

Linear Apelin Receptor Agonists

This invention relates to a class of novel peptide compounds, their salts, pharmaceutical compositions containing them and their use in therapy of the human body. In particular, the invention is directed to a class of compounds which are agonists of Apelin receptors. The
5 invention also relates to the manufacture and use of these compounds and compositions in the prevention or treatment of such diseases in which Apelin receptors are involved.

The compounds relates to metabolically stable apelin analogs, covering a range of G protein-dependent and independent pharmacological profiles, and their use under both acute and chronic administration protocols, for the prevention or the treatment of disease
10 mediated by the apelin receptor, in particular of cardiovascular disease (heart failure, kidney failure, hypertension, pulmonary hypertension, acute and chronic kidney injury and thrombotic diseases), diabetes, liver and gastrointestinal disease.

Background of the Invention

Apelin is the endogenous ligand of the apelin receptor (also known as APJ, APLNR or angiotensin receptor-like 1). The Apelin receptor is a class A GPCR located on chromosome
15 11 consisting of 377 amino acids. To date only one apelin receptor has been identified in mammals, although two subtypes are present in amphibians and fish, and there are no closely related (homologous) genes.

In humans the APLN gene resides on chromosome X and encodes a 77 amino acid precursor preproapelin which is subsequently proteolytically cleaved to generate several
20 isoforms: apelin-36, apelin-17, apelin-13 and [Pyr1] apelin-13. Among the isoforms [Pyr1] apelin-13 is the predominant isoform detected in human heart and plasma, however the plasma half life of apelin is very short (<5minutes) and therefore it is feasible additional short-lived isoforms with alternative structures and/or pharmacological properties may exist
25 and potentially contribute to the physiological effects associated with the parent peptide apelin-36. Binding of the apelins to the apelin receptor can result in activation of multiple intracellular signaling pathways mediated by Gai/o, Ga13 and possibly Gq G proteins leading to recruitment of several signal transduction cascades including, but not limited to, phospholipase C (PLC), protein kinase C (PKC), AMP-activated protein kinase (AMPK),
30 endothelial nitric oxide synthase, regulation of ERK1/2 phosphorylation and PI3K/Akt/p70S6 kinase signaling.

A second peptide of 54 amino acids Elabela/Toddler (ELABELA, or ELA, also known as Toddler, or Apela) has been identified which also activates the apelin receptor. The primary

amino acid sequence of ELA does not demonstrate similarity to APJ however like APJ, ELA also undergoes rapid proteolytical cleavage to generate shorter isoforms. Both ligands are critical regulators of cardiovascular development and function.

5 Activation of the apelin receptor by endogenous ligands has also been demonstrated to result in the of β -arrestin, a protein that initiates receptor internalisation, desensitisation as well as downstream signalling. Recruitment of β -arrestin results in apparent short duration responses and an apelin receptor population that are refractory to further ligand-mediated activation. In various embodiments the identified examples can binding to and/or activate G
10 protein-signalling either alone or in combination with recruitment of β -arrestin thereby providing unique pharmacological profiles useful in the treatment of diseases related to apelin dysfunction.

Both apelin and APJ are relatively widely expressed across the central nervous system (CNS), peripheral tissues and blood, suggesting roles in multiple complex physiological processes. Based on multiple literature publications the apelin system has been implicated
15 in roles in CNS disorders, thermoregulation, glucose homeostasis, angiogenesis, diabetes, pancreatitis, cardiovascular function, hepatic function and renal function, cancer (including but not limited to glioblastoma and colon cancer),

The APJ receptor and its ligands (apelin and ELA) have been implicated in the pathophysiology of human heart failure. Apelin receptors are present on endothelial cells,
20 vascular smooth muscle cells and cardiomyocytes. Initial studies identified apelin as one of the most potent inotropic agents identified to date through direct actions on cardiomyocyte contractility without evidence of cardiac hypertrophy. Apelin has also been demonstrated to increase left ventricular contractility.

Apelin expression has been demonstrated to be altered in the setting of cardiovascular disease. An increase in apelin immunoreactivity has been observed in the plasma of patients
25 in the early stages of heart failure, whereas a decrease is observed at later, more severe stages. Moreover, apelin receptor mRNA has been shown to be decreased in rat hypertrophied and failing hearts. Apelin gene-deficient mice were shown to develop an impaired heart contractility and progressive heart failure associated with aging and pressure
30 overload. Therefore, down-regulation of the apelin system seems to coincide with declining cardiac performance raising the possibility that apelin could be a protective agent for cardiac function.

Systemic injection of apelin in rodents and humans has been demonstrated to result in significant decreases in blood pressure (BP) in rats via nitric oxide production. These data demonstrate that apelin exerts a hypotensive effect in vivo. However these effects on both blood pressure and inotropic cardiac output are short-lived, lasting only a few minutes, and
5 demonstrating a degree of desensitization (also known as tachyphalaxis) leaving the apelin receptor refractory to further stimulation.

In chronic models of right ventricular failure apelin had inotropic effects and long-term treatment led to improved right ventricular mass, increased contractile force with decreased cardiac loading and hemodynamic measurements. Consistent with these findings apelin
10 infusion has been demonstrated to improve pulmonary vascular hemodynamics in multiple preclinical models of pulmonary arterial hypertension (PAH) and these benefits have been confirmed to translate into PAH patients.

In zebrafish, ELA signalling is required for normal heart and vasculature development and its deficiency lead to severe defects in heart development and lymphogenesis. In humans ELA
15 is expressed in adult embryonic stem cells and kidney and activates the human apelin receptor in respect of its activities to suppress cAMP production and to induce ERK1/2 phosphorylation and calcium mobilization. Functionally Elabela stimulates angiogenesis in human HUVECs and relaxes mouse aortic vessels.

In addition to a cardiovascular action of apelin, apelin receptor mRNA has been detected in
20 all renal zones, most abundantly in the inner stripe of the outer medulla, in the glomeruli and a moderate expression was observed in all nephron segments, especially in collecting ducts. In agreement with this localization, the intravenous (iv) injection of apelin in increasing doses, dose-dependently increases diuresis.

Apelin expression has also been confirmed in human endothelial tissue where a key role in
25 controlling fatty acid transport across the endothelial layer through apelin-induced inactivation of the transcription factor Forkhead box protein O1 (FOXO1) and subsequent inhibition of endothelial fatty acid binding protein 4 (FABP4) expression. These actions are consistent with predicted benefits on glucose utilisation and improved insulin sensitivity in diseases such as type 2 diabetes (T2DM).

30 Apelin receptor agonists may be useful alone and/or in combination with current standard of care treatments in the treatment of pulmonary arterial hypertension (PAH) increasing cardiac output, reducing pulmonary vessel hypertension, reducing inflammation, improve pulmonary tissue remodelling and preserving right heart ventricular function. PAH is a rare, progressive

disorder characterized by high blood pressure (hypertension) in the arteries of the lungs (pulmonary artery) for no apparent reason. Symptoms of PAH include shortness of breath (dyspnea) especially during exercise, chest pain, and fainting episodes. The exact cause of PAH is unknown and although treatable, there is no known cure for the disease. PAH occurs
5 twice as frequently in females as in males. It tends to affect females between the ages of 30 and 60. New cases are estimated to occur in one to two individuals per million each year in the U.S. The incidence is estimated to be similar in Europe. Approximately 500-1000 new cases of PAH are diagnosed each year in the U.S. There is no ethnic or racial group that is known to have a higher frequency of patients with PAH. Individuals with PAH may go years
10 without a diagnosis, either because their symptoms are mild, nonspecific, or only present during demanding exercise. However, it is important to treat PAH because without treatment high blood pressure in the lungs causes the right heart to work much harder, and over time, this heart muscle may weaken or fail. The progressive nature of this disease means that an individual may experience only mild symptoms at first, but will eventually require treatment
15 and medical care to maintain a normal lifestyle.

Apelin receptor agonists are agents useful in the treatment of cardiovascular conditions such as heart failure, acute decompensated heart failure, congestive heart failure, cardiomyopathy, ischemia, ischemia/reperfusion injury, fluid homeostasis, kidney failure,
20 hypertension, pulmonary hypertension, polycystic kidney disease, hyponatremia and SIADH to increase cardiac output, improve cardiac function, stabilise cardiac function, limit further decrease in cardiac function, reduce systemic and portal hypertension, promote angiogenesis and new blood vessel formation in ischemic tissue, treat abnormalities in thrombosis and platelet function and improve kidney function and diuresis. Heart failure
25 constitutes a major and growing health burden. In Europe there are at least 15 million patients with heart failure and in the United States, heart failure affects nearly 5,800,000 people. Heart failure incidence approaches 10 per 1,000 population after age 65. In the United States, heart failure causes 280,000 deaths annually, and the estimated direct and indirect cost of heart failure for 2010 is \$39,2 billion. Treatment options depend on the type,
30 cause, symptoms and severity of the heart failure, including treating the underlying causes and lifestyle changes. A number of medications are prescribed for heart failure, and most patients will take more than one drug. Apelin receptor agonists are likely to be used on top of existing agents. Despite the advancements obtained in medical therapy, the death rate of heart failure remains high: almost 50% of people diagnosed with heart failure will die within 5
35 years.

Abnormalities in platelet function are associated with a range of thrombotic diseases such as peripheral arterial disease (PAD), acute coronary syndrome (ACS), myocardial infarction (MI), heart attacks (HA), stroke and atherosclerosis. Apelin and APJNR are expressed in human and mouse platelets and apelin knockout mice displayed a prothrombotic phenotype with increased platelet aggregation. Stimulation of platelets with apelin has been demonstrated to engage signalling pathways associated with calcium, nitric oxide and thromboxane production consistent with predicted benefits in these conditions.

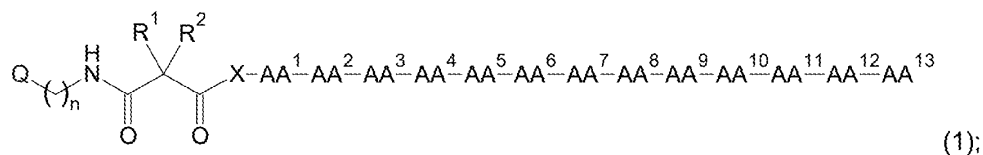
Apelin receptor agonists are also agents useful for the treatment and management of diabetes and associated related metabolic conditions, diabetic complications (for example diabetic nephropathy, retinopathy, neuropathy, non-alcoholic fatty liver disease, non-alcoholic steatosis, portal hypertension) and conditions where stimulation and/or growth and/or endurance of muscle mass may be considered beneficial. Apelin has been demonstrated to be expressed in endothelial cells and improved glucose tolerance, enhances glucose utilisation by muscle, increases muscle insulin sensitivity and improves angiogenesis in tissue with poor local blood supply. Apelin-neuroprotection, where administration of apelin peptides promote neuronal survival and/or increased numbers of neurons, will be useful in conditions with neuronal loss of function, such as diabetic neuropathy.

The half-life of apelin in the blood circulation is around one minute, this invention aims at designing, synthesising and testing novel potent and stable drugs that activate the apelin/apelin receptor pathway. Embodiments contained herein exemplify the potential to specifically activate intracellular signaling pathways in a manner independent of β -arrestin activation and consistent with sustained receptor activation in the absence of desensitisation and/or tachyphalaxis. Such a compound constitutes a potential new therapeutic agent to treat diseases mediated by the apelin receptor as described in this invention.

Summary of the Invention

The present invention relates to novel compounds with agonist activity at the Apelin receptor, pharmaceutical compositions comprising these, and use of the compounds for the manufacture of medicaments for treatment of diseases.

Accordingly, in one embodiment the invention provides a compound of the formula (1):



5 wherein;

Q is selected from phenyl or a monocyclic heteroaryl ring each of which may be optionally substituted with one or more R^q groups; or Q is a polyether chain of formula -
 (OCH₂CH₂)_mOCH₃, wherein m is 1 to 5;

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R^q is selected from halogen, hydroxyl, amino or C₁₋₆ alkyl having an alkyl chain optionally containing one or more heteroatoms selected from O, N, or S;

n is 1 to 3;

15

R^1 and R^2 are independently selected from hydrogen or a C₁₋₆ alkyl group, or together with the carbon to which they are attached join to form a C₃₋₈ cycloalkyl or a heterocyclyl group;

X is -DArg- or a bond;

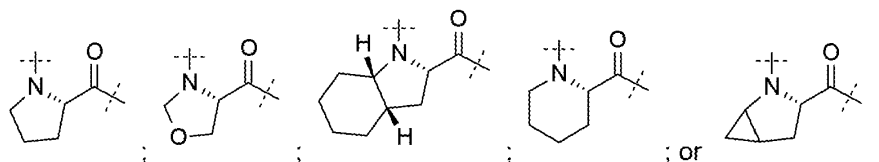
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AA^1 is -NHCR^{3a}R^{3b}CO- or -N(Me)CR^{3a}R^{3b}CO-; wherein R^{3a} is hydrogen or C₁₋₃ alkyl; and R^{3b} is -CH₂(CH₂)_pCONH₂ or -(CH₂)_pbenzyl, where p is 0 or 1;

AA^2 is -Arg-, -DArg- or a homoarginine residue;

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AA^3 is a residue selected from:



AA^4 is -Arg- or -DArg-;

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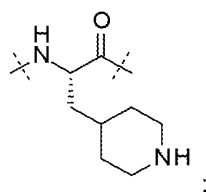
AA⁵ is -NHCH(CH₂R⁴)CO- or -N(Me)CH(CH₂R⁴)CO-; wherein R⁴ is C₁₋₆ alkyl, C₁₋₆ cycloalkyl or C₁₋₆ branched alkyl;

AA⁶ is -Aib-, -DAla- or -Ser-;

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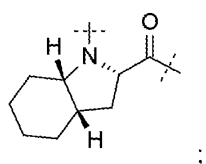
AA⁷ is -NHCR^{5a}R^{5b}CO- or -N(Me)CR^{5a}R^{5b}CO-; wherein R^{5a} is hydrogen or C₁₋₃ alkyl and R^{5b} is C₁₋₃ alkyl, CH₂-aryl or CH₂-heteroaryl optionally substituted with one or more halo groups or C₁₋₃ alkyl groups;

10 AA⁸ is the residue:



AA⁹ is -Gly-, -Ala-, -DAla- or an N-methyl glycine residue;

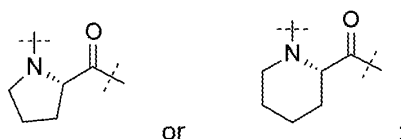
15 AA¹⁰ is the residue:



AA¹¹ is -NHCHR⁶CO-; wherein R⁶ is C₁₋₆ alkyl, benzyl, -CH₂-naphthyl or -CH₂-biphenyl optionally substituted with one or more halo groups;

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AA¹² is a residue selected from:



25 AA¹³ is -NHCR^{7a}R^{7b}CO- or -N(Me)CR^{7a}R^{7b}CO-; wherein R^{7a} is hydrogen or C₁₋₃ alkyl and R^{7b} is C₁₋₁₀ alkyl, -CH₂-naphthyl, -CH₂-biphenyl or benzyl optionally substituted with one or more R⁸ groups, wherein R⁸ is selected from halo, -O-aryl or -O-benzyl;

wherein the AA¹³ C-terminus is a carboxyl group or a carboxamide group;

or a tautomeric or stereochemically isomeric form thereof or a prodrug, salt or zwitterion thereof.

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Detailed Description of the Invention

This invention relates to novel compounds. The invention also relates to the use of novel compounds as agonists of Apelin receptors. The invention further relates to the use of novel compounds in the manufacture of medicaments for use as Apelin receptor agonists or for the treatment of disorders associated with Apelin receptors.

The invention further relates to compounds, compositions and medicaments useful for the treatment of disorders associated with Apelin receptors. Such disorders include cardiovascular disease, acute decompensated heart failure, congestive heart failure, myocardial infarction, cardiomyopathy, ischemia, ischemia/reperfusion injury, pulmonary hypertension, diabetes, obesity, cancer, metastatic disease, fluid homeostasis, pathological angiogenesis, retinopathy, HIV infection, treatment of pulmonary arterial hypertension (PAH) increasing cardiac output, reducing pulmonary vessel hypertension, reducing inflammation, improve pulmonary tissue remodelling, preserving right heart ventricular function, heart failure, congestive heart failure, cardiomyopathy, ischemia, ischemia/reperfusion injury, fluid homeostasis, kidney failure, hypertension, pulmonary hypertension, polycystic kidney disease, hyponatremia, SIADH, platelet function are associated with a range of thrombotic diseases such as peripheral arterial disease (PAD), acute coronary syndrome (ACS), myocardial infarction (MI), heart attacks (HA), stroke, atherosclerosis, treatment and management of diabetes and associated related metabolic conditions, diabetic complications (for example diabetic nephropathy, retinopathy, neuropathy, non-alcoholic fatty liver disease, non-alcoholic steatosis, portal hypertension) and conditions where stimulation and/or growth and/or endurance of muscle mass may be considered beneficial.

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Another aspect of the invention is a method of treating the symptoms of various forms of central nervous system disorders including, dementia, including senile dementia and cerebrovascular dementia, depression, hyperkinetic (minimal brain damage) syndrome, disturbance of consciousness, anxiety disorder, schizophrenia, phobia, epilepsy, amyotrophic lateral sclerosis; Impairments of growth hormone secretion and/or function including but not limited to hyperphagia, polyphagia, hypercholesterolemia, hyperglyceridemia, hyperlipidemia, hyperprolactinemia, hypoglycemia, hypopituitarism,

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pituitary dwarfism; cancers, pancreatitis, renal diseases, Turner's syndrome, rheumatoid arthritis, spinal injury, spinocerebellar deformation, bone fractures, wounds, atopic dermatitis, osteoporosis, asthma, infertility, arteriosclerosis, pulmonary emphysema, pulmonary edema, and milk secretion insufficiency, and can also be used as a hypnotic sedative, a
 5 postoperative nutritional status improving agent, a preventive or therapeutic drug for HIV infection, AIDS, etc., and the like, comprising administering a Apelin acting polypeptide to a patient in need thereof.

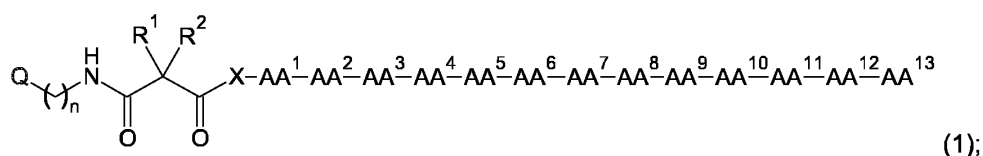
Diseases or conditions for which the compounds may be beneficial include those selected
 10 from the group consisting of, treatment of pulmonary arterial hypertension (PAH) increasing cardiac output, reducing pulmonary vessel hypertension, reducing inflammation, improve pulmonary tissue remodelling and preserving right heart ventricular function, heart failure, congestive heart failure, cardiomyopathy, ischemia, ischemia/reperfusion injury, fluid homeostasis, kidney failure, hypertension, pulmonary hypertension, polycystic kidney
 15 disease, hyponatremia and SIADH, treatment and management of diabetes and associated related metabolic conditions, diabetic complications (for example diabetic nephropathy, retinopathy, neuropathy, non-alcoholic fatty liver disease, non-alcoholic steatosis, portal hypertension) and conditions where stimulation and/or growth and/or endurance of muscle mass.

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In a further aspect, the present invention provides the use of a compound as outlined above for the manufacture of a medicament for the treatment of any of the indications listed above.

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Accordingly, in one embodiment the invention provides a compound of the formula (1):



wherein;

Q is selected from phenyl or a monocyclic heteroaryl ring each of which may be optionally
 30 substituted with one or more R^a groups; or Q is a polyether chain of formula -
 $(\text{OCH}_2\text{CH}_2)_m\text{OCH}_3$, wherein m is 1 to 5;

R^a is selected from halogen, hydroxyl, amino or C_{1-6} alkyl having an alkyl chain optionally containing one or more heteroatoms selected from O, N, or S;

n is 1 to 3;

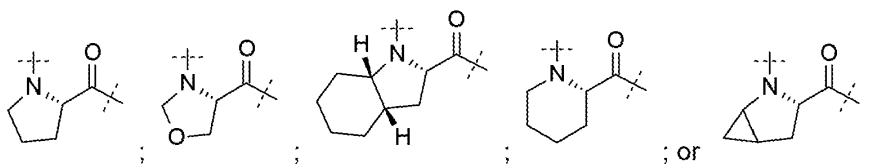
R¹ and R² are independently selected from hydrogen or a C₁₋₆ alkyl group, or together with the carbon to which they are attached join to form a C₃₋₈ cycloalkyl or a heterocyclyl group;

X is -DArg- or a bond;

- 5 AA¹ is -NHCR^{3a}R^{3b}CO- or -N(Me)CR^{3a}R^{3b}CO-; wherein R^{3a} is hydrogen or C₁₋₃ alkyl; and R^{3b} is -CH₂(CH₂)_pCONH₂ or -(CH₂)_pbenzyl, where p is 0 or 1;

AA² is -Arg-, -DArg- or a homoarginine residue;

AA³ is a residue selected from:



- 10 AA⁴ is -Arg- or -DArg-;

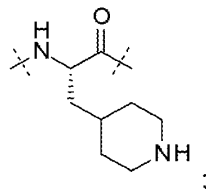
AA⁵ is -NHCH(CH₂R⁴)CO- or -N(Me)CH(CH₂R⁴)CO-; wherein R⁴ is C₁₋₆ alkyl, C₁₋₆ cycloalkyl or C₁₋₆ branched alkyl;

AA⁶ is -Aib-, -DAla- or -Ser-;

AA⁷ is -NHCR^{5a}R^{5b}CO- or -N(Me)CR^{5a}R^{5b}CO-; wherein R^{5a} is hydrogen or C₁₋₃ alkyl and R^{5b}

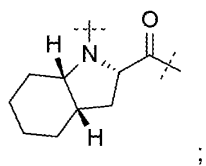
- 15 is C₁₋₃ alkyl, CH₂-aryl or CH₂-heteroaryl optionally substituted with one or more halo groups or C₁₋₃ alkyl groups;

AA⁸ is the residue:



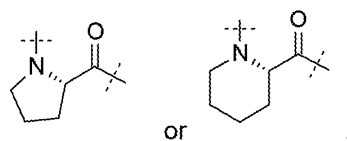
AA⁹ is -Gly-, -Ala-, -DAla- or an N-methyl glycine residue;

- 20 AA¹⁰ is the residue:



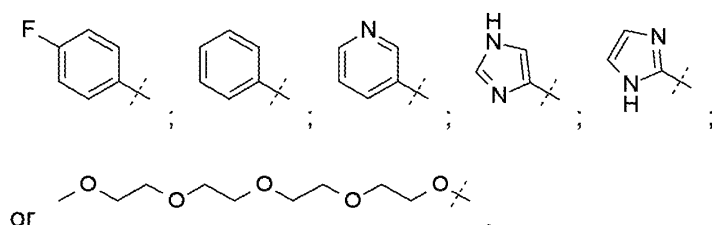
AA¹¹ is -NHCHR⁶CO-; wherein R⁶ is C₁₋₆ alkyl, benzyl, -CH₂-naphthyl or -CH₂-biphenyl optionally substituted with one or more halo groups;

AA¹² is a residue selected from:

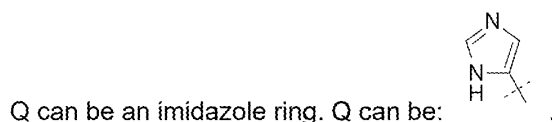


- AA¹³ is -NHCR^{7a}R^{7b}CO- or -N(Me)CR^{7a}R^{7b}CO-; wherein R^{7a} is hydrogen or C₁₋₃ alkyl and R^{7b} is C₁₋₁₀ alkyl, -CH₂-naphthyl, -CH₂-biphenyl or benzyl optionally substituted with one or more R⁸ groups, wherein R⁸ is selected from halo, -O-aryl or -O-benzyl; wherein the AA¹³ C-terminus is a carboxyl group or a carboxamide group; or a tautomeric or stereochemically isomeric form thereof or a prodrug, salt or zwitterion thereof.

- 10 Q can be selected from:



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Q can be an imidazole ring. Q can be:

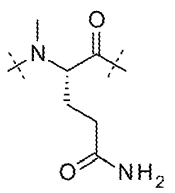
n can be 1. n can be 2. n can be 3.

- 20 R¹ and R² may be independently selected from hydrogen or a C₁₋₆ alkyl group. R¹ can be hydrogen or a C₁₋₆ alkyl group. R² can be hydrogen or a C₁₋₆ alkyl group. R¹ and R² can both be methyl. R¹ can be methyl. R² can be methyl.

X can be -DArg-. X can be a bond.

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AA¹ can be a glutamine residue, a D-glutamine residue, a homophenylalanine residue or an N-methyl glutamine residue of the formula:

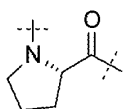


AA¹ can be a glutamine residue.

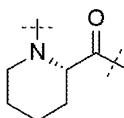
AA² can be -Arg-. AA² can be -DArg-. AA² can be a homoarginine residue.

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AA³ can be:



AA³ can be:



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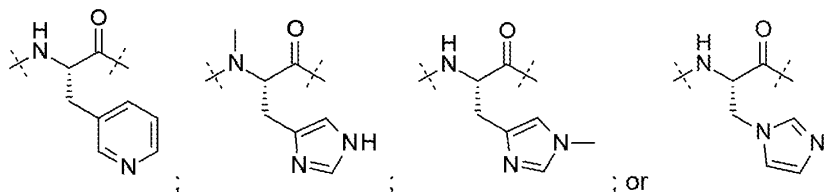
AA⁴ can be -Arg-. AA⁴ can be -DArg-.

AA⁵ can be a leucine residue, a D-leucine residue, a *tert*-butylalanine residue, a cyclobutylalanine residue or an N-methyl leucine residue. AA⁵ can be a leucine residue.

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AA⁶ can be -Aib-. AA⁶ can be -DAla-. AA⁶ can be -Ser-.

AA⁷ can be a 2-aminoisobutyric acid residue, a histidine residue, a 4-bromophenylalanine residue or is a residue selected from:



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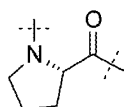
AA⁷ can be a histidine residue.

AA⁹ can be -Gly-. AA⁹ can be -Ala-. AA⁹ can be -DAla-. AA⁹ can be an N-methyl glycine residue;

AA¹¹ can be a phenylalanine residue, a 2-naphthylalanine residue, a 3-chlorophenylalanine residue, a 4-bromophenylalanine residue, a 4-chlorophenylalanine residue, a norleucine residue or a 4-phenylphenylalanine residue. AA¹¹ can be a 4-bromophenylalanine residue.

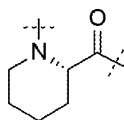
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AA¹² can be:



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AA¹² can be:

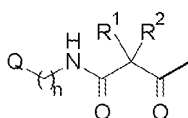


AA¹³ can be an O-benzyl-D-tyrosine residue, a 4-bromo-D-phenylalanine residue, a 4-phenoxy-D-phenylalanine residue, a 2-naphthyl-D-alanine residue, a 4-phenyl-D-phenylalanine residue, an N-methyl 4-phenyl-D-phenylalanine residue or a beta-cyclohexyl-D-alanine residue. AA¹³ can be a 4-phenyl-D-phenylalanine residue.

The AA¹³ C-terminus can be a carboxamide group. The AA¹³ C-terminus can be a carboxyl group.

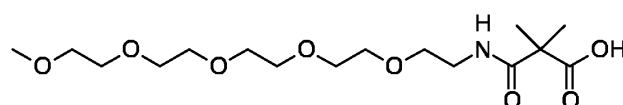
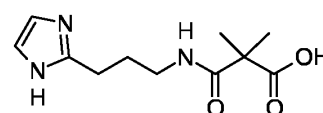
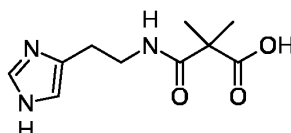
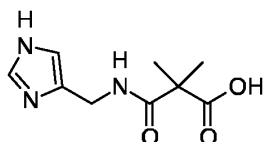
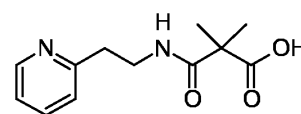
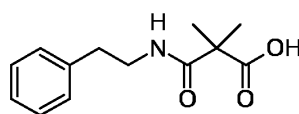
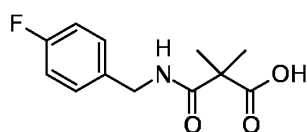
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Particular examples of moiety



include caps 1-7 as shown below where the COOH group is coupled to the amine of the peptide X or AA¹ where X is a bond:

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The compound can be selected from any one of Examples 1 to 62 shown in Table 1.

- 5 Specific examples of compounds include compounds having Apelin receptor agonist activity.

The compounds of the invention may be used in a pharmaceutical composition comprising a compound of the invention and a pharmaceutically acceptable excipient.

- 10 The compounds of the invention may be used in medicine.

The compounds of the invention may be used in the treatment of disorders associated with Apelin receptors listed above.

- ## 15 Definitions

In this application, the following definitions apply, unless indicated otherwise.

The term “alkyl”, “aryl”, “halogen”, “cycloalkyl”, “heterocyclyl” and “heteroaryl” are used in their conventional sense (e.g. as defined in the IUPAC Gold Book) unless indicated otherwise.

The term “treatment”, in relation to the uses of any of the compounds described herein, including those of the formula (1), is used to describe any form of intervention where a

compound is administered to a subject suffering from, or at risk of suffering from, or potentially at risk of suffering from the disease or disorder in question. Thus, the term "treatment" covers both preventative (prophylactic) treatment and treatment where measurable or detectable symptoms of the disease or disorder are being displayed.

5

The term "effective therapeutic amount" as used herein (for example in relation to methods of treatment of a disorder, disease or condition) refers to an amount of the compound which is effective to produce a desired therapeutic effect. For example, if the condition is pain, then the effective therapeutic amount is an amount sufficient to provide a desired level of pain relief. The desired level of pain relief may be, for example, complete removal of the pain or a reduction in the severity of the pain.

To the extent that any of the compounds described have chiral centres, the present invention extends to all optical isomers of such compounds, whether in the form of racemates or resolved enantiomers. The invention described herein relates to all crystal forms, solvates and hydrates of any of the disclosed compounds however so prepared. To the extent that any of the compounds disclosed herein have acid or basic centres such as carboxylates or amino groups, then all salt forms of said compounds are included herein. In the case of pharmaceutical uses, the salt should be seen as being a pharmaceutically acceptable salt.

20

Salts or pharmaceutically acceptable salts that may be mentioned include acid addition salts and base addition salts. Such salts may be formed by conventional means, for example by reaction of a free acid or a free base form of a compound with one or more equivalents of an appropriate acid or base, optionally in a solvent, or in a medium in which the salt is insoluble, followed by removal of said solvent, or said medium, using standard techniques (e.g. in vacuo, by freeze-drying or by filtration). Salts may also be prepared by exchanging a counter-ion of a compound in the form of a salt with another counter-ion, for example using a suitable ion exchange resin.

Examples of pharmaceutically acceptable salts include acid addition salts derived from mineral acids and organic acids, and salts derived from metals such as sodium, magnesium, potassium and calcium.

Examples of acid addition salts include acid addition salts formed with acetic, 2,2-dichloroacetic, adipic, alginic, aryl sulfonic acids (e.g. benzenesulfonic, naphthalene-2-sulfonic, naphthalene-1,5-disulfonic and p-toluenesulfonic), ascorbic (e.g. L-ascorbic), L-aspartic, benzoic, 4-acetamidobenzoic, butanoic, (+) camphoric, camphor-sulfonic, (+)-(1S)-

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camphor-10-sulfonic, capric, caproic, caprylic, cinnamic, citric, cyclamic, dodecylsulfuric, ethane-1,2-disulfonic, ethanesulfonic, 2-hydroxyethanesulfonic, formic, fumaric, galactaric, gentisic, glucoheptonic, gluconic (e.g. D-gluconic), glucuronic (e.g. D-glucuronic), glutamic (e.g. L-glutamic), α -oxoglutaric, glycolic, hippuric, hydrobromic, hydrochloric, hydriodic, isethionic, lactic (e.g. (+)-L-lactic and ($\pm$)-DL-lactic), lactobionic, maleic, malic (e.g. (-)-L-malic), malonic, ($\pm$)-DL-mandelic, metaphosphoric, methanesulfonic, 1-hydroxy-2-naphthoic, nicotinic, nitric, oleic, orotic, oxalic, palmitic, pamoic, phosphoric, propionic, L-pyroglutamic, salicylic, 4-amino-salicylic, sebacic, stearic, succinic, sulfuric, tannic, tartaric (e.g. (+)-L-tartaric), thiocyanic, undecylenic and valeric acids.

10

Also encompassed are any solvates of the compounds and their salts. Preferred solvates are solvates formed by the incorporation into the solid state structure (e.g. crystal structure) of the compounds of the invention of molecules of a non-toxic pharmaceutically acceptable solvent (referred to below as the solvating solvent). Examples of such solvents include water, alcohols (such as ethanol, isopropanol and butanol) and dimethylsulfoxide. Solvates can be prepared by recrystallising the compounds of the invention with a solvent or mixture of solvents containing the solvating solvent. Whether or not a solvate has been formed in any given instance can be determined by subjecting crystals of the compound to analysis using well known and standard techniques such as thermogravimetric analysis (TGA), differential scanning calorimetry (DSC) and X-ray crystallography.

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The solvates can be stoichiometric or non-stoichiometric solvates. Particular solvates may be hydrates, and examples of hydrates include hemihydrates, monohydrates and dihydrates. For a more detailed discussion of solvates and the methods used to make and characterise them, see Bryn *et al*, Solid-State Chemistry of Drugs, Second Edition, published by SSCI, Inc of West Lafayette, IN, USA, 1999, ISBN 0-967-06710-3.

25

The term "pharmaceutical composition" in the context of this invention means a composition comprising an active agent and comprising additionally one or more pharmaceutically acceptable carriers. The composition may further contain ingredients selected from, for example, diluents, adjuvants, excipients, vehicles, preserving agents, fillers, disintegrating agents, wetting agents, emulsifying agents, suspending agents, sweetening agents, flavouring agents, perfuming agents, antibacterial agents, antifungal agents, lubricating agents and dispersing agents, depending on the nature of the mode of administration and dosage forms. The compositions may take the form, for example, of tablets, dragees, powders, elixirs, syrups, liquid preparations including suspensions, sprays, inhalants, tablets,

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lozenges, emulsions, solutions, cachets, granules, capsules and suppositories, as well as liquid preparations for injections, including liposome preparations.

The compounds of the invention may contain one or more isotopic substitutions, and a
5 reference to a particular element includes within its scope all isotopes of the element. For
example, a reference to hydrogen includes within its scope ^1H , ^2H (D), and ^3H (T). Similarly,
references to carbon and oxygen include within their scope respectively ^{12}C , ^{13}C and ^{14}C and
 ^{16}O and ^{18}O . In an analogous manner, a reference to a particular functional group also
10 includes within its scope isotopic variations, unless the context indicates otherwise. For
example, a reference to an alkyl group such as an ethyl group or an alkoxy group such as a
methoxy group also covers variations in which one or more of the hydrogen atoms in the
group is in the form of a deuterium or tritium isotope, e.g. as in an ethyl group in which all
five hydrogen atoms are in the deuterium isotopic form (a perdeuteroethyl group) or a
15 methoxy group in which all three hydrogen atoms are in the deuterium isotopic form (a
trideuteromethoxy group). The isotopes may be radioactive or non-radioactive.

Therapeutic dosages may be varied depending upon the requirements of the patient, the
severity of the condition being treated, and the compound being employed. Determination of
the proper dosage for a particular situation is within the skill of the art. Generally, treatment
20 is initiated with the smaller dosages which are less than the optimum dose of the compound.
Thereafter the dosage is increased by small increments until the optimum effect under the
circumstances is reached. For convenience, the total daily dosage may be divided and
administered in portions during the day if desired.

25 The magnitude of an effective dose of a compound will, of course, vary with the nature of the
severity of the condition to be treated and with the particular compound and its route of
administration. The selection of appropriate dosages is within the ability of one of ordinary
skill in this art, without undue burden. In general, the daily dose range may be from about 10
 μg to about 30 mg per kg body weight of a human and non-human animal, preferably from
30 about 50 μg to about 30 mg per kg of body weight of a human and non-human animal, for
example from about 50 μg to about 10 mg per kg of body weight of a human and non-human
animal, for example from about 100 μg to about 30 mg per kg of body weight of a human
and non-human animal, for example from about 100 μg to about 10 mg per kg of body
weight of a human and non-human animal and most preferably from about 100 μg to about 1
35 mg per kg of body weight of a human and non-human animal.

Pharmaceutical Formulations

While it is possible for the active compound to be administered alone, it is preferable to present it as a pharmaceutical composition (e.g. formulation).

- 5 Accordingly, in another embodiment of the invention, there is provided a pharmaceutical composition comprising at least one compound of the formula (1) as defined above together with at least one pharmaceutically acceptable excipient.

- The composition may be a composition suitable for injection. The injection may be intra-
10 venous (IV) or subcutaneous. The composition may be supplied in a sterile buffer solution or as a solid which can be suspended or dissolved in sterile buffer for injection.

- The pharmaceutically acceptable excipient(s) can be selected from, for example, carriers (e.g. a solid, liquid or semi-solid carrier), adjuvants, diluents (e.g. solid diluents such as fillers
15 or bulking agents; and liquid diluents such as solvents and co-solvents), granulating agents, binders, flow aids, coating agents, release-controlling agents (e.g. release retarding or delaying polymers or waxes), binding agents, disintegrants, buffering agents, lubricants, preservatives, anti-fungal and antibacterial agents, antioxidants, buffering agents, tonicity-adjusting agents, thickening agents, flavouring agents, sweeteners, pigments, plasticizers,
20 taste masking agents, stabilisers or any other excipients conventionally used in pharmaceutical compositions.

- The term "pharmaceutically acceptable" as used herein means compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment,
25 suitable for use in contact with the tissues of a subject (e.g. a human subject) without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Each excipient must also be "acceptable" in the sense of being compatible with the other ingredients of the formulation.

- 30 Pharmaceutical compositions containing compounds of the formula (1) can be formulated in accordance with known techniques, see for example, Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA, USA.

- Suitable formulations typically contain 0-20% (w/w) buffers, 0-50% (w/w) cosolvents, and/or
35 0-99% (w/w) Water for Injection (WFI) (depending on dose and if freeze dried). Formulations for intramuscular depots may also contain 0-99% (w/w) oils.

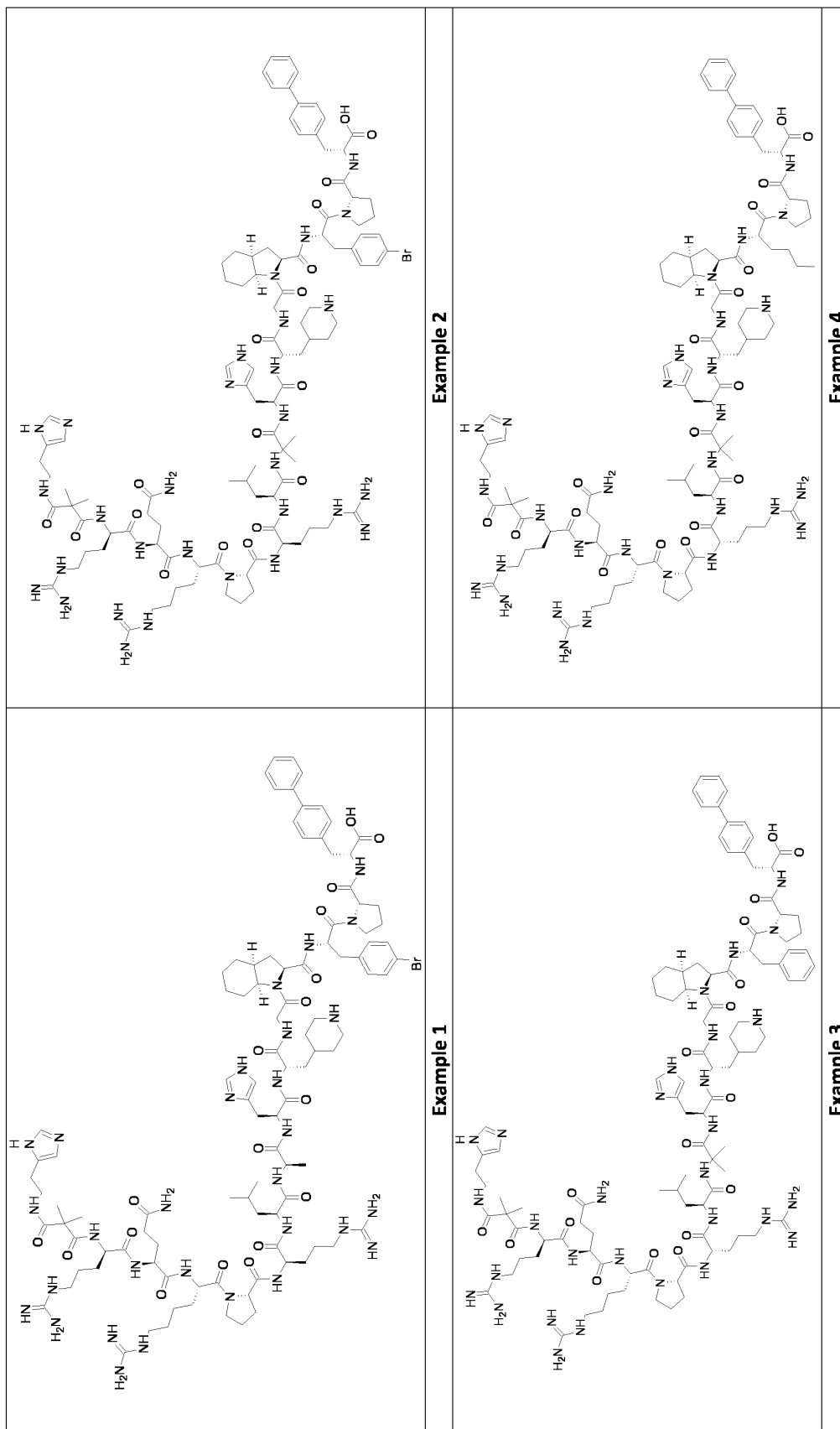
- The compounds of the formula (1) will generally be presented in unit dosage form and, as such, will typically contain sufficient compound to provide a desired level of biological activity. For example, a formulation may contain from 1 nanogram to 2 grams of active ingredient, e.g. from 1 nanogram to 2 milligrams of active ingredient. Within these ranges,
- 5 particular sub-ranges of compound are 0.1 milligrams to 2 grams of active ingredient (more usually from 10 milligrams to 1 gram, e.g. 50 milligrams to 500 milligrams), or 1 microgram to 20 milligrams (for example 1 microgram to 10 milligrams, e.g. 0.1 milligrams to 2 milligrams of active ingredient).
- 10 The active compound will be administered to a patient in need thereof (for example a human or animal patient) in an amount sufficient to achieve the desired therapeutic effect (effective amount). The precise amounts of compound administered may be determined by a supervising physician in accordance with standard procedures.

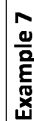
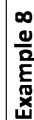
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EXAMPLES

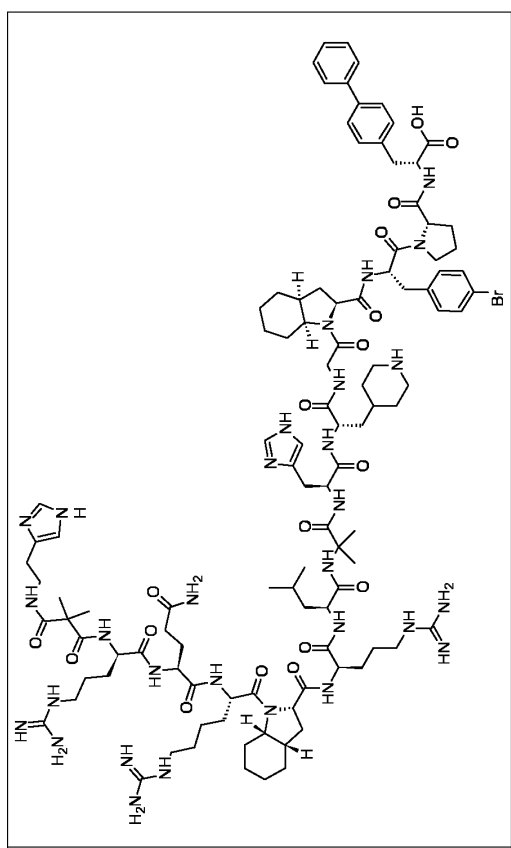
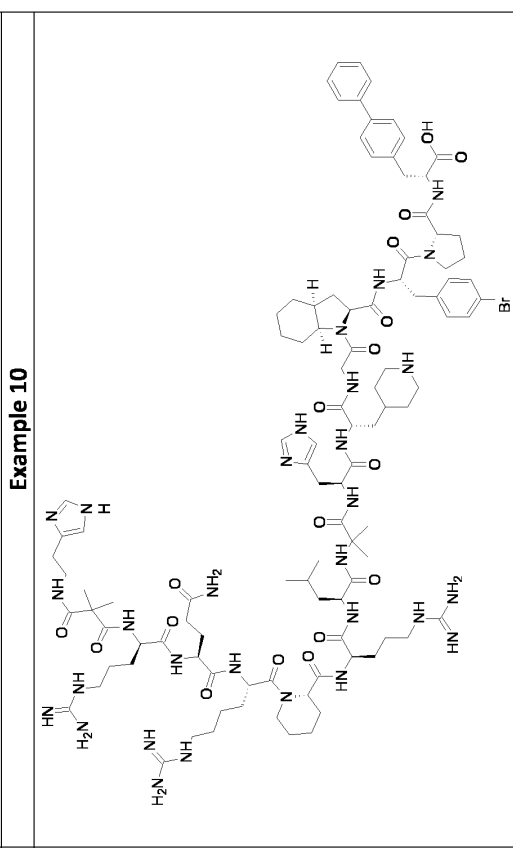
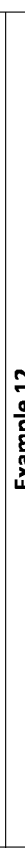
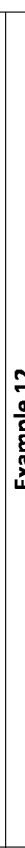
The invention will now be illustrated, but not limited, by reference to the specific embodiments described in the following examples.

EXAMPLES 1 TO 62



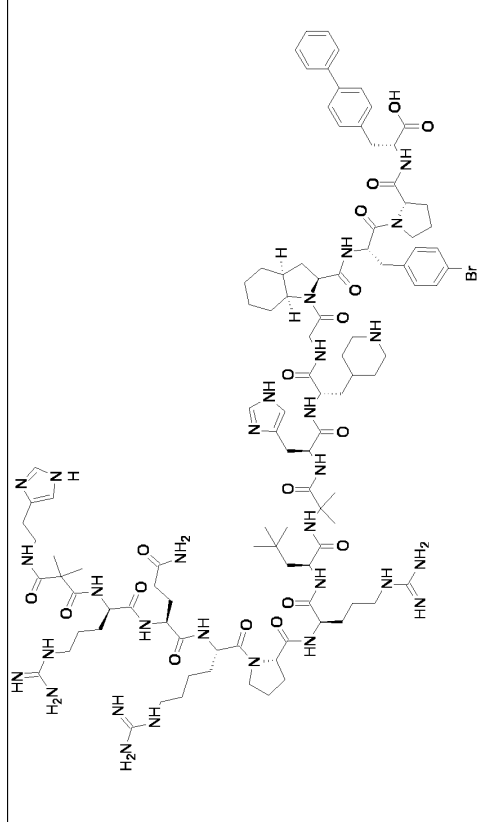
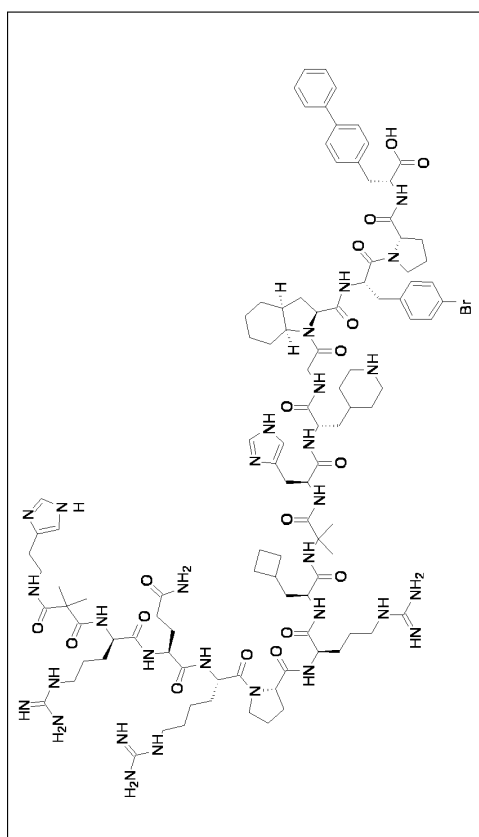
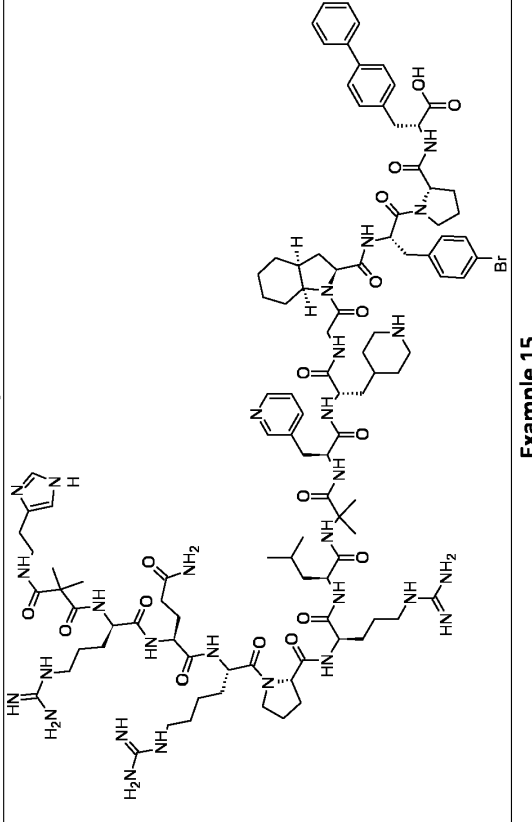
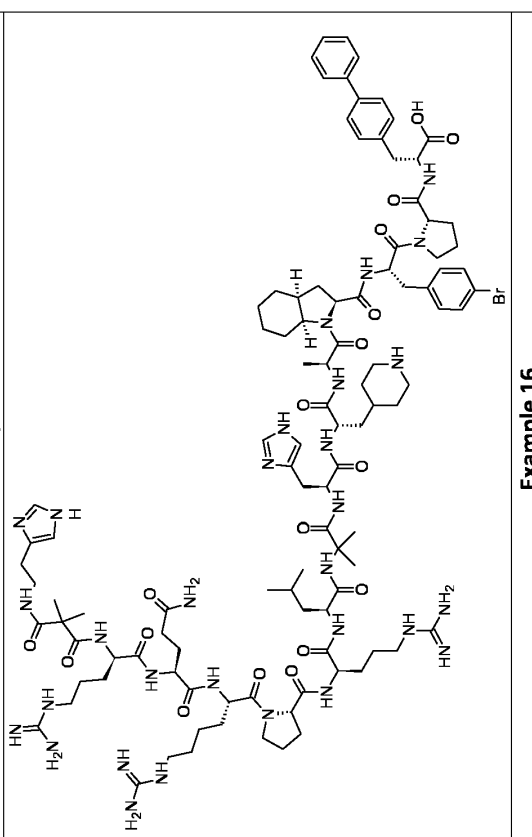


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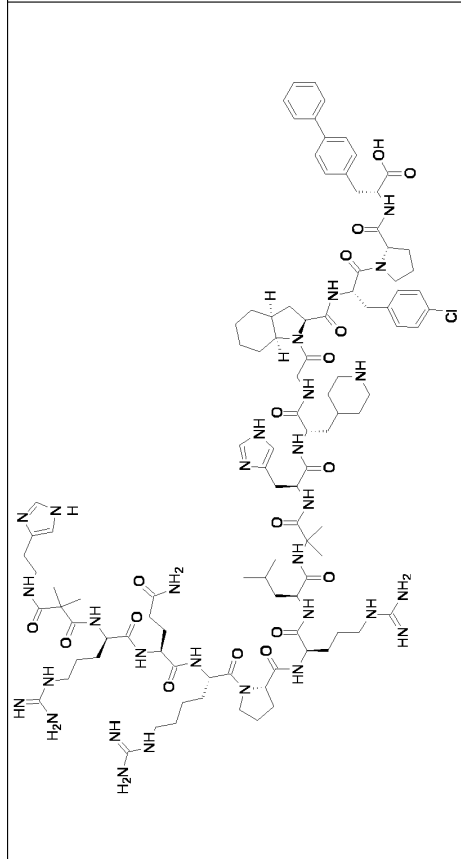
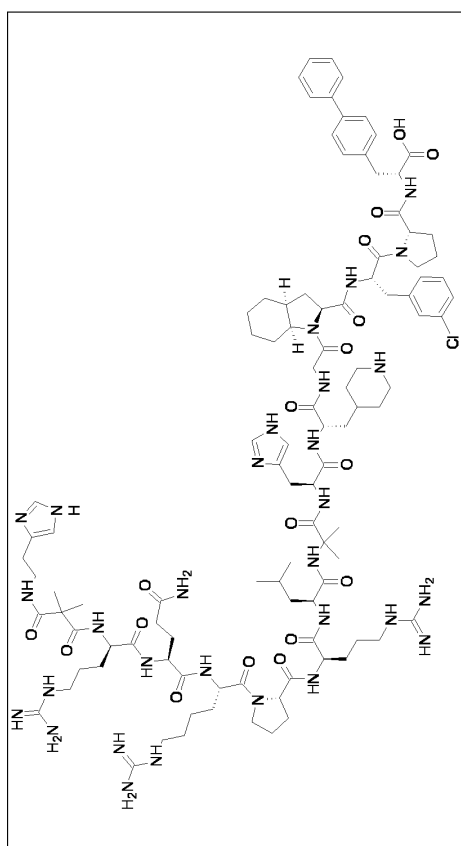
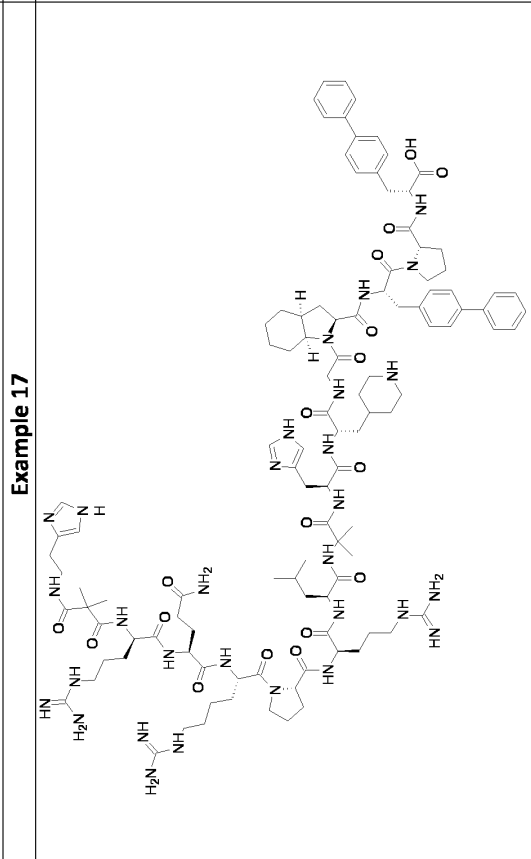
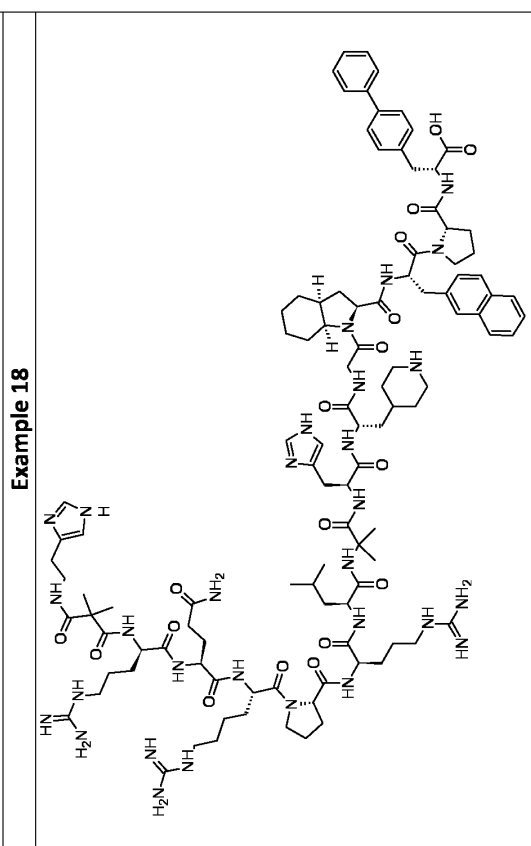
P30726WO1  Chemical structure of Example 9, a complex molecule featuring multiple amide linkages, a pyrazole ring, a bromophenyl group, and a carboxylic acid moiety.	Example 9
 Chemical structure of Example 10, a complex molecule featuring multiple amide linkages, a pyrazole ring, a bromophenyl group, and a carboxylic acid moiety.	Example 10
 Chemical structure of Example 11, a complex molecule featuring multiple amide linkages, a pyrazole ring, a bromophenyl group, and a carboxylic acid moiety.	Example 11
 Chemical structure of Example 12, a complex molecule featuring multiple amide linkages, a pyrazole ring, a bromophenyl group, and a carboxylic acid moiety.	Example 12

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P30726WO1

	
Example 13	Example 14
	
Example 15	Example 16

P30726WO1

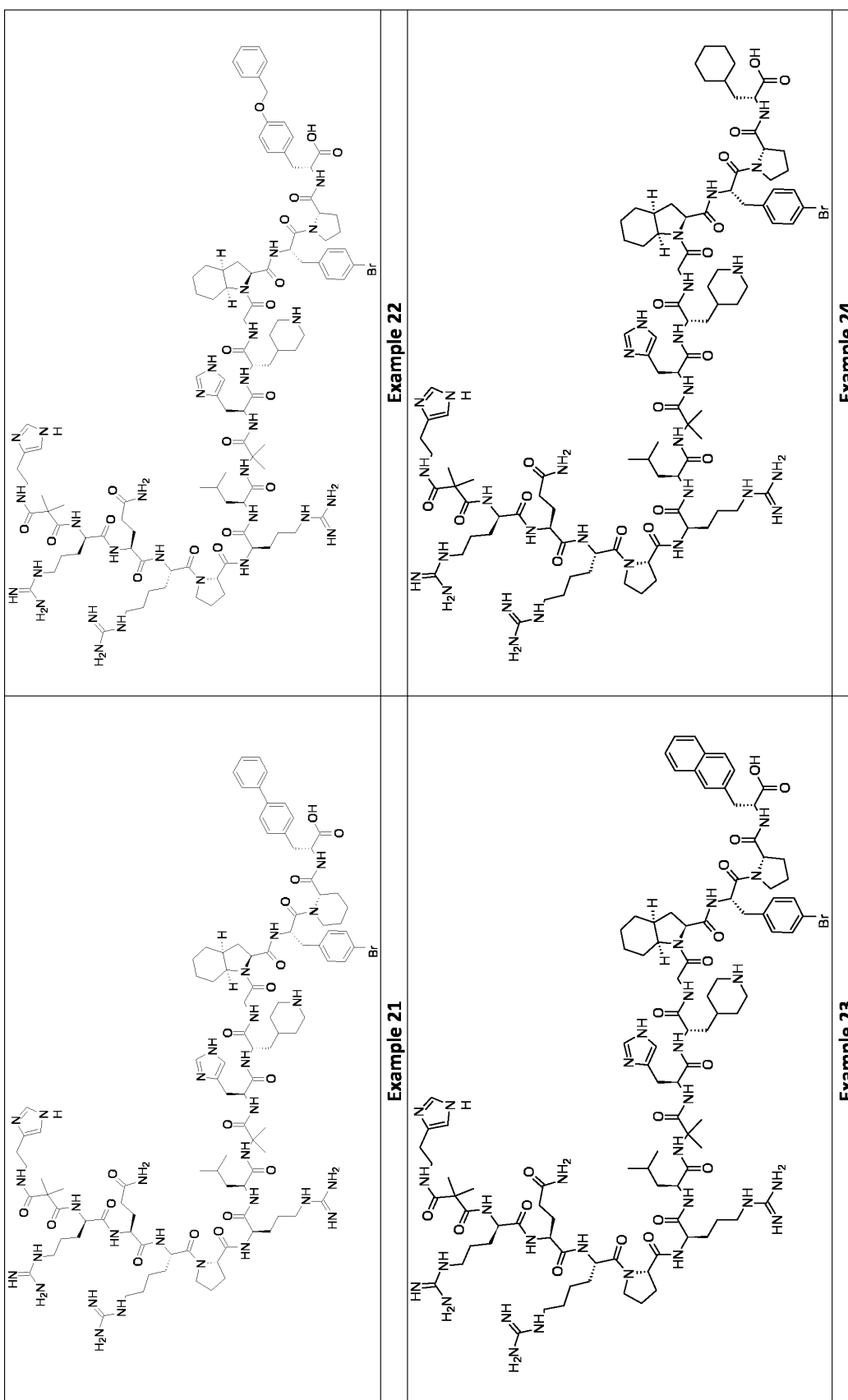
 Chemical structure of Example 17, a complex molecule featuring multiple amide bonds, a pyrazole ring, a cyclohexyl group, and a 4-chlorophenyl group.	 Chemical structure of Example 18, a complex molecule featuring multiple amide bonds, a pyrazole ring, a cyclohexyl group, and a 4-chlorophenyl group.
 Chemical structure of Example 19, a complex molecule featuring multiple amide bonds, a pyrazole ring, a cyclohexyl group, and a 4-chlorophenyl group.	 Chemical structure of Example 20, a complex molecule featuring multiple amide bonds, a pyrazole ring, a cyclohexyl group, and a 4-chlorophenyl group.

Example 18

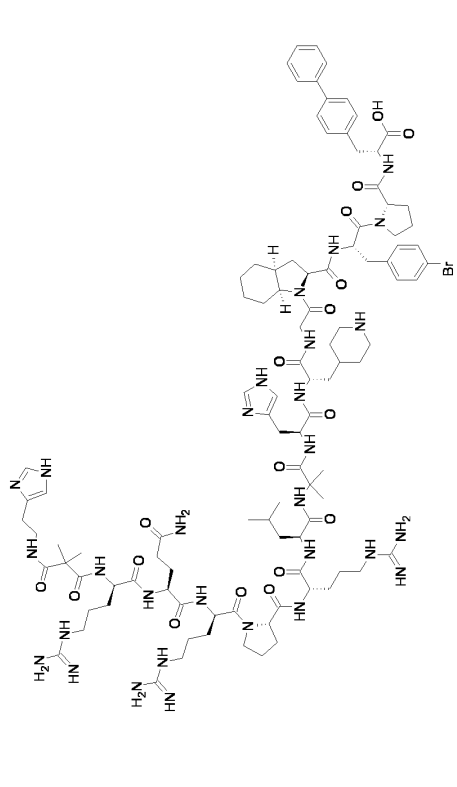
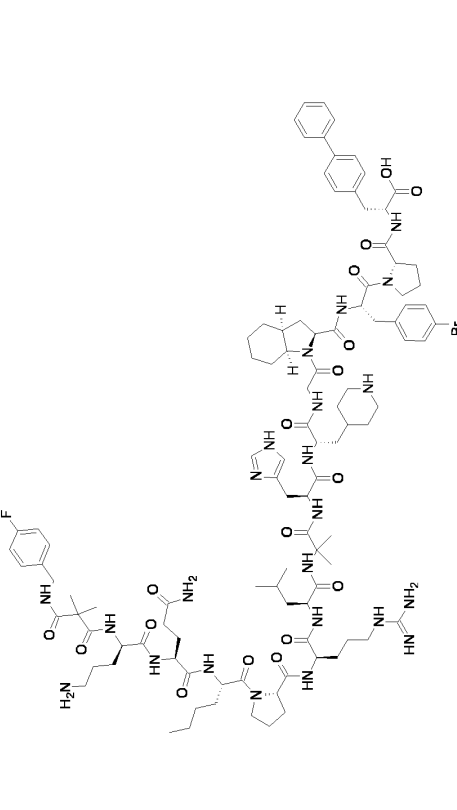
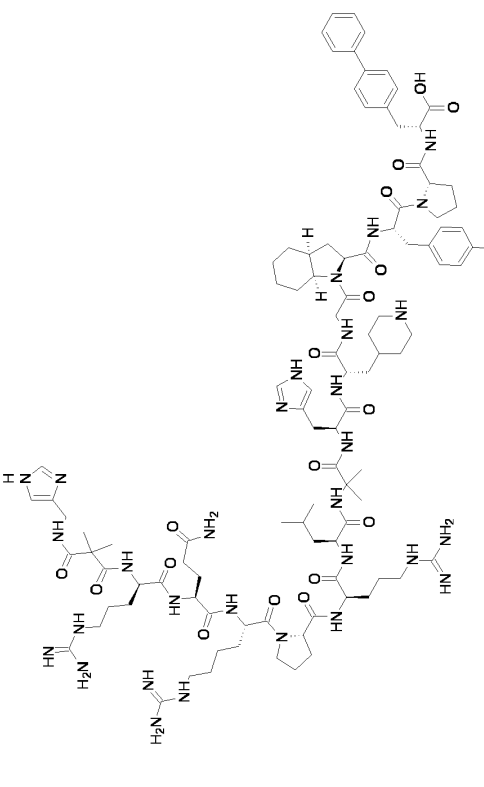
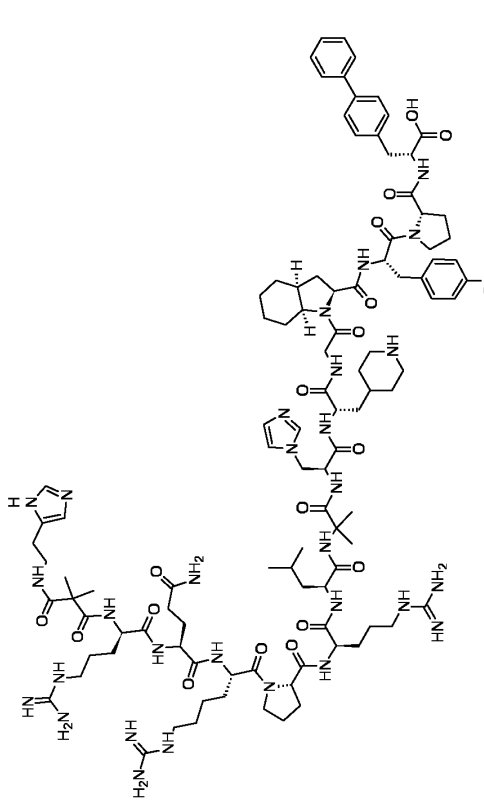
Example 17

Example 20

Example 19

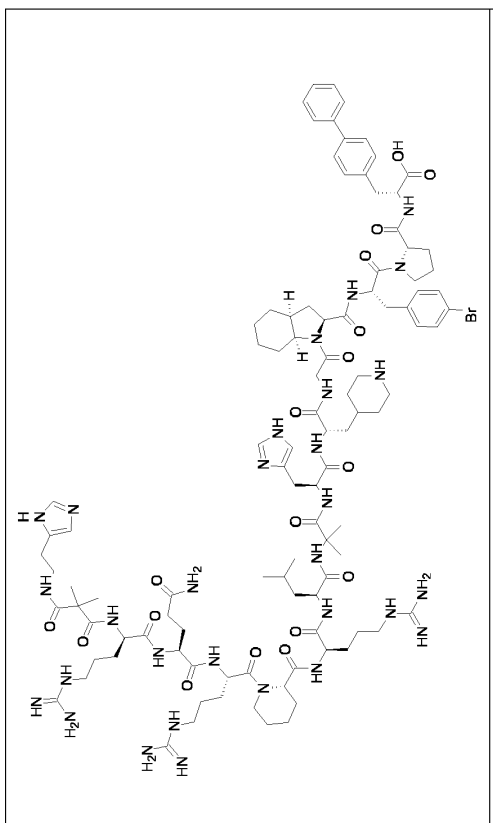
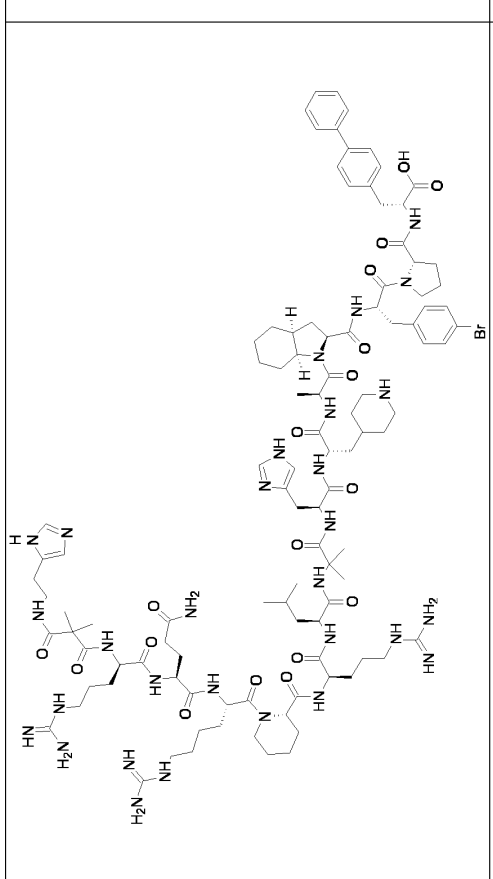
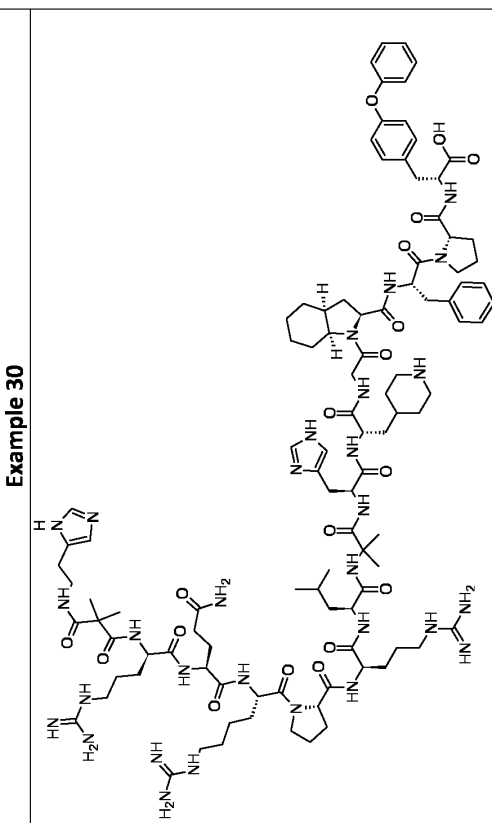
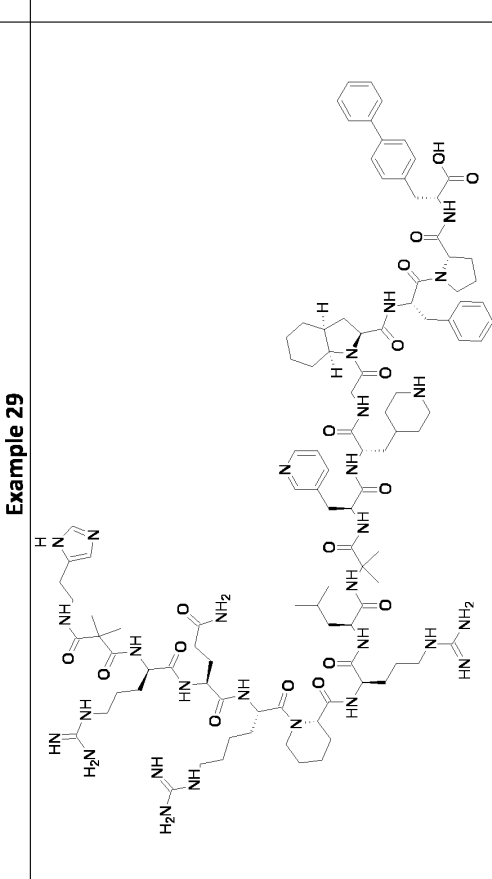


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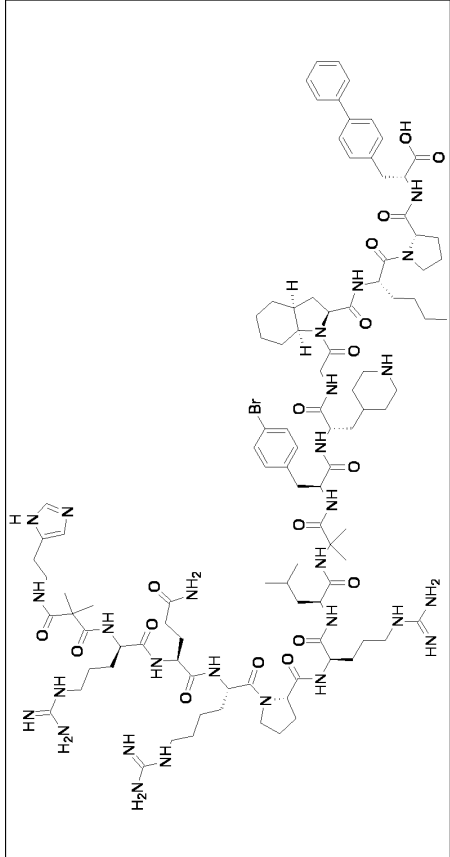
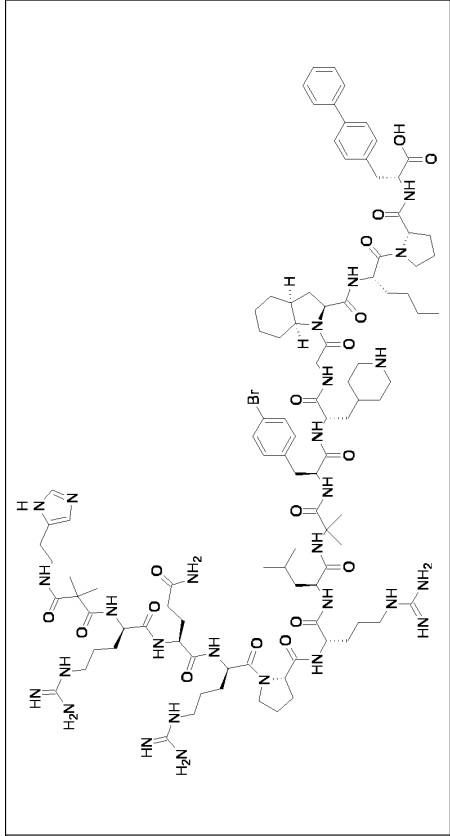
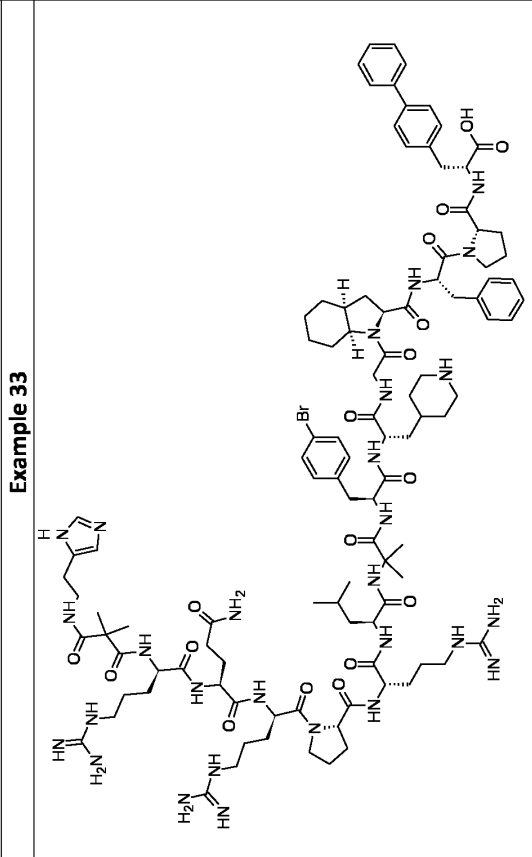
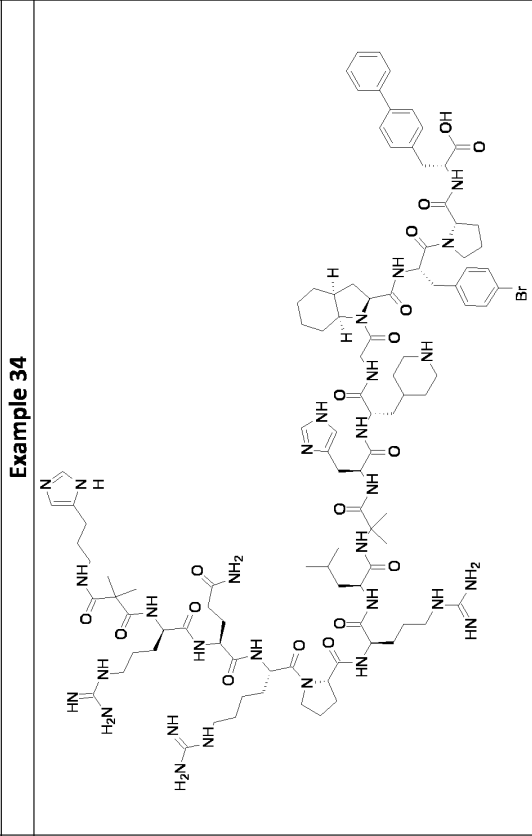
P30726WO1  Chemical structure of Example 25, a complex molecule featuring multiple amide, urea, and imine linkages, along with various functional groups including a fluorophenyl group, a bromophenyl group, and a hydroxybenzoyl group.	Example 25
 Chemical structure of Example 26, a complex molecule featuring multiple amide, urea, and imine linkages, along with various functional groups including a fluorophenyl group, a bromophenyl group, and a hydroxybenzoyl group.	Example 26
 Chemical structure of Example 27, a complex molecule featuring multiple amide, urea, and imine linkages, along with various functional groups including a fluorophenyl group, a bromophenyl group, and a hydroxybenzoyl group.	Example 27
 Chemical structure of Example 28, a complex molecule featuring multiple amide, urea, and imine linkages, along with various functional groups including a fluorophenyl group, a bromophenyl group, and a hydroxybenzoyl group.	Example 28

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P30726WO1

 Chemical structure of Example 29, a complex molecule featuring multiple amide, urea, and imine linkages, a bromophenyl group, and a 4-phenylphenyl group.	 Chemical structure of Example 30, a complex molecule featuring multiple amide, urea, and imine linkages, a bromophenyl group, and a 4-phenylphenyl group.
Example 29	Example 30
 Chemical structure of Example 31, a complex molecule featuring multiple amide, urea, and imine linkages, a bromophenyl group, and a 4-phenylphenyl group.	 Chemical structure of Example 32, a complex molecule featuring multiple amide, urea, and imine linkages, a bromophenyl group, and a 4-phenylphenyl group.
Example 31	Example 32

P30726WO1

 Chemical structure of Example 33, a complex molecule featuring multiple amide linkages, a bromophenyl group, a pyrazole ring, and a hydroxybenzoic acid derivative.	 Chemical structure of Example 34, a complex molecule featuring multiple amide linkages, a bromophenyl group, a pyrazole ring, and a hydroxybenzoic acid derivative.
 Chemical structure of Example 35, a complex molecule featuring multiple amide linkages, a bromophenyl group, a pyrazole ring, and a hydroxybenzoic acid derivative.	 Chemical structure of Example 36, a complex molecule featuring multiple amide linkages, a bromophenyl group, a pyrazole ring, and a hydroxybenzoic acid derivative.

Example 34

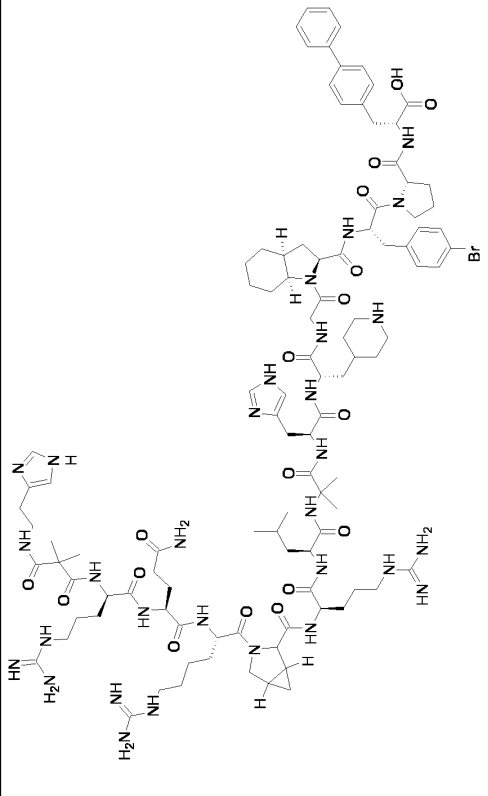
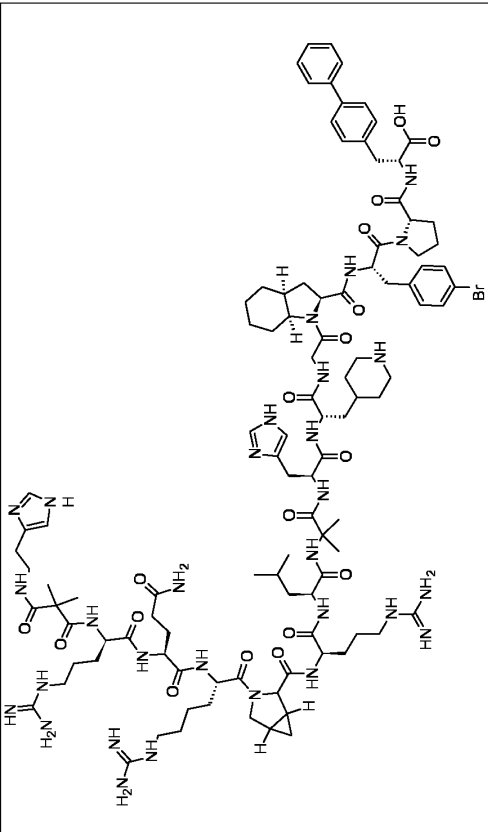
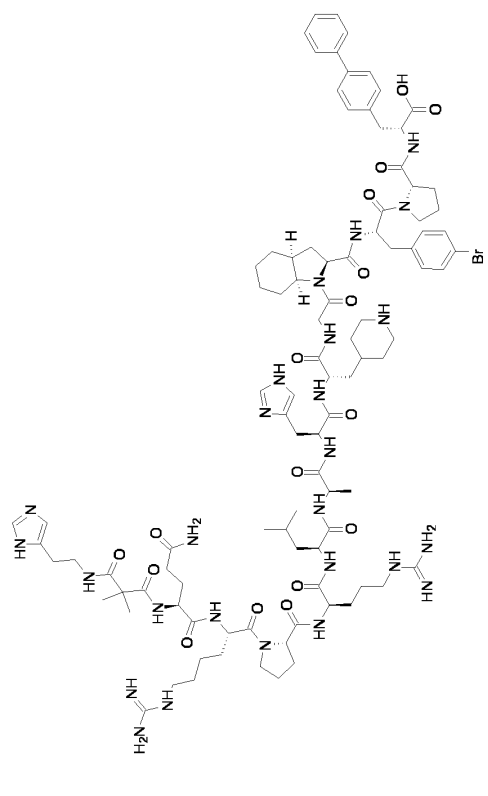
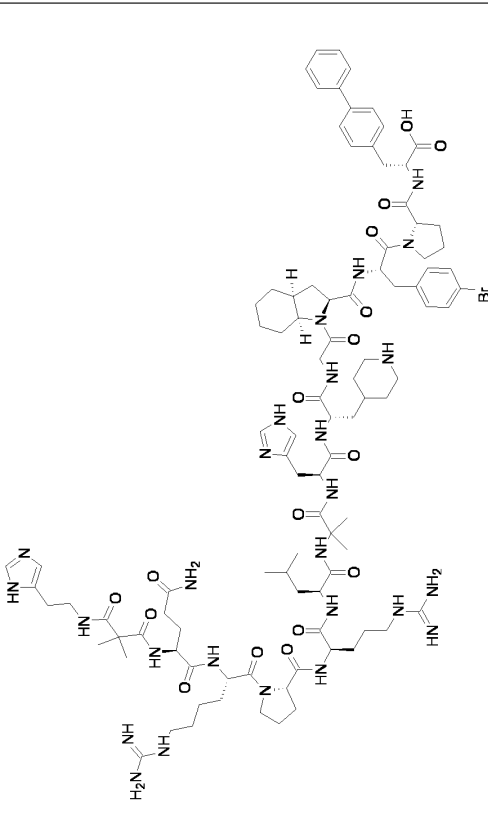
Example 33

Example 36

Example 35

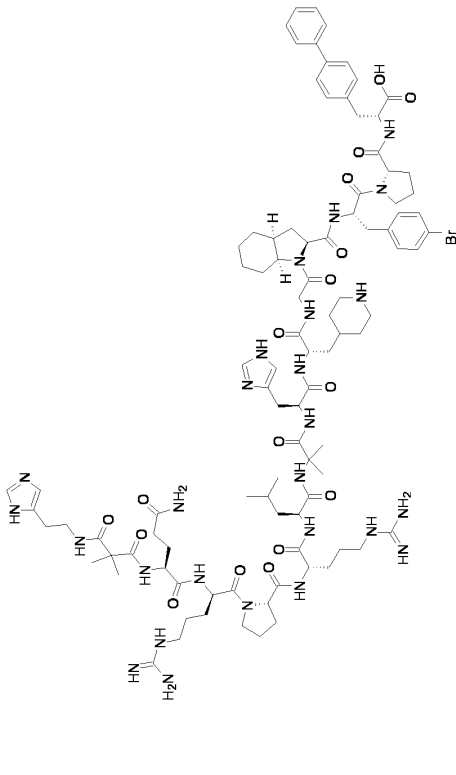
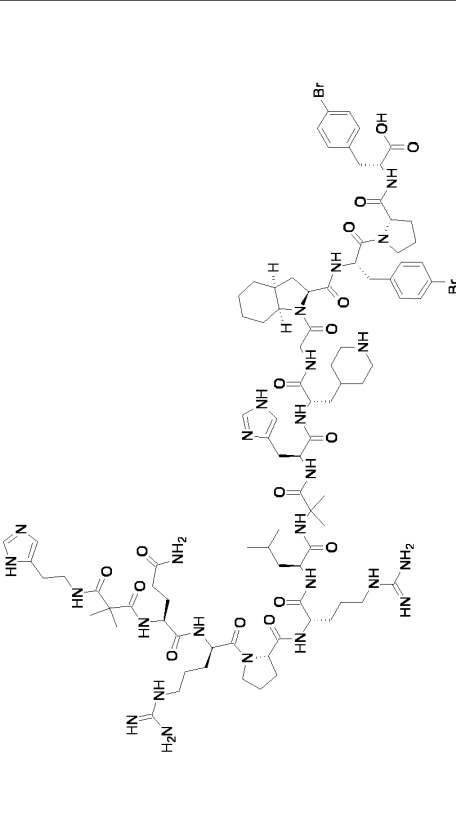
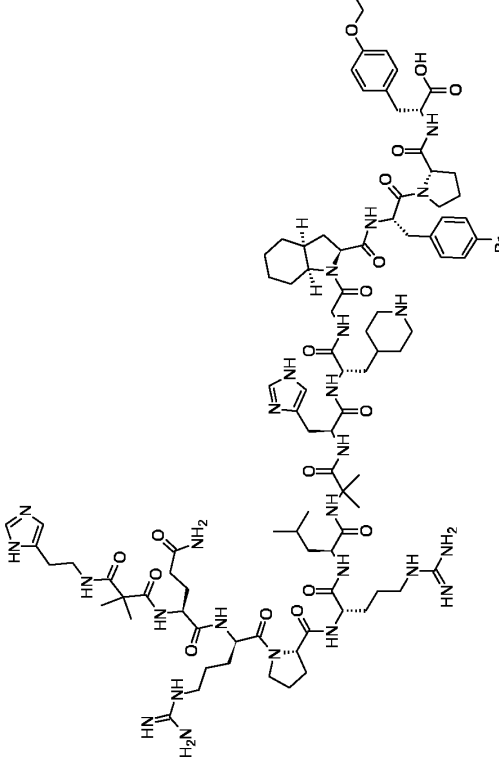
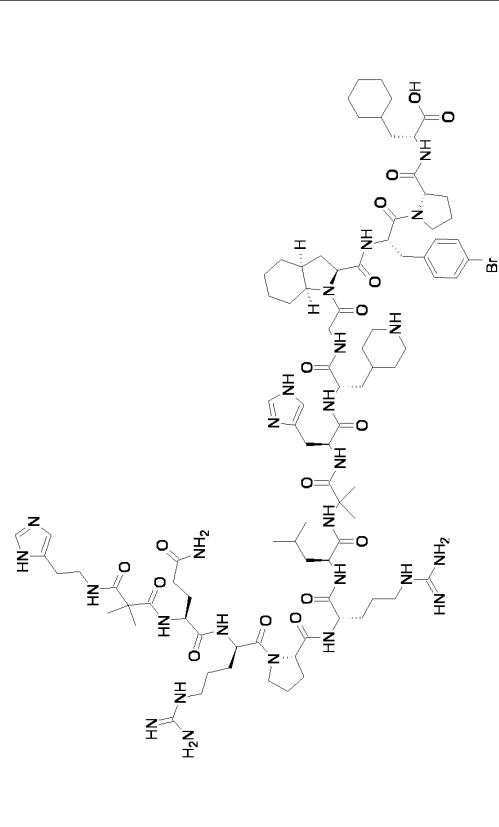
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P30726WO1

 Chemical structure of Example 37 isomer 1, a complex molecule featuring multiple amide, urea, and imine linkages, a bromophenyl group, and a 4-phenylphenyl group.	 Chemical structure of Example 37 isomer 2, a complex molecule featuring multiple amide, urea, and imine linkages, a bromophenyl group, and a 4-phenylphenyl group.
Example 37 isomer 1	Example 37 isomer 2
 Chemical structure of Example 38, a complex molecule featuring multiple amide, urea, and imine linkages, a bromophenyl group, and a 4-phenylphenyl group.	 Chemical structure of Example 39, a complex molecule featuring multiple amide, urea, and imine linkages, a bromophenyl group, and a 4-phenylphenyl group.
Example 38	Example 39

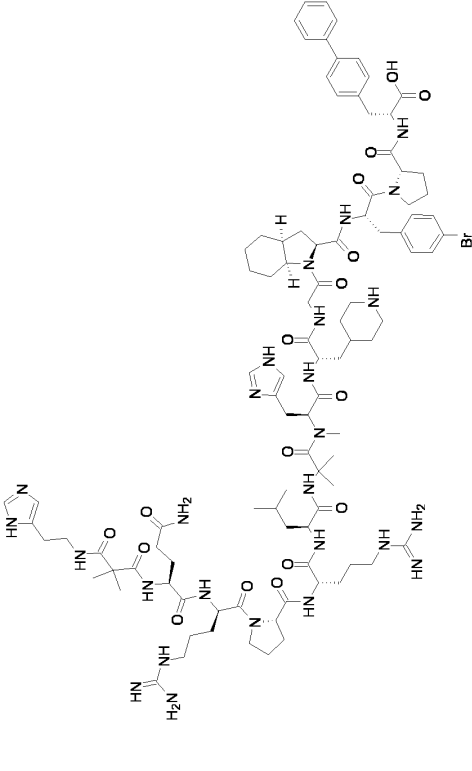
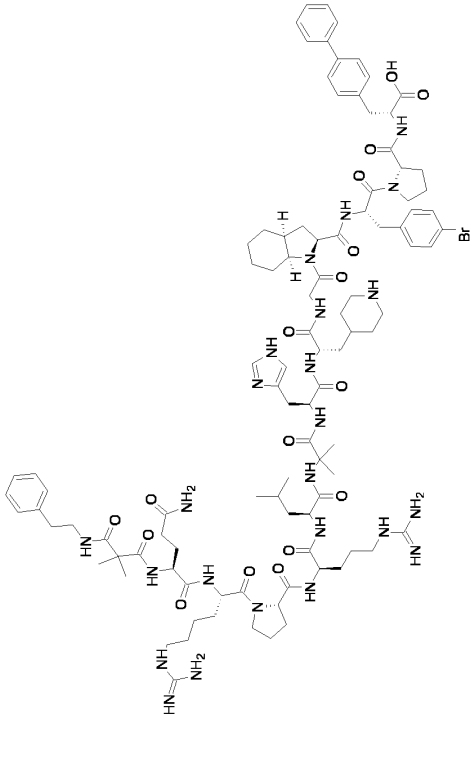
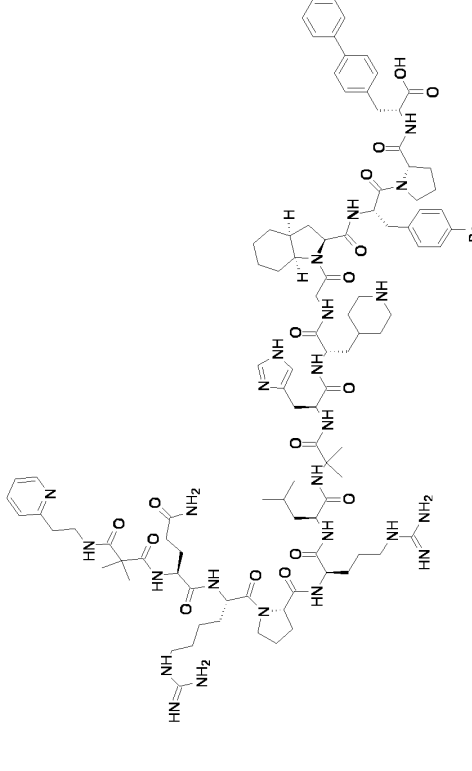
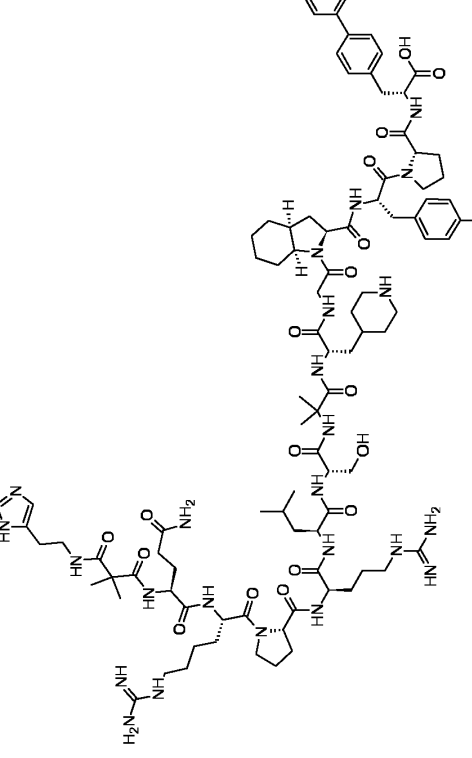
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P30726WO1

	
Example 40	Example 41
	
Example 42	Example 43

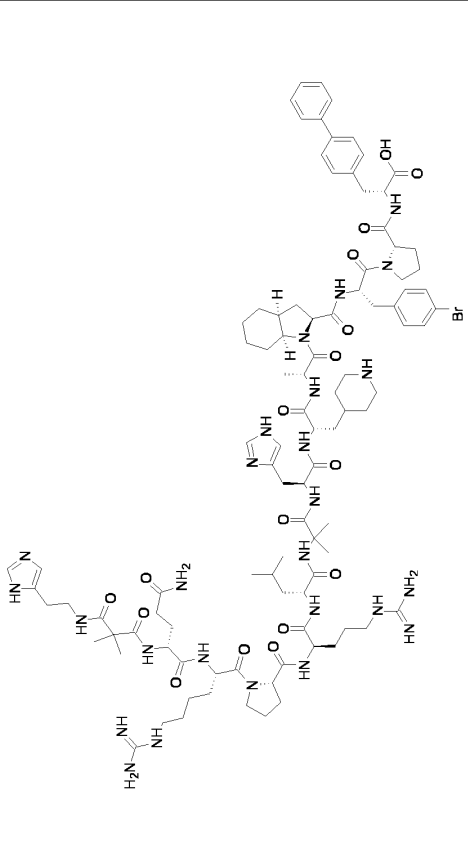
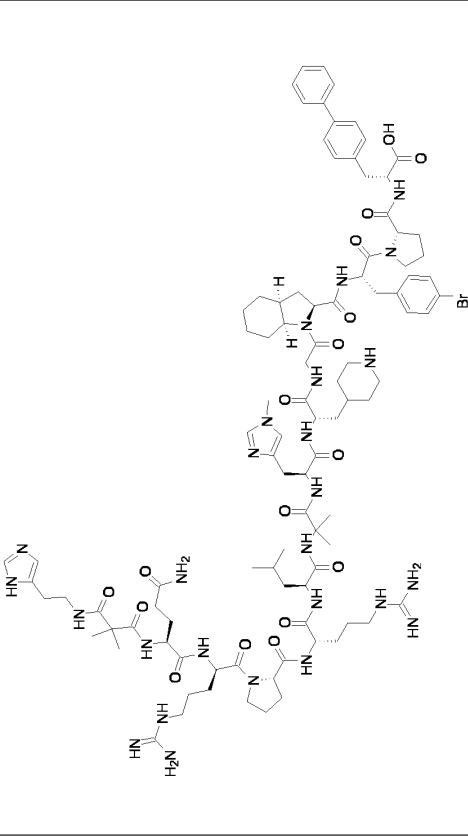
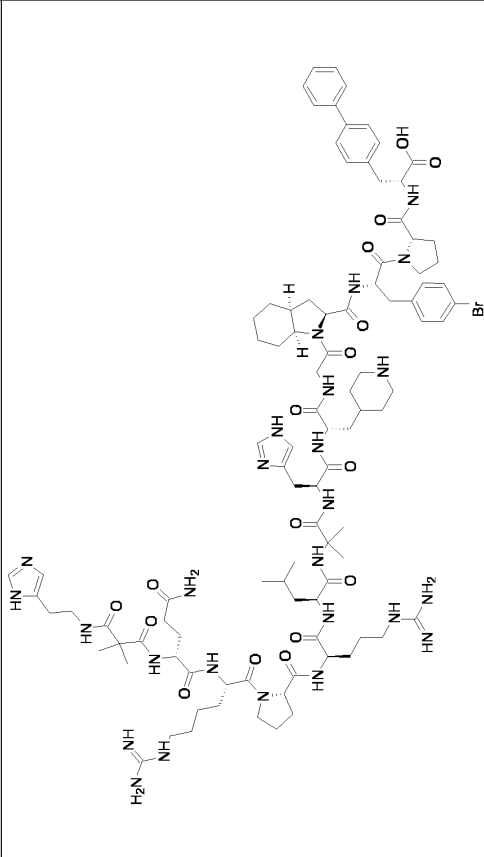
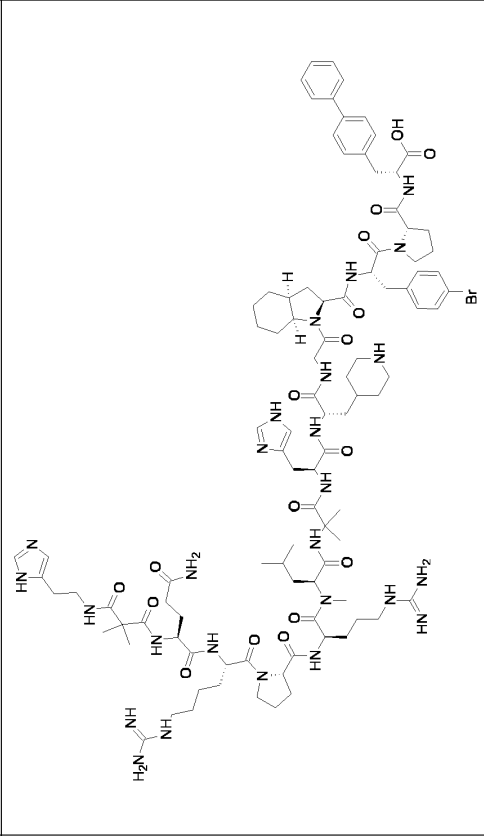
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P30726WO1

 Chemical structure of Example 44, a complex molecule featuring multiple amide, urea, and hydroxamic acid linkages, along with various side chains including a bromophenyl group and a 4-phenylbutanoic acid derivative.	 Chemical structure of Example 45, a complex molecule featuring multiple amide, urea, and hydroxamic acid linkages, along with various side chains including a bromophenyl group and a 4-phenylbutanoic acid derivative.
Example 44	Example 45
 Chemical structure of Example 46, a complex molecule featuring multiple amide, urea, and hydroxamic acid linkages, along with various side chains including a bromophenyl group and a 4-phenylbutanoic acid derivative.	 Chemical structure of Example 47, a complex molecule featuring multiple amide, urea, and hydroxamic acid linkages, along with various side chains including a bromophenyl group and a 4-phenylbutanoic acid derivative.
Example 46	Example 47

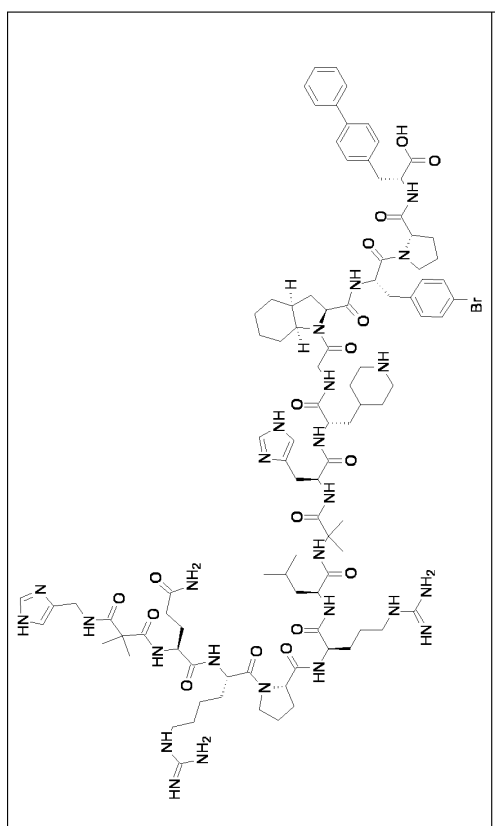
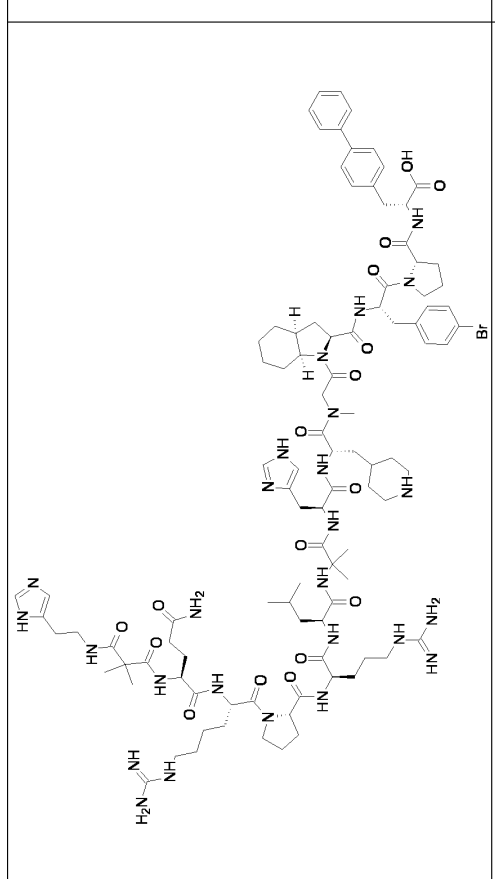
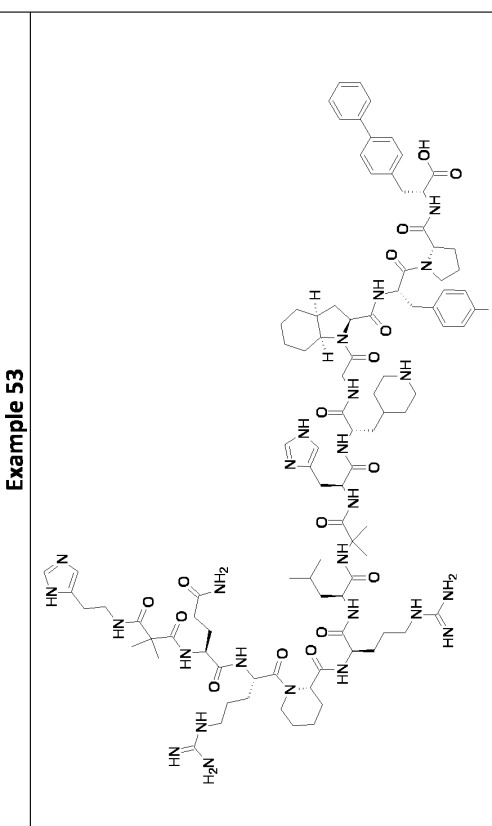
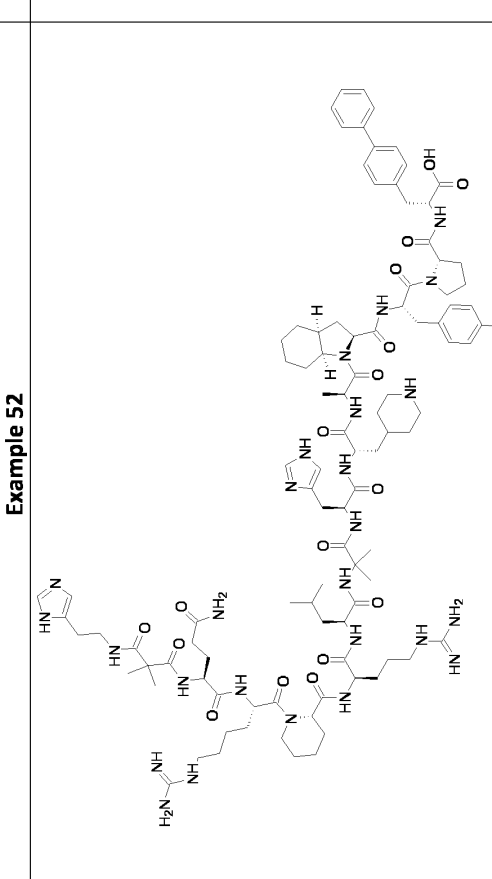
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 Chemical structure of Example 48, a complex molecule featuring multiple amide, urea, and imine linkages, a bromophenyl group, and a biphenyl-3-carboxylic acid moiety.	 Chemical structure of Example 49, a complex molecule featuring multiple amide, urea, and imine linkages, a bromophenyl group, and a biphenyl-3-carboxylic acid moiety.
Example 48	Example 49
 Chemical structure of Example 50, a complex molecule featuring multiple amide, urea, and imine linkages, a bromophenyl group, and a biphenyl-3-carboxylic acid moiety.	 Chemical structure of Example 51, a complex molecule featuring multiple amide, urea, and imine linkages, a bromophenyl group, and a biphenyl-3-carboxylic acid moiety.
Example 50	Example 51

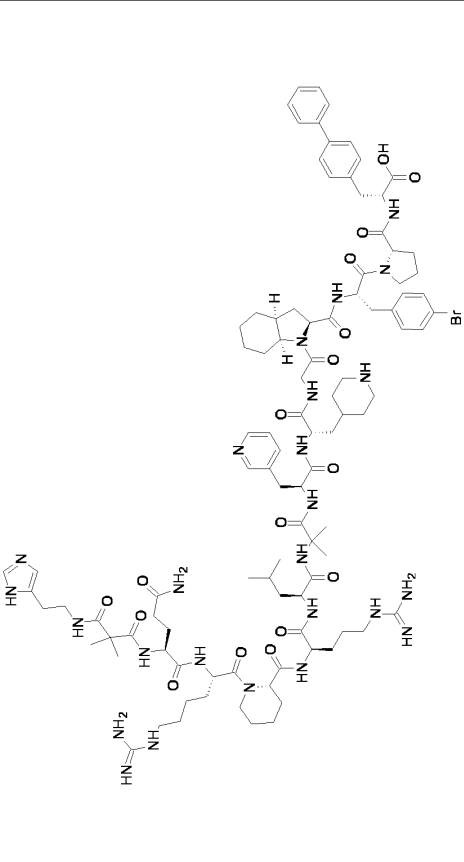
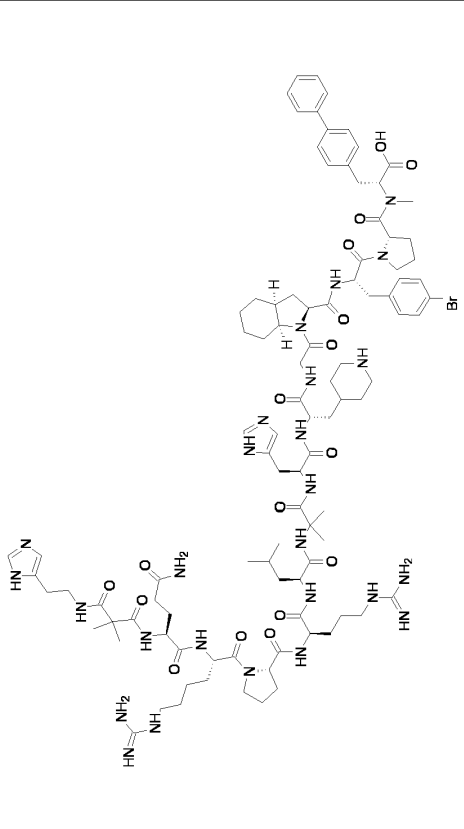
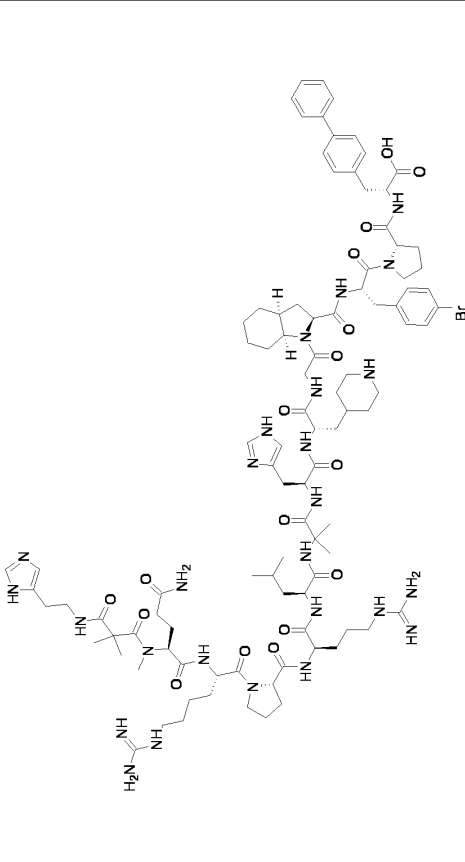
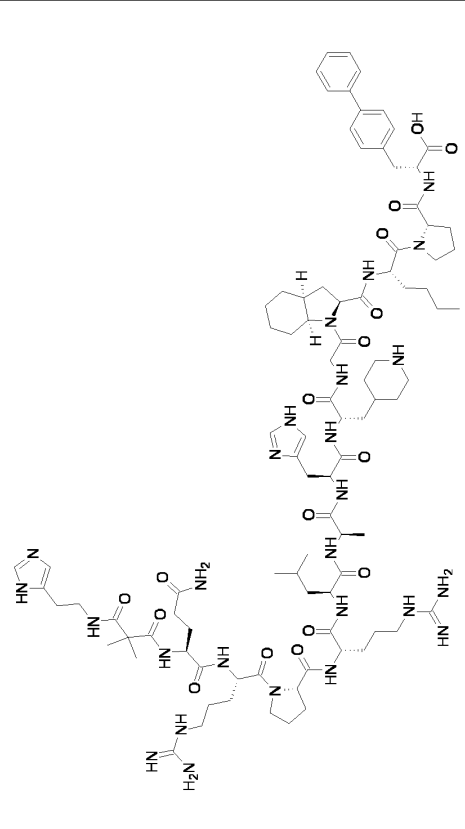
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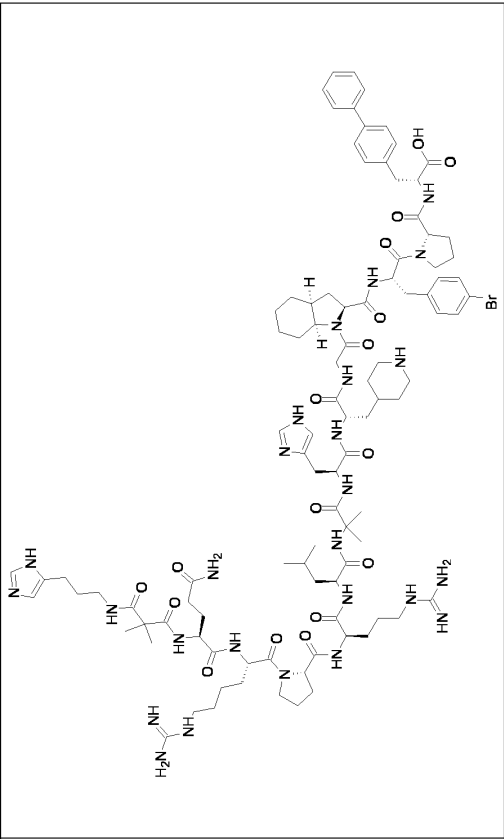
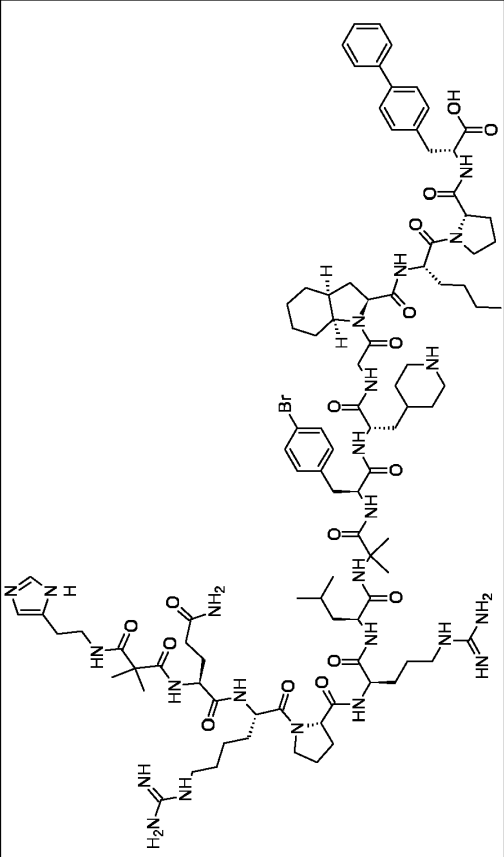
	
Example 52	Example 53
	
Example 54	Example 55

34

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 Chemical structure of Example 56: A complex molecule featuring a central core with multiple amide and urea linkages. It includes a pyridine ring, a bromophenyl group, and a 4-phenyl-4-oxobutanoic acid moiety.	 Chemical structure of Example 57: A complex molecule featuring a central core with multiple amide and urea linkages. It includes a pyridine ring, a bromophenyl group, and a 4-phenyl-4-oxobutanoic acid moiety.
Example 56	Example 57
 Chemical structure of Example 58: A complex molecule featuring a central core with multiple amide and urea linkages. It includes a pyridine ring, a bromophenyl group, and a 4-phenyl-4-oxobutanoic acid moiety.	 Chemical structure of Example 59: A complex molecule featuring a central core with multiple amide and urea linkages. It includes a pyridine ring, a bromophenyl group, and a 4-phenyl-4-oxobutanoic acid moiety.
Example 58	Example 59

35

P30726WO1  Chemical structure of Example 60: A complex molecule featuring a central core with multiple amide and ester linkages. It includes a pyrazole ring, a bromophenyl group, a cyclohexyl group, and a 4-phenylbutanoic acid moiety. Stereochemistry is indicated with wedges and dashes.	Example 60
 Chemical structure of Example 61: A complex molecule featuring a central core with multiple amide and ester linkages. It includes a pyrazole ring, a bromophenyl group, a cyclohexyl group, and a 4-phenylbutanoic acid moiety. Stereochemistry is indicated with wedges and dashes.	Example 61
	Example 62

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The compounds of Examples 1 to 62 shown in Table 1 below have been prepared. Their LCMS properties and the methods used to prepare them are set out in Table 2. The starting materials for each of the Examples are commercial unless indicated otherwise.

5

Table 1

	Q	X	AA1	AA2	AA3	AA4	AA5	AA6	AA7	AA8	AA9	AA10	AA11	AA12	AA13	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Example 1	CAP 5	D-ARG	GLN	homoARG	PRO	D-ARG	LEU	D-ALA	HIS	PipALA	GLY	OIC	4-BrPHE	PRO	D-BIP	OH
Example 2	CAP 5	D-ARG	GLN	homoARG	PRO	D-ARG	LEU	AIB	HIS	PipALA	GLY	OIC	4-BrPHE	PRO	D-BIP	OH
Example 3	CAP 5	D-ARG	GLN	D-ARG	PRO	ARG	LEU	AIB	HIS	PipALA	GLY	OIC	PHE	PRO	D-BIP	OH
Example 4	CAP 5	D-ARG	GLN	D-ARG	PRO	ARG	LEU	AIB	HIS	PipALA	GLY	OIC	NorLEU	PRO	D-BIP	OH
Example 5	CAP 2	D-ARG	GLN	homoARG	PRO	D-ARG	LEU	AIB	HIS	PipALA	GLY	OIC	4-BrPHE	PRO	D-BIP	OH
Example 6	CAP 3	D-ARG	GLN	homoARG	PRO	D-ARG	LEU	AIB	HIS	PipALA	GLY	OIC	4-BrPHE	PRO	D-BIP	OH
Example 7	CAP 7	D-ARG	GLN	homoARG	PRO	D-ARG	LEU	AIB	HIS	PipALA	GLY	OIC	4-BrPHE	PRO	D-BIP	OH
Example 8	CAP 5	D-ARG	homophE	homoARG	PRO	D-ARG	LEU	AIB	HIS	PipALA	GLY	OIC	4-BrPHE	PRO	D-BIP	OH
Example 9	CAP 5	D-ARG	GLN	ARG	PRO	D-ARG	LEU	AIB	HIS	PipALA	GLY	OIC	4-BrPHE	PRO	D-BIP	OH
Example 10	CAP 5	D-ARG	GLN	homoARG	OIC	D-ARG	LEU	AIB	HIS	PipALA	GLY	OIC	4-BrPHE	PRO	D-BIP	OH
Example 11	CAP 5	D-ARG	GLN	homoARG	Oxa	D-ARG	LEU	AIB	HIS	PipALA	GLY	OIC	4-BrPHE	PRO	D-BIP	OH
Example 12	CAP 5	D-ARG	GLN	homoARG	homopRO	D-ARG	LEU	AIB	HIS	PipALA	GLY	OIC	4-BrPHE	PRO	D-BIP	OH
Example 13	CAP 5	D-ARG	GLN	homoARG	PRO	D-ARG	tBuALA	AIB	HIS	PipALA	GLY	OIC	4-BrPHE	PRO	D-BIP	OH

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Example 14	CAP 5	D-ARG	GLN	homoARG	PRO	D-ARG	cycloBu ALA	AIB	HIS	PipALA	GLY	OIC	4- BrPHE	PRO	D-BIP	OH
Example 15	CAP 5	D-ARG	GLN	homoARG	PRO	D-ARG	LEU	AIB	3-PAL	PipALA	GLY	OIC	4- BrPHE	PRO	D-BIP	OH
Example 16	CAP 5	D-ARG	GLN	homoARG	PRO	D-ARG	LEU	AIB	HIS	PipALA	ALA	OIC	4- BrPHE	PRO	D-BIP	OH
Example 17	CAP 5	D-ARG	GLN	homoARG	PRO	D-ARG	LEU	AIB	HIS	PipALA	GLY	OIC	4-Cl- PHE	PRO	D-BIP	OH
Example 18	CAP 5	D-ARG	GLN	homoARG	PRO	D-ARG	LEU	AIB	HIS	PipALA	GLY	OIC	3-Cl- PHE	PRO	D-BIP	OH
Example 19	CAP 5	D-ARG	GLN	homoARG	PRO	D-ARG	LEU	AIB	HIS	PipALA	GLY	OIC	BIP	PRO	D-BIP	OH
Example 20	CAP 5	D-ARG	GLN	homoARG	PRO	D-ARG	LEU	AIB	HIS	PipALA	GLY	OIC	2-Nal	PRO	D-BIP	OH
Example 21	CAP 5	D-ARG	GLN	homoARG	PRO	D-ARG	LEU	AIB	HIS	PipALA	GLY	OIC	4- BrPHE	homo PRO	D-BIP	OH
Example 22	CAP 5	D-ARG	GLN	homoARG	PRO	D-ARG	LEU	AIB	HIS	PipALA	GLY	OIC	4- BrPHE	PRO	D-(4- Bn)TYR	OH
Example 23	CAP 5	D-ARG	GLN	homoARG	PRO	D-ARG	LEU	AIB	HIS	PipALA	GLY	OIC	4- BrPHE	PRO	D-2-Nal	OH
Example 24	CAP 5	D-ARG	GLN	homoARG	PRO	D-ARG	LEU	AIB	HIS	PipALA	GLY	OIC	4- BrPHE	PRO	D-CHA	OH
Example 25	CAP 5	D-ARG	GLN	D-ARG	PRO	ARG	LEU	AIB	HIS	PipALA	GLY	OIC	4- BrPHE	PRO	D-BIP	OH
Example 26	CAP 1	D-ARG	GLN	homoARG	PRO	D-ARG	LEU	AIB	HIS	PipALA	GLY	OIC	4- BrPHE	PRO	D-BIP	OH
Example 27	CAP 4	D-ARG	GLN	homoARG	PRO	D-ARG	LEU	AIB	HIS	PipALA	GLY	OIC	4- BrPHE	PRO	D-BIP	OH
Example 28	CAP 5	D-ARG	GLN	homoARG	PRO	D-ARG	LEU	AIB	beta- imidazol yl-L-Ala	PipALA	GLY	OIC	4- BrPHE	PRO	D-BIP	OH
Example 29	CAP 5	D-ARG	GLN	homoARG	homoPR O	D-ARG	LEU	AIB	HIS	PipALA	ALA	OIC	4- BrPHE	PRO	D-BIP	OH
Example 30	CAP 5	D-ARG	GLN	ARG	homoPR O	D-ARG	LEU	AIB	HIS	PipALA	GLY	OIC	4- BrPHE	PRO	D-BIP	OH
Example 31	CAP 5	D-ARG	GLN	homoARG	homoPR O	D-ARG	LEU	AIB	3-PAL	PipALA	GLY	OIC	4- BrPHE	PRO	D-BIP	OH
Example 32	CAP 5	D-ARG	GLN	homoARG	PRO	D-ARG	LEU	AIB	HIS	PipALA	GLY	OIC	4- BrPHE	PRO	D-(4- Oph)PH E	OH

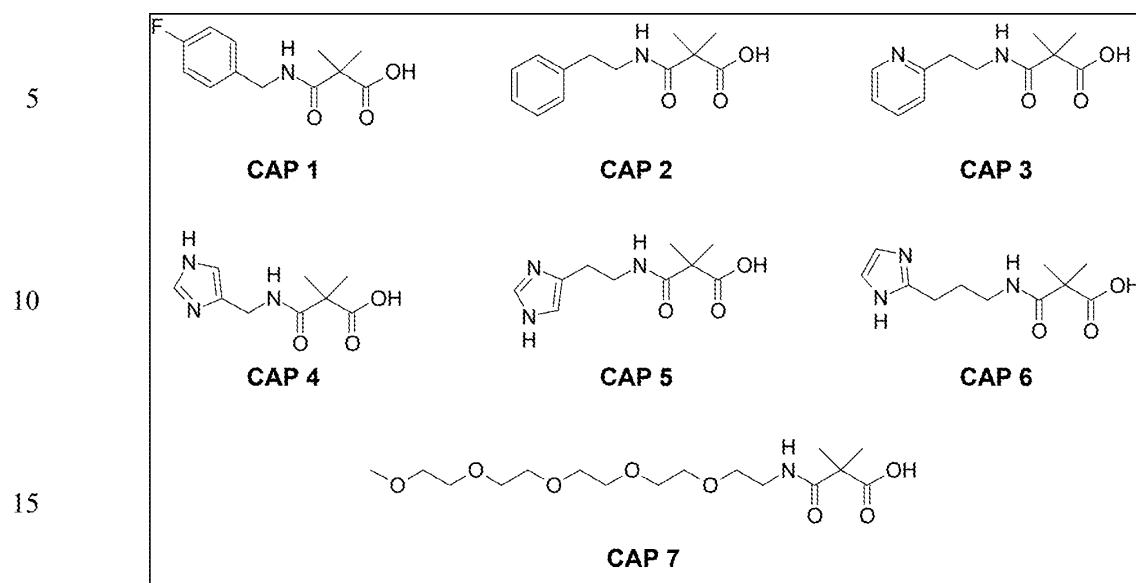
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Example 33	CAP 5	D-ARG	GLN	homoARG	PRO	D-ARG	LEU	AIB	4-BrPHE	PipALA	GLY	OIC	NorLEU	PRO	D-BIP	OH
Example 34	CAP 5	D-ARG	GLN	D-ARG	PRO	ARG	LEU	AIB	4-BrPHE	PipALA	GLY	OIC	NorLEU	PRO	D-BIP	OH
Example 35	CAP 5	D-ARG	GLN	D-ARG	PRO	ARG	LEU	AIB	4-BrPHE	PipALA	GLY	OIC	PHE	PRO	D-BIP	OH
Example 36	CAP 6	D-ARG	GLN	homoARG	PRO	D-ARG	LEU	AIB	HIS	PipALA	GLY	OIC	4-BrPHE	PRO	D-BIP	OH
Example 37 isomer 1	CAP 5	D-ARG	GLN	HomoARG	cis-methanoproline	D-ARG	LEU	AIB	HIS	PipALA	GLY	OIC	4-BrPHE	PRO	D-BIP	OH
Example 37 isomer 2	CAP 5	D-ARG	GLN	HomoARG	cis-methanoproline	D-ARG	LEU	AIB	HIS	PipALA	GLY	OIC	4-BrPHE	PRO	D-BIP	OH
Example 38		CAP 5	GLN	homoARG	PRO	D-ARG	LEU	D-ALA	HIS	PipALA	GLY	OIC	4-BrPHE	PRO	D-BIP	OH
Example 39		CAP 5	GLN	homoARG	PRO	D-ARG	LEU	AIB	HIS	PipALA	GLY	OIC	4-BrPHE	PRO	D-BIP	OH
Example 40		CAP 5	GLN	D-ARG	PRO	ARG	LEU	AIB	HIS	PipALA	GLY	OIC	4-BrPHE	PRO	D-BIP	OH
Example 41		CAP 5	GLN	D-ARG	PRO	ARG	LEU	AIB	HIS	PipALA	GLY	OIC	4-BrPHE	PRO	D-(4-Br)-PHE	OH
Example 42		CAP 5	GLN	D-ARG	PRO	ARG	LEU	AIB	HIS	PipALA	GLY	OIC	4-BrPHE	PRO	D-(4-Bn)TYR	OH
Example 43		CAP 5	GLN	D-ARG	PRO	ARG	LEU	AIB	HIS	PipALA	GLY	OIC	4-BrPHE	PRO	D-CHA	OH
Example 44		CAP 5	GLN	D-ARG	PRO	ARG	LEU	AIB	NMeHIS	PipALA	GLY	OIC	4-BrPHE	PRO	D-BIP	OH
Example 45		CAP 2	GLN	homoARG	PRO	D-ARG	LEU	AIB	HIS	PipALA	GLY	OIC	4-BrPHE	PRO	D-BIP	OH
Example 46		CAP 3	GLN	homoARG	PRO	D-ARG	LEU	AIB	HIS	PipALA	GLY	OIC	4-BrPHE	PRO	D-BIP	OH
Example 47		CAP 5	GLN	homoARG	PRO	D-ARG	LEU	SER	AIB	PipALA	GLY	OIC	4-BrPHE	PRO	D-BIP	OH
Example 48		CAP 5	D-GLN	homoARG	PRO	D-ARG	D-LEU	AIB	HIS	PipALA	D-ALA	OIC	4-BrPHE	PRO	D-BIP	OH
Example 49		CAP 5	GLN	D-ARG	PRO	ARG	LEU	AIB	HIS(NMe)	PipALA	GLY	OIC	4-BrPHE	PRO	D-BIP	OH

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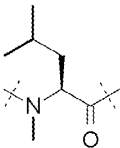
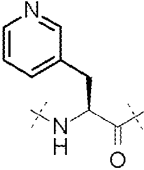
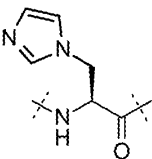
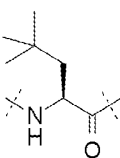
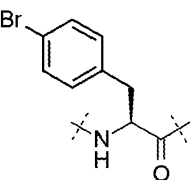
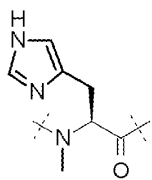
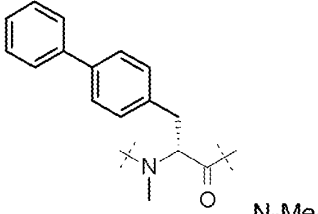
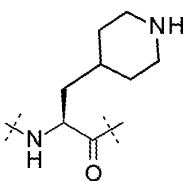
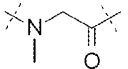
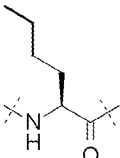
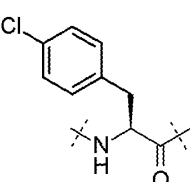
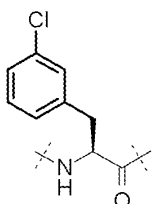
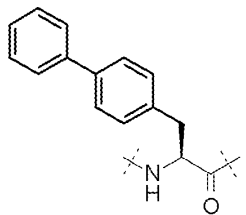
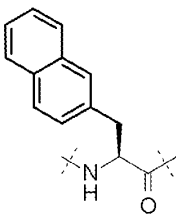
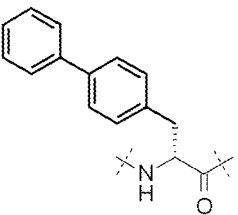
Example 50		CAP 5	D-GLN	homoARG	PRO	D-ARG	LEU	AIB	HIS	PipALA	GLY	OIC	4-BrPHE	PRO	D-BIP	OH
Example 51		CAP 5	GLN	homoARG	PRO	D-ARG	N-Me-LEU	AIB	HIS	PipALA	GLY	OIC	4-BrPHE	PRO	D-BIP	OH
Example 52		CAP 5	GLN	homoARG	PRO	D-ARG	LEU	AIB	HIS	PipALA	N-Me-Gly	OIC	4-BrPHE	PRO	D-BIP	OH
Example 53		CAP 4	GLN	homoARG	PRO	D-ARG	LEU	AIB	HIS	PipALA	GLY	OIC	4-BrPHE	PRO	D-BIP	OH
Example 54		CAP 5	GLN	homoARG	homoPRO	D-ARG	LEU	AIB	HIS	PipALA	ALA	OIC	4-BrPHE	PRO	D-BIP	OH
Example 55		CAP 5	GLN	ARG	homoPRO	D-ARG	LEU	AIB	HIS	PipALA	GLY	OIC	4-BrPHE	PRO	D-BIP	OH
Example 56		CAP 5	GLN	homoARG	homoPRO	D-ARG	LEU	AIB	3-PAL	PipALA	GLY	OIC	4-BrPHE	PRO	D-BIP	OH
Example 57		CAP 5	GLN	homoARG	PRO	D-ARG	LEU	AIB	HIS	PipALA	GLY	OIC	4-BrPHE	PRO	N-Me-D-BIP	OH
Example 58		CAP 5	N-Me-GLN	homoARG	PRO	D-ARG	LEU	AIB	HIS	PipALA	GLY	OIC	4-BrPHE	PRO	D-BIP	OH
Example 59		CAP 5	GLN	D-ARG	PRO	ARG	LEU	D-ALA	HIS	PipALA	GLY	OIC	NorLEU	PRO	D-BIP	OH
Example 60		CAP 5	GLN	homoARG	PRO	D-ARG	LEU	AIB	4-BrPHE	PipALA	GLY	OIC	NorLEU	PRO	D-BIP	OH
Example 61		CAP 6	GLN	homoARG	PRO	D-ARG	LEU	AIB	HIS	PipALA	GLY	OIC	4-BrPHE	PRO	D-BIP	OH
Example 62		CAP 5	GLN	HomoARG	HomoPRO	D-ARG	LEU	AIB	4-BrPHE	PipALA	ALA	OIC	NLE	PRO	D-BIP	OH

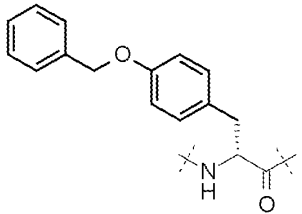
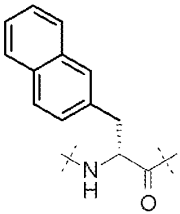
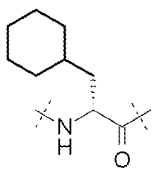
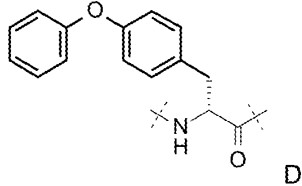
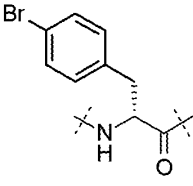
Standard amino acid symbols are used in Table 1 where appropriate. In cases where a standard symbol is not available, the following representations are used:



Standard amino acid symbols are used in Table 1 where appropriate. In cases where a standard symbol is not available, the following representations are used:

HomoPHE	N-Me-GLN	homoARG
OIC	Oxa	homoPRO
Methanoproline 1	Methanoproline 2	cycloBuALA

 N-Me-LEU	 3-PAL	 beta-imidazolyl-L-Ala
 tBuALA	 4-BrPHE	 NMeHIS
 D-BIP	 PipALA	 N-Me-Gly
 NorLEU	 4-CIPHE	 3-CIPHE
 BIP	 2-Nal	 D-BIP

 D-(4-Bn)TYR	 D-2-Nal	 D-CHA
 (4-OPh)PHE	 D-(4-Br)-PHE	

General procedures

Where no preparative routes are included, the relevant intermediate is commercially available. Commercial reagents were utilized without further purification. Room temperature (rt) refers to approximately 20-27°C. ¹H NMR spectra were recorded at 400 MHz on a Bruker instrument. Chemical shift values are expressed in parts per million (ppm), i.e. (δ)-values. The following abbreviations are used for the multiplicity of the NMR signals: s=singlet, br=broad, d=doublet, t=triplet, q=quartet, quint=quintet, td=triplet of doublets, tt= triplet of triplets, qd=quartet of doublets, ddd=doublet of doublet of doublets, ddt=doublet of doublet of triplets, m=multiplet. Coupling constants are listed as *J* values, measured in Hz. NMR and mass spectroscopy results were corrected to account for background peaks. Chromatography refers to column chromatography performed using 60 – 120 mesh silica gel and executed under nitrogen pressure (flash chromatography) conditions.

Analytical Methods

LCMS analysis of compounds was performed under electrospray conditions

LCMS Method A

Instruments: Waters Acquity UPLC, Waters 3100 PDA Detector, SQD; Column: Acquity HSS-T3, 1.8 micron, 2.1 x 100 mm; Gradient [time (min)/solvent B in A (%]): 0.00/10, 1.00/10, 2.00/15, 4.50/55, 6.00/90, 8.00/90, 9.00/10, 10.00/10; Solvents: solvent A = 0.1% trifluoroacetic acid in water; solvent B = acetonitrile; Injection volume 1 µL; Detection wavelength 214 nm; Column temperature 30 °C; Flow rate 0.3 mL per min.

Analytical Method B

MS ion determined using LCMS method below under electrospray conditions, HPLC retention time (R_T) determined using HPLC method below, purity > 95% by HPLC unless indicated.

- 5 LCMS: Agilent 1200 HPLC&6410B Triple Quad, Column: Xbridge C18 3.5 μ m 2.1*30mm. Gradient [time (min)/solvent B(%)]:0.0/10,0.9/80,1.5/90,8.5/5,1.51/10. (Solvent A=1mL of TFA in 1000 mL Water; Solvent B=1mL of TFA in 1000 mL of MeCN); Injection volume 5 μ L (may vary); UV detection 220 nm 254 nm 210 nm; Column temperature 25°C; 1.0 mL/min.
- 10 HPLC: Agilent Technologies 1200, Column: Sepax GP-C18 5 μ m 120A 4.6*150mm. Gradient [time (min)/solvent B(%)]:0.0/40,20/55,20.1/90,23/90. (Solvent A=1mL of TFA in 1000 mL Water; Solvent B=1mL of TFA in 1000 mL of 80%MeCN+20%H₂O); Injection volume 30 μ L (may vary); UV detection 220 nm; Column temperature 25°C; 1.0 mL/min

Analytical Method C

MS ion determined using LCMS method below under electrospray conditions, HPLC

- 15 retention time (R_T) determined using HPLC method below, purity > 95% by HPLC unless indicated.

- LCMS: Agilent 1200 HPLC&6410B Triple Quad, Column: Xbridge C18 3.5 μ m 2.1*30mm. Gradient [time (min)/solvent B(%)]:0.0/10,0.9/80,1.5/90,8.5/5,1.51/10. (Solvent A=1mL of TFA in 1000 mL Water; Solvent B=1mL of TFA in 1000 mL of MeCN); Injection volume 5 μ L (may vary); UV detection 220 nm 254 nm 210 nm; Column temperature 25°C; 1.0 mL/min.
- 20 HPLC: Agilent Technologies 1200, Column: Gemini-NX C18 5 μ m 110A 150*4.6mm. Gradient [time (min)/solvent B(%)]:0.0/30,20/60,20.1/90,23/90. (Solvent A=1mL of TFA in 1000 mL Water; Solvent B=1mL of TFA in 1000 mL of MeCN); Injection volume 5 μ L (may vary); UV detection 220 nm 254 nm; Column temperature 25°C; 1.0 mL/min

- 25 **Analytical Method D**

- Instrument: Thermo Scientific Orbitrap Fusion; Column: Phenomenex Kinetex Biphenyl 100 Å, 2.6 μ m, 2.1 x 50 mm; Gradient [time (min)/solvent B in A (%)]: 0.00/10, 0.30/10, 0.40/60, 1.10/90, 1.70/90, 1.75/10, 1.99/10, 2.00/10; Solvents: Solvent A = 0.1% formic acid in water; Solvent B = 0.1% formic acid in acetonitrile; Injection volume 5 μ L; Column temperature 25 °C; Flow rate 0.8 mL/min.
- 30

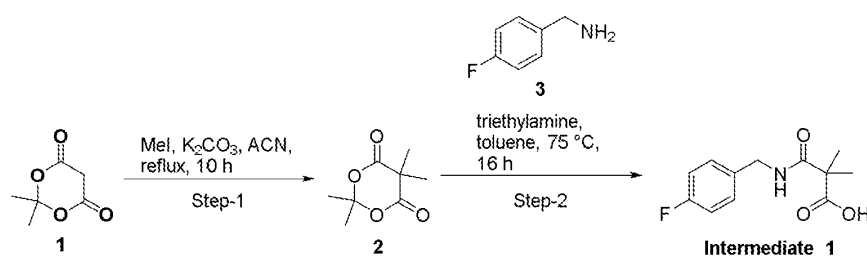
Synthesis of Intermediates and Compounds

- 35 The following examples are provided to illustrate preferred aspects of the invention and are not intended to limit the scope of the invention.

Synthesis of Intermediates

All Fmoc-amino acids are commercially available except for Intermediates 1 to 7, synthesis of which are outlined below

5 Synthesis of 3-((4-fluorobenzyl)amino)-2,2-dimethyl-3-oxopropanoic acid (Intermediate 1)



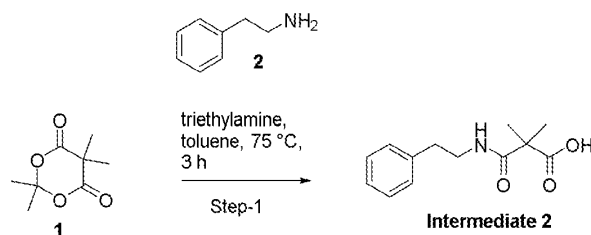
Step-1: Synthesis of 2,2,5,5-tetramethyl-1,3-dioxane-4,6-dione (2): To a solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (**1**, 20.0 g, 138.8 mmol) in ACN (200 mL), K₂CO₃ (96 g, 694.0 mmol) and MeI (26 mL, 416.6 mmol) were added at rt and reaction mixture was refluxed for 10 h. After completion, the reaction mixture was cooled to room temperature, filtered through a pad of celite, washed with EtOAc (3 x 50 mL). The organic layer was washed with 10% aq Na₂S₂O₃ (100 mL), dried, (Na₂SO₄) and concentrated in *vacuo* to give 2,2,5,5-tetramethyl-1,3-dioxane-4,6-dione (**2**, 21 g, 88%) as a yellow solid. The crude residue was used for the next step without further purification.

¹H-NMR (400 MHz; CDCl₃): δ 1.63 (s, 6H), 1.73 (s, 6H).

Step-2: Synthesis of 3-((4-fluorobenzyl)amino)-2,2-dimethyl-3-oxopropanoic acid (Intermediate 1): To a stirred solution of 2,2,5,5-tetramethyl-1,3-dioxane-4,6-dione (**2**, 9.9 g, 57.0 mmol) in toluene (60 mL) was heated at 75°C. The reaction mixture was stirred for 10 min at same temperature and added a solution of Et₃N (34.6 mL, 240 mmol) and (4-fluorophenyl)methanamine (**1**, 6 g, 48.0 mmol) in toluene (60 mL) drop wise over 10 min. The reaction mixture was further stirred at same temperature for 16 h. After completion, the reaction mixture was concentrated in *vacuo*. The residue was triturated diethyl ether (70 mL) and ether was decanted off. The obtained material was dried in *vacuo* to give 3-((4-fluorobenzyl)amino)-2,2-dimethyl-3-oxopropanoic acid (**Intermediate 1**, 1.58 g, 14%) as a yellow solid.

LCMS (Method A): m/z 240.13 [M+H]⁺ (ES⁺), at 4.77 min, 98.85%.

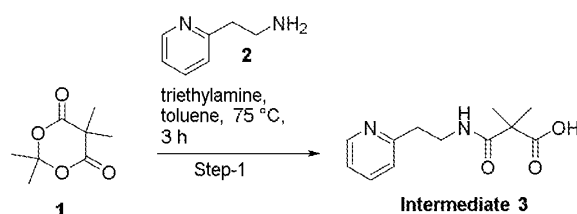
¹H-NMR (400 MHz; DMSO-d₆): δ 1.31 (s, 6H), 4.25 (d, *J* = 5.8 Hz, 2H), 7.07 - 7.15 (m, 2H), 7.20 - 7.30 (m, 2H), 8.23 (br s, 1H), 12.49 (br s, 1H).

Synthesis of 2,2-dimethyl-3-oxo-3-(phenethylamino)propanoic acid (Intermediate 2)**Step-1: Synthesis of 2,2-dimethyl-3-oxo-3-(phenethylamino)propanoic acid (Intermediate 2):**

To a stirred solution of 2,2,5,5-tetramethyl-1,3-dioxane-4,6-dione (**1**, 5.1 g, 29.7 mmol) in toluene (30 mL) was heated at 75°C. The reaction mixture was stirred for 10 min at same temperature and solution of Et₃N (16.4 mL, 123.7 mmol) and 2-phenylethan-1-amine (**2**, 3.1 g, 24.7 mmol) in toluene (50 mL) was added drop wise over 10 min. The resulting mixture was further stirred at same temperature for 3 h. After consumption of starting material, the reaction mixture was concentrated in *vacuo* to get crude. The crude material was triturated with diethyl ether (80 mL) and ether was decanted off. The obtained material was dried under *vacuo* to give 2,2-dimethyl-3-oxo-3-(phenethylamino)propanoic acid (**Intermediate 2**, 3.2 g, 55%) as a white solid.

LCMS (Method A): m/z 236.18 [M+H]⁺ (ES⁺), at 5.01 min, 99.61%.

¹H-NMR (400 MHz; DMSO- d₆): δ 1.24 (s, 6H), 2.70 (t, J = 7.6 Hz, 2H), 3.24 (t, J = 7.6 Hz, 2H), 7.17 - 7.20 (m, 3H), 7.26 - 7.29 (m, 2H), 7.72 (br s, 1H), 12.48 (br s, 1H).

Synthesis of 2,2-dimethyl-3-oxo-3-((2-(pyridin-2-yl)ethyl)amino)propanoic acid (Intermediate 3)**Step-1: Synthesis of 2,2-dimethyl-3-oxo-3-((2-(pyridin-2-yl)ethyl)amino)propanoic acid (Intermediate 3):**

To a stirred solution of 2,2,5,5-tetramethyl-1,3-dioxane-4,6-dione (**1**, 3.3 g, 19.6 mmol) in toluene (30 mL) was heated at 75°C. The reaction mixture stirred for 10 min at same temperature and solution of Et₃N (11.4 mL, 81.9 mmol) and 2-(pyridin-2-yl)ethan-1-amine (**2**, 2 g, 16.4 mmol) in toluene (50 mL) was added drop wise over 10 min. The reaction mixture was further stirred at same temperature for 3 h. After consumption of starting material, the reaction mixture was concentrated in *vacuo* to get crude material which was triturated with diethyl ether (50 mL) and ether was decanted off. The obtained material was dried under *vacuo* to give 2,2-dimethyl-3-oxo-3-((2-(pyridin-2-yl)ethyl)amino)propanoic acid

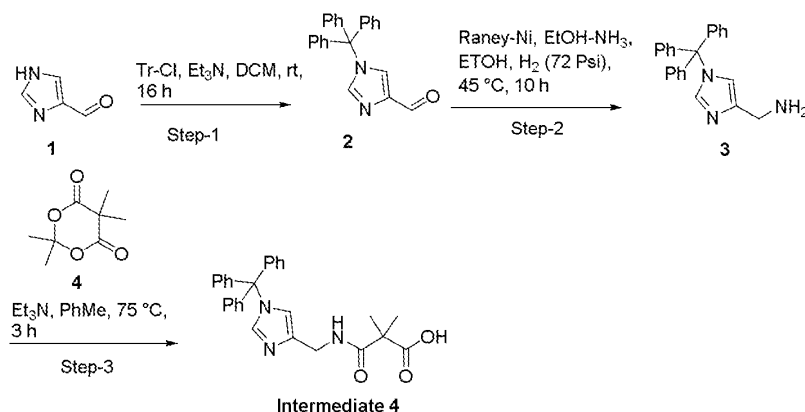
(Intermediate 3, 1.9 g, 50%) as a white solid.

LCMS (Method A): m/z 237.23 $[M+H]^+$ (ES^+), at 4.07 min, 97.85%.

^1H -NMR (400 MHz; $DMSO-d_6$): δ 1.22 (s, 6H), 2.80 - 2.90 (m, 2H), 3.33 - 3.43 (m, 2H), 7.18 - 7.22 (m, 2H), 7.61 - 7.71 (m, 1H), 7.79 (br s, 1H), 8.45 (d, J = 4.4 Hz, 1H), 12.00 (br s, 1H).

5

Synthesis of 2,2-dimethyl-3-oxo-3-((3-(1-trityl-1H-imidazol-4-yl)propyl)amino)propanoic acid (Intermediate 4)



Step-1: Synthesis of 1-trityl-1H-imidazole-4-carbaldehyde (2): To a solution of 1H-imidazole-4-carbaldehyde (**1**, 10.0 g, 104 mmol) in DCM (100 mL), Et_3N (28.9 mL, 110 mmol) was added to it. The reaction mixture was stirred for 10 min at 0 °C and added trityl chloride (34.7 g, 124.0 mmol) at same temperature. The resulting mixture was further stirred for 16 h. After completion, water was added and the aqueous layer was extracted with DCM (3 x 100 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to get crude material. The obtained material was triturated with hexane (200 mL) and hexane was decanted off. The resulting material was dried under *vacuo* to give 1-trityl-1H-imidazole-4-carbaldehyde (**2**, 11.2 g, 32%) as an off white solid.

^1H NMR (400 MHz; $DMSO-d_6$): δ 7.06 - 7.18 (m, 6H), 7.37 - 7.50 (m, 9H), 7.65 (s, 1H), 7.79 (s, 1H), 9.72 (s, 10H).

Step-2: Synthesis of (1-trityl-1H-imidazol-4-yl)methanamine (3): 1-trityl-1H-imidazole-4-carbaldehyde (**2**, 4.0 g, 11.8 mmol) was dissolved in EtOH (100 mL) and transferred to parr apparatus then raney Ni (1.5 g) was added followed by addition of ethanolic ammonia (100 mL). The resulting mixture was stirred at 45 °C for 10 h under H_2 atmosphere (72 Psi). After consumption of starting material, reaction mixture was filtered through a pad of celite, washed with MeOH and concentrated in *vacuo* to give (1-trityl-1H-imidazol-4-yl)methanamine (**3**, 4.1 g, 99%). This was used for the next step reaction without purification.

MS (ESI +ve): 341.24

^1H NMR (400 MHz; $DMSO-d_6$): δ 3.40 - 3.50 (m, 2H), 4.08 (br s, 2H), 6.71 (s, 1H), 7.00 -

7.11 (m, 6H), 7.24 (s, 1H), 7.30 - 7.45 (m, 9H).

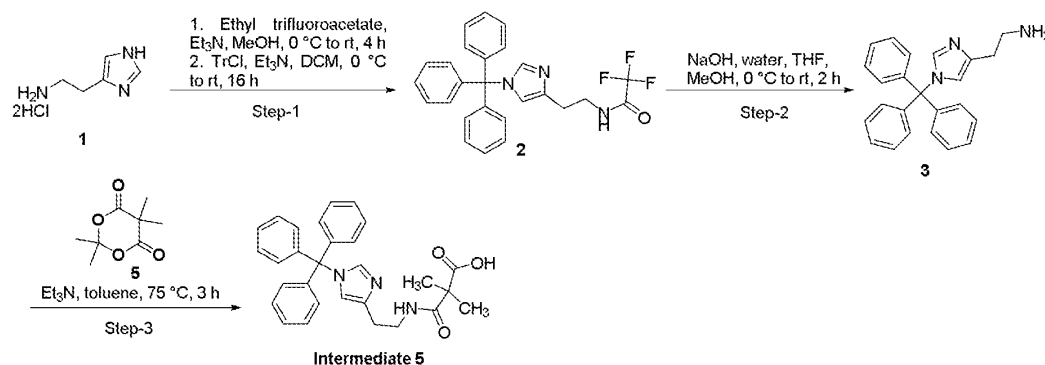
Step-3: Synthesis of 2,2-dimethyl-3-oxo-3-(((1-trityl-1H-imidazol-4-yl)methyl)amino)propanoic acid (Intermediate 4):

To a stirred solution of 2,2,5,5-tetramethyl-1,3-dioxane-4,6-dione (**4**, 3.1 g, 18.1 mmol) in toluene (30 mL) was heated at 75 °C. The reaction mixture was stirred at same temperature for 10 min and solution of Et₃N (8.4 mL, 60.4 mmol) and (1-trityl-1H-imidazol-4-yl)methanamine (**3**, 4.1 g, 12.1 mmol) in toluene (50 mL) was added drop wise over 10 min. The reaction mixture was further continued at same temperature for 3 h. After completion, the reaction mixture was concentrated in *vacuo*. The residue was dissolved in chloroform (80 mL) and washed with 10% of aqueous citric acid (pH ~ 6 - 6.5). The organic layer was dried over Na₂SO₄ and concentrated in *vacuo*. The obtained residue was triturated diethyl ether / n-hexane (35 mL) and the suspension was stirred at room temperature for 16 h. The solid was filtered, washed with methanol (30 mL) and dried in *vacuo* to give 2,2-dimethyl-3-oxo-3-((3-(1-trityl-1H-imidazol-4-yl)propyl)amino)propanoic acid (**Intermediate 4**, 1.7 g, 43%) as a white solid.

LCMS (Method A): m/z 454.26 [M+H]⁺ (ES⁺), at 4.73 min, 99.42%.

¹H-NMR (400 MHz; DMSO- d₆): δ 1.20 (s, 6H), 4.11 (d, J = 4.8 Hz, 2H), 6.68 (s, 1H), 6.98 - 7.10 (m, 6H), 7.25 (s, 1H), 7.30 - 7.50 (m, 2H), 8.00 (br s, 1H), 12.33 (br s, 1H)

Synthesis of 2,2-dimethyl-3-oxo-3-((2-(1-trityl-1H-imidazol-4-yl)ethyl)amino)propanoic acid (Intermediate 5)



Step-1: Synthesis of 2,2,2-trifluoro-N-(2-(1-trityl-1H-imidazol-4-yl)ethyl)acetamide (2):

To a solution of 2-(1H-imidazol-4-yl)ethan-1-amine dihydrochloride (**1**, 25.0 g, 136.6 mmol) in MeOH (100 mL), Et₃N (67 mL, 464.4 mmol) was added at rt and the reaction mixture was cooled to 0 °C. A solution of ethyl trifluoroacetate (20 mL, 164.0 mmol) in MeOH (50 mL) was added to the reaction mixture over 30 min at 0 °C and the reaction mixture was stirred at rt for 4 h. This reaction mixture was diluted with dry DCM (200 mL) and Et₃N (60 mL, 409.8 mmol) and the reaction mixture was cooled to 0 °C. Tr-Cl (76 g, 273.2 mmol) was added portion wise and the resulting reaction mixture was stirred at rt for 16 h. After

completion, the reaction mixture was quenched with water (300 mL) and the aq layer was extracted with chloroform (3 x 150 mL). The organic layers were combined, dried (Na₂SO₄) and concentrated in *vacuo*. The crude residue was triturated with *n*-hexane to give 2,2,2-trifluoro-*N*-(2-(1-trityl-1*H*-imidazol-4-yl)ethyl)acetamide (**2**, 50.10 g, 81%) as a white solid.

5 **MS (ESI +ve):** 450

¹H-NMR (400 MHz; CDCl₃): δ 2.75 (t, *J* = 5.9 Hz, 2H), 3.60 - 3.65 (m, 2H), 6.61 (s, 1H), 7.08 - 7.15 (m, 6H), 7.31 - 7.38 (m, 9H), 7.40 (s, 1H), 8.41 (br s, 1H).

Step-2: Synthesis of 2-(1-trityl-1*H*-imidazol-4-yl)ethan-1-amine (3**):** To a solution of 2,2,2-trifluoro-*N*-(2-(1-trityl-1*H*-imidazol-4-yl)ethyl)acetamide (**2**, 50.0 g, 111.3 mmol) in THF (150 mL) and MeOH (180 mL), NaOH (22.0 g, 556.7 mmol) in water (100 mL) was slowly added at 0 °C and the reaction mixture was stirred at room temperature for 2 h. After completion, the reaction mixture was quenched with water (300 mL) and the aq layer was extracted with chloroform (3 x 150 mL). The organic layers were combined, dried (Na₂SO₄) and concentrated in *vacuo* to give 2-(1-trityl-1*H*-imidazol-4-yl)ethan-1-amine (**3**, 34.0 g, 86%) as a yellowish sticky solid. The crude residue was used for the next step without further purification.

MS (ESI +ve): 354

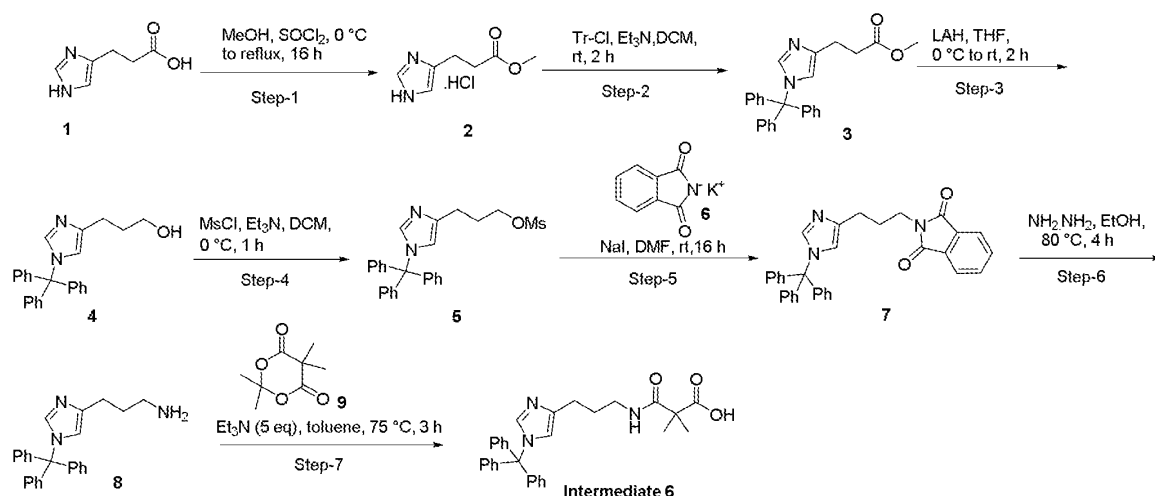
¹H-NMR (400 MHz; CDCl₃): δ 1.53 (bs, 2H), 2.65 (t, *J* = 6.5 Hz, 2H), 2.95 (t, *J* = 6.5 Hz, 2H), 6.58 (s, 1H), 7.11 - 7.16 (m, 6H), 7.28 - 7.38 (m, 10H).

20 **Step-4: Synthesis of 2,2-dimethyl-3-oxo-3-((2-(1-trityl-1*H*-imidazol-4-yl)ethyl)amino)propanoic acid (Intermediate **5**):** A solution of 2-(1-trityl-1*H*-imidazol-4-yl)ethan-1-amine (**3**, 8.0 g, 22.6 mmol) and Et₃N (16.0 mL, 113.0 mmol) in toluene (100 mL) was added drop wise over 60 min to a solution of 2,2,5,5-tetramethyl-1,3-dioxane-4,6-dione (**5**, 5.8 g, 29.76 mmol) in toluene (50 mL) at 75 °C. The reaction mixture was further stirred at same temperature was 3 h. After completion, the reaction mixture was concentrated in *vacuo*. The residue was dissolved in chloroform (100 mL) and washed with 10% aq citric acid (pH ~ 6 - 6.5). The organic layer was dried (Na₂SO₄) and concentrated in *vacuo*. The crude residue obtained was triturated with hot chloroform (150 mL) and *n*-hexane (75 mL) and the suspension was stirred at rt for 16 h. The solid was filtered, washed with chloroform : *n*-hexane (1:1, 2 x 50 mL) and dried in *vacuo* to give 2,2-dimethyl-3-oxo-3-((2-(1-trityl-1*H*-imidazol-4-yl)ethyl)amino)propanoic acid (**Intermediate 5**, 6.8 g, 64%) as a white solid.

LCMS (Method A): *m/z* 468 [M+H]⁺ (ES⁺), at 5.38 min, 99.31%

35 **¹H-NMR** (400 MHz; DMSO-*d*₆): δ 1.21 (s, 6H), 2.57 (t, *J* = 6.8 Hz, 2H), 3.22 - 3.27 (m, 2H), 6.66 (s, 1H), 7.06 - 7.11 (m, 6H), 7.28 (s, 1H), 7.35 - 7.42 (m, 8H), 7.64 (t, *J* = 5.4 Hz, 1H), 8.31 (s, 1H), 12.44 (br s, 1H).

Synthesis of 2,2-dimethyl-3-oxo-3-((3-(1-trityl-1H-imidazol-4-yl)propyl)amino)propanoic acid (Intermediate 6)



- 5 **Step-1: Synthesis of methyl 3-(1H-imidazol-4-yl)propanoate.HCl (2):** To a mixture of 3-(1H-imidazol-4-yl)propanoic acid (**1**, 5 g, 38.7 mmol) in MeOH (80 mL), SOCl₂ (7.7 mL, 107.1 mmol) was added at 0 °C. After allowing the reaction mixture at room temperature, the reaction was further heated at reflux for 5 h. After completion, the reaction mixture was concentrated *in vacuo* and the reaction mixture was triturated with diethylether (200 mL) to give methyl 3-(1H-imidazol-4-yl)propanoate.HCl (**2**, 7 g, 97%) as a white solid.

MS (ESI +ve): 155.14.

- 15 **Step-2: Synthesis of methyl 3-(1-trityl-1H-imidazol-4-yl)propanoate (3):** To a solution of methyl 3-(1H-imidazol-4-yl)propanoate.HCl salt (**2**, 7 g, 44.02 mmol) in DCM (80 mL), Et₃N (19 mL, 132 mmol) was added. After 10 min stirring at 0 °C, trityl chloride (18.3 g, 66 mmol) was added at same temperature and the reaction was further stirred for 2 h. After completion, water was added and the aqueous layer was extracted with DCM (3 x 100 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. The crude material was triturated with hexane (200 mL) and hexane was decanted off. The obtained material was dried under *vacuo* to give methyl 3-(1-trityl-1H-imidazol-4-yl)propanoate (**3**, 15 g, 88%) as white solid.

MS (ESI +ve): 397

¹H NMR (400 MHz; DMSO-*d*₆): δ 2.51 - 2.73 (m, 4H), 3.52 (s, 3H), 6.60 (s, 1H), 7.00 - 7.11 (m, 6H), 7.17 - 7.45 (m, 10H).

- 25 **Step-3: Synthesis of 3-(1-trityl-1H-imidazol-4-yl)propan-1-ol (4):** To a solution methyl 3-(1-trityl-1H-imidazol-4-yl)propanoate (**3**, 15 g, 37.8 mmol) in THF (300 mL), LAH (2.5M in THF, 60 mL, 151.2 mmol) was slowly added at 0 °C. After 10 min stirring at 0 °C, the

reaction was allowed to warm room temperature for 2h. After completion, the reaction was quenched with saturated NH₄Cl solution (60 mL) and solid suspension was filtered through celite pad and washed with ethyl acetate (200 mL). The filtrate was concentrated *in vacuo* to give 3-(1-trityl-1H-imidazol-4-yl)propan-1-ol (**4**, 10.2 g, 73%) as white solid. This was used for the next step reaction without purification.

MS (ESI -ve): 367

¹H NMR (400 MHz; DMSO-*d*₆): δ 1.60 - 1.70 (m, 2H), 2.40 - 2.53 (m, 2H), 3.30 - 3.42 (m, 2H), 4.40 (bs, 1H), 6.57 (s, 1H), 7.00 - 7.11 (m, 6H), 7.24 (s, 1H), 7.30 - 7.45 (m, 9H).

Step-4: Synthesis of 3-(1-trityl-1H-imidazol-4-yl)propyl methanesulfonate (5): To a solution of 3-(1-trityl-1H-imidazol-4-yl)propan-1-ol (**4**, 10 g, 27.1 mmol) in DCM (60 mL), Et₃N (5.9 mL, 29.8 mmol) was added. After 10 min stirring at 0 °C, mesyl chloride (3.08 mL, 47 mmol) was added and the reaction was further stirred for 1h at same temperature. After consumption of starting material, water was added and extracted with DCM (3 x 100 mL). The combined organic layer was washed with brine, dried over Na₂SO₄ and concentrated *in vacuo* to give 3-(1-trityl-1H-imidazol-4-yl)propyl methane sulfonate (**5**, 14 g crude) as a sticky liquid. This was used for the next step reaction without purification.

Step-5: Synthesis of 2-(3-(1-trityl-1H-imidazol-4-yl)propyl)isoindoline-1,3-dione (7): To a solution of 3-(1-trityl-1H-imidazol-4-yl)propyl methanesulfonate (**5**, 14 g, 28 mmol) in DMF (50 mL), NaI (1.2 g, 8.4 mmol) and potassium phthalimide (**6**, 7.3 g, 39.2 mmol) was added. The resulting mixture was stirred at room temperature for 16 h. After consumption of starting material, water was added and solid was filtered. The filtrate was dried *in vacuo* to give 2-(3-(1-trityl-1H-imidazol-4-yl)propyl)isoindoline-1,3-dione (**7**, 7.5 g, 51%) as a white solid. This was used for the next step reaction without purification.

MS (ESI+ -ve): 498.31

¹H NMR (400 MHz; DMSO-*d*₆): δ 1.80 - 1.90 (m, 2H), 2.80 - 3.00 (m, 4H), 6.40 (s, 1H), 7.00 - 7.11 (m, 3H), 7.12 - 7.47 (m, 16H), 7.82 (s, 1H).

Step-6: Synthesis of 3-(1-trityl-1H-imidazol-4-yl)propan-1-amine (8): To a solution of 2-(3-(1-trityl-1H-imidazol-4-yl)propyl)isoindoline-1,3-dione (**7**, 7.5 g, 15.1 mmol) in EtOH : THF (2:1, 75 mL), hydrazine monohydrate (9.4 mL) was added drop wise and then heated the reaction at 75 °C for 4 h. After completion, the reaction mixture was filtered and filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography [normal phase, silica gel (100-200 mesh), gradient 2% MeOH in DCM (saturated NH₄OH) to give 3-(1-trityl-1H-imidazol-4-yl)propan-1-amine (**8**, 3 g, 54%) as a white solid.

¹H NMR (400 MHz; DMSO-*d*₆): δ 1.50 - 1.60 (m, 2H), 2.20 - 2.30 (m, 2H), 2.48 - 2.67 (m, 2H), 4.08 (bs, 2H), 6.56 (s, 1H), 7.00 - 7.12 (m, 6H), 7.22 (s, 1H), 7.32 - 7.45 (m, 9H).

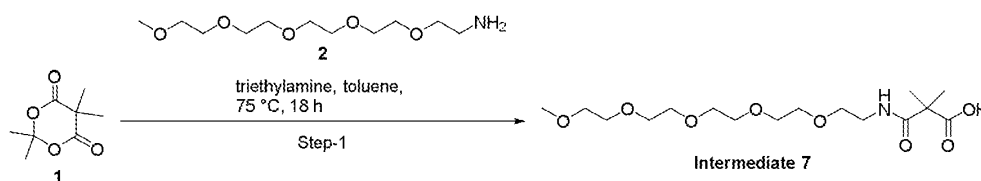
Step-7: Synthesis of 2,2-dimethyl-3-oxo-3-((3-(1-trityl-1H-imidazol-4-yl)propyl)amino)

propanoic acid (Intermediate 6): To a stirred solution of 2,2,5,5-tetramethyl-1,3-dioxane-4,6-dione^[1] (**9**, 2.1 g, 12.2 mmol) in toluene (30 mL) was heated at 75°C. The reaction mixture was stirred for 10 min at same temperature and solution of Et₃N (5.8 mL, 40.8 mmol) and 3-(1-trityl-1H-imidazol-4-yl)propan-1-amine (**8**, 3 g, 8.1 mmol) in toluene (50 mL) was added over 10 min at 75 °C. The reaction mixture was further stirred at same temperature for 3 h. After completion, the reaction mixture was concentrated in *vacuo*. The residue was dissolved in chloroform (100 mL) and washed with 10% of aqueous citric acid (pH ~ 6 - 6.5). The organic layer was dried over Na₂SO₄ and concentrated in *vacuo*. The crude material was washed with diethyl ether (50 mL) and ether was decanted off. The resulting material was dried in *vacuo* to give 2,2-dimethyl-3-oxo-3-((3-(1-trityl-1H-imidazol-4-yl)propyl)amino)propanoic acid (**Intermediate 6**, 1.7 g, 43%) as a white solid.

LCMS (Method A): m/z 482.09 [M+H]⁺ (ES⁺), at 4.98 min, 97.99%.

¹H-NMR (400 MHz; DMSO- d₆): δ 1.24 (s, 6H), 2.70 (t, *J* = 7.6 Hz, 2H), 3.24 (t, *J* = 7.6 Hz, 2H), 7.17 - 7.24 (m, 3H), 7.23 - 7.33 (m, 2H), 7.72 (br s, 1H).

Synthesis of 19,19-dimethyl-18-oxo-2,5,8,11,14-pentaoxa-17-azaicosan-20-oic acid (**Intermediate 7**)



Synthesis of 19,19-dimethyl-18-oxo-2,5,8,11,14-pentaoxa-17-azaicosan-20-oic acid (**Intermediate 7**):

To a stirred solution of 2,2,5,5-tetramethyl-1,3-dioxane-4,6-dione (**1**, 986 mg, 5.73 mmol) in toluene (30 mL) was heated at 75°C. The reaction mixture was stirred for 10 min at same temperature and added solution of Et₃N (3.0 mL, 23.4 mmol) and 2,5,8,11,14-pentaoxahexadecan-16-amine (**2**, 1.2 g, 4.71 mmol) in toluene (30 mL) drop wise over 10 min. The reaction mixture was further stirred at same temperature for 18 h. After completion, the reaction mixture was concentrated in *vacuo*. The residue was triturated with diethyl ether (50 mL) and ether was decanted off. The obtained material was dried in *vacuo* to give 19,19-dimethyl-18-oxo-2,5,8,11,14-pentaoxa-17-azaicosan-20-oic acid (**Intermediate 7**, 1.9 g, 90%) as yellow viscous liquid.

LCMS (Method A): m/z 383.2 [M+H]⁺ (ES⁺), at 3.85 min, 99.3%.

¹H-NMR (400 MHz; DMSO- d₆): δ 1.04 (t, *J* = 7.1 Hz, 1H), 1.25 (s, 6H), 2.70 - 2.85 (m, 2H), 3.15 - 3.23 (m, 2H), 3.23 (s, 1H), 3.32 - 3.45 (m, 6H), 3.46 - 3.55 (m, 7H), 7.80 (br s, 1H), 12.00 (br s, 1H).

Synthesis of Examples 1-62

Standard Fmoc solid phase peptide synthesis (SPPS) was used to synthesize the linear peptides which were then cleaved from the resin and purified.

5 General method for Peptide Synthesis:

The peptide was synthesized using standard Fmoc chemistry.

Method a – Exemplified by the Synthesis of Example 39

- 10 1) Add DCM to the vessel containing CTC Resin (sub: 0.35 mmol/g, 5 mmol, 14.29 g) and swell for 2 hours.
- 2) Drain and wash resin with DMF (5 times, drain between each wash).
- 3) A solution of 20% piperidine in DMF was added, agitate with N₂ bubbling for 30 min.
- 4) Drain and wash with DMF (5 times, drain between each wash).
- 15 5) Add Fmoc-amino acid solution (2.0 equivalents in DMF) and mix for 30 seconds, then add activation buffer (HBTU (1.9 equivalents) and DIEA (4 equivalents) in DMF), agitate with N₂ bubbling for 1 hour.
- 6) The coupling reaction was monitored by ninhydrin test
- 7) If required repeat steps 4 to 5 for same amino acid coupling if inefficient coupling occurs
- 20 8) Repeat steps 2 to 6 for next amino acid coupling.

Note: for the amino acids in the table below different equivalents and coupling agents were used

Amino acids from C-terminus	Materials	Coupling reagents
14	Intermediate 5 (1.5 eq)	HOAT (1.5eq) and DIC (1.5 eq)

- 9) The resin was washed with MeOH three times and dried *in vacuo*.
- 25

Peptide Cleavage and Purification:

- 1) Add cleavage buffer (92.5%TFA/2.5%EDT/2.5%TIS/2.5%H₂O) to the flask containing the side chain protected peptide on the resin at room temperature and stir for 3 hours.
- 2) The peptide is precipitated with cold tert-butyl methyl ether and centrifuged (3 min at
- 30 3000 rpm).
- 3) Reaction mixture was filtered and the filtrate was collected and reduced *in vacuo*.
- 4) Residue was washed with tert-butyl methyl ether (2 times).
- 5) Crude peptide dried *in vacuo* for 2 hours.
- 6) The crude peptide was purified by prep-HPLC (A: 0.5% ACOH in H₂O, B: MeCN). Prep-
- 35 HPLC Conditions: Gilson 281. Solvent: A- 0.075% TFA in H₂O, B- acetonitrile, Column: Luna C18 (200×25 mm; 10 μm) and Gemini C18 (150×30 mm; 5 μm) in series. Gradient

[time (min)/solvent B (%]): 0.0/25, 60.0/55, 60.1/90, 70/90, 70.1/10. Then re-purified by prep-HPLC (A: 0.5% ACOH in H₂O, B: MeCN), Prep-HPLC Conditions: Instrument: Gilson 281. Solvent: A- 0.5% AcOH in H₂O, B- acetonitrile, Column: Luna C18 (200×25 mm; 10 μm) and Gemini C18 (150×30 mm; 5 μm) in series. Gradient [time (min)/solvent B (%]): 0.0/25, 60.0/55, 60.1/90, 70/90, 70.1/10 to give Example 39 (2.94 g, 28.04% yield).

Table 2 - HRMS and LCMS properties of purify peptides represented by Examples 1-23

Example	HRMS (Method D)	Analytical Method	LCMS / HPLC Data
1	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C ₁₀₂ H ₁₄₉ BrN ₃ O ₁₈ 2161.085; Found 721.3708	B	m/z 1082.6 [M+2H] ²⁺ , R _T = 9.59 min
2	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C ₁₀₃ H ₁₅₁ BrN ₃ O ₁₈ 2175.1006; Found 726.0467	C	m/z 726.2 [M+3H] ³⁺ , R _T = 9.06 min
3	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C ₁₀₂ H ₁₅₀ N ₃ O ₁₈ 2083.1743; Found 521.8047	B	m/z 695.8 [M+3H] ³⁺ , R _T = 12.39 min
4	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C ₉₉ H ₁₅₂ N ₃ O ₁₈ 2049.1902; Found 513.3062	B	m/z 684.4 [M+3H] ³⁺ , R _T = 10.61 min
5	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C ₁₀₆ H ₁₅₃ BrN ₂ O ₁₈ 2185.1101; Found 729.3819	B	m/z 730.4 [M+3H] ³⁺ , R _T = 10.34 min
6	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C ₁₀₅ H ₁₅₂ BrN ₂ O ₁₈ 2186.1052; Found 547.5363	B	m/z 730.6 [M+3H] ³⁺ , R _T = 10.17 min
7	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C ₁₀₉ H ₁₆₇ BrN ₂ O ₂₃ 2315.1943; Found 579.8084	B	m/z 773.5 [M+3H] ³⁺ , R _T = 10.51 min
8	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C ₁₀₈ H ₁₅₄ BrN ₂ O ₁₇ 2208.126; Found 553.0409	B	m/z 737.6 [M+3H] ³⁺ , R _T = 9.00 min
9	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C ₁₀₂ H ₁₄₉ BrN ₃ O ₁₈ 2161.085; Found 541.2803	B	m/z 722.1 [M+3H] ³⁺ , R _T = 11.51 min
10	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C ₁₀₇ H ₁₅₇ BrN ₃ O ₁₈ 2229.1475; Found 558.2966	B	m/z 744.7 [M+3H] ³⁺ , R _T = 10.70 min
11	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C ₁₀₂ H ₁₄₉ BrN ₃ O ₁₉ 2177.0798; Found 545.2795	B	m/z 545.9 [M+4H] ⁴⁺ , R _T = 8.63 min
12	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C ₁₀₄ H ₁₅₃ BrN ₃ O ₁₈ 2189.1162; Found 548.2884	B	m/z 731.6 [M+3H] ³⁺ , R _T = 8.90 min
13	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C ₁₀₄ H ₁₅₃ BrN ₃ O ₁₈ 2189.1162; Found 548.2889	B	m/z 731.5 [M+3H] ³⁺ , R _T = 10.11 min
14	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C ₁₀₄ H ₁₅₁ BrN ₃ O ₁₈ 2187.1006; Found 547.7851	B	m/z 730.8 [M+3H] ³⁺ , R _T = 13.04 min
15	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for	B	m/z 548.2 [M+4H] ⁴⁺ ,

	C105H152BrN29O18 2186.1052; Found 547.5359		R _T = 9.44 min
16	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C104H153BrN30O18 2189.1162; Found 548.2891	B	m/z 731.5 [M+3H] ³⁺ , R _T = 12.17 min
17	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C103H151CIN30O18 2131.1511; Found 533.7979	B	m/z 712.1 [M+3H] ³⁺ , R _T = 12.36 min
18	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C103H151CIN30O18 2131.1511; Found 533.7974	B	m/z 712.1 [M+3H] ³⁺ , R _T = 10.54 min
19	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C109H156N30O18 2173.2214; Found 544.3148	B	m/z 726.0 [M+3H] ³⁺ , R _T = 11.28 min
20	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C107H154N30O18 2147.2058; Found 537.8120	B	m/z 717.3 [M+3H] ³⁺ , R _T = 10.36 min
21	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C104H153BrN30O18 2189.1162; Found 730.7173	B	m/z 731.7 [M+3H] ³⁺ , R _T = 8.87 min
22	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C104H153BrN30O19 2205.1111; Found 552.2873	B	m/z 553.0 [M+4H] ⁴⁺ , R _T = 7.52 min
23	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C101H149BrN30O18 2149.085; Found 538.2819	B	m/z 718.3 [M+3H] ³⁺ , R _T = 8.05 min
24	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C97H153BrN30O18 2105.1162; Found 527.2892	B	m/z 703.4 [M+3H] ³⁺ , R _T = 10.20 min
25	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C102H149BrN30O18 2161.085; Found 541.2816	B	m/z 722.2 [M+3H] ³⁺ , R _T = 8.44 min
26	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C105H150BrFN28O18 2189.085; Found 548.2808	B	m/z 731.6 [M+3H] ³⁺ , R _T = 8.45 min
27	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C102H149BrN30O18 2161.085; Found 541.2802	B	m/z 1085.4 [M+2H] ²⁺ , R _T = 10.18 min
28	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C103H151BrN30O18 2175.1006; Found 544.7855	B	m/z 545.4 [M+4H] ⁴⁺ , R _T = 7.79 min
29	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C105H155BrN30O18 2203.1318; Found 551.7931	C	m/z 731.1 [M+3H] ³⁺ , R _T = 9.20 min
30	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C103H151BrN30O18 2175.1006; Found 544.7841	B	m/z 545.4 [M+4H] ⁴⁺ , R _T = 10.45 min
31	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C106H154BrN29O18 2200.1211; Found 551.0403	B	m/z 551.5 [M+4H] ⁴⁺ , R _T = 11.13 min
32	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C103H151BrN30O19 2191.0955; Found 548.7840	B	m/z 549.5 [M+4H] ⁴⁺ , R _T = 8.94 min
33	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C103H155BrN28O18 2151.1257; Found 538.7893	B	m/z 719.0 [M+3H] ³⁺ , R _T = 11.49 min
34	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C102H153BrN28O18 2137.1101; Found 535.2855	B	m/z 714.1 [M+3H] ³⁺ , R _T = 9.36 min

35	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C105H151BrN28O18 2171.0945; Found 543.7814	B	m/z 544.4 [M+4H] ⁴⁺ , R _T = 11.01 min
36	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C104H153BrN30O18 2189.1162; Found 548.2872	B	m/z 548.9 [M+4H] ⁴⁺ , R _T = 9.93 min
37 Isomer 1	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C104H151BrN30O18 2187.1006; Found 547.7830	B	m/z 548.3 [M+4H] ⁴⁺ , R _T = 10.23 min
37 Isomer 2	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C104H151BrN30O18 2187.1006; Found 547.7830	B	m/z 548.3 [M+4H] ⁴⁺ , R _T = 10.57 min
38	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C96H137BrN26O17 2004.9839; Found 669.3384	B	m/z 670.0 [M+3H] ³⁺ , R _T = 9.38 min
39	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C97H139BrN26O17 2018.9995; Found 674.0107	C	m/z 1011.3 [M+2H] ²⁺ , R _T = 9.40 min
40	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C96H137BrN26O17 2004.9839; Found 669.3396	B	m/z 670.1 [M+3H] ³⁺ , R _T = 8.59 min
41	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C90H132BrN26O17 2006.863; Found 669.9656	B	m/z 670.8 [M+3H] ³⁺ , R _T = 10.95 min
42	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C97H139BrN26O18 2034.9944; Found 679.3414	B	m/z 680.0 [M+3H] ³⁺ , R _T = 10.26 min
43	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C90H139BrN26O17 1934.9995; Found 646.0105	B	m/z 485.4 [M+4H] ⁴⁺ , R _T = 9.89 min
44	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C97H139BrN26O17 2018.9995; Found 674.0110	B	m/z 506.5 [M+4H] ⁴⁺ , R _T = 11.36 min
45	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C100H141BrN24O17 2029.009; Found 677.3454	B	m/z 678.0 [M+3H] ³⁺ , R _T = 8.80 min
46	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C99H140BrN25O17 2030.0043; Found 677.6786	B	m/z 678.4 [M+3H] ³⁺ , R _T = 8.54 min
47	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C94H137BrN24O18 1968.9727; Found 657.3340	B	m/z 657.9 [M+3H] ³⁺ , R _T = 11.04 min
48	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C98H141BrN26O17 2033.0151; Found 678.6827	B	m/z 679.5 [M+3H] ³⁺ , R _T = 10.33 min
49	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C97H139BrN26O17 2018.9995; Found 674.0111	C	m/z 674.8 [M+3H] ³⁺ , R _T = 9.79 min
50	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C97H139BrN26O17 2018.9995; Found 505.7581	B	m/z 1011.8 [M+2H] ²⁺ , R _T = 9.09 min
51	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C98H141BrN26O17 2033.0151; Found 509.2636	C	m/z 679.3 [M+3H] ³⁺ , R _T = 9.71 min
52	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C98H141BrN26O17 2033.0151; Found 678.6829	C	m/z 679.3 [M+3H] ³⁺ , R _T = 9.57 min
53	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C96H137BrN26O17 2004.9839; Found	B	m/z 1004.7 [M+2H] ²⁺ , R _T = 7.77 min

	669.3397		
54	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C ₉₉ H ₁₄₃ BrN ₂₆ O ₁₇ 2047.0308; Found 683.3554	C	m/z 1025.5 [M+2H] ²⁺ , R _T = 10.34 min
55	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C ₉₇ H ₁₃₉ BrN ₂₆ O ₁₇ 2018.9995; Found 674.0106	B	m/z 674.6 [M+3H] ³⁺ , R _T = 8.48 min
56	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C ₁₀₀ H ₁₄₂ BrN ₂₅ O ₁₇ 2044.0199; Found 512.0138	B	m/z 1024.5 [M+2H] ²⁺ , R _T = 9.41 min
57	HRMS (HESI/FT) m/z: [M+3H] ³⁺ Calcd for C ₉₈ H ₁₄₁ BrN ₂₆ O ₁₇ 2033.0151; Found 678.6834	B	m/z 679.6 [M+3H] ³⁺ , R _T = 7.29 min
58	HRMS (HESI/FT) m/z: [M+2H] ²⁺ Calcd for C ₉₈ H ₁₄₁ BrN ₂₆ O ₁₇ 2033.0151; Found 1017.5146	C	m/z 679.4 [M+3H] ³⁺ , R _T = 10.31 min
59	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C ₉₂ H ₁₃₈ N ₂₆ O ₁₇ 1879.0734; Found 470.7759	B	m/z 471.2 [M+4H] ⁴⁺ , R _T = 11.20 min
60	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C ₉₇ H ₁₄₃ BrN ₂₄ O ₁₇ 1995.0247; Found 499.7643	B	m/z 666.7 [M+3H] ³⁺ , R _T = 11.43 min
61	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C ₉₈ H ₁₄₁ BrN ₂₆ O ₁₇ 2033.0151; Found 509.2617	B	m/z 509.7 [M+4H] ⁴⁺ , R _T = 9.63 min
62	HRMS (HESI/FT) m/z: [M+4H] ⁴⁺ Calcd for C ₉₉ H ₁₄₇ BrN ₂₄ O ₁₇ 2023.0559; Found 506.7721	B	m/z 675.8 [M+3H] ³⁺ , R _T = 10.67 min

ND – Not determined

Biological Activity

- 5 The following examples are provided to illustrate preferred aspects of the invention and are not intended to limit the scope of the invention.

Example A. In vitro pharmacological characterization of Apelin peptides - Functional agonism of human Apelin receptors, cAMP accumulation assay:

- 10 **cAMP functional assay.** cAMP production was quantified using the Homogeneous Time-Resolved Fluorescence (HTRF) cAMP dynamic-2 assay (Cisbio, France). CHO cells stably expressing the human Apelin receptor were seeded at a density of 12,500 cells/well in solid walled 96 well half area plates (Costar). After 16 h incubation at 37°C media was removed and cells were incubated at 37°C for 30 min in serum free media containing 500 µM IBMX
- 15 (Tocris), 3uM forskolin to raise cAMP levels and increasing concentrations of test agonist. cAMP production was determined as manufacturer's instructions before plates were

read on a PheraStar fluorescence plate reader (BMG LabTech) and EC₅₀ values were determined using Graphpad Prism.

Example	Human Apelin agonist cAMP assay		Example	Human Apelin agonist cAMP assay	
	pEC ₅₀	E _{max}		pEC ₅₀	E _{max}
Apelin	8.9	112.8	32	7.8	141.4
1	7.8	27.2	33	7.6	63.0
2	7.7	50.8	34	7.6	60.6
3	8.0	69.5	35	7.2	35.3
4	8.1	79.0	36	8.3	55.7
5	7.8	47.2	37 Isomer 1	8.0	68.6
6	7.7	53.9	37 Isomer 2	8.3	68.9
7	7.7	59.2	38	7.5	27.9
8	7.8	56.1	39	7.5	62.1
9	8.2	86.9	40	7.6	84.8
10	7.7	52.5	41	7.3	46.1
11	7.9	90.6	42	8.1	106.7
12	8.1	98.9	43	7.0	95.7
13	7.6	72.9	44	7.3	34.7
14	8.1	77.0	45	7.4	59.0
15	8.1	86.4	46	7.4	55.0
16	8.3	64.8	47	7.9	94.2
17	7.6	78.8	48	7.0	33.5
18	7.1	47.5	49	8.1	87.2
19	7.7	97.0	50	7.4	56.5
20	7.9	84.1	51	7.1	27.6
21	8.0	54.5	52	7.2	20.4
22	8.1	98.1	53	7.5	79.2
23	7.6	43.4	54	8.9	61.2
24	7.5	87.9	55	7.9	85.9
25	7.8	92.7	56	7.7	68.1
26	7.5	64.4	57	7.2	45.9
27	8.2	66.1	58	6.1	33.0
28	7.8	27.4	59	7.0	48.1
29	8.6	69.7	60	7.3	59.0
30	8.3	106.3	61	8.0	41.8
31	8.0	75.4	62	7.0	31.7

5 **Example B. In vitro pharmacological characterization of Apelin peptides - Functional agonism of human Apelin receptors, β -arrestin accumulation assay:**

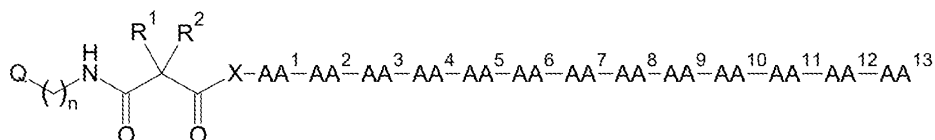
β -arrestin assay. CHO-K1 cells engineered to overexpress the human Apelin receptor and β -arrestin (DiscoverRx) were seeded at a density of 12,500 cells/well in solid walled 96 well half area plates (Costar). After 16 h incubation at 37°C media was removed and cells were
 10 incubated at 37°C for 90 min in serum free media containing increasing concentrations of test agonist. The assay reaction was stopped by adding detection reagent (DiscoverRx) and incubation for 60 min in the dark. Levels of receptor activation were then measured on a

PheraStar fluorescence plate reader (BMG LabTech) and EC₅₀ values were determined using Graphpad Prism. Emax value only reported for active compounds

Example	Human Apelin agonist β -arrestin assay	Example	Human Apelin agonist β -arrestin assay
	pEC ₅₀ (Emax)		pEC ₅₀ (Emax)
Apelin	8.6 (165.8)	32	<5
1	<5	33	<5
2	<5	34	<5
3	<5	35	<5
4	<5	36	<4
5	<5	37 Isomer 1	<4
6	<5	37 Isomer 2	<4
7	<5	38	<5
8	<5	39	<5
9	<5	40	<5
10	<5	41	<5
11	<5	42	7.1 (26)
12	<5	43	<5
13	<5	44	<5
14	<5	45	<5
15	<5	46	<5
16	<6	47	<6
17	<5	48	<5
18	<5	49	<5
19	<5	50	<5
20	<5	51	<5
21	<6	52	<5
22	<5	53	<5
23	<5	54	<5
24	<5	55	<5
25	<5	56	<5
26	<5	57	<5
27	<5	58	<4
28	<5	59	<5
29	<5	60	<5
30	<5	61	<4
31	<5	62	<5

Claims

1. A compound comprising the sequence of formula (1):



5 (1);

wherein;

Q is selected from phenyl or a monocyclic heteroaryl ring each of which may be optionally substituted with one or more R^q groups; or Q is a polyether chain
 10 of formula $-(\text{OCH}_2\text{CH}_2)_m\text{OCH}_3$, wherein m is 1 to 5;

R^q is selected from halogen, hydroxyl, amino or C_{1-6} alkyl having an alkyl chain optionally containing one or more heteroatoms selected from O, N, or S;

15 n is 1 to 3;

R^1 and R^2 are independently selected from hydrogen or a C_{1-6} alkyl group, or together with the carbon to which they are attached join to form a C_{3-8} cycloalkyl or a heterocyclyl group;

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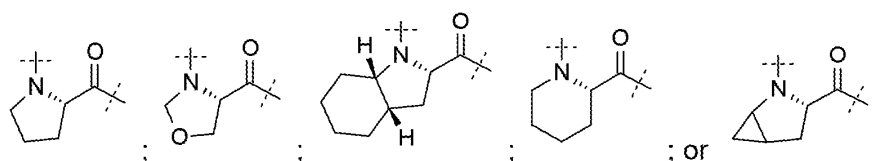
X is -DArg- or a bond;

AA^1 is $-\text{NHCR}^{3a}\text{R}^{3b}\text{CO}-$ or $-\text{N}(\text{Me})\text{CR}^{3a}\text{R}^{3b}\text{CO}-$; wherein R^{3a} is hydrogen or C_{1-3} alkyl; and R^{3b} is $-\text{CH}_2(\text{CH}_2)_p\text{CONH}_2$ or $-(\text{CH}_2)_p\text{benzyl}$, where p is 0 or 1;

25

AA^2 is -Arg-, -DArg- or a homoarginine residue;

AA^3 is a residue selected from:



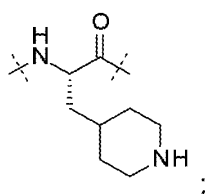
AA⁴ is -Arg- or -DArg-;

AA⁵ is -NHCH(CH₂R⁴)CO- or -N(Me)CH(CH₂R⁴)CO-; wherein R⁴ is C₁₋₆ alkyl,
 5 C₁₋₆ cycloalkyl or C₁₋₆ branched alkyl;

AA⁶ is -Aib-, -DAla- or -Ser-;

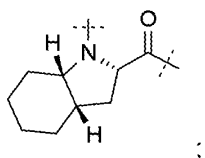
AA⁷ is -NHCR^{5a}R^{5b}CO- or -N(Me)CR^{5a}R^{5b}CO-; wherein R^{5a} is hydrogen or C₁₋₃
 10 alkyl and R^{5b} is C₁₋₃ alkyl, CH₂-aryl or CH₂-heteroaryl optionally substituted
 with one or more halo groups or C₁₋₃ alkyl groups;

AA⁸ is the residue:



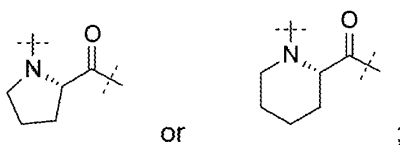
AA⁹ is -Gly-, -Ala-, -DAla- or an N-methyl glycine residue;

AA¹⁰ is the residue:



AA¹¹ is -NHCHR⁶CO-; wherein R⁶ is C₁₋₆ alkyl, benzyl, -CH₂-naphthyl or -CH₂-
 20 biphenyl optionally substituted with one or more halo groups;

AA¹² is a residue selected from:

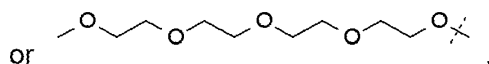
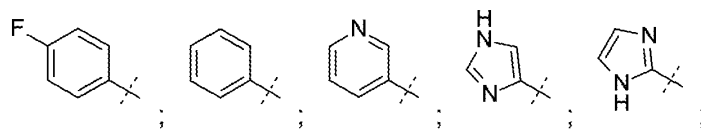


AA¹³ is -NHCR^{7a}R^{7b}CO- or -N(Me)CR^{7a}R^{7b}CO-; wherein R^{7a} is hydrogen or C₁₋₃ alkyl and R^{7b} is C₁₋₁₀ alkyl, -CH₂-naphthyl, -CH₂-biphenyl or benzyl optionally substituted with one or more R⁸ groups, wherein R⁸ is selected from halo, -O-aryl or -O-benzyl;

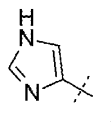
wherein the AA¹³ C-terminus is a carboxyl group or a carboxamide group;

or a tautomeric or stereochemically isomeric form thereof or a prodrug, salt or zwitterion thereof.

2. The compound according to claim 1, wherein Q is selected from:



3. The compound according to claim 2, wherein Q is:



4. The compound according to claim 3, wherein n is 2.

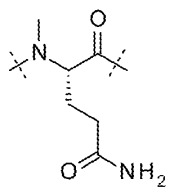
5. The compound according to any one of claims 1 to 4, wherein R¹ and R² are independently selected from hydrogen or a C₁₋₆ alkyl group.

6. The compound according to claim 5, wherein R¹ and R² are both methyl.

7. The compound according to any one of claims 1 to 6, wherein X is -DArg-.

8. The compound according to any one of claims 1 to 6, wherein X is a bond.

9. The compound according to any one of claims 1 to 8, wherein AA¹ is a glutamine residue, a D-glutamine residue, a homophenylalanine residue or an N-methyl glutamine residue of the formula:



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10. The compound according to claim 9, wherein AA¹ is a glutamine residue.

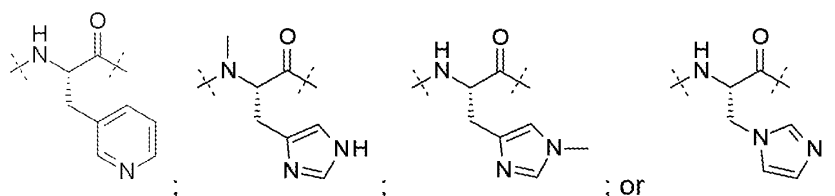
11. The compound according to any one of claims 1 to 10, wherein AA⁵ is a leucine residue, a D-leucine residue, a *tert*-butylalanine residue, a cyclobutylalanine residue or an N-methyl leucine residue.

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12. The compound according to claim 11, wherein AA⁵ is a leucine residue.

13. The compound according to any one of claims 1 to 12, wherein AA⁷ is a 2-aminoisobutyric acid residue, a histidine residue, a 4-bromophenylalanine residue or is a residue selected from:

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14. The compound according to claim 13, wherein AA⁷ is a histidine residue.

20

15. The compound according to any one of claims 1 to 14, wherein AA¹¹ is a phenylalanine residue, a 2-naphthylalanine residue, a 3-chlorophenylalanine residue, a 4-bromophenylalanine residue, a 4-chlorophenylalanine residue, a norleucine residue or a 4-phenylphenylalanine residue.

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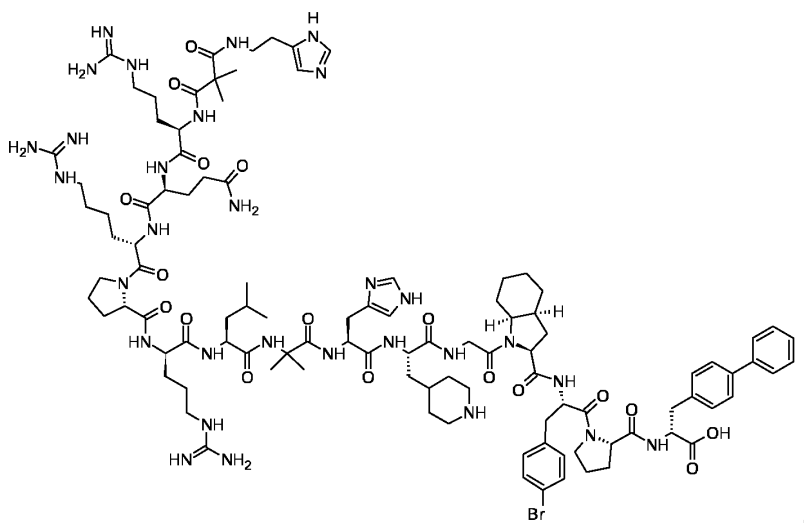
16. The compound according to claim 15, wherein AA¹¹ is a 4-bromophenylalanine residue.

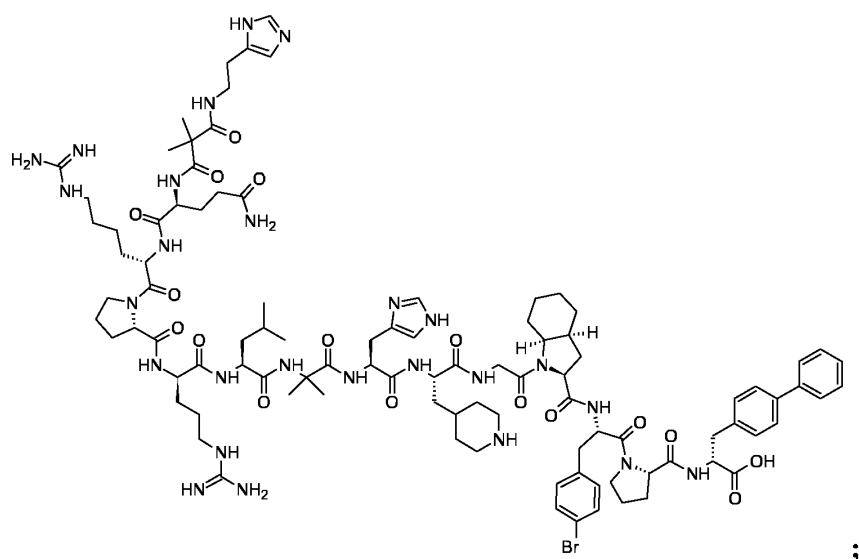
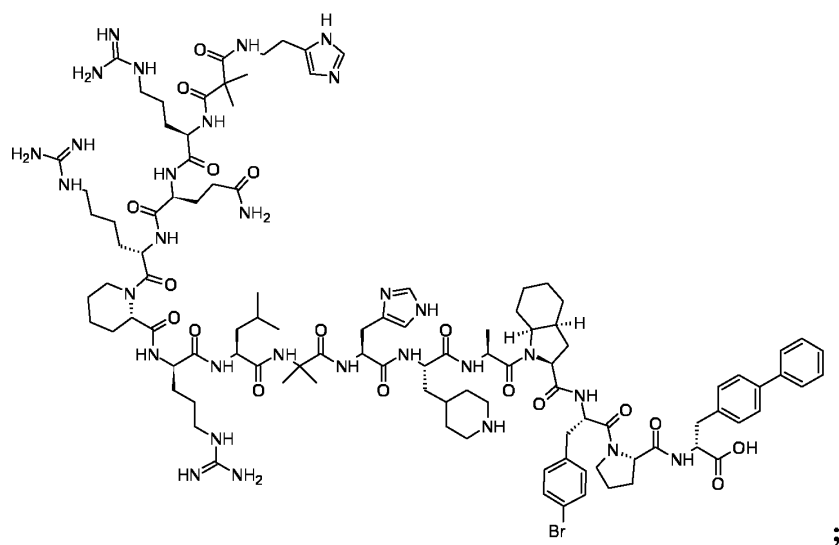
17. The compound according to any one of claims 1 to 16, wherein AA¹³ is an O-benzyl-D-tyrosine residue, a 4-bromo-D-phenylalanine residue, a 4-phenoxy-D-phenylalanine residue, a 2-naphthyl-D-alanine residue, a 4-phenyl-D-phenylalanine residue, an N-methyl 4-phenyl-D-phenylalanine residue or a beta-cyclohexyl-D-alanine residue.

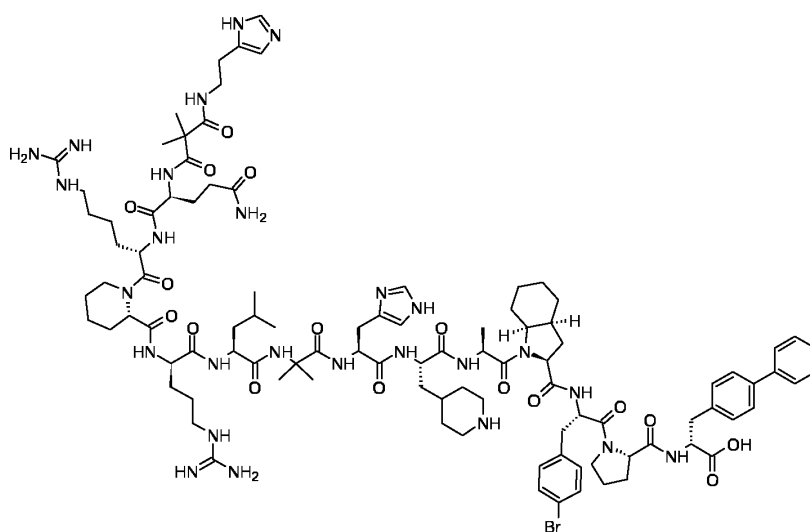
18. The compound according to claim 17, wherein AA¹³ is a 4-phenyl-D-phenylalanine residue.

19. The compound according to any one of claims 1 to 18, wherein the AA¹³ C-terminus is a carboxyl group.

20. The compound according to claim 1 which is selected from:







21. The compound according to any one of claims 1 to 20 having apelin receptor agonist activity.

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22. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 21 and a pharmaceutically acceptable excipient.

23. The compound according to any one of claims 1 to 22 for use in medicine.

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24. The compound or composition according to any one of claims 1 to 23 for use in the treatment of cardiovascular disease, acute decompensated heart failure, congestive heart failure, myocardial infarction, cardiomyopathy, ischemia, ischemia/reperfusion injury, pulmonary hypertension, diabetes, obesity, cancer, metastatic disease, fluid homeostasis, pathological angiogenesis, retinopathy, HIV infection, treatment of pulmonary arterial hypertension (PAH) increasing cardiac output, reducing pulmonary vessel hypertension, reducing inflammation, improve pulmonary tissue remodelling, preserving right heart ventricular function, heart failure, congestive heart failure, cardiomyopathy, ischemia, ischemia/reperfusion injury, fluid homeostasis, kidney failure, hypertension, pulmonary hypertension, polycystic kidney disease, hyponatremia, SIADH, platelet function are associated with a range of thrombotic diseases such as peripheral arterial disease (PAD), acute

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5 coronary syndrome (ACS), myocardial infarction (MI), heart attacks (HA), stroke, atherosclerosis, treatment and management of diabetes and associated related metabolic conditions, diabetic complications (for example diabetic nephropathy, retinopathy, neuropathy, non-alcoholic fatty liver disease, non-alcoholic steatosis, portal hypertension) and conditions where stimulation and/or growth and/or endurance of muscle mass may be considered beneficial.