicals, when present, include $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, -CH=CH-, $-CH=CHCH_2-$, $-CH_2CH=CH-$, $CH_2CH=CHCH_2-C\equiv C-$, $-C\equiv CCH_2-$, $CH_2C\equiv C-$, and $CH_2C\equiv CCH_2$. Additional examples of Alk^1 and Alk^2 include $-CH_2W-$, $-CH_2CH_2W-$, $-CH_2CH_2WCH_2-$, $-CH_2CH_2WCH(CH_3)-$, $-CH_2WCH_2CH_2-$, $-CH_2WCH_2CH_2WCH_2-$ and $-WCH_2CH_2-$ where W is -O-, -S-, -NH-, $-N(CH_3)-$, or $-CH_2CH_2N(CH_2CH_2OH)CH_2-$. Further examples of Alk^1 and Alk^2 include divalent cyclopropyl, cyclopentyl and cyclohexyl radicals.

In L^1, when n is 0, the radical is a hydrocarbon chain (optionally substituted and perhaps having an ether, thioether or amino linkage). Presently it is preferred that there be no optional substituents in L^1. When both m and p are 0, L^1 is a divalent mono- or bicyclic carbocyclic or heterocyclic radical with 5 - 13 ring atoms (optionally substituted). When n is 1 and at least one of m and p is 1, L^1 is a divalent radical including a hydrocarbon chain or chains and a mono- or bicyclic carbocyclic or heterocyclic radical with 5 - 13 ring atoms (optionally substituted). When present, Q may be, for example, a divalent phenyl, naphthyl, cyclopropyl, cyclopentyl, or cyclohexyl radical, or a mono-, or bi-cyclic heterocyclic radical having 5 to13 ring members, such as piperidinyl, piperazinyl, indolyl, pyridyl, thienyl, or pyrrolyl radical, but 1,4-phenylene is presently preferred.

Specifically, in some embodiments of the invention, L^1, m and p may be 0 with n being 1. In other embodiments, n and p may be 0 with m being 1. In further embodiments, m, n and p may be all 0. In still further embodiments m may be 0, n may be 1 with Q being a monocyclic heterocyclic radical, and p may be 0 or 1. Alk^1 and Alk^2, when present, may be selected from $-CH_2-$, $-CH_2CH_2-$, and-$CH_2CH_2CH_2-$ and Q may be 1,4-phenylene.

[0040] Specific examples of the radical-Y-L^1-X^1-$[CH_2]_z$- include -C(=O)- and -C(=O)NH- as well as $-(CH_2)_v-$, $-(CH_2)_vO-$, $-C(=O)-(CH_2)_v-$, $-C(=O)-(CH_2)_vO-$, $-C(=O)-MH-(CH_2)_w-$, $-C(=O)-NH-(CH_2)_wO-$



wherein v is 1, 2, 3 or 4 and w is 1, 2 or 3, such as -Y-L^1-X^1-$[CH_2]_z$-, is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2O-$, $-CH_2CH_2O-$, $-CH_2CH_2CH_2O-$,$-CH_2CH_2CH_2CH_2O-$, $-C(=O)-CH_2-$, - $C(=O)-CH_2O-$, $-C(=O)-NH-CH_2-$, or $-C(=O)-NH-CH_2O-$.

The group R_1

[0041] The ester group R_1 must be one which in the compound of the invention is hydrolysable by one or more intracellular carboxylesterase enzymes to a carboxylic acid group. Intracellular carboxylesterase enzymes capable of hydrolysing the ester group of a compound of the invention to the corresponding acid include the three known human enzyme isotypes hCE-1, hCE-2 and hCE-3. Although these are considered to be the main enzymes, other enzymes such as biphenylhydrolase (BPH) may also have a role in hydrolysing the ester. In general, if the carboxylesterase hydrolyses the free amino acid ester to the parent acid it will also hydrolyse the ester motif when covalently conjugated to the inhibitor. Hence, the broken cell assay and/or the isolated carboxylesterase assay described herein provide a straightforward, quick and simple first screen for esters which have the required hydrolysis profile. Ester motifs selected in that way may then be re-assayed in the same carboxylesterase assay when conjugated to the inhibitor via the chosen conjugation chemistry, to confirm that it is still a carboxylesterase substrate in that background.

[0042] Subject to the requirement that they be hydrolysable by intracellular carboxylesterase enzymes, examples of particular ester groups R_1 include those of formula $-(C=O)OR_{14}$ wherein R_{14} is $R_8R_9R_{10}C-$ wherein

(i) R_8 is hydrogen or optionally substituted $(C_1\text{-}C_3)$alkyl-$(Z^1)_a$-$[(C_1\text{-}C_3)\text{alkyl}]_b$- or $(C_2\text{-}C_3)$alkenyl-$(Z^1)_a$-$[(C_1\text{-}C_3)\text{alkyl}]_b$- wherein a and b are independently 0 or 1 and Z^1 is -O-, -S-, or $-NR_{11}$- wherein R_{11} is hydrogen or $(C_1\text{-}C_3)$alkyl; and R_9 and R_{10} are independently hydrogen or $(C_1\text{-}C_3)$alkyl-;

(ii) R_8 is hydrogen or optionally substituted $R_{12}R_{13}N$-$(C_1\text{-}C_3)$alkyl- wherein R_{12} is hydrogen or $(C_1\text{-}C_3)$alkyl and R_{13} is hydrogen or $(C_1\text{-}C_3)$alkyl; or R_{12} and R_{13} together with the nitrogen to which they are attached form an optionally substituted monocyclic heterocyclic ring of 5- or 6- ring atoms or bicyclic heterocyclic ring system of 8 to 10 ring atoms, and R_9 and R_{10} are independently hydrogen or $(C_1\text{-}C_3)$alkyl-;or

(iii) R_8 and R_9 taken together with the carbon to which they are attached form an optionally substituted monocyclic carbocyclic ring of from 3 to 7 ring atoms or bicyclic carbocyclic ring system of 8 to 10 ring atoms, and R_{10} is hydrogen.

[0043] Within these classes, R_{10} is often hydrogen. Specific examples of R_{14} include methyl, ethyl, n- or iso-propyl, n-, sec- or tert-butyl, cyclohexyl, allyl, phenyl, benzyl, 2-, 3- or 4-pyridylmethyl, N-methylpiperidin-4-yl, tetrahydrofuran-3-yl or methoxyethyl. Currently preferred is where R_{14} is cyclopentyl.

[0044] Macrophages are known to play a key role in inflammatory disorders through the release of cytokines in particular TNFα and IL-1 (van Roon et al, Arthritis and Rheumatism, 2003, 1229-1238). In rheumatoid arthritis they are major contributors to the maintenance of joint inflammation and joint destruction. Macrophages are also involved in tumour growth and development (Naldini and Carraro, Curr Drug Targets Inflamm Allergy, 2005, 3-8). Hence agents that selectively target macrophage cell proliferation could be of value in the treatment of cancer and autoimmune disease. Targeting specific cell types would be expected to lead to reduced side-effects. The inventors have discovered a method of targeting p38 kinase inhibitors to macrophages which is based on the observation that the way in which the esterase motif is linked to the p38 kinase inhibitor determines whether it is hydrolysed, and hence whether or not it accumulates in different cell types. Specifically it has been found that macrophages contain the human carboxylesterase hCE-1 whereas other cell types do not. In the general formula (I) when the nitrogen of the esterase motif $R_1CH(R_2)NH$- is not directly linked to a carbonyl (-C(=O)-), ie when Y is not a -C(=O), -C(=O)O- or $-C(=O)NR_3$- radical, the ester will only be hydrolysed by hCE-1 and hence the inhibitors will only accumulate in macrophages. Herein, unless "monocyte" or "monocytes" is specified, the term macrophage or macrophages will be used to denote macrophages (including tumour associated macrophages) and/or monocytes.

The amino acid side chain R_2

[0045] Subject to the requirement that the ester group R_1 be hydrolysable by intracellular carboxylesterase enzymes, the identity of the side chain group R_2 is not critical.

[0046] Amino acid side chains are:

C_1-C_6 alkyl, phenyl, 2,- 3-, or 4-hydroxyphenyl, 2,- 3-, or 4-methoxyphenyl, 2,-3-, or 4-pyridylmethyl, benzyl, phenylethyl, 2-, 3-, or 4-hydroxybenzyl, 2,- 3-, or 4-benzyloxybenzyl, 2,- 3-, or 4- C_1-C_6 alkoxybenzyl, and benzyloxy(C_1-C_6alkyl)-groups;

the characterising group of a natural α amino acid, in which any functional group may be protected;

groups $-[Alk]_nR_6$ where Alk is a $(C_1\text{-}C_6)$alkyl or $(C_2\text{-}C_6)$alkenyl group optionally interrupted by one or more -O-, or -S- atoms or $-N(R_7)$- groups [where R_7 is a hydrogen atom or a $(C_1\text{-}C_6)$alkyl group], n is 0 or 1, and R_6 is an optionally substituted cycloalkyl or cycloalkenyl group;

a benzyl group substituted in the phenyl ring by a group of formula $-OCH_2COR_{15}$ where R_{15} is hydroxyl, amino, $(C_1\text{-}C_6)$alkoxy, phenyl$(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkylamino, di$((C_1\text{-}C_6)\text{alkyl})$amino, phenyl$(C_1\text{-}C_6)$alkylamino, the residue of an amino acid or acid halide, ester or amide derivative thereof, said residue being linked via an amide bond, said amino acid being selected from glycine, α or β alanine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan, serine, threonine, cysteine, methionine, asparagine, glutamine, lysine, histidine, arginine, glutamic acid, and aspartic acid;

a heterocyclic$(C_1\text{-}C_6)$alkyl group, either being unsubstituted or mono- or di-substituted in the heterocyclic ring with halo, nitro, carboxy, $(C_1\text{-}C_6)$alkoxy, cyano, $(C_1\text{-}C_6)$alkanoyl, trifluoromethyl $(C_1\text{-}C_6)$alkyl, hydroxy, formyl, amino, $(C_1\text{-}C_6)$alkylamino, di-$(C_1\text{-}C_6)$alkylamino, mercapto, $(C_1\text{-}C_6)$alkylthio, hydroxy$(C_1\text{-}C_6)$alkyl, mercapto$(C_1\text{-}C_6)$alkyl or $(C_1\text{-}C_6)$alkylphenylmethyl; and

a group $-CR_aR_bR_c$ in which:

each of R_a, R_b and R_c is independently hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, phenyl$(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl; or

R_c is hydrogen and R_a and R_b are independently phenyl or heteroaryl such as pyridyl; or

R_c is hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, phenyl$(C_1\text{-}C_6)$alkyl, or $(C_3\text{-}C_8)$cycloalkyl, and R_a and R_b together with the carbon atom to which they are attached form a 3 to 8 membered cycloalkyl or a 5- to 6-membered heterocyclic ring; or

R_a, R_b and R_c together with the carbon atom to which they are attached form a tricyclic ring (for example adamantyl); or

R_a and R_b are each independently $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, phenyl$(C_1\text{-}C_6)$alkyl, or a group as defined for R_c below other than hydrogen, or R_a and R_b together with the carbon atom to which they are attached form a cycloalkyl or heterocyclic ring, and R_c is hydrogen, -OH, -SH, halogen, -CN, $-CO_2H$, $(C_1\text{-}C_4)$perfluoroalkyl, $-CH_2OH$, $-CO_2(C_1\text{-}C_6)$alkyl, $-O(C_1\text{-}C_6)$alkyl, $-O(C_2\text{-}C_6)$alkenyl, $-S(C_1\text{-}C_6)$alkyl, $-SO(C_1\text{-}C_6)$alkyl, $-SO_2(C_1\text{-}C_6)$ alkyl, $-S(C_2\text{-}C_6)$alkenyl,$-SO(C_2\text{-}C_6)$alkenyl, $-SO_2(C_2\text{-}C_6)$alkenyl or a group $-Q^2$-W wherein Q^2 represents a bond or -O-, -S-, -SO- or $-SO_2$- and W represents a phenyl, phenylalkyl, $(C_3\text{-}C_8)$cycloalkyl, $(C_3\text{-}C_8)$cycloalkylalkyl, $(C_4\text{-}C_8)$cycloalkenyl, $(C_4\text{-}C_8)$cycloalkenylalkyl, heteroaryl or heteroarylalkyl group, which group W may optionally be substituted by one or more substituents independently selected from, hydroxyl, halogen, -CN, $-CO_2H$, $-CO_2(C_1\text{-}C_6)$alkyl, $-CONH_2$, $-CONH(C_1\text{-}C_6)$alkyl, $-CONH(C_1\text{-}C_6\text{alkyl})_2$, -CHO, $-CH_2OH$, $(C_1\text{-}C_4)$perfluoroalkyl, $-O(C_1\text{-}C_6)$alkyl, $-S(C_1\text{-}C_6)$alkyl, $-SO(C_1\text{-}C_6)$alkyl, $-SO_2(C_1\text{-}C_6)$alkyl, $-NO_2$, $-NH_2$, $-NH(C_1\text{-}C_6)$alkyl, $-N((C_1\text{-}C_6)\text{alkyl})_2$, $-NHCO(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_3\text{-}C_8)$cycloalkyl, $(C_4\text{-}C_8)$cycloalkenyl, phenyl or benzyl.

[0047] Examples of particular R_2 groups include hydrogen (the glycine "side chain"), benzyl, phenyl, cyclohexylmethyl, cyclohexyl, pyridin-3-ylmethyl, tert-butoxymethyl, iso-butyl, sec-butyl, tert-butyl, 1-benzylthio-1-methylethyl, 1-methylthio-1-methylethyl, 1-mercapto-1-methylethyl, and phenylethyl. Presently preferred R_2 groups include phenyl, benzyl, isobutyl, cyclohexyl and t-butoxymethyl.

[0048] For compounds of the invention which are to be administered systemically, esters with a slow rate of carboxylesterase cleavage are preferred, since they are less susceptible to pre-systemic metabolism. Their ability to reach their target tissue intact is therefore increased, and the ester can be converted inside the cells of the target tissue into the acid product. However, for local administration, where the ester is either directly applied to the target tissue or directed there by, for example, inhalation, it will often be desirable that the ester has a rapid rate of esterase cleavage, to minimise systemic exposure and consequent unwanted side effects. In the compounds of this invention, if the carbon adjacent to the alpha carbon of the alpha amino acid ester ester is monosubstituted, ie R_2 is CH_2R^z (R^z being the mono-substituent) then the esters tend to be cleaved more rapidly than if that carbon is di- or tri-substituted, as in the case where R_2 is, for example, phenyl or cyclohexyl.

[0049] As mentioned above, the compounds with which the invention is concerned are inhibitors of p38 MAK kinase activity, and are therefore of use in the treatment of diseases such as psoriasis, inflammatory bowel disease, Crohns disease, ulcerative colitis, chronic obstructive pulmonary disease, asthma, multiple sclerosis, diabetes, atopic dermatitis, graft versus host disease, or systemic lupus erythematosus and rheumatoid arthritis, in which p38 MAP kinase activity plays a part.

[0050] It will be understood that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing treatment. Optimum dose levels and frequency of dosing will be determined by clinical trial.

[0051] The compounds with which the invention is concerned may be prepared for administration by any route consistent with their pharmacokinetic properties. The orally administrable compositions may be in the form of tablets, capsules, powders, granules, lozenges, liquid or gel preparations, such as oral, topical, or sterile parenteral solutions or suspensions. Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricant, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants for example potato starch, or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions,

solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, glucose syrup, gelatin hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

[0052] For topical application to the skin, the drug may be made up into a cream, lotion or ointment. Cream or ointment formulations which may be used for the drug are conventional formulations well known in the art, for example as described in standard textbooks of pharmaceutics such as the British Pharmacopoeia.

[0053] For topical application by inhalation, the drug may be formulated for aerosol delivery for example, by pressure-driven jet atomizers or ultrasonic atomizers, or preferably by propellant-driven metered aerosols or propellant-free administration of micronized powders, for example, inhalation capsules or other "dry powder" delivery systems. Excipients, such as, for example, propellants (e.g. Frigen in the case of metered aerosols), surface-active substances, emulsifiers, stabilizers, preservatives, flavorings, and fillers (e.g. lactose in the case of powder inhalers) may be present in such inhaled formulations. For the purposes of inhalation, a large number of apparata are available with which aerosols of optimum particle size can be generated and administered, using an inhalation technique which is appropriate for the patient. In addition to the use of adaptors (spacers, expanders) and pear-shaped containers (e.g. Nebulator®, Volumatic®), and automatic devices emitting a puffer spray (Autohaler®), for metered aerosols, in particular in the case of powder inhalers, a number of technical solutions are available (e.g. Diskhaler®, Rotadisk®, Turbohaler® or the inhalers for example as described in European Patent Application EP 0 505 321).

[0054] For topical application to the eye, the drug may be made up into a solution or suspension in a suitable sterile aqueous or non aqueous vehicle. Additives, for instance buffers such as sodium metabisulphite or disodium edeate; preservatives including bactericidal and fungicidal agents such as phenyl mercuric acetate or nitrate, benzalkonium chloride or chlorhexidine, and thickening agents such as hypromellose may also be included.

[0055] The active ingredient may also be administered parenterally in a sterile medium. Depending on the vehicle and concentration used, the drug can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as a local anaesthetic, preservative and buffering agent can be dissolved in the vehicle.

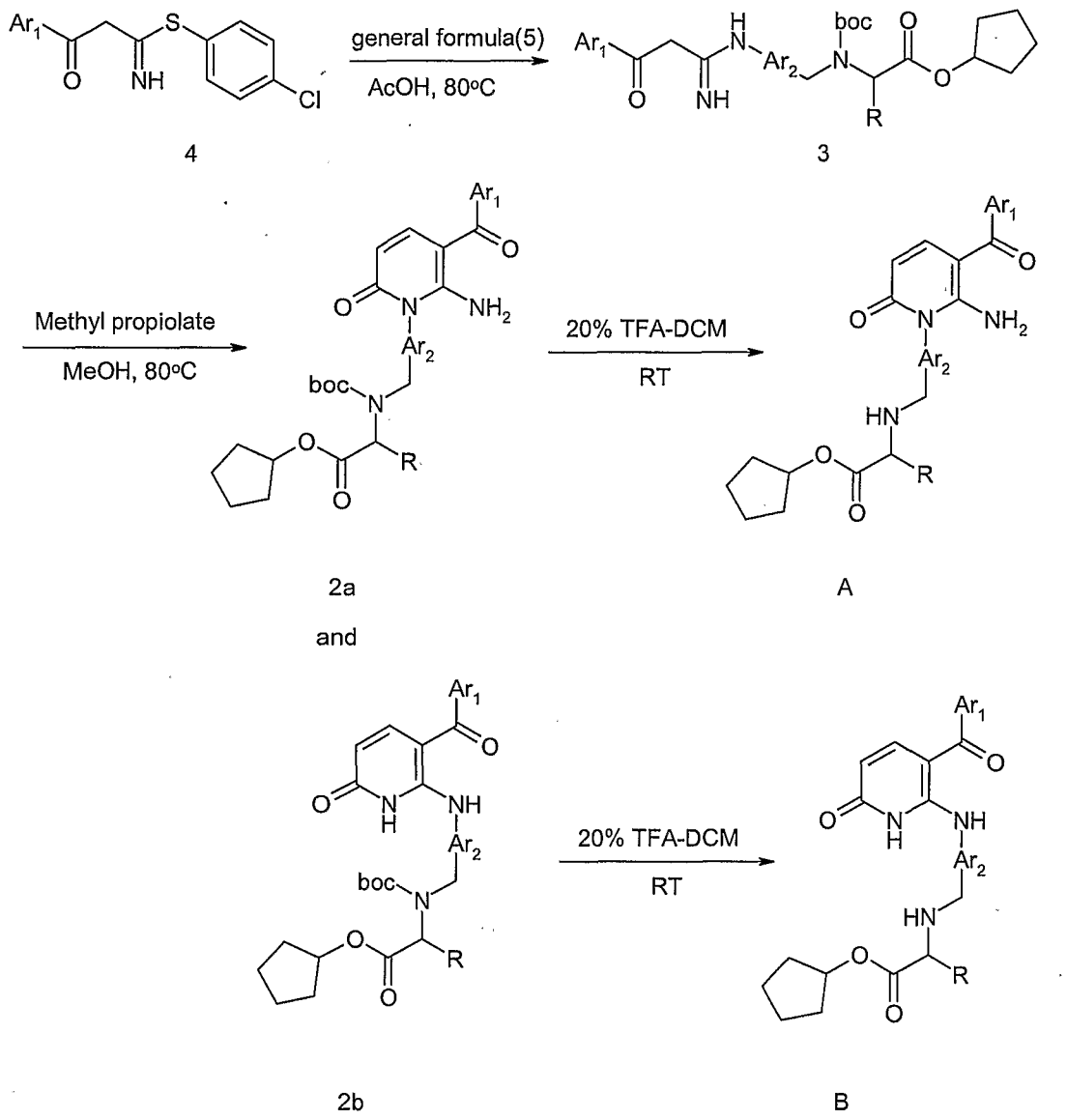
Synthesis

[0056] There are multiple synthetic strategies for the synthesis of the compounds (I) with which the present invention is concerned, but all rely on known chemistry, known to the synthetic organic chemist. Thus, compounds according to formula (I) can be synthesised according to procedures described in the standard literature and are well-known to those skilled in the art. Typical literature sources are "Advanced organic chemistry", 4th Edition (Wiley), J March, "Comprehensive Organic Transformation", 2nd Edition (Wiley), R.C. Larock , "Handbook of Heterocyclic Chemistry", 2nd Edition (Pergamon), A.R. Katritzky), review articles such as found in "*Synthesis*", "*Acc. Chem. Res.*", "*Chem. Rev*", or primary literature sources identified by standard literature searches online or from secondary sources such as *"Chemical Abstracts"* or *"Beilstein"*.

[0057] The compounds of the invention may be prepared by a number of processes generally described below and more specifically in the Examples hereinafter. In the reactions described below, it may be necessary to protect reactive functional groups, for example hydroxyl, amino and carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions [see for example Greene, T.W., "Protecting Groups in Organic Synthesis", John Wiley and Sons, 1999]. Conventional protecting groups may be used in conjunction with standard practice. In some instances deprotection may be the final step in the synthesis of a compound of general formula (I) and the processes according to the invention described herein after are understood to extend to such removal of protecting groups.

[0058] Examples of such methods that may be employed to the synthesis of compounds of general formula (I) are set out, but not limited to the reactions shown in Scheme 1 below.

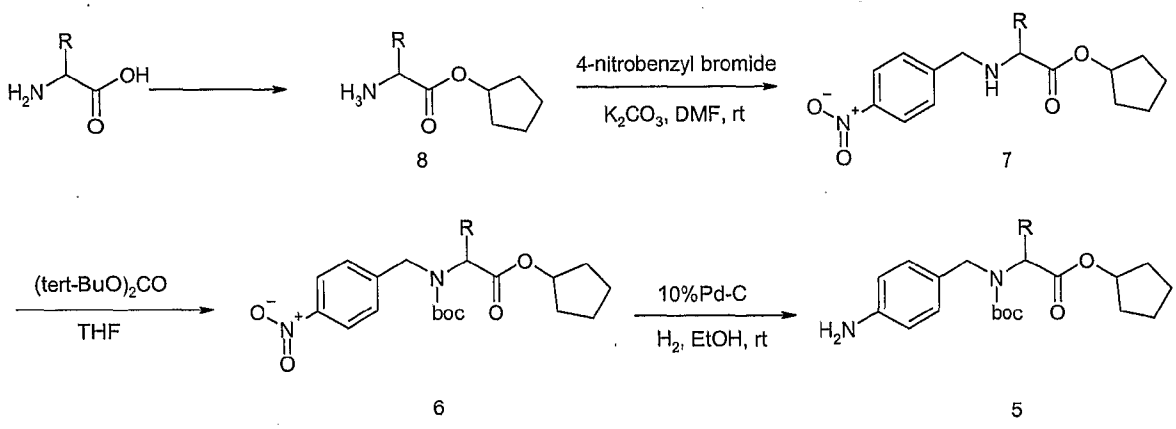
Scheme 1



[0059] Thus, amino esters of general formula (A) may be prepared by treatment of the tert-butylcarbamate of general formula (2a) with trifluoroacetic acid in dichloromethane. Intermediates of general formula (2) may be prepared by methods described in WO 03/076405 and references therein. Amino esters of general formula (2b) may be formed as a bi-product in the synthesis of compounds of formula (2a) and treated with trifluoroacetic acid to give compounds of general formula (B).

[0060] Intermediate esters of general formula (5) may be prepared by the procedures shown in Scheme 2.

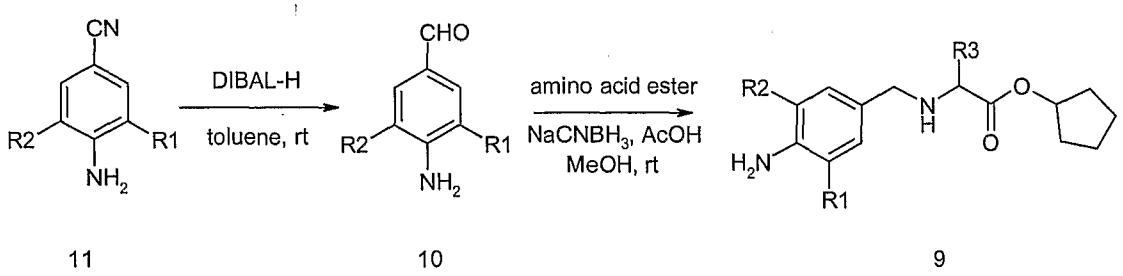
Scheme 2



[0061] Hydrogenation of the nitrobenzyl intermediate (6) over palladium-carbon catalyst in THF provides amines of general formula (5). Intermediates of formula (6) may be prepared by the reaction of the corresponding amine with di-tert-butoxycarbonate in inert solvent such as THF at ambient temperature. Intermediates of general formula (7) may be produced by the alkylation of amino esters of formula (8) with 4-nitrobenzyl bromide. The reaction may be performed in a dialkylamide solvent such as DMF in the presence of an inorganic base such as potassium or ceasium carbonate Such reactions are set forth in March's Advanced Organic Chemistry [John Wiley and Sons, 1992].

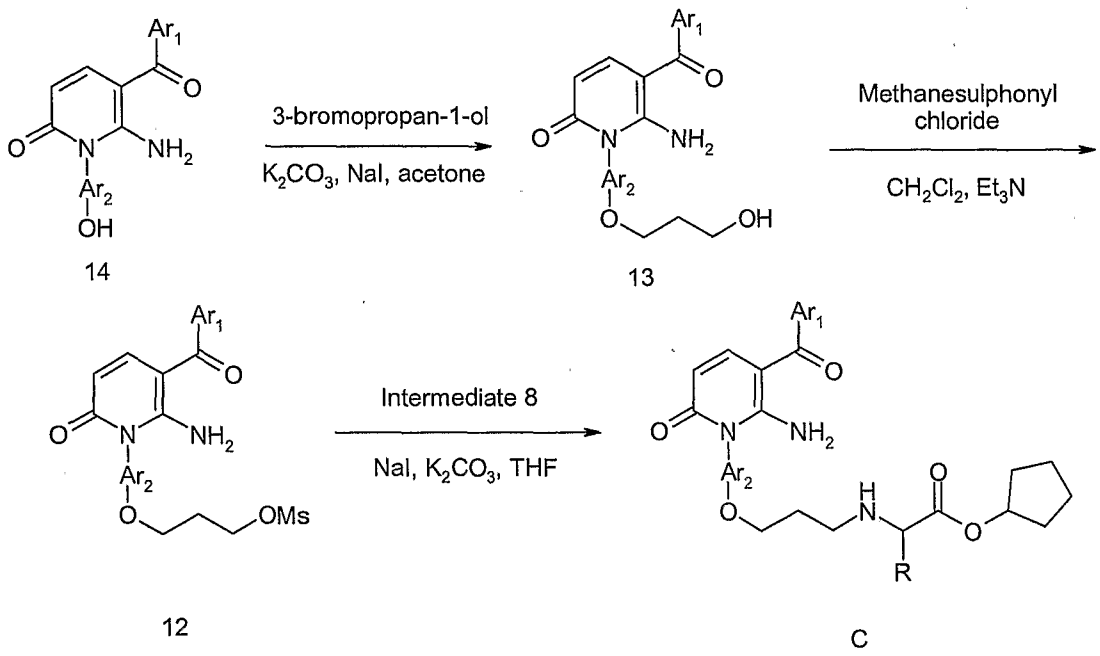
[0062] An alternative general method for the synthesis of N-benzylamino acid esters of general formula (9), where further functionalisation is required on the aryl ring of the benzyl substituent is set out in Scheme 3.

Scheme 3



[0063] In a further aspect of the invention, amino esters of general formula (9) may be prepared by, but not limited to, the reactions set out in Scheme 3. Thus benzonitriles of general formula (11), which are either commercially available or can be readily synthesized by methods known to those skilled in the art, may be converted to the corresponding benzaldehyde of general formula (10) by reduction with an appropriate metal hydride such as DIBAL-H and acid hydrolysis of the intermediate imine [see for Example LeBel J. Am. Chem. Soc., 1964, 86, 3759]. The N-benzyl amino acid ester of general formula (9) may be prepared by reaction with the said benzaldehyde under conditions of reductive alkylation, employing borohydride reagents such as $NaBH_3CN$ or $NaBH(OAc)_3$ under acidic conditions in a protic solvent such as methanol [see for example Borsch et al, J.Am. Chem. Soc., 1971, 93, 2897].

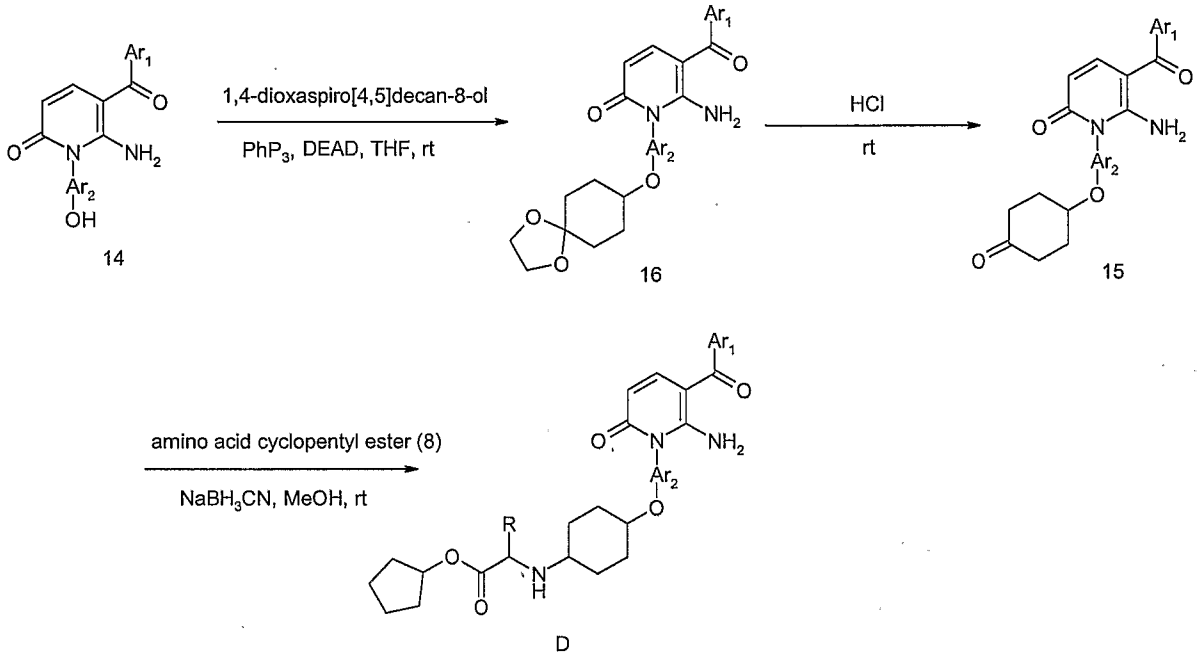
Scheme 4



[0064] In a further aspect of the invention, compounds of general formula (C) may be prepared by methods set out in Scheme 4, from the alkylation of intermediates of general formula (8) with mesylates of general formula (12). The alkylation may be carried out in an inert ether solvent such as THF, in the presence of sodium iodide and inorganic bases such as potassium carbonate. It will be recognized by those skilled in the art that the corresponding alkylbromides or alkylchlorides will be of utility in this process. The preparation of mesylate (12) may be performed by treatment of the primary alcohol (13) with methanesulphonyl chloride in an inert solvent such as dichloromethane and in the presence of organic base such as triethylamine. Compounds of general formula (14) may be prepared by methods described in WO 03/076405 and references therein.

[0065] In a further aspect to the invention compounds of general formula (D) may be prepared by, but not limited to, the reactions in Scheme 5.

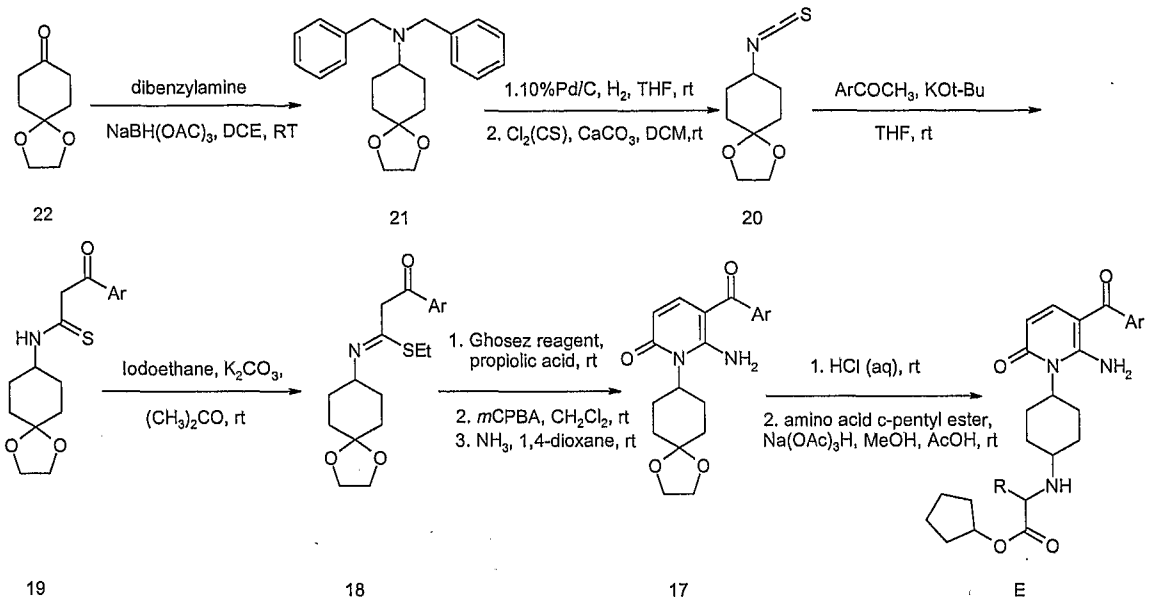
Scheme 5



[0066] Thus, alcohols of general formula (14) can be alkylated with an appropriately protected cycloalkanol derivative such as 1,4-dioxaspiro[4,5]decan-8-ol using triphenylphosphine and a dialkyl azadicarboxylate such as DEAD in an inert ethereal solvent [see for example Mitsunobu et al, Bull. Chem. Soc. Jpn., 1967, 40, 2380]. Ketals of general formula (16) may be deprotected to the corresponding ketone under aqueous acidic conditions. Reductive amination of compounds of formula (16) may be achieved by treatment with amino acid esters of general formula (8) in the presence of borohydride reagents such as sodium cyanoborohydride and sodium triacetoxyborohydride under acid conditions to give compounds of general formula (D).

[0067] In a further aspect to the invention compounds of general formula (E) may be prepared by, but not limited to, the reactions in Scheme 6.

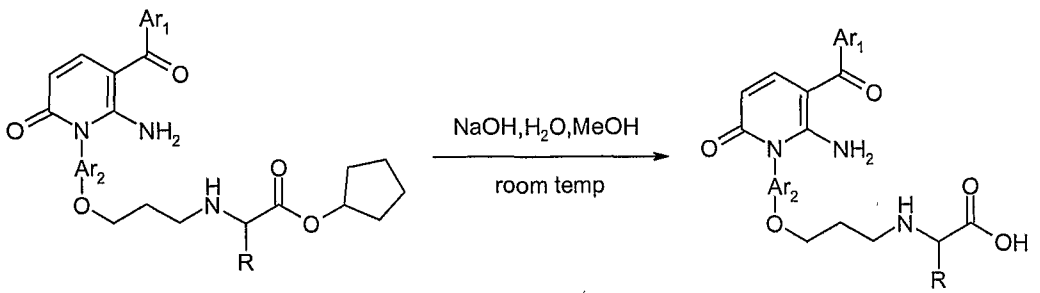
Scheme 6



[0068] Reductive amination of compounds of formula (22) may be achieved by treatment with dibenzylamine in the presence of borohydride reagents such as sodium cyanoborohydride and sodium triacetoxyborohydride under acid conditions to give compounds of general formula (21). Hydrogenation of (21) and subsequent reaction with thiophosgene can give the isocyanate of general formula (20). Compounds of general formula (19) may be prepared by reaction of (20) with the corresponding acetophenone using sodium tert-butoxide. Alkylation of (19) with iodoethane may be carried out using an inorganic base such as potassium carbonate in a solvent such as acetone. Compounds of general formula (18) may be subjected to cyclisation, oxidation and then subsequent ammonia displacement to give ketals of general formula (17). Thus ketals of general formula (17) may be deprotected to the corresponding cyclohexanone intermediate under aqueous acidic conditions, the cycohexanone then reacted with amino acid esters of general formula (8) under conditions of reductive amination employing borohydride reagents such as sodium cyanoborohydride and sodium triacetoxyborohydride.

[0069] In another aspect of the invention, amino acids of general formula (F) may be prepared by, but not restricted to methods set out in Scheme 7.

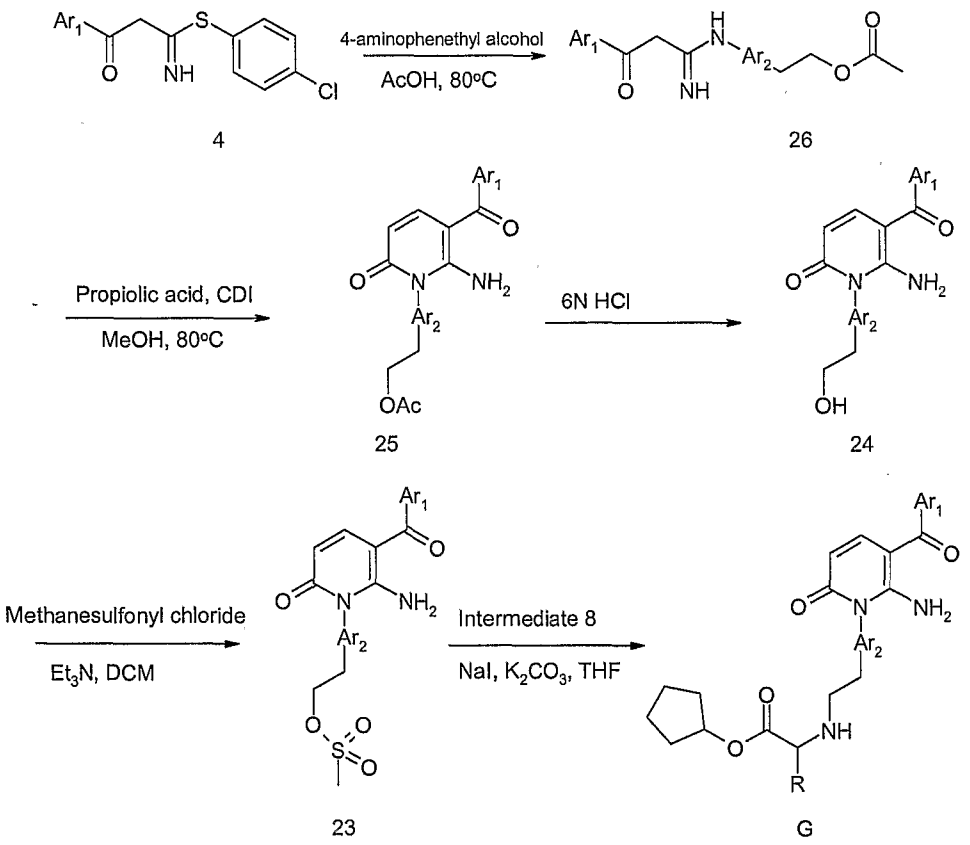
Scheme 7



[0070] Thus, for example, amino acid esters of general formula (C) may be hydrolysed to the corresponding amino acids (F) by treatment with aqueous sodium or potassium hydroxide, or any appropriate base, at ambient temperature in a co-solvent such as methanol or ethanol.

[0071] In another aspect of the invention, amino acids of general formula (G) may be prepared by, but not restricted to methods set out in Scheme 8.

Scheme 8



[0072] Thus, amino esters of general formula G may be prepared by the alkylation of intermediates of general formula (8) with mesylates of general formula (23). The alkylation may be carried out in an inert ether solvent such as THF, in the presence of sodium iodide and inorganic bases such as potassium carbonate. The preparation of mesylate (23) may be performed by treatment of the primary alcohol (24) with methanesulphonyl chloride in an inert solvent such as dichloromethane and in the presence of organic base such as triethylamine. The alcohol (24) may be prepared by deprotection of the acetyl group of intermediate (25) under acidic conditions such as HCl. Intermediates of general formula (4), (25) and (26) may be prepared by similar methods described in WO 03/076405 and references therein.

[0073] The following examples illustrate the invention. All temperatures are in °C. The following abbreviations are used:

MeOH	= methanol
EtOH	= ethanol
EtOAc	= ethyl acetate
Boc	= tert-butoxycarbonyl
CDI	= 1,1'-carbonyl diimidazole
DCM	= dichloromethane
DMF	= dimethylformamide
DMSO	= dimethyl sulfoxide
TFA	= trifluoroacetic acid
THF	= tetrahydrofuran
Na_2CO_3	= sodium carbonate
HCl	= hydrochloric acid
DIPEA	= diisopropylethylamine
NaH	= sodium hydride
NaOH	= sodium hydroxide
$NaHCO_3$	= sodium hydrogen carbonate
Pd/C	= palladium on carbon
TME	= tert-butyl methyl ether

N_2	= nitrogen
Na_2SO_4	= sodium sulphate
Et_3N	= triethylamine
NH_3	= ammonia
TMSCl	= trimethylchlorosilane
TBME	= tertiary butyl methyl ether
NH_4Cl	= ammonium chloride
$LiAlH_4$	= lithium aluminium hydride
$MgSO_4$	= magnesium sulfate
^nBuLi	= n-butyllithium
CO_2	= carbon dioxide
EDCI	= *N*-(3-Dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride
Et_2O	= diethyl ether
LiOH	= lithium hydroxide
HOBt	= 1-hydroxybenzotriazole
ELS	= Evaporative Light Scattering
TLC	= thin layer chromatography
ml	= milliliter(s)
g	= gram(s)
mg	= milligram(s)
mol	= moles
mmol	= millimole(s)
LCMS	= high performance liquid chromatography/mass spectrometry
NMR	= nuclear magnetic resonance
RT	= room temperature

[0074] Microwave irradiation was carried out using a CEM Discover focused microwave reactor. Solvents were removed using a GeneVac Series I without heating or a Genevac Series

[0075] II with VacRamp at 30 °Cor a Buchi rotary evaporator. Purification of compounds by flash chromatography column was performed using silica gel, particle size 40-63 μm (230-400 mesh) obtained from Silicycle. Purification of compounds by preparative HPLC was performed on Gilson systems using reverse phase ThermoHypersil-Keystone Hyperprep HS C18 columns (12 μm, 100 x 21.2 mm), gradient 20-100% B (A= water/ 0.1 % TFA, B= acetonitrile/ 0.1 % TFA) over 9.5 min, flow = 30 ml/min, injection solvent 2:1 DMSO:acetonitrile (1.6 ml), UV detection at 215 nm.

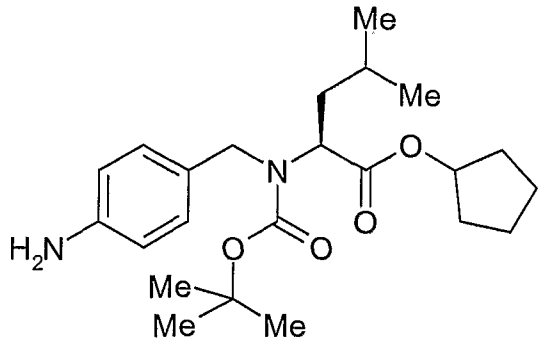
[0076] ^1H NMR spectra were recorded on a Bruker 400 MHz AV or a Bruker 300 MHz AV spectrometer in deuterated solvents. Chemical shifts (δ) are in parts per million. Thin-layer chromatography (TLC) analysis was performed with Kieselgel 60 F_{254} (Merck) plates and visualized using UV light.

[0077] Analytical HPLCMS was performed on Agilent HP1100, Waters 600 or Waters 1525 LC systems using reverse phase Hypersil BDS C18 columns (5 μm, 2.1 x 50 mm), gradient 0-95% B (A= water/ 0.1% TFA, B= acetonitrile/ 0.1% TFA) over 2.10 min, flow = 1.0 ml/min. UV spectra were recorded at 215 nm using a Gilson G1315A Diode Array Detector, G1214A single wavelength UV detector, Waters 2487 dual wavelength UV detector, Waters 2488 dual wavelength UV detector, or Waters 2996 diode array UV detector. Mass spectra were obtained over the range m/z 150 to 850 at a sampling rate of 2 scans per second or 1 scan per 1.2 seconds using Micromass LCT with Z-spray interface or Micromass LCT with Z-spray or MUX interface. Data were integrated and reported using OpenLynx and OpenLynx Browser software.

Intermediates

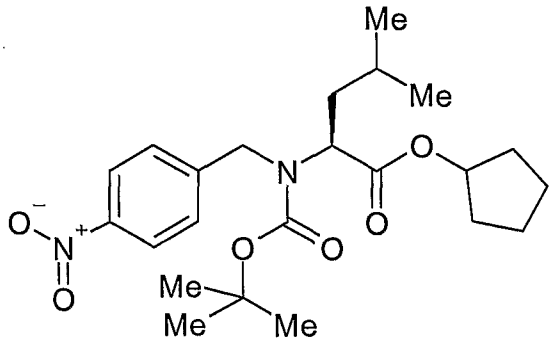
Intermediate 1A Cyclopentyl (S)-2-[(4-Aminobenzyl)-tert-butoxycarbonyl amino]-4-methylpentanoate

[0078]



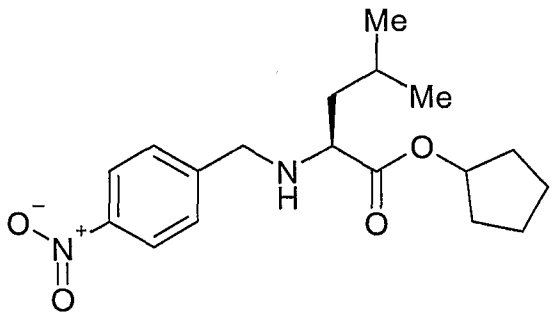
[0079] Cyclopentyl (S)-2-[tert-Butoxycarbonyl-(4-nitrobenzyl)amino]-4-methylpentanoate (3.8g, 8.74mmol) was dissolved in EtOH (100ml) before addition of Pd/C (10% wet) catalyst (100mg) and hydrogenated under balloon pressure at room temperature for 18 h. The reaction mixture was filtered through a pad of celite and evaporated to dryness to give a pink coloured solid (3.15g, 89% yield). LCMS purity 100%, m/z 405 $[M+H]^+$.

[0080] The nitrobenzyl carbamate starting material for this procedure was prepared as follows:



[0081] Cyclopentyl (S)-(4-nitrobenzyl)amino]-4-methylpentanoate (15.8g; 47.4mmol) was dissolved in THF (250ml) before addition of potassium carbonate (7.58g, 56.9mmol) and water (150ml). Di-tert-butyldicarbonate (15.5g, 71.1 mmol) was added and the reaction mixture heated to 50°C for 18 h. The reaction mixture was concentrated under reduced pressure to remove volatiles giving an aqueous residue which was extracted with EtOAc (200ml). The EtOAc layer was washed consecutively with 0.1 M HCl (150ml), sat. aq. $NaHCO_3$ and water (150 ml). The organic layer was dried (Na_2SO_4), filtered and concentrated to dryness. After purification by flash column chromatography (10% EtOAc/ hexane) the product was isolated (9.36g, 46% yield). LC purity 94%, m/z 435 $[M+H]^+$.

[0082] The nitrobenzylamino starting material used in this procedure was prepared as follows

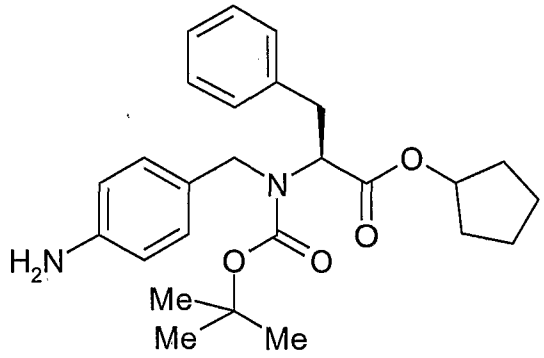


[0083] 4-Nitrobenzyl bromide (11g, 50 mmol) was dissolved in DMF (180ml) and potassium carbonate (13.6g, 99 mmol) added, followed by L-leucine cyclopentyl ester (Intermediate 8) (16g, 43 mmol). The reaction was stirred for 18 h at RT. The residue was diluted with EtOAc (500ml) and washed with water (3x100ml), dried (Na_2SO_4) filtered and concentrated to dryness to give the crude product (15.8g) which was used in the next step without further purification. LCMS purity 60%, m/z 335 $[M+H]^+$.

[0084] The following compounds were prepared in a similar manner:

Intermediate 1B Cyclopentyl (S)-2-[(4-Aminobenzyl)-tert-butoxycarbonyl amino]-3-phenylpropionate

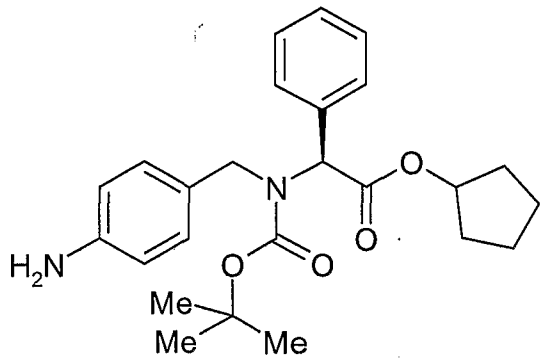
[0085]



LCMS purity 75%, m/z 439 $[M+H]^+$.

Intermediate 1C Cyclopentyl (S)-[(4-Aminobenzyl)-tert-butoxycarbonyl amino]-phenylacetate

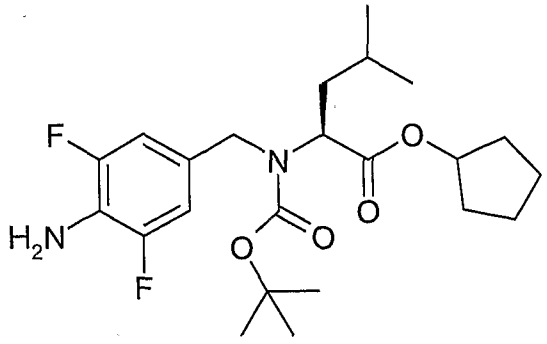
[0086]



LCMS purity 100%, m/z 425 $[M+H]^+$.

Intermediate 1D Cyclopentyl (S)-2-[(4-Amino-3,5-difluorobenzyl)-tert-butoxycarbonyl amino]-4-methylpentanoate

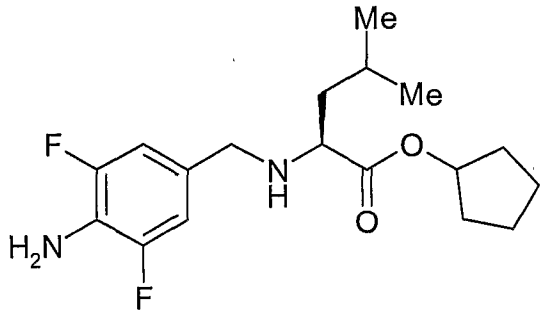
[0087]



[0088] Cyclopentyl 2(S)-(4-amino-3,5-difluorobenzyl)amino]-4-methylpentanoate (2.54g crude, assume 5.73mmol) was dissolved in a mixture of THF (25ml) and water (25ml). K_2CO_3 (5.15g, 37.3mmol) and Boc_2O (8.14g, 37.2mmol) were added and stirring at RT was continued for 18h. The volatiles were removed under reduced pressure and the

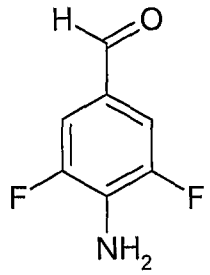
residual aqueous layer was extracted with EtOAc (50ml). The organic layer dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash chromatography (5% EtOAc/ heptane) gave the N-Boc-protected product (1.0g, 40%). LCMS purity 89% m/z 441 $[M+H]^+$.

[0089] The benzylamino carbamate used as starting material was prepared as follows



[0090] To a solution of 4-amino-3,5-difluorobenzaldehyde (0.90g, 5.73mmol) in 1/1 MeOH/ DMF (16ml), L-leucine cyclopentyl ester **(Intermediate 8)** (3.19g, 8.59mmol) and K_2CO_3 (1.19g, 8.59mmol) were added. The reaction mixture was adjusted to pH 5-6 using glacial acetic acid (dropwise) and was stirred for 1 h before addition of $NaCNBH_3$ (0.72g, 11.46mmol). Stirring was continued at room temperature for 18h. The reaction mixture was concentrated to remove MeOH, diluted with EtOAc (20ml), washed with $NaHCO_3$ (5ml) followed by water (10ml). The organic layer dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the crude product (2.54g) which was reacted in the next step without purification. LC purity= 68%.

[0091] The benzaldehyde used as starting material was prepared as follows;

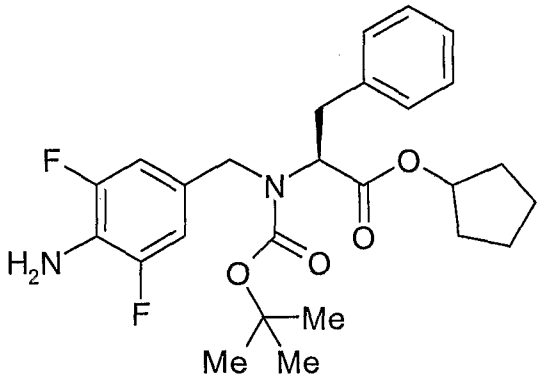


[0092] To a stirred solution of 4-amino-3,5-difluorobenzonitrile (2.0g, 12.98mmol) in toluene (16ml) was added dropwise DIBAL (1.5M in toluene) at 0°C. The reaction mixture was warmed to RT and stirring continued for 2h. The reaction was quenched by dropwise addition to 10% aq citric acid (10ml). EtOAc (50ml) and saturated aq potassium sodium tartrate (Rochelle's salt) (30ml) were added and the mixture was vigorously stirred for 20min. The organic layer was isolated and washed with water (10ml), dried (Na_2SO_4), filtered and concentrated to dryness to give a pale yellow solid (1.9g, 93%). LCMS purity 92%, m/z 158 $[M+H]^+$.

[0093] The following compounds were prepared in a similar manner:

Intermediate 1E Cyclopentyl (S)-2-[(4-Amino-3,5-difluorobenzyl)-tert-butoxy carbonylamino]-3-phenylpropionate

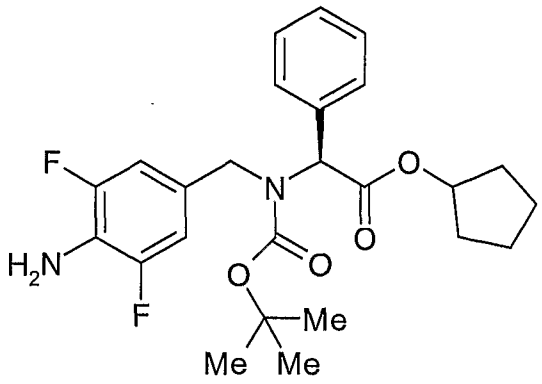
[0094]



LCMS purity 86%, m/z 475 $[M+H]^+$.

Intermediate 1F Cyclopentyl (S)-2-[(4-Amino-3,5-difluorobenzyl)-tert-butoxy carbonylamino]-phenylacetate

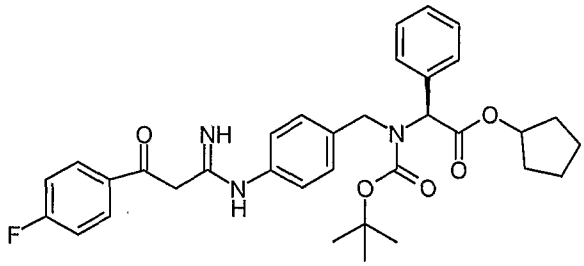
[0095]



LCMS purity 86%, m/z 461 $[M+H]^+$.

Intermediate 2A Cyclopentyl (S)-[tert-Butoxycarbonyl-(-4{[3-(4-fluoro phenyl)-3-oxopropionimidoyl]aminobenzyl)aminophenylacetate

[0096]

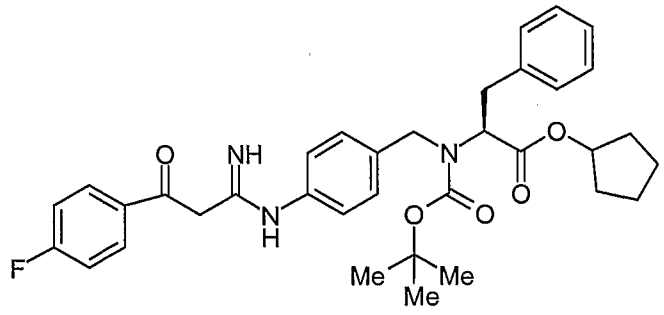


[0097] A mixture of 3-(4-fluorophenyl)-3-oxothiopropionimidic acid 4-chlorophenyl ester [WO 03/076405] (300mg, 0.874mmol), **Intermediate 1C** (0.41g, 0.961mmol) and glacial acetic acid (3 ml) was stirred at 80 °C for 2h. Reaction mixture was evaporated to dryness under reduced pressure to give a thick residue which was triturated with ether (3ml). The resultant solid was collected by suction filtration. The product was neutralised by partitioning between EtOAc (20ml) and sat aq $NaHCO_3$ (10ml). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo.* Yield =305mg (59%). LCMS purity= 75%, m/z 588 $[M+H]^+$. The product was used in the next step without further purification.

[0098] The following starting materials were prepared in an analogous manner:

Intermediate 2B Cyclopentyl (S)-2-[tert-Butoxycarbonyl-(4-{[3-(4-fluoro phenyl)-3-oxoproplonimidoyl]amino}benzyl)amino]-3-phenylpropionate

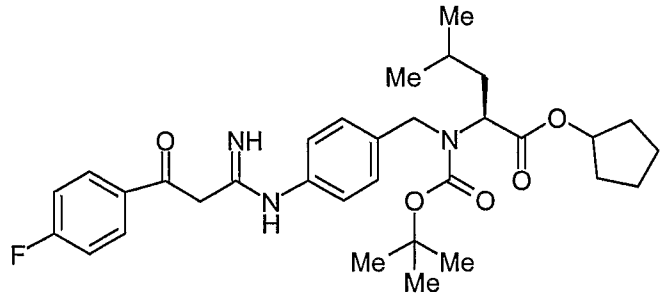
[0099]



From Intermediate 1 B, LCMS purity 76%, m/z 602 $[M+H]^+$.

Intermediate 2C Cyclopentyl (S)-2-[tert-Butoxycarbonyl-(4-{[3-(4-fluoro phenyl)-3-oxopropionimidoyl]amino}benzyl)amino]-1-4-methylpentanoate

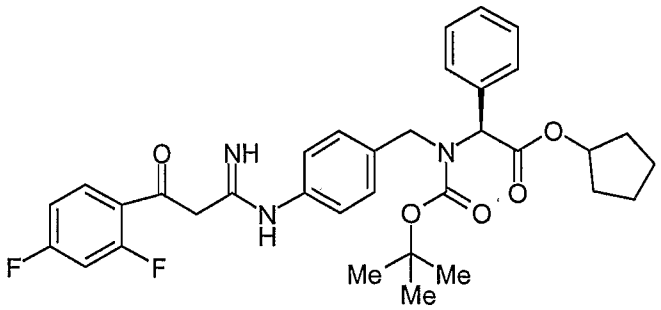
[0100]



From Intermediate 1A, LCMS purity 55%, m/z 568 $[M+H]^+$.

Intermediate 2D Cyclopentyl (S)-[tert-Butoxycarbonyl-(-4-[3-(2,4-fluorophenyl)-3-oxopropionimidoyl]aminobenzyl)aminophenylacetate

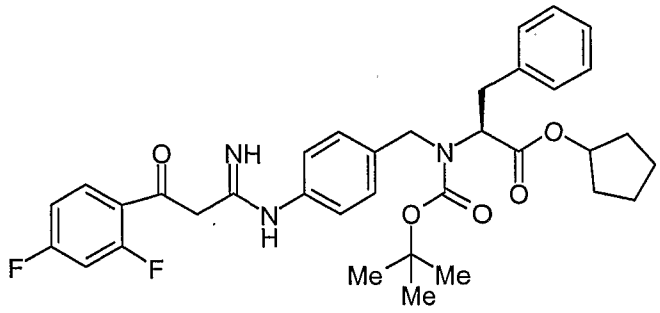
[0101]



From Intermediate 1C, LCMS purity 76%, m/z 606 $[M+H]^+$.

Intermediate 2E Cyclopentyl (S)-2-[tert-Butoxycarbonyl-(4-{[3-(2,4-difluoro phenyl)-3-oxopropionimidoyl]amino}benzyl)aminol-3-phenylpropionate

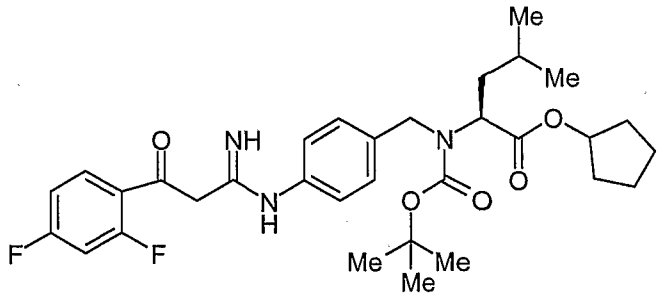
[0102]



From Intermediate 1B, LCMS purity 78%, m/z 620 $[M+H]^+$.

Intermediate 2F Cyclopentyl (S)-2-[tert-Butoxycarbonyl-(4-{[3-(2,4-difluoro phenyl)-3-oxopropionimidoyl]amino}benzyl)amino]-4-methylpentanoate

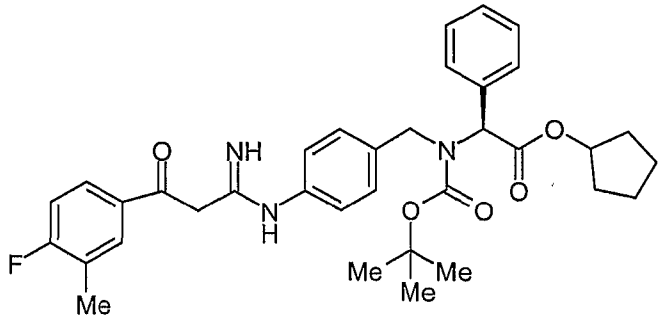
[0103]



From Intermediate 1A, LCMS purity 76%, m/z 586 $[M+H]^+$.

Intermediate 2G Cyclopentyl (S)-[tert-Butoxycarbonyl-(-4-[3-(3-methyl-4-fluorophenyl)-3-oxopropionimidoyl]aminobenzyl)aminophenylacetate

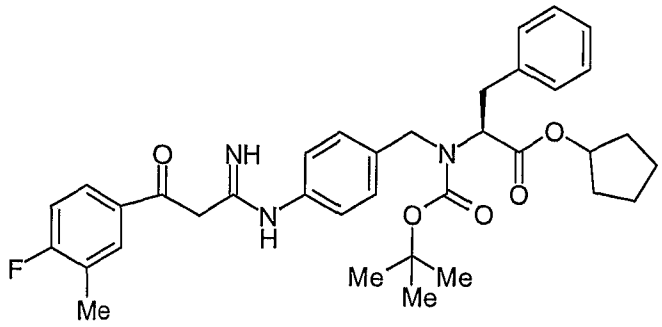
[0104]



From Intermediate 1C, LCMS purity 77%, m/z 602 $[M+H]^+$.

Intermediate 2H Cyclopentyl (S)-2-[tert-Butoxycarbonyl-(4-{[H3-(3-methyl-4-fluorophenyl)-3-oxopropionimidoyl]amino}benzyl)amino]-3-phenyl propionate

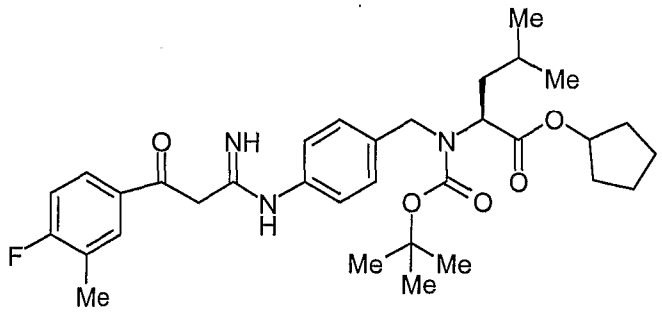
[0105]



From **Intermediate 1B,** LCMS purity 77%, m/z 616 $[M+H]^+$.

Intermediate 2I Cyclopentyl (S)-2-[tert-Butoxycarbonyl-(4-{[3-(3-methyl-4-fluorophenyl)-3-oxopropionimidoyl]amino}benzyl)amino]1-4-methyl pentanoate

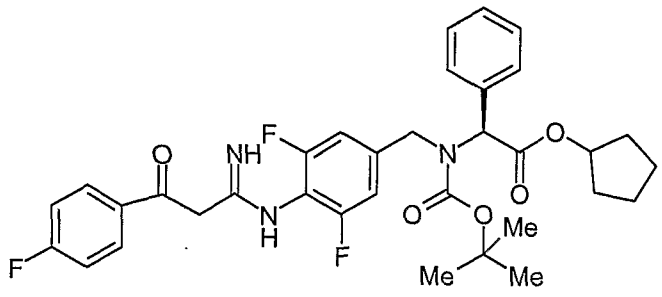
[0106]



From **Intermediate 1A,** LCMS purity77 %, m/z 582 $[M+H]^+$.

Intermediate 2J Cyclopentyl (S)-[tert-Butoxycarbonyl-(3,5-difluoro-4-{[3-(4-fluorophenyl)-3-oxo-propionimidoyl]amino}benzyl)amino]phenylacetate

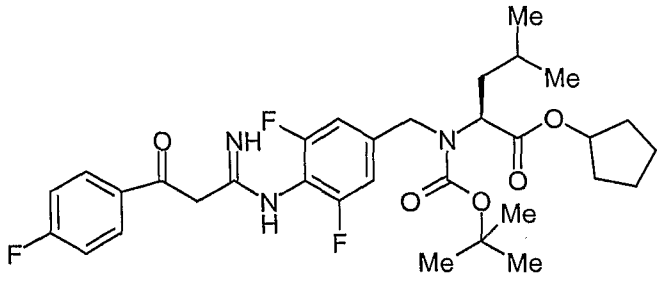
[0107]



From **Intermediate 1 F,** LCMS purity %, m/z 624$[M+H]^+$.

Intermediate 2K Cyclopentyl (S)-2-[tert-Butoxycarbonyl-(3,5-difluoro-4-{[3-(4-fluoro-phenyl)-3-oxopropionimidoyl]amino}benzyl)amino]-4-methyl pentanoate

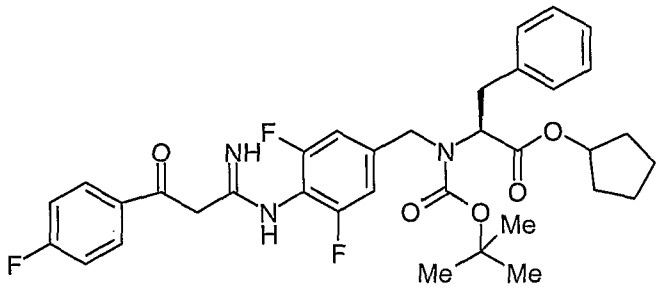
[0108]



From **Intermediate 1 D,** LCMS purity %, m/z 604 $[M+H]^+$.

Intermediate 2L Cyclopentyl (S)2-[tert-Butoxycarbonyl-(3,5-difluoro-4-{[3-(4-fluoro-phenyl)-3-oxo-propionimidoyl]amino}benzyl)-amino]-3-phenyl propionate

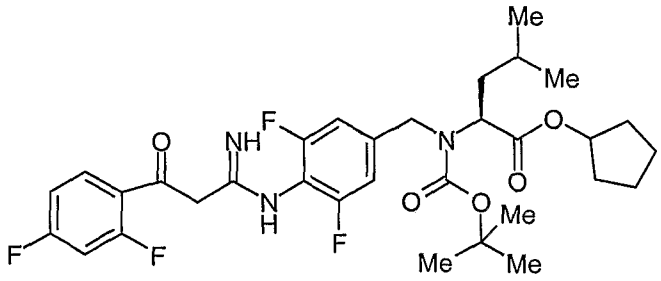
[0109]



From **Intermediate 1E,** LCMS purity 100%, m/z 638 $[M+H]^+$.

Intermediate 2M Cyclopentyl (S)-2-[tert-Butoxycarbonyl-(3,5-difluoro-4-{[3-(2,4-difluorophenyl)-3-oxopropionimidoyl]amino}benzyl)amino]-4-methylpentanoate

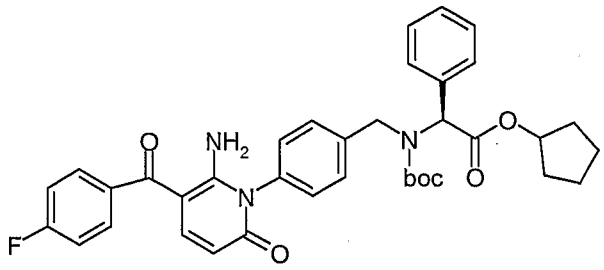
[0110]



From **Intermediate 1D,** LCMS purity 86%, m/z 622 $[M+H]^+$.

Intermediate 3A Cyclopentyl (S)-({4-[6-Amino-5-(4-fluorobenzoyl)-2-oxo-2H-pyridinyl-1-yl]benzyl}-tert-butoxycarbonylamino)phenylacetate

[0111]

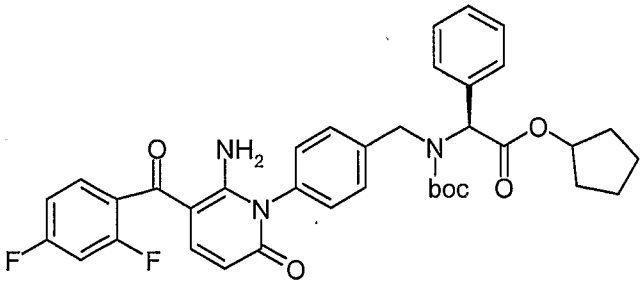


[0112] To a solution of **Intermediate 2A** (305mg, 0.52mmol) in MeOH (5ml) was added methyl propiolate (70µl, 0.78mmol). The mixture was heated at 80 °C for 3h. The reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography (30% EtOAc/ heptane). Yield= 200mg (60%). LCMS purity 80%, m/z 640 $[M+H]^+$.

[0113] The following compounds were produced in a similar fashion:

Intermediate 3B Cyclopentyl (S)-({4-[6-Amino-5-(2,4-difluorobenzoyl)-2-oxo-2H-pyridinyl-1-yl]benzyl}-tert-butoxycarbonylamino)phenylacetate

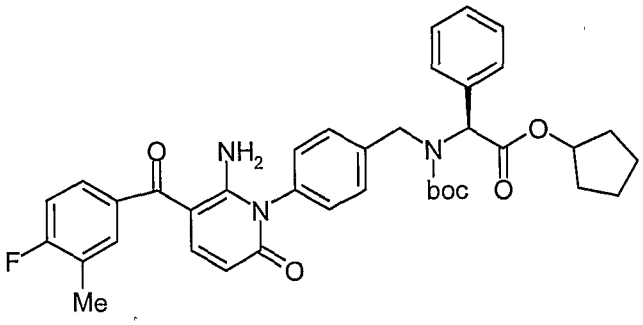
[0114]



From **Intermediate 2D,** LCMS purity 71%, m/z 658 $[M+H]^+$.

Intermediate 3C Cyclopentyl (S)-({4-[6-Amino-5-(3-methyl-4-fluorobenzoyl)-2-oxo-2H-pyridinyl-1-yl]benzyl}-tert-butoxycarbonylamino)phenylacetate

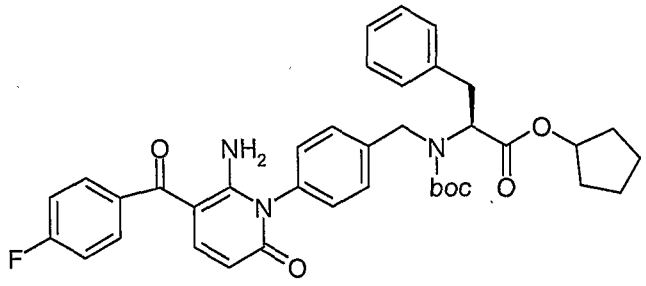
[0115]



From **Intermediate 2G,** LCMS purity 73%, m/z 654 $[M+H]^+$.

Intermediate 3D Cyclopentyl (S)-2-({4-[6-Amino-5-(4-fluorobenzoyl)-2-oxo-2H-pyridin-1-yl]benzyl}-tert-butoxycarbonylamino)-3-phenylpropionate

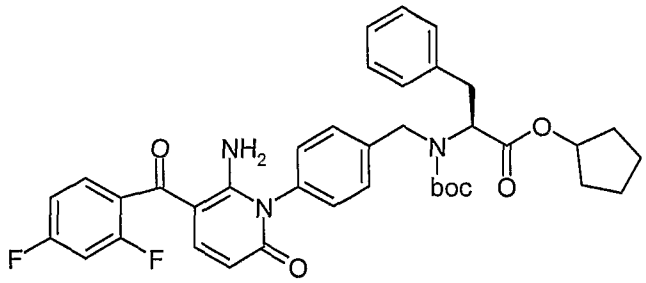
[0116]



From **Intermediate 2B,** LCMS purity 64%, m/z 654 $[M+H]^+$.

Intermediate 3E Cyclopentyl (S)-2-({4-[6-Amino-5-(2,4-difluorobenzoyl)-2-oxo-2H-pyridin-1-yl]-benzyl}tert-butoxycarbonylamino)-3-phenylpropionate

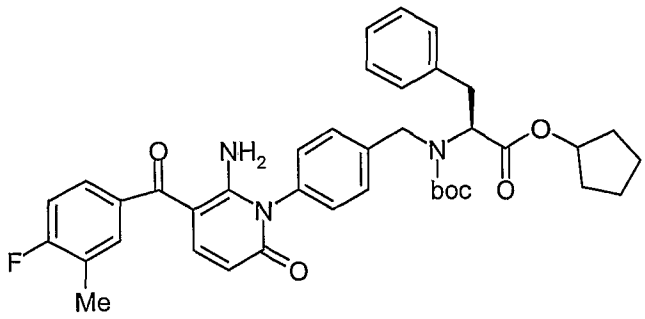
[0117]



From **Intermediate 2E,** LCMS purity 59%, m/z 672 $[M+H]^+$.

Intermediate 3F Cyclopentyl (S)-2-({4-[6-Amino-5-(3-methyl-4-fluorobenz oyl)-2-oxo-2H-pyridin-1-yl]-benzyl}-tert-butoxycarbonylamino)-3-phenyl propionate

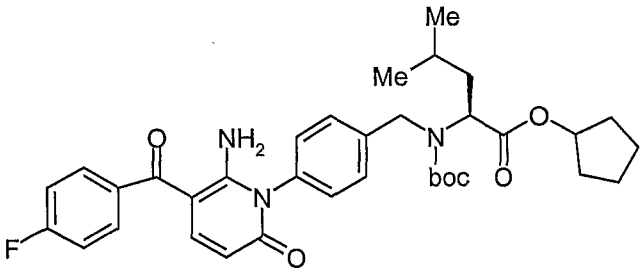
[0118]



From **Intermediate 2H,** LCMS purity 87%, m/z 668 $[M+H]^+$.

Intermediate 3G Cyclopentyl (S)-2-({d4-[6-Amino-5-(4-fluorobenzoyl)-2-oxo-2H-pyridin-1-yl]benzyl}-tert-butoxycarbonylamino)-4-methylpentanoate

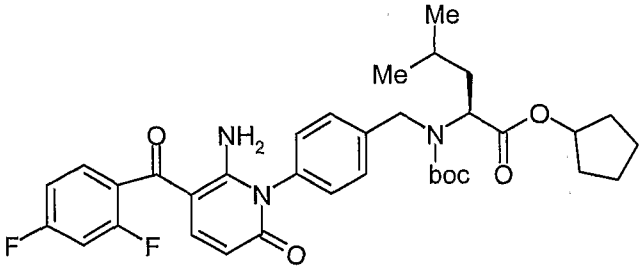
[0119]



From **Intermediate 2C,** LCMS purity 82%, m/z 620 $[M+H]^+$.

Intermediate 3I Cyclopentyl (S)-2-({4-[6-Amino-5-(2,4-difluorobenzoyl-2-oxo-2H-pyridin-1-yl]benzyl}-tert-butoxycarbonylamino)-4-methylpentanoate

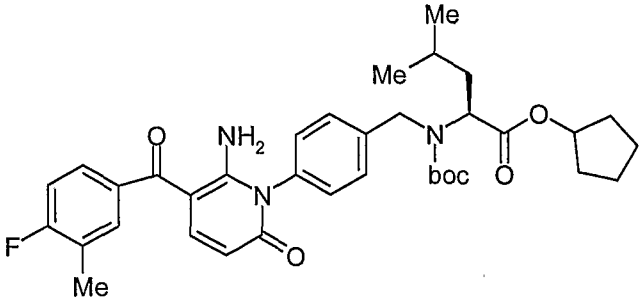
[0120]



From **Intermediate 2F,** LCMS purity 84%, m/z 638 $[M+H]^+$.

Intermediate 3J Cyclopentyl (S)-2-({4-[-Amino-5-(3-methyl-4-fluorobenzoyl)-2-oxo-2H-pyridin-1-yl]benzyl}-tert-butoxycarbonylamino)-4-methylpentanoate

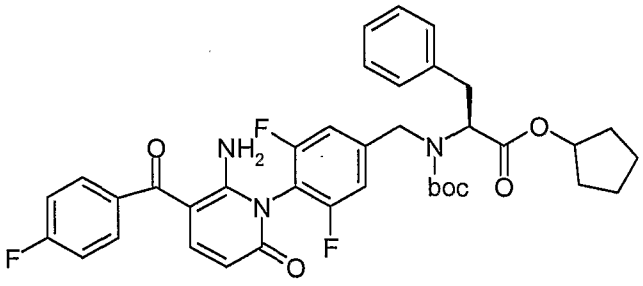
[0121]



From **Intermediate** 21, LCMS purity 90 %, m/z 634 $[M+H]^+$.

Intermediate 3K Cyclopentyl (S)-2-({4-[6-Amino-5-(4-fluorobenzoyl)-2-oxo-2H-pyridin-1-yl]-3,5-difluorobenzyl}-tert-butoxycarbonylamino)-3-phenyl propionate

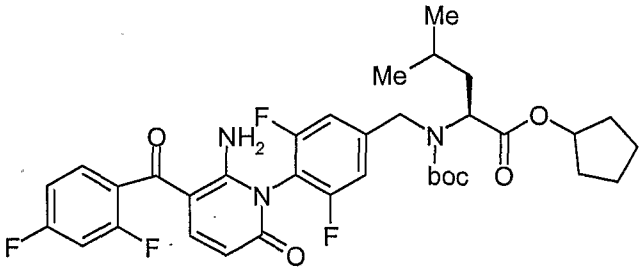
[0122]



From **Intermediate 2L,** LCMS purity 92%, m/z 690 $[M+H]^+$.

Intermediate 3L Cyclopentyl (S)-2-({4-[6-Amino-5-(2,4-difluorobenzoyl)-2-oxo-2H-pyridin-1-yl]-3,5-difluorobenzyl}-tert-butoxycarbonylamino)-4-methyl pentanoate

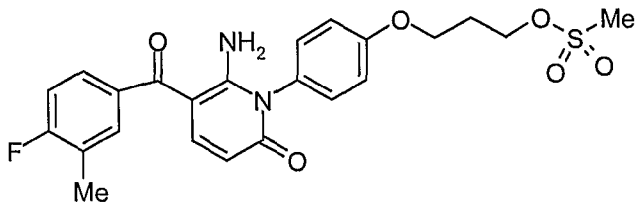
[0123]



From **Intermediate 2M,** LCMS purity 92%, m/z 674 $[M+H]^+$.

Intermediate 4A Methanesulfonic acid 3-{4-[6-amino-5-(4-fluoro-3-methyl-benzoyl)-2-oxo-2H-pyridin-1-yl]phenoxy}propyl ester

[0124]



[0125] To a suspension of 6-Amino-5-(4-fluoro-3-methyl-benzoyl)-1-[4-(3-hydroxy-propoxy)-phenyl]-1H-pyridin-2-one (100mg, 0.25mmol) in anhydrous DCM (1ml) at 0 °C was added methanesulfonyl chloride (21.5µl, 0.28mmol) followed by Et_3N (70µl, 0.50mmol). The reaction mixture was allowed to warm up to RT and stirred for 10-20min to completion, monitored by TLC (5% MeOH/ DCM). The reaction mixture was diluted with DCM (10ml), washed with 10% citric acid (5ml), followed by sat aq $NaHCO_3$ (5ml) and water (5ml). The DCM layer was dried (Na_2SO_4), filtered and concentrated *in vacuo.* Yield= 105mg (88%). LCMS purity = 79% m/z= 475 $[M+H]^+$. This material was used in the next step without further purification.

[0126] The alcohol used as starting material was prepared as follows:

The 6-Amino-5-(4-fluoro-3-methyl-benzoyl)-1-[4-(3-hydroxy-propoxy)-phenyl]-1H-pyridin-2-one was prepared as shown below.

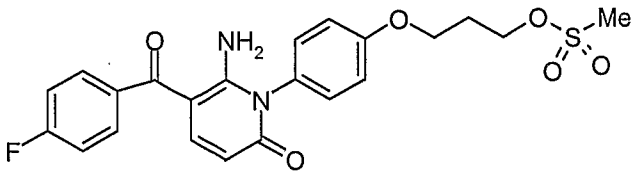
[0127] A mixture of 6-Amino-5-(4-fluoro-3-methyl-benzoyl)-1-[4-hydroxy-phenyl]-1 H-pyridin-2-one [WO 03/076405] (0.80g, 2.37mmol), 3-bromo-1-propanol (0.23 ml, 2.60mmol), K_2CO_3 (1.37g, 9.46mmol), NaI (0.73g, 4.86mmol) in acetone (20ml) was heated at 70 °C for 18h under N_2. The reaction mixture was concentrated under reduced pressure,

suspended in water (20ml) and the resulting solid was filtered and washed with ether (0.5ml). Yield= 0.8g (85%). LCMS purity= 96%, m/z 397 $[M+H]^+$

[0128] The following methanesulphonate intermediates were prepared in a similar manner to Intermediate 4A using methods described in WO 03/076405 for the synthesis of the corresponding 4-hydroxyphenyl intermediates.

Intermediate 4B Methanesulfonic acid 3{4-[6-amino-5-(4-fluorobenzoyl)-2-oxo-2H-pyridin-1-yl]phenoxy}propyl ester

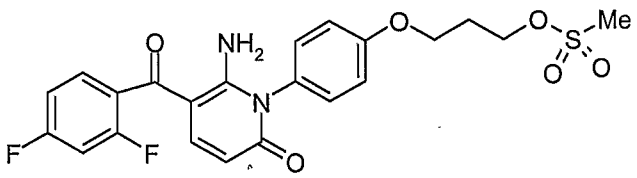
[0129]



LCMS purity 66%, m/z 461 $[M+H]^+$.

Intermediate 4C Methanesulfonic acid 3-{4-[6-amino-5-(2,4-difluorobenzoyl)-2-oxo-2H-pyridin-1-yl]phenoxy}propyl ester

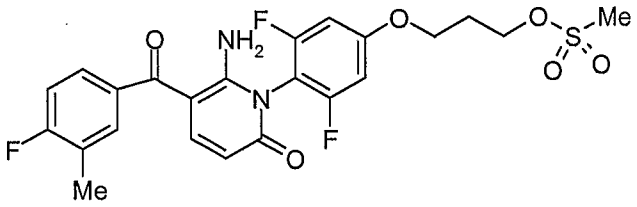
[0130]



LCMS purity 88%, m/z 479 $[M+H]^+$.

Intermediate 4D Methanesulfonic acid 3-{4-[6-amino-5-(4-fluoro-3-methyl-benzoyl)-2-oxo-2H-pyridin-1-yl]-3,5-difluorophenoxy}propyl ester

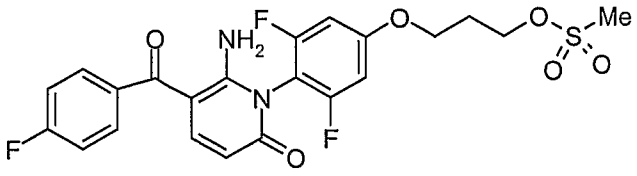
[0131]



LCMS purity 51%, m/z 511 $[M+H]^+$.

Intermediate 4E Methanesulfonic acid 3-{4-[6-amino-5-(4-fluorobenzoyl)-2-oxo-2H-pyridin-1-yl]-3,5-difluorophenoxy}-propyl ester

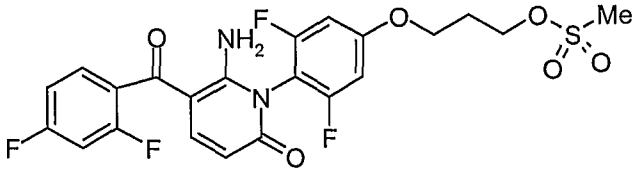
[0132]



LCMS purity 72%, m/z 497 $[M+H]^+$.

Intermediate 4F Methanesulfonic acid 3-{4-[6-amino-5-(2,4-difluorobenzoyl)-2-oxo-2H-pyridin-1-yl]-3,5-difluorophenoxy}propyl ester

[0133]

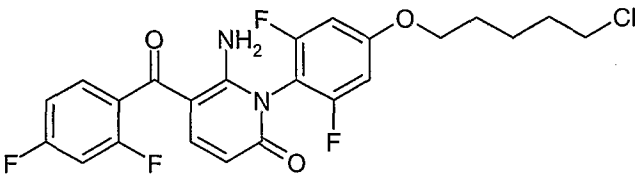


LCMS purity 81%, m/z 515 $[M+H]^+$.

[0134] The following intermediates were prepared by direct alkylation of the 4-hydroxyphenyl intermediates (described within WO03/076405 with 1-bromo-5-chloropentane.

Intermediate 4G 6-Amino-1-{4-[(5-chloropentyl)oxy]-2,6-difluorophenyl}-5-(2,4-difluoro-benzoyl)pyridin-2(1*H*)-one

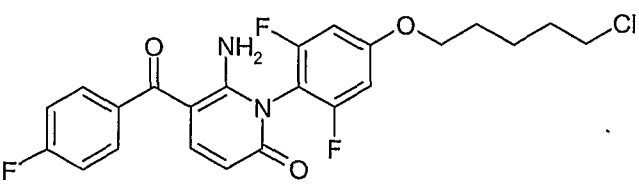
[0135]



[0136] To a solution of 6-amino-5-(2,4-difluorobenzoyl)-1-(2,6-difluoro-4-hydroxyphenyl)-pyridin-2(1*H*)-one (300 mg, 0.79 mmol) in acetone (6 ml) under an atmosphere of nitrogen was added 1-bromo-5-chloropentane (0.115 ml, 0.87 mmol, 1.1 eq), sodium iodide (238 mg, 1.59 mmol, 2 eq) and potassium carbonate (438 mg, 3.17 mmol, 4 eq). The mixture was heated at 70°C for 16 hours, before being allowed to cool to room temperature and partitioned between EtOAc (50 ml) and water (50 ml). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (30 % EtOAc in heptane) afforded a 3:2 mixture of the title compound and 6-amino-1-{4-[(5-iodopentyl)oxy]-2,6-difluorophenyl}-5-(2,4-difluorobenzoyl)pyridin-2(1*H*)-one (142 mg) which was used without further purification.
LC/MS: m/z 483, 575 $[M+H]^+$.

Intermediate 4H 6-Amino-1-{4-[(5-chloropentyl)oxy]-2,6-difluorophenyl}-5-(4-fluoro-benzoyl)pyridin-2(1*H*)-one

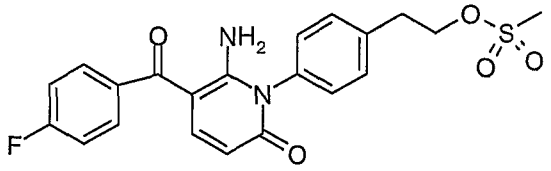
[0137]



[0138] To a solution of 6-amino-5-(2,4-fluorobenzoyl)-1-(2,6-difluoro-4-hydroxyphenyl)-pyridin-2(1*H*)-one (200 mg, 0.56 mmol) in anhydrous DMF (6 ml) under an atmosphere of nitrogen was added 1-bromo-5-chloropentane (0.088 ml, 0.67 mmol, 1.2 eq) and potassium carbonate (115 mg, 0.83 mmol, 1.5 eq). The mixture was heated at 40°C for 19 hours, before being allowed to cool to room temperature and diluted with EtOAc (20 ml). The solution was washed with water (3 x 20 ml) and brine (20 ml). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (20-40 % EtOAc in heptane) afforded the title compound as a yellow solid (104 mg) which was used without further purification.
LC/MS: m/z 465 $[M+H]^+$. ^1H NMR (300 MHz, CD_3OD) δ: 7.60 (2H, m), 7.53 (1 H, d, J=9.4 Hz), 7.33 (2H, m), 7.05 (2H, m), 5.72 (1H, d, J=9.8 Hz), 4.11 (2H, t, J=6.3 Hz), 3.68 (2H, t, J=6.5 Hz), 1.84-1.77 (4H, m), 1.56 (2H, m).

Intermediate 4J Methanesulfonic acid 2-{4-[6-amino-5-(4-fluoro-benzoyl)-2-oxo-2H-pyridin-1-yl]-phenyl}-ethyl ester

[0139]



[0140] To a suspension of 6-Amino-5-(4-fluoro-3-methyl-benzoyl)-1-[4-(2-hydroxy-ethyl)-phenyl]-1H-pyridin-2-one (150mg, 0.43mmol) in anhydrous DCM (3ml) at 0 °C was added methanesulfonyl chloride (34µl, 0.47mmol) followed by Et_3N (120µl, 0.85mmol). The reaction mixture was allowed to warm up to RT and stirred for 24 hours to completion. The reaction mixture was diluted with DCM (10ml), washed with 10% citric acid (5ml), followed by sat aq $NaHCO_3$ (5ml) and water (5ml). The DCM layer was dried ($MgSO_4$), filtered and concentrated *in vacuo.* Yield= 183mg (crude). LCMS purity = 85% m/z= 431 $[M+H]^+$. This material was used in the next step without further purification. The alcohol used as starting material was prepared as follows:

Acetic acid 2-{4-[6-amino-5-(4-fluoro-benzoyl)-2-oxo-2H-pyridin-1-yl]-phenyl}-ethyl ester (300mg) was dissolved in water (5ml) and conc HCl (5ml) and heated to 100°C for 1 hour. The reaction was then cooled, diluted with 10ml water and filtered. The resulting solid was then dried under reduced pressure to give 264mg of product, m/z= 353 $[M+H]^+$.

[0141] The acetic acid 2-{4-[6-amino-5-(4-fluoro-benzoyl)-2-oxo-2H-pyridin-1-yl]-phenyl}-ethyl ester used as starting material was prepared as follows:

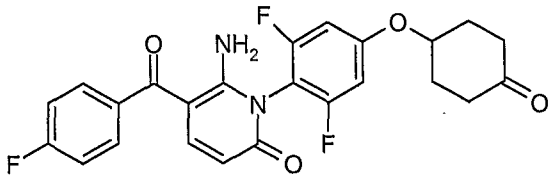
A solution of propiolic acid (270µl, 4.39mmol) and CDI (712mg, 4.34mmol) in THF (13ml) was warmed from 0°C to RT and stirred for 1.5 hours. To this solution was added acetic acid 2-(4={[3-(4-fluoro-phenyl)-3-oxo-propionimidoyl]-amino}-phenyl)-ethyl ester (1g, 2.92mmol) in THF (6ml) and the reaction heated to 80°C for a period of 2 hours maximum. After cooling and evaporation under reduced pressure, the crude residue was sonicated with methanol (7ml) before filtration, washing with a minimum amount of methanol. An off-white solid was collected (350mg crude).

[0142] The acetic acid 2-(4-{[3-(4-fluoro-phenyl)-3-oxo-propionimidoyl]-amino}-phenyl)-ethyl ester used as starting material was prepared as follows:

3-(4-Fluoro-phenyl)-3-oxo-thiopropionimidic acid 4-chloro-phenyl ester (1 g, 2.9mmol) and 4-aminophenethyl alcohol (418mg, 3.08mmol) were dissolved in acetic acid (5ml) and heated to 80°C for a period of 24 hours. The reaction was cooled to RT and evaporated under reduced pressure. The crude residue was partitioned between DCM and Na_2CO_3. The DCM layer was further washed with brine and dried over $MgSO_4$ before evaporation under reduced pressure. The product was isolated (1g crude) as a 3:1 mixture of the acetylated product: alcohol. This was taken through unpurified into the above cyclisation reaction. Product m/z= 343 $[M+H]^+$, alcohol m/z= 301 $[M+H]^+$.

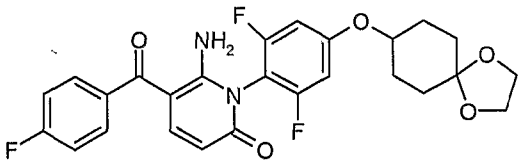
Intermediate 5 6-Amino-1-[2,6-difluoro-4-(4-oxo-cyclohexyloxy)phenyl]-5-(4-fluorobenzoyl)-1H-pyridin-2-one

[0143]



[0144] To a solution of 6-amino-1-[4-(1,4-dioxa-spiro[4.5]dec-8-yloxy)-2,6-difluoro-phenyl]-5-(4-fluorobenzoyl)-1H-pyridin-2-one (0.55g, 1.10mmol) in 1,4-dioxane (10ml) was added 2M aq HCl (5ml) at room temperature. Stirring was continued for 18h. Upon completion of reaction the reaction mixture was diluted with water (10ml) before evaporation of dioxane under reduced pressure. The residual aqueous solution was extracted with EtOAc (2 x 10ml). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to dryness under reduced pressure to give the desired ketone as a white solid (0.43g, 86%). LCMS purity 98%, m/z 457 $[M+H]^+$, ^1H NMR (400 MHz, $CDCl_3$), δ: 2.05-2.15 (2H, m), 2.25-2.45 (4H, m), 2.55-2.70 (2H, m), 4.65-4.75 (1H, m), 5.85 (1H, d), 6.70-6.75 (2H, m), 7.05-7.15 (2H, m), 7.50-7.65 (3H, m),

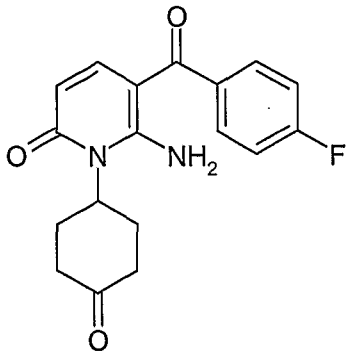
[0145] The ketal used as starting material was prepared as follows:



[0146] To a stirred solution of 1,4-dioxa-spiro[4.5]decan-8-ol (0.5g, 1.45mmol) in THF (1.5ml) was added 6-Amino-1-(2,6-difluoro-4-hydroxyphenyl)-5-(4-fluoro-benzoyl)-1H-pyridin-2-one (prepared by methods described in WO 03/076405) (0.5g, 1.39mmol) and triphenylphosphine (0.38g, 1.45mmol) at RT. Diisopropyl azodicarboxylate (0.29ml, 1.45mmol) was added dropwise and stirring was continued for 18h. The reaction mixture was evaporated to dryness and purified by column chromatography to afford the desired material as a white solid (0.55g, 79%). LCMS purity 99%, m/z 501 $[M+H]^+$, ^{1}HNMR (400 MHz, $CDCl_3$), δ: 1.55-1.65 (2H, m), 1.75-2.00 (6H, m), 3.85-3.90 (4H, m,), 4.35-4.40 (1 H, m), 5.85 (1H, d), 6.10-6.20 (2H, m), 7.05-7.15 (2H, m), 7.45-7.60 (3H, m).

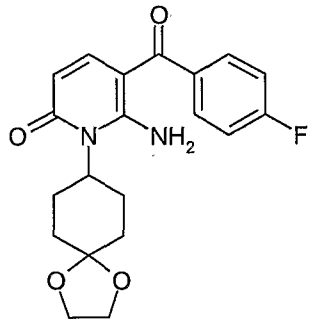
Intermediate 6 6-Amino-5-(4-fluorobenzoyl)-1-(4-oxo-cyclohexyl)-1H-pyridin -2-one

[0147]



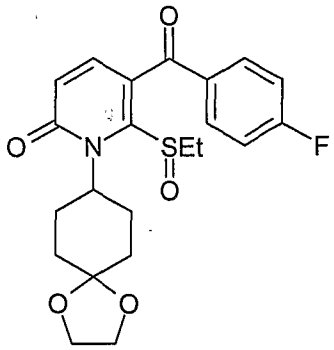
[0148] 2M HCl (14ml) was added to a yellow solution of 6-Amino-1-(1,4-dioxa-spiro[4.5]dec-8-yl)-5-(4-fluorobenzoyl)-1H-pyridin-2-one (664mg, 1.78mmol) in 1,4-dioxane (60ml) at RT. The resultant yellow solution was stirred at RT for 24h and then diluted with H_2O (30ml) and concentrated *im vacuo* to remove the 1,4-dioxane giving a yellow crystalline solid. The solid was isolated by filtration, washed with $H_2O$and air dried giving a yellow crystalline solid. Yield = 479mg, 82%. LCMS purity 92%, m/z 329 $[M+H]^+$, ^1H NMR (400 MHz, $CDCl_3$), δ: 1.90-2.30 (8H, m), 5.35 (1H, m), 5.65 (1H, d), 7.05-7.15 (2H, m), 7.30 (1 H, d), 7.35-7.45 (2H, m), 11.45 (1 H, s).

[0149] The pyridone acetal used as starting material in the above procedure was prepared as follows



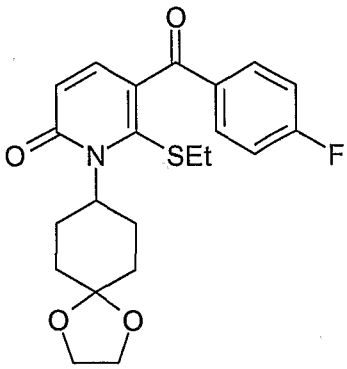
[0150] Triethylamine was added (0.74ml, 5.31mmol) to a solution of 1-(1,4-Dioxa-spiro[4.5]dec-8-yl)-6-ethanesulfinyl-5-(4-fluorobenzoyl)-1H-pyridin-2-one (1.046g,2.42 mmol) in 0.5M NH_3 in 1,4-dioxane (30ml) at RT under N_2. The resultant yellow solution was stirred at RT overnight and then concentrated *in vacuo* giving a yellow solid, which was triturated with TBME, isolated by filtration and washed with TBME giving a pale yellow solid. Yield = 802mg, 89%. LCMS purity 100%, m/z 373 $[M+H]^+$, ^1H NMR (400 MHz, $CDCl_3$), 5:1.90-2.00 (6H, m), 2.60 (2H, m), 4.15 (4H, m), 5.90 (1 H, d), 7.25 (2H, m), 7.55 (1 H, d), 7.65 (2H, m).

[0151] The sulphoxide used in the above procedure was prepared as follows



[0152] m-Chloroperbenzoic acid (583mg, 2.60mmol) was added in one portion to a yellow solution of 1-(1,4-Dioxaspiro[4.5]dec-8-yl)-6-ethylsulfanyl-5-(4-fluorobenzoyl)-1H-pyridin-2-one (986mg, 2.36mmol) in CH_2Cl_2 (30ml) at RT under N_2. The resultant yellow solution was stirred at RT overnight and then diluted with CH_2Cl_2 (25ml) and washed with sat. Na_2SO_3 (2 x 30ml), sat. $NaHCO_3$ (2 x 30ml), H_2O (30ml), dried (Na_2SO_4), filtered and concentrated *in vacuo* giving a light yellow oil. Yield = 1.046g, 102%. LCMS purity 96%, m/z 434 $[M+H]^+$.

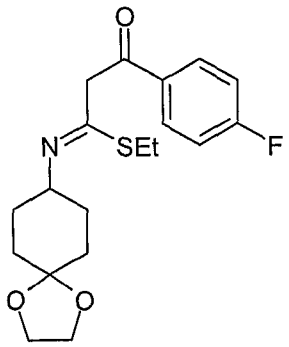
[0153] The sulphide used in the procedure above was prepared as follows



[0154] 1-Chloro-N,N-2-trimethylpropenylamine (2.03ml, 15.34mmol) was added to a colourless solution of propiolic acid (0.94ml, 15.34mmol) in anhydrous THF (50ml) at 0°C under N_2. The resultant colourless solution was stirred at 0°C for 2h after which time a yellow solution of the N-(1,4-Dioxa-spiro[4.5]dec-8-yl)-3-(4-fluorophenyl)-3-oxo-thiopropionimidic acid (4.667g, 12.79mmol) in anhydrous THF (50ml) was added over 5 min at 0°C. The resultant yellow solution was then allowed to warm to RT and stirred for 24h. The reaction mixture was concentrated *in vacuo* giving a dark brown

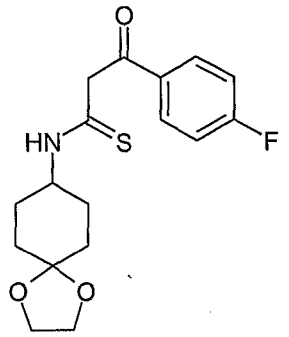
oil, which was diluted with EtOAc (20ml) and allowed to stand at RT overnight giving a crystalline solid which was isolated by filtration and washed with heptane and TBME. Yield = 216mg. The filtrate was concentrated *in vacuo* giving a brown solid which was dissolved in CH_2Cl_2 (100ml) and washed with sat. Na_2CO_3 (3 x 100ml), H_2O (2 x 100ml), dried (Na_2SO_4), filtered and concentrated *in vacuo* giving a brown oil. Purification by flash column chromatography (silica, 100% CH_2Cl2 to 30% EtOAc/CH_2Cl_2) gave the cyclised product after trituration with TBME. Yield = 770mg. Overall yield = 986mg, 19%. LCMS purity 100%, m/z 418 $[M+H]^+$.

[0155] The thiopropionimidic acid used in the above procedure was prepared as follows:



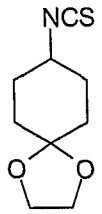
[0156] K_2CO_3 (16.1g, 117mmol) was added to a solution of N-(1,4-Dioxaspiro[4.5]dec-8-yl)-3-(4-fluorophenyl)-3-oxo-thiopropionamide (18.8g, 55.7mmol) in acetone (200ml) at RT/N_2 followed by the ethyl iodide (6.68ml, 83.6mmol). The reaction mixture was stirred at RT/N_2 for 2h and then concentrated *in vacuo* giving a brown paste which was taken up in EtOAc (300ml) and washed with H_2O (250ml). The organic phase was separated and the aqueous phase was extracted with EtOAc (2 x 150ml). The combined organic phases were dried (Na_2SO_4), filtered and concentrated *in vacuo* a brown oil. Purification by flash column chromatography (silica, 15% EtOAc/Heptane) gave a yellow oil. Yield = 9.94g, 49%. LCMS purity 94%, m/z 366 $[M+H]^+$.

[0157] The thiopropionamide used in the above process was prepared as follows:



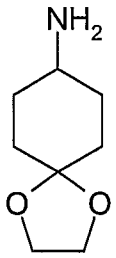
[0158] A solution of 4-fluoroacetophenone (6.76ml, 55.7mmol) in THF (50ml) was added slowly over 5 min to a stirred suspension of KO^{t}Bu (6.56g, 58.5mmol) in THF (40ml) at 0°C. A solution of 8-isothiocyanato-1,4-dioxaspiro[4.5]decane (11.1 g, 55.7mmol) in THF (30ml) was added at 0°C over 5 min and the resulting mixture was stirred at 0°C for 90 min. The reaction mixture was evaporated to dryness giving a dark brown solid which was used crude in the next stage. Yield = 18.8g, 100%. LCMS purity 55%, m/z 338 $[M+H]^+$.

[0159] The isothiocyanate used in the above procedure was prepared as follows



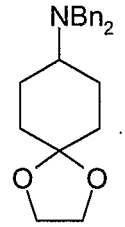
[0160] Calcium carbonate (13.75g, 137.4mmol) was added to a solution of 1,4-dioxaspiro[4.5]dec-8-ylamine (13.5g, 85.9mmol) in CH_2Cl_2 (675ml) and H_2O (330ml) with vigorous stirring at RT. The thiophosgene (8.5ml, 111.6mmol) was added dropwise over 5 min and upon complete addition the reaction mixture was stirred at RT for 2h. The reaction mixture was diluted with H_2O (600ml) and extracted into CH_2Cl_2 (300ml). The organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo* giving the product. Yield = 8.5g, 50%. LCMS purity 47%, m/z 200 $[M+H]^+$.

[0161] The cyclohexylamine used in the above process was prepared as follows:



[0162] 10% $Pd(OH)_2/C$ (1g) was added to a fine suspension of N,N-dibenzyl-N-1,4-dioxaspiro[4.5]dec-8-ylamine (21.13g, 62.7mmol) in EtOH (400ml) at RT. The resultant mixture was evacuated and purged three times with H_2 and then held under an atmosphere of H_2 (balloon) overnight. The reaction mixture was evacuated and purged three times with N_2 and then the catalyst was removed by filtration. The filtrate was concentrated *in vacuo* giving the amine as a colourless oil. Yield = 14.34g, 99%. LC-MS (ELS detection) purity 100%, m/z 158 $[M+H]^+$.

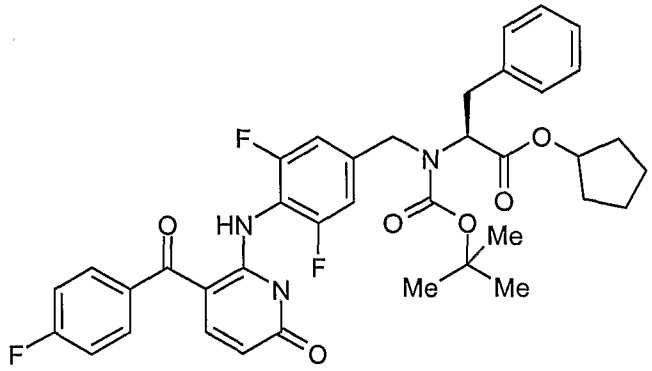
[0163] The dibenzylamine used in the above process was prepared as follows:



[0164] Dibenzylamine (27.8ml, 145mmol) was added to a solution of 1,4-dioxaspiro[4.5]decan-8-one (21.5g, 138mmol) in DCE (350ml) at RT under N_2 and stirred for 1 h. Sodium triacetoxyborohydride (46.7g, 220mmol) was added portion wise over 10min and upon complete addition the reaction was stirred at RT/N_2 overnight. Saturated $NaHCO_3$ (300ml) was added followed by DCM (300ml) and the reaction mixture was stirred for 30 min. The organic phase was separated and washed with $NaHCO_3$ (300ml), brine (300ml), dried (Na_2SO_4), filtered and concentrated *in vacuo* giving an oil which upon trituration with heptane gave a white solid which was isolated by filtration. Yield = 30.95g, 67%. LCMS purity 100%, m/z 338 $[M+H]^+$.

Intermediate 7 Cyclopentyl (S)-2-(tert-Butoxycarbonyl-{3,5-difluoro-4-[3-(4-fluoro-benzoyl)-6-oxo-1,6-dihydro-pyridin-2-ylamino]benzyl}amino)-3-phenyl propionate

[0165]

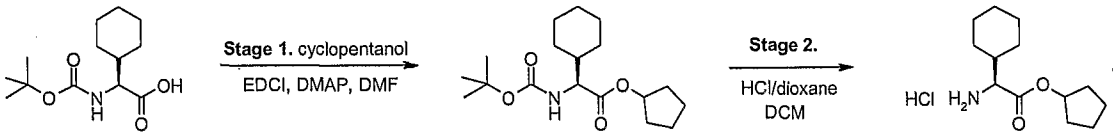


[0166] The pyridone was formed as a side product of the procedure described for the synthesis of **Intermediate 3K.** LCMS purity 80%, m/z 690 $[M+H]^+$.

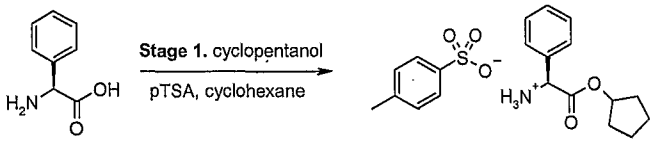
Preparation of aminoacid esters (intermediates 8 to 16)

[0167]

Route I. Used for the preparation of Intermediates 8, 9, 13, 14 and 15

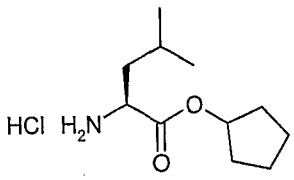


Route II. Used for the preparation of Intermediate 10, 11,12 and 16

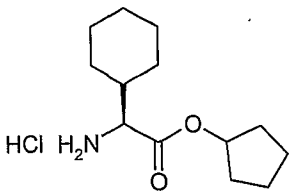


Intermediates prepared:

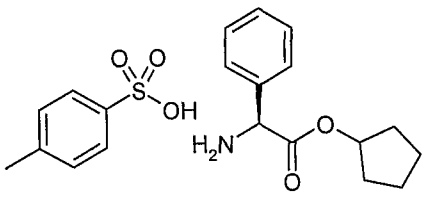
[0168]



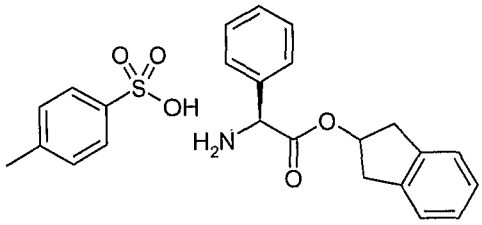
Intermediate **8**



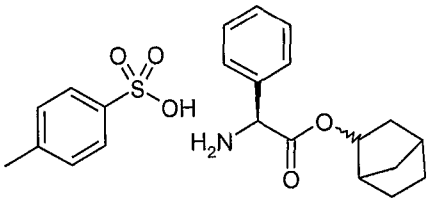
Intermediate **9**



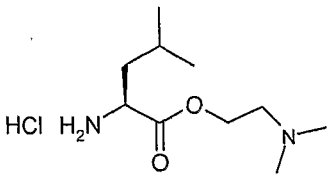
Intermediate **10**



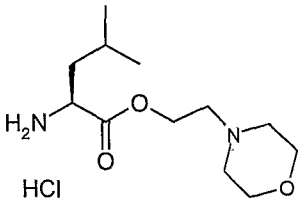
Intermediate **11**



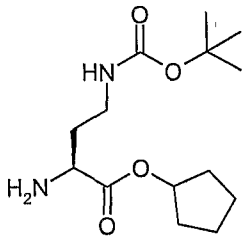
Intermediate **12**



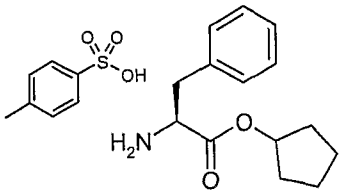
Intermediate **13**



Intermediate **14**



Intermediate **15**



Intermediate **16**

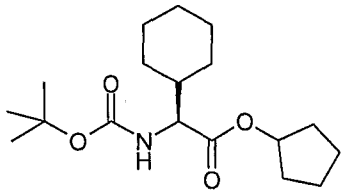
Figure 1

Synthesis of compounds outlined in Figure 1

*Route I (exemplified for Intermediate **9**)*

Stage 1 - Ester formation

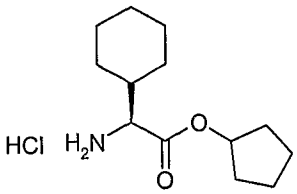
[0169]



[0170] To a solution of (S)-2-*tert*-butoxycarbonylamino-3-cyclohexyl-propionic acid (5g, 19.4mmol) in DMF (50ml) at 0°C was added cyclopentanol (8.8ml, 97.15mmol), EDCI (4.09g, 21.37mmol) and finally DMAP (237mg, 1.94mmol). The reaction mixture was warmed to RT and stirred for 18h. The DMF was removed *in vacuo* to give a clear oil. This was separated between water and EtOAc. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo.* The crude extract was purified by column chromatography (25% EtOAC in heptane) to yield the desired product as a clear oil (14.87g, 55%). ^{1}H NMR (300 MHz, d_6-DMSO) δ; 7.09 (1H, d), 5.08 (1H, t), 3.76 (1H, t), 1.50-1.85 (10H, br m), 1.39 (9H, s), 1.00-1.25 (9H, br m).

Stage 2- Boc deprotection to yield cyclopentyl (2S)-amino(cyclohexyl)acetate hydrochloride **(Intermediate 9)**

[0171]

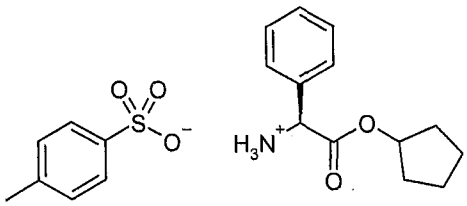


[0172] Stage 1 product (14.87g, 45.69mmol) was dissolved in DCM (100ml) and treated with 4M HCl/dioxane (22.8ml, 91.38mmol) and the reaction mixture was stirred at RT for 24h. The crude mixture was concentrated under reduced pressure to give an orange oil. This was triturated with Et_2O to give a white precipitate. This was further washed with Et_2O to give the desired product as a white powder (7.78g, 65%). ^1H NMR (300MHz, d_6-DMSO) δ; 8.45 (3H, br s), 5.22 (1 H, t), 3.28 (1 H, d), 1.95-1.50 (10H, br m), 1.30-0.90 (9H, br m).

Route II (exemplified for Intermediates 10)

Stage 1 -Ester formation to yield (1S)-2-(cyclopentyloxy)-2-oxo-1-phenylethanaminium 4-methylbenzenesulfonate **(Intermediate 10)**

[0173]



[0174] To a slurry of (S)-phenylglycine (5g, 33.1mmol) in cyclohexane (150ml) was added cyclopentanol (29.84ml, 331mmol) and p-toluene sulfonic acid (6.92g, 36.4mmol). The reaction was fitted with a Dean-Stark receiver and heated to 135°C for complete dissolution. After 12h, the reaction was cooled to RT leading to the precipitation of a white solid. The solid was filtered and washed with EtOAc before drying under reduced pressure to give the required product as a white powder (11.01g, 85%). ^1H NMR (300MHz, *d*6-DMSO) δ; 8.82 (2H, brs), 8.73 (1H, brs), 7.47 (7H, m), 7.11 (2H, d), 5.25 (1 H, br s), 5.18 (1H, m), 2.29 (3H, s), 1.87-1.36 (8H, m).

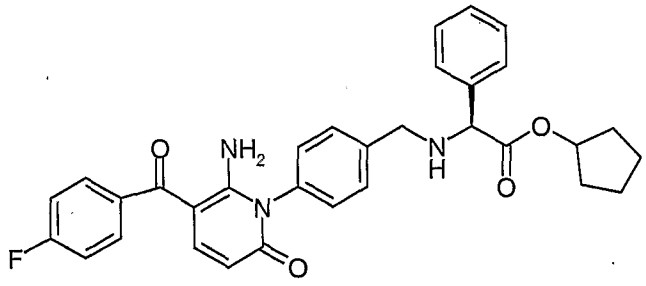
[0175] Intermediates **11** and **12** were prepared using 2-indanol and α-norborneol respectively, instead of cyclopentanol (via Route II). In a similar manner, intermediates **13** and **14** were prepared using dimethylaminoethanol and 4-(2-hydroxyethyl)-morpholine respectively (via Route I). Intermediate **15** was prepared via route I using commercially available Z-Dab(Boc)-OH (N-α-Z-N-y-Boc-L-2,4-diaminobutyric acid).

[0176] The corresponding (R)-amino acid esters of the above intermediates can be prepared in a similar manner to shown above, starting from the relevant commercially available (R)-amino acids. In addition, the corresponding Leucine and Phenylglycine tert-butyl esters are commercially available and are used directly where appropriate.

Examples

Example 1 Cyclopentyl (S)-{4-[6-Amino-5-(4-fluorobenzoyl)-2-oxo-2H-pyridin-1-yl]benzylamino}phenylacetate

[0177]

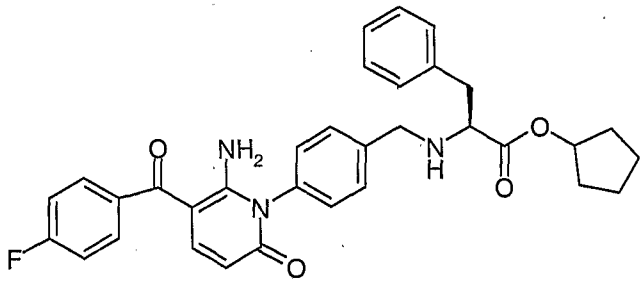


[0178] A mixture of **Intermediate 3A** (80mg, 0.125mmol) in 20% TFA/DCM solution (5ml) was allowed to stir at RT for 1 h. The reaction mixture was evaporated to dryness and purified by preparative HPLC to give the desired product, yield = 33mg (40%), LCMS purity= 100% m/z 540 $[M+H]^+$, ^1H NMR (400 MHz, DMSO), δ: 1.21-1.82 (8H, m), 4.01-4.14 (2H, m), 5.11-5.21 (2H, m), 5.64 (1 H, d), 7.21-7.54 (13H, m), 7.62 (1 H, d), 10.16 (2H, br s).

[0179] The following examples were prepared in a similar manner to Example 1.

Example 2 Cyclopentyl (S)-2-{4-[6-Amino-5-(4-fluorobenzoyl)-2-oxo-2H-pyridin-1-yl]benzylamino} -3-phenylpropionate

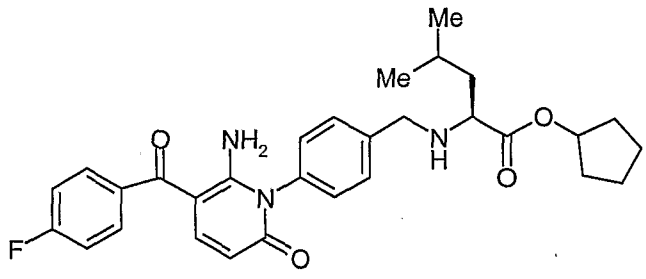
[0180]



[0181] From the **Intermediate 3D .** LCMS purity 100%, m/z 554 $[M+H]^+$, ^1H NMR (400 MHz, DMSO), δ: 1.22-1.83 (8H, m), 3.10 (1H, m), 4.45 (3H, m), 5.19 (1H, m), 5.85 (1H, d), 7.35-7.74 (14H, m), 7.82 (1H, br s), 9.96 (1H, br s).

Example 3 Cyclopentyl (S)-2-{4-[6-Amino-5-(4-fluorobenzoyl)-2-oxo-2H-pvridin-1-yl]benzylamino}-4-methylpentanoate

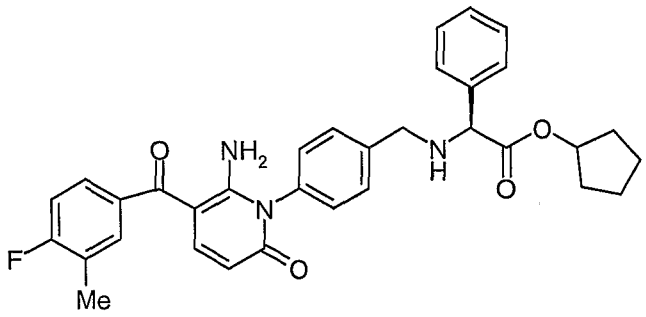
[0182]



[0183] From **Intermediate 3G.** LCMS purity 100%, m/z 520 $[M+H]^+$, ^1H NMR (400 MHz, DMSO), δ: 1.10 (6H, m), 1.70-2.11 (11H, m), 4.14-4.53 (3H, m), 5.42 (1H, m, CH), 5.90 (1H, d), 7.49-7.91 (9H, m), 9.83 (2H, br s).

Example 4 Cyclopentyl (S)-{4-[6-Amino-5-(3-methyl-4-fluoro benzoyl)-2-oxo-2H-pyridin-1-yl]benzylamino}phenylacetate

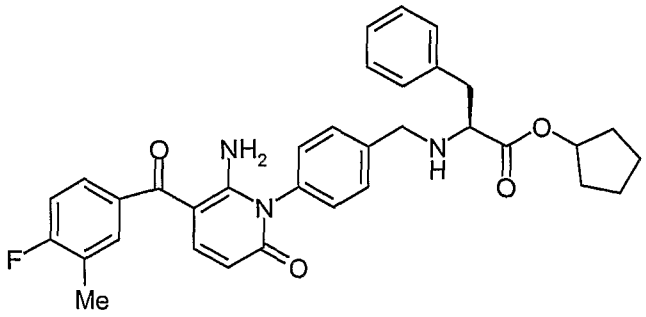
[0184]



[0185] From **Intermediate 3C**, LCMS purity 97%, m/z 554 $[M+H]^+$, ^1H NMR (400 MHz, CD_3OD), δ: 1.30-1.81 (8H, m), 2.25 (3H, s), 3.72 (2H, s), 4.34 (1 H, s), 5.08 (1 H, m), 5.70 (1 H, d), 7.03-7.38 (10H, m), 7.46-7.61 (3H, m).

Example 5 Cyclopentyl (S)-2-{4-[6-Amino-5-(3-methyl-4-fluorobenzoyl)-2-oxo-2H-pyridin-1-yl]benzylamino}-3-phenylpropionate

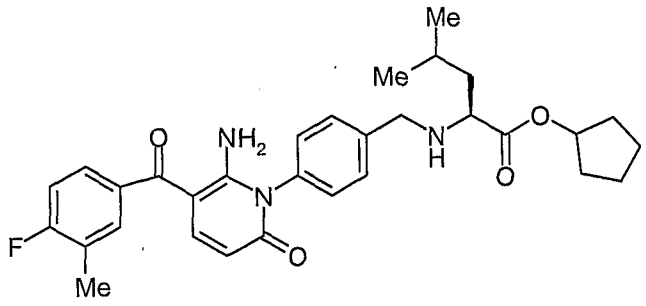
[0186]



[0187] From **Intermediate 3F**. LCMS purity 100%, m/z 568 $[M+H]^+$, ^1H NMR (400 MHz, DMSO), δ: 1.09-1.77 (8H, m), 2.30 (3H, s), 2.95 (1H, m), 3.14 (2H, s), 4.19-4.42 (3H, m), 5.02 (1 H, m), 5.69 (1 H, d), 7.19-7.51 (11 H, m), 7.68 (2H, m), 9.79 (2H, br s).

Example 6 Cyclopentyl (S)-2-{4-[6-Amino-5-(3-Methyl-4-fluorobenzoyl)-2-oxo-2H-pyridin-1-yl]benzylamino}-4-methylpentanoate

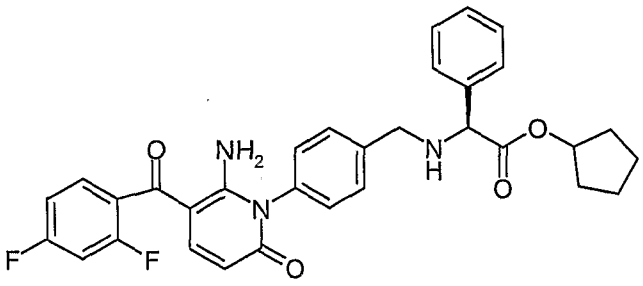
[0188]



[0189] From **Intermediate 3J.** LCMS purity 100%, m/z 534 $[M+H]^+$, ^1H NMR (400 MHz, DMSO), δ: 0.71 (6H, m), 1.32-1.70 (11 H, m), 2.09 (3H, s), 3.72-4.14 (3H, m), 5.03 (1 H, m), 5.50 (1 H, d), 7.00-7.29 (6H, m), 7.46 (2H, m), 9.40 (2H, br s).

Example 7 Cyclopentyl (S)-{4-[6-Amino-5-(2,4-difluorobenzoyl)-2-oxo-2H-pyridin-1-yl]benzylamino}phenylacetate

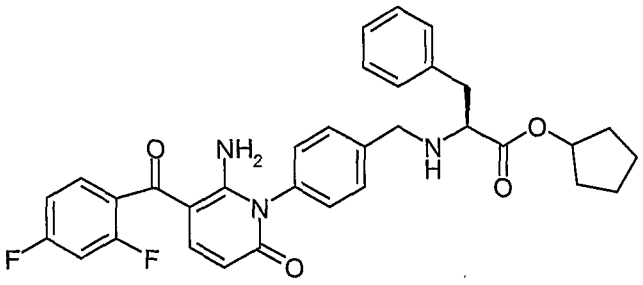
[0190]



[0191] From **Intermediate 3B.** LCMS purity 100%, m/z 558 $[M+H]^+$, ^1H NMR (400 MHz, DMSO), δ: 1.33-1.89 (8H, m), 3.71 (2H, m), 4.28 (1 H, s), 5.04 (1 H, m), 5.61 (1 H, d), 6.91 (1H, brs), 7.18-7.60 (13H, m), 10.05 (1H, br s).

Example 8 Cyclopentyl (S)-2-{4-[6-Amino-5-(2.4-difluorobenzoyl)-2-oxo-2H-pyridin-1-yl]benzylamino}-3-phenylpropionate

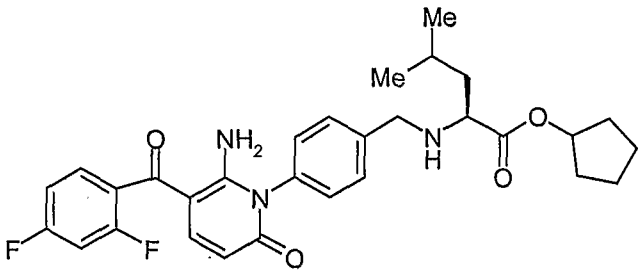
[0192]



[0193] From **Intermediate 3E.** LCMS purity 100%, m/z 572 $[M+H]^+$, ^1H NMR (400 MHz, DMSO), δ: 1.08-1.76 (8H, m), 2.95 (1H, t), 4.11-4.40 (3H, m), 4.98 (1H, m), 5.68 (1H, d), 6.89 (1H, brs), 7.13-7.50 (12H, m), 7.65 (1H, m), 9.64-10.12 (2H, br s).

Example 9 Cyclopentyl (S)-2-{4-[6-Amino-5-(2,4-difluorobenzoyl)-2-oxo-2H-pyridin-1-yl]benzylamino}-4-methylpentanoate

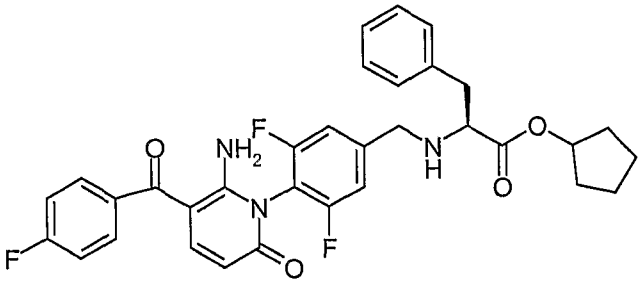
[0194]



[0195] From **Intermediate 3I**.LCMS purity 100%, m/z 538 $[M+H]^+$, ^1H NMR (400 MHz, DMSO), δ: 0.79 (6H, m), 1.39-1.78 (11H, m), 3.84-4.22 (3H, m), 5.10 (1H, m), 5.59 (1H, d), 6.79 (1 H, br s), 7.03-7.18 (2H, m), 7.21-7.42 (4H, m), 7.56 (2H, m), 9.54 (1 H, br s), 9.92 (1 H, br s).

Example 10 Cyclopentyl (S)-2-{-4-[6-Amino-5-(2,4-fluorobenzoyl)-2-oxo-2H-pyridin-1-yl]-3,5-difluorobenzylamino}-3-phenylpropionate

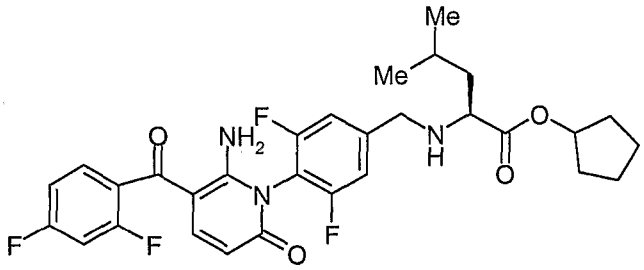
[0196]



[0197] From **Intermediate 3K.** LCMS purity 94%, m/z 591 $[M+H]^+$, ^1H NMR (400 MHz, d_6-DMSO), δ: 1.20-1.90 (10H, m), 3.10 (1 H, m), 3.50-3.60 (2H, m), 4.40-4.50 (4H, m), 5.20 (1 H, m), 5.90 (1 H, d), 7.35-7.50 (7H, m), 7.65-7.70 (5H, m), 9.50 (1 H, br)

Example 11 Cyclopentyl (S)-2-{4-[6-Amino-5-(4-fluorobenzoyl)-2-oxo-2H-pyridin-1-yl]-3,5-difluorobenzylamino}-4-methylpentanoate

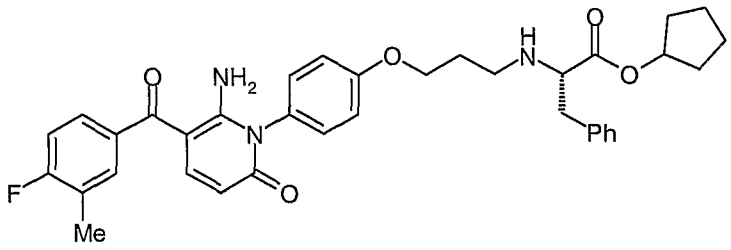
[0198]



[0199] From **Intermediate 3L** .LCMS purity 96%, m/z 574 $[M+H]^+$, ^1H NMR (400 MHz, CD_3OD), δ: 0.95-1.15 (6H, m), 1.65-2.05 (11H, m), 4.15-4.25 (1H, m), 4.35-4.45 (2H, m), 5.35-5.45 (1H, m), 5.85 (1H, d), 7.10-7.20 (2H, m), 7.45-7.55 (4H, m).

Example 12 Cyclopentyl (S)-2-(3-{4-[6-Amino-5-(3-methyl-4-fluoro benzoyl)-2-oxo-2H-pyridin-1-yl]phenoxy}propylamino)-3-phenyl propionate

[0200]



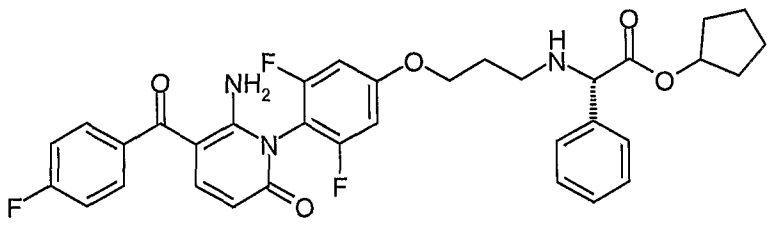
[0201] To a mixture of L-phenylalanine cyclopentyl ester tosylate salt **(Intermediate 16)** (218mg, 0.54mmol), K_2CO_3 (192mg, 1.39mmol), NaI (108mg, 0.72mmol) was added a solution of mesylate **Intermediate 4A** (170mg, 0.35mmol) in THF (2ml). The reaction mixture was diluted with DMF (2ml) and heated at 70 °C for 18h with stirring. The reaction mixture was cooled to RT, THF was removed by concentration under reduced pressure. The residue was diluted with EtOAc (20ml) and washed with water (10ml), dried (Na_2SO_4), filtered and evaporated to dryness. Purification by pre-

parative HPLC afforded the desired product, yield= 57mg, 15%. LCMS purity 97%, m/z 612 $[M+H]^+$, ^1H NMR (400 MHz, CD_3OD), δ: 1.30-2.00 (8H, m), 2.30 (2H, m), 3.10 (1H, m), 3.40 (1H, m), 4.25 (2 H, m), 4.40 (1H, m), 5.20 (1H, m), 5.85 (1H, d), 6.90 (2H, m), 7.10 (2H, d), 7.20-7.45 (7H, m), 7.65 (2H, m), 7.75 (1H, m).

[0202] The following compounds were prepared in a similar manner

Example 13 Cyclopentyl (S)-(3-{4-[6-Amino-5-(4-fluorobenzoyl)-2-oxo-2H-pyridin-1-yl]-3,5-difluorophenoxy}propylamino)phenylacetate

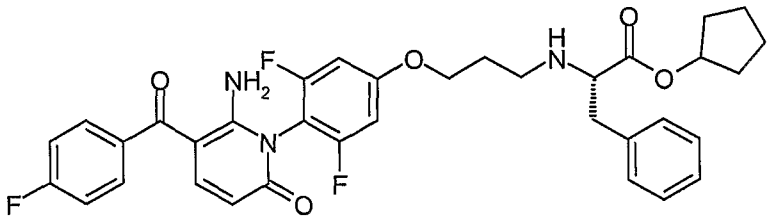
[0203]



[0204] From **Intermediate 4E** and L-phenylglycine cyclopentyl ester tosylate salt **(Intermediate 10),** LCMS purity 96%, m/z 620 $[M+H]^+$, ^1H NMR (400 MHz, CD_3OD), δ: 1.40-1.65 (5H, m), 1.80 (2H, m), 1.95 (1 H, m), 2.30 (2H, m), 3.15 (1 H, m), 3.30 (1 H, m), 4.25 (2H, m), 5.25 (1 H, s), 5.40 (1 H, m), 5.90 (1 H, d), 6.90 (2H, d), 7.30 (2H, t), 7.55 - 7.60 (5H, m), 7.65 (2H, m) 7.75 (1 H, d).

Example 14 Cyclopentyl (S)-(3-{4-[6-Amino-5-(4-fluorobenzoyl)-2-oxo-2H-pyridin-1-yl]-3,5-difluorophenoxy}propylamino)phenylacetate

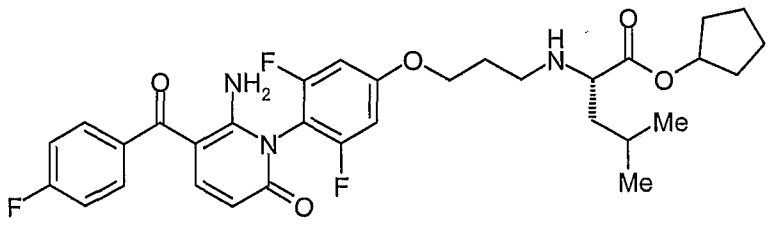
[0205]



[0206] From **Intermediate 4E** and L-phenylalanine cyclopentyl ester tosylate salt **(Intermediate 16),** LCMS purity 97%, m/z 634 $[M+H]^+$, ^1H NMR (400 MHz, CD_3OD), δ: 1.30-2.00 (8H, m), 2.30 (2H, m), 3.10 (1 H, m), 3.40 (1 H, m), 4.25 (2H, m), 4.40 (1 H, m), 5.20 (1 H, m), 5.85 (1H, d), 6.90 (2H, m), 7.10 (2H, d), 7.20-7.45 (7H, m), 7.65 (2H, m), 7.75 (1H, m).

Example 15 Cyclopentyl (S)-2-(3-{4-[6-Amino-5-(4-fluorobenzoyl)-2-oxo-2H-pyridin-1-yl]-3,5-difluorophenoxy-phenoxy}propylamino)-4-methyl pentanoate

[0207]

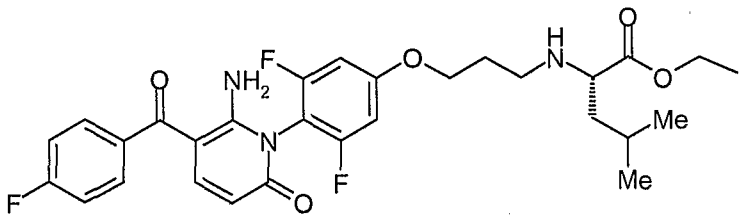


[0208] From **Intermediate 4E** and L-leucine cyclopentyl ester **(Intermediate 8),** LCMS purity 96%, m/z 600 $[M+H]^+$,

^{1}H NMR (400 MHz, CD_3OD), δ: 1.10 (6H, m), 1.70-2.0 (12H, m), 2.30 (2 H, m), 4.10 (1 H, m), 4.25 (2H, m), 4.40 (1 H, m), 5.40 (1 H, m), 5.85 (1 H, d), 6.90 (2H, m). 7.10 (2H, d), 7.60. (2H, m), 7.65 (2H, m), 7.75 (1H, m).

Example 16 Ethyl *N*-(3-{4-[6-amino-5-(4-fluorobenzoyl)-2-oxopyridin-1(2*H*)-yl]-3,5-difluorophenoxy}propyl)-L-leucinate

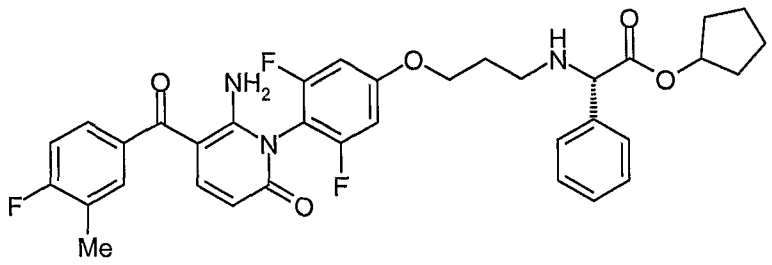
[0209]



[0210] From **Intermediate 4E** and L-leucine ethyl ester LCMS purity 98%, m/z 560 $[M+H]^+$, ^{1}H NMR (400 MHz, CD_3OD), δ: 1.10-1.20 (6H, m), 1.45-1.55 (3H, t), 1.65-1.85 (2H, m), 1.90-2.00 (1 H, m), 2.15-2.30 (2H, m), 2.85-3.05 (2H, m), 3.55 (1 H, m), 4.35-4.50 (4H, m), 6.00 (1H, d), 7.10 (1H, d), 7.45-7.55 (1H, m), 7.80-7.85 (1H, m), 7.95 (1H, d).

Example 17 Cyclopentyl (S)-(3-{[6-Amino-5-(4-fluoro-3-methylbenzoyl)-2-oxo-2H-pyridin-1-yl]-3,5-difluorophenoxy}propylamino) phenylacetate

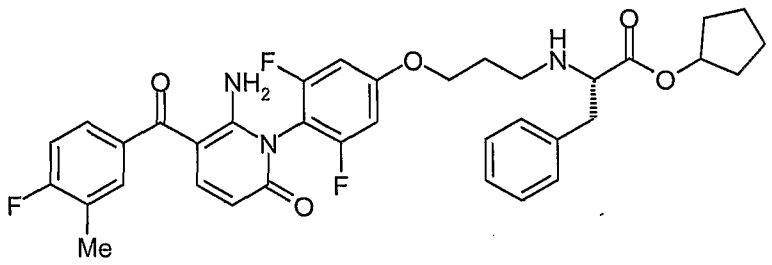
[0211]



[0212] From **Intermediate 4D** and L-phenylglycine cyclopentyl ester tosylate salt **(Intermediate 10),** LCMS purity 100%, m/z 634 $[M+H]^+$, ^{1}H NMR (400 MHz, d_6-DMSO), δ: 1.20-1.80 (8H, m), 2.0 (2H, m), 2.20 (3H, m), 2.80-3.00 (2H, m), 4.10 (2H, m), 5.10 (1H, m), 5.30 (1H, s), 5.60 (1H, d), 6.95 (1H, d), 7.20 (1H, m), 7.30 (1H, m), 7.40-7.50 (8H, m), 9.65 (1 H, m).

Example 18 Cyclopentyl (S)-2-(3-{4-[6-Amino-5-(4-fluoro-3-methylbenzoyl)-2-oxo-2H-pyridin-1-yl]-3,5-difluorophenoxy}propylamino)-3-phenylpropionate

[0213]

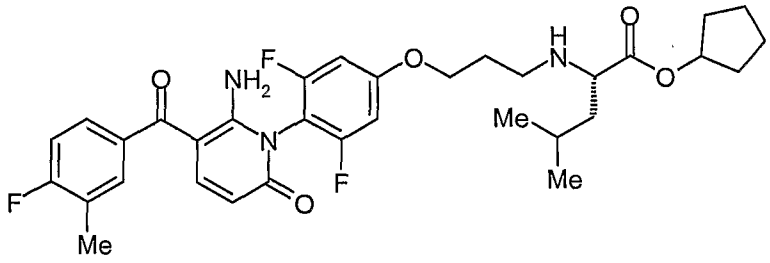


[0214] From **Intermediate 4D** and L-phenylalanine cyclopentyl ester tosylate salt **(Intermediate 16),** LCMS purity 97%, m/z 648 $[M+H]^+$, ^{1}H NMR (400 MHz, CD_3OD), δ: 1.20-1.90 (9H, m), 2.25 (2H, m), 2.35 (3H, s), 3.15 (1H, m), 3.45

(1H, m), 4.25 (2H, m), 4.40 (1H, d), 5.20 (2H, m), 5.82 (1H, d), 6.95 (2H, m), 7.20 (1H, m), 7.30-7.50 (7H, m), 7.75 (1H, d).

Example 19 Cyclopentyl (S)-2-(3-{4-[6-Amino-5-(4-fluoro-3-methylbenzoyl)-2-oxo-2H-pyridin-1-yl]-3,5-difluorophenoxy}propylamino)-4-methylpentanoate

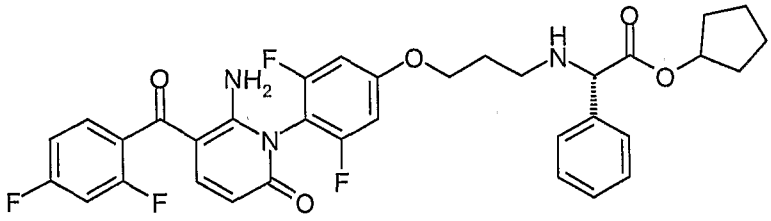
[0215]



[0216] From **Intermediate 4D** and L-leucine cyclopentyl ester **(intermediates 8)**, LCMS purity 100%, m/z 614 $[M+H]^+$, ^1H NMR (400 MHz, d_6-DMSO), δ: 0.90 (6H, m), 1.60-1.70 (10H, m), 1.90 (2H, m), 2.15 (2H, m), 2.30 (3H, s), 3.00-3.20 (2H, m), 4.10 (1 H, s), 4.20 (2H, m), 5.25 (1H, m), 5.70 (1H, d), 7.05 (1H, d), 7.25 (1H, m), 7.40 (1H, m), 7.50 (1H, m), 7.60 (1 H, d).

Example 20 Cyclopentyl (S)-(3-{4-[6-Amino-5-(2,4-difluoro benzoyl)-2-oxo-2H-pyridin-1-yl]-3,5-difluorophenoxy}propylamino)phenyl acetate

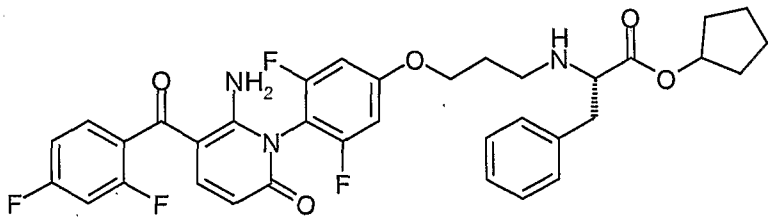
[0217]



[0218] From **Intermediate 4F** and L-phenylglycine cyclopentyl ester tosylate salt **(Intermediate 10)**, LCMS purity 91%, m/z 638 $[M+H]^+$, ^1H NMR (400 MHz, d_6-DMSO), δ: 1.50-2.10 (8H, m), 2.30 (2H, m), 3.10-3.25 (2H, m), 4.33 (2H, m), 5.40 (1 H, m), 5.56 (1 H, m), 5.90 (1 H, d), 7.20 (1 H, d) 7.40-7.75 (9H, m), 9.85 (2H, m).

Example 21 Cyclopentyl (S)-2-(3-{4-[6-Amino-5-(2,4-difluorobenz oyl)-2-oxo-2H-pyridin-1-yl]-3,5-difluorophenoxy}-propylamino)-3-phenyl propionate

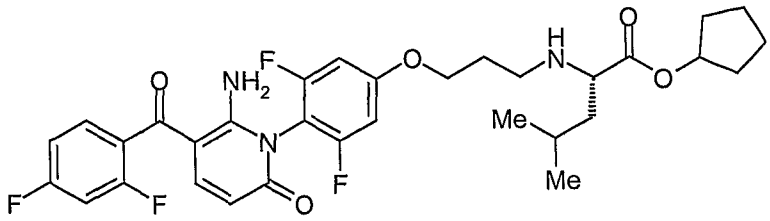
[0219]



[0220] From **Intermediate 4F** and L-phenylalanine cyclopentyl ester tosylate salt **(Intermediate 16)**.LCMS purity 100%, m/z 652 $[M+H]^+$, ^1H NMR (400 MHz, d_6-DMSO), δ: 1.10-1.80 (9H, m), 2.15 (2H, m), 2.95-3.20 (2H, m), 4.20 (2H, m), 4.40 (1H, m), 5.10 (1H, m), 5.75 (1 H, d), 7.06 (2H, d), 7.25-7.58 (9H, m), 9.34 (2H, m).

Example 22 Cyclopentyl (S)-2-(3-{4-[6-Amino-5-(2,4-difluoro benzoyl)-2-oxo-2H-pyridin-1-yl]-3,5-difluorophenoxy}propylamino)-4-methyl pentanoate

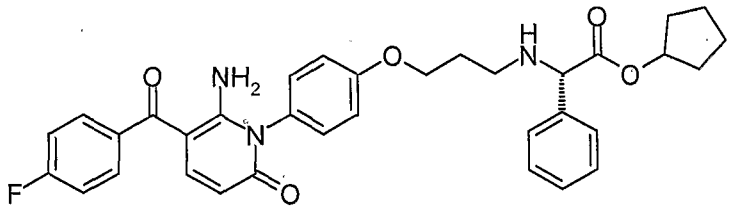
[0221]



[0222] From **Intermediate 4F** and L-leucine cyclopentyl ester **(Intermediate 8),** LCMS purity 87%, m/z 618 $[M+H]^+$, ^1H NMR (400 MHz, d_6-DMSO), δ: 1.0 (6H, m), 1.75 (9H, m), 1.95 (2H, m), 2.20 (2H, m), 3.10-3.30 (2H, m), 4.16 (1H, m), 4.26 (2H, m), 5.33 (1H, m), 5.80 (1H, d), 7.15 (2H, d), 7.40-7.65 (4H, m), 9.13- 9.25 (2H, m).

Example 23 Cyclopentyl (S)-(3-{-[6-Amino-5-(4-fluorobenzoyl)-2-oxo-2H-pyridin-1-yl]-phenoxy}propylamino)phenulacetate

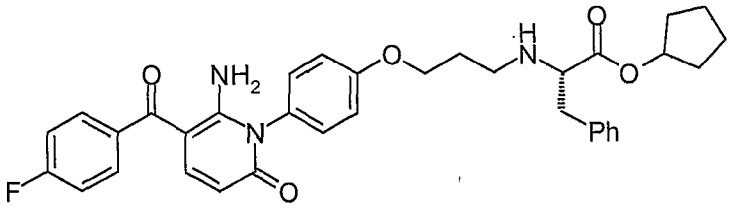
[0223]



[0224] From **Intermediate 4B** and L-phenylglycine cyclopentyl ester tosylate salt **(Intermediate 10),** LCMS purity 95%, m/z 584 $[M+H]^+$, ^1H NMR (400 MHz, CD_3OD), δ: 1.25-1.55 (5H, m), 1.60-1.85 (3H, m), 2.15 (2H, m), 3.00 (1 H, m), 3.15 (1 H, m), 4.05 (2H, m), 5.10 (1H, s), 5.25 (1H, m), 5.70 (1H, d), 7.00 (2H, m), 7.15 (4H, m), 7.40-7.50 (7H, m), 7.55 (1H, d).

Example 24 Cyclopentyl (S)-2-(3-{4-[6-Amino-5-(4-fluorobenzoyl)-2-oxo-2H-pyridin-1-yl]phenoxy}propylamino)-3-phenylpropionate

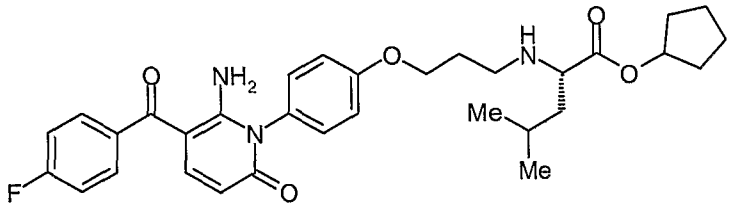
[0225]



[0226] From **Intermediate 4B** and L-phenylalanine cyclopentyl ester **(Intermediate 16),** LCMS purity 93%, m/z 598 $[M+H]^+$, ^1H NMR (400 MHz, CD_3OD), δ: 1.50-2.10 (8H, m), 2.50 (2H, m), 3.35-3.40 (1 H, m), 3.55-3.70 (2H, m), 4.40-4.50 (2H, m), 4.60 (1 H, m), 5.40-5.45 (1 H, m), 6.05-6.10 (1 H, d), 7.40-7.65 (11H, m), 7.85 (2H, m). 7.90 (1 H, m).

Example 25 Cyclopentyl (S)-2-(3-{4-[6-Amino-5-(4-fluorobenzoyl)-2-oxo-2H-pyridin-1-yl]phenoxy}propylamino)-4-methylpentanoate

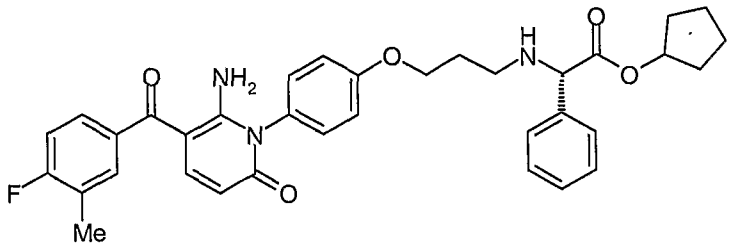
[0227]



[0228] From **Intermediate 4B** and L-leucine cyclopentyl ester **(Intermediate 8),** LCMS purity 97%, m/z 564 $[M+H]^+$, ^1H NMR (400 MHz, d_6-DMSO), δ: 0.90 (6H, m), 1.60-1.75 (10H, m), 1.90 (2H, m), 2.15 (2H, m), 3.10-3.30 (2H, m), 4.10 (1H, m), 4.15 (2H, m), 5.30 (1H, m), 5.70 (1H, d). 7.15 (2H, d), 7.30 (2H, d), 7.35 (2H, t), 7.50 (1H, d), 7.55 (1H, m) 9.05-30 (2H, m).

Example 26 Cyclopentyl (S)-(3-{4[6-Amino-5-(4-fluoro-3-methylbenzoyl)-2-oxo-2H-pyridin-1-yl-phenoxy}propylamino)phenylacetate

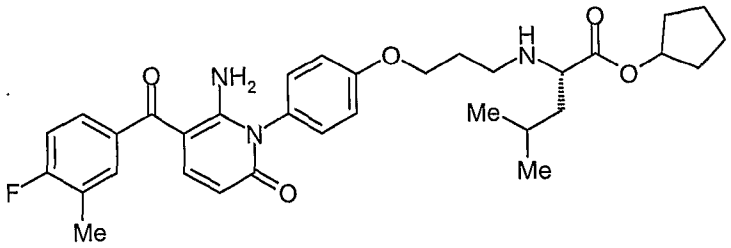
[0229]



[0230] From **Intermediate 4A** and L-phenylglycine cyclopentyl ester tosylate salt **(Intermediate 10),** LCMS purity 95%, m/z 598 $[M+H]^+$, ^1H NMR (400 MHz, d_6-DMSO), δ: 1.30 2.20 (10H, m), 2.30 (3H, m), 2.90-3.10 (2H, m), 4.15 (2H, m), 5.20 (1H, m), 5.30 (1H, m), 5.70 (1H, d), 7.10 (2H, d), 7.25-7.40 (5H, m), 7.40-7.50 (3H, m), 7.55 (5H, m), 9.70 (2H, m).

Example 27 Cyclopentyl (S)-2-(3-{4-[6-Amino-5-(4-fluoro-3-methyl benzoyl-2-oxo-2H-pyridin-1-yl]phenoxy}propylamino)-4-methylpentanoate

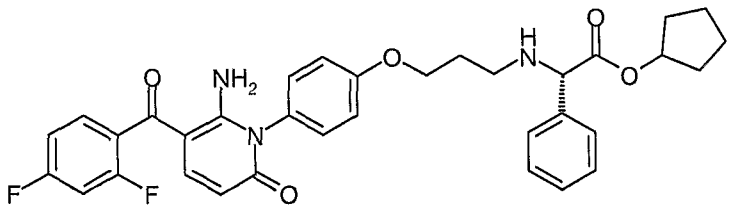
[0231]



[0232] From **Intermediate 4A** and L-leucine cyclopentyl ester **(Intermediate 8),** LCMS purity 89%, m/z 578 $[M+H]^+$, ^1H NMR (400 MHz, d_6-DMSO), δ: 0.95 (6H, m), 1.55-2.25 (12H, m), 2.30 (3H, m), 2.75-3.30 (2H, m), 4.15 (3H, m), 5.25 (1H, m), 5.70 (1H, d). 7.15 (2H, d), 7.30-7.40 (4H, m), 7.40 - 7.50 (2H, m).

Example 28 Cyclopentyl (S)-(3-{4-[6-Amino-5-(2,4-difluoro benzoyl)-2-oxo-2H-pyridin-1-yl]-phenoxy}propylamino)phenyl acetate

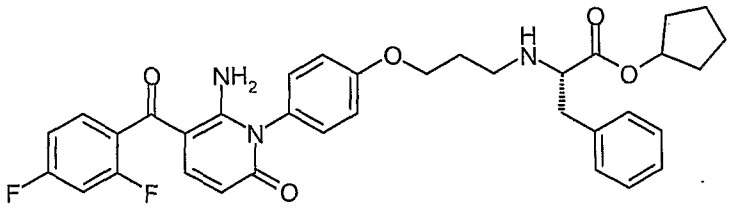
[0233]



[0234] From **Intermediate 4C** and L-phenylglycine cyclopentyl ester tosylate salt **(Intermediate 10),** LCMS purity 99%, m/z 602 $[M+H]^+$, ^1H NMR (400 MHz, d_6-DMSO), δ: 1.35-2.15 (10H, m), 2.90-3.10 (2H, m), 4.10 (2H, m), 5.25 (1H, m), 5.40 (1H, m), 5.70 (1H, d), 7.10 (2H, d), 7.25-7.30 (4H, m), 7.40-7.50 (2H, m), 7.55 (5H, m), 9.70 (2H, m).

Example 29 Cyclopentyl (S)-2-(3-{4-[6-Amino-5-(2,4-difluoro benzoyl)-2-oxo-2H-pyridin-1-yl]phenoxy}propylamino)-3-phenyl propionate

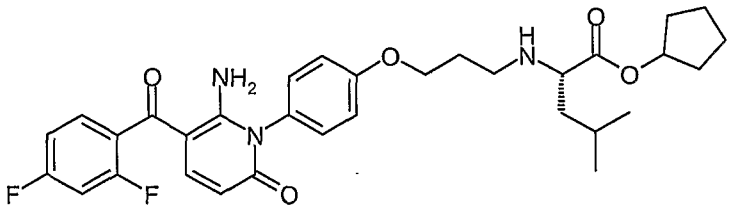
[0235]



[0236] From **Intermediate 4C** and L-phenylalanine cyclopentyl ester tosylate salt **(Intermediate 16),** LCMS purity 99%, m/z 616 $[M+H]^+$, ^1H NMR (400 MHz, d_6-DMSO), δ: 1.10-1.80 (8H, m), 2.20 (2H, m), 2.95 (1H, m), 3.10-3.30 (2H, m), 3.40 (2H, m), 4.20 (2H, m), 4.40 (1H, m), 5.05 (1 H, m), 5.70 (1 H, d), 7.15 (2H, d), 7.20-7.55 (11 H, m), 9.70 (2H, m).

Example 30 Cyclopentyl (S)-2-(3-{4-[6-Amino-5-(2,4difluoro benzoyl)-2-oxo-2H-pyridin-1-yl]phenoxy}propylamino)-4-methyl pentanoate

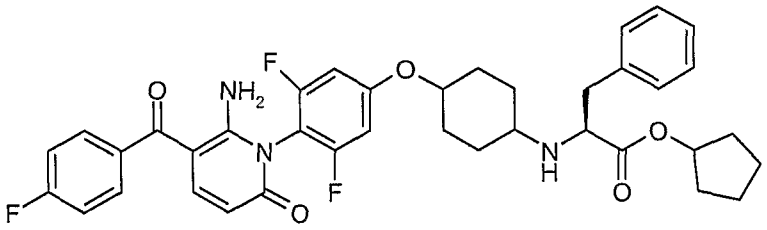
[0237]



[0238] From **Intermediate 4C** and L-leucine cyclopentyl ester **(Intermediate 8),** LCMS purity 99%, m/z 582 $[M+H]^+$, ^1H NMR (400 MHz, d_6-DMSO), δ: 0.95 (6H, m), 1.65-2.15 (13H, m), 3.10-3.20 (2H, m), 4.15 (3H, m), 5.30 (1H, m), 5.70 (1H, d), 7.15 (2H, d), 7.25-7.55 (6H, m), 9.24 (2H, m)

Example 31 Cyclopentyl (S)-2-(4-{4-[6-Amino-5-(4-fluorobenzoyl)-2-oxo-2H-pyridin-1-yl]-3,5-difluorophenoxy}cyclohexylamino)-4-methylpentanoate trifluoroacetate

[0239]

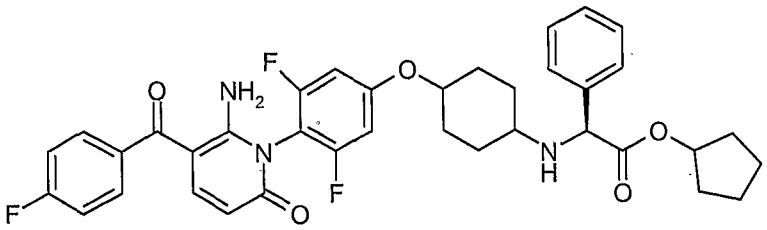


[0240] A suspension of **Intermediate 5** (120mg, 0.263mmol) and L-Phenylalanine cyclopentyl ester tosylate salt **(Intermediate 16)** (98mg, 0.263mmol) in MeOH (1.2ml) was allowed to stir at RT for 1 h before addition of $NaCNBH_3$ (66mg, 1.05mmol). Stirring was continued at RT for 18h. Upon completion of reaction the reaction mixture was concentrated to dryness and partitioned between EtOAc (10ml) and water (10ml). The organic layer was dried (Na_2SO_4), filtered and concentrated to dryness under reduced pressure and was purified by preparative HPLC. This gave the desired product as a TFA salt. Yield= 37mg (18%).
LCMS purity 97%, m/z 674 $[M+H]^+$, ^1H NMR (400 MHz, CD_3OD), δ: 1.10-2.20 (16H, m), 2.35-2.45 (1 H, m), 2.70-3.00 (2H, m), 3.50-3.55 (1 H, m), 4.25-4.35 (1 H, m), 4.95-5.05 (1H, m), 5.70 (1H, d), 6.75 (2H, dd), 7.05-7.25 (7H, m), 7.45-7.55 (2H, m), 7.65 (1H, d)

[0241] The following examples were prepared in a similar manner:

Example 32 Cyclopentyl (2S)-[(4-{4[6-amino-5-(4-fluorobenzoyl)-2-oxopyridin-1(2*H*)-yl]-3,5-difluorophenoxy}cyclohexyl)amino](phenyl)acetate

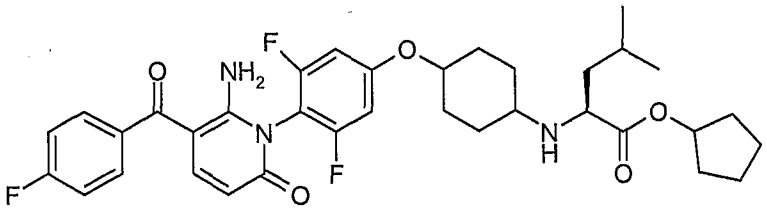
[0242]



[0243] From **Intermediate 5** (120mg, 0.263mmol) and L-phenylglycine cyclopentyl ester **(Intermediate 10).** LCMS purity 97%, m/z 660 $[M+H]^+$, ^1H NMR (400 MHz, CD_3OD), δ: 1.30-1.80 (14H, m), 1.90-2.05 (2H, m), 2.35-2.50 (1 H, m), 4.35-4.45 (1 H, m), 4.50-4.60 (1H, m), 5.05-5.10 (1H, m), 5.70 (1H, d), 6.75-6.85 (2H, m), 7.10-7.15 (2H, m), 7.20-7.35 (5H, m), 7.45-7.55 (2H, m), 7.55-7.60 (1 H, m).

Example 33 Cyclopentyl (S)-2-(4-{4-[6-Amino-5-(4-fluorobenzoyl)-2-oxo-2H-pyridin-1-yl]-3,5-difluorophenoxy}cyclohexylamino)-4-methylpentanoate

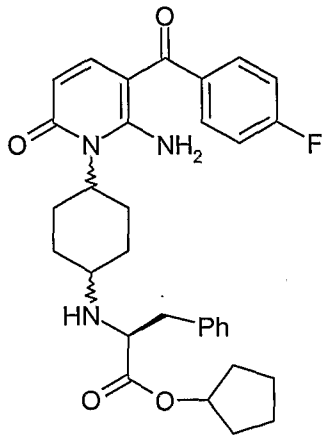
[0244]



[0245] From **Intermediate 5** (120mg, 0.263mmol) and L-Leucine cyclopentyl ester **(Intermediate 8).** LCMS purity 100%, m/z 640 $[M+H]^+$, ^1H NMR (400 MHz, CD_3OD), δ: 0.95-1.05 (6H, m), 1.50-2.00 (16H, m), 2.10-2.35 (3H, m), 3.15-3.20 (1 H, m), 4.00-4.15 (1 H, m), 4.40 and 4.75 (0.5H each, m), 5.25-5.35 (1 H, m), 5.75 (1 H, d), 6.85-6.95 (2H, m), 7.15-7.25 (2H, m), 7.55-7.65 (2H, m), 7.65-7.70 (1H, m).

Examples 34 and 35 Cyclopentyl (S)-2-{4-[6-Amino-5-(4-fluorobenzoyl)-2-oxo-2H-pyridin-1-yl]clohexyl amino}-3-phenylpropionate

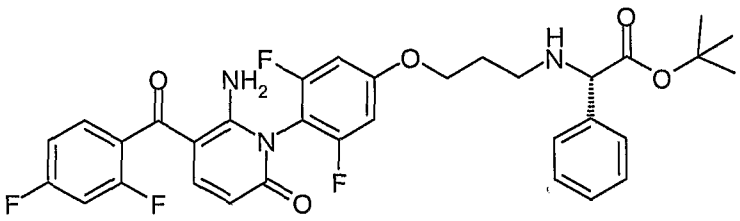
[0246]



[0247] **Intermediate 6** (50mg, 0.15mmol) was added to a colourless solution of L-phenylalanine cyclopentyl ester (89mg, 0.38mmol) in MeOH (10ml) at RT/N_2 and stirred at RT for 1 h. AcOH glacial was added dropwise to adjust the pH to 6 followed by the $NaCNBH_3$ (38mg, 0.61 mmol). The resultant colourless solution was stirred at RT overnight and then carefully quenched with sat. $NaHCO_3$ (20ml) and extracted into CH_2Cl_2 (3 x 15ml). The combined organic phases were washed with 2M HCl (2 x 20ml), brine (20ml), dried (Na_2SO_4), filtered and concentrated *in vacuo* giving a cream coloured solid. Purification by flash column chromatography (silica, gradient elution 40-100% EtOAc/ heptane) gave the desired material, separable as two isomers, isomer 1 (**Example 34**) as a white solid (Yield = 39mg, 47%) LCMS purity 100%, m/z 546 $[M+H]^+$, ^1H NMR (400 MHz, CD_3OD), δ: 1.40-2.05 (16H, m), 2.85-3.10 (3H, m), 3.60-3.70 (1H, m), 4.55-4.65 (1H, m), 5.10-5.20 (1H, m), 5.70 (1H, d), 7.15-7.40 (7H, m), 7.45-7.50 (1H, m), 7.50-7.60 (2H, m) and isomer 2 (**Example 35**) LCMS purity 97%, m/z 546 $[M+H]^+$, ^1H NMR (400 MHz, CD_3OD), δ: 1.25-1.85 (12H, m), 1.95-2.20 (2H, m), 2.45-2.95 (4H, m), 3.00-3.10 (1H, m), 3.65-3.75 (1H, m), 4.55-4.65 (1H, m), 5.05-5.15 (1H, m), 5.65 (1H, d), 7.20-7.35 (7H, m), 7.40-7.50 (1H, m), 7.50-7.60 (2H, m) as a colourless film (Yield = 15mg, 18%).

Example 36 tert-Butyl (S)-(3-{4-[6-Amino-5-(2,4-difluoro benzoyl)-2-oxo-2H-pyridin-1-yl]-3,5-difluorophenoxy}propylamino)phenyl acetate

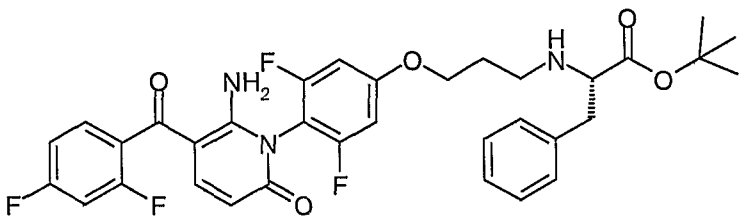
[0248]



[0249] From **Intermediate 4F** and L-phenylglycine tert-butyl ester, LCMS purity 93%, m/z 626 $[M+H]^+$, ^1H NMR (400 MHz, CD_3OD), δ: 1.30 (9H, s), 2.15 (2H, m), 3.00-3.15 (2H, m), 4.06 (2H, m), 5.02 (1H, s), 5.70 (1H, d), 6.75 (2H, d), 7.02 (2H, m), 7.30-7.50 (7H, m).

Example 37 tert-Butyl (S)-2-(3-{4-[6-Amino-5-(2,4-difluorobenz oyl)-2-oxo-2H-pyridin-1yl]-3,5-difluorophenoxy}-propylamino)-3-phenyl propionate

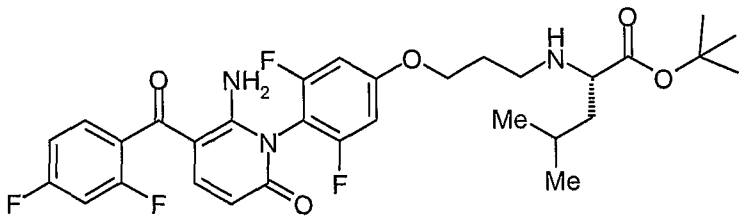
[0250]



[0251] From **Intermediate 4F** and L-phenylalanine tert-butyl ester. LCMS purity 97%, m/z 640 $[M+H]^+$, ^1H NMR (400 MHz, CD_3OD), δ: 1.25 (9H, s), 2.16 (2H, m), 3.00 (1H, dd), 3.15-3.25 (2H, m), 3.35 (1H, dd), 4.10 (2H, m), 4.20 (1H, m), 5.71 (1H, d), 6.79 (2H, d), 7.02 (2H, t), 7.20-7.30 (5H, m), 2H (2H, m).

Example 38 tert-Butyl (S)-2-(3-{4-[6-Amino-5-(2,4-difluoro benzoyl-2-oxo-2H-pyridin-1-yl]-3,5-difluorophenoxy}propylamino)-4-methyl pentanoate

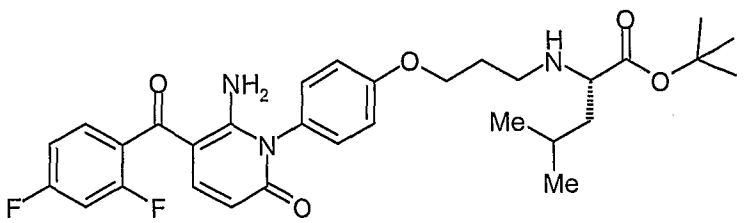
[0252]



[0253] From **Intermediate 4F** and L-leucine tert-butyl ester, LCMS purity 97%, m/z 606 $[M+H]^+$, ^1H NMR (400 MHz, CD_3OD), δ: 0.95 (6H, m), 1.41 (9H, s), 1.61 (1H, m), 1.75 (2H, m), 2.15 (2H, m), 3.22-3.25 (2H, m), 3.88 (1H, m), 4.13 (2H, m), 4.20 (1H, m), 5.40 (1H, s), 5.75 (1 H, d), 6.85 (2H, d), 7.00 (2H, t), 7.40 (2H, m).

Example 39 tert-Butyl (S)-2-(3-{4-[6-Amino-5-(2,4-difluoro benzoyl)-2-oxo-2H-pyridin-1-yl]phenoxy}propylamino)-4-methyl pentanoate

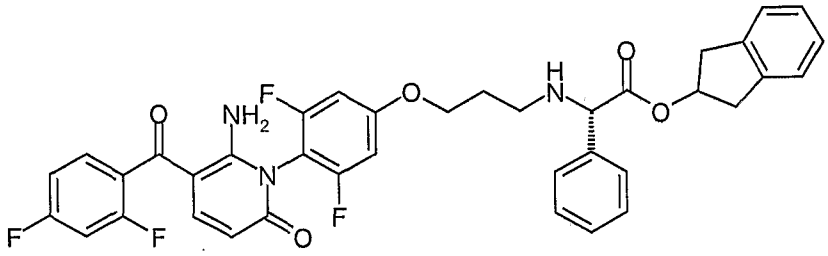
[0254]



[0255] From **Intermediate 4C** and L-leucine tert-butyl ester, LCMS purity 91 %, m/z 570 $[M+H]^+$, ^1H NMR (400 MHz, CD_3OD), δ: 0.95 (6H, m), 1.45 (9H, s), 1.65 (1H, m), 2.15 (2H, m), 3.15-3.30 (2H, m), 3.85 (1H, m), 4.15 (2H, m), 5.75 (1H, d), 7.00-7.20 (6H, m), 7.35 (2H, m).

Example 40 2,3-Dihydro-1*H*-inden-2-yl (2*S*)-[(3-{4-[6-amino-5-(2,4-difluorobenzoyl)-2-oxopyridin-1(2*H*)-yl]-3,5-difluorophenoxy}propyl)amino](phenyl) acetate

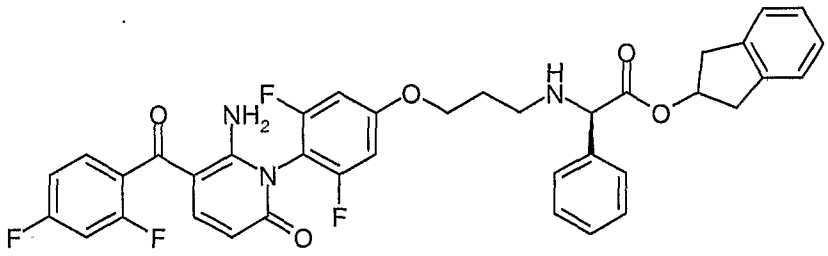
[0256]



[0257] From **Intermediate 4F** and L-phenylglycine indanyl ester **(Intermediate 11),** LCMS purity 96%, m/z 686 $[M+H]^+$, ^1H NMR (300 MHz, CD_3OD), δ: 7.55-7.47 (2H, m), 7.46-7.31 (5H, m), 7.22-7.10 (6H, m), 6.85 (2H, d, J=9.6 Hz), 5.82 (1 H, d, J=9.6 Hz), 5.57-5.51 (1 H, m), 4.37 (1 H, s), 4.13 (1 H, t, J=6.0 Hz), 3.32-3.21 (2H, m), 3.05-2.98 (1 H, m), 2.80-2.63 (3H, m), 2.05-1.97 (2H, m).

Example 41 2,3-dihydro-1*H*-inden-2-yl (2*R*)-[(3-{4-[6-amino-5-(2,4-difluorobenzoyl-2-oxopyridin-1(2*H*)-yl]-3,5-difluorophenoxy}propyl)amino](phenyl)acetate

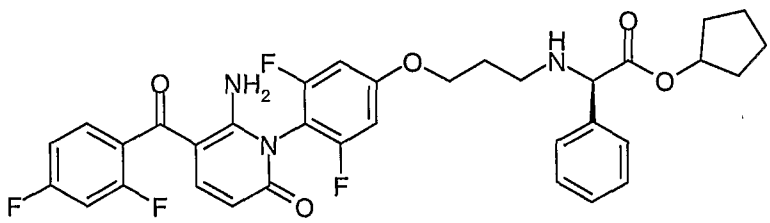
[0258]



[0259] From **Intermediate 4F** and D-phenylglycine indanyl ester, LCMS purity 94%, m/z 686 $[M+H]^+$, ^1H NMR (300 MHz, CD_3OD), δ: 7.56-7.47 (2H, m), 7.38-7.31 (5H, m), 7.28-7.14 (6H, m), 6.85 (2H, d, J=9.6 Hz), 5.82 (1H, d, J=9.6 Hz), 5.57-5.52 (1H, m), 4.37 (1H, s), 4.13 (1H, t, J=6.0 Hz), 3.31-3.21 (2H, m), 3.09-2.99 (1H, m), 2.78-2.64 (3H, m), 2.06-1.99 (2H, m).

Example 42 Cyclopentyl (2*R*)-[(3-{4-[6-amino-5-(2,4-difluorobenzoyl)-2-oxopyridin-1(2*H*)-yl]-3,5-difluorophenoxy}propyl)amino](phenyl)acetate

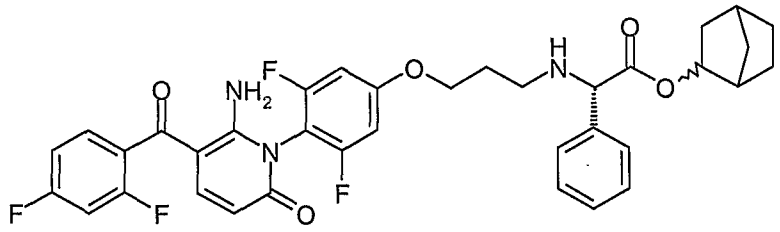
[0260]



[0261] From **Intermediate 4F** and D-phenylglycine cyclopentyl ester, LCMS purity 95%, m/z 638 $[M+H]^+$.

Example 43 Bicyclo[2.2.1]hept-2-yl (2*S*)-[(3-{4-[6-amino-5-(2,4-difluorobenzoyl}-2-oxopyridin-1(2*H*)-yl]-3,5-difluorophenoxy}propyl)amino](phenyl)acetate

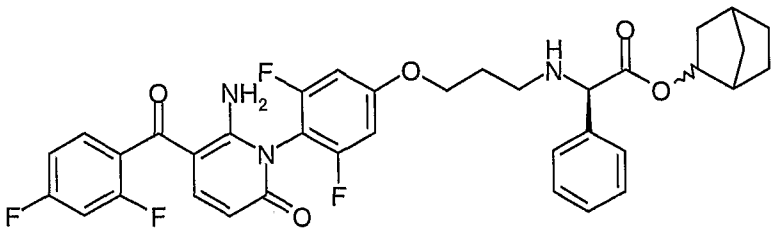
[0262]



[0263] From **Intermediate 4F** and L-phenylglycine norborneyl ester **(Intermediate 12),** LCMS purity 97%, m/z 664 $[M+H]^+$, ^1H NMR (300 MHz, CD_3OD), δ: 7.50-7.21 (7H, m), 7.02 (2H, t, J=8.6 Hz), 6.75 (2H, d, J=9.6 Hz), 5.70 (1 H, d, J=9.6 Hz), 4.50 (1 H, d, J=6.6 Hz), 4.32-4.26 (1H, m), 4.05 (2H, t, J=5.9 Hz), 2.71-2.56 (2H, m), 2.24-1.90 (4H, m), 1.64-1.06 (8H, m).

Example 44 Bicyclo[2.2.1]hept-2-yl (2*R*)-[(3-{4-[6-amino-5-(2,4-difluorobenzoyl)-2-oxopydin-1(2*H*)-yl]-3,5-difluorophenoxy}propyl)amino](phenyl)acetate

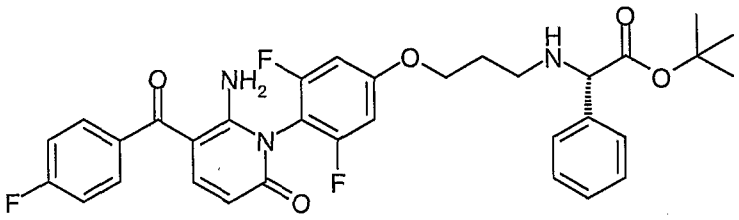
[0264]



[0265] From **Intermediate 4F** and D-phenylglycine norborneyl ester, LCMS purity 98%, m/z 664 $[M+H]^+$, ^1H NMR (300 MHz, CD_3OD), δ: 7.42-7.17 (7H, m), 7.00 (2H, t, J=8.6 Hz), 6.74 (2H, d, J=9.1 Hz), 5.69 (1H, d, J=9.8 Hz), 4.49 (1H, d, J=6.8 Hz), 4.32-4.26 (1H, m), 4.03 (2H, t, J=6.0 Hz), 2.70-2.52 (2H, m), 2.18-1.86 (4H, m), 1.63-0.92 (8H, m).

Example 45 tert-Butyl (S)-(3-{4-[6-Amino-5-(4-difluoro benzoyl)-2-oxo-2H-pyridin-1-yl]-3,5-difluorophenoxy}propylamino)phenyl acetate

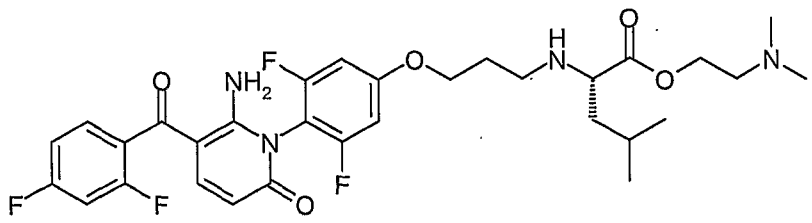
[0266]



[0267] From **Intermediate 4E** and L-phenylglycine tert-butyl ester, LCMS purity 100%, m/z 608 $[M+H]^+$, ^1H NMR (300 MHz, CD_3OD), δ: 7.55-7.47 (3H, m), 7.30-7.21 (6H, m), 7.09 (1H, t, J=8.7 Hz), 6.61 (2H, d, J=9.3 Hz), 5.81 (1H, d, J=9.6 Hz), 4.18 (1H, s), 4.03 (2H, t, J=6.0 Hz), 2.75-2.69 (1 H, m), 2.65-2.58 (1 H, m), 1.96-1.88 (1 H, m), 1.96-1.88 (2H, m); 1.32 (9H, s)

Example 46 2-(Dimethylamino)ethyl *N*-(3-{4-[6-amino-5-(2,4-difluorobenzoyl)-2-oxopyridin-1(2*H*)-yl]-3,5-difluorophenoxy}propyl)-L-leucinate

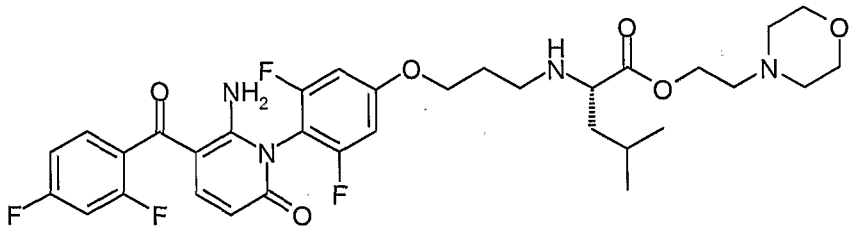
[0268]



[0269] From **Intermediate 4F** and **Intermediate 13,** LCMS purity 90%, m/z 621 $[M+H]^+$, ^1H NMR (300 MHz, DMSO), δ: 10.18 (1H,br s), 9.50 (1H, br s),7.57 (1 H, q, J=7.8Hz), 7.39 (2H, m),7.37-7.15 (3H, m), 7.04 (2H, m), 5.73 (1H, d, J=9.6Hz), 4.59-4.46 (2H, m), 4.21 (2H, t, J=9.0Hz), 4.11 (1H, m), 3.14 (2H, m), 2.86 (6H, s), 2.14 (2H, m), 1.74 (2H, m), 0.92 (8H, m).

Example 47 2-Morpholin-4-ylethyl *N*-(3-{4-[6-amino-5-(2,4-difluorobenzoyl)-2-oxopyridin-1(2*H*)-yl]-3,5-difluorophenoxy}propyl)-L-leucinate

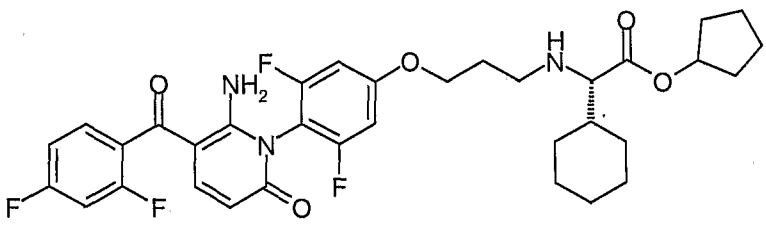
[0270]



[0271] From **Intermediate 4F** and **Intermediate 14,** LCMS purity 90%, m/z 621 $[M+H]^+$, ^1H NMR (300 MHz, DMSO), δ: 7.57 (1H, q, J=7.5 Hz), 7.40 (2H, m), 7.26-7.17 (3H, m), 7.06 (2H, d, J=10.8 Hz), 5.74 (1 H, d, J=9.9 Hz), 4.53 (2H, m), 4.21 (4H, m), 3.80 (4H, m), 3.37 (2H, m), 3.17 (4H, m), 2.15 (2H, m), 1.75 (3H, m), 0.94 (6H, br s).

Example 48 Cyclopentyl (2*S*)-[(3-{4-[6-amino-5-(2,4-difluorobenzoyl)-2-oxopyridin-1(2*H*)-yl]-3,5-difluorophenoxy}propyl)amino](cyclohexyl)acetate

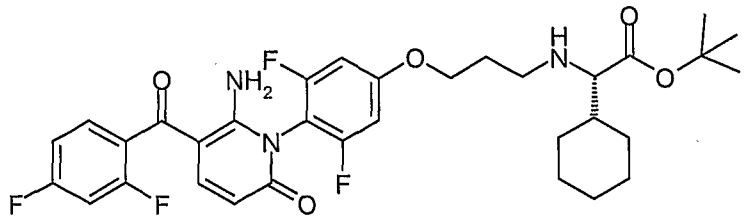
[0272]



[0273] From **Intermediate 4F** and L-cyclohexylglycine cyclopentyl ester **(Intermediate 9)**, LCMS purity 95%, m/z 664 $[M+H]^+$, ^1H NMR (300 MHz, DMSO), δ: 9.15 (1H, br s), 8.95 (1 H, br s), 7.62-7.52 (1 H, m), 7.46-7.31 (2H, m),7.27-7.20 (1 H, m), 7.05 (2H, d, J=10.2Hz), 5.74 (1H, d, J=9.6Hz), 5.30-5.25 (1H, m), 4.20 (2H, t, J=5.7Hz), 4.10-3.95 (1 H, m), 3.25 -2.95 (2H, m), 2.20-2.07 (2H, m), 2.00-1.50 (15H, m),1.30-1.00 (4H, m), 0.95-0.75 (1 H, m)

Example 49 *tert*-Butyl (2*S*)-[(3-{4-[6-amino-5-(2,4-difluorobenzoyl)-2-oxopyridin-1(2*H*)-yl]-3,5-difluorophenoxy}propyl)amino](cyclohexyl)acetate

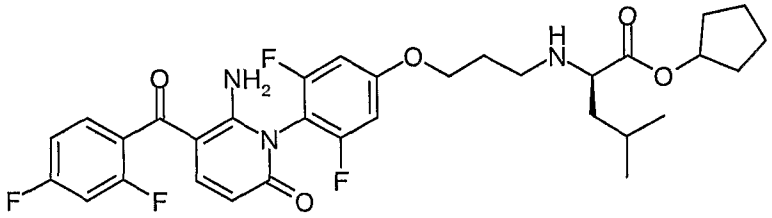
[0274]



[0275] From **Intermediate 4F** and L-cyclohexylglycine tert-butyl ester, LCMS purity 95%, m/z 632 $[M+H]^+$, ^1H NMR (300 MHz, DMSO), δ: 9.10 (1H, br s), 8.85 (1H, brs), 7.62-7.52 (1H, m), 7.45-7.31 (2H, m), 7.28-7.20 (1H, m), 7.06 (2H, d, J=10.2Hz), 5.74 (1H, d, J=9.6Hz), 4.20 (2H, t, J=5.9Hz), 3.95-3.85 (1 H, m), 3.25-2.95 (2H, m),2.20-2.07 (2H, m), 2.00-1.60 (6H, m), 1.51 (9H, s),1.35-1.07 (4H, m),1.00-0.85 (1H, m).

Example 50 Cyclopentyl *N*-(3-{4-[6-amino-5-(2,4-difluorobenzoyl}-2-oxopyridin-1(2*H*)-yl]-3,5-difluorophenoxy}propyl)-D-leucinate

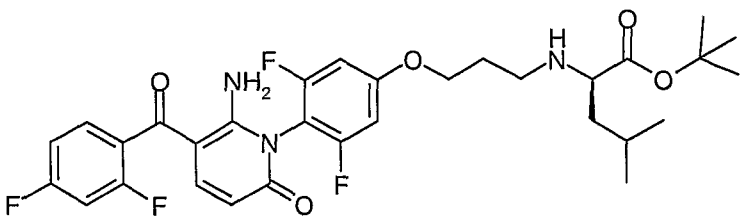
[0276]



[0277] From **Intermediate 4F** and D-Leucine cyclopentyl ester, LCMS purity 95%, m/z 618 $[M+H]^+$, ^1H NMR (300 MHz, DMSO), δ: 10.10 (1 H, br s), 9.40-9.10 (2H, m), 8.15 (1 H, br s), 7.62-7.52 (1H, m), 7.47-7.31 (2H, m), 7.28-7.12 (1H, m), 7.07 (2H, d, J=10.5Hz), 5.73 (1H, d, J=9.6Hz), 5.30-5.20 (1H, m), 4.25-4.00 (3H, m), 3.30-3.00 (2H, m), 2.20-2.00 (2H, m), 1.95-1.80 (2H, m), 1.75-1.55 (10H, m), 1.00-0.90 (6H, m).

Example 51 *tert*-Butyl *N*-(3-{4-[6-amino-5-(2,4-difluorobenzoyl)-2-oxopyridin-1(2*H*)-yl]-3,5-difluorophenoxy}propyl)-D-leucinate

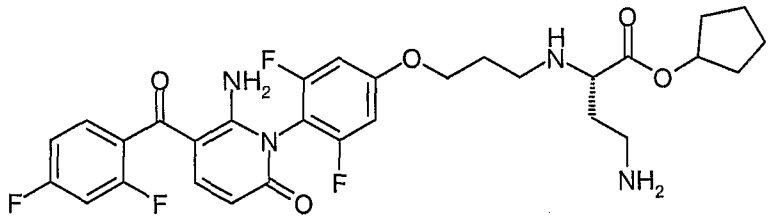
[0278]



[0279] From **Intermediate 4F** and D-Leucine tert-butyl ester, LCMS purity 95%, m/z 606 $[M+H]^+$, ^1H NMR (300 MHz, DMSO), δ: 9.30-9.00 (2H, m), 7.62-7.52 (1H,m), 7.47-7.32 (2H, m), 7.28-7.12 (1 H, m), 7.06 (2H, d, J=10.2Hz), 5.73 (1 H, d, J=9.6Hz), 4.20 (2H, t, J=5.7Hz), 3.99 (1 H, br s), 3.25-2.95 (2H, m), 2.20-2.05 (2H, m), 1.80-1.60 (3H, m), 1.49 (9H, s), 0.95 (6H, d, J=4.8Hz).

Example 52 Cyclopentyl (2*S*)-4-amino-2-[(3-{4-[6-amino-5-(2,4-difluorobenzoyl)-2-oxopyridin-1(2*H*)-yl]-3,5-difluorophenoxy}propyl)amino]butanoate

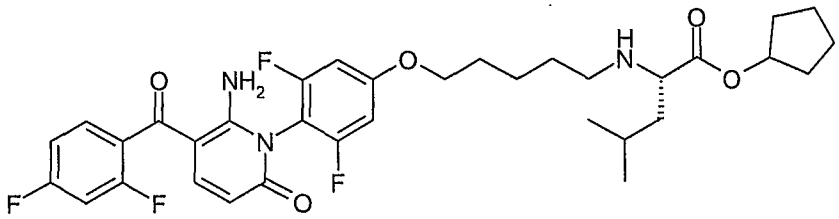
[0280]



[0281] From **Intermediate 4F** and **Intermediate 15,** LCMS purity 90%, m/z 605 $[M+H]^+$, ^1H NMR (300 MHz, CD_3OD), δ: 7.46 - 7.55 (2H, m), 7.12 (2H, t, J=8.7 Hz), 6.93 (2H, d, J=9.6 Hz), 5.81 (1H, d, J=9.6 Hz), 5.37 - 5.44 (1H, m), 4.20 - 4.31 (4H, m), 3.33 - 3.42 (1 H, m), 2.25 - 2.49 (4H, m), 1.91-2.08 (2H, m), 1.65 - 1.89 (7H, m).

Example 53 Cyclopentyl *N*-(5-{4-[6-amino-5-(2,4-difluorobenzoyl)-2-oxopyridin-1(2*H*)-yl]-3,5-difluorophenoxy}pentyl)-L-leucinate

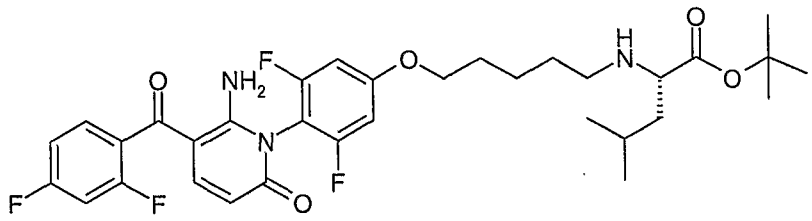
[0282]



[0283] From **Intermediate 4G.** To a solution of 6-Amino-1-{4-[(5-chloropentyl)oxy]-2,6-difluorophenyl}-5-(2,4-difluorobenzoyl)pyridin-2(1*H*)-one (138mg, 0.29mmol) in anhydrous DMF (3ml) under an atmosphere of nitrogen was added cyclopentyl L-leucinate **(Intermediate 8)** (284mg, 1.43mmol, 5 eq), sodium iodide (86mg, 0.57mmol, 2eq) and *N,N*-diisopropylethylamine (0.052ml, 0.29mmol, 1eq). The mixture was heated at 90°C for 16 hours, before being allowed to cool to room temperature and diluted with EtOAc (25ml). The solution was washed with water (2 x 25ml) and brine (25ml). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (3-4 % MeOH in DCM) followed by preparative HPLC afforded the title compound as a cream coloured solid (96mg, 52% yield).
LC/MS: m/z 646 $[M+H]^+$. ^1H NMR (300 MHz, CD_3OD) δ: 7.56-7.47 (2H, m), 7.13 (2H, m), 6.88 (2H, m), 5.82 (1 H, d, J=9.8 Hz), 5.23 (1 H, t, J=4.1 Hz), 4.11 (2H, t, J=6.3 Hz), 3.28 (1 H, m), 2.61-2.51 (2H, m), 1.95-1.41, (17H, br m), 0.98-0.93 (6H, m).

Example 54 *tert*-Butyl *N*-(5-{4-[6-amino-5-(2,4-difluorobenzoy)-2-oxopyridin-1(2*H*)-yl]-3,5-difluorophenoxy}pentyl)-L-leucinate

[0284]

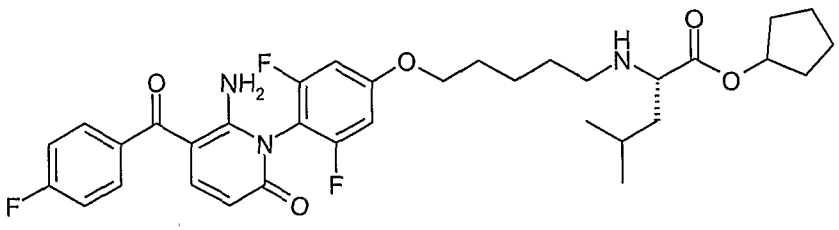


[0285] From **Intermediate 4G.** To a solution of 6-Amino-1-{4-[(5-chloropentyl)oxy]-2,6-difluorophenyl}-5-(2,4-difluorobenzoyl)pyridin-2(1*H*)-one (96mg, 0.20mmol) in anhydrous DMF (3ml) under an atmosphere of nitrogen was added *tert*-butyl L-leucinate hydrochloride (198mg, 0.99mmol, 5eq), sodium iodide (60mg, 0.40mmol, 2eq) and *N,N*-diisopropylethylamine (0.072ml, 0.40mmol, 2eq). The mixture was heated at 90°C for 20 hours, before being allowed to cool to room temperature and diluted with EtOAc (20ml). The solution was washed with water (2 x20ml) and brine (20ml). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (1-3 % MeOH in DCM) followed by preparative HPLC afforded the title compound as a white solid (23mg,

18% yield).
LC/MS: m/z 634 $[M+H]^+$. ^1H NMR (300 MHz, CD_3OD) δ: 7.56-7.47 (2H, m), 7.14 (2H, m), 6.89 (2H, m), 5.81 (1 H, d, J=9.6 Hz), 4.11 (2H, t, J=6.2 Hz), 3.19 (1 H, m), 2.60-2.53 (2H, m), 1.89-1.84 (2H, m), 1.72-1.41 (16H, m), 0.96 (6H, m).

Example 55 Cyclopentyl *N*-(5-{4-[6-amino-5-(4-fluorobenzoyl)-2-oxopyridin-1(2*H*)-yl]-3,5-difluorophenoxy}pentyl)-L-leucinate

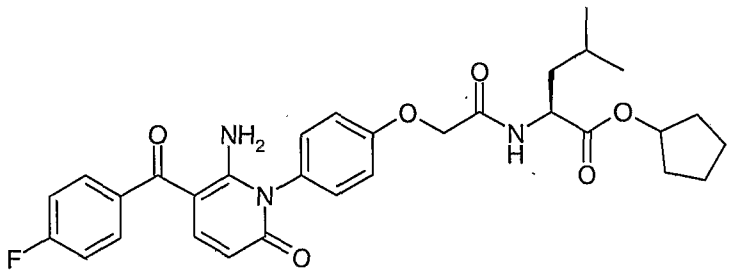
[0286]



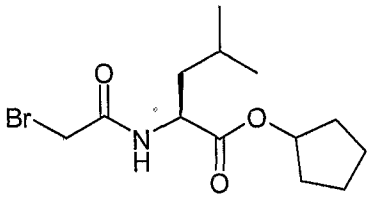
[0287] From **Intermediate 4H.** To a solution of 6-amino-1-{4-[(5-chloropentyl)oxy]-2,6-difluorophenyl}-5-(4-fluorobenzoyl)pyridin-2(1*H*)-one (99 mg, 0.21 mmol) in anhydrous DMF (3 ml) under an atmosphere of nitrogen was added cyclopentyl L-leucinate **(Intermediate 8)** (212 mg, 1.06 mmol, 5 eq), sodium iodide (64mg, 0.43mmol, 2eq) and *N,N*-diisopropylethylamine (0.039ml, 0.21mmol, 1eq). The mixture was heated at 90°C for 20 hours, before being allowed to cool to room temperature and diluted with EtOAc (25ml). The solution was washed with water (2 x 25ml) and brine (25ml). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (2 % MeOH in DCM) followed by preparative HPLC afforded the title compound as a yellow solid (64mg, 48% yield).
LC/MS: m/z 628 $[M+H]^+$. ^1H NMR (300 MHz, CD_3OD) δ: 7.71 (1H, d, J=9.6 Hz), 7.62 (2H, m), 7.26 (2H, m), 6.89 (2H, m), 5.81 (1 H, d, J=9.6 Hz), 5.23 (1 H, t, J=5.3 Hz), 4.11 (2H, t, J=6.4 Hz), 3.28 (1H, m), 2.55 (2H, m), 1.91-1.48 (17H, m), 0.98-0.93 (6H, m).

Example 56 Cyclopentyl *N*-({4-[6-amino-5-(4-fluorobenzoyl)-2-oxopyridin-1(2*H*)-yl]phenoxy}acetyl)-L-leucinate

[0288]



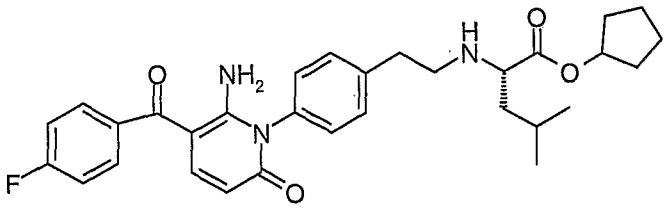
[0289] LC/MS: m/z 564 $[M+H]^+$. ^1HNMR (300 MHz, DMSO-d_6) δ: 8.47 (1H, d, J=7.7 Hz), 7.56 (2H, m), 7.45 (1 H, d, J=9.6 Hz), 7.38-7.24 (4H, m), 7.15 (2H, m), 5.69 (1 H, d, J=9.8 Hz), 5.09 (1 H, t, J=5.3 Hz), 4.63 (2H, m), 4.31 (1 H, m), 1.84-1.79 (2H, m), 1.66-1.53 (9H, m), 0.92-0.86 (6H, m).
[0290] To a solution of 6-amino-5-(4-fluorobenzoyl)-1-(4-hydroxyphenyl)pyridin-2(1*H*)-one [WO 03/076405] (100mg, 0.31mmol) in anhydrous DMF (3ml) under an atmosphere of nitrogen was added cyclopentyl *N*-(bromoacetyl)-L-leucinate (109ml, 0.34mmol, 1.1 eq) and potassium carbonate (51 mg, 0.37mmol, 1.2eq). The mixture was heated at 40C for 16 hours, before being allowed to cool to room temperature and added to water (20 ml). The mixture was extracted with EtOAc (3 x 1 5ml), and the combined extracts washed with water (2 x 40ml) and brine (40ml). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (2-3 % MeOH in DCM) followed by trituration with minimal MeOH afforded the title compound as a white solid (91 mg, 52% yield).
[0291] The cyclopentyl *N*-(bromoacetyl)-L-leucinate was synthesised from cyclopentyl L-leucinate in one step, the details of which are outlined below.



[0292] To a solution of cyclopentyl L-leucinate **(Intermediate 8)** (568mg, 2.84mmol) in DCM (6ml) was added triethylamine (0.24ml, 2.84mmol, 1eq) and bromoacetyl chloride (1.44ml, 3.13mmol, 1.1eq) dropwise. The mixture was stirred at room temperature for 20 hours, diluted with DCM (50ml) and washed with water (50ml) and brine (50ml). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a crude mixture containing the title compound (902mg) that was used without further purification. LC/MS: m/z 320/322 $[M+H]^+$.

Example 57 Cyclopentyl *N*-[2-(4-{6-amino-5-[(4-fluorophenyl)carbonyl]-2-oxopyridin-1(2*H*)-yl}phenyl)ethyl]-L-leucinate

[0293]

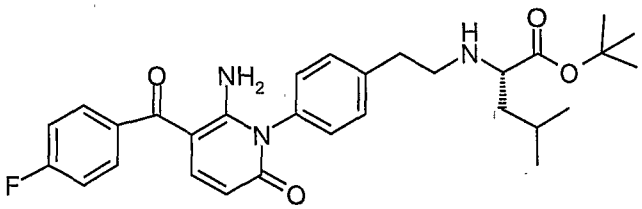


[0294] From **Intermediate 4J** and L-Leucine cyclopentyl ester **(Intermediate 8).** LC/MS: m/z 534 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ: 8.47 (1 H, d, J=7.7 Hz), 7.56 (2H, m), 7.45 (1 H, d, J=9.6 Hz), 7.38-7.24 (4H, m), 7.15 (2H, m), 5.69 (1 H, d, J=9.8 Hz), 5.09 (1 H, t, J=5.3 Hz), 4.63 (2H, m), 4.31 (1 H, m), 1.84-1.79 (2H, m), 1.66-1.53 (9H, m), 0.92-0.86 (6H, m).

[0295] The following examples were synthesised in a similar manner:

Example 58 *tert*-Butyl *N*-[2-(4-{6-amino-5-[(4-fluorophenyl)carbonyl]-2-oxopyridin-1(2*H*)-yl}phenyl)ethyl]-L-leucinate

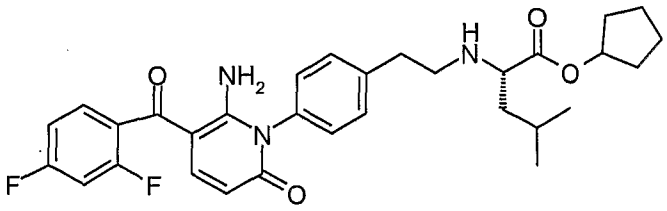
[0296]



[0297] From **Intermediate 4J** and L-Leucine tbutyl ester. LC/MS: m/z 522 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ: 9.40-9.10 (2H,m), 7.59-7.44 (5H, m), 7.38-7.30 (4H, m), 5.71 (1 H, d, J=9.6Hz), 4.00 (1 H, br s), 3.40-3.28 (1 H, m), 3.25-3.15 (1 H, m), 3.10-3.00 (2H, m), 1.80-1.70 (3H, m), 0.96 (6H, d, J=5.1Hz).

Example 59 Cyclopentyl *N*-[2-(4-{6-amino-5-[(2,4-difluorophenyl)carbonyl]-2-oxopyridin-1(2*H*)-yl}phenyl)ethyl]-L-leucinate

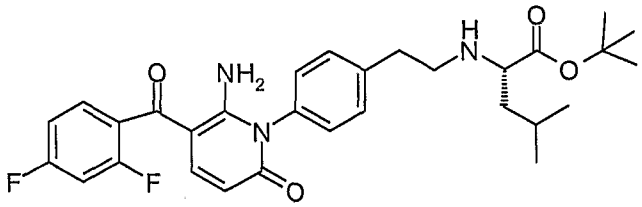
[0298]



[0299] **Example 59** was synthesised via a similar route to **Example 57** using 3-(2,4-difluoro-phenyl)-3-oxo-thiopropionimidic acid 4-chloro-phenyl ester. LC/MS: m/z 552 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ: 10.07 (1 H, br s), 9.35 (2H, br s), 7.55-6.95 (8H, m), 5.72 (1H, d, J=9.9Hz), 5.27 (1H, t, J=5.7Hz), 4.15-4.00 (1H, m), 3.41-3.15 (2H, m), 3.10-3.00 (2H, m), 1.96-1.80 (2H, m), 1.78-1.55 (9H, m), 0.95 (6H, d, J=5.1Hz).

Example 60 *tert*-Butyl *N*-[2-(4-{6-amino-5-[(2,4-difluoropheny)carbonyl]-2-oxopyridin-1(2*H*)-yl}phenyl)ethyl]-L-leucinate

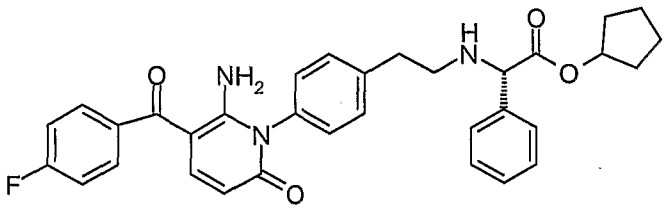
[0300]



[0301] **Example 60** was synthesised via a similar route to **Example 57** using 3-(2,4-difluorophenyl)-3-oxo-thiopropionimidic acid 4-chloro-phenyl ester. LC/MS: m/z 540 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ: 10.07 (1 H, br s), 9.30 (2H, br s), 7.55-6.94 (8H, m), 5.72 (1 H, d, J=9.6Hz), 4.05-3.93 (1 H, m), 3.40-3.10 (2H, m), 3.08-3.00 (2H, m), 1.80-1.65 (3H, m), 1.50 (9H, s), 0.96 (6H, d, J=5.1 Hz).

Example 61 Cyclopentyl (2*S*)-{[2-(4-{6-amino-5-[(4-fluorophenyl)carbonyl]-2-oxopyridin-1(2*H*)-yl}phenyl)ethyl]amino}(phenyl) ethanoate

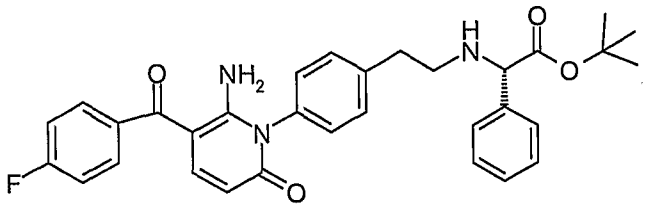
[0302]



[0303] From **Intermediate 4J** and L-Phenylglycine cyclopentyl ester **(Intermediate 10).** LC/MS: m/z 554 $[M+H]^+$, ^1H NMR (300 MHz, $CDCl_3$) δ: 10.35 (1 H, br s), 7.60-7.13 (14H, m), 5.91 (1H, d, J=10.2Hz), 5.22-5.14 (1H, m), 4.36 (1H, s), 3.00-2.85 (4H, m), 2.16 (1H, br s), 1.99-1.43 (8H, m).

Example 62 *tert*-Butyl (2*S*)-{[2-(4-{6-amino-5-[(4-fluorophenyl)carbonyl]-2-oxopyridin-1(2*H*)-yl}phenyl)ethyl]amino}(phenyl) ethanoate

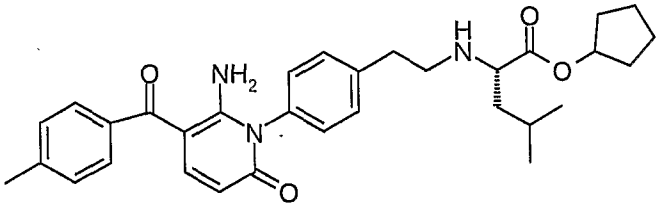
[0304]



[0305] From **Intermediate 4J** and L-Phenylglycine tbutyl ester. LC/MS: m/z 542 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$) δ: 10.30 (1H, br s), 7.51-7.45 (3H, m), 7.38 (2H, d, J=6.9Hz), 7.27-7.04 (9H, m), 5.82 (1 H, d, J=9.6Hz), 4.20 (1 H, s), 2.86-2.75 (4H, m), 2.04 (1 H, br s), 1.31 (9H, s).

Example 63 Cyclopentyl *N*-[2-(4-{6-amino-5-[(4-methylphenyl)carbonyl]-2-oxopyridin-1(2*H*)-yl}phenyl)ethyl]-L-leucinate

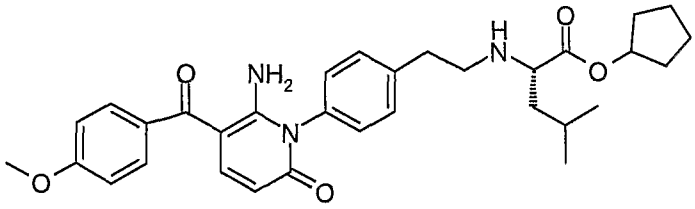
[0306]



[0307] **Example 63** was prepared by similar methodolgy to **Example 59** using 3-(4-methylphenyl)-3-oxo-thiopropionimidic acid 4-chloro-phenyl ester, prepared by a similar method used for **Intermediate 4J**. LC/MS: m/z 530 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.65 (1 H, d, J=9.9Hz), 7.47 (4H, m), 7.26 (4H, m), 5.89 (1 H, d, J=9.9Hz), 5.20 (1 H, m), 3.25 (1H, t, J=7.2Hz), 2.87 (4H, m), 2.44 (3H, s), 1.99-1.53 (9H, m), 1.42 (2H, t, J=6.3Hz), 0.91 (6H, m).

Example 64 Cyclopentyl *N*-[2-(4-{6-amino-5-[(4-methoxyphenyl)carbonyl]-2-oxopyridin-1(2*H*)-yl}phenyl)ethyl]-L-leucinate

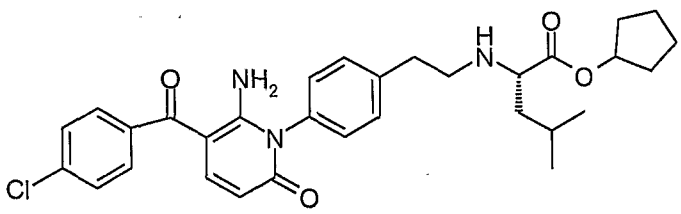
[0308]



[0309] **Example 64** was prepared by similar methodolgy to **Example 59** using 3-(4-methoxy-phenyl)-3-oxo-thiopropionimidic acid 4-chloro-phenyl ester, prepared by a similar method used for **Intermediate 4J.** LC/MS: m/z 546 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.67 (1 H, d, J=9.9Hz), 7.55 (2H, d), 7.46 (2H, d), 7.24 (2H, d, J=8.4Hz), 6.98 (2H, d, J=6.9 Hz), 5.90 (1 H, d, J=9.6 Hz), 5.18 (1 H, m), 3.88 (3H, s), 3.24 (1 H, t, J=7.2 Hz), 2.87 (4H, m), 1.97-1.53 (9H, m), 1.43 (2H, t), 0.90 (6H, m).

Example 65 Cyclopentyl *N*-[2-(4-{6-amino-5-[(4-chlorophenyl)carbonyl]-2-oxopyridin-1(2*H*)-yl}phenyl)ethyl]-L-leucinate

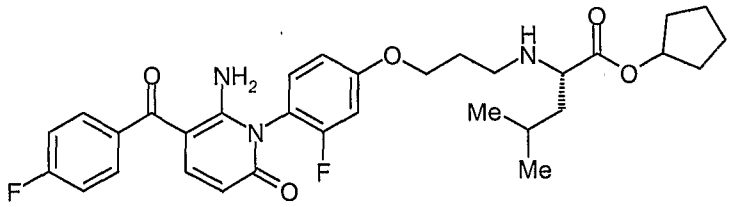
[0310]



[0311] **Example 65** was prepared by similar methodolgy to **Example 59** using 3-(4-chloro-phenyl)-3-oxo-thiopropion-imidic acid 4-chloro-phenyl ester, prepared by a similar method used for **Intermediate 4J**. LC/MS: m/z 551 $[M+H]^+$. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.40 (7H, m), 7.16 (2H, d, J=8.4Hz), 5.82 (1H, d, J=9.9 Hz), 5.11 (1H, m), 3.17 (1H, t, J=7.5 Hz), 2.78 (4H, m), 1.92-1.43 (9H, m), 1.35 (2H, t), 0.82 (6H, dd).

Example 66 Cyclopentyl *N*-[3-(4-{6-amino-5-[(4-fluorophenyl)carbonyl]-2-oxopyridin-1(2*H*)-yl}-3-fluorophenoxy)propyl]-L-leucinate

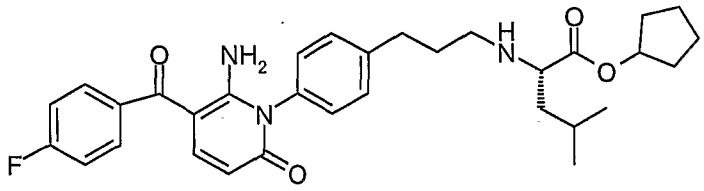
[0312]



[0313] **Example 66** was prepared by similar methodolgy to **Example 25** using 6-Amino-5-(4-fluoro-3-methyl-benzoyl)-1-[2-fluoro-4-hydroxy-phenyl]-1H-pyridin-2-one [WO 03/076405]. LCMS purity 97%, m/z 582 $[M+H]^+$, ^1H NMR (400 MHz, d_6-DMSO), δ: 7.57 (2H, m), 7.48 (1H, d, J=9.6Hz), 7.34 (3H, m), 7.10 (1H, dd, J=11.9, 2.3Hz), 7.00 (1H, dd,J= 9.7, 2.3Hz), 5.70 (1 H, d, J=9.6Hz), 5.12 (1 H, m), 4.11 (2H, t, J=6.2Hz), 3.14 (1 H, m), 2.68 (1 H, m), 1.98 (1 H, m), 1.88-1.82 (4H, m), 1.67-1.57 (7H, m), 0.88 (6H, t, J=7.2Hz).

Example 67 Cyclopentyl *N*-[3-(4-{6-amino-5-[(4-fluorophenyl)carbonyl]-2-oxopyridin-1(2*H*)-yl}phenyl)propyl]-L-leucinate

[0314]



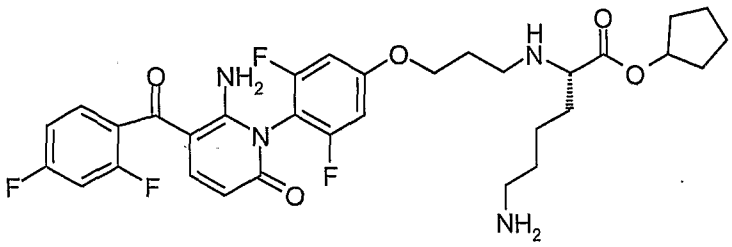
[0315] **Example 61** was synthesised via a similar route to **Example 57** using 3-(4-Amino-phenyl)-propan-1-ol. LC/MS: m/z 548 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ: 9.13 (2H, br s), 7.59-7.52 (2H, m), 7.50-7.42 (3H, m), 7.39-7.25 (4H, m), 5.70 (1 H, d, J=9.6Hz), 5.28-5.24 (1 H, m), 4.04 (1H, br s), 3.35-2.85 (2H, m), 2.80-2.70 (2H, m), 2.10-1.80 (4H, m), 1.75-1.55 (10H, m), 0.93 (6H, d, J=3.4Hz).

[0316] The 3-(4-Amino-phenyl)-propan-1-ol was synthesised in a one step process from 4-nitro cinnamyl alcohol as shown below:

To a solution of 4-nitro cinnamyl alcohol (2g, 11.1 mmol) in methanol (30ml) under a nitrogen atmosphere was added Raney Nickel (2ml slurry in water). The reaction was then exposed to hydrogen gas and stirred under a hydrogen atmosphere for 12 hours for complete reaction. The reaction mixture was filtered through Celite, washing with methanol and ethyl acetate. The filtrate was then concentrated under reduced pressure before purification by column chromatography (8:2 EtOAc:Hexane) to give the required product (1.68g, 95%) as a yellow solid.

Example 68 Cyclopentyl N^2-[3-(4-{6-amino-5-[(2,4-difluorophenyl)carbonyl]-2-oxopyridin-1 (2*H*)-yl}-3,5-difluorophenoxy)propyl]-L-lysinate

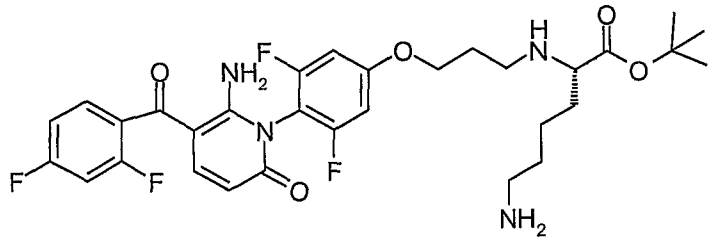
[0317]



[0318] **Example 68** was synthesised via a similar route to **Example 52** using L-Lysine(Z)-cyclopentyl ester. LC/MS: m/z 633 $[M+H]^+$. ^1H NMR (300 MHz, CD_3OD) δ: 7.45 - 7.54 (2H, m), 7.12 (2H, t, J=8.6 Hz), 6.93 (2H, d, J=9.8 Hz), 5.81 (1H, d, J=9.8 Hz), 5.33-5.40 (1 H, m), 4.25 (2H, t, J=5.1 Hz), 4.10 - 4.16 (1 H, m), 2.96 (2H, t), 2.27 - 2.35 (2H, m), 1.63 - 2.12 (16H, m).

Example 69 *tert*-Butyl N^2-[3-(4-{6-amino-5-[(2,4-difluorophenyl)carbonyl]-2-oxopyridin-1(2*H*)-yl}-3,5-difluorophenoxy)propyl]-L-lysinate

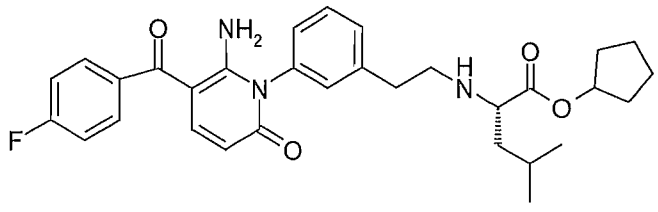
[0319]



[0320] **Example 69** was synthesised via a similar route to **Example 52** using L-Lysine(Z)- tbutyl ester. LC/MS: m/z 621 $[M+H]^+$, ^1H NMR (300 MHz, CD_3OD) δ: 7.48 (2H, dd, J=9.7, 2.7 Hz), 7.12 (2H, t, J=8.6Hz), 6.88 (2H, d, J=9.2 Hz), 5.81 (1H, d, J=9.6 Hz), 4.18 (2H, t, J=6.2 Hz), 3.15 (H, t, J=6.6 Hz), 2.76 - 2.87 (3H, m), 2.68 (1 H, dt, J=11.5, 6.9 Hz), 1.97 - 2.05 (4H, m), 1.64 (4H, dt, J= 6.1 Hz), 1.01 (9H, s).

Example 70 Cyclopentyl *N*-[2-(3-{6-amino-5-[(4-fluorophenyl)carbonyl-2-oxopyridin-1(2*H*)-yl}phenyl)ethyl]-L-leucinate

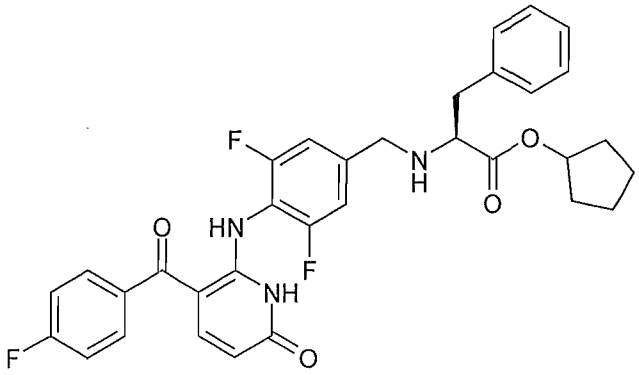
[0321]



[0322] **Example 70** was synthesised using similar methodology to **Intermediate 4J** (instead using 3-aminophenethyl alcohol) and L-Leucine cyclopentyl ester **(Intermediate 8).**
LC/MS: m/z 534 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ: 9.40-9.00 (2H, m), 7.65-7.44 (5H, m), 7.38-7.11 (4H, m), 5.72 (1 H, d, J=9.9Hz), 5.30-5.20 (1 H, m), 4.10-4.00 (1H, m), 3.45-3.15 (2H, m), 3.10-3.00 (2H, m), 1.95-1.80 (2H, m), 1.75-1.55 (9H, m), 9.93 (6H, d, J=4.8Hz).

Example 71 Cyclopentyl (S)-2-{3,5-Difluoro-4-[3-(4-fluorobenzoyl)-6-oxo-1,6-dihydro pyridin-2-ylamino]benzylamino}-3-phenylpropionate

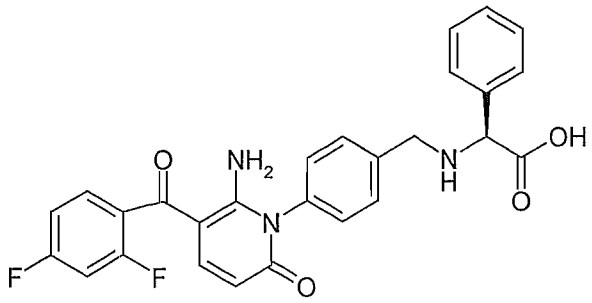
[0323]



[0324] A solution of **Intermediate 7** (20mg) in 20% TFA/ DCM (0.5ml) was allowed to stand at RT for 1h. Upon completion the reaction mixture was evaporated to dryness by blowing under a gentle flow of N_2. DCM (0.5ml) was added and was blown under N_2. Drying under N_2 was continued overnight. Yield =20mg, 98%.
LCMS purity 96%, m/z 590 $[M+H]^+$, ^1H NMR (400 MHz, d_6-DMSO), δ: 0.75 -1.33 (8H, m), 2.90 (1H, m), 3.50 (2H, m), 4.25 (3H, m), 4.93 (1H, m), 5.70, (1H, m), 5.98 (1H, m), 7.15-7.62 (11 H, m), 9.7 (1H, br s), 10.42 (0.5H br s)

Reference Example 72 (S)-{4-[6-Amino-5-(2,4-difluorobenzoyl)-2-oxo-2H-pyridin-1-yl]benzylamino}phenylacetic acid

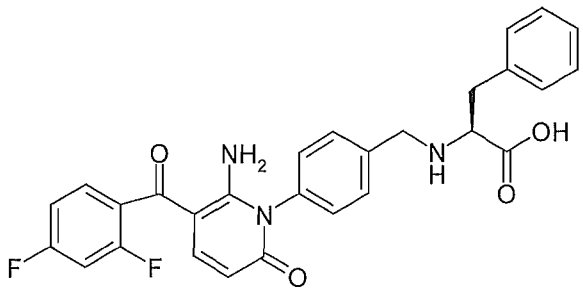
[0325]



[0326] To a solution of **Example 7** (100mg, 0.179mmol) in THF (1 ml) and MeOH (0.5ml) was added 2M NaOH (aq, 1ml). The mixture was allowed to stir at RT for 3h, evaporated to near dryness, acidified using dropwise addition of 1M HCl and extracted with EtOAc (5ml). EtOAc layer was concentrated *in vacuo* to give the crude acid. LCMS shows 80% product m/z = 490 $[M+H]^+$and 20% impurity m/z 470 $[M+H]^+$. Purification by preparative HPLC afforded the desired product. Yield= 34mg, 31%). LCMS purity 100%, m/z 490 $[M+H]^+$, ^1H NMR (400 MHz, DMSO), δ: 3.64 (2H, m, CH_2), 4.06 (1H, s, CH), 5.50 (1H, d, Ar), 6.75(1H, br s, NH), 6.96 (13H, m, Ar), 9.84 (1H, br s, NH).
[0327] The following compounds were prepared in a similar manner:

Reference Example 73 (S)-2-{4-[6-Amino-5-(2,4-difluorobenzoyl)-2-oxo-2H-pyridin-1-yl]benzylamino}-3-phenylpropionic acid

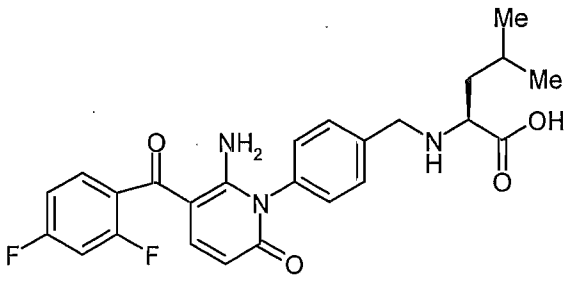
[0328]



[0329] From **Example 8.** LCMS purity 99%, m/z 504 $[M+H]^+$, ^1H NMR (400 MHz, DMSO), δ: 2.96-3.09 (3H, m), 3.81 (1H, d), 3.98 (1H, d), 5.76 (1H, d), 7.00 (1H, br s), 7.22-7.40 (9H, m), 7.41-7.61 (4H, m), 10.11 (1H, brs).

Reference Example 74 (S)-2-{4-[6-Amino-5-(2,4-difluorobenzoyl)-2-oxo-2H-pyridin-1-yl]benzylamino}-4-methyl-pentanoic acid

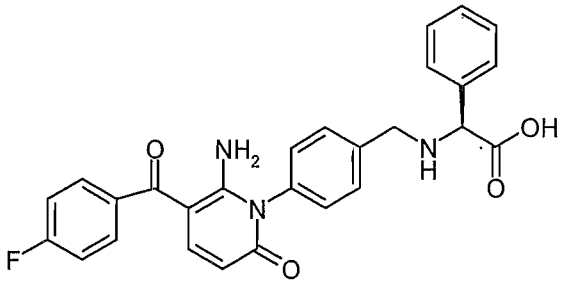
[0330]



[0331] From **Example 9.** LCMS purity 91%, m/z 470 $[M+H]^+$, ^1H NOR (400 MHz, DMSO), δ: 0.71 (6H, m), 1.40 (2H, m), 1.60 (1 H, m), 3.44 (1 H, m), 3.89 (2H, s), 5.49 (1H, d), 6.70 (1 H, br s), 6.94-7.08 (2H, m), 7.14-7.33 (4H, m), 7.46 (2H, m), 9.86 (1 H, br s).

Reference Example 75 (S)-{4-[6-Amino-5-(4-fluorobenzoyl)-2-oxo-2H-pyridin-1-yl]benzylamino}phenylacetic acid

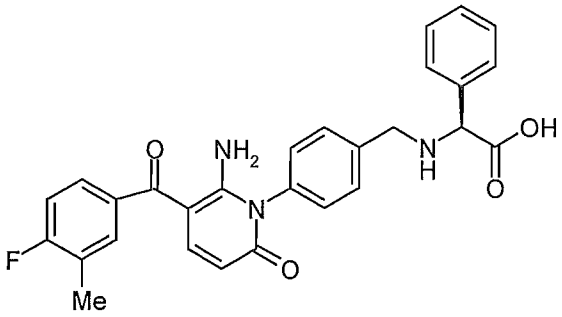
[0332]



[0333] From **Example 1.** LCMS purity 100%, m/z 472 $[M+H]^+$, ^1H NMR (400 MHz, DMSO), δ: 4.13 (1H, d), 4.22 (1H, d), 5.18 (1H, s), 5.73 (1H, d), 7.30-7.61 (13H, m), 7.73 (1H, d), 10.09 (2H, br s).

Reference Example 76 (S)-{4-[6-Amino-5-(3-methyl-4-fluoro benzoyl)-2-oxo-2H-pyridin-1-yl]benzylamino}phenylacetic acid

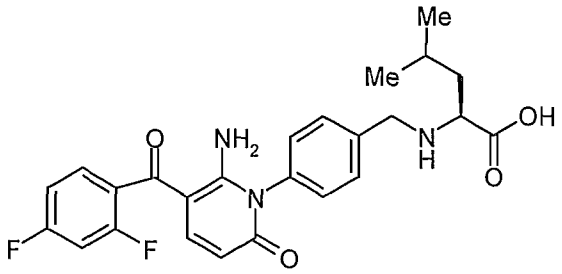
[0334]



[0335] From **Example 4.** LCMS purity 86%, m/z 486 $[M+H]^+$, ^1H NMR (400 MHz, DMSO), δ: 2.20 (3H, s), 3.98 (1H, d), 4.06 (1H, d), 5.07 (1H, s), 5.62 (1H, d), 7.12-7.50 (12H, m), 7.61 (1 H, d), 9.90 (2H, br s).

Reference Example 77 (S)-2-{4-[6-Amino-5-(2,4-difluorobenzoyl)-2-oxo-2H-pyridin-1-yl]benzylamino}-4-methylpentanoic acid

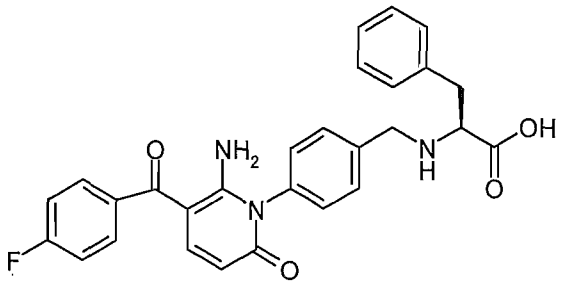
[0336]



[0337] From **Example 9.** LCMS purity 91%, m/z 470 $[M+H]^+$, 1H NMR (400 MHz, DMSO), δ: 0.71 (6H, m), 1.40 (2H, m), 1.60 (1H, m), 3.44 (1H, m), 3.89 (2H, s), 5.49 (1H, d), 6.70 (1H, br s), 6.94-7.08 (2H, m), 7.14-7.33 (4H, m), 7.46 (2H, m), 9.86 (1H, br s).

Reference Example 78 (S)-2-{4-[6-Amino-5-(4-fluorobenzoyl)-2-oxo-2H-pyridin-1-yl]benzylamino}-3-phenylpropionic acid

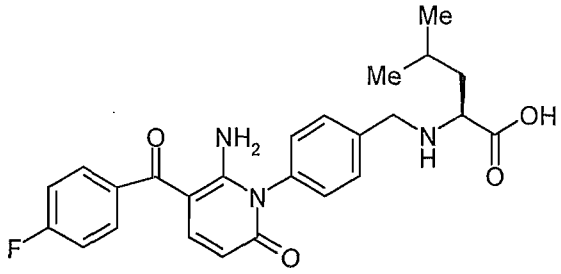
[0338]



[0339] From **Example 2.** LCMS purity 100%, m/z 486 $[M+H]^+$, ^1H NMR (400 MHz, DMSO), δ: 3.00 (2H, m), 3.98 (3H, m), 5.65 (1H, d), 7.15-7.34 (11 H, m), 7.40 (1 H, d), 7.51 (2H, m).

Reference Example 79 (S)-2-{4-[6-Amino-5-(4-fluorobenzoyl)-2-oxo-2H-pyridin-1-yl]benzylamino}-4-methylpentanoic acid

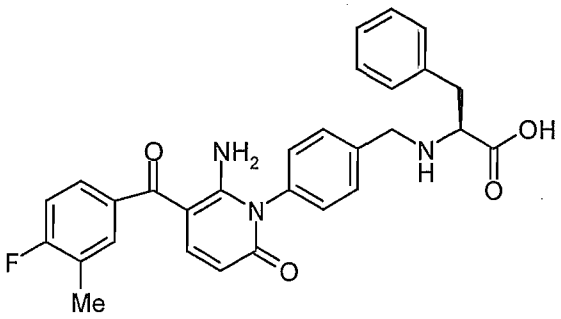
[0340]



[0341] From **Example 3.** LCMS purity 100%, m/z 452 $[M+H]^+$, ^1H NMR (400 MHz, DMSO), δ: 0.81 (6H, m), 1.51 (2H, m), 1.72 (1 H, m), 3.95 (2H, m), 5.61 (1 H, d), 7.21-7.30 (4H, m), 7.39 (1 H, d), 7.48 (2H, m), 7.52 (2H, m).

Reference Example 80 (S)-2-{4-[6-Amino-5-(3-methyl-4-fluorobenzoyl)-2-oxo-2H-pyridin-1-yl]benzylamino}-3-phenylpropionic acid

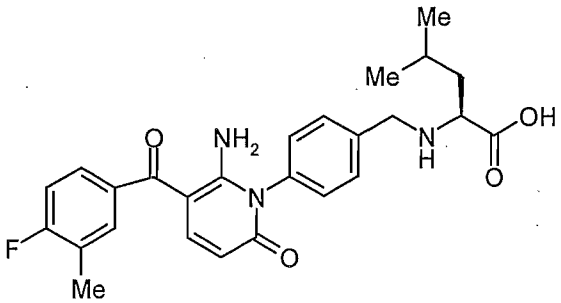
[0342]



[0343] From **Example 5.** LCMS purity 100%, m/z 500 $[M+H]^+$, ^1H NMR (400 MHz, DMSO), δ: 2.33 (3H, s), 2.90-3.07 (3H, m), 3.76 (1 H, d), 3.92 (1 H, d), 5.72 (1 H, d), 7.20-7.42 (9H, m), 7.49 (4H, m).

Reference Example 81 (S)-2-{4-[6-Amino-5-(3-Methyl-4-fluorobenzoyl)-2-oxo-2H-Pyridin-1-yl]benzylamino}-4-methylpentanoic acid

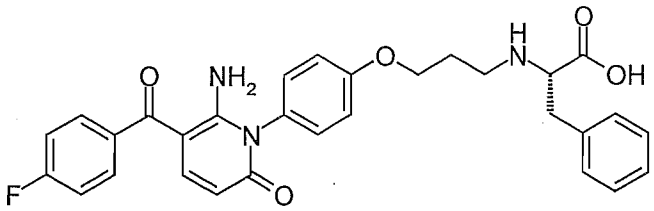
[0344]



[0345] From **Example 6.** LCMS purity 98%, m/z 500 $[M+H]^+$.

Reference Example 82 Cyclopentyl (S)-2-(3-{4-[6-Amino-5-(4-fluorobenzoyl)-2-oxo-2H-pyridin-1-yl]phenoxy}propylamino)-3-phenylpropionic acid

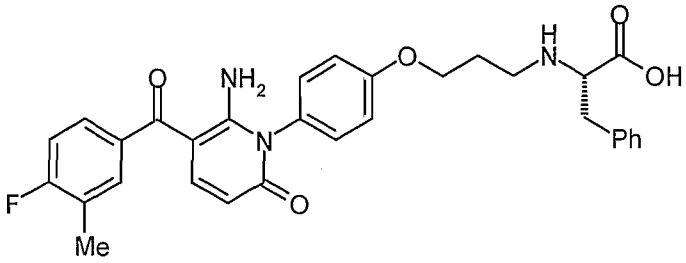
[0346]



[0347] From **Example 24.** LCMS purity 93%, m/z 530 $[M+H]^+$, ^1H NMR (400 MHz, d_6-DMSO), δ: 1.90 (2H, m), 2.80-2.90 (2H, m), 3.00 (2H, m), 3.40 (1H, m), 4.05 (2H, m), 5.70 (1 H, d), 7.10 (1H, d), 7.20 (2H, d). 7.30 (5H, m), 7.35 (1H, d), 7.45 (1H, d), 7.60 (1H, d).

Reference Example 83 (S)-2-(3-{4-[6-Amino-5-(3-methyl-4-fluoro benzoyl)-2-oxo-2H-pyridin-1-yl]phenoxy}propylamino)-3-phenyl propionic acid

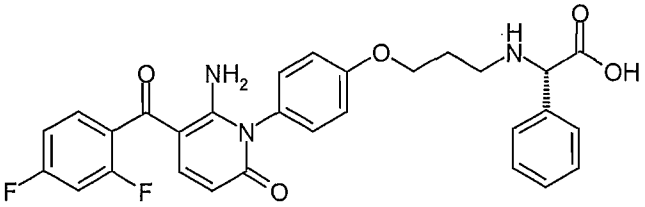
[0348]



[0349] From **Example 12.** LCMS purity 96%, m/z 544 $[M+H]^+$, ^1H NMR (400 MHz, d_6-DMSO), δ: 2.30 (2H, m), 2.40 (3H, s), 3.30 (1 H, m), 4.30 (2H, m), 4.45 (1 H, m), 5.85 (1 H, d), 5.40 (1H, m), 5.85 (1 H, d), 7.25 (2H, d), 7.40-7.55 (9H, m), 7.60-7.70 (2H, m).

Reference Example 84 (S)-(3-{4-[6-Amino-5-(2,4-difluoro benzoyl)-2-oxo-2H-pyridin-1-yl]-phenoxy}propylamino)phenyl acetic acid

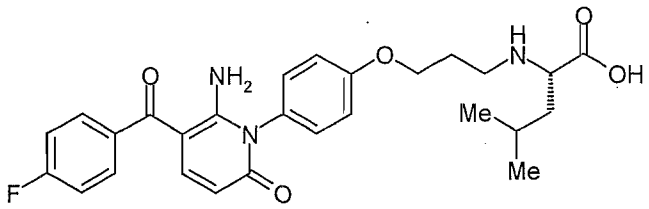
[0350]



[0351] From **Example 28.** LCMS purity 82%, m/z 534 $[M+H]^+$, ^1H NMR (400 MHz, CD_3OD), δ: 2.25 (2H, m), 3.10 (1H, m), 3.25 (1H, m), 4.20 (1 H, m), 5.83 (1H, d), 7.15 - 7.60 (13H, d).

Reference Example 85 (S)-2-(3-{4-[6-Amino-5-(4-fluorobenzoyl)-2-oxo-2H-pyridin-1-yl]phenoxy}propylamino)-4-methylpentanoic acid

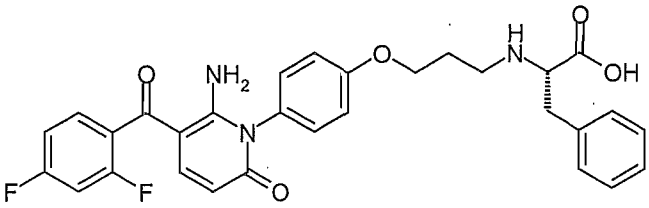
[0352]



[0353] From **Example 25.** LCMS purity 100%, m/z 496 $[M+H]^+$, ^1H NMR (400 MHz, d_6-DMSO), δ: 1.00 (6H, m), 1.75-1.90 (3H, m), 2.30 (2H, m), 3.10-3.30 (2H, m), 4.00 (1H, m), 4.25 (2H, m), 5.85 (1 H, d), 5.40 (1 H, m), 5.85 (1 H, d), 7.20 (2H, d), 7.30 (2H, d), 7.40 (2H, t), 7.55 (1 H, m), 7.65 (2H, m).

Reference Example 86 (S)-2-(3-{4-[6-Amino-5-(2,4-difluoro benzoyl)-2-oxo-2H-pyridin-1-yl]phenoxy}propylamino)-3-phenyl propionic acid

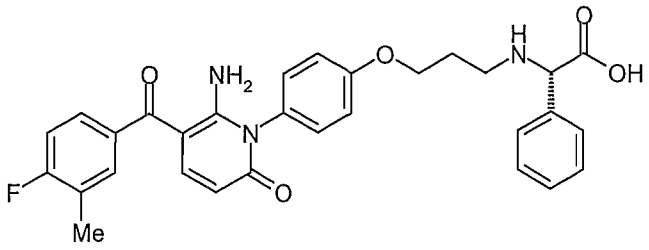
[0354]



[0355] From **Example 29.** LCMS purity 100%, m/z 548 $[M+H]^+$, ^1H NMR (400 MHz, d_6-DMSO), δ: 2.15 (2H, m), 3.15-3.30 (3H, m), 3.35 (1 H, m), 4.10 (2H, m), 4.20 (1 H, m), 5.65 (1 H, d), 7.15 (2H, d), 7.20-7.35 (11 H, m)

Reference Example 87 (S)-(3-{4-[6-Amino-5-(4-fluoro-3-methylbenzoyl)-2-oxo-2H-pyridin-1-yl-phenoxy}propylamino)phenylacetic acid

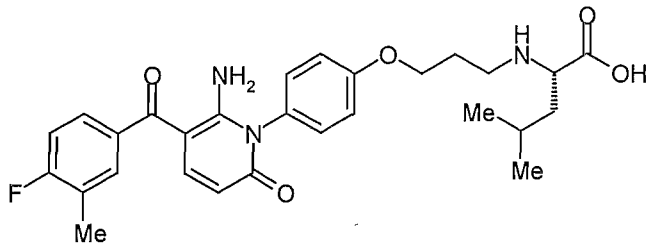
[0356]



[0357] From **Example 26.** LCMS purity 95%, m/z 530 $[M+H]^+$, ^1H NMR (400 MHz, d_6-DMSO), δ: 2.15 (3H, s) -2.35 (2H, m), 2.85 (2H, m), 3.05 (2H, m), 4.10 (2H, m), 5.25 (1H, m), 5.70 (1H, d), 4.25 (2H, m), 5.85 (1 H, d), 5.40 (1H, m), 5.85 (1 H, d), 7.10 (2H, d), 7.25 (2H, d), 7.3 (1 H, d), 7.35 (1 H, m), 7.40-7.55 (5H, m), 7.60 (2H, m).

Reference Example 88 (S)-2-(3-{4-[6-Amino-5-(4-fluoro-3-methyl benzoyl)-2-oxo-2H-pyridin-1-yl]phenoxy}propylamino)-4-methylpentanoic acid

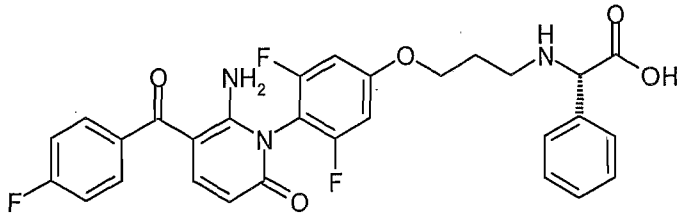
[0358]



From **Example 27.** LCMS purity 94%, m/z 510 $[M+H]^+$, ^1H NMR (400 MHz, d_6-DMSO), δ: 0.90 (6H, br s), 1.65-1.80 (3H, m), 2.1-2.30 (3H, s+ 2H, m), 3.0-3.20 (2H, m), 3.90 (1H, m), 4.15 (2H, m), 5.65 (1H, d), 7.15 (2H, d), 7.20-7.30 (3H, m), 7.30 (1H, m), 7.40 (1H, d), 7.45 (2H, s).

Reference Example 89 S)-(3-{4-[6-Amino-5-(4-fluorobenzoyl)-2-oxo-2H-pyridin-1-yl]-3,5-difluorophenoxy}propylamino)phenylacetic acid

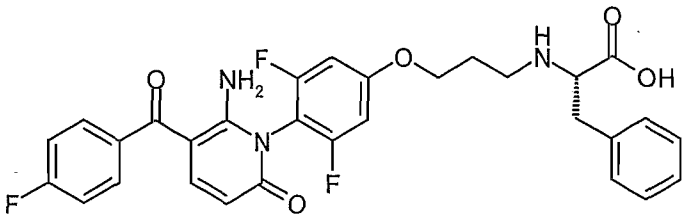
[0359]



[0360] From **Example 13.** LCMS purity 91%, m/z 552 $[M+H]^+$, ^1H NMR (400 MHz, d_6-DMSO), δ: 2.10-2.25 (2H, br m), 2.80 (1 H, m), 3.00 (1 H, m), 4.15 (2H, d), 5.20 (1 H, s), 5.70 (1 H, d), 5.65 (1H, d), 6.95 (2H, d), 7.30 (2H, t), 7.30 (1H, m), 7.40 -7.60 (8H, m).

Reference Example 90 (S)-(3-{4-[6-Amino-5-(4-fluorobenzoyl)-2-oxo-2H-pyridin-1-yl]-3,5-difluorophenoxy}propylamino)phenylacetic acid

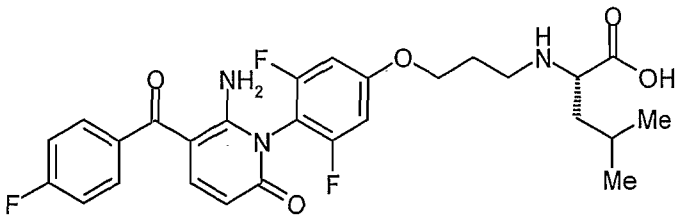
[0361]



[0362] From **Example 14.** LCMS purity 98%, m/z 566 $[M+H]^+$, ^1H NMR (400 MHz, d_6-DMSO), δ: 2.35 (2H, m), 3.1-3.3 (3H, m), 3.50 (1H, m), 4.25-4.40 (3H, m), 5.80 (1H, d), 5.70 (1H, d), 7.10 (2H, d), 7.30-7.45 (7H, m), 7.60-7.70 (3H, m).

Reference Example 91 (S)-2-(3-{4-[6-Amino-5-(4-fluorobenzoyl)-2-oxo-2H-pyridin-1-yl]-3,5-difluorophenoxyphenoxy}propylamino)-4-methyl pentanoic acid

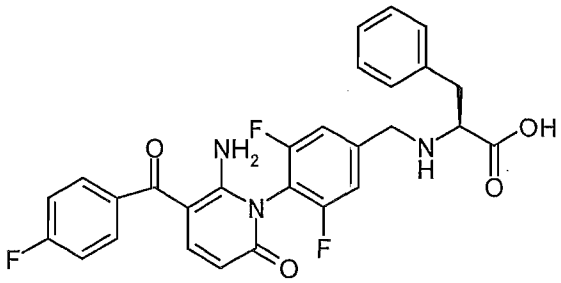
[0363]



[0364] From **Example 15.** LCMS purity 92%, m/z 532 $[M+H]^+$, ^1H NMR (400 MHz, d_6-DMSO), δ: 0.95 (6H, m), 1.8 (3H, m), 2.30 (2H, m), 3.10-3.25 (2H, m), 3.95 (1H, m), 4.25 (2H, m), 5.80 (1 H, d), 7.10 (2H, m), 7.40 (2H, m), 7.60 (1 H, m), 7.65 (2H, m).

Reference Example 92 (S)-2-{4-[6-Amino-5-(2,4-fluorobenzoyl)-2-oxo-2H-pyridin-1-yl]-3,5-difluorobenzylamino}-3-phenylpropionic acid

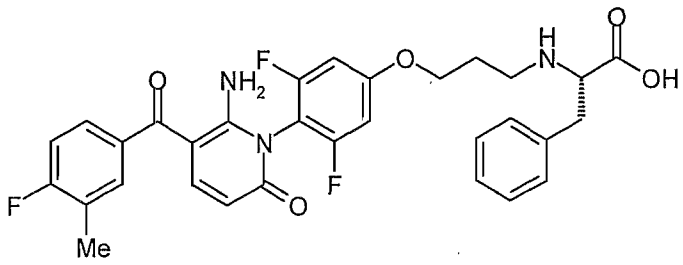
[0365]



[0366] From **Example 10.** LCMS purity 95%, m/z 522 $[M+H]^+$, ^1H NMR (400 MHz, CD_3OD), δ: 3.30 (2H, m), 4.15 (1H, m), 4.25 (2H, m), 5.75 (1H, d), 7.15-7.35 (9H, m), 5.20 (1 H, m), 5.90 (1H, d), 7.35-7.50 (9H, m), 7.55 (2H, m), 7.65 (1H, d).

Reference Example 93 (S)-2-(3-{4-[6-Amino-5-(4-fluoro-3-methylbenzoyl)-2-oxo-2H-pyridin-1-yl]-3,5-difluorophenoxy}propylamino)-3-phenylpropionic acid

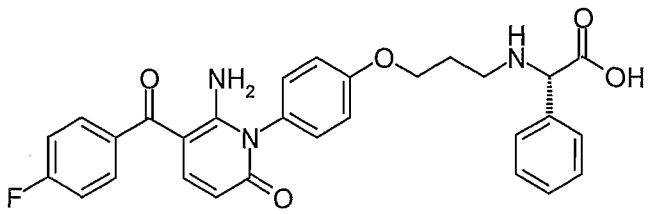
[0367]



[0368] From **Example 18.** LCMS purity 92%, m/z 580 $[M+H]^+$, ^1H NMR (400 MHz, d_6-DMSO), δ: 2.30 (2H, m), 2.40 (3H, s), 3.15-3.35 (4H, m), 3.50 (1 H, m), 4.30 (2H, m), 4.35 (1 H, m), 5.80 (1 H, d), 7.10 (2H, m), 7.35-7.50 (7H, m), 7.55 (1 H, m), 7.65 (1 H, m).

Reference Example 94 (S)-(3-{4-[6-Amino-5-(4-fluorobenzoyl)-2-oxo-2H-pyridin-1-yl]-phenoxy}propylamino)phenylacetic acid

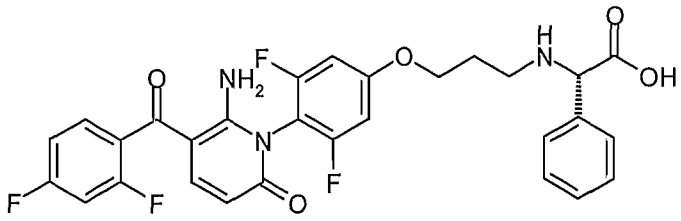
[0369]



[0370] From **Example 23.** LCMS purity 87%, m/z 516 $[M+H]^+$, ^1H NMR (400 MHz, d_6-DMSO), δ: 2.25 (2H, m), 2.80 (1H, m), 3.10 (1H, m), 4.15 (2H, m), 5.30 (1H, s), 5.75 (2H, d), 7.15 (2H, d), 7.25 (2H, d), 7.40 (2H, t), 7.50-7.70 (7H, m).

Reference Example 95 (S)-(3-{4-[6-Amino-5-(2,4-difluoro benzoyl)-2-oxo-2H-pyridin-1-yl]-3,5-difluorophenoxy}propylamino)phenyl acetic acid

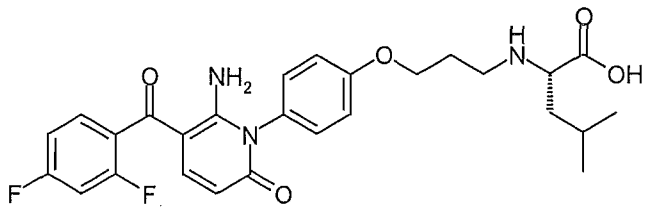
[0371]



[0372] From **Example 20.** LCMS purity 84%, m/z 570 $[M+H]^+$, ^1H NMR (400 MHz, d_6-DMSO), δ: 2.30 (2H, m), 2.90 (1H, m), 3.15 (1H, m), 4.23 (2H, m), 5.32 (1 H, s), 5.85 (1 H, d), 7.10 (2H, d), 7.50 (3H, m), 7.60-7.65 (6H, m).

Reference Example 96 (S)-2-(3-{4-[6-Amino-5-(2,4difluoro benzoyl)-2-oxo-2H-pyridin-1-yl]phenoxy}propylamino)-4-methyl pentanoic acid

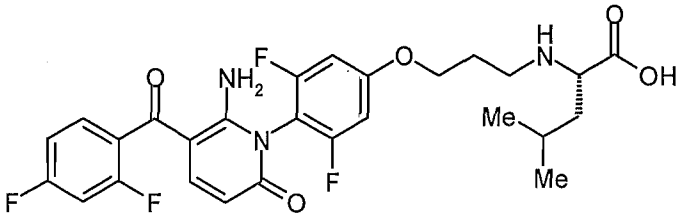
[0373]



[0374] From **Example 30.** LCMS purity 93%, m/z 514 $[M+H]^+$, ^1H NMR (400 MHz, d_6-DMSO), δ: 0.95 (6H, m), 1.85 (3H, m), 2.30 (2H, m), 3.15-3.22 (2H, m), 3.99 (1 H, m), 4.21 (2H, m), 5.77 (1H, d), 7.20 (2H, d), 7.30 (4H, m), 7.45 (1H, m), 7.55 (1H, m).

Reference Example 97 (S)-2-(3-{4-[6-Amino-5-(2,4-difluoro benzoyl)-2-oxo-2H-pyridin-1-yl]-3,5-difluorophenoxy}propylamino)-4-methyl pentanoic acid

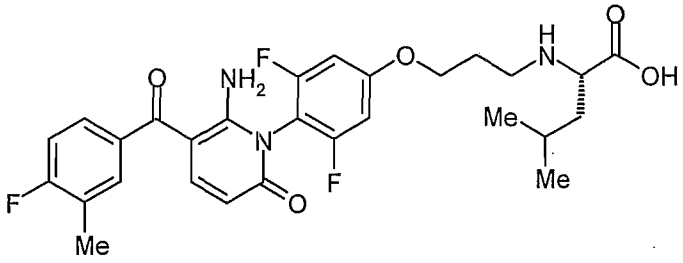
[0375]



[0376] From **Example 22.** LCMS purity 88%, m/z 550 $[M+H]^+$, ^1H NMR (400 MHz, d_6-DMSO), δ: 0.80-0.95 (6H, m),1.50-1.85 (3H, m), 1.95-2.10 (2H, m), 2.95-3.05 (2H, m), 3.75-3.85 (1H, m), 4.05-4.15 (2H, m), 5.65 (1H, d), 7.00 (1H, d), 7.10-7.20 (1H, m), 7.25-7.30 (1H, m), 7.30-7.40 (1 H, m), 7.45-7.55 (1 H, m), 7.80-8.25 (1H, br s), 9.90-10.20 (1 H, br s).

Reference Example 98 (S)-2-(3-{4-[6-Amino-5-(4-fluoro-3-methylbenzoyl)-2-oxo-2H-pyridin-1-yl]-3,5-difluorophenoxy}propylamino)-4-methylpentanoic acid

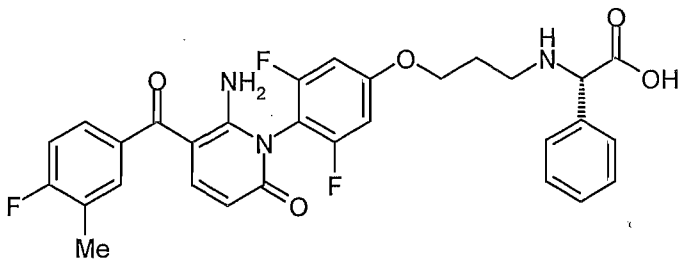
[0377]



[0378] From **Example 19.** LCMS purity 93%, m/z 546 $[M+H]^+$, ^1H NMR (400 MHz, d_6-DMSO), δ: 0.95-1.05 (6H, m), 1.55-1.75 (2H, m), 1.80-1.90 (1H, m), 2.10-2.25 (2H, m), 2.35 (3H, s), 3.00-3.15 (2H, m), 3.70 (1H, m), 4.15-4.30 (2H, m), 5.80 (1H, d), 7.10 (1H, d), 7.25-7.35 (1H, m), 7.40-7.45 (1H, m), 7.50-7.55 (1H, m), 7.55-7.65 (1H, m), 8.90-10.70 (2H, brs).

Reference Example 99 (S)-(3-{4-[6-Amino-5-(4-fluoro-3-methylbenzoyl)-2-oxo-2H-pyridin-1-yl]-3,5-difluorophenoxy}propylamino) phenylacetic acid

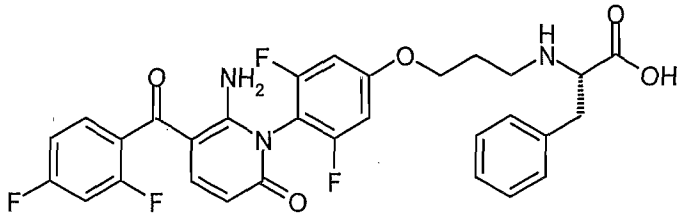
[0379]



[0380] From **Example 17.** LCMS purity 100%, m/z 566 $[M+H]^+$, ^1H NMR (400 MHz, d_6-DMSO), δ: 2.05-2.20 (2H, m), 2.30 (3H, s), 2.75-3.05 (2H, m), 4.05-4.20 (2H, m), 4.65-4.85 (1 H, m), 5.70 (1H, d), 7.00 (1H, d), 7.25-7.35 (1H, m), 7.35-7.60 (8H, m).

Reference Example 100 (S)-2-(3-{4-[6-Amino-5-(2,4-difluorobenz oyl)-2-oxo-2H-pyridin-1-yl]-3,5-difluorophenoxy}-propylamino)-3-phenyl propionic acid

[0381]

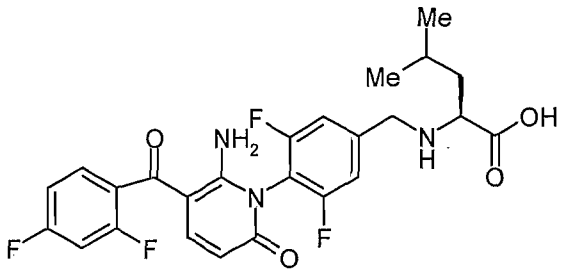


[0382] From **Example 21.** LCMS purity 100%, m/z 584 $[M+H]^+$, ^1H NMR (400 MHz, DMSO), δ: 2.05-2.15 (2H, m),

3.00-3.10 (3H, m), 4.00-4.25 (4H, m), 5.75 (1H, d), 7.05 (1H, d), 7.25-7.50 (8H, m), 7.55-7.65 (1 H, m).

Reference Example 101 (S)-2-{4-[6-Amino-5-(4-fluorobenzoyl)-2-oxo-2H-pyridin-1-yl]-3,5-difluorobenzylamino}-4-methylpentanoic acid

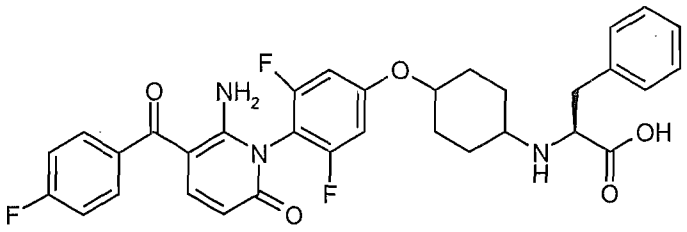
[0383]



[0384] From **Example 11.** LCMS purity 92%, m/z 506 $[M+H]^+$, ^1H NMR (400 MHz, MeOD), δ: 0.85-1.05 (6H, m), 1.65-1.85 (3H, m), 3.95-4.05 (1 H, m), 4.25-4.35 (2H, m), 5.75 (1 H, d), 6.90 (1H, d), 7.00-7.10 (2H, m), 7.35-7.45 (4H, m).

Reference Example 102 (S)-2-(4-{4-[6-Amino-5-(4-fluorobenzoyl)-2-oxo-2H-pyridin-1-yl]-3,5-difluorophenoxy}cyclohexylamino)-4-methylpentanoic acid

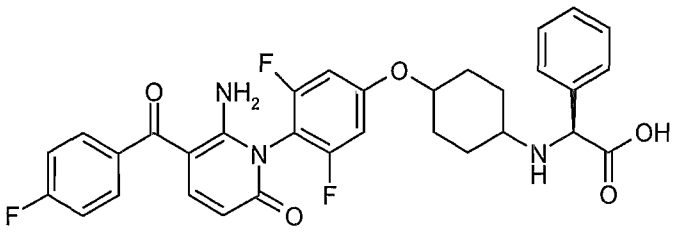
[0385]



[0386] From **Example 31.** LCMS purity 91%, m/z 606 $[M^+ +H]$, ^1H NMR (400 MHz, CD_3OD), δ: 1.55-2.55 (8H, m), 3.20-3.40 (2H, m), 4.25-4.35 (1 H, m), 4.45-4.55 (1 H, m), 4.85-4.95
[0387] (1H, m), 5.95 (1H, d), 6.95-7.10 (2H, m), 7.35-7.55 (6H, m), 7.70-7.80 (2H, m), 7.80-7.85 (1H, d).

Reference Example 103 (2S)-[(4-{4-[6-amino-5-(4-fluorobenzoyl)-2-oxopyridin-1(2*H*)-yl]-3,5-difluorophenoxy}cyclohexyl)aminol(phenyl)acetic acid

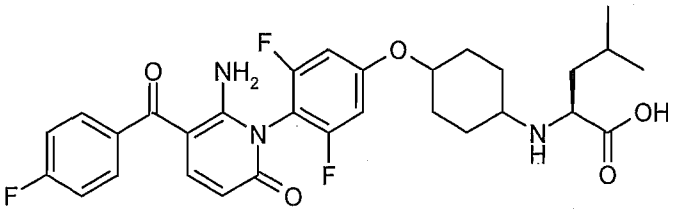
[0388]



[0389] From **Example 32.** LCMS purity 89%, m/z 592 $[M+H]^+$, ^1H NMR (400 MHz, CD_3OD), δ: 1.60-1.75 (2H, m), 1.80-1.95 (2H, m), 2.00-2.15 (2H, m), 2.15-2.30 (2H, m), 3.05-3.20 (1H, m), 4.65-4.75 (1H, m), 4.75-4.80 (1H, m), 5.80 (1H, d), 6.85-6.95 (2H, m), 7.20-7.30 (2H, m), 7.40-7.50 (3H, m), 7.55-7.65 (4H, m), 7.65-7.70 (1 H, m).

Reference Example 104 *N*-(4-{4-[6-amino-5-(4-fluorobenzoyl)-2-oxopyridin-1(2*H*)-yl]-3,5-difluorophenoxy}cyclohexyl)-L-leucine

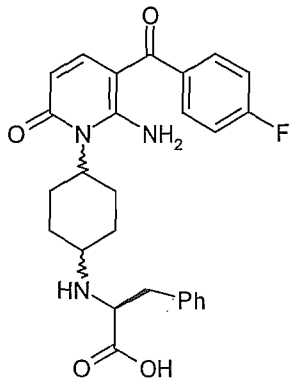
[0390]



[0391] From **Example 33.** LCMS purity 93%, m/z 572 $[M+H]^+$, ^1H NMR (400 MHz, CD_3OD), δ: 0.85-1.00 (6H, m), 1.45-2.00 (9H, m), 2.05-2.25 (3H, m), 3.05-3.15 (1H, m), 3.60-3.75 (1H, m), 4.30 and 4.65 (0.5H each, m), 5.70 (1H, d), 6.75-6.85 (2H, m), 7.10-7.15 (2H, m), 7.45-7.55 (2H, m), 7.55-7.65 (1H, m).

Reference Example 105 (S)-2-{4-[6-Amino-5-(4-fluorobenzoyl)-2-oxo-2H-pyridin-1-yl]cyclohexyl amino}-3-phenylpropionic acid

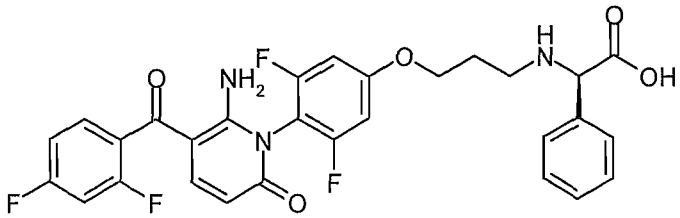
[0392]



[0393] From **Example 34.** LCMS purity 98%, m/z 478 $[M+H]^+$, ^1H NMR (400 MHz, CD_3OD), δ: 1.55-1.85 (4H, m), 1.95-2.20 (2H, m), 2.30-2.75 (2H, m), 3.15-3.20 (1 H, m), 3.25-3.35 (2H, m), 4.05-4.15 (1 H, m), 5.60 (1 H, d), 7.05-7.15 (2H, m), 7.15-7.35 (5H, m), 7.35-7.45 (3H, m).

Reference Example 106 (R)-(3-{4-[6-Amino-5-(2,4-difluoro benzoyl)-2-oxo-2H-pyridin-1-yl]-3,5-difluorophenoxy}propylamino)phenyl acetic acid

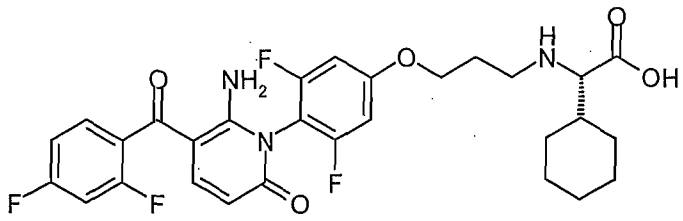
[0394]



[0395] From **Example 42.** LCMS purity 88%, m/z 570 $[M+H]^+$, ^1H NMR (400 MHz, DMSO), δ: 2.05-2.20 (2H, m), 2.75-2.95 (2H, m), 4.10-4.20 (2H, m), 4.30-4.50 (1H, m), 5.75 (1H, d), 7.00-7.10 (2H, m), 7.20-7.30 (1H, m), 7.35-7.50 (7H, m), 7.55-7.65 (1H, m).

Reference Example 107 (2*S*)-[(3-{4-[6-amino-5-(2,4-difluorobenzoyl)-2-oxopyridin-1(2*H*)-yl]-3,5-difluorophenoxy}propyl)amino](cyclohexyl)acetic acid

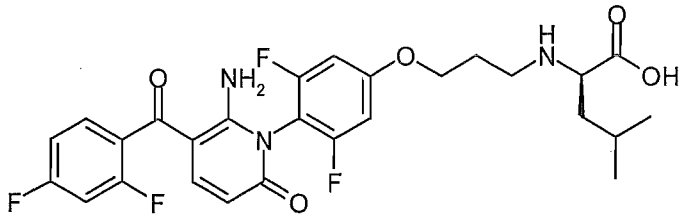
[0396]



[0397] From **Example 48,** LCMS purity 95%, m/z 576 $[M+H]^+$, 1H NMR (300 MHz, DMSO), δ: 10.16 (1 H, br s),8.78 (1 H, br s), 8.12 (1 H, br s), 7.62-7.53 (1 H, m), 7.47-7.32 (2H, m), 7.27-7.21 (1H, m), 7.07 (2H, d, J=10.2Hz), 5.74 (1H, d, J=9.6Hz), 4.19 (2H, t, J=5.7Hz), 3.85-3.75 (1H, m),3.15-3.00 (2H, m), 2.20-2.05 (2H, m),1.95-1.60 (6H, m), 1.40-0.90 (5H, m).

Reference Example 108 *N*-(3-{4-[6-amino-5-(2,4-difluorobenzoyl)-2-oxopyridin-1(2*H*)-yl]-3,5-difluorophenoxy}propyl)-D-leucine

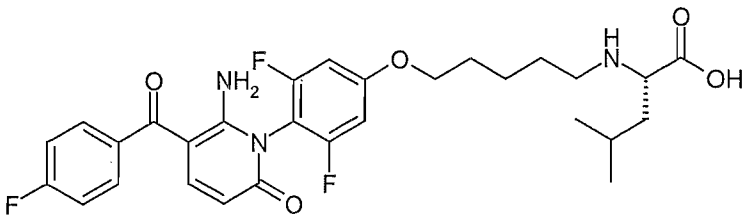
[0398]



[0399] From **Example 50.** LCMS purity 90%, m/z 550 $[M+H]^+$, 1H NMR (300 MHz, DMSO), δ: 7.63-7.52 (1H, m), 7.46-7.32 (2H, m), 7.28-7.10 (1H, m), 7.06 (2H, d, J=10.2Hz), 5.73 (1 H, d, J=9.9Hz), 4.25-4.15 (2H, m), 3.90-3.80 (1 H, m), 3.20-3.00 (2H, m), 2.20-2.05 (2H, m), 1.80-1.55 (3H, m), 0.98-0.90 (6H, m).

Reference Example 109 *N*-(5-{4-[6-amino-5-(4-fluorobenzoyl)-2-oxopyridin-1(2*H*)-yl]-3,5-difluorophenoxy}pentyl)-L-leucine

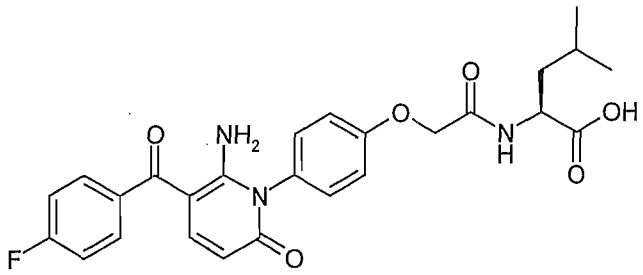
[0400]



[0401] From **Example 55.** To a solution of cyclopentyl *N*-(5-{4-[6-amino-5-(4-fluorobenzoyl)-2-oxopyridin-1(2*H*)-yl]-3,5-difluorophenoxy}pentyl)-L-leucinate (33mg, 0.05mmol) in THF (1 ml) and water (1ml) was added LiOH (25mg, 1.05mmol, 20eq). The mixture was stirred at room temperature for 16 hours, before being heated at 80 °C for 10 hours. The mixture was concentrated under reduced pressure and water (5 ml) added. The pH was adjusted to 7 using 1M HCl and the aqueous layer extracted with 1-butanol (3 x 5ml). The combined organic extracts were concentrated under reduced pressure. The solid residue was triturated with Et_2O, collected by filtration and purified by preparative HPLC to provide the title compound as a white solid as the mono-TFA salt (7mg, 24% yield). LC/MS: m/z 560 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ: 7.62-7.51 (3H, m), 7.34 (2H, m), 7.05 (2H, m), 5.72 (1 H, d, J=9.8 Hz), 4.09 (2H, t, J=5.7 Hz), 3.23 (1 H, m), 2.80 (2H, m), 1.79-1.43 (9H, m), 0.89 (6H, t, J=6.7 Hz).

Reference Example 110 *N*-({4-[6-Amino-5-(4-fluorobenzoyl)-2-oxopyridin-1(2*H*)-yl]phenoxy}-acetyl)-L-leucine

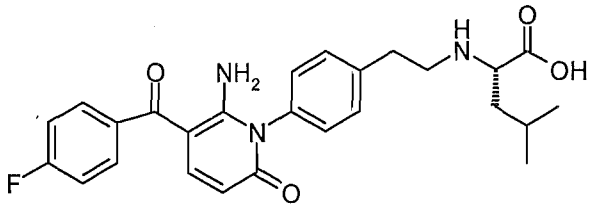
[0402]



[0403] From **Example 56.** To a solution of cyclopentyl *N*-({4-[6-amino-5-(4-fluorobenzoyl)-2-oxopyridin-1(2*H*)-yl]phenoxy}acetyl)-L-leucinate (35mg, 0.06mmol) in THF (1ml) and water (1 ml) was added LiOH (30mg, 1.24mmol, 20eq). The mixture was stirred at room temperature for 16 hours, concentrated under reduced pressure and water (5ml) added. The pH was adjusted to 7 using 1M HCl and the aqueous layer extracted with 1-butanol (3 x 5ml). The combined organic extracts were concentrated under reduced pressure. The solid residue was triturated with Et_2O, filtered and dried under reduced pressure to provide the title compound as a cream solid (11mg, 36% yield).
LC/MS: m/z 496 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ: 7.58-7.53 (3H, m), 7.43 (1 H, d, J=9.6 Hz), 7.36-6.98 (6H, m), 5.68 (1 H, d, J=9.6 Hz), 4.58 (2H, s), 3.90 (1 H, m), 1.67-1.31 (3H, m), 0.86 (6H, m).

Reference Example 111 *N*-[2-(4-{6-amino-5-[(4-fluorophenyl)carbonyl]-2-oxopyridin-1(2*H*)-yl}phenyl)ethyl]-L-leucine

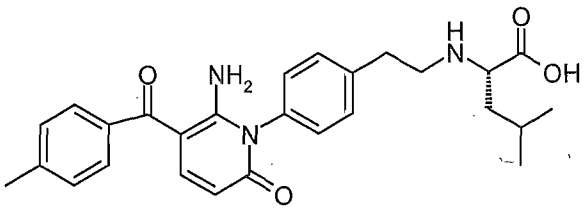
[0404]



[0405] From **Example 58.** LC/MS: m/z 466 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ: 8.21 (1H, br s), 7.60-7.44 (4H, m), 7.39-7.30 (4H, m), 5.76-5.69 (1 H, m), 4.00-3.85 (1 H, m), 3.10-2.95 (2H, m), 1.85-1.60 (3H, m), 1.30-1.10 (2H, m), 0.95 (6H, d, J=6Hz).

Reference Example 112 *N*-[2-(4-{6-amino-5-[(4-methylphenyl)carbonyl]-2-oxopyridin-1(2*H*)-yl}phenyl)ethyl]-L-leucine

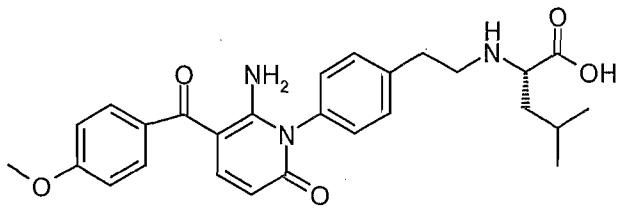
[0406]



[0407] From **Example 63.** LC/MS: m/z 462 $[M+H]^+$. ^1H NMR (300 MHz, CD_3OD) δ: 7.69 (1H, d, J=9.6Hz), 7.53 (2H, d, J=7.2 Hz), 7.45 (2H, d, J=8.1 Hz), 7.34 (2H, d, J=7.8 Hz), 7.25 (2H, d, J=8.4 Hz), 5.80 (1H, d, J=9.6 Hz), 3.15 (1H, m), 3.02-2.75 (4H, m), 2.45 (3H, s), 1.73 (1 H, m), 1.56-1.22 (2H, m), 0.96 (6H, dd).

Reference Example 113 ***N*****-[2-(4-{6-amino-5-[(4-methoxyphenyl)carbonyl]-2-oxopyridin-1(2*H*)-yl}phenyl)ethyl]-L-leucine**

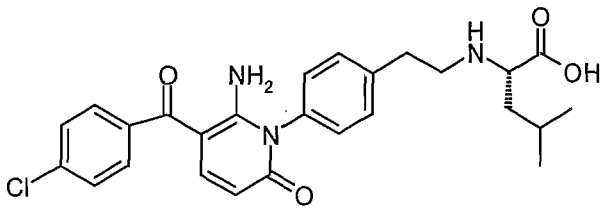
[0408]



[0409] From **Example 64.** LC/MS: m/z 478 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ: 7.28 (2H, d, J=8.7Hz), 7.15 (2H, d, J=8.1Hz), 7.04 (1H, d, J=9.3 Hz), 6.89 (4H, m), 4.87 (1H, d, J=9.3Hz), 3.78 (1H, m), 3.41 (3H, s), 2.75 (2H, m), 1.78 (1 H, m), 1.24 (2H, m), 0.86 (6H, t).

Reference Example 114 ***N*****-[2-(4-{6-amino-5-[(4-chlorophenyl)carbonyl]-2-oxopyridin-1(2*H*)-yl}phenyl)ethyl]-L-leucine**

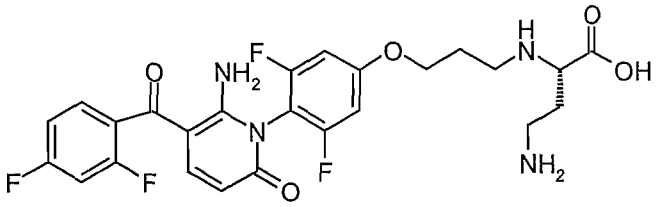
[0410]



[0411] From **Example 65.** LC/MS: m/z 482 $[M+H]^+$. ^1H NMR (300 MHz, CD_3OD) δ: 7.16 (1H, d), 7.52 (6H, m), 7.23 (2H, d), 6.82 (1 H, d), 3.15 (1 H, t), 1.74 (1 H, m), 1.44 (2H, m), 0.93 (6H, dd).

Reference Example 115 (2*S*)-4-amino-2-[(3-{4-[6-amino-5-(2,4-difluorobenzoyl)-2-oxopyridin-1(2*H*)-yl]-3,5-difluorophenoxy}propyl)amino]butanoate

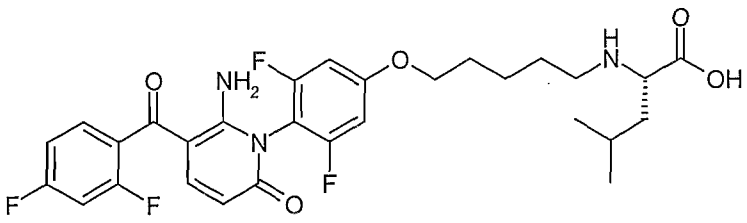
[0412]



[0413] From **Example 52.** LC/MS: m/z 537 $[M+H]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ: 7.52-7.75 (2H, m), 7.30 - 7.48 (2H, m), 7.20 - 7.29 (1H, m), 7.09 (2 H, d, J=9.7 Hz), 4.23 (1H, t, J=6.1 Hz), 4.07 - 4.17 (2H, m), 2.14 - 2.32 (2H, m), 1.22 - 1.41 (6H, m), 0.88 (4H, t, J=7.3 Hz)

Reference Example 116 ***N*****-(5-{4-[6-amino-5-(2,4-difluorobenzoyl)-2-oxopyridin-1(2*H*)-yl]-3,5-difluorophenoxy}pentyl)-L-leucine**

[0414]

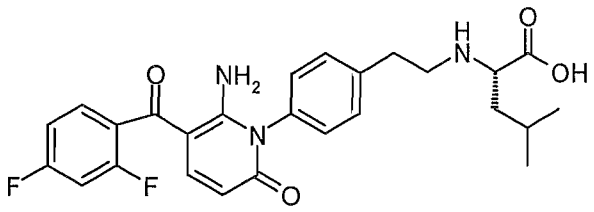


[0415] From **Example 54.** To a solution of *tert*-butyl *N*-(5-{4-[6-amino-5-(2,4-difluorobenzoyl)-2-oxopyridin-1(2*H*)-yl]-3,5-difluorophenoxy}pentyl)-L-leucinate (21 mg, 0.04mmol) in DCM (2.5ml) was added TFA (2.5ml). The mixture was stirred at room temperature for 20 hours, before concentrating under reduced pressure. The residue was dissolved in minimal MeOH and azeotroped with 1:1 toluene/DCM three times. The title compound was afforded as a cream coloured solid as the mono-TFA salt (21 mg, 92% yield). LC/MS: m/z 634 $[M+H]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.14 (1 H, br s), 8.21 (1 H, br s), 7.57 (1 H, m), 7.46 (1 H, m), 7.34 (1 H, dd, J=9.6, 2.4 Hz), 7.21 (1 H, m), 7.06 (2H, d, J=10.2 Hz), 5.73 (1 H, d, J=9.9 Hz), 4.10 (2H, t, J=5.7 Hz), 3.40 (1 H, m), 2.84 (2H, t, J=6.6 Hz), 1.79-1.48 (9H, m), 0.90 (6H, t, J=6.3 Hz).

[0416] The following examples were prepared in a similar manner:

Reference Example 117 *N*-[2-(4-{6-amino-5-[(2,4-difluorophenyl)carbonyl]-2-oxopyridin-1(2*H*)-yl}phenyl)ethyl]-L-leucine

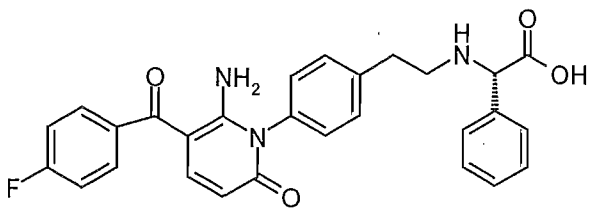
[0417]



[0418] From **Example 60.** LC/MS: m/z 484 $[M+H]^+$: ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.06 (1 H, br s), 9.17 (2H, br s), 7.55-6.94 (8H, m), 5.72 (1H, d, J=9.6Hz), 4.05-3.93 (1H, m), 3.40-3.10 (3H, m), 1.85-1.65 (4H, m), 0.95 (6H, d, J=5.7Hz).

Reference Example 118 (2*S*)-{[2-(4-{6-amino-5-[(4-fluorophenyl)carbonyl]-2-oxopyridin-1(2*H*)-yl}phenyl)ethyl]amino}(phenyl)ethanoic acid

[0419]



[0420] From **Example 62.** LC/MS: m/z 486 $[M+H]^+$, ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.80 (2H, br s), 7.70-7.20 (14H, m), 5.70 (1 H, d, J=9.6Hz), 5.24 (1 H, s), 3.20-2.90 (4H, m).

Measurement of biological activities

p38 MAP Kinase activity

[0421] The ability of compounds to inhibit p38 MAP a Kinase activity was measured in an assay performed by Upstate (Dundee UK). In a final reaction volume of 25μL, p38 MAP Kinase a (5-10 mU) is incubated with 25mM Tris pH 7.5, 0.002 mMEGTA, 0.33 mg/mL myelin basic protein, 10mM MgAcetate and [g-33p-ATP] (specific activity approx. 500cpm/pmol, concentration as required). The reaction is initiated by the addition of the MgATP mix. After incubation

for 40 minutes at room temperature, the reaction is stopped by the addition of 5μL of a 3% phosphoric acid solution. 1μL of the reaction is then spotted onto a P30 filtermat and washed three times for 5 minutes in 75 mM phosphoric acid and once in methanol prior to drying and scintillation counting.

[0422] Duplicate data points are generated from a 1/3 log dilution series of a stock solution in DMSO. Nine dilutions steps are made from a top concentration of 10μM, and a 'no compound' blank is included. The standard radiometric filter-binding assay is performed at an ATP concentration at, or close to, the Km. Data from scintillation counts are collected and subjected to free-fit analysis by Prism software. From the curve generated, the concentration giving 50% inhibition is determined and reported.

LPS-stimulation of THP-1 cells

[0423] THP-1 cells were plated in 100μl at a density of 4 x 10^4 cells/well in V-bottomed 96 well tissue culture treated plates and incubated at 37°C in 5% CO_2 for 16hrs. 2hrs after the addition of the inhibitor in 100μl of tissue culture media, the cells were stimulated with LPS (*E coli* strain 005:B5, Sigma) at a final concentration of 1μg/ml and incubated at 37°C in 5% CO_2 for 6hrs. TNF-α levels were measured from cell-free supernatants by sandwich ELISA (R&D Systems #QTA00B).

LPS-stimulation of human whole blood

[0424] Whole blood was taken by venous puncture using heparinised vacutainers (Becton Dickinson) and diluted in an equal volume of RPMI1640 tissue culture media (Sigma). 100μl was plated in V-bottomed 96 well tissue culture treated plates. 2hrs after the addition of the inhibitor in 100μl of RPMI1640 media, the blood was stimulated with LPS (*E coli* strain 005:B5, Sigma) at a final concentration of 100ng/ml and incubated at 37°C in 5% CO_2 for 6hrs. TNF-α levels were measured from cell-free supernatants by sandwich ELISA (R&D Systems #QTA00B)

[0425] IC50 values were allocated to one of three ranges as follows:

Range A: IC50 < 100nM
Range B: 100nM < IC50 <1000nM
Range C: IC50 >1000nM

Results Table

[0426]

Example	Inhibitor activity versus p38 MAPKa	Inhibitor activity versus THP-1 TNFα release	Inhibitor activity versus human whole blood TNFα release
1	B	C	NT
2	B	C	NT
3	B	C	C
4	B	C	NT
5	B	C	NT
6	B	C	NT
7	A	C	NT
8	A	B	NT
9	A	B	C
10	A	B	NT
11	A	B	C
12	A	B	NT
13	A	A	NT
14	A	A	NT

(continued)

Example	Inhibitor activity versus p38 MAPKa	Inhibitor activity versus THP-1 TNFα release	Inhibitor activity versus human whole blood TNFα release
15	A	A	C
16	A	A	NT
17	A	A	NT
18	A	A	NT
19	A	A	C
20	A	A	B
21	A	A	C
22	A	A	B
23	A	B	NT
24	A	B	NT
25	A	B	C
26	A	B	NT
27	B	B	C
28	A	A	NT
29	A	B	NT
30	A	A	NT
31	A	A	NT
32	A	A	NT
33	A	A	NT
34	B	C	NT
35	B	C	NT
36	A	A	C
37	A	B	NT
38	A	A	C
39	A	B	NT
40	A	A	NT
41	B	A	C
42	A	A	B
43	A	A	NT
44	B	A	NT
45	A	A	NT
46	B	A	B
47	A	A	B
48	A	A	C
49	A	B	C
50	A	A	NT
51	A	A	NT

(continued)

Example	Inhibitor activity versus p38 MAPKa	Inhibitor activity versus THP-1 TNFα release	Inhibitor activity versus human whole blood TNFα release
52	A	A	B
53	A	A	B
54	A	A	NT
55	B	A	NT
56	B	C	NT
57	B	A	B
58	B	A	B
59	B	A	B
60	B	A	NT
61	B	A	NT
62	B	B	NT
63	C	A	NT
64	C	B	NT
65	B	A	NT
66	B	B	NT
67	B	B	C
68	NT	NT	NT
69	NT	NT	NT
70	NT	NT	NT
71	A	C	NT
72	A	NT	NT
73	A	NT	NT
74	A	NT	NT
75	B	NT	NT
76	B	NT	NT
77	A	NT	NT
78	B	NT	NT
79	B	NT	NT
80	A	NT	NT
81	B	NT	NT
82	A	NT	NT
83	A	NT	NT
84	A	NT	NT
85	A	NT	NT
86	C	NT	NT
87	B	NT	NT
88	A	NT	NT

(continued)

Example	Inhibitor activity versus p38 MAPKa	Inhibitor activity versus THP-1 TNFα release	Inhibitor activity versus human whole blood TNFα release
89	A	NT	NT
90	A	NT	NT
91	A	NT	NT
92	A	NT	NT
93	A	NT	NT
94	A	NT	NT
95	A	NT	NT
96	A	NT	NT
97	A	NT	NT
98	A	NT	NT
99	A	NT	NT
100	A	NT	NT
101	A	NT	NT
102	A	NT	NT
103	A	NT	NT
104	A	NT	NT
105	B	NT	NT
106	A	NT	NT
107	A	NT	NT
108	A	NT	NT
109	A	NT	NT
110	B	NT	NT
111	B	NT	NT
112	NT	NT	NT
113	NT	NT	NT
114	NT	NT	NT
115	NT	NT	NT
116	A	NT	NT
117	A	NT	NT
118	A	NT	NT

Broken Cell Carboxylesterase Assay

[0427] Any given compound of the present invention wherein R_1 is an ester group may be tested to determine whether it meets the requirement that it be hydrolysed by intracellular esterases, by testing in the following assay.

Preparation of cell extract

[0428] U937 or Hut78 tumour cells (~ 10^9) were washed in 4 volumes of Dulbeccos PBS (~ 1 litre) and pelleted at 525 g for 10 min at 4°C. This was repeated twice and the final cell pellet was resuspended in 35 ml of cold homogenising

buffer (Trizma 10 mM, NaCl 130 mM, $CaCl_2$ 0.5 mM pH 7.0 at 25°C). Homogenates were prepared by nitrogen cavitation (700 psi for 50 min at 4°C). The homogenate was kept on ice and supplemented with a cocktail of inhibitors at final concentrations of:

Leupeptin	1 μM
Aprotinin	0.1 μM
E64	8 μM
Pepstatin	1.5 μM
Bestatin	162 μM
Chymostatin	33 μM

[0429] After clarification of the cell homogenate by centrifugation at 525 g for 10 min, the resulting supernatant was used as a source of esterase activity and was stored at -80°C until required.

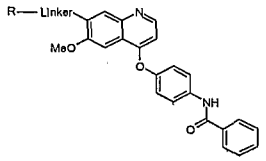
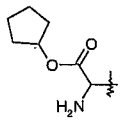
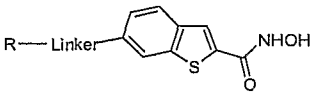
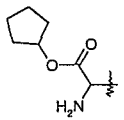
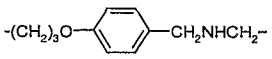
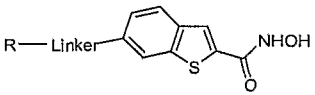
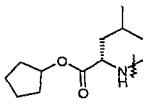
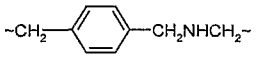
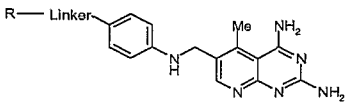
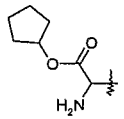
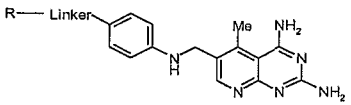
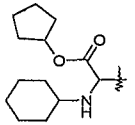
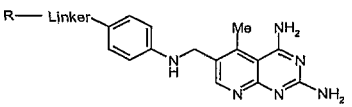
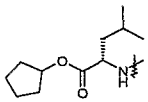
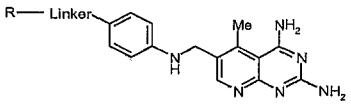
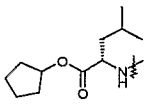
Measurement of ester cleavage

[0430] Hydrolysis of esters to the corresponding carboxylic acids can be measured using the cell extract, prepared as above. To this effect cell extract (~30 μg / total assay volume of 0.5 ml) was incubated at 37°C in a Tris- HCl 25 mM, 125 mM NaCl buffer, pH 7.5 at 25°C. At zero time the ester (substrate) was then added at a final concentration of 2.5 μM and the samples were incubated at 37°C for the appropriate time (usually 0 or 80 min). Reactions were stopped by the addition of 3 x volumes of acetonitrile. For zero time samples the acetonitrile was added prior to the ester compound. After centrifugation at 12000 g for 5 min, samples were analysed for the ester and its corresponding carboxylic acid at room temperature by LCMS (Sciex API 3000, HP1100 binary pump, CTC PAL). Chromatography was based on an AceCN (75x2.1 mm) column and a mobile phase of 5-95 % acetonitrile in water /0.1 % formic acid.

[0431] Rates of hydrolysis are expressed in pg/mL/min.

[0432] Table 1 presents data showing that several amino acid ester motifs, conjugated to various intracellular enzyme inhibitors by several different linker chemistries are all hydrolysed by intracellular carboxyesterases to the corresponding acid.

Table 1

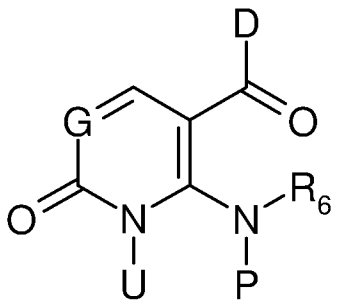
Structure of amino acid ester conjugate	R	Linker	Hydrolysis Rate Range U937Cells (pg/mL/min)	Preparation of amino ester conjugate
		-CH2CH2O-	100-1000	WO2006117552
			1000-50000	WO2006117548
			>50000	WO2006117549
		-CH2CH2O-	>50000	WO2006117567
		-CH2CH2O-	1000-50000	WO2006117567
		-CH2-	1000-50000	WO2006117667
		~CO~	>50000	WO200611756

(continued)

Structure of amino acid ester conjugate	R	Linker	Hydrolysis Rate Range U937Cells (pg/mL/min)	Preparation of amino ester conjugate
			>50000	WO2006117549
			>50000	WO200611754

Claims

1. A compound of formula (I):



(I)

wherein:

G is-CH=
D is an optionally substituted phenyl ring;
$\mathbf{R_6}$ is hydrogen;
P represents hydrogen **and U** represents a radical of formula (IA); or **U** represents hydrogen **and P** represents a radical of formula (IA);

$$-A-(CH_2)_2-X^1-L^1-Y-NH-CHR_1R_2 \qquad (IA)$$

wherein

A represents an optionally substituted phenyl or cyclohexyl ring;
z is or 1;
Y is a bond, -C(=O)-, $-S(=O)_2-$, $-C(=O)NR_3-$, $-C(=S)-NR_3$, $-C(=NH)NR_3$ or $-S(=O)_2NR_3-$ wherein R_3 is hydrogen or optionally substituted C_1-C_6 alkyl;

$\mathbf{L^1}$ is a divalent radical of formula $-(Alk^1)_m(Q)_n(Alk^2)_p-$ wherein

m, n and p are independently 0 or 1,
Q is (i) an optionally substituted divalent mono- or bicyclic carbocyclic or heterocyclic radical having 5 - 13 ring members, or (ii), in the case where both m and p are 0, a divalent radical of formula $-X^2-Q^1-$ or $-Q^1-X^2-$ wherein X^2 is-O-, S- or NR^A- wherein R^A is hydrogen or optionally substituted C_1-C_3 alkyl, and Q^1 is an optionally substituted divalent mono- or bicyclic carbocyclic or heterocyclic radical having 5 - 13 ring members,
$\mathbf{Alk^1}$ and $\mathbf{Alk^2}$ independently represent optionally substituted divalent C_3-C_7 cycloalkyl radicals, or optionally substituted straight or branched, C_1-C_6 alkylene, C_2-C_6 alkenylene ,or C_2-C_6 alkynylene radicals which may optionally contain or terminate in an ether (-O-), thioether (-S-) or amino ($-NR^A-$) link wherein R^A is hydrogen or optionally substituted C_1-C_3 alkyl; and

$\mathbf{X^1}$ represents a bond; -C(=O); or $-S(=O)_2-$; $-NR_4C(=O)-$, $-C(=O)NR_4-$,$-NR_4C(=O)NR_5-$, $-NR_4S(=O)_2-$, or $-S(=O)_2NR_4-$ wherein R_4 and R_5 are independently hydrogen or optionally substituted C_1-C_6 alkyl;
$\mathbf{R_1}$ is an ester group which is hydrolysable by one or more intracellular carboxylesterase enzymes to a carboxylic acid group;
$\mathbf{R_2}$ is the side chain of a natural or non-natural alpha amino acid selected from:

(i) C_1-C_6 alkyl, phenyl, 2,- 3-, or 4-hydroxyphenyl, 2,- 3-, or 4-methoxyphenyl, 2,-3-, or 4-pyridylmethyl, benzyl, phenylethyl, 2-, 3-, or 4-hydroxybenzyl, 2,- 3-, or 4-benzyloxybenzyl, 2,- 3-, or 4- C_1-C_6 alkoxybenzyl, and benzyloxy(C_1-C_6alkyl)-groups;
(ii) the characterising group of a natural α amino acid, in which any functional group may be protected;
(iii) groups $-[Alk]_nR_6$ where Alk is a (C_1-C_6)alkyl or (C_2-C_6)alkenyl group optionally interrupted by one or more -O-, or -S- atoms or $-N(R_7)-$ groups [where R_7 is a hydrogen atom or a (C_1-C_6)alkyl group], n is 0 or 1, and R_6 is an optionally substituted cycloalkyl or cycloalkenyl group;

(iv) a benzyl group substituted in the phenyl ring by a group of formula-OCH_2COR_{15} where R_{15} is hydroxyl, amino, (C_1-C_6)alkoxy, phenyl(C_1-C_6)alkoxy, (C_1-C_6)alkylamino, di((C_1-C_6)alkyl)amino, phenyl(C_1-C_6)alkylamino, the residue of an amino acid or acid halide, ester or amide derivative thereof, said residue being linked via an amide bond, said amino acid being selected from glycine, α or β alanine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan, serine, threonine, cysteine, methionine, asparagine, glutamine, lysine, histidine, arginine, glutamic acid, and aspartic acid;

(v) a heterocyclic(C_1-C_6)alkyl group, either being unsubstituted or mono- or disubstituted in the heterocyclic ring with halo, nitro, carboxy, (C_1-C_6)alkoxy, cyano, (C_1-C_6)alkanoyl, trifluoromethyl (C_1-C_6)alkyl, hydroxy, formyl, amino, (C_1-C_6)alkylamino, di-(C_1-C_6)alkylamino, mercapto, (C_1-C_6)alkylthio, hydroxy(C_1-C_6)alkyl, mercapto(C_1-C_6)alkyl or (C_1-C_6)alkylphenylmethyl; and

(vi) a group -$CR_aR_bR_c$ in which:

each of R_a, R_b and R_c is independently hydrogen, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, phenyl(C_1C_6)alkyl, (C_3-C_8)cycloalkyl; or

R_c is hydrogen and R_a and R_b are independently phenyl or heteroaryl such as pyridyl; or

R_c is hydrogen, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, phenyl(C_1-C_6)alkyl, or (C_3-C_8)cycloalkyl, and R_a and R_b together with the carbon atom to which they are attached form a 3 to 8 membered cycloalkyl or a 5- to 6-membered heterocyclic ring; or

R_a, R_b and R_c together with the carbon atom to which they are attached form a tricyclic ring (for example adamantyl); or

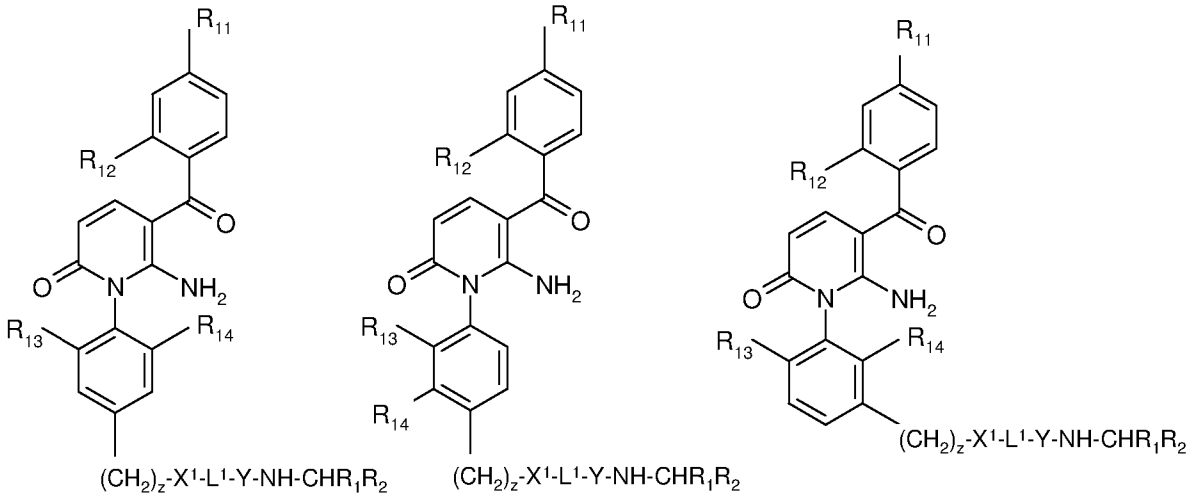
R_a and R_b are each independently (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, phenyl(C_1-C_6)alkyl, or a group as defined for R_c below other than hydrogen, or R_a and R_b together with the carbon atom to which they are attached form a cycloalkyl or heterocyclic ring, and R_c is hydrogen, -OH, -SH, halogen, -CN,-CO_2H, (C_1-C_4)perfluoroalkyl, -CH_2OH -CO_2(C_1-C_6)alkyl, -O(C_1-C_6)alkyl,-O(C_2-C_6)alkenyl, -S(C_1-C_6)alkyl, -SO(C_1-C_6)alkyl, -SO_2(C_1-C_6) alkyl, -S(C_2-C_6)alkenyl, -SO(C_2-C_6)alkenyl, -SO_2(C_2-C_6)alkenyl or a group -Q^2-W wherein Q^2 represents a bond or -O-, -S-, -SO- or -SO_2- and W represents a phenyl, phenylalkyl, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkylalkyl, (C_4-C_8)cycloalkenyl, (C_4-C_8)cycloalkenylalkyl, heteroaryl or heteroarylalkyl group, which group W may optionally be substituted by one or more substituents independently selected from, hydroxyl, halogen, -CN, -CO_2H -CO_2(C_1-C_2)alkyl, -$CONH_2$, -CONH(C_1-C_6)alkyl, -CONH(C_1-C_6alkyl)$_2$, -CHO, -CH_2OH (C_1-C_4)perfluoroalkyl, -O(C_1-C_6)alkyl, -S(C_1-C_6)alkyl, -SO(C_1-C_6)alkyl, -SO_2(C_1-C_6)alkyl, -NO_2, -NH_2,-NH(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, -NHCO(C_1-C_6)alkyl, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_8)cycloalkyl, (C_4-C_8)cycloalkenyl, phenyl or benzyl; and

unless otherwise specified in the context in which it occurs, the term "substituted" as applied to any moiety herein means substituted with up to four compatible substituents, each of which independently selected from (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxy, hydroxy(C_1-C_6)alkyl, mercapto, mercapto(C_1-C_6)alkyl, (C_1-C_6)alkylthio, phenyl, halo including fluoro, bromo and chloro, trifluoromethyl, trifluoromethoxy, nitro, nitrile (-CN), oxo, -COOH, -$COOR^A$, -COR^A, -SO_2R^A, -$CONH_2$, -SO_2NH_2,-$CONHR^A$, -SO_2NHR^A, -$CONR^AR^B$, -$SO_2NR^AR^B$, -NH_2, -NHR^A, -NR^AR^B, -$OCONH_2$,-$OCONHR^A$, -$OCONR^AR^B$, -$NHCOR^A$, -$NHCOOR^A$, -NR^BCOOR^A, -$NHSO_2OR^A$,-NR^BSO_2OH, -$NR^BSO_2OR^A$, -$NHCONH_2$, -NR^ACONH_2,-$NHCONHR^B$,-NR^ACONHR^B,-$NHCONR^AR^B$, or -$NR^ACONR^AR^B$ wherein R^A and R^B are independently a (C_1-C_6)alkyl, (C_3-C_6) cycloalkyl , phenyl or monocyclic heteroaryl having 5 or 6 ring atoms.

2. A compound as claimed in claim 1 wherein P is hydrogen and U is a radical of formula (IA) as defined in claim 1.

3. A compound as claimed in any of the preceding claims wherein A is optionally substituted 1,4 phenylene.

4. A compound as claimed in claim 1 which has formula (IIA), (IIB) and (IIC):



(IIA) (IIB) (IIC)

wherein R_{11} = F, R_{12} = H, R_{13} = H and R_{14} = H; or
R_{11} = F, R_{12} = F, R_{13} = H and R_{14} = H; or
R_{11} = F, R_{12} = H, R_{13} = F and R_{14} = F; or
R_{11} = F, R_{12} = F, R_{13} = F and R_{14} = F; or
R_{11} = F, R_{12} 2 = F, R_{13} = F and R_{14} = H
and wherein z, X^1, L^1, Y, R^1 and R^2 are as defined in claim 1

5. A compound as claimed in any of claims 1 to 4 wherein the radical -Y-L^1-X^1-$[CH_2]_z$-, is -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2$-, -CH_2O-, -CH_2CH_2O-, -$CH_2CH_2CH_2O$-, -$CH_2CH_2CH_2CH_2O$-, -C(=O)-CH_2-, -C(=O)-CH_2O-, -C(=O)-NH-CH_2-, or -C(=O)-NH-CH_2O-.

6. A compound as claimed in any of the preceding claims wherein R_1 is an ester group of formula -(C=O)OR_{14} wherein R_{14} is $R_8R_9R_{10}C$- wherein

(i) R_8 is hydrogen or optionally substituted (C_1-C_3)alkyl-(Z^1),-[(C_1-C_3)alkyl]$_b$- or (C_2-C_3)alkenyl-(Z^1)$_a$-[(C_1-C_3)alkyl]$_b$- wherein a and b are independently 0 or 1 and Z^1 is -O-, -S-, or -NR_{11}- wherein R_{11} is hydrogen or (C_1-C_3)alkyl; and R_9 and R_{10} are independently hydrogen or (C_1-C_3)alkyl-;
(ii) R_8 is hydrogen or optionally substituted $R_{12}R_{13}$N-(C_1-C_3)alkyl- wherein R_{12} is hydrogen or (C_1-C_3)alkyl and R_{13} is hydrogen or (C_1-C_3)alkyl; or R_{12} and R_{13} together with the nitrogen to which they are attached form an optionally substituted monocyclic heterocyclic ring of 5- or 6- ring atoms or bicyclic heterocyclic ring system of 8 to 10 ring atoms, and R_9 and R_{10} are independently hydrogen or (C_1-C_3)alkyl-;or
(iii) R_8 and R_9 taken together with the carbon to which they are attached form an optionally substituted monocyclic carbocyclic ring of from 3 to 7 ring atoms or bicyclic carbocyclic ring system of 8 to 10 ring atoms, and R_{10} is hydrogen.

7. A compound as claimed in claim 6 wherein wherein R_{14} is methyl, ethyl, n- or iso-propyl, n-, sec- or tert-butyl, cyclohexyl, allyl, phenyl, benzyl, 2-, 3- or 4-pyridylmethyl, N-methylpiperidin-4-yl, tetrahydrofuran-3-yl or methoxyethyl.

8. A compound as claimed in any of the preceding claims wherein R_2 is phenyl, benzyl, iso-butyl, cyclohexyl or t-butoxymethyl.

9. A compound as claimed in any of claims 1 to 5 wherein R_1 is an ester group of formula -(C=O)OR_{14} wherein R_{14} is cyclopentyl, and R_2 is phenyl, benzyl, iso-butyl, cyclohexyl or t-butoxymethyl.

10. A compound as claimed in claim 1 selected from the group consisting of

Cyclopentyl (S)-(3-{4-[6-Amino-5-(2,4-difluoro benzoyl)-2-oxo-2H-pyridin-1-yl]-3,5-difluorophenoxy}propylami-

no)phenyl acetate
Cyclopentyl (S)-2-(3-{4-[6-Amino-5-(2,4-difluoro benzoyl)-2-oxo-2H-pyridin-1-yl]-3,5-difluorophenoxy}propylamino)-4-methyl pentanoate
Example 42 Cyclopentyl (2*R*)-[(3-{4-[6-amino-5-(2,4-difluorobenzoyl)-2-oxopyridin-1(2*H*)-yl]-3,5-difluorophenoxy}propyl)amino](phenyl)acetate
2-Morpholin-4-ylethyl *N*-(3-{4-[6-amino-5-(2,4-difluorobenzoyl)-2-oxopyridin-1-(2*H*)-yl]-3,5-difluorophenoxy}propyl)-L-leucinate
2-(Dimethylamino)ethyl *N*-(3-{4-[6-amino-5-(2,4-difluorobenzoyl)-2-oxopyridin-1-(2*H*)-yl]-3,5-difluorophenoxy}propyl)-L-leucinate
Cyclopentyl *N*-[2-(4-{6-amino-5-[(4-fluorophenyl)carbonyl]-2-oxopyridin-1(2*H*)-yl}phenyl)ethyl]-L-leucinate
Cyclopentyl *N*-(5-{4-[6-amino-5-(2,4-difluorobenzoyl)-2-oxopyridin-1(2*H*)-yl]-3,5-difluorophenoxy}pentyl)-L-leucinate
Cyclopentyl *N*-[3-(4-{6-amino-5-[(4-fluorophenyl)carbonyl]-2-oxopyridin-1(2*H*)-yl}phenyl)propyl]-L-leucinate
Cyclopentyl (2*S*)-4-amino-2-[(3-{4-[6-amino-5-(2,4-difluorobenzoyl)-2-oxopyridin-1(2*H*-yl]-3,5-difluorophenoxy}propyl)amino]butanoate
Cyclopentyl *N*-(5-{4-[6-amino-5-(4-fluorobenzoyl)-2-oxopyridin-1(2*H*)-yl]-3,5-difluorophenoxy}pentyl)-L-leucinate
Cyclopentyl *N*-[2-(4-{6-amino-5-[(2,4-difluorophenyl)carbonyl]-2-oxopyridin-1(2*H*)-yl}phenyl)ethyl]-L-leucinate
tert-Butyl *N*-[2-(4-{6-amino-5-[(2,4-difluorophenyl)carbonyl]-2-oxopyridin-1(2*H*)-yl}phenyl)ethyl]-L-leucinate
Cyclopentyl (2*S*)-{[2-(4-{6-amino-5-[(4-fluorophenyl)carbonyl]-2-oxopyridin-1(2*H*)-yl}phenyl)ethyl]amino}(phenyl) ethanoate
Cyclopentyl *N*-[2-(4-{6-amino-5-[(4-methylphenyl)carbonyl]-2-oxopyridin-1(2*H*)-yl}phenyl)ethyl]-L-leucinate
Cyclopentyl *N*-[2-(4-{6-amino-5-[(4-chlorophenyl)carbonyl]-2-oxopyridin-1(2*H*)-yl}phenyl)ethyl]-L-leucinate.

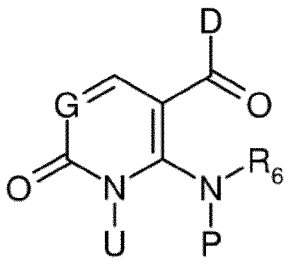
11. A compound as claimed in any of the preceding claims which is in the form of a pharmaceutically acceptable salt.

12. A pharmaceutical composition comprising a compound as claimed in any of the preceding claims, together with a pharmaceutically acceptable carrier.

13. A compound as claimed in any of claims 1 to 10 for the treatment of autoimmune or inflammatory disease.

Patentansprüche

1. Verbindung der Formel (I):



(I)

wobei:

G -CH= ist
D ein optional substituierter Phenylring ist;
$\mathbf{R_6}$ Wasserstoff ist;
P Wasserstoff darstellt **und U** eine Radikale der Formel (IA) darstellt; oder **U** Wasserstoff darstellt **und P** eine Radikale der Formel (IA) darstellt;

$$-A-(CH_2)_Z-X^1-L^1-Y-NH-CHR_1R_2 \qquad (IA)$$

wobei

A einen optional substituierten Phenyl- oder Cyclohexylring darstellt;
z 0 oder 1 ist;
Y eine Bindung, -C(=O)-, -$S(=O)_2$-, -C(=O)NR_3-, -C(=S)-NR_3, -C(=NH)NR_3 oder-$S(=O)_2NR_3$- ist, wobei R_3 Wasserstoff oder optional substituiertes C_1-C_6-Alkyl ist;
$\mathbf{L^1}$ eine zweiwertige Radikale der Formel -$(Alk^1)_m(Q)_n(Alk^2)_p$- ist, wobei

m, **n** und **p** unabhängig voneinander 0 oder 1 sind,
Q (i) eine optional substituierte zweiwertige mono- oder bizyklische carbozyklische oder heterozyklische Radikale mit 5 bis 13 Ringelementen ist, oder (ii) im Fall, in dem m und p 0 sind, eine zweiwertige Radikale der Formel -X^2-Q^1- oder -Q^1-X^2- ist, wobei X^2 -O-, S- oder NR^A- ist, wobei R^A Wasserstoff oder optional substituiertes C_1-C_3-Alkyl ist und Q^1 eine optional substituierte zweiwertige mono- oder bizyklische carbozyklische oder heterozyklische Radikale mit 5 bis 13 Ringelementen ist,
$\mathbf{Alk^1}$ und $\mathbf{Alk^2}$ unabhängig voneinander optional substituierte zweiwertige C_3-C_7-Cycloalkylradikale darstellen oder optional substituierte gerade oder verzweigte C_1-C_6-Alkylen-, C_2-C_6-Alkenylen- oder C_2-C_6-Alkynylenradikale, die optional eine Ether- (-O-), Thioether- (-S-) oder Amino- (-NR^A-) -Verbindung enthalten können oder darin enden können, wobei R^A Wasserstoff oder optional substituiertes C_1-C_3-Alkyl ist; und

$\mathbf{X^1}$ eine Bindung; -C(=O); oder -$S(=O)_2$-; -NR_4C(=O)-, -C(=O)NR_4-, -NR_4C(=O)NR_5-, -$NR_4S(=O)_2$- oder -$S(=O)_2NR_4$- darstellt, wobei R_4 und R_5 unabhängig voneinander Wasserstoff oder optional substituiertes C_1-C_6-Alkyl sind;
$\mathbf{R_1}$ eine Estergruppe ist, die durch ein oder mehrere intrazelluläre Carboxylesterase-Enzyme in eine Carbonsäuregruppe hydrolisiert werden kann;
$\mathbf{R_2}$ die Seitenkette einer natürlichen oder nicht natürlichen Alpha-Aminosäure ist, die ausgewählt ist aus:

(i) C_1-C_6-Alkyl-, Phenyl, 2,- 3-, oder 4-Hydroxyphenyl-, 2,- 3-, oder 4-Methoxyphenyl-, 2-, - 3-, oder 4-Pyridylmethyl-, Benzyl-, Phenylethyl-, 2-, 3-, oder 4-Hydroxybenzyl-, 2,- 3-, oder 4- Benzyloxybenzyl-, 2,- 3-, oder 4-C_1-C_6-Alkoxybenzyl- und Benzyloxy(C_1-C_6-Alkyl)-Gruppen;
(ii) der kennzeichnenden Gruppe einer natürlichen α-Aminosäure, in der eine jegliche funktionelle Gruppe geschützt sein kann;
(iii) den Gruppen -$[Alk]_nR_6$, wobei Alk eine (C_1-C_6)-Alkyl- oder (C_2-C_6)-Alkenylgruppe ist, die optional von einem oder mehreren -O-, oder -S-Atomen oder -$N(R_7)$-Gruppen unterbrochen wird [wobei R_7 ein Wasserstoffatom oder eine (C_1-C_6)-Alkylgruppe ist], n 0 oder 1 ist und R_6 eine optional substituierte Cycloalkyl- oder Cycloalkenylgruppe ist;
(iv) einer Benzylgruppe, substituiert im Phenylring durch eine Gruppe der Formel-OCH_2COR_{15}, wobei R_{15} Hydroxyl, Amino, (C_1-C_6)-Alkoxy, Phenyl(C_1-C_6)alkoxy, (C_1-C_6)-Alkylamino, di((C_1-C_6)-alkyl)amino, Phenyl(C_1-C_6)alkylamino, der Rest eines Aminosäureoder Säurehalogenid-, Ester- oder Amidderivats davon ist, wobei der Rest über eine Amidbindung verbunden ist, wobei die Aminosäure ausgewählt ist aus Glycin, α- oder β-Alanin, Valin, Leucin, Isoleucin, Phenylalanin, Tyrosin, Tryptophan, Serin, Threonin, Cystein, Methionin, Asparagin, Glutamin, Lysin, Histidin, Arginin, Glutaminsäure und Asparaginsäure;
(v) einer heterozyklischen (C_1-C_6)-Alkylgruppe, entweder nicht substituiert oder im heterozyklischen Ring mit Halogen, Nitro, Carboxy, (C_1-C_6)-Alkoxy, Cyano, (C_1-C_6)-Alkanoyl, Trifluormethyl(C_1-C_6)alkyl, Hydroxy, Formyl, Amino, (C_1-C_6)-Alkylamino, di-(C_1-C_6)-Alkylamino, Mercapto, (C_1-C_6)-Alkylthio, Hydroxy(C_1-C_6)alkyl, Mercapto(C_1-C_6)alkyl oder (C_1-C_6)-Alkylphenylmethyl mono- oder di-substituiert; und
(vi) einer Gruppe -$CR_aR_bR_c$, in der:

jedes von R_a, R_b und R_c unabhängig Wasserstoff, (C_1-C_6)-Alkyl, (C_2-C_6)-Alkenyl, (C_2-C_6)-Alkynyl, Phenyl(C_1-C_6)alkyl, (C_3-C_8)-Cycloalkyl ist; oder

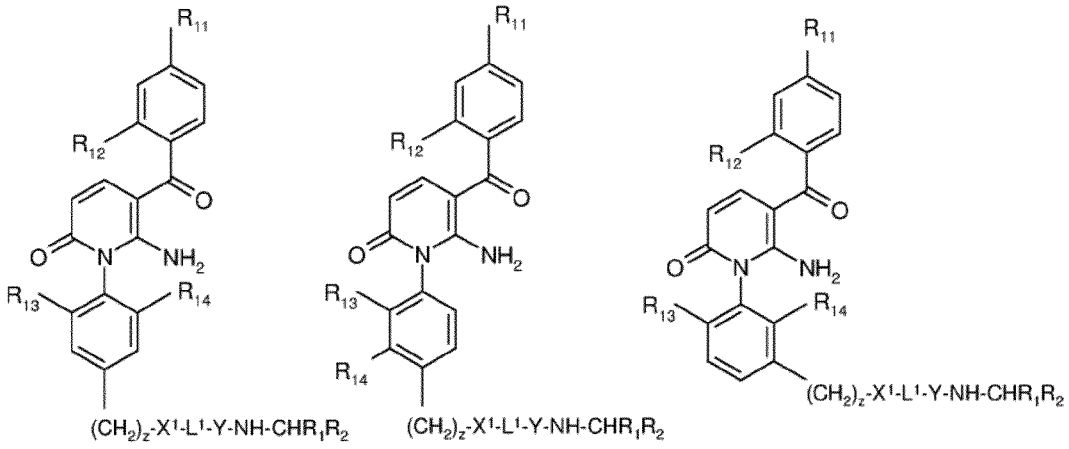
R_c Wasserstoff ist und R_a und R_b unabhängig voneinander Phenyl oder Heteroaryl sind, wie z. B. Pyridyl; oder
R_c Wasserstoff, (C_1-C_6)-Alkyl, (C_2-C_6)-Alkenyl, (C_2-C_6)-Alkynyl, Phenyl(C_1-C_6)alkyl oder (C_3-C_8)-Cycloalkyl ist, und R_a und R_b zusammen mit dem Kohlenstoffatom, an das sie gebunden sind, einen 3- bis 8-gliedrigen Cycloalkyl- oder einen 5- bis 6-gliedrigen heterozyklischen Ring bilden; oder
R_a, R_b und R_c zusammen mit dem Kohlenstoffatom, an das sie gebunden sind, einen trizyklischen Ring (z. B. Adamantyl) bilden; oder
R_a und R_b jeweils unabhängig voneinander (C_1-C_6)-Alkyl, (C_2-C_6)-Alkenyl, (C_2-C_6)-Alkynyl, Phenyl(C_1-C_6)alkyl

oder eine nachfolgend für R_c definierte Gruppe außer Wasserstoff sind, oder wobei R_a und R_b zusammen mit dem Kohlenstoffatom, an das sie gebunden sind, einen Cycloalkyl- oder heterozyklischen Ring bilden, und R_c Wasserstoff, -OH, -SH, Halogen,-CN, - CO_2H, (C_1-C_4)-Perfluoralkyl, -CH_2OH, -CO_2(C_1-C_6)-Alkyl, -O(C_1-C_6)-Alkyl, -O(C_2-C_6)-Alkenyl, -S(C_1-C_6)-Alkyl, -SO(C_1-C_6)-Alkyl, -SO_2(C_1-C_6)-Alkyl, -S(C_2-C_6)-Alkenyl,-SO(C_2-C_6)-Alkenyl, -SO_2(C_2-C_6)-Aalkenyl oder eine Gruppe -Q^2-W ist, wobei Q^2 eine Bindung oder -O-, -S-, -SO- oder -SO_2- und W eine Phenyl-, Phenylalkyl, (C_3-C_8)-Cycloalkyl-, (C_3-C_8)-Cycloalkylalkyl-, (C_4-C_8)-Cycloalkenyl-, (C_4-C_8)-Cycloalkenylalkyl-, Heteroaryl- oder Heteroarylalkylgruppe darstellt, wobei die Gruppe W optional von einem oder mehreren Substituenten substituiert sein kann, die unabhängig voneinander ausgewählt sind aus Hydroxyl, Halogen, -CN, -CO_2H, -CO_2(C_1-C_6)-Alkyl, -$CONH_2$, -CONH(C_1-C_6)-Alkyl, -CONH(C_1-C_6-Alkyl)$_2$, -CHO, -CH_2OH, (C_1-C_4)-Perfluoralkyl, -O(C_1-C_6)-Alkyl,-S(C_1-C_6)-Alkyl, -SO(C_1-C_6)-Alkyl, -SO2(C_1-C_6)-Alkyl, -NO_2, -NH_2, -NH(C_1-C_6)-Alkyl,-N((C_1-C_6)-Alkyl)$_2$, -NHCO(C_1-C_6)-Alkyl, (C_1-C_6)-Alkyl, (C_2-C_6)-Alkenyl, (C_2-C_6)-Alkynyl, (C_3-C_8)-Cycloalkyl, (C_4-C_8)-Cycloalkenyl, Phenyl oder Benzyl; und
sofern nicht anders im Zusammenhang angegeben, bedeutet der Begriff "substituiert", wie auf eine jegliche Einheit hier angewandt, substituiert mit bis zu vier passenden Substituenten, jeweils unabhängig voneinander ausgewählt aus (C_1-C_6)-Alkyl, (C_1-C_6)-Alkoxy, Hydroxy, Hydroxy(C_1-C_6)alkyl, Mercapto, Mercapto(C_1-C_6)alkyl, (C_1-C_6)-Alkylthio, Phenyl, Halogen, einschließlich Fluor, Brom und Chlor, Trifluormethyl, Trifluormethoxy, Nitro, Nitril (-CN), Oxo, -COOH, -$COOR^A$, -COR^A, -SO_2R^A, -$CONH_2$, -SO_2NH_2, - $CONHR^A$, -SO_2NHR^A,-$CONR^AR^B$, -$SO_2NR^AR^B$, -NH_2, -NHR^A, -NR^AR^B, -OCONNH$_2$, -$OCONHR^A$, -$OCONR^AR^B$,-$NHCOR^A$, -$NHCOOR^A$, -NR^B-$COOR^A$, -$NHSO_2OR^A$, -NR^BSO_2OH, -$NR^BSO_aOR^A$,-$NHCONH_2$, -NR^ACONH_2, -$NHCONHR^B$, -NR^ACONHR^B, - $NHCONR^AR^B$ oder-$NR^ACONR^AR^B$, wobei Rand R^B unabhängig voneinander ein (C_1-C_6)-Alkyl, (C_3-C_6)-Cycloalkyl, Phenyl oder monozyklisches Heteroaryl mit 5 oder 6 Ringatomen sind.

2. Verbindung nach Anspruch 1, wobei P Wasserstoff und U eine Radikale der Formel (IA), wie definiert in Anspruch 1, ist.

3. Verbindung nach einem der vorstehenden Ansprüche, wobei A optional substituiertes 1,4-Phenylen ist.

4. Verbindung nach Anspruch 1, die die Formel (IIA), (IIB) und (IIC) aufweist:



(IIA) (IIB) (IIC)

wobei R_{11} = F, R_{12} = H, R_{13} = H und R_{14} = H; oder
R_{11} = F, R_{12} = F, R_{13} = H und R_{14} = H; oder
R_{11} = F, R_{12} = H, R_{13} = F und R_{14} = F; oder
R_{11} = F, R_{12} = F, R_{13} = F und R_{14} = F; oder
R_{11} = F, R_{12} = F, R_{13} = F und R_{14} = H
und wobei z, X^1, L^1, Y, R^1 und R^2 wie in Anspruch 1 definiert sind.

5. Verbindung nach einem der Ansprüche 1 bis 4, wobei die Radikale -Y-L^1-X^1-[CH_2]$_z$-Folgendes ist: -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$, -$CH_2CH_2CH_2CH_2$, -CH_2O-, -CH_2CH_2O-,-$CH_2CH_2CH_2O$-, -$CH_2CH_2CH_2CH_2O$-, -C(=O)-CH_2-, -C(=O)-CH_2O-, -C(=O)-NH-CH_2 oder-C(=O)-NH-CH_2O-.

6. Verbindung nach einem der vorstehenden Ansprüche, wobei R_1 eine Estergruppe der Formel -C(=O)OR_{14} ist, wobei R_{14} $R_8R_9R_{10}C$- ist, wobei

(i) R_8 Wasserstoff oder optional substituiertes (C_1-C_3)-Alkyl-(Z^1)$_a$-[(C_1-C_3)-alkyl]$_b$- oder (C_2-C_3)-Alkenyl-(Z^1)$_a$-[(C_1-C_3)-alkyl]$_b$- ist, wobei a und b unabhängig voneinander 0 oder 1 sind und Z^1 -O-, -S- oder -NR_{11} ist, wobei R_{11} Wasserstoff oder (C_1-C_3)-Alkyl ist; und R_9 und R_{10} unabhängig voneinander Wasserstoff oder (C_1-C_3)-Alkyl sind;
(ii) R_8 Wasserstoff oder optional substituiertes $R_{12}R_{13}$N-(C_1-C_3)-Alkyl- ist, wobei R_{12} Wasserstoff oder (C_1-C_3)-Alkyl ist und R_{13} Wasserstoff oder (C_1-C_3)-Alkyl ist; oder R_{12} und R_{13} zusammen mit dem Stickstoff, an den sie gebunden sind, einen optional substituierten monozyklischen heterozyklischen Ring aus 5 oder 6 Ringatomen oder ein bizyklisches heterozyklisches Ringsystem aus 8 bis 10 Ringatomen bilden, und R_9 und R_{10} unabhängig voneinander Wasserstoff oder (C_1-C_3)-Alkyl sind; oder
(iii) R_8 und R_9 zusammen mit dem Kohlenstoff, an den sie gebunden sind, einen optional substituierten monozyklischen carbozyklischen Ring aus 3 bis 7 Ringatomen oder ein bizyklisches carbozyklisches Ringsystem aus 8 bis 10 Ringatomen bilden und R_{10} Wasserstoff ist.

7. Verbindung nach Anspruch 6, wobei R_{14} Methyl, Ethyl, n- oder iso-Propyl, n-, sec-oder tert-Butyl, Cyclohexyl, Allyl, Phenyl, Benzyl, 2-, 3- oder 4-Pyridylmethyl, N-Methylpiperididn-4-yl, Tetrahydrofuran-3-yl oder Metoxyethyl ist.

8. Verbindung nach einem der vorstehenden Ansprüche, wobei R_2 Phenyl, Benzyl, iso-Butyl, Cyclohexyl oder t-Butoxymethyl ist.

9. Verbindung nach einem der Ansprüche 1 bis 5, wobei R_1 eine Estergruppe der Formel -(C=O)OR_{14} ist, wobei R_{14} Cyclopentyl ist und R_2 Phenyl, Benzyl, iso-Butyl, Cyclohexyl oder t-Butoxymethyl ist.

10. Verbindung nach Anspruch 1, ausgewählt aus der Gruppe bestehend aus:

Cyclopentyl (S)-(3-{4-[6-Amino-5-(2,4-difluor-benzoyl)-2-oxo-2H-pyridin-1-yl]-3,5-difluorphenoxy}propylamino)phenyl-acetat
Cyclopentyl (S)-2-(3-{4-[6-Amino-5-(2,4-difluor-benzoyl)-2-oxo-2H-pyridin-1-yl]-3,5-difluorphenoxy}propylamino)-4-methyl-pentanoat Beispiel 42 Cyclopentyl (2R)-[(3-{4-[6-amino-5-(2,4-difluorbenzoyl)-2-oxopyridin-1(2*H*)-y1]-3,5-difluorphenoxy}propyl)amino](phenyl)acetat
2-Morpholin-4-ylethyl-*N*-(3-{4-[6-amino-5-(2,4-difluorbenzoyl)-2-oxopyridin-1(2*H*)-yl]-3,5-difluorphenoxy}propyl)-L-leucinat 2-(Dimethylamino)ethyl *N*-(3-{4-[6-amino-5-(2,4-difluorbenzoyl)-2-oxopyridin-1(2*H*)-yl]-3,5-difluorphenoxy}propyl)-L-leucinat
Cyclopentyl *N*-[2-(4-{6-amino-5-[(4-fluorphenyl)carbonyl]-2-oxopyridin-1(2*H*)-yl}phenyl)ethyl]-L-leucinate
Cyclopentyl *N*-(5-{4-[6-amino-5-(2,4-difluorbenzoyl)-2-oxopyridin-1(2*H*)-yl]-3,5-difluorphenoxy}pentyl)-L-leucinate
Cyclopentyl N-[3-(4-{6-amino-5-[(4-fluorphenyl)carbonyl]-2-oxopyridin-1(2*H*)-yl}phenyl)propyl]-L-leucinat
Cyclopentyl (2S)-4-amino-2-[(3-{4-[6-amino-5-(2,4-difluorbenzoyl)-2-oxopyridin-1(2*H*)-yl]-3,5-difluorphenoxy}propyl)amino]butanoat
Cyclopentyl *N*-(5-{4-[6-amino-5-(4-fluorbenzoyl)-2-oxopyridin-1(2*H*)-yl]-3,5-difluorphenoxy}pentyl)-L-leucinat
Cyclopentyl *N*-[2-(4-{6-amino-5-[(2,4-difluorphenyl)carbonyl]-2-oxopyridin-1(2*H*)-yl}phenyl)ethyl]-L-leucinate
tert-Butyl *N*-[2-(4-{6-amino-5-[(2,4-difluorphenyl)carbonyl]-2-oxopyridin-1(2*H*)-yl}phenyl)ethyl]-L-leucinat
Cyclopentyl (2*S*)-{[2-(4-{6-amino-5-[(4-fluorphenyl)carbonyl]-2-oxopyridin-1(2*H*)-yl}phenyl)ethyl]amino}(phenyl)-ethanoat
Cyclopentyl *N*-[2-(4-{6-amino-5-[(4-methylphenyl)carbonyl]-2-oxopyridin-1(2*H*)-yl}phenyl)ethyl]-L-leucinate
Cyclopentyl *N*-[2-(4-{6-amino-5-[(4-chlorphenyl)carbonyl]-2-oxopyridin-1(2*H*)-yl}phenyl)ethyl]-L-leucinat.

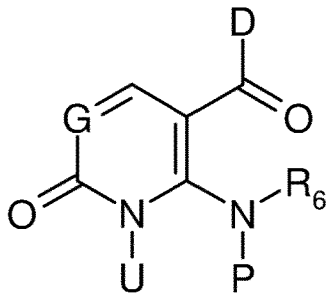
11. Verbindung nach einem der vorstehenden Ansprüche, die in der Form eines pharmazeutisch akzeptablen Salzes vorliegt.

12. Pharmazeutische Zusammensetzung, umfassend eine Verbindung nach einem der vorstehenden Ansprüche, zusammen mit einer pharmazeutisch akzeptablen Trägersubstanz.

13. Verbindung nach einem der Ansprüche 1 bis 10 für die Behandlung von Autoimmun- oder Entzündungskrankheiten.

Revendications

1. Composé de formule (I)



(I)

dans laquelle :

G est -CH=
D est un cycle phényle éventuellement substitué ;
$\mathbf{R_6}$ est un atome d'hydrogène ;
P représente un atome d'hydrogène **et U** représente un radical de formule (IA) ; ou **U** représente un atome d'hydrogène **et P** représente un radical de formule (IA) ;

$$-A-(CH_2)_2-X^1-L^1-Y-NH-CHR_1R_2 \qquad (IA)$$

dans laquelle

A représente un cycle phényle ou cyclohexyle éventuellement substitué ;
z vaut 0 ou 1 ;
Y est une liaison, -C(=O)-, $-S(=O)_2-$, $-C(=O)NR_3-$, $-C(=S)-NR_3$, $-C(=NH)NR_3$ ou $-S(=O)_2NR_3$-dans laquelle R_3 est un atome d'hydrogène ou un groupe alkyle en C_1 à C_6 éventuellement substitué ;
$\mathbf{L^1}$ est un radical divalent de formule $-(Alk^1)_m(Q)n(Alk^2)_p-$, où

m, n et **p** valent indépendamment 0 ou 1,
Q est (i) un radical carbocyclique ou hétérocyclique monocyclique ou bicyclique divalent éventuellement substitué ayant 5 à 13 éléments, ou (ii) dans le cas où m et p valent tous deux 0, un radical divalent de formule $-X^2-Q^1-$ ou $-Q^1-X^2-$ où X^2 est -O-, S- ou NR^A-, où R^A est un atome d'hydrogène ou un groupe alkyle en C_1 à C_3 éventuellement substitué, et Q^1 est un radical carbocyclique ou hétérocyclique monocyclique ou bicyclique divalent éventuellement substitué ayant 5 à 13 éléments,
$\mathbf{Alk^1}$ et $\mathbf{Alk^2}$ représentent indépendamment des radicaux cycloalkyle en C_3 à C_7 divalents éventuellement substitués ou des radicaux alkylène en C_1 à C_6, alcénylène en C_2 à C_6 ou alcynylène en C_2 à C_6 linéaires ou ramifiés éventuellement substitués qui peuvent éventuellement contenir ou se terminer sous la forme d'une liaison éther (-O-), thioéther (-S-) ou amino ($-NR^A-$), où R^A est un atome d'hydrogène ou un groupe alkyle en C_1 à C_3 éventuellement substitué ; et

$\mathbf{X^1}$ représente une liaison ; -C(=O) ; ou $-S(=O)_2-$; $-NR_4C(=O)-$, $-C(=O)NR_4-$, $-NR_4C(=O)NR_5-$,

$-NR_4S(=O)_2-$ ou $-S(=O)_2NR_4-$, où R_4 et R_5 sont indépendamment un atome d'hydrogène ou un groupe alkyle en C_1 à C_6 éventuellement substitué ;

$\mathbf{R_1}$ est un groupe ester qui peut être hydrolysé par au moins une enzyme carboxylestérase intracellulaire en un groupe acide carboxylique ;
$\mathbf{R_2}$ est la chaîne latérale d'un acide alpha-aminé naturel ou non naturel choisi parmi :

(i) les groupes alkyle en C_1 à C_6, phényle, 2-, 3- ou 4-hydroxyphényle, 2-, 3- ou 4-méthoxyphényle, 2-, 3- ou 4-pyridylméthyle, benzyle, phényléthyle, 2-, 3- ou 4-hydroxybenzyle, 2-, 3- ou 4-benzyloxybenzyle, 2-, 3- ou 4-alcoxybenzyle en C_1 à C_6 et benzyloxy(alkyle en C_1 à C_6)- ;
(ii) le groupe caractérisant d'un acide aminé naturel, dans lequel tout groupe fonctionnel peut être

protégé ;
(iii) les groupes -[Alk]$_n$R$_6$ où Alk est un groupe alkyle (en C_1 à C_6) ou alcényle (en C_2 à C_6) éventuellement interrompu par au moins atome de -O- ou -S- ou les groupes -N(R_7)- [où R_7 est un atome d'hydrogène ou un groupe alkyle(en C_1 à C_6)], n vaut 0 ou 1 et R_6 est un groupe cycloalkyle ou cycloalcényle éventuellement substitué ;
(iv) un groupe benzyle substitué dans le cycle phényle par un groupe de formule -OCH_2COR_{15} où R_{15} est un groupe hydroxyle, amino, alcoxy(en C_1 à C_6), phényl-alcoxy(en C_1 à C_6), alkylamino(en C_1 à C_6), di(alkyl(en C_1 à C_6))amino, phényl-alkylamino(en C_1 à C_6), le résidu d'un acide aminé ou un dérivé halogénure, ester ou amide d'acide de celui-ci, ledit résidu étant lié via une liaison amide, ledit acide aminé étant choisi parmi la glycine, l'α ou β-alanine, la valine, la leucine, l'isoleucine, la phénylalanine, la tyrosine, le tryptophane, la sérine, la thréonine, la cystéine, la méthionine, l'asparagine, la glutamine, la lysine, l'histidine, l'arginine, l'acide glutamique et l'acide aspartique ;
(v) un groupe hétérocyclique-alkyle(en C_1 à C_6), soit non substitué soit mono- ou di-substitué dans de cycle hétérocyclique par un groupe halogéno, nitro, carboxy, alcoxy(en C_1 à C_6), cyano, alcanoyle(en C_1 à C_6), trifluorométhyl-alkyle(en C_1 à C_6), hydroxy, formyle, amino, alkylamino(en C_1 à C_6), di-alkylamino(en C_1 à C_6), mercapto, alkylthio(en C_1 à C_6), hydroxy-alkyle(en C_1 à C_6), mercapto-alkyle(en C_1 à C_6) ou alkylphénylméthyle(en C_1 à C_6) ; et
(vi) un groupe -$CR_aR_bR_c$ dans lequel :

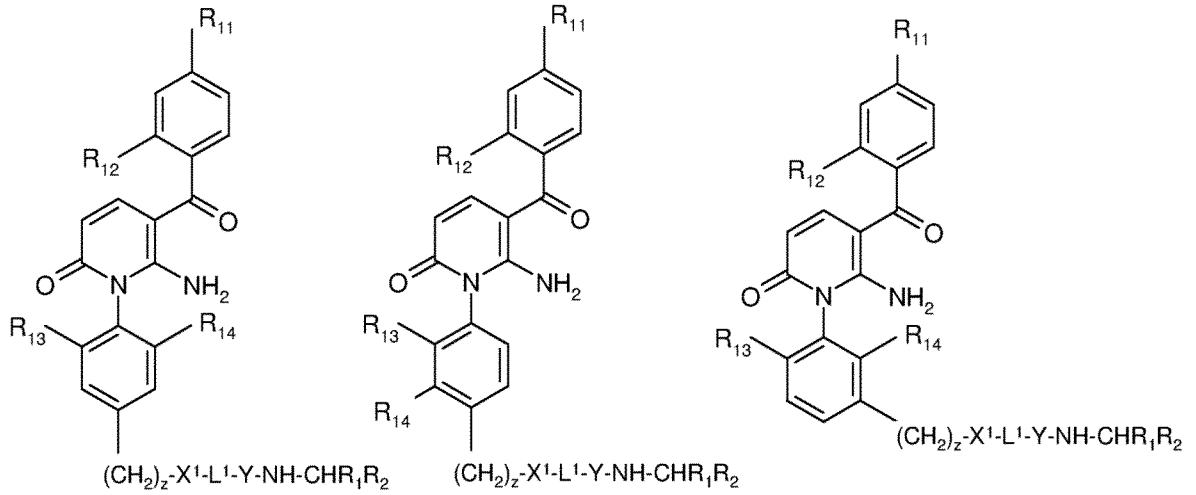
chacun de R_a, R_b et R_c est indépendamment un atome d'hydrogène, un groupe alkyle(en C_1 à C_6), alcényle(en C_2 à C_6), alcynyle(en C_2 à C_6), phényl-alkyle(en C_1 à C_6), cycloalkyle(en C_3 à C_8) ; ou
R_c est un atome d'hydrogène et R_a et R_b sont indépendamment un groupe phényle ou hétéroaryle tel qu'un groupe pyridyle ; ou
R_c est un atome d'hydrogène, un groupe alkyle(en C_1 à C_6), alcényle(en C_2 à C_6), alcynyle(en C_2 à C_6), phényl-alkyle(en C_1 à C_6) ou cycloalkyle(en C_3 à C_8), et R_a et R_b, conjointement avec l'atome de carbone auquel ils sont attachés, forment un cycle cycloalkyle à 3 à 8 éléments ou hétérocyclique à 5 à 6 éléments ; ou
R_a, R_b et R_c, conjointement avec l'atome de carbone auquel ils sont attachés, forment un cycle tricyclique (par exemple adamantyle) ; ou
R_a et R_b sont chacun indépendamment un groupe alkyle(en C_1 à C_6), alcényle(en C_2 à C_6), alcynyle(en C_2 à C_6), phényl-alkyle(en C_1 à C_6), ou un groupe tel que défini pour R_c ci-dessous autre qu'un atome d'hydrogène, ou R_a et R_b, conjointement avec l'atome de carbone auquel ils sont attachés, forment un cycle cycloalkyle ou hétérocyclique, et R_c est un atome d'hydrogène, un groupe -OH, -SH, un atome d'halogène, un groupe -CN, -CO_2H, perfluoroalkyle(en C_1 à C_4), -CH_2OH, -CO_2-alkyle(en C_1 à C_6), -O-alkyle(en C_1 à C_6), -O-alcényle(en C_2 à C_6), -S-alkyle(en C_1 à C_6), -SO-alkyle(en C_1 à C_6), -SO_2-alkyle(en C_1 à C_6), -S-alcényle(en C_2 à C_6), -SO-alcényle(en C_2 à C_6), -SO_2-alcényle(en C_2 à C_6) ou un groupe -Q^2-W, où Q^2 représente une liaison ou -O-, -S-, -SO- ou -SO_2- et W représente un groupe phényle, phénylalkyle, cycloalkyle(en C_3 à C_8), cycloalkylalkyle(en C_3 à C_8), cycloalcényle(en C_4 à C_8), cycloalcénylalkyle(en C_4 à C_8), hétéroaryle ou hétéroarylalkyle, ledit groupe W pouvant éventuellement être substitué par au moins un substituant indépendamment choisi parmi un groupe hydroxyle, un atome d'halogène, un groupe -CN, -CO_2H, -CO_2-alkyle(en C_1 à C_6), -$CONH_2$, -CONH-alkyle(en C_1 à C_6), -CONH-(alkyle en C_1 à C_6)$_2$, -CHO, -CH_2OH, perfluoroalkyle(en C_1 à C_4), -O-alkyle(en C_1 à C_6), -S-alkyle(en C_1 à C_6), -SO-alkyle(en C_1 à C_6), -SO_2-alkyle(en C_1 à C_6), -NO_2, -NH_2, -NH-alkyle(en C_1 à C_6), -N(alkyle(en C_1 à C_6))$_2$, -NHCO-alkyle(en C_1 à C_6), alkyle(en C_1 à C_6), alcényle(en C_2 à C_6), alcynyle(an C_2 à C_6), cycloalkyle(en C_3 à C_8), cycloalcényle(en C_4 à C_8), phényle ou benzyle ; et

sauf indication contraire dans le contexte dans lequel il est utilisé, le terme « substitué » tel qu'appliqué à tout fragment dans le présent document signifie substitué par jusqu'à quatre substituants compatibles, chacun d'entre eux étant indépendamment choisi parmi les groupes alkyle(en C_1 à C_6), alcoxy(en C_1 à C_6), hydroxy, hydroxy-alkyle(en C_1 à C_6), mercapto, mercapto-alkyle(en C_1 à C_6), alkylthio(en C_1 à C_6), phényle, halogéno notamment fluoro, bromo et chloro, trifluorométhyle, trifluorométhoxy, nitro, nitrile (-CN), oxo, -COOH, -$COOR^A$, -COR^A, -SO_2R^A, -$CONH_2$, -SO_2NH_2, - $CONHR^A$, -SO_2NHR^A, -$CONR^AR^B$, -$SO_2NR^AR^B$, -NH_2, -NHR^A, -NR^AR^B, -$OCONH_2$, -$OCONHR^A$, -$OCONR^AR^B$, -$NHCOR^A$, $NHCOOR^A$, -$NRBCOOR^A$, -$NHSO_2R^A$, -$NRBSO_2OH$, -$NR^BSO_2OR^A$, -$NHCONH_2$, NR^ACONH_2, -$NHCONHR^B$, -NR^ACONHR^B, -$NHCONR^AR^B$ ou -$NR^ACONR^AR^B$, où R^A et R^B sont indépendamment un groupe alkyle(en C_1 à C_6), cycloalkyle(en C_3 à C_6), phényle ou hétéroaryle monocyclique ayant 5 ou 6 atomes dans le cycle.

2. Composé tel que revendiqué dans la revendication 1 dans lequel P est un atome d'hydrogène et U est un radical de formule (IA) tel que défini dans la revendication 1.

3. Composé tel que revendiqué dans l'une quelconque des revendications précédentes dans lequel A est un groupe 1,4-phénylène éventuellement substitué.

4. Composé tel que revendiqué dans la revendication 1 qui répond aux formules (IIA), (IIB) et (IIC) :



(IIA) (IIB) (IIC)

dans lesquelles R_{11} = F, R_{12} = H, R_{13} = H et R_{14} = H ; ou
R_{11}=F, R_{12}=F, R_{13}=H et R_{14}=H ; ou
R_{11}=F, R_{12}=H, R_{13}=F et R_{14}=F; ou
R_{11}=F, R_{12}=F, R_{13}=F et R_{14}=F; ou
R_{11}=F, R_{12}=F, R_{13}=F et R_{14}=H
et dans lesquelles z, X^1, L^1, Y, R^1 et R^2 sont tels que définis dans la revendication 1.

5. Composé tel que revendiqué dans l'une quelconque des revendications 1 à 4 dans lequel le radical -Y-L^1-X^1-$[CH_2]_z$- est $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2O-$, $-CH_2CH_2O-$, $-CH_2CH_2CH_2O-$, $-CH_2CH_2CH_2CH_2O-$, $-C(=O)-CH_2-$, $-C(=O)-CH_2O-$, $-C(=O)-NH-CH_2-$ ou $-C(=O)-NH-CH_2O-$.

6. Composé tel que revendiqué dans l'une quelconque des revendications précédentes dans lequel R_1 est un groupe ester de formule $-(C=O)OR_{14}$, où R_{14} est $R_8R_9R_{10}C-$, où

(i) R_8 est un atome d'hydrogène ou un groupe alkyle(en C_1 à C_3)-$(Z^{10})_a$-[alkyle(en C_1 à C_3)]$_b$- ou alcényle(en C_2 à C_3)-$(Z^1)_a$-[alkyle(en C_1 à C_3)]$_b$- éventuellement substitué, où a et b valent indépendamment 0 ou 1 et Z^1 est -O-, -S- ou $-NR_{11}$, où R_{11} est un atome d'hydrogène ou un groupe alkyle(en C_1 à C_3) ; et R_9 et R_{10} sont indépendamment un atome d'hydrogène ou un groupe alkyle(en C_1 à C_3)- ;
(ii) R_8 est un atome d'hydrogène ou un groupe $R_{12}R_{13}N$-alkyle(en C_1 à C_3)-éventuellement substitué, où R_{12} est un atome d'hydrogène ou un groupe alkyle(en C_1 à C_3) et R_{13} est un atome d'hydrogène ou un groupe alkyle(en C_1 à C_3) ; ou R_{12} et R_{13}, conjointement avec l'atome d'azote auquel ils sont attachés, forment un cycle monocyclique hétérocyclique éventuellement substitué de 5 ou 6 atomes dans le cycle ou un système de cycle hétérocyclique bicyclique de 8 à 10 atomes dans le cycle, et R_9 et R_{10} sont indépendamment un atome d'hydrogène ou un groupe alkyle(en C_1 à C_3)- ;ou
(iii) R_8 et R_9, pris conjointement avec l'atome de carbone auquel ils sont attachés, forment un cycle carbocyclique monocyclique éventuellement substitué de 3 à 7 atomes dans le cycle ou un système de cycle carbocyclique bicyclique de 8 à 10 atomes dans le cycle, et R_{10} est un atome d'hydrogène.

7. Composé tel que revendiqué dans la revendication 6 dans lequel R_{14} est un groupe méthyle, éthyle, n- ou iso-propyle, n-, sec- ou tert-butyle, cyclohexyle, allyle, phényle, benzyle, 2-, 3- ou 4-pyridylméthyle, N-méthylpipéridin-

4-yle, tétrahydrofuran-3-yle ou méthoxyéthyle.

8. Composé tel que revendiqué dans l'une quelconque des revendications précédentes dans lequel R_2 est un groupe phényle, benzyle, iso-butyle, cyclohexyle ou t-butoxyméthyle.

9. Composé tel que revendiqué dans l'une quelconque des revendications 1 à 5 dans lequel R_1 est un groupe ester de formule -(C=O)OR_{14}, où R_{14} est un groupe cyclopentyle, et R_2 est un groupe phényle, benzyle, iso-butyle, cyclohexyle ou t-butoxyméthyle.

10. Composé tel que revendiqué dans la revendication 1, choisi dans le groupe constitué par

le (S)-(3-{4-[6-amino-5-(2,4-difluoro benzoyl)-2-oxo-2H-pyridin-1-yl]-3,5-difluorophénoxy}propylamino)phénylacétate de cyclopentyle
le (S)-2-(3-{4-[6-amino-5-(2,4-difluoro benzoyl)-2-oxo-2H-pyridin-1-yl]-3,5-difluorophénoxy}propylamino)-4-méthylpentanoate de cyclopentyle
Exemple 42 (2*R*)-[(3-{4-[6-amino-5-(2,4-difluorobenzoyl)-2-oxopyridin-1(2*H*)-yl]-3,5-difluorophénoxy}p ropyl)amino](phényl)acétate de cyclopentyle
le *N*-(3-{4-[6-amino-5-(2,4-difluorobenzoyl)-2-oxopyridin-1(2*H*)-yl]-3,5-difluorophénoxy}prop yl)-L-leucinate de 2-morpholin-4-yléthyle
le *N*-(3-{4-[6-amino-5-(2,4-difluorobenzoyl)-2-oxopyridin-1(2*H*)-yl]-3,5-difluorophénoxy}prop yl)-L-leucinate de 2-(diméthylamino)éthyle
le *N*-[2-(4-{6-amino-5-[(4-fluorophényl)carbonyl]-2-oxopyridin-1(2*H*)-yl}phényl)éthyl]-L-leuci nate de cyclopentyle
le *N*-(5-{4-[6-amino-5-(2,4-difluorobenzoyl)-2-oxopyridin-1(2*H*)-yl]-3,5-difluorophénoxy}pent yl)-L-leucinate de cyclopentyle
le *N*-[3-(4-{6-amino-5-[(4-fluorophényl)carbonyl]-2-oxopyridin-1(2*H*)-yl}phényl)propyl]-L-leu cinate de cyclopentyle
le (2*S*)-4-amino-2-[(3-{4-[6-amino-5-(2,4-difluorobenzoyl)-2-oxopyridin-1(2*H*)-yl]-3,5-difluoro phénoxy}propyl)amino]butanoate de cyclopentyle
le *N*-(5-{4-[6-amino-5-(4-fluorobenzoyl)-2-oxopyridin-1(2*H*)-yl]-3,5-difluorophéenoxy}pentyl) -L-leucinate de cyclopentyle
le *N*-[2-(4-{6-amino-5-[(2,4-difluorophényl)carbonyl]-2-oxopyridin-1*(2H)*-yl}phényl)éthyl]-L-1 eucinate de cyclopentyle
le *N*-[2-(4-{6-amino-5-[(2,4-difluorophényl)carbonyl]-2-oxopyridin-1(2*H*)-yl}phényl)éthyl]-L-1 eucinate de tert-butyle
le (2*S*)-{[2-(4-{6-amino-5-[(4-fluorophényl)carbonyl]-2-oxopyridin-1(2*H*)-yl}phényl)éthyl]ami no}(phényl)éthanoate de cyclopentyle
le *N*-[2-(4-{6-amino-5-[(4-méthylphényl)carbonyl]-2-oxopyridin-1(2*H*)-yl}phényl)éthyl]-L-leuc inate de cyclopentyle
le *N*-[2-(4-{6-amino-5-[(4-chlorophényl)carbonyl]-2-oxopyridin-1(2*H*)-yl}phényl)éthyl]-L-leuci nate de cyclopentyle .

11. Composé tel que revendiqué dans l'une quelconque des revendications précédentes qui se présente sous la forme d'un sel pharmaceutiquement acceptable.

12. Composition pharmaceutique comprenant un composé tel que revendiqué dans l'une quelconque des revendications précédentes, associé à un support pharmaceutiquement acceptable.

13. Composé tel que revendiqué dans l'une quelconque des revendications 1 à 10 destiné au traitement d'une maladie auto-immune ou inflammatoire.

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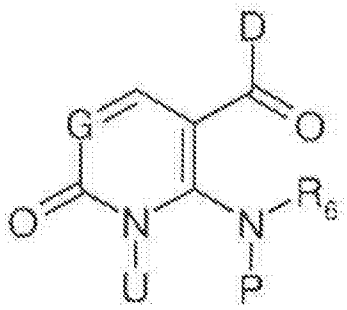
p38 MITOGÉN-AKTIVÁLT PROTEIN (MAP) KINÁZ INHIBITOROK

SZABADALMI IGÉNYPONTOK

1. Vegyület az (I)-es képlet szerint:



(I)

ahol:

G jelentése -CH=

SZTNH-100021015

D jelentése egy opcionálisan szubsztituált fenilgyűrű;

R_6 jelentése hidrogén;

P jelentése hidrogén és U jelentése (IA) képlet szerinti gyök; vagy U jelentése hidrogén és P jelentése (IA) képlet gyöke;

$$-A-(CH_2)_z-X^1-L^1-Y-NH-CHR_1R_2 \qquad (IA)$$

ahol

A jelentése egy opcionálisan szubsztituált fenilgyűrű vagy ciklohexil-gyűrű;

z értéke 0 vagy 1;

Y jelentése kovalens kötés, -C(=O)-, $-S(=O)_2-$, $-C(=O)NR_3-$, $-C(=S)-NR_3-$, $-C(=NH)NR_3$ vagy $-S(=O)_2NR_3-$ ahol R_3 jelentése hidrogén vagy opcionálisan szubsztituált C_1-C_6 alkilcsoport;

L^1 jelentése $-(Alk^1)_m(Q)_n(Alk^2)_p-$ képlet szerinti két vegyértékű gyök, ahol

m, n és p értéke egymástól függetlenül 0 vagy 1,

Q jelentése (i) opcionálisan szubsztituált két vegyértékű mono- vagy biciklusos karbociklikus vagy heterociklusos gyök, amely 5-13 gyűrűtaggal rendelkezik, vagy (ii) abban az esetben, ha m és p értéke 0, akkor az $-X^2-Q^1-$ or $-Q^1-X^2-$ képlet szerinti két vegyértékű gyök, ahol X^2 jelentése -O-, -S- vagy $-NR^4-$, ahol R^4 jelentése hidrogén vagy opcionálisan szubsztituált C_1-C_3 alkilcsoport, és Q^1 jelentése opcionálisan szubsztituált két vegyértékű mono- vagy biciklusos karbociklikus vagy heterociklusos gyök, amely 5-13 gyűrűtaggal rendelkezik,

Alk^1 és Alk^2 jelentése egymástól függetlenül opcionálisan szubsztituált két vegyértékű C_3-C_7 cikloalkil-gyök vagy opcionálisan szubsztituált egyenesláncú vagy elágazó láncú C_1-C_8 alkilén-, C_2-C_8 alkenilén- vagy C_2-C_8 alkinilléngyök, amelyek opcionálisan tartalmaznak éter- (-O-), tioéter- (-S-) vagy aminokötést ($-NR^A-$), vagy abban terminálnak, ahol R^A jelentése hidrogén vagy opcionálisan szubsztituált C_1-C_3 alkilcsoport; és

X^1 jelentése kovalens kötés; $-C(=O)-$; $-S(=O)_2-$; $-NR_4C(=O)-$, $-C(=O)NR_4-$, $-NR_4C(=O)NR_5-$, $-NR_4S(=O)_2-$, vagy $-S(=O)_2NR_4-$, ahol R_4 és R_5 jelentése egymástól függetlenül hidrogén vagy opcionálisan szubsztituált C_1-C_6 alkil;

R_1 jelentése észtercsoport, amely hidrolizálható egy vagy több intracelluláris karboxil-észteráz enzimmmel karbonsav-csoporttá;

R_2 jelentése az alábbiak közül kiválasztott természetes vagy mesterséges alfa-aminosav oldallánca:

(i) C_1-C_6 alkil-, fenil-, 2,- 3-, or 4-hidroxifenil-, 2,- 3-, vagy 4-metoxifenil-, 2,- 3-, vagy 4-piridilmetil-, benzil-, feniletil-, 2-, 3-, vagy 4-hidroxibenzil-, 2,- 3-, vagy 4-benzilioxi-benzil-, 2,- 3-, vagy 4-C_1-C_6 alkoxibenzil- és benziloxi(C_1-C_6alkil)-csoport;

(ii) természetes α-aminosavak jellemző csoportja, amelyben bármely funkcióscsoport védett lehet;

(iii) -[Alk]$_n$$R_6$-csoportok, ahol Alk jelentése (C_1-C_6)alkilcsoport vagy (C_2-C_6)alkenilcsoport opcionálisan megszakítva egy vagy több -O- vagy -S- atommal vagy $-N(R_7)$-csoporttal [ahol R_7 jelentése hidrogénatom vagy (C_1-C_6)alkilcsoport], n értéke 0 vagy 1 és R_6 jelentése opcionálisan szubsztituált cikloalkil- vagy cikloalkenil-csoport;

(iv) $-OCH_2COR_{15}$ képletcsoport által meghatározott fenilgyűrűben szubsztituált benzilcsoport, ahol R_{15} jelentése hidroxi-, amino-, (C_1-C_6)alkoxi-, fenil(C_1-C_6)alkoxi-, (C_1-C_6)alkilamino-, di((C_1-C_6)alkil)amino-, fenil(C_1-C_6)alkilamino-csoport, aminosav-maradék vagy annak sav-halid-, észter- vagy amid-származéka, ahol az említett savmaradék egy amidkötéssel kapcsolódik, ahol az aminosav glicin, α vagy β alanin, valin, leucin, izoleucin, fenilalanin, tirozin, triptofán, szerin, treonin, cisztein, metionin, aszparagin, glutamin, lizin, hisztidin, arginin, glutaminsav vagy aszparaginsav közül kiválasztott;

(v) heterociklusos (C_1-C_6)alkilcsoport, szubsztituálatlan vagy a heterociklusos gyűrűben mono- vagy diszubsztituált halogén-, nitro-, karboxi-, (C_1-C_6)alkoxi-, ciano-, (C_1-C_6)alkanoil-, trifluor-metil (C_1-C_6)alkil-, hidroxi-, formil-, amino-, (C_1-C_6)alkilamino-, di-(C_1-C_6)alkilamino-, merkapto-, (C_1-C_6)alkiltio-, hidroxi(C_1-C_6)alkil-, merkapto(C_1-C_6)alkil- vagy (C_1-C_6)alkilfenilmetil-csoporttal; és

(vi) $-CR_8R_9R_{10}$ csoport, amelyben:

R_8, R_9 és R_{10} mindegyikének jelentése egymástól függetlenül hidrogén, (C_1-C_6)alkil-, (C_2-C_6)alkenil-, (C_2-C_6)alkinil-, fenil(C_1-C_3)alkil-, (C_3-C_6)cikloalkil-csoport; vagy

R_c jelentése hidrogén, R_a és R_b jelentése egymástól függetlenül fenilcsoport vagy heteroaril-csoport, mint például piridilcsoport; vagy

R_c jelentése hidrogén, (C_1-C_6)alkil-, (C_2-C_6)alkenil-, (C_2-C_6)alkinil-, fenil(C_1-C_6)alkil, vagy (C_3-C_8)cikloalkil-csoport, R_a és R_b együttesen azzal a szénatommal, amelyhez csatlakoznak, 3-8-tagú cikloalkilcsoportot vagy 5-6-tagú heterociklikus gyűrűt alkotnak; vagy

R_a, R_b és R_c együttesen azzal a szénatommal, amelyhez csatlakoznak, triciklikus gyűrűt alkotnak (például adamantil); vagy

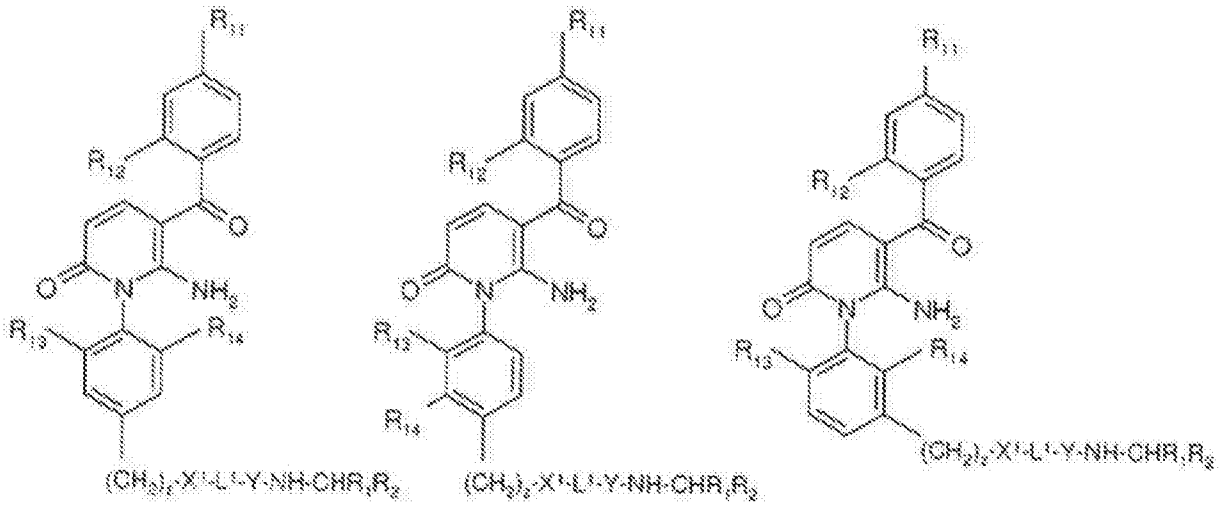
R_a és R_b jelentése egymástól függetlenül (C_1-C_6)alkil-, (C_2-C_6)alkenil-, (C_2-C_6)alkinil-, fenil(C_1-C_6)alkilcsoport vagy R_c által lejjebb definiált csoport, amely nem hidrogén, vagy R_a és R_b együttesen a szénatommal, amelyhez csatlakoznak, cikloalkilcsoportot vagy heteroheterociklusos gyűrűt alkotnak, és R_c jelentése hidrogén, -OH, -SH, halogén-, -CN, - CO_2H, (C_1-C_4)perfluoralkil-, -CH_2OH, -CO_2(C_1-C_6)alkil-, -O(C_1-C_6)alkil-, -O(C_2-C_6)alkenil-, -S(C_1-C_6)alkil-, -SO(C_1-C_6)alkil-, -SO_2(C_1-C_6)alkil-, -S(C_2-C_6)alkenil-, -SO(C_2-C_6)alkenil-, -SO_2(C_2-C_6)alkenil-csoport vagy -Q^2-W csoport, ahol Q^2 jelentése kovalens kötés vagy -O-, -S-, -SO- or -SO_2- kötés és W jelentése fenil-, fenilalkil-, (C_3-C_8)cikloalkil-, (C_3-C_8)cikloalkil-alkil-, (C_4-C_8)cikloalkenil-, (C_4-C_8)cikloalkenil-alkil-, heteroaril- vagy heteroaril-alkil-csoport, amely W csoport opcionálisan szubsztituált lehet egy vagy több szubsztituenssel hidroxi-, halogén-, -CN, -CO_2H, -CO_2(C_1-C_6)alkil, -$CONH_2$, -CONH(C_1-C_6)alkil-, -CONH(C_1-C_6-alkil)$_2$, -CHO, -CH_2OH, (C_1-C_4)perfluoralkil-, -O(C_1-C_6)alkil-, -S(C_1-C_6)alkil-, -SO(C_1-C_6)alkil-, -SO_2(C_1-C_6)alkil-, -NO_2, -NH_2, -NH(C_1-C_6)alkil-, -N((C_1-C_6)alkil)$_2$, -NHCO(C_1-C_6)alkil-, (C_1-C_6)alkil-, (C_2-C_6)alkenil-, (C_2-C_6)alkinil-, (C_3-C_8)cikloalkil-, (C_4-C_8)cikloalkenil-, fenil- vagy benzilcsoport közül egymástól függetlenül kiválasztva; és

ha a kontextus által, amelyben előfordul, máshogy nem meghatározott, akkor a „szubsztituált" kifejezés bármely csoportra alkalmazva azt jelenti, hogy szubsztituált legfeljebb négy kompatibilis szubsztituenssel, amelyek mindegyike egymástól függetlenül (C_1-C_6)alkil-, (C_1-C_6)alkoxi-, hidroxi-, hidroxi(C_1-C_6)alkil-, merkapto-, merkapto(C_1-C_6)alkil-, (C_1-C_6)alkiltio-, fenil-, halogéncsoport közül kiválasztott, beleértve fluor-, bróm- és klór-, trifluormetil-, trifluormetoxi-, nitro-, nitril (-CN), oxo, -COOH, -$COOR^A$, -COR^A, -SO_3R^A, -$CONH_2$, -SO_2NH_2, -$CONHR^A$, -SO_2NHR^A, -$CONR^AR^B$, -$SO_2NR^AR^B$, -NH_2, -NHR^A, -NR^AR^B, -$OCONH_2$, -$OCONHR^A$, -$OCONR^AR^B$, -$NHCOR^A$, -$NHCOOR^A$, -NR^BCOOR^A, -$NHSO_2OR^A$, -NR^BSO_2OH, -$NR^BSO_2OR^A$, -$NHCONH_2$, -NR^ACONH_2, -$NHCONHR^B$, -NR^ACONHR^B, -$NHCONR^AR^B$ vagy -$NR^ACONR^AR^B$ csoportokat, ahol R^A és R^B jelentése egymástól függetlenül (C_1-C_6)alkil-, (C_3-C_8) cikloalkil-, fenil- vagy 5-6 gyűrűatommal rendelkező monociklusos heteroaril-csoport.

2. Vegyület az 1-es igénypont szerint, ahol P jelentése hidrogén és U jelentése az 1-es igénypont szerinti (IA) képlet gyöke.

3. Vegyület az eddigi igénypontok bármelyike szerint, ahol A jelentése opcionálisan szubsztituált 1,4-fenilén.

4. Vegyület az 1-es igénypont szerint, amelynek képlete (IIA), (IIB), illetve (IIC) szerinti:



(IIA) (IIB) (IIC)

ahol R_{11} = F, R_{12} = H, R_{13} = H és R_{14} = H; vagy

R_{11} = F, R_{12} = F, R_{13} = H és R_{14} = H; vagy

R_{11} = F, R_{12} = H, R_{13} = F és R_{14} = F; vagy

R_{11} = F, R_{12} = F, R_{13} = F és R_{14} = F; vagy

R_{11} = F, R_{12} = F, R_{13} = F és R_{14} = H

és ahol z, X^1, L^1, Y, R^1 és R^2 jelentése az 1-es igénypont szerint meghatározott.

5. Vegyület az 1-4 igénypontok bármelyike szerint, ahol az -Y-L^1-X^1-$[CH_2]_z$- gyök jelentése -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2$-, -CH_2O-, -CH_2CH_2O-, -$CH_2CH_2CH_2O$-, -$CH_2CH_2CH_2CH_2O$-, -C(=O)-CH_2-, -C(=O)-CH_2O-, -C(=O)-NH-CH_2- vagy -C(=O)-NH-CH_2O-.

6. Vegyület az eddigi igénypontok bármelyike szerint, ahol R_1 jelentése -(C=O)OR_{14} képlet szerinti észtercsoport, ahol R_{14} jelentése $R_aR_bR_cC$-, ahol

(i) R_a jelentése hidrogén vagy opcionálisan szubsztituált (C_1-C_3)alkil-$(Z^1)_a$-[(C_1-C_3)alkil]$_b$- vagy (C_2-C_3)alkenil-$(Z^1)_a$-[(C_1-C_3)alkil]$_b$-csoport, ahol a és b értéke egymástól függetlenül 0 vagy 1, és Z^1 jelentése -O-, -S- vagy -NR_{11}- kötés, ahol R_{11} jelentése hidrogén vagy (C_1-C_3)alkilcsoport; valamint R_b és R_{bb} jelentése egymástól függetlenül hidrogén vagy (C_1-C_3)alkyl-csoport;

(ii) R_a jelentése hidrogén vagy opcionálisan szubsztituált $R_{12}R_{13}N$-(C_1-C_3)alkilcsoport, ahol R_{12} jelentése hidrogén vagy (C_1-C_3)alkilcsoport és R_{13} jelentése hidrogén vagy (C_1-C_3)alkilcsoport, vagy R_{12} és R_{13} együttesen a nitrogén atommal, amelyhez kapcsolódnak, egy opcionálisan szubsztituált, 5-6 gyűrűatommal rendelkező, monociklusos heterociklusos gyűrűt vagy 8-10 gyűrűatommal rendelkező, biciklusos heterociklusos gyűrűrendszert alkotnak, valamint R_c és R_{cc} jelentése egymástól függetlenül hidrogén vagy (C_1-C_3)alkilcsoport; vagy

(iii) R_8 és R_9 együttesen a szénatommal, amelyhez kapcsolódnak, egy opcionálisan szubsztituált, 3-7 gyűrűatommal rendelkező, monociklusos karbociklusos gyűrűt vagy biciklusos karbociklusos, 8-10 gyűrűatommal rendelkező, gyűrűrendszert alkotnak, és R_{10} jelentése hidrogén.

7. Vegyület a 6-os igénypont szerint, ahol R_{14} jelentése metil-, etil-, n- vagy izopropil-, n-, sec- vagy terbutil-, ciklohexil-, allil-, fenil-, benzil-, 2-, 3- vagy 4- piridilmetil-, *N*-metilpiperidin-4-il-, tetrahidrofurán-3-il- vagy metoxietil-csoport.

8. Vegyület az eddigi igénypontok bármelyike szerint, ahol R_2 jelentése fenil-, benzil-, izobutil-, ciklohexil- vagy t-butoximetil-csoport.

9. Vegyület az 1-5 igénypontok bármelyike szerint, ahol R_1 jelentése -(C=O)OR_{14} képlet által meghatározott észtercsoport, ahol R_{14} jelentése ciklopentil-csoport és R_2 jelentése fenil-, benzil-, izobutil-, ciklohexil- vagy t-butoximetil-csoport.

10. Vegyület az 1-es igénypont szerint az alábbiakat tartalmazó csoportból kiválasztva:

Ciklopentil (*S*)-(3-[4-[6-Amino-5-(2,4-difluor benzoil)-2-oxo-2H-pirdin-1-il]-3,5-difluorfenoxi]propilamino)fenil acetát

Ciklopentil (*S*)-2-(3-[4-[6-Amino-5-(2,4-difluor benzoil)-2-oxo-2H-piridin-1-il]-3,5-difluorfenoxi]propilamino)-4-metil pentanoát

Példa 42 Ciklopentil (2*R*)-[(3-{4-[6-amino-5-(2,4-difluorbenzoil)-2-oxopiridin-1(2*H*)-il]-3,5-difluorfenoxi}propil)amino](fenil)acetát

2-Morfolin-4-iletil *N*-(3-[4-[6-amino-5-(2,4-difluorbenzoil)-2-oxopiridin-1(2*H*)-il]-3,6-difluorfenoxi]propil)-L-leucinát

2-(Dimetilamino)etil *N*-(3-{4-[6-amino-5-(2,4-difluorbenzoil)-2-oxopiridin-1(2*H*)-il]-3,5-difluorfenoxi}propil)-L-leucinát

Ciklopentil *N*-[2-(4-[6-amino-5-[(4-fluorfenil)karbonil]-2-oxopiridin-1(2*H*)-il]fenil)etil]-L-leucinát

Ciklopentil *N*-(5-{4-[6-amino-5-(2,4-difluorbenzoil)-2-oxopiridin-1(2*H*)-il]-3,5-difluorfenoxi}pentil)-L-leucinát

Ciklopentil *N*-[3-(4-[6-amino-5-[(4-fluorfenil)karbonil]-2-oxopiridin-1(2*H*)-il]fenil}propil]-L-leucinát

Ciklopentil (2*S*)-4-amino-2-{(3-{4-[6-amino-5-(2,4-difluorbenzoil)-2-oxopiridin-1(2*H*)-il]-3,5-difluorfenoxi}propil)amino}butanoát

Ciklopentil *N*-(5-{4-[6-amino-5-(4-fluorbenzoil)-2-oxopiridin-1(2*H*)-il]-3,5-difluorfenoxi}pentil)-L-leucinát

Ciklopentil *N*-[2-(4-[6-amino-5-[(2,4-difluorfenil)karbonil]-2-oxopiridin-1(2*H*)-il]fenil)etil]-L-leucinát

tert-Butil *N*-[2-(4-{6-amino-5-[(2,4-difluorfenil)karbonil]-2-oxopiridin-1(2*H*)-il}fenil)etil]-L-leucinát

Ciklopentil (2*S*)-{[2-(4-{6-amino-5-[(4-fluorfenil)karbonil]-2-oxopiridin-1(2*H*)-il}fenil)etil]amino}(fenil)etanoát

Ciklopentil *N*-[2-(4-{6-amino-5-[(4-metilfenil)karbonil]-2-oxopiridin-1(2*H*)-il}fenil)etil]-L-leucinát

Ciklopentil *N*-[2-(4-{6-amino-5-[(4-klórfenil)karbonil]-2-oxopiridin-1(2*H*)-il}fenil)etil]-L-leucinát.

11. Vegyület az eddigi igénypontok bármelyike szerint, ahol a vegyület gyógyszerészetileg elfogadható só formájában van jelen.

12. Gyógyszerészeti összetétel, amely tartalmazza a vegyületet az eddigi igénypontok bármelyike szerint együttesen egy gyógyszerészetileg elfogadható hordozóanyaggal.

13. Vegyület az 1-10 igénypontok bármelyike szerint autoimmun vagy gyulladásos megbetegedés kezelésére.