

HDAC Inhibitors

This invention relates to compounds which inhibit members of the histone deacetylase family of enzymes and to their use in the treatment of cell proliferative diseases, including cancers, polyglutamine diseases, for example Huntingdon disease, neurogenerative diseases for example Alzheimer disease, autoimmune disease for example rheumatoid arthritis and organ transplant rejection, diabetes, haematological disorders, inflammatory disease, cardiovascular disease, atherosclerosis, and the inflammatory sequelae of infection.

Background to the Invention

In eukaryotic cells DNA is packaged with histones, to form chromatin. Approximately 150 base pairs of DNA are wrapped twice around an octamer of histones (two each of histones 2A, 2B, 3 and 4) to form a nucleosome, the basic unit of chromatin. The ordered structure of chromatin needs to be modified in order to allow transcription of the associated genes. Transcriptional regulation is key to differentiation, proliferation and apoptosis, and is, therefore, tightly controlled. Control of the changes in chromatin structure (and hence of transcription) is mediated by covalent modifications to histones, most notably of the N-terminal tails. Covalent modifications (for example methylation, acetylation, phosphorylation and ubiquitination) of the side chains of amino acids are enzymatically mediated (A review of the covalent modifications of histones and their role in transcriptional regulation can be found in S. L. Berger, *Oncogene*, 2001, **20**, 3007-3013. See M. Grunstein, *Nature*, 1997, **389**, 349-352; A. P. Wolffe, *Science*, 1996, **272**, 371-372; and P. A. Wade *et al*, *Trends Biochem. Sci.*, 1997, **22**, 128-132 for reviews of histone acetylation and transcription).

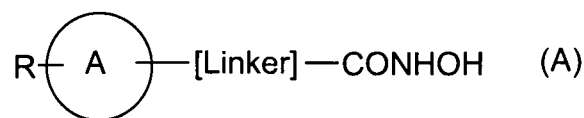
Acetylation of histones is associated with areas of chromatin that are transcriptionally active, whereas nucleosomes with low acetylation levels are, typically, transcriptionally silent. The acetylation status of histones is controlled by two enzyme classes of opposing activities; histone acetyltransferases (HATs) and histone deacetylases (HDACs). In transformed cells it is believed that inappropriate expression of HDACs results in silencing of tumour suppressor genes (For a review of the potential roles of HDACs in tumorigenesis see S. G. Gray and B. T. The, *Curr. Mol. Med.*, 2001, **1**, 401-429). Inhibitors of HDAC enzymes have been described in the literature and shown to induce transcriptional reactivation of certain genes resulting in the inhibition of cancer cell proliferation, induction of apoptosis and inhibition of tumour growth in animals (For review see W. K. Kelly *et al*, *Expert Opin. Investig. Drugs*, 2002, **11**, 1695-1713). Such findings suggest that HDAC inhibitors have therapeutic potential in the treatment of proliferative diseases such as cancer (O. H. Kramer *et al*, *Trends Endocrinol.*, 2001, **12**, 294-300; D. M. Vigushin and R. C. Coombes, *Anticancer Drugs*, 2002, **13**, 1-13).

In addition, others have proposed that aberrant HDAC activity or histone acetylation is implicated in the following diseases and disorders; polyglutamine disease, for example Huntingdon disease (R. E. Hughes, *Curr Biol*, 2002, **12**, R141-R143; A. McCampbell *et al*, *Proc. Soc. Natl. Acad. Sci.*, 2001, **98**, 15179-15184; E. Hockly *et al*, *Proc. Soc. Natl. Acad. Sci.*, 2003, **100**, 2041-2046), other neurodegenerative diseases, for example Alzheimer disease (B. Hempen and J. P. Brion, *J. Neuropathol. Exp. Neurol.*, 1996, **55**, 964-972), autoimmune disease and organ transplant rejection (S. Skov *et al*, *Blood*, 2003, **101**, 1430-1438; N. Mishra *et al*, *J. Clin. Invest.*, 2003, **111**, 539-552), diabetes (A. L. Mosley and S. Ozcan, *J. Biol. Chem.*, 2003, **278**, 19660 - 19666) and diabetic complications, infection (including protozoal infection (S. J. Darkin-Rattray *et al*, *Proc. Soc. Natl. Acad. Sci.*, 1996, **93**, 13143-13147)) and haematological disorders including thalassemia (O. Witt *et al*, *Blood*, 2003, **101**, 2001-2007). The observations contained in these manuscripts suggest that HDAC inhibition should have therapeutic benefit in these, and other related, diseases.

Many types of HDAC inhibitor compounds have been suggested, and several such compounds are currently being evaluated clinically, for the treatment of cancers. For example, the following patent publications disclose such compounds:

US 5,369,108	WO 01/70675	WO 02/30879
WO 01/18171	WO 01/38322	WO 02/26703
US 4,254,220	WO 02/069947	WO 02/26696
WO 03/082288	WO 02/22577	WO 03/075929
WO 03/076395	WO 03/076400	WO 03/076401
WO 03/076421	WO 03/076430	WO 03/076422
WO 03/082288	WO 03/087057	WO 03/092686
WO 03/066579	WO 03/011851	WO 04/013130
WO 04/110989	WO 04/092115	WO 04/224991
WO 04/076386	WO 05/014588	WO 05/018578
WO 05/019174	WO 05/004861	WO 05/007091
WO 05/030704	WO 05/013958	WO 05/028447
WO 05/026907	WO 06/0166	

Many of the HDAC inhibitors known in the art have a structural template, which may be represented as in formula (A):



wherein ring A is a carbocyclic or heterocyclic ring system with optional substituents R, and [Linker] is a linker radical of various types. The hydroxamate group functions as a metal binding group, interacting with the metal ion at the active site of the HDAC enzyme, which lies at the base of a pocket in the folded enzyme structure. The ring or ring system A lies within or at the entrance to the pocket containing the metal ion, with the –[Linker]- radical extending deeper into that pocket linking A to the metal binding hydroxamic acid group. In the art, and occasionally herein, the ring or ring system A is sometimes informally referred to as the “head group” of the inhibitor.

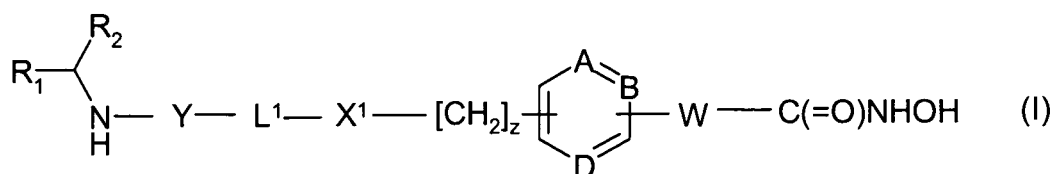
The use of prodrugs to enhance the delivery to target organs and tissues, or to overcome poor pharmacokinetic properties of the parent drug, is a well known medicinal chemistry approach. Administration of ester prodrugs, for example, which are hydrolysed by serum carboxyesterases *in vivo* to the active parent acids, can result in higher serum levels of the parent acid than administration of the acid itself.

Brief Description of the Invention

This invention makes available a new class of HDAC inhibitors having pharmaceutical utility in the treatment of diseases such as cancers or inflammation which benefit from intracellular inhibition of HDAC, one subset of which has an alpha amino acid ester grouping which facilitates penetration of the agent through the cell wall, and thereby allows intracellular carboxyesterase activity to hydrolyse the ester to release the parent acid. Being charged, the acid is not readily transported out of the cell, where it therefore accumulates to increase the intracellular concentration of active HDAC inhibitor. This leads to increases in potency and duration of action. This subset of compounds of the invention is therefore characterised by having an alpha amino acid ester moiety which is a substrate for intracellular carboxyesterase (also referred to herein as an “esterase motif”) covalently linked to the parent molecular template, and to the corresponding de-esterified parent acids.

Detailed Description of the Invention

According to the invention there is provided a compound of formula (I), or a salt, N-oxide, hydrate or solvate thereof:



wherein

A, **B** and **D** independently represent =C- or =N-;

W is a divalent radical $-\text{CH}=\text{CH}-$ or $-\text{CH}_2\text{CH}_2-$;

R₁ is a carboxylic acid group ($-\text{COOH}$), or an ester group which is hydrolysable by one or more intracellular carboxyesterase enzymes to a carboxylic acid group;

R₂ is the side chain of a natural or non-natural alpha amino acid;

Y is a bond, $-\text{C}(=\text{O})-$, $-\text{S}(=\text{O})_2-$, $-\text{C}(=\text{O})\text{O}-$, $-\text{C}(=\text{O})\text{NR}_3-$, $-\text{C}(=\text{S})-\text{NR}_3$, $-\text{C}(=\text{NH})\text{NR}_3$ or $-\text{S}(=\text{O})_2\text{NR}_3-$ wherein **R**₃ is hydrogen or optionally substituted C₁-C₆ alkyl;

L¹ is a divalent radical of formula $-(\text{Alk}^1)_m(\text{Q})_n(\text{Alk}^2)_p-$ 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 $-\text{X}^2-\text{Q}^1-$ or $-\text{Q}^1-\text{X}^2-$ wherein **X**² is $-\text{O}-$, $-\text{S}-$ or $-\text{NR}^{\text{A}}-$ wherein **R**^A is hydrogen or optionally substituted C₁-C₃ alkyl, and **Q**¹ is an optionally substituted divalent mono- or bicyclic carbocyclic or heterocyclic radical having 5 - 13 ring members,

Alk¹ and **Alk**² independently represent optionally substituted divalent C₃-C₇ cycloalkyl radicals, or optionally substituted straight or branched, C₁-C₆ alkylene, C₂-C₆ alkenylene, or C₂-C₆ alkynylene radicals which may optionally contain or terminate in an ether ($-\text{O}-$), thioether ($-\text{S}-$) or amino ($-\text{NR}^{\text{A}}-$) link wherein **R**^A is hydrogen or optionally substituted C₁-C₃ alkyl;

X¹ represents a bond; $-\text{C}(=\text{O})$; or $-\text{S}(=\text{O})_2$; $-\text{NR}_4\text{C}(=\text{O})-$, $-\text{C}(=\text{O})\text{NR}_4-$, $-\text{NR}_4\text{C}(=\text{O})\text{NR}_5-$, $-\text{NR}_4\text{S}(=\text{O})_2-$, or $-\text{S}(=\text{O})_2\text{NR}_4-$ wherein **R**₄ and **R**₅ are independently hydrogen or optionally substituted C₁-C₆ alkyl; and

z is 0 or 1;

PROVIDED THAT, when A, B and D are each =C- and W is -CH=CH- and R₁ is a carboxylic acid group or a methyl or tert-butyl ester thereof, then R₂ is not the side chain of tryptophan, namely indol-3-ylmethyl.

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.

In another broad aspect the invention provides the use of a compound of the invention in the preparation of a composition for inhibiting the activity of histone deacetylase.

The compounds with which the invention is concerned may be used for the inhibition of histone deacetylase activity, *ex vivo* or *in vivo*.

In one aspect of the invention, the compounds of the invention may be used in the preparation of a composition for the treatment of cell-proliferation disease, polyglutamine disease, neurodegenerative disease, autoimmune disease, inflammatory disease, organ transplant rejection, diabetes, haematological disorders or infection,.

In another aspect, the invention provides a method for the treatment of the foregoing disease types, which comprises administering to a subject suffering such disease an effective amount of a compound of the invention.

Terminology

The term "ester" or "esterified carboxyl group" means a group R₉O(C=O)- in which R₉ is the group characterising the ester, notionally derived from the alcohol R₉OH.

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.

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.

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.

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.

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. For a = 2 and b = 6, this term would include for example, ethynyl, 1-propynyl, 1- and 2-butyne, 2-methyl-2-propynyl, 2-pentyne, 3-pentyne, 4-pentyne, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl.

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.

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.

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.

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 naphthyl.

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.

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, morpholinyl, piperazinyl, indolyl, benzfuranyl, pyranyl, isoxazolyl, benzimidazolyl, methylenedioxyphenyl, ethylenedioxyphenyl, maleimido and succinimido groups.

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, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, hydroxy, hydroxy(C₁-C₆)alkyl, mercapto, mercapto(C₁-C₆)alkyl, (C₁-C₆)alkylthio, phenyl, halo (including fluoro, bromo and chloro), trifluoromethyl, trifluoromethoxy, nitro, nitrile (-CN), oxo, -COOH, -COOR^A, -COR^A, -SO₂R^A, -CONH₂, -SO₂NH₂, -CONHR^A, -SO₂NHR^A, -CONR^AR^B, -SO₂NR^AR^B, -NH₂, -NHR^A, -NR^AR^B, -OCONH₂, -OCONHR^A, -OCONR^AR^B, -NHCOR^A, -NHCOOR^A, -NR^BCOOR^A, -NH₂SO₂OR^A, -NR^BSO₂OH, -NR^BSO₂OR^A, -NHCONH₂, -NR^ACONH₂, -NHCONHR^B, -NR^ACONHR^B, -NHCONR^AR^B, or -NR^ACONR^AR^B wherein R^A and R^B are independently a (C₁-C₆)alkyl, (C₃-C₆) cycloalkyl, phenyl or monocyclic heteroaryl having 5 or 6 ring atoms, or RA and RB when attached to the same nitrogen atom form a cyclic amino group (for example morpholino, piperidinyl, piperazinyl, or tetrahydropyrrolyl). An "optional substituent" may be one of the foregoing substituent groups.

As used herein, the term "nitrogen substituent" means a substituent on a nitrogen atom which is selected from the following:

amino (C₁-C₆)alkyl eg aminoethyl, (C₁-C₃)alkylamino-(C₁-C₆)alkyl-, (C₁-C₃)dialkylamino-(C₁-C₆)alkyl, hydroxy(C₁-C₆)alkyl eg hydroxyethyl, (C₁-C₃)alkoxy-(C₁-C₆)alkyl- eg methoxyethyl, mercapto(C₁-C₃)alkyl, (C₁-C₃)alkylmercapto-(C₁-C₆)alkyl-, carboxamido(C₁-C₆)alkyl e.g. -CH₂CONH₂, aminosulphonyl(C₁-C₆)alkyl- e.g. -CH₂SO₂NH₂, (C₁-C₃)alkylaminosulphonyl- (C₁-C₆)alkyl- e.g. -CH₂SO₂NHMe, (C₁-C₃)dialkylaminosulphonyl- (C₁-C₆)alkyl e.g. -CH₂SO₂NMe₂, (C₁-C₆)alkanoyl, (C₁-C₆)alkylsulphonyl, aminosulphonyl (-SO₂NH₂), (C₁-C₆)alkylaminosulphonyl e.g. -SO₂NHMe, (C₁-C₆)dialkylaminosulphonyl e.g. -SO₂NMe₂, optionally substituted phenylaminosulphonyl, carboxamido (-CONH₂), (C₁-C₆)alkylaminocarbonyl, (C₁-C₆)dialkylaminocarbonyl, morpholinyl(C₁-C₆)alkyl,

imidazolyl(C₁-C₆)alkyl, triazolyl(C₁-C₆)alkyl, or monocyclic heterocycloalkyl(C₁-C₆)alkyl, optionally substituted in the imidazolyl, triazolyl or heterocyclyl ring, eg piperidinyl(C₁-C₆)alkyl, piperazinyl(C₁-C₆)alkyl or 4-((C₁-C₆)alkyl)piperazinyl(C₁-C₆)alkyl.

The term "side chain of a natural or non-natural alpha-amino acid" refers to the group R₂ in a natural or non-natural amino acid of formula NH₂-CH(R₂)-COOH.

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-amino adipic acid, α-amino-n-butyric acid, 3,4-dihydroxyphenylalanine, homoserine, β-methylserine, ornithine, pipecolic acid, and thyroxine.

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 R₂ in the compounds of the invention is one of those side chains, the functional substituent may optionally be protected.

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 C₁-C₆ alkyl ester), amino groups may be converted to amides (for example as a NHCOC₁-C₆ alkyl amide) or carbamates (for example as an NHC(=O)OC₁-C₆ alkyl or NHC(=O)OCH₂Ph carbamate), hydroxyl groups may be converted to ethers (for example an OC₁-C₆ alkyl or a O(C₁-C₆ alkyl)phenyl ether) or esters (for example a OC(=O)C₁-C₆ 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)C₁-C₆ alkyl thioester).

Examples of side chains of non-natural alpha amino acids include those referred to below in the discussion of suitable R₂ groups for use in compounds of the present invention.

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.

It is expected that compounds of the invention may be recovered in hydrate or solvate form. 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.

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 a number of diastereoisomers with R or S stereochemistry at each chiral centre. The invention includes all such diastereoisomers and mixtures thereof.

Further Discussion

As stated above, the esters of the invention are primarily prodrugs of the corresponding carboxylic acids to which they are converted by intracellular esterases. However, for so long as they remain unhydrolysed, the esters may have HDAC inhibitory activity in their own right. The compounds of the invention include not only the ester, but also the corresponding carboxylic and hydrolysis products.

The hydroxamate group $-C(=O)NHOH$

In the compounds of the invention, the hydroxamate group functions as a metal binding group, interacting with the metal ion at the active site of the HDAC enzyme, which lies at the base of a pocket in the folded enzyme structure.

The ring containing A, B and D

Each of **A**, **B** and **D** may be $-C=$, or at least one of **A**, **B** and **D** may be $-N=$, or **A** may be $-C=$ and **B** and **D** may each be $-N=$;

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

L¹ may be selected from:

- (i) a bond;
- (ii) $-O-$, $-S-$, $-C(=O)-$, $-S(=O)_2-$, $-NR^1-$, $-C(=O)NR^1-$, $-S(=O)_2NR^1-$,

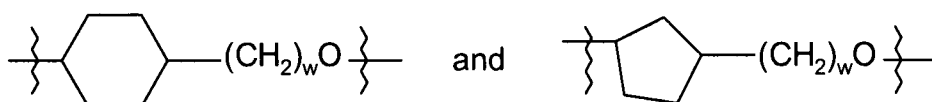
$-\text{NR}^1\text{C}(=\text{O})-$, $-\text{NR}^1\text{S}(=\text{O})_2-$, $-\text{NR}^1(\text{CH}_2)_m-$, $-\text{NR}^1\text{C}(=\text{O})(\text{CH}_2)_m-$,
 $-\text{NR}^1\text{S}(=\text{O})_2(\text{CH}_2)_m-$, $-\text{NR}^2\text{C}(=\text{O})\text{NR}^1-$, $-\text{NR}^1\text{C}(=\text{O})(\text{CH}_2)_m\text{Ar}-$, or
 $-\text{NR}^1\text{S}(=\text{O})_2(\text{CH}_2)_m\text{Ar}-$ wherein R^1 and R^2 are independently hydrogen, C_1 - C_4
 alkyl, or a nitrogen substituent, m is 0, 1, 2 or 3, and Ar is a divalent phenyl
 radical or a divalent mono-, or bi-cyclic heteroaryl radical having 5 to 13 ring
 members; and
 (iii) an optionally substituted, straight or branched, C_1 - C_6 alkylene, C_2 - C_6
 alkenylene or C_2 - C_6 alkynylene radical which may optionally contain or terminate
 in an ether ($-\text{O}-$), thioether ($-\text{S}-$) or amino ($-\text{NR}^A-$) link wherein R^A is hydrogen,
 C_1 - C_3 alkyl, or a nitrogen substituent;

In the radical L^1 , Alk^1 and Alk^2 , when present, may be selected from, for example,
 $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{O}-$, $-\text{CH}_2\text{CH}_2\text{O}-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$, and divalent
 cyclopropyl, cyclopentyl and cyclohexyl radicals.

Also in the radical L^1 , Q^1 may be, for example, 1,4-phenylene.

Also in the radical L^1 , m and p may both be 0, or n and p may be 0 while m is 1, or m , n
 and p may all be 0.

Specific examples of the radical $-\text{Y}-\text{L}^1-\text{X}^1-[\text{CH}_2]_z-$ are $-\text{C}(=\text{O})-$, $-\text{C}(=\text{O})\text{NH}-$, $-(\text{CH}_2)_v-$, $-(\text{CH}_2)_v\text{O}-$, $-\text{C}(=\text{O})-(\text{CH}_2)_v-$, $-\text{C}(=\text{O})(\text{CH}_2)_v\text{O}-$, $-\text{C}(=\text{O})\text{NH}(\text{CH}_2)_w-$, $-\text{C}(=\text{O})\text{NH}(\text{CH}_2)_w\text{O}-$



wherein v is 1, 2, 3 or 4 and w is 1, 2 or 3.

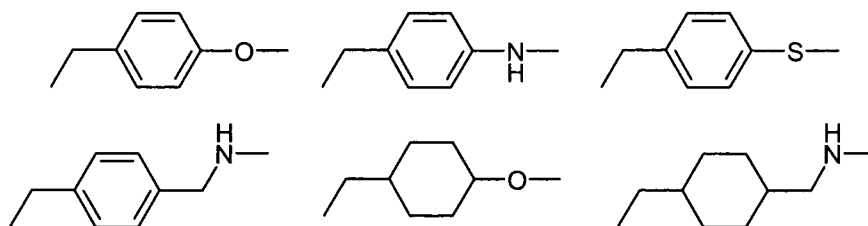
Amongst preferred $-\text{Y}-\text{L}^1-\text{X}^1-[\text{CH}_2]_z-$ radicals are $-\text{CH}_2-$, $-\text{CH}_2\text{O}-$, $-\text{C}(=\text{O})-\text{CH}_2-$,
 $-\text{C}(=\text{O})-\text{CH}_2\text{O}-$, $-\text{C}(=\text{O})-\text{NH}-\text{CH}_2-$, or $-\text{C}(=\text{O})-\text{NH}-\text{CH}_2\text{O}-$.

X^1 may be, for example, $-\text{NR}_3-$, $-\text{S}-$, $-\text{O}-$, $-\text{C}(=\text{O})\text{NR}_3-$, $-\text{NR}_3\text{C}(=\text{O})-$, or $-\text{C}(=\text{O})\text{O}-$, wherein
 R_3 is hydrogen, C_1 - C_6 alkyl, or a nitrogen substituent, or in other cases a bond.

In the radical L^1 , Alk^1 and Alk^2 , when present, may be selected from $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$,
 $-\text{CH}_2\text{CH}_2\text{CH}_2-$, and divalent cyclopropyl, cyclopentyl and cyclohexyl radicals.

In the radical L^1 , Q^1 may be, for example, a divalent phenyl radical or a mono-, or bi-cyclic heteroaryl radical having 5 to 13 ring members, such as 1,4-phenylene.

Specific examples of the radical $-L^1-X^1-[CH_2]_z-$ are $-(CH_2)_3NH-$, $-CH_2C(=O)NH-$, $-CH_2CH_2C(=O)NH-$, $-CH_2C(O)O-$, $-CH_2S-$, $-CH_2CH_2C(O)O-$, $-(CH_2)_4NH-$, $-CH_2CH_2S-$, $-CH_2O-$, $-CH_2CH_2O-$



In a simple subset of compounds of the invention, the radical $-YL^1X^1[CH_2]_z-$ is $-CH_2-$.

The ester group R_1

The ester group R_1 must be one which in the compound of the invention is hydrolysable by one or more intracellular carboxyesterase enzymes to a carboxylic acid group. Intracellular carboxyesterase 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 carboxyesterase hydrolyses the free amino acid ester to the parent acid it will, subject to the N-carbonyl dependence of hCE-2 and hCE-3 discussed below, also hydrolyse the ester motif when covalently conjugated to the HDAC inhibitor. Hence, the broken cell assay provides 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 carboxyesterase assay when conjugated to the inhibitor *via* the chosen conjugation chemistry, to confirm that it is still a carboxyesterase substrate in that background.

Subject to the requirement that they be hydrolysable by intracellular carboxyesterase enzymes, examples of particular ester groups R_1 include those of formula $-(C=O)OR_9$ wherein R_9 is $R_{20}R_{21}R_{22}C-$ wherein

- (i) R_{20} is hydrogen or optionally substituted $(C_1-C_3)alkyl-(Z^1)_a-[(C_1-C_3)alkyl]_b-$ 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_C- wherein R_C is hydrogen or (C₁-C₃)alkyl; and R₂₁ and R₂₂ are independently hydrogen or (C₁-C₃)alkyl-;

(ii) R₂₀ is hydrogen or optionally substituted R₁₂R₁₃N-(C₁-C₃)alkyl- wherein R₁₂ is hydrogen or (C₁-C₃)alkyl and R₁₃ is hydrogen or (C₁-C₃)alkyl; or R₁₂ and R₁₃ 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 R₂₁ and R₂₂ are independently hydrogen or (C₁-C₃)alkyl-; or

(iii) R₂₀ and R₂₁ 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 R₂₂ is hydrogen.

Within these classes, R₉ may be, for example, 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, methoxyethyl, indonyl, norbonyl, dimethylaminoethyl, morpholinoethyl. Currently preferred is where R₉ is cyclopentyl.

Macrophages are known to play a key role in inflammatory disorders through the release of cytokines in particular TNF α 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 and function 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 inhibitors to cells that express hCE-1, in particular macrophages and other cells derived from the myelo-monocytic lineage such as monocytes, osteoclasts and dendritic cells. This is based on the observation that the way in which the esterase motif is linked to the inhibitor determines whether it is hydrolysed by all three human carboxylesterases or just by hCE-1, and hence whether or not it accumulates in different cell types. Specifically it has been found that macrophages and other cells derived from the myelo-monocytic lineage, both normal and cancerous, contain the human carboxylesterase hCE-1 whereas other cell types do not. In the general formula (I) when the nitrogen of the esterase motif R₁CH(R₂)NH- is not directly linked to a carbonyl (-C(=O)-), ie when Y is not a -C(=O), -C(=O)O- or -C(=O)NR₃- radical, the ester will only be hydrolysed by hCE-1 and hence the inhibitors selectively accumulate in macrophage-related cells.

The amino acid side chain R₂

Subject to the requirement that the ester group R₁ be hydrolysable by intracellular carboxylesterase enzymes, the identity of the side chain group R₂ is not critical for non-macrophage selective compounds.

Examples of amino acid side chains include:

C₁-C₆ 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-C₁-C₆ alkoxybenzyl, and benzyloxy(C₁-C₆alkyl)-groups;

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

groups -[Alk]_nR₆ where Alk is a (C₁-C₆)alkyl or (C₂-C₆)alkenyl group optionally interrupted by one or more -O-, or -S- atoms or -N(R₇)- groups [where R₇ is a hydrogen atom or a (C₁-C₆)alkyl group], n is 0 or 1, and R₆ is an optionally substituted cycloalkyl or cycloalkenyl group;

a benzyl group substituted in the phenyl ring by a group of formula -OCH₂COR₈ where R₈ is hydroxyl, amino, (C₁-C₆)alkoxy, phenyl(C₁-C₆)alkoxy, (C₁-C₆)alkylamino, di((C₁-C₆)alkyl)amino, phenyl(C₁-C₆)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(C₁-C₆)alkyl group, either being unsubstituted or mono- or di-substituted in the heterocyclic ring with halo, nitro, carboxy, (C₁-C₆)alkoxy, cyano, (C₁-C₆)alkanoyl, trifluoromethyl (C₁-C₆)alkyl, hydroxy, formyl, amino, (C₁-C₆)alkylamino, di-(C₁-C₆)alkylamino, mercapto, (C₁-C₆)alkylthio, hydroxy(C₁-C₆)alkyl, mercapto(C₁-C₆)alkyl or (C₁-C₆)alkylphenylmethyl; and

a group -CR_aR_bR_c in which:

each of R_a, R_b and R_c is independently hydrogen, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, phenyl(C₁-C₆)alkyl, (C₃-C₈)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, -CO₂H, (C_1-C_4) perfluoroalkyl, -CH₂OH, -CO₂ (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, -SO₂ (C_1-C_6) alkyl, -S (C_2-C_6) alkenyl, -SO (C_2-C_6) alkenyl, -SO₂ (C_2-C_6) alkenyl or a group -Q-W wherein Q represents a bond or -O-, -S-, -SO- or -SO₂- 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, -CO₂H, -CO₂ (C_1-C_6) alkyl, -CONH₂, -CONH (C_1-C_6) alkyl, -CONH (C_1-C_6) alkyl₂, -CHO, -CH₂OH, (C_1-C_4) perfluoroalkyl, -O (C_1-C_6) alkyl, -S (C_1-C_6) alkyl, -SO (C_1-C_6) alkyl, -SO₂ (C_1-C_6) alkyl, -NO₂, -NH₂, -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.

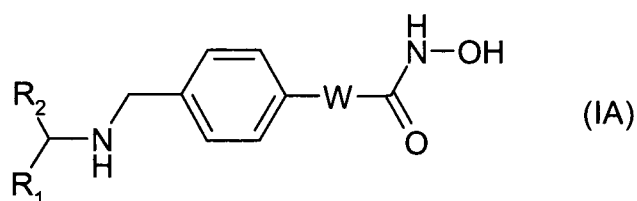
Examples of particular R_2 groups include hydrogen (the glycine "side chain"), benzyl, phenyl, cyclohexylmethyl, cyclohexyl, pyridin-3-ylmethyl, tert-butoxymethyl, iso-butyl, sec-butyl, tert-butyl, 1-benzylthio-1-methylethyl, 1-methylthio-1-methylethyl, 1-mercapto-1-methylethyl, and phenylethyl. Presently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

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.

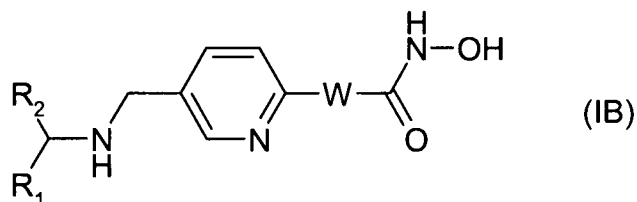
For macrophage selective compounds, side chains such as those of valine (ie $-CH(CH_3)_2$), cyclohexylglycine (ie cyclohexyl), t-butylserine (ie $-CH_2O(t-Bu)$), t-butylcysteine (ie $-CH_2S(t-Bu)$), and phenylglycine (ie phenyl) are currently preferred.

One subset of the compounds of the invention has formula (IA):



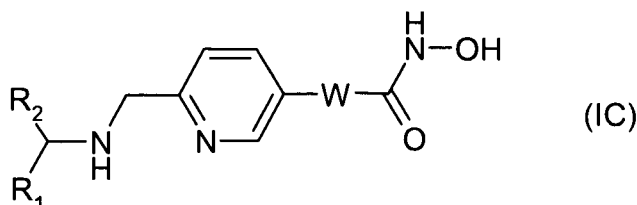
wherein W, R_1 and R_2 are as defined and further discussed above.

Another subset of the compounds of the invention has formula (IB):



wherein W, R_1 and R_2 are as defined and further discussed above.

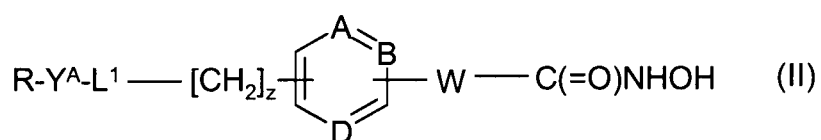
Yet another subset of the compounds of the invention has formula (IC):



wherein W, R_1 and R_2 are as defined and further discussed above.

Alternative embodiments

The compounds of formula (I) of the invention are characterised by the attachment of the alpha amino acid or esterase-hydrolysable alpha amino acid ester motif R^1R^2CHNH- to the ring containing A, B and D via a linker radical $-YL^1X^1[CH_2]_z-$. Instead of being N-linked in this way, the alpha amino acid or esterase-hydrolysable alpha amino acid ester motif may be C-linked to the ring containing A, B and D via a linker radical attached to its alpha carbon. Thus, an alternative embodiment of the invention comprises compounds of formula (II) and salts, N-oxides, hydrates and solvates thereof:



wherein A, B, D, W, L^1 and z are as defined and discussed above in relation to compounds of formula (I)

Y^A is a bond, $-(C=O)-$, $-S(O_2)-$, $-(C=O)NR_3-$, $-NR_3(C=O)-$, $-S(O_2)NR_3-$, $-NR_3S(O_2)-$, or $-NR_3(C=O)NR_5-$, wherein R_3 and R_5 are as defined and discussed above in relation to compounds of formula (I); and

R is a radical of formula (X) or (Y)



wherein

R₁ as defined and discussed above in relation to compounds of formula (I), and

R₆ is hydrogen; or optionally substituted C₁-C₆ alkyl, C₃-C₇ cycloalkyl, aryl or heteroaryl or $-(C=O)R_3$, $-(C=O)OR_3$, or $-(C=O)NR_3$ wherein R_3 is as defined and discussed above in relation to compounds of formula (I).

In compounds (II), when the nitrogen of the ester motif is substituted but not directly bonded to a carbonyl i.e. when in formula X, **R**₆ is not H, or a group linked to the nitrogen through a $-(C=O)-$,

-C(=O)O- or -C(=O)NR₃- radical, or in formula Y the ring system does not directly link a -C(=O), -C(=O)O- or -C(=O)NH- radical to the nitrogen of the esterase motif, the ester will only be hydrolysed by hCE-1 and hence the inhibitors will only accumulate in macrophages.

R₆ may be, *inter alia*, optionally substituted C₁-C₆ alkyl, C₃-C₇ cycloalkyl, aryl or heteroaryl, for example methyl, ethyl, n- or isopropyl, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, or pyridyl. In cases where macrophage specificity is not required, R₆ may be hydrogen, or -(C=O)R₇, wherein R₇ is optionally substituted C₁-C₆ alkyl such as methyl, ethyl, n- or isopropyl, or n-, iso- or sec-butyl, C₃-C₇ cycloalkyl such as cyclopropyl, cyclopentyl, cyclohexyl, phenyl, pyridyl, thienyl, phenyl(C₁-C₆ alkyl)-, thienyl(C₁-C₆ alkyl)- or pyridyl(C₁-C₆ alkyl)- such as benzyl, 4-methoxyphenylmethylcarbonyl, thienylmethyl or pyridylmethyl.

R₆ may also be, for example -(C=O)OR₇, or -(C=O)NHR₇ wherein R₇ is hydrogen or optionally substituted (C₁-C₆)alkyl such as methyl, ethyl, or n- or iso-propyl.

For compounds (II) which are to be administered systemically, esters with a slow rate of esterase 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. If a carbon atom to which the group R in formula (II) is attached is unsubstituted, ie R is attached to a methylene (-CH₂)- radical, then the esters tend to be cleaved more rapidly than if that carbon is substituted, or is part of a ring system such as a phenyl or cyclohexyl ring.

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 is monosubstituted, ie R₂ is CH₂R^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 R₂ is, for example, phenyl or cyclohexyl.

Utilities

As mentioned above, the compounds with which the invention is concerned are inhibitors of HDAC activity, and are therefore of use in the treatment of diseases such as cancers, 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.

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. However, it is expected that a typical dose will be in the range from about 0.001 to 50 mg per kg of body weight.

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 polyvinyl-pyrrolidone; fillers for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tableting 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.

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 pharmaceuticals such as the British Pharmacopoeia.

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 apparatus 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).

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.

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

There are multiple synthetic strategies for the synthesis of the compounds with which the present invention is concerned, but all rely on known chemistry, known to the synthetic organic chemist. Thus, compounds according to the invention can be synthesised according to procedures described in the standard literature and are well-known to the one 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*". The synthetic routes used in the preparation of the compounds of the Examples below may be adapted for the preparation of analogous compounds.

The following Examples illustrate the preparation of specific compounds of the invention, and the HDAC inhibitory properties thereof:

Abbreviations

MeOH = methanol

EtOH = ethanol

EtOAc = ethyl acetate

Boc = *tert*-butoxycarbonyl

DCM = dichloromethane

DMF = dimethylformamide

DCE = 1,2-dichloroethane

TMSOK = potassium trimethylsilanoxide

DMSO = dimethyl sulfoxide

TFA = trifluoroacetic acid

THF = tetrahydrofuran

Na₂CO₃ = sodium carbonate

K₂CO₃ = potassium carbonate

HCl = hydrochloric acid

aq = aqueous solution

sat = saturated

DIPEA = diisopropylethylamine

NaH = sodium hydride

NaOH = sodium hydroxide

STAB = sodium triacetoxymethylborohydride

NaCNBH₃ = sodium cyanoborohydride

NaHCO₃ = sodium hydrogen carbonate

Pd/C = palladium on carbon

TBME = *tert*-butyl methyl ether

TPAP = tetrapropyl ammonium perruthenate

(COCl)₂ = oxalyl chloride

N₂ = nitrogen

PyBop = benzotriazole-1-yl-oxy-*tris*-pyrrolidino-phosphonium hexafluorophosphate

Na₂SO₄ = sodium sulphate

Et₃N = triethylamine

NH₃ = ammonia

TMSCl = trimethylchlorosilane

NH₄Cl = ammonium chloride

LiAlH₄ = lithium aluminium hydride

PyBrOP = Bromo-*tris*-pyrrolidino phosphoniumhexafluorophosphate

MgSO₄ = magnesium sulfate

ⁿBuLi = n-butyllithium

CO₂ = carbon dioxide

EDCI = *N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride

Et₂O = diethyl ether

LiOH = lithium hydroxide

HOBt = 1-hydroxybenzotriazole

TLC = thin layer chromatography

LCMS = liquid chromatography / mass spectrometry

mL = millilitre(s)

g = gram(s)

mg = milligram(s)

mol = mole(s)

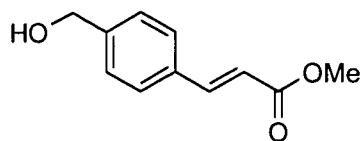
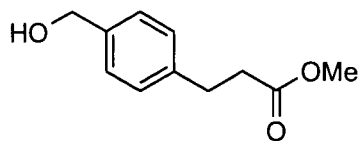
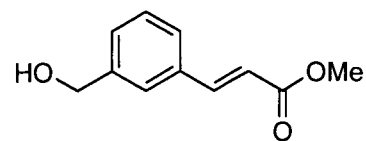
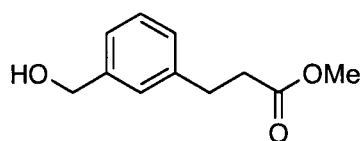
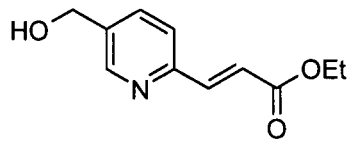
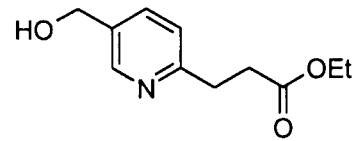
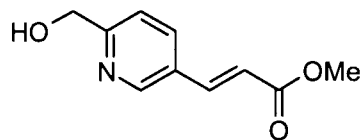
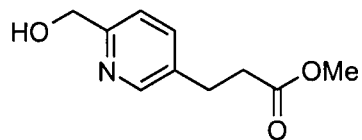
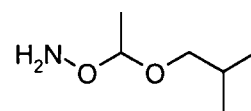
mmol = millimole(s)

HPLC = high performance liquid chromatography

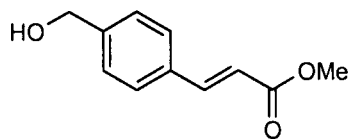
NMR = nuclear magnetic resonance

RT = room temperature

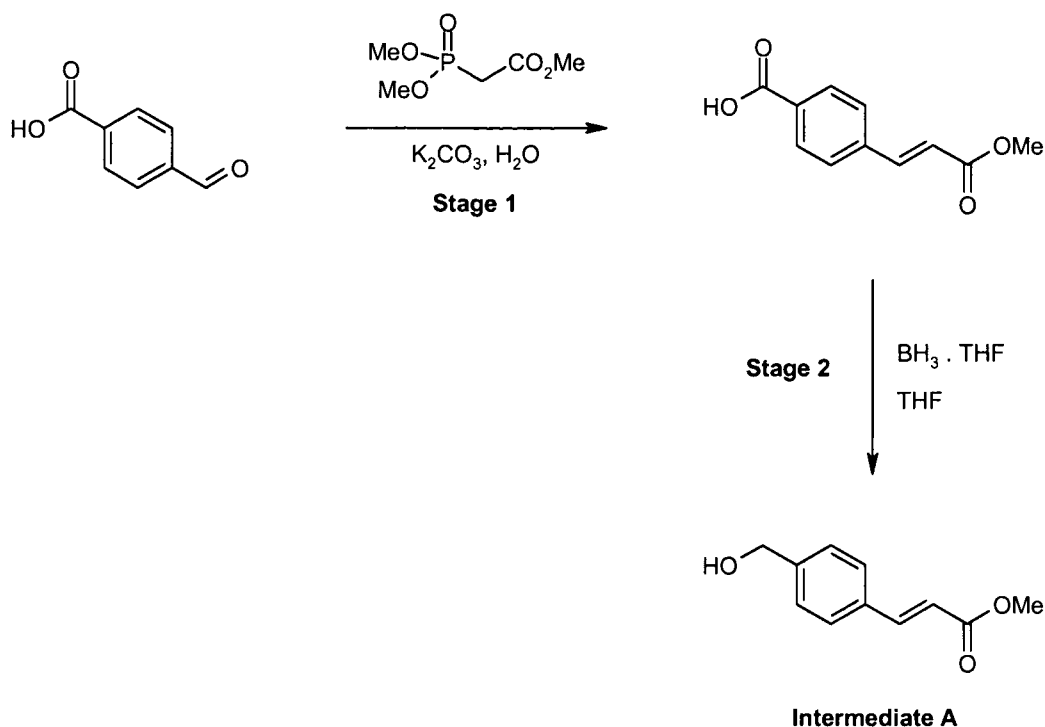
h = hour(s)

Scaffold intermediates:**Intermediate A****Intermediate B****Intermediate C****Intermediate D****Intermediate E****Intermediate F****Intermediate G****Intermediate H****Intermediate I***Preparation:***Intermediate A:**

Methyl (2E)-3-[4-(hydroxymethyl)phenyl]acrylate



The title compound was prepared by the following methodology:



Stage 1 – Preparation of 4-[(1E)-3-methoxy-3-oxoprop-1-en-1-yl]benzoic acid

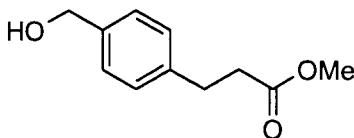
4-Formylbenzoic acid (20g, 0.133mol) and K_2CO_3 (55g, 0.398mol) were added to water (350mL) and cooled to 0-5°C. Trimethyl phosphonoacetate (26mL, 0.160mol) was charged dropwise maintaining the reaction temperature below 15°C. The reaction was then warmed and stirred at RT for 1.5h before acidifying to pH ~ 1. The resulting precipitate was filtered and dried *in vacuo* to afford the title product as a pale yellow solid (29.5g, quant). 1H NMR (300MHz, d_6 -DMSO) δ : 7.89-7.52 (5H, m), 6.59 (1H, d, $J=16.2$ Hz), 3.7 (3H, s).

Stage 2 – Preparation of methyl (2E)-3-[4-(hydroxymethyl)phenyl]acrylate (Intermediate A**)**

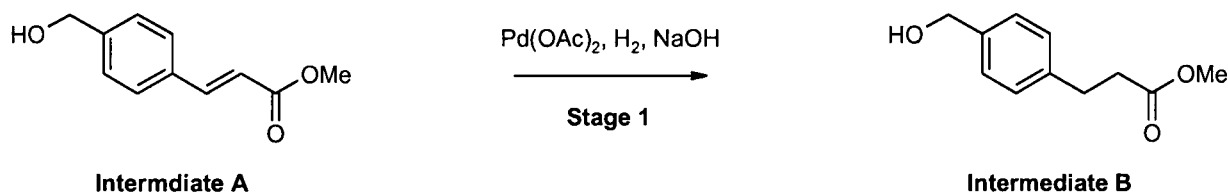
Stage 1 product (10g, 48mmol) was added to THF (80mL) and cooled to 0-5°C. Borane-THF complex, 1M in THF (97mL, 96mmol) was added dropwise and the reaction allowed to warm to RT and stirred for 2h. It was then quenched with 1:1 10% HCl_{aq} /THF, then the organics removed *in vacuo*. The residue was extracted with EtOAc (2 x 50mL) and the combined organics washed with sat. $NaHCO_3$ solution (50mL) then brine (50mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the title product as a yellow oil (2.75g, 30%). 1H NMR (300MHz, CD_3OD) δ : 7.75-7.70 (5H, m), 6.54 (1H, d, $J=16.2$ Hz), 4.64 (2H, s), 3.80 (3H, s).

Intermediate B:

Methyl 3-[4-(Hydroxymethyl)phenyl]propanoic acid



The title compound was prepared by the following methodology:

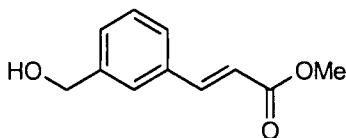


Stage 1 – Preparation of methyl 3-[4-(hydroxymethyl)phenyl]propanoic acid (**Intermediate B**)

Intermediate A (3g, 15.6mmol) and palladium acetate (0.3g, 1.3mmol) were added to 0.5N NaOH_{aq} (50mL), purged with and stirred under hydrogen for 4.5h. The reaction was filtered through celite, washed with DCM (30mL), acidified to pH ~ 1 with 10% HCl_{aq} and extracted with EtOAc (2 x 30mL). The combined organics were dried (MgSO₄) and concentrated *in vacuo* to afford the title product as a pale yellow solid (2.85g, 94%). ¹H NMR (300MHz, CD₃OD) δ: 7.25 (4H, ABq, J=10.9, 22.9Hz), 4.57 (2H, s), 3.68 (3H, s), 2.92 (2H, t, J=9.8Hz), 2.60 (2H, t, J=9.8Hz).

Intermediate C:

Methyl (2E)-3-[3-(hydroxymethyl)phenyl]acrylic acid

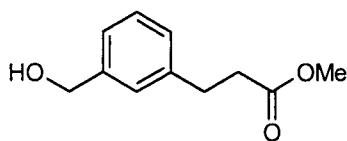


The title compound was prepared from 3-formylbenzoic acid by the same methodology used to make **Intermediate A**.

¹H NMR (300MHz, CDCl₃) δ: 7.63 (1H, d, J=15.9Hz), 7.42 (2H, d, J=8.4Hz), 7.30 (2H, d, J=8.1Hz), 6.37 (1H, d, J=15.9Hz), 4.61 (2H, s), 3.77 (3H, s).

Intermediate D:

Methyl 3-[3-(Hydroxymethyl)phenyl]propanoic acid

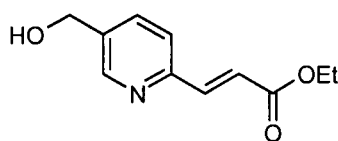


The title compound was prepared from **Intermediate C** by the same methodology used to make **Intermediate B**.

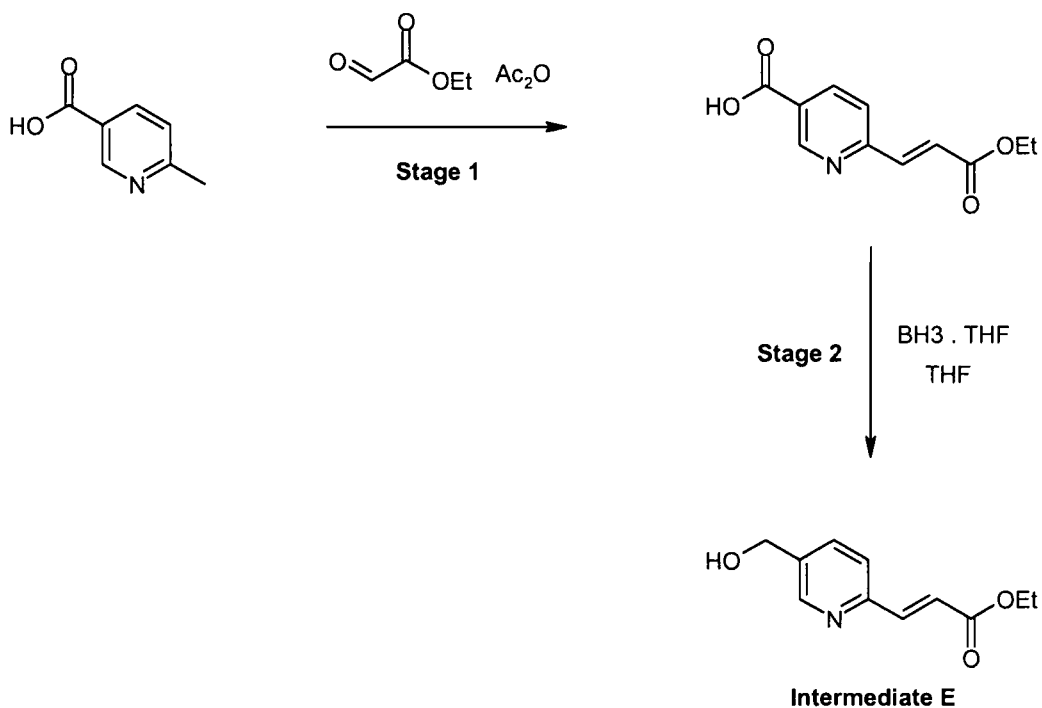
^1H NMR (300MHz, d_6 -DMSO) δ : 6.73-7.25 (4H, m), 5.13 (1H, t, $J=5.7\text{Hz}$), 4.76 (2H, d, $J=5.7\text{Hz}$), 3.60 (3H, m), 2.84 (2H, t, $J=7.5\text{Hz}$), 2.62 (2H, m, $J=7.5\text{Hz}$).

Intermediate E:

Ethyl (2E)-3-[5-(Hydroxymethyl)pyridin-2-yl]acrylic acid



The title compound was prepared by the following methodology:

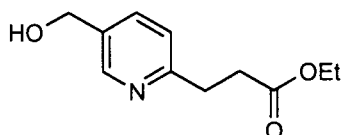


Stage 1 – Preparation of 6-[(1E)-3-ethoxy-3-oxoprop-1-en-1-yl]nicotinic acid

6-Methylnicotinic acid (5g, 36mmol) and ethyl glyoxalate (50% solution in toluene – 8.7mL, 44mmol) were added to Ac₂O (25mL) and stirred under a nitrogen atmosphere. The reaction was heated at 130°C for 3h then allowed to cool to RT over 17h. The reaction was then quenched with water (10mL) and concentrated to dryness *in vacuo* to afford the product as a brown solid (11.6g, >100%). m/z = 222 [M+H]⁺.

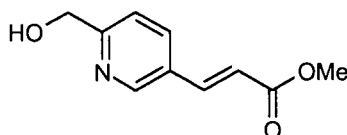
Stage 2 – Preparation of ethyl (2E)-3-[5-(hydroxymethyl)pyridin-2-yl]acrylate (Intermediate E)

Borane-THF complex (1M in THF – 84mL, 0.084mol) was added dropwise to a slurry of stage 1 product (11.6g, 52mmol) in THF (100mL), under a nitrogen atmosphere. The reaction was stirred at RT for 1.5h then quenched with 2N HCl_{aq} (20mL). The THF was removed *in vacuo*, the residue basified to pH ~ 9 with K₂CO₃ then extracted with EtOAc (3 x 30mL). The organic phases were combined, dried (MgSO₄) then concentrated *in vacuo* to afford the crude product as a brown oil. Purification by column chromatography gave the desired product as a yellow solid (1.86g, 25%). ¹H NMR (300MHz, CD₃OD) δ: 8.59 (1H, s), 7.91-7.63 (3H, m), 6.88 (1H, d, J=15.9Hz), 4.70 (2H, s), 4.28 (2H, q), 1.35 (3H, t).

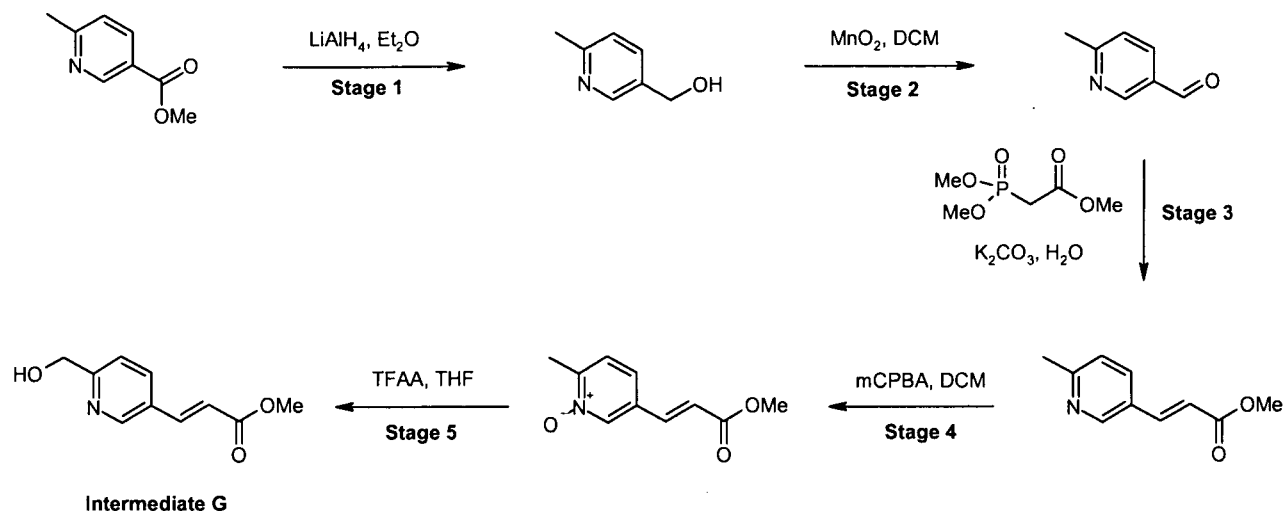
Intermediate F:Ethyl 3-[5-(Hydroxymethyl)pyridin-2-yl]propanoic acid

The title compound was prepared from **Intermediate E** by the same methodology used to make **Intermediate B**.

¹H NMR (300MHz, CDCl₃) δ: 8.49 (1H, s), 7.65 (1H, d, J=5.7Hz), 7.21 (1H, d, J=7.8Hz), 4.68 (2H, s), 4.13 (2H, q, J=7.2Hz), 3.12 (2H, t, J=7.5Hz), 2.77 (2H, t, J=7.2Hz), 1.24 (3H, t, J=7.2Hz).

Intermediate G:Methyl (2E)-3-[6-(Hydroxymethyl)pyridin-3-yl]acrylic acid

The title compound was prepared by the following methodology:



Stage 1 – Preparation of (6-methylpyridin-3-yl)methanol

To a suspension of lithium aluminium hydride (7.24g, 191mmol) in Et₂O (400ml) at -78°C was added *via* cannula over a period of one hour a solution of methyl 6-methylnicotinate (19.62g, 130mmol) in Et₂O (200mL). Once addition was completed, the mixture was stirred for a further 3h. Excess lithium aluminium hydride was quenched by dropwise addition of EtOAc (40 ml). The mixture was then warmed using a water-ice bath, and further quenched with sat NH₄Cl (500mL). The ethereal layer was decanted, and EtOAc was added (500mL). The mixture was stirred vigorously, and the organic layer was again decanted. The extraction procedure was repeated twice (500mL EtOAc). The combined organic extracts were dried (MgSO₄) and concentrated to yield the desired product (13.6g, 85%). ¹H NMR (300MHz, CDCl₃) δ: 8.39 (1H, s), 7.62 (1H, dd, J=2.1, 8.1Hz), 7.14 (1H, d, J=7.8Hz), 4.68 (2H, s), 2.54 (3H, s).

Stage 2 – Preparation of 6-methylnicotaldehyde

To a cooled (ice bath) solution of stage 1 product (14.85g, 120.6mmol) in DCM (1000mL) was added manganese oxide (100g) in 10g portions over a period of 30 minutes. The mixture was warmed to RT and stirred for 45 minutes and was then filtered through Celite. The residues were washed with DCM (500mL), and the combined DCM portions were concentrated to yield the desired product. ¹H NMR (300MHz, CDCl₃) δ: 10.00 (1H, s), 8.88 (1H, d, J=1.8Hz), 8.00 (1H, dd, J=2.4, 8.1Hz), 7.26 (1H, d, J=8.1Hz), 2.60 (3H, s).

Stage 3 – Preparation of methyl (2E)-3-(6-methylpyridin-3-yl)acrylate

To a solution of stage 2 product (14.60 g, 120mmol) in water (600mL) was added K₂CO₃ (55g, 398mmol). The mixture was cooled (ice bath) and trimethylphosphonoacetate (25mL,

154mmol) was added dropwise over a period of 10 minutes. The mixture was stirred for 5 minutes and then warmed to RT and stirred for a further hour. The product was collected by filtration and washed with water (250mL), then dried under vacuum to yield the desired product (15.708g, 73% over two steps). ^1H NMR (300MHz, d_6 -DMSO) δ : 8.74 (1H, d, $J=2.1\text{Hz}$), 8.08 (1H, dd, $J=2.4, 8.1\text{Hz}$), 7.66 (1H, d, $J=16.2\text{Hz}$), 7.32 (1H, d, $J=8.1\text{Hz}$), 6.74 (1H, d, $J=16.2\text{Hz}$), 3.73 (3H, s), 2.50 (3H, s).

Stage 4 – Preparation of methyl (2E)-3-(6-methyl-1-oxidopyridin-3-yl)acrylate

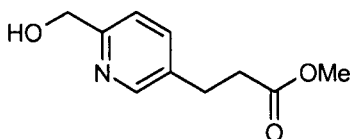
To a solution of stage 3 product (10.04g, 57mmol) in DCM (250mL) was added mCPBA (10.1g, 10.7g, 4.7g, 147mmol) in three portions over a period of 1 hour. The mixture was dried by addition of anhydrous magnesium sulfate, and filtered, washing with a further portion of DCM (200mL). The mixture was concentrated, then loaded directly onto a silica gel column and eluted with 10% methanol-DCM to yield the desired product (10.35g, 94%). ^1H NMR (300MHz, d_6 -DMSO) δ : 8.70 (1H, s), 7.68 (1H, dd, $J=1.3, 7.9\text{Hz}$), 7.59 (1H, d, $J=16.2\text{Hz}$), 7.52 (1H, d, $J=8.1\text{Hz}$), 3.74 (3H, s), 2.34 (3H, s).

Stage 5 – Preparation of methyl (2E)-3-[6-(hydroxymethyl)pyridin-3-yl]acrylate (Intermediate G**)**

To a cooled (ice bath) solution of stage 4 product (24.60g, 127mmol) in THF (500mL) was added trifluoroacetic anhydride (25mL, 180mmol). The mixture was stirred for 15 minutes and then warmed to RT. After stirring for 1 hour, the solution was cooled (ice bath) and the mixture was quenched by careful addition of sat NaHCO_3 (1000mL). The product was extracted with DCM (3 x 500mL) then purified by flash column chromatography (10% MeOH in DCM) to yield the desired product (13.97g, 57%). ^1H NMR (300MHz, CDCl_3) δ : 8.70 (1H, s), 7.87 (1H, dd, $J=2.1, 8.1\text{Hz}$), 7.71 (1H, d, $J=16.2\text{Hz}$), 7.32 (1H, d, $J=8.1\text{Hz}$), 8.52 (1H, d, $J=15.9\text{Hz}$), 4.81 (2H, s), 3.85 (3H, s).

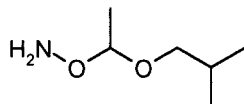
Intermediate H:

Methyl 3-[6-(Hydroxymethyl)pyridin-3-yl]propanoic acid

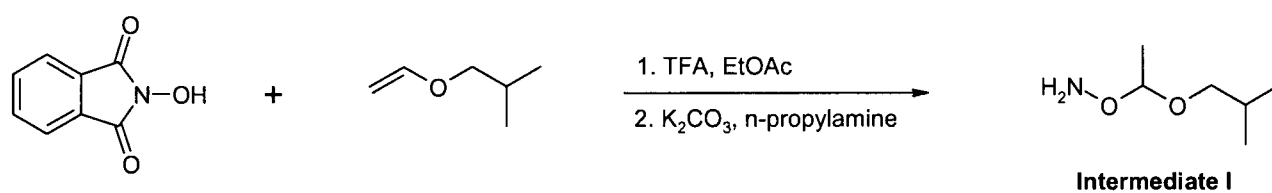


The title compound was prepared from **Intermediate G** acid by the same methodology used to make **Intermediate B**.

^1H NMR (300MHz, CDCl_3) δ : 8.44 (1H, s), 7.55 (1H, dd, $J=2.1, 8.1\text{Hz}$), 7.20 (1H, d, $J=8.1\text{Hz}$), 4.75 (2H, s), 3.69 (3H, s), 2.98 (2H, t, $J=7.5\text{Hz}$), 2.67 (2H, t, $J=7.5\text{Hz}$).

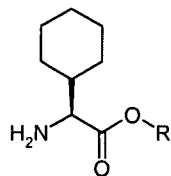
Intermediate I:O-(1-Isobutoxyethyl)hydroxylamine

The title compound was prepared by the following methodology:

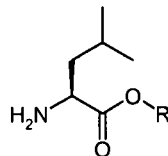


Intermediate I was prepared following the methodology described in WO 01/60785.

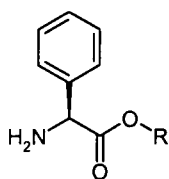
¹H NMR (300MHz, d₆-DMSO) δ: 0.85 (6H, d), 1.15 (3H, d), 1.75 (1H, m), 3.18 (1H, dd), 3.42 (1H, dd), 4.53 (1H, q), 5.82 (2H, s).

Aminoacid intermediates:

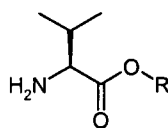
Int. J1 R = cyclopentyl
 Int. J2 R = t-butyl
 Int. J3 R = ethyl
 Int. J4 R = allyl
 Int. J5 R = 2-methylcyclopentyl
 Int. J6 R = indanyl
 Int. J7 R = norbonyl
 Int. J8 R = 3-methylcyclopentyl
 Int. J9 R = benzyl
 Int. J10 R = ethylmorpholino
 Int. J11 R = ethyldimethylamino
 Int. J12 R = (+)-menthyl
 Int. J13 R = (-)-menthyl



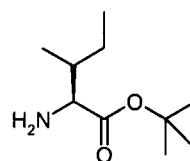
Int. K1 R = cyclopentyl
 Int. K2 R = t-butyl
 Int. K3 R = ethylmorpholino
 Int. K4 R = norbonyl
 Int. K5 R = indanyl
 Int. K6 R = ethyldimethylamino
 Int. K7 R = (-)-menthyl



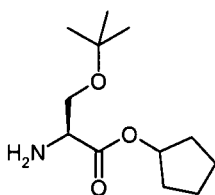
Intermediate L1 R = cyclopentyl
Intermediate L2 R = t-butyl



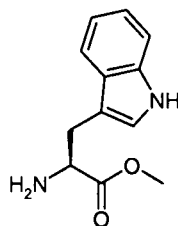
Intermediate M1 R = cyclopentyl
Intermediate M2 R = t-butyl



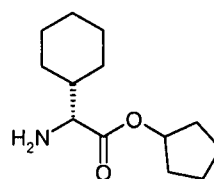
Intermediate N



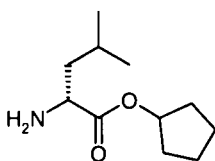
Intermediate O



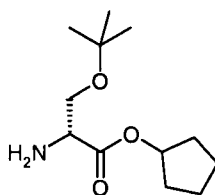
Intermediate P



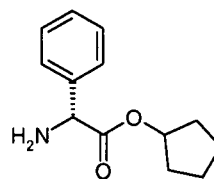
Intermediate Q



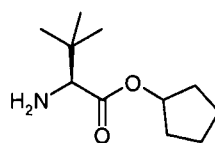
Intermediate R



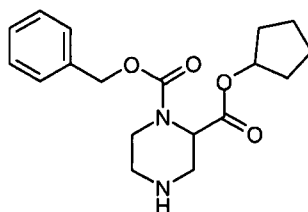
Intermediate S



Intermediate T



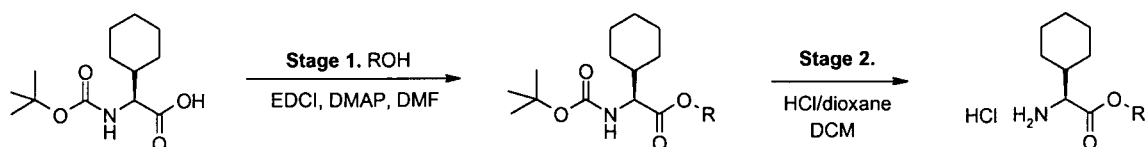
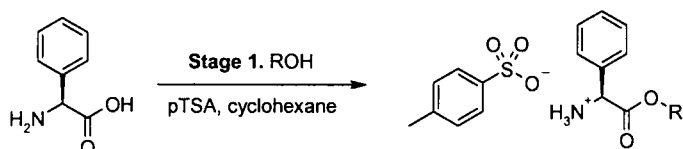
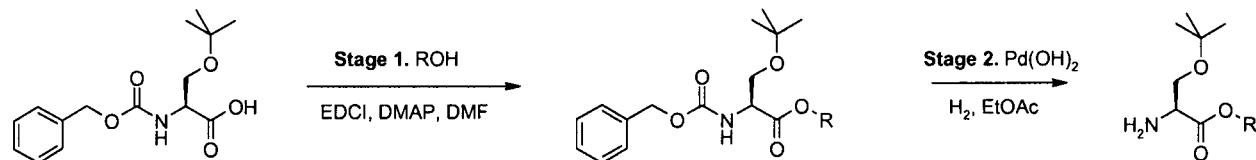
Intermediate U



Intermediate V

Preparation:

The intermediates above were prepared from the corresponding aminoacids and alcohols according to the methods described below:

Method I.**Method II.****Method III.****Method I (exemplified for Intermediate J1)****Stage 1 – Preparation of cyclopentyl (2S)-[(tert-butoxycarbonyl)amino](cyclohexyl)acetate**

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), EDC (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 (MgSO₄) 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%). ¹H NMR (300MHz, d₆-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 – Preparation of cyclopentyl (2S)-amino(cyclohexyl)acetate hydrochloride

(Intermediate J1)

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 Et₂O to give a white precipitate. This was further washed with Et₂O to give the desired product as a white powder (7.78g, 65%). ¹H NMR (300MHz, d₆-DMSO) δ: 8.45 (3H, br s), 5.22 (1H, t), 3.28 (1H, d), 1.95-1.50 (10H, br m), 1.30-0.90 (9H, br m).

Method II (exemplified for Intermediate L1)

Stage 1 – Ester formation to yield cyclopentyl (2S)-amino(phenyl)acetate tosylate salt

(Intermediate L1)

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, d₆-DMSO) δ: 8.82 (2H, br s), 8.73 (1H, br s), 7.47 (7H, m), 7.11 (2H, d), 5.25 (1H, br s), 5.18 (1H, m), 2.29 (3H, s), 1.87-1.36 (8H, m).

Method III (exemplified for Intermediate O)

Stage 1 – Preparation of [(2S)-2-{[(benzyloxy)carbonyl]amino}-3-*tert*-butoxypropanoyl]oxy

To a solution of (S)-2-benzyloxycarbonylamino-3-*tert*-butoxy-propionic acid (25g, 84.65mmol) in DMF (250mL) at 0°C was added cyclopentanol (15.36mL, 169.3mmol), EDCI (17.85g, 93.11mmol) and finally DMAP (1.03g, 8.46mmol). The reaction mixture was warmed to RT and stirred for 18h. The DMF was removed *in vacuo* to give a yellow oil. This was partitioned between water and EtOAc. The organic phase was dried (MgSO₄) 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. This was used directly in the next stage without characterization.

Stage 2 – Preparation of cyclopentyl *O*-*tert*-butyl-L-serinate **(Intermediate O)**

Stage 1 product was dissolved in EtOAc (150mL), treated with Pd(OH)₂ (10 mol%) and stirred under an atmosphere of hydrogen for 32h. Upon completion, the catalyst was removed by filtration through celite and the filtrate concentrated *in vacuo* to yield the desired product as a clear oil (15.96g, 82% over two steps). ¹H NMR (300MHz, d₆-DMSO) δ: 5.17 (1H, t), 3.45 (1H, m), 3.34 (2H, q), 1.90-1.50 (9H, br m), 1.08 (9H, s).

Characterisation:

Intermediate number	Chemical name	Method for preparation	Analytical data
J1	Cyclopentyl (2S)-amino(cyclohexyl)acetate	I	¹ H NMR (300MHz, <i>d</i> ₆ -DMSO) δ: 8.45 (3H, br s), 5.22 (1H, t), 3.28 (1H, d), 1.95-1.50 (10H, br m), 1.30-0.90 (9H, br m).
J2	<i>tert</i> -Butyl (2S)-amino(cyclohexyl)acetate	I	<i>m/z</i> = 214 [M+H] ⁺ .
J3	Ethyl (2S)-amino(cyclohexyl)acetate	I	¹ H NMR (300MHz, <i>d</i> ₆ -DMSO) δ: 3.99-4.35 (3H, m), 1.02-1.86 (12H, m), 1.06 (3H, t, <i>J</i> =7.2Hz).
J4	Allyl (2S)-amino(cyclohexyl)acetate	I	¹ H NMR (300MHz, <i>d</i> ₆ -DMSO) δ: 5.92 (1H, ddd, <i>J</i> =5.4, 10.5, 17.4Hz), 5.34 (1H, dd, <i>J</i> =1.8, 17.4Hz), 5.22 (1H, dd, <i>J</i> =3.0, 10.5Hz), 4.51-4.62 (2H, m), 3.12 (1H, d, <i>J</i> =5.7Hz), 0.95-1.70 (11H, m).
J5	2-Methylcyclopentyl (2S)-amino(cyclohexyl)acetate	I	¹ H NMR (300MHz, <i>d</i> ₆ -DMSO) δ: 4.61 (1H, d, <i>J</i> =6.0Hz), 3.06 (1H, d, <i>J</i> =2.4Hz), 1.00-2.01 (20H, m), 0.90 (3H, d, <i>J</i> =5.7Hz).
J6	2,3-Dihydro-1 <i>H</i> -inden-2-yl (2S)-amino(cyclohexyl)acetate	I	<i>m/z</i> = 274.25 [M+H] ⁺
J7	Bicyclo[2.2.1]hept-2-yl (2S)-amino(cyclohexyl)acetate	I	¹ H NMR (300MHz, <i>d</i> ₆ -DMSO) δ: 4.86 (1H, t, <i>J</i> =3.6Hz), 3.03 (1H, d, <i>J</i> =3.9Hz), 2.22 (2H, m), 0.93-1.70 (21H, m).
J8	3-Methylcyclopentyl (2S)-amino(cyclohexyl)acetate	I	¹ H NMR (300MHz, <i>d</i> ₆ -DMSO) δ: 5.02-5.11 (1H, m), 3.02-3.05 (1H, m), 0.80-2.20 (23H, m).
J9	Benzyl (2S)-amino(cyclohexyl)acetate	I	¹ H NMR (300MHz, <i>d</i> ₆ -DMSO) δ: 7.23-7.43 (5H, m), 5.05-5.16 (2H, m), 3.15 (1H, t, <i>J</i> =3.0Hz), 1.42-1.80 (7H, m), 0.92-1.27 (5H, m).

Intermediate number	Chemical name	Method for preparation	Analytical data
J10	2-Morpholin-4-ylethyl (2S)-amino(cyclohexyl)acetate	I	¹ H NMR (300MHz, <i>d</i> ₆ -DMSO) δ: 8.71 (3H, br s), 4.47-4.62 (1H, m), 3.85-4.00 (6H, m), 3.42-3.55 (4H, m), 3.15-3.20 (2H, m), 1.60-1.85 (6H, m), 1.01-1.25 (5H, m).
J11	2-(Dimethylamino)ethyl (2S)-amino(cyclohexyl)acetate	I	¹ H NMR (300MHz, CDCl ₃) δ: 4.20-4.29 (3H, m), 2.60 (2H, t, J=6.0Hz), 2.30 (6H, s), 1.52-1.80 (6H, m), 1.05-1.25 (5H, m).
J12	(1S,2R,5S)-2-Isopropyl-5-methylcyclohexyl (2S)-amino(cyclohexyl)acetate	I	¹ H NMR (300MHz, <i>d</i> ₆ -DMSO) δ: 8.24 (3H, br s), 7.47 (2H, d, J=7.8Hz), 7.12 (2H, d, J=7.8Hz), 4.65-4.73 (1H, m), 3.94 (1H, br s), 2.29 (3H, s), 1.00-2.00 0.89 (6H, d, J=6.3Hz), 0.71 (3H, d, J=6.6Hz).
J13	(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl (2S)-amino(cyclohexyl)acetate	I	<i>m/z</i> = 296 [M+H] ⁺ .
K1	Cyclopentyl L-leucinate	I	<i>m/z</i> = 200 [M+H] ⁺ ; ¹ H NMR (300 MHz, CDCl ₃) δ: 0.90 (6H, t, J=6.4 Hz), 1.23-1.94 (11H, m), 3.38 (1H, dd, J=8.4, 5.9 Hz), 5.11-5.22 (1H, m).
K2	<i>tert</i> -Butyl L-leucinate	Commercial source	n/a
K3	2-Morpholin-4-ylethyl L-leucinate	I	¹ H NMR (300MHz, <i>d</i> ₆ -DMSO) δ: 8.96 (2H, br s), 4.52 (1H, m), 3.97 (4H, br s), 3.59-3.41 (6H, m), 3.18 (2H, br s), 1.80-1.68 (3H, m), 0.88 (6H, br s).
K4	Bicyclo[2.2.1]hept-2-yl L-leucinate	I	¹ H NMR (300MHz, <i>d</i> ₆ -DMSO) δ: 8.58 (2H, br s), 4.64 (1H, d, J=7.6Hz), 2.43 (1H, br s), 2.28 (2H, br s), 1.99 (1H, m), 1.79-1.02 (10H, m), 0.93-0.87 (6H, m).
K5	2,3-Dihydro-1 <i>H</i> -inden-2-yl L-leucinate	I	¹ H NMR (300MHz, <i>d</i> ₆ -DMSO) δ: 8.72 (3H, br s), 7.25 (2H, br s), 7.18 (2H, br s), 5.55 (1H, br s), 3.80 (1H, br s), 3.33 (2H, dd, J=6.5, 16.3Hz), 2.99 (2H, t, J=16.3Hz), 1.72-1.55 (3H, m), 0.82 (6H, s).

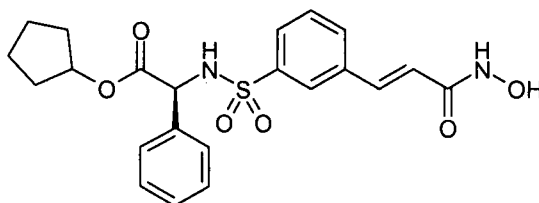
Intermediate number	Chemical name	Method for preparation	Analytical data
K6	2-(Dimethylamino)ethyl L-leucinate	I	^1H NMR (300MHz, CDCl_3) δ : 3.50-3.40 (2H, m), 2.94 (2H, s), 2.52 (2H, t, $J=5.4\text{Hz}$), 1.48 (1H, m), 1.35 (1H, m), 0.93-0.82 (12H, m).
K7	(1 <i>R</i> ,2 <i>S</i> ,5 <i>R</i>)-2-Isopropyl-5-methylcyclohexyl L-leucinate	I	^1H NMR (300MHz, d_6 -DMSO) δ : 8.58 (2H, br s), 4.70 (1H, dt, $J=5.4$, 10.9Hz), 3.91 (1H, t, $J=8.7\text{Hz}$), 1.92-1.82 (2H, m), 1.80-1.55 (5H, m), 1.46-1.35 (2H, m), 1.02 (2H, t, $J=10.9\text{Hz}$), 0.93-0.82 (13H, m), 0.70 (3H, d, $J=8.7\text{Hz}$).
L1	Cyclopentyl (2 <i>S</i>)-amino(phenyl)acetate	II	^1H NMR (300MHz, d_6 -DMSO) δ : 8.82 (2H, br s), 8.73 (1H, br s), 7.47 (7H, m), 7.11 (2H, d), 5.25 (1H, br s), 5.18 (1H, m), 2.29 (3H, s), 1.87-1.36 (8H, m).
L2	<i>tert</i> -Butyl (2 <i>S</i>)-amino(phenyl)acetate	Commercial source	n/a
M1	Cyclopentyl L-valinate	I	$m/z = 186$ $[\text{M}+\text{H}]^+$; ^1H NMR (300MHz, d_6 -DMSO) δ : 8.26 (1H, br s), 7.49 (2H, d, $J=8.1\text{Hz}$), 7.13 (2H, d, $J=8.1\text{Hz}$), 5.21 (1H, t, $J=5.5\text{Hz}$), 3.86 (1H, br s), 3.42 (1H, br s), 2.29 (3H, s), 2.13 (1H, td, $J=6.9$, 4.7Hz), 1.90-1.79 (2H, m), 1.70-1.57 (6H, m), 0.98 (3H, d, $J=7.0\text{Hz}$), 0.94 (3H, d, $J=7.0\text{Hz}$).
M2	<i>tert</i> -Butyl L-valinate	Commercial source	n/a
N	<i>tert</i> -Butyl L-isoleucinate	Commercial source	n/a
O	Cyclopentyl <i>O-tert</i> -butyl-L-serinate	III	^1H NMR (300MHz, d_6 -DMSO) δ : 5.17 (1H, t), 3.45 (1H, m), 3.34 (2H, q), 1.90-1.50 (9H, br m), 1.08 (9H, s).
P	Methyl L-tryptophanate	Commercial source	n/a
Q	Cyclopentyl (2 <i>R</i>)-amino(cyclohexyl)acetate	I	^1H NMR (300MHz, CDCl_3) δ : 8.63 (3H, s), 5.22 (1H, m), 5.16 (1H, m), 2.08-0.90 (19H, m).
R	Cyclopentyl D-leucinate	I	^1H NMR (300MHz, CDCl_3) δ : 8.90 (3H, s), 5.28 (1H, m), 3.97 (1H, m), 2.10-1.50 (11H, m), 1.01 (6H, d, $J=4.5\text{Hz}$).

Intermediate number	Chemical name	Method for preparation	Analytical data
S	Cyclopentyl <i>O</i> - <i>tert</i> -butyl-D-serinate	III	¹ H NMR (300MHz, CDCl ₃) δ: 5.14 (1H, m), 3.50 (3H, m), 1.90-1.39 (8H, m), 1.09 (9H, s).
T	Cyclopentyl (2 <i>R</i>)-amino(phenyl)acetate	II	¹ H NMR (300MHz, <i>d</i> ₆ -DMSO) δ: 8.80 (2H, br s), 8.74 (1H, br s), 7.44 (7H, m), 7.13 (2H, d), 5.28 (1H, br s), 5.21 (1H, m), 2.26 (3H, s), 1.85-1.30 (8H, m).
U	Cyclopentyl 3-methyl-L-valinate	I	<i>m/z</i> = 200 [M+H] ⁺ ; ¹ H NMR (300MHz, <i>d</i> ₆ -DMSO) δ: 8.51 (3H, br s), 5.20 (1H, t, <i>J</i> =5.7Hz), 5.21-4.89 (1H, m), 3.63 (1H, s), 1.84 (2H, t, <i>J</i> =5.6Hz), 1.75-1.55 (6H, m), 1.00 (9H, s).
V	1-Benzyl 2-cyclopentyl piperazine-1,2-dicarboxylate	I	¹ H NMR (300MHz, CDCl ₃) δ: 7.40-7.29 (5H, m), 5.19 (2H, br s), 4.64-4.97 (2H, m), 4.07-3.85 (2H, m), 3.31 (1H, m), 3.08 (1H, m), 2.84 (1H, m), 2.06 (1H, s), 1.92-1.56 (8H, m), 1.27 (1H, t, <i>J</i> =6.5Hz).

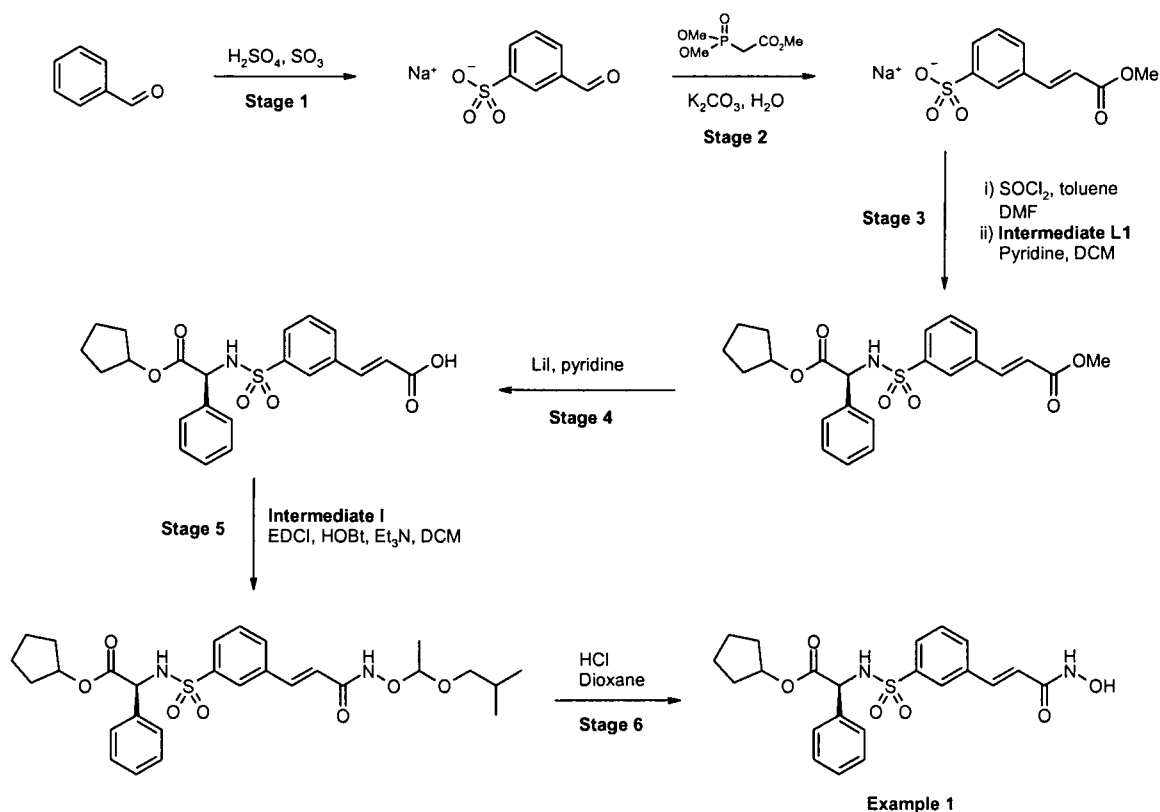
All the above intermediates were used in aminoacid coupling reactions as free bases. To an individual skilled in the art, it will be apparent that each free base can be prepared by titration of the salts described above with a suitable inorganic base (eg NaHCO₃).

Example 1:

(2*S*)-[({3-[(1*E*)-3-(Hydroxyamino)-3-oxoprop-1-en-1-yl]phenyl)sulfonyl]amino](phenyl)acetate



The title compound was prepared by the following methodology:



Stage 1 – Preparation of 3-formylbenzenesulfonate sodium salt

Benzaldehyde (10g, 94mmol) was added dropwise to 20% sulfur trioxide in fuming sulfuric acid (25mL) and stirred under an atmosphere of nitrogen, maintaining the reaction temperature below 40°C. The reaction was stirred at 40°C for 18h. The reaction was then quenched onto ice (60g) and the aqueous extracted with EtOAc (100mL). The aqueous phase was treated with CaCO₃ until the evolution of CO₂ ceased (pH ~ 6). The resultant precipitate was filtered, washed with water and the filtrate basified with Na₂CO₃ to pH ~ 8. The precipitate was removed by filtration and the filtrate evaporated to dryness *in vacuo*. The residue was washed with MeOH, filtered and the washings concentrated to give the desired product as a white solid (7.94g, 81%). ¹H NMR (300MHz, CD₃OD) δ: 9.88 (1H, s), 8.19 (1H, s), 7.99 (2H, dd), 7.63 (1H, t, J=7.8Hz).

Stage 2 – Preparation of 3-[(1*E*)-3-methoxy-3-oxoprop-1-en-1-yl]benzenesulfonate sodium salt

Stage 1 product (13.8g, 66mmol) and K₂CO₃ (18.3g, 132mmol) were dissolved in water (70mL). Trimethyl phosphonoacetate (14.51g, 80mmol) was added dropwise and the reaction stirred at RT for 15h. The resulting precipitate was filtered, washed with MeOH and dried *in vacuo* to

afford the desired product as a white solid (5.75g, 33%). ¹H NMR (300MHz, *d*₆-DMSO) δ: 7.84 (1H, s), 7.65-7.70 (3H, m), 7.40 (1H, t, J=7.5Hz), 6.60 (1H, d, J=16.2Hz), 3.73 (1H, s).

Stage 3 – Preparation of methyl (2E)-3-[3-({[(1S)-2-(cyclopentyloxy)-2-oxo-1-phenylethyl]amino}sulfonyl)phenyl]acrylate

Stage 2 product (5.75g, 22mmol) was added to toluene (17.5mL) and DMF (6 drops) under an atmosphere of nitrogen. Thionyl chloride (4.75mL, 66mmol) was added dropwise then the reaction heated at reflux for 1h. This was then concentrated to dryness and the residue was dissolved in toluene (50mL), filtered and the filtrate concentrated to dryness to afford a yellow solid. This was dissolved in DCM (7mL) and added to a solution of **Intermediate L1** (1.91g, 4.9mmol) in pyridine (2.5mL) and DCM (10mL). The reaction was stirred for 2h at RT and then concentrated to dryness *in vacuo* and the residue separated between EtOAc (50mL) and 10% HCl_{aq} (50mL). The organic phase was washed with water (50mL), saturated NaHCO₃ (50mL) and brine (50mL) then dried (MgSO₄) and concentrated *in vacuo* to afford the product as a yellow oil (1.77g, 54%). m/z = 442 [M-H]⁺.

Stage 4 – Preparation of (2E)-3-[3-({[(1S)-2-(cyclopentyloxy)-2-oxo-1-phenylethyl]amino}sulfonyl)phenyl]acrylic acid

Stage 3 product (1.77g, 4mmol) and lithium iodide (2.67g, 20mmol) were added to pyridine (17.7mL) and heated at reflux for 24h. The reaction was cooled, quenched to pH ~ 1 with 10% HCl_{aq} and extracted with DCM (2 x 20mL). The combined organics were washed with 10% HCl_{aq} (40mL) then brine (40mL), dried (MgSO₄) and concentrated *in vacuo* to afford a brown oil (1.19g, 73%). m/z = 428 [M-H]⁺.

Stage 5 – Preparation of cyclopentyl (2S)-[3-({[(1E)-3-[(1-isobutoxyethoxy)amino]-3-oxoprop-1-en-1-yl]phenyl)sulfonyl]amino}(phenyl)acetate

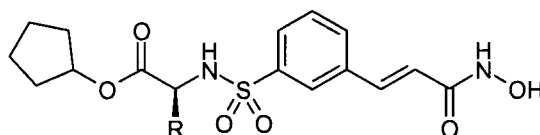
Stage 4 product (1.19g, 2.8mmol), EDCI (0.64g, 3.3mmol) and HOBt (0.45g, 3.3mmol) were added to DCM (10mL) and stirred at RT for 30 minutes. **Intermediate I** (2.0mL, 14mmol) and triethylamine (2.0mL, 14mmol) were added and the reaction stirred at RT for 1.5h. The reaction was separated with water, the aqueous phase extracted with DCM (20mL) and the combined organics concentrated *in vacuo*. The crude material was purified by column chromatography to afford the product as a brown oil (0.17g, 11%). m/z = 543 [M-H]⁺.

*Stage 6 – Preparation of cyclopentyl (2S)-[3-({[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]phenyl)sulfonyl]amino}(phenyl)acetate (**Example 1**)*

Stage 5 product (170mg, 0.31mmol) was dissolved in anhydrous DCM (5mL). 4N HCl in dioxane (0.16mL, 0.63mmol) was added and the reaction stirred at RT for 1h. The reaction was

concentrated to dryness *in vacuo* to afford a brown solid. Purification by preparative HPLC afforded a yellow solid (9mg, 5%). LCMS purity >95%, $m/z = 558.5$ $[M+H]^+$, 1H NMR (300MHz, d_6 -DMSO) δ : 7.95 (1H, s), 7.89 (2H, m), 7.65 (1H, d, $J=15.9$ Hz), 7.52 (1H, t), 7.26 (5H, s), 6.54 (1H, d, $J=15.9$ Hz), 4.94 (1H, m), 1.22-1.70 (8H, m).

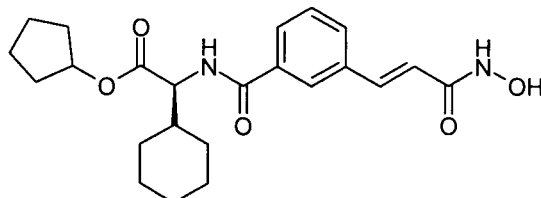
The following examples were prepared using the same methodology:



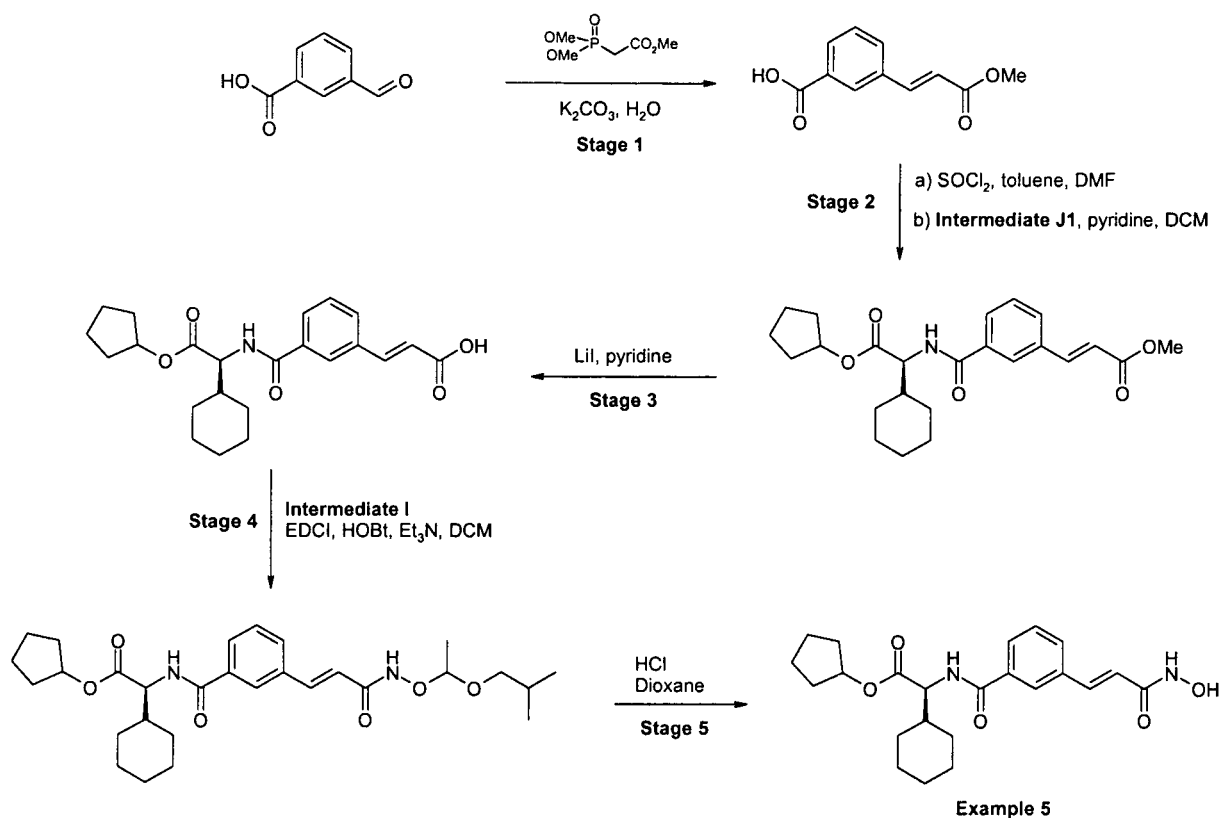
Example	R	Chemical name	Intermediate used	Analytical data
2		Cyclopentyl (2S)-cyclohexyl[[(3-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]phenyl)sulfonyl]amino]acetate	J1	LCMS purity 98%, $m/z = 449$ $[M-H]^-$, 1H NMR (300MHz, d_6 -DMSO) δ : 0.70-1.90 (19H, m), 3.56 (1H, m), 4.66 (1H, s), 6.55 (1H, d), 7.40-8.05 (4H, m), 8.30 (1H, d), 10.82 (1H, s).
3		Cyclopentyl N-({3-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]phenyl)sulfonyl)-L-leucinate	K1	LCMS purity >95%, $m/z = 425$ $[M+H]^+$; 1H NMR (300MHz, d_6 -DMSO) δ : 0.80 (6H, dd), 1.20-1.71 (11H, m), 3.74 (1H, m), 4.69 (1H, m), 6.56 (1H, d, $J=15.9$ Hz), 7.48-7.84 (4H, m), 7.90 (1H, s), 8.39 (1H, d, $J=9$ Hz), 9.13 (1H, s), 10.82 (1H, s).
4		Cyclopentyl O-tert-butyl-N-({3-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]phenyl)sulfonyl)-L-serinate	O	LCMS purity >95%, $m/z = 455$ $[M+H]^+$; 1H NMR (300MHz, d_6 -DMSO) δ : 1.01 (9H, s), 1.33-1.75 (8H, m), 3.32-3.48 (2H, m), 6.56 (1H, d, $J=15.9$ Hz), 7.49-7.63 (2H, m), 7.79 (2H, t), 8.36 (1H, d, $J=9.3$ Hz), 9.13 (1H, s), 10.83 (1H, s).

Example 5:

Cyclopentyl (2S)-cyclohexyl({3-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzoyl}amino)acetate



The title compound was prepared by the following methodology:



Stage 1 – Preparation of 3-[(1E)-3-methoxy-3-oxoprop-1-en-1-yl]benzoic acid

3-Carboxybenzaldehyde (25g, 0.167mol) and K_2CO_3 (69g, 0.499mol) were added to water (250mL) and cooled to 0-5°C. Trimethyl phosphonoacetate (32.3mL, 0.2mol) was charged dropwise maintaining the reaction temperature below 15°C. The reaction was warmed and stirred at RT for 17h. The mixture was acidified to pH ~ 1, filtered and dried *in vacuo* to afford the product as an off-white solid (37.25g, >100% - slightly wet). 1H NMR (300MHz, CD_3OD) δ : 8.23 (1H, s), 8.06 (1H, d, J=7.8Hz), 7.86 (1H, d, J=7.5Hz), 7.75 (1H, d, J=15.9Hz), 6.61 (1H, d, J=16.2Hz), 7.54 (1H, t), 3.81 (3H, s).

Stage 2 – Preparation of methyl (2E)-3-(3-(((1S)-1-cyclohexyl-2-(cyclopentyloxy)-2-oxoethyl]carbamoyl]phenyl)acrylate

Stage 1 product (5g, 24mmol) was added to toluene (20mL) and DMF (6 drops) under an atmosphere of nitrogen. Thionyl chloride (5.3mL, 72mmol) was charged dropwise to the reaction which was then heated at reflux for 1h. The reaction was then cooled and concentrated to dryness *in vacuo*, the residue was dissolved in toluene (40mL), filtered and the filtrate concentrated to give the product as a pale yellow solid (6.1g, >100% - some DMF).

Intermediate J1 (0.5g, 1.9mmol) was added to pyridine (1mL) and DCM (10mL). The pale yellow solid (0.51g, 2.3mmol) was dissolved in DCM (5mL) and charged to the reaction which was stirred for 18h at RT. It was then concentrated to dryness *in vacuo* and the residue separated between EtOAc (20mL) and 10% HCl_{aq} (20mL). The organic phase was washed with water (20mL), sat. NaHCO₃ solution (20mL) and brine (20mL) then concentrated *in vacuo* to afford the product as a yellow oil (0.83g, quant.). This was carried through to the next stage without further purification or characterization.

Stage 3 – Preparation of (2E)-3-(3-(((1S)-1-cyclohexyl-2-(cyclopentyloxy)-2-oxoethyl]carbamoyl]phenyl)acrylic acid

Stage 2 product (0.83g, 2.0mmol) and lithium iodide (1.34g, 10mmol) were added to pyridine (8.3mL) and heated at reflux for 3 days. The reaction was cooled, quenched to pH ~ 1 with 10% HCl_{aq} and extracted with DCM (2 x 20mL). The combined organics were washed with 10% HCl_{aq} (20mL) then brine (20mL), dried (MgSO₄) and concentrated *in vacuo* to afford a brown oil (0.22g, 23% over three steps). *m/z* = 400 [M+H]⁺.

Stage 4 – Preparation of cyclopentyl (2S)-cyclohexyl[(3-((1E)-3-((1-isobutoxyethoxy)amino)-3-oxoprop-1-en-1-yl)benzoyl)amino]acetate

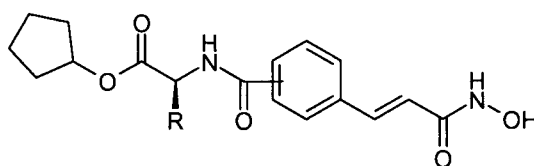
Stage 3 product (0.22g, 0.55mmol), EDCI (0.13g, 0.66mmol) and HOBt (0.09g, 0.66mol) were added to DCM (10mL) and stirred at RT for 30 minutes. **Intermediate I** (0.23mL, 1.65mmol) and triethylamine (0.23mL, 1.65mmol) were charged and the reaction stirred at RT for 3.5h. The reaction was separated with water, the aqueous phase extracted with DCM (20mL) and the combined organics concentrated *in vacuo*. The crude material was purified by column chromatography to afford the product as a brown oil (0.14g, 50%). *m/z* = 537 [M+Na]⁺.

Stage 5 – Preparation of cyclopentyl (2S)-cyclohexyl[(3-((1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl)benzoyl)amino]acetate (Example 5)

Stage 4 product (140mg, 0.27mmol) was dissolved in anhydrous DCM (5mL). 4N HCl in dioxane (0.16mL, 0.54mol) was charged and the reaction stirred at RT for 1h. The mixture was

concentrated to dryness *in vacuo* to afford a yellow oil. Purification by preparative HPLC afforded a pink solid (68mg, 61%). LCMS purity 98%, $m/z = 415$ $[M+H]^+$, 1H NMR (300MHz, d_6 -DMSO) δ : 10.82 (1H, s), 9.08 (1H, s), 8.61 (1H, d, $J=7.5$ Hz), 8.06 (1H, s), 7.85 (1H, d, $J=8.4$ Hz), 7.72 (1H, d, $J=8.4$ Hz), 7.54-7.49 (2H, m), 6.55 (1H, d, $J=15.9$ Hz), 5.11 (1H, m), 4.25 (1H, t, $J=7.8$ Hz), 1.92-1.47 (13H, m), 1.35-1.00 (6H, m).

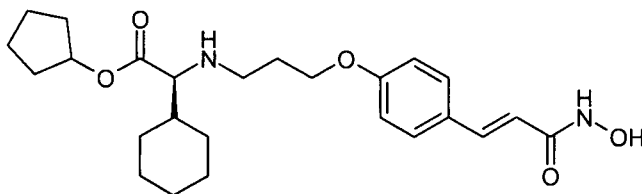
The following examples were prepared using the same methodology:



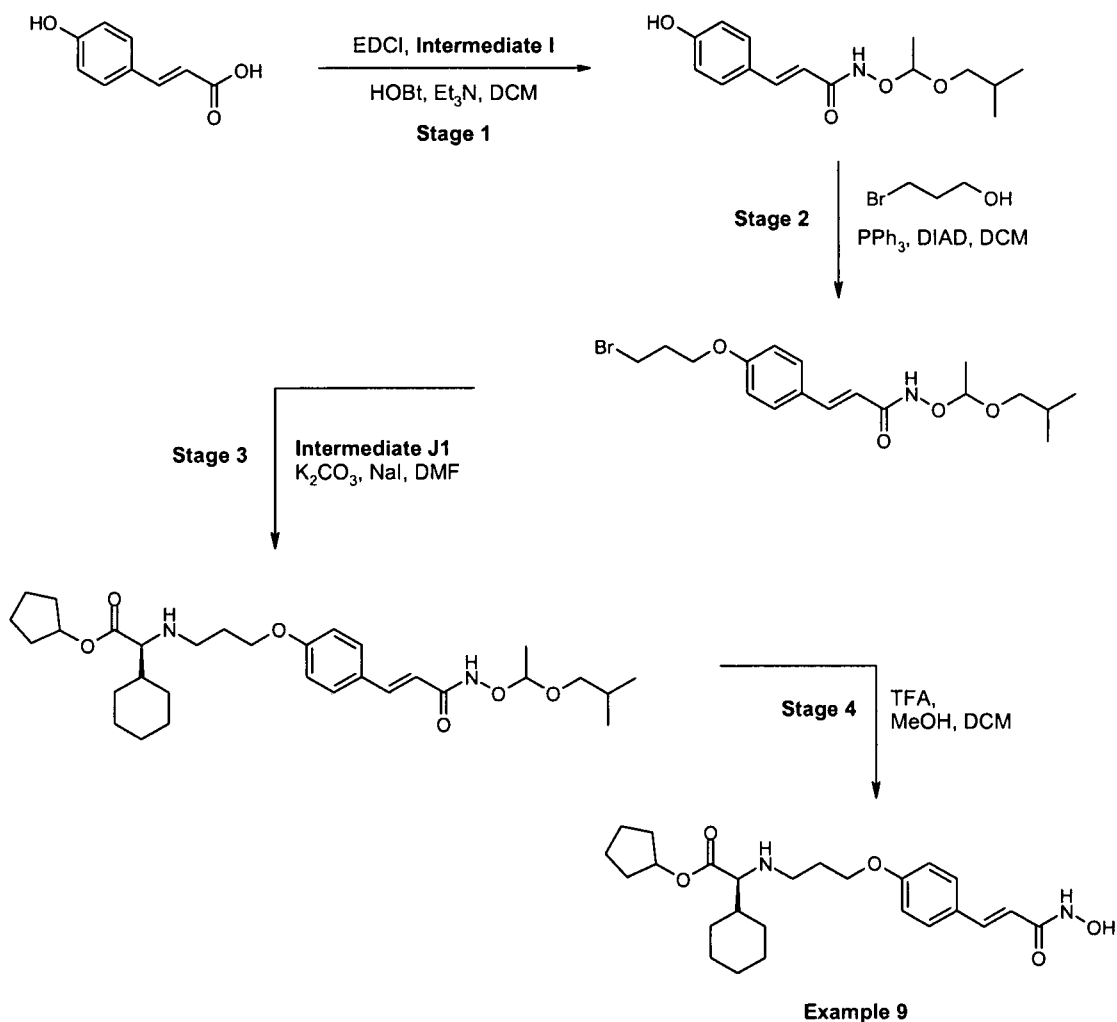
Example	R	Chemical name	Intermediates used	Analytical data
6		Cyclopentyl (2S)-({3-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzoyl}amino)(phenyl)acetate	3-Carboxy benzaldehyde and L1	LCMS purity 95%, $m/z = 409$ $[M+H]^+$, 1H NMR (300MHz, CD_3OD) δ : 9.04 (1H, m), 8.06 (1H, s), 7.90-7.25 (9H, m), 6.56 (1H, d, $J=15.6$ Hz), 5.64 (1H, m), 5.24 (1H, m), 3.68 (1H, s), 1.97-0.82 (8H, m).
7		Cyclopentyl (2S)-cyclohexyl({4-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzoyl}amino)acetate	4-Carboxy benzaldehyde and J1	LCMS purity 96%, $m/z = 528.5$ $[M+H]^+$, 1H NMR (300MHz, CD_3OD) δ : 8.51 (1H, d), 7.87 (2H, d), 7.67 (2H, d), 6.58 (1H, d), 5.23 (1H, m), 4.42 (1H, t), 1.55-2.03 (13H, m), 1.08-1.42 (6H, m).
8		Cyclopentyl N-{4-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzoyl}-L-leucinate	4-Carboxy benzaldehyde and K1	LCMS purity 98%, $m/z = 389$ $[M+H]^+$, 1H NMR (300MHz, d_6 -DMSO) δ : 0.90 (6H, dd), 1.45-1.90 (11H, m), 4.40 (1H, m), 5.09 (1H, m), 6.55 (1H, d, $J=15.9$ Hz), 7.50 (1H, d, $J=16.2$ Hz), 7.67 (2H, d, $J=8.1$ Hz), 7.89 (2H, d, $J=8.1$ Hz), 8.71 (1H, d, $J=7.5$ Hz), 10.82 (1H, s).

Example 9:

Cyclopentyl (2S)-cyclohexyl[(3-{4-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]phenoxy}propyl)amino]acetate



The title compound was prepared by the following methodology:



Stage 1 – Preparation of (2E)-3-(4-hydroxyphenyl)-N-(1-isobutoxyethoxy)acrylamide

4-Hydroxycinnamic acid (1g, 6.1mmol), EDCI (1.76g, 9.1mmol) and HOBt (1.24g, 9.1mmol) were added to DCM (20mL) and stirred at RT for 45 minutes. **Intermediate I** (4.2mL, 30.5mmol) and triethylamine (4.1mL, 30.5mmol) were added and the reaction stirred at RT for 1.5h. The

reaction was separated with water, the aqueous phase extracted with DCM (20mL) and the combined organics dried (MgSO_4) and concentrated *in vacuo*. The crude material was purified by column chromatography to afford the product as a clear oil (1.39g, 82%). $m/z = 278$ $[\text{M-H}]^-$.

Stage 2 – Preparation of (2E)-3-[4-(3-bromopropoxy)phenyl]-N-(1-isobutoxyethoxy)acrylamide
Stage 1 product (0.66g, 2.4mmol), 3-bromopropan-1-ol (0.24mL, 2.6mmol) and triphenylphosphine (0.96g, 4.8mmol) were added to DCM (20mL) and stirred under nitrogen for 10 minutes. DIAD (0.56mL, 2.9mmol) was charged dropwise and the reaction stirred at RT for 1h. The reaction was concentrated to dryness *in vacuo* to afford a pale yellow oil. Purification by column chromatography gave the product as a white solid (0.68g, 72%). $m/z = 398/400$ $[\text{M-H}]^-$.

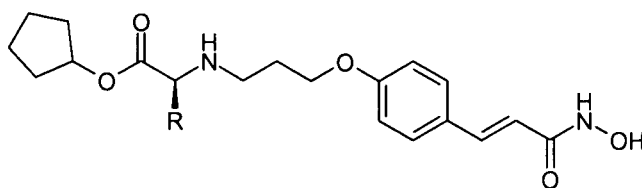
Stage 3 – Preparation of cyclopentyl (2S)-cyclohexyl[3-(4-((1E)-3-[(1-isobutoxyethoxy)amino]-3-oxoprop-1-en-1-yl)phenoxy)propyl]amino]acetate

Intermediate J1 (0.14g, 0.54mmol), K_2CO_3 (0.3g, 2.2mmol) and sodium iodide (0.16g, 1.07mmol) were added to DMF (5mL) and heated to 70°C. Stage 2 product (0.22g, 0.55mmol) was dissolved in DMF (2mL) and charged to the reaction which was stirred at 70-80°C under nitrogen for 24h. Further stage 2 product (0.1g, 0.25mmol) was charged and the reaction stirred at 80°C for 4.5h. The reaction was then concentrated to dryness *in vacuo*, the residue was separated with water (10mL) and EtOAc (10mL) and the aqueous phase extracted with EtOAc (10mL). The combined organics were washed with brine (10mL), dried (MgSO_4) and concentrated *in vacuo* to give the crude product as a yellow oil. Purification by column chromatography afforded the product as a clear oil (0.1g, 34%). $m/z = 546$ $[\text{M+H}]^+$.

Stage 4 – Preparation of cyclopentyl (2S)-cyclohexyl[3-(4-((1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl)phenoxy)propyl]amino]acetate

Stage 3 product (100mg, 0.31mmol) was dissolved in anhydrous DCM (0.4mL) and MeOH (0.5mL). TFA (0.1mL) was charged and the reaction stirred at RT for 1h. It was then concentrated to dryness *in vacuo* to afford a yellow oil. Purification by preparative HPLC afforded the product as a white solid (10mg, 12%). LCMS purity 100%, $m/z = 445$ $[\text{M+H}]^+$, ^1H NMR (300MHz, CD_3OD) δ : 7.53 (3H, m), 6.97 (2H, d, $J=8.4\text{Hz}$), 6.35 (1H, d, $J=15.9\text{Hz}$), 5.33 (2H, m), 4.16 (2H, m), 3.90 (1H, m), 3.83 (1H, d, $J=4.5\text{Hz}$), 2.23 (2H, m), 2.09-1.57 (12H, m), 1.45-0.98 (6H, m), 0.92 (2H, m).

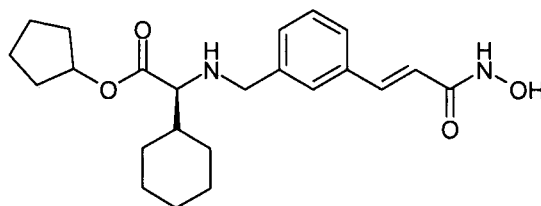
The following examples were prepared using the same methodology:



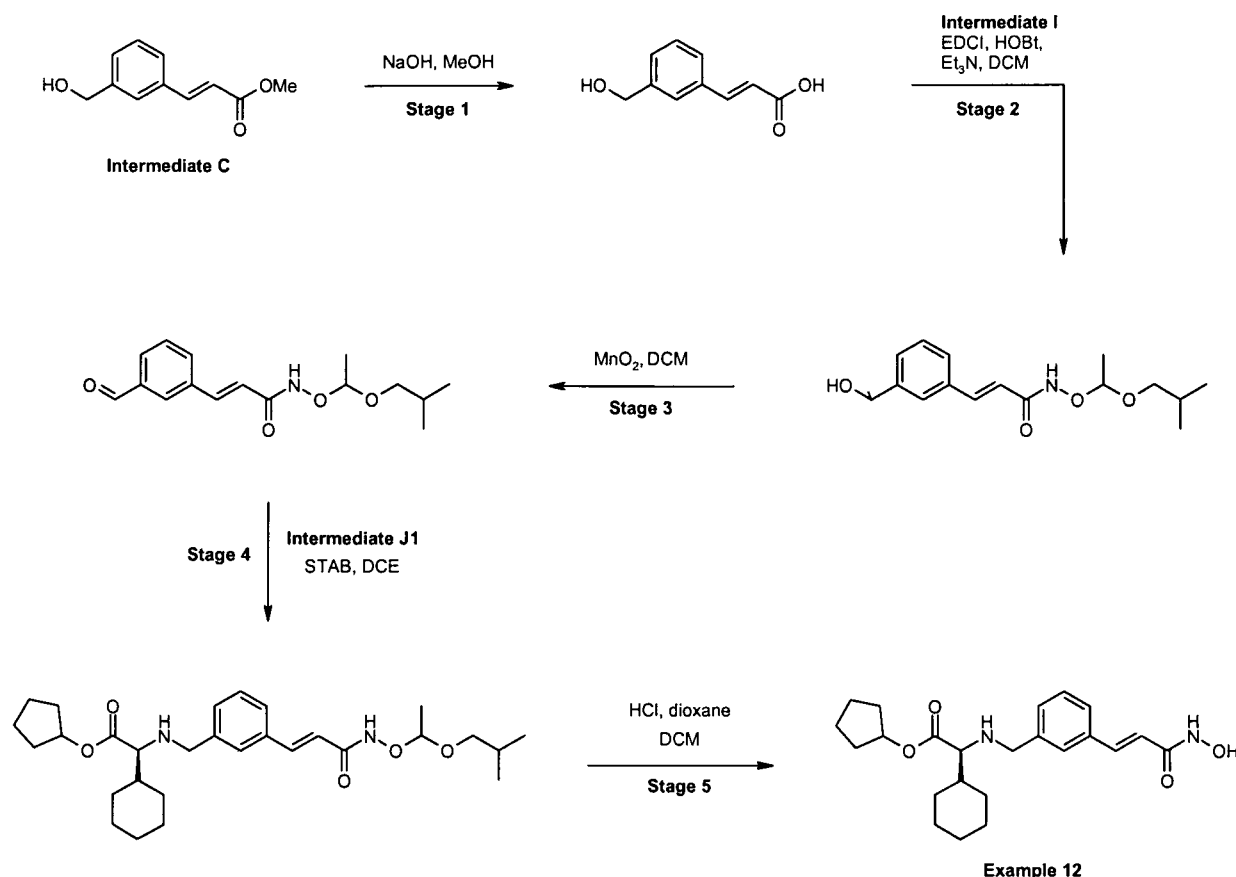
Example	R	Chemical name	Intermediate used	Analytical data
10		Cyclopentyl O- <i>tert</i> -butyl-N-(3-{4-[(1 <i>E</i>)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]phenoxy}propyl)-L-serinate	O	LCMS purity 95%, $m/z = 449$ $[M+H]^+$, 1H NMR (300MHz, CD_3OD) δ : 7.53 (3H, m), 6.99 (2H, m), 6.36 (1H, m), 5.34 (1H, m), 4.29 (1H, m), 4.19 (2H, m), 3.92 (2H, m), 2.26 (2H, m), 2.03-1.59 (8H, m), 1.31 (1H, m), 1.23 (9H, s), 0.90 (1H, m).
11		Cyclopentyl N-(3-{4-[(1 <i>E</i>)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]phenoxy}propyl)-L-leucinate	K1	LCMS purity 100%, $m/z = 419$ $[M+H]^+$, 1H NMR (300MHz, CD_3OD) δ : 7.53 (3H, m), 6.98 (2H, d, $J=8.4$ Hz), 6.35 (1H, d, $J=15.6$ Hz), 5.36 (1H, m), 4.18 (2H, m), 4.05 (1H, m), 2.23 (2H, m), 2.07-1.58 (10H, m), 1.31 (1H, m), 1.11-0.78 (8H, m).

Example 12:

Cyclopentyl (2*S*)-cyclohexyl({3-[(1*E*)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}amino)acetate



The title compound was prepared by the following methodology:



Stage 1 – Preparation of (2E)-3-[3-(hydroxymethyl)phenyl]acrylic acid

Intermediate C (16.04g, 83.5mmol) was added to 1M NaOH_{aq} (28mL) and MeOH (41mL) and stirred at RT for 15.5h. The MeOH was removed *in vacuo* and the residue washed with EtOAc. The aqueous phase was acidified to pH ~ 1 and the resulting precipitate was filtered and dried *in vacuo* to afford the title product as a white solid (7.29g, 49%). *m/z* = 179 [M+H]⁺.

Stage 2 – Preparation of (2E)-3-[3-(1-hydroxyethyl)phenyl]-N-(1-isobutoxyethoxy)acrylamide

Stage 1 product (7.29g, 41mmol), EDCI (9.4g, 49mmol) and HOBt (6.6g, 49mmol) were added to DCM (100mL) and stirred at RT for 30 minutes. **Intermediate I** (17.3mL, 123mmol) and triethylamine (28.5mL, 205mmol) were charged and the reaction stirred at RT for 2.5h. The reaction was separated with water, the aqueous phase extracted with DCM (50mL) and the combined organics dried (MgSO₄) and concentrated *in vacuo*. The crude material was purified by column chromatography to afford the product as a pale yellow oil (6.54g, 54%). ¹H NMR (300MHz, CD₃OD) δ: 7.71-7.33 (5H, m), 6.57 (2H, d, J=15.6Hz), 5.01 (1H, m), 4.65 (2H, s), 3.32 (2H, m), 1.40 (3H, d, J=5.4Hz), 0.93 (6H, m).

Stage 3 – Preparation of (2E)-3-(3-formylphenyl)-N-(1-isobutoxyethoxy)acrylamide

Stage 2 product (6.5g, 22mmol) and manganese dioxide (9.6g, 110mmol) were stirred in DCM (100mL) at RT for 16h. The reaction was filtered through celite and the filtrate concentrated to dryness to afford the product as a grey solid (4.8g, 75%). ¹H NMR (300MHz, CDCl₃) δ: 10.05 (1H, s), 8.06 (1H, s), 7.97-7.52 (4H, m), 6.55 (1H, d), 5.05 (1H, m), 3.35 (2H, m), 1.47-1.44 (3H, m) 0.94 (6H, m).

Stage 4 – Preparation of cyclopentyl (2S)-cyclohexyl[(3-[(1E)-3-[(1-isobutoxyethoxy)amino]-3-oxoprop-1-en-1-yl]benzyl)amino]acetate

Stage 3 product (0.3g, 1.03mmol) and **Intermediate J1** (0.32g, 1.22mmol) were dissolved in 1,2-dichloroethane (10mL). STAB (0.33g, 1.56mmol) was charged and the reaction stirred under nitrogen for 1h. It was then quenched with sat. NaHCO₃ solution (10mL). The aqueous phase was extracted with DCM (2 x 10mL) and the combined organics dried (MgSO₄) and concentrated to dryness *in vacuo* to afford the product as a brown oil (0.59g, >100%). m/z = 501 [M+H]⁺.

Stage 5 – Preparation of cyclopentyl (2S)-cyclohexyl[(3-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl)amino]acetate (Example 12)

4N HCl in dioxane (0.59mL, 2.4mmol) was added to a solution of stage 4 product (0.59g, 1.2mmol) in DCM and the reaction stirred for 3h. The reaction was concentrated to dryness *in vacuo* to afford a yellow oil. Purification by preparative HPLC afforded the desired product as a white solid (11.5mg, 2.4%). LCMS purity >95%, m/z = 400.5 [M+H]⁺, ¹H NMR (300MHz, d₆-DMSO) δ: 10.75 (1H, s), 9.03 (1H, s), 7.25-7.51 (5H, m), 6.45 (1H, d, J=15.6Hz), 5.09 (1H, m), 3.64 (2H, dd), 2.83 (1H, m), 1.42-1.93 (13H, m), 0.92-1.25 (6H, m).

The following examples were prepared using the same methodology:

Example	Chemical name	Intermediates used	Analytical data
13	Cyclopentyl (2S)-({3-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}amino)(phenyl)acetate	C, L1	LCMS purity >95%, ¹ H NMR (300MHz, d ₆ -DMSO) δ: 1.30-1.85 (8H, m), 3.10 (1H, m), 3.66 (2H, d, J=5.1Hz), 4.28 (1H, d, J=8.7Hz), 5.05 (1H, m), 6.45 (1H, d, J=15.9Hz), 7.22-7.57 (10H, m), 9.03 (1H, s), 10.74 (1H, s).
14	Cyclopentyl (2S)-cyclohexyl({4-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}amino)acetate	A, J1	LCMS purity 98%, m/z = 401 [M+H] ⁺ , ¹ H NMR (300MHz, d ₆ -DMSO) δ: 9.41 (1H, s), 8.99 (1H, s), 8.31 (1H, s), 7.32-7.75 (5H, m), 6.53 (1H, d), 5.23 (1H, m), 5.11 (1H, s), 4.16 (2H, m), 3.60-3.95 (2H, m), 2.97 (1H, m), 1.40-2.05 (12H, m), 0.70-1.32 (6H, m).

Example	Chemical name	Intermediates used	Analytical data
15	Cyclopentyl <i>N</i> -{4-[(1 <i>E</i>)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}-L-leucinate	A, K1	LCMS purity 99%, $m/z = 375$ [M+H] ⁺ , ¹ H NMR (300MHz, <i>d</i> ₆ -DMSO) δ : 0.91 (6H, d), 1.20 (1H, t), 1.55-1.76 (10H, m), 1.78-1.95 (2H, m), 3.85-4.30 (2H, m), 5.19 (1H, m), 6.50 (1H, d), 7.35-7.70 (5H, m), 9.08 (1H, s), 9.45 (1H, s).
16	Cyclopentyl <i>O</i> - <i>tert</i> -butyl- <i>N</i> -{4-[(1 <i>E</i>)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}-L-serinate	A, O	LCMS purity 100%, $m/z = 405$ [M+H] ⁺ , ¹ H NMR (300MHz, CD ₃ OD) δ : 7.72-7.50 (5H, m), 6.58 (1H, m), 5.33 (1H, m), 4.32 (2H, m), 4.22 (1H, m), 3.99-3.80 (3H, m), 3.14 (1H, m), 2.03-1.60 (8H, m), 1.24 (9H, s), 0.92 (1H, m).
17	Cyclopentyl (2 <i>S</i>)-({4-[(1 <i>E</i>)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}amino)(phenyl)acetate	A, L1	LCMS purity 100%, $m/z = 395$ [M+H] ⁺ , ¹ H NMR (300MHz, <i>d</i> ₆ -DMSO) δ : 7.69-7.46 (10H, m), 6.49 (1H, d, <i>J</i> =15.6Hz), 5.15 (1H, m), 4.07 (2H, m), 1.88-1.13 (8H, m).
18	Cyclopentyl <i>N</i> -{4-[(1 <i>E</i>)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}-D-leucinate	A, R	LCMS purity 100%, $m/z = 375$ [M+H] ⁺ , ¹ H NMR (300MHz, CD ₃ OD) δ : 7.67-7.45 (3H, m), 7.37 (2H, d, <i>J</i> =7.8Hz), 6.47 (1H, d, <i>J</i> =15.6Hz), 5.19 (1H, m), 3.71 (2H, q), 3.23 (1H, t), 2.02-1.18 (11H, m), 1.01-0.75 (6H, m).
19	Cyclopentyl (2 <i>R</i>)-cyclohexyl({4-[(1 <i>E</i>)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}amino)acetate	A, Q	LCMS purity 100%, $m/z = 401$ [M+H] ⁺ , ¹ H NMR (300MHz, CD ₃ OD) δ : 7.70-7.43 (3H, m), 7.36 (2H, d, <i>J</i> =8.1Hz), 6.47 (1H, d, <i>J</i> =15.6Hz), 5.18 (1H, m), 3.72 (2H, q), 2.96 (1H, d, <i>J</i> =6Hz), 2.00-1.45 (13H, m), 1.39-0.82 (6H, m).
20	Cyclopentyl <i>O</i> - <i>tert</i> -butyl- <i>N</i> -{4-[(1 <i>E</i>)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}-D-serinate	A, S	LCMS purity 100%, $m/z = 405$ [M+H] ⁺ , ¹ H NMR (300MHz, CD ₃ OD) δ : 7.63-7.48 (3H, m), 7.39 (2H, d, <i>J</i> =7.8Hz), 6.48 (1H, d, <i>J</i> =15.6Hz), 5.20 (1H, m), 3.80 (2H, q), 3.61 (2H, m), 3.38 (1H, t), 1.95-1.57 (8H, m), 1.31 (1H, m), 1.17 (9H, s).
21	Ethyl (2 <i>S</i>)-cyclohexyl({4-[(1 <i>E</i>)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}amino)acetate	A, J3	LCMS purity >98%, $m/z = 361$ [M+H] ⁺ , ¹ H NMR (300MHz, <i>d</i> ₆ -DMSO) δ : 7.49 (2H, d, <i>J</i> =7.9Hz), 7.44 (1H, d, <i>J</i> =15.8Hz), 7.33 (2H, d, <i>J</i> =8.0Hz), 6.42 (1H, d, <i>J</i> =15.8Hz), 4.10 (2H, q, <i>J</i> =7.0Hz), 3.77 (1H, d, <i>J</i> =15.8Hz), 3.50 (1H, d, <i>J</i> =9.3Hz), 2.87 (1H, m), 1.82 (1H, d, <i>J</i> =11.4Hz), 1.35-1.65 (5H, m), 1.19 (3H, t, <i>J</i> =7.1Hz), 0.9-1.25 (5H, m).
22	Cyclopentyl (2 <i>R</i>)-({4-[(1 <i>E</i>)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}amino)(phenyl)acetate	A, L1	LCMS purity 100%, $m/z = 395$ [M+H] ⁺ , ¹ H NMR (300MHz, <i>d</i> ₆ -DMSO) δ : 7.69-7.46 (10H, m), 6.49 (1H, d, <i>J</i> =15.6Hz), 5.15 (1H, m), 4.07 (2H, m), 1.88-1.13 (8H, m).

Example	Chemical name	Intermediates used	Analytical data
23	2,3-Dihydro-1 <i>H</i> -inden-2-yl (2 <i>S</i>)-cyclohexyl({4-[(1 <i>E</i>)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}amino)acetate	A, J6	LCMS purity >98%, $m/z = 449$ [M+H] ⁺ , ¹ H NMR (300MHz, <i>d</i> ₆ -DMSO) δ : 10.72 (1H, br s), 9.00 (1H, br s), 7.38-7.46 (3H, m), 7.22-7.27 (4H, m), 7.15-7.19 (2H, m), 6.41 (1H, d, <i>J</i> =15.8Hz), 5.44-5.50 (1H, m), 3.74 (1H, d, <i>J</i> =14Hz), 3.50 (1H, d, <i>J</i> =14Hz), 2.75-2.95 (3H, m), 1.77 (1H, d, <i>J</i> =12.2Hz), 0.86-1.65 (11H, m).
24	Benzyl (2 <i>S</i>)-cyclohexyl({4-[(1 <i>E</i>)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}amino)acetate	A, J9	LCMS purity >98%, $m/z = 423$ [M+H] ⁺ , ¹ H NMR (300MHz, <i>d</i> ₆ -DMSO) δ : 10.72 (1H, br s), 9.00 (1H, br s), 7.15-7.55 (10H, m), 6.42 (1H, d, <i>J</i> =15.6Hz), 5.13 (2H, s), 3.76 (1H, d, <i>J</i> =14.6Hz), 3.50 (1H, d, <i>J</i> =14.0Hz), 2.90-3.0 (1H, m), 1.40-1.82 (7H, m), 0.85-1.25 (7H, m).
25	Allyl (2 <i>S</i>)-cyclohexyl({4-[(1 <i>E</i>)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}amino)acetate	A, J4	LCMS purity >98%, $m/z = 373$ [M+H] ⁺ , ¹ H NMR (300MHz, <i>d</i> ₆ -DMSO) δ : 10.72 (1H, br s), 9.00 (1H, br s), 7.49 (2H, <i>J</i> =8.1Hz), 7.43 (1H, d, <i>J</i> =15.9Hz), 7.33 (2H, d, <i>J</i> =8.1Hz), 6.43 (1H, d, <i>J</i> =15.8Hz), 5.85-6.0 (1H, m), 5.32 (1H, dd, <i>J</i> =1.7, 17.2Hz), 5.22 (1H, dd, <i>J</i> =1.7, 10.4Hz), 4.54-4.62 (2H, m), 3.79 (1H, d, <i>J</i> =14Hz), 3.52 (1H, d, <i>J</i> =14Hz), 2.94 (1H, br s), 0.9-1.9 (10H, m).
26	Bicyclo[2.2.1]hept-2-yl (2 <i>S</i>)-cyclohexyl({4-[(1 <i>E</i>)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}amino)acetate	A, J7	LCMS purity >95%, $m/z = 427$ [M+H] ⁺ , ¹ H NMR (300MHz, <i>d</i> ₆ -DMSO) δ : 7.49 (2H, <i>J</i> =8.1Hz), 7.43 (1H, d, <i>J</i> =15.9Hz), 7.33 (2H, d, <i>J</i> =8.1Hz), 6.43 (1H, d, <i>J</i> =15.8Hz), 4.50-4.11 (1H, m), 3.79 (1H, d, <i>J</i> =14Hz), 3.52 (1H, d, <i>J</i> =14Hz), 2.66 (1H, m), 0.65-2.40 (22H, m).
27	2-Methylcyclopentyl (2 <i>S</i>)-cyclohexyl({4-[(1 <i>E</i>)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}amino)acetate	A, J5	LCMS purity >95%, $m/z = 415$ [M+H] ⁺ , ¹ H NMR (300MHz, <i>d</i> ₆ -DMSO) δ : 10.72 (1H, br s), 9.00 (1H, br s), 7.49 (2H, d, <i>J</i> =8Hz), 7.43 (1H, d, <i>J</i> =15.8Hz), 7.32 (2H, d, <i>J</i> =8Hz), 6.43 (1H, d, <i>J</i> =15.8Hz), 4.63 (1H, m), 3.76 (1H, d, <i>J</i> =14Hz), 3.50 (1H, d, <i>J</i> =14Hz), 2.85 (1H, m), 0.95-2.04 (18H, m), 0.94 (3H, d, <i>J</i> =6.2Hz).
28	3-Methylcyclopentyl (2 <i>S</i>)-cyclohexyl({4-[(1 <i>E</i>)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}amino)acetate	A, J8	LCMS purity >95%, $m/z = 415$ [M+H] ⁺ , ¹ H NMR (300MHz, <i>d</i> ₆ -DMSO) δ : 10.71 (1H, br s), 9.00 (1H, br s), 7.48 (2H, d, <i>J</i> =8Hz), 7.38 (1H, d, <i>J</i> =14Hz), 7.32 (1H, d, <i>J</i> =7.9Hz), 6.42 (1H, d, <i>J</i> =15.7Hz), 5.05 (1H, m), 3.75 (1H, d, <i>J</i> =14Hz), 3.52 (1H, d, <i>J</i> =16.2Hz), 2.84 (1H, m), 1.00-2.80 (18H, m), 1.00 (3H, d, <i>J</i> =6.7Hz).

Example	Chemical name	Intermediates used	Analytical data
29	Methyl <i>N</i> -{4-[(1 <i>E</i>)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}-L-tryptophanate	A, P	LCMS purity 98%, $m/z = 393.4$ $[M+H]^+$, 1H NMR (300MHz, d_6 -DMSO) δ : 10.81 (1H, br s), 7.45 (2H, d, $J=8.1$ Hz), 7.39 (2H, d, $J=8.9$ Hz), 7.30 (3H, m), 7.00-7.14 (2H, m), 6.95-6.98 (1H, m), 6.42 (1H, d, $J=15.8$ Hz), 4.32 (1H, m), 3.77 (1H, d, $J=13.6$ Hz), 3.62 (1H, d, $J=17.3$ Hz), 3.51 (3H, s), 3.04 (2H, d, $J=6.6$ Hz).
30	2-Morpholin-4-ylethyl (2 <i>S</i>)-cyclohexyl({4-[(1 <i>E</i>)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}amino)acetate	A, J10	LCMS purity >98%, $m/z = 446.2$ $[M+H]^+$, 1H NMR (300MHz, d_6 -DMSO) δ : 7.48 (2H, d, $J=7.2$ Hz), 7.38 (1H, d, $J=14.7$ Hz), 7.32 (2H, d, $J=7.5$ Hz), 6.43 (1H, d, $J=13.4$ Hz), 4.10-4.28 (2H, m), 3.78 (1H, d, $J=13.9$ Hz), 3.45-3.62 (5H, m), 3.16 (1H, s), 2.87 (1H, br s), 2.38 (4H, m), 1.83 (1H, d, $J=11.3$ Hz), 0.80-1.75 (10H, m).
31	2-(Dimethylamino)ethyl (2 <i>S</i>)-cyclohexyl({4-[(1 <i>E</i>)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}amino)acetate	A, J11	LCMS purity >98%, $m/z = 404.2$ $[M+H]^+$, 1H NMR (300MHz, d_6 -DMSO) δ : 10.75 (1H, br s), 9.06 (1H, br s), 7.49 (2H, d, $J=8.0$ Hz), 7.42 (1H, d, $J=15.6$ Hz), 7.32 (2H, d, $J=8.0$ Hz), 6.42 (1H, d, $J=15.8$ Hz), 4.09-4.16 (3H, m), 3.77 (1H, d, $J=13.8$ Hz), 3.49 (1H, d, $J=13.7$ Hz), 2.86 (1H, m), 2.45 (2H, t, $J=5.5$ Hz), 2.15 (6H, s), 0.94-1.88 (11H, m).
32	<i>tert</i> -Butyl (2 <i>S</i>)-cyclohexyl({4-[(1 <i>E</i>)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}amino)acetate	A, J2	LCMS purity 98%, $m/z = 389$ $[M+H]^+$, 1H NMR (300MHz, d_6 -DMSO) δ : 0.88 (1H, m), 1.18 (4H, m), 1.42 (9H, s), 1.67 (5H, m), 1.73 (1H, m), 3.75 (1H, m), 4.13 (2H, m), 6.50 (1H, d, $J=15.9$ Hz), 7.49 (3H, m), 7.63 (2H, d, $J=7.8$ Hz), 9.08 (1H, m), 9.28 (1H, m), 10.81 (1H, m).
33	Cyclopentyl (2 <i>S</i>)-cyclohexyl({4-[3-(hydroxyamino)-3-oxopropyl]benzyl}amino)acetate	B, J1	LCMS purity 100%, $m/z = 403$ $[M+H]^+$, 1H NMR (300MHz, d_6 -DMSO) δ : 10.35 (1H, s), 8.68 (1H, s), 7.15 (4H, q), 5.11 (1H, m), 3.70 (1H, d), 3.44 (1H, d), 2.78 (2H, m), 2.39 (2H, m), 1.90-0.91 (19H, m).
34	Cyclopentyl <i>N</i> -{4-[3-(hydroxyamino)-3-oxopropyl]benzyl}-L-leucinate	B, K1	LCMS purity 100%, $m/z = 377$ $[M+H]^+$, 1H NMR (300MHz, d_6 -DMSO) δ : 10.34 (1H, s), 8.68 (1H, s), 7.15 (4H, q), 5.10 (1H, m), 3.68 (1H, d), 3.49 (1H, d), 3.06 (1H, m), 2.78 (2H, t), 2.24 (2H, t), 1.91-1.28 (11H, m), 0.83 (6H, dd).

Example	Chemical name	Intermediates used	Analytical data
35	2-Morpholin-4-ylethyl <i>N</i> -(4-[3-(hydroxyamino)-3-oxopropyl]benzyl)-L-leucinate	B, K3	LCMS purity 90%, $m/z = 422$ $[M+H]^+$, 1H NMR (300MHz, CD_3OD) δ : 7.46 (2H, d, $J=8.1$ Hz), 7.32 (2H, d, $J=7.9$ Hz), 4.57 (2H, m), 4.27 (2H, dd, $J=12.9, 22.8$ Hz), 4.14 (1H, m), 3.97 (4H, br s), 3.59 (2H, t, $J=5.1$ Hz), 3.42 (3H, br s), 2.97 (2H, t, $J=7.4$ Hz), 2.45 (2H, t, $J=7.4$ Hz), 1.96-1.68 (4H, m), 0.99 (6H, t, $J=6.8$ Hz).
36	Bicyclo[2.2.1]hept-2-yl <i>N</i> -(4-[3-(hydroxyamino)-3-oxopropyl]benzyl)-L-leucinate	B, K4	LCMS purity 98%, $m/z = 403$ $[M+H]^+$, 1H NMR (300MHz, CD_3OD) δ : 7.43 (2H, d, $J=7.9$ Hz), 7.33 (2H, d, $J=7.9$ Hz), 4.76 (1H, t, $J=7.4$ Hz), 4.21 (2H, qd, $J=3.0, 12.9$ Hz), 3.98 (1H, m), 2.96 (2H, t, $J=7.5$ Hz), 2.41 (2H, t, $J=7.6$ Hz), 2.35 (2H, m), 1.77 (4H, m), 1.52 (3H, m), 1.22 (3H, m), 0.99 (7H, m).
37	2,3-Dihydro-1 <i>H</i> -inden-2-yl <i>N</i> -(4-[3-(hydroxyamino)-3-oxopropyl]benzyl)-L-leucinate	B, K5	LCMS purity 87%, $m/z = 425$ $[M+H]^+$, 1H NMR (300MHz, CD_3OD) δ : 7.35-7.16 (8H, m), 5.65 (1H, m), 5.48 (1H, s), 4.17 (1H, q, $J=12.8$ Hz), 3.94 (1H, m), 3.39 (1H, d, $J=5.7$ Hz), 3.39 (1H, t, $J=5.7$ Hz), 3.07 (2H, m), 2.94 (1H, t, $J=7.6$ Hz), 2.39 (1H, t, $J=8.6$ Hz), 1.86-1.58 (4H, m), 0.88 (7H, m).
38	2-(Dimethylamino)ethyl <i>N</i> -(4-[3-(hydroxyamino)-3-oxopropyl]benzyl)-L-leucinate	B, K6	LCMS purity 90%, $m/z = 380$ $[M+H]^+$, 1H NMR (300MHz, CD_3OD) δ : 7.46 (2H, d, $J=8.1$ Hz), 7.34 (2H, d, $J=8.1$ Hz), 4.70-4.44 (2H, m), 4.29 (2H, m), 4.15 (1H, m), 3.56 (2H, t, $J=4.99$ Hz), 2.96 (6H, s), 2.93 (1H, m), 2.43 (2H, t, $J=7.44$ Hz), 1.85 (4H, m), 0.99 (6H, t, $J=6.78$ Hz).
39	Cyclopentyl (2 <i>S</i>)-({4-[3-(hydroxyamino)-3-oxopropyl]benzyl}amino)(phenyl)acetate	B, L1	LCMS purity 95%, $m/z = 397$ $[M+H]^+$, 1H NMR (300MHz, d_6 -DMSO) δ : 1.36-1.90 (8H, m), 2.27 (2H, t, $J=7.6$ Hz), 2.83 (2H, t, $J=7.6$ Hz), 3.91 (1H, m), 4.08 (1H, m), 5.16 (2H, m), 7.24 (2H, d, $J=7.9$ Hz), 7.37 (2H, d, $J=7.9$ Hz), 7.50 (5H, m), 8.71 (1H, br s), 10.01 (1H, m), 10.42 (1H, s).
40	<i>tert</i> -Butyl (2 <i>S</i>)-cyclohexyl({4-[3-(hydroxyamino)-3-oxopropyl]benzyl}amino)acetate	B, J2	LCMS purity 99%, $m/z = 391$ $[M+H]^+$, 1H NMR (300MHz, d_6 -DMSO) δ : 0.87 (1H, m), 1.15 (4H, m), 1.43 (9H, s), 1.71 (4H, m), 1.91 (1H, m), 2.26 (2H, t, $J=8.1$ Hz), 2.82 (2H, t, $J=8.1$ Hz), 3.73 (1H, m), 4.07 (2H, m), 7.26 (2H, d, $J=7.8$ Hz), 7.36 (2H, d, $J=7.8$ Hz), 8.74 (1H, m), 9.18 (2H, m), 10.40 (1H, m).

Example	Chemical name	Intermediates used	Analytical data
41	<i>tert</i> -Butyl <i>N</i> -{4-[3-(hydroxyamino)-3-oxopropyl]benzyl}-L-leucinate	B, K2	LCMS purity 95%, $m/z = 365$ $[M+H]^+$, 1H NMR (300MHz, CD_3OD) δ : 7.45-7.40 (2H, m), 7.37-7.33 (2H, m), 4.26-4.13 (2H, m), 3.91 (1H, t, $J=4.6$ Hz), 2.97 (2H, t, $J=7.5$ Hz), 2.41 (2H, t, $J=7.5$ Hz), 1.89-1.63 (3H, m), 1.56 (9H, s), 1.01 (6H, dd, $J=7.7, 6.2$ Hz).
42	Cyclopentyl <i>N</i> -{4-[3-(hydroxyamino)-3-oxopropyl]benzyl}-L-valinate	B, M1	LCMS purity 100%, $m/z = 363$ $[M+H]^+$, 1H NMR (300MHz, d_6 -DMSO) δ : 10.38 (1H, s), 9.23 (2H, br s), 8.71 (1H, br s), 7.38 (2H, d, $J=7.7$ Hz), 7.27 (2H, d, $J=7.7$ Hz), 5.13 (1H, t, $J=5.4$ Hz), 4.17-4.08 (2H, m), 3.86 (1H, br s), 2.83 (2H, t, $J=7.5$ Hz), 2.54-2.53 (1H, m), 2.46-2.36 (1H, m), 2.27 (2H, t, $J=7.6$ Hz), 1.91-1.76 (2H, m), 1.67-1.52 (6H, m), 1.01 (3H, d, $J=7.0$ Hz), 0.91 (3H, d, $J=6.8$ Hz).
43	Cyclopentyl <i>N</i> -{4-[3-(hydroxyamino)-3-oxopropyl]benzyl}-3-methyl-L-valinate	B, U	LCMS purity 96%, $m/z = 377$ $[M+H]^+$, 1H NMR (300MHz, CD_3OD) δ : 7.44 - 7.32 (4H, m), 5.14-5.05 (1H, m), 4.32-4.17 (2H, m), 3.53 (1H, s), 2.98 (2H, t, $J=7.6$ Hz), 2.41 (2H, t, $J=7.5$ Hz), 1.94-1.61 (8H, m), 1.08 (9H, s).
44	<i>tert</i> -Butyl <i>N</i> -{4-[3-(hydroxyamino)-3-oxopropyl]benzyl}isoleucinate	B, N	LCMS purity 92%, $m/z = 365$ $[M+H]^+$, 1H NMR (300MHz, CD_3OD) δ : 7.46-7.32 (4H, m), 4.22 (2H, s), 3.86 (1H, d, $J=3.2$ Hz), 2.97 (2H, t, $J=7.5$ Hz), 2.41 (2H, t, $J=7.5$ Hz), 2.04-1.97 (1H, m), 1.52 (9H, s), 1.65-1.38 (2H, m), 1.03-0.98 (6H, m).
45	(1 <i>R</i> ,2 <i>S</i> ,5 <i>R</i>)-2-Isopropyl-5-methylcyclohexyl <i>N</i> -{4-[3-(hydroxyamino)-3-oxopropyl]benzyl}-L-leucinate	B, K7	LCMS purity 97%, $m/z = 447$ $[M+H]^+$, 1H NMR (300MHz, CD_3OD) δ : 0.94 (3H, d, $J=5.1$ Hz), 0.98 (14H, m), 1.51 (2H, m), 1.72-1.92 (6H, m), 2.04 (1H, m), 2.41 (2H, t, $J=7.5$ Hz), 2.97 (2H, t, $J=7.5$ Hz), 4.02 (1H, m), 4.18 (2H, dd, $J=36.6, 12.9$ Hz), 7.37 (4H, m).
46	(1 <i>R</i> ,2 <i>S</i> ,5 <i>R</i>)-2-Isopropyl-5-methylcyclohexyl (2 <i>S</i>)-cyclohexyl({4-[3-(hydroxyamino)-3-oxopropyl]benzyl}amino)acetate	B, J13	LCMS purity 98%, $m/z = 473$ $[M+H]^+$, 1H NMR (300MHz, CD_3OD) δ : 0.72 (3H, d, $J=7.2$ Hz), 0.8-1.9 (26H, m), 2.29 (2H, t, $J=7.8$ Hz), 2.85 (2H, t, $J=7.8$ Hz), 3.54 (1H, m), 4.01 (2H, m), 4.89 (1H, m), 7.25 (1H, m).
47	<i>tert</i> -Butyl <i>N</i> -{4-[3-(hydroxyamino)-3-oxopropyl]benzyl}-L-valinate	B, M2	LCMS purity 100%, $m/z = 351$ $[M+H]^+$, 1H NMR (300MHz, d_6 -DMSO) δ : 10.41 (1H, s), 9.27 (2H, br s), 7.39 (2H, d, $J=8.1$ Hz), 7.27 (2H, d, $J=7.9$ Hz), 4.18-4.03 (2H, m), 3.74 (1H, br s), 2.83 (2H, t, $J=7.6$ Hz), 2.36-2.32 (1H, m), 2.27 (2H, t), 1.43 (9H, s), 1.04 (3H, d, $J=7.0$ Hz), 0.93 (3H, d, $J=6.8$ Hz).

Example	Chemical name	Intermediates used	Analytical data
48	(1 <i>S</i> ,2 <i>R</i> ,5 <i>S</i>)-2-Isopropyl-5-methylcyclohexyl (2 <i>S</i>)-cyclohexyl({4-[3-(hydroxyamino)-3-oxopropyl]benzyl}amino)acetate	B, J12	LCMS purity 98%, $m/z = 473$ [M+H] ⁺ , ¹ H NMR (300MHz, <i>d</i> ₆ -DMSO) δ : 10.37 (1H, br s), 8.70 (1H, br s), 7.15-7.43 (4H, m), 4.61-4.74 (1H, m), 4.00-4.23 (1H, m), 3.22-3.45 (2H, m), 2.82 (2H, t, <i>J</i> =6.6Hz), 2.26 (2H, t, <i>J</i> =7.7Hz), 1.33-2.01 (15H, m), 0.94-1.30 (14H, m), 0.90 (3H, d, <i>J</i> =6.6Hz), 0.88 (3H, d, <i>J</i> =4.2Hz), 0.71 (3H, d, <i>J</i> =6.9Hz).
49	<i>tert</i> -Butyl (2 <i>S</i>)-({3-[3-(hydroxyamino)-3-oxopropyl]benzyl}amino)(phenyl)acetate	D, L2	LCMS purity 98%, $m/z = 485$ [M+H] ⁺ , ¹ H NMR (300MHz, <i>d</i> ₆ -DMSO) δ : 10.39 (1H, br s), 7.48-7.55 (5H, m), 7.23-7.39 (4H, m), 5.13 (1H, br s), 3.99 (2H, ABq, <i>J</i> =13.2Hz), 2.82 (2H, t, <i>J</i> =8.1Hz), 2.26 (2H, t, <i>J</i> =8.0Hz), 1.35 (9H, s).
50	Cyclopentyl (2 <i>S</i>)-cyclohexyl({3-[3-(hydroxyamino)-3-oxopropyl]benzyl}amino)acetate	D, J1	LCMS purity 98%, $m/z = 403$ [M+H] ⁺ , ¹ H NMR (300MHz, <i>d</i> ₆ -DMSO) δ : 10.40 (1H, br s), 7.23-7.40 (4H, m), 5.16 (1H, m), 4.11 (2H, m), 3.82 (1H, br s), 2.83 (2H, t, <i>J</i> =8.3Hz), 2.27 (2H, t, <i>J</i> =7.5Hz), 0.73-2.00 (19H, m).
51	Cyclopentyl (2 <i>S</i>)-({3-[3-(hydroxyamino)-3-oxopropyl]benzyl}amino)(phenyl)acetate	D, L1	LCMS purity 98%, $m/z = 397$ [M+H] ⁺ , ¹ H NMR (300MHz, <i>d</i> ₆ -DMSO) δ : 10.39 (1H, br s), 7.51 (4H, m), 7.23-7.38 (5H, m), 5.15-5.23 (2H, m), 4.00 (2H, ABq, <i>J</i> =12.3Hz), 2.82 (2H, t, <i>J</i> =8.1Hz), 2.27 (2H, t, <i>J</i> =7.4Hz), 1.27-1.90 (8H, m).
52	Cyclopentyl <i>N</i> -{3-[3-(hydroxyamino)-3-oxopropyl]benzyl}-L-leucinate	D, K1	LCMS purity 95%, $m/z = 377$ [M+H] ⁺ , ¹ H NMR (300MHz, <i>d</i> ₆ -DMSO) δ : 10.41 (1H, br s), 9.46 (1H, br s), 7.24-7.41 (4H, m), 5.21 (1H, t, <i>J</i> =5.5Hz), 4.13 (1H, ABq, <i>J</i> =12.2Hz), 3.93 (1H, m), 2.83 (2H, t, <i>J</i> =7.2Hz), 2.27 (2H, t, <i>J</i> =8.0Hz), 1.53-1.95 (11H, m), 0.90 (6H, d, <i>J</i> =5.8Hz).
53	Cyclopentyl (2 <i>S</i>)-cyclohexyl[({6-[(1 <i>E</i>)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]pyridin-3-yl}methyl)amino]acetate	E, J1	LCMS purity >95%, $m/z = 402$ [M+H] ⁺ , ¹ H NMR (300MHz, CD ₃ OD) δ : 8.53 (1H, s), 7.89-7.48 (3H, m), 6.87 (1H, d, <i>J</i> =15.6Hz), 5.17 (1H, m), 3.77 (2H, q), 2.97 (1H, d, <i>J</i> =6Hz), 2.01-0.97 (19H, m).
54	Cyclopentyl <i>N</i> -({6-[(1 <i>E</i>)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]pyridin-3-yl}methyl)-L-leucinate	E, K1	LCMS purity 100%, $m/z = 376$ [M+H] ⁺ , ¹ H NMR (300MHz, CD ₃ OD) δ : 8.54 (1H, s), 7.87-7.49 (3H, m), 6.87 (1H, d, <i>J</i> =15.6Hz), 5.20 (1H, m), 3.78 (2H, q), 3.24 (1H, t), 2.00-1.20 (11H, m), 0.90 (6H, dd).
55	2,3-Dihydro-1 <i>H</i> -inden-2-yl (2 <i>S</i>)-cyclohexyl[({6-[(1 <i>E</i>)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]pyridin-3-yl}methyl)amino]acetate	E, J6	LCMS purity 99%, $m/z = 450$ [M+H] ⁺ , ¹ H NMR (300MHz, CD ₃ OD) δ : 8.62 (1H, s), 7.87 (1H, d, <i>J</i> =8.4Hz), 7.64 (1H, d, <i>J</i> =8.5Hz), 7.60 (1H, s), 7.31-7.18 (5H, m), 6.97 (1H, d, <i>J</i> =15.5Hz), 5.59 (1H, m), 4.15 (2H, s), 1.88-1.58 (7H, m), 1.39-0.88 (9H, m).

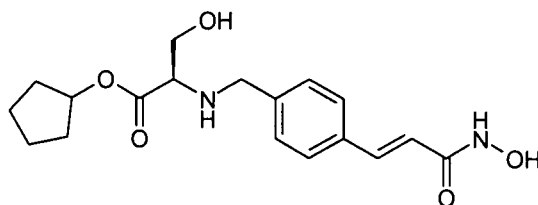
Example	Chemical name	Intermediates used	Analytical data
56	2-Morpholin-4-ylethyl (2 <i>S</i>)-cyclohexyl[({6-[(1 <i>E</i>)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]pyridin-3-yl)methyl}amino]acetate	E, J10	LCMS purity 96%, $m/z = 447 [M+H]^+$, 1H NMR (300MHz, CD_3OD) δ : 8.72(1H, s), 8.02 (1H, dd, $J=7.9$, 1.8Hz), 7.66 (1H, d, $J=5.6$ Hz), 7.65 (1H, d, $J=29.1$ Hz), 6.99 (1H, d, $J=15.4$ Hz), 4.64 (2H, m), 4.36 (2H, s), 4.10 (1H, d, $J=3.8$ Hz), 3.97 (4H, br s), 3.60 (2H, m), 3.40 (3H, br s), 3.36 (3H, s), 2.07 (1H, m), 1.84 (4H, br s), 1.73 (1H, d, $J=11.1$ Hz), 1.42-1.02 (5H, m).
57	2-(Dimethylamino)ethyl (2 <i>S</i>)-cyclohexyl[({6-[(1 <i>E</i>)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]pyridin-3-yl)methyl}amino]acetate	E, J11	LCMS purity 94%, $m/z = 405 [M+H]^+$, 1H NMR (300MHz, CD_3OD) δ : 8.74 (1H, s), 8.07 (1H, d, $J=7.63$), 7.70 (1H, d, $J=7.82$ Hz), 7.58 (1H, d, $J=15.35$ Hz), 4.65 (2H, m), 4.41 (2H, s), 3.01 (6H, s), 2.12 (1H, m), 1.84 (4H, d, $J=7.91$ Hz), 1.71 (1H, d, $J=11.87$ Hz), 1.41-1.04 (5H, m).
58	Bicyclo[2.2.1]hept-2-yl (2 <i>S</i>)-cyclohexyl[({6-[(1 <i>E</i>)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]pyridin-3-yl)methyl}amino]acetate	E, J7	LCMS purity 97%, $m/z = 428 [M+H]^+$, 1H NMR (300MHz, CD_3OD) δ : 8.73 (1H, s), 8.05 (1H, d, $J=7.25$ Hz), 7.68 (1H, d, $J=7.82$ Hz), 7.56 (1H, d, $J=15.54$ Hz), 6.97 (1H, d, $J=15.45$ Hz), 4.67 (1H, dd, $J=24.63$, 6.55Hz), 4.36 (2H, m), 4.02 (1H, m), 2.40-0.94 (22H, m).
59	<i>tert</i> -Butyl (2 <i>S</i>)-cyclohexyl[({6-[(1 <i>E</i>)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]pyridin-3-yl)methyl}amino]acetate	E, J2	LCMS purity 98%, $m/z = 390 [M+H]^+$, 1H NMR (300MHz, d_6 -DMSO) δ : 1.14 (6H, m), 1.41 (9H, s), 1.61 (4H, m), 1.79 (1H, m), 2.73 (1H, m), 3.32 (1H, m), 3.54 (1H, d, $J=13.8$ Hz), 3.80 (1H, d, $J=13.8$ Hz), 6.90 (1H, d, $J=15.3$ Hz), 7.45 (1H, d, $J=15.3$ Hz), 7.52 (1H, d, $J=7.8$ Hz), 7.73 (1H, dm, $J=7.8$ Hz), 8.51 (1H, s), 9.12 (1H, s), 10.90 (1H, s).
60	Cyclopentyl (2 <i>S</i>)-[({6-[(1 <i>E</i>)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]pyridin-3-yl)methyl}amino](phenyl)acetate	E, L1	LCMS purity 98%, $m/z = 396 [M+H]^+$, 1H NMR (300MHz, d_6 -DMSO) δ : 10.97 (1H, br s), 8.59 (1H, s), 7.88 (1H, dd, $J=2.0$, 7.9Hz), 7.64 (1H, d, $J=8.0$ Hz), 7.43-7.57 (6H, m), 6.96 (1H, d, $J=15.4$ Hz), 5.31 (1H, br s), 5.11-5.20 (1H, m), 4.14 (2H, ABq, $J=13.6$ Hz), 1.26-1.90 (8H, m).
61	<i>tert</i> -Butyl (2 <i>S</i>)-[({6-[(1 <i>E</i>)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]pyridin-3-yl)methyl}amino](phenyl)acetate	E, L2	LCMS purity 98%, $m/z = 384 [M+H]^+$, 1H NMR (300MHz, d_6 -DMSO) δ : 8.76 (1H, br s), 7.88 (1H, dd, $J=2.1$, 8.2Hz), 7.64 (1H, d, $J=8.1$ Hz), 7.41-7.70 (6H, m), 6.95 (1H, d, $J=15.4$ Hz), 5.12-5.31 (2H, m), 4.02-4.21 (2H, m), 1.34 (9H, s).

Example	Chemical name	Intermediates used	Analytical data
62	Cyclopentyl (2S)-cyclohexyl[({6-[3-(hydroxyamino)-3-oxopropyl]pyridin-3-yl)methyl}amino]acetate	F, J1	LCMS purity 93%, m/z = 404 [M+H] ⁺ , ¹ H NMR (300MHz, d ₆ -DMSO) δ: 10.41 (1H, s), 8.70 (1H, s), 8.34 (1H, s), 7.59 (1H, d, J=6Hz), 7.19 (1H, d, J=7.8Hz), 5.08 (1H, m), 3.80-3.41 (2H, q), 2.92 (2H, t, J=7.2Hz), 2.81 (1H, m), 2.37 (2H, t, J=8.1Hz), 1.91-0.87 (19H, m).
63	<i>tert</i> -Butyl (2S)-cyclohexyl[({6-[3-(hydroxyamino)-3-oxopropyl]pyridin-3-yl)methyl}amino]acetate	F, J2	LCMS purity 92%, m/z = 392 [M+H] ⁺ , ¹ H NMR (300MHz, CD ₃ OD) δ: 8.65 (1H, d, J=1.7Hz), 8.03 (1H, dd, J=8.1, 2.3Hz), 7.56 (1H, d, J=8.1Hz), 4.37-4.23 (2H, m), 3.87 (1H, d, J=3.6Hz), 3.18 (2H, t, J=7.4Hz), 2.59 (2H, t, J=7.4Hz), 2.05-1.97 (1H, m), 1.89-1.75 (5H, m), 1.54 (9H, s), 1.45-1.24 (3H, m), 1.23-1.04 (2H, m).
64	<i>tert</i> -Butyl (2S)-[({6-[3-(hydroxyamino)-3-oxopropyl]pyridin-3-yl)methyl}amino](phenyl)acetate	F, L2	LCMS purity 98%, m/z = 386 [M+H] ⁺ , ¹ H NMR (300MHz, d ₆ -DMSO) δ: 10.43 (1H, br s), 10.13 (1H, br s), 8.49 (1H, s), 7.80 (1H, d, J=7.2Hz), 7.51 (5H, m), 7.38 (1H, t, J=6.3Hz), 5.21 (1H, br s), 4.06 (2H, ABq, J=13.2Hz), 2.99 (2H, t, J=6.9Hz), 2.68 (2H, t, J=7.3Hz), 2.40 (2H, t, J=7.8Hz), 1.35 (9H, s).
65	Cyclopentyl (2S)-[({6-[3-(hydroxyamino)-3-oxopropyl]pyridin-3-yl)methyl}amino](phenyl)acetate	F, L1	LCMS purity 95%, m/z = 398 [M+H] ⁺ , ¹ H NMR (300MHz, d ₆ -DMSO) δ: 10.42 (1H, br s), 10.10 (1H, br s), 8.49 (1H, s), 7.88 (1H, d, J=8.3Hz), 7.45-7.60 (5H, m), 7.37 (1H, t, J=6.4Hz), 5.20 (1H, br s), 5.16 (1H, t, J=5.7Hz), 4.08 (2H, ABq, J=15.4Hz), 3.00 (2H, t, J=7.6Hz), 2.42 (2H, t, J=7.6Hz), 1.27-1.87 (8H, m).
66	<i>tert</i> -Butyl <i>N</i> -({6-[3-(hydroxyamino)-3-oxopropyl]pyridin-3-yl)methyl}-L-leucinate	F, K2	LCMS purity 97%, m/z = 366 [M+H] ⁺ , ¹ H NMR (300MHz, CD ₃ OD) δ: 8.29 (1H, dd, J=1.8, 0.7Hz), 7.63 (1H, dt, J=8.1, 1.1Hz), 7.21 (1H, d, J=8.1Hz), 3.69 (1H, d, J=13.4Hz), 3.52 (1H, d, J=13.4Hz), 3.02 (1H, t), 2.96 (2H, dd, J=8.1, 7.5Hz), 2.34 (2H, t, J=7.8Hz), 1.69-1.56 (1H, m), 1.38 (9H, s), 0.82 (3H, d, J=6.6Hz), 0.76 (3H, d, J=6.6Hz).
67	(1 <i>R</i> ,2 <i>S</i> ,5 <i>R</i>)-2-Isopropyl-5-methylcyclohexyl <i>N</i> -({6-[3-(hydroxyamino)-3-oxopropyl]pyridin-3-yl)methyl}-L-leucinate	F, K7	LCMS purity 97%, m/z = 448 [M+H] ⁺ , ¹ H NMR (300MHz, d ₆ -DMSO) δ: 10.44 (1H, s), 9.60 (1H, br s), 8.54 (1H, d, J=1.9Hz), 7.81 (1H, dd, J=8.1, 2.1Hz), 7.43-7.35 (1H, m), 4.82-4.71 (1H, m), 4.03 (3H, q, J=7.2Hz), 2.99 (1H, t, J=7.6Hz), 2.71 (1H, d, J=13.6Hz), 2.41 (1H, t, J=7.6Hz), 1.93-1.76 (2H, m), 1.74-1.62 (6H, m), 1.43 (2H, t, J=12.4Hz), 1.18 (6H, t, J=7.2Hz), 1.06 (2H, t, J=11.5Hz), 0.91 (8H, dd, J=6.9, 2.7Hz), 0.74 (3H, d, J=7.0Hz).

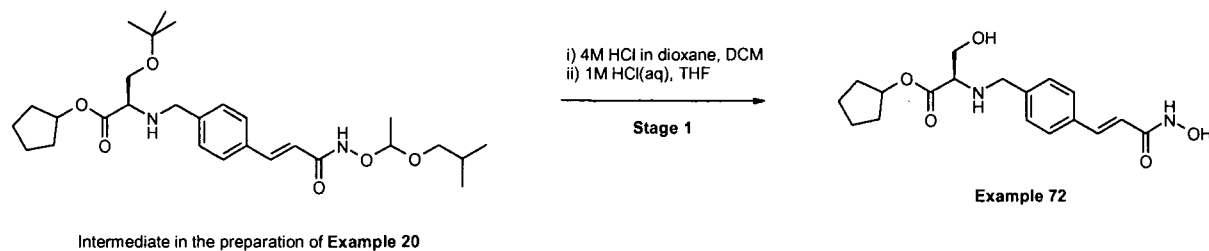
Example	Chemical name	Intermediates used	Analytical data
68	Cyclopentyl (2S)-cyclohexyl[({5-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]pyridin-2-yl)methyl}amino]acetate	G, J1	LCMS purity 95%, m/z = 402 [M+H] ⁺ , ¹ H NMR (300MHz, CD ₃ OD) δ: 8.81 (1H, s), 8.09 (1H, d, J=7.7Hz), 7.63 (1H, d, J=15.9Hz), 7.50 (1H, d, J=8.2Hz), 5.31-5.39 (1H, m), 4.46 (2H, ABq, J=13Hz), 3.98 (1H, d, J=4.0Hz), 1.07-2.14 (18H, m).
69	<i>tert</i> -Butyl N-({5-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]pyridin-2-yl)methyl}-L-leucinate	G, K2	LCMS purity 98%, m/z = 364 [M+H] ⁺ , ¹ H NMR (300MHz, d ₆ -DMSO) δ: 10.87 (1H, br s), 9.55 (2H, br s), 9.14 (1H, br s), 8.84 (1H, s), 8.10 (1H, d, J=8.4Hz), 7.50-7.60 (2H, m), 6.62 (1H, d, J=15.7Hz), 4.35 (2H, ABq, J=16.4Hz), 3.84-3.99 (2H, m), 1.64-1.78 (3H, m), 1.46 (9H, s), 0.93 (6H, d, J=5.8Hz).
70	Cyclopentyl (2S)-cyclohexyl[({5-[3-(hydroxyamino)-3-oxopropyl]pyridin-2-yl)methyl}amino]acetate	H, J1	LCMS purity 95%, m/z = 404 [M+H] ⁺ , ¹ H NMR (300MHz, d ₆ -DMSO) δ: 10.41 (1H, br s), 8.48 (1H, d, J=1.6Hz), 7.73 (1H, dd, J=2.1, 8.0Hz), 7.44 (1H, d, J=8.0Hz), 5.19 (1H, t, J=5.5Hz), 4.30 (2H, br s), 3.88 (2H, t, J=3.6 Hz), 2.87 (2H, t, J=7.3Hz), 2.31 (2H, t, J=7.4Hz), 1.53-2.07 (14H, m), 0.79-1.31 (5H, m).
71	<i>tert</i> -Butyl N-({5-[3-(hydroxyamino)-3-oxopropyl]pyridin-2-yl)methyl}-L-leucinate	H, K2	LCMS purity 99%, m/z = 366 [M+H] ⁺ , ¹ H NMR (300MHz, d ₆ -DMSO) δ: 10.37 (1H, br s), 8.73 (1H, br s), 8.31 (1H, d, J=1.8Hz), 7.56 (1H, dd, J=8.1, 2.2Hz), 7.31 (1H, d, J=8.1Hz), 3.76 (1H, d, J=13.6Hz), 3.62 (1H, dd, J=2.9, 14.0Hz), 3.03-3.11 (1H, m), 2.80 (2H, t, J=7.5Hz), 2.30-2.45 (1H, m), 2.26 (2H, t, J=7.3Hz), 1.66-1.79 (1H, m), 1.40 (9H, s), 0.88 (3H, d, J=7.0Hz), 0.82 (3H, d, J=6.5Hz).

Example 72:

Cyclopentyl N-{4-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}-D-serinate



The title compound was prepared by the following methodology:

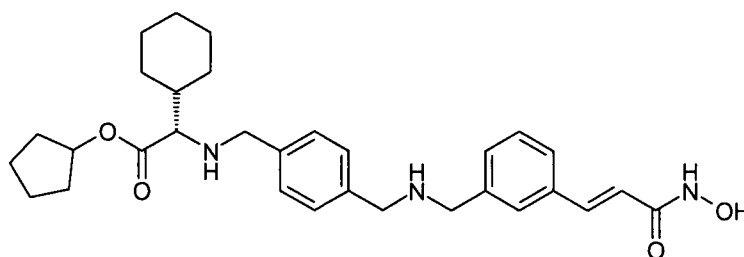


Stage 1 – Preparation of cyclopentyl N-{4-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}-D-serinate (Example 72**)**

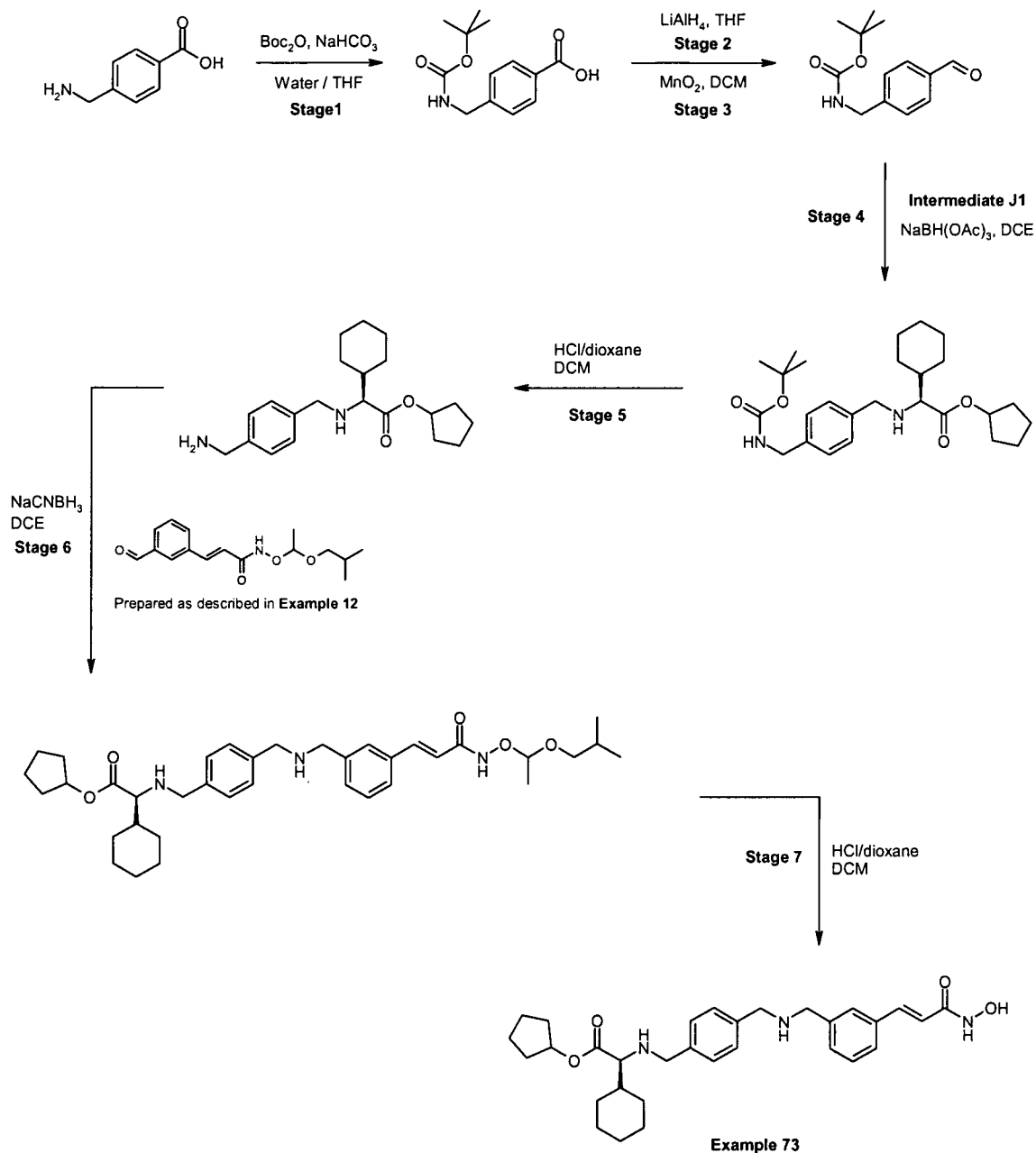
The intermediate in the preparation of **Example 20** (100mg, 0.20mmol) was dissolved in DCM (10mL) and 4N HCl in dioxane (0.15mL, 0.60mmol) charged. The reaction was concentrated to dryness, the residue dissolved in THF (10mL), 1N aqueous HCl (10mL) was charged and the reaction stirred at 50°C for 18h. The solvent was then removed *in vacuo* and the residue purified by prep HPLC to afford the desired product (12mg, 17%). LCMS purity 100%, $m/z = 349$ $[M+H]^+$, 1H NMR (300MHz, CD_3OD) δ : 7.80-7.44 (5H, m), 6.55 (1H, d, $J=15.3$ Hz), 5.33 (1H, s), 4.32 (2H, s), 4.06 (3H, s), 2.03-1.20 (8H, m).

Example 73:

Cyclopentyl (2S)-cyclohexyl({4-[(3-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}amino)methyl]benzyl}amino)acetate



The title compound was prepared by the following methodology:



Stage 1 – Preparation of 4-[(tert-butoxycarbonyl)amino]methyl}benzoic acid

4-(Aminomethyl)benzoic acid (10.00g, 65.36mmol) was stirred with Boc_2O (28.00g, 130.72mmol) in H_2O (100mL) and THF (100mL) at RT. Sat. NaHCO_3 solution was added until pH ~ 6 was reached and the reaction was allowed to stir for 16h. The reaction was then carefully acidified to pH ~ 3 with 1M HCl_{aq} which caused a solid to precipitate out. This was filtered and dried to give the product as a white solid (16.1g, 97%). $m/z = 274 [\text{M}+\text{Na}]^+$.

Stage 2 – Preparation of *tert*-butyl [4-(hydroxymethyl)benzyl]carbamate

Stage 1 product (16.1g, 64.14mmol) was stirred in THF (300mL) and dioxane (200mL) at 0°C under a nitrogen atmosphere. LiAlH₄ was then added and the reaction allowed to warm to RT and stir for 16h. It was then cooled to 0°C and quenched with sat. NH₄Cl_{aq}. Na₂SO₄ was added and the mixture stirred for 30 minutes. It was then filtered through celite and the filtrate concentrated *in vacuo* to give the product as a light yellow solid (13.1g, 94%). *m/z* = 260 [M+Na]⁺.

Stage 3 – Preparation of *tert*-butyl (4-formylbenzyl)carbamate

Stage 2 product (5.87g, 24.73mmol) was stirred in DCM (200mL) with MnO₂ (16.71g, 192.2mmol) for 16h at RT. The reaction was then filtered through celite and the solvent removed *in vacuo* to give the product as a yellow oil (4.63g, 80%). *m/z* = 258 [M+Na]⁺.

Stage 4 – Preparation of cyclopentyl (2S)-[4-[[*tert*-butoxycarbonyl)amino]methyl]benzyl]amino](cyclohexyl)acetate

Stage 3 product (650mg, 2.70mmol) was stirred in DCE (20mL), **Intermediate J1** (707mg, 2.70mmol) and STAB (918mg, 4.33mmol) at RT under a nitrogen atmosphere for 3h. After this time the reaction was diluted with H₂O (50mL) and extracted with Et₂O (2 x 100mL). The combined organic extracts were dried (MgSO₄) and solvent removed *in vacuo* to give the product as a brown oil (1.13g, 95%). *m/z* = 445 [M+H]⁺.

Stage 5 – Preparation of cyclopentyl (2S)-[4-(aminomethyl)benzyl]amino](cyclohexyl)acetate

Stage 4 product (1.13g, 2.56mmol) was stirred in DCM (5mL) with 4M HCl in dioxane (2mL) at RT under a nitrogen atmosphere for 3h. The solvent was removed *in vacuo* and the residue dried to give the product as a brown solid as the HCl salt (971mg, 99%). *m/z* = 345 [M+H]⁺.

Stage 6 – Preparation of cyclopentyl (2S)-cyclohexyl[[4-[[3-[(1*E*)-3-[(1-isobutoxyethoxy)amino]-3-oxoprop-1-en-1-yl]benzyl]amino]methyl]benzyl]amino]acetate

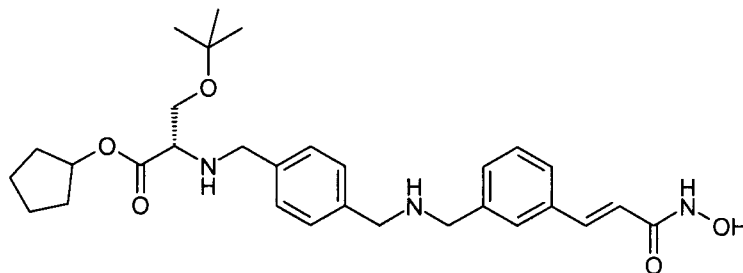
(2*E*)-3-(3-Formylphenyl)-*N*-(1-isobutoxyethoxy)acrylamide (prepared as described in **Example 12** – 0.2g, 0.69mmol) and stage 5 product (0.26g, 0.68mmol) were dissolved in DCE (10mL) and stirred under nitrogen for 17h. NaBH₃CN (0.087g, 1.4mmol) was charged and the reaction stirred for 2h. After this time the reaction was quenched with water (10mL) then separated. The aqueous phase was extracted with DCM (2 x 10mL) and the combined organics dried (MgSO₄) and concentrated to dryness *in vacuo* to afford the product as a yellow oil. Purification by column chromatography (1:1 EtOAc in heptane) gave a pale yellow oil (0.07g, 16%). *m/z* = 642 [M+Na]⁺.

Stage 7 – Preparation of cyclopentyl (2S)-cyclohexyl({4-[(3-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}amino)methyl]benzyl}amino)acetate (Example 73**)**

4N HCl in dioxane (0.03mL, 0.12mmol) was charged to a solution of stage 6 product (0.07g, 0.11mmol) in DCM (10mL) and the reaction stirred for 3h. The reaction was concentrated to dryness *in vacuo* to afford a yellow oil. Purification by preparative HPLC afforded the desired product as a white solid (15mg, 26%). LCMS purity >95%, $m/z = 520$ $[M+H]^+$, 1H NMR (300MHz, CD_3OD) δ : 7.78-7.47 (9H, m), 6.54 (1H, d, $J=15.6$ Hz), 5.31 (1H, m), 4.38-4.20 (6H, m), 3.79 (1H, m), 2.04-1.18 (19H, m).

Example 74:

Cyclopentyl O-*tert*-butyl-N-{4-[(3-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}amino)methyl]benzyl}-L-serinate

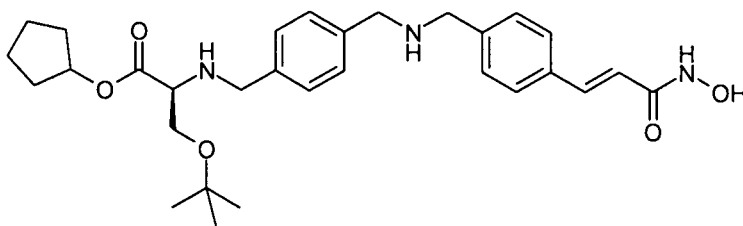


The title compound was prepared from **Intermediate O** by the same methodology used to make **Example 73**.

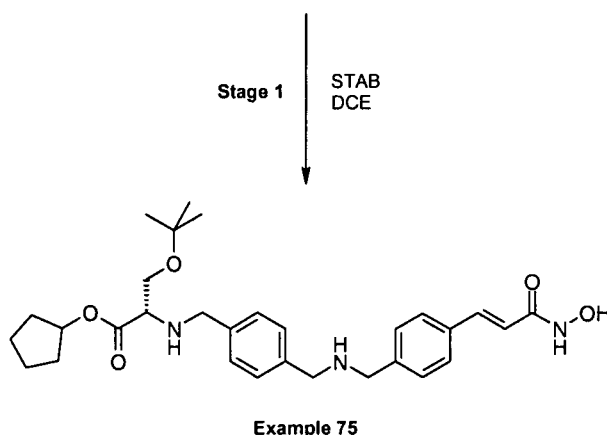
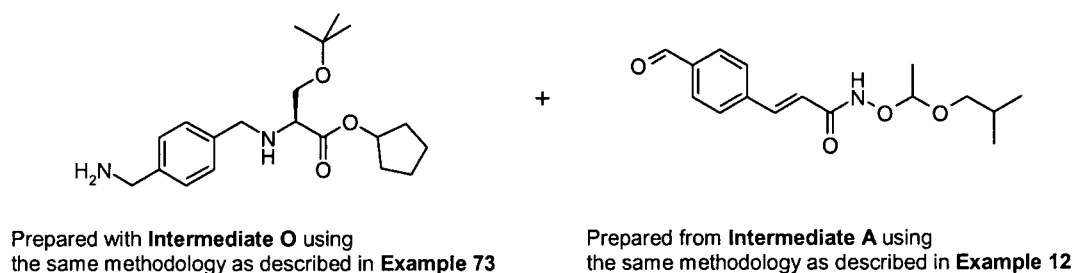
LCMS purity 100%, $m/z = 520$ $[M+H]^+$, 1H NMR (300MHz, CD_3OD) δ : 7.78-7.47 (9H, m), 6.54 (1H, d, $J=15.6$ Hz), 5.31 (1H, m), 4.38-4.20 (6H, m), 3.79 (1H, m), 2.04-1.18 (19H, m).

Example 75:

Cyclopentyl O-*tert*-butyl-N-{4-[(4-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}amino)methyl]benzyl}-L-serinate



The title compound was prepared by the following methodology:



Stage 1 – Preparation of cyclopentyl O-tert-butyl-N-[4-[(4-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl]amino)methyl]benzyl]-L-serinate (Example 75**)**

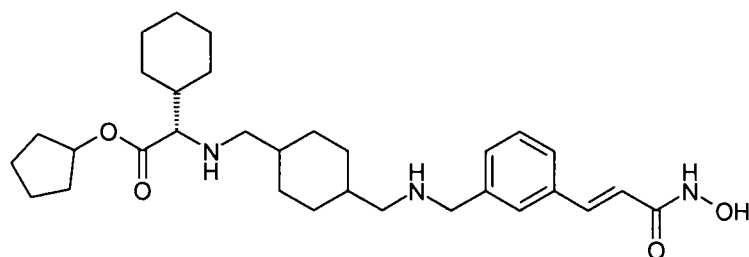
To a suspension of cyclopentyl N-[4-(aminomethyl)benzyl]-O-tert-butyl-L-serinate (prepared as described in **Example 73** – 0.282g, 0.67mmol) and (2E)-3-(4-formylphenyl)-N-(1-isobutoxyethoxy)acrylamide (prepared as described in **Example 12** – 0.230g, 0.79mmol) in DCE (25mL) was added STAB (0.700g, 3.3mmol). The mixture was stirred at RT for 3h, and then quenched with sat. NaHCO₃ solution (75mL). The product was then extracted with DCM (3 x 100mL) and the combined organic extracts were dried (MgSO₄), concentrated and purified by preparative HPLC to yield the desired product (5mg, 2%). LCMS purity 98%, m/z = 524.25 [M+H]⁺, ¹H NMR (300MHz, CD₃OD) δ: 7.41 (2H, d, J=7.9Hz), 7.24 (2H, d, J=7.7Hz), 7.20 (3H, br s), 6.37 (1H, d, J=15.6Hz), 5.09 (1H, t, J=5.7Hz), 3.44-3.75 (8H, m), 3.25 (1H, t, J=3Hz), 1.45-1.90 (8H, m), 1.04 (9H, s).

The following examples were prepared using the same methodology:

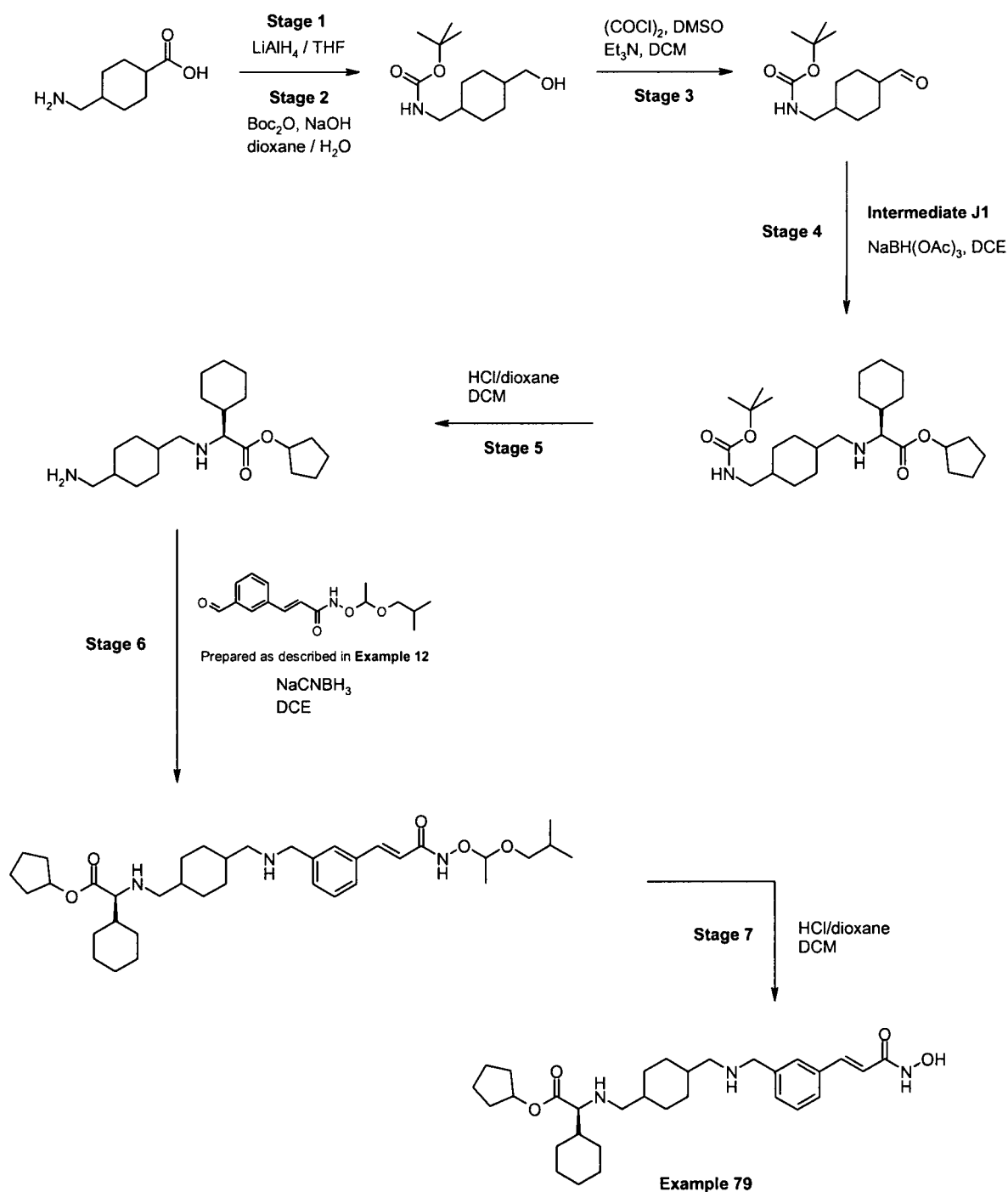
Example	Chemical name	Intermediates used	Analytical data
76	<i>tert</i> -Butyl <i>N</i> -4-[[[4-[(1 <i>E</i>)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl]amino) methyl]benzyl]-L-leucinate	A, K2	LCMS purity 97%, $m/z = 482$ $[M+H]^+$, 1H NMR (300MHz, d_6 -DMSO) δ : 0.91 (6H, m), 1.47 (9H, s), 1.71 (3H, m), 3.81 (1H, m), 4.15 (6H, m), 6.52 (1H, d, $J=15.9$ Hz), 7.50 (7H, m), 7.63 (2H, d, $J=8.4$ Hz), 9.51 (3H, m), 10.85 (1H, s).
77	Cyclopentyl (2 <i>S</i>)-cyclohexyl[({4-[[{4-[3-(hydroxyamino)-3-oxopropyl]benzyl}amino) methyl]benzyl}amino)acetate	B, J1	LCMS purity 98%, $m/z = 522$ $[M+H]^+$, 1H NMR (300MHz, CD_3OD) δ : 0.96-1.45 (6H, m), 1.75-2.00 (13H, m), 2.41 (2H, t, $J=7.2$ Hz), 2.96 (2H, t, $J=7.2$ Hz), 3.82 (1H, d, $J=3.9$ Hz), 4.23 (2H, s), 4.29 (4H, s), 5.31 (1H, t, $J=5.7$ Hz), 7.33 (2H, d, $J=8.1$ Hz), 7.41 (2H, d, $J=8.1$ Hz), 7.59 (4H, m).
78	<i>tert</i> -Butyl <i>N</i> -4-[[[4-[3-(hydroxyamino)-3-oxopropyl]benzyl]amino)methyl]benzyl]-L-leucinate	B, K2	LCMS purity 97%, $m/z = 484$ $[M+H]^+$, 1H NMR (300MHz, CD_3OD) δ : 1.01 (6H, t, $J=6.0$ Hz), 1.57 (9H, s), 1.80 (3H, m), 2.41 (2H, t, $J=7.2$ Hz), 2.96 (2H, t, $J=7.2$ Hz), 3.95 (1H, m), 4.25 (6H, m), 7.32 (2H, d, $J=8.1$ Hz), 7.42 (2H, d, $J=8.1$ Hz), 7.61 (4H, s).

Example 79:

Cyclopentyl (2*S*)-cyclohexyl[({4-[[{3-[(1*E*)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl]amino)methyl]cyclohexyl)methyl]amino]acetate



The title compound was prepared by the following methodology:



Stage 1 – Preparation of [4-(aminomethyl)cyclohexyl]methanol

4-(Aminomethyl)cyclohexanecarboxylic acid (4.00g, 25.44mmol) was stirred in THF (100mL) at 0°C under a nitrogen atmosphere. LiAlH_4 (2.90g, 76.33mmol) was then added and the reaction allowed to warm to RT and stir for 3h. It was then cooled to 0°C and quenched with H_2O . Na_2SO_4 was then added and the mixture stirred for 10 minutes. It was then filtered through

celite and the filtrate concentrated *in vacuo* to give the product as a colourless oil which solidified on standing to give the product as a white solid (3.72g, 100%). ^1H NMR (300MHz, d_6 -DMSO) δ : 0.95 (4H, m), 1.22-1.47 (5H, m), 1.86 (4H, m), 2.55 (2H, d, $J=6.6\text{Hz}$), 4.46 (2H, d, $J=6.3\text{Hz}$).

Stage 2 – Preparation of *tert*-butyl {[4-(hydroxymethyl)cyclohexyl]methyl}carbamate

Stage 1 product (3.72g, 26.01mmol) was stirred with NaOH (1.00g, 26.01mmol) and di-*tert*-butyl-dicarbonate (6.24g, 28.61mmol) in H_2O (50mL) and dioxane (50mL) at RT for 16h. The reaction was then concentrated *in vacuo*. When approximately 50% had been evaporated, a solid precipitated out of solution and was collected and dried to give the product as a white solid (5.5g, 87%). $m/z = 266$ $[\text{M}+\text{Na}]^+$, ^1H NMR (300MHz, CDCl_3) δ : 0.82 (4H, m), 1.28 (2H, m), 1.37 (9H, s), 1.70 (4H, m), 2.76 (2H, t, $J=6.3\text{Hz}$), 3.19 (2H, d, $J=6.3\text{Hz}$), 4.32 (1H, br s), 6.75 (1H, m).

Stage 3 – Preparation of *tert*-butyl [(4-formylcyclohexyl)methyl]carbamate

A solution of DCM (100mL) and $(\text{COCl})_2$ (1.58mL, 18.14mmol) was stirred under a nitrogen atmosphere and cooled to -78°C . DMSO (2.27mL, 32.02mmol) was then added whilst maintaining the temperature below -65°C . A solution of stage 2 product (4.5g, 17.79mmol) in DCM (50mL) was then prepared and added slowly to the reaction mixture, again maintaining the temperature below -65°C . When addition was complete Et_3N (9.99mL, 71.69mmol) was slowly added, again maintaining the temperature below -65°C . When addition was complete the reaction was allowed to warm to RT and then the solvent removed *in vacuo*. The residue was purified by column chromatography (0 to 10% MeOH in DCM) to give the product as a light yellow oil (5g, >100% - contains some Et_3N). $m/z = 266$ $[\text{M}+\text{Na}]^+$, ^1H NMR (300MHz, CDCl_3) δ : 1.02 (2H, m), 1.30 (2H, m), 1.45 (9H, s), 1.90 (2H, m), 2.03 (2H, m), 3.01 (2H, t, $J=6.3\text{Hz}$), 4.57 (1H, br s), 9.63 (1H, s).

Stage 4 – Preparation of cyclopentyl (2S)-{[4-[[*tert*-butoxycarbonyl]amino]methyl]cyclohexyl)methyl]amino}(cyclohexyl)acetate

Stage 3 product (1.00g, 4.14mmol) was stirred with **Intermediate J1** (1.08g, 4.14mmol) and STAB (1.33g, 6.21mmol) in DCE (20mL) at RT for 16h. The reaction was then diluted with H_2O (100mL) and extracted with DCM (2 x 100mL). The combined organic extracts were dried (MgSO_4) and the solvent removed *in vacuo* to give the product as a grey solid which was used in the next step without further purification (1.74g, 94%). $m/z = 451$ $[\text{M}+\text{H}]^+$.

Stage 5 – Preparation of cyclopentyl (2S)-([4-(aminomethyl)cyclohexyl)methyl]amino) (cyclohexyl)acetate

Stage 4 product (1.74g, 3.87mmol) was stirred in DCM (10mL) with 4M HCl in dioxane (3mL) at RT for 16h. The solvent was then removed *in vacuo* and the residue dried under vacuum to give the product as a white solid (1.36g, 98%). $m/z = 351$ $[M+H]^+$, 1H NMR (300MHz, d_6 -DMSO) δ : 0.90-1.20 (9H, m), 1.50-2.00 (21H, m), 2.65 (4H, m), 3.85 (1H, m), 5.25 (1H, m), 7.83 (2H, m).

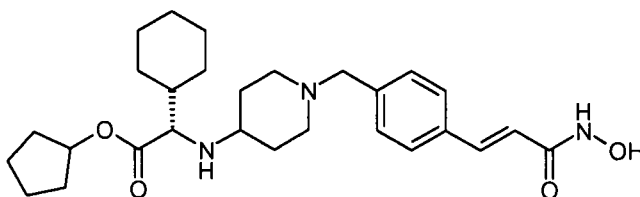
Stage 6 – Preparation of cyclopentyl (2S)-cyclohexyl{[(4-[(3-[(1E)-3-[(1-isobutoxyethoxy)amino]-3-oxoprop-1-en-1-yl]benzyl)amino)methyl]cyclohexyl)methyl]amino}acetate (2E)-3-(3-Formylphenyl)-N-(1-isobutoxyethoxy)acrylamide (prepared as described in **Example 12 – 0.3g, 1mmol) and stage 5 product (0.40g, 1mmol) were dissolved in DCE (10mL) and stirred for 2h. $NaBH_3CN$ (0.13g, 2.1mmol) was charged and the reaction stirred for 15h. After this time the reaction was quenched with water (10mL) then separated. The aqueous phase was extracted with DCM (2 x 10mL) and the combined organics dried ($MgSO_4$) and concentrated to dryness *in vacuo* to afford the product as a yellow oil (0.91g, 143%). $m/z = 626$ $[M+H]^+$.**

Stage 7 – Preparation of cyclopentyl (2S)-cyclohexyl{[(4-[(3-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl)amino)methyl]cyclohexyl)methyl]amino}acetate (Example 79**)**

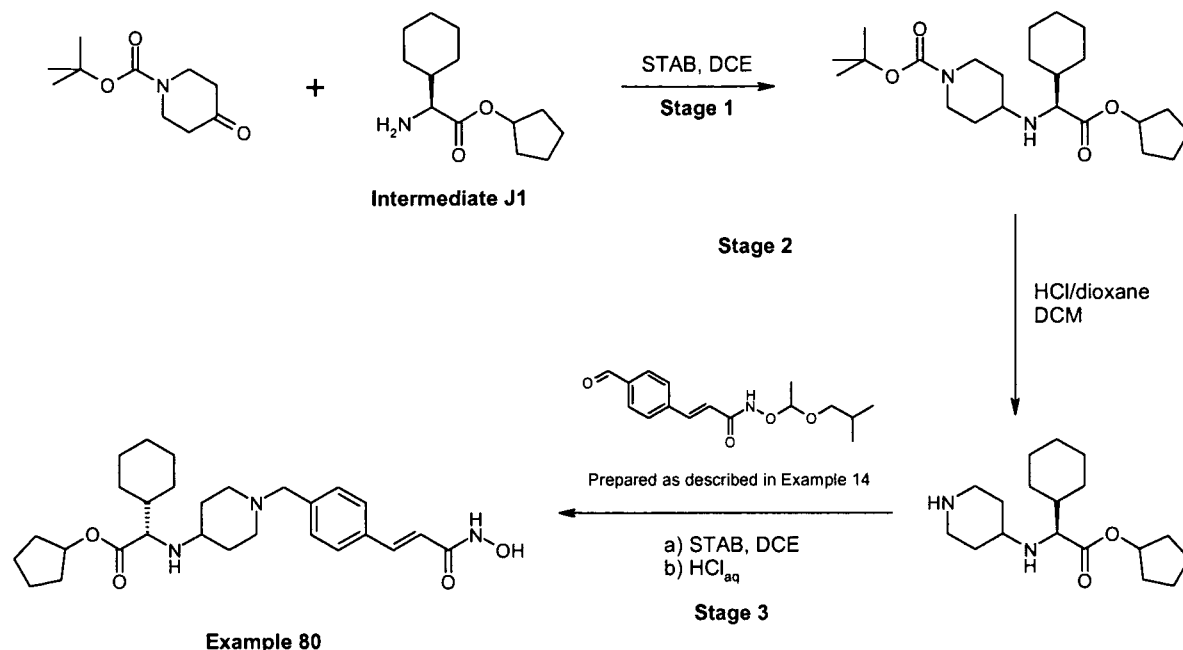
4N HCl in dioxane (0.52mL, 2mmol) was charged to a solution of stage 6 product (0.65g, 1mmol) in DCM (10mL) and the reaction stirred for 5 minutes. The reaction was concentrated to dryness *in vacuo* to afford a yellow oil. Purification by preparative HPLC afforded the desired product as a white solid (20mg, 4%). LCMS purity >95%, $m/z = 526$ $[M+H]^+$, 1H NMR (300MHz, CD_3OD) δ : 7.80-7.42 (5H, m), 6.56 (1H, d, $J=15.6Hz$), 5.36(1H, m), 4.26 (1H, s), 3.85 (1H, d), 3.12-2.75 (4H, m), 2.12-0.87 (29H, m).

Example 80:

Cyclopentyl (2S)-cyclohexyl[(1-{4-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}piperidin-4-yl)amino]acetate



The title compound was prepared by the following methodology:



Stage 1 – Preparation of *tert*-butyl 4-[[[(1*S*)-1-cyclohexyl-2-(cyclopentyloxy)-2-oxoethyl]amino]piperidine-1-carboxylate

To a solution of **Intermediate J1** (1.15g, 4.4mmol) in DCE (20mL) was added *tert*-butyl 4-oxopiperidine-1-carboxylate (800mg, 4.01mmol) and STAB (1.73g, 8.2mmol). The mixture was stirred for 4h and then quenched by addition of sat. NaHCO₃ solution (50mL). The product was extracted with DCM (2 x 50mL), and the combined extracts were dried (MgSO₄) and concentrated, and then purified by column chromatography (1% MeOH in DCM) to yield the desired product (1.05g, 61%). *m/z* = 409.25 [M+H]⁺, ¹H NMR (300MHz, CDCl₃) δ: 5.32 (1H, s), 5.22-5.25 (1H, m), 3.87-4.00 (2H, m), 3.50 (1H, d, J=4.3Hz), 3.06 (1H, t, J=5.3Hz), 2.81-2.94 (2H, m), 2.46-2.57 (1H, m), 0.91-1.95 (23H, m), 1.46 (9H, s).

Stage 2 – Preparation of cyclopentyl (2*S*)-cyclohexyl(piperidin-4-ylamino)acetate dihydrochloride

To stage 1 product (1.058g, 2.4mmol) in DCM (2mL) was added 4M HCl in dioxane (5mL). The mixture was stirred for 2h, and then Et₂O (50mL) was added to induce precipitation. The product was collected by filtration to give an off white solid (952mg, quant.). *m/z* = 309.25 [M+H]⁺.

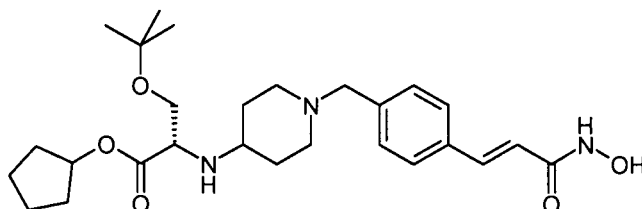
Stage 3 – Preparation of cyclopentyl (2*S*)-cyclohexyl[(1-{4-[(1*E*)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}piperidin-4-yl)amino]acetate (Example 80**)**

To a solution of stage 2 product (0.396g, 1.03mmol) in DCE (5mL) was added (2*E*)-3-(4-formylphenyl)-*N*-(1-isobutoxyethoxy)acrylamide (prepared as described in **Example 14** –

0.324g, 1.11mmol) in DCE (5mL). STAB (0.325g, 1.53mmol) was then added, and the mixture was stirred for 3h. The reaction was quenched by addition of 2M HCl (10mL), and stirred for 30 minutes. The mixture was then poured into sat. NaHCO₃ solution (100mL), and the product extracted with DCM (3 x 75mL). The mixture was then dried (MgSO₄), concentrated and purified by preparative HPLC to yield the desired product (35mg, 7%). LCMS purity >98%, m/z = 488 [M+H]⁺, ¹H NMR (300MHz, CD₃OD) δ: 7.48-7.65 (3H, m), 7.36 (2H, d, J=7.8Hz), 6.48 (1H, d, J=15.7Hz), 5.20 (1H, m), 3.45-3.65 (6H, m), 3.30-3.35 (2H, m), 2.87 (2H, d, J=11.5Hz), 2.50 (1H, m), 1.30-2.15 (12H, m), 1.16 (9H, s).

Example 81:

Cyclopentyl O-tert-butyl-N-(1-{4-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}piperidin-4-yl)-L-serinate

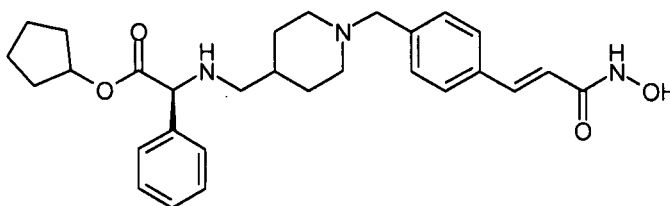


The title compound was prepared from **Intermediate O** by the same methodology used to make **Example 80**.

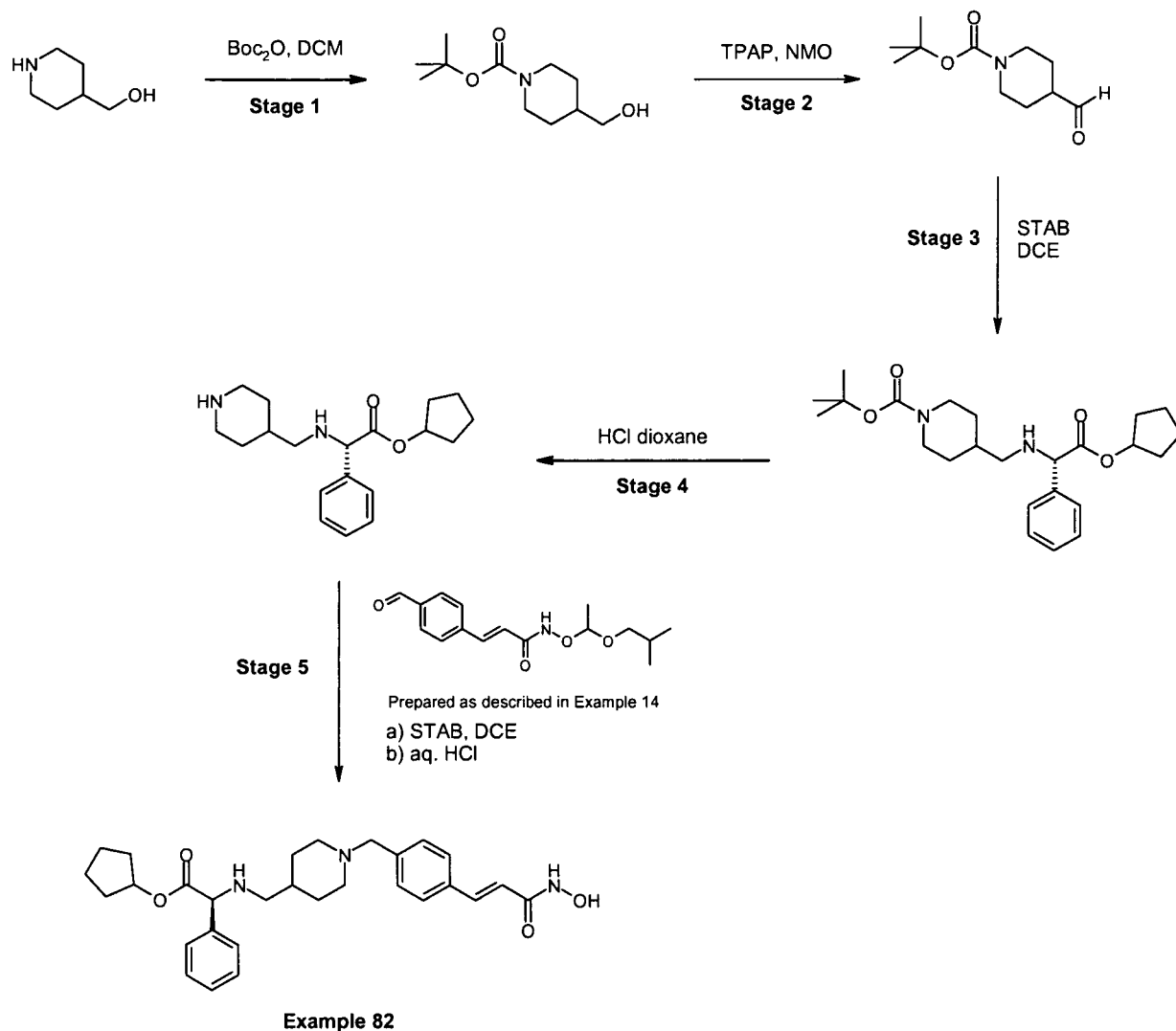
LCMS purity >98%, m/z = 488.25 [M+H]⁺, ¹H NMR (300MHz, d₆-DMSO) δ: 7.48-7.65 (3H, m), 7.36 (2H, d, J=7.8Hz), 6.48 (1H, d, J=15.7Hz), 5.20 (1H, m), 3.45-3.65 (6H, m), 3.30-3.35 (2H, m), 2.87 (2H, d, J=11.5Hz), 2.50 (1H, m), 1.30-2.15 (12H, m), 1.16 (9H, s).

Example 82:

Cyclopentyl (2S)-{[(1-{4-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}piperidin-4-yl)methyl]amino}(phenyl)acetate



The title compound was prepared by the following methodology:



Stage 1 – Preparation of *tert*-butyl 4-(hydroxymethyl)piperidine-1-carboxylate

To a solution of piperidin-4-ylmethanol (5.122g, 44.5mmol) in DCM (70mL) was added di-*tert*-butyl dicarbonate (8.91g, 40.8mmol). The solution was stirred at RT for 3h and then poured into Et₂O (250mL). The solution was then washed with 0.5M HCl_{aq} (3 x 75mL), brine (50mL) and then dried (MgSO₄) and concentrated *in vacuo* to give the desired product (9.78g, quant.). ¹H NMR (300MHz, CDCl₃) δ: 4.14 (2H, d, J=13.2Hz), 3.52 (2H, d, J=6.1Hz), 2.72 (2H, dt, J=2.2, 14.6Hz), 1.65-1.77 (2H, m), 1.47 (9H, s), 1.13-1.26 (3H, m).

Stage 2 – Preparation of *tert*-butyl 4-formylpiperidine-1-carboxylate

To stage 1 product (9.78g, 44.5mmol) in DCM (250mL) was added *N*-methylmorpholine-*N*-oxide (6.60g, 55.3mmol) and TPAP (260mg, 0.74mmol). The mixture was stirred for 24h, then further NMO (3.37g, 28.3mmol) and TPAP (30mg, 0.08mmol) were added. The mixture was stirred for a further 48h, and then further NMO (2.60g, 21.8mmol) was added. After stirring for a further

5h, the mixture was poured into Et₂O (500mL) and washed with 0.5M HCl_{aq} (4 x 100mL) and brine (100mL). The organic fraction was then dried (MgSO₄) concentrated and purified by column chromatography to yield the desired product (3.14g, 35%). ¹H NMR (300MHz, CDCl₃) δ: 9.68 (1H, s), 3.97 (2H, d, J=17.1Hz), 2.95 (2H, dt, J=3.1, 11.0Hz), 2.41-2.46 (2H, m), 1.85-1.90 (2H, m), 1.53-1.59 (1H, m), 1.47 (9H, s).

Stage 3 – Preparation of tert-butyl 4-(((1S)-2-(cyclopentyloxy)-2-oxo-1-phenylethyl)amino)methyl)piperidine-1-carboxylate

To a solution of stage 2 product (0.748g, 3.5mmol) in DCE (20mL) was added **Intermediate L1** (1.63g, 4.2mmol) and STAB (1.76g, 8.3mmol). The mixture was stirred for 4h and was then quenched by addition of sat. NaHCO₃ solution (50mL). The product was then extracted with DCM (2 x 50mL), the combined extracts were dried (MgSO₄) concentrated *in vacuo* and purified by column chromatography (1% MeOH in DCM) to yield the desired product. m/z = 417.25 [M+H]⁺, ¹H NMR (300MHz, CDCl₃) δ: 7.28-7.39 (5H, m), 5.20 (1H, m), 4.08 (2H, d, J=9.6Hz), 2.70 (2H, t, J=12.5Hz), 2.50 (1H, dd, J=6.6, 11.3Hz), 2.38 (1H, dd, J=6.8, 11.5Hz), 1.47-1.88 (14H, m), 1.47 (9H, s).

Stage 4 – Preparation of cyclopentyl (2S)-phenyl[(piperidin-4-ylmethyl)amino]acetate dihydrochloride

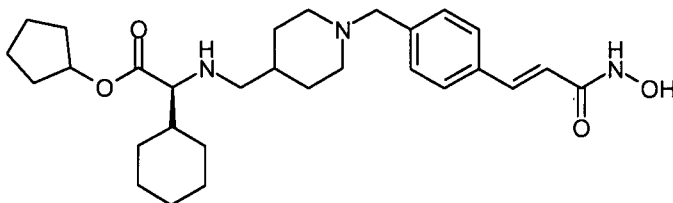
To stage 3 product was added 4M HCl in dioxane (5mL). The mixture was stirred for 3h and then concentrated under vacuum to yield the desired product (891mg, 80% over 2 steps). ¹H NMR (300MHz, d₆-DMSO) δ: 7.24-7.40 (5H, m), 5.06 (1H, m), 4.28 (1H, s), 3.14 (2H, d, J=11.7Hz), 2.70 (2H, t, J=12.5Hz), 2.20-2.40 (2H, m), 1.08-1.86 (14H, m).

*Stage 5 – Preparation of cyclopentyl (2S)-{[(1-{4-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}piperidin-4-yl)methyl]amino}(phenyl)acetate (**Example 82**)*

To a solution of stage 4 product (236mg, 0.74mmol) in DCE (5mL) was added (2E)-3-(4-formylphenyl)-N-(1-isobutoxyethoxy)acrylamide (prepared as described in **Example 14** – 218mg, 0.75mmol) and STAB (157mg, 0.74mmol). The mixture was stirred for 3h then quenched with 0.5M HCl_{aq} (20mL) for 30 minutes. The solution was neutralized with sat. NaHCO₃ solution, and then extracted with DCM (3 x 100mL). The combined extracts were dried (MgSO₄) concentrated *in vacuo* and purified by preparative HPLC to yield the desired product (18mg, 5%). LCMS purity >95%, m/z = 492.25 [M+H]⁺, ¹H NMR (300MHz, CD₃OD) δ: 7.45-7.65 (3H, m), 7.25-7.45 (7H, m), 6.47 (1H, d, J=13.8Hz), 5.15 (1H, m), 4.30 (1H, s), 3.45-3.57 (2H, m), 2.89 (2H, d, J=9.5Hz), 2.30-2.50 (2H, m), 1.13-2.11 (15H, m).

Example 83:

Cyclopentyl (2S)-cyclohexyl[(1-{4-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}piperidin-4-yl)methyl]amino]acetate

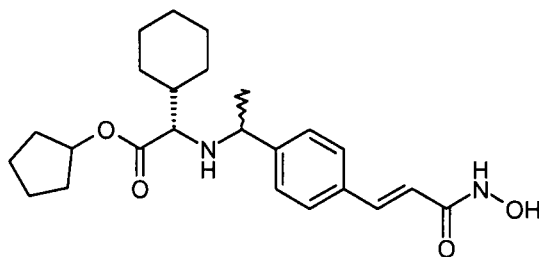


The title compound was prepared from **Intermediate J1** by the same methodology used to make **Example 82**.

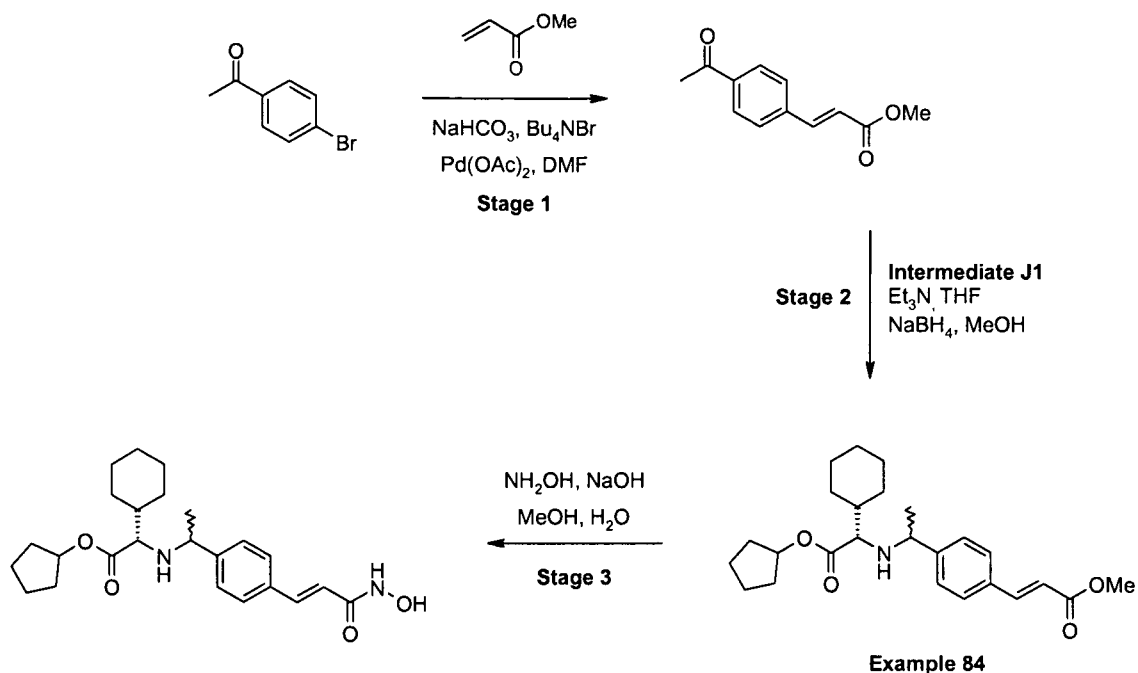
LCMS purity >98%, $m/z = 498.25$ $[M+H]^+$, 1H NMR (300MHz, d_6 -DMSO) δ : 7.48 (2H, d, $J=7.9$ Hz), 7.33 (1H, d, $J=10.8$ Hz), 7.30 (2H, d, $J=8.0$ Hz), 6.42 (1H, d, $J=13.5$ Hz), 5.10 (1H, m), 4.07 (2H, q, $J=5.1$ Hz), 3.43 (2H, br s), 3.17 (6H, m), 2.70-2.85 (3H, m), 2.10-2.42 (2H, m), 0.96-1.94 (18H, m).

Example 84:

Cyclopentyl (2S)-cyclohexyl[(1-{4-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]phenyl}ethyl)amino]acetate



The title compound was prepared by the following methodology:



Stage 1 – Preparation of methyl (2E)-3-(4-acetylphenyl)acrylate

To 4-bromoacetophenone (1g, 5mmol) in anhydrous DMF (30mL) were added methyl acrylate (450μL, 5mmol), sodium bicarbonate (420mg, 5mmol) tetrabutylammonium bromide (1.61g, 5mmol) and palladium acetate (56mg, 0.25mmol) and the reaction mixture was heated at 130°C for 2 h. The DMF was removed by concentration under reduced pressure, the crude was dissolved in EtOAc (100mL) and washed with water (100mL) then brine (100mL). The organic layer was dried (MgSO₄), filtered and concentrated under vacuum to afford the crude product. This was purified by flash chromatography (1:1 heptane/EtOAc) to yield the desired product (784mg, 77%). *m/z* = 205 [M+H]⁺; ¹H NMR (300MHz, CDCl₃) δ: 7.99 (2H, d, J=8.3Hz), 7.73 (1H, d, J=16.2Hz), 7.63 (2H, d, J=8.3Hz), 6.55 (1H, d, J=16.0Hz), 3.85 (3H, s), 2.64 (3H, s).

Stage 2 – Preparation of methyl (2E)-3-[4-(1-[(1S)-1-cyclohexyl-2-(cyclopentyloxy)-2-oxoethyl]amino}ethyl)phenyl]acrylate

To stage 1 product (500mg, 2.45mmol) in anhydrous THF (10mL) were added **Intermediate J1** (946mg, 2.45mmol), Et₃N (341μL, 2.45mmol), AcOH (4 drops) and 4Å molecular sieves and the reaction mixture was heated at 50°C N₂ atmosphere for 18h. The reaction was cooled to RT and anhydrous MeOH (5mL) was added, followed by NaBH₄ (93mg, 2.45mmol). The reaction was left stirring at RT until completion, after which the solvents were removed *in vacuo*. The crude was poured into EtOAc (25mL), washed with water (25mL), 1M HCl (25mL) then brine (25mL). The organic layer was dried (MgSO₄), filtered and concentrated under vacuum to afford the desired product (1g, 97%) *m/z* = 414 [M+H]⁺.

Stage 3 – Preparation of cyclopentyl (2S)-cyclohexyl[(1-{4-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]phenyl}ethyl)amino]acetate (Example 84)

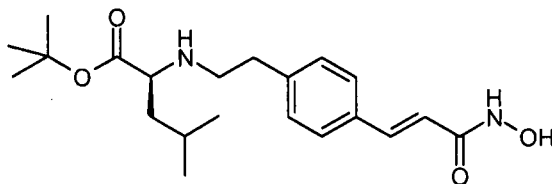
To stage 2 product (60mg, 0.14mmol) in MeOH (1mL) were added hydroxylamine in water (100μL) and NaOH (60mg) and the reaction mixture was left stirring at RT for 2h. The reaction was quenched by addition of a sat NH₄Cl (2mL), and the product was purified by preparative HPLC after concentration of solvents and filtration of the undesired salts (21mg, 36%). LCMS purity >99%, m/z = 415 [M+H]⁺, ¹H NMR (300MHz, CD₃OD) δ: 7.67 (2H, dd, J=11.4, 8.6Hz), 7.55 (2H, t, J=8.3Hz), 7.48 (2H, d, J=8.1Hz), 6.61-6.46 (1H, m), 5.30 (1H, t, J=5.9Hz), 4.58-4.45 (1H, m), 3.41-3.38 (1H, m), 1.99-1.78 (6H, m), 1.75 (3H, d, J=6.8Hz), 1.72-1.44 (4H, m), 1.38-0.92 (8H, m).

The following examples were prepared using the same methodology:

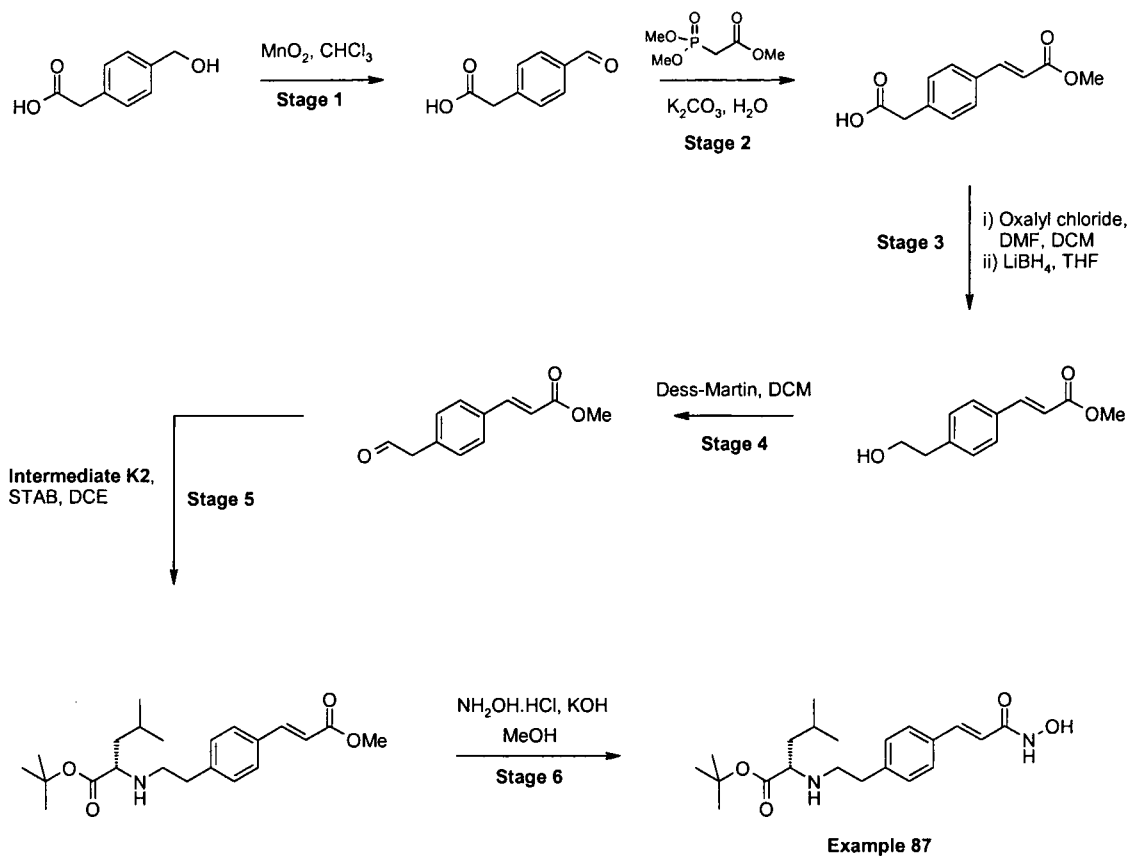
Example	Chemical name	Intermediates used	Analytical data
85	<i>tert</i> -Butyl <i>N</i> -(1-{4-[(1 <i>E</i>)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]phenyl}ethyl)-L-leucinate	A, K2	LCMS purity 93%, m/z = 377 [M+H] ⁺ , ¹ H NMR (300MHz, CD ₃ OD) δ: 7.74-7.69 (2H, m), 7.68-7.56 (1H, m), 7.49 (2H, d, J=8.3Hz), 6.58 (1H, d, J=16.0Hz), 4.51 (1H, q, J=6.7Hz), 1.73 (3H, d, J=6.8Hz), 1.69-1.61 (1H, m), 1.55 (9H, s), 1.06-0.98 (2H, m), 0.95-0.91 (1H, m), 0.88 (3H, d, J=2.8Hz), 0.86 (3H, d, J=2.6 Hz).
86	<i>tert</i> -Butyl <i>N</i> -(1-{4-[3-(hydroxyamino)-3-oxopropyl]phenyl}ethyl)-L-leucinate	B, K2	LCMS purity 100%, m/z = 379 [M+H] ⁺ , ¹ H NMR (300MHz, CD ₃ OD) δ: 7.41-7.33 (4H, m), 4.43 (1H, t, J=7.0Hz), 2.99 (2H, t, J=7.5Hz), 2.42 (2H, t, J=7.5Hz), 1.82-1.75 (2H, m), 1.71 (3H, d, J=7.0Hz), 1.64-1.56 (2H, m), 1.55 (9H, s), 0.86 (6H, d, J=6.2Hz).

Example 87:

tert-Butyl *N*-(2-{4-[(1*E*)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]phenyl}ethyl)-L-leucinate



The title compound was prepared by the following methodology:



Stage 1 – Preparation of (4-formylphenyl)acetic acid

To [4-(hydroxymethyl)phenyl]acetic acid (3g, 18mmol) in CHCl_3 (50mL) under N_2 was added manganese dioxide (7.7g, 90mmol) and the reaction mixture was stirred at 50°C for 18h. The crude was filtered through a pad of celite, washed with DCM (50mL) and concentrated under reduced pressure to give the desired product (1.76g, 59%). ^1H NMR (300MHz, d_6 -DMSO) δ : 12.49 (1H, br s), 9.99 (1H, s), 7.89-7.84 (2H, m), 7.50 (2H, d, $J=7.9\text{Hz}$), 3.72 (2H, s).

Stage 2 – Preparation of {4-[(1E)-3-methoxy-3-oxoprop-1-en-1-yl]phenyl}acetic acid

To stage 1 product (1.03g, 6.3mmol) in water (100mL) were added K_2CO_3 (2.61g, 18.9mmol) then trimethylphosphonoacetate (1.23mL, 7.6mmol) at 0°C . Addition was carried out over 10 minutes to avoid the reaction temperature rising above 15°C . The reaction mixture was then stirred at RT for 72h. A solution of 1M HCl was added until pH $\sim$ 1. The white precipitate was isolated by filtration, washed with water (100mL), concentrated and dried on the freeze drier to afford the desired product as a white solid (784 mg, 57%). ^1H NMR (300MHz, d_6 -DMSO) δ : 12.46 (1H, br s), 7.69-7.63 (2H, m), 7.31 (2H, d, $J=8.1\text{Hz}$), 6.74 (1H, d, $J=16.0\text{Hz}$), 6.63 (1H, d, $J=16.0\text{Hz}$), 3.72 (3H, s), 3.62 (2H, s).

Stage 3 – Preparation of methyl (2E)-3-[4-(2-hydroxyethyl)phenyl]acrylate

To stage 2 product (784mg) in DCM (20mL) under N₂ atmosphere, were added oxalyl chloride (2mL) and DMF (3 drops). The reaction was left stirring for 1h at RT. The crude was concentrated under reduced pressure. Anhydrous THF (10mL) was then added, followed by a solution of lithium borohydride in THF (3mL, 2M in THF) at 0°C. This was left stirring for 1h, then quenched with sat NH₄Cl (15mL) and extracted with EtOAc (50mL). The organic layer was washed with brine (50mL), dried (MgSO₄), filtered and concentrated under reduced pressure. The crude was purified on a Biotage automated purification system to afford the pure product (250mg, 34%). ¹H NMR (300MHz, CDCl₃) δ: 7.70 (1H, d, J=16.0Hz), 7.50 (2H, d, J=8.3Hz), 7.28 (2H, d, J=8.1Hz), 6.44 (1H, d, J=16.0Hz), 3.90 (2H, t, J=6.5Hz), 3.82 (3H, s), 2.91 (2H, t).

Stage 4 – Preparation of methyl (2E)-3-[4-(2-oxoethyl)phenyl]acrylate

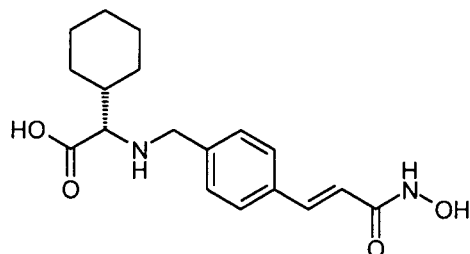
To stage 3 product (200mg, 0.97mmol) in DCM (10mL) at 0°C was added Dess-Martin periodinane (492mg, 1.16mmol) and the reaction mixture was stirred at RT for 2h. The reaction was quenched by addition of a 1/1 mixture of sat NaHCO₃ and sodium dithionite solutions (5mL) and left stirring vigorously for 30 minutes. The mixture was extracted with DCM (2 x 10mL) and washed with brine (10mL). The organic was dried (MgSO₄), and concentrated under reduced pressure to afford the desired product (198mg, quant.). m/z = 205 [M+H]⁺.

Stage 5 – Preparation of *tert*-butyl N-(2-{4-[(1E)-3-methoxy-3-oxoprop-1-en-1-yl]phenyl}ethyl)-L-leucinate

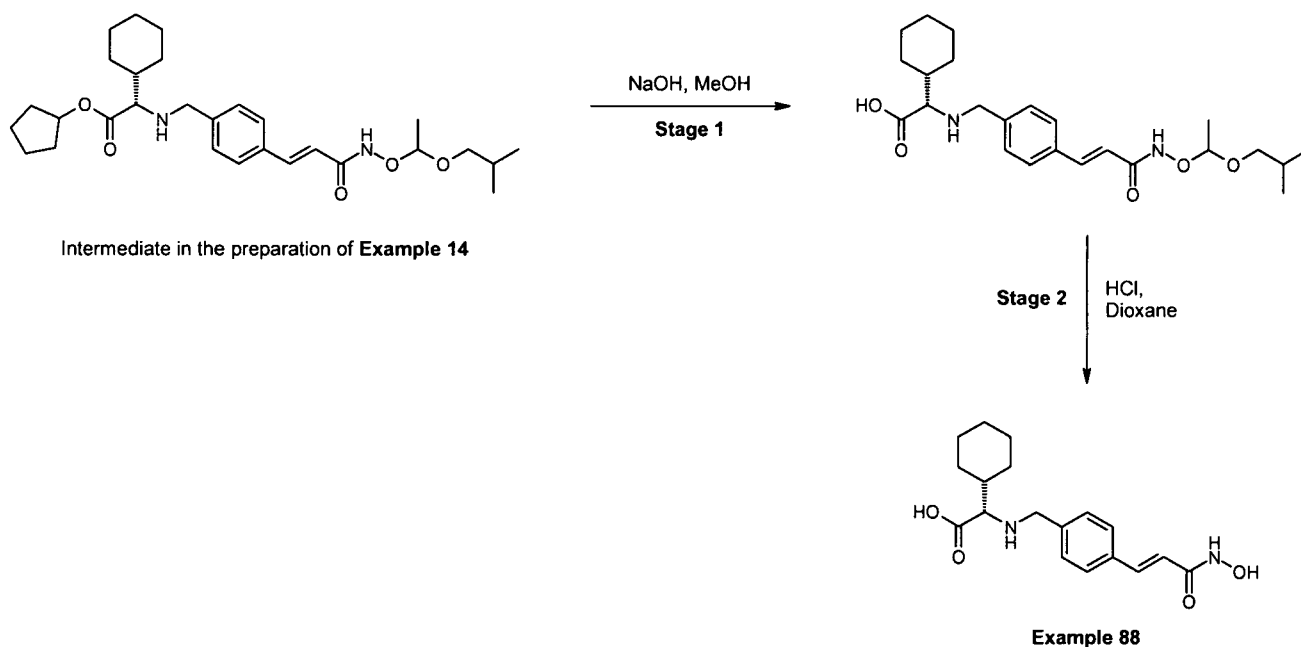
To stage 4 product (88mg, 0.43mmol) in DCE (3mL) was added **Intermediate K2** (81mg, 0.43mmol) followed by sodium triacetoxyborohydride (109mg, 0.51mmol) and the reaction mixture was stirred at RT under N₂ atmosphere for 72h. DCM (10mL) and water (10mL) were added. The organic layer was separated, washed with sat NaHCO₃ (15mL) and brine (15mL), dried (MgSO₄), filtered and concentrated under reduced pressure to afford the desired product (162mg, quant.). This was used directly in the final step without further purification. m/z = 376 [M+H]⁺.

Stage 6 – Preparation of *tert*-butyl N-(2-{4-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]phenyl}ethyl)-L-leucinate (Example 87**)**

To a solution of crude stage 5 product (162mg, 0.43mmol) in MeOH (2mL) was added hydroxylamine hydrochloride (120mg, 1.72mmol) and the reaction mixture was cooled to -5°C. A solution of KOH (193mg, 3.44mmol) in water (0.5mL) was prepared, cooled and added slowly to the reaction mixture. After 30 minutes stirring at -5°C, the reaction was complete. A solution of 1M HCl was added to neutralise the pH. The crude was purified by preparative HPLC to yield the desired product (16mg, 9%). LCMS purity 96%, m/z = 377 [M+H]⁺.

Example 88:(2S)-Cyclohexyl({4-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}amino)acetic acid

The title compound was prepared by the following methodology:



Stage 1 – Preparation of (2S)-cyclohexyl[4-[(1E)-3-[(1-isobutoxyethoxy)amino]-3-oxoprop-1-en-1-yl]benzyl]amino]acetic acid

1N NaOH_{aq} (3mL) was charged to a solution of cyclopentyl (2S)-cyclohexyl[4-[(1E)-3-[(1-isobutoxyethoxy)amino]-3-oxoprop-1-en-1-yl]benzyl]amino]acetate (prepared as described in **Example 14** – 0.3g, 0.6mmol) in MeOH (5mL) and stirred at 45°C for 4 days. The MeOH was removed *in vacuo* and the residue washed with EtOAc (10mL). The aqueous phase was acidified to pH ~ 2 with saturated citric acid solution, extracted with EtOAc (2 x 10mL) and the organic phase dried (MgSO₄) and concentrated *in vacuo* to afford the product as a yellow oil (0.14g, 53%). m/z = 433 [M+H]⁺.

Stage 2 – Preparation of (2S)-Cyclohexyl({4-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}amino)acetic acid (Example 88)

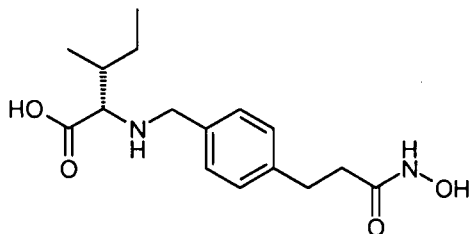
4N HCl in dioxane (0.18mL, 0.72mmol) was added to a solution of stage 1 product (0.14g, 0.32mmol) in DCM and the reaction stirred for 5 minutes. The reaction was then concentrated to dryness *in vacuo* to afford a yellow solid. Purification by preparative HPLC afforded the desired product as an off-white solid (4mg, 2%). ¹H NMR (300MHz, *d*₆-DMSO) δ: 10.80 (1H, s), 9.08 (1H, m), 7.73 (2H, d, J=7.8Hz), 7.52-7.45 (3H, m), 6.50 (1H, d, J=16.2Hz), 4.16 (2H, m), 3.70 (1H, m), 1.91 (1H, m), 1.81-1.50 (5H, m), 1.32-0.86 (5H, m).

The following examples were prepared using the same methodology:

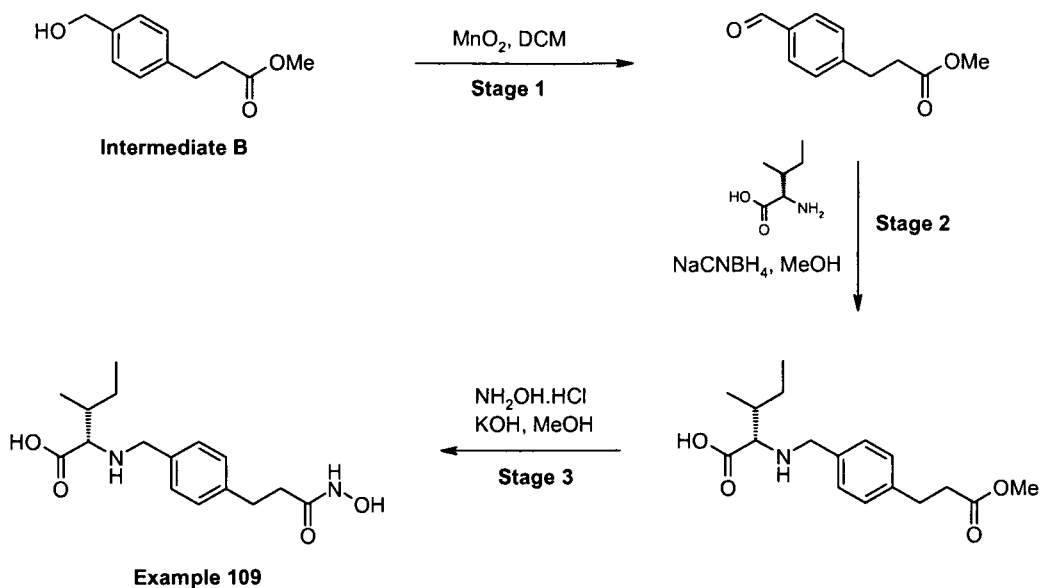
Example	Chemical name	Intermediate from Example number	Analytical data
89	<i>N</i> -{4-[(1E)-3-(Hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}-L-leucine	15	LCMS purity 97%, <i>m/z</i> = 307 [M+H] ⁺ , ¹ H NMR (300MHz, CD ₃ OD) δ: 7.79-7.44 (5H, m), 6.55 (1H, d, J=15.9Hz), 4.28 (2H, s), 4.00 (1H, m), 1.96-1.65 (3H, m), 1.00 (6H, m).
90	<i>O</i> - <i>tert</i> -Butyl- <i>N</i> -{4-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}-L-serine	16	LCMS purity 100%, <i>m/z</i> = 337 [M+H] ⁺ , ¹ H NMR (300MHz, CD ₃ OD) δ: 7.77-7.50 (5H, m), 6.55 (1H, d, J=15.9Hz), 4.32 (1H, s), 3.88 (2H, s), 1.31 (2H, s), 1.25 (9H, s).
91	(2S)-({4-[(1E)-3-(Hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}amino)(phenyl)acetic acid	17	LCMS purity >95%, <i>m/z</i> = 327 [M+H] ⁺ , ¹ H NMR (300MHz, CD ₃ OD) δ: 7.75-7.41 (10H, m), 6.55 (1H, d, J=15.6Hz), 5.10 (1H, s), 4.21 (2H, q).
92	<i>N</i> -{4-[(1E)-3-(Hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}-D-leucine	18	LCMS purity 100%, <i>m/z</i> = 307 [M+H] ⁺ , ¹ H NMR (300MHz, CD ₃ OD) δ: 7.76-7.48 (5H, m), 6.54 (1H, d, J=15.6Hz), 4.16 (2H, m), 3.62 (1H, m), 1.91-0.74 (9H, m).
93	(2R)-Cyclohexyl({4-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}amino)acetic acid	19	LCMS purity 100%, <i>m/z</i> = 333 [M+H] ⁺ , ¹ H NMR (300MHz, CD ₃ OD) δ: 7.78-7.43 (5H, m), 6.54 (1H, d, J=15.9Hz), 4.24 (2H, m), 3.57 (1H, m), 2.03-1.01 (11H, m).
94	<i>O</i> - <i>tert</i> -Butyl- <i>N</i> -{4-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}-D-serine	20	LCMS purity 100%, <i>m/z</i> = 337 [M+H] ⁺ , ¹ H NMR (300MHz, CD ₃ OD) δ: 7.72-7.51 (5H, m), 6.55 (1H, d, J=15.6Hz), 4.33 (2H, s), 4.12 (1H, m), 3.93 (2H, m), 1.25 (9H, s).
95	(2R)-({4-[(1E)-3-(Hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}amino)(phenyl)acetic acid	22	LCMS purity 100%, <i>m/z</i> = 327 [M+H] ⁺ , ¹ H NMR (300MHz, CD ₃ OD) δ: 7.75-7.34 (10H, m), 6.54 (1H, d, J=15.9Hz), 4.53 (1H, s), 4.18 (2H, q).

Example	Chemical name	Intermediate from Example number	Analytical data
96	(2S)-Cyclohexyl({4-[3-(hydroxyamino)-3-oxopropyl]benzyl}amino)acetic acid	33	LCMS purity 100%, m/z = 335 [M+H] ⁺ , ¹ H NMR (300MHz, CD ₃ OD) δ: 7.45-7.22 (4H, m), 4.12 (2H, q), 2.95 (2H, t), 2.39 (2H, t), 1.91-1.04 (11H, m).
97	N-{4-[3-(Hydroxyamino)-3-oxopropyl]benzyl}-L-leucine	34	LCMS purity 100%, m/z = 309 [M+H] ⁺ , ¹ H NMR (300MHz, CD ₃ OD) δ: 7.50-7.15 (4H, m), 4.57 (1H, s), 4.12 (2H, q), 2.94 (2H, t), 2.39 (2H, t), 1.80 (2H, m), 1.59 (1H, m), 0.93 (6H, dd).
98	(2S)-({4-[3-(Hydroxyamino)-3-oxopropyl]benzyl}amino)(phenyl)acetic acid	39	LCMS purity 90%, m/z = 329 [M+H] ⁺ , ¹ H NMR (300MHz, d ₆ -DMSO) δ: 10.38 (1H, s), 9.83 (1H, br s), 8.72 (1H, br s), 7.6-7.4 (5H, m), 7.29 (4H, dd), 5.09 (1H, s), 4.00 (2H, dd), 2.84 (2H, t), 2.27 (2H, t). □
99	N-{4-[3-(Hydroxyamino)-3-oxopropyl]benzyl}-L-valine	42	LCMS purity 90%, m/z = 295 [M+H] ⁺ , ¹ H NMR (300MHz, CD ₃ OD) δ: 7.46-7.39 (2H, m), 7.38-7.30 (2H, m), 4.23 (2H, d, J=9.6Hz), 3.81 (1H, d, J=3.6Hz), 2.97 (2H, t, J=7.4Hz), 2.41 (2H, t, J=7.5Hz), 2.36-2.27 (1H, m), 1.18-1.10 (3H, m), 1.08-1.00 (3H, m).
100	N-{4-[3-(Hydroxyamino)-3-oxopropyl]benzyl}-3-methyl-L-valine	43	LCMS purity 90%, m/z = 309 [M+H] ⁺ , ¹ H NMR (300MHz, CD ₃ OD) δ: 7.49-7.28 (4H, m), 4.32 (1H, d, J=13.6Hz), 4.13 (1H, d, J=13.6Hz), 3.40 (1H, s), 2.98 (2H, t, J=7.5Hz), 2.41 (2H, t, J=7.5Hz), 1.08 (9 H, s).
101	(2S)-Cyclohexyl[({6-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]pyridin-3-yl}methyl)amino]acetic acid	53	LCMS purity 100%, m/z = 334 [M+H] ⁺ , ¹ H NMR (300MHz, CD ₃ OD) δ: 8.65 (1H, s), 7.93 (1H, m), 7.60 (2H, m), 6.92 (1H, d, J=15.6Hz), 4.02 (2H, q), 1.90-1.09 (11H, m).
102	N-({6-[(1E)-3-(Hydroxyamino)-3-oxoprop-1-en-1-yl]pyridin-3-yl}methyl)-L-leucine	54	LCMS purity >95%, m/z = 308 [M+H] ⁺ , ¹ H NMR (300MHz, CD ₃ OD) δ: 8.65 (1H, s), 7.93 (1H, dd), 7.59 (2H, dd), 6.91 (1H, d, J=15.6Hz), 4.54 (1H, s), 4.02 (2H, q), 1.97-1.19 (3H, m), 0.95 (6H, dd).
103	(2S)-Cyclohexyl[({6-[3-(hydroxyamino)-3-oxopropyl]pyridin-3-yl}methyl)amino]acetic acid	62	LCMS purity 95%, m/z = 336 [M+H] ⁺ , ¹ H NMR (300MHz, CD ₃ OD) δ: 8.72 (1H, d, J=2.1Hz), 8.19 (1H, dd, J=8.2, 2.2Hz), 7.70 (1H, d, J=8.1Hz), 4.37 (2H, s), 3.94 (1H, d), 3.22 (2H, t, J=7.2Hz), 2.85 (2H, t, J=7.2Hz), 2.07-1.96 (1H, m), 1.88-1.80 (4H, m), 1.75-1.69 (1H, m), 1.47-1.17 (5H, m).

Example	Chemical name	Intermediate from Example number	Analytical data
104	(2S)-Cyclohexyl[({5-[3-(hydroxyamino)-3-oxopropyl]pyridin-2-yl)methyl}amino]acetic acid	70	LCMS purity 98%, m/z = 336 [M+H] ⁺ , ¹ H NMR (300MHz, d ₆ -DMSO) δ: 10.39 (1H, br s), 8.49 (1H, s), 7.72 (1H, dd, J=2.2, 8.0Hz), 7.44 (1H, d, J=8.0Hz), 4.30 (2H, s), 3.82 (1H, d, J=3.3Hz), 2.87 (2H, t, J=7.3Hz), 2.31 (2H, t, J=7.3Hz), 1.57-2.04 (6H, m), 0.92-1.38 (5H, m).
105	(2S)-Cyclohexyl[({4-[(3-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl)amino)methyl]cyclohexyl)methyl}amino]acetic acid	79	LCMS purity 97%, m/z = 458 [M+H] ⁺ , ¹ H NMR (300MHz, CD ₃ OD) δ: 7.78-7.47 (5H, m), 6.57 (1H, m), 4.26 (2H, s), 3.59 (1H, s), 3.04-2.75 (4H, m), 2.06-0.78 (19H, m).
106	(2S)-Cyclohexyl[1-{4-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}piperidin-4-yl)amino]acetic acid	80	LCMS purity 98%, m/z = 416 [M+H] ⁺ , ¹ H NMR (300MHz, CD ₃ OD) δ: 7.67 (2H, d, J=7.5Hz), 7.60 (1H, obs d), 7.57 (2H, d, J=7.0Hz), 6.56 (1H, d, J=15.6Hz), 4.35 (2H, s), 3.94 (1H, d, J=3.1Hz), 3.40-3.65 (3H, m), 3.12 (2H, br m), 2.39 (2H, t, J=15.4Hz), 1.90-2.22 (3H, m), 1.60-1.80 (5H, m), 1.05-1.50 (5H, m).
107	(2S)-{[(1-{4-[(1E)-3-(Hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}piperidin-4-yl)methyl]amino}(phenyl)acetic acid	82	LCMS purity 98%, m/z = 424 [M+H] ⁺ , ¹ H NMR (300MHz, CD ₃ OD) δ: 7.68 (2H, d, J=7.8Hz), 7.46-7.64 (8H, m), 6.58 (1H, d, J=16.0Hz), 5.02 (1H, s), 4.35 (2H, s), 3.44-3.55 (2H, m), 2.80-3.15 (3H, m), 2.00-2.25 (3H, m), 1.47-1.65 (2H, m).
108	(2S)-Cyclohexyl[1-{4-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]phenyl}ethyl)amino]acetic acid	84	LCMS purity 92%, m/z = 347 [M+H] ⁺ , ¹ H NMR (300MHz, CD ₃ OD) δ: 7.69 (2H, d, J=7.8Hz), 7.61 (1H, d, J=15.9Hz), 7.52-7.37 (2H, m), 6.55 (1H, d, J=15.6Hz), 4.52-4.50 (1H, m), 3.26-3.23 (1H, m), 1.76 (3H, d, J=6.6Hz), 1.60-1.43 (4H, m), 1.38-0.92 (6H, m).

Example 109:*N*-{4-[3-(Hydroxyamino)-3-oxopropyl]benzyl}-L-isoleucine

The title compound was prepared by the following methodology:



Stage 1 – Preparation of methyl 3-(4-formylphenyl)propanoate

To a solution of **Intermediate B** (300mg, 1.54mmol) in DCM (25mL) was added manganese dioxide (2.98g, 34mmol). The mixture was stirred for 15 minutes, and then filtered through Celite and washed with additional DCM (100mL). The filtrate was concentrated to yield the desired product. This was used directly in the next stage without further purification or characterisation.

Stage 2 – Preparation of *N*-{4-[(1*E*)-3-methoxy-3-oxopropyl]benzyl}-*L*-isoleucine

To stage 1 product (150mg, 0.78mmol) in anhydrous MeOH (5mL) were added *L*-isoleucine (103mg, 0.78mmol) and sodium cyanoborohydride (49mg, 0.78mmol). The resulting mixture was stirred overnight at RT. The solvent was removed by concentration and the residue partitioned between DCM (20mL) and water (20mL). The organic layer was washed with water (20mL) and brine (20mL), dried (MgSO₄) and concentrated under reduced pressure to afford the desired product as a colourless oil (140mg, 58%). *m/z* = 308 [M+H]⁺; ¹H NMR (300MHz, CD₃OD) δ: 7.42-7.35 (1H, m), 7.28 (2H, d, *J*=7.7Hz), 7.22-7.16 (1H, m), 4.57 (1H, s), 3.64 (3H, s), 3.33 (1H, dt, *J*=3.3, 1.6Hz), 2.92 (2H, t, *J*=7.5Hz), 2.64 (2H, t, *J*=3.8Hz), 2.17 (2H, s), 1.41-1.27 (2H, m), 0.97 (3H, d, *J*=6.6Hz), 0.91 (3H, t, *J*=7.3Hz).

Stage 3 – Preparation of *N*-{4-[3-(Hydroxyamino)-3-oxopropyl]benzyl}-*L*-isoleucine (**Example 109**)

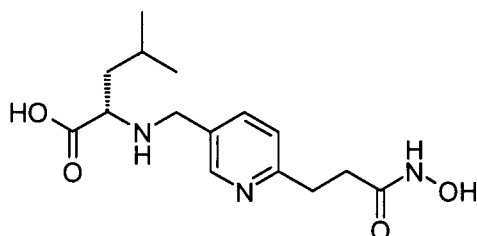
To stage 2 product (110mg, 0.36mmol) in MeOH (1mL) was added hydroxylamine hydrochloride at -5°C. KOH was dissolved in the minimum amount of water, cooled and added to the solution.

The resulting mixture was stirred at -5°C for 70 minutes. The pH was adjusted to 7 by addition of 1M HCl solution. The solution was then concentrated to dryness, MeOH was added and the suspension was filtered to remove excess salts. The filtrate was purified by preparative HPLC to afford the title compound as a white solid (31mg, 28%).

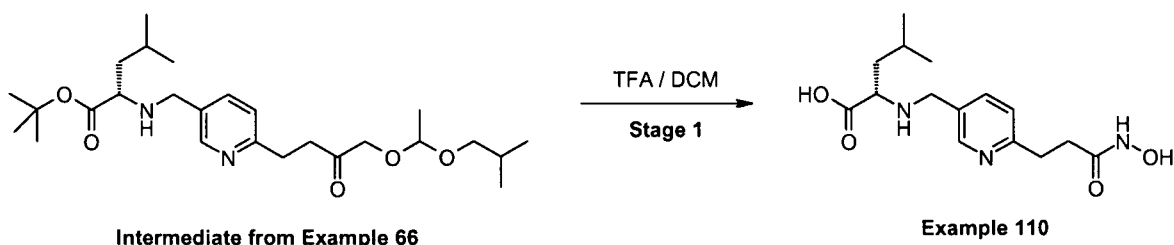
LCMS purity 93%, $m/z = 309$ $[M+H]^+$, 1H NMR (300MHz, CD_3OD) δ : 7.46-7.32 (4H, m), 4.22 (2H, s), 3.86 (1H, d, $J=3.2$ Hz), 2.97 (2H, t, $J=7.5$ Hz), 2.41 (2H, t, $J=7.5$ Hz), 2.04-1.97 (1H, m), 1.52 (9H, s), 1.65-1.38 (2H, m), 1.03-0.98 (6H, m).

Example 110:

N-({6-[3-(hydroxyamino)-3-oxopropyl]pyridin-3-yl}methyl)-L-leucine



The title compound was prepared by the following methodology:



Stage 1 – Preparation of *N*-({6-[3-(hydroxyamino)-3-oxopropyl]pyridin-3-yl}methyl)-L-leucine (Example 110)

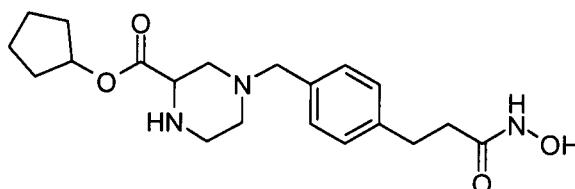
The intermediate to **Example 66** (50mg, 0.1mmol) was treated with 25% TFA in DCM (3mL) and stirred at RT for 3h. The solvents were removed *in vacuo* and the TFA azeotroped with toluene (3 x 25mL) to afford the title compound as a white solid (30mg, quant.). LCMS purity 80%, $m/z = 310$ $[M+H]^+$, 1H NMR (300MHz, CD_3OD) δ : 8.64 (1H, d, $J=0.8$ Hz), 7.98 (1H, dd, $J=8.1, 2.4$ Hz), 7.51 (1H, d, $J=7.9$ Hz), 4.32 (2H, s), 4.04 (1H, dd, $J=8.6, 5.2$ Hz), 3.17 (2H, t, $J=7.3$ Hz), 2.57 (2H, t, $J=7.4$ Hz), 1.95-1.82 (2H, m), 1.81-1.69 (1H, m), 1.04 (3H, d, $J=6.2$ Hz), 1.02 (3H, d, $J=6.2$ Hz).

The following examples were prepared using the same methodology:

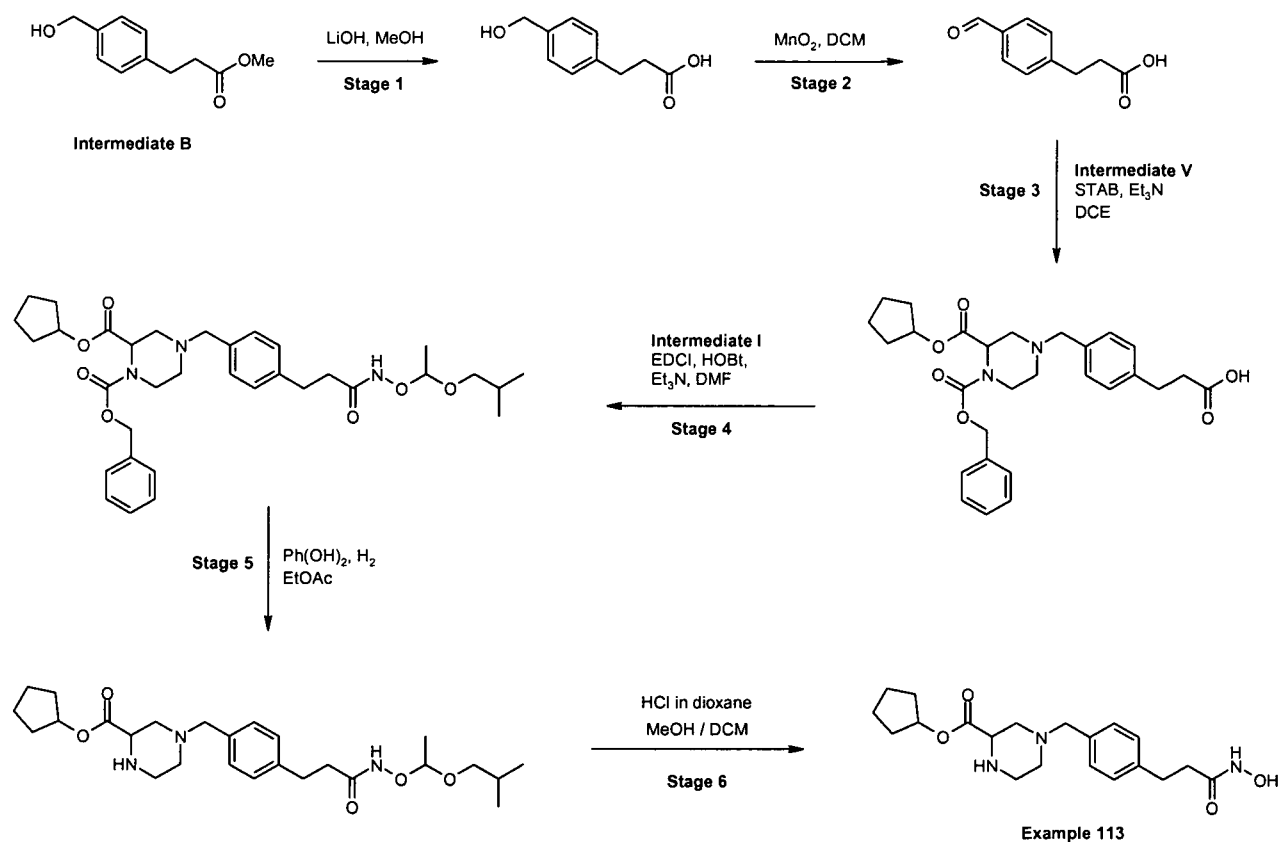
Example	Chemical name	Intermediate from Example number	Analytical data
111	<i>N</i> -({5-[3-(Hydroxyamino)-3-oxopropyl]pyridin-2-yl)methyl)-L-leucine	71	LCMS purity 98%, $m/z = 311$ $[M+H]^+$, 1H NMR (300MHz, CD_3OD) δ : 8.53 (1H, s), 7.76 (1H, d, $J=7.9$ Hz), 7.41 (1H, d, $J=7.9$ Hz), 4.41 (2H, s), 4.07 (1H, t, $J=5.8$ Hz), 3.00 (2H, t, $J=7.3$ Hz), 2.44 (2H, t, $J=7.4$ Hz), 1.74-1.99 (3H, m), 1.02 (3H, d, $J=6.0$ Hz), 1.01 Hz (3H, d, $J=6.0$ Hz).
112	<i>N</i> -(1-{4-[(1 <i>E</i>)-3-(Hydroxyamino)-3-oxoprop-1-en-1-yl]phenyl}ethyl)-L-leucine	85	LCMS purity 100%, $m/z = 321$ $[M+H]^+$, 1H NMR (300MHz, CD_3OD) δ : 7.71 (2H, d, $J=8.1$ Hz), 7.61 (1H, d, $J=15.8$ Hz), 7.53 (2H, d, $J=8.3$ Hz), 6.57 (1H, d, $J=15.8$ Hz), 4.55 (1H, q, $J=6.7$ Hz), 3.44 (1H, d), 2.02 (1H, d, $J=8.7$ Hz), 2.03-2.00 (1H, m), 1.75 (3H, d, $J=7.0$ Hz), 1.71-1.60 (2H, m), 1.26 (1H, t, $J=7.2$ Hz), 0.87 (3H, d, $J=6.2$ Hz), 0.84 (3H, d, $J=6.2$ Hz).

Example 113:

Cyclopentyl 4-{4-[3-(hydroxyamino)-3-oxopropyl]benzyl}piperazine-2-carboxylate



The title compound was prepared by the following methodology:



Stage 1 – Preparation of 3-[4-(hydroxymethyl)phenyl]propanoic acid

Intermediate B (5g, 25.7mmol) was dissolved in MeOH (50mL) and water (10mL). LiOH (1.85g, 77.2mmol) was added and the reaction stirred at RT for 18h. The reaction mixture was acidified to pH ~ 3 with 1M HCl, the resulting precipitate was isolated by filtration to afford the desired product (4.57g, quant.). $^1\text{H NMR}$ (300MHz, d_6 -DMSO) δ : 7.18 (4H, q), 4.45 (2H, d), 2.81 (2H, t), 2.62 (2H, t).

Stage 2 – Preparation of 3-(4-formylphenyl)propanoic acid

Stage 1 product (2g, 11mmol) was dissolved in anhydrous DCM (100mL) and treated with MnO_2 (10g, 115mmol). The reaction was stirred at 35°C for 18h. The resulting suspension was filtered through celite and the filtrate concentrated under reduced pressure to afford the title compound as a white solid (1.64g, 84%). $^1\text{H NMR}$ (300MHz, CDCl_3) δ : 10.00 (1H, s), 7.84 (2H, d, $J=8.7\text{Hz}$), 7.41 (2H, d, $J=8.7\text{Hz}$), 3.08 (2H, t, $J=7.6\text{Hz}$), 2.25 (2H, t, $J=7.6\text{Hz}$).

Stage 3 – Preparation of 3-[4-({4-[(benzyloxy)carbonyl]-3-[(cyclopentyloxy)carbonyl]piperazin-1-yl)methyl}phenyl]propanoic acid

Stage 2 product (137mg, 0.77mmol), **Intermediate V** (256mg, 0.69mmol), STAB (196mg, 0.92mmol) and Et_3N (104 μL , 0.77mmol) were added to anhydrous DCE (4mL) and stirred at RT

for 18h. The reaction mixture was partitioned between DCM (50mL) and water (50mL). The organic layer was washed with brine (50mL), dried (MgSO_4) and concentrated under reduced pressure to afford the desired product (341mg, 90%). $m/z = 495$ $[\text{M}+\text{H}]^+$.

Stage 4 – Preparation of 1-benzyl 2-cyclopentyl 4-(4-{3-[(1-isobutoxyethoxy)amino]-3-oxopropyl}benzyl)piperazine-1,2-dicarboxylate

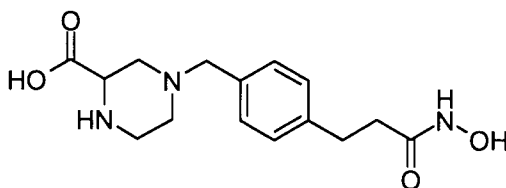
To a solution of stage 3 product (341mg, 0.69mmol) in DMF (5mL) were added EDCI (159mg, 0.83mmol), HOBt (112mg, 0.83mmol), Et₃N (480 μ L, 3.45mmol) and **Intermediate I** (477 μ L, 3.45mmol). The reaction was stirred at RT for 18h and then heated to 50°C for a further 3h. The reaction mixture was then diluted with DCM (50mL) and washed with sat NaHCO_3 (50mL) and brine (50mL). The organic layer was dried (MgSO_4) and concentrated in vacuo. The resulting residue was purified by column chromatography (Heptane / EtOAc 6:1) to afford the title compound as a white solid (300mg, 72%). $m/z = 610$ $[\text{M}+\text{H}]^+$.

Stage 5 – Preparation of cyclopentyl 4-(4-{3-[(1-isobutoxyethoxy)amino]-3-oxopropyl}benzyl)piperazine-2-carboxylate

Stage 4 product (150mg, 0.24mmol) was dissolved in EtOAc (25mL) and the solution degassed. $\text{Pd}(\text{OH})_2$ (50mg, 0.35mmol) was added and the reaction stirred under H_2 atmosphere for 1h. The catalyst was removed by filtration through celite and the solvent removed under reduced pressure to afford the desired product. This was carried on to the next stage without further purification or characterization.

Stage 6 – Preparation of cyclopentyl 4-(4-[3-(hydroxyamino)-3-oxopropyl]benzyl)piperazine-2-carboxylate (Example 113)

Stage 5 crude product (~0.24mmol) was dissolved in DCM (5mL) and MeOH (1mL). 4M HCl solution in dioxane (125 μ L, 0.25mmol) was added and the reaction stirred at RT under N_2 atmosphere for 1h. The reaction mixture was then concentrated under reduced pressure and the residue purified by prep HPLC to afford the title compound (11mg, 12% over two steps). LCMS purity 99%, $m/z = 376$ $[\text{M}+\text{H}]^+$, ^1H NMR (300MHz, d_6 -DMSO) δ : 10.39 (1H, br s), 9.22 (1H, br s), 7.26-7.14 (4H, m), 7.20 (2H, d, $J=2.6\text{Hz}$), 5.23-5.15 (1H, m), 4.34-4.28 (1H, m), 3.68 (1H, d, $J=14.0\text{Hz}$), 3.52 (1H, d, $J=14.0\text{Hz}$), 3.35-3.23 (1H, m), 3.12-3.01 (1H, m), 2.96-2.89 (1H, m), 2.80 (2H, t, $J=7.7\text{Hz}$), 2.75-2.62 (2H, m), 2.60-2.54 (1H, m), 2.48-2.41 (1H, m), 2.25 (2H, t, $J=7.6\text{Hz}$), 1.89-1.78 (2H, m), 1.68-1.48 (6H, m).

Example 114:4-{4-[3-(Hydroxyamino)-3-oxopropyl]benzyl}piperazine-2-carboxylic acid

The title compound was prepared from **Example 113** by the same methodology used to make **Example 88**.

LCMS purity 95%, $m/z = 308$ $[M+H]^+$, 1H NMR (300MHz, CD_3OD) δ : 5.94 (2H, d, $J=8.1$ Hz), 5.79 (2H, d, $J=8.1$ Hz), 3.03 (1H, dd, $J=11.1, 3.6$ Hz), 2.85-2.72 (2H, m), 2.31 (1H, d, $J=11.9$ Hz), 2.16-2.09 (1H, m), 2.02-1.94 (2H, m), 1.85-1.79 (1H, m), 1.70-1.62 (1H, m), 1.40 (2H, t, $J=7.4$ Hz), 0.84 (2H, t, $J=7.5$ Hz).

Measurement of biological activities***Histone deacetylase activity***

The ability of compounds to inhibit histone deacetylase activities was measured using the commercially available HDAC fluorescent activity assay from Biomol. In brief, the *Fluor de LysTM* substrate, a lysine with an epsilon-amino acetylation, is incubated with the source of histone deacetylase activity (HeLa nuclear extract) in the presence or absence of inhibitor. Deacetylation of the substrate sensitises the substrate to *Fluor de LysTM* developer, which generates a fluorophore. Thus, incubation of the substrate with a source of HDAC activity results in an increase in signal that is diminished in the presence of an HDAC inhibitor.

Data are expressed as a percentage of the control, measured in the absence of inhibitor, with background signal being subtracted from all samples, as follows:

$$\% \text{ activity} = [(S^I - B)/(S^o - B)] \times 100$$

where S^I is the signal in the presence of substrate, enzyme and inhibitor, S^o is the signal in the presence of substrate, enzyme and the vehicle in which the inhibitor is dissolved, and B is the background signal measured in the absence of enzyme.

IC₅₀ values were determined by non-linear regression analysis, after fitting the results of eight data points to the equation for sigmoidal dose response with variable slope (% activity against log concentration of Compound), using Graphpad Prism software.

Histone deacetylase activity from crude nuclear extract derived from HeLa cells was used for screening. The preparation, purchased from 4C (Seneffe, Belgium), was prepared from HeLa cells harvested whilst in exponential growth phase. The nuclear extract was prepared according to the methodology described by J. D. Dignam, *Nucl. Acid. Res.*, 1983, **11**, 1475-1489, snap frozen in liquid nitrogen and stored at -80°C. The final buffer composition was 20mM Hepes, 100mM KCl, 0.2mM EDTA, 0.5mM DTT, 0.2mM PMSF and 20 % (v/v) glycerol.

IC₅₀ results were allocated to one of 3 ranges as follows:

Range **A**: IC₅₀<100nM,

Range **B**: IC₅₀ from 101nM to 1000nM;

and Range **C**: IC₅₀ >1001Nm;

nt = not tested.

U937 and HUT cell inhibition assay

Cancer cell lines (U937 and HUT) growing in log phase were harvested and seeded at 1000 – 2000 cells/well (100µl final volume) into 96-well tissue culture plates. Following 24h of growth cells were treated with Compound. Plates were then re-incubated for a further 72 – 96h before a WST-1 cell viability assay was conducted according to the suppliers (Roche Applied Science) instructions.

Data were expressed as a percentage inhibition of the control, measured in the absence of inhibitor, as follows:

$$\% \text{ inhibition} = 100 - [(S^i/S^o) \times 100]$$

where Sⁱ is the signal in the presence of inhibitor and S^o is the signal in the presence of DMSO.

Dose response curves were generated from 8 concentrations (top final concentration 10µM, with 3-fold dilutions), using 6 replicates.

IC₅₀ values were determined by non-linear regression analysis, after fitting the results to the equation for sigmoidal dose response with variable slope (% activity against log concentration of Compound), using Graphpad Prism software.

IC₅₀ results were allocated to one of 3 ranges as follows:

Range **A**: IC₅₀<330nM,

Range **B**: IC₅₀ from 331nM to 3300nM;

and Range **C**: IC₅₀ >3301nM;

nt = not tested.

HeLa cell inhibition Assay

HeLa cells growing in log phase were harvested and seeded at 1000 cells/well (200µl final volume) into 96-well tissue culture plates. Following 24h of cell growth cells were treated with compounds (final concentration of 20µM). Plates were then re-incubated for a further 72h before a sulphorhodamine B (SRB) cell viability assay was conducted according to the methodology described by Skehan *et al*, *J. Natl. Canc. Inst.*, 1990, **82**, 1107-1112.

Data were expressed as a percentage inhibition of the control, measured in the absence of inhibitor, as follows:-

$$\% \text{ inhibition} = 100 - [(S^i/S^o) \times 100]$$

where Sⁱ is the signal in the presence of inhibitor and S^o is the signal in the presence of DMSO.

IC₅₀ values were determined by non-linear regression analysis, after fitting the results of eight data points to the equation for sigmoidal dose response with variable slope (% activity against log concentration of Compound), using Graphpad Prism software.

IC₅₀ results were allocated to one of 3 ranges as follows:

Range **A**: IC₅₀<330nM,

Range **B**: IC₅₀ from 331nM to 3300nM;

and Range **C**: IC₅₀ >3301nM;

nt = not tested.

Results Table:

Example	HDAC activity	U937 activity	HUT activity	HeLa activity
1	B	C	C	C
2	A	B	B	B

Example	HDAC activity	U937 activity	HUT activity	HeLa activity
3	A	B	B	B
4	A	B	B	B
5	A	B	B	B
6	B	B	B	C
7	B	B	B	C
8	B	B	B	B
9	C	C	C	C
10	B	B	B	B
11	B	B	B	C
12	B	B	B	C
13	C	C	B	C
14	A	A	A	B
15	A	A	A	B
16	B	B	B	C
17	B	A	B	C
18	B	B	B	C
19	B	B	C	C
20	B	A	B	C
21	A	A	A	B
22	B	B	B	nt
23	B	A	B	nt
24	A	A	A	nt
25	A	A	B	B
26	B	A	B	B
27	B	A	B	B
28	B	A	B	B

Example	HDAC activity	U937 activity	HUT activity	HeLa activity
29	B	B	B	B
30	B	A	A	nt
31	A	A	B	nt
32	A	B	B	nt
33	B	A	B	nt
34	B	A	A	nt
35	C	A	B	C
36	B	A	A	B
37	B	A	A	B
38	B	B	C	C
39	B	A	B	nt
40	A	B	B	nt
41	B	A	B	nt
42	C	A	B	nt
43	C	B	B	nt
44	B	B	B	nt
45	C	A	B	nt
46	C	C	C	nt
47	C	C	B	nt
48	C	B	B	nt
49	C	C	C	nt
50	B	B	B	nt
51	C	C	C	nt
52	C	B	C	nt
53	A	A	A	nt
54	A	A	B	nt

Example	HDAC activity	U937 activity	HUT activity	HeLa activity
55	A	A	A	B
56	A	A	A	B
57	A	A	A	C
58	A	A	A	B
59	A	A	A	nt
60	A	A	A	nt
61	A	A	A	nt
62	A	A	A	nt
63	A	A	A	nt
64	B	B	B	nt
65	B	A	B	nt
66	A	A	B	nt
67	B	A	B	nt
68	A	A	B	nt
69	B	B	B	nt
70	B	A	B	nt
71	C	B	B	nt
72	B	B	B	nt
73	B	B	B	B
74	B	A	B	C
75	B	A	A	B
76	A	A	A	nt
77	B	A	B	nt
78	B	A	B	nt
79	C	B	B	B
80	B	A	A	B

Example	HDAC activity	U937 activity	HUT activity	HeLa activity
81	B	A	A	B
82	A	B	B	B
83	B	B	A	B
84	C	C	C	nt
85	A	A	A	nt
86	B	A	B	nt
87	B	B	B	nt
88	A	nt	nt	nt
89	A	nt	nt	nt
90	B	nt	nt	nt
91	B	nt	nt	nt
92	B	nt	nt	nt
93	B	nt	nt	nt
94	B	nt	nt	nt
95	B	nt	nt	nt
96	B	nt	nt	nt
97	A	nt	nt	nt
98	C	nt	nt	nt
99	C	nt	nt	nt
100	C	nt	nt	nt
101	A	nt	nt	nt
102	A	nt	nt	nt
103	A	nt	nt	nt
104	B	nt	nt	nt
105	C	nt	nt	nt
106	B	nt	nt	nt

Example	HDAC activity	U937 activity	HUT activity	HeLa activity
107	C	nt	nt	nt
108	A	nt	nt	nt
109	C	nt	nt	nt
110	B	nt	nt	nt
111	C	nt	nt	nt
112	A	nt	nt	nt
113	B	B	B	nt
114	C	nt	nt	nt

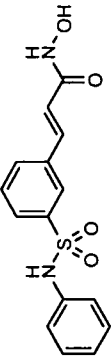
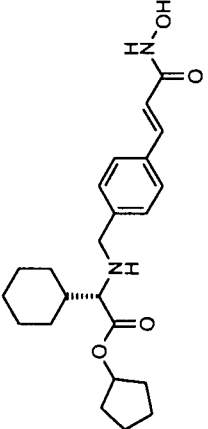
"nt" means "not tested to date".

Macrophage Selectivity:

Table A illustrates the way in which the addition of an esterase motif can significantly increase macrophage(monocyte) selectivity.

Example 14 is 30 fold more potent as an anti-proliferative agent in the monocytic cell line U937 than the known HDAC inhibitor belinostat which is currently in Phase II clinical trials (Glaser KB, Biochem. Pharmacol., 2007, **74**, 659-671). This macrophage(monocyte) selectivity results from selective cleavage of the ester as shown by the accumulation of the resultant acid inside the U937 cell line but not the HUT cell line. Only the theU937 cell line expresses HCE-1. Furthermore, the potency of **Example 14** in the non-monocytic cell line HUT is what would be expected based on its enzyme activity i.e. the ratio of enzyme to cell potency is the same for **Example 14** and belinostat.

TABLE A

Compound	Structure	Inhibition of HDAC (IC ₅₀ – nM)	Inhibition of U937 cell proliferation (IC ₅₀ – nM)	Ratio U937 / enzyme	Acid accumulation at 6h in U937 (ng/ml)	Inhibition of HUT78 cell proliferation (IC ₅₀ – nM)	Ratio HUT78 / enzyme	Acid accumulation at 6h in HUT78 (ng/ml)
Belinostat		13	180	14	-	31	2.4	-
Example 14		59	5	0.08	27	230	3.8	0

Broken Cell Carboxylesterase Assay

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

U937 or Hut78 tumour cells ($\sim 10^9$) were washed in 4 volumes of Dulbeccos PBS (~ 1 litre) and pelleted at 525g for 10 min at 4°C. This was repeated twice and the final cell pellet was resuspended in 35mL of cold homogenising buffer (Trizma 10mM, NaCl 130mM, CaCl_2 0.5mM pH 7.0 at 25°C). Homogenates were prepared by nitrogen cavitation (700psi 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 μ M
Aprotinin 0.1 μ M
E64 8 μ M
Pepstatin 1.5 μ M
Bestatin 162 μ M
Chymostatin 33 μ M

After clarification of the cell homogenate by centrifugation at 525g 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

Hydrolysis of esters to the corresponding carboxylic acids can be measured using the cell extract, prepared as above. To this effect cell extract ($\sim 30\mu\text{g}$ / total assay volume of 0.5ml) was incubated at 37°C in a Tris- HCl 25mM, 125mM NaCl buffer, pH 7.5 at 25°C. At zero time the ester (substrate) was then added at a final concentration of 2.5 μ M 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 12000g 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 (75x2.1mm) column and a mobile phase of 5-95 % acetonitrile in water/0.1% formic acid.

Rates of hydrolysis are expressed in pg/mL/min.

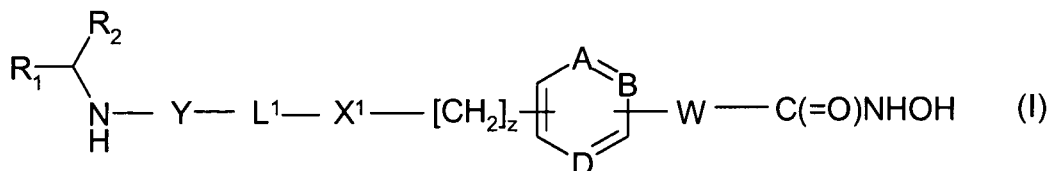
HDACs are intracellular enzymes. The following Table B presents data showing that several amino acid ester motifs, conjugated to various intracellular enzyme inhibitors by several different linker chemistries are all hydrolysed by intracellular carboxyesterases to the corresponding acid.

TABLE B

Structure of amino acid ester conjugate	R	Linker	Hydrolysis Rate Range U937Cells (pg/mL/min)	Preparation of amino ester conjugate
		~CH ₂ CH ₂ O~	100-1000	WO2006117552
		~(CH ₂) ₃ O~~CH ₂ NHCH ₂ ~	1000-50000	WO2006117548
		~CH ₂ ~~CH ₂ NHCH ₂ ~	>50000	WO2006117549
		~CH ₂ CH ₂ O~	>50000	WO2006117567
		~CH ₂ CH ₂ O~	1000-50000	WO2006117567
		~CH ₂ ~	1000-50000	WO2006117567
		~CO~	>50000	WO2006117567
		~CH ₂ ~~CH ₂ NHCH ₂ ~	>50000	WO2006117549
		~CH ₂ ~~CH ₂ NHCH ₂ ~	>50000	WO2006117549

Claims

1. A compound of formula (I) or a salt, N-oxide, hydrate or solvate thereof:



wherein

A, **B** and **D** independently represent =C- or =N-;

W is a divalent radical –CH=CH- or –CH₂CH₂-;

R₁ is a carboxylic acid group (–COOH), or an ester group which is hydrolysable by one or more intracellular carboxyesterase enzymes to a carboxylic acid group;

R₂ is the side chain of a natural or non-natural alpha amino acid;

Y is a bond, –C(=O)-, –S(=O)₂-, –C(=O)O-, –C(=O)NR₃-, –C(=S)-NR₃, –C(=NH)NR₃ or –S(=O)₂NR₃- wherein R₃ is hydrogen or optionally substituted C₁-C₆ alkyl;

L¹ is a divalent radical of formula –(Alk¹)_m(Q)_n(Alk²)_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 –X²-Q¹- or –Q¹-X²- wherein X² is –O-, S- or NR^A- wherein R^A is hydrogen or optionally substituted C₁-C₃ alkyl, and Q¹ is an optionally substituted divalent mono- or bicyclic carbocyclic or heterocyclic radical having 5 - 13 ring members,

Alk¹ and **Alk**² independently represent optionally substituted divalent C₃-C₇ cycloalkyl radicals, or optionally substituted straight or branched, C₁-C₆ alkylene, C₂-C₆ alkenylene, or C₂-C₆ 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 C₁-C₃ alkyl;

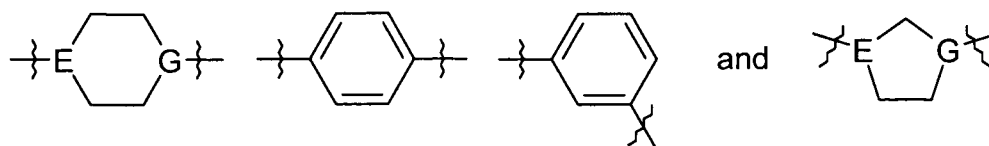
X^1 represents a bond; $-C(=O)$; or $-S(=O)_2-$; $-NR_4C(=O)-$, $-C(=O)NR_4-$, $-NR_4C(=O)NR_5-$, $-NR_4S(=O)_2-$, or $-S(=O)_2NR_4-$ wherein R_4 and R_5 are independently hydrogen or optionally substituted C_1 - C_6 alkyl; and

z is 0 or 1;

PROVIDED THAT, when A, B and D are each $=C-$ and W is $-CH=CH-$ and R_1 is a carboxylic acid group or a methyl or tert-butyl ester thereof, then R_2 is not the side chain of tryptophan, namely indol-3-ylmethyl.

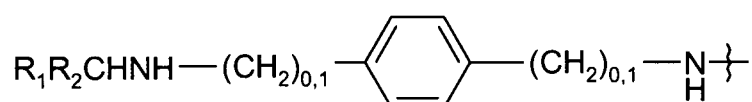
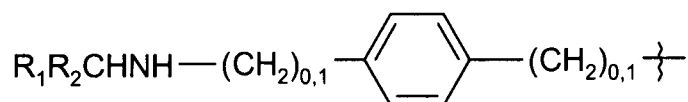
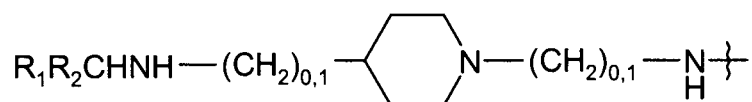
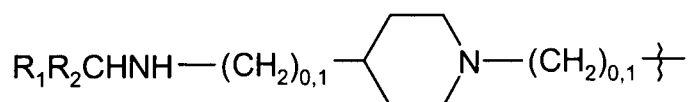
2. A compound as claimed in claim 1 wherein A, B and D are each $=C-$.
3. A compound as claimed in claim 1 wherein one of A, B and D is $=N-$ and the others are each $=C-$.
4. A compound as claimed in any of the preceding claims wherein the radical $HONHC(=O)-W-$ is attached to the ring containing A, B and C in a position meta- or para- to the radical $R_1R_2CHNHYL^1X^1[CH_2]_z-$.
5. A compound as claimed in any of the preceding claims wherein, in the radical $R_1R_2CHNHYL^1X^1[CH_2]_z-$, z is 0.
6. A compound as claimed in any of the preceding claims wherein, in the radical $R_1R_2CHNHYL^1X^1[CH_2]_z-$, Y is a bond.
7. A compound as claimed in any of claims 1 to 6 wherein, in the radical $R_1R_2CHNHYL^1X^1[CH_2]_z-$, X^1 is a bond.
8. A compound as claimed in any of claims 1 to 5 wherein, in the radical $R_1R_2CHNHYL^1X^1[CH_2]_z-$, one of Y and X^1 is other than a bond, and L^1 is a bond.
9. A compound as claimed in any of claims 1 to 4 wherein, in the radical $R_1R_2CHNHYL^1X^1[CH_2]_z-$, z is 0, Y and X^1 are each a bond, and L^1 is a divalent radical of formula $-(Alk^1)_m(Q)_n(Alk^2)_p-$ wherein one of m and p is 0 and the other is 1, and n is 1.

10. A compound as claimed in claim 9 wherein Q is selected from:



wherein E and G are independently CH or N

11. A compound as claimed in any of claims 1 to 4 wherein the radical $R_1R_2CHNHYL^1X^1[CH_2]_z-$, is selected from: $R_1R_2CHNHOSO_2-$, $R_1R_2CHNHCO-$, $R_1R_2CHNHCH_2-$, $R_1R_2CHNH(CH_2)_3O-$, and the following:



12. A compound as claimed in any of claims 1 to 4 wherein the radical $-YL^1X^1[CH_2]_z-$ is $-CH_2-$.
13. A compound as claimed in any of the preceding claims wherein R_1 is an ester group of formula $-(C=O)OR_9$ wherein R_9 is $R_{20}R_{21}R_{22}C$ wherein
- (i) R_{20} is hydrogen or optionally substituted $(C_1-C_3)\text{alkyl}-(Z^1)_a-[(C_1-C_3)\text{alkyl}]_b-$ or $(C_2-C_3)\text{alkenyl}-(Z^1)_a-[(C_1-C_3)\text{alkyl}]_b-$ wherein a and b are independently 0 or 1 and Z^1 is $-O-$, $-S-$, or $-NR_C-$ wherein R_C is hydrogen or $(C_1-C_3)\text{alkyl}$; and R_{21} and R_{22} are independently hydrogen or $(C_1-C_3)\text{alkyl}$;

- (ii) R_{20} 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_{21} and R_{22} are independently hydrogen or $(C_1-C_3)alkyl-$; or
- (iii) R_{20} and R_{21} 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_{22} is hydrogen.
14. A compound as claimed in claim 13 wherein R_9 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.
15. A compound as claimed in claim 13 wherein R_9 is cyclopentyl.
16. A compound as claimed in any of the preceding claims wherein R_2 is cyclohexylmethyl, cyclohexyl, pyridin-3-ylmethyl, sec-butyl, tert-butyl, 1-benzylthio-1-methylethyl, 1-methylthio-1-methylethyl, or 1-mercapto-1-methylethyl.
17. A compound as claimed in any of claims 1 to 15 wherein R_2 is phenyl, benzyl, phenylethyl, tert-butoxymethyl or iso-butyl.
18. A compound as claimed in any of claims 1 to 15 wherein R_2 is $-CH(CH_3)_2$, cyclohexyl, $-CH_2O(t-Bu)$, $-CH_2S(t-Bu)$, or phenyl.
19. A compound as claimed in claim 1 selected from the group consisting of:
- Cyclopentyl (2S)-cyclohexyl({4-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}amino)acetate,
- Cyclopentyl N-{4-[(1E)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]benzyl}-L-leucinate,
- Cyclopentyl (2S)-cyclohexyl({4-[3-(hydroxyamino)-3-oxopropyl]benzyl}amino)acetate,
- Cyclopentyl N-{4-[3-(hydroxyamino)-3-oxopropyl]benzyl}-L-leucinate,

tert-Butyl *N*-{4-[3-(hydroxyamino)-3-oxopropyl]benzyl}-L-leucinate,

Cyclopentyl (2*S*)-cyclohexyl[({6-[(1*E*)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]pyridin-3-yl)methyl}amino]acetate,

Cyclopentyl *N*-({6-[(1*E*)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]pyridin-3-yl)methyl}-L-leucinate,

Cyclopentyl (2*S*)-cyclohexyl[({6-[3-(hydroxyamino)-3-oxopropyl]pyridin-3-yl)methyl}amino]acetate,

tert-Butyl *N*-({6-[3-(hydroxyamino)-3-oxopropyl]pyridin-3-yl)methyl}-L-leucinate,

Cyclopentyl (2*S*)-cyclohexyl[({5-[(1*E*)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]pyridin-2-yl)methyl}amino]acetate,

tert-Butyl *N*-({5-[(1*E*)-3-(hydroxyamino)-3-oxoprop-1-en-1-yl]pyridin-2-yl)methyl}-L-leucinate,

Cyclopentyl (2*S*)-cyclohexyl[({5-[3-(hydroxyamino)-3-oxopropyl]pyridin-2-yl)methyl}amino]acetate,

tert-Butyl *N*-({5-[3-(hydroxyamino)-3-oxopropyl]pyridin-2-yl)methyl}-L-leucinate,

and salts, N-oxides, hydrates or solvates thereof.

20. A pharmaceutical composition comprising a compound as claimed in any of the preceding claims, together with a pharmaceutically acceptable carrier.
21. The use of a compound as claimed in any of claims 1 to 19 in the preparation of a medicament for the treatment of cell-proliferation disease, polyglutamine disease, neurodegenerative disease, autoimmune disease, inflammatory disease, organ transplant rejection, diabetes, haematological disorders or infection.
22. A method for the treatment of cell-proliferation disease, polyglutamine disease, neurodegenerative disease, autoimmune disease, inflammatory disease, organ

transplant rejection, diabetes, haematological disorders or infection, which comprises administering to a subject suffering such disease an effective amount of a compound as claimed in any of claims 1 to 19.

23. The use as claimed in claim 21, or a method as claimed in claim 22 wherein the treatment is of cancer cell proliferation, Huntingdon disease, or Alzheimer disease.
24. The use as claimed in claim 21, or a method as claimed in claim 22 wherein the treatment is of rheumatoid arthritis.
25. A pharmaceutical composition as claimed in claim 20 which is adapted for topical administration and wherein, in the compound, R_2 is linked to the carbon atom to which it is attached through a methylene radical $-CH_2-$.