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(54) **Titre : COMPOSES HETEROCYCLIQUES COMME ANTAGONISTES DU RECEPTEUR DE TYPE 2 DE L'ANGIOTENSINE II**
(54) **Title: HETEROCYCLIC COMPOUNDS AS ANGIOTENSIN II TYPE 2 RECEPTOR ANTAGONISTS**

(57) **Abrégé/Abstract:**

The present invention relates to heterocyclic compounds useful for antagonising angiotensin II Type 2 (AT₂) receptor. More particularly the invention relates to pyrrolidine and azetidine compounds, compositions containing them and their use in methods of treating or preventing disorders or diseases associated with AT₂ receptor function including neuropathic pain, inflammatory pain, conditions associated with neuronal hypersensitivity, impaired nerve conduction velocity, cell proliferation disorders, disorders associated with an imbalance between bone resorption and bone formation and disorders associated with aberrant nerve regeneration.

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(54) Title: HETEROCYCLIC COMPOUNDS AND METHODS FOR THEIR USE

(57) Abstract: The present invention relates to heterocyclic compounds useful for antagonising angiotensin II Type 2 (AT₂) receptor. More particularly the invention relates to pyrrolidine and azetidine compounds, compositions containing them and their use in methods of treating or preventing disorders or diseases associated with AT₂ receptor function including neuropathic pain, inflammatory pain, conditions associated with neuronal hypersensitivity, impaired nerve conduction velocity, cell proliferation disorders, disorders associated with an imbalance between bone resorption and bone formation and disorders associated with aberrant nerve regeneration.



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Heterocyclic Compounds As Angiotensin II Type 2 Receptor Antagonists

Fields of the Invention

The present invention relates generally to compounds that are useful in antagonizing the
5 angiotensin II type 2 (AT₂) receptor. More particularly, the invention relates to
heterocyclic compounds of formula (I) and their use as AT₂ receptor antagonists.
Pharmaceutical compositions comprising the compounds and their use in modulating the
AT₂ receptor and therapies that require modulation of the AT₂ receptor are described.

10 Background of the Invention

Although AT₂ receptor has been known since the 1980s, much less is known about its
biological function than the angiotensin II type 1 (AT₁) receptor, which has been studied
for its functional effects on vasoconstriction, aldosterone release and cardiovascular
growth [Wexler *et al.*, 1996]. However, more recently the AT₂ receptor has been
15 implicated in the differentiation and regeneration of neuronal tissue [Steckelings *et al.*,
2005; Chakrabarty *et al.*, 2008], cell proliferation and angiogenesis [Clere *et al.*, 2010] and
maintenance of bone mass [Izu *et al.*, 2009].

AT₂ receptor antagonists have also recently been associated with the treatment of pain,
20 particularly inflammatory pain [WO 2007/106938] and neuropathic pain [WO
2006/066361], two types of pain which are difficult to treat or relieve. Impaired nerve
conduction velocity is also associated with nerve damage and has been implicated in
peripheral neuropathies, Carpel Tunnel Syndrome, ulnar neuropathy, Guillian-Barré
Syndrome, fascioscapulohumeral muscular dystrophy and spinal disc herniation. Impaired
25 nerve conduction velocity can result in diminished reflex responses and altered peripheral
sensation such as parathesia and in some cases pain and AT₂ receptor antagonists have
been shown to restore nerve conduction velocity [WO 2011/088504].

While there are effective therapies for treating nociceptive pain, inflammatory and
30 neuropathic pain are often resistant to these therapies. In addition, current therapies of
neuropathic pain, inflammatory pain, impaired nerve conduction velocity and other types

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of pain that are difficult to treat, have serious side effects, for example, cognitive changes, sedation, nausea and in the case of narcotic drugs, tolerance and dependence. There is a need for further therapies that treat or prevent neuropathic pain, inflammatory pain, impaired nerve conduction velocity and other painful conditions that are currently difficult
5 to treat.

Cell proliferation and angiogenesis are important biological functions in normal tissue. However, uncontrolled cell proliferation and angiogenesis can lead to tumors and other proliferative disorders. While there are some effective chemotherapies available for
10 tumors, many result in unpleasant side effects and/or have high toxicity for normal cells. Further therapies for reducing or preventing abnormal cell proliferation in a controlled manner are required and AT₂ receptor antagonists have been shown to have antiproliferative activity [Clere *et al.*, 2010].

15 Osteoporosis is a significant problem in older populations, especially in post-menopausal women. Current therapies for osteoporosis rely on calcium supplementation. However, the control of bone formation and bone resorption is complex and further therapies for improving bone mass are required and AT₂ receptor antagonists have been shown to increase bone mass [Izu *et al.*, 2009].

20

The role of the AT₂ receptor in modulating neuronal outgrowth and associated effects of AT₂ receptor antagonists on reducing neuronal outgrowth, indicates that AT₂ receptor antagonists may be useful therapeutics in diseases characterized by aberrant nerve regeneration [Chakrabarty *et al.*, 2008].

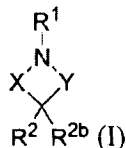
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The present invention is predicated in part on the discovery of heterocyclic azetidine and pyrrolidine compounds that have AT₂ receptor antagonist activity.

Summary of the Invention

30 In a first aspect of the present invention there is provided a compound of formula (I):

- 3 -



wherein:

X is absent and Y is $-\text{CHR}^3\text{CH}_2-$, $-\text{CH}_2\text{CHR}^3-$, $-\text{CHR}^3\text{CHR}^4\text{CH}_2-$, $-\text{CH}_2\text{CHR}^3\text{CHR}^4-$, $-\text{CH}_2\text{CH}_2\text{CHR}^3-$, $-\text{CR}^3=\text{CHCH}_2-$, $-\text{CH}=\text{CHR}^3\text{CH}_2-$ or $-\text{CH}_2\text{CH}=\text{CR}^3-$; or

5 X is $-\text{CHR}^5$ and Y is $-\text{CHR}^3-$, $-\text{CHR}^3\text{CHR}^4-$, $-\text{CH}_2\text{CHR}^3-$, $-\text{CHR}^3\text{CR}^4=$, $-\text{CR}^3=\text{CH}-$ or $-\text{CH}=\text{CR}^3-$; wherein when Y is $-\text{CHR}^3\text{CR}^4=$, R^{2b} is absent; or

X is $-\text{CH}_2\text{CHR}^5-$ or $\text{C}(=\text{O})\text{CHR}^5-$ and Y is $-\text{CHR}^3-$;

R^1 is $-\text{C}(=\text{O})\text{CHR}^6\text{R}^7$, $-\text{C}(=\text{O})\text{NR}^6\text{R}^7$, $-\text{C}(=\text{O})\text{CH}_2\text{CHR}^6\text{R}^7$, $-\text{C}(=\text{O})\text{CH}=\text{CR}^6\text{R}^7$, $-\text{C}(=\text{S})\text{CHR}^6\text{R}^7$, $-\text{C}(=\text{S})\text{NR}^6\text{R}^7$, $-\text{C}(=\text{S})\text{CH}_2\text{CHR}^6\text{R}^7$, $-\text{C}(=\text{S})\text{CH}=\text{CR}^6\text{R}^7$, $-\text{C}(=\text{NR}^8)\text{CHR}^6\text{R}^7$, $-\text{C}(=\text{NR}^8)\text{NR}^6\text{R}^7$, $-\text{C}(=\text{NR}^8)\text{CH}_2\text{CHR}^6\text{R}^7$ and $-\text{C}(=\text{NR}^8)\text{CH}=\text{CR}^6\text{R}^7$;

R^2 is $-\text{C}_{1-6}\text{alkyl}$, $-\text{C}_{2-6}\text{alkenyl}$, $-\text{C}_{2-6}\text{alkynyl}$, $-\text{OR}^8$, $-\text{SR}^8$, $-\text{N}(\text{R}^8)_2$, $-\text{C}(=\text{O})\text{R}^8$, $-\text{C}(=\text{O})\text{N}(\text{R}^8)_2$, $-\text{N}(\text{R}^8)\text{C}(=\text{O})\text{R}^8$, $-\text{N}(\text{R}^8)\text{C}(=\text{O})\text{N}(\text{R}^8)_2$, $-\text{N}(\text{R}^8)\text{SO}_2\text{R}^8$, $-\text{SO}_2\text{N}(\text{R}^8)_2$, $-\text{N}(\text{R}^8)\text{SO}_2\text{N}(\text{R}^8)_2$, $-\text{W}$ -cycloalkyl, $-\text{W}$ -cycloalkenyl, $-\text{W}$ -aryl, $-\text{W}$ -heterocyclyl, $-\text{W}$ -heteroaryl, $-\text{W}$ -Z-W-cycloalkyl, $-\text{W}$ -Z-W-cycloalkenyl, $-\text{W}$ -Z-W-aryl, $-\text{W}$ -Z-W-heterocyclyl or $-\text{W}$ -Z-W-

15 heteroaryl, $=\text{CH}-\text{C}(=\text{O})-\text{J}-\text{R}^{10}$, $=\text{CHC}(=\text{O})\text{NH}-\text{J}-\text{R}^{10}$, $-\text{OCH}_2\text{CHR}^{10}\text{CH}_2\text{R}^{10}$ or $-\text{OCH}_2\text{C}(\text{R}^{10})=\text{CHR}^{10}$;

R^{2b} is hydrogen;

R^3 is a carboxylic acid, $-\text{CH}_2\text{CO}_2\text{H}$, $-\text{C}(=\text{O})\text{C}(=\text{O})\text{OH}$, $-\text{CH}_2\text{OH}$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{CN}$, $-\text{CH}_2\text{C}(\text{O})\text{NH}_2$, $-\text{CH}_2\text{CN}$, a carboxylic acid bioisostere or $-\text{CH}_2\text{carboxylic acid}$

20 bioisostere;

R^4 is hydrogen or R^3 and R^4 together form a group:



where R^{11} is a carboxylic acid, $-\text{CH}_2\text{CO}_2\text{H}$, $-\text{C}(=\text{O})\text{C}(=\text{O})\text{OH}$, $-\text{CH}_2\text{OH}$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{CN}$, $-\text{CH}_2\text{C}(\text{O})\text{NH}_2$, $-\text{CH}_2\text{CN}$, a carboxylic acid bioisostere or $-\text{CH}_2\text{carboxylic acid bioisostere}$;

25 R^5 is hydrogen or together with R^2 forms a fused aryl, heterocyclyl or heteroaryl ring, optionally substituted with one or two optional substituents selected from $-\text{C}_{1-6}\text{alkyl}$, $-\text{C}_{2-6}\text{alkenyl}$, $-\text{C}_{2-6}\text{alkynyl}$, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, $-\text{C}_{1-6}\text{alkyleneR}^{10}$, $-\text{C}_{2-6}\text{alkenyleneR}^{10}$, $-\text{C}_{2-6}\text{alkynyleneR}^{10}$, $-\text{OCF}_3$, $-\text{OCHF}_2$, $-\text{OR}^9$,

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- OC₁₋₆alkyleneR¹⁰, -OC₂₋₆alkenyleneR¹⁰, -OC₂₋₆alkynyleneR¹⁰, -SO₂NHR⁹, -NHSO₂R⁹, -NHC(=O)NHR⁹, -NHC(=O)OR⁹ or -CH(OH)CH(OH)R⁹;
- R⁶ and R⁷ are independently hydrogen, -C₁₋₆alkyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, -CH₂aryl, -CH₂cycloalkyl, -CH₂cycloalkenyl, -CH₂heterocyclyl or
- 5 -CH₂heteroaryl; provided that R⁶ and R⁷ are not both hydrogen;
- R⁸ is hydrogen, -C₁₋₈alkyl, -C₁₋₈fluoroalkyl, aryl, -C₁₋₈alkylenearyl, -C₂₋₈alkenylenearyl or -C₂₋₈alkynylenearyl;
- R⁹ is -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, arylcycloalkyl-, arylcycloalkenyl-, arylaryl-, arylheterocyclyl- or
- 10 arylheteroaryl-;
- W is a covalent bond, -O-, -S-, -SO-, -SO₂-, -N(R⁸)-, -C(=O)-, -N(R⁸)C(=O)-, -C(=O)N(R⁸)-, -C₁₋₄alkylene-, -C₂₋₄alkenylene-, -C₂₋₄alkynylene-, -C₁₋₃alkyleneQC₁₋₃alkylene-, -QC₁₋₄alkylene-, -QC₂₋₄alkenylene-, -QC₂₋₄alkynylene-, -C₁₋₄alkyleneQ-, -C₂₋₄alkenyleneQ-, -C₂₋₄alkynyleneQ-, -QC₁₋₄alkyleneQ-, -QC₂₋₄alkenyleneQ- or
- 15 -OC₂₋₄alkynyleneQ-;
- Q is -O-, -S-, -SO-, -SO₂-, -N(R⁸)-, -C(=O)-, -N(R⁸)C(=O)-, -C(=O)N(R⁸)-,
- Z is -cycloalkyl-, -cycloalkenyl-, -aryl-, -heterocyclyl- or -heteroaryl-;
- J is a covalent bond or -C₁₋₆alkylene-, -C₂₋₆alkenylene- or -C₂₋₆alkynylene, in which one -CH₂- group in the alkylene, alkenylene or alkynylene group may be replaced by -O-, -S-,
- 20 -S(O)-, -S(O)₂-, -N(R⁸)-, -C(=O)-, -C(=O)NH- or -NHC(=O)-;
- R¹⁰ is cycloalkyl, cycloalkenyl, aryl, heterocyclyl or heteroaryl; and
- wherein each cycloalkyl, cycloalkenyl, aryl, heterocyclyl and heteroaryl may be optionally substituted;
- or a pharmaceutically acceptable salt thereof.

25

In another aspect, the present invention provides a pharmaceutical composition comprising the compounds of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

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In a further aspect of the invention, there is provided a method of treating or preventing neuropathic pain in a subject comprising administering a compound of formula (I) or a pharmaceutically acceptable salt thereof.

- 5 In yet a further aspect of the invention there is provided a method of treating or preventing a condition characterized by neuronal hypersensitivity in a subject comprising administering a compound of formula (I) or a pharmaceutically acceptable salt thereof.

- 10 In yet another aspect of the invention, there is provided a method of treating or preventing inflammatory pain in a subject comprising administering a compound of formula (I) or a pharmaceutically acceptable salt thereof.

- 15 In a further aspect, the present invention provides a method of treating or preventing impaired nerve conduction velocity in a subject comprising administering a compound of formula (I) or a pharmaceutically acceptable salt thereof.

- 20 In yet a further aspect of the invention there is provided a method of producing analgesia in a subject comprising administering a compound of formula (I) or a pharmaceutically acceptable salt thereof.

- In still another aspect of the invention there is provided a method of treating or preventing a cell proliferative disorder in a subject comprising administering a compound of formula (I) or a pharmaceutically acceptable salt thereof.

- 25 In a further aspect the present invention provides a method of treating or preventing a disorder associated with an imbalance between bone resorption and bone formation in a subject comprising administering a compound of formula (I) or a pharmaceutically acceptable salt thereof.

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In yet another aspect the present invention provides a method of treating a disorder associated with aberrant nerve regeneration in a subject comprising administering a compound of formula (I) or a pharmaceutically acceptable salt thereof.

5 Description of the Invention

Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by those of ordinary skill in the art to which the invention belongs. Although any methods and materials similar or equivalent to those
10 described herein can be used in the practice or testing of the present invention, preferred methods and materials are described. For the purposes of the present invention, the following terms are defined below.

The articles "a" and "an" are used herein to refer to one or to more than one (i.e. to at least
15 one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

As used herein, the term "about" refers to a quantity, level, value, dimension, size, or amount that varies by as much as 30%, 25%, 20%, 15% or 10% to a reference quantity,
20 level, value, dimension, size, or amount.

As used herein, the term "AT₂ receptor" means an angiotensin II type 2 (AT₂) receptor polypeptide that can bind angiotensin II and/or one or more other ligands. The term "AT₂ receptor" encompasses vertebrate homologs of AT₂ receptor family members, including,
25 but not limited to, mammalian, reptilian and avian homologs. Representative mammalian homologs of AT₂ receptor family members include, but are not limited to, murine and human homologs.

The term "antagonist" as used herein refers to a compound that decreases or inhibits the
30 biological activity and/or function of an AT₂ receptor, including binding to the AT₂ receptor and blocking access to angiotensin II, inhibiting a gene that expresses AT₂

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receptor, or inhibiting an expression product of that gene. By the term "selective", is meant that the compound binds to and/or inhibits AT₂ receptor activity to a greater extent than binding and inhibition of the AT₁ receptor. In some instances, selective refers to binding and/or inhibition of the AT₂ receptor with little or no binding at the AT₁ receptor.

5

The term "allodynia" as used herein refers to the pain that results from a non-noxious stimulus i.e. pain due to a stimulus that does not normally provoke pain. Examples of allodynia include, but are not limited to, cold allodynia, tactile allodynia (pain due to light pressure or touch), and the like.

10

The term "analgesia" is used herein to describe states of reduced pain perception, including absence from pain sensations as well as states of reduced or absent sensitivity to noxious stimuli. Such states of reduced or absent pain perception are induced by the administration of a pain-controlling agent or agents and occur without loss of consciousness, as is commonly understood in the art. The term analgesia encompasses the term "antinociception", which is used in the art as a quantitative measure of analgesia or reduced pain sensitivity in animal models.

15

The term "anti-allodynia" is used herein to describe states of reduced pain perception, including absence from pain sensations as well as states of reduced or absent sensitivity to non-noxious stimuli. Such states of reduced or absent pain perception are induced by the administration of a pain-controlling agent or agents and occur without loss of consciousness, as is commonly understood in the art.

20

The term "causalgia" as used herein refers to the burning pain, allodynia, and hyperpathia after a traumatic nerve lesion, often combined with vasomotor and sudomotor dysfunction and later trophic changes.

25

By "complex regional pain syndromes" is meant the pain that includes, but is not limited to, reflex sympathetic dystrophy, causalgia, sympathetically maintained pain, and the like.

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By "condition characterized by neuronal hypersensitivity" is meant conditions that have symptoms of pain related to neuronal hypersensitivity and/or allodynia. Examples of this type of condition include fibromyalgia and irritable bowel syndrome.

- 5 By "disorder associated with aberrant nerve regeneration" is meant disorders in which there is abnormal axon outgrowth in neurons. This abnormal outgrowth may be associated with painful conditions including breast pain, interstitial cystitis, vulvodynia and cancer chemotherapy-induced neuropathies.
- 10 Throughout this specification, unless the context requires otherwise, the words "comprise", "comprises" and "comprising" will be understood to imply the inclusion of a stated step or element or group of steps or elements but not the exclusion of any other step or element or group of steps or elements.
- 15 By "hyperalgesia" is meant an increased response to a stimulus that is normally painful. A hyperalgesia condition is one that is associated with pain caused by a stimulus that is not normally painful.

- By "neuropathic pain" is meant any pain syndrome initiated or caused by a primary lesion or dysfunction in the peripheral or central nervous system. Examples of neuropathic pain include, but are not limited to, thermal or mechanical hyperalgesia, thermal or mechanical allodynia, diabetic pain, entrapment pain, and the like.
- 20

- The term "nociceptive pain" refers to the normal, acute pain sensation evoked by activation of nociceptors located in non-damaged skin, viscera and other organs in the absence of sensitization.
- 25

- As used herein "inflammatory pain" refers to pain induced by inflammation. Such types of pain may be acute or chronic and can be due to any number of conditions characterized by inflammation including, without limitation, burns including chemical, frictional or thermal burns, autoimmune diseases such as rheumatoid arthritis, osteoarthritis and inflammatory
- 30

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bowel disease including Crohn's disease and colitis, as well as other inflammatory diseases including carditis, dermatitis, myositis, neuritis and collagen vascular diseases.

The term "pain" as used herein is given its broadest sense and includes an unpleasant
5 sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage and includes the more or less localized sensation of discomfort, distress, or agony, resulting from the stimulation of specialized nerve endings. There are many types of pain, including, but not limited to, lightning pains, phantom pains, shooting pains, acute pain, inflammatory pain, neuropathic pain, complex regional pain,
10 neuralgia, neuropathy, and the like (Dorland's Illustrated Medical Dictionary, 28th Edition, W. B. Saunders Company, Philadelphia, Pa.). The goal of treatment of pain is to reduce the degree of severity of pain perceived by a treatment subject.

By the phrases "impaired NCV" or "impaired nerve conduction velocity" and the like is
15 meant any nerve conduction demonstrably abnormal in any one of the parameters assessed for normal nerve signal conduction. Whether the various parameters of NCV are normal is typically an assessment made by the relevant trained clinician. General background, terminology and procedures known to those in the art for evaluating NCV are described in "Proper performance and interpretation of electrodiagnostic studies' Muscle Nerve. (2006)
20 33(3):436-439 and "Electrodiagnostic medicine listing of sensory, motor, and mixed nerves." Appendix J of Current Procedural Terminology (CPT) 2007, authored by The American Association of Neuromuscular & Electrodiagnostic Medicine and published by the American Medical Association. Impaired or abnormal nerve conduction velocity is a symptom of nerve dysfunction or damage and may be causal to or a symptom of a large
25 number of diseases or disorders, particularly diseases or disorders that exhibit diminished reflex responses and altered peripheral sensation including paresthesia. As used herein, "paresthesia" refers to a sensation of tingling, prickling, weakness or numbness in a subject's skin. It is also known as "pins and needles" or a limb "falling asleep". Paresthesia may be transient, acute or chronic and may occur alone or be accompanied by
30 other symptoms such as pain.

- 10 -

As used herein, the term "cell proliferative disorder" refers to diseases or conditions where unwanted or damaged cells are not removed by normal cellular process, or diseases or conditions in which cells undergo aberrant, unwanted or inappropriate proliferation. Disorders characterized by inappropriate cell proliferation include, for example, 5 inflammatory conditions such as inflammation arising from acute tissue injury including, for example, acute lung injury, cancer including cancers characterized by tumors, autoimmune disorders, tissue hypertrophy and the like.

The term "disorder associated with an imbalance between bone resorption and bone 10 formation" includes disorders where there is insufficient development of bone mass, excessive bone resorption and insufficient bone formation during remodelling. An exemplary disorder associated with an imbalance between bone resorption and bone formation is osteoporosis.

15 As used herein, the term "alkyl" refers to a straight chain or branched saturated hydrocarbon group having 1 to 10 carbon atoms. Where appropriate, the alkyl group may have a specified number of carbon atoms, for example, C₁₋₆alkyl which includes alkyl groups having 1, 2, 3, 4, 5 or 6 carbon atoms in a linear or branched arrangement. Examples of suitable alkyl groups include, but are not limited to, methyl, ethyl, *n*-propyl, 20 *i*-propyl, *n*-butyl, *i*-butyl, *t*-butyl, *n*-pentyl, 2-methylbutyl, 3-methylbutyl, 4-methylbutyl, *n*-hexyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 5-methylpentyl, 2-ethylbutyl, 3-ethylbutyl, heptyl, octyl, nonyl and decyl.

The term "fluoroalkyl" as used herein refers to an alkyl group in which one or more 25 hydrogen atoms of the alkyl group is replaced with a fluoro atom. Where appropriate, the alkyl group may have a specified number of carbon atoms, for example, C₁₋₆fluoroalkyl which includes fluoroalkyl groups having 1, 2, 3, 4, 5 or 6 carbon atoms in a linear or branched arrangement. Examples of fluoroalkyl groups include fluoromethyl, difluoromethyl, trifluoromethyl, 1-fluoroethyl, 2-fluoroethyl, 1,1-difluoroethyl, 2,2- 30 fluoroethyl, 1,1,2-trifluoroethyl, 2,2,2-trifluoroethyl, 1,1,2,2,2-pentafluoroethyl, 3-fluoropropyl, 3,3-difluoropropyl, 3,3,3-trifluoropropyl, 4-fluorobutyl, 4,4-difluorobutyl,

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4,4,4-trifluorobutyl, 5-fluoropentyl, 5,5-difluoropentyl, 5,5,5-trifluoropentyl, 6-fluorohexyl, 6,6-difluorohexyl or 6,6,6-trifluorohexyl and the like.

As used herein, the term "alkenyl" refers to a straight-chain or branched hydrocarbon group having one or more double bonds between carbon atoms and having 2 to 10 carbon atoms. Where appropriate, the alkenyl group may have a specified number of carbon atoms. For example, C₂-C₆ as in "C₂-C₆alkenyl" includes groups having 2, 3, 4, 5 or 6 carbon atoms in a linear or branched arrangement. Examples of suitable alkenyl groups include, but are not limited to, ethenyl, propenyl, isopropenyl, butenyl, butadienyl, pentenyl, pentadienyl, hexenyl, hexadienyl, heptenyl, octenyl, nonenyl and decenyl.

As used herein, the term "alkynyl" refers to a straight-chain or branched hydrocarbon group having one or more triple bonds and having 2 to 10 carbon atoms. Where appropriate, the alkynyl group may have a specified number of carbon atoms. For example, C₂-C₆ as in "C₂-C₆alkynyl" includes groups having 2, 3, 4, 5 or 6 carbon atoms in a linear or branched arrangement. Examples of suitable alkynyl groups include, but are not limited to ethynyl, propynyl, butynyl, pentynyl and hexynyl.

As used herein, the term "cycloalkyl" refers to a saturated cyclic hydrocarbon. The cycloalkyl ring may include a specified number of carbon atoms. For example, a 3 to 8 membered cycloalkyl group includes 3, 4, 5, 6, 7 or 8 carbon atoms. Examples of suitable cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

As used herein, the term "cycloalkenyl" refers to an unsaturated cyclic hydrocarbon. The cycloalkenyl ring may include a specified number of carbon atoms. For example, a 5 to 8 membered cycloalkenyl group includes 5, 6, 7 or 8 carbon atoms. The cycloalkenyl group has one or more double bonds and when more than one double bond is present, the double bonds may be unconjugated or conjugated, however the cycloalkenyl group is not aromatic. Examples of suitable cycloalkenyl groups include, but are not limited to,

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cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, cycloheptatrienyl, cyclooctenyl, cyclooctadienyl and cyclooctatrienyl rings.

As used herein, the term "aryl" is intended to mean any stable, monocyclic, bicyclic or
 5 tricyclic carbon ring system of up to 7 atoms in each ring, wherein at least one ring is aromatic. Examples of such aryl groups include, but are not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, fluorenyl, phenanthrenyl, biphenyl and binaphthyl.

As used herein, the term "alkylene" refers to a divalent saturated hydrocarbon chain having
 10 1 to 6 carbon atoms. Where appropriate, the alkylene group may have a specified number of carbon atoms, for example, C₁₋₆alkylene includes alkylene groups having 1, 2, 3, 4, 5 or 6 carbon atoms in a linear arrangement. Examples of suitable alkylene groups include, but are not limited to, -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, -CH₂CH₂CH₂CH₂-, -CH₂CH₂CH₂CH₂CH₂- and -CH₂CH₂CH₂CH₂CH₂CH₂-.

15 As used herein, the term "alkenylene" refers to a divalent unsaturated hydrocarbon chain having 2 to 6 carbon atoms and at least one double bond. Where appropriate, the alkenylene group may have a specified number of carbon atoms, for example, C₂₋₆alkenylene includes alkenylene groups having 2, 3, 4, 5 or 6 carbon atoms in a linear
 20 arrangement. The double bonds may be in either *E* or *Z* configuration. Examples of suitable alkenylene groups include, but are not limited to, -CH=CH-, -CH=CHCH₂-, -CH₂CH=CH-, -CH=CHCH₂CH₂-, -CH₂CH=CHCH₂-, -CH₂CH₂CH=CH-, -CH=CHCH₂CH₂CH₂-, -CH₂CH=CHCH₂CH₂-, -CH₂CH₂CH=CHCH₂-, -CH=CHCH₂CH₂CH₂CH₂-, -CH₂CH=CHCH₂CH₂CH₂-,
 25 -CH₂CH₂CH=CHCH₂CH₂-, -CH₂CH₂CH₂CH=CHCH₂- and -CH₂CH₂CH₂CH₂CH=CH-.

As used herein, the term "alkynylene" refers to a divalent unsaturated hydrocarbon chain having 2 to 6 carbon atoms and at least one triple bond. Where appropriate, the alkynylene group may have a specified number of carbon atoms, for example, C₂₋₆alkynylene includes
 30 alkynylene groups having 2, 3, 4, 5 or 6 carbon atoms in a linear arrangement. Examples of suitable alkynylene groups include, but are not limited to, -C≡C-, -C≡CCH₂-, -CH₂C≡C-

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, -C≡CCH₂CH₂-, -CH₂C≡CCH₂-, -CH₂CH₂C≡C-, -C≡CCH₂CH₂CH₂-, -CH₂C≡CCH₂CH₂-,
-CH₂CH₂C≡CCH₂-, -CH₂CH₂CH₂C≡C-, -C≡CCH₂CH₂CH₂CH₂-, -CH₂C≡CCH₂CH₂CH₂-,
-CH₂CH₂C≡CCH₂CH₂-, -CH₂CH₂CH₂C≡CCH₂- and -CH₂CH₂CH₂CH₂C≡C-.

- 5 In some embodiments, one or more "-CH₂-" groups in an alkylene, alkenylene or alkynylene group may be replaced by a heteroatom or a group containing a heteroatom including -O-, -S-, -NH-, -NR-, -S(O)-, -S(O)₂-, -C(=O)-, -C(=O)NH- and -NHC(=O)-.

The term "benzyl" where used herein refers to a phenylmethylene group, C₆H₅CH₂-.

10

As used herein, the term "halogen" or "halo" refers to fluorine (fluoro), chlorine (chloro), bromine (bromo) and iodine (iodo).

- The term "heterocyclic" or "heterocyclyl" as used herein, refers to a cyclic hydrocarbon in
15 which one to four carbon atoms have been replaced by heteroatoms independently selected from the group consisting of N, N(R), S, S(O), S(O)₂ and O. A heterocyclic ring may be saturated or unsaturated but not aromatic. A heterocyclic group may also be part of a spirocyclic group containing 1, 2 or 3 rings, two of which are in a "spiro" arrangement. Examples of suitable heterocyclyl groups include azetidine, tetrahydrofuranyl,
20 tetrahydrothiophenyl, pyrrolidinyl, 2-oxopyrrolidinyl, pyrrolinyl, pyranyl, dioxolanyl, piperidinyl, 2-oxopiperidinyl, pyrazolinyl, imidazolinyl, thiazolinyl, dithiolyl, oxathiolyl, dioxanyl, dioxinyl, dioxazolyl, oxathiozolyl, oxazolonyl, piperazinyl, morpholino, thiomorpholinyl, 3-oxomorpholinyl, dithianyl, trithianyl and oxazinyl.

- 25 The term "heteroaryl" as used herein, represents a stable monocyclic, bicyclic or tricyclic ring of up to 7 atoms in each ring, wherein at least one ring is aromatic and at least one ring contains from 1 to 4 heteroatoms selected from the group consisting of O, N and S. Heteroaryl groups within the scope of this definition include, but are not limited to, acridinyl, carbazolyl, cinnolinyl, quinoxalinyl, quinazolinyl, pyrazolyl, indolyl, isoindolyl,
30 1H,3H-1-oxoisoindolyl, benzotriazolyl, furanyl, thienyl, thiophenyl, benzothienyl, benzofuranyl, benzodioxane, benzodioxin, quinolinyl, isoquinolinyl, oxazolyl, isoxazolyl,

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imidazolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetrahydroquinolinyl, thiazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,4-oxadiazolyl, 1,2,4-thiadiazolyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,4,5-tetrazinyl and tetrazolyl. Particular heteroaryl groups have 5- or 6-membered rings, such as pyrazolyl, furanyl, thienyl, oxazolyl, indolyl, 5 isoindolyl, 1H,3H-1-oxoisoindolyl, isoxazolyl, imidazolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, thiazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl and 1,2,4-oxadiazolyl and 1,2,4-thiadiazolyl.

Each alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl and heteroaryl 10 whether an individual entity or as part of a larger entity may be optionally substituted with one or more optional substituents selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₃₋₆cycloalkyl, oxo (=O), -OH, -SH, C₁₋₆alkylo-, C₂₋₆alkenylO-, C₃₋₆cycloalkylo-, C₁₋₆alkylS-, C₂₋₆alkenylS-, C₃₋₆cycloalkylS-, -CO₂H, -CO₂C₁₋₆alkyl, -NH₂, -NH(C₁₋₆alkyl), -N(C₁₋₆alkyl)₂, -NH(phenyl), -N(phenyl)₂, oxo, -CN, -NO₂, 15 -halogen, -CF₃, -OCF₃, -SCF₃, -CHF₂, -OCHF₂, -SCHF₂, -phenyl, -heterocyclyl, -heteroaryl, -Oheteroaryl, -Oheterocyclyl, -Ophenyl, -C(O)phenyl, -C(O)C₁₋₆alkyl. Examples of suitable substituents include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *tert*-butyl, vinyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, methylthio, ethylthio, propylthio, isopropylthio, butylthio, hydroxy, 20 hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, fluoro, chloro, bromo, iodo, cyano, nitro, -CO₂H, -CO₂CH₃, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, difluoromethyl, difluoromethoxy, difluoromethylthio, morpholino, amino, methylamino, dimethylamino, phenyl, phenoxy, phenylcarbonyl, benzyl and acetyl.

25 The term "carboxylic acid bioisotere" refers to a group which is physiochemically or topologically similar to carboxylic acid or carboxylate group. Examples of suitable carboxylic acid or carboxylate isosteres include, but are not limited to, tetrazole, tetrazolate, -CONH-tetrazole, oxadiazole, phosphate (-PO₃H₂), -C(OH)(CF₃)₂, N-(aryl or heteroaryl)-sulfonamides, acylsulfonamides and sulfonic acid (-SO₃H) [See Patani and 30 LaVoie, 1996]. Examples of sulfonamide isosteric equivalents of carboxy groups include -CONHSO₂R^a, -CONHSO₂N(R^a)₂, -SO₂NHCOR^a, -SO₂NHCONHR^a, -SO₂NHR^a and

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-NHSO₂R^a, where R^a is selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₃₋₈cycloalkyl, aryl, heterocyclyl, heteroaryl and -CF₃.

The compounds of the invention may be in the form of pharmaceutically acceptable salts.

- 5 It will be appreciated however that non-pharmaceutically acceptable salts also fall within the scope of the invention since these may be useful as intermediates in the preparation of pharmaceutically acceptable salts or may be useful during storage or transport. Suitable pharmaceutically acceptable salts include, but are not limited to, salts of pharmaceutically acceptable inorganic acids such as hydrochloric, sulphuric, phosphoric, nitric, carbonic, boric, sulfamic, and hydrobromic acids, or salts of pharmaceutically acceptable organic acids such as acetic, propionic, butyric, tartaric, maleic, hydroxymaleic, fumaric, maleic, citric, lactic, mucic, gluconic, benzoic, succinic, oxalic, phenylacetic, methanesulphonic, toluenesulphonic, benzenesulphonic, salicylic, sulphanilic, aspartic, glutamic, edetic, stearic, palmitic, oleic, lauric, pantothenic, tannic, ascorbic and valeric acids.

15

Base salts include, but are not limited to, those formed with pharmaceutically acceptable cations, such as sodium, potassium, lithium, calcium, magnesium, ammonium and alkylammonium.

- 20 Basic nitrogen-containing groups may be quaternized with such agents as lower alkyl halide, such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl and diethyl sulfate; and others.

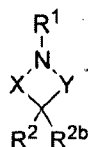
- It will also be recognised that compounds of the invention may possess asymmetric centres and are therefore capable of existing in more than one stereoisomeric form. The invention thus also relates to compounds in substantially pure isomeric form at one or more asymmetric centres eg., greater than about 90% ee, such as about 95% or 97% ee or greater than 99% ee, as well as mixtures, including racemic mixtures, thereof. Such isomers may be prepared by asymmetric synthesis, for example using chiral intermediates, or by chiral resolution. The compounds of the invention may exist as geometric isomers. The
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invention also relates to compounds in substantially pure *cis* (Z) or *trans* (E) or mixtures thereof.

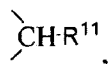
Compounds of the Invention

- 5 In a first aspect of the present invention there is provided a compound of formula (I):



wherein:

- X is absent and Y is $-\text{CHR}^3\text{CH}_2-$, $-\text{CH}_2\text{CHR}^3-$, $-\text{CHR}^3\text{CHR}^4\text{CH}_2-$, $-\text{CH}_2\text{CHR}^3\text{CHR}^4-$,
 10 $-\text{CH}_2\text{CH}_2\text{CHR}^3-$, $-\text{CR}^3=\text{CHCH}_2-$, $-\text{CH}=\text{CHR}^3\text{CH}_2-$ or $-\text{CH}_2\text{CH}=\text{CR}^3-$; or
 X is $-\text{CHR}^5$ and Y is $-\text{CHR}^3-$, $-\text{CHR}^3\text{CHR}^4-$, $-\text{CH}_2\text{CHR}^3-$, $-\text{CHR}^3\text{CR}^4=$, $-\text{CR}^3=\text{CH}-$ or
 $-\text{CH}=\text{CR}^3-$; wherein when Y is $-\text{CHR}^3\text{CR}^4=$, R^{2b} is absent; or
 X is $-\text{CH}_2\text{CHR}^5-$ or $\text{C}(=\text{O})\text{CHR}^5-$ and Y is $-\text{CHR}^3-$;
 R^1 is $-\text{C}(=\text{O})\text{CHR}^6\text{R}^7$, $-\text{C}(=\text{O})\text{NR}^6\text{R}^7$, $-\text{C}(=\text{O})\text{CH}_2\text{CHR}^6\text{R}^7$, $-\text{C}(=\text{O})\text{CH}=\text{CR}^6\text{R}^7$,
 15 $-\text{C}(=\text{S})\text{CHR}^6\text{R}^7$, $-\text{C}(=\text{S})\text{NR}^6\text{R}^7$, $-\text{C}(=\text{S})\text{CH}_2\text{CHR}^6\text{R}^7$, $-\text{C}(=\text{S})\text{CH}=\text{CR}^6\text{R}^7$, $-\text{C}(=\text{NR}^8)\text{CHR}^6\text{R}^7$,
 $-\text{C}(=\text{NR}^8)\text{NR}^6\text{R}^7$, $-\text{C}(=\text{NR}^8)\text{CH}_2\text{CHR}^6\text{R}^7$ and $-\text{C}(=\text{NR}^8)\text{CH}=\text{CR}^6\text{R}^7$;
 R^2 is $-\text{C}_{1-6}\text{alkyl}$, $-\text{C}_{2-6}\text{alkenyl}$, $-\text{C}_{2-6}\text{alkynyl}$, $-\text{OR}^8$, $-\text{SR}^8$, $-\text{N}(\text{R}^8)_2$, $-\text{C}(=\text{O})\text{R}^8$, $-\text{C}(=\text{O})\text{N}(\text{R}^8)_2$,
 $-\text{N}(\text{R}^8)\text{C}(=\text{O})\text{R}^8$, $-\text{N}(\text{R}^8)\text{C}(=\text{O})\text{N}(\text{R}^8)_2$, $-\text{N}(\text{R}^8)\text{SO}_2\text{R}^8$, $-\text{SO}_2\text{N}(\text{R}^8)_2$, $-\text{N}(\text{R}^8)\text{SO}_2\text{N}(\text{R}^8)_2$, $-\text{W}-$
 cycloalkyl , $-\text{W}-\text{cycloalkenyl}$, $-\text{W}-\text{aryl}$, $-\text{W}-\text{heterocyclyl}$, $-\text{W}-\text{heteroaryl}$, $-\text{W}-\text{Z}-\text{W}-$
 20 cycloalkyl , $-\text{W}-\text{Z}-\text{W}-\text{cycloalkenyl}$, $-\text{W}-\text{Z}-\text{W}-\text{aryl}$, $-\text{W}-\text{Z}-\text{W}-\text{heterocyclyl}$ or $-\text{W}-\text{Z}-\text{W}-$
 heteroaryl , $=\text{CH}-\text{C}(=\text{O})-\text{J}-\text{R}^{10}$, $=\text{CHC}(=\text{O})\text{NH}-\text{J}-\text{R}^{10}$, $-\text{OCH}_2\text{CHR}^{10}\text{CH}_2\text{R}^{10}$ or
 $-\text{OCH}_2\text{C}(\text{R}^{10})=\text{CHR}^{10}$;
 R^{2b} is hydrogen;
 R^3 is a carboxylic acid, $-\text{CH}_2\text{CO}_2\text{H}$, $-\text{C}(=\text{O})\text{C}(=\text{O})\text{OH}$, $-\text{CH}_2\text{OH}$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{CN}$,
 25 $-\text{CH}_2\text{C}(\text{O})\text{NH}_2$, $-\text{CH}_2\text{CN}$, a $-\text{carboxylic acid bioisostere}$ or $-\text{CH}_2\text{carboxylic acid bioisostere}$;
 R^4 is hydrogen or R^3 and R^4 together form a group:

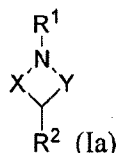


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- where R^{11} is a carboxylic acid, $-\text{CH}_2\text{CO}_2\text{H}$, $-\text{C}(=\text{O})\text{C}(=\text{O})\text{OH}$, $-\text{CH}_2\text{OH}$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{CN}$, $-\text{CH}_2\text{C}(\text{O})\text{NH}_2$, $-\text{CH}_2\text{CN}$, a carboxylic acid bioisostere or $-\text{CH}_2$ carboxylic acid bioisostere;
- R^5 is hydrogen or together with R^2 forms a fused aryl, heterocyclyl or heteroaryl ring, optionally substituted with one or two optional substituents selected from $-\text{C}_{1-6}$ alkyl,
- 5 $-\text{C}_{2-6}$ alkenyl, $-\text{C}_{2-6}$ alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, $-\text{C}_{1-6}$ alkylene R^{10} , $-\text{C}_{2-6}$ alkenylene R^{10} , $-\text{C}_{2-6}$ alkynylene R^{10} , $-\text{OCF}_3$, $-\text{OCHF}_2$, $-\text{OR}^9$, $-\text{OC}_{1-6}$ alkylene R^{10} , $-\text{OC}_{2-6}$ alkenylene R^{10} , $-\text{OC}_{2-6}$ alkynylene R^{10} , $-\text{SO}_2\text{NHR}^9$, $-\text{NHSO}_2\text{R}^9$, $-\text{NHC}(=\text{O})\text{NHR}^9$, $-\text{NHC}(=\text{O})\text{OR}^9$ or $-\text{CH}(\text{OH})\text{CH}(\text{OH})\text{R}^9$;
- R^6 and R^7 are independently hydrogen, $-\text{C}_{1-6}$ alkyl, cycloalkyl, cycloalkenyl, aryl,
- 10 heterocyclyl, heteroaryl, $-\text{CH}_2$ aryl, $-\text{CH}_2$ cycloalkyl, $-\text{CH}_2$ cycloalkenyl, $-\text{CH}_2$ heterocyclyl or $-\text{CH}_2$ heteroaryl; provided that R^6 and R^7 are not both hydrogen;
- R^8 is hydrogen, $-\text{C}_{1-8}$ alkyl, C_{1-8} fluoroalkyl, aryl, $-\text{C}_{1-8}$ alkylenearyl, $-\text{C}_{2-8}$ alkenylenearyl or $-\text{C}_{2-8}$ alkynylenearyl;
- R^9 is $-\text{C}_{1-6}$ alkyl, $-\text{C}_{2-6}$ alkenyl, $-\text{C}_{2-6}$ alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl,
- 15 heteroaryl, arylcycloalkyl-, arylcycloalkenyl-, arylaryl-, arylheterocyclyl- or arylheteroaryl-;
- W is a covalent bond, $-\text{O}-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$, $-\text{N}(\text{R}^8)-$, $-\text{C}(=\text{O})-$, $-\text{N}(\text{R}^8)\text{C}(=\text{O})-$, $-\text{C}(=\text{O})\text{N}(\text{R}^8)-$, $-\text{C}_{1-4}$ alkylene-, $-\text{C}_{2-4}$ alkenylene-, $-\text{C}_{2-4}$ alkynylene-, $-\text{C}_{1-3}$ alkylene QC_{1-3} alkylene-, $-\text{QC}_{1-4}$ alkylene-, $-\text{QC}_{2-4}$ alkenylene-, $-\text{QC}_{2-4}$ alkynylene-, $-\text{C}_{1-4}$ alkyleneQ-,
- 20 $-\text{C}_{2-4}$ alkenyleneQ-, $-\text{C}_{2-4}$ alkynyleneQ-, $-\text{QC}_{1-4}$ alkyleneQ-, $-\text{QC}_{2-4}$ alkenyleneQ- or $-\text{OC}_{2-4}$ alkynyleneQ-;
- Q is $-\text{O}-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$, $-\text{N}(\text{R}^8)-$, $-\text{C}(=\text{O})-$, $-\text{N}(\text{R}^8)\text{C}(=\text{O})-$, $-\text{C}(=\text{O})\text{N}(\text{R}^8)-$,
- Z is $-\text{cycloalkyl}-$, $-\text{cycloalkenyl}-$, $-\text{aryl}-$, $-\text{heterocyclyl}-$ or $-\text{heteroaryl}-$;
- J is a covalent bond or $-\text{C}_{1-6}$ alkylene-, $-\text{C}_{2-6}$ alkenylene- or $-\text{C}_{2-6}$ alkynylene, in which one
- 25 $-\text{CH}_2-$ group in the alkylene, alkenylene or alkynylene group may be replaced by $-\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{N}(\text{R}^8)-$, $-\text{C}(=\text{O})-$, $-\text{C}(=\text{O})\text{NH}-$ or $-\text{NHC}(=\text{O})-$;
- R^{10} is cycloalkyl, cycloalkenyl, aryl, heterocyclyl or heteroaryl; and
- wherein each cycloalkyl, cycloalkenyl, aryl, heterocyclyl and heteroaryl may be optionally substituted;
- 30 or a pharmaceutically acceptable salt thereof.

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In a particular embodiment, the compound of formula (I) is a compound of formula (Ia):



5

wherein:

X is absent and Y is $-\text{CHR}^3\text{CH}_2-$, $-\text{CH}_2\text{CHR}^3-$, $-\text{CHR}^3\text{CHR}^4\text{CH}_2-$, $-\text{CH}_2\text{CHR}^3\text{CHR}^4-$, $-\text{CH}_2\text{CH}_2\text{CHR}^3-$, $-\text{CR}^3=\text{CHCH}_2-$, $-\text{CH}=\text{CHR}^3\text{CH}_2-$ or $-\text{CH}_2\text{CH}=\text{CR}^3-$; or

X is $-\text{CHR}^5$ and Y is $-\text{CHR}^3-$, $-\text{CHR}^3\text{CHR}^4-$, $-\text{CH}_2\text{CHR}^3-$, $-\text{CR}^3=\text{CH}-$ or $-\text{CH}=\text{CR}^3-$; or

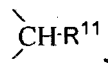
10 X is $-\text{CH}_2\text{CHR}^5-$ or $\text{C}(=\text{O})\text{CHR}^5-$ and Y is $-\text{CHR}^3-$;

R^1 is $-\text{C}(=\text{O})\text{CHR}^6\text{R}^7$, $-\text{C}(=\text{O})\text{NR}^6\text{R}^7$, $-\text{C}(=\text{CH}_2)\text{CHR}^6\text{R}^7$, $-\text{C}(=\text{O})\text{CH}=\text{CR}^6\text{R}^7$, $-\text{C}(=\text{S})\text{CHR}^6\text{R}^7$, $-\text{C}(=\text{S})\text{NR}^6\text{R}^7$, $-\text{C}(=\text{S})\text{CH}_2\text{CR}^6\text{R}^7$, $-\text{C}(=\text{S})\text{CH}=\text{CR}^6\text{R}^7$, $-\text{C}(=\text{NR}^8)\text{CHR}^6\text{R}^7$, $-\text{C}(=\text{NR}^8)\text{NR}^6\text{R}^7$, $-\text{C}(=\text{NR}^8)\text{CH}_2\text{CHR}^6\text{R}^7$ or $-\text{C}(=\text{NR}^8)\text{CH}=\text{CR}^6\text{R}^7$;

15 R^2 is $-\text{C}_{1-6}\text{alkyl}$, $-\text{C}_{2-6}\text{alkenyl}$, $-\text{C}_{2-6}\text{alkynyl}$, $-\text{OR}^8$, $-\text{SR}^8$, $-\text{N}(\text{R}^8)_2$, $-\text{C}(=\text{O})\text{R}^8$, $-\text{C}(=\text{O})\text{N}(\text{R}^8)_2$, $-\text{N}(\text{R}^8)\text{C}(=\text{O})\text{R}^8$, $-\text{N}(\text{R}^8)\text{C}(=\text{O})\text{N}(\text{R}^8)_2$, $-\text{N}(\text{R}^8)\text{SO}_2\text{R}^8$, $-\text{SO}_2\text{N}(\text{R}^8)_2$, $-\text{N}(\text{R}^8)\text{SO}_2\text{N}(\text{R}^8)_2$, $-\text{W}$ -cycloalkyl, $-\text{W}$ -cycloalkenyl, $-\text{W}$ -aryl, $-\text{W}$ -heterocyclyl, $-\text{W}$ -heteroaryl, $-\text{W}$ -Z-W-cycloalkyl, $-\text{W}$ -Z-W-cycloalkenyl, $-\text{W}$ -Z-W-aryl, $-\text{W}$ -Z-W-heterocyclyl or $-\text{W}$ -Z-W-heteroaryl, $=\text{CH}-\text{C}(=\text{O})-\text{J}-\text{R}^{10}$, $=\text{CHC}(=\text{O})\text{NH}-\text{J}-\text{R}^{10}$, $-\text{OCH}_2\text{CHR}^{10}\text{CH}_2\text{R}^{10}$ or $-\text{OCH}_2\text{C}(\text{R}^{10})=\text{CHR}^{10}$;

20 R^3 is a carboxylic acid, $-\text{CH}_2\text{CO}_2\text{H}$, $-\text{C}(=\text{O})\text{C}(=\text{O})\text{OH}$ or a carboxylic acid bioisostere;

R^4 is hydrogen or R^3 and R^4 together form a group:



where R^{11} is a carboxylic acid, $-\text{CH}_2\text{CO}_2\text{H}$, $-\text{C}(=\text{O})\text{C}(=\text{O})\text{OH}$, or carboxylic acid bioisostere;

25 R^5 is hydrogen or together with R^2 forms a fused aryl, heterocyclyl or heteroaryl ring, optionally substituted with one or two optional substituents selected from $-\text{C}_{1-6}\text{alkyl}$, $-\text{C}_{2-6}\text{alkenyl}$, $-\text{C}_{2-6}\text{alkynyl}$, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, $-\text{C}_{1-6}\text{alkyleneR}^{10}$, $-\text{C}_{2-6}\text{alkenyleneR}^{10}$, $-\text{C}_{2-6}\text{alkynyleneR}^{10}$, $-\text{OCF}_3$, $-\text{OCHF}_2$, $-\text{OR}^9$,

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- OC₁₋₆alkyleneR¹⁰, -OC₂₋₆alkenyleneR¹⁰, -OC₂₋₆alkynyleneR¹⁰, -SO₂NHR⁹, -NHSO₂R⁹, -NHC(=O)NHR⁹, -NHC(=O)OR⁹ or -CH(OH)CH(OH)R⁹;
- R⁶ and R⁷ are independently hydrogen, -C₁₋₆alkyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, -CH₂aryl, -CH₂cycloalkyl, -CH₂cycloalkenyl, -CH₂heterocyclyl or
- 5 -CH₂heteroaryl; provided that R⁶ and R⁷ are not both hydrogen;
- R⁸ is hydrogen, -C₁₋₆alkyl, aryl or -C₁₋₆alkylenearyl;
- R⁹ is -C₁₋₆alkyl, -C₂₋₆alkenyl, -C₂₋₆alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, arylcycloalkyl-, arylcycloalkenyl-, arylaryl-, arylheterocyclyl- or arylheteroaryl-;
- 10 W is a covalent bond, -O-, -S-, -SO-, -SO₂-, -N(R⁸)-, -C(=O)-, -N(R⁸)C(=O)-, -C(=O)N(R⁸)-, -C₁₋₄alkylene-, -C₂₋₄alkenylene-, -C₂₋₄alkynylene-, -C₁₋₃alkyleneQC₁₋₃alkylene-, -QC₁₋₄alkylene-, -QC₂₋₄alkenylene-, -QC₂₋₄alkynylene-, -C₁₋₄alkyleneQ-, -C₂₋₄alkenyleneQ-, -C₂₋₄alkynyleneQ-, -QC₁₋₄alkyleneQ-, -QC₂₋₄alkenyleneQ- or -OC₂₋₄alkynyleneQ-;
- 15 Q is -O-, -S-, -SO-, -SO₂-, -N(R⁸)-, -C(=O)-, -N(R⁸)C(=O)-, -C(=O)N(R⁸)-,
- Z is -cycloalkyl-, -cycloalkenyl-, -aryl-, -heterocyclyl- or -heteroaryl-;
- J is a covalent bond or -C₁₋₆alkylene-, -C₂₋₆alkenylene- or -C₂₋₆alkynylene, in which one -CH₂- group in the alkylene, alkenylene or alkynylene group may be replaced by -O-, -S-, -S(O)-, -S(O)₂-, -N(R⁸)-, -C(=O)-, -C(=O)NH- or -NHC(=O)-;
- 20 R¹⁰ is cycloalkyl, cycloalkenyl, aryl, heterocyclyl or heteroaryl; and
- wherein each cycloalkyl, cycloalkenyl, aryl, heterocyclyl and heteroaryl may be optionally substituted;
- or a pharmaceutically acceptable salt thereof.
- 25 In particular embodiments of formula (I) or formula (Ia), one or more of the following applies:
- X is absent and Y is -CHR³CH₂-;
- X is -CH₂- or -CHR⁵- and Y is -CHR³-, -CHR³CH₂-, -CHR³CR⁴=, -CH₂CHR³-, -CH=CR³-
- 30 or -CR³=CH-, wherein when Y is -CHR³CR⁴=, R^{2b} is absent,

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X is $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CHR}^5-$ or $-\text{C}(=\text{O})\text{CHR}^5-$ and Y is $-\text{CHR}^3-$;

R^1 is $-\text{C}(=\text{O})\text{CHR}^6\text{R}^7$, $-\text{C}(=\text{O})\text{NR}^6\text{R}^7$, especially $-\text{C}(=\text{O})\text{CH}(\text{aryl})(\text{aryl})$,
 5 $-\text{C}(=\text{O})\text{CH}(\text{aryl})(\text{cycloalkyl})$, $-\text{C}(=\text{O})\text{CH}(\text{cycloalkyl})(\text{cycloalkyl})$, $-\text{C}(=\text{O})\text{CH}(\text{aryl})(\text{alkyl})$,
 $-\text{C}(=\text{O})\text{N}(\text{aryl})(\text{aryl})$, $-\text{C}(=\text{O})\text{N}(\text{aryl})(\text{cycloalkyl})$, $-\text{C}(=\text{O})\text{N}(\text{cycloalkyl})(\text{cycloalkyl})$ or
 $-\text{C}(=\text{O})\text{N}(\text{aryl})(\text{alkyl})$, where each aryl or cycloalkyl group is optionally substituted; more
 especially $-\text{C}(=\text{O})\text{CH}(\text{phenyl})(\text{phenyl})$, $-\text{C}(=\text{O})\text{CH}(\text{phenyl})(\text{cyclohexyl})$,
 $-\text{C}(=\text{O})\text{N}(\text{phenyl})(\text{phenyl})$ or $-\text{C}(=\text{O})\text{N}(\text{phenyl})(\text{cyclohexyl})$, wherein each phenyl or
 10 cyclohexyl group is optionally substituted with one or more substituents selected from
 $-\text{C}_{1-3}\text{alkyl}$, $-\text{OC}_{1-3}\text{alkyl}$ and halo, especially methyl, methoxy and fluoro; most especially
 where R^1 is $-\text{C}(=\text{O})\text{CH}(\text{phenyl})(\text{phenyl})$ and $-\text{C}(=\text{O})\text{N}(\text{phenyl})(\text{phenyl})$;

R^2 is cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, heterocyclylaryl,
 15 $-\text{heterocyclylC}_{1-3}\text{alkylenearyl}$, $-\text{C}_{1-4}\text{alkylenecycloalkyl}$, $-\text{C}_{1-4}\text{alkylenecycloalkenyl}$,
 $-\text{C}_{1-4}\text{alkylenearyl}$, $-\text{C}_{1-4}\text{alkyleneheterocyclyl}$, $-\text{C}_{1-4}\text{alkyleneheteroaryl}$,
 $-\text{C}_{2-4}\text{alkenylenecycloalkyl}$, $-\text{C}_{2-4}\text{alkenylenecycloalkenyl}$, $-\text{C}_{2-4}\text{alkylenearyl}$,
 $-\text{C}_{2-4}\text{alkyleneheterocyclyl}$, $-\text{C}_{2-4}\text{alkyleneheteroaryl}$, $-\text{C}_{2-4}\text{alkynylenecycloalkyl}$,
 $-\text{C}_{2-4}\text{alkynylenecycloalkenyl}$, $-\text{C}_{2-4}\text{alkynylenearyl}$, $-\text{C}_{2-4}\text{alkynyleneheterocyclyl}$,
 20 $-\text{C}_{2-4}\text{alkynyleneheteroaryl}$, $=\text{CHC}(=\text{O})\text{NHCH}_2\text{cycloalkyl}$, $=\text{CHC}(=\text{O})\text{NHCH}_2\text{cycloalkenyl}$,
 $=\text{CHC}(=\text{O})\text{NHCH}_2\text{aryl}$, $=\text{CHC}(=\text{O})\text{NHCH}_2\text{heterocyclyl}$, $=\text{CHC}(=\text{O})\text{NHCH}_2\text{heteroaryl}$,
 $-\text{Ocycloalkyl}$, $-\text{Ocycloalkenyl}$, $-\text{Oaryl}$, $-\text{Oheterocyclyl}$, $-\text{Oheteroaryl}$,
 $-\text{OC}_{1-3}\text{alkylenecycloalkyl}$, $-\text{OC}_{1-3}\text{alkylenecycloalkenyl}$, $-\text{OC}_{1-3}\text{alkylenearyl}$,
 $-\text{OC}_{1-3}\text{alkyleneheterocyclyl}$, $-\text{OC}_{1-3}\text{alkyleneheteroaryl}$, $-\text{OC}_{2-3}\text{alkenylenecycloalkyl}$,
 25 $-\text{OC}_{2-3}\text{alkenylenecycloalkenyl}$, $-\text{OC}_{2-3}\text{alkylenearyl}$, $-\text{OC}_{2-3}\text{alkyleneheterocyclyl}$,
 $-\text{OC}_{2-3}\text{alkyleneheteroaryl}$, $-\text{OC}_{2-3}\text{alkynylenecycloalkyl}$, $-\text{OC}_{2-3}\text{alkynylenecycloalkenyl}$,
 $-\text{OC}_{2-3}\text{alkynylenearyl}$, $-\text{OC}_{2-3}\text{alkynyleneheterocyclyl}$, $-\text{OC}_{2-3}\text{alkynyleneheteroaryl}$,
 $-\text{OC}_{1-3}\text{alkylenecycloalkylaryl}$, $-\text{OarylOaryl}$, $-\text{OarylOC}_{1-3}\text{alkylenearyl}$, $-\text{Scycloalkyl}$,
 $-\text{Scycloalkenyl}$, $-\text{Saryl}$, $-\text{Sheterocyclyl}$, $-\text{Sheteroaryl}$, $-\text{SC}_{1-3}\text{alkylenecycloalkyl}$,
 30 $-\text{SC}_{1-3}\text{alkylenecycloalkenyl}$, $-\text{SC}_{1-3}\text{alkylenearyl}$, $-\text{SC}_{1-3}\text{alkyleneheterocyclyl}$,

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- SC₁₋₃alkyleneheteroaryl, -SC₂₋₃alkenyleneecycloalkyl, -SC₂₋₃alkenyleneecycloalkenyl,
 -SC₂₋₃alkenylenearyl, -SC₂₋₃alkenyleneheterocyclyl, -SC₂₋₃alkenyleneheteroaryl,
 -SC₂₋₃alkynyleneecycloalkyl, -SC₂₋₃alkynyleneecycloalkenyl, -SC₂₋₃alkynylenearyl,
 -SC₂₋₃alkynyleneheterocyclyl, -SC₂₋₃alkynyleneheteroaryl, -SC₁₋₃alkyleneecycloalkylaryl,
 5 -SO₂cycloalkyl, -SO₂cycloalkenyl, -SO₂aryl, -SO₂heterocyclyl, -SO₂heteroaryl,
 -SO₂C₁₋₃alkyleneecycloalkyl, -SO₂C₁₋₃alkyleneecycloalkenyl, -SO₂C₁₋₃alkylenearyl,
 -SO₂C₁₋₃alkyleneheterocyclyl, -SO₂C₁₋₃alkyleneheteroaryl, -SO₂C₂₋₃alkenyleneecycloalkyl,
 -SO₂C₂₋₃alkenyleneecycloalkenyl, -SO₂C₂₋₃alkenylenearyl, -SO₂C₂₋₃alkenyleneheterocyclyl,
 -SO₂C₂₋₃alkenyleneheteroaryl, -SO₂C₂₋₃alkynyleneecycloalkyl,
 10 -SO₂C₂₋₃alkynyleneecycloalkenyl, -SO₂C₂₋₃alkynylenearyl, -SO₂C₂₋₃alkynyleneheterocyclyl,
 -SO₂C₂₋₃alkynyleneheteroaryl, -SO₂C₁₋₃alkyleneecycloalkylaryl, -NHC₁₋₈alkyl, -NHC₂₋₈
 alkenyl, -NHC₂₋₈alkynyl, -NHcycloalkyl, -NHcycloalkenyl, -NHaryl, -NHheterocyclyl, -
 NHheteroaryl, -NHC₁₋₃alkyleneecycloalkyl, -NHC₁₋₃alkyleneecycloalkenyl,
 -NHC₁₋₃alkylenearyl, -NHC₁₋₃alkyleneheterocyclyl, -NHC₁₋₃alkyleneheteroaryl,
 15 -NHC₂₋₃alkenyleneecycloalkyl, -NHC₂₋₃alkenyleneecycloalkenyl, -NHC₂₋₃alkenylenearyl,
 -NHC₂₋₃alkenyleneheterocyclyl, -NHC₂₋₃alkenyleneheteroaryl,
 -NHC₂₋₃alkynyleneecycloalkyl, -NHC₂₋₃alkynyleneecycloalkenyl, -NHC₂₋₃alkynylenearyl,
 -NHC₂₋₃alkynyleneheterocyclyl, -NHC₂₋₃alkynyleneheteroaryl, -NHC(=O)cycloalkyl,
 -NHC(=O)cycloalkenyl, -NHC(=O)aryl, -NHC(=O)heterocyclyl, -NHC(=O)heteroaryl,
 20 -NHC(=O)C₁₋₃alkyleneecycloalkyl, -NHC(=O)C₁₋₃alkyleneecycloalkenyl,
 -NHC(=O)C₁₋₃alkylenearyl, -NHC(=O)C₁₋₃alkyleneheterocyclyl,
 -NHC(=O)C₁₋₃alkyleneheteroaryl, -NHC(=O)C₂₋₃alkenyleneecycloalkyl,
 -NHC(=O)C₂₋₃alkenyleneecycloalkenyl, -NHC(=O)C₂₋₃alkenylenearyl,
 -NHC(=O)C₂₋₃alkenyleneheterocyclyl, -NHC(=O)C₂₋₃alkenyleneheteroaryl,
 25 -NHC(=O)C₂₋₃alkynyleneecycloalkyl, -NHC(=O)C₂₋₃alkynyleneecycloalkenyl,
 -NHC(=O)C₂₋₃alkynylenearyl, -NHC(=O)C₂₋₃alkynyleneheterocyclyl,
 -NHC(=O)C₂₋₃alkynyleneheteroaryl, -N(CH₃)C₁₋₈alkyl, -N(CH₃)C₂₋₈alkenyl, -N(CH₃)C₂₋₈
 alkynyl, -N(CH₃)cycloalkyl, -N(CH₃)cycloalkenyl, -N(CH₃)aryl, -N(CH₃)heterocyclyl,
 -N(CH₃)heteroaryl, -N(CH₃)C₁₋₃alkyleneecycloalkyl, -N(CH₃)C₁₋₃alkyleneecycloalkenyl,
 30 -N(CH₃)C₁₋₃alkylenearyl, -N(CH₃)C₁₋₃alkyleneheterocyclyl,
 -N(CH₃)C₁₋₃alkyleneheteroaryl, -N(CH₃)C₂₋₃alkenyleneecycloalkyl,

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- N(CH₃)C₂₋₃alkenyleneecycloalkenyl, -N(CH₃)C₂₋₃alkenylenearyyl,
 -N(CH₃)C₂₋₃alkenyleneheterocyclyl, -N(CH₃)C₂₋₃alkenyleneheteroaryyl,
 -N(CH₃)C₂₋₃alkynyleneecycloalkyl, -N(CH₃)C₂₋₃alkynyleneecycloalkenyl,
 -N(CH₃)C₂₋₃alkynylenearyyl, -N(CH₃)C₂₋₃alkynyleneheterocyclyl,
 5 -N(CH₃)C₂₋₃alkynyleneheteroaryyl, -N(CH₃)C(=O)cycloalkyl, -N(CH₃)C(=O)cycloalkenyl,
 -N(CH₃)C(=O)aryl, -N(CH₃)C(=O)heterocyclyl, -N(CH₃)C(=O)heteroaryyl,
 -N(CH₃)C(=O)C₁₋₃alkyleneecycloalkyl, -N(CH₃)C(=O)C₁₋₃alkyleneecycloalkenyl,
 -N(CH₃)C(=O)C₁₋₃alkylenearyyl, -N(CH₃)C(=O)C₁₋₃alkyleneheterocyclyl,
 -N(CH₃)C(=O)C₁₋₃alkyleneheteroaryyl, -N(CH₃)C(=O)C₂₋₃alkenyleneecycloalkyl,
 10 -N(CH₃)C(=O)C₂₋₃alkenyleneecycloalkenyl, -N(CH₃)C(=O)C₂₋₃alkenylenearyyl,
 -N(CH₃)C(=O)C₂₋₃alkenyleneheterocyclyl, -N(CH₃)C(=O)C₂₋₃alkenyleneheteroaryyl,
 -N(CH₃)C(=O)C₂₋₃alkynyleneecycloalkyl, -N(CH₃)C(=O)C₂₋₃alkynyleneecycloalkenyl,
 -N(CH₃)C(=O)C₂₋₃alkynylenearyyl, -N(CH₃)C(=O)C₂₋₃alkynyleneheterocyclyl,
 -N(CH₃)C(=O)C₂₋₃alkynyleneheteroaryyl, -N(C(=O)CH₃)cycloalkyl,
 15 -N(C(=O)CH₃)cycloalkenyl, -N(C(=O)CH₃)aryl, -N(C(=O)CH₃)heterocyclyl,
 -N(C(=O)CH₃)heteroaryyl, -N(C(=O)CH₃)C₁₋₃alkyleneecycloalkyl,
 -N(C(=O)CH₃)C₁₋₃alkyleneecycloalkenyl, -N(C(=O)CH₃)C₁₋₃alkylenearyyl,
 -N(C(=O)CH₃)C₁₋₃alkyleneheterocyclyl, -N(C(=O)CH₃)C₁₋₃alkyleneheteroaryyl,
 -N(C(=O)CH₃)C₂₋₃alkenyleneecycloalkyl, -N(C(=O)CH₃)C₂₋₃alkenyleneecycloalkenyl,
 20 -N(C(=O)CH₃)C₂₋₃alkenylenearyyl, -N(C(=O)CH₃)C₂₋₃alkenyleneheterocyclyl,
 -N(C(=O)CH₃)C₂₋₃alkenyleneheteroaryyl, -N(C(=O)CH₃)C₂₋₃alkynyleneecycloalkyl,
 -N(C(=O)CH₃)C₂₋₃alkynyleneecycloalkenyl, -N(C(=O)CH₃)C₂₋₃alkynylenearyyl,
 -N(C(O)CH₃)C₂₋₃alkynyleneheterocyclyl, -N(C(O)CH₃)C₂₋₃alkynyleneheteroaryyl,
 -N(SO₂CH₃)cycloalkyl, -N(SO₂CH₃)cycloalkenyl, -N(SO₂CH₃)aryl,
 25 -N(SO₂CH₃)heterocyclyl, -N(SO₂CH₃)heteroaryyl, -N(SO₂CH₃)C₁₋₃alkyleneecycloalkyl,
 -N(SO₂CH₃)C₁₋₃alkyleneecycloalkenyl, -N(SO₂CH₃)C₁₋₃alkylenearyyl,
 -N(SO₂CH₃)C₁₋₃alkyleneheterocyclyl, -N(SO₂CH₃)C₁₋₃alkyleneheteroaryyl,
 -N(SO₂CH₃)C₂₋₃alkenyleneecycloalkyl, -N(SO₂CH₃)C₂₋₃alkenyleneecycloalkenyl,
 -N(SO₂CH₃)C₂₋₃alkenylenearyyl, -N(SO₂CH₃)C₂₋₃alkenyleneheterocyclyl,
 30 -N(SO₂CH₃)C₂₋₃alkenyleneheteroaryyl, -N(SO₂CH₃)C₂₋₃alkynyleneecycloalkyl,
 -N(SO₂CH₃)C₂₋₃alkynyleneecycloalkenyl, -N(SO₂CH₃)C₂₋₃alkynylenearyyl,

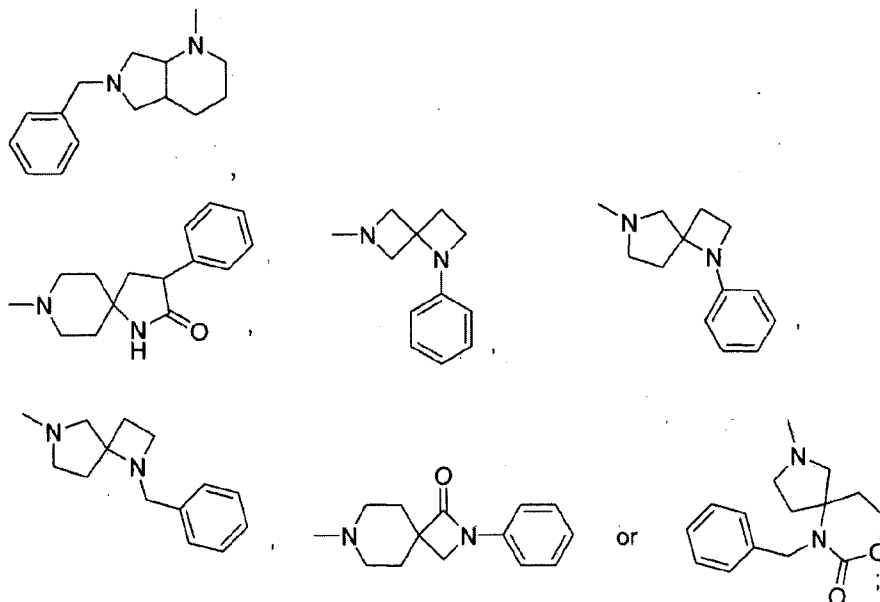
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- N(SO₂CH₃)C₂₋₃alkynyleneheterocyclyl, -N(SO₂CH₃)C₂₋₃alkynyleneheteroaryl,
 -N(CH₂CF₃)cycloalkyl, -N(CH₂CF₃)cycloalkenyl, -N(CH₂CF₃)aryl,
 -N(CH₂CF₃)heterocyclyl, -N(CH₂CF₃)heteroaryl, -N(CH₂CF₃)C₁₋₃alkylenecycloalkyl,
 -N(CH₂CF₃)C₁₋₃alkylenecycloalkenyl, -N(CH₂CF₃)C₁₋₃alkylenearyl,
 5. -N(CH₂CF₃)C₁₋₃alkyleneheterocyclyl, -N(CH₂CF₃)C₁₋₃alkyleneheteroaryl,
 -N(CH₂CF₃)C₂₋₃alkenylenecycloalkyl, -N(CH₂CF₃)C₂₋₃alkenylenecycloalkenyl,
 -N(CH₂CF₃)C₂₋₃alkylenearyl, -N(CH₂CF₃)C₂₋₃alkyleneheterocyclyl,
 -N(CH₂CF₃)C₂₋₃alkyleneheteroaryl, -N(CH₂CF₃)C₂₋₃alkynyleneheterocyclyl,
 -N(CH₂CF₃)C₂₋₃alkynyleneheteroaryl, -N(CH₂CF₃)C₂₋₃alkynyleneheteroaryl,
 10 -N(CH₂CF₃)C₂₋₃alkynyleneheterocyclyl, -N(CH₂CF₃)C₂₋₃alkynyleneheteroaryl,
 -OCH₂CH(phenyl)CH₂(phenyl), -OCH₂C(phenyl)=CH(phenyl),
 -CH₂C(=O)NHCH₂cycloalkyl, -CH₂C(=O)NHCH₂cycloalkenyl, -CH₂C(=O)NHCH₂aryl,
 -CH₂C(=O)NHCH₂heterocyclyl, -CH₂C(=O)NHCH₂heteroaryl,
 -C(=O)NHC₁₋₃alkylenecycloalkyl, -C(=O)NHC₁₋₃alkylenecycloalkenyl,
 15 -C(=O)NHC₁₋₃alkylenearyl, -C(=O)NHC₁₋₃alkyleneheterocyclyl,
 -C(=O)NHC₁₋₃alkyleneheteroaryl, -CH₂SO₂C₀₋₃alkylenecycloalkyl,
 -CH₂SO₂C₀₋₃alkylenecycloalkenyl, -CH₂SO₂C₀₋₃alkylenearyl,
 -CH₂SO₂C₀₋₃alkyleneheterocyclyl, -CH₂SO₂C₀₋₃alkyleneheteroaryl,
 -CH₂OC₁₋₃alkylenecycloalkyl, -CH₂OC₁₋₃alkylenecycloalkenyl, -CH₂OC₁₋₃alkylenearyl,
 20 -CH₂OC₁₋₃alkyleneheterocyclyl, -CH₂OC₁₋₃alkyleneheteroaryl,
 -CH₂SC₁₋₃alkylenecycloalkyl, -CH₂SC₁₋₃alkylenecycloalkenyl, -CH₂SC₁₋₃alkylenearyl,
 -CH₂SC₁₋₃alkyleneheterocyclyl, -CH₂SC₁₋₃alkyleneheteroaryl,
 -CH₂SC₂₋₃alkenylenecycloalkyl, -CH₂SC₂₋₃alkenylenecycloalkenyl,
 -CH₂SC₂₋₃alkylenearyl, -CH₂SC₂₋₃alkyleneheterocyclyl,
 25 -CH₂SC₂₋₃alkyleneheteroaryl, -CH₂SC₂₋₃alkynyleneheterocyclyl,
 -CH₂SC₂₋₃alkynyleneheteroaryl, -CH₂SC₂₋₃alkynyleneheteroaryl,
 -CH₂SC₂₋₃alkynyleneheterocyclyl, -CH₂SC₂₋₃alkynyleneheteroaryl or -NHC(=O)N(aryl)₂,
 especially -OCH₂phenyl, -CH₂Ophenyl, -OCH₂CH₂phenyl, -OCH₂CH₂CH₂phenyl,
 -OCH₂CH₂CH₂-(4-fluorophenyl), -CH₂CH=CHphenyl, -OCH₂CH=CHphenyl,
 30 -C≡CCH₂CH₂phenyl, =CHC(=O)NHCH₂phenyl, -OCH₂cyclopropyl, -OCH₂-(2-phenyl)cyclopropyl,
 -OCH₂-4-oxazole, -CH₂-4-(3-methyl-2-phenyl)oxazole, -1-azetidine,

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- 1-(3-benzyloxy)azetidine, -1-(3-phenyl)azetidine, -N(CH₃)(CH₂CH₂CH₃),
 -N(CH₃)(CH₂CH₂CH₂C(CH₃)₃), -N(CH₃)(CH₂C≡CH), -N(CH₃)(CH₂C≡CC(CH₃)₃),
 -N(CH₃)CH₂CH₂CH₂phenyl, -N(CH₂CF₃)CH₂CH₂CH₂-(4-fluorophenyl),
 -N(CH₃)CH₂CH₂phenyl, -N(CH₃)CH₂CH₂CH₂-(4-fluorophenyl), -N(CH₃)CH₂CH₂-(4-
 5 fluorophenyl), -N(CH₃)CH₂CH₂O-(4-fluorophenyl), -N(CH₃)CH₂C≡C-(3-methyl-4-
 methoxyphenyl), -1-piperazine, -1-(4-phenyl)piperazine, -1-(4-benzyl)piperazine, -1-(3-
 benzyl)piperazine, -1-(4-methyl-3-phenyl)piperazine, -4-morpholine, -4-(2-
 phenyl)morpholine, -4-(2-benzyl)morpholine, -4-(3-benzyl)morpholine,
 -N(CH₃)cyclopropyl, -N(CH₃)-(2-phenyl)cyclopropyl, -OCH₂C(phenyl)=CH(phenyl),
 10 -OCH₂CH(phenyl)CH₂(phenyl), -Ophenyl, -O-(4-benzyloxy)phenyl, -O-(3-
 benzyloxy)phenyl, -O-(2-benzyloxy)phenyl, -O-(4-phenoxy)phenyl, -O-(3-
 phenoxy)phenyl, -O-(2-phenoxy)phenyl; -OCH₂-C≡Cphenyl, -CH₂C(=O)NHCH₂phenyl,
 -C(=O)NHCH₂phenyl, -C(=O)NHCH₂CH₂phenyl, -NHCH₂CH₂CH₂phenyl,
 -NHCH₂CH₂phenyl, -CH₂CH₂CH₂phenyl, -CH₂CH₂CH₂CH₂phenyl, -CH₂OCH₂phenyl,
 15 -CH₂Ophenyl, -1-piperidine, -1-(4-phenyl)piperidine, -1-(3-phenyl)piperidine, -1-(3-
 benzyl)piperidine, -2-(phenyl)pyrrolidine, -3-(phenyl)pyrrolidine, -CH₂OCH₂CH₂phenyl,
 -CH₂CH₂OCH₂phenyl, -2-oxazole, -2-(5-phenyl)oxazole, -2-(5-benzyl)oxazole,
 -CH₂SO₂CH₂CH₂phenyl, -1-pyrrolidine, -1-(2-benzyl)pyrrolidine,
 -N(CH₃)CH₂cyclopropyl, -N(CH₃)CH₂-(2-phenyl)cyclopropyl, -N(CH₃)(CH₂)₃phenyl,
 20 -N(CH₃)(CH₂)₃(4-fluorophenyl), -N(CH₃)(CH₂)₃(4-methoxy-3-methylphenyl),
 -N(CH₃)(CH₂)₄phenyl,
 -N(CH₃)(CH₂)₃pyridine, -NHC(=O)N(phenyl)(phenyl), -OCH₂-4-oxazole, -OCH₂-4-(2-
 phenyl)oxazole, -O-4-oxazole, -O-4-(2-phenyl)oxazole, -NHC(=O)CH=CHphenyl,
 -N(CH₃)C(=O)CH=CHphenyl, -NHC(O)CH₂CH₂phenyl, -N(CH₃)C(=O)CH₂CH₂phenyl,
 25 -N(C(=O)CH₃)CH₂CH₂CH₂phenyl, N(SO₂CH₃)CH₂CH₂CH₂phenyl, -CH₂SO₂CH₂phenyl,
 -CH₂SO₂phenyl, -CH₂SCH₂CH₂phenyl, -CH₂SCH₂phenyl, -CH₂Sphenyl,
 -CH₂SCH₂CH₂CH₂phenyl, -SO₂CH₂CH₂CH₂phenyl, -SCH₂CH₂phenyl,
 -SO₂CH₂CH₂phenyl, -SCH₂CH₂-(4-fluorophenyl), -SO₂CH₂CH₂CH₂-(4-fluorophenyl), -1-
 (5-phenyl-1,2,3-triazolyl), -1-(5-benzyl-1,2,3-triazolyl), -4-(5-benzyl-3-oxo-morpholinyl),
 30 -2-(3-phenylthiophenyl), -2-(4-phenyl-1,3-thiazolyl),

- 25 -

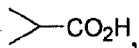


R^{2b} is hydrogen,

R^3 is $-\text{CO}_2\text{H}$, $-\text{CH}_2\text{CO}_2\text{H}$, $-\text{C}(=\text{O})\text{C}(=\text{O})\text{OH}$, $-\text{C}(=\text{O})\text{NHSO}_2\text{C}_{1-6}\text{alkyl}$, $-\text{C}(=\text{O})\text{NHSO}_2\text{N}(\text{C}_{1-6}\text{alkyl})_2$, $-\text{C}(=\text{O})\text{NHSO}_2\text{phenyl}$, $-\text{C}(=\text{O})\text{NHSO}_2\text{CF}_3$, $-\text{SO}_3\text{H}$, $-\text{PO}_3\text{H}_2$, tetrazolyl, $-\text{CH}_2\text{NHSO}_2\text{C}_{1-6}\text{alkyl}$, $-\text{CH}_2\text{OH}$, $-\text{C}(=\text{O})\text{NH}_2$ or $-\text{CN}$, especially $-\text{CO}_2\text{H}$, $-\text{CH}_2\text{CO}_2\text{H}$, $-\text{CH}_2\text{OH}$, $-\text{C}(=\text{O})\text{NHSO}_2\text{C}_{1-4}\text{alkyl}$, $-\text{C}(=\text{O})\text{NHSO}_2\text{N}(\text{C}_{1-3}\text{alkyl})_2$, $-\text{C}(=\text{O})\text{NHSO}_2\text{phenyl}$, tetrazolyl, $-\text{CH}_2\text{NHSO}_2(\text{C}_{1-4}\text{alkyl})$, $-\text{C}(=\text{O})\text{NH}_2$ or $-\text{CN}$, $-\text{C}(=\text{O})\text{NHSO}_2\text{CF}_3$, more especially $-\text{CO}_2\text{H}$;

10

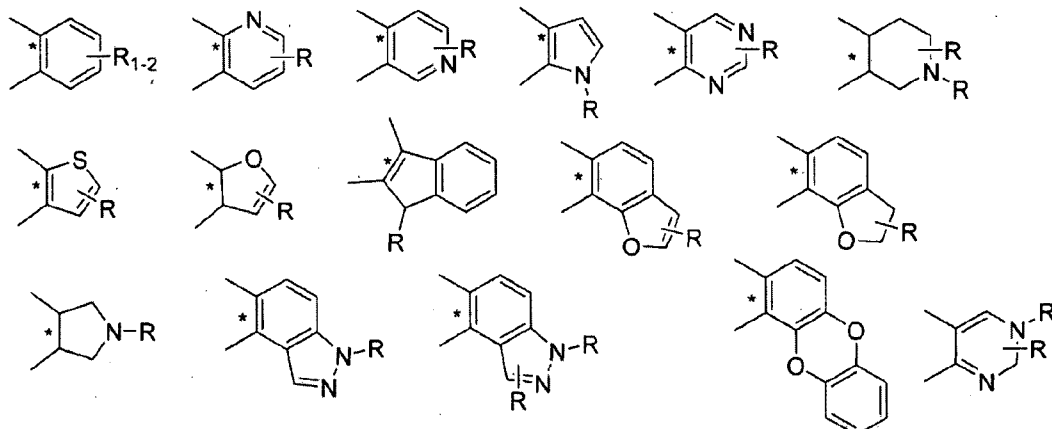
R^4 is hydrogen or R^3 and R^4 together form:



especially where R^4 is hydrogen;

15 R^5 is hydrogen or together with R^2 forms an aryl, heteroaryl or heterocyclyl ring selected from:

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where* indicates the fused bond, and R is selected from -C₁₋₃alkyl, -OC₁₋₃alkyl, -OCF₃, -OCHF₂, -OCH₂phenyl, -CH=CHphenyl, -CH₂CH₂phenyl, -CH(OH)CH(OH)phenyl, -C≡Cphenyl, -SO₂NHphenyl, -NHSO₂phenyl, -NHC(O)NHphenyl, -NHC(O)Ophenyl, -CH₂phenyl, -Ophenyl, -OCH₂CH=CHphenyl, -OCH₂CH₂phenyl, -OCH₂CH₂CH₂phenyl and -phenyl;

R⁶ and R⁷ are independently selected from phenyl and cyclohexyl, especially where both R⁶ and R⁷ are phenyl;

R⁸ is hydrogen, methyl, ethyl or phenyl.

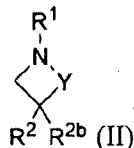
In some embodiments, especially when R³ appears on the carbon atom of Y that is adjacent in the ring to the ring nitrogen, R³ has an *S* stereochemistry.

In some embodiments, R² and R³ are *cis* relative to one another, that is, they are positioned on the same face of the N-containing 4- or 5-membered ring.

In some embodiments, the group R² contains at least one stereocentre. In embodiments where R² comprises a cyclohexyl or 6-membered heterocyclyl ring, substituted in the position adjacent to the attachment to the azetidine or pyrrolidine ring, one stereoisomer may be preferred over the other stereoisomer.

In one embodiment, the compound of formula (I) is a compound of formula (II):

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wherein X is absent and Y is $-\text{CHR}^3\text{CHR}^4\text{CH}_2-$, $-\text{CH}_2\text{CHR}^3\text{CHR}^4-$ or $-\text{CH}_2\text{CH}_2\text{CHR}^3-$ or
 X is $-\text{CHR}^5-$ and Y is $-\text{CHR}^3-$, $-\text{CHR}^3\text{CHR}^4-$, $-\text{CHR}^3\text{CR}^4=$, $-\text{CH}_2\text{CHR}^3-$, $-\text{CR}^3=\text{CH}-$ or
 5 $-\text{CH}=\text{CR}^3-$, wherein when Y is $-\text{CHR}^3\text{CR}^4=$, R^{2b} is absent; or
 X is $-\text{CH}_2\text{CH}^5-$ and Y is $-\text{CHR}^3-$ and
 R^1 , R^2 , R^3 , R^4 and R^5 are as defined for formula (I).

In particular embodiments of compound of formula (II): R^1 is $-\text{C}(=\text{O})\text{CH}(\text{phenyl})(\text{phenyl})$,
 10 $-\text{C}(=\text{O})\text{CH}(\text{phenyl})(\text{cycloalkyl})$, $-\text{C}(=\text{O})\text{CH}(\text{cycloalkyl})(\text{cycloalkyl})$,
 $-\text{C}(=\text{O})\text{N}(\text{phenyl})(\text{phenyl})$, $-\text{C}(=\text{O})\text{N}(\text{phenyl})(\text{cycloalkyl})$ or
 $-\text{C}(=\text{O})\text{N}(\text{cycloalkyl})(\text{cycloalkyl})$, especially $-\text{C}(=\text{O})\text{CH}(\text{phenyl})(\text{phenyl})$ or
 $-\text{C}(=\text{O})\text{N}(\text{phenyl})(\text{phenyl})$;

15 R^2 is cycloalkyl, cycloalkenyl, aryl, heterocyclyl, heteroaryl, -heterocyclylaryl,
 -heterocyclyl C_{1-3} alkylenearyl, $-\text{C}_{1-4}$ alkylenecycloalkyl, $-\text{C}_{1-4}$ alkylenecycloalkenyl,
 $-\text{C}_{1-4}$ alkylenearyl, $-\text{C}_{1-4}$ alkyleneheterocyclyl, $-\text{C}_{1-4}$ alkyleneheteroaryl,
 $-\text{C}_{2-4}$ alkenylenecycloalkyl, $-\text{C}_{2-4}$ alkenylenecycloalkenyl, $-\text{C}_{2-4}$ alkylenearyl,
 $-\text{C}_{2-4}$ alkyleneheterocyclyl, $-\text{C}_{2-4}$ alkyleneheteroaryl, $-\text{C}_{2-4}$ alkynylenecycloalkyl,
 20 $-\text{C}_{2-4}$ alkynylenecycloalkenyl, $-\text{C}_{2-4}$ alkynylenearyl, $-\text{C}_{2-4}$ alkynyleneheterocyclyl,
 $-\text{C}_{2-4}$ alkynyleneheteroaryl, $=\text{CHC}(=\text{O})\text{NHCH}_2\text{cycloalkyl}$, $=\text{CHC}(=\text{O})\text{NHCH}_2\text{cycloalkenyl}$,
 $=\text{CHC}(=\text{O})\text{NHCH}_2\text{aryl}$, $=\text{CHC}(=\text{O})\text{NHCH}_2\text{heterocyclyl}$, $=\text{CHC}(=\text{O})\text{NHCH}_2\text{heteroaryl}$,
 $-\text{Ocycloalkyl}$, $-\text{Ocycloalkenyl}$, $-\text{Oaryl}$, $-\text{Oheterocyclyl}$, $-\text{Oheteroaryl}$,
 $-\text{OC}_{1-3}$ alkylenecycloalkyl, $-\text{OC}_{1-3}$ alkylenecycloalkenyl, $-\text{OC}_{1-3}$ alkylenearyl,
 25 $-\text{OC}_{1-3}$ alkyleneheterocyclyl, $-\text{OC}_{1-3}$ alkyleneheteroaryl, $-\text{OC}_{2-3}$ alkenylenecycloalkyl,
 $-\text{OC}_{2-3}$ alkenylenecycloalkenyl, $-\text{OC}_{2-3}$ alkylenearyl, $-\text{OC}_{2-3}$ alkyleneheterocyclyl,
 $-\text{OC}_{2-3}$ alkyleneheteroaryl, $-\text{OC}_{2-3}$ alkynylenecycloalkyl, $-\text{OC}_{2-3}$ alkynylenecycloalkenyl,
 $-\text{OC}_{2-3}$ alkynylenearyl, $-\text{OC}_{2-3}$ alkynyleneheterocyclyl, $-\text{OC}_{2-3}$ alkynyleneheteroaryl,
 $-\text{OC}_{1-3}$ alkylenecycloalkylaryl, $-\text{OarylOaryl}$, $-\text{OarylOC}_{1-3}$ alkylenearyl, $-\text{Scycloalkyl}$,

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- Scycloalkenyl, -Saryl, -Sheterocyclyl, -Sheteroaryl, -SC₁₋₃alkylenecycloalkyl,
 -SC₁₋₃alkylenecycloalkenyl, -SC₁₋₃alkylenearyl, -SC₁₋₃alkyleneheterocyclyl,
 -SC₁₋₃alkyleneheteroaryl, -SC₂₋₃alkenylenecycloalkyl, -SC₂₋₃alkenylenecycloalkenyl,
 -SC₂₋₃alkylenearyl, -SC₂₋₃alkyleneheterocyclyl, -SC₂₋₃alkyleneheteroaryl,
 5 -SC₂₋₃alkynylenecycloalkyl, -SC₂₋₃alkynylenecycloalkenyl, -SC₂₋₃alkynylenearyl,
 -SC₂₋₃alkynyleneheterocyclyl, -SC₂₋₃alkynyleneheteroaryl, -SC₁₋₃alkylenecycloalkylaryl,
 -SO₂cycloalkyl, -SO₂cycloalkenyl, -SO₂aryl, -SO₂heterocyclyl, -SO₂heteroaryl,
 -SO₂C₁₋₃alkylenecycloalkyl, -SO₂C₁₋₃alkylenecycloalkenyl, -SO₂C₁₋₃alkylenearyl,
 -SO₂C₁₋₃alkyleneheterocyclyl, -SO₂C₁₋₃alkyleneheteroaryl, -SO₂C₂₋₃alkenylenecycloalkyl,
 10 -SO₂C₂₋₃alkenylenecycloalkenyl, -SO₂C₂₋₃alkylenearyl, -SO₂C₂₋₃alkyleneheterocyclyl,
 -SO₂C₂₋₃alkyleneheteroaryl, -SO₂C₂₋₃alkynylenecycloalkyl,
 -SO₂C₂₋₃alkynylenecycloalkenyl, -SO₂C₂₋₃alkynylenearyl, -SO₂C₂₋₃alkynyleneheterocyclyl,
 -SO₂C₂₋₃alkynyleneheteroaryl, -SO₂C₁₋₃alkylenecycloalkylaryl, -NHC₁₋₈alkyl, -NHC₂₋₈
 8alkenyl, -NHC₂₋₈alkynyl, -NHcycloalkyl, -NHcycloalkenyl, -NHaryl, -NHheterocyclyl, -
 15 NHheteroaryl, -NHC₁₋₃alkylenecycloalkyl, -NHC₁₋₃alkylenecycloalkenyl,
 -NHC₁₋₃alkylenearyl, -NHC₁₋₃alkyleneheterocyclyl, -NHC₁₋₃alkyleneheteroaryl,
 -NHC₂₋₃alkenylenecycloalkyl, -NHC₂₋₃alkenylenecycloalkenyl, -NHC₂₋₃alkylenearyl,
 -NHC₂₋₃alkyleneheterocyclyl, -NHC₂₋₃alkyleneheteroaryl,
 -NHC₂₋₃alkynylenecycloalkyl, -NHC₂₋₃alkynylenecycloalkenyl, -NHC₂₋₃alkynylenearyl,
 20 -NHC₂₋₃alkynyleneheterocyclyl, -NHC₂₋₃alkynyleneheteroaryl, -NHC(=O)cycloalkyl,
 -NHC(=O)cycloalkenyl, -NHC(=O)aryl, -NHC(=O)heterocyclyl, -NHC(=O)heteroaryl,
 -NHC(=O)C₁₋₃alkylenecycloalkyl, -NHC(=O)C₁₋₃alkylenecycloalkenyl,
 -NHC(=O)C₁₋₃alkylenearyl, -NHC(=O)C₁₋₃alkyleneheterocyclyl,
 -NHC(=O)C₁₋₃alkyleneheteroaryl, -NHC(=O)C₂₋₃alkenylenecycloalkyl,
 25 -NHC(=O)C₂₋₃alkenylenecycloalkenyl, -NHC(=O)C₂₋₃alkylenearyl,
 -NHC(=O)C₂₋₃alkyleneheterocyclyl, -NHC(=O)C₂₋₃alkyleneheteroaryl,
 -NHC(=O)C₂₋₃alkynylenecycloalkyl, -NHC(=O)C₂₋₃alkynylenecycloalkenyl,
 -NHC(=O)C₂₋₃alkynylenearyl, -NHC(=O)C₂₋₃alkynyleneheterocyclyl,
 -NHC(=O)C₂₋₃alkynyleneheteroaryl, -N(CH₃)C₁₋₈alkyl, -N(CH₃)C₂₋₈alkenyl, -N(CH₃)C₂₋₈
 30 8alkynyl, -N(CH₃)cycloalkyl, -N(CH₃)cycloalkenyl, -N(CH₃)aryl, -N(CH₃)heterocyclyl,
 -N(CH₃)heteroaryl, -N(CH₃)C₁₋₃alkylenecycloalkyl, -N(CH₃)C₁₋₃alkylenecycloalkenyl,

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- | | |
|--|--|
| -N(CH ₃)C ₁₋₃ alkylenearyl, | -N(CH ₃)C ₁₋₃ alkyleneheterocyclyl, |
| -N(CH ₃)C ₁₋₃ alkyleneheteroaryl, | -N(CH ₃)C ₂₋₃ alkenyleneecycloalkyl, |
| -N(CH ₃)C ₂₋₃ alkenyleneecycloalkenyl, | -N(CH ₃)C ₂₋₃ alkenylenearyl, |
| -N(CH ₃)C ₂₋₃ alkenyleneheterocyclyl, | -N(CH ₃)C ₂₋₃ alkenyleneheteroaryl, |
| 5 -N(CH ₃)C ₂₋₃ alkynyleneecycloalkyl, | -N(CH ₃)C ₂₋₃ alkynyleneecycloalkenyl, |
| -N(CH ₃)C ₂₋₃ alkynylenearyl, | -N(CH ₃)C ₂₋₃ alkynyleneheterocyclyl, |
| -N(CH ₃)C ₂₋₃ alkynyleneheteroaryl, | -N(CH ₃)C(=O)cycloalkyl, |
| -N(CH ₃)C(=O)aryl, | -N(CH ₃)C(=O)cycloalkenyl, |
| -N(CH ₃)C(=O)heterocyclyl, | -N(CH ₃)C(=O)heteroaryl, |
| -N(CH ₃)C(=O)C ₁₋₃ alkyleneecycloalkyl, | -N(CH ₃)C(=O)C ₁₋₃ alkyleneecycloalkenyl, |
| 10 -N(CH ₃)C(=O)C ₁₋₃ alkylenearyl, | -N(CH ₃)C(=O)C ₁₋₃ alkyleneheterocyclyl, |
| -N(CH ₃)C(=O)C ₁₋₃ alkyleneheteroaryl, | -N(CH ₃)C(=O)C ₂₋₃ alkenyleneecycloalkyl, |
| -N(CH ₃)C(=O)C ₂₋₃ alkenyleneecycloalkenyl, | -N(CH ₃)C(=O)C ₂₋₃ alkenylenearyl, |
| -N(CH ₃)C(=O)C ₂₋₃ alkenyleneheterocyclyl, | -N(CH ₃)C(=O)C ₂₋₃ alkenyleneheteroaryl, |
| -N(CH ₃)C(=O)C ₂₋₃ alkynyleneecycloalkyl, | -N(CH ₃)C(=O)C ₂₋₃ alkynyleneecycloalkenyl, |
| 15 -N(CH ₃)C(=O)C ₂₋₃ alkynylenearyl, | -N(CH ₃)C(=O)C ₂₋₃ alkynyleneheterocyclyl, |
| -N(CH ₃)C(=O)C ₂₋₃ alkynyleneheteroaryl, | -N(C(=O)CH ₃)cycloalkyl, |
| --N(C(=O)CH ₃)cycloalkenyl, | -N(C(=O)CH ₃)aryl, |
| -N(C(=O)CH ₃)heterocyclyl, | -N(C(=O)CH ₃)heteroaryl, |
| -N(C(=O)CH ₃)C ₁₋₃ alkyleneecycloalkyl, | -N(C(=O)CH ₃)C ₁₋₃ alkyleneecycloalkenyl, |
| -N(C(=O)CH ₃)C ₁₋₃ alkylenearyl, | -N(C(=O)CH ₃)C ₁₋₃ alkyleneheterocyclyl, |
| 20 -N(C(=O)CH ₃)C ₁₋₃ alkyleneheteroaryl, | -N(C(=O)CH ₃)C ₂₋₃ alkenyleneecycloalkyl, |
| -N(C(=O)CH ₃)C ₂₋₃ alkenyleneecycloalkenyl, | -N(C(=O)CH ₃)C ₂₋₃ alkenyleneheterocyclyl, |
| -N(C(=O)CH ₃)C ₂₋₃ alkenylenearyl, | -N(C(=O)CH ₃)C ₂₋₃ alkenyleneheteroaryl, |
| -N(C(=O)CH ₃)C ₂₋₃ alkynyleneecycloalkyl, | -N(C(=O)CH ₃)C ₂₋₃ alkynyleneecycloalkenyl, |
| -N(C(=O)CH ₃)C ₂₋₃ alkynylenearyl, | -N(C(=O)CH ₃)C ₂₋₃ alkynyleneheterocyclyl, |
| 25 -N(C(O)CH ₃)C ₂₋₃ alkynyleneheterocyclyl, | -N(C(O)CH ₃)C ₂₋₃ alkynyleneheteroaryl, |
| -N(SO ₂ CH ₃)cycloalkyl, | -N(SO ₂ CH ₃)cycloalkenyl, |
| -N(SO ₂ CH ₃)heterocyclyl, | -N(SO ₂ CH ₃)heteroaryl, |
| -N(SO ₂ CH ₃)C ₁₋₃ alkyleneecycloalkyl, | -N(SO ₂ CH ₃)C ₁₋₃ alkyleneecycloalkenyl, |
| -N(SO ₂ CH ₃)C ₁₋₃ alkylenearyl, | -N(SO ₂ CH ₃)C ₁₋₃ alkyleneheterocyclyl, |
| -N(SO ₂ CH ₃)C ₁₋₃ alkyleneheteroaryl, | -N(SO ₂ CH ₃)C ₂₋₃ alkenyleneecycloalkyl, |
| 30 -N(SO ₂ CH ₃)C ₂₋₃ alkenyleneecycloalkenyl, | -N(SO ₂ CH ₃)C ₂₋₃ alkenyleneheterocyclyl, |
| -N(SO ₂ CH ₃)C ₂₋₃ alkenylenearyl, | |

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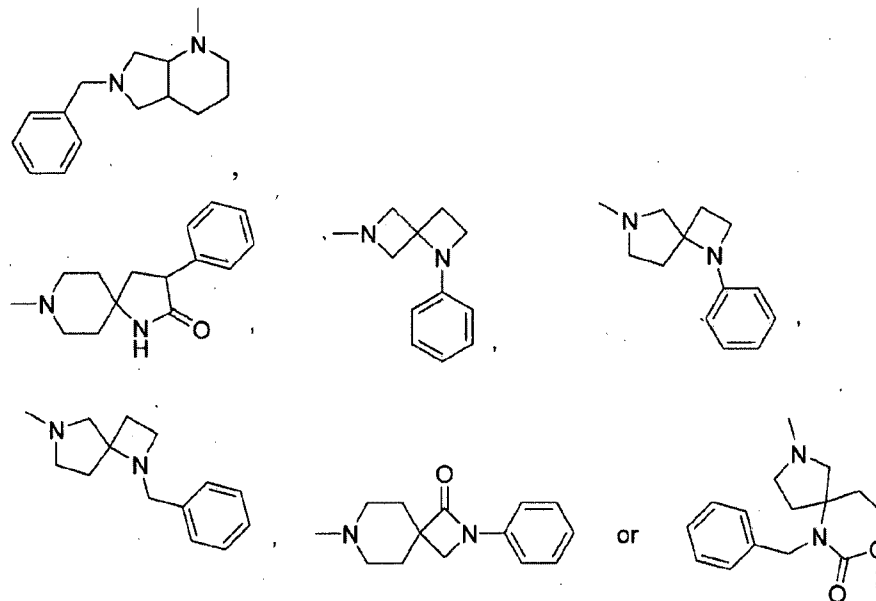
- $-N(SO_2CH_3)C_{2-3}alkenyleneheteroaryl,$ $-N(SO_2CH_3)C_{2-3}alkynyleneecycloalkyl,$
 $-N(SO_2CH_3)C_{2-3}alkynyleneecycloalkenyl,$ $-N(SO_2CH_3)C_{2-3}alkynylenearyl,$
 $-N(SO_2CH_3)C_{2-3}alkynyleneheterocyclyl,$ $-N(SO_2CH_3)C_{2-3}alkynyleneheteroaryl,$
 $-N(CH_2CF_3)cycloalkyl,$ $-N(CH_2CF_3)cycloalkenyl,$ $-N(CH_2CF_3)aryl,$
5 $-N(CH_2CF_3)heterocyclyl,$ $-N(CH_2CF_3)heteroaryl,$ $-N(CH_2CF_3)C_{1-3}alkyleneecycloalkyl,$
 $-N(CH_2CF_3)C_{1-3}alkyleneecycloalkenyl,$ $-N(CH_2CF_3)C_{1-3}alkylenearyl,$
 $-N(CH_2CF_3)C_{1-3}alkyleneheterocyclyl,$ $-N(CH_2CF_3)C_{1-3}alkyleneheteroaryl,$
 $-N(CH_2CF_3)C_{2-3}alkenyleneecycloalkyl,$ $-N(CH_2CF_3)C_{2-3}alkenyleneecycloalkenyl,$
 $-N(CH_2CF_3)C_{2-3}alkenylenearyl,$ $-N(CH_2CF_3)C_{2-3}alkenyleneheterocyclyl,$
10 $-N(CH_2CF_3)C_{2-3}alkenyleneheteroaryl,$ $-N(CH_2CF_3)C_{2-3}alkynyleneecycloalkyl,$
 $-N(CH_2CF_3)C_{2-3}alkynyleneecycloalkenyl,$ $-N(CH_2CF_3)C_{2-3}alkynylenearyl,$
 $-N(CH_2CF_3)C_{2-3}alkynyleneheterocyclyl,$ $-N(CH_2CF_3)C_{2-3}alkynyleneheteroaryl,$
 $-OCH_2CH(phenyl)CH_2(phenyl),$ $-OCH_2C(phenyl)=CH(phenyl),$
 $-CH_2C(=O)NHCH_2cycloalkyl,$ $-CH_2C(=O)NHCH_2cycloalkenyl,$ $-CH_2C(=O)NHCH_2aryl,$
15 $-CH_2C(=O)NHCH_2heterocyclyl,$ $-CH_2C(=O)NHCH_2heteroaryl,$
 $-C(=O)NHC_{1-3}alkyleneecycloalkyl,$ $-C(=O)NHC_{1-3}alkyleneecycloalkenyl,$
 $-C(=O)NHC_{1-3}alkylenearyl,$ $-C(=O)NHC_{1-3}alkyleneheterocyclyl,$
 $-C(=O)NHC_{1-3}alkyleneheteroaryl,$ $-CH_2SO_2C_{0-3}alkyleneecycloalkyl,$
 $-CH_2SO_2C_{0-3}alkyleneecycloalkenyl,$ $-CH_2SO_2C_{0-3}alkylenearyl,$
20 $-CH_2SO_2C_{0-3}alkyleneheterocyclyl,$ $-CH_2SO_2C_{0-3}alkyleneheteroaryl,$
 $-CH_2OC_{1-3}alkyleneecycloalkyl,$ $-CH_2OC_{1-3}alkyleneecycloalkenyl,$ $-CH_2OC_{1-3}alkylenearyl,$
 $-CH_2OC_{1-3}alkyleneheterocyclyl,$ $-CH_2OC_{1-3}alkyleneheteroaryl,$
 $-CH_2SC_{1-3}alkyleneecycloalkyl,$ $-CH_2SC_{1-3}alkyleneecycloalkenyl,$ $-CH_2SC_{1-3}alkylenearyl,$
 $-CH_2SC_{1-3}alkyleneheterocyclyl,$ $-CH_2SC_{1-3}alkyleneheteroaryl,$
25 $-CH_2SC_{2-3}alkenyleneecycloalkyl,$ $-CH_2SC_{2-3}alkenyleneecycloalkenyl,$
 $-CH_2SC_{2-3}alkenylenearyl,$ $-CH_2SC_{2-3}alkenyleneheterocyclyl,$
 $-CH_2SC_{2-3}alkenyleneheteroaryl,$ $-CH_2SC_{2-3}alkynyleneecycloalkyl,$
 $-CH_2SC_{2-3}alkynyleneecycloalkenyl,$ $-CH_2SC_{2-3}alkynylenearyl,$
 $-CH_2SC_{2-3}alkynyleneheterocyclyl,$ $-CH_2SC_{2-3}alkynyleneheteroaryl$ or $-NHC(=O)N(aryl)_2,$
30 especially $-OCH_2phenyl,$ $-CH_2Ophenyl,$ $-OCH_2CH_2phenyl,$ $-OCH_2CH_2CH_2phenyl,$
 $-OCH_2CH_2CH_2-(4-fluorophenyl),$ $-CH_2CH=CHphenyl,$ $-OCH_2CH=CHphenyl,$

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$\text{-C}\equiv\text{CCH}_2\text{CH}_2\text{phenyl}$, $\text{=CHC(=O)NHCH}_2\text{phenyl}$, $\text{-OCH}_2\text{cyclopropyl}$, $\text{-OCH}_2\text{-(2-phenyl)cyclopropyl}$, $\text{-OCH}_2\text{-4-oxazole}$, $\text{-CH}_2\text{-4-(3-methyl-2-phenyl)oxazole}$, -1-azetidine ,
 $\text{-1-(3-benzyloxy)azetidine}$, $\text{-1-(3-phenyl)azetidine}$, $\text{-N(CH}_3\text{)(CH}_2\text{CH}_2\text{CH}_3\text{)}$,
 $\text{-N(CH}_3\text{)(CH}_2\text{CH}_2\text{CH}_2\text{C(CH}_3\text{)}_3\text{)}$, $\text{-N(CH}_3\text{)(CH}_2\text{C}\equiv\text{CH)}$, $\text{-N(CH}_3\text{)(CH}_2\text{C}\equiv\text{CC(CH}_3\text{)}_3\text{)}$,
5 $\text{-N(CH}_3\text{)CH}_2\text{CH}_2\text{CH}_2\text{phenyl}$, $\text{-N(CH}_2\text{CF}_3\text{)CH}_2\text{CH}_2\text{CH}_2\text{-(4-fluorophenyl)-N(CH}_3\text{)CH}_2\text{CH}_2\text{phenyl}$,
 $\text{-N(CH}_3\text{)CH}_2\text{CH}_2\text{CH}_2\text{-(4-fluorophenyl)}$,
 $\text{-N(CH}_3\text{)CH}_2\text{C}\equiv\text{Cphenyl}$, $\text{-N(CH}_3\text{)CH}_2\text{C}\equiv\text{C-(3-methyl-4-methoxyphenyl)}$,
 $\text{-N(CH}_3\text{)CH}_2\text{CH}_2\text{-(4-fluorophenyl)}$, $\text{-N(CH}_3\text{)CH}_2\text{CH}_2\text{-(4-fluorophenyl)}$,
 -1-piperazine , $\text{-1-(4-phenyl)piperazine}$, $\text{-1-(4-benzyl)piperazine}$, $\text{-1-(3-benzyl)piperazine}$,
10 $\text{-1-(4-methyl-3-phenyl)piperazine}$, -4-morpholine , $\text{-4-(2-phenyl)morpholine}$, $\text{-4-(2-benzyl)morpholine}$,
 $\text{-4-(3-benzyl)morpholine}$, $\text{-N(CH}_3\text{)cyclopropyl}$, $\text{-N(CH}_3\text{)-(2-phenyl)cyclopropyl}$,
 $\text{-OCH}_2\text{C(phenyl)=CH(phenyl)}$, $\text{-OCH}_2\text{CH(phenyl)CH}_2\text{(phenyl)}$,
 -Ophenyl , $\text{-O-(4-benzyloxy)phenyl}$, $\text{-O-(3-benzyloxy)phenyl}$, $\text{-O-(2-benzyloxy)phenyl}$,
 $\text{-O-(4-phenoxy)phenyl}$, $\text{-O-(3-phenoxy)phenyl}$, $\text{-O-(2-phenoxy)phenyl}$, $\text{-OCH}_2\text{-}$
15 $\text{C}\equiv\text{Cphenyl}$, $\text{-CH}_2\text{C(=O)NHCH}_2\text{phenyl}$, $\text{-C(=O)NHCH}_2\text{phenyl}$, $\text{-C(=O)NHCH}_2\text{CH}_2\text{phenyl}$,
 $\text{-NHCH}_2\text{CH}_2\text{CH}_2\text{phenyl}$, $\text{-NHCH}_2\text{CH}_2\text{phenyl}$, $\text{-CH}_2\text{CH}_2\text{CH}_2\text{phenyl}$,
 $\text{-CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{phenyl}$, $\text{-CH}_2\text{OCH}_2\text{phenyl}$, $\text{-CH}_2\text{Ophenyl}$, -1-piperidine , $\text{-1-(4-phenyl)piperidine}$,
 $\text{-1-(3-phenyl)piperidine}$, $\text{-1-(3-benzyl)piperidine}$, $\text{-2-(phenyl)pyrrolidine}$, $\text{-3-(phenyl)pyrrolidine}$,
 $\text{-CH}_2\text{OCH}_2\text{CH}_2\text{phenyl}$, $\text{-CH}_2\text{CH}_2\text{OCH}_2\text{phenyl}$,
20 -2-oxazole , $\text{-2-(5-phenyl)oxazole}$, $\text{-2-(5-benzyl)oxazole}$, $\text{-CH}_2\text{SO}_2\text{CH}_2\text{CH}_2\text{phenyl}$, -1-pyrrolidine ,
 $\text{-1-(2-benzyl)pyrrolidine}$, $\text{-N(CH}_3\text{)CH}_2\text{cyclopropyl}$, $\text{-N(CH}_3\text{)CH}_2\text{-(2-phenyl)cyclopropyl}$,
 $\text{-N(CH}_3\text{)(CH}_2\text{)}_3\text{phenyl}$, $\text{-N(CH}_3\text{)(CH}_2\text{)}_3\text{(4-fluorophenyl)}$,
 $\text{-N(CH}_3\text{)(CH}_2\text{)}_3\text{(4-methoxy-3-methylphenyl)}$, $\text{-N(CH}_3\text{)(CH}_2\text{)}_4\text{phenyl}$,
 $\text{-N(CH}_3\text{)(CH}_2\text{)}_3\text{pyridine}$, $\text{-NHC(=O)N(phenyl)(phenyl)}$, $\text{-OCH}_2\text{-4-oxazole}$, $\text{-OCH}_2\text{-4-(2-phenyl)oxazole}$,
25 -O-4-oxazole , $\text{-O-4-(2-phenyl)oxazole}$, $\text{-NHC(=O)CH=CHphenyl}$,
 $\text{-N(CH}_3\text{)C(=O)CH=CHphenyl}$, $\text{-NHC(O)CH}_2\text{CH}_2\text{phenyl}$, $\text{-N(CH}_3\text{)C(=O)CH}_2\text{CH}_2\text{phenyl}$,
 $\text{-N(C(=O)CH}_3\text{)CH}_2\text{CH}_2\text{CH}_2\text{phenyl}$, $\text{N(SO}_2\text{CH}_3\text{)CH}_2\text{CH}_2\text{CH}_2\text{phenyl}$, $\text{-CH}_2\text{SO}_2\text{CH}_2\text{phenyl}$,
 $\text{-CH}_2\text{SO}_2\text{phenyl}$, $\text{-CH}_2\text{SCH}_2\text{CH}_2\text{phenyl}$, $\text{-CH}_2\text{SCH}_2\text{phenyl}$, $\text{-CH}_2\text{Sphenyl}$,
 $\text{-CH}_2\text{SCH}_2\text{CH}_2\text{CH}_2\text{phenyl}$, $\text{-SO}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{phenyl}$, $\text{-SCH}_2\text{CH}_2\text{phenyl}$,
30 $\text{-SO}_2\text{CH}_2\text{CH}_2\text{phenyl}$, $\text{-SCH}_2\text{CH}_2\text{-(4-fluorophenyl)}$, $\text{-SO}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{-(4-fluorophenyl)}$, -1-

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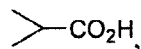
(5-phenyl-1,2,3-triazolyl), -1-(5-benzyl-1,2,3-triazolyl), -4-(5-benzyl-3-oxo-morpholinyl),
-2-(3-phenylthiophenyl), -2-(4-phenyl-1,3-thiazolyl),



5 R^{2b} is hydrogen;

R^3 is $-\text{CO}_2\text{H}$, $-\text{CH}_2\text{CO}_2\text{H}$, $-\text{CH}_2\text{OH}$, $-\text{C}(=\text{O})\text{C}(=\text{O})\text{OH}$, $-\text{C}(=\text{O})\text{NHSO}_2\text{C}_{1-6}\text{alkyl}$,
 $-\text{C}(=\text{O})\text{NHSO}_2\text{N}(\text{C}_{1-6}\text{alkyl})_2$, $-\text{C}(=\text{O})\text{NHSO}_2\text{phenyl}$, $-\text{C}(=\text{O})\text{NHSO}_2\text{CF}_3$, $-\text{SO}_3\text{H}$,
 $-\text{PO}_3\text{H}_2$, tetrazolyl, $-\text{CH}_2\text{NHSO}_2\text{C}_{1-6}\text{alkyl}$, $-\text{CH}_2\text{OH}$, $-\text{C}(=\text{O})\text{NH}_2$ or $-\text{CN}$ especially
 $-\text{CO}_2\text{H}$, $-\text{CH}_2\text{CO}_2\text{H}$, $-\text{C}(=\text{O})\text{NHSO}_2\text{C}_{1-4}\text{alkyl}$, $-\text{C}(=\text{O})\text{NHSO}_2(\text{C}_{1-3}\text{alkyl})_2$,
10 $-\text{C}(=\text{O})\text{NHSO}_2\text{phenyl}$, tetrazolyl, $-\text{CH}_2\text{NHSO}_2\text{C}_{1-4}\text{alkyl}$, $-\text{C}(=\text{O})\text{NH}_2$, $-\text{CN}$ or
 $-\text{C}(=\text{O})\text{NHSO}_2\text{CF}_3$, more especially $-\text{CO}_2\text{H}$;

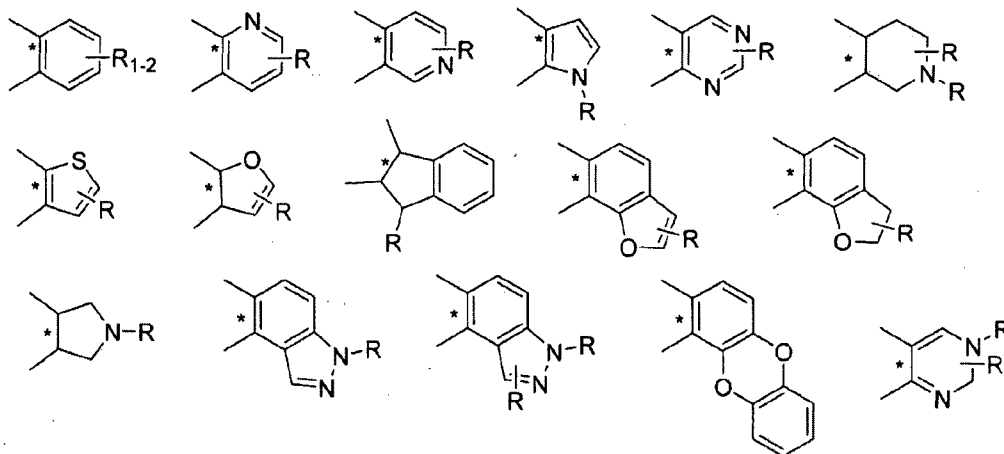
R^4 is hydrogen or R^3 and R^4 together form:



15 especially hydrogen;

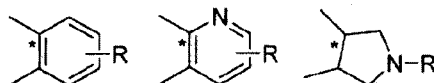
R^5 is hydrogen or together with R^2 forms an aryl, heteroaryl or heterocyclyl ring selected from:

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where* indicates the fused bond, and R is selected from -C₁₋₃alkyl, -OC₁₋₃alkyl, -OCF₃, -OCHF₂, -OCH₂phenyl, -CH=CHphenyl, -CH₂CH₂phenyl, -CH(OH)CH(OH)phenyl, -C≡Cphenyl, -SO₂NHphenyl, -NHSO₂phenyl, -NHC(O)NHphenyl, -NHC(O)Ophenyl, -CH₂phenyl, -Ophenyl, -OCH₂CH=CHphenyl, -OCH₂CH₂phenyl, -OCH₂CH₂CH₂phenyl and -phenyl;

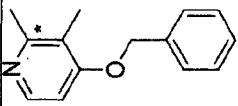
especially where R⁵ and R² together forms one of:



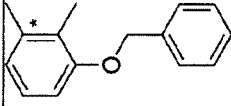
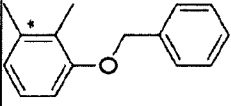
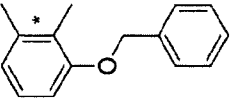
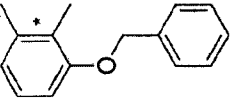
where R is selected from -C₁₋₃alkyl, -OC₁₋₃alkyl, -OCF₃, -OCHF₂, -OCH₂phenyl, -CH=CHphenyl, -CH₂CH₂phenyl, -CH(OH)CH(OH)phenyl, -C≡Cphenyl, -SO₂NHphenyl, -NHSO₂phenyl, -NHC(O)NHphenyl, -NHC(O)Ophenyl, -CH₂phenyl, -Ophenyl, -OCH₂CH=CHphenyl, -OCH₂CH₂phenyl, -OCH₂CH₂CH₂phenyl and -phenyl especially -OCH₂phenyl or -CH₂phenyl;

Particular compounds of formula (II) are:

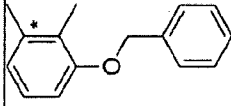
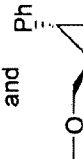
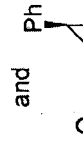
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Compound	X	Y	R ¹	R ²	R ³	Relative R ² /R ³	R ⁴	R ³ /R ⁴	R ⁵	R ² /R ⁵
1	-CR ⁵ -	-CH=CR ⁵ -	-C(O)CH (phenyl) ₂	-	-CO ₂ H	-	H	-	-	
2	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	benzyloxy	-CO ₂ H (S)	cis	H	-	H	-
3	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	benzyloxy	-CO ₂ H (S)	trans	H	-	H	-
4	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	phenylCH ₂ CH ₂ O-	-CO ₂ H (S)	cis	H	-	H	-
5	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	phenylCH=CHCH ₂ O-	-CO ₂ H (S)	cis	H	-	H	-
6	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	phenylCH ₂ CH ₂ CH ₂ O- CH ₂ O-	-CO ₂ H (S)	cis	H	-	H	-
7	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	phenylCH ₂ CH ₂ O-	-CO ₂ H (S)	trans	H	-	H	-
8	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	phenylCH=CHCH ₂ O-	-CO ₂ H (S)	trans	H	-	H	-
9	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	phenylCH ₂ CH ₂ CH ₂ O- CH ₂ O-	-CO ₂ H (S)	trans	H	-	H	-
10	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	=CHC(O)NHCH ₂ phenyl	-CO ₂ H (S)	-	H	-	H	-

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Compound	X	Y	R ¹	R ²	R ³	Relative R ² /R ³	R ⁴	R ³ /R ⁴	R ⁵	R ² /R ⁵
11	-CR ⁵ -	-CR ³ =CH-	-C(O)CH (phenyl) ₂	-	-CO ₂ H	-	-	-	-	
12	-CR ⁵ -	-CR ³ =CH-	-C(O)CH (phenyl) ₂	-	-C(O)C(O)OH	-	-	-	H	
13	-CR ⁵ -	-CR ³ =CH-	-C(O)N (phenyl) ₂	-	-CO ₂ H	-	-	-	-	
14	-CR ⁵ -	-CH=CR ³ -	-C(O)N (phenyl) ₂	-	-C(O)C(O)OH	-	-	-	-	

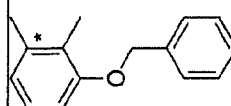
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Compound	X	Y	R ¹	R ²	R ³	Relative R ² /R ³	R ⁴	R ³ /R ⁴	R ⁵	R ² /R ⁵
15	-OR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-	-CO ₂ H (R/S)	-	H	-	-	
16	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	 and 	-CO ₂ H (S)	cis	H	-	H	
17	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	 and 	-CO ₂ H (S)	cis	H	-	H	
18	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-OCH ₂ -(2-phenyl)- 5-methyl-4-oxazole	-CO ₂ H (S)	cis	H	-	H	-
19	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-1-(3-benzylloxy) azetidine	-CO ₂ H (S)	cis	H	-	H	-
20	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-1-(3-phenyl) azetidine	-CO ₂ H (S)	cis	H	-	H	-
21	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-N(CH ₃)CH ₂ CH ₂ CH ₂ phenyl	-CO ₂ H (S)	cis	H	-	H	-
22	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH	-N(CH ₃)CH ₂ CH ₂	-CO ₂ H (S)	cis	H	-	H	-

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Compound	X	Y	R ¹	R ²	R ³	Relative R ² /R ³	R ⁴	R ³ /R ⁴	R ⁵	R ² /R ⁵
23	-CHR ⁵ -	-CHR ³ CHR ⁴ -	(phenyl) ₂ -C(O)CH (phenyl) ₂	phenyl -1-(4-phenyl)- piperazine	-CO ₂ H (S)	cis	H	-	H	-
24	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-1-(4-methyl-3R- phenyl)piperazine	-CO ₂ H (S)	cis	H	-	H	-
25	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-1-(4-methyl-3S- phenyl)piperazine	-CO ₂ H (S)	cis	H	-	H	-
26	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	4-(2R-phenyl) morpholine	-CO ₂ H (S)	cis	H	-	H	-
27	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	4-(2S-phenyl) morpholine	-CO ₂ H (S)	cis	H	-	H	-
28	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	4-(2S-benzyl) morpholine	-CO ₂ H (S)	cis	H	-	H	-
29	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	N(CH ₃)-(2-phenyl) cyclopropyl	-CO ₂ H (S)	cis	H	-	H	-
30	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	N(CH ₃)-(2-phenyl) Cyclopropyl	-CO ₂ H (S)	cis	H	-	H	-
31	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-OCH ₂ C(phenyl) =CH(phenyl)	-CO ₂ H (S)	cis	H	-	H	-
32	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-OCH ₂ CH(phenyl) CH ₂ (phenyl)	-CO ₂ H (S)	cis	H	-	H	-
33	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-O-(2-benzoyloxy) phenyl	-CO ₂ H (S)	cis	H	-	H	-
34	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-O-(3-phenoxy) phenyl	-CO ₂ H (S)	cis	H	-	H	-
35	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-O-(2-phenoxy) phenyl	-CO ₂ H (S)	cis	H	-	H	-

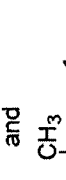
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Compound	X	Y	R ¹	R ²	R ³	Relative R ² /R ³	R ⁴	R ³ /R ⁴	R ⁵	R ² /R ⁵
36	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-OCH ₂ C≡C-phenyl	-CO ₂ H (S)	cis	H	-	H	-
37	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-OCH ₂ CH=CH phenyl	-CO ₂ H (R)	cis	H	-	H	-
38	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-OCH ₂ CH ₂ CH ₂ phenyl	-CO ₂ H (R)	cis	H	-	H	-
39	-CH ₂ CHR ⁵ -	-CHR ³ -	-C(O)CH (phenyl) ₂	-OCH ₂ CH=CH phenyl	-CO ₂ H (S)	cis	H	-	H	-
40	-CH ₂ CHR ⁵ -	-CHR ³ -	-C(O)CH (phenyl) ₂	-OCH ₂ CH ₂ CH ₂ phenyl	-CO ₂ H (S)	cis	H	-	H	-
41	-	-CHR ³ CHR ⁴ CH ₂ -	-C(O)CH (phenyl) ₂	-CH ₂ CH=CHphenyl	-CO ₂ H (S)	cis	H	-	H	-
42	-	-CHR ³ CHR ⁴ CH ₂ -	-C(O)CH (phenyl) ₂	-CH ₂ CH ₂ CH ₂ phenyl	-CO ₂ H (S)	cis	-	-	-	-
43	-CR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-	-	-	-	-CH (CO ₂ H))	-	
44	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-C(O)NHCH ₂ phenyl	-CO ₂ H (S)	cis	H	-	H	-
45	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-C(O)NHCH ₂ CH ₂ phenyl	-CO ₂ H (S)	cis	H	-	H	-
46	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-NHCH ₂ CH ₂ phenyl	-CO ₂ H (S)	cis	H	-	H	-

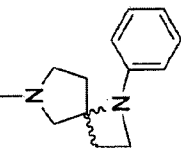
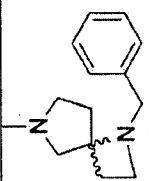
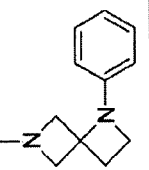
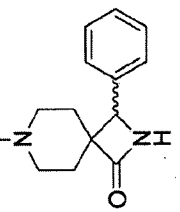
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Compound	X	Y	R ¹	R ²	R ³	Relative R ² /R ³	R ⁴	R ³ /R ⁴	R ⁵	R ² /R ⁵
47	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-1-(4-phenyl) piperidine	-CO ₂ H (S)	cis	H	-	H	-
48	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-1-(3S-phenyl) piperidine	-CO ₂ H (S)	cis	H	-	H	-
49	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-1-(3R-phenyl) piperidine	-CO ₂ H (S)	cis	H	-	H	-
50	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-1-(3R/S-phenyl) piperidine	-CO ₂ H (S)	cis	H	-	H	-
51	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-1-(3R-benzyl) piperidine	-CO ₂ H (S)	cis	H	-	H	-
52	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-1-(3S-benzyl) piperidine	-CO ₂ H (S)	cis	H	-	H	-
53	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-1-(3R/S-benzyl) piperidine	-CO ₂ H (S)	cis	H	-	H	-
54	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-CH ₂ OCH ₂ phenyl	-CO ₂ H (S)	cis	H	-	H	-
55	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-CH ₂ CH ₂ OCH ₂ phenyl	-CO ₂ H (S)	cis	H	-	H	-
56	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-2-(5-phenyl) oxazoly	-CO ₂ H (S)	cis	H	-	H	-
57	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-2-(5-benzyl) oxazoly	-CO ₂ H (S)	cis	H	-	H	-
58	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-CH ₂ SO ₂ CH ₂ CH ₂ phenyl	-CO ₂ H (S)	cis	H	-	H	-
59	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-1-(2S-benzyl) pyrrolidinyl	-CO ₂ H (S)	cis	H	-	H	-
60	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH	-1-(2R-benzyl)	-CO ₂ H (S)	cis	H	-	H	-

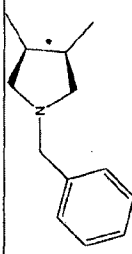
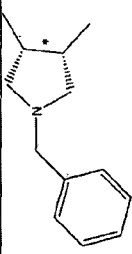
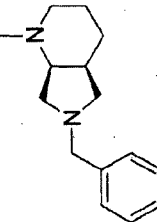
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Compound	X	Y	R ¹	R ²	R ³	Relative R ² /R ³	R ⁴	R ³ /R ⁴	R ³	R ² /R ³
61	-CHR ⁵ -	-CHR ³ CHR ⁴ -	(phenyl) ₂ -C(O)CH (phenyl) ₂	pyrrolidinyl -1-(2R/S-benzyl) pyrrolidinyl	-CO ₂ H (S)	cis	H	-	H	-
62	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) (cyclohexyl)	-N(CH ₃)CH ₂ CH ₂ CH ₂ phenyl	-CO ₂ H (S)	cis	H	-	H	-
63	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	 and  -NHC(O)N(phenyl) ₂	-CO ₂ H (S)	cis	H	-	H	-
64	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-NHC(O)N(phenyl) ₂	-CO ₂ H (S)	cis	H	-	H	-
65	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	 -NHC(O)N(phenyl) ₂	-CO ₂ H (S)	cis	H	-	H	-
66	-CHR ⁵ -	-CH ₂ CHR ³ -	-C(O)CH (phenyl) ₂	-N(CH ₃)CH ₂ CH ₂ CH ₂ phenyl	-CO ₂ H (S/R)	cis	-	-	H	-
67	-CHR ⁵ -	-CH ₂ CHR ³ -	-C(O)CH (phenyl) ₂	-N(CH ₃)CH ₂ CH ₂ CH ₂ phenyl	-CO ₂ H (S/R)	trans	-	-	H	-
68	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	1-(2S-benzyl) piperidine	-CO ₂ H (S)	cis	H	-	H	-
69	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH	1-(2R-benzyl)	-CO ₂ H (S)	cis	H	-	H	-

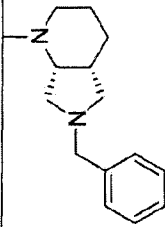
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Compound	X	Y	R ¹	R ²	R ³	Relative R ² /R ³	R ⁴	R ³ /R ⁴	R ⁵	R ² /R ⁵
70	-CHR ⁵ -	-CHR ³ CHR ⁴ -	(phenyl) ₂ -C(O)CH (phenyl) ₂	piperidine 1-(2R/S-benzyl) piperidine	-CO ₂ H (S)	cis	H	-	H	-
71	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-OCH ₂ -4-(2-phenyl) oxazoly	-CO ₂ H (S)	cis	H	-	H	-
72	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂		-CO ₂ H (S)	cis	H	-	H	-
73	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂		-CO ₂ H (S)	cis	H	-	H	-
74	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂		-CO ₂ H (S)	cis	H	-	H	-
75	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂		-CO ₂ H (S)	cis	H	-	H	-
76	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-OCH ₂ CH ₂ CH ₂ phenyl	-CO ₂ H (R)	cis	H	-	H	-

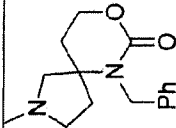
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Compound	X	Y	R ¹	R ²	R ³	Relative R ² /R ³	R ⁴	R ³ /R ⁴	R ⁵	R ² /R ⁵
77	-CH ₂ CHR ⁵	-CHR ³ -	-C(O)CH (phenyl) ₂	-	-CO ₂ H (R)		-	-	-	
78	-CH ₂ CHR ⁵	-CHR ³ -	-C(O)CH (phenyl) ₂	-	-CO ₂ H (R)		-	-	-	
79	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-O-4-(2-phenyl) oxazoly	-CO ₂ H (S)	cis	H	-	H	-
80	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)N (phenyl) ₂	-OCH ₂ CH ₂ CH ₂ phenyl	-CO ₂ H (S)	cis	H	-	H	-
81	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-1-(3R-benzyl) piperidine	-CO ₂ H (S)	trans	H	-	H	-
82	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-1-(3R/S-benzyl) piperidine	-CO ₂ H (S)	trans	H	-	H	-
83	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-1-(3S-benzyl) piperidine	-CO ₂ H (S)	trans	H	-	H	-
84	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂		-CO ₂ H (S)	cis	H	-	H	-

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Compound	X	Y	R ¹	R ²	R ³	Relative R ² /R ³	R ⁴	R ¹ /R ⁴	R ⁵	R ² /R ⁵
85	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂		-CO ₂ H (S)	cis	H	-	H	-
86	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-3-R-phenylpyrrolidine	-CO ₂ H (S)	cis	H	-	H	-
87	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-3-S-phenylpyrrolidine	-CO ₂ H (S)	cis	H	-	H	-
88	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-4-(2S-benzyl)morpholine	-CO ₂ H (S)	cis	H	-	H	-
89	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-4-(2R-benzyl)morpholine	-CO ₂ H (S)	cis	H	-	H	-
90	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-N(CH ₃)(CH ₂) ₄ -phenyl	-CO ₂ H (S)	cis	H	-	H	-
91	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-N(CH ₃)(CH ₂) ₃ (4-fluorophenyl)	-CO ₂ H (S)	cis	H	-	H	-
92	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-N(CH ₃)(CH ₂) ₃ (4-methoxy-3-methylphenyl)	-CO ₂ H (S)	cis	H	-	H	-
93	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH (phenyl) ₂	-N(CH ₃)(CH ₂) ₃ (3-pyridine)	-CO ₂ H (S)	cis	H	-	H	-
94	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH(Phenyl) ₂	-NHC(O)CH=CHphenyl	-CO ₂ H (S)	cis	H	-	H	-
95	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH(Phenyl) ₂	-N(CH ₃)C(O)CH=CHphenyl	-CO ₂ H (S)	cis	H	-	H	-
96	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH(Phenyl) ₂	-NHC(O)CH ₂ CH ₂ phenyl	-CO ₂ H (S)	cis	H	-	H	-
97	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH(Phenyl) ₂	-N(CH ₃)C(O)CH ₂ CH ₂ phenyl	-CO ₂ H (S)	cis	H	-	H	-
98	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH(Phenyl) ₂	-N(C(O)CH ₃)CH ₂ CH ₂ CH ₂ phenyl	-CO ₂ H (S)	cis	H	-	H	-

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Compound	X	Y	R ¹	R ²	R ³	Relative R ² /R ³	R ⁴	R ³ /R ⁴	R ⁵	R ² /R ⁵
99	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH(Phenyl) ₂	-N(SO ₂ CH ₃)CH ₂ CH ₂ CH ₂ phenyl	-CO ₂ H (S)	cis	H	-	H	-
100	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH(Phenyl) ₂	-1-(5-phenyl-1,2,3-triazolyl)	-CO ₂ H (S)	cis	H	-	H	-
101	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH(Phenyl) ₂	-1-(5-benzyl-1,2,3-triazolyl)	-CO ₂ H (S)	cis	H	-	H	-
102	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH(Phenyl) ₂	-4-(5-benzyl-3-oxo-morpholinyl)	-CO ₂ H (S)	cis	H	-	H	-
103	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH(Phenyl) ₂	-OCH ₂ CH ₂ CH ₂ phenyl	-CH ₂ OH (S)	cis	H	-	H	-
104	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH(Phenyl) ₂	-OCH ₂ CH ₂ CH ₂ CH ₂ (4-fluorophenyl)	-CO ₂ H (S)	cis	H	-	H	-
105	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH(Phenyl) ₂	-N(CH ₃)CH ₂ C≡C-(3-methyl-4-methoxyphenyl)	-CO ₂ H (S)	cis	H	-	H	-
106	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH(Phenyl) ₂	-CH ₂ CH ₂ CH ₂ CH ₂ phenyl	-CO ₂ H (S)	cis	H	-	H	-
107	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH(Phenyl) ₂	-2-(3-phenylthiophenyl)	-CO ₂ H (S)	cis	H	-	H	-
108	-CHR ⁵ -	-CHR ³ -	-C(O)CH(Phenyl) ₂	-OCH ₂ CH ₂ CH ₂ phenyl	-CH ₂ OH (S/R)	trans	H	-	H	-
109	-CHR ⁵ -	-CHR ³ -	-C(O)CH(Phenyl) ₂	-OCH ₂ CH ₂ CH ₂ phenyl	-CH ₂ OH (S/R)	cis	H	-	H	-
110	-CH ₂ CHR ⁵	-CHR ³ -	-C(O)CH(Phenyl) ₂	-OCH ₂ CH=CHphenyl	-CO ₂ H (S)	trans	H	-	H	-
111	-CH ₂ CHR ⁵	-CHR ³ -	-C(O)CH(Phenyl) ₂	-OCH ₂ CH ₂ CH ₂ phenyl	-CO ₂ H (S)	trans	H	-	H	-
112	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH(Phenyl) ₂	-OCH ₂ CH ₂ CH ₂ phenyl	-C(O)NH ₂ SO ₂	cis	H	-	H	-
113	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH(Phenyl) ₂	-N(CH ₃)CH ₂ CH ₂ CH ₂ phenyl	N(CH ₃) ₂ (S)	cis	H	-	H	-
114	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH(Phenyl) ₂	-N(CH ₃)CH ₂ CH ₂ CH ₂ CH ₂ -(4-fluorophenyl)	-C(O)NH ₂ SO ₂	cis	H	-	H	-
115	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH(Phenyl) ₂		-CO ₂ H (S)	cis	H	-	H	-
116	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH(Phenyl) ₂	-N(CH ₃)CH ₂ C≡C-phenyl	-CO ₂ H (S)	cis	H	-	H	-
117	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH(Phenyl) ₂	-CH ₂ Ophenyl	-CO ₂ H (S)	cis	H	-	H	-

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Compound	X	Y	R ¹	R ²	R ³	Relative R ² /R ³	R ⁴	R ³ /R ⁴	R ⁵	R ² /R ⁵
118	-CHR ⁵ -	-CHR ³ CHR ⁴ -	C(O)CH(Phenyl) ₂	-CH ₂ SO ₂ CH ₂ phenyl	-CO ₂ H (S)	cis	H	-	H	-
119	-CHR ⁵ -	-CHR ³ CHR ⁴ -	C(O)CH(Phenyl) ₂	-CH ₂ SO ₂ phenyl	-CO ₂ H (S)	cis	H	-	H	-
120	-CHR ⁵ -	-CHR ³ CHR ⁴ -	C(O)CH(Phenyl) ₂	-CH ₂ SCH ₂ CH ₂ phenyl	-CO ₂ H (S)	cis	H	-	H	-
121	-CHR ⁵ -	-CHR ³ CHR ⁴ -	C(O)CH(Phenyl) ₂	-CH ₂ SCH ₂ phenyl	-CO ₂ H (S)	cis	H	-	H	-
122	-CHR ⁵ -	-CHR ³ CHR ⁴ -	C(O)CH(Phenyl) ₂	-CH ₂ Sphenyl	-CO ₂ H (S)	cis	H	-	H	-
123	-CHR ⁵ -	-CHR ³ CHR ⁴ -	C(O)CH(Phenyl) ₂	-2-(4-phenyl-1,3-thiazolyl)	-CO ₂ H (S)	cis	H	-	H	-
124	-CHR ⁵ -	-CHR ³ CHR ⁴ -	C(O)CH(Phenyl) ₂	-SCH ₂ CH ₂ CH ₂ phenyl	-CO ₂ H (S)	cis	H	-	H	-
125	-CHR ⁵ -	-CHR ³ CHR ⁴ -	C(O)CH(Phenyl) ₂	-SO ₂ CH ₂ CH ₂ CH ₂ phenyl	-CO ₂ H (S)	cis	H	-	H	-
126	-CHR ⁵ -	-CHR ³ CHR ⁴ -	C(O)CH(Phenyl) ₂	-N(CH ₃)CH ₂ CH ₂ O-(4-fluorophenyl)	-CO ₂ H (S)	cis	H	-	H	-
127	-CHR ⁵ -	-CHR ³ CHR ⁴ -	C(O)CH(Phenyl) ₂	-CH ₂ N(CH ₃)CH ₂ CH ₂ -(4-fluorophenyl)	-CO ₂ H (S)	cis	H	-	H	-
128	-CHR ⁵ -	-CHR ³ CHR ⁴ -	C(O)CH(Phenyl) ₂	-N(CH ₂ CF ₃)CH ₂ CH ₂ CH ₂ -(4-fluorophenyl)	-CO ₂ H (S)	cis	H	-	H	-
129	-CHR ⁵ -	-CHR ³ CHR ⁴ -	C(O)CH(Phenyl) ₂	-OCH ₂ CH ₂ CH ₂ phenyl	-tetrazolyl (S)	cis	H	-	H	-
130	-CHR ⁵ -	-CHR ³ CHR ⁴ -	C(O)CH(Phenyl) ₂	-OCH ₂ CH ₂ CH ₂ phenyl	-CH ₂ NHSO ₂ CH ₃ (S)	cis	H	-	H	-
131	-CHR ⁵ -	-CHR ³ CHR ⁴ -	C(O)CH(Phenyl) ₂	-SCH ₂ CH ₂ phenyl	-CO ₂ H (S)	cis	H	-	H	-
132	-CHR ⁵ -	-CHR ³ CHR ⁴ -	C(O)CH(Phenyl) ₂	-SO ₂ CH ₂ CH ₂ phenyl	-CO ₂ H (S)	cis	H	-	H	-
133	-CHR ⁵ -	-CHR ³ CHR ⁴ -	C(O)CH(Phenyl) ₂	-SCH ₂ CH ₂ CH ₂ -(4-fluorophenyl)	-CO ₂ H (S)	cis	H	-	H	-
134	-CHR ⁵ -	-CHR ³ CHR ⁴ -	C(O)CH(Phenyl) ₂	-SO ₂ CH ₂ CH ₂ CH ₂ -(4-fluorophenyl)	-CO ₂ H (S)	cis	H	-	H	-
135	-CHR ⁵ -	-CHR ³ CHR ⁴ -	C(O)CH(Phenyl) ₂	-OCH ₂ CH ₂ CH ₂ phenyl	-C(O)NH ₂ CH ₃ (S)	cis	H	-	H	-
136	-CHR ⁵ -	-CHR ³ CHR ⁴ -	C(O)CH(Phenyl) ₂	-N(CH ₃)CH ₂ CH ₂ CH ₂ -(4-fluorophenyl)	-C(O)NH ₂ (S)	cis	H	-	H	-
137	-CHR ⁵ -	-CHR ³ CHR ⁴ -	C(O)CH(Phenyl) ₂	-N(CH ₃)CH ₂ CH ₂ CH ₂ -(4-fluorophenyl)	-CN (S)	cis	H	-	H	-

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Compound	X	Y	R ¹	R ²	R ³	Relative R ² /R ³	R ⁴	R ³ /R ⁴	R ⁵	R ² /R ⁵
138	-CHR ⁵ -	-CHR ³ CHR ⁴ -	C(O)CH(Phenyl) ₂	fluorophenyl) -N(CH ₃)CH ₂ CH ₂ CH ₂ -4- fluorophenyl)	-tetrazolyl (S)	cis	H	-	H	-
139	-CHR ⁵ -	-CHR ³ CR ⁴ =	-C(O)CH(phenyl) ₂	-2-(3-phenylthiophenyl)	-CO ₂ H (S)	-	H	-	H	-
140	-CHR ⁵ -	-CHR ³ CR ⁴ =	-C(O)CH(phenyl) ₂	-C≡CCCH ₂ CH ₂ phenyl	-CO ₂ H (S)	-	H	-	H	-
141	-CHR ⁵ -	-CHR ³ CR ⁴ =	-C(O)CH(phenyl) ₂	-2-(4-phenyl-1,3-thiazolyl)	-CO ₂ H (S)	-	H	-	H	-
142	-CHR ⁵ -	-CHR ³ -	-C(O)CH(phenyl) ₂	-OCH ₂ CH ₂ CH ₂ phenyl	-CO ₂ H (S/R)	trans	H	-	H	-
143	-CHR ⁵ -	-CHR ³ -	-C(O)CH(phenyl) ₂	-OCH ₂ CH ₂ CH ₂ phenyl	-CO ₂ H (S/R)	cis	H	-	H	-
144	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH(phenyl) ₂	4-(2R-phenyl)morpholine	-CO ₂ H (S)	cis	H	-	H	-
145	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH(phenyl) ₂	4-(2S-phenyl)morpholine	-CO ₂ H (S)	cis	H	-	H	-
146	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH(phenyl) ₂	-N(CH ₃)(CH ₂ C≡CH	-CO ₂ H (S)	cis	H	-	H	-
147	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH(phenyl) ₂	-N(CH ₃)(CH ₂ CH ₂ CH ₃	-CO ₂ H (S)	cis	H	-	H	-
148	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH(phenyl) ₂	-N(CH ₃)(CH ₂ C≡CC(CH ₃) ₃	-CO ₂ H (S)	cis	H	-	H	-
149	-CHR ⁵ -	-CHR ³ CHR ⁴ -	-C(O)CH(phenyl) ₂	-N(CH ₃)(CH ₂ CH ₂ CH ₂ C(CH ₃) ₃	-CO ₂ H (S)	cis	H	-	H	-

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Particular compounds of the formula (II) include compounds 2, 3, 5, 6, 8, 9, 15, 16, 17, 21, 22, 23, 28, 34, 35, 36, 46, 48, 49, 50, 51, 53, 54, 55, 56, 58, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 75, 76, 84, 85, 86, 87, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 112, 114, 115, 116, 118, 119, 120, 121, 122, 124, 125, 126, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 142 and 143, especially 2, 3, 5, 6, 9, 15, 16, 21, 22, 23, 28, 48, 49, 50, 51, 53, 54, 55, 56, 58, 61, 63, 70, 84, 85, 87, 90, 91, 92, 93, 97, 98, 100, 101, 102, 106, 107, 112, 114, 115, 118, 121, 122, 124, 126, 135, 136, 137, 138, and 143.

10 In some embodiments, the compounds of formula (I) are selective AT₂ receptor antagonists. In particular embodiments, the selective AT₂ receptor antagonists have an IC₅₀ at the AT₂ receptor of ≤ 100 nM and an IC₅₀ at the AT₁ receptor of $>100,000$ nM (10 μ M) using the assay methodologies described in Biological Examples 1 and 2.

15 The compounds of the invention are made by methods known in the art from commercially available starting materials.

For preparation of pyrrolidine derivatives, starting materials include suitably protected carboxylic acids such as *trans*-4-hydroxyproline ethyl ester and 4-hydroxy-indol-2-yl carboxylic acid methyl ester. For preparation of azetidine derivatives, a suitable starting material includes 3-hydroxy-azetidine-2-carboxylic acid methyl ester.

R² may be introduced by alkylation reactions such as reaction of an alkyl or aryl chloride in the presence of base. In some instances, the base used may be a hindered alkoxide such as *tert*-butoxide. In some instances where epimerization of a group alpha to the carboxylic acid is a problem, silver oxide mediated alkylation may be used.

R¹ may be introduced either before the introduction of R² or after the introduction of R². If R² is introduced prior to the introduction of R¹, it may be necessary to protect the ring nitrogen during the alkylation reaction. Suitable nitrogen protecting groups are known in the art, for example, in Greene & Wutz, Protective Groups in Organic Synthesis, Third

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Edition, John Wiley & Sons, 1999. A suitable nitrogen protecting group is *t*-butoxycarbonyl (Boc). Alternatively other reactive alkyl or aryl groups, such as phenoxy groups may be introduced by reaction of the 4-hydroxy substituent with the phenolic hydroxyl group in the presence of triphenylphosphine (PPh₃) and DBAD.

5

R¹ may be introduced by amide formation with a suitable carboxylic acid and the ring nitrogen. Amide formation is well known in the art and may involve the activation of the carboxylic acid, for example, the carboxy group is activated by formation of a carbodiimide, triazole or a uronium or phosphonium salt of a non-nucleophilic anion.

- 10 Suitable activating groups are well known in the art including dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC), 1-ethyl-3-(dimethylaminopropyl)carbodiimide (EDCI), 1-hydroxybenzotriazole (HOBt), 1-hydroxy-7-aza-benzotriazole (HOAt), ethyl-2-cyano-2-cyano-2-(hydroxyimino)acetate (Oxyma Pure), O-benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), O-(6-chloro-1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluorophosphate (HCTU), O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU), (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP); (benzotriazol-1-yloxy)-tris-(dimethylamino)phosphonium hexafluorophosphate (BOP), (1-cyano-2-ethoxy-2-oxoethylidenaminoxy)-dimethylamino-morpholino-carbenium hexafluorophosphate (COMU) and O-[(ethoxycarbonyl)-cyanomethyleneamino]-N,N,N',N'-tetramethyluronium tetrafluoroborate (TOTU).
- 15
- 20

- Compounds in which R² is a substituted amino group may be prepared from 4-aminoproline. 4-Aminoproline may be prepared from commercially available 4-hydroxyproline by reductive amination of a ketone resulting from the oxidation of the 4-hydroxy group. The amino group may be further alkylated, acylated or sulfonated with one or two substituents. When the amine is bulky, for example, a secondary amine or the amino of a heterocyclic ring, this method provides good yields. In an alternative approach,
- 30 the hydroxyl group of the 4-hydroxyproline may be mesylated and reacted with an amine nucleophile. This approach may be used when the amino nucleophile is a primary amine

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group. After introduction of the amino substituent, the amino group may be alkylated to provide a tertiary amine such as a N-methylalkylphenyl substituent.

In some cases, where the bond to R^2 is with the nitrogen atom of a heterocyclic ring, the starting material may be 4-oxo-proline methyl ester or an N-protected or N-derivative thereof and the reaction proceeds at elevated temperature, such as between 100 and 110 °C.

The mesylate may also be used to prepare compounds in which R^2 is a thiol or sulfoxide group. For example the mesylate formed from 4-hydroxy-proline methyl ester may be reacted with PhC(O)SH to provide a protected thiol group as R^2 . The thiol may be deprotected with mild base such as K_2CO_3 . The free thiol may then be alkylated or arylated by methods known in the art such as reaction with an alkyl halide. The thio group may also be oxidised to provide a sulfoxide, for example, with m-CPBA.

When the pyrrolidine ring has a double bond in the 3,4-position, this may also be formed from reaction of 4-oxo-proline with a compound such as PhNTf_2 . The triflate formed may then be further reacted with another group such as a heterocycle via its borate or an alkyne in the presence of a catalyst such as CuI , $\text{Pd(PPh)}_2\text{Cl}_2$.

In some instances, R^2 may be formed into a heterocyclyl ring *in situ* by cyclization of a disubstituted amino group. For example, the 4-oxo-proline may be aminated with a hydroxy containing alkyl amine, followed by acylation of the nitrogen atom with an chloroalkylacyl chloride. The remaining chloride is able to be used in a cyclization reaction in the presence of Cs_2CO_3 .

25

Triazoles may be prepared by reaction of 4-azo-proline with an alkyne in the presence of a suitable catalyst such as $\text{Cp}^*\text{Ru (COD)Cl}$.

R^3 may be a carboxy group or may be manipulated, for example by reduction with a reagent such as LiAlH_2Cl , $\text{NaBH}_4/\text{ClCO}_2\text{Et}$ or BH_3 THF, to give a primary alcohol. Acyl

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sulfonamides may also be prepared by reaction with appropriate amines such as $\text{NH}_2\text{SO}_2\text{N}(\text{CH}_3)_2$.

The substituents of R^2 and R^5 that have reactive functional groups such as double bonds or triple bonds may be further manipulated to provide variation in the R^2 or R^5 substituents. For example, double bonds may be reduced to alkylene groups, or may be oxidized such as with *meta*-chloroperoxybenzoic acid (MCPBA) to give epoxides or reacted with diiodomethane to provide cyclopropyl groups. Triple bonds may be selectively reduced to provide double bonds and catalysts may be selected to provide either *cis* or *trans* geometric isomers as known in the art.

Substituents may be introduced onto a ring formed by R^2 and R^5 in a similar manner as discussed for the introduction of R^2 above.

15 ***Methods of the Invention***

In one aspect of the present invention, there is provided a method of treating or preventing the symptoms of a neuropathic condition in a subject comprising administering a compound of formula (I) or a pharmaceutically acceptable salt thereof.

20 The compounds of formula (I) are effective in the prevention or attenuation of the symptoms of neuropathic conditions including primary and secondary neuropathic conditions. In accordance with the present invention, the compounds of formula (I) can act to treat, prevent or attenuate one or more symptoms associated with neuropathic conditions including, but not limited to, hyperesthesia, hyperalgesia, allodynia and/or spontaneous
25 burning pain. In some embodiments, the compound of formula (I) is used to prevent or attenuate one or more symptoms associated with peripheral neuropathic conditions, illustrative examples of which include numbness, weakness, burning pain, shooting pain, and loss of reflexes. The pain may be severe and disabling. In some embodiments, the symptom, which is the subject of the prevention and/or attenuation, is neuropathic pain.
30 Accordingly, in a related aspect, the invention provides methods for preventing and/or attenuating neuropathic pain in an individual, comprising administering to the individual a

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pain-preventing or -attenuating effective amount of an AT₂ receptor antagonist, which is suitably in the form of a pharmaceutical composition.

There are many possible causes of neuropathy and neuropathic pain and it will be understood that the present invention contemplates the treatment or prevention of symptoms of any neuropathic condition regardless of the cause. In some embodiments, the neuropathic conditions are a result of diseases of the nerves (primary neuropathy) and neuropathy that is caused by systemic disease (secondary neuropathy) such as but not limited to: diabetic neuropathy; Herpes Zoster (shingles)-related neuropathy; uremia-associated neuropathy; amyloidosis neuropathy; HIV sensory neuropathies; hereditary motor and sensory neuropathies (HMSN); hereditary sensory neuropathies (HSNs); hereditary sensory and autonomic neuropathies; hereditary neuropathies with ulcero-mutilation; nitrofurantoin neuropathy; toxic neuropathy; neuropathy caused by nutritional deficiency, neuropathy caused by kidney failure and complex regional pain syndrome. Other causes include repetitive activities such as typing or working on an assembly line, medications known to cause peripheral neuropathy such as several antiretroviral drugs ddC (zalcitabine) and ddI (didanosine), antibiotics (metronidazole, an antibiotic used for Crohn's disease, isoniazid used for tuberculosis), gold compounds (used for rheumatoid arthritis), some chemotherapy drugs (such as vincristine and others) and many others. Chemical compounds are also known to cause peripheral neuropathy including alcohol, lead, arsenic, mercury and organophosphate pesticides. Some peripheral neuropathies are associated with infectious processes (such as Guillian-Barre syndrome). In certain embodiments, the neuropathic condition is a peripheral neuropathic condition, which is suitably pain secondary to mechanical nerve injury or painful diabetic neuropathy (PDN) or related condition.

The neuropathic condition may be acute or chronic and, in this connection, it will be understood by persons of skill in the art that the time course of a neuropathy will vary, based on its underlying cause. With trauma, the onset of symptoms may be acute, or sudden; however, the most severe symptoms may develop over time and persist for years. Inflammatory and some metabolic neuropathies have a subacute course extending over

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days to weeks. A chronic course over weeks to months usually indicates a toxic or metabolic neuropathy. A chronic, slowly progressive neuropathy over many years such as occurs with painful diabetic neuropathy or with most hereditary neuropathies or with a condition termed chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).
5 Neuropathic conditions with symptoms that relapse and remit include the Guillian-Barre syndrome.

In another aspect of the invention there is provided a method of treating or preventing a condition characterized by neuronal hypersensitivity in a subject comprising administering
10 a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In some embodiments, the condition characterized by neuronal hypersensitivity is a hyperalgesic condition such as fibromyalgia. In other embodiments, the condition is irritable bowel syndrome which is characterized by neuronal hypersensitivity in the gut.
15

In another aspect of the invention there is provided a method of treating or preventing a disorder associated with aberrant nerve regeneration comprising administering a compound of formula (I) or a pharmaceutically acceptable salt thereof.

20 In some embodiments, the disorder associated with aberrant nerve regeneration also includes neuronal hypersensitivity. For example, disorders associated with aberrant nerve regeneration are breast pain, interstitial cystitis and vulvodynia. In other embodiments, the disorder is a cancer chemotherapy-induced neuropathy.

25 In another aspect of the invention, there is provided a method of treating or preventing inflammatory pain in a subject comprising administering a compound of formula (I) or a pharmaceutically acceptable salt thereof.

Pain related to inflammation may be acute or chronic and can be due to a number of
30 conditions that are characterized by inflammation including, without limitation, burns such as chemical, frictional or chemical burns, autoimmune diseases such as rheumatoid

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arthritis and osteoarthritis, inflammatory bowel disease such as Crohn's disease and colitis, and other inflammatory diseases such as inflammatory bowel disease, carditis, dermatitis, myositis, neuritis and collagen vascular diseases.

- 5 In a further aspect, the present invention provides a method of treating or preventing impaired nerve conduction velocity in a subject comprising administering a compound of formula (I) or a pharmaceutically acceptable salt thereof.

- Impaired neuronal conduction velocity is a symptom of nerve dysfunction or damage and
10 may be present as a symptom of a large number of diseases or disorders, particularly diseases or disorders that exhibit paresthesia as a symptom. In some embodiments, the impaired nerve conduction velocity is associated with a neuropathic condition as described above. In other embodiments, the impaired nerve conduction velocity is associated with
Carpel Tunnel Syndrome, ulnar neuropathy, Guillian-Barré Syndrome,
15 fascioscapulohumeral muscular dystrophy and spinal disc herniation.

- Nerve conduction velocity is assessed by evaluating the electrical conduction of motor and sensory nerves in the body. Motor nerve conduction velocity is measured by stimulation of a peripheral nerve and measuring the time taken for the electrical impulse to be detected
20 in the muscle associated with the nerve. The time taken is measured in milliseconds and is converted to a velocity (m/s) by taking into account the distance travelled. Sensory nerve conduction is assessed in a similar manner with stimulation of a peripheral nerve and recording at a sensory site such as a finger or paw pad.

- 25 In yet a further aspect of the invention there is provided a method of producing analgesia in a subject comprising administering a compound of formula (I) or a pharmaceutically acceptable salt thereof.

- In some embodiments, the subject is a subject having a neuropathic condition, an
30 inflammatory condition, impaired nerve conduction velocity, a condition characterized by neuronal hypersensitivity or a disorder associated with aberrant nerve regeneration. In

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other embodiments, the subject is a subject at risk of developing neuropathic pain, inflammatory pain, pain related to impaired nerve conduction velocity, a condition characterized by neuronal hypersensitivity or a disorder associated with aberrant nerve regeneration.

5

In still another aspect of the invention there is provided a method of treating or preventing a cell proliferative disorder in a subject comprising administering a compound of formula (I) or a pharmaceutically acceptable salt thereof.

10 In some embodiments, the cell proliferative disorder is a cancer, especially where the cancer is selected from leukaemia, melanoma, prostate cancer, breast cancer, ovarian cancer, basal cell carcinoma, squamous cell carcinoma, sarquoides, fibrosarcoma, colon cancer, lung cancer and other solid tumour cancers.

15 In other embodiments, the cell proliferative disorder is a non-cancerous proliferative disorder. Examples of such non-cancerous proliferative disorders include dermatological disorders such as warts, keloids, psoriasis, proud flesh disorder and also the reduction in scar tissue and cosmetic remodelling.

20 In a further aspect the present invention provides a method of treating or preventing a disorder associated with an imbalance between bone resorption and bone formation in a subject comprising administering a compound of formula (I) or a pharmaceutically acceptable salt thereof.

25 In some embodiments, the disorder associated with an imbalance between bone resorption and bone formation is osteoporosis.

The subjects, individuals or patients to be treated are mammalian subjects including but not limited to humans, primates, livestock animals such as sheep, cattle, pigs, horses,
30 donkeys and goats; laboratory test animals such as mice, rats, rabbits and guinea pigs;

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companion animals such as cats and dogs or captive wild animals such as those kept in zoos. In a particular embodiment, the subject is a human.

An "effective amount" means an amount necessary at least partly to attain the desired response, or to delay the onset or inhibit progression or halt altogether, the onset or progression of a particular condition being treated. The amount varies depending upon the health and physical condition of the individual to be treated, the taxonomic group of individual to be treated, the degree of protection desired, the formulation of the composition, the assessment of the medical situation, and other relevant factors. It is expected that the amount will fall in a relatively broad range that can be determined through routine trials. An effective amount in relation to a human patient, for example, may lie in the range of about 0.1 ng per kg of body weight to 1 g per kg of body weight per dosage. The dosage is preferably in the range of 1 μ g to 1 g per kg of body weight per dosage, such as is in the range of 1 mg to 1 g per kg of body weight per dosage. In one embodiment, the dosage is in the range of 1 mg to 500 mg per kg of body weight per dosage. In another embodiment, the dosage is in the range of 1 mg to 250 mg per kg of body weight per dosage. In yet another embodiment, the dosage is in the range of 1 mg to 100 mg per kg of body weight per dosage, such as up to 50 mg per kg of body weight per dosage. In yet another embodiment, the dosage is in the range of 1 μ g to 1 mg per kg of body weight per dosage. Dosage regimes may be adjusted to provide the optimum therapeutic response. For example, several divided doses may be administered daily, weekly, monthly or other suitable time intervals, or the dose may be proportionally reduced as indicated by the exigencies of the situation.

Reference herein to "treatment" and "prophylaxis" is to be considered in its broadest context. The term "treatment" does not necessarily imply that a subject is treated until total recovery. "Treatment" may also reduce the severity of an existing condition. The term "prophylaxis" does not necessarily mean that the subject will not eventually contract a disease condition. The term "prophylaxis" may be considered to include delaying the onset of a particular condition. Accordingly, treatment and prophylaxis include amelioration of

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the symptoms of a particular condition or preventing or otherwise reducing the risk of developing a particular condition.

In some embodiments, the compounds of formula (I) or their pharmaceutically acceptable salts thereof may be administered together with another therapy. Administration may be in
5 a single composition or in separate compositions simultaneously or sequentially such that both compounds or therapies are active at the same time in the body.

In some embodiments, the compounds of formula (I) or their pharmaceutically acceptable salts are administered together with another therapy to treat neuropathic or inflammatory
10 pain or the underlying condition that is causing the neuropathic or inflammatory pain or another therapy to treat conditions characterized by neuronal sensitivity, disorders associated with aberrant nerve regeneration, proliferative disorders or disorders associated with an imbalance between bone resorption and bone formation. In some embodiments,
15 the amount of the second drug may be reduced when administration is together with a compound of formula (I) or a pharmaceutically acceptable salt thereof.

Suitable additional drugs to treat pain include opiates such as morphine, codeine, dihydrocodeine, hydrocodone, acetyldihydrocodeine, oxycodone, oxymorphone and
20 buprenorphine, and non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen, naproxen, acetaminophen, diflunisal, salsalate, phenacetin, fenoprofen, ketoprofen, flurbiprofen, oxaprozin, loxoprofen, indomethacin, sulindac, etodolac, ketorolac, diclofenac, nabumetone, mefenamic acid, meclofenamic acid, flufenamic acid, tolfenamic acid, celecoxib, parecoxib, lumoxicob, etoricoxib, firocoxib, rimesulide and
25 licofelone.

Examples of drugs to treat neuropathies include duloxetine, pregabalin, gabapentin, phenytoin, carbamazepine, levocarnitine, tricyclic antidepressants such as amitriptyline and sodium channel blockers such as lidocaine.

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Examples of chemotherapy drugs for proliferative disorders include cisplatin, carboplatin, camptothecin, carmustine, cyclophosphamide, dactinomycin, daunorubicin, dexamethasone, docetaxel, doxorubicin, etoposide, epirubicin, everolimus, gemcitabine, goserelin, trastuzumab (Herceptin[®]), idarubicin, interferon-alfa, irinotecan, methotrexate, 5 mitomycin, oxaliplatin, paclitaxel, raloxifene, streptozocin, tamoxifen, topotecan, vinblastine, vincristine, abiraterone, fluorouracil, denosumab, imatinib, gefitinib, lapatinib, pazopanib, rituximab, sunitinib, erlotinib and vorinostat.

Examples of drugs to treat disorders associated with an imbalance between bone formation 10 and bone resorption include bisphosphonates such as sodium alendronate, risedronate and ibandronate, raloxifene, calcitonin, teriparatide, strontium ranelate or calcium supplements.

Examples of drugs used to treat conditions characterized by neuronal hypersensitivity, such as irritable bowel syndrome, include 5HT₃ receptor antagonists such as alosetron 15 (Lotronex[®]).

The AT₂ receptor antagonists of the invention are also useful in combination with radiotherapy in cancer patients.

20 *Compositions of the Invention*

While it is possible that, for use in therapy, a compound of the invention may be administered as a neat chemical, it is preferable to present the active ingredient as a pharmaceutical composition.

25 Thus, in a further aspect of the invention, there is provided a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable carrier.

The carrier(s) must be "acceptable" in the sense of being compatible with the other 30 ingredients of the composition and not deleterious to the recipient thereof.

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Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation. The compounds of the invention, together with a conventional adjuvant, carrier, excipient, or diluent, may thus be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. Formulations containing ten (10) milligrams of active ingredient or, more broadly, 0.1 to two hundred (200) milligrams, per tablet, are accordingly suitable representative unit dosage forms. The compounds of the present invention can be administered in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise, as the active component, either a compound of the invention or a pharmaceutically acceptable salt or derivative of the compound of the invention.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

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In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as admixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated as solutions in aqueous polyethylene glycol solution.

The compounds according to the present invention may thus be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain

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formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

5

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavours, stabilizing and thickening agents, as desired.

- 10 Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well known suspending agents.

- Also included are solid form preparations which are intended to be converted, shortly
15 before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavours, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

- 20 For topical administration to the epidermis the compounds according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing
25 agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

- Formulations suitable for topical administration in the mouth include lozenges comprising active agent in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose
30 and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

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- Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in single or multidose form. In the latter case of a dropper or pipette, this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension.
- 5 In the case of a spray, this may be achieved for example by means of a metering atomizing spray pump. To improve nasal delivery and retention the compounds according to the invention may be encapsulated with cyclodextrins, or formulated with their agents expected to enhance delivery and retention in the nasal mucosa.
- 10 Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurised pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example, dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide, or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug
- 15 may be controlled by provision of a metered valve.

Alternatively the active ingredients may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP).

20

Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of, e.g., gelatin, or blister packs from which the powder may be administered by means of an inhaler.

25

In formulations intended for administration to the respiratory tract, including intranasal formulations, the compound will generally have a small particle size for example of the order of 1 to 10 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization.

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When desired, formulations adapted to give sustained release of the active ingredient may be employed.

5 The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

10

The invention will now be described with reference to the following Examples which illustrate some preferred aspects of the present invention. However, it is to be understood that the particularity of the following description of the invention is not to supersede the generality of the preceding description of the invention.

15

Brief Description of the Figures

Figure 1 is a graphical representation of the inhibition of neurite outgrowth in the presence of angiotensin II 0.1 μM and known selective AT_2 receptor antagonist PD-126,055 at 0.003 μM , 0.01 μM , 0.03 μM , 0.1 μM , 0.3 μM , 1 μM , 3 μM and 10 μM .

20

Figure 2 is a graphical representation of the inhibition of neurite outgrowth in the presence of angiotensin II 0.1 μM and compound 6 at 0.003 μM , 0.01 μM , 0.03 μM , 0.1 μM , 0.3 μM , 1 μM , 3 μM and 10 μM .

25 Figure 3 is a graphical representation of the inhibition of neurite outgrowth in the presence of angiotensin II 0.1 μM and compound 16 at 0.003 μM , 0.01 μM , 0.03 μM , 0.1 μM , 0.3 μM , 1 μM , 3 μM and 10 μM .

30 Figure 4 is a graphical representation of the inhibition of neurite outgrowth in the presence of angiotensin II 0.1 μM and compound 29 at 0.003 μM , 0.01 μM , 0.03 μM , 0.1 μM , 0.3 μM , 1 μM , 3 μM and 10 μM .

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Figure 5 is a graphical representation of the inhibition of neurite outgrowth in the presence of angiotensin II 0.1 μM and compound 38 at 0.003 μM , 0.01 μM , 0.03 μM , 0.1 μM , 0.3 μM , 1 μM , 3 μM and 10 μM .

5

EXAMPLES

Abbreviations:

DCM	dichloromethane
DBAD	dibenzyl azodicarboxylate
RT	room temperature
PE	petroleum ether
EA or EtOAc	ethyl acetate
THF	tetrahydrofuran
Et ₂ O	diethyl ether
MeOH	methanol
Et ₃ N	triethylamine
DMAP	4-dimethylaminopyridine
DMSO	dimethylsulfoxide
Bn	benzyl
Bz	benzoyl
TLC	thin layer chromatography
DCE	1,2-dichloroethane
DMF	dimethylformamide
NaH	sodium hydride
TFA	trifluoroacetic acid
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
AcOH	acetic acid
TEA	triethylamine
Boc	<i>t</i> -butyloxycarbonyl
TBAI	tetrabutylammonium iodide

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HCHO	formaldehyde
MsCl	mesyl chloride
PCC	pyridinium chlorochromate
EDTA	ethylenediamine tetraacetic acid
DIPEA	diisopropylethylamine
CuI	copper iodide
IPA	isopropylamine
CDI	1,1-carbonyldiimidazole
LDA	Lithium diisopropylamide
HATU	O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate

General Methods Used in the Synthesis Examples

LC-MS (Agilent):

1. LC: Agilent Technologies 1200 series, Binary Pump, Diode Array Detector.
5 Ultimate AQ-C18, 3 μ m, 2.1 $\times$ 50 mm column. Mobile phase: B (MeOH) and A (0.07% HCOOH aqueous solution). Flow Rate: 0.4 mL/min at 25°C. Detector: 214 nm, 254 nm. Gradient stop time, 5 min. Timetable:

T (min)	B(%)	A(%)
0	10	90
0.2	10	90
1.2	95	5
2.8	95	5
3	10	90
5	10	90

- 10 2. MS: G6110A, Quadrupole LC/MS, Ion Source: ES-API, TIC: 50~900 m/z, Fragmentor: 60, Drying gas flow: 10 L/min, Nebulizer pressure: 35 psi, Drying gas temperature: 350°C, Vcap: 3500V.
3. Sample preparation: samples were dissolved in methanol at 1~10 μ g/mL, then filtered through a 0.22 μ m filter membrane. Injection volume: 1~10 μ L.

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LC-MS (Waters):

1. LC: Waters 2695, Quaternary Pump, Waters 2996 Photodiode Array Detector. Xbridge-C18, 3.5 μ m, 2.1×50mm column. Mobile Phase: B (MeOH) and A (0.07% HCOOH aqueous solution). Flow Rate: 0.3 mL/min at 30°C. Detector: 214 nm, 254 nm. Gradient stop time, 10 min. Timetable:

T (min)	B(%)	A(%)
0	10	90
2.5	75	25
5.0	95	5
7.5	95	5
7.6	10	90
10	10	90

2. MS: Micromass QZ, TIC: 100~900 m/z, Ion Source: ES, Capillary: 3kV, Cone: 3V, Extractor: 3V, Drying gas flow: 600 L/hr, cone: 50 L/hr, Desolvation temperature: 300°C, Source temperature: 100°C.
3. Sample preparation: samples were dissolved in methanol at 1~10 μ g/mL, then filtered through a 0.22 μ m filter membrane. Injection volume: 1~10 μ L.

LC-MS (Agilent, P-2) (Positive Ion mode) or LC-MS (Agilent, N-2) (Negative Ion Mode):

1. LC: Agilent Technologies 1200 series, Binary Pump, Diode Array Detector. Xbridge-C18, 2.5 μ m, 2.1×30 mm column. Mobile phase: B (MeOH) and A (0.07% HCOOH aqueous solution). Flow Rate: 0.5 mL/min at 30 °C. Detector: 214 nm, 254 nm. Gradient stop time, 5 min. Timetable:

T (min)	B(%)	A(%)
0	80	20
0.2	80	20
0.8	5	95
2.8	5	95
3	80	20
5	80	20

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4. MS: G6110A, Quadrupole LC/MS, Ion Source: ES-API, TIC: 50~900 m/z, Fragmentor: 60, Drying gas flow: 10 L/min, Nebulizer pressure: 35 psi, Drying gas temperature: 350 °C, Vcap: 3500V.

5. Sample preparation: samples were dissolved in methanol at 1~10 µg/mL, then filtered through a 0.22 µm filter membrane. Injection volume: 1~10 µL.

LC-MS (Agilent, P-1) (Positive Ion mode) or LC-MS (Agilent, N-1) (Negative Ion mode) (low polarity samples):

1. LC: Agilent Technologies 1200 series, Binary Pump, Diode Array Detector. Xbridge-C18, 2.5 µm, 2.1×30 mm column. Mobile phase: B (MeOH) and A (0.07% HCOOH aqueous solution). Flow Rate: 0.4 mL/min at 30 °C. Detector: 214 nm, 254 nm. Gradient stop time, 6 min. Timetable:

T (min)	B(%)	A(%)
0	80	20
0.2	80	20
0.8	5	95
3.8	5	95
4	80	20
6	80	20

2. MS: G6110A, Quadrupole LC/MS, Ion Source: ES-API, TIC: 50~900 m/z, Fragmentor: 60, Drying gas flow: 10 L/min, Nebulizer pressure: 35 psi, Drying gas temperature: 350 °C, Vcap: 3500V.

3. Sample preparation: samples were dissolved in methanol at 1~10 µg/mL, then filtered through a 0.22 µm filter membrane. Injection volume: 1~10 µL.

Analytical HPLC:

1. (Referred to as "Aligent") Agilent Technologies 1200 series, Quaternary Pump, Diode Array Detector. Ultimate AQ-C18, 5 µm, 4.6×250 mm column. Mobile Phase: B (MeOH) and A (0.07% TFA aqueous solution). Flow Rate: 1.00 mL/min at 30°C. Detector: 214 nm, 254 nm. Gradient stop time: 20 min. Timetable:

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T (min)	B(%)	A(%)
0	40	60
3	40	60
5	60	40
7	80	20
8	95	5
15	95	5
17	40	60
20	40	60

2. Sample preparation: samples were dissolved in methanol at ~1 mg/mL, then filtered through a 0.22 µm filter membrane. Injection volume: 1~10 µL.

5 Referred to as "July-L" or "SYN-001"

1. Agilent Technologies 1200 series, Quaternary Pump, Diode Array Detector. Waters Nova-pak C18, 4 µm, 3.9×150 mm column. Mobile Phase: C (MeOH) and D (0.07%TFA aqueous solution). Flow Rate: 1.00 mL/min at 30 °C. Detector: 214 nm, 254 nm. Gradient stop time: 15 min. Timetables:

10

Method name: SYN-001 (high polarity)

T (min)	C(%)	D(%)
0	5	95
2	5	95
5	12	88
6	40	60
7	95	5
10	95	5
12	60	40
13	5	95
15	5	95

Method name: JULY-L (average and low polarity)

T (min)	C(%)	D(%)
0	20	80
2	20	80
4	40	60
5	70	30
6	95	5
10	95	5
11	70	20

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12	20	80
15	20	80

2. Sample preparation: samples were dissolved in methanol at ~1 mg/mL, then filtered through a 0.22 μ m filter membrane. Injection volume: 1~10 μ L.

5 Referred to as "ZSJ-2"

1. Agilent Technologies 1200 series, Quaternary Pump, Diode Array Detector. Waters Nova-pak C18, 4 μ m, 3.9 $\times$ 150 mm column. Mobile Phase: C (MeOH) and D (0.07% TFA aqueous solution). Flow Rate: 1.00 mL/min at 30°C. Detector: 214 nm, 254 nm. Gradient stop time: 30 min. Timetable:

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Method name: ZSJ-2

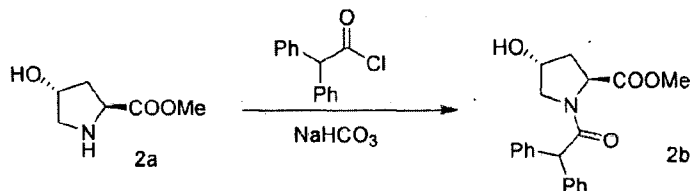
T (min)	C(%)	D(%)
0	20	80
28	95	5
30	70	30

2. Sample preparation: samples were dissolved in methanol at ~1 mg/mL, then filtered through a 0.22 μ m filter membrane. Injection volume: 1~10 μ L.

15

Example 1: Compound 2 (2*S*,4*S*)-4-(benzyloxy)-1-(2,2-diphenylacetyl)pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of Compound 2b



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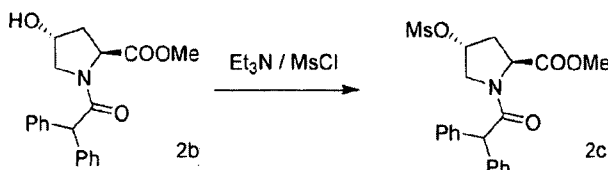
- A solution of diphenylacetic acid (5.0 g, 23.6 mmol) in thionyl chloride (30 mL) was heated at reflux for 30 min. The mixture was then concentrated *in vacuo* and the residue was dissolved in ether (10 mL) and added to a mixture of compound 2a (3.76 g, 25.9 mmol) and NaHCO₃ (5.95 g, 70.8 mmol) in water (50 mL) and ether (20 mL) at 0°C. After addition, the mixture was stirred at RT for 2 h, TLC (EA:PE=1:1) showed the starting material was consumed. The product was collected by filtration and the obtained filter cake

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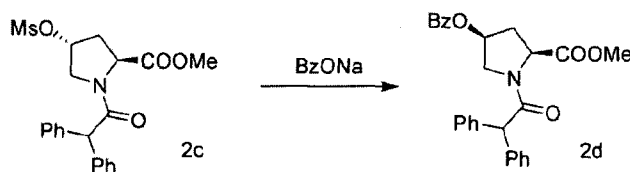
was dissolved in EA (50 mL), washed with brine (30 mL x 3), dried over Na₂SO₄, filtered and concentrated *in vacuo* to give 2b as a white solid (6.5 g, 74%). LC-MS (Agilent): R_t 4.86 min; m/z calculated for C₂₀H₂₁NO₄ [M+H]⁺ 340.2, [M+Na]⁺ 362.1, found [M+H]⁺ 340.2, [M+Na]⁺ 362.1.

5 2. Procedure for the preparation of Compound 2c



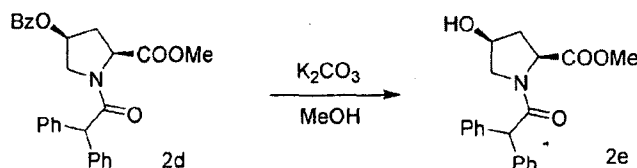
To a stirred solution of 2b (2.0 g, 5.9 mmol) and Et₃N (1.2 g, 11.8 mmol) in DCM (20 mL) was added MsCl (0.81 g, 7.1 mmol) at 0°C. After addition, the reaction was stirred at RT for 1 h. TLC (PE:EA=2:1) showed the starting material was consumed. DCM (10 mL) and
 10 water (20 mL) were added and the DCM layer was separated, washed with brine (20 mL x 3) then dried over Na₂SO₄. The solvent was removed *in vacuo* to give 2c as a yellow solid (2.0 g, 81%). LC-MS (Agilent): R_t 4.82 min; m/z calculated for C₂₁H₂₃NO₆S [M+H]⁺ 418.1, [M+Na]⁺ 440.1, found [M+H]⁺ 418.0, [M+Na]⁺ 440.0.

3. Procedure for the preparation of Compound 2d



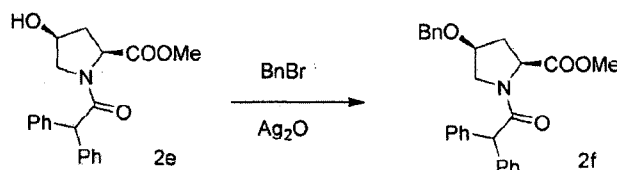
15 To a stirred solution of 2c (2.0 g, 4.8 mmol) in DMSO (20 mL) was added BzONa (1.4g, 9.6 mmol) at RT. The mixture was then heated at 90°C overnight. TLC (PE:EA=2:1) showed the starting material was consumed. The mixture was cooled to RT, added to EA (30 mL) and washed with cold water (200 mL). The organic phase was washed with brine
 20 (2 x 20 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=10:1) to give 2d as an off-white solid (1.5g, 70%). LC-MS (Agilent): R_t 5.25 min; m/z calculated for C₂₇H₂₅NO₅ [M+H]⁺ 444.2, [M+Na]⁺ 466.2, found [M+H]⁺ 444.1, [M+Na]⁺ 466.1.

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4. Procedure for the preparation of Compound 2e

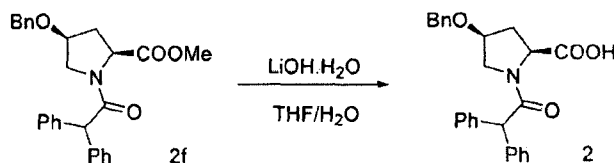
To a stirred solution of 2d (8.0 g, 18.0 mmol) in MeOH (150 mL) was added K_2CO_3 (2.5 g, 18.0 mmol) at 0°C and the mixture was stirred at RT for 1 h, TLC (PE:EA=2:1) showed the starting material was consumed. The mixture was poured into EA (200ml), washed with water (300 mL) and brine (150 mL x 2), then dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE: EA = 3:1) to give 2e as an off-white solid (5.6 g, 88%). LC-MS (Agilent): R_t 4.78 min; m/z calculated for $\text{C}_{20}\text{H}_{21}\text{NO}_4$ $[\text{M}+\text{H}]^+$ 340.2, $[\text{M}+\text{Na}]^+$ 362.1, found $[\text{M}+\text{H}]^+$ 340.0, $[\text{M}+\text{Na}]^+$ 362.0.

10

5. Procedure for the preparation of Compound 2f

To a stirred suspension of Ag_2O (409 mg, 1.77 mmol) in DCM (10 mL) was added 2e (500 mg, 1.47 mmol) at 0°C . BnBr (303 mg, 1.77 mmol) was added to the reaction mixture at 0°C . After addition, the reaction was stirred at RT overnight. TLC (PE:EA=1:1) showed the starting material was consumed. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=0:1 to 5:1) to give the product as a clear oil (250 mg, 40%). LC-MS (Agilent): R_t 5.30 min; m/z calculated for $\text{C}_{27}\text{H}_{27}\text{NO}_4$ $[\text{M}+\text{H}]^+$ 430.2, $[\text{M}+\text{Na}]^+$ 452.2, found $[\text{M}+\text{H}]^+$ 430.1, $[\text{M}+\text{Na}]^+$ 452.1.

20

6. Procedure for the preparation of Compound 2

To a stirred solution of 2f (250 mg, 0.58 mmol) in THF (7 mL) was added an solution of $\text{LiOH}\cdot\text{H}_2\text{O}$ (37 mg, 0.87 mmol) in water (3 mL) at 0°C . After addition, the reaction was

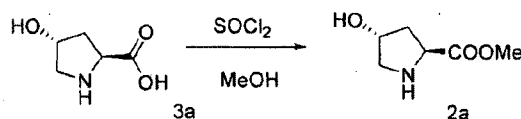
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stirred overnight at 25°C. TLC (MeOH:DCM=1:10) showed the starting material was consumed. Water (5 mL) and Et₂O (10 mL) were added to the mixture and the organic phase separated. The aqueous phase was acidified with 1M HCl to pH 3-4 and the solution was extracted with EA (2 x 10mL). The organic layer was washed with brine (3 x 10mL) and the organic phase dried (Na₂SO₄) and evaporated to give 200 mg of the crude product. 100 mg of the crude product was purified by preparative TLC (MeOH:DCM= 1:20) to give 59 mg of pure 2. LC-MS (Agilent): R_t 5.09 min; m/z calculated for C₁₉H₂₅NO₅ [M+H]⁺ 416.2, [M+Na]⁺ 438.2, found [M+H]⁺ 416.2, [M+Na]⁺ 438.1. HPLC (214 and 254 nm): R_t 13.38 min.

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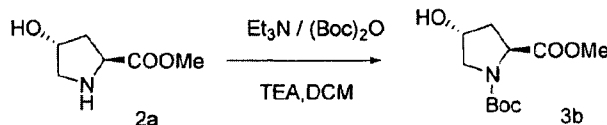
Example 2: Compound 3 (2*S*,4*R*)-4-(benzyloxy)-1-(2,2-diphenylacetyl)pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of Compound 2a



To a stirred mixture of 3a (5.0 g, 38.1 mmol) in MeOH (50 mL) was added SOCl₂ (5 mL) dropwise and the mixture was heated at reflux for 7 h, TLC (DCM:MeOH=10:1) showed the starting material was consumed. The MeOH was removed *in vacuo* to give 2a (6.0 g) as white solid, which was used for the next step directly. LC-MS (Agilent): R_t 0.87 min; m/z calculated for C₆H₁₁NO₃ [M+H]⁺ 146.1, found [M+H]⁺ 146.1.

2. Procedure for the preparation of Compound 3b



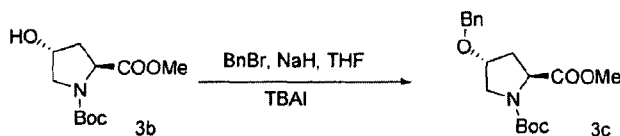
To a stirred solution of 2a (4.0 g, 27.5 mmol) and Et₃N (3.3 g, 33.1 mmol) in DCM (40 mL) was added (Boc)₂O (7.22 g, 33.1 mmol) at 0°C under N₂ and the mixture was stirred at RT for 5 h, TLC (DCM:MeOH=20:1) showed the starting material was consumed. The reaction was quenched with water (30 mL), the layers were separated and the aqueous phase was extracted with DCM (20 mL x 2). The combined organic extracts were washed by brine, dried over Na₂SO₄ and concentrated *in vacuo*. Recrystallization from hexane/DCM then gave 3b as white solid (4.2 g, 62%). LC-MS (Agilent): R_t 4.96 min; m/z

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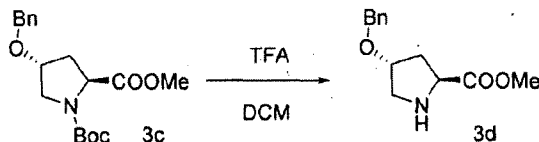
calculated for $C_{11}H_{19}NO_5$ $[M+Na]^+$ 268.1, $[2M+Na]^+$ 513.3, found $[M+Na]^+$ 268.1, $[2M+Na]^+$ 513.3.

3. Procedure for the preparation of Compound 3c



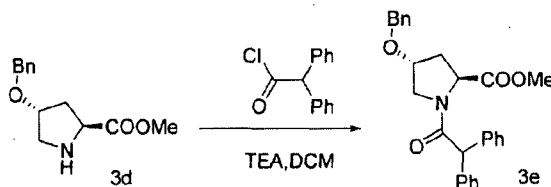
- 5 To a stirred suspension of 3b (2.5 g, 10.2 mmol), BnBr (1.5 mL, 12.2 mmol) and TBAI (1.13 g, 3.06 mmol) in THF (50 mL) was added NaH (60% w/w dispersion in mineral oil, 0.45 g, 11.2 mmol) at 0°C and the mixture was stirred at RT overnight, TLC (PE:EA=2:1) showed that the starting material was consumed. The mixture was poured into water (40 mL) and extracted with EA (30 mL x 2). The combined organic extracts were washed with
- 10 brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by silica column (PE: EA = 10:1 to 4:1) gave 3c as yellow oil (1.7 g, 50%). LC-MS (Agilent): R_t 5.35 min; m/z calculated for $C_{18}H_{25}NO_5$ $[M+Na]^+$ 358.2, $[2M+Na]^+$ 693.3, found $[M+Na]^+$ 358.2, $[2M+Na]^+$ 693.4.

4. Procedure for the preparation of Compound 3d

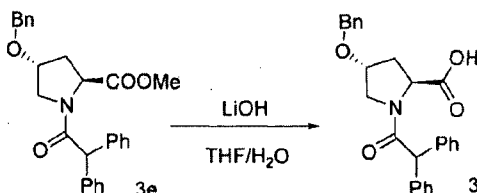


- 15 To a stirred solution of 3c (800 mg, 2.38 mmol) in DCM (6 mL) was added TFA (1.36 g, 12.0 mmol) and the mixture was stirred at RT for 2 h, then heated at 35°C for 3 h, TLC (DCM:MeOH=20:1) showed that the starting material was consumed. Water (15 mL) and DCM (15 mL) were added and the aqueous phase was adjusted to pH 8 with $NaHCO_3$ (aq).
- 20 The layers were separated and the aqueous layer was extracted with DCM (10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and the solvent was removed *in vacuo* to give 3d (380 mg, 67%) as a yellow oil. LC-MS (Agilent): R_t 4.12 min; m/z calculated for $C_{13}H_{17}NO_3$ $[M+H]^+$ 236.1, found $[M+H]^+$ 236.1.

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5. Procedure for the preparation of Compound 3e

To a solution of diphenylacetic acid (1.14 g, 5.3 mmol) in DCM (15 mL) at 0°C was added two drops of DMF followed by oxalyl chloride (1.0 g, 8.0 mmol) and the mixture was stirred at RT for 5 h then concentrated *in vacuo*. The residue was dissolved in DCM (15 mL) and a mixture of 3d (1.15 g, 4.8 mmol) and Et₃N (0.73 g, 7.1 mmol) in DCM (20 mL) was added at 0°C. The mixture was then stirred at RT overnight, TLC (PE:EA=2:1) showed that the starting material was consumed. Water (30 mL) was added and the layers were separated. The aqueous phase was extracted with DCM (20 mL) and the combined organic extracts were washed with NaHCO₃ (saturated aqueous solution), brine and dried over Na₂SO₄. The solvent was removed *in vacuo* and purification by silica column (PE:EA=20:1 to 4:1) gave the product as a yellow oil (600 mg, 30%). LC-MS (Agilent): R_t 5.25 min; m/z calculated for C₂₇H₂₇NO₄ [M+H]⁺ 430.1, found [M+H]⁺ 430.1.

6. Procedure for the preparation of Compound 3

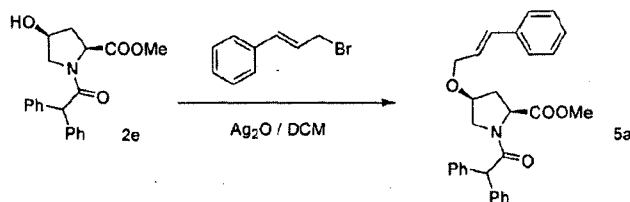
To a stirred mixture of 3e (600 mg, 1.4 mmol) in THF (5 mL) and H₂O (2 mL) was added LiOH (146.7 mg, 3.5 mmol) and the mixture was stirred at RT for 5 h, TLC (PE:EA=1:1) showed that the starting material was consumed. Most of the THF was removed *in vacuo*, water (10 mL) was added and the mixture was acidified to pH 2-3 with 1 M aqueous HCl and extracted with EA (10 mL x 2). The combined organic extracts were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification by column chromatography then prep-TLC (EA: DCM = 1:1) gave 3 (90 mg, 17%) as a white solid. LC-MS (Agilent): R_t 5.22 min; m/z calculated for C₂₆H₂₅NO₄ [M+H]⁺ 416.1, found [M+H]⁺ 416.1. HPLC (214 and 254 nm): R_t 13.49 min.

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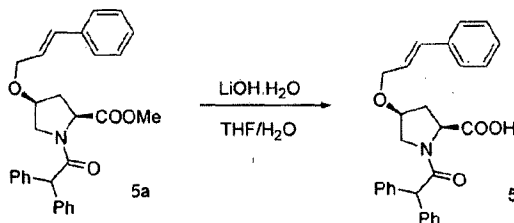
Example 3: Compound 5 (2S,4S)-4-cinnamyloxy-1-(2,2-diphenylacetyl)pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of Compound 5a



- 5 To a stirred suspension of 2e (2.0 g, 5.89 mmol) and Ag_2O (1.64 g, 7.07 mmol) in DCM (25 mL) at 0°C was added cinnamyl bromide (1.4 g, 7.07 mmol) at 0°C and the mixture was stirred at RT overnight, TLC (PE:EA=1:1) showed most of the starting material was consumed. The reaction was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=10:1 to 5:1) to give 5a as a colorless oil
- 10 (270 mg, 10%). LC-MS (Agilent): R_t 5.43 min; m/z calculated for $\text{C}_{29}\text{H}_{29}\text{NO}_4$ $[\text{M}+\text{H}]^+$ 456.2, $[\text{M}+\text{Na}]^+$ 478.2, found $[\text{M}+\text{H}]^+$ 456.1, $[\text{M}+\text{Na}]^+$ 478.1.

2. Procedure for the preparation of Compound 5

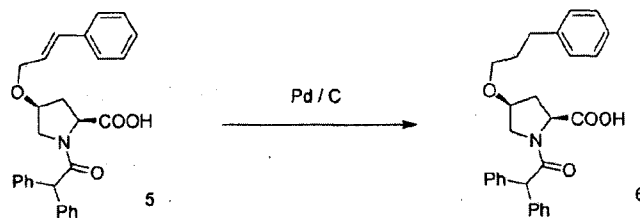


- 15 To a stirred solution of 5a (270 mg, 0.59 mmol) in THF (7 mL) and H_2O (3 mL) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (37 mg, 0.87 mmol) at 0°C and the mixture was stirred at 0°C for 0.5 hour, TLC (MeOH:DCM=1:10) showed the starting material was consumed. The mixture was concentrated *in vacuo* to remove most of the THF and water (10 mL) and Et_2O (10 mL) were added. The mixture was acidified with 1M HCl to pH 7 and then basified with
- 20 sodium bicarbonate to pH 10 and the phases separated. DCM (10 mL) was added to the aqueous phase and the mixture was acidified to pH 3-4 with 1M HCl and the organic layer was separated, washed with water (5 mL x 1), brine (5 mL x 2), dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give the product (150 mg) as a white solid. The crude product was purified by prep-TLC to give 5 as a white solid (130mg). LC-MS (Agilent): R_t

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5.26 min; m/z calculated for $C_{28}H_{27}NO_4$ $[M+H]^+$ 442.2, $[M+Na]^+$ 464.2, found $[M+H]^+$ 442.1, $[M+Na]^+$ 464.1. HPLC (214 and 254 nm): R_t 13.63 min.

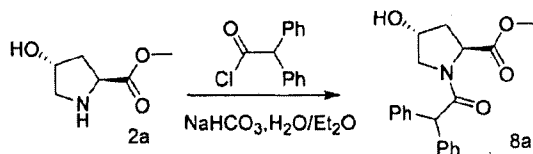
Example 4: Compound 6 (2*S*,4*S*)-1-2,2-diphenylacetyl-4-(3-phenylpropoxy)pyrrolidine carboxylic acid



To a stirred solution of 5 (120 mg, 0.27 mmol) in EA (3 mL) was added 10% Pd/C (12 mg) and the mixture was stirred at RT under a H_2 atmosphere (1 atm pressure) overnight, TLC (MeOH:DCM=1:20) showed the starting material was consumed. The mixture was filtered and the filtrate was concentrated *in vacuo* to give the crude product, which was purified by column chromatography (DCM:EA=10:1 to 8:1) to give 6 (60 mg, 50%) as a colorless oil. LC-MS (Agilent): R_t 5.26 min; m/z calculated for $C_{28}H_{29}NO_4$ $[M+H]^+$ 444.2, found 444.2. HPLC (214 and 254 nm): R_t 13.75 min.

Example 5: Compound 8 (2*S*,4*R*)-4-(cinnamyloxy)-1-(2,2-diphenylacetyl)pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of Compound 8a

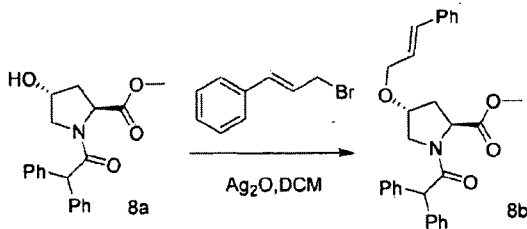


A solution of diphenylacetic acid (5.0 g, 23.6 mmol) in thionyl chloride (30 mL) was heated at reflux for 30 min. The mixture was then concentrated *in vacuo* and the residue was dissolved in ether (10 mL) and added to a mixture of 2a (3.76 g, 25.9 mmol) and $NaHCO_3$ (5.95 g, 70.8 mmol) in water (50 mL) and ether (20 mL) at 0°C. After addition, the mixture was stirred at RT for 2 h, TLC (EA:PE=1:1) showed the starting material was consumed. The product was collected by filtration and the obtained cake was dissolved in EA (50 mL), washed with brine (30 mL x 3), dried over Na_2SO_4 , filtered and concentrated

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in vacuo to give 8a (6.5 g, 74%) as a white solid. LC-MS (Agilent): R_t 4.86 min; m/z calculated for $C_{20}H_{21}NO_4$ $[M+H]^+$ 340.2, $[M+Na]^+$ 362.1, found $[M+H]^+$ 340.2, $[M+Na]^+$ 362.1.

2. Procedure for the preparation of Compound 8b

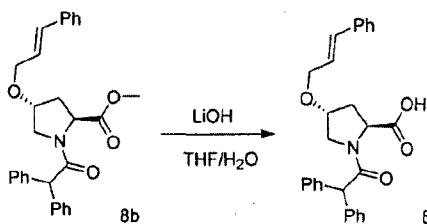


5

To a solution of 8a (1.0 g, 2.9 mmol) in DCM (10 mL) was added Ag_2O (806 mg, 3.48 mmol) at $0^\circ C$ and the mixture was stirred at RT for 30 min. A solution of cinnamyl bromide (685.8 mg, 3.48 mmol) in DCM (2 mL) was then added and the mixture was stirred at RT overnight. The Ag_2O was removed by filtration and the filtrate was concentrated *in vacuo*. Purification by silica column (PE:EA=10:1 to 4:1) gave 8b as yellow solid (100 mg, 8%). LC-MS (Agilent): R_t 5.34 min; m/z calculated for $C_{29}H_{29}NO_4$ $[M+H]^+$ 456.1, $[M+Na]^+$ 478.1, found $[M+H]^+$ 456.1, $[M+23]^+$ 478.1.

10

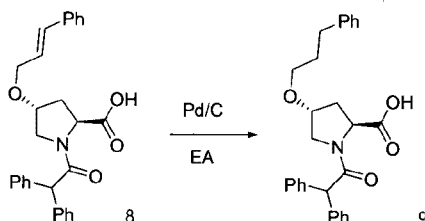
3. Procedure for the preparation of Compound 8



To a mixture of 8b (170 mg, 0.37 mmol) in THF/H₂O (3 mL/1 mL) was added LiOH (40 mg, 0.93 mmol) and the mixture was stirred at RT for 5h, TLC (PE:EA=2:1) showed that the starting material was consumed. Most of the THF was removed *in vacuo*, water (10 mL) and Et₂O (10 mL) were added and the layers were separated. The aqueous phase was adjusted to pH 2-3 with 1 M aqueous HCl and extracted with DCM (15 mL x 2). The combined organic extracts were washed with brine, dried over Na₂SO₄ and the solvent was removed *in vacuo*. Purification by prep-TLC (DCM:MeOH=10:1) gave 8 as a white solid (80 mg, 49%). LC-MS (Agilent): R_t 5.34 min; m/z calculated for $C_{28}H_{27}NO_4$ $[M+H]^+$ 442.1, found $[M+H]^+$ 442.1. HPLC (214 and 254 nm): R_t 13.71 min.

20

Example 6: Compound 9 (2S,4R)-1-(2,2-diphenylacetyl)-4-(3-phenylpropoxy)pyrrolidine-2-carboxylic acid

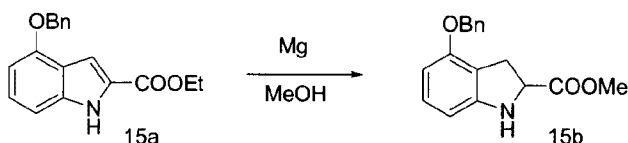


To a solution of 8 (100 mg, 0.23 mmol) in EA (5 mL) was added 10% Pd/C (10 mg) and the mixture was stirred at RT under a hydrogen atmosphere (1 atm pressure) overnight. The mixture was filtered through Celite™ and the filtrate was concentrated *in vacuo*. Purification by prep-TLC (DCM:MeOH=10:1) gave 9 as a white solid (93 mg, 93%). LC-MS (Agilent): R_t 5.40 min; m/z calculated for $C_{28}H_{29}NO_4$ $[M+H]^+$ 444.2, $[M+Na]^+$ 466.2, found $[M+H]^+$ 444.2, $[M+Na]^+$ 466.2. HPLC (214 and 254 nm): R_t 13.86 min.

10

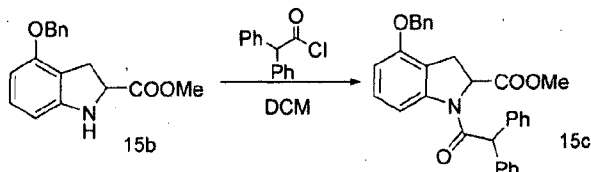
Example 7: Compound 15 4-(benzyloxy)-1-(2,2-diphenylacetyl)indoline-2-carboxylic acid

1. Procedure for the preparation of Compound 15b

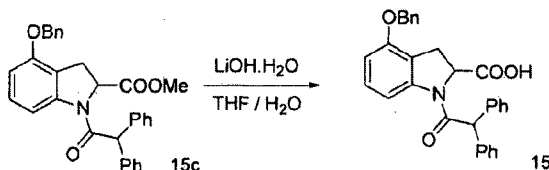


To a stirred solution of 15a (200 mg, 0.68 mmol) in MeOH (10 mL) was added Mg pieces (65 mg, 2.7 mmol) at RT under N_2 and the mixture was stirred overnight at RT. TLC (EA: PE=1:10) showed the starting material was consumed. The mixture was poured into a cold 2 M aqueous HCl solution (4 mL) and then stirred until it became a clear solution. The mixture was basified to pH 8~9 with a saturated aqueous $NaHCO_3$ solution and then concentrated *in vacuo* to remove most of the MeOH. The residue was dissolved in EA, washed with water (5 mL) and brine (5 mL x 2), dried over Na_2SO_4 , then filtered and concentrated *in vacuo* to give 15b (180 mg, 94%) as an off-white solid. LC-MS (Agilent): R_t 4.96 min; m/z calculated for $C_{17}H_{17}NO_3$ $[M+H]^+$ 284.1, $[M+Na]^+$ 306.1, found $[M+H]^+$ 284.1, $[M+Na]^+$ 306.1.

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2. Procedure for the preparation of Compound 15c

To a solution of 15b (180 mg, 0.64 mmol), Et₃N (129 mg, 1.28 mmol), and DMAP (8 mg, 0.06 mmol) in DCM (10 mL) was added diphenylacetyl chloride (175 mg, 0.76 mmol) at 0°C. The mixture was then warmed to RT and stirred for 5 h, TLC (DCM) showed the starting material was consumed. Iced water was added to quench the reaction, the organic layer was separated, washed with brine (5 mL x 2), dried over Na₂SO₄, then filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:DCM=10:1 to 1:2) to give 15c (220 mg, 56%) as an off-white solid. LC-MS (Agilent): R_t 5.50 min; m/z calculated for C₃₁H₂₇NO₄ [M+H]⁺ 478.2, [M+Na]⁺ 500.2, found [M+H]⁺ 478.2, [M+Na]⁺ 500.2.

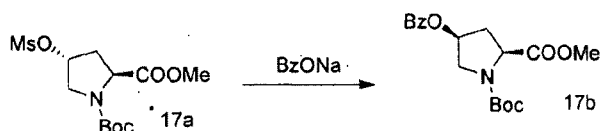
3. Procedure for the preparation of Compound 15

To a solution of 15c (50 mg, 0.10 mmol) in THF (0.7 mL) was added a solution of LiOH.H₂O (7 mg, 0.16 mmol) in water (0.3 mL) at 0°C and the mixture was stirred at RT overnight, TLC (MeOH:DCM=1:10) showed the starting material was consumed. The reaction was repeated on a larger batch of ester (170 mg, 0.36 mmol) and the reaction mixtures were combined and concentrated *in vacuo* to remove most of the THF. The residue was dissolved in EA (10 mL), acidified to pH 4-5 using 1 M HCl and the organic phase washed with water (5 mL), brine (5 mL x 2) and dried over Na₂SO₄. The solvent was removed *in vacuo* and the crude product was washed with hexane and Et₂O to give pure 15 (150 mg, 70%) as a white solid. LC-MS (Agilent): R_t 5.52 min; m/z calculated for C₃₀H₂₅NO₄ [M+H]⁺ 464.2, [M+Na]⁺ 486.2, found [M+H]⁺ 464.2, [M+Na]⁺ 486.1. HPLC (214 and 254 nm): R_t 14.08 min.

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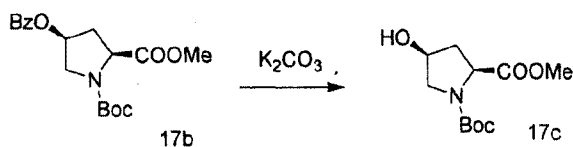
Example 8: Compound 17 (2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-(((1*R*,2*S*)-2-phenylcyclopropyl)methoxy)pyrrolidine-2-carboxylic acid and (2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-(((1*S*,2*R*)-2-phenylcyclopropyl)methoxy)pyrrolidine-2-carboxylic acid

5 1. Procedure for the preparation of Compound 17b



To a stirred solution of 17a (2.0 g, 6.2 mmol) in DMSO (20 mL) was added BzONa (1.8 g, 12.4 mmol) at RT and the mixture was stirred at 90°C for 6h, TLC (PE:EA=2:1) showed the starting material was consumed. The mixture was cooled to RT. The reaction was repeated (140 g, 434 mmol) and the two reaction mixtures were combined and poured into water (10 L) and EA (2 L). The layers were separated and the aqueous phase was extracted with EA (0.5 L). The combined organic extracts were washed with brine (1 L x 3), dried over Na₂SO₄, filtered and concentrated *in vacuo* to give crude 17b (150 g) as an off-white solid which was used in next step directly. LC-MS (Agilent): R_t 3.20 min; m/z calculated for C₁₈H₂₃NO₆ [M+H-Boc]⁺ 250.1, [M+Na]⁺ 372.1, found [M+H-Boc]⁺ 250.1, [M+Na]⁺ 372.1.

2. Procedure for the preparation of Compound 17c

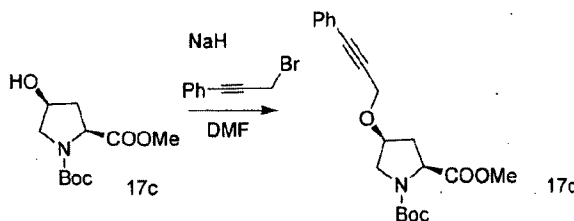


To a stirred solution of 17b (1.0 g, 2.86 mmol) in MeOH (20 mL) was added K₂CO₃ (0.4 g, 2.86 mmol) at 0°C and the mixture was stirred at RT for 0.5 h, TLC (PE:EA=1:1) showed the reaction was complete. The reaction was repeated (150 g, 429 mmol) and the two reaction mixtures were combined and filtered. The filtrate was concentrated *in vacuo* to remove most of the MeOH, the residue was dissolved in EA (500 mL), washed with water (250 mL), brine (250 mL x 2), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=1:0 to 0:1) to give 17c as an off-white solid (70 g, 65%). LC-MS (Agilent): R_t 2.97 min; m/z calculated for C₁₁H₁₉NO₅ [M+H-

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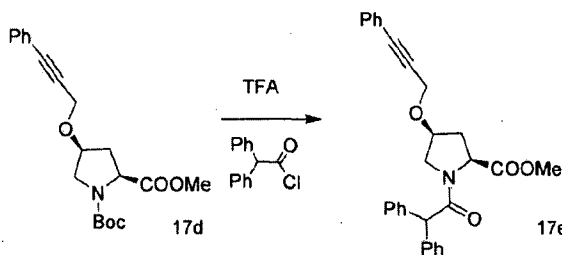
Boc]⁺ 146.1, [M+H- *t*-Bu]⁺ 190.1, [M+Na]⁺, 268.1, found [M+H-Boc]⁺ 146.1, [M+H- *t*-Bu]⁺ 190.1, [M+Na]⁺, 268.1.

3. Procedure for the preparation of Compound 17d



- 5 To a stirred solution of the 17c (3.5 g, 14.3 mmol) in DMF (35 mL) was added NaH (60% w/w dispersion in mineral oil, 0.63 g, 15.7 mmol) at 0°C under a N₂ atmosphere and the mixture was stirred at RT for 1 hour then re-cooled to 0°C. The bromide (3.1 g, 15.7 mmol) was added and the mixture was warmed to RT slowly and then stirred overnight, TLC (PE:EA=1:1) showed the starting material was consumed. The mixture was
- 10 partitioned between EA (100 mL) and water (300 mL), the layers were separated and the aqueous layer was extracted with EA (80 mL x 2). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo* and the residue was purified by chromatography (PE:EA=10:0 to 1:20) to give 17d as a colorless oil (1.0 g, 19%). LC-MS (Agilent): R_t 3.25 min; m/z calculated for C₂₀H₂₅NO₅ [M+H-Boc]⁺ 260.1,
- 15 [M+Na]⁺ 382.2, found [M+H-Boc]⁺ 260.1, [M+Na]⁺ 382.1.

4. Procedure for the preparation of Compound 17e

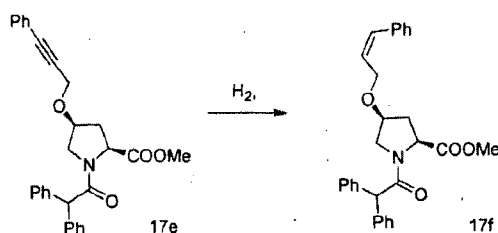


- To a stirred solution of compound 17d (1.0 g, 3.8 mmol) in DCM (10 mL) was added TFA (1.7 g, 15.2 mmol) at 0°C and the mixture was stirred at 0°C for 4 hour, TLC (PE:EA=4:1)
- 20 showed the starting material was consumed. The mixture was concentrated *in vacuo*, the residue was partitioned between DCM (30 mL) and a saturated aqueous NaHCO₃ solution (30 mL). The organic layer was separated and washed with brine, dried over Na₂SO₄ and filtered. The filtrate was treated with Et₃N (422 mg, 4.17 mmol), cooled to 0°C and

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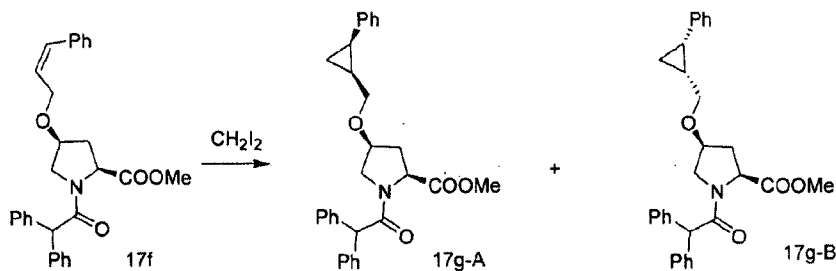
diphenylacetyl chloride (867 mg, 3.8 mmol) was added in portions. The mixture was stirred at 0~5°C for 10 min, TLC (PE:EA=2:1) showed the reaction was complete. Ice-water (40 mL) was added and the DCM layer was separated, washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=50:0 to 10:1) to give 17e (300 mg, 17%). LC-MS (Agilent): R_t 3.04 min; m/z calculated for C₂₉H₂₇NO₄ [M+H]⁺ 454.2, found [M+H]⁺ 454.2.

5. Procedure for the preparation of Compound 17f



To a stirred solution of 17e (150 mg, 0.33 mmol) in EA (3 mL) was added Lindlar catalyst (15 mg) and the mixture was stirred at RT under a H₂ balloon overnight, LCMS showed the reaction was complete. The mixture was filtered and the filtrate was concentrated *in vacuo* to give 17f as a thick oil (150 mg). LC-MS (Agilent): R_t 3.37 min; m/z calculated for C₂₉H₂₉NO₄ [M+H]⁺ 456.2, [M+Na]⁺ 478.2, found [M+H]⁺ 456.2, [M+Na]⁺ 478.2.

6. Procedure for the preparation of Compound 17g

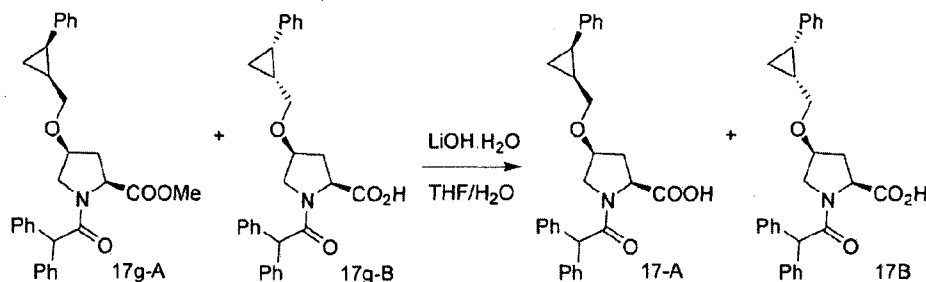


A stirred solution of compound 17f (100 mg, 0.22 mmol) in dry DCE (10 mL) was cooled to -5°C under a N₂ atmosphere. A ZnEt₂ solution (1 M in hexane, 0.44 mL, 0.44 mmol) was added followed by CH₂I₂ (235 mg, 0.88 mmol) and the mixture was warmed to RT slowly and stirred overnight, TLC showed the reaction was complete. The mixture was concentrated *in vacuo*, the residue was partitioned between ether (20 mL) and water (20 mL) and the aqueous phase was acidified to pH 2-3 with a 1 M aqueous HCl solution. The layers were separated and the aqueous layer was extracted again with ether (20 mL). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and

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concentrated *in vacuo* to give crude product as the two indicated diastereoisomers (100 mg) as a yellow oil, which was used in next step directly.

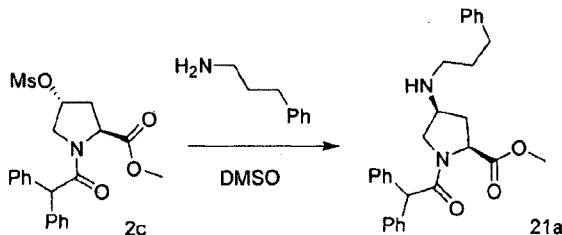
7. **Procedure for the preparation of Compound 17**



- 5 To a stirred solution of 17g-A and 17g-B (100 mg, 0.20 mmol) in THF (5 mL) and was added LiOH.H₂O/H₂O (25 mg, 0.6 mmol/1 mL) and the mixture was stirred at RT overnight, TLC (PE:EA=4:1) showed the reaction was complete. The mixture was concentrated *in vacuo* to remove most of the THF and the residue was partitioned between DCM (20 mL) and water (20 mL). The aqueous layer was acidified to pH 3~4 with a 1 M
- 10 aqueous HCl solution, the layers were separated and the aqueous layer was extracted again with DCM (20 mL). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (DCM: MeOH = 50:1) to give the product as a mixture of the indicated diastereoisomers as a white solid (80 mg, 77%). LC-MS (Agilent): R_t 3.28 min; m/z calculated for C₂₉H₂₉NO₄ [M+H]⁺ 456.2, [M+Na]⁺ 478.2, found [M+H]⁺ 456.2, [M+Na]⁺ 478.2. HPLC (214 and 254 nm): R_t 13.70 min.
- 15

Example 9: Compound 21 (2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-(methyl(3-phenylpropyl)amino)pyrrolidine-2-carboxylic acid

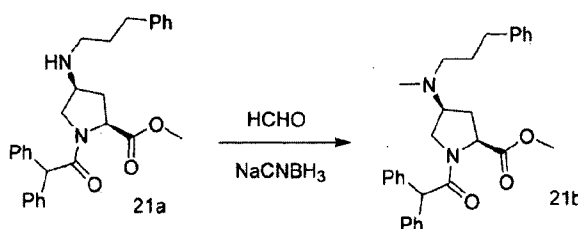
20 **1. Procedure for the preparation of Compound 21a**



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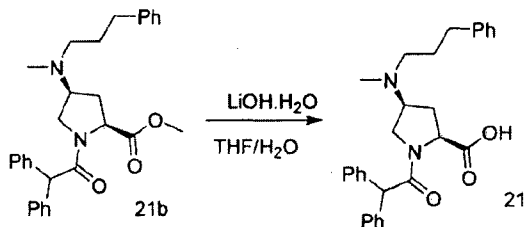
A mixture of 2c (500 mg, 1.2 mmol) and 3-phenylpropylamine (487 mg, 3.6 mmol) in DMSO/DMA/NMP (1:1:1, 10 mL) was heated at 110°C overnight, TLC (DCM:MeOH=20:1) showed that most of the starting material was consumed. The mixture was poured into water (50 mL) and extracted with EA (20 mL x 2). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by silica column gave 21a (300 mg, 55%) as a yellow oil. LC-MS (Agilent): R_t 2.96 min; m/z calculated for C₂₉H₃₂N₂O₃ [M+H]⁺ 457.2, found [M+H]⁺ 457.2.

2. Procedure for the preparation of Compound 21b



To a solution of compound 21a (300 mg, 0.66 mmol) in CH₃CN (8 mL) was added 37% aqueous HCHO (160.0 mg, 1.97 mmol) and NaCNBH₃ (103.9 mg, 1.65 mmol) and the mixture was stirred at RT for 3h, TLC (DCM:MeOH=20:1) showed that the starting material was consumed. Water (20 mL) was added and the mixture was extracted with EA (15 mL x 2). The combined organic extracts were washed with brine, dried over Na₂SO₄, concentrated *in vacuo* and the residue was purified by silica column (DCM:MeOH=100:1 to 50:1) to give 21b (280 mg, 90%) as a yellow solid. LC-MS (Agilent): R_t 2.95 min; m/z calculated for C₃₀H₃₄N₂O₃ [M+H]⁺ 471.2, found [M+H]⁺ 471.3.

3. Procedure for the preparation of Compound 21



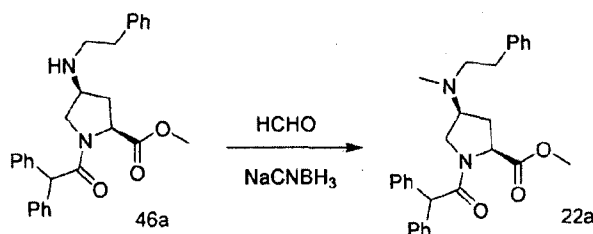
To a stirred mixture of 21b (280 mg, 0.6 mmol) in THF/water (6 mL/2 mL) was added LiOH.H₂O (75.0 mg, 1.8 mmol) and the mixture was stirred at RT overnight, TLC showed that the starting material was consumed. Most of the THF was removed *in vacuo* and the residue was partitioned between water (20 mL) and Et₂O (10 mL). The Et₂O layer was discarded, DCM (10 mL) was added and the aqueous layer was acidified to pH 2-3 with a

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1 M aqueous HCl solution. The organic layer was separated and the aqueous layer was extracted again with DCM (10 mL). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to give crude 21 (180 mg). Purification by prep-HPLC gave pure 21 (60.0 mg, 22%) as a white solid. LC-MS (Agilent): R_t 3.14 min; m/z calculated for C₂₉H₃₂N₂O₃ [M+H]⁺ 457.2, found [M+H]⁺ 457.2. HPLC (214 and 254 nm): R_t 14.30 min.

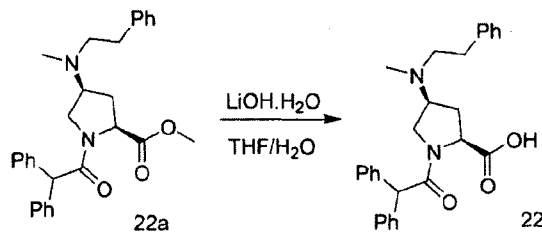
Example 10: Compound 22 (2S,4S)-1-(2,2-diphenylacetyl)-4-(methyl(phenylethylamino)pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of Compound 22a



The reaction of Example 9, 2. was repeated with 46a (380.0 mg, 0.86 mmol) in CH₃CN (8 mL), 37% aqueous HCHO (210 mg, 2.6 mmol) and NaCNBH₃ (135.0 mg, 2.2 mmol) to give 22a (260 mg, 66%) as a yellow solid. LC-MS (Agilent): R_t 2.60 min; m/z calculated for C₂₉H₃₂N₂O₃ [M+H]⁺ 457.3, found [M+H]⁺ 457.3.

2. Procedure for the preparation of Compound 22

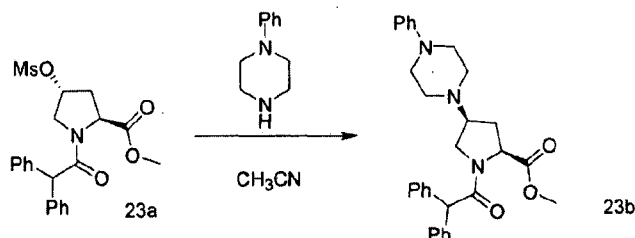


Hydrolysis of 22a (260 mg, 0.57 mmol) as performed using the method of Example 9, 3. using 3 equivalents of LiOH.H₂O (71.8 mg, 1.71 mmol). Purification by prep-HPLC gave 22 (160.0 mg, 64%) as a white solid. LC-MS (Agilent): R_t 3.09 min; m/z calculated for C₂₈H₃₀N₂O₃ [M+H]⁺ 443.3, found [M+H]⁺ 443.3. HPLC (214 and 254 nm): R_t 12.66 min.

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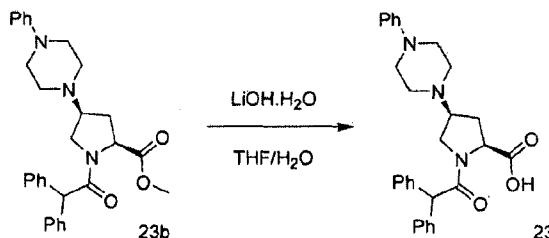
Example 11: Compound 23 (2S,4S)-1-(2,2-diphenylacetyl)-4-(4-phenylpiperazine)pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of Compound 23b



- 5 A mixture of compound 23a (1.5 g, 3.5 mmol) and N-phenylpiperazine (1.75 g, 10.7 mmol) in CH₃CN (10 mL) was heated at 110°C overnight, TLC (DCM:MeOH=20:1) showed that the reaction was complete. The mixture was poured into water (50 mL) and extracted with EA (20 mL x 2). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to give 23b (600 mg 35%) as a
- 10 yellow solid. LC-MS (Agilent): R_t 3.16 min; m/z calculated for C₃₀H₃₃N₃O₃ [M+H]⁺ 484.3, found [M+H]⁺ 484.3.

2. Procedure for the preparation of Compound 23

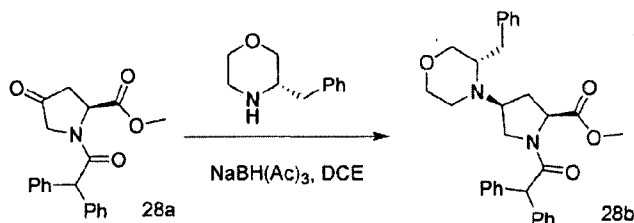


- Hydrolysis of 23b (450 mg, 0.93 mmol) was performed using the method of Example 9, 3.
- 15 using about 3 equivalents of LiOH.H₂O (117.4 mg, 2.8 mmol). Recrystallization from DCM/hexane gave 23 (200 mg, 45%) as a white solid. LC-MS (Agilent): R_t 3.17 min; m/z calculated for C₂₉H₃₁N₃O₃ [M+H]⁺ 470.3, found [M+H]⁺ 470.3. HPLC (214 and 254 nm): R_t 14.25 min.

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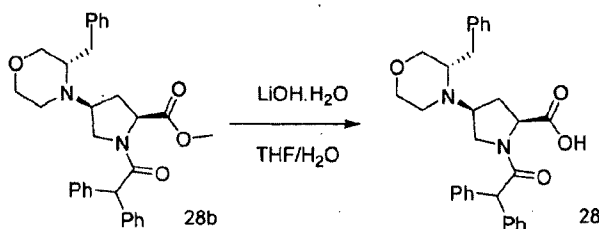
Example 12: Compound 28 ((2S,4S)-4-((S)-3-benzylmorpholino)-1-(2,2-diphenylacetyl)pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of Compound 28b



- 5 To a solution of 28a (762 mg, 2.26 mmol) and (S)-3-benzylmorpholine (400 mg, 2.26 mmol) in DCE (10 mL) was added AcOH (0.2 mL) and the mixture was stirred at RT for 40 min. The mixture was cooled to 0°C, NaBH(OAc)₃ (954 mg, 4.5 mmol) was added and stirring was continued at RT overnight, TLC (PE:EA=2:1) showed that the starting material was consumed. Water (20 mL) was added and the pH was adjusted to 7-8 with
- 10 Na₂CO₃. The organic phase was separated and the aqueous layer was extracted with DCM (20 mL). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by silica column (PE:EA=10:1 to 4:1) gave 28b (400 mg, 36%) as a white solid. LC-MS (Agilent): R_t 3.26 min; m/z calculated for C₃₁H₃₄N₂O₄ [M+H]⁺ 499.3, found [M+H]⁺ 499.3.

15 **2. Procedure for the preparation of Compound 28**



- To a mixture of compound 28b (400 mg, 0.8 mmol) in THF/water (6 mL/2 mL) was added LiOH.H₂O (101 mg, 2.4 mmol) and the mixture was stirred at RT overnight, TLC showed the starting material was consumed. Most of the THF was removed *in vacuo* and the
- 20 residue was partitioned between water (20 mL) and Et₂O (15 mL) and the aqueous phase was adjusted to pH 2-3 with 1 M aqueous HCl solution, then to pH 8 with Na₂CO₃. The Et₂O phase was separated and discarded, DCM (10 mL) was added and the aqueous layer was acidified to pH 2-3 with a 1 M aqueous HCl solution. The organic layer was separated and the aqueous layer was extracted with DCM (20 mL). The combined organic extracts

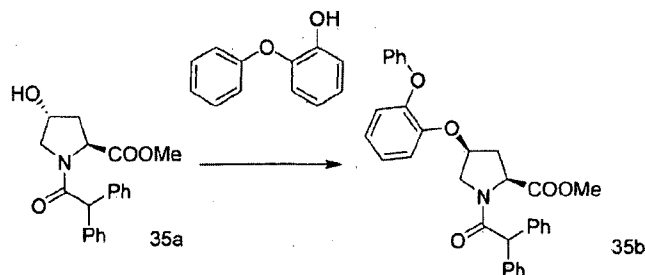
- 87 -

were washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Recrystallization from DCM/hexane gave 28 (200 mg, 51%) as a white solid. LC-MS (Agilent): R_t 3.10 min; m/z calculated for $\text{C}_{30}\text{H}_{32}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$ 485.3, found $[\text{M}+\text{H}]^+$ 485.3. HPLC (214 and 254 nm): R_t 12.08 min

5

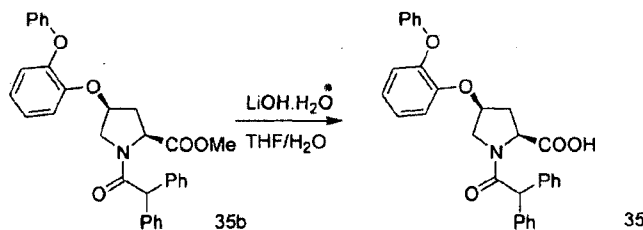
Example 13: Compound 35 (2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-(2-phenoxyphenoxy)-pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of Compound 35b



- 10 To a stirred solution of 35a (3.00 g, 8.84 mmol), 2-phenoxyphenol (2.40 g 13.3 mmol) prepared by the method described in *Synthesis*, (1994, 1, p28) and PPh_3 (4.6 g, 17.7 mmol) in DCM (60 mL) was added a solution of DBAD (5.3 g, 17.7 mmol) in DCM (30 mL) slowly at 0°C under a N_2 atmosphere and the mixture was stirred at RT overnight, TLC (PE:EA=2:1) showed the starting material was consumed. The mixture was concentrated *in*
- 15 *vacuo* and the residue was partially purified by chromatography (PE:EA=1:0 to 5:1) to give 35b (6.00 g) as a colorless oil, which was used in next step directly. LC-MS (Waters): R_t 6.32 min; m/z calculated for $\text{C}_{32}\text{H}_{29}\text{NO}_5$ $[\text{M}+\text{H}]^+$ 508.2, $[\text{M}+\text{Na}]^+$ 530.2, found $[\text{M}+\text{H}]^+$ 508.1, $[\text{M}+\text{Na}]^+$ 530.1.

2. Procedure for the preparation of Compound 35



20

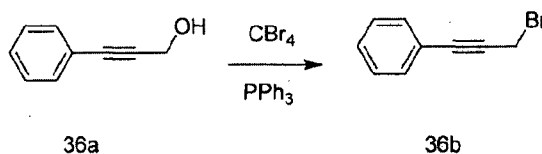
To a solution of compound 35b (6.00 g, 11.8 mmol) in THF (35 mL) was added a solution of $\text{LiOH}\cdot\text{H}_2\text{O}$ (0.74 g, 17.7 mmol) in water (15 mL) and the mixture was stirred at RT overnight, TLC (PE:EA=2:1) showed the starting material was consumed. Most of the

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THF was removed *in vacuo* and the residue was dissolved in water H₂O (10 mL) and washed with Et₂O (20 mL x 2). EtOAc (20 mL) was added and the aqueous layer was acidified to pH 3~4 with a 1 M aqueous HCl solution. The layers were separated and the organic layer was washed with water (20 mL), brine (20 mL x 2), dried over Na₂SO₄,
 5 filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE to PE:EA=5:1) then prep-HPLC to give 35 (120 mg, 2%) as a white solid. LC-MS (Agilent): R_t 3.43 min; m/z calculated for C₃₁H₂₇NO₅ [M+H]⁺ 494.2, [M+Na]⁺ 516.2, found [M+H]⁺ 494.2, [M+Na]⁺ 516.2. HPLC (JULY-L) (214 and 254 nm): R_t 8.44 min.

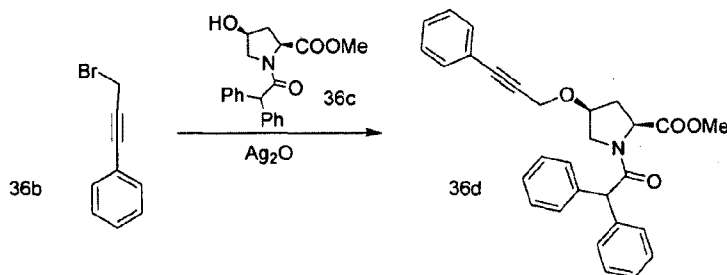
10 **Example 14: Compound 36 (2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-((3-phenylprop-2-yn-1-yl)-oxy)pyrrolidine-2-carboxylic acid**

1. Procedure for the preparation of Compound 36b



To a stirred solution of 36a (200 mg, 1.5 mmol) and PPh₃ (430 mg, 1.65 mmol) in THF (4
 15 mL) was added CBr₄ (600 mg, 1.8 mmol) at 0°C and the mixture was stirred at 0°C for 2 h, TLC (PE:EA=1:1) showed the starting material was consumed. The reaction was repeated (4.8 g, 36 mmol) and the reaction mixtures were combined, then most of the THF was removed *in vacuo* and the residue was partitioned between EA (50 mL) and water (30 mL). The organic layer was separated, washed with brine (30 mL x 2), dried over Na₂SO₄,
 20 filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE) to give 36b (6.5 g, 90 %) as a colorless oil.

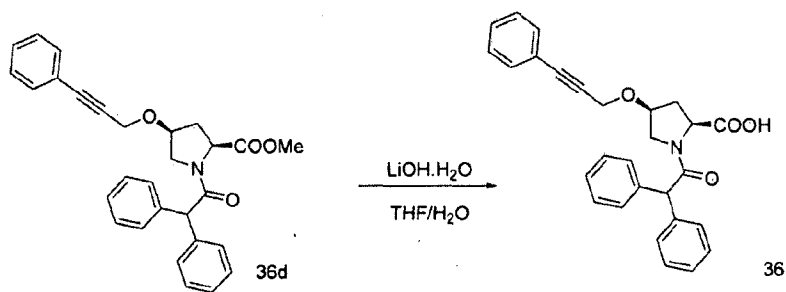
2. Procedure for the preparation of Compound 36d



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To a stirred suspension of 36c (100 mg, 0.29 mmol) and Ag₂O (81 mg, 0.35 mmol) in DCM (2 mL) was added compound 36b (67 mg, 0.35 mmol) at 0°C and the mixture was stirred in the dark at RT overnight. The reaction was repeated (0.9 g, 2.6 mmol) and the reaction mixtures were combined, then the mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=10:1 to 5:1) to give 36d (100 mg, 8%) as a colorless oil. LC-MS (Agilent): R_t 3.29 min; m/z calculated for C₂₉H₂₇NO₄ [M+H]⁺ 454.2, [M+Na]⁺ 476.2, found [M+H]⁺ 454.2, [M+Na]⁺ 476.2.

3. Procedure for the preparation of Compound 36

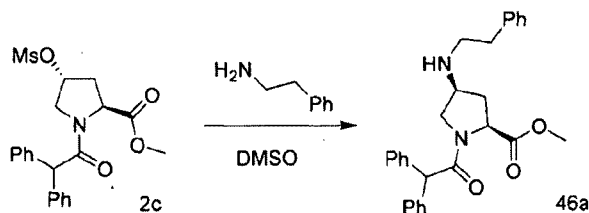


To a mixture of compound 36d (80 mg, 0.18 mmol) in THF/water (5 mL/2 mL) was added LiOH.H₂O (11 mg, 0.26 mmol) at 0°C and the mixture was stirred at RT overnight, TLC (MeOH:DCM=1:10) showed the starting material was consumed. The mixture was concentrated *in vacuo* to remove most of the THF and the residue was partitioned between EA and water. The aqueous layer was acidified to pH 3~4 with a 1 M aqueous HCl solution and the EA layer was separated, washed with water (3 mL), brine (3 mL x 2), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by chromatography (DCM:MeOH=50:1) to give 36 (50 mg, 61%) as a white solid. LC-MS (Agilent): R_t 3.29 min; m/z calculated for C₂₈H₂₅NO₄ [M-H]⁻ 438.2, found [M-H]⁻ 438.1. HPLC (214 and 254 nm): R_t 13.55 min.

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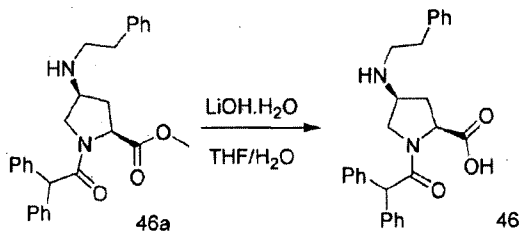
Example 15: Compound 46 (2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-(phenethylamino)-pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of Compound 46a



- 5 A mixture of 2c (1.5 g, 3.5 mmol) and phenethylamine (1.3 g, 10.8 mmol) in DMSO (10 mL) was heated at 100°C overnight, TLC (DCM:MeOH=20:1) showed that most of the starting material was consumed. The mixture was poured into water and extracted with EA. The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to give 46a (500 mg, 31%) as a yellow solid. LC-MS (Agilent):
- 10 R_t 2.92 min; m/z calculated for C₂₈H₃₀N₂O₃ [M+H]⁺ 443.2, found [M+H]⁺ 443.2.

2. Procedure for the preparation of Compound 46

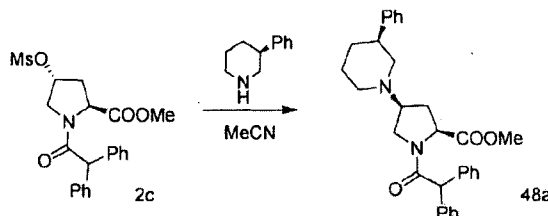


- To a mixture of compound 46a (200 mg, 0.45 mmol) in THF/water (6 mL/2 mL) was added LiOH·H₂O (56.9 mg, 1.36 mmol) and the mixture was stirred at RT for 3h, TLC
- 15 showed that the starting material was consumed. Most of the THF was removed *in vacuo* and the residue was partitioned between water (20 mL) and Et₂O (10 mL). The pH of the aqueous phase was adjusted to 3-4 with a 1 M aqueous HCl solution and then to pH 8 with a saturated aqueous Na₂CO₃ solution. The layers were separated and the Et₂O layer discarded. DCM (10 mL) was added and the aqueous layer was acidified to pH 2-3 with a
- 20 1 M aqueous HCl solution. The layers were separated and the organic extract was washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by prep-HPLC gave 46 (60.0 mg, 31%) as a white solid. LC-MS (Agilent): R_t 3.10 min; m/z calculated for C₂₇H₂₈N₂O₃ [M+H]⁺ 429.2, found [M+H]⁺ 429.2. HPLC (214 and 254 nm): R_t 11.78 min.

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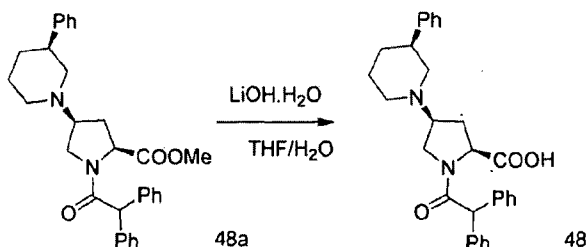
Example 16: Compound 48 (2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-((*S*)-3-phenylpiperidine-1-yl)pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of Compound 48a



5 A mixture of 2c (450 mg, 1.08 mmol) and (*S*)-3-phenyl piperidine (348 mg 2.16 mmol) in CH₃CN (5 mL) heated at 105°C in a sealed tube overnight, TLC (PE:EA=1:1) showed most of the starting material was consumed. The mixture was cooled to RT, concentrated *in vacuo* and the residue was purified by chromatography (PE:EA=1:0 to 2:1) to give 48a
10 (150 mg, 28%) as a white solid. LC-MS (Agilent): R_t 3.40 min; m/z calculated for C₃₁H₃₄N₂O₃ [M+H]⁺ 483.3, found [M+H]⁺ 483.3.

2. Procedure for the preparation of Compound 48

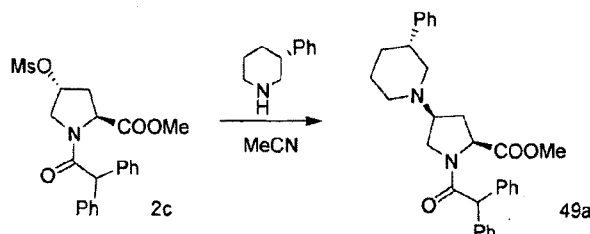


To a mixture of compound 48a (150 mg, 0.31 mmol) in THF/water (5 mL/1 mL) was
15 added LiOH·H₂O (33 mg, 0.77 mmol) and the mixture was stirred at RT overnight, TLC (PE:EA=1:1) showed the starting material was consumed. Most of the THF was removed *in vacuo* and the residue was dissolved in water (15 mL), acidified to pH 3~4 with a 1 M aqueous HCl solution and extracted with chloroform (15 mL x 2). The combined organic
20 extracts were washed with brine (15 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* to give 48 (130 mg, 89%) as a white solid. LC-MS (Agilent): R_t 3.55 min; m/z calculated for C₃₀H₃₂N₂O₃ [M+H]⁺ 469.2, found [M+H]⁺ 469.3. HPLC (JULY-L) (214 and 254 nm): R_t 8.87 min.

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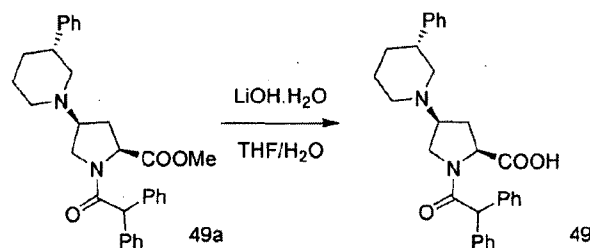
Example 17: Compound 49 (2S,4S)-1-(2,2-diphenylacetyl)-4-((R)-3-phenylpiperidin-1-yl)pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of Compound 49a



- 5 A mixture of 2c (450 mg, 1.08 mmol) and (R)-3-phenyl piperidine (348 mg 2.16 mmol) in CH₃CN (5 mL) was heated at 105°C in a sealed tube overnight, TLC (PE:EA=1:1) showed most of the starting material was consumed. The mixture was cooled to RT, concentrated *in vacuo* and the residue was purified by chromatography (PE:EA=1:0 to 2:1) to give 49a (170 mg, 31%) as a colorless oil. LC-MS (Agilent): R_t 3.42 min; m/z
- 10 calculated for C₃₁H₃₄N₂O₃ [M+H]⁺ 483.3, found [M+H]⁺ 483.3

2. Procedure for the preparation of Compound 49

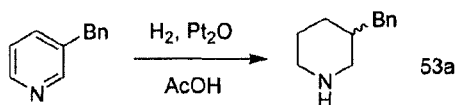


- Hydrolysis of 49a (170 mg, 0.35 mmol) as performed with about 2 equivalents of LiOH·H₂O (37 mg, 0.77 mmol) as described in Example 16, 2. The resulting precipitate
- 15 was collected by filtration, washed with water (5 mL x 2), then ether (5 mL x 2) and dried at 45°C overnight to give 49 (90 mg, 55%) as a white solid. LC-MS (Agilent): R_t 3.40 min; m/z calculated for C₃₀H₃₂N₂O₃ [M+H]⁺ 469.2, found [M+H]⁺ 469.3. HPLC (JULY-L) (214 and 254 nm): R_t 8.61 min.

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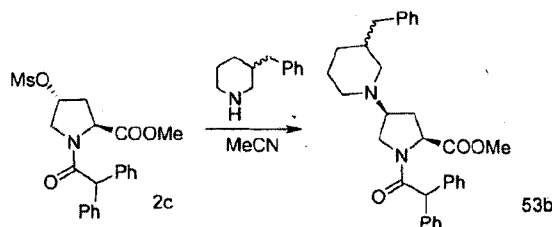
Example 18: Compound 53 (2*S*,4*S*)-4-(3-benzylpiperidin-1-yl)-1-(2,2-diphenylacetyl)-pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of Compound 53a



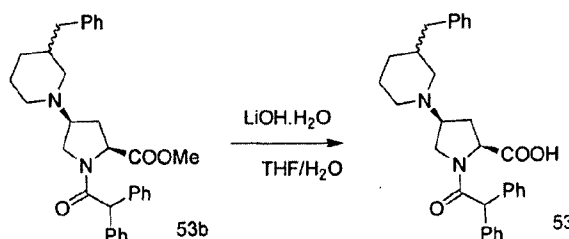
- 5 A mixture of 3-benzyl pyridine (1.0 g, 5.9 mmol) and PtO₂ (100 mg, 0.36 mmol) in AcOH (20 mL) was stirred at 30°C under a H₂ atmosphere (0.6 Mpa) overnight, TLC (PE:EA=4:1) showed the starting material was consumed. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was partitioned between EA (30 mL) and a saturated aqueous Na₂CO₃ solution (30 mL), the organic layer was separated, washed with
- 10 brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to give 53a (1.0 g, 97%) as a yellow oil. LC-MS (Waters): R_t 2.79 min; m/z calculated for C₁₂H₁₇N [M+H]⁺ 176.1, found [M+H]⁺ 176.2.

2. Procedure for the preparation of Compound 53b



- 15 A mixture of compound 2c (1.2 g, 2.88 mmol) and 3-benzyl piperidine (compound 53a) (1.0 g 5.76 mmol) in CH₃CN (40 mL) was heated at 110°C in a sealed tube overnight, TLC (PE:EA=1:1) showed the starting material was consumed. The mixture was cooled to RT, diluted with water and extracted with EA. The combined organic extracts were washed with brine (20 mL x 2), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The
- 20 reaction was repeated (600 mg, 1.43 mmol) and the two crude products were combined and purified by chromatography (PE:EA=1:0 to 1:1) to give 53b as the indicated mixture of diastereoisomers (300 mg, 14%) as a yellow oil. LC-MS (Waters): R_t 5.03 min; m/z calculated for C₃₂H₃₆N₂O₃ [M+H]⁺ 497.3, found [M+H]⁺ 497.1.

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3. Procedure for the preparation of Compound 53

To a mixture of 53b (300 mg, 0.60 mmol) in THF/water (6 mL/2 mL) was added LiOH.H₂O (25.4 mg, 1.8 mmol) and the mixture was stirred at RT overnight, TLC (PE: EA=1:1) showed the starting material was consumed. Most of the THF was removed *in vacuo* and the residue was partitioned between EA and water. The aqueous layer was acidified to pH 2-3 with a 1 M aqueous HCl solution. The organic layer was separated, washed with water (10 mL), brine (10 mL x 2), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was suspended in EA then heated at reflux for 30 min, cooled, the solid filtered and dried to give 53 as the indicated mixture of diastereoisomers (80 mg, 27%) as a white solid. LC-MS (Agilent): R_t 3.26 min; m/z calculated for C₃₁H₃₄N₂O₃ [M+H]⁺ 483.3, found [M+H]⁺ 483.2. HPLC (JULY-L) (214 and 254 nm): R_t 7.51 min

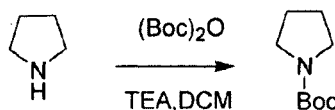
Each enantiomer of 3-benzylpiperidine was prepared using methodology described in L. Micouin et al, *Tetrahedron Letters*, 1994, 35 (16), p. 2529-2532. Compounds 51 and 52 were prepared using the respective single enantiomer of 3-benzylpiperidine as starting material and applying the same methodology as for the preparation of Compound 53.

Example 19: Compound 61 (3'S,5'S)-2-benzyl-1'-(2,2-diphenylacetyl)-[1,3'-bipyrrolidine]-5'-carboxylic acid

1. Procedure for the preparation of 2-benzyl pyrrolidine.

Racemic 2-benzyl pyrrolidine was synthesized using a modified literature procedure (the Sparteine chiral ligand was omitted), see: *J. Am. Chem. Soc.* **1994**, 116, 3231 as follows:

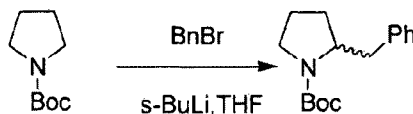
A) Procedure for the preparation of Boc-protected pyrrolidine



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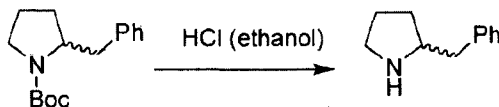
To a stirred mixture of pyrrolidine (10.0 g, 0.14 mol) in DCM (150 mL) at 0°C was added TEA (15.6 g, 0.15 mol) followed by (Boc)₂O (30.6 g, 0.14 mol) and the mixture was stirred at RT for 1 h, TLC showed that pyrrolidine had disappeared. The mixture was washed with a 1 M aqueous HCl solution (100 mL), brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the product (24.0 g, 100%) as a colorless oil, which was used in the next step directly.

B) Procedure for the preparation of Boc-protected 2-benzyl pyrrolidine.



To a stirred solution of Boc-protected pyrrolidine (14.0 g, 80.0 mmol) in THF (200 mL) at -60°C under N₂ was added *s*-BuLi (1.3 M solution in hexanes, 67.8 mL, 88 mmol) and the mixture was stirred at -60°C for 1 h. A solution of BnBr (15.4 g, 0.09 mol) in THF (5 mL) was then added at -60°C and stirring was continued at -60°C for a further 3 h then at RT overnight. The reaction was quenched at 0°C with a saturated aqueous NH₄Cl solution and extracted with EA. The organic extract was washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by silica column (PE:EA=50:1 to 20:1) gave the product (6.0 g, 30%) as a yellow oil. LC-MS (Agilent): R_t 3.55 min; m/z calculated for C₁₆H₂₃NO₂ [M-56+H]⁺ 206.1, [M+H]⁺ 262.2, [M+Na]⁺ 284.1, found [M-56+H]⁺ 206.1, [M+Na]⁺ 284.1.

C) Procedure for the preparation of benzyl pyrrolidine

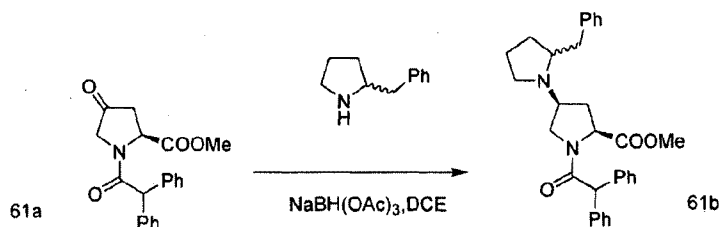


A mixture of Boc-protected 2-benzyl pyrrolidine (6.0 g, 23.0 mmol) in a 4 M HCl/ethanol solution (30 mL) was stirred at RT for 6 h, TLC (PE:EA=10:1) showed that most of the starting material had disappeared. The solvent was removed *in vacuo*, water (30 mL) and Et₂O (20 mL) were added and the layers were separated. The aqueous phase was basified to pH 7-8 with a saturated aqueous Na₂CO₃ solution and extracted with DCM (2 x 20 mL) and CHCl₃/IPA = 3:1 (v/v) (2 x 20 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated *in vacuo* to give the product (2.0 g, 54%) as a

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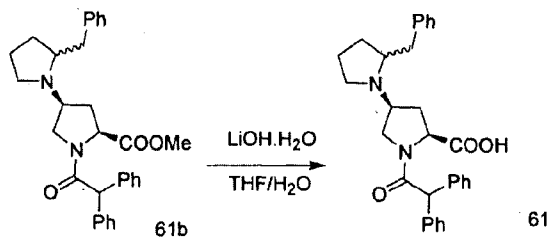
colorless oil. LC-MS (Agilent): R_t 2.82 min; m/z calculated for $C_{11}H_{15}N$ $[M+H]^+$ 162.1, found $[M+H]^+$ 162.1.

2. Procedure for the preparation of Compound 61b



- 5 To a solution of compound 61a (1.0 g, 2.96 mmol) and 2-benzyl pyrrolidine (0.47 g, 2.96 mmol) in DCE (20 mL) was added AcOH (0.2 mL) and the mixture was stirred at RT for 1 h. NaBH(OAc)₃ (0.94 g, 4.44 mmol) was then added at 0°C and the mixture was stirred at RT overnight, TLC (PE:EA=1:1) showed that the starting material was consumed. Water (20 mL) was added, the layers were separated and the aqueous layer was extracted with
- 10 DCM. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by silica column (PE:EA=10:1 to 3:1) gave 61b as the indicated mixture of diastereoisomers (320 mg, 23%) as a white solid. LC-MS (Agilent): R_t 3.17 min; m/z calculated for $C_{31}H_{34}N_2O_3$ $[M+H]^+$ 483.2, found $[M+H]^+$ 483.2.

15 3. Procedure for the preparation of Compound 61



- Hydrolysis of 61b (300 mg, 0.62 mmol) as performed as described in Example 9, 3. with about 3 equivalents of LiOH.H₂O (78.4 mg, 1.87 mmol), to give 61 (200 mg, 69%) as a yellow solid. The two diastereoisomers were separated by prep-HPLC to give compound
- 20 61-A (35 mg) and compound 61-B (35 mg) as white solids. The absolute stereochemistry of these diastereoisomers was not determined and therefore are referred to as 61-A and 61-B.

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Data for Compound 61-A:

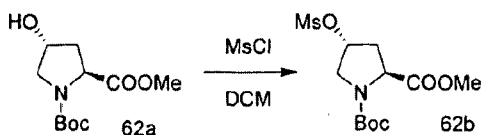
LC-MS (Agilent): R_t 3.44 min; m/z calculated for $C_{30}H_{32}N_2O_3$ $[M+H]^+$ 469.2, found $[M+H]^+$ 469.2. HPLC (JULY-L) (214 and 254 nm): R_t 7.39 min.

Data for Compound 61-B:

- 5 LC-MS (Agilent): R_t 3.45 min; m/z calculated for $C_{30}H_{32}N_2O_3$ $[M+H]^+$ 469.2, found $[M+H]^+$ 469.2. HPLC (JULY-L) (214 and 254 nm): R_t 7.61 min.

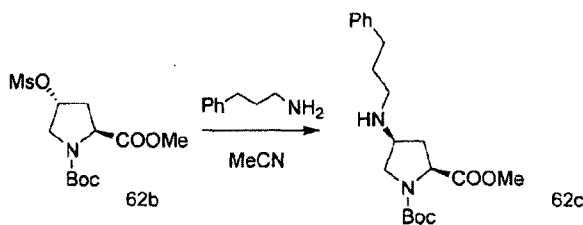
Example 20: Compound 62 (2*S*,4*S*)-1-(2-cyclohexyl-2-phenylacetyl)-4-(methyl(3-phenylpropyl)amino)pyrrolidine-2-carboxylic acid

10 **1. Procedure for the preparation of Compound 62b**



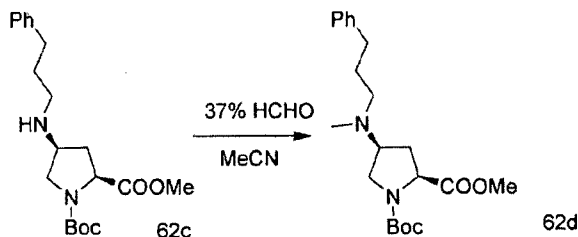
- To a stirred solution of 62a (3.0 g, 12.2 mmol) and Et_3N (1.35 g, 13.4 mmol) in DCM (30 mL) at $0^\circ C$ was added $MsCl$ (1.47 g, 12.8 mmol) and the mixture was stirred at $0^\circ C$ for 2 h, TLC (PE:EA=1:1) showed the starting material was consumed. The mixture was washed with water (20 mL x 2), brine (20 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give 62b (3.9 g, 100%) as a yellow thick oil, which was used directly in next step.

2. Procedure for the preparation of Compound 62c

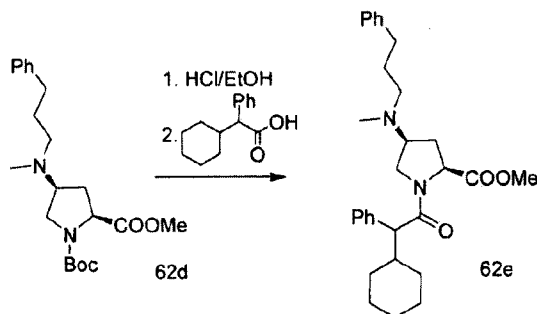


- A solution of 62b (500 mg, 1.54 mmol) and 3-phenylpropylamine (522 mg, 3.86 mmol) in CH_3CN (5 mL) was heated at $110^\circ C$ in a sealed tube overnight and then allowed to cool to RT. The reaction was repeated (1.00 g, 3.08 mmol) and the reaction mixtures were combined and concentrated *in vacuo*. The residue was dissolved in EA, washed with brine then dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by chromatography (PE:EA=10:1 to 2:1) gave 62c (450 mg, 28%) as a yellow oil. LC-MS (Agilent): R_t 3.11 min; m/z calculated for $C_{20}H_{30}N_2O_4$ $[M+H]^+$ 363.2, found $[M+H]^+$ 363.2.

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3. Procedure for the preparation of Compound 62d

To a stirred solution of 62c (450 mg, 1.24 mmol) in MeCN (10 mL) was added a 37% aqueous solution of formaldehyde (252 mg, 3.10 mmol) followed by AcOH (2 drops) and the mixture was stirred at RT for 1 h. NaCNBH₃ (195 mg, 3.10 mmol) was added and the mixture was stirred at RT overnight, TLC (DCM:MeOH=10:1) showed the starting material was consumed. The mixture was partitioned between EA (30 mL) and water (20 mL), the organic layer was collected and washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=10:1 to 2:1) to give 62d (90 mg, 19%) as a yellow oil. LC-MS (Agilent): R_t 2.88 min; m/z calculated for C₂₁H₃₂N₂O₄ [M+H]⁺ 377.2, found [M+H]⁺ 377.2.

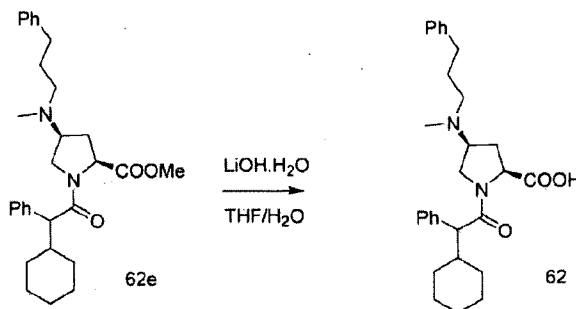
4. Procedure for the preparation of Compound 62e

A suspension of compound 62d (90 mg, 0.24 mmol) in 4 M HCl/EtOH (10 mL) was stirred at RT for 4 h, TLC (DCM:MeOH=10:1) showed the starting material was consumed. The mixture was concentrated *in vacuo*, the residue was dissolved in water (10 mL) and washed with ether (10 mL x 2). The aqueous layer was then basified to pH 9-10 with K₂CO₃ and extracted with DCM (10 mL x 2). The combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo*. The residue was dissolved in DCM (10 mL) and cyclohexylphenyl acetic acid (50.4 mg, 0.23 mmol) and EDCI.HCl (76.6 mg, 0.40 mmol) were added followed by a catalytic amount of DMAP. The mixture was then stirred at RT overnight, TLC (DCM:MeOH=20:1) showed the reaction was complete. The mixture was

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washed with a saturated aqueous NaHCO_3 solution (10 mL x 2), brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by chromatography (DCM:MeOH=1:0 to 20:1) gave 62e (60 mg, 52%) as a white solid. LC-MS (Agilent): R_t 3.24 min; m/z calculated for $\text{C}_{30}\text{H}_{40}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$ 477.3 found $[\text{M}+\text{H}]^+$ 477.3.

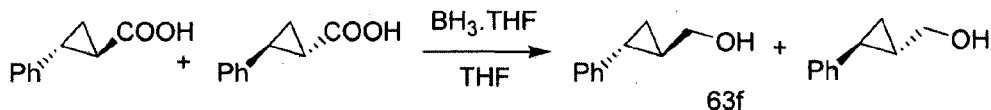
5. Procedure for the preparation of Compound 62



Hydrolysis of 62e (60 mg, 0.16 mmol) was performed as described in Example 2, 6. with 3 equivalents of $\text{LiOH}\cdot\text{H}_2\text{O}$ (15.8 mg, 0.48 mmol). After acidification, the organic layer was collected and washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give 62 (36 mg, 49%) as a white solid. LC-MS (Agilent): R_t 3.43 min; m/z calculated for $\text{C}_{29}\text{H}_{28}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$ 463.3, found $[\text{M}+\text{H}]^+$ 463.3. HPLC (JULY-L) (214 and 254 nm): R_t 7.96 min.

Example 21: Compound 63 (2S,4S)-1-(2,2-diphenylacetyl)-4-(methyl((2-phenylcyclopropyl)methyl)amino)pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of Compound 63f

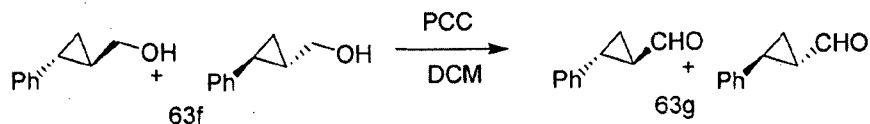


To a stirred solution of racemic *trans*-2-phenyl-1-cyclopropanecarboxylic acid (2.00 g, 12.3 mmol) in dry THF (20 mL) at 0°C was added $\text{BH}_3\cdot\text{THF}$ (1 M solution in THF, 14.8 mL, 14.8 mmol) and the mixture was allowed to warm slowly to RT and stirred for 4 h. More $\text{BH}_3\cdot\text{THF}$ (1 M solution in THF, 7.4 mL, 7.4 mmol) was added and stirring was continued at RT for 2 h, TLC (DCM:MeOH=20:1) showed the reaction was complete. The reaction was quenched with MeOH, water was added and the mixture was extracted with EA. The organic layer was separated and washed with brine (30 mL x 2), dried over

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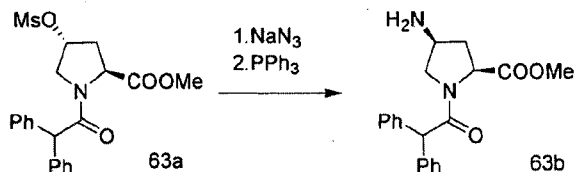
Na₂SO₄, filtered and concentrated to give 63f (1.6 g, 88%) as a yellow oil. LC-MS (Agilent): R_t 3.27 min; m/z calculated for C₁₀H₁₂O [M+Na]⁺ 171.1, found [M+Na]⁺ 171.1

2. Procedure for the preparation of Compound 63g



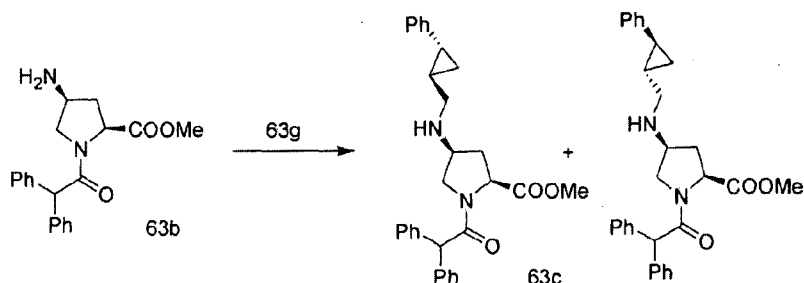
To a solution of 63f (0.8 g, 5.39 mmol) in THF (30 mL) was added Celite (~ 3 g) followed by PCC (3.49 g, 16.2 mmol) and the mixture was stirred at RT overnight, TLC (PE:EtOAc =4:1) showed the reaction was complete. The mixture was then filtered through a plug of silica gel and rinsed with DCM. The filtrate was concentrated *in vacuo* to give the product (0.62 g, 78%) as a yellow oil.

3. Procedure for the preparation of Compound 63b

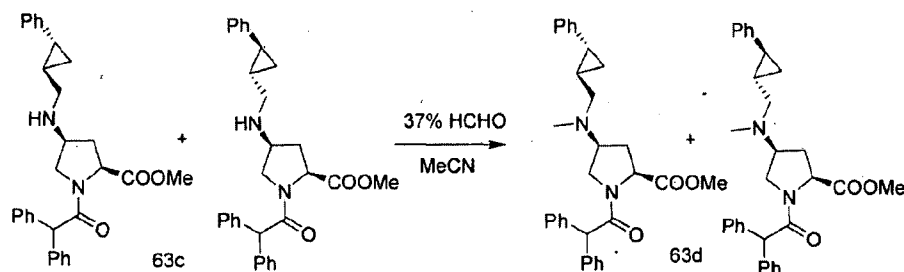


To a solution of compound 63a (1.4 g, 3.35 mmol) in DMSO (15 mL) was added NaN₃ (0.43 g, 6.70 mmol) and the mixture was heated at 90°C overnight, TLC (PE:EA=2:1) showed the reaction was complete. The reaction was partitioned between EA (30 mL) and water (60 mL), the layers were separated and the aqueous layer was extracted with EA (20 mL x 2). The combined organic extracts were washed with brine (30 mL x 2), dried over Na₂SO₄, filtered and concentrated to a volume of ~2 mL. A mixture of THF/H₂O (10 mL/1 mL) was added followed by PPh₃ (1.4 g, 5.35 mmol) and the mixture was heated at reflux for 3 h, TLC (PE:EA=2:1) showed the starting material was consumed. The mixture was concentrated *in vacuo* to remove most of the THF and the residue was dissolved in a 0.5 M aqueous HCl solution (20 mL) and washed with EA (20 mL x 2). The aqueous layer was then basified to pH 8 with K₂CO₃ and extracted with DCM (20 mL x 4). The combined organic extracts were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo* to give 63b (1.0 g, 90%) as a white solid. LC-MS (Agilent): R_t 3.02 min; m/z calculated for C₂₀H₂₂N₂O₃ [M+H]⁺ 339.2, found [M+H]⁺ 339.2

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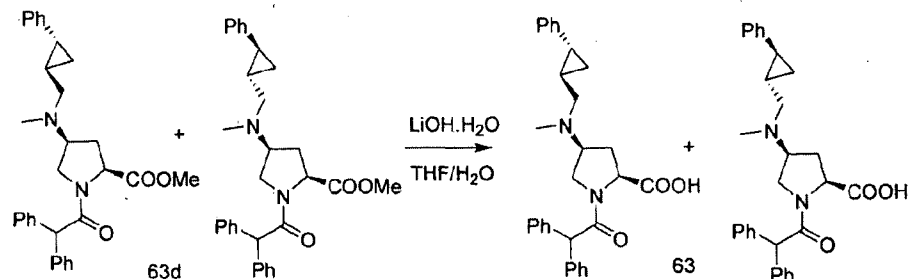
4. Procedure for the preparation of Compound 63c

To solution of compound 63b (600 mg, 1.77 mmol) and compound 63g (260 mg, 1.77 mmol) in DCE (30 mL) was added 2 drops of AcOH and the mixture was stirred at RT for 1 h. NaBH(OAc)₃ (451 mg, 2.13 mmol) was then added and stirring was continued at RT overnight, TLC (PE:EA=1:2) showed most of the starting material was consumed. The mixture was washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by chromatography to give 63c as a mixture of the indicated diastereoisomers (500 mg, 60%) as a yellow oil. LC-MS (Agilent): R_t 3.22 min; m/z calculated for C₂₀H₃₂N₂O₃ [M+H]⁺ 469.2, found [M+H]⁺ 469.2.

5. Procedure for the preparation of Compound 63d

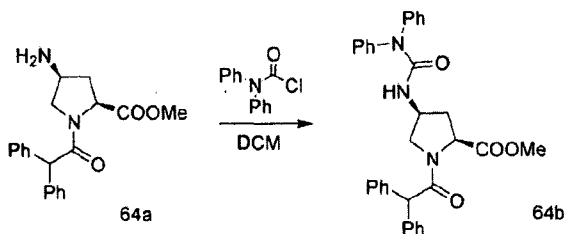
To a solution of compound 63c (500 mg, 1.06 mmol) in MeCN (10 mL) was added a 37% aqueous formaldehyde solution (220 mg, 2.66 mmol) followed by 2 drops of AcOH and the mixture was stirred at RT for 1 h. NaCNBH₃ (168 mg, 2.66 mmol) was then added and stirring was continued at RT overnight, TLC (PE:EA=1:2) showed the starting material was consumed. To the reaction mixture was added 3-5 drops of NaHCO₃ to neutralize the mixture which was partitioned between EA and water. The organic layer was separated and washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=10:1 to 2:1) to give 63d as a mixture of the indicated diastereoisomers (185 mg, 36%) as a yellow oil. LC-MS (Agilent): R_t 3.48 min; m/z calculated for C₃₁H₃₄N₂O₃ [M+H]⁺ 483.3, found [M+H]⁺ 483.2.

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6. Procedure for the preparation of Compound 63

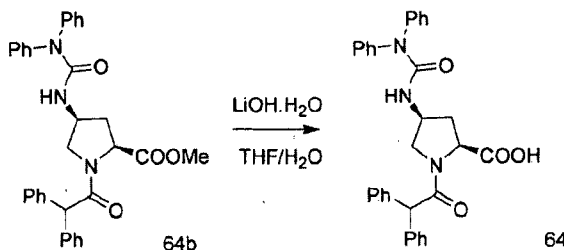
Hydrolysis of 63d (185 mg, 0.38 mmol) as performed as described in Example 16, 2. ith about 2.8 equivalents of LiOH.H₂O and the resulting precipitate was collected by filtration, washed with water (5 mL x 2), then purified by prep-HPLC to give 63 as a mixture of the indicated diastereoisomers (51 mg, 28%) as a white solid. LC-MS (Agilent): R_t 3.50 min; m/z calculated for C₃₀H₃₂N₂O₃ [M+H]⁺ 469.2, found [M+H]⁺ 469.3. HPLC (JULY-L) (214 and 254 nm): R_t 8.76 min.

10 Example 22: Compound 64 (2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-(3,3-diphenyluriedo)-pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of Compound 64b

To a stirred solution of compound 64a (300 mg, 0.88 mmol) and Et₃N (96 mg, 0.96 mmol) in DCM (5 mL) was added diphenylcarbamoyl chloride (246 mg, 0.96 mmol) followed a catalytic amount of DMAP and the mixture was stirred at RT overnight, TLC (DCM: MeOH=10:1) showed the starting material was consumed. Water (10 mL) was added, the layers were separated and the aqueous layer was extracted with DCM (10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=4:1 to 2:1) to give 64b (210 mg, 44%) as a white solid. LC-MS (Agilent): R_t 3.50 min; m/z calculated for C₃₁H₃₃N₃O₄ [M+H]⁺ 534.2, [M+Na]⁺ 556.2, found [M+H]⁺ 534.2, [M+Na]⁺ 556.2.

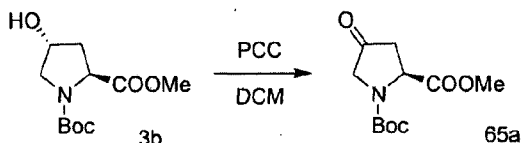
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2. Procedure for the preparation of Compound 64

To a mixture of compound 64b (200 mg, 0.37 mmol) in THF (5 mL) and H₂O (1 mL) was added LiOH.H₂O (40 mg, 0.94 mmol) and the mixture was stirred at RT overnight, TLC (PE:EA=1:1) showed the starting material was consumed. Most of the THF was removed *in vacuo* and the residue was dissolved in water (20 mL), cooled to 0°C and acidified to pH 2-3 with a 3 M aqueous HCl solution. The resulting precipitate was collected by filtration, washed with water (10 mL x 2) and dried at 50°C overnight to give 64 (140 mg, 72%) as a white solid. LC-MS (Agilent): R_t 3.52 min; m/z calculated for C₃₂H₂₉N₃O₄ [M+H]⁺ 520.2, [M+Na]⁺ 542.2, found [M+H]⁺ 520.2, [M+Na]⁺ 542.2. HPLC (JULY-L) (214 and 254 nm): R_t 8.15 min.

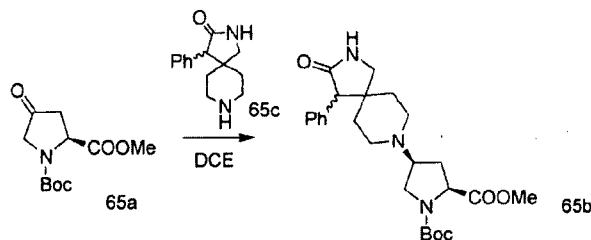
Example 23: Compound 65 (2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-(3-oxo-4-phenyl-2,8-diazaspiro[4,5]decan-8-yl)pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of Compound 65a

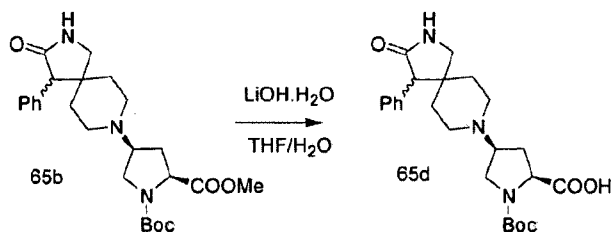


To a stirred solution of compound 3b (5.0 g, 20.4 mmol) in DCM (60 mL) was added Celite (8 g) then PCC (13.2 g, 61.2 mmol) and the mixture was stirred at RT overnight, TLC (PE:EA=2:1) showed the starting material was consumed. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=1:0 to 4:1) to give 65a (3.6 g, 72%) as a thick yellow oil. LC-MS (Agilent): R_t 3.17 min; m/z calculated for C₁₁H₁₇NO₅ [M+H-Boc]⁺ 144.1, [M+H-*t*-Bu]⁺ 188.1, found [M+H-Boc]⁺ 144.1, [M+H-*t*-Bu]⁺ 188.1.

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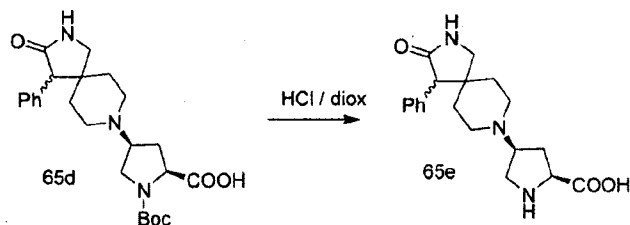
2. Procedure for the preparation of Compound 65b

A solution of compound 65a (900 mg, 3.70 mmol) and the racemic piperidine 65c (710 mg, 3.08 mmol) in MeOH (15 mL) was stirred at RT for 30 min. NaCNBH₃ (233 mg, 3.70 mmol) was added followed by 3 drops of AcOH and stirring was continued at RT overnight, TLC (DCM:MeOH=10:1) showed the starting material was consumed. The mixture was concentrated *in vacuo* and the residue was partitioned between DCM (20 mL) and a saturated aqueous NaHCO₃ solution (10 mL). The organic layer was collected, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by chromatography (DCM:MeOH=1:0 to 50:1) to give 65b as the indicated mixture of diastereoisomers (450 mg, 26%) as a white solid. LC-MS (Agilent): R_t 3.13 min; m/z calculated for C₂₅H₃₅N₃O₅ [M+H]⁺ 458.3, found [M+H]⁺ 458.3.

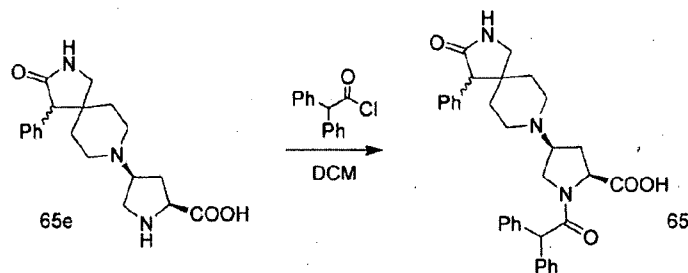
3. Procedure for the preparation of Compound 65d

To a mixture of 65b (450 mg, 0.98 mmol) in THF (10 mL) and H₂O (2 mL) was added LiOH.H₂O (104 mg, 2.46 mmol) and the mixture was stirred at RT overnight, TLC (DCM:MeOH= 10:1) showed the starting material was consumed. Most of the THF was removed *in vacuo* and the residue was dissolved in water (15 mL), cooled to 0°C, acidified to pH 2-3 with a 3 M aqueous HCl solution and then freeze-dried. Purification by flash chromatography (DCM:MeOH=10:1) gave 65d as the indicated mixture of diastereoisomers (320 mg, 73%) as a white solid. LC-MS (Agilent): R_t 3.20 min; m/z calculated for C₂₄H₃₃N₃O₅ [M+H]⁺ 444.2, found [M+H]⁺ 444.2. HPLC (JULY-L) (214 and 254 nm): R_t 8.08 min.

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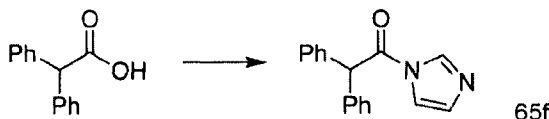
4. Procedure for the preparation of Compound 65e

To a stirred suspension of 65d (270 mg, 0.61 mmol) in a 4 M HCl/dioxane solution (5 mL) was added a 6 M aqueous HCl solution (0.5 mL). The resulting homogeneous mixture was then stirred at RT for 2 h, LCMS analysis showed the reaction was complete. The mixture was concentrated *in vacuo* to give crude 65e (250 mg) and a portion (80 mg) was purified by prep-HPLC to give pure 65e as the indicated mixture of diastereoisomers (40 mg, 59%) as a white solid. The remaining crude product was used directly in the next step. LC-MS (Agilent): R_t 0.97 min; m/z calculated for $C_{19}H_{25}N_3O_3$ $[M+H]^+$ 344.2, found $[M+H]^+$ 344.2. HPLC (JULY-L) (214 and 254 nm): R_t 3.19 min.

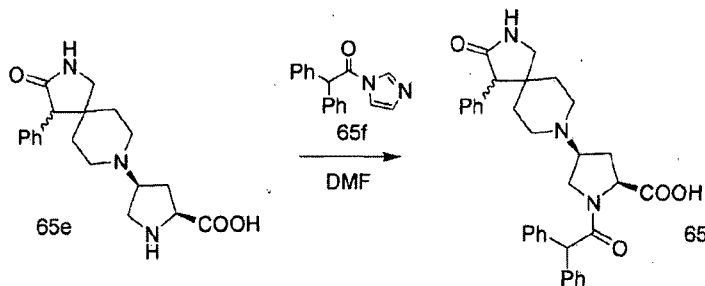
5. Procedure for the preparation of Compound 65

To a stirred mixture of crude 65e (130 mg, 0.34 mmol) and Et_3N (86 mg, 0.85 mmol) in DCM (10 mL) at 0°C was added diphenylacetyl chloride (94 mg, 0.41 mmol) in DCM (2 mL) under a N_2 atmosphere and the mixture was stirred at 0°C for 1 h, TLC (DCM:MeOH=10:1) showed a new product was formed. The mixture was partitioned between DCM/water (10 mL/15 mL) and the aqueous layer was acidified to pH 3 with a 6 M aqueous HCl solution. The organic layer was collected, concentrated *in vacuo* and the residue was purified by prep-HPLC to give 65 as the indicated mixture of diastereoisomers (8.5 mg, 5%) as a white solid. LC-MS (Agilent): R_t 3.47 min; m/z calculated for $C_{33}H_{35}N_3O_4$ $[M+H]^+$ 538.3, found $[M+H]^+$ 538.3. HPLC (JULY-L) (214 and 254 nm): R_t 8.50 min.

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Example 24: Alternative Synthesis of Compound 65**1. Procedure for the preparation of Compound 65f**

To a stirred solution of diphenyl acetic acid (5.0 g, 23.5 mmol) in DCM (50 mL) at 0°C was added CDI (4.6 g, 28.3 mmol) in portions and the mixture was stirred at RT for 1 h, TLC (DCM:MeOH=20:1) showed the starting material was consumed. The mixture was washed with water (30 mL x 2) and brine (30 mL x 2), dried over Na₂SO₄, filtered and concentrated *in vacuo* to give 65f (5.6 g, 90%) as a white solid. LC-MS (Agilent): R_t 3.70 min; m/z calculated for C₁₇H₁₄N₂O [M+H]⁺ 263.1, found [M+H]⁺ 263.1.

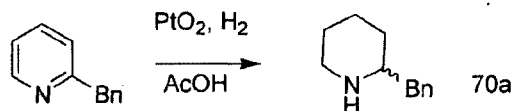
2. Procedure for the preparation of Compound 65

To a stirred solution of pure 65e (27 mg, 0.079 mmol) in DMF (1 mL) was added tetramethyl guanidine (9.3 mg, 0.081 mmol) under a N₂ atmosphere and the mixture was stirred at RT for 1 h. Compound 65f (25 mg, 0.094 mmol) was added and stirring was continued at RT overnight. More compound 65f (24.7 mg, 0.094 mmol) was added stirring was continued at RT for another day. Water (10 mL) was added and the mixture was basified to pH 9 with K₂CO₃ and washed with ether. The aqueous layer was then acidified to pH 3-4 with a 1 M aqueous HCl solution and extracted with CHCl₃/*i*-PrOH (v/v = 3/1, 15 mL x 3). The combined organic extracts were concentrated *in vacuo* and the residue was purified by prep-HPLC to give 65 as the indicated mixture of diastereoisomers (7 mg, 16%) as a white solid. LC-MS (Agilent): R_t 3.41 min; m/z calculated for C₃₃H₃₅N₃O₄ [M+H]⁺ 538.3, found [M+H]⁺ 538.3. HPLC (JULY-L) (214 and 254 nm): R_t 8.50 min.

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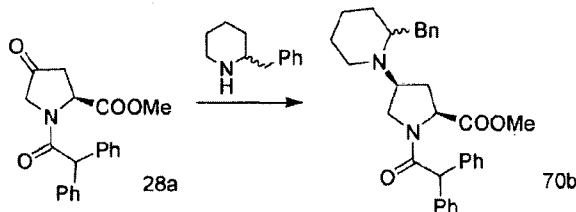
Example 25: Compound 70 (2*S*,4*S*)-4-(2-benzylpiperidin-1-yl)-1-(2,2-diphenylacetyl)-pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of Compound 70a



5 A mixture of 2-benzyl pyridine (2.0 g, 1.08 mmol) and PtO_2 (200 mg, 0.72 mmol) in AcOH (20 mL) was stirred at RT under a H_2 atmosphere (0.6 Mpa) for 6 h, TLC (PE:EA=4:1) showed the starting material was consumed. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was partitioned between DCM (30 mL) and water (30 mL) and the aqueous layer was basified to pH 8-9 with K_2CO_3 . The organic layer was
 10 separated, washed with brine (15 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give 70a (1.9 g, 94%) as a colorless oil. LC-MS (Agilent): R_t 2.77 min; m/z calculated for $\text{C}_{12}\text{H}_{17}\text{N}$ $[\text{M}+\text{H}]^+$ 176.1, found $[\text{M}+\text{H}]^+$ 176.2.

2. Procedure for the preparation of Compound 70b



15 To a stirred solution of compound 28a (900 mg, 2.67 mmol) and 2-benzyl piperidine (compound 70a) (468 mg 2.67 mmol) in DCE (10 mL) was added AcOH (0.5 mL) and the mixture was stirred at RT for 30 min then cooled to 0°C . $\text{NaBH}(\text{OAc})_3$ (849 mg, 4.01 mmol) was added and stirring was continued at RT overnight, TLC (PE:EA=1:1) showed most of the starting material was consumed. The mixture was partitioned between DCM
 20 (20 mL) and a saturated aqueous NaHCO_3 solution (20 mL). The organic layer was separated, washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by chromatography (DCM:EA=1:0 to 5:1) to give one diastereoisomer 70b-A (170 mg, 13%) as a white solid. Further elution then gave the other diastereoisomer 70b-B (150 mg, 12%) as a white solid. The absolute stereochemistry of
 25 these diastereoisomers was not determined and therefore are referred to as 70-A and 70-B.

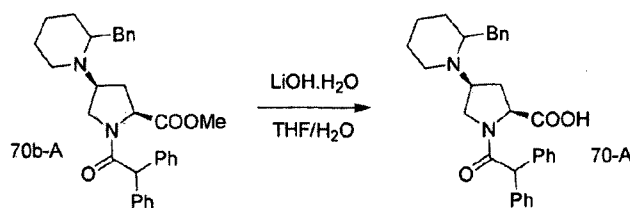
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LCMS for Compound 70b-A

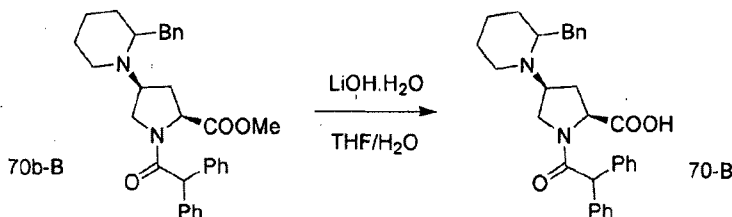
LC-MS (Agilent): R_t 3.42 min; m/z calculated for $C_{32}H_{36}N_2O_3$ $[M+H]^+$ 497.3, found $[M+H]^+$ 497.3.

LCMS for Compound 70b-B

5 LC-MS (Agilent): R_t 3.39 min; m/z calculated for $C_{32}H_{36}N_2O_3$ $[M+H]^+$ 497.3, found $[M+H]^+$ 497.3.

3. Procedure for the preparation of Compound 70-A

To a stirred solution of compound 70b-A (170 mg, 0.34 mmol) in THF/water (5 mL/1 mL) at 0°C was added LiOH.H₂O (36 mg, 0.85 mmol) and the mixture was stirred at RT overnight, TLC (PE:EA=1:1) showed the starting material was consumed. Most of the THF was removed *in vacuo* and the residue was dissolved in water (15 mL), cooled in an ice-water bath and acidified to pH 3~4 with a 1 M aqueous HCl solution. The resulting precipitate was collected by filtration and re-crystallized from EA (20 mL) to give 70-A (23 mg, 14 %) as a white solid. LC-MS (Agilent): R_t 3.51 min; m/z calculated for $C_{31}H_{34}N_2O_3$ $[M+H]^+$ 483.3, found $[M+H]^+$ 483.3. HPLC (214 and 254 nm): R_t 8.76 min.

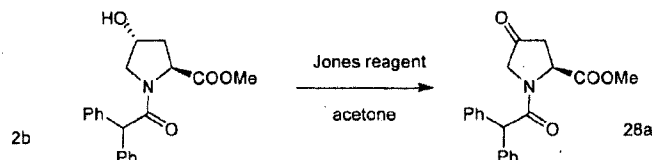
4. Procedure for the preparation of Compound 70-B

The hydrolysis reaction from 3. above was repeated for 70b-B (150 mg, 0.30 mmol) and after acidification, the aqueous mixture was then extracted with chloroform (15 mL x 3) and the combined organic extracts were washed with brine (15 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* to give 70-B (120 mg, 83%) as a thick oil. LC-MS (Agilent): R_t 3.68 min; m/z calculated for $C_{31}H_{34}N_2O_3$ $[M+H]^+$ 483.3, found $[M+H]^+$ 483.3. HPLC (JULY-L) (214 and 254 nm): R_t 8.96 min.

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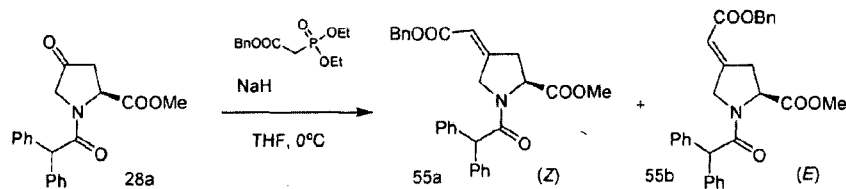
Example 26: Compound 55 (2*S*,4*R*)-4-(2-(benzyloxy)ethyl)-1-(2,2-diphenylacetyl)-pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of 28a



To a solution of 2b (7.00 g, 20.6 mol) in acetone (70 mL) at 0°C was added Jones reagent (2.6 M, 9.00 mL, 28.9 mol) and the mixture was allowed to warm to RT and stirred for 20 min, TLC (PE:EA=2:1) showed the starting material was consumed. The reaction was quenched with isopropanol, Celite (3 g) was added and the mixture was filtered. The filtrate was concentrated *in vacuo* and the residue was partitioned between EA (40 mL) and water (40 mL). The layers were separated and the organic phase was washed with a saturated aqueous NaHCO₃ solution (30 mL), brine (30 mL x 2) then dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=1:0 to 2:1) to give 28a (5.95 g, 85%) as a white solid. LC-MS (Agilent, P-2): R_t 2.79 min; m/z calculated for C₂₀H₁₉NO₄ [M+H]⁺ 338.1, found [M+H]⁺ 338.1.

2. Procedure for the preparation of 55a

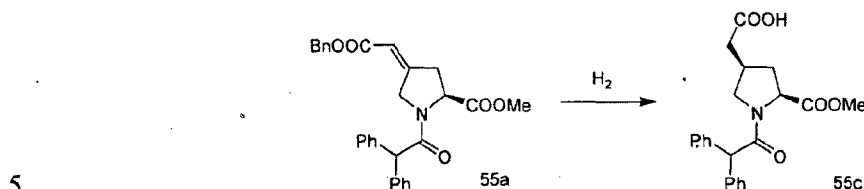


To a solution of benzyl 2-(diethoxyphosphoryl)acetate (1.68 g, 6.52 mmol) in dry THF (10 mL) at 0°C was added NaH (60% dispersion in mineral oil, 260 mg, 6.52 mmol) in portions and the mixture was stirred at 0°C for 30 min. A solution of 28a (2.00 g, 5.93 mmol) in THF (10 mL) was then added and stirring was continued at 0°C for a further 40 min, TLC (PE:EA=2:1) showed that the starting material was consumed. The reaction was quenched with ice-water (40 mL) and the mixture was extracted with EA (20 mL x 2). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=1:0 to 5:1) to give the first eluting product 55a (1.0 g, 36%) and second eluting product 55b (1.8 g, 64%) as thick oils, which were assigned as Z and E isomers respectively. LC-MS (Agilent, P-2)

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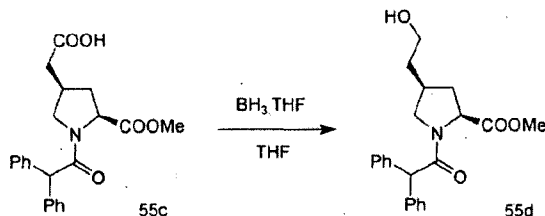
for 55a: R_t 3.02 min; m/z calculated for $C_{29}H_{27}NO_5$ $[M+H]^+$ 470.2, found $[M+H]^+$ 470.2.
 LC-MS (Agilent, P-2) for 55b: R_t 3.01 min; m/z calculated for $C_{29}H_{27}NO_5$ $[M+H]^+$ 470.2,
 found $[M+H]^+$ 470.2.

3. Procedure for the preparation of 55c



A mixture of 55a (1.00 g, 2.1 mmol) and 10% Pd/C (100 mg) in MeOH (20 mL) was stirred at RT under a H_2 atmosphere (1 atm) overnight, TLC (PE:EA=2:1) showed that the starting material was consumed. The mixture was filtered and the filtrate was concentrated *in vacuo* to give 55c (0.75 g, 87%) as a white solid. LC-MS (Agilent, P-2): R_t 2.70 min;
 10 m/z calculated for $C_{22}H_{23}NO_5$ $[M+H]^+$ 382.1, found $[M+H]^+$ 382.1.

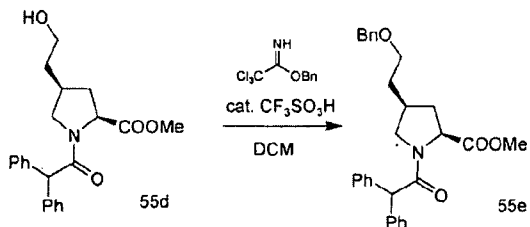
4. Procedure for the preparation of 55d



To a solution of 55c (0.70 g, 1.8 mmol) in dry THF (20 mL) at $0^\circ C$ under N_2 was added BH_3 /THF (1 M solution in THF, 2.00 mL, 2.00 mmol) and the mixture was stirred at $0^\circ C$
 15 for 1 h, TLC (DCM:MeOH=10:1) showed that the starting material was consumed. The reaction was quenched with MeOH (2 mL), a 3 M aqueous HCl solution (5 mL) was added and the mixture was stirred at RT for 1 h then partitioned between EA and brine. The layers were separated and the organic phase was dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE: EA= 1:0 to 1:1)
 20 to give 55d (500 mg, 76%) as a colorless oil. LC-MS (Agilent, P-2): R_t 2.74 min; m/z calculated for $C_{22}H_{25}NO_4$ $[M+H]^+$ 368.2, found $[M+H]^+$ 368.2.

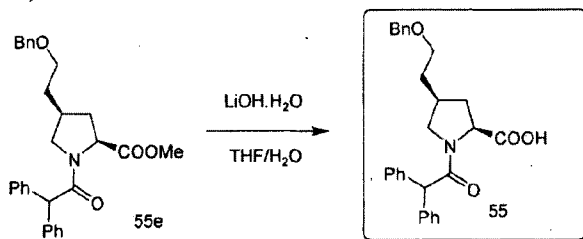
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5. Procedure for the preparation of 55e



To a solution of 55d (200 mg, 0.54 mmol) and benzyl 2,2,2-trichloroacetimidate (151 mg, 0.59 mmol) in DCM (10 mL) at RT was added 1 drop of $\text{CF}_3\text{SO}_3\text{H}$ and the mixture was stirred at RT overnight, TLC (DCM:MeOH=10:1) showed that the starting material was consumed. The mixture was washed with brine then dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=1:0 to 4:1) to give 55e (120 mg, 50%) as a colorless oil. LC-MS (Agilent, P-2): R_t 3.05 min; m/z calculated for $\text{C}_{29}\text{H}_{31}\text{NO}_4$ $[\text{M}+\text{H}]^+$ 458.2, found $[\text{M}+\text{H}]^+$ 458.2.

6. Procedure for the preparation of 55

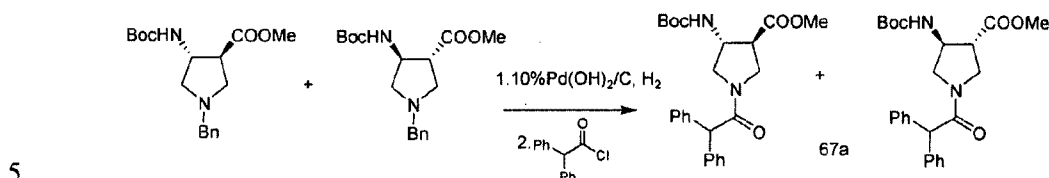


A mixture of 55e (120 mg, 0.26 mmol) and $\text{LiOH}\cdot\text{H}_2\text{O}$ (33 mg, 0.78 mmol) in THF/water (3 mL/1 mL) was stirred at RT overnight, TLC (PE:EA=2:1) showed that the starting material was consumed. Most of the THF was removed *in vacuo* and the residue was dissolved in water (20 mL), acidified to pH 3 with a 3 M aqueous HCl solution and extracted with DCM (20 mL x 2). The combined organic extracts were washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by preparative HPLC to give 55 (90 mg, 78%) as a white solid. LC-MS (Agilent, P-2): R_t 2.95 min; m/z calculated for $\text{C}_{28}\text{H}_{29}\text{NO}_4$ $[\text{M}+\text{H}]^+$ 444.2, found $[\text{M}+\text{H}]^+$ 444.2. HPLC (JULY-L) (214 and 254 nm): R_t 9.25 min.

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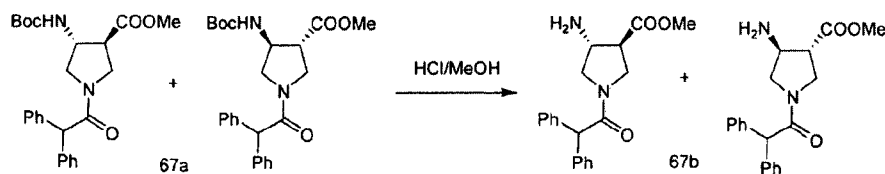
Example 27: Compound 67 (3*R*,4*S*)-1-(2,2-diphenylacetyl)-4-(methyl(3-phenylpropyl) amino)pyrrolidine-3-carboxylic acid and (3*S*,4*R*)-1-(2,2-diphenylacetyl)-4-(methyl(3-phenylpropyl) amino)pyrrolidine-3-carboxylic acid

1. Procedure for the preparation of 67a



To a solution of (3*R*,4*S*)-methyl-1-benzyl-4-(tert-butoxycarbonyl)amino-pyrrolidine-3-carboxylate (500 mg, 1.49 mmol) in MeOH (20 mL) was added Pearlman's catalyst (50 mg) and the mixture was stirred at RT under a H₂ atmosphere (1 atm) overnight, TLC (PE:EA=2:1) showed that the starting material was consumed. The mixture was filtered, the
 10 filtrate was concentrated *in vacuo* and the residue was dissolved in DCM (20 mL). Diphenyl acetic acid (347 mg, 1.64 mmol) and EDCI.HCl (343 mg, 1.79 mmol) were added and the mixture was stirred at RT overnight, TLC (DCM:MeOH=10:1) showed the starting material was consumed. The mixture was washed with brine (15 mL x 2), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by
 15 chromatography (PE:EA=1:0 to 4:1) to give 67a (150 mg, 23%) as a colorless oil. LC-MS (Agilent): R_t 4.37 min; m/z calculated for C₂₅H₃₀N₂O₅ [M+H]⁺ 439.2, [M+Na]⁺ 461.2, found [M+H]⁺ 439.2, [M+Na]⁺ 461.2.

2. Procedure for the preparation of 67b

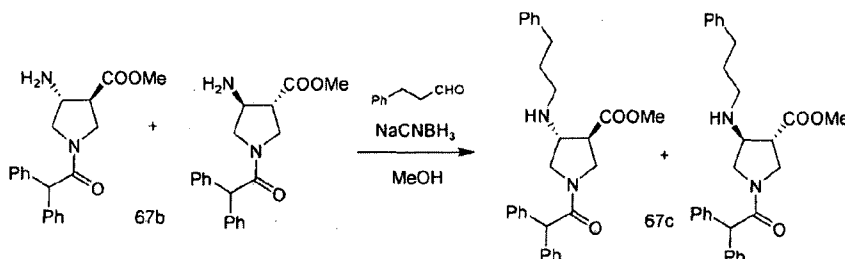


20 67a (150 mg, 0.34 mmol) was dissolved in a 4 M HCl/MeOH solution (10 mL) and the mixture was stirred at RT overnight, TLC (PE:EA=2:1) showed that the starting material was consumed. The mixture was concentrated *in vacuo* and the residue was partitioned between DCM (20 mL) and water (15 mL). The aqueous phase was basified to pH 9 with K₂CO₃ and the layers were separated. The aqueous layer was further extracted with DCM
 25 (10 mL x 3) and the combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to give 67b (130 mg, 100%) as a colorless oil

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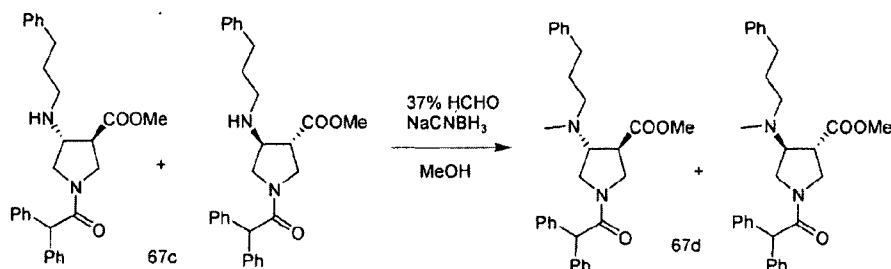
which was used directly in the next step. LC-MS (Agilent): R_t 4.13 min; m/z calculated for $C_{20}H_{22}N_2O_3$ $[M+H]^+$ 339.2, found $[M+H]^+$ 339.2.

3. Procedure for the preparation of 67c



- 5 To solution of 67b (130 mg, 0.34 mmol) and 3-phenylpropanal (45 mg, 0.34 mmol) in MeOH (10 mL) was added 1 drop of AcOH and the mixture was stirred at RT for 0.5 h. NaCNBH₃ (28 mg, 0.44 mmol) was then added and stirring was continued at RT overnight, TLC (DCM:MeOH=10:1) showed the starting material was consumed. The mixture was concentrated *in vacuo* and the residue was partitioned between DCM and
- 10 brine. The organic layer was collected, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=1:0 to 2:1) to give 67c (120 mg, 77%) as a colorless oil. LC-MS (Agilent): R_t 3.85 min; m/z calculated for $C_{29}H_{32}N_2O_3$ $[M+H]^+$ 457.2, found $[M+H]^+$ 457.2.

4. Procedure for the preparation of 67d



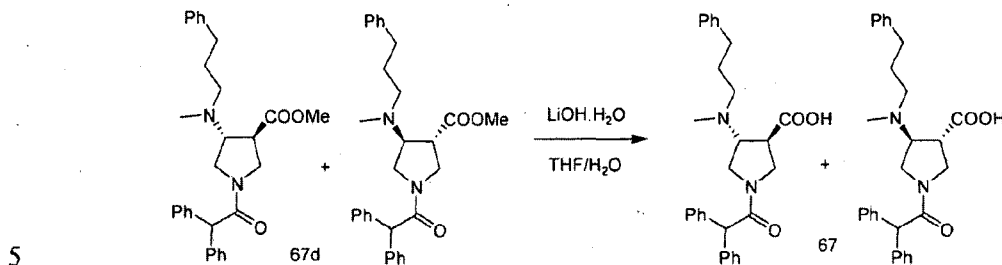
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- To solution of 67c (120 mg, 0.26 mmol) and 37% aqueous formaldehyde (25 mg, 0.32 mmol) in MeOH (15 mL) at 0°C was added 2 drops of AcOH and the mixture was stirred at 0°C for 30 min. NaCNBH₃ (20 mg, 0.32 mmol) was added and stirring was continued at RT overnight, TLC (PE:EA=2:1) showed that the starting material was consumed. The
- 20 mixture was concentrated *in vacuo* and the residue was partitioned between water (10 mL) and EA (20 mL). The layers were separated and the organic phase was washed with brine (10 mL x 2), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was

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purified by chromatography (PE:EA=5:1 to 3:1) to give 67d (65 mg, 53%) as a colorless oil. LC-MS (Agilent): R_t 3.97 min; m/z calculated for $C_{30}H_{34}N_2O_3$ $[M+H]^+$ 471.3, found $[M+H]^+$ 471.3.

5. Procedure for the preparation of 67



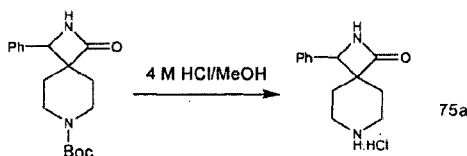
A mixture of 67d (65 mg, 0.14 mmol) and $LiOH \cdot H_2O$ (18 mg, 0.41 mmol) in THF/water (10 mL/2 mL) was stirred at RT overnight, TLC (PE:EA=2:1) showed the starting material was consumed. Most of the THF was removed *in vacuo* and the residue was dissolved in water H_2O (10 mL), acidified to pH 4~5 with a 3 M aqueous HCl solution and extracted with DCM (10 mL x 2). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by preparative HPLC to give 67 (40 mg, 63%) as a white solid. LC-MS (Agilent): R_t 3.78 min; m/z calculated for $C_{28}H_{30}N_2O_3$ $[M+H]^+$ 457.3, found $[M+H]^+$ 457.3. HPLC (JULY-L) (214 and 254 nm): R_t 8.79 min.

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Example 28: Compound 75 (2S,4S)-1-(2,2-diphenylacetyl)-4-(1-oxo-3-phenyl-2,7-diazaspiro[3,5]nonan-7-yl)pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of 75a



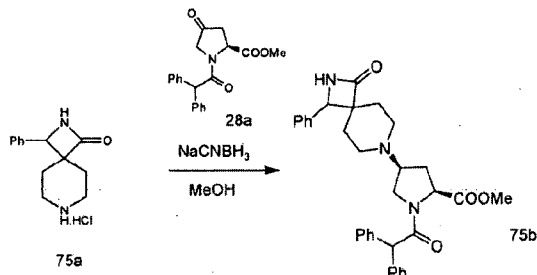
tert-Butyl 1-oxo-3-phenyl-2,7-diazaspiro[3.5]nonane-7-carboxylate (300 mg, 0.94 mmol) was added to a 4 M HCl/MeOH solution (5 mL) at 0°C and the mixture was stirred at RT for 3 h, after which time a white suspension formed. LCMS analysis showed that the starting material was consumed. EA (3 mL) and diethyl ether (10 mL) were added and the solid material was collected by filtration, washed with diethyl ether (5 mL x 2) and dried to

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give 75a (280 mg, >100%) as a white solid, which was used in the following step without further purification. LC-MS (Agilent): R_t 2.75 min; m/z calculated for $C_{13}H_{16}N_2O$ $[M+H]^+$ 217.1, found $[M+H]^+$ 217.1.

2. Procedure for the preparation of 75b

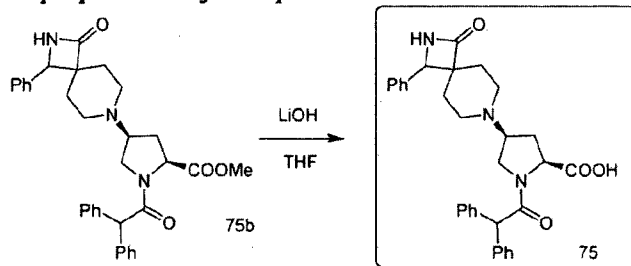


5

A solution of 28a (100 mg, 0.29 mmol), 75a (75 mg, 0.29 mmol) and Et_3N (33 mg, 0.32 mmol) in MeOH (10 mL) was stirred at RT for 30 min before adding 1 drop of AcOH and $NaCNBH_3$ (20 mg, 0.32 mmol). The mixture was then allowed to stir at RT overnight, TLC (PE:EA=1:1) showed that the starting material was consumed and 75b was confirmed by LCMS analysis. The reaction was repeated on a larger amount of 75a (200 mg, 0.59 mmol) and the two reaction mixtures were combined and concentrated *in vacuo*. The residue was dissolved in DCM (30 mL), washed with brine (30 mL) then dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Purification by column chromatography (DCM:MeOH=1:0 to 20:1) gave 75b (60 mg, 12%) as a colorless oil. LC-MS (Agilent): R_t 3.41 min; m/z calculated for $C_{33}H_{35}N_3O_4$ $[M+H]^+$ 538.3, $[M+Na]^+$ 560.3, found $[M+H]^+$ 538.3, $[M+Na]^+$ 560.3.

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3. Procedure for the preparation of Compound 75



To a mixture of 75b (60 mg, 0.11 mmol) in THF/water (5 mL/1 mL) was added $LiOH \cdot H_2O$ (14 mg, 0.33 mmol) and the mixture was stirred at RT overnight, TLC (DCM:MeOH=10:1) showed that the starting material was consumed. Most of THF was removed *in vacuo* and the residue was dissolved in water (20 mL), acidified to pH 3-4 with a 3 M aqueous

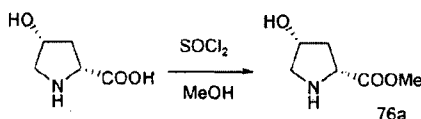
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HCl solution and extracted with DCM (15 mL x 3). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to give 50 mg of crude product which was suspended in EA (5 mL). The obtained mixture was heated at reflux for 30 min, cooled to RT and the precipitate was collected by filtration then dried to give 75 (25 mg, 43%) as a white solid. LC-MS (Agilent): R_t 3.67 min; m/z calculated for C₃₂H₃₃N₃O₄ [M+H]⁺ 524.3, found [M+H]⁺ 524.3. HPLC (214 and 254 nm): R_t 8.53 min.

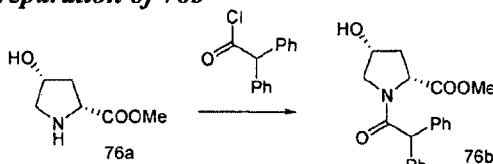
Example 29: Compound 76 (2R,4R)-1-(2,2-diphenylacetyl)-4-(3-phenylpropoxy)-pyrrolidine-2-carboxylic acid

10 **1. Procedure for the preparation of Compound 76a**



cis-4-Hydroxy-D-proline was prepared using the procedure described in *Tetrahedron Asymmetry*, **2002**, 13, 197. To a solution of *cis*-4-Hydroxy-D-proline (20 g, 0.15 mol) in MeOH (200 mL) at 0°C was added SOCl₂ (19.9 g, 0.17 mol) dropwise and the mixture was then heated at 70°C overnight, LCMS analysis showed that the starting material was consumed. The mixture was cooled to RT and concentrated *in vacuo* to give 76a (22 g, 100%) as brown solid. LC-MS (Agilent): R_t 0.64min; m/z calculated for C₆H₁₁NO₃ [M+H]⁺ 146.1, found [M+H]⁺ 146.1.

20 **2. Procedure for the preparation of 76b**

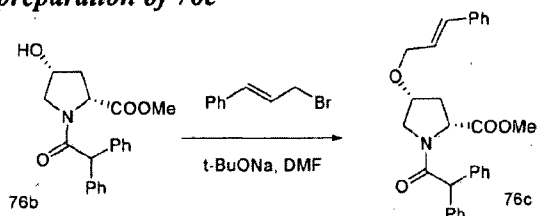


To a solution of diphenylacetic acid (15.9 g, 75.2 mmol) in DCM (150 mL) at 0°C was added DMF (2 drops) and SOCl₂ (11.6 g, 87.7 mmol) and the mixture was heated at reflux for 2 h. The solvent was removed *in vacuo* and the residue was dissolved in ether (20 mL) and added slowly to a mixture of 76a (15 g, 83 mmol) and K₂CO₃ (15.6 g, 113 mmol) in water (250 mL) and ether (100 mL) at 0°C. The mixture was stirred at 0°C for 2 h, TLC (PE:EA=1:1) showed a major new product was formed. The layers were separated and the aqueous layer was extracted with EA (80 mL x 2). The combined organic extracts were

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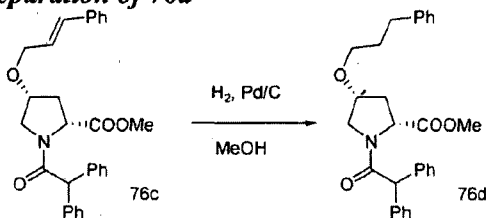
washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by column chromatography (PE:EA=10:1 to 3:1) to give 76b (20 g, 80%) as a yellow solid. LC-MS (Agilent): R_t 3.53 min; m/z calculated for $\text{C}_{20}\text{H}_{21}\text{NO}_4$ $[\text{M}+\text{H}]^+$ 340.1 found $[\text{M}+\text{H}]^+$ 340.1.

3. Procedure for the preparation of 76c



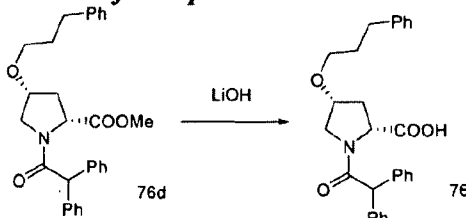
To a stirred solution of 76b (1.0 g, 2.9 mmol) and cinnamyl bromide (0.87 g, 4.4 mmol) in DMF (20 mL) -40°C was added *t*-BuONa (0.28 g, 2.9 mmol) in portions and the mixture was stirred at -40°C for 2 h, TLC (PE:EA=1:1) showed that the starting material was consumed. The mixture was allowed to warm to 0°C , water (100 mL) was added and extracted with EA (30 mL x 2). The combined organic extracts were washed with water (20 mL), brine (20 mL x 2), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by column chromatography (PE:EA=10:1 to 3:1) to give 76c (0.8 g, 62%) as a white solid. LC-MS (Agilent): R_t 4.03 min; m/z calculated for $\text{C}_{29}\text{H}_{29}\text{NO}_4$ $[\text{M}+\text{H}]^+$ 456.2, found $[\text{M}+\text{H}]^+$ 456.1.

4. Procedure for the preparation of 76d



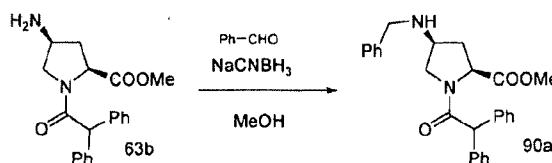
To a solution of 76c (400 mg, 0.88 mmol) in MeOH (15 mL) was added 10% Pd/C (40 mg) and the mixture was stirred at RT under a H_2 atmosphere (1 atm) overnight, TLC (PE:EA=2:1) showed that the starting material was consumed. The mixture was filtered through Celite and the filtrate was concentrated *in vacuo* to give 76d (370 mg, 92%) as a colorless oil. LC-MS (Agilent): R_t 4.12 min; m/z calculated for $\text{C}_{29}\text{H}_{31}\text{NO}_4$ $[\text{M}+\text{H}]^+$ 458.2, found $[\text{M}+\text{H}]^+$ 458.2.

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5. Procedure for the preparation of Compound 76

To a stirred solution of 76d (370 mg, 0.8 mmol) in THF/H₂O (10 mL/3 mL) was added LiOH.H₂O (102 mg, 2.4 mmol) and the mixture was heated at 30°C overnight, TLC (PE: EA=2:1) showed that the starting material was consumed. Most of the THF was removed *in vacuo* and the residue was dissolved in water (20 mL) and washed with Et₂O (15 mL x 2). DCM (15 mL) was added and the aqueous layer was acidified to pH 2-3 with a 3 M aqueous HCl solution. The layers were separated and the aqueous layer was further extracted with DCM (15 mL). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to give compound 76 (300 mg, 85%) as a white solid. LC-MS (Agilent): R_t 3.99 min; m/z calculated for C₂₈H₂₉NO₄ [M+H]⁺ 444.2, found [M+H]⁺ 444.2. HPLC (214 and 254 nm): R_t 9.36 min.

Example 30: Compound 90 (2S,4S)-1-(2,2-diphenylacetyl)-4-(methyl(4-phenylbutyl)-amino)pyrrolidine-2-carboxylic acid

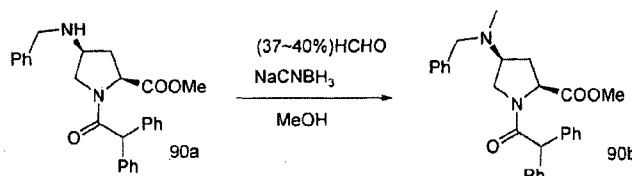
1. Procedure for the preparation of 90a

To a stirred solution of 63b (100 mg, 0.29 mmol) and benzaldehyde (25 mg, 0.24 mmol) in MeOH (5 mL) under nitrogen was added 2 drops of AcOH and the mixture was stirred for 1 h then cooled to 0°C. NaCNBH₃ (22 mg, 0.35 mmol) was added and the mixture was allowed to warm slowly to RT and stirred overnight, TLC (DCM:MeOH=10:1) showed that most of the starting material was consumed. Most of the MeOH was removed *in vacuo*, water (15 mL) was added and the mixture was extracted with EA (15 mL x 2). The combined organic extracts were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo* to give the crude 90a (150 mg) as a yellow oil. The procedure was repeated and the crude batches were combined and purified by column chromatography (PE:EA=10:1 to

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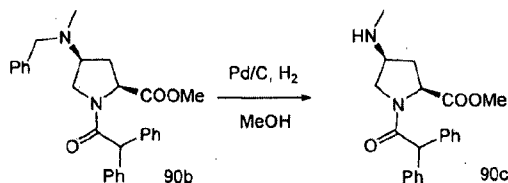
1:1) to give 90a (2.0 g, 66%) as a white solid. LC-MS (Agilent): R_t 3.42 min; m/z calculated for $C_{27}H_{28}N_2O_3$ $[M+H]^+$ 429.2, found $[M+H]^+$ 429.2.

2. Procedure for the preparation of 90b



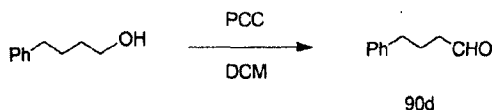
- 5 To a stirred solution of 90a (2.00 g, 4.67 mmol) and formaldehyde (37~40% solution in water, 0.56 g, 7.01mmol) in MeOH (40 mL) under nitrogen was added 3 drops of AcOH and the mixture was stirred for 1 h then cooled to 0°C. NaCNBH₃ (0.35 g, 5.60 mmol) was added and the mixture was allowed to warm slowly to RT and stirred overnight, TLC (DCM:MeOH=20:1) showed that most of the starting material was consumed. Most of the
- 10 MeOH was removed *in vacuo*, water (20 mL) was added and the mixture was extracted with DCM (30 mL). The organic layer was washed with brine (25 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=10:1 to 4:1) to give 90b (1.86 g, 90%) as a white solid. LC-MS (Agilent): R_t 3.50 min; m/z calculated for $C_{28}H_{30}N_2O_3$ $[M+H]^+$ 443.3, found $[M+H]^+$ 443.3.

15 3. Procedure for the preparation of 90c



- A mixture of 90b (1.86 g, 4.20 mmol) and 10% Pd/C (200 mg) in MeOH (30 mL) was stirred at RT under a H₂ atmosphere (1 atm) for 2 days, TLC (DCM:MeOH=10:1) showed that the starting material was consumed. The mixture was filtered and the filtrate was
- 20 concentrated *in vacuo* to give 90c (1.40 g, 95%) as colorless oil. LC-MS (Agilent): R_t 3.34 min; m/z calculated for $C_{21}H_{24}N_2O_3$ $[M+H]^+$ 353.2, found $[M+H]^+$ 353.2.

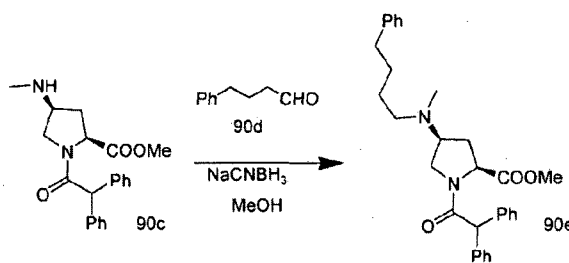
4. Procedure for the preparation of 90d



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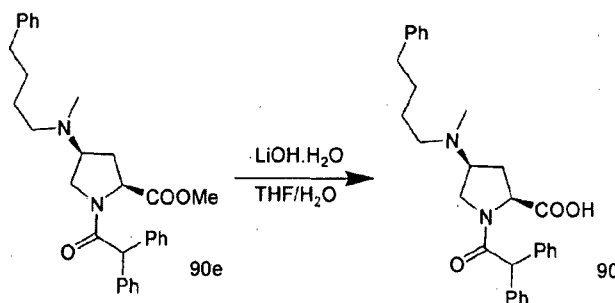
To a solution of 4-phenyl-1-butanol (0.5 g, 3.3 mmol) in DCM (10 mL) was added Celite (0.5 g) followed by PCC (1.8 g, 8.3 mmol) and the mixture was stirred at RT for 3 h, TLC (PE:EA=2:1) showed that the starting material was consumed. The mixture was filtered through a short plug of silica gel using DCM to wash. The filtrate was concentrated *in vacuo* to give 90d (0.5 g, 100%) as a yellow oil.

5. Procedure for the preparation of 90e



To a stirred solution of 90c (202 mg, 0.57 mmol) and the aldehyde 90d (102 mg, 0.68 mmol) in MeOH (10 mL) at RT was added AcOH (1 drop) and the mixture was stirred for 1 h then cooled to at 0°C. NaCNBH₃ (43 mg, 0.68 mmol) was added and the mixture was allowed to warm to RT and stirred overnight, TLC (DCM:MeOH=20:1) showed that the starting material was consumed. The mixture was concentrated *in vacuo* and the residue was dissolved in water (15 mL) and extracted with DCM. The organic extracts were washed with brine (15 mL x 2), dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification by column chromatography (PE:EA=4:1 to 1:1) gave 90e (198 mg, 71%) as thick colorless oil. LC-MS (Agilent): R_t 3.61 min; m/z calculated for C₃₁H₃₆N₂O₃ [M+H]⁺ 485.3, found [M+H]⁺ 485.3.

6. Procedure for the preparation of Compound 90



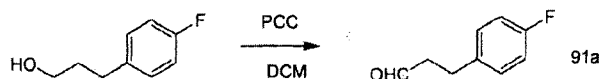
Hydrolysis of 90e (198 mg, 0.41 mmol) was performed as described in Example 27, 5. with 3 equivalents of LiOH.H₂O (52 mg, 1.23 mmol) and the mixture was stirred at RT overnight, TLC (DCM: MeOH=20:1). The combined organic extracts were washed with

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brine (10 mL x 2), dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give 90 (185 mg, 96%) as white solid. LC-MS (Agilent): R_t 3.67 min; m/z calculated for $\text{C}_{31}\text{H}_{36}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$ 471.3, found $[\text{M}+\text{H}]^+$ 471.3. HPLC (214 and 254 nm): R_t 8.93 min.

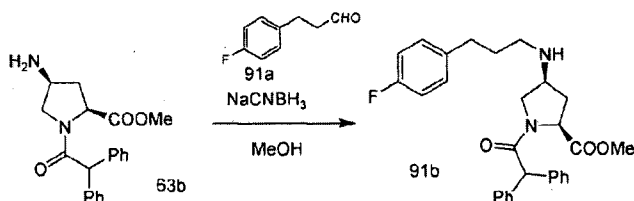
5 Example 31: Compound 91 (2S,4S)-1-(2,2-diphenylacetyl)-4-((3-(4-fluorophenyl)-propyl)(methyl)amino)pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of 91a



To a solution of the alcohol (1.0 g, 6.5 mmol) in DCM (20 mL) was added Celite (1.5 g) and PCC (3.5 g, 16.2 mmol) and the mixture was stirred at RT for 3 h. TLC (PE:EA=4:1) showed the starting material was consumed. The mixture was charged on to a silica column and flushed with DCM to give 91a (0.8 g, 79%) as a yellow oil, which was used directly in the next step.

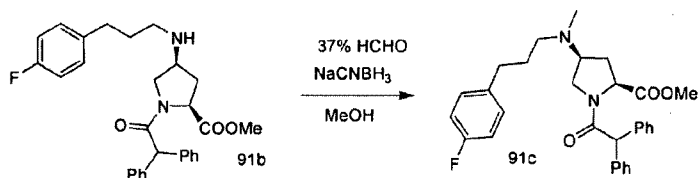
2. Procedure for the preparation of 91b



To a solution of 63b (113 mg, 0.33 mmol) and 91a (41 mg 0.27 mmol) in MeOH (10 mL) at 0°C under a N_2 atmosphere was added a drop of AcOH and the mixture was stirred for 30 min. NaCNBH_3 (21 mg, 0.33 mmol) was then added and the mixture was allowed to warm slowly to RT and stirred overnight, TLC (DCM:MeOH=10:1) showed most of starting material was consumed. The mixture was concentrated *in vacuo* to give crude 91b (150 mg) as a yellow oil. The reaction was repeated on a larger batch of 63b (509 mg, 1.5 mmol) and the crude products were combined and purified by column chromatography (DCM:MeOH=50:1 to 20:1) to give 91b (500 mg, 57%) as a white solid. LC-MS (Agilent): R_t 3.37 min; m/z calculated for $\text{C}_{29}\text{H}_{31}\text{FN}_2\text{O}_3$ $[\text{M}+\text{H}]^+$ 475.2, found $[\text{M}+\text{H}]^+$ 475.3.

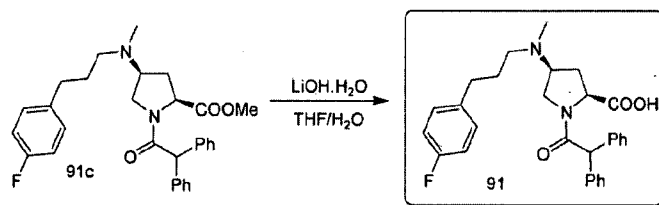
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3. Procedure for the preparation of 91c



To a solution of 91b (210 mg, 0.44 mmol) and formaldehyde (37% aqueous solution, 72 mg, 0.88 mmol) in MeOH (10 mL) at 0°C under a N₂ atmosphere was added 2 drops of AcOH and the mixture was stirred for 30 min. NaCNBH₃ (56 mg, 0.88 mmol) was then added and the mixture was allowed to warm slowly to RT and stirred overnight, TLC (DCM:MeOH=10:1) showed the starting material was consumed. The mixture was concentrated *in vacuo* and the residue was dissolved in EA (15 mL), washed with water (10 mL), saturated aqueous NaHCO₃ solution (15 mL), brine (15 mL) and dried over Na₂SO₄. The solvent was removed *in vacuo* and the residue was purified by column chromatography (DCM:MeOH=100:1 to 50:1) to give 91c (170 mg, 79%) as a colorless oil. LC-MS (Agilent): R_t 3.76 min; m/z calculated for C₃₀H₃₃FN₂O₃ [M+H]⁺ 489.3, found [M+H]⁺ 489.3.

4. Procedure for the preparation of Compound 91



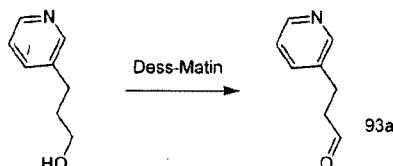
15

Hydrolysis of 91c (170 mg, 0.35 mmol) was performed using the procedure of Example 9, 3. with about 3 equivalents of LiOH.H₂O (44 mg, 1.04 mmol) at RT and the mixture was stirred overnight, TLC (MeOH:DCM=1:10) showed the starting material was consumed. Most of the THF was removed *in vacuo* and the residue was dissolved in water (15 mL) and washed with Et₂O (10 mL x 2). The aqueous layer was acidified to pH 2-3 with a 3 M aqueous HCl solution and the resulting precipitate was collected by filtration and dried to give 91 (90 mg, 54%) as a white solid. LC-MS (Agilent): R_t 3.52 min; m/z calculated for C₂₉H₃₁FN₂O₃ [M+H]⁺ 475.2, found [M+H]⁺ 475.3. HPLC (214 and 254 nm): R_t 8.86 min.

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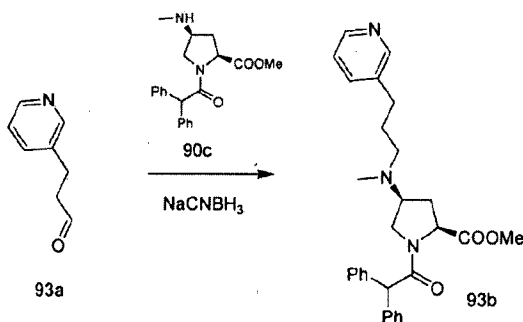
Example 32: Compound 93 (2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-(methyl(3-pyridinyl)propyl)amino)pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of 93a



- 5 To a solution of 3-(pyridin-3-yl)propan-1-ol (500 mg, 3.6 mmol) in DCM (10 mL) was added Dess-Martin reagent (1.7 g, 4.0 mmol) and the mixture was stirred at RT overnight, TLC (DCM:MeOH=10:1) showed that the starting material was consumed. Water (20 mL) was added and the solid was removed by filtration. The filtrate layers were separated and the aqueous layer was extracted with DCM (15 mL). The combined organics layers were
- 10 washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by chromatography (DCM:MeOH=150:0 to 50:1) to give 93a (200 mg, 40%) as a white solid. LC-MS (Agilent): R_t 0.58 min; m/z calculated for C₈H₉NO [M+H]⁺ 136.1, found [M+H]⁺ 136.1.

2. Procedure for the preparation of 93b.

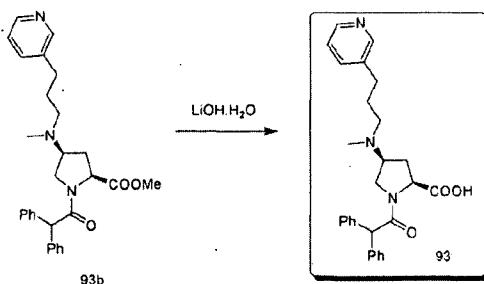


- 15 To a solution of 93a (57 mg, 0.42 mmol) and 90c (100 mg, 0.28 mmol) in MeOH (10 mL) was added 2 drops of AcOH and the mixture was stirred at RT for 1 h. NaCNBH₃ (27 mg, 0.42 mmol) was added and stirring was continued at RT overnight, TLC (DCM:MeOH=10:1) showed that the starting material was consumed. The mixture was
- 20 concentrated *in vacuo* and the residue suspended in water (20 mL) and extracted with EA (15 mL x 2). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by chromatography (DCM:MeOH=100:1 to 50:1) to give 93b (100 mg, 75%) as a yellow oil. LC-MS

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(Agilent): R_t 3.52 min; m/z calculated for $C_{29}H_{33}N_3O_3$ $[M+H]^+$ 472.3, found $[M+H]^+$ 472.3.

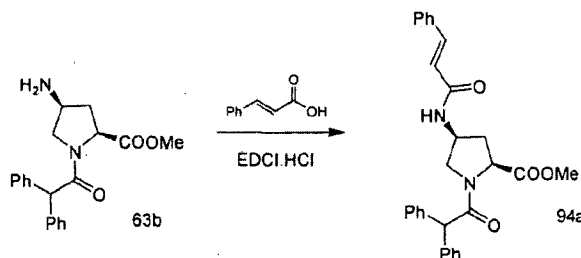
3. Procedure for the preparation of Compound 93



- 5 A mixture of 93b (100 mg, 0.21 mmol) and $\text{LiOH}\cdot\text{H}_2\text{O}$ (18 mg, 0.42 mmol) in THF/water (6 mL/2 mL) was stirred at RT overnight, TLC (DCM:MeOH=10:1) showed that the starting material was consumed. Most of the THF was removed *in vacuo* and the residue was dissolved in water (15 mL) and washed with ether (10 mL). The aqueous layer was acidified to pH 5 with a 3 M aqueous HCl solution and freeze dried to give a white solid,
- 10 which was suspended in DCM/MeOH and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by preparative HPLC to give 93 (70 mg, 74%) as a white solid. LC-MS (Agilent): R_t 3.59 min; m/z calculated for $C_{28}H_{31}N_3O_3$ $[M+H]^+$ 458.2, found $[M+H]^+$ 458.2. HPLC (JULY-L) (214 and 254 nm): R_t 8.33 min.

15 Example 33: Compound 94 (2S,4S)-4-cinnamamido-1-(2,2-diphenylacetyl)-pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of 94a

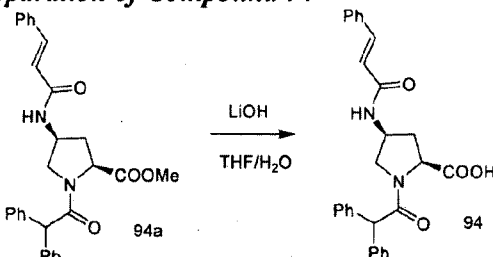


- To a solution of 63b (1.05 g, 3.1 mmol) and cinnamic acid (0.46 g, 3.10 mmol) in DCM (40 mL) at RT under nitrogen was added $\text{EDCI}\cdot\text{HCl}$ (0.65 g, 3.39 mmol) and the mixture was stirred overnight, TLC (DCM:MeOH=10:1) showed the reaction was complete. The mixture was washed with brine (20 mL x 2), dried over Na_2SO_4 , filtered and concentrated
- 20

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in vacuo. The residue was purified by column chromatography (PE:EA=1:0 to 1:1) to give 94a (1.28 g, 88%) as a white solid. LC-MS (Agilent): R_t 3.84 min; m/z calculated for $C_{29}H_{28}N_2O_4$ $[M+H]^+$ 469.2, $[M+Na]^+$ 491.2, found $[M+H]^+$ 469.2, $[M+Na]^+$ 491.2.

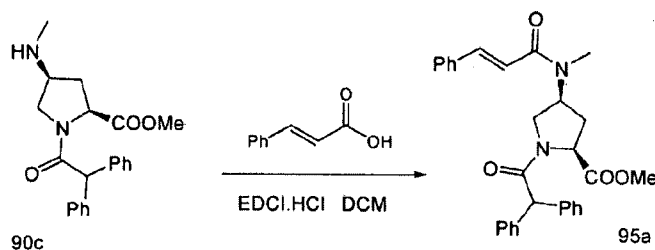
2. Procedure for the preparation of Compound 94



To a mixture of 94a (300 mg, 0.64 mmol) in THF/H₂O (15 mL/2 mL) was added LiOH.H₂O (81 mg, 1.92 mmol) and the mixture was stirred at RT overnight, TLC (DCM: MeOH=10:1) showed the starting material was consumed. Most of the THF was removed *in vacuo* and the residue was dissolved in water H₂O (20 mL), acidified to pH 2-3 with a 3 M aqueous HCl solution and extracted with DCM (25 mL x 2). The combined organic extracts were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* to give 94 (286 mg, 98%) as a white solid. LC-MS (Agilent): R_t 3.71 min; m/z calculated for $C_{28}H_{26}N_2O_4$ $[M+H]^+$ 455.2, found $[M+H]^+$ 455.2. HPLC (214 and 254 nm): R_t 9.08 min.

Example 34: Compound 95 (2S,4S)-1-(2,2-diphenylacetyl)-4-(N-methylcinnamamido)-pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of 95a

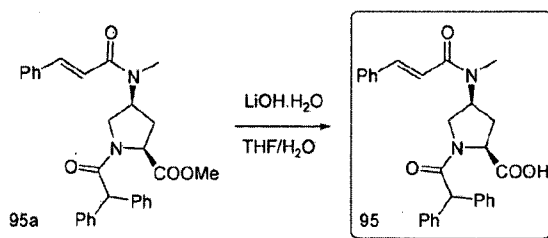


To a stirred solution of 90c (300 mg, 0.85 mmol) and cinnamic acid (126 mg, 0.85 mmol) in DCM (15 mL) at RT under nitrogen was added EDCI.HCl (180 mg, 0.94 mmol) and the mixture was stirred overnight, TLC (DCM:MeOH=10:1) showed that the starting material was consumed. The mixture was washed with a saturated aqueous NaHCO₃ solution (15

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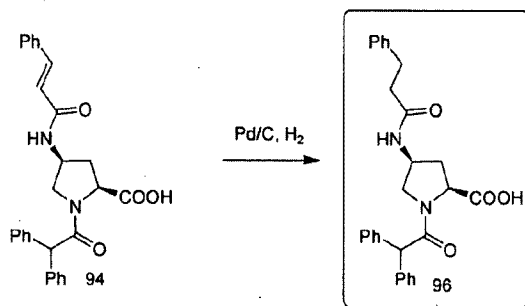
mL x 2), a 0.5 M aqueous HCl solution (15 mL x 2), brine (15 mL x 2), dried over Na₂SO₄ and filtered. The solvent was removed *in vacuo* and the residue was purified by column chromatography (PE:EA=2:1) to give 95a (300 mg, 73%) as a white solid. LC-MS (Agilent): R_t 3.93 min; m/z calculated for C₃₀H₃₀N₂O₄ [M+H]⁺ 483.2, [M+Na]⁺ 505.2, found [M+H]⁺ 483.2, [M+Na]⁺ 505.2.

2. Procedure for the preparation of 95



To a stirred solution of 95a (300 mg, 0.62 mmol) in THF/water (15 mL/2 mL) was added LiOH.H₂O (78 mg, 1.87 mmol) and the mixture was stirred at RT overnight, TLC (DCM: MeOH=10:1) showed the starting material was consumed. Most of the THF was removed *in vacuo* and the residue was dissolved in water (20 mL). The solution was acidified to pH=3~4 with a 3 M aqueous HCl solution and extracted with EA (15 mL x 2). The combined organic extracts were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo* to give 95 (270 mg, 93%) as a white solid. LC-MS (Agilent): R_t 3.88 min; m/z calculated for C₂₉H₂₈N₂O₄ [M+H]⁺ 469.2, [M+Na]⁺ 491.2, found [M+H]⁺ 469.2, [M+Na]⁺ 491.2. HPLC (214 and 254 nm): R_t 9.12 min.

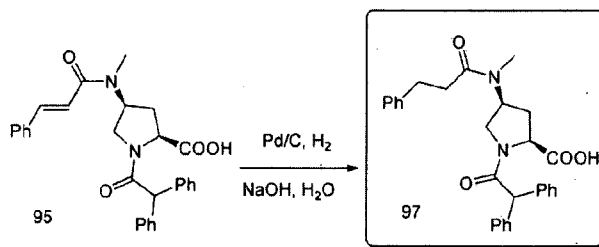
Example 35: Compound 96 (2S,4S)-1-(2,2-diphenylacetyl)-4-(3-phenylpropanamido)-pyrrolidine-2-carboxylic acid



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To a solution of 94 (170 mg, 0.37 mmol) in EA (30 mL) was added 10% Pd/C (20 mg) and the mixture was stirred at RT under a H₂ atmosphere (1 atm pressure) overnight, TLC (DCM:MeOH=10:1) showed the starting material was consumed. The mixture was filtered and the filtrate was concentrated *in vacuo* to give 96 (150 mg, 88%) as a white solid. LC-MS (Agilent): R_t 3.80 min; m/z calculated for C₂₈H₂₈N₂O₄ [M+H]⁺ 457.2, [M+Na]⁺ 479.2, found [M+H]⁺ 457.2, [M+Na]⁺ 479.2. HPLC (214 and 254 nm): R_t 9.06 min.

Example 36: Compound 97 (2S,4S)-1-(2,2-diphenylacetyl)-4-(N-methyl-3-phenylpropanamido)pyrrolidine-2-carboxylic acid



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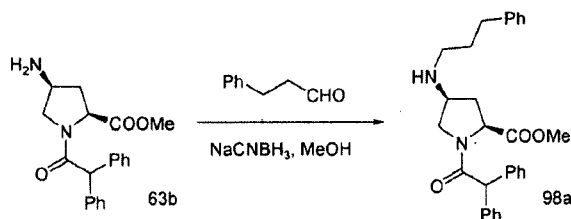
To a mixture of 95 (80 mg, 0.17 mmol) and 10% Pd/C (20 mg) in H₂O (20 mL) was added NaOH (10 mg, 0.26 mmol) and the mixture was stirred at RT under a H₂ atmosphere (1 atm pressure) overnight, LCMS analysis showed the starting material was consumed. The mixture was filtered and the filtrate was acidified to pH=3~4 with a 3 M aqueous HCl solution and extracted with EA (10 mL x 3). The combined organic extracts were washed with brine (20 mL x 2), dried over Na₂SO₄ and concentrated *in vacuo*. The residue was re-crystallized from Et₂O to give 97 (15 mg, 19%) as a white solid. LC-MS (Agilent): R_t 3.86 min; m/z calculated for C₂₉H₃₀N₂O₄ [M+H]⁺ 471.2, [M+Na]⁺ 493.2, found [M+H]⁺ 471.2, [M+Na]⁺ 493.2. HPLC (214 and 254 nm): R_t 9.12 min.

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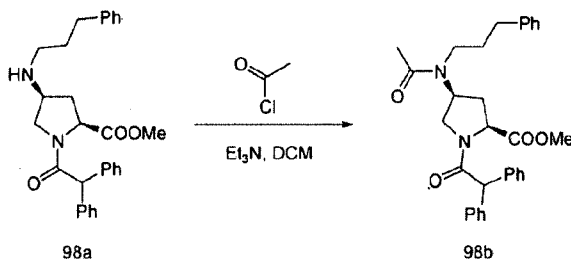
Example 37: Compound 98 (2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-(*N*-3-phenylpropyl)-acetamido)pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of 98a



- 5 To a solution of 63b (500 mg, 1.5 mmol) and 3-phenylpropanal (161 mg, 1.2 mmol) in MeOH (10 mL) at RT was added AcOH (2 drops) and the mixture was stirred for 1 h. The mixture was cooled to 0°C, NaCNBH₃ (113 mg, 1.8 mmol) was added and stirring was continued at RT overnight, TLC (DCM:MeOH=20:1) showed that the starting material was consumed. Most of the MeOH was removed *in vacuo* and the residue was partitioned
- 10 between water (20 mL) and EA (15 mL). The layers were separated and the aqueous phase was further extracted with EA (20 mL). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (DCM:MeOH=100:1 to 50:1) to give 98a (320 mg, 58%) as a yellow oil. LC-MS (Agilent): R_t 3.46 min; m/z calculated for C₂₉H₃₄N₂O₃ [M+H]⁺ 457.3,
- 15 found [M+H]⁺ 457.3.

2. Procedure for the preparation of 98b

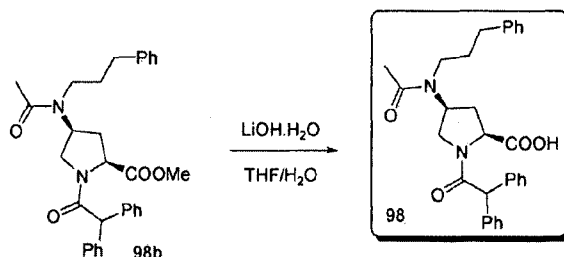


- To a solution of 98a (150 mg, 0.33 mmol) in DCM (5 mL) at 0°C was added Et₃N (40 mg, 0.4 mmol) followed by acetyl chloride (28 mg, 0.36 mmol). The mixture was then stirred
- 20 at RT for 15 min, TLC (DCM:MeOH=20:1) showed that the starting material was consumed. The mixture was washed with brine (10 mL x 2) and the organic layer was concentrated *in vacuo*. Purification by column chromatography (PE:EA=4:1 to 1:1) gave

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98b (130 mg, 79%) as a yellow oil. LC-MS (Agilent): R_t 3.89 min; m/z calculated for $C_{31}H_{34}N_2O_4$ $[M+Na]^+$ 521.25, found $[M+Na]^+$ 521.3.

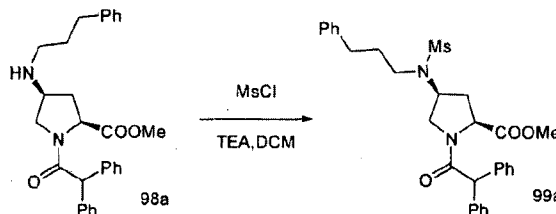
3. Procedure for the preparation of Compound 98



- 5 Hydrolysis of 98b (130 mg, 0.26 mmol) was performed as described in Example 5, 3. using 3 equivalents of LiOH.H₂O (32 mg, 0.78 mmol) to give 98 (100 mg, 80%) as a light yellow solid. LC-MS (Agilent): R_t 3.85 min; m/z calculated for $C_{30}H_{32}N_2O_4$ $[M+H]^+$ 485.25, found $[M+H]^+$ 485.3. HPLC (214 and 254 nm): R_t 9.19 min.

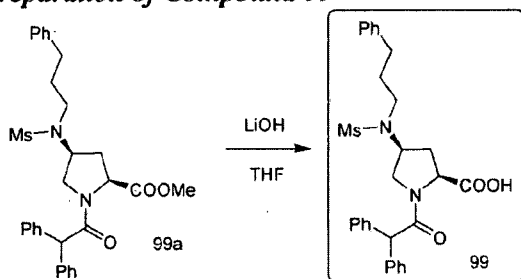
10 Example 38: Compound 99 (2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-(*N*-(3-phenylpropyl)-methylsulfonamido)pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of 99a



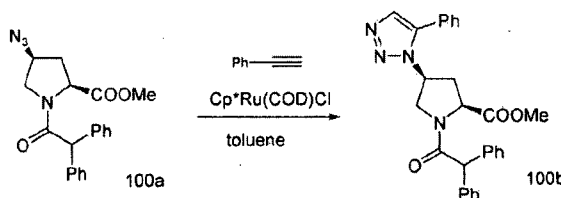
- To a cooled mixture of 98a (150 mg, 0.33 mmol) in DCM (5 mL) and TEA (40mg, 0.4mmol) at 0 °C, was added MsCl (41 mg, 0.36 mmol). The mixture was stirred at RT for 15 min. TLC (DCM:MeOH=20:1) showed that 99a had disappeared, and the mixture was washed with brine. The organic phase was dried over Na₂SO₄, and evaporated *in vacuo*. The resulting mixture was purified by silica column (PE:EA=4:1 to 2:1) to give 99a (140 mg, 79%) as white solid. LC-MS (Agilent): R_t 3.86 min; m/z calculated for $C_{30}H_{34}N_2O_5S$ $[M+H]^+$ 535.24, found $[M+H]^+$ 535.3.

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2. Procedure for the preparation of Compound 99

Hydrolysis of 99a (140 mg, 0.26 mmol) was performed as described in Example 25, 3, with about 3 equivalents of LiOH.H₂O (33 mg, 0.79 mmol). The precipitate was collected by filter, washed with water (5 mL x 2), dried at 50°C overnight to give 99 (120 mg, 88%) as a white solid. LC-MS (Agilent): R_t 3.87 min; m/z calculated for C₂₉H₃₂N₂O₅S [M+H]⁺ 521.2, [M+Na]⁺ 543.2, found [M+H]⁺ 521.3, [M+Na]⁺ 543.2. HPLC (214 and 254 nm): R_t 9.15 min.

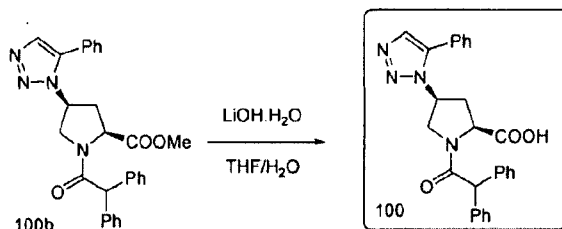
10 Example 39: Compound 100 (2S,4S)-1-(2,2-diphenylacetyl)-4-(5-phenyl-1H-1,2,3-triazol-1-yl)pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of 100b

A mixture of 100a (100 mg, 0.27 mmol), phenyl acetylene (42 mg, 0.41 mmol) and Cp*Ru(COD)Cl (10 mg, 0.027 mmol) in toluene (5 mL) was heated at 80°C under a N₂ atmosphere overnight, TLC (PE:EA=1:1) showed that the starting material was consumed. The mixture was cooled to RT, concentrated *in vacuo* and the residue was purified by column chromatography (PE:EA=1:0 to 1:1) to give 100b (130 mg, 100%) as a white solid. LC-MS (Agilent): R_t 3.80 min; m/z calculated for C₂₈H₂₆N₄O₃ [M+H]⁺ 467.2, [M+Na]⁺ 489.2, found [M+H]⁺ 467.2, [M+Na]⁺ 489.2.

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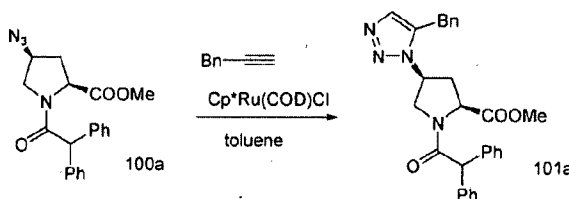
2. Procedure for the preparation of 100



To a mixture 100b (130 mg, 0.28 mmol) in THF/water (10 mL/1.5 mL) was added LiOH.H₂O (35 mg, 0.84 mmol) and the mixture was stirred at RT overnight, TLC (DCM: MeOH=10:1) showed that the starting material was consumed. Most of the THF was removed *in vacuo* and the residue was dissolved in water (15 mL). The aqueous mixture was acidified to pH=5-6 with a 3 M aqueous HCl solution and extracted with DCM (20 mL x 2). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to give 100 (120 mg, 95%) as a white solid. LC-MS (Agilent): R_t 3.87 min; m/z calculated for C₂₇H₂₄N₄O₃ [M+H]⁺ 453.2, [M+Na]⁺ 475.2, found [M+H]⁺ 453.2, [M+Na]⁺ 475.2. HPLC (214 and 254 nm): R_t 8.98 min.

Example 40: Compound 101 (2*S*,4*S*)-4-(5-benzyl-1*H*-1,2,3-triazol-1-yl)-1-(2,2-diphenylacetyl)pyrrolidine-2-carboxylic acid

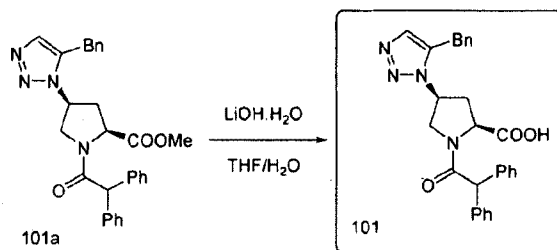
1. Procedure for the preparation of 101a



A mixture of 100a (100 mg, 0.27 mmol), 1-(prop-2-ynyl)benzene (48 mg, 0.41 mmol) and Cp*Ru(COD)Cl (10 mg, 0.027 mmol) in toluene (5 mL) was heated at 80°C under a N₂ atmosphere overnight, TLC (PE:EA=1:1) showed that the starting material was consumed. The reaction was cooled to RT and concentrated *in vacuo* to give 140 mg of crude product. The reaction was repeated and the two batches of crude product were combined and purified by column chromatography (PE:EA=1:0 to 1:1) to give 101a (230 mg, 88%) as a white solid. LC-MS (Agilent): R_t 3.89 min; m/z calculated for C₂₉H₂₈N₄O₃ [M+H]⁺ 481.2, [M+Na]⁺ 503.2, found [M+H]⁺ 481.2, [M+Na]⁺ 503.2.

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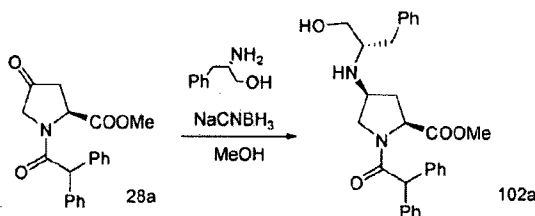
2. Procedure for the preparation of 101



Hydrolysis of 101a (230 mg, 0.48 mmol) was performed as described in Example 39, 2, using about 3 equivalents of LiOH.H₂O (64 mg, 1.53 mmol) to give 101 (190 mg, 97%) as a white solid. LC-MS (Agilent): R_t 3.82 min; m/z calculated for C₂₈H₂₆N₄O₃ [M+H]⁺ 467.2, [M+Na]⁺ 489.2, found [M+H]⁺ 467.2, [M+Na]⁺ 489.2. HPLC (214 and 254 nm): R_t 9.00 min.

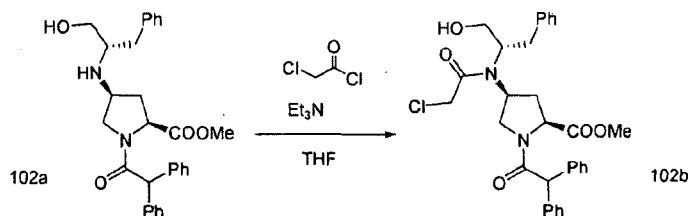
Example 41: Compound 102 (2*S*,4*S*)-4-((*S*)-3-benzyl-5-oxomorpholino)-1-(2,2-diphenylacetyl)pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of 102a.

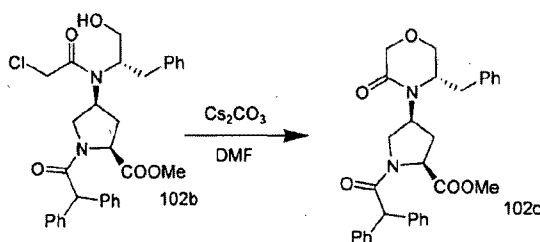


To a solution of 28a (980 mg, 2.90 mmol) and L-phenylglycinol (483 mg, 3.20 mmol) in MeOH (20 mL) at RT under N₂ was added AcOH (one drop) and the mixture was stirred for 1 h then cooled to 0°C. NaCNBH₃ (219 mg, 3.49 mmol) was added and the mixture was allowed to warm to RT and stirred overnight, TLC (DCM:MeOH=10:1) showed that the starting material was consumed. The mixture was concentrated *in vacuo* and the residue was dissolved in water (20 mL) and extracted with DCM (25 mL). The organic layer was washed with brine (15 mL x 2), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (DCM:EA=3:1 to 1:1) to give 102a (395 mg, 29%) as a white solid. LC-MS (Agilent): R_t 3.47 min; m/z calculated for C₂₉H₃₂N₂O₄ [M+H]⁺ 473.3, found [M+H]⁺ 473.3.

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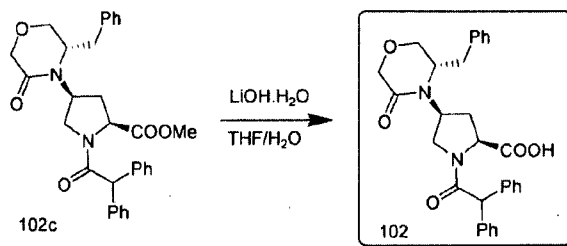
2. Procedure for the preparation of 102b.

To a stirred solution of 102a (385 mg, 0.83 mmol) and Et_3N (101 mg, 1.00 mmol) in THF (15 mL) at 0°C was added chloroacetyl chloride (95 mg, 0.83 mmol) and the mixture was
 5 allowed to warm to RT and stirred overnight, TLC (PE:EA=1:1) showed that the starting material was consumed. Most of the THF was removed *in vacuo* and the residue was diluted with water (15 mL) and extracted with EA (15 mL x 2). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by column chromatography (PE:EA=10:1 to 3:2) to give
 10 102b (190 mg, 43%) as a white solid. LC-MS (Agilent): R_t 3.83 min; m/z calculated for $\text{C}_{31}\text{H}_{33}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$ 549.2, $[\text{M}+\text{Na}]^+$ 571.2, found $[\text{M}+\text{H}]^+$ 549.2, $[\text{M}+\text{Na}]^+$ 571.2.

3. Procedure for the preparation of 102c

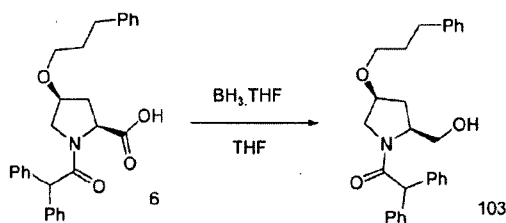
A stirred mixture of 102b (160 mg, 0.30 mmol) and Cs_2CO_3 (151 mg, 0.46 mmol) in
 15 DMF (15 mL) was heated to 90°C under a N_2 atmosphere for 4 h, TLC (PE:EA=1:2) showed that the starting material was consumed. The mixture was cooled to RT, poured into ice-water (100 mL) and extracted with EA (20 mL x 2). The combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give 102c (100 mg, 67%) as a yellow solid. LC-MS (Agilent): R_t
 20 3.94 min; m/z calculated for $\text{C}_{31}\text{H}_{32}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$ 512.2, $[\text{M}+\text{Na}]^+$ 535.2, found $[\text{M}+\text{H}]^+$ 512.2, $[\text{M}+\text{Na}]^+$ 535.2.

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4. Procedure for the preparation of 102

To a solution of 102c (100 mg, 0.20 mmol) in THF/water (10 mL/2 mL) was added LiOH·H₂O (25 mg, 0.59 mmol) and the mixture was stirred at RT overnight, TLC (DCM: MeOH=10:1) showed that the starting material was consumed. Most of the THF was removed *in vacuo* and the residue was dissolved in water (10 mL) and washed with Et₂O. The aqueous layer was acidified to pH 4–5 with a 3 M aqueous HCl solution and extracted with DCM (15 mL x 2). The combined organic extracts were washed with brine (15 mL x 2), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by preparative HPLC to give 102 (28 mg, 29%) as white solid. LC-MS (Agilent): R_t 4.03 min; m/z calculated for C₂₉H₂₈N₄O₃ [M+H]⁺ 499.2, found [M+H]⁺ 499.2. HPLC (214 and 254 nm): R_t 9.14 min.

Example 42: Compound 103 1-((2S,4S)-2-(hydroxymethyl)-4-(3-phenylpropoxy)-pyrrolidine-1-yl)-diphenylethanoate



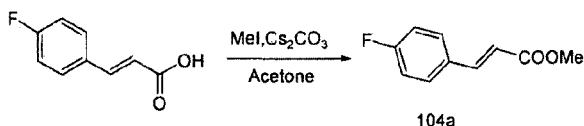
To a solution of Compound 6 (400 mg, 0.9 mmol) in THF (10 mL) at -10°C under N₂ was added BH₃.THF (1.0 M solution in THF, 1.0 mL, 1.0 mmol) dropwise and the mixture was stirred at -10°C for 1 h, TLC (DCM:MeOH=20:1) showed there was no reaction. The reaction mixture was allowed to warm to RT and stirred for 30 min, TLC showed most of the starting material remained. More BH₃.THF (1.0 M solution in THF, 0.9 mL, 0.9 mmol) was added and the mixture was stirred at RT overnight, TLC (DCM:MeOH=20:1) showed that most of the starting material was consumed. The mixture was cooled to 0°C, quenched with MeOH, diluted with water (20 mL) and extracted with EA (20 mL x 2). The

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combined organic extracts were washed with a saturated aqueous NaHCO_3 solution, a 1 M aqueous HCl solution, brine and dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by column chromatography (PE:EA=10:1 to 5:1) followed by preparative HPLC to give 103 (30 mg, 7%) as a white solid. LC-MS (Agilent): R_t 4.02 min; m/z calculated for $\text{C}_{28}\text{H}_{31}\text{NO}_3$ $[\text{M}+\text{H}]^+$ 430.3, $[\text{2M}+\text{Na}]^+$ 881.5, found $[\text{M}+\text{H}]^+$ 430.3, $[\text{2M}+\text{Na}]^+$ 881.5. HPLC (214 and 254 nm): R_t 9.42 min.

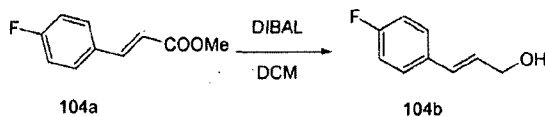
Example 43: Compound 104 (2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-(3-(4-fluorophenyl)propoxy)pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of 104a



To a solution of 4-fluorocinnamic acid (2.0 g, 12 mmol) in acetone (30 mL) was added Cs_2CO_3 (4.7 g, 14.4 mmol) and iodomethane (2.5 g, 18 mmol) and the mixture was stirred at RT for 3 h, TLC (PE:EA=2:1) showed that the starting material was consumed. The mixture was concentrated *in vacuo* and the residue was partitioned between water (30 mL) and DCM (20 mL). The organic layer was separated, washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give 104a (1.9 g, 90%) as a yellow solid. LC-MS (Agilent): R_t 3.85 min; m/z calculated for $\text{C}_{10}\text{H}_9\text{FO}_2$ $[\text{M}+\text{H}]^+$ 180.1, found $[\text{M}+\text{H}]^+$ 180.1.

2. Procedure for the preparation of 104b

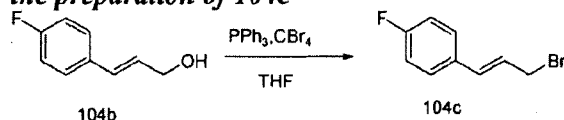


To a solution of 104a (1.9 g, 10.0 mmol) in DCM (20 mL) at -65°C under N_2 was added DIBAL-H (1.2 M solution in toluene, 10.0 mL, 12.0 mmol) dropwise and the mixture was stirred at -65°C for 1 h, TLC (PE:EA=2:1) showed incomplete reaction. More DIBAL-H (1.2 M solution in toluene, 8.3 mL, 10.0 mmol) was added and stirring was continued for 30 min, TLC (PE:EA=2:1) showed that some starting material remained. More DIBAL-H (1.2 M solution in toluene, 2.5 mL, 3.0 mmol) was added and stirring was continued for 30 min, TLC (PE:EA=2:1) showed that the starting material was consumed. The mixture was allowed to warm to -10°C and quenched with a 2.5 M aqueous NaOH solution (2.5 eq)

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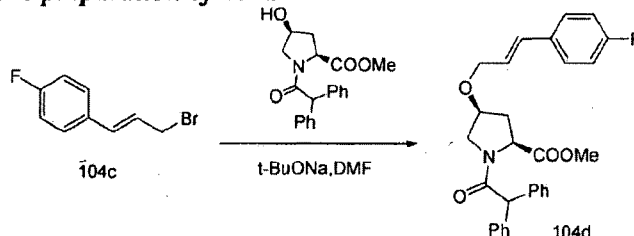
then water (50 mL). DCM (30 mL) was added and the resulting precipitate was removed by filtration. The filtrate was collected and the phases were separated. The aqueous layer was extracted with DCM (30 mL) and the combined organic extracts were washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give 104b (1.4 g, 93%) as an off-white solid.

3. Procedure for the preparation of 104c



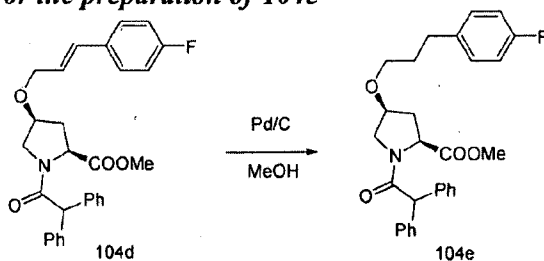
To a stirred suspension of 104b (0.7 g, 4.6 mmol) in THF (10 mL) was added PPh_3 (1.4 g, 5.5 mmol) and CBr_4 (2.3 g, 6.9 mmol) and the mixture was stirred at RT for 1 h, TLC (PE:EA=10:1) showed that the starting material was consumed. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography (100% PE) to give 104c (0.9 g, 90%) as a yellow oil.

4. Procedure for the preparation of 104d

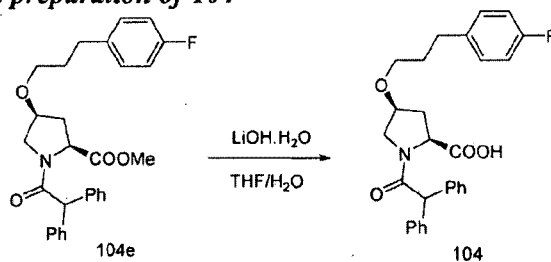


To a stirred solution of 104c (353 mg, 1.6 mmol) and 2e (380 mg, 1.1 mmol) in DMF (10 mL) at -45°C was added t-BuONa (108 mg, 1.1 mmol) in portions and the mixture was stirred at -40°C for 1.5 h, TLC (PE:EA=1:1) showed that the starting material was consumed. The reaction was quenched with AcOH and then allowed to warm to -10°C . Water (50 mL) was added and the mixture was extracted with EA (20 mL). The organic layer was washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=10:1 to 5:1) to give 104d (110 mg, 21%) as a yellow oil. LC-MS (Agilent): R_t 4.05 min; m/z calculated for $\text{C}_{13}\text{H}_{17}\text{NO}_3$ $[\text{M}+\text{H}]^+$ 474.2, found $[\text{M}+\text{H}]^+$ 474.2.

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5. Procedure for the preparation of 104e

To a stirred solution of 104d (110 mg, 0.23 mmol) in MeOH (10 mL) was added 10% Pd/C (11 mg) and the mixture was stirred at RT under a H₂ atmosphere (1 atm) overnight, TLC (PE:EA=2:1) showed that the starting material was consumed. The mixture was filtered and the filtrate was concentrated *in vacuo* to give 104e (100 mg, 90%) as a colorless oil. LC-MS (Agilent): R_t 4.08 min; m/z calculated for C₂₉H₂₈FNO₄ [M+H]⁺ 476.2, found [M+H]⁺ 476.2.

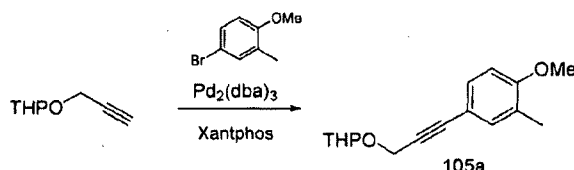
6. Procedure for the preparation of 104

To a mixture of 104e (100 mg, 0.2 mmol) in THF/water (8 mL/3 mL) was added LiOH.H₂O (26 mg, 0.6 mmol) and the mixture was stirred at RT overnight, TLC (PE:EA=2:1) showed that the starting material was consumed. Most of the THF was removed *in vacuo* and the residue was dissolved in water (15 mL) and washed with Et₂O (15 mL). DCM (15 mL) was added and the aqueous layer was acidified to pH 2-3 with a 1 M aqueous HCl solution. The layers were separated and the aqueous layer was further extracted with DCM (15 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to give 104 (60 mg, 65%) as a white solid. LC-MS (Agilent): R_t 3.96 min; m/z calculated for C₂₈H₂₈FNO₄ [M+H]⁺ 461.2, found [M+H]⁺ 462.2. HPLC (214 and 254 nm): R_t 9.34 min.

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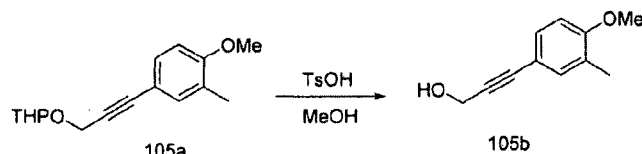
Example 44: Compound 105 (2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-((3-(4-methoxy-3-methylphenyl)prop-2-yn-1-yl)(methyl)amino)pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of 105a



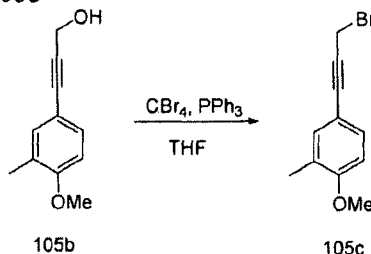
- 5 A mixture of 2-(prop-2-ynyloxy)-tetrahydro-2H-pyran (1.4 g, 10.0 mmol), Cs₂CO₃ (4.8 g, 15.0 mmol), 4-bromo-1-methoxy-2-methylbenzene (2.0 g, 10.0 mmol), Pd₂(dba)₃ (180 mg, 0.2 mmol) and Xantphos (100 mg, 0.17 mmol) in MeCN (30 mL) was stirred at 80°C under a N₂ atmosphere overnight. TLC (PE:EA=10:1) showed that the starting material was consumed. The mixture was cooled to RT, water (50 mL) was added and extracted with EA (30 mL x 2). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (PE:EA=1:0 to 50:1) to give 105a (450 mg, 17 %) as a yellow oil. LC-MS (Agilent): R_t 4.49 min; m/z calculated for C₁₆H₂₀O₃ [M+H]⁺ 261.1, [M+Na]⁺ 283.1, found [M+H]⁺ 261.2, [M+Na]⁺ 283.1.

2. Procedure for the preparation of 105b

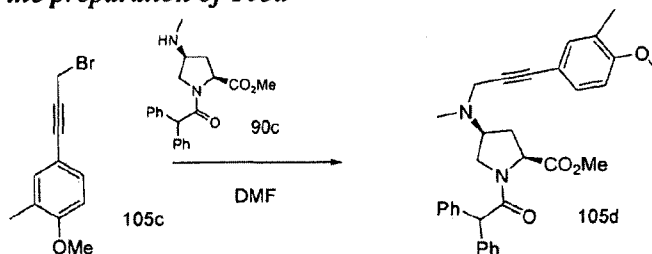


- To a stirred solution of 105a (450 mg, 1.7 mmol) in MeOH (10 mL) was added TsOH.H₂O (5 mg, 0.03 mmol) and the mixture was stirred at RT overnight, TLC (PE:EA=2:1) showed some of the starting material remained. More TsOH.H₂O (5 mg, 0.03 mmol) was added and stirring was continued at RT for 24 h, TLC showed that the starting material was consumed. Most of the MeOH was removed *in vacuo* and the residue was partitioned between water (30 mL) and EA (20 mL). The layers were separated and the aqueous layer was further extracted EA (20 mL). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to give 105b (330 mg, >100%) as a yellow oil, which was used directly in the next step. LC-MS (Agilent): R_t 3.56 min; m/z calculated for C₁₁H₁₂O₃ [M+H]⁺ 177.1, [M+Na]⁺ 199.1, found [M+H]⁺ 177.1, [M+Na]⁺ 199.1.

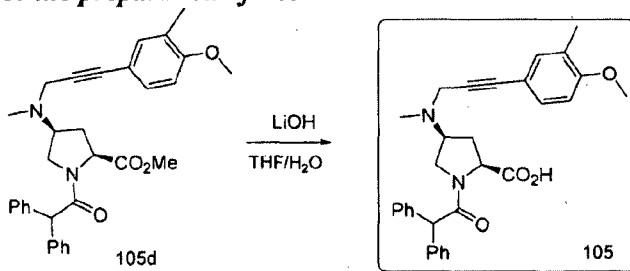
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3. Procedure for the preparation of 105c

- To a stirred suspension of 105b (320 mg, 1.8 mmol) in THF (10 mL) was added PPh₃ (518 mg, 1.9 mmol) and CBr₄ (782 mg, 2.4 mmol) and the mixture was stirred at RT for 4 h, TLC (PE:EA=4:1) showed that the starting material was consumed. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography (100% PE) to give 105c (400 mg, 93%) as a yellow oil.

4. Procedure for the preparation of 105d

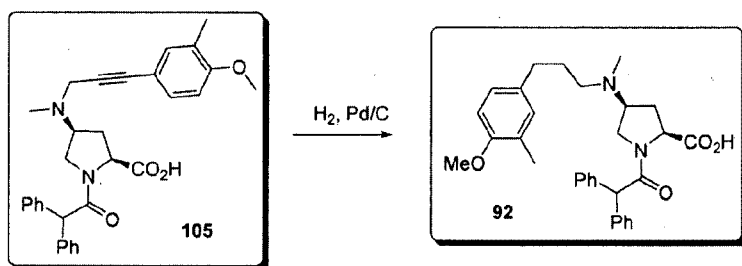
- To a solution of 105c (350 mg, 1.0 mmol) and 90c (353 mg, 1.48 mmol) in DMF (10 mL) was added Cs₂CO₃ (480 mg, 1.48 mmol) and the mixture was heated at 60°C for 4 h, TLC (DCM:MeOH=20:1) showed that most of 90c was consumed. The mixture was cooled to RT, poured into ice-water (100 mL) and extracted with EA (30 mL x 2). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (PE:EA=5:1 to 2:1) to give 105d (250 mg, 49%) as a yellow oil. LC-MS (Agilent): R_t 4.07 min; m/z calculated for C₃₂H₃₄N₂O₄ [M+H]⁺ 511.3, found [M+H]⁺ 511.3.

5. Procedure for the preparation of 105

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Hydrolysis of 105d (250 mg, 0.49 mmol) was performed as described in Example 9, 3. with 3 equivalents of LiOH.H₂O (62 mg, 1.47 mmol). After acidification, the layers were separated and the aqueous layer was further extracted with DCM (20 mL). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to give 105 (200 mg, 82%) as a yellow solid. LC-MS (Agilent): *R*_t 3.89 min; *m/z* calculated for C₃₁H₃₂N₂O₄ [M+H]⁺ 497.2, found [M+H]⁺ 497.3. HPLC (214 and 254 nm): *R*_t 9.09 min.

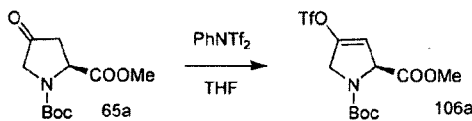
Example 45: Compound 92 (2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-((3-(4-methoxy-3-methylphenyl)propyl)(methyl)amino)pyrrolidine-2-carboxylic acid



A mixture of Compound 105 (140 mg, 0.28 mmol) and 10% Pd/C (14 mg) in EA (10 mL) was stirred at 30°C under a H₂ atmosphere (1 atm) overnight, LCMS analysis showed that the starting material was consumed. The mixture was filtered through Celite and the filtrate was concentrated *in vacuo*. The residue was purified by preparative HPLC to give 92 (30 mg, 21%) as a white solid. LC-MS (Agilent): *R*_t 3.84 min; *m/z* calculated for C₃₁H₃₆N₂O₄ [M+H]⁺ 501.3, found [M+H]⁺ 501.3. HPLC (214 and 254 nm): *R*_t 8.99 min.

Example 46: Compound 106 (2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-(4-phenylbutyl)-pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of 106a

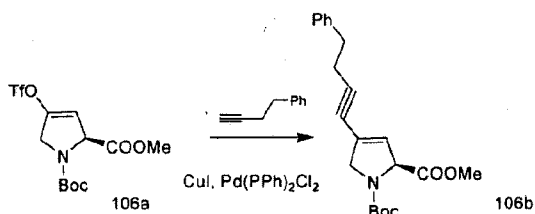


To a solution of 65a (500 mg, 2.05 mmol) in THF (5 mL) at -65°C was added LiHMDS (1 M solution in THF, 2.26 mL, 2.26 mmol) and the mixture was stirred at -65°C for 0.5 h. A solution of PhNTf₂ (807 mg, 2.26 mmol) in THF (1 mL) was then added slowly and stirring was continued at -65°C for 3 h before allowing to warm to -30°C and stirred for a

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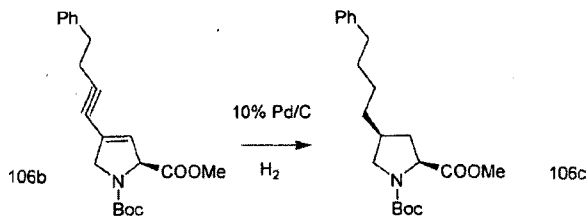
further 2 h. The mixture was then allowed to warm to RT and stirred overnight, TLC (PE:EA=1:1) showed that most of the starting material was consumed. The reaction was quenched with a saturated aqueous NaHCO_3 solution and then partitioned between EA and brine. The organic layer was separated, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=1:0 to 4:1) to give 106a (400 mg, 52%) as a thick colorless oil.

2. Procedure for the preparation of 106b



To a solution of 106a (250 mg, 0.66 mmol) in THF (5 mL) at RT under N_2 was added 1-(but-3-ynyl)benzene (104 mg, 0.80 mmol), DIPEA (425 mg, 3.30 mmol), CuI (13 mg, 0.068 mmol) and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (21 mg, 0.033 mmol) and the mixture was stirred at RT for 3 h, TLC (PE:EA=10:1) showed that the starting material was consumed. The mixture was partitioned between brine (20 mL) and EA (20 mL) and the organic layer was separated, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=1:0 to 20:1) to give 106b (120 mg, 51%) as a yellow oil and an impure fraction of 106b (40 mg). LC-MS (Agilent): R_t 4.42 min; m/z calculated for $\text{C}_{21}\text{H}_{25}\text{NO}_4$ $[\text{M}+\text{Na}]^+$ 378.2, $[\text{M}-t\text{-Bu}]^+$ 300.1, found $[\text{M}+\text{Na}]^+$ 378.2, $[\text{M}-t\text{-Bu}]^+$ 300.1.

3. Procedure for the preparation of 106c

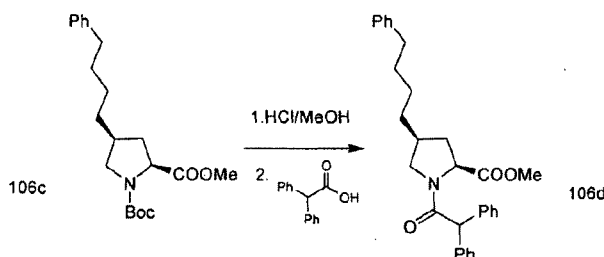


To a solution of 106b (170 mg, 0.48 mmol) in MeOH (5 mL) was added 10% Pd/C (20 mg) and the mixture was stirred under a H_2 atmosphere (1 atm) at RT overnight, TLC (PE:EA=10:1) showed that the starting material was consumed. The mixture was filtered and the filtrate was concentrated *in vacuo* to give 106c (160 mg, 94%) as colorless oil. LC-MS

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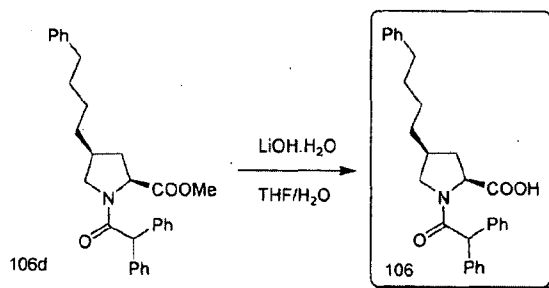
(Agilent): R_t 4.48 min; m/z calculated for $C_{21}H_{31}NO_4$ $[M+Na]^+$ 384.2, $[M-t-Bu]^+$ 306.2, $[M-boc]^+$ 262.2, found $[M+Na]^+$ 384.2, $[M-t-Bu]^+$ 306.2, $[M-boc]^+$ 262.2.

4. Procedure for the preparation of 106d



- 5 A solution of 106c (160 mg, 0.44 mmol) in a 4 M HCl/MeOH solution (5 mL) was stirred at RT for 3 h, TLC (PE:EA=4:1) showed that the starting material was consumed. The mixture was concentrated *in vacuo*, the residue was dissolved in water (15 mL), basified to pH 7-8 with K_2CO_3 and extracted with DCM (15 mL x 3). The combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give the product (90 mg) as a yellow oil. NMR analysis revealed the cis/trans ratio to be ~6.1:1. To a solution of the deprotected amine (90 mg) in DCM (10 mL) was added diphenyl acetic acid (90 mg, 0.44 mmol) and EDCl.HCl (95 mg, 0.49 mmol) and the mixture was stirred at RT overnight, TLC (DCM:MeOH=10:1) showed that the starting material was consumed. The mixture was washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=1:0 to 4:1) to give 106d (120 mg, 59%) as a colorless oil. LC-MS (Agilent): R_t 4.54 min; m/z calculated for $C_{30}H_{33}NO_3$ $[M+H]^+$ 455.2, found $[M+H]^+$ 455.2.

5. Procedure for the preparation of Compound 106



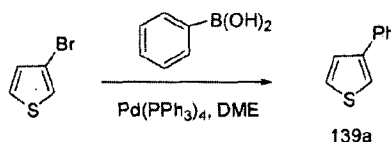
- 20 Hydrolysis of 106d (120 mg, 0.26 mmol) was performed as described in Example 53, 2, with about 3 equivalents of $LiOH.H_2O$ (33 mg, 0.79 mmol). The combined organic extracts were washed with brine (10 mL x 2), dried over Na_2SO_4 , filtered and concentrated

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in vacuo to give 106 (110 mg, 94%) as a colorless gum. LC-MS (Agilent): R_t 4.55 min; m/z calculated for $C_{29}H_{31}NO_3$ $[M+H]^+$ 442.2, found $[M+H]^+$ 442.2. HPLC (214 and 254 nm): R_t 9.62 min.

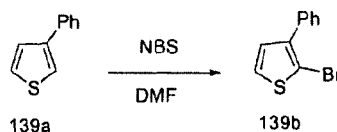
5 Example 47: Compound 139 (*S*)-1-(2,2-diphenylacetyl)-4-(3-phenylthiophen-2-yl)-2,5-dihydro-1H-pyrrole-2-carboxylic acid

1. Procedure for the preparation of 139a



To a solution of 3-bromo thiophene (15.0 g, 92 mmol) and phenyl boronic acid (16.8 g, 138 mmol) in DME (150 mL) was added $Pd(PPh_3)_4$ (1.0 g, 0.87 mmol) and the mixture was heated at reflux overnight under a N_2 atmosphere, TLC (PE) showed most of the starting material was consumed. The mixture was cooled to RT, washed with brine (100 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by column chromatography (PE) to give 139a (4.0 g, 27%) as light yellow solid, which was used directly in the next step.

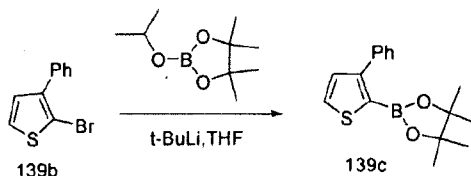
2. Procedure for the preparation of 139b



To a stirred solution of 139a (2.0 g, 12.5 mmol) in DMF (40 mL) at $0^\circ C$ under N_2 was added a solution of NBS (2.43 g, 13.7 mmol) in DMF (20 mL) dropwise and the mixture was stirred at RT overnight, TLC analysis (hexane) showed that the starting material was consumed. The mixture was poured into water (300 mL), extracted with EA (50 mL x 2) and the combined organic extracts were washed with water (40 mL), brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give 139b (3.0 g, 100%) as a yellow oil.

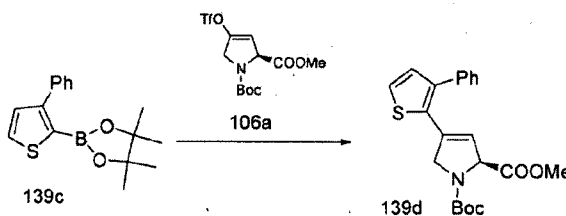
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3. Procedure for the preparation of 139c



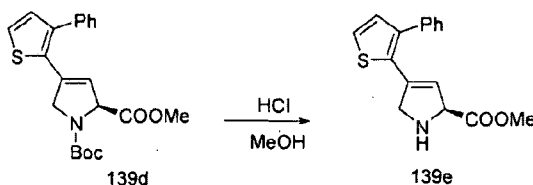
To a stirred solution of 139b (1.0 g, 4.2 mmol) in THF (20 mL) at -70°C , under N_2 was added $t\text{-BuLi}$ (1.3 M solution in hexane, 3.5 mL, 4.6 mmol) dropwise and the mixture was stirred at -70°C for 2 h. 2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (950 mg, 5.1 mmol) was added dropwise and stirring was continued at -70°C for a further 3 h. The mixture was allowed to warm to RT and stirred for a further 1 h, TLC (PE) showed that the starting material was consumed. The mixture was cooled to 0°C , water was added (30 mL) and extracted with EA (20 mL x 2). The combined organic extracts were washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by column chromatography (PE:EA=1:0 to 50:1) to give 139c (700 mg, 58%) as yellow solid. LC-MS (Agilent): R_t 4.64 min; m/z calculated for $\text{C}_{16}\text{H}_{19}\text{BO}_2\text{S}$ $[\text{M}+\text{H}]^+$ 287.1, $[\text{M}+\text{Na}]^+$ 309.1, found $[\text{M}+\text{H}]^+$ 287.1, $[\text{M}+\text{Na}]^+$ 309.1.

4. Procedure for the preparation of 139d

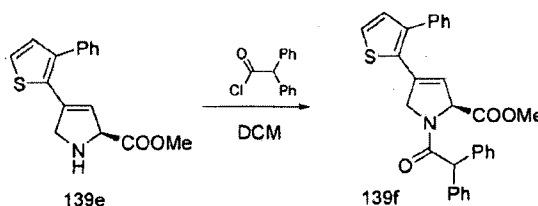


To a mixture of 139c (515 mg, 1.8 mmol) and 106a (675 mg, 1.8 mmol) in toluene (10 mL) was added a 2 M aqueous Na_2CO_3 solution (2.7 mL, 5.4 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (104 mg, 0.09 mmol, 5 mol%) and the mixture was heated at 105°C overnight under a N_2 atmosphere, TLC (PE:EA=10:1) showed that most of the starting materials were consumed. The mixture was cooled to RT, diluted with water (20 mL) and extracted with EA (15 mL x 2). The combined organic extracts were washed with brine, concentrated *in vacuo* and the residue was purified by column chromatography (PE to PE:EA=40:1) to give 139d (600 mg, 86%) as yellow oil. LC-MS (Agilent): R_t 4.60 min; m/z calculated for $\text{C}_{21}\text{H}_{23}\text{NO}_4\text{S}$ $[\text{M}-100]^+$ 286.1, $[\text{M}+\text{Na}]^+$ 408.1, $[\text{M}-56]^+$ 330.1, found $[\text{M}-100]^+$ 286.1, $[\text{M}+\text{Na}]^+$ 408.1, $[\text{M}-56]^+$ 330.1.

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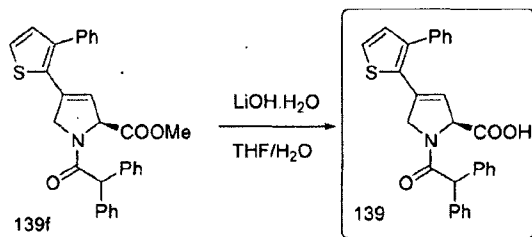
5. Procedure for the preparation of 139e

139d (600 mg, 1.56 mmol) was dissolved in a 4 M HCl/MeOH solution (15 mL) and the mixture was stirred at RT overnight, TLC (PE:EA=2:1) showed that the starting material
 5 was consumed. Most of the MeOH was removed *in vacuo* and the residue was diluted with water (20 mL) and washed with Et₂O (15 mL x 2). The aqueous layer was basified to pH 8 with a saturated aqueous Na₂CO₃ solution and extracted with DCM (15 mL x 2). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* and the residue was purified by column chromatography
 10 (PE:EA=15:1 to 5:1) to give 139e (170 mg, 38%) as a yellow oil. LC-MS (Agilent): R_t 3.51 min; m/z calculated for C₁₇H₁₇NO₂S [M+H]⁺ 286.1, found [M+H]⁺ 286.1.

6. Procedure for the preparation of 139f

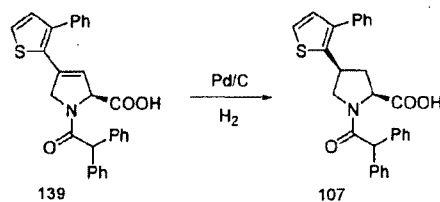
To a solution of 139e (160 mg, 0.56 mmol) and Et₃N (85 mg, 0.84 mmol) in DCM (5 mL)
 15 at 0°C was added a solution of diphenylacetyl chloride (155 mg, 0.67 mmol) in DCM (2 mL) and the mixture was stirred at RT for 15 min, TLC (PE:EA=4:1) showed that the starting material was consumed. The mixture was washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (PE:EA=15:1 to 8:1) to give 139f (130 mg, 48%) as a yellow solid. LC-MS (Agilent): R_t
 20 4.37 min; m/z calculated for C₃₀H₂₅NO₃S [M+H]⁺ 480.2, found [M+H]⁺ 480.2.

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7. Procedure for the preparation of 139

To a mixture of 139f (130 mg, 0.27 mmol) in THF/water (6 mL/2 mL) was added LiOH·H₂O (23 mg, 0.54 mmol) and the mixture was stirred at RT overnight, TLC (PE: EA=2:1) showed that the starting material was consumed. Most of the THF was removed *in vacuo* and the residue was partitioned between water (15 mL) and DCM (15 mL) and the aqueous phase was acidified to pH 2-3 with a 1 M aqueous HCl solution. The layers were separated and the aqueous phase was extracted with DCM (15 mL). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to give 139 (100 mg, 80%) as white solid. LC-MS (Agilent): R_t 4.43 min; m/z calculated for C₂₉H₂₃NO₃S [M+H]⁺ 466.1 found [M+H]⁺ 466.1. HPLC (JULY-L) (214 and 254 nm): R_t 9.46 min.

Example 48: Compound 107 (2S,4S)-1-(2,2-diphenylacetyl)-4-(3-phenylthiophen-2-yl)-pyrrolidine-2-carboxylic acid

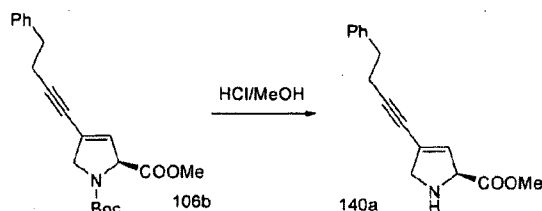


A mixture of 139 (60 mg, 0.13 mmol) and 10 % Pd/C (6 mg) in MeOH (10 mL) was stirred at RT under a H₂ atmosphere (1 atm) overnight, TLC (DCM:MeOH=10:1) showed that the starting material was consumed. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by preparative HPLC to give 107 (15 mg, 25%) as white solid. LC-MS (Agilent): R_t 4.51 min; m/z calculated for C₂₉H₂₃NO₃S [M+H]⁺ 468.1 found [M+H]⁺ 468.1. HPLC (JULY-L) (214 and 254 nm): R_t 9.44 min.

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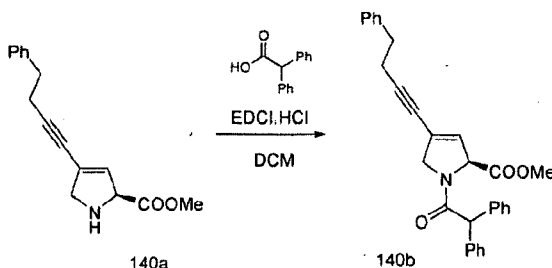
Example 49: Compound 140 (*S*)-1-(2,2-diphenylacetyl)-4-(4-phenylbut-1-yn-1-yl)-2,5-dihydro-1H-pyrrole-2-carboxylic acid

1. Procedure for the preparation of 140a



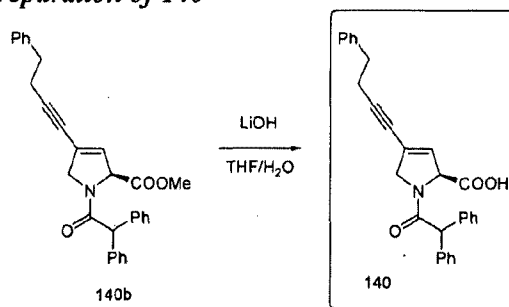
- 5 106b (40 mg, 0.089 mmol) was dissolved in a 4 M HCl/MeOH solution (5 mL) at RT and the mixture was stirred for 4 h, TLC (PE:EA=4:1) showed that the starting material was consumed. The mixture was concentrated *in vacuo* and the residue was dissolved in water (20 mL) and washed with ether (15 mL). DCM (15 mL) was added and the aqueous layer was basified to pH 8 with a saturated aqueous NaHCO₃ solution. The layers were separated and the aqueous phase was extracted with DCM (15 mL). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to give 140a (30 mg, 98%) as a yellow oil. LC-MS (Agilent): R_t 3.55 min; m/z calculated for C₁₆H₁₇NO₂ [M+H]⁺ 256.04, found [M+H]⁺ 256.1.

2. Procedure for the preparation of 140b



- 15 To solution of 140a (30 mg, 0.11 mmol) and diphenylacetic acid (25 mg, 0.11 mmol) in DCM (5 mL) at RT was added EDCI.HCl (32 mg, 0.16 mmol) and the mixture was stirred overnight, TLC (PE:EA=2:1) showed that most of the starting material was consumed. The mixture was washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*.
- 20 The residue was purified by chromatography (PE:EA=1:0 to 4:1) to give 140b (40 mg, 81%) as a yellow solid. LC-MS (Agilent): R_t 4.52 min; m/z calculated for C₃₀H₂₇NO₃ [M+H]⁺ 450.2, found [M+H]⁺ 450.2.

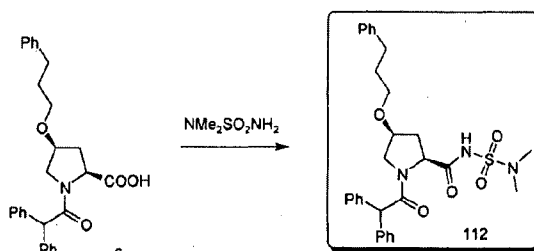
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3. Procedure for the preparation of 140

Hydrolysis of 140b (40 mg, 0.089 mmol) was performed as described in Example 9, 3, with about 2 equivalents of LiOH.H₂O (7 mg, 0.18 mmol). After acidification, the layers were separated and the aqueous phase was extracted with DCM (10 mL). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by preparative HPLC to give 140 (10 mg, 26%) as a white solid. LC-MS (Agilent): R_t 3.95 min; m/z calculated for C₂₉H₂₅NO₃ [M+H]⁺ 436.2, found [M+H]⁺ 436.2. HPLC (214 and 254 nm): R_t 9.49 min.

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Example 50: Compound 112 (2S,4S)-N-(N,N-dimethylsulfamoyl)-1-(2,2-diphenylacetyl)-4-(3-phenylpropoxy)pyrrolidine-2-carboxamide



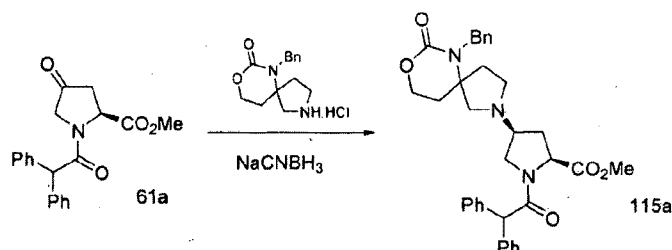
To a solution of Compound 6 (50 mg, 0.11 mmol) and N,N-dimethylsulfamide (15 mg, 0.12 mmol) in DCM (1 mL) was added DCC (27 mg, 0.13 mmol) and the mixture was stirred in a sealed flask at RT overnight, LCMS analysis showed that the starting material was consumed. DCM (5 mL) and PE (3 mL) were added to the mixture and the white solid was removed by filtration. The filtrate was concentrated *in vacuo* and the residue was purified by preparative HPLC to give 112 (15 mg, 25%) as a white solid. LC-MS (Agilent): R_t 3.25 min; m/z calculated for C₃₀H₃₅N₃O₅S [M+H]⁺ 550.2, found [M+H]⁺ 550.3. HPLC (JULY-L) (214 and 254 nm): R_t 9.27 min.

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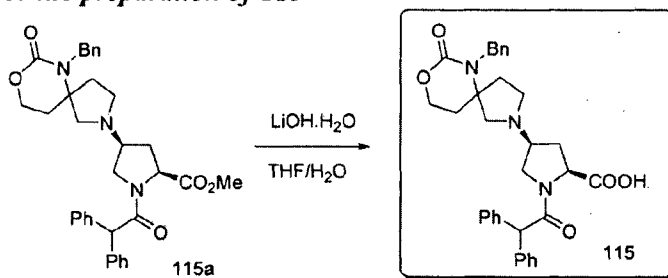
Example 51: Compound 115 (2S,4S)-4-(6-benzyl-7-oxa-2,6-diazaspiro[4,5]decan-2-yl)-1-(2,2-diphenylacetyl)pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of 115a



To a solution of 61a (142 mg, 0.42 mmol) and 6-benzyl-8-oxa-2,6-diazaspiro[4.5]decan-7-one hydrochloride (100 mg, 0.42 mmol) in MeOH (10 mL) was added Et₃N (43 mg, 0.42 mmol) followed by 2 drops of AcOH and the mixture was stirred at RT for 1 h. NaCNBH₃ (40 mg, 0.63 mmol) was added and stirring was continued at RT overnight, TLC (DCM: MeOH=10:1) showed that the starting material was consumed. The mixture was concentrated *in vacuo* and the residue was purified by column chromatography (DCM:MeOH=100:1 to 50:1) to give 115a (100 mg, 42%) as a light yellow solid. LC-MS (Agilent): R_t 3.96 min; m/z calculated for C₃₄H₃₇N₃O₅ [M+H]⁺ 568.3, found [M+H]⁺ 568.3.

2. Procedure for the preparation of 115

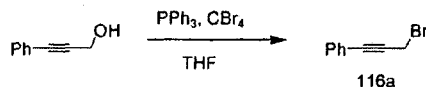


Hydrolysis of 115a (20 mg, 0.035 mmol) was performed as described in Example 9, 3, with 2 equivalents of LiOH.H₂O (3 mg, 0.07 mmol). The organic layer was separated, washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by preparative HPLC to give 115 (10 mg, 50%) as a white solid. LC-MS (Agilent): R_t 3.94 min; m/z calculated for C₃₃H₃₅N₃O₅ [M+H]⁺ 554.3 found [M+H]⁺ 554.3. HPLC (JULY-L) (214 and 254 nm): R_t 8.77 min.

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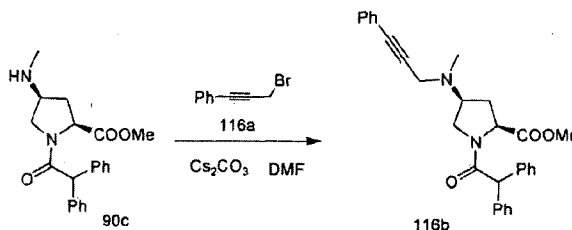
Example 52: Compound 116 (2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-(methyl(3-phenylprop-2-yn-1-yl)amino)pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of 116a



- 5 To a solution of 3-phenylprop-2-yn-1-ol (930 mg, 7.04 mmol) and PPh₃ (1.85 g, 7.04 mmol) in THF (20 mL) was added CBr₄ (2.10 g, 6.33 mmol) portion-wise and the mixture was stirred at RT overnight, TLC (100% PE) showed that most of the starting material was consumed. PE (15 mL) was added and the resulting precipitate was removed by filtration.
- 10 The filtrate was concentrated *in vacuo* and the residue was purified by chromatography (100% PE) to give 116a (1.10 g, 81%) as a colorless oil.

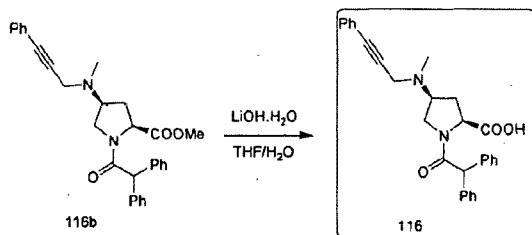
2. Procedure for the preparation of 116b



- A mixture of 90c (80 mg, 0.23 mmol), 116a (53 mg, 0.27 mmol) and Cs₂CO₃ (89 mg, 0.27 mmol) in DMF (8 mL) was heated at 60°C overnight, TLC (DCM:MeOH=20:1) showed that most of the starting material was consumed. The mixture was poured into ice-water (40 mL), extracted with EA (20 mL x 2) and the combined organic extracts were washed with brine (15 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=1:0 to 2:1) to give 116b (60 mg, 57%) as thick colorless oil. LC-MS (Agilent): R_t 4.24 min; m/z calculated for C₃₀H₃₀N₂O₃ [M+H]⁺ 467.2, found [M+H]⁺ 467.2.
- 15
- 20

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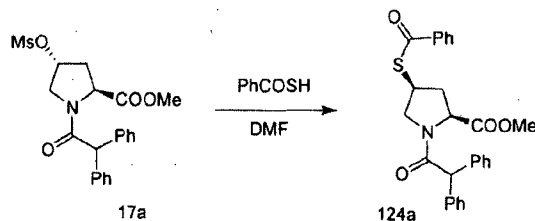
3. Procedure for the preparation of 116



A mixture of 116b (60 mg, 0.13 mmol) and LiOH.H₂O (16 mg, 0.39 mmol) in THF/water (8 mL/2 mL) was stirred at RT overnight, TLC (PE:EA=1:1) showed that the starting material was consumed. Most of the THF was removed *in vacuo*, the residue was dissolved in water (8 mL) and washed with MTBE (6 mL x 2). The aqueous layer was then acidified to pH 4~5 with a 4 M aqueous HCl solution. The resulting precipitate was collected by filtration and purified by preparative HPLC to give 116 (32 mg, 55%) as a white solid. LC-MS (Agilent): R_t 3.81 min; m/z calculated for C₂₉H₂₈N₂O₃ [M+H]⁺ 453.2, found [M+H]⁺ 453.2. HPLC (JULY-L) (214 and 254 nm): R_t 8.91 min.

Example 53: Compound 124 (2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-((3-phenylpropyl)thio)-pyrrolidine-2-carboxylic acid

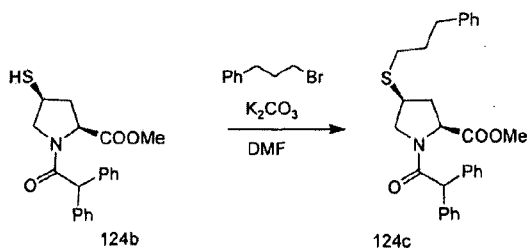
1. Procedure for the preparation of 124a



To a solution of PhCOSH (1.42 g, 9.60 mmol) in DMF (70 mL) at 0°C under N₂ was added NaH (0.39 g, 9.60 mmol) slowly and the mixture was stirred at RT for 30 min. 17a (2.00 g, 4.8 mmol) was then added and the mixture was stirred at RT overnight, TLC (PE:EA=1:1) showed that the starting material was consumed. The mixture was poured into water, extracted with EA and the organic extract was washed with a saturated aqueous NaHCO₃ solution, brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=1:0 to 5:1) to give 124a (1.61 g, 73%) as a yellow

solid. LC-MS (Agilent, P-2): R_t 3.14 min; m/z calculated for $C_{24}H_{25}NO_4S$ $[M+H]^+$ 460.1, $[M+Na]^+$ 482.1, found $[M+H]^+$ 460.1, $[M+Na]^+$ 482.1.

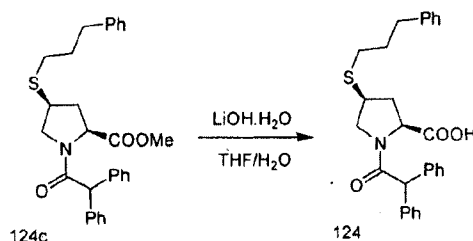
3. Procedure for the preparation of 124c



To a stirred mixture of 124b (600 mg, 1.69 mmol) and K_2CO_3 (257 mg, 1.86 mmol) in DMF (20 mL) was added 1-bromo-3-phenylpropane (370 mg, 1.86 mmol) and the mixture was heated at 80°C overnight, TLC (PE:EA=2:1) showed that the starting material was consumed. The mixture was poured into ice-water (100 mL) and EA (40 mL). The organic layer was separated, washed with brine (30 mL x 2), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=1:0 to 4:1) to give 124c (448 mg, 71%) as a colorless oil. LC-MS (Agilent, P-2): R_t 3.26 min; m/z calculated for $C_{29}H_{31}NO_3S$ $[M+H]^+$ 472.2, $[M+Na]^+$ 496.2, found $[M+H]^+$ 472.2, $[M+Na]^+$ 496.2.

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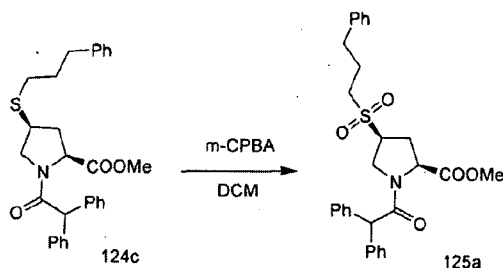
4. Procedure for the preparation of 124



A mixture of 124c (146 mg, 0.31 mmol) and LiOH.H₂O (39 mg, 0.93 mmol) in THF/water (8 mL/2 mL) was stirred at RT overnight, TLC (PE:EA=2:1) showed that the starting material was consumed. Most of the THF was removed *in vacuo*, the residue was dissolved in water (10 mL), acidified to pH 4~5 with a 4 M aqueous HCl solution and extracted with DCM (15 mL x 2). The combined organic extracts were washed with brine (10 mL x 2), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=4:0 to 2:1) to give 124 (97 mg, 68%) as a colorless oil. LC-MS (Agilent, P-2): R_t 2.87 min; m/z calculated for C₂₈H₂₉NO₃S [M+H]⁺ 460.2, [M+Na]⁺ 482.2, found [M+H]⁺ 460.2, [M+Na]⁺ 482.2. HPLC (JULY-L) (214 and 254 nm): R_t 9.41 min

Example 54: Compound 125 (2*S*,4*S*)—1-(2,2-diphenylacetyl)-4-((3-phenylpropyl)-sulfonyl)pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of 125a.

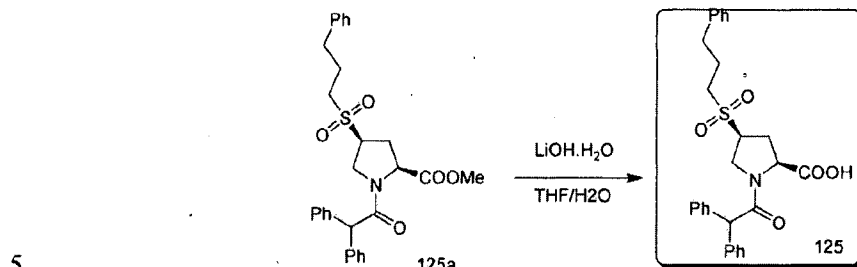


To a solution of 124c (260 mg, 0.55 mmol) in DCM (15 mL) was added 80% m-CPBA (296 mg, 1.37 mmol) and the mixture was stirred at RT overnight, TLC (PE:EA=2:1) showed that the starting material was consumed. The mixture was washed with a saturated aqueous Na₂CO₃ solution (15 mL), brine (15 mL x 2), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=8:1 to 2:1) to

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give 125a (245 mg, 88%) as a thick colorless oil. LC-MS (Agilent, P-2): R_t 3.03 min; m/z calculated for $C_{29}H_{31}NO_5S$ $[M+H]^+$ 506.2, $[M+Na]^+$ 528.2, found $[M+H]^+$ 506.2, $[M+Na]^+$ 528.2.

2. Procedure for the preparation of 125



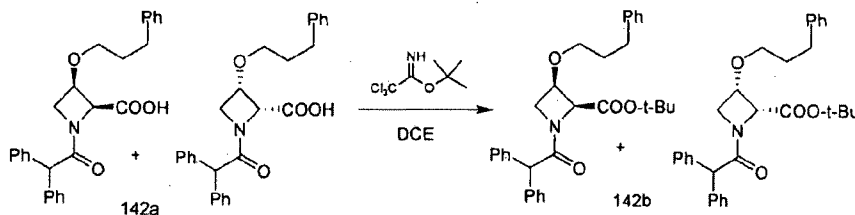
Hydrolysis of 125a (245 mg, 0.48 mmol) was performed as described in Example 53, 2., with about 3 equivalents of $LiOH \cdot H_2O$ (61 mg, 1.45 mmol). The organic extract was washed with brine (15 mL x 2), dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give 125 (215 mg, 90%) as a white solid. LC-MS (Agilent, P-2): R_t 2.73 min; m/z calculated for $C_{28}H_{29}NO_5S$ $[M+H]^+$ 492.2, $[M+Na]^+$ 514.2, found $[M+H]^+$ 492.2, $[M+Na]^+$ 514.2. HPLC (JULY-L) (214 and 254 nm): R_t 8.95 min.

10

Example 55: Compound 142 (2S,3S)-1-(2,2-diphenylacetyl)-3-(3-phenylpropoxy)-azetidine-2-carboxylic acid and (2R,3R)-1-(2,2-diphenylacetyl)-3-(3-phenylpropoxy)-azetidine-2-carboxylic acid

15

1. Procedure for the preparation of 142b



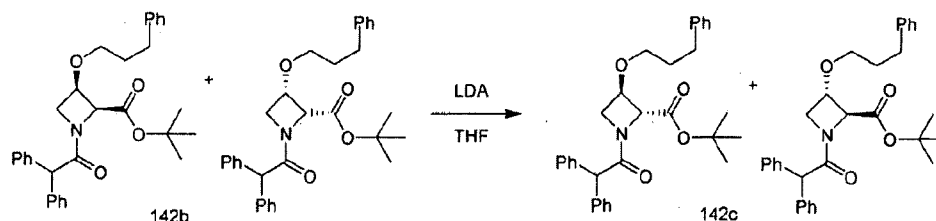
To a mixture of 142a (300 mg, 0.69 mmol) in DCE (10 mL) was added tert-butyl 2,2,2-trichloroacetimidate (168 mg, 0.77 mmol) and the mixture was heated at 60°C overnight, TLC(DCM:MeOH=10:1) showed that the starting material was consumed. The mixture was washed with brine (10 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=1:0 to 4:1) to give 142b (270 mg,

20

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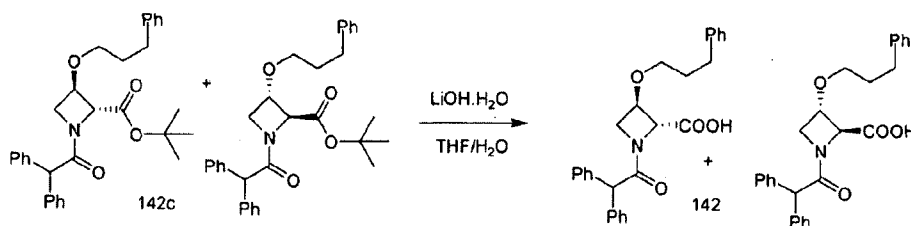
81%) as a white solid. LC-MS (Agilent): R_t 4.81 min; m/z calculated for $C_{31}H_{35}NO_4$ $[M+H]^+$ 486.3, $[M-t-Bu]^+$ 430.2, found $[M+H]^+$ 486.3, $[M-t-Bu]^+$ 430.2.

2. Procedure for the preparation of 142c



- 5 To a stirred solution of 142b (170 mg, 0.35 mmol) in THF (10 mL) at -65°C under N_2 was added LDA (1 M in THF, 0.7 mL, 0.70 mmol) and the mixture was allowed to warm slowly to RT and stirred overnight. The mixture was cooled in an ice-water bath and the reaction was quenched with a saturated aqueous NH_4Cl solution. The mixture was partitioned between EA (20 mL) and brine (30 mL), the organic layer was separated, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=1:0 to 10:1) to give the trans-product (70 mg, 41%) as a colorless oil and the cis starting material (50 mg, 29%) as a white solid. LC-MS (Agilent): R_t 4.47 min; m/z calculated for $C_{31}H_{35}NO_4$ $[M+H]^+$ 486.3, $[M-t-Bu]^+$ 430.2, found $[M+H]^+$ 486.3, $[M-t-Bu]^+$ 430.2.

15 3. Procedure for the preparation of 142

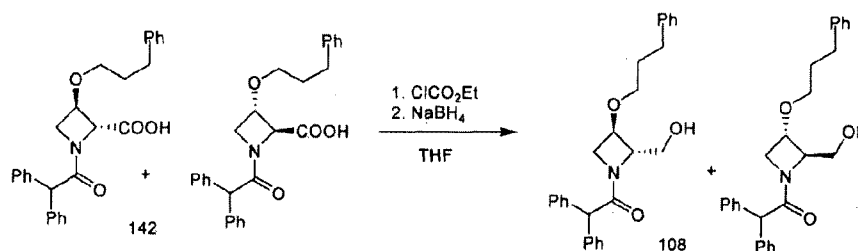


- To a stirred mixture of 142c (70 mg, 0.14 mmol) in THF/water (3 mL/1 mL) was added $LiOH \cdot H_2O$ (18 mg, 0.43 mmol) and the mixture was stirred at RT overnight, TLC (PE:EA=4:1) showed that the starting material was consumed. Most of the THF was removed *in vacuo*, the residue was dissolved in water (15 mL) and acidified to pH 3-4 with a 3 M aqueous HCl solution. The aqueous mixture was extracted with DCM (15 mL x 2) and the combined organic extracts were washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give 142 (60 mg, 92%) as a white solid. LC-MS (Agilent): R_t

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4.36 min; m/z calculated for $C_{27}H_{27}NO_4$ $[M+H]^+$ 430.2, found $[M+H]^+$ 430.2. HPLC (JULY-L) (214 and 254 nm): R_t 9.33 min.

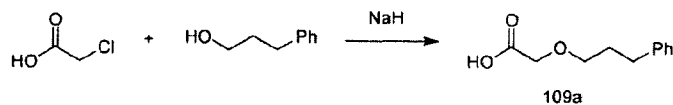
Example 56: Compound 108 1-((2*R*,3*S*)-2-(hydroxymethyl)-3-(3-phenylpropoxy)-azetidin-1-yl)-2,2-diphenylethanone and 1-((2*S*,3*R*)-2-(hydroxymethyl)-3-(3-phenylpropoxy)-azetidin-1-yl)-2,2-diphenylethanone



To a solution of 142 (30 mg, 0.07 mmol) in dry THF (10 mL) at 0°C under N_2 was added Et_3N (7 mg, 0.07 mmol) followed by $ClCO_2Et$ (7.6 mg, 0.07 mmol) and the mixture was stirred at 0°C for 1 h. $NaBH_4$ (8 mg, 0.21 mmol) was added and stirring was continued at 0°C for 1 h before allowing to warm slowly to RT and stirred overnight, TLC (PE:EA=2:1) showed that the starting material was consumed. The reaction was quenched with water (30 mL) and the mixture was extracted with EA (15 mL x 2). The combined organic extracts were washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by preparative HPLC to give 108 (15 mg, 51%) as a colorless oil. LC-MS (Agilent): R_t 4.34 min; m/z calculated for $C_{27}H_{29}NO_3$ $[M+H]^+$ 416.2, found $[M+H]^+$ 416.2. HPLC (JULY-L) (214 and 254 nm): R_t 9.32 min.

Example 57: Compound 109 (1-((2*R*,3*R*)-2-(hydroxymethyl)-3-(3-phenylpropoxy)-azetidin-1-yl)-2,2-diphenylethanone and (1-((2*S*,3*S*)-2-(hydroxymethyl)-3-(3-phenylpropoxy)-azetidin-1-yl)-2,2-diphenylethanone

1. Procedure for the preparation of 109a

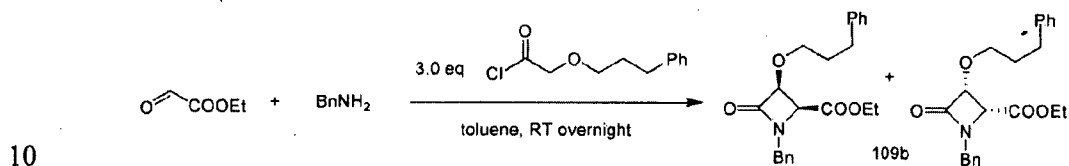


To a solution of 3-phenylpropan-1-ol (54.0 g, 0.40 mol) in DMF (250 mL) at RT was added NaH (60% dispersion in oil, 15.6 g, 0.40 mol) and the mixture was stirred at RT for 1 h, then heated at 61°C for 1 h. The mixture was cooled to 5°C and 2-chloroacetic acid

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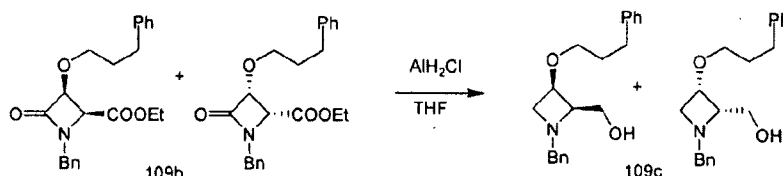
(15.0 g, 0.16 mol) was added. The mixture was stirred at RT for 0.5 h, then heated at 60°C for 3 h, TLC (DCM:MeOH=10:1) showed that a new product was formed. The mixture was allowed to cool to RT, stirred overnight then poured into ice-water (1.5 L) and washed with EA (300 mL x 4). The aqueous layer was acidified to pH 5 with a 3 M aqueous HCl solution and extracted with EA (500 mL x 2). The combined organic extracts were washed with brine (300 mL x 2), dried over Na₂SO₄, filtered and concentrated *in vacuo* to give 109a (25 g, 81%) as a pale yellow solid. LC-MS (Agilent): R_t 3.74 min; m/z calculated for C₁₁H₁₄O₃ [M+Na]⁺ 217.1, found [M+Na]⁺ 217.1.

2. Procedure for the preparation of 109b



To a solution of 109a (17.1 g, 87.9 mmol) in DCM (150 mL) was added SOCl₂ (11.0 g, 92.3 mmol) and the mixture was heated at reflux for 0.5 h, then cooled to RT and concentrated *in vacuo* to give the acid chloride which was used directly in the next step. To a solution of ethyl glyoxylate (6.00 g, 50% toluene solution, 29.3 mmol) in toluene (60 mL) was added benzyl amine (3.15 g, 29.3 mmol) and the mixture was stirred at RT for 1 h. Triethylamine (10.4 g, 103 mmol) was added and the mixture was cooled in an ice-water bath. A solution of the above-prepared acid chloride in toluene (45 mL) was then added dropwise and the mixture was stirred at RT overnight, TLC (PE:EA=4:1) showed that the product was formed. The mixture was partitioned between EA (60 mL) and brine (100 mL). The organic layer was separated and washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=1:0 to 10:1) to give 109b (1.2 g, 11%) as a colorless oil. LC-MS (Agilent): R_t 4.15 min; m/z calculated for C₂₂H₂₅NO₄ [M+H]⁺ 368.2, [M+Na]⁺ 390.2, found [M+H]⁺ 368.2, [M+Na]⁺ 390.2.

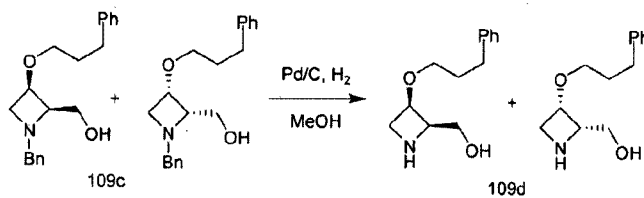
25 3. Procedure for the preparation of 109c



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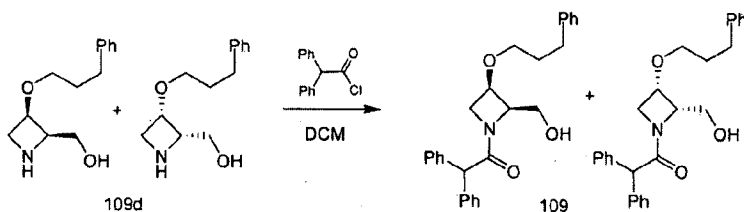
To a mixture of AlCl_3 (333 mg, 2.49 mmol) in dry THF (5 mL) at 0°C under N_2 was added LiAlH_4 (95 mg, 2.49 mmol) and the mixture was heated at 35°C for 0.5 h then re-cooled to 0°C . A solution of 109b (200 mg, 0.54 mmol) in THF (2 mL) was then added and the mixture was heated at 35°C for 3 h, TLC (PE:EA=2:1) showed that the starting material was consumed. The mixture was cooled to 0°C , the reaction was quenched with water (1 mL) and then partitioned between EA and brine. The organic layer was separated, dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give 109c (160 mg, 95%) as a yellow oil. LC-MS (Agilent): R_t 3.37 min; m/z calculated for $\text{C}_{20}\text{H}_{25}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 312.2, found $[\text{M}+\text{H}]^+$ 312.2.

4. Procedure for the preparation of 109d



A mixture of 109c (160 mg, 0.51 mmol) and 10% Pd/C (20 mg) in MeOH (5 mL) was stirred at RT under a H_2 atmosphere (1 atm) at 35°C overnight, TLC (DCM:MeOH=10:1) showed that the starting material was consumed. The mixture was filtered and the filtrate was concentrated *in vacuo* to give 109d (100 mg, 87%) as a colorless oil. LC-MS (Agilent): R_t 3.53 min; m/z calculated for $\text{C}_{13}\text{H}_{19}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 222.1, found $[\text{M}+\text{H}]^+$ 222.1.

5. Procedure for the preparation of 109

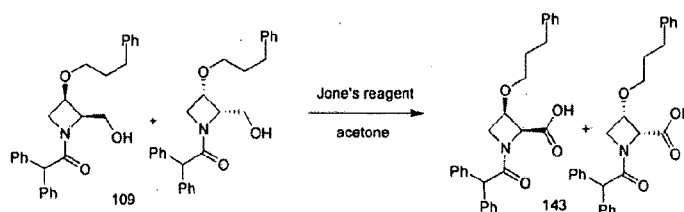


To a solution of 109d (100 mg, 0.45 mmol) and Et_3N (50 mg, 0.49 mmol) in DCM (10 mL) at 0°C was added a solution of diphenylacetyl chloride (104 mg, 0.45 mmol) in DCM (1 mL) and the mixture was stirred at 0°C for 1 h, TLC (DCM:MeOH=10:1) showed that the starting material was consumed. The mixture was washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=1:0 to 4:1) to give 109 (80 mg, 43%) as a colorless oil. LC-MS (Agilent): R_t 3.80

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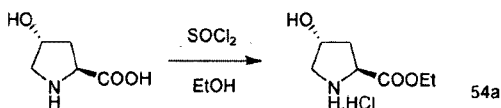
min; m/z calculated for $C_{27}H_{29}NO_3$ $[M+H]^+$ 416.2, found $[M+H]^+$ 416.2. HPLC (214 and 254 nm): R_t 9.36 min.

Example 58: Compound 143 (2*R*,3*R*)-3-(3-phenylpropoxy)-1-(2,2-diphenylacetyl)-azetidine-2-carboxylic acid and (2*S*,3*S*)-3-(3-phenylpropoxy)-1-(2,2-diphenylacetyl)-azetidine-2-carboxylic acid



To a stirred solution of 109 (250 mg, 0.60 mmol) in acetone (5 mL) at 0°C was added Jones's reagent (0.92 mL, 2.40 mmol) and the mixture was stirred at 0°C for 2 h, TLC (PE: EA=2:1) showed that the starting material was consumed. The reaction was quenched with iso-propanol (1 mL) then diluted with EA (20 mL) and filtered. The filtrate was concentrated *in vacuo* and the residue was dissolved in EA (20 mL), washed with water (15 mL x 2), saturated aqueous EDTA solution (10 mL x 2), brine (15 mL x 2), then dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give crude 143t (240 mg) as a brown oil. A portion (40 mg) of the crude product was purified by preparative TLC (DCM: MeOH= 10:1) to give pure 143 (20 mg) as a white solid. LC-MS (Agilent): R_t 4.27 min; m/z calculated for $C_{27}H_{27}NO_4$ $[M+H]^+$ 430.2, found $[M+H]^+$ 430.2. HPLC (214 and 254 nm): R_t 9.24 min.

Example 59: Compound 54 (2*S*,4*S*)-4-((benzyloxymethyl)-1-(2,2-diphenylacetyl)pyrrolidine-2-carboxylic acid
1. Procedure for the preparation of 54a

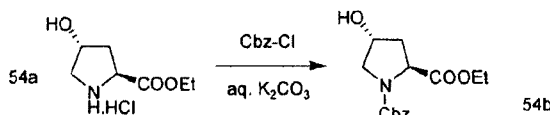


To a stirred solution of *trans*-4-hydroxy-L-proline (100 g, 0.76 mol) in EtOH (1 L) was added $SOCl_2$ (95.2 g, 0.8 mol) dropwise and the mixture was heated at reflux overnight. The mixture was cooled to RT and concentrated *in vacuo* to give 54a (140 g, 94%) as a

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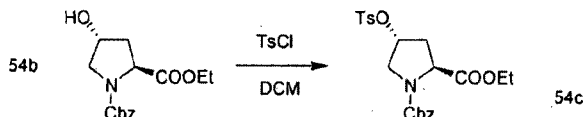
white solid. LC-MS (Agilent): R_t 0.56 min; m/z calculated for $C_{13}H_{17}NO_3$ $[M+H]^+$ 160.1, found $[M+H]^+$ 160.1.

2. Procedure for the preparation of 54b



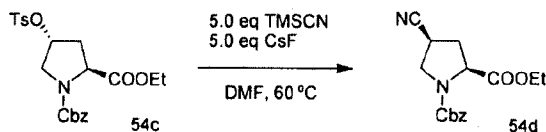
- 5 To a stirred mixture 54a (60.0 g, 0.30 mol) in diethyl ether/ H_2O (100 mL/600 mL) at $0^\circ C$ was added K_2CO_3 (104 g, 0.75 mol) and CbzCl (48.0 g, 0.28 mol) dropwise and the mixture was stirred at RT for 2 h, TLC (PE:EA=2:1) showed that a major new product was formed. The layers were separated and the aqueous phase was extracted with EA (100 mL x 2) and the combined organic extracts were washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give 54b (75.0 g, 83%) as a yellow oil. LC-MS (Agilen, P-2): R_t 2.86 min; m/z calculated for $C_{15}H_{19}NO_3$ $[M+H]^+$ 294.1, $[M+Na]^+$ 316.1, found $[M+H]^+$ 294.1, $[M+Na]^+$ 316.1.

3. Procedure for the preparation of 54c



- 15 To a stirred solution of 54b (145 g, 0.49 mol) and Et_3N (60.05 g, 0.59 mol) in DCM (1 L) at RT was added TsCl (104 g, 0.54 mol) in portions over 20 min and the mixture was heated at $40^\circ C$ overnight, TLC (PE:EA=2:1) showed that the starting material was consumed. The mixture was cooled to RT, washed with water (200 mL x 2), brine (200 mL x 2), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=20:1 to 1:1) to give 54c (128 g, 58%) as a yellow oil. LC-MS (Agilent, P-2): R_t 3.025 min; m/z calculated for $C_{22}H_{25}NO_7S$ $[M+H]^+$ 448.1, $[M+Na]^+$ 470.1, found $[M+H]^+$ 448.2, $[M+Na]^+$ 470.1.

4. Procedure for the preparation of 54d

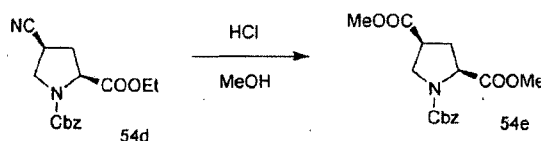


- 25 A mixture 54c (34.4 g, 76.8 mmol), CsF (58.4 g, 384 mmol) and TMSCN (38.1 g, 384 mmol) in DMF (300 mL) was heated at $60^\circ C$ for 40 h, TLC (PE:EA=2:1) showed about

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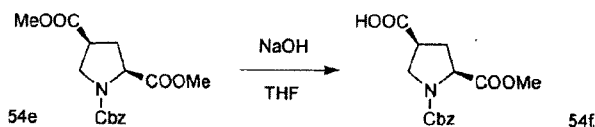
half of the starting material remained. The mixture was cooled to RT and poured into EA/H₂O (2 L/800 mL). The organic layer was collected and washed with water (400 mL x 2), brine (500 mL x 2), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=10:0 to 1:1) to give 54d (8.00 g, 34%) as a yellow oil and recovered starting material (7.0 g, 20%). LC-MS (Waters): R_t 5.73 min; m/z calculated for C₁₆H₁₈N₂O₄ [M+H]⁺ 303.1, [M+Na]⁺ 325.1, found [M+H]⁺ 303.1, [M+Na]⁺ 325.1

5. Procedure for the preparation of 54e



Acetyl chloride (20.8 g, 0.264 mol) was added to MeOH (40 mL) drop-wise at 0°C and the mixture was stirred at RT for 1 h. 54d (8.00 g, 26.4 mmol) was then added and stirring was continued at RT for 2 days, TLC (PE:EA=4:1) showed that the starting material was consumed. The reaction was neutralised with solid NaHCO₃ until pH ~7 and the mixture was filtered. The filtrate was concentrated *in vacuo* and the residue was partitioned between water (30 mL) and EA (30 mL). The organic layer was collected, washed with brine (30 mL x 2), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=10:1 to 3:1) to give 54e (7.5 g, 88%) as a brown oil. LC-MS (Waters): R_t 5.81 min; m/z calculated for C₁₆H₁₉NO₆ [M+H]⁺ 322.1, [M+Na]⁺ 344.1, found [M+H]⁺ 322.2, [M+Na]⁺ 344.1.

6. Procedure for the preparation of 54f

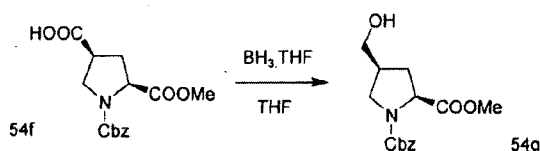


The following procedure was carried out in five parallel reactions using 54e (total of 7.5 g, 23.3 mmol): To a solution of 54e (1.5 g, 4.67 mmol) in THF (10 mL) at 0°C was added a 1 M aqueous NaOH solution (4.7 mL, 4.7 mmol) and the mixture was stirred at 0°C for 30 min, then allowed to warm to RT and stirred for a further 1 h, LCMS showed most of the starting material was consumed. The five reaction mixtures were combined and concentrated *in vacuo* to remove most of the THF and the residue was dissolved in a

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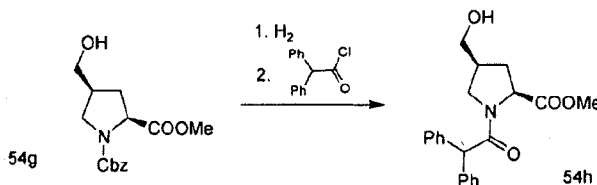
saturated aqueous NaHCO_3 solution and washed with ether. The aqueous layer was acidified to pH 3-4 with a 3 M aqueous HCl solution and extracted with EA. The organic layer was dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give 54f (6.3 g, 86%) as a yellow oil. LC-MS (Agilent, P-2): R_t 3.71 min; m/z calculated for $\text{C}_{15}\text{H}_{17}\text{NO}_6$ $[\text{M}+\text{Na}]^+$ 330.1, found $[\text{M}+\text{Na}]^+$ 330.1.

7. Procedure for the preparation of 54g



To a stirred solution 54f (3.80 g, 12.4 mmol) in THF (30 mL) at 0°C under a N_2 atmosphere was added $\text{BH}_3\cdot\text{THF}$ (1 M solution in THF, 37 mL, 37 mmol) and the mixture was stirred at 0°C for 30 min, TLC (DCM:MeOH=10:1) showed that the starting material was consumed. The reaction was quenched with MeOH followed by a 3 M aqueous HCl solution and the mixture was concentrated *in vacuo* to remove most of THF. The residue was partitioned between EA and brine, the organic layer was separated, dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give 54g (3.2 g, 88%) as a colorless oil. LC-MS (Agilent, P-2): R_t 2.82 min; m/z calculated for $\text{C}_{15}\text{H}_{19}\text{NO}_5$ $[\text{M}+\text{H}]^+$ 294.1, found $[\text{M}+\text{H}]^+$ 294.1.

8. Procedure for the preparation of 54h

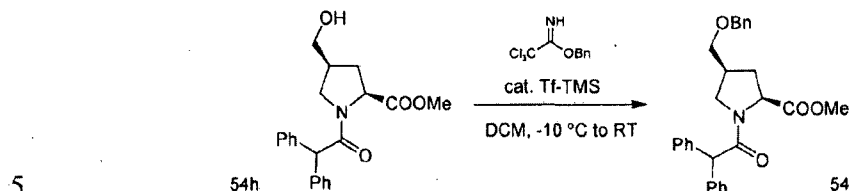


A mixture of 54g (3.20 g, 11 mmol) and 10% $\text{Pd}(\text{OH})_2/\text{C}$ (300 mg) in MeOH (30 mL) was stirred at RT under a H_2 atmosphere (1 atm) overnight, TLC (DCM:MeOH=10:1) showed that the starting material was consumed. The mixture was filtered, the filtrate was concentrated *in vacuo* and the residue was dissolved in EA/ H_2O (20 mL/20 mL) then cooled to 0°C . KHCO_3 (2.75 g, 2.75 mmol) was added followed by diphenyl acetyl chloride (3.0 g, 13.2 mmol) and the mixture was stirred at 0°C for 30 min, TLC (DCM:MeOH=10:1) showed that the starting material was consumed. The organic layer was separated, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was

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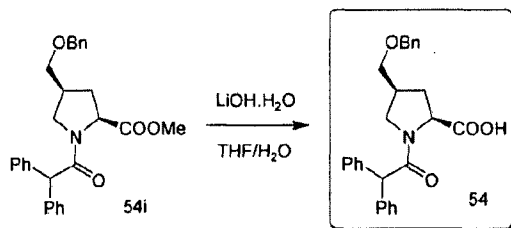
purified by chromatography (PE:EA=1:0 to 1:1) to give 54h (2.1 g, 55% overall) as a white solid. LC-MS (Agilent, P-2): R_t 2.88 min; m/z calculated for $C_{21}H_{23}NO_4$ $[M+H]^+$ 354.2, $[M+Na]^+$ 376.2, found $[M+H]^+$ 354.1, $[M+Na]^+$ 376.2.

9. Procedure for the preparation of 54i



To a solution of 54h (100 mg, 0.28 mmol) and benzyl trichloroacetimidate (143 mg, 0.56 mmol) in DCM (15 mL) at -10°C under a N_2 atmosphere was added TMS triflate (18 mg, 0.08 mmol) and the mixture was allowed to warm slowly to RT and stirred overnight, TLC (PE:EA=1:1) showed that the starting material was consumed. The mixture was washed with a saturated aqueous $NaHCO_3$ solution, brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=1:0 to 2:1) to give 54i (90 mg, 72%) as a colorless oil. LC-MS (Agilent, P-2): R_t 2.98 min; m/z calculated for $C_{28}H_{29}NO_4$ $[M+H]^+$ 444.2, $[M+Na]^+$ 466.2, found $[M+H]^+$ 444.2, $[M+Na]^+$ 466.2.

10. Procedure for the preparation of 54



A mixture of 54i (90 mg, 0.20 mmol) and $LiOH \cdot H_2O$ (25 mg, 0.60 mmol) in THF/water (3 mL/1 mL) was stirred at RT overnight, TLC (PE:EA=1:1) showed that the starting material was consumed. The mixture was concentrated *in vacuo*, the residue was dissolved in water (10 mL), acidified to pH 3-4 with a 3 M aqueous HCl solution and extracted with DCM. The organic extracts were washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by preparative HPLC to give 54 (57 mg, 68%) as a white solid. LC-MS (Agilent, P-2): R_t 3.09 min; m/z calculated for $C_{27}H_{27}NO_4$ $[M+H]^+$ 430.2, found $[M+H]^+$ 430.3. HPLC (JULY-L) (214 and 254 nm): R_t 9.14 min. HPLC (ZSJ-2) (214 and 254 nm): R_t 20.56 min.

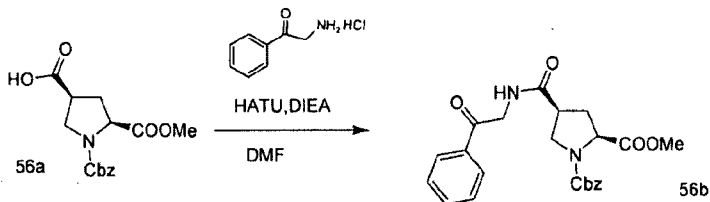
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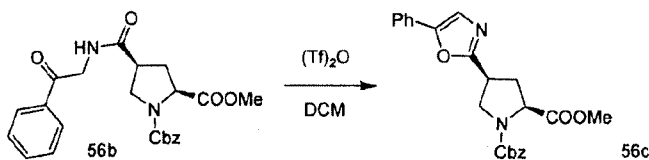
Example 60: Compound 56 (2S,4S)-1-(2,2-diphenylacetyl)-4-5-phenyloxazol-2-yl)pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of 56b



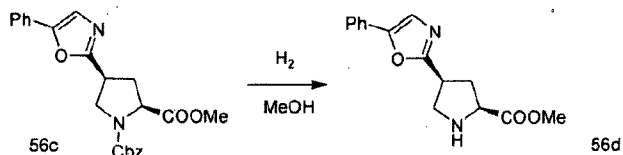
To a stirred solution of 56a (0.5 g, 1.63 mmol) in DMF (20 mL) was added DIPEA (0.63 mL, 4.89 mmol) and HATU (0.74 g, 1.96 mmol) and the mixture was stirred at RT for 30 min. 2-amino-1-phenylethanone hydrochloride (0.36 g, 2.12 mmol) was then added and stirring was continued at RT overnight, TLC (PE:EA=1:1) showed that the starting material was consumed. The mixture was poured into ice-water (40 mL), extracted with EA (40 mL x 2) and the combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=1:0 to 1:1) to give 56b (260 mg, 37%) as a thick oil. LC-MS (Waters): R_t 5.99 min; m/z calculated for C₂₃H₂₄N₂O₆ [M+H]⁺ 425.2, [M+Na]⁺ 447.2, found [M+H]⁺ 425.2, [M+Na]⁺ 447.2.

2. Procedure for the preparation of 56c

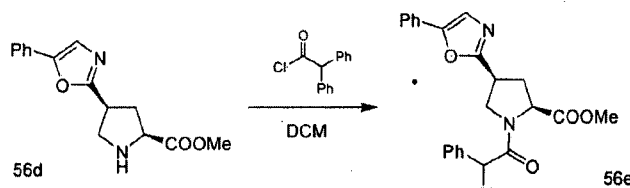


To a solution of 56b (250 mg, 0.59 mmol) in DCM (15 mL) at 0°C was added pyridine (71 mg, 0.89 mmol) then TFAA (0.2 g, 0.71 mmol) and the mixture was stirred at 0°C for 15 min then at RT for 3 hours, TLC (PE:EA=2:1) showed that the starting material was consumed. The reaction was quenched with a saturated aqueous NaHCO₃ solution, the layers were separated and the aqueous layer was extracted with DCM (30 mL x 2). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=100:0 to 3:1) to give 56c (100 mg, 41%) as a brown oil. LC-MS (Waters): R_t 6.93 min; m/z calculated for C₂₃H₂₂N₂O₅ [M+H]⁺ 407.2, [M+Na]⁺ 429.2, found [M+H]⁺ 407.2, [M+Na]⁺ 429.2.

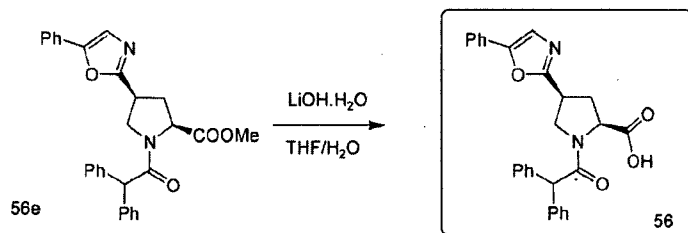
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3. Procedure for the preparation of 56d

A mixture of 56c (120 mg, 0.3 mmol) and 10% Pd(OH)₂/C (20 mg) in methanol (20 mL) was stirred at RT under a H₂ atmosphere (1 atm) for 2 h, LC-MS analysis showed that the starting material was consumed. The mixture was filtered and the filtrate was concentrated *in vacuo* to give 56d (60 mg, 75%) as a white solid. LC-MS (Waters): R_t 4.97 min; m/z calculated for C₁₅H₁₆N₂O₃ [M+H]⁺ 273.1, found [M+H]⁺ 273.2.

4. Procedure for the preparation of 56e

To a solution of 56d (60 mg, 0.22 mmol) in DCM (20 mL) at 0°C was added DIPEA (85 mg, 0.66 mmol) then 2,2-diphenylacetyl chloride (76 mg, 0.33 mmol) and the mixture was allowed to warm to RT and stirred for 30 min, TLC (PE:EA=2:1) showed that the starting material was consumed. Water was added and the mixture was extracted with DCM (30 mL x 2). The combined organic extracts were washed with brine (20 mL x 2), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=10:1 to 3:1) to give 56e (56 mg, 55%) as a yellow oil. LC-MS (Waters): R_t 7.02 min; m/z calculated for C₂₉H₂₆N₂O₄ [M+H]⁺ 467.2, found [M+H]⁺ 467.2.

5. Procedure for the preparation of 56

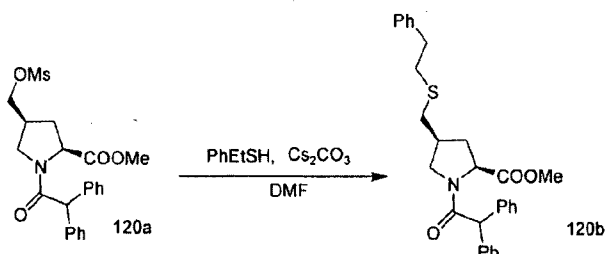
A mixture of 56e (56 mg, 0.12 mmol) and LiOH.H₂O (16 mg, 0.38 mmol) in THF/H₂O (2.5 mL/0.5 mL) was stirred at RT overnight. The mixture was concentrated *in vacuo*, the residue was dissolved in water, acidified to pH 4~5 with a 3 M aqueous HCl solution and

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extracted with DCM (30 mL x 3). The combined organic extracts were washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by preparative HPLC to give 56 (30 mg, 55%) as a white solid. LC-MS (Agilent, P-2): R_t 3.00 min; m/z calculated for $\text{C}_{28}\text{H}_{24}\text{N}_2\text{O}_4$ $[\text{M}+\text{H}]^+$ 453.2, found $[\text{M}+\text{H}]^+$ 453.2. HPLC (JULY-L) (214 and 254 nm): R_t 9.12 min. HPLC (ZSJ-2) (214 and 254 nm): R_t 20.50 min.

Example 61: Compound 120 (2S,4S)-1-(2,2-diphenylacetyl)-4-((phenethylthio)methyl)pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of 120b

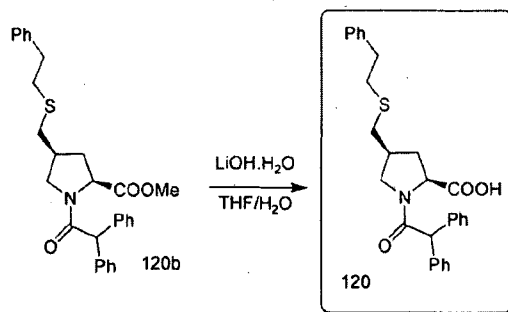


10

A mixture of 120a (600 mg, 1.39 mmol), 2-phenylethanethiol (385 mg, 2.78 mmol) and Cs_2CO_3 (906 mg, 2.78 mmol) in DMF (10 mL) was heated at 80°C overnight, TLC (PE:EA=1:1) showed the starting material was consumed. The mixture was poured into ice-water (50 mL) and extracted with EA (20 mL x 2). The combined organic extracts were washed with brine (25 mL x 2), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=10:1 to 3:1) to give 120b (197 mg, 30%) as a colorless oil. LC-MS (Agilent, P-2): R_t 3.30 min; m/z calculated for $\text{C}_{29}\text{H}_{31}\text{NO}_3\text{S}$ $[\text{M}+\text{H}]^+$ 474.2, found $[\text{M}+\text{H}]^+$ 474.2.

15

2. Procedure for the preparation of 120



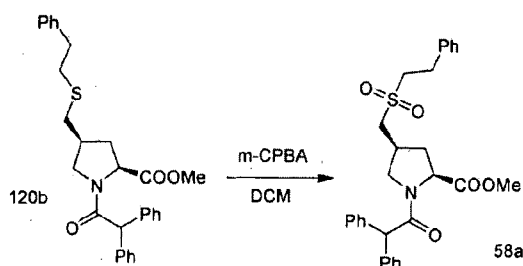
20

Hydrolysis of 120b (70 mg, 0.15 mmol) was performed as described in Example 60, 5, with about 3 equivalents of $\text{LiOH}\cdot\text{H}_2\text{O}$ (18 mg, 0.44 mmol) to give 120 (60 mg, 88%) as a

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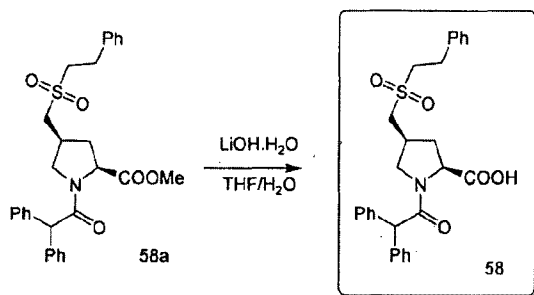
white solid. LC-MS (Agilent, P-2): R_t 3.21 min; m/z calculated for $C_{28}H_{29}NO_3S$ $[M+H]^+$ 460.2, found $[M+H]^+$ 460.2. HPLC (JULY-L) (214 and 254 nm): R_t 9.35 min. HPLC (ZSJ-2) (214 and 254 nm): R_t 22.86min.

5 Example 62: Compound 58 (2S,S)-1-(2,2-diphenylacetyl)-4-((phenethylsulfonyl)methyl)pyrrolidine-2-carboxylic acid
1. Procedure for the preparation of 58a



To a solution of 120b (120 mg, 0.25 mmol) in DCM (6 mL) was added 80% m-CPBA (137 mg, 0.63 mmol) and the mixture was stirred at RT overnight, TLC (PE:EA=2:1) showed that the starting material was consumed. The mixture was washed with a saturated aqueous Na_2CO_3 solution, brine (10 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=8:1 to 1.5:1) to give 58a (102 mg, 82%) as a white solid. LC-MS (Agilent, P-2): R_t 2.98 min; m/z calculated for $C_{29}H_{31}NO_5S$ $[M+H]^+$ 506.2, $[M+Na]^+$ 528.2, found $[M+H]^+$ 506.2, $[M+Na]^+$ 528.2.

2. Procedure for the preparation of 58

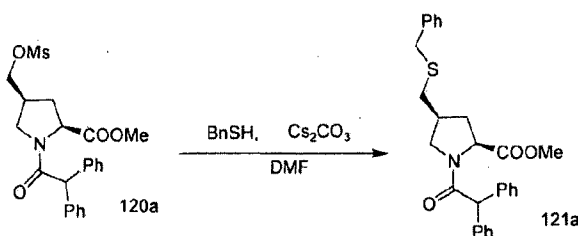


A mixture of 58a (102 mg, 0.20 mmol) and $LiOH \cdot H_2O$ (25 mg, 0.60 mmol) in THF/ H_2O (4 mL/1 mL) was stirred at RT overnight, TLC (PE:EA=1:1) showed that the starting material was consumed. The mixture was concentrated *in vacuo*, the residue was dissolved in water (4 mL), acidified to pH 4~5 with a 3 M aqueous HCl solution and the resulting precipitate was collected by filtration and dried at 60°C to give 58 (77 mg, 77%) as a white solid. LC-

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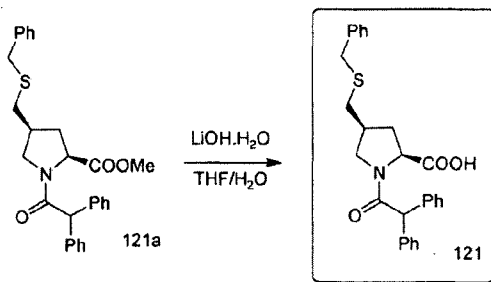
MS (Agilent, P-2): R_t 2.77 min; m/z calculated for $C_{28}H_{29}NO_5S$ $[M+H]^+$ 492.2, $[M+Na]^+$ 514.2, found $[M+H]^+$ 492.2, $[M+Na]^+$ 514.2. HPLC (JULY-L) (214 and 254 nm): R_t 8.89 min. HPLC (ZSJ-2) (214 and 254 nm): R_t 18.32 min.

5 **Example 63: Compound 121 (2S,4S)-4-((benzylthio)methyl)-1-(2,2-diphenylacetyl)pyrrolidine-2-carboxylic acid**
1. Procedure for the preparation of 121a



A mixture of 120a (600 mg, 1.39 mmol), BnSH (345 mg, 2.78 mmol) and Cs_2CO_3 (906 mg, 2.78 mmol) in DMF (10 mL) was heated at 80°C overnight, TLC (PE:EA= 1:1) showed that the 120a was consumed. The mixture was poured into ice-water (50 mL) and extracted with EA (20 mL x 2). The combined organic extracts were washed with brine (15 mL x 2), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=10:1 to 4:1) to give 121a (140 mg, 21%) as colorless oil. LC-MS (Agilent, P-2): R_t 3.10 min; m/z calculated for $C_{28}H_{29}NO_3S$ $[M+H]^+$ 460.2, found $[M+H]^+$ 460.2.

2. Procedure for the preparation of 121



A mixture of 121a (56 mg, 0.12 mmol) and LiOH.H₂O (15 mg, 0.37 mmol) in THF/H₂O (3 mL/1 mL) was stirred at RT overnight, TLC (PE:EA=2:1) showed that the starting material was consumed. The mixture was concentrated *in vacuo*, the residue was dissolved in water (10 mL), acidified to pH 4~5 with a 3 M aqueous HCl solution and extracted with DCM (10 mL x 2). The combined organic extracts were washed with brine (10 mL), dried over

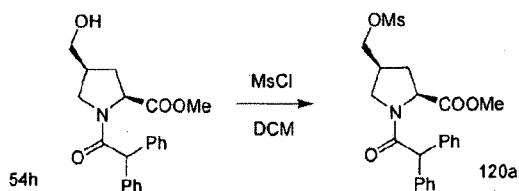
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Na₂SO₄, filtered and concentrated *in vacuo* to give 121 (50 mg, 92%) as white solid. LC-MS (Agilent, P-2): R_t 3.16 min; m/z calculated for C₂₇H₂₇NO₃S [M+H]⁺ 446.2, found [M+H]⁺ 446.2. HPLC (JULY-L) (214 and 254 nm): R_t 9.26 min. HPLC (ZSJ-2) (214 and 254 nm): R_t 21.92 min.

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Example 64: Compound 122 (2S,4S)-1-(2,2-diphenylacetyl)-4-((phenylthio)methyl)pyrrolidine-2-carboxylic acid

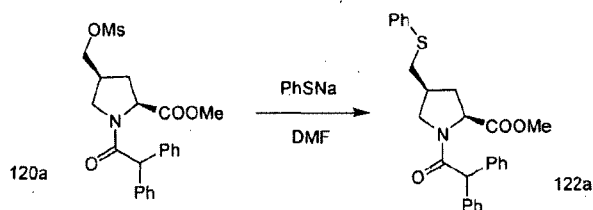
1. Procedure for the preparation of 120a



10 To a solution of 54h (1.90 g, 5.37 mmol) and Et₃N (0.71 g, 6.98 mmol) in DCM (15 mL) at 0°C was added MsCl (0.67 g, 5.91 mmol) and the mixture was stirred at 0°C for 30 min, TLC (PE:EA=1:1) showed that the starting material was consumed. The mixture was washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=1:0 to 1:1) to give 120a (2.2 g, 95%) as a white solid.

15 LC-MS (Agilent, P-2): R_t 2.85 min; m/z calculated for C₂₂H₂₆NO₆S [M+H]⁺ 432.2, [M+Na]⁺ 454.1, found [M+H]⁺ 432.2, [M+Na]⁺ 454.1.

2. Procedure for the preparation of 122a

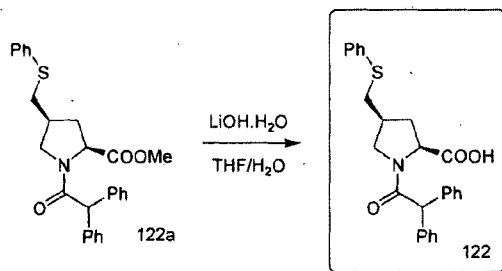


20 A mixture of 120a (500 mg, 1.39 mmol), and PhSNa (229 mg, 1.74 mmol) in DMF (10 mL) was heated at 80°C overnight, TLC (PE:EA=2:1) showed that most of the starting material was consumed. The mixture was cooled to RT, poured into ice-water (60 mL) and extracted with EA (20 mL x 3). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=1:0 to 2:1) to give 122a (150 mg, 29%) as a viscous colorless oil.

25 LC-MS (Agilent, P-2): R_t 3.30 min; m/z calculated for C₂₇H₂₇NO₃S [M+H]⁺ 446.2, found [M+H]⁺ 446.2.

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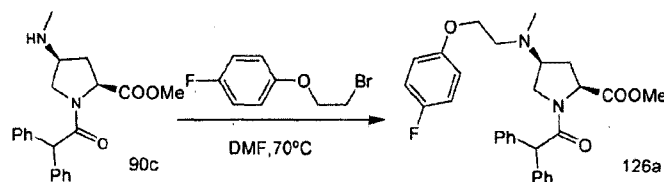
3. Procedure for the preparation of 122



A mixture of 122a (50 mg, 0.11 mmol) and LiOH.H₂O (14 mg, 0.33 mmol) in THF/H₂O (3 mL/1 mL) was stirred at RT overnight, TLC (PE:EA=2:1) showed that the starting material
 5 was consumed. The mixture was concentrated *in vacuo* and the residue was dissolved in water (10 mL), washed with ether then acidified to pH 3~4 with a 3 M aqueous HCl solution and extracted with DCM. The organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to give 122 (30 mg, 62%) as a white solid. LC-MS (Agilent, P-2): R_t 3.18 min; m/z calculated for C₂₆H₂₅NO₃S [M+H]⁺ 432.2, [M+Na]⁺
 10 454.2, found [M+H]⁺ 432.2, [M+Na]⁺ 454.1. HPLC (JULY-L) (214 and 254 nm): R_t 9.24 min. HPLC (ZSJ-2) (214 and 254 nm): R_t 21.70 min.

Example 65: Compound 126 (2S,4S)-1-(2,2-diphenylacetyl)-4-((2-fluorophenoxy)ethyl)(methylamino)pyrrolidine-2-carboxylic acid

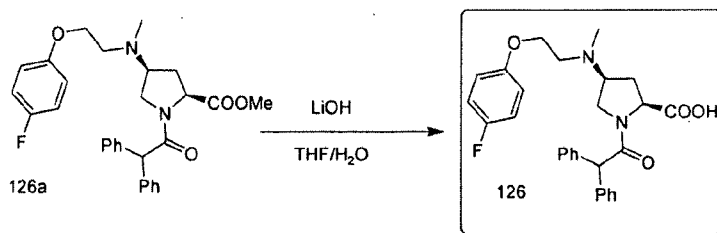
1. Procedure for the preparation of 126a



A mixture of 90c (50 mg, 0.14 mmol), Cs₂CO₃ (68 mg, 0.21 mmol) and 4-fluorophenylethyl bromide (37 mg, 0.17 mmol) in DMF (2 mL) was heated at 70°C overnight, TLC (DCM:MeOH=20:1) showed that the starting material was consumed.
 20 The mixture was cooled to RT, partitioned between EA (30 mL) and H₂O (30 mL) and the organic layer was separated, washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA =10: 1 to 1: 2) to give 126a (40 mg, 58%) as a yellow oil. LC-MS (Waters): R_t 6.07 min; m/z calculated for C₂₉H₃₁FN₂O₄ [M+H]⁺ 491.1, found [M+H]⁺ 491.1.

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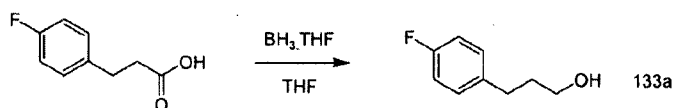
2. Procedure for the preparation of 126



A mixture of 126a (127 mg, 0.26 mmol) and LiOH.H₂O (44 mg, 1.04 mmol) in THF/H₂O (3 mL/0.5 mL) was stirred at RT overnight, TLC (DCM:MeOH=20:1) showed that the starting material was consumed. The mixture was concentrated *in vacuo*, the residue was dissolved in H₂O (3 mL), acidified to pH ~5 with a 3 M aqueous HCl solution and extracted with DCM (10 mL x 2). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by preparative HPLC to give 126 (20 mg, 18%) as a white solid. LC-MS (Agilent, P-2): R_t 2.824 min; m/z calculated for C₂₈H₂₉FN₂O₄ [M+H]⁺ 477.2, found [M+H]⁺ 477.2. HPLC (ZSJ-2) (214 and 254 nm): R_t 16.13 min.

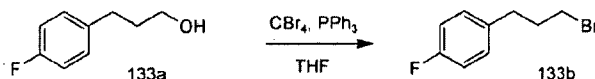
Example 66: Compound 133 (2S,4S)-1-(2,2-diphenylacetyl)-4((3-(4-fluorophenyl)propyl)thio)pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of 133a

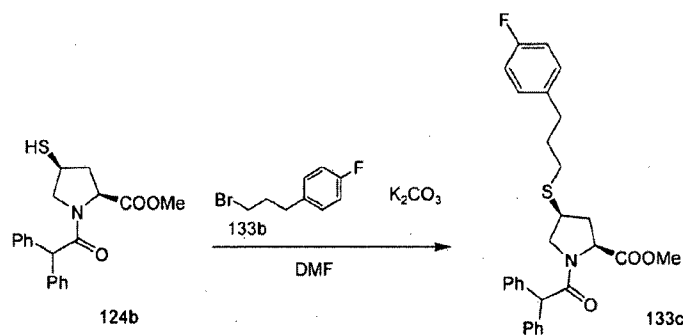


To a solution of 3-(4-fluorophenyl) propanoic acid (6.0 g) in THF (30 mL) at 0°C under a N₂ atmosphere was added BH₃.THF (1 M in THF, 42.8 mL, 42.8 mmol) dropwise and the mixture was allowed to warm slowly to RT and stirred for 3 h, TLC (PE:EA=2:1) showed that the starting material was consumed. The mixture was re-cooled to 0°C, quenched with MeOH (5 mL) then water (10 mL) and concentrated *in vacuo*. The residue was diluted with water (20 mL) and extracted with EA. The organic phase was washed with a saturated aqueous NaHCO₃ solution (20 mL) then brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to give 133a (5.0 g, 90%) as a colorless oil.

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2. Procedure for the preparation of 133b

To a solution of 133a (937 mg, 6.08 mmol) and PPh₃ (1.59 g, 6.08 mmol) in THF (20 mL) at 0°C was added CBr₄ (2.11 g, 6.38 mmol) in portions and the mixture was allowed to warm slowly to RT and stirred for 3 h, TLC (PE:EA=10:1) showed that most of the starting material was consumed. The mixture was filtered the filtrate was concentrated *in vacuo*. The residue was purified by chromatography (100% PE) to give 133b (724 mg, 54%) as a colorless oil.

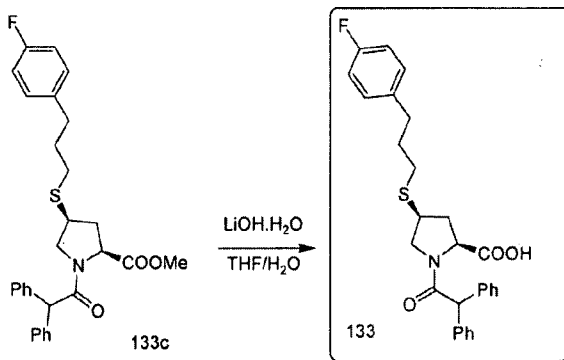
3. Procedure for the preparation of 133c

10

To a solution of 124b (202 mg, 0.57 mmol) in DMF (10 mL) was added K₂CO₃ (87 mg, 0.63 mmol) and 133b (136 mg, 0.63 mmol) and the mixture was heated at 80°C overnight, TLC (PE:EA=2:1) showed that the starting material was consumed. The mixture was poured into ice-water (30 mL) and extracted with EA (15 mL x 2). The combined organic extracts were washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE: EA=8:1 to 5:1) to give 133c (232 mg, 83%) as a colorless oil. LC-MS (Agilent, P-2): R_t 3.26 min; m/z calculated for C₂₉H₃₀FNO₃S [M+H]⁺ 492.2, found [M+H]⁺ 492.2.

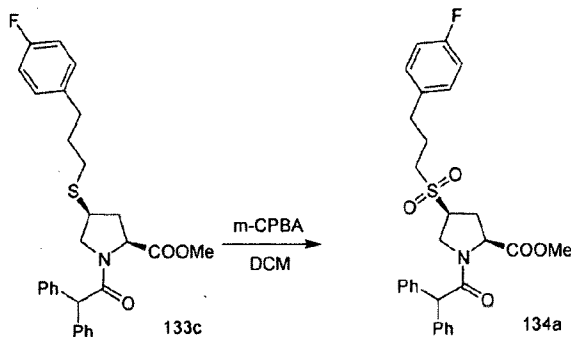
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4. Procedure for the preparation of 133

A mixture of 133c (105 mg, 0.21 mmol) and LiOH.H₂O (27 mg, 0.63 mmol) in THF/H₂O (3 mL/ 1 mL) was stirred at RT overnight, TLC (PE:EA=1:1) showed that the starting material was consumed. The mixture was concentrated *in vacuo*, the residue was dissolved in water (10 mL), acidified to pH 4~5 with a 3 M aqueous HCl solution and extracted with DCM. The organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* to give 133 (100 mg, 98%) as a white solid. LC-MS (Agilent, P-2): R_t 3.29 min; m/z calculated for C₂₈H₂₈FNO₃S [M+H]⁺ 478.2, found [M+H]⁺ 478.2. HPLC (JULY-L) (214 and 254 nm): R_t 9.34 min.

Example 67: Compound 134 (2S,4S)-1-(2,2-diphenylacetyl)-4-((3-(4-fluorophenyl)propyl)sulfonyl)pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of 134a

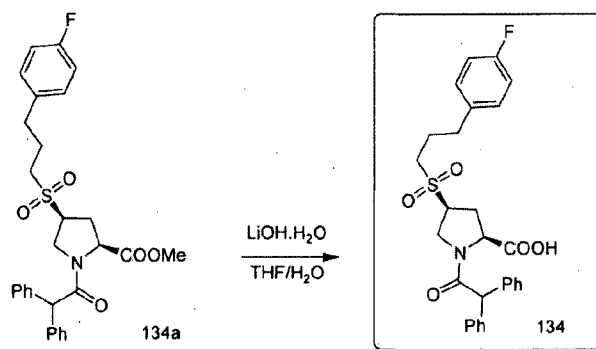
To a solution of 133c (105 mg, 0.21 mmol) in DCM (5 mL) was added 80% m-CPBA (115 mg, 0.53 mmol) and the mixture was stirred at RT overnight, TLC (PE:EA=1:1) showed that the starting material was consumed. The reaction was quenched with a saturated aqueous NaHSO₃ solution and the mixture was washed with a saturated aqueous Na₂CO₃

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solution (5 mL), then brine (5 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=8:1 to 2:1) to give 134a (100 mg, 90%) as a colorless oil. LC-MS (Agilent, P-2): R_t 3.04 min; m/z calculated for $\text{C}_{29}\text{H}_{30}\text{FNO}_5\text{S}$ $[\text{M}+\text{H}]^+$ 524.2, $[\text{M}+\text{Na}]^+$ 546.2, found $[\text{M}+\text{H}]^+$ 524.2, $[\text{M}+\text{Na}]^+$ 546.2.

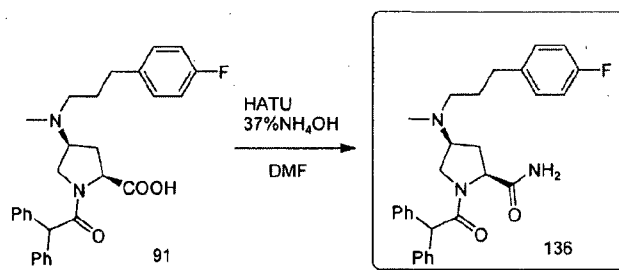
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2. Procedure for the preparation of 134



A mixture of 134a (100 mg, 0.19 mmol) and $\text{LiOH}\cdot\text{H}_2\text{O}$ (24 mg, 0.57 mmol) in THF/ H_2O (3 mL/ 1 mL) was stirred at RT overnight, TLC (PE:EA=1:1) showed that the starting material was consumed. The mixture was concentrated *in vacuo*, the residue was dissolved in water (3 mL), washed with Et_2O then acidified to pH 4~5 with a 3 M aqueous HCl solution. The resulting precipitate was collected by filtration and dried at 55°C to give 134 (60 mg, 61%) as a white solid. LC-MS (Agilent, P-2): R_t 2.94 min; m/z calculated for $\text{C}_{28}\text{H}_{28}\text{FNO}_5\text{S}$ $[\text{M}+\text{H}]^+$ 510.2, $[\text{M}+\text{Na}]^+$ 532.2, found $[\text{M}+\text{H}]^+$ 510.2, $[\text{M}+\text{Na}]^+$ 532.2. HPLC (JULY-L) (214 and 254 nm): R_t 8.91 min.

Example 68: Compound 136 (2S,4S)-1-(2,2-diphenylacetyl)-4-((3-(4-fluorophenyl)propyl)(methyl)amino)pyrrolidine-2-carboxamide



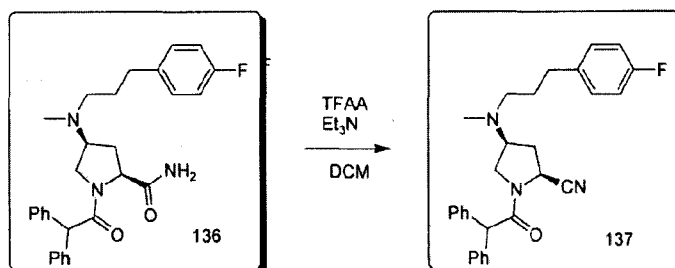
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To a solution of 91 (1.2 g, 2.53 mmol) in DMF (20 mL) was added DIPEA (645 mg, 5.03 mmol) and HATU (1.54 g, 4.05 mmol) and the mixture was stirred at RT for 1 h. A 37% aqueous NH_4OH solution (1 mL) was then added and stirring was continued at RT overnight, TLC (DCM:MeOH=10:1) showed that the starting material was consumed.

5 Water (30 mL) was added and the mixture was extracted with EA (30 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by column chromatography (DCM:MeOH=1:0 to 20:1) to afford 136 (500 mg, 40%) as a white solid. LC-MS (Agilent, P-2): R_t 2.825 min; m/z calculated for $\text{C}_{29}\text{H}_{32}\text{FN}_3\text{O}_2$ $[\text{M}+\text{H}]^+$ 474.3, found

10 $[\text{M}+\text{H}]^+$ 474.3. HPLC (JULY-L) (214 and 254 nm): R_t 9.032 min.

Example 69: Compound 137 (2S,4S)-1-(2,2diphenylacetyl)-4-((3-(4-fluorophenyl)propyl)(methyl)amino)pyrrolidine-2-carbonitrile



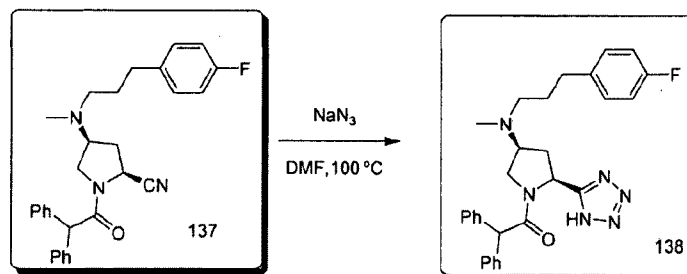
15 To a solution of 136 (430 mg, 0.91 mmol) in DCM (5 mL) at 0°C was added TEA (139 mg, 1.37 mmol) and the mixture was stirred at 0°C for 15 min. TFAA (231 mg, 1.1 mmol) was then added drop-wise at 0°C and the mixture was stirred at that temperature for 30 min before allowing to warm slowly to RT and stirred overnight, TLC (PE:EA=1:2) showed that the starting material was consumed. The reaction was quenched with a saturated

20 aqueous NaHCO_3 solution, the layers were separated and the aqueous layer was extracted with DCM (15 mL x 2). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by column chromatography (PE:EA=10:1 to 1:1) to give 137 (320 mg, 77%) as a brown oil. LC-MS (Agilent, P-2): R_t 2.761 min; m/z calculated for $\text{C}_{29}\text{H}_{30}\text{FN}_3\text{O}$ $[\text{M}+\text{H}]^+$ 456.2, found $[\text{M}+\text{H}]^+$

25 456.2. HPLC (JULY-L) (214 and 254 nm): R_t 8.894 min.

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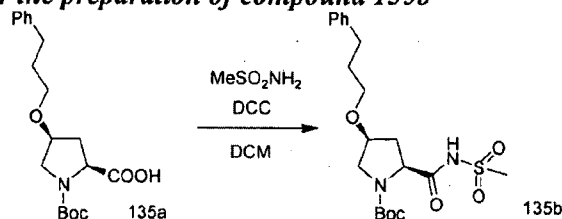
Example 70: Compound 138 1-(2*S*,4*S*)-4-((3-(4-fluorophenyl)propyl)(methyl)amino)-2-(1*H*-tetrazol-5-yl)pyrrolidin-1-yl)-2,2-diphenylethanoate



To a solution of 137 (240 mg, 0.53 mmol) in DMF (3 mL) was added NaN_3 (172 mg, 2.64 mmol) and NH_4Cl (192 mg, 3.55 mmol) and the flask was sealed and heated at 100°C overnight, TLC (DCM:MeOH=50:1) showed that the starting material was consumed. The mixture was partitioned between EA (30 mL) and water (30 mL), the organic layer was collected and washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by chromatography (DCM:MeOH=20:1) to afford 138 (165 mg, 65 %) as a white solid. LC-MS (Agilent, P-2): R_t 2.879 min; m/z calculated for $\text{C}_{29}\text{H}_{31}\text{FN}_6\text{O}$ $[\text{M}+\text{H}]^+$ 499.3, found $[\text{M}+\text{H}]^+$ 499.3. HPLC (JULY-L) (214 and 254 nm): R_t 8.871 min.

Example 71: Compound 135 (2*S*,4*S*)-1-(2,2-diphenylacetyl)-*N*-(methylsulfonyl)-4-(phenylpropoxy)pyrrolidine-2-carboxamide

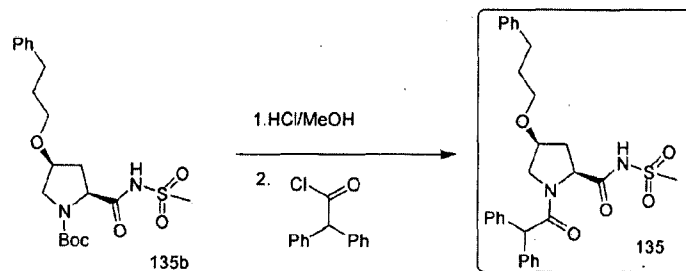
1. Procedure for the preparation of compound 135b



To a stirred solution of 135a (20 mg, 0.057 mmol) in DCM (0.2 mL) was added MeSO_2NH_2 (6 mg, 0.062 mmol), DCC (14 mg, 0.068 mmol) and DMAP (2.0 mg, 0.017 mmol). The flask was sealed and the mixture was stirred at RT for 2 days, LCMS analysis showed that the starting material was consumed. The mixture was concentrated *in vacuo* to give 135b (50 mg) as a white solid, which was used directly in the next step without purification. LC-MS (Agilent, P-2): R_t 2.78 min; m/z calculated for $\text{C}_{20}\text{H}_{30}\text{N}_2\text{O}_6\text{S}$ $[\text{M}+\text{Na}]^+$ 449.2, found $[\text{M}+\text{Na}]^+$ 449.3.

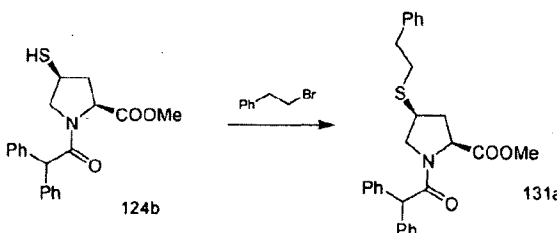
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2. Procedure for the preparation of 135



A mixture of 135b (50 mg, assumed 0.057 mmol) and a 4 M HCl/MeOH solution (5 mL) was stirred at RT overnight, LCMS analysis showed that the starting material was consumed. The mixture was concentrated *in vacuo*, the residue was dissolved in water, basified to pH 8 with K_2CO_3 and extracted with DCM. The organic layer was then dried over Na_2SO_4 and filtered. To the filtrate was added Et_3N (9 mg, 0.085 mmol) then diphenyl acetyl chloride (16 mg, 0.068 mmol) and the mixture was stirred at RT for 1 h, TLC (DCM:MeOH=10:1) showed a that a major new product formed. The mixture was washed with a 20% aqueous K_2CO_3 solution, brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by preparative HPLC to give 135 (11 mg, 38% over three steps) as a white solid. LC-MS (Agilent, P-2): R_t 2.68 min; m/z calculated for $C_{29}H_{32}N_2O_5S$ $[M+H]^+$ 521.2, found $[M+H]^+$ 521.2. HPLC (JULY-L) (214 and 254 nm): R_t 9.17 min.

Example 72: Compound 131 (2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-(phenethylthio)pyrrolidine-2-carboxylic acid
1. Procedure for the preparation of 131a



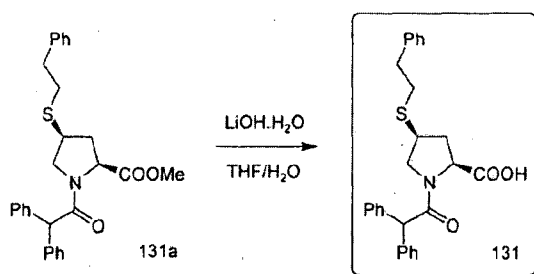
A mixture of 124b (190 mg, 0.53 mmol), 1-(2-bromoethyl)benzene (109 mg, 0.58 mmol) and K_2CO_3 (81 mg, 0.58 mmol) in DMF (10 mL) was heated at 80°C overnight, TLC (PE:EA= 2:1) showed that the starting material was consumed. The mixture was cooled to RT, poured into ice-water (60 mL) and extracted with ether (30 mL x 2). The combined

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organic extracts were washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=1:0 to 4:1) to give 131a (200 mg, 83%) as a colorless oil. LC-MS (Agilent, P-2): R_t 3.15 min; m/z calculated for $\text{C}_{28}\text{H}_{29}\text{NO}_3\text{S}$ $[\text{M}+\text{H}]^+$ 460.2, found $[\text{M}+\text{H}]^+$ 460.2.

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2. Procedure for the preparation of 131



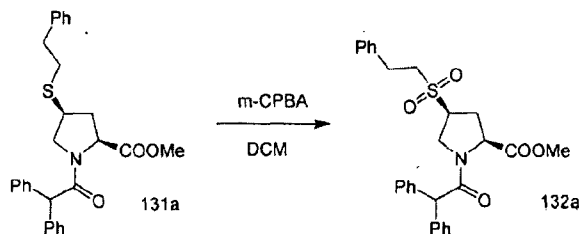
A mixture of 131a (80 mg, 0.17 mmol) and $\text{LiOH}\cdot\text{H}_2\text{O}$ (29 mg, 0.69 mmol) in THF/water (3 mL/1 mL) was stirred at RT overnight, TLC (PE:EA=2:1) showed that the starting material was consumed. The mixture was concentrated *in vacuo*, the residue was dissolved in water (10 mL), acidified to pH=3-4 with a 3 M aqueous HCl solution and extracted with DCM (10 mL x 2). The combined organic extracts were washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give 131 (70 mg, 93%) as a white solid. LC-MS (Agilent, P-2): R_t 3.20 min; m/z calculated for $\text{C}_{27}\text{H}_{27}\text{NO}_3\text{S}$ $[\text{M}+\text{H}]^+$ 446.2, found $[\text{M}+\text{H}]^+$ 446.2. HPLC (JULY-L) (214 and 254 nm): R_t 9.27 min.

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Example 73: Compound 132 (2S,4S)-1-(2,2-diphenylacetyl)-4-(phenethylsulfonyl)pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of 132a

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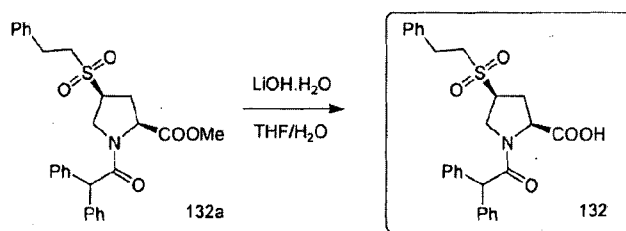
To a stirred solution of 131a (120 mg, 0.26 mmol) in DCM (10 mL) at 0°C was added 80% m-CPBA (140 mg, 0.65 mmol) in three portions and the mixture was allowed to warm slowly to RT and stirred overnight, TLC (PE:EA=2:1) showed that the starting material

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was consumed. The mixture was washed with a saturated aqueous Na_2CO_3 solution (5 mL x 2), brine (5 mL x 2) then dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=1:0 to 3:1) to give 132a (110 mg, 86%) as a colorless oil. LC-MS (Agilent, P-2): R_t 3.01 min; m/z calculated for $\text{C}_{28}\text{H}_{29}\text{NO}_5\text{S}$ $[\text{M}+\text{H}]^+$ 492.2, $[\text{M}+\text{Na}]^+$ 514.2, found $[\text{M}+\text{H}]^+$ 492.2, $[\text{M}+\text{Na}]^+$ 514.2.

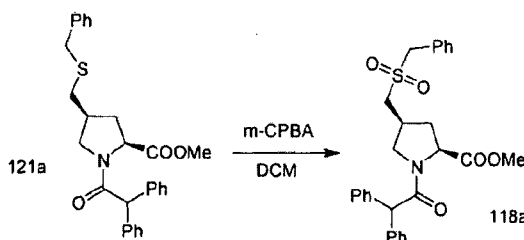
2. Procedure for the preparation of 132



A mixture of 132a (110 mg, 0.22 mmol) and $\text{LiOH}\cdot\text{H}_2\text{O}$ (37 mg, 0.88 mmol) in THF/water (3 mL/1 mL) was stirred at RT overnight, TLC (PE:EA=1:1) showed that the starting material was consumed. The mixture was concentrated *in vacuo*, the residue was dissolved in water (10 mL) and acidified to pH 3-4 with a 3 M aqueous HCl solution. The resulting precipitate was collected by filtration then dried to give 132 (80 mg, 77%) as a white solid. LC-MS (Agilent, P-2): R_t 2.84 min; m/z calculated for $\text{C}_{27}\text{H}_{27}\text{NO}_5\text{S}$ $[\text{M}+\text{H}]^+$ 478.2, found $[\text{M}+\text{H}]^+$ 478.2. HPLC (JULY-L) (214 and 254 nm): R_t 8.84 min.

Example 74: Compound 118 (2S,4S)-4-((benzylsulfonyl)methyl)-1-(diphenylacetyl)-pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of 118a

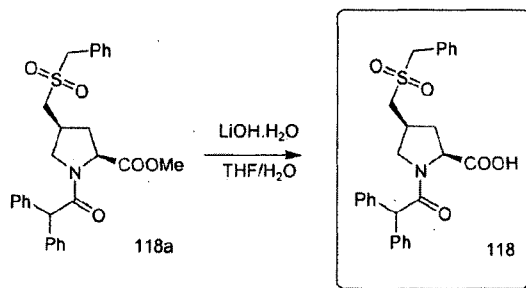


To a solution of 121a (80 mg, 0.17 mmol) in DCM (6 mL) was added 80% m-CPBA (94 mg, 0.43 mmol) and the mixture was stirred at RT overnight, TLC (PE:EA=2:1) showed that the 121a was consumed. The mixture was washed with a saturated aqueous Na_2CO_3 solution, brine (10 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue

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was purified by chromatography (PE:EA=8:1 to 1.5:1) to give 118a (77 mg, 90%) as a white solid. LC-MS (Agilent, P-2): R_t 3.12 min; m/z calculated for $C_{31}H_{32}N_2O_3$ $[M+H]^+$ 492.2, $[M+Na]^+$ 514.2, found $[M+H]^+$ 492.2, $[M+Na]^+$ 514.2.

5 2. Procedure for the preparation of 118

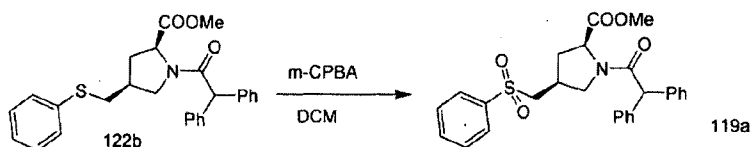


A mixture of 118a (77 mg, 0.16 mmol) and $\text{LiOH}\cdot\text{H}_2\text{O}$ (20 mg, 0.47 mmol) in THF/ H_2O (4 mL/1 mL) was stirred at RT overnight, TLC (PE:EA=1:1) showed that the starting material was consumed. The mixture was concentrated *in vacuo*, the residue was dissolved in water (5 mL), acidified to pH 4~5 with a 3 M aqueous HCl solution and the resulting precipitate was collected by filtration and dried at 60°C to give 118 (40 mg, 54%) as a white solid. LC-MS (Agilent, P-2): R_t 2.88 min; m/z calculated for $C_{27}H_{27}NO_5S$ $[M+H]^+$ 478.2, $[M+Na]^+$ 500.2, found $[M+H]^+$ 478.2, $[M+Na]^+$ 500.2. HPLC (JULY-L) (214 and 254 nm): R_t 8.75 min. HPLC (ZSJ-2) (214 and 254 nm): R_t 16.68 min.

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Example 75: Compound 119 (2S,4S)-4-((phenylsulfonyl)methyl)-1-(diphenylacetyl)-pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of 119a



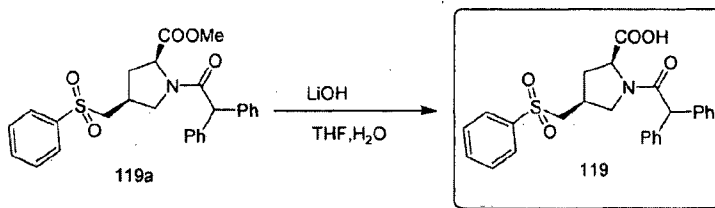
To a solution of 122b (80 mg, 0.18 mmol) in DCM (5 mL) at 0°C was added 80% m-CPBA (97 mg, 0.45 mmol) and the mixture was allowed to warm slowly to RT and stirred for 3 h, TLC (PE:EA=1:1) showed that the starting material was consumed. A saturated aqueous Na_2CO_3 solution was added, the layers were separated and the aqueous layer was extracted with DCM (20 mL x 3). The combined organic extracts were washed

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with brine, dried over Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by chromatography (PE:EA=1:0 to 1:1) to give 119a (55 mg, 64%) as a white solid. LC-MS (Waters): R_t 6.27 min; m/z calculated for $\text{C}_{27}\text{H}_{27}\text{NO}_5\text{S}$ $[\text{M}+\text{H}]^+$ 478.0, $[\text{M}+\text{Na}]^+$ 500.1 found $[\text{M}+\text{H}]^+$ 478.0, $[\text{M}+\text{Na}]^+$ 500.0.

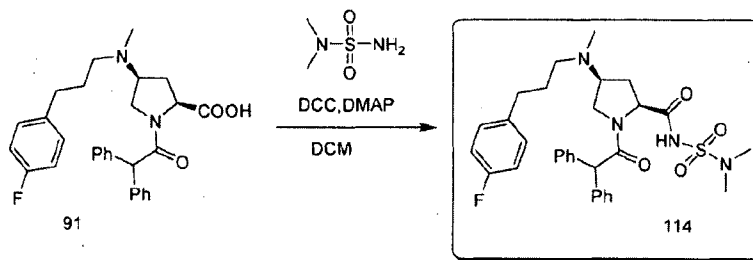
5 2. Procedure for the preparation of 119



A mixture of 119a (55 mg, 0.12 mmol) and $\text{LiOH} \cdot \text{H}_2\text{O}$ (15 mg, 0.35 mmol) in THF/ H_2O (2 mL/0.5 mL) was stirred at RT overnight, TLC (PE:EA=1:1) showed that the starting material was consumed. The mixture was concentrated *in vacuo*, the residue was dissolved in water, acidified to pH 3~4 with a 3 M aqueous HCl solution and the resulting precipitate was collected by filtration then purified by preparative HPLC to give 119 (30 mg, 50%) as a white solid. LC-MS (Agilent, P-2): R_t 2.917 min; m/z calculated for $\text{C}_{26}\text{H}_{25}\text{NO}_5\text{S}$ $[\text{M}+\text{H}]^+$ 464.2, found $[\text{M}+\text{H}]^+$ 464.2. HPLC (JULY-L) (214 and 254 nm): R_t 8.73 min. HPLC (ZSJ-2) (214 and 254 nm): R_t 16.36 min.

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Example 76: Compound 114 (2S,4S)-N-(N,N-dimethylsulfamoyl)-1-(2,2-diphenylacetyl)-4-((3-(4-fluorophenyl)propyl)(methyl)amino)pyrrolidine-2-carboxylic acid



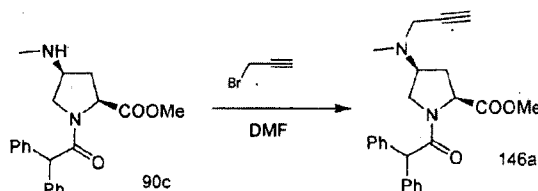
To a solution of 91 (100 mg, 0.21 mmol) in DCM (5 mL) was added *N,N*-dimethylsulfamide (28.8 mg, 0.23 mmol), DMAP (6.3 mg, 0.063 mmol) and DCC (52 mg, 0.25 mmol) and the mixture was stirred at RT for 72 h, TLC (DCM:MeOH= 20:1) showed that the starting material was consumed. The mixture was filtered, the filtrate was concentrated *in vacuo* and the residue was purified by preparative HPLC to give 114 (56

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mg, 46%) as a white solid. LC-MS (Agilent, P-2): R_t 2.86 min; m/z calculated for $C_{31}H_{37}FN_4O_4S$ $[M+H]^+$ 581.3, found $[M+H]^+$ 581.3. HPLC (JULY-L) (214 and 254 nm): R_t 8.88 min.

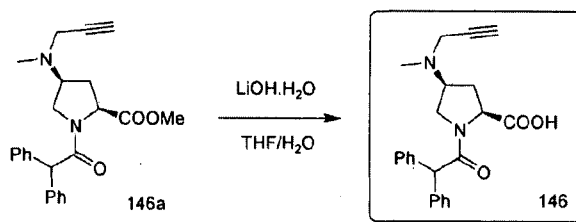
5 Example 77: Compound 146 (2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-methyl(prop-2-yn-1-yl)amino)pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of 146a



To a solution of 90c (200 mg, 0.57 mmol) in DMF (8 mL) was added CS_2CO_3 (222 mg, 0.68 mmol) then 3-bromoprop-1-yne (68 mg, 0.57 mmol). The flask was sealed and the mixture was heated at 40°C overnight, TLC (PE:EA=1:2) showed that the starting material was consumed. The mixture was poured into ice-water (30 mL) and extracted with EA (15 mL x 4). The combined organic extracts were washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=10:1 to 3:1) to give 146a (61 mg, 27%) as a colorless oil. LC-MS (Agilent, P-2): R_t 2.592 min; m/z calculated for $C_{24}H_{26}N_2O_3$ $[M+H]^+$ 391.2, found $[M+H]^+$ 391.2.

2. Procedure for the preparation of 146



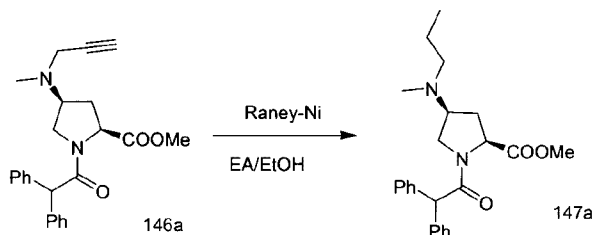
A mixture of 146a (61 mg, 0.21 mmol) and $LiOH \cdot H_2O$ (20 mg, 0.47 mmol) in THF/ H_2O (3 mL/1 mL) was stirred at RT overnight, TLC (PE:EA=1:2) showed that the starting material was consumed. The mixture was concentrated *in vacuo* to remove THF, the residue was dissolved in water (5 mL), acidified to pH ~ 4 with a 4 M aqueous HCl solution and extracted with DCM (5 mL x 5). The combined organic extracts were washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give crude 146 (57 mg) and 27

mg of this crude material was purified by preparative HPLC to give pure 146 (20 mg, ~53%) as a viscous colorless oil. LC-MS (Agilent, P-2): R_t 2.51 min; m/z calculated for $C_{23}H_{24}N_2O_3$ $[M+H]^+$ 377.2, found $[M+H]^+$ 377.2. HPLC (JULY-L) (214 and 254 nm): R_t 8.50 min.

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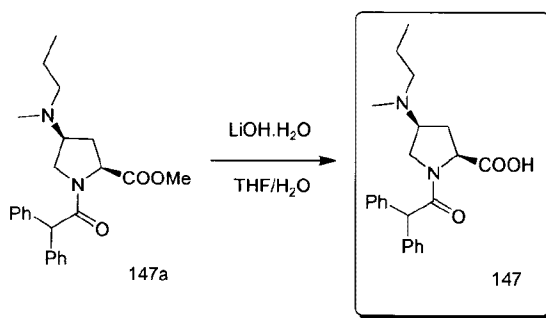
Example 78: Compound 147 (2S,4S)-1-(2,2-diphenylacetyl)-4-(methyl(propyl)amino)pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of 147a



10 A mixture of 146a (29 mg, 0.074 mmol) and RaneyTM-Ni (50 mg) in EA/EtOH (10 mL/10 mL) was stirred under a H_2 atmosphere (1 atm) at 30°C overnight, LCMS analysis showed that the starting material was consumed. The mixture was filtered and the filtrate was concentrated *in vacuo* to give 147a (22 mg, 75%) as a colorless oil. LC-MS (Agilent, P-2): R_t 2.75 min; m/z calculated for $C_{24}H_{30}N_2O_3$ $[M+H]^+$ 395.2, found $[M+H]^+$ 395.2.

15 **2. Procedure for the preparation of 147**



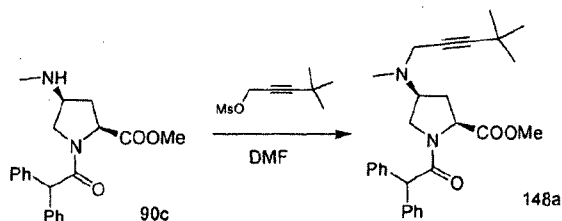
A mixture of 147a (22 mg, 0.056 mmol) and LiOH.H₂O (7 mg, 0.168 mmol) in THF/H₂O (3 mL/1 mL) was stirred at RT for 2 days, LCMS analysis showed that the starting material was consumed. The mixture was concentrated *in vacuo* to remove the THF, the residue was dissolved in water (5 mL), acidified to pH 4 with a 4 M aqueous HCl solution and concentrated *in vacuo*. The residue was purified by preparative HPLC to give 147 (7 mg, 33%) as a white solid. LC-MS (Agilent, P-2): R_t 2.47 min; m/z calculated for $C_{23}H_{28}N_2O_3$ $[M+H]^+$ 381.2, found $[M+H]^+$ 381.2. HPLC (JULY-L) (214 and 254 nm): R_t 8.55 min.

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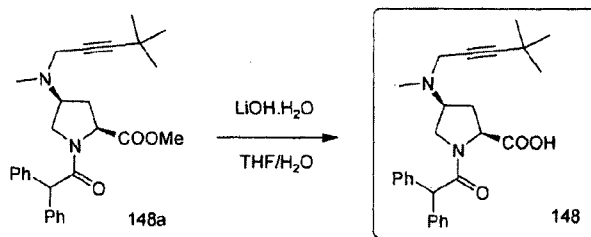
Example 79: Compound 148 ((2*S*,4*S*)-4-((4,4-dimethylpent-2-yn-1-yl)(methyl)amino)-1-(2,2-diphenylacetyl)pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of 148a



To a solution of 90c (300 mg, 0.85 mmol) in DMF (8 mL) was added Cs_2CO_3 (333 mg, 1.02 mmol) then 4,4-dimethylpent-2-ynyl methanesulfonate (194 mg, 1.02 mmol) and the mixture was heated at 40°C overnight, TLC (PE:EA=1:1) showed that the starting material was consumed. The mixture was poured into ice-water (30 mL) and extracted with EA (15 mL x 3). The combined organic extracts were washed with brine (20 mL x 2), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=10:1 to 4:1) to give 148a (100 mg, 26%) as a colorless oil. LC-MS (Agilent, P-2): R_t 3.60 min; m/z calculated for $\text{C}_{28}\text{H}_{34}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$ 447.3, found $[\text{M}+\text{H}]^+$ 447.3.

2. Procedure for the preparation of 148

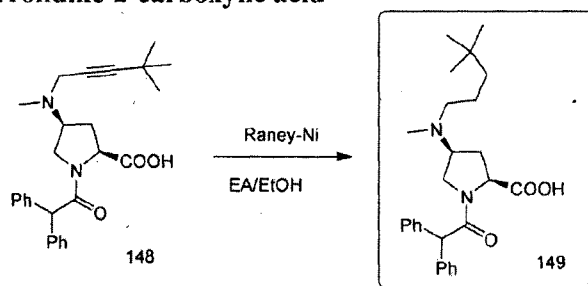


A mixture of 148a (100 mg, 0.22 mmol) and $\text{LiOH}\cdot\text{H}_2\text{O}$ (28 mg, 0.67 mmol) in THF/ H_2O (5 mL/1 mL) was stirred at RT overnight, TLC (PE:EA=1:1) showed that the starting material was consumed. The mixture was concentrated *in vacuo* to remove THF, the residue was dissolved in water (5 mL), acidified to pH ~4 with a 4 M aqueous HCl solution and extracted with DCM (5 mL x 4). The combined organic extracts were washed with brine (10 mL x 2), dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give crude 148 (95 mg) and 35 mg of the crude material was purified by preparative HPLC to give pure 148 (25 mg, 71%) as a white solid. LC-MS (Agilent, P-2): R_t 3.08 min; m/z

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calculated for $C_{27}H_{32}N_2O_3$ $[M+H]^+$ 433.2, found $[M+H]^+$ 433.2. HPLC (JULY-L) (214 and 254 nm): R_t 9.08 min.

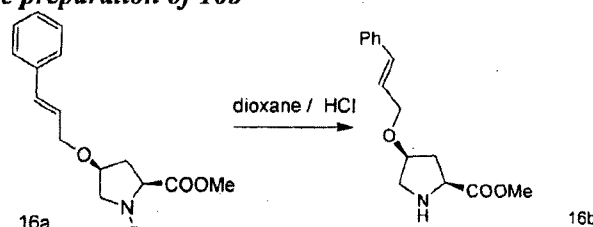
Example 80: Compound 149 ((2S,4S)-4-((4,4-dimethylpentyl)methyl)amino)-1-(2,2-diphenylacetyl)pyrrolidine-2-carboxylic acid



A mixture of 148 (30 mg, 0.069 mmol) and Raney-Ni (50 mg) in EA/EtOH (10 mL/10 mL) was stirred under a H_2 atmosphere (1 atm) at $38^\circ C$ overnight, LCMS analysis showed that the starting material was consumed. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by preparative HPLC to give 149 (12 mg, 40%) as a white solid. LC-MS (Agilent, P-2): R_t 2.63 min; m/z calculated for $C_{27}H_{36}N_2O_3$ $[M+H]^+$ 437.3, found $[M+H]^+$ 437.3. HPLC (JULY-L) (214 and 254 nm): R_t 9.15 min.

Example 81: Compound 16 ((2S,4S)-1-(2,2-diphenylacetyl)-4-(((1R,2R)-2-phenylcyclopropyl)methoxy)pyrrolidine-2-carboxylic acid and (2S,4S)-1-(2,2-diphenylacetyl)-4-(((1S,2S)-2-phenylcyclopropyl)methoxy)pyrrolidine-2-carboxylic acid

1. Procedure for the preparation of 16b

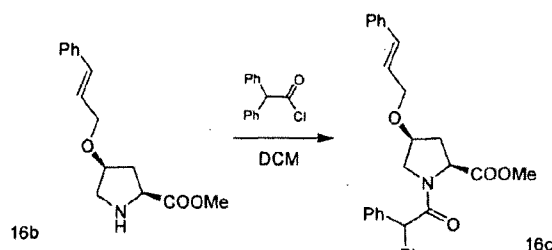


A solution of 16a (12.0 g, 48.8 mmol) in 4 M HCl/diox (60 mL) was stirred at RT overnight, TLC (MeOH:DCM=1:10) showed the starting material was consumed. The mixture was concentrated *in vacuo*, the residue was dissolved in water (50 mL) and extracted with diethyl ether (100 mL x 2). The aqueous layer was basified to pH=9~10 with a saturated aqueous Na_2CO_3 solution and extracted with EA (100 mL x 2). The

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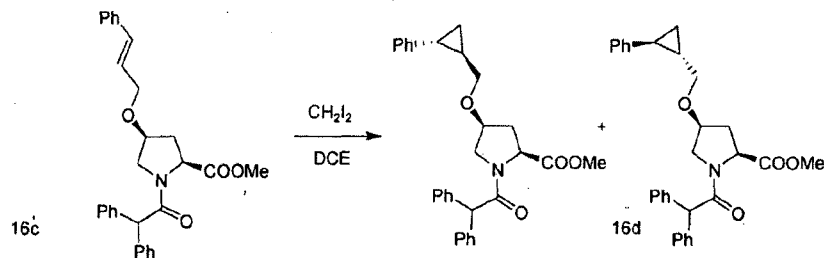
combined organic extracts were washed with brine (100 mL x 2), dried over Na₂SO₄, filtered and concentrated *in vacuo* to give 16b as a colorless oil (5.0 g, 78%). LC-MS (Agilent): R_t 2.81 min; m/z calculated for C₁₉H₁₅NO₃ [M+H]⁺ 262.1, [M+Na]⁺ 284.1, found [M+H]⁺ 262.1, [M+Na]⁺ 284.1.

5 2. Procedure for the preparation of 16c



To a solution of 16b (300 mg, 1.15 mmol) and Et₃N (175 mg, 1.72 mmol) in DCM (5 mL) was added diphenylacetyl chloride (318 mg, 1.38 mmol) at 0°C under N₂ and the mixture was stirred at 0°C for 30 min, TLC (PE:EA=1:1) showed the starting material was consumed. The mixture was washed with brine (3 mL x 2), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE: EA=10:0 to 4:1) to give 16c as a thick oil (300 mg, 57%). LC-MS (Agilent): R_t 3.38 min; m/z calculated for C₂₉H₂₉NO₄ [M+H]⁺ 456.2, [M+Na]⁺ 478.2, found [M+H]⁺ 456.2, [M+Na]⁺ 478.2.

3. Procedure for the preparation of 16d

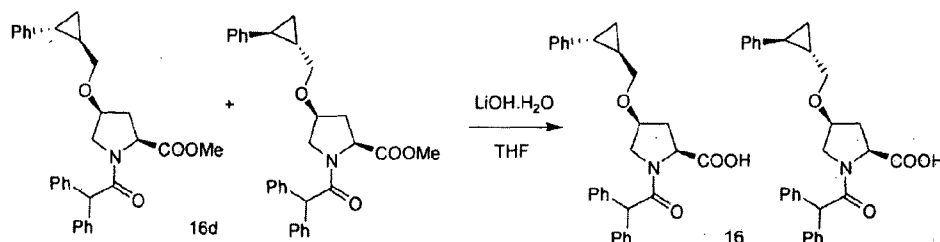


A stirred solution of 16c (150 mg, 0.33 mmol) in dry DCE (5 mL) was cooled to 0°C under a N₂ atmosphere. A ZnEt₂ solution (1 M in hexane, 0.66 mL, 0.66 mmol) was added followed by CH₂I₂ (354 mg, 1.32 mmol) and the mixture was warmed to RT slowly and stirred overnight. The mixture was re-cooled to 0°C, quenched with a saturated aqueous NH₄Cl solution (10 mL) and extracted with DCM (20 mL). The organic layer was separated, washed with brine, dried over Na₂SO₄ then filtered and concentrated *in vacuo*. The residue was purified by chromatography (PE:EA=4:1) to give 16d as a thick oil (120

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mg, 78%). LC-MS (Agilent): R_t 3.38 min; m/z calculated for $C_{30}H_{31}NO_4$ $[M+H]^+$ 470.2, $[M+Na]^+$ 492.2, found $[M+H]^+$ 470.2, $[M+Na]^+$ 492.2.

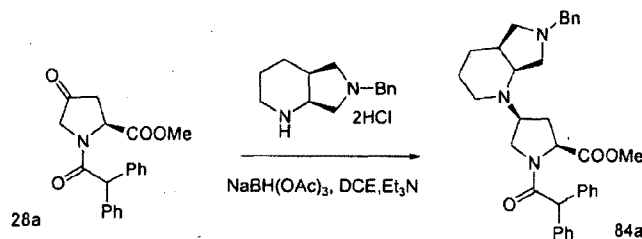
4. Procedure for the preparation of 16



- 5 To a stirred solution of 16d (110 mg, 0.23 mmol) in THF (3 mL) was added a solution of LiOH.H₂O (33 mg, 0.79 mmol) in water (1 mL) and the mixture was stirred at RT overnight, TLC (PE:EtOAc=1:1) showed the starting material was consumed. The mixture was concentrated *in vacuo* to remove most of the THF and the residue was partitioned between DCM (15 mL) and water (15 mL). The aqueous layer was acidified with a 1 M aqueous HCl solution to pH=3~4, the DCM layer was separated and the aqueous layer was extracted again with DCM (15 mL). The combined organic extracts were washed with brine (30 mL x 2), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (DCM: MeOH=50:1 to 20:1) to give the product as a white solid (80 mg, 77%). LC-MS (Agilent): R_t 3.39 min; m/z calculated for $C_{29}H_{29}NO_4$ $[M+H]^+$ 456.2, $[M+Na]^+$ 478.2, found $[M+H]^+$ 456.2, $[M+Na]^+$ 478.2. HPLC (214 and 254 nm): R_t 13.75 min.

Example 82: Compound 84 (2*S*,4*S*)-4-((4*aS*,7*aS*)-6-benzooctahydro-1*H*-pyrrolo[3,4-*b*]pyridin-1-yl)-1-(2,2-diphenylacetyl)pyrrolidine-2-carboxylic acid

6. Procedure for the preparation of 84a

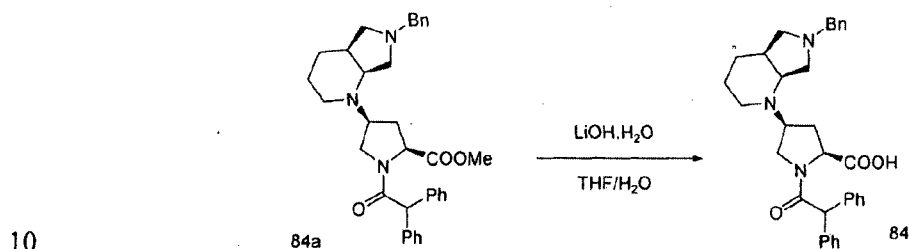


A solution of the amine (257 mg, 0.89 mmol) in DCE (10 mL) was cooled to 0°C and Et₃N (181 mg, 1.78 mmol) was added followed by a solution of 28a (300 mg, 0.89 mmol) in DCE (5 mL). AcOH (0.5 mL) and the mixture was stirred at RT for 30 min. NaBH(OAc)₃

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(282 mg, 1.34 mmol) was added and stirring was continued at RT overnight, TLC (DCM:MeOH=10:1) showed that some of the 28a remained. NaCNBH₃ (1.2 equiv) was added and the mixture was heated at 40°C overnight, TLC (DCM:MeOH=10:1) showed that most of the ketone was consumed. The mixture was washed twice with brine, dried
 5 over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica column (DCM: MeOH=100:1 to 50:1) to give 84a (90 mg, 18%) as a yellow solid. LC-MS (Agilent): R_t 3.28 min; m/z calculated for C₃₄H₃₉N₃O₃ [M+H]⁺ 538.4, found [M+H]⁺ 538.4.

7. Procedure for the preparation of 84

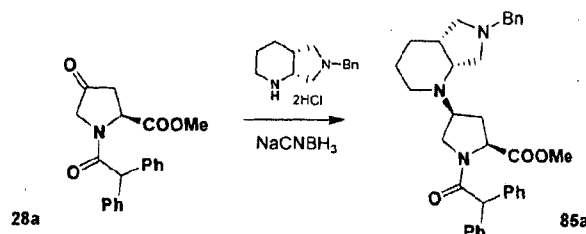


To a mixture of 84a (90 mg, 0.17 mmol) in THF/water (6 mL/2 mL) was added LiOH.H₂O (21 mg, 0.51 mmol) and the mixture was stirred at RT overnight, TLC (DCM:MeOH=20:1) showed the starting material was consumed. Most of the THF was removed *in vacuo*, the residue was dissolved in water (15 mL) and washed with Et₂O (10 mL x 2). The
 15 aqueous layer was then acidified to pH=2-3 with a 1 M aqueous HCl solution and extracted with DCM (10 mL x 3). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo* and the residue was purified by prep-HPLC to give 84 (25 mg, 28%) as a white solid. LC-MS (Agilent): R_t 3.29 min; m/z calculated for C₃₃H₃₇N₃O₃ [M+H]⁺ 524.28, found [M+H]⁺ 524.3. HPLC (JULY-L) (214 and 254 nm): R_t
 20 8.67 min.

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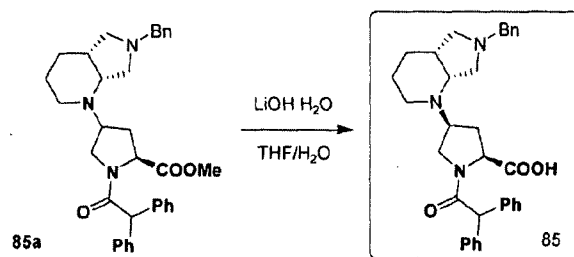
Example 83: Compound 85 (2*S*,4*S*)-4-((4*aR*,7*aR*)-6-benzooctahydro-1*H*-pyrrolo[3,4-*b*]pyridin-1-yl)-1-(2,2-diphenylacetyl)pyrrolidine-2-carboxylic acid

2. Procedure for the preparation of 85a



- 5 To a solution of 28a (417 mg, 1.24 mmol), amine (300 mg, 1.00 mmol) and Et₃N (230 mg, 2.28 mmol) in MeOH (15 mL) was added AcOH (1.0 mL) and the mixture was stirred at RT for 1 h. NaCNBH₃ (80 mg, 1.24 mmol) was then added and the mixture was stirred at RT overnight; TLC (DCM:MeOH=10:1) showed that the starting material was consumed. Most of the MeOH was removed *in vacuo* and the residue was dissolved in water (10 mL)
- 10 and extracted with DCM (10 mL). The organic layer was washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica column (DCM:MeOH=80:1) to give 85a (220 mg, 33%) as a white solid. LC-MS (Agilent): R_t 3.30 min; m/z calculated for C₃₄H₃₉N₃O₃ [M+H]⁺ 538.3, found [M+H]⁺ 538.3.

3. Procedure for the preparation of 85

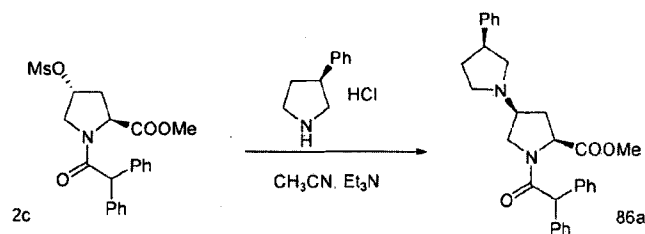


- 15 To a mixture of 85a (220 mg, 0.41 mmol) in THF/water (10 mL/1.5 mL) was added LiOH·H₂O (52 mg, 1.23 mmol) and the mixture was stirred at RT overnight, TLC (DCM:MeOH=10:1) showed that the starting material was consumed. Most of the THF was removed *in vacuo* and the residue was dissolved in water (15 mL) and acidified to
- 20 pH=3-4 with a 3 M aqueous HCl solution. The resulting precipitate was collected by filtration then purified by prep-HPLC to give 85 (66 mg, 30%) as a white solid. LC-MS (Agilent): R_t 3.28 min; m/z calculated for C₃₃H₃₇N₃O₃ [M+H]⁺ 524.3, found [M+H]⁺ 524.3. HPLC (JULY-L) (214 and 254 nm): R_t 8.75 min.

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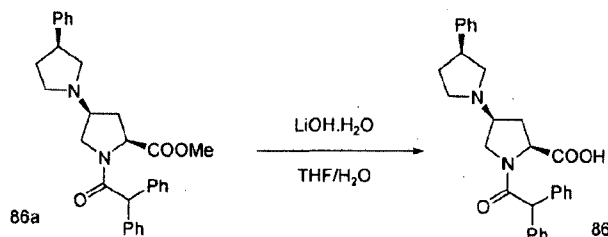
Example 84: Compound 86 (3*S*,3'*S*,5'*S*)-1-(2,2-diphenylacetyl)-3-(phenyl-[1,3'-bipyrrolidine]-5'-carboxylic acid

1. Procedure for the preparation of 86a



To a stirred mixture of (*S*)-3-phenyl-pyrrolidine.hydrochloride (528 mg, 2.8 mmol) in CH₃CN (10 mL) was added Et₃N (285 mg, 2.8 mmol) followed by 2c (600 mg, 1.4 mmol) and the mixture was heated at 110°C in a sealed tube overnight. The solvent was removed *in vacuo* and the residue was partitioned between water (20 mL) and EA (15 mL). The aqueous layer was separated and further extracted with EA (15 mL). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica column (DCM:MeOH= 100:1 to 50:1) to give 86a (230 mg, 35%) as a yellow solid. LC-MS (Agilent): R_t 3.27 min; m/z calculated for C₃₀H₃₂N₂O₃ [M+H]⁺ 469.24, found [M+H]⁺ 469.3.

2. Procedure for the preparation of 86



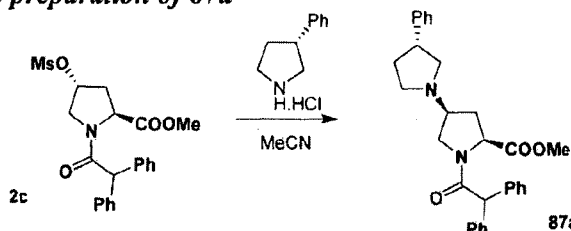
To a mixture of 86a (220 mg, 0.47 mmol) in THF/water (8 mL/3 mL) was added LiOH.H₂O (59 mg, 1.41 mmol) and the mixture was stirred at RT overnight, TLC (DCM:MeOH=20:1) showed the starting material was consumed. Most of the THF was removed *in vacuo* and the residue was dissolved in water (20 mL) and washed with Et₂O (15 mL x 2). The aqueous layer was then acidified to pH=2-3 with a 1 M aqueous HCl solution and extracted with DCM (15 mL x 2). The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by prep-HPLC to give 86 (50 mg, 23%) as a white solid. LC-MS (Agilent): R_t

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3.53 min; m/z calculated for $C_{29}H_{30}N_2O_3$ $[M+H]^+$ 455.24, found $[M+H]^+$ 455.3. HPLC (JULY-L) (214 and 254 nm): R_t 8.80 min.

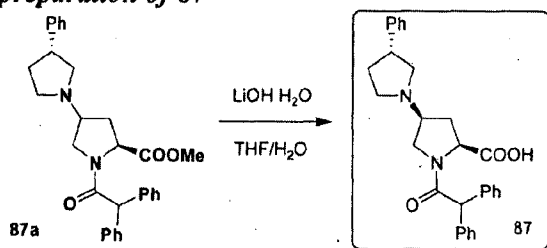
Example 85: Compound 87 (3*R*,3'*S*,5'*S*)-1-(2,2-diphenylacetyl)-3-(phenyl-[1,3'-bipyrrolidine]-5'-carboxylic acid

1. Procedure for the preparation of 87a



A mixture of 2c (500 mg, 1.19 mmol), (*R*)-3-phenylpyrrolidine hydrochloride (660 mg, 3.59 mmol) and Et_3N (363 mg, 3.59 mmol) in CH_3CN (10 mL) was heated at $110^\circ C$ in a sealed tube overnight, TLC (DCM:MeOH=10:1) showed most of the starting material was consumed. The mixture was cooled to RT, concentrated *in vacuo* and the residue was purified by chromatography (DCM:MeOH = 1:0 to 50:1) to give 87a (200 mg, 35%) as a white solid. LC-MS (Agilent): R_t 3.35 min; m/z calculated for $C_{30}H_{32}N_2O_3$ $[M+H]^+$ 469.2, found $[M+H]^+$ 469.3.

2. Procedure for the preparation of 87



To a mixture of 87a (200 mg, 0.43 mmol) in THF/water (5 mL/1 mL) was added $LiOH \cdot H_2O$ (54 mg, 1.28 mmol) and the mixture was stirred at RT overnight, TLC (DCM:MeOH=10:1) showed the starting material was consumed. Most of the THF was removed *in vacuo* and the residue was dissolved in water (15 mL) and washed with ether (15 mL x 2). The aqueous layer was then cooled in an ice water bath and acidified to pH=3~4 with a 1 M aqueous HCl solution. The resulting precipitate was collected by filtration, washed with water (5 mL x 3) and dried at $45^\circ C$ overnight to give 87 (70 mg, 36%) as a white solid. LC-MS (Agilent): R_t 3.48 min; m/z calculated for $C_{29}H_{30}N_2O_3$ $[M+H]^+$ 455.2, found $[M+H]^+$ 455.3. HPLC (JULY-L) (214 and 254 nm): R_t 8.77 min.

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Biological Example 1: AT₂ receptor binding*Media and Solutions*

1. Trypsin-EDTA (for preparation of 100 mL)

5 Trypsin 0.25 g
 2% EDTA 2 mL
 PBS 98 mL

Dissolve trypsin in 2% EDTA and PBS completely; sterilize the solution by passing through a 0.20 µm membrane filter; store at 4°C.

10

2. DMEM medium (for preparation of 1L)

The powder was dissolved into 950 mL of distilled water with gentle stirring until the solution becomes clear.

Add NaHCO₃ 1.176 g for DMEM medium.

15 Adjust pH of medium to 0.2-0.3 below final working pH using 1 M NaOH or 1 M HCl. Add slowly with stirring.

Dilute to 1 liter with ddH₂O.

Sterilize the medium immediately by filtration.

Store at 4°C.

20

3. TE buffer

20 mM Tris-HCl, pH 7.4,
5 mM EDTA

- 25 4. Binding Assay Buffer

50 mM Hepes, pH 7.4
5 mM MgCl₂
1 mM CaCl₂
0.2% BSA

30

5. Wash Buffer

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50 mM Hepes, pH 7.4

Procedures for HEK293/AT₂ receptor transient cell

Transfection

- 5 • Cells were plated into 150 mm dish at 50% density for transient transfection. Cells were ready for transfection after overnight incubation (the confluence reaches around 80%).
- 75 μ L LipofectamineTM2000 diluted in 6.25 mL OptiMEM I Reduced Serum Medium, was mixed gently, and incubated at room temperature for 5 minutes. 50
- 10 • 50 μ g expression plasmid DNA diluted in 6.25 mL OptiMEM I Reduced Serum Medium without serum was mixed gently.
- After the 5 minute incubation, the diluted DNA was combined with the diluted LipofectamineTM2000 (total volume is 12.5 mL). The mixture was mixed gently and incubated for 30 minutes at room temperature to allow the DNA-
- 15 • LipofectamineTM2000 complexes to form.
- The 12.5 mL DNA- LipofectamineTM2000 complexes were added into the 150 mm dish and mixed gently by rocking the dish back and forth.
- The cells were incubated at 37°C with 5% CO₂ for 48 hours.
- Cells were collected and stored frozen at -80°C.

20

Procedures for HEK293/AT₂ receptor cell membrane preparation

- Frozen HEK293/AT₂ receptor (transient transfected) cells were homogenized in ice cold TE buffer for 10s.
- The homogenate was centrifuged at 25,000g for 30 minutes.
- 25 • The pellet was resuspended in ice cold tissue buffer.
- Protein concentrations were determined using Bradford assay method with BSA as standard.
- The membrane protein was frozen under -80°C.

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Compound preparation

Solutions of all compounds were prepared by microplate liquid handling equipment such as Janus or Precision 2000. Compounds, dissolved in DMSO were stored in a Freezer. Compounds were prepared from 30 mM in 100% DMSO.

5

Step 1 : Dose plate preparation (96 well plate)

- Add the 3 μ L [30mM] compound stock to column 1 on the plate.
- Add 15 μ L of 100% DMSO to column 1.
- Add 10.81 μ L of 100% DMSO to column 2-12.
- 10 • Transfer 5 μ L from column 1 into column 2 (half log dilution).
- Transfer 5 μ L from column 2 into column 3 (half log dilution).
- Transfer 5 μ L from column 3 into column 4 (half log dilution).
- Transfer 5 μ L from column 4 into column 5 (half log dilution).
- Transfer 5 μ L from column 5 into column 6 (half log dilution).
- 15 • Transfer 5 μ L from column 6 into column 7 (half log dilution).
- Transfer 5 μ L from column 7 into column 8 (half log dilution).
- Transfer 5 μ L from column 8 into column 9 (half log dilution).
- Transfer 5 μ L from column 9 into column 10 (half log dilution)
- Transfer 5 μ L from column 10 into column 11 (half log dilution)
- 20 • Transfer 5 μ L from column 11 into column 12 (half log dilution).

All the compounds were diluted using Precision 2000 microplate liquid handling equipment. The top concentration of compound was 5 mM with 100% DMSO.

25 Step 2 : Working plate preparation (96 well plate)

- Compounds were diluted 50-fold with buffer.
- 49 μ L buffer was added to the well of 96 well plate.
- 1 μ L compound solution from dose plate was transferred to the corresponding well of working plate.

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- The top concentration of compound was 100 μ M with 2% DMSO.

Step 3 : Assay plate preparation (96 well plate)

15 μ L of compound solution was transferred from each well of working plate to the well of
5 assay plate by Janus. Each compound was assayed in duplicate in each plate and there
were 4 compounds per plate.

Procedures for AT₂ receptor binding assay

- 120 μ L membrane (5 mg protein/well) was incubated with 15 μ L of [¹²⁵I]-
10 CGP42112A and 15 μ L of compound at RT for 1.5 hrs.
- The binding reaction was stopped by rapid filtration through Unifilter GF/C plates
(presoaked in 0.3% (v:v) BSA).
- Plate was washed three times with ice cold wash buffer.
- The filtration plates were dried at 37°C overnight.
- 15 • 50 μ L of scintillation cocktail was added to each well.
- Radioactivity was determined using MicroBetaTriluxmicroplate scintillation
counter.

Data analysis

20 Data was analyzed through 4 parameter logic using Prism 5.0 software.

The results are shown in the following Table:

Compound	IC ₅₀ (nM)	Compound	IC ₅₀ (nM)	Compound	IC ₅₀ (nM)
2	113.9	67	3665	115	321.3
3	192.9	70-B	1340	116	649.6
5	89.96	70-A	49.08	118	313.7
6	181.3	75	3829	119	2647
9	98.62	76	3604	120	1199
15	54.47	84	75.75	121	57.67
16	6654	85	102.6	122	142.6
17	3974	86	817.4	124	363.4
21	62.14	87	43.6	125	1244

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22	384.1	90	64.23	126	20.48
23	290.3	91	12.01	131	652.1
28	86.86	92	133.8	133	1738
35	539.9	93	125.6	134	954.5
36	1664	8	512.1	135	240.2
46	2257	96	2248	136	89.03
48	89.43	97	457.5	137	173.4
49	58.81	98	240.5	138	3.519
50	67.27	99	535.5	139	2533
51	50.33	100	18	140	673.7
53	43.88	101	400.5	142	992.9
54	154.8	102	498.6	143	372.3
55	386.4	104	1316		
56	315.5	105	2489		
58	3050	106	426.2		
61-A	83.34	107	461		
61-B	107.0	108	2054		
62	540.2	109	650.4		
63	482.9	112	255.1		
64	3358	114	17.05		
65	1605	52	63.23		

Biological Example 2: AT₁ receptor binding

The same media, solutions, cell procedures and compound preparation was used as for Biological Example 1 but using HEK293/AT₁ Receptor Transient Cells. The binding assay was then performed as follows:

- 120 μ L membrane (5 mg protein/well) was incubated with 15 μ L of [¹²⁵I]-Sar1-Ile8-Angiotensin II and 15 μ L of compound at RT for 1.5 hrs.
- The binding reaction was stopped by rapid filtration through Unifilter GF/C plates (presoaked in 0.3% (v:v) BSA).
- Plate was washed three times with ice cold wash buffer.
- The filtration plates were dried at 37°C overnight.
- 50 μ L of scintillation cocktail was added to each well.

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- Radioactivity was determined using MicroBetaTriluxmicroplate scintillation counter.

The IC₅₀ binding results for a known selective AT₂ receptor antagonist PD-126,055, known selective AT₁ receptor antagonist, Losartin, angiotensin II and compound 21 are shown in the following Table.

Compound	IC ₅₀ (nM)	Ki (nM)
PD-126,055	-	-
Compound 21	-	-
Losartin	11.01	5.505
Angiotensin II	1.797	0.8985

- : No significant inhibition of binding of the radiolabelled ligand even at top concentration tested (10 μ M). Compounds 6, 112, 136 and 138 were also analysed in a similar assay and showed no AT₁ receptor binding at 10 μ M.

10 Biological Example 3: AT₂ receptor neurite outgrowth assay

The general methodology of Wallinder (2008) and references cited therein was used to assess the effect of the compounds of the present invention on neurite outgrowth. The assay was adapted for high content screening.

- 15 The compounds screened against NG108-15 neurite cells were the known AT₂ selective antagonist PD-126,055, compound 6, compound 15, compound 21 and compound 28. The controls used were naïve cells, DMSO 0.2% treated cells, cells treated with Angiotensin II (Ang II) 0.1 μ M, EMA1087 0.1 μ M and Ang II 0.1 μ M + PD-123,319 (PD-123) 1 μ M. EMA1087 is a known AT₂ receptor agonist described as "compound 21" in Wan *et al.*
- 20 2004. PD-123,319 is a known, commercially available AT₂ receptor antagonist. The results were analyzed by immunofluorescence quantitative analysis. Neurite outgrowth was quantified with neurite average length using Cellomics software. Results are expressed as the mean $\pm$ SEM, each conducted in triplicate. Statistical significance, compared with Ang II control : *p<0.05, **p<0.01, and ***p<0.001. NS : no significant
- 25 difference. ND: not determined. Figures 1 to 5 show neurite outgrowth was inhibited by the AT₂ receptor antagonists, PD-126,055 and compounds 6, 15, 21 and 28.

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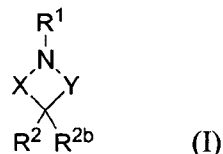
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CLAIMS

1. A compound of formula (I):



5 wherein:

X is absent and Y is $-\text{CHR}^3\text{CH}_2-$, $-\text{CH}_2\text{CHR}^3-$, $-\text{CHR}^3\text{CHR}^4\text{CH}_2-$, $-\text{CH}_2\text{CHR}^3\text{CHR}^4-$, $-\text{CH}_2\text{CH}_2\text{CHR}^3-$, $-\text{CR}^3=\text{CHCH}_2-$, or $-\text{CH}_2\text{CH}=\text{CR}^3-$; or

X is $-\text{CHR}^5$ and Y is $-\text{CHR}^3-$, $-\text{CHR}^3\text{CHR}^4-$, $-\text{CHR}^3\text{CR}^4=$, $-\text{CH}_2\text{CHR}^3-$, $-\text{CR}^3=\text{CH}-$ or $-\text{CH}=\text{CR}^3-$, wherein when Y is $-\text{CHR}^3\text{CR}^4=$, R^{2b} is absent, or

10 X is $-\text{CH}_2\text{CHR}^5-$ or $-\text{C}(=\text{O})\text{CHR}^5-$ and Y is $-\text{CHR}^3-$;

R^1 is $-\text{C}(=\text{O})\text{CH}(\text{aryl})(\text{aryl})$, $-\text{C}(=\text{O})\text{CH}(\text{aryl})(\text{cycloalkyl})$, $-\text{C}(=\text{O})\text{CH}(\text{cycloalkyl})(\text{cycloalkyl})$, $-\text{C}(=\text{O})\text{N}(\text{aryl})(\text{aryl})$, $-\text{C}(=\text{O})\text{N}(\text{aryl})(\text{cycloalkyl})$ or $-\text{C}(=\text{O})\text{N}(\text{cycloalkyl})(\text{cycloalkyl})$;

R^2 is heterocyclyl, heteroaryl, $-\text{C}_{1-4}\text{alkylenearyl}$, $-\text{OC}_{1-3}\text{alkylenearyl}$, $-\text{OC}_{2-3}\text{alkenylenearyl}$, $-\text{OC}_{2-3}\text{alkynylenearyl}$, $-\text{OC}_{1-3}\text{alkylenecycloalkylaryl}$, $-\text{OarylOaryl}$,

15 $-\text{SC}_{1-3}\text{alkylenearyl}$, $-\text{SO}_2\text{C}_{1-3}\text{alkylenearyl}$, $-\text{NHC}_{1-8}\text{alkyl}$,

$-\text{NHC}_{1-3}\text{alkylenearyl}$, $-\text{NHC}_{1-3}\text{alkyleneheteroaryl}$, $-\text{NHC}_{2-3}\text{alkynylenearyl}$,

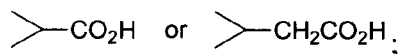
$-\text{N}(\text{CH}_3)\text{C}_{1-8}\text{alkyl}$, $-\text{N}(\text{CH}_3)\text{C}_{1-3}\text{alkylenearyl}$, $-\text{N}(\text{CH}_3)\text{C}_{1-3}\text{alkyleneheteroaryl}$,

$-\text{N}(\text{CH}_3)\text{C}_{2-3}\text{alkynylenearyl}$, $-\text{CH}_2\text{OC}_{1-3}\text{alkylenearyl}$, $-\text{N}(\text{CH}_3)\text{C}_{1-3}\text{alkylenecycloalkyl}$ or $-\text{NHC}_{1-3}\text{alkylenecycloalkyl}$;

20 R^{2b} is hydrogen;

R^3 is CO_2H , $-\text{CH}_2\text{CO}_2\text{H}$, $-\text{C}(=\text{O})\text{C}(=\text{O})\text{OH}$, $-\text{C}(=\text{O})\text{NHSO}_2\text{C}_{1-6}\text{alkyl}$, $-\text{C}(=\text{O})\text{NHSO}_2\text{phenyl}$, $-\text{C}(=\text{O})\text{NHSO}_2\text{CF}_3$, $-\text{SO}_3\text{H}$ or $-\text{PO}_3\text{H}_2$

R^4 is hydrogen or R^3 and R^4 together form a group:



25

R^5 is hydrogen; and

wherein each cycloalkyl, aryl, heterocyclyl and heteroaryl may be optionally substituted with one or more optional substituents selected from the group consisting of $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{2-6}\text{alkenyl}$,

30 $\text{C}_{3-6}\text{cycloalkyl}$, $=\text{O}$, $-\text{OH}$, $-\text{SH}$, $\text{C}_{1-6}\text{alkylO}-$, $\text{C}_{2-6}\text{alkenylO}-$, $\text{C}_{3-6}\text{cycloalkylO}-$, $\text{C}_{1-6}\text{alkylS}-$, $\text{C}_{2-6}\text{alkenylS}-$, $\text{C}_{3-6}\text{cycloalkylS}-$, $-\text{CO}_2\text{H}$, $-\text{CO}_2\text{C}_{1-6}\text{alkyl}$, $-\text{NH}_2$, $-\text{NH}(\text{C}_{1-6}\text{alkyl})$, $-\text{N}(\text{C}_{1-6}\text{alkyl})_2$,

-NH(phenyl), -N(phenyl)₂, -CN, -NO₂, -halogen, -CF₃, -OCF₃, -SCF₃, -CHF₂, -OCHF₂, -SCHF₂, -phenyl, -heterocyclyl, -heteroaryl, -Oheteroaryl, -Oheterocyclyl, -Ophenyl, -C(O)phenyl and -C(O)C₁₋₆alkyl;

wherein heterocyclyl is selected from the group consisting of azetidiny, tetrahydrofuranyl, tetrahydrothiophenyl, pyrrolidinyl, 2-oxopyrrolidinyl, pyrrolinyl, pyranyl, dioxolanyl, piperidinyl, 2-oxopiperidinyl, pyrazolinyl, imidazolinyl, thiazolinyl, dithiolyl, oxathiolyl, dioxanyl, dioxinyl, dioxazolyl, oxathiozolyl, oxazolonyl, piperazinyl, morpholinyl, thiomorpholinyl, 3-oxomorpholinyl, dithianyl, trithianyl and oxazinyl; or a pharmaceutically acceptable salt thereof.

10

2. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein X is absent and Y is -CHR³CH₂- or X is -CH₂- and Y is -CHR³-.

3. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein X is absent and Y is -CHR³CHR⁴CH₂-, -CH₂CHR³CHR⁴- or -CH₂CH₂CHR³- or X is -CHR⁵- and Y is -CHR³CHR⁴- or -CH₂CHR³-, or X is -CH₂CHR⁵- and Y is -CHR³-.

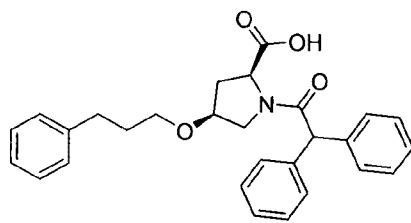
4. A compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein R¹ is -C(=O)CH(phenyl)(phenyl), -C(=O)CH(phenyl)(cyclohexyl), -C(=O)CH(cyclohexyl)(cyclohexyl), -C(=O)N(phenyl)(phenyl), -C(=O)N(phenyl)(cyclohexyl) or -C(=O)N(cyclohexyl)(cyclohexyl) wherein each phenyl or cyclohexyl is optionally substituted with one or more substituents selected from the group consisting of -C₁₋₃alkyl, -OC₁₋₃alkyl and halo.

5. A compound according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein R³ is -CO₂H.

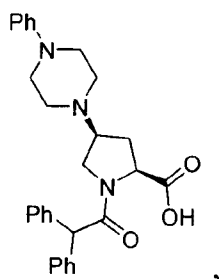
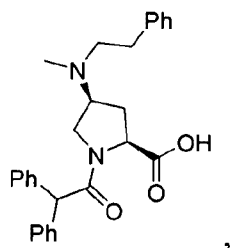
6. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R⁴ is H.

30

7. A compound according to claim 1 selected from the group consisting of:
 (2*S*,4*S*)-4-(benzyloxy)-1-(2,2-diphenylacetyl)pyrrolidine-2-carboxylic acid,
 (2*S*,4*R*)-4-(benzyloxy)-1-(2,2-diphenylacetyl)pyrrolidine-2-carboxylic acid,
 (2*S*,4*S*)-4-cinnamyloxy-1-(2,2-diphenylacetyl)pyrrolidine-2-carboxylic acid,



(2*S*,4*R*)-4-(cinnamyloxy)-1-(2,2-diphenylacetyl)pyrrolidine-2-carboxylic acid,
 (2*S*,4*R*)-1-(2,2-diphenylacetyl)-4-(3-phenylpropoxy)pyrrolidine-2-carboxylic acid,
 (2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-(((1*R*,2*S*)-2-phenylcyclopropyl)methoxy)
 pyrrolidine-2-carboxylic acid,
 (2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-(((1*S*,2*R*)-2-phenylcyclopropyl)methoxy)
 pyrrolidine-2-carboxylic acid,
 (2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-(methyl(3-phenylpropyl)amino)pyrrolidine-2-
 carboxylic acid,



(2*S*,4*S*)-4-((*S*)-3-benzylmorpholino)-1-(2,2-diphenylacetyl)pyrrolidine-2-
 carboxylic acid,
 (2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-(2-phenoxyphenoxy)-pyrrolidine-2-carboxylic
 acid,
 (2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-((3-phenylprop-2-yn-1-yl)-oxy)pyrrolidine-2-
 carboxylic acid,
 (2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-(phenethylamino)-pyrrolidine-2-carboxylic acid,
 (2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-((*S*)-3-phenylpiperidine-1-yl)pyrrolidine-2-
 carboxylic acid,

(2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-((*R*)-3-phenylpiperidin-1-yl)pyrrolidine-2-carboxylic acid,

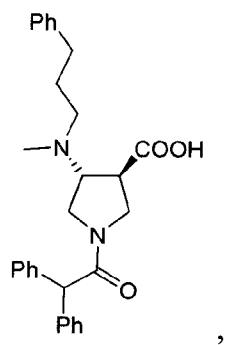
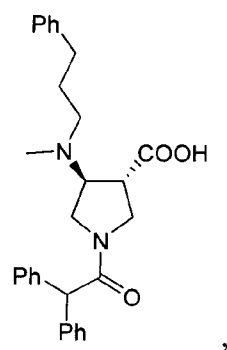
(2*S*,4*S*)-4-(3-benzylpiperidin-1-yl)-1-(2,2-diphenylacetyl)-pyrrolidine-2-carboxylic acid,

5 (3'*S*,5'*S*)-2-benzyl-1'-(2,2-diphenylacetyl)-[1,3'-bipyrrolidine]-5'-carboxylic acid,

(2*S*,4*S*)-1-(2-cyclohexyl-2-phenylacetyl)-4-(methyl(3-phenylpropyl)amino)pyrrolidine-2-carboxylic acid,

(2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-(methyl((2-phenylcyclopropyl)methyl)amino)pyrrolidine-2-carboxylic acid,

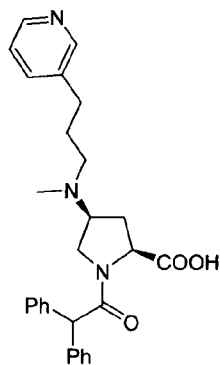
10 (2*S*,4*S*)-4-(2-benzylpiperidin-1-yl)-1-(2,2-diphenylacetyl)-pyrrolidine-2-carboxylic acid,



(2*R*,4*R*)-1-(2,2-diphenylacetyl)-4-(3-phenylpropoxy)-pyrrolidine-2-carboxylic acid,

15

(2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-((3-(4-fluorophenyl)-propyl)(methyl)amino)pyrrolidine-2-carboxylic acid,



(2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-(5-phenyl-1*H*-1,2,3-triazol-1-yl)pyrrolidine-2-carboxylic acid,

5

(2*S*,4*S*)-4-(5-benzyl-1*H*-1,2,3-triazol-1-yl)-1-(2,2-diphenylacetyl)pyrrolidine-2-carboxylic acid,

(2*S*,4*S*)-4-((*S*)-3-benzyl-5-oxomorpholino)-1-(2,2-diphenylacetyl)pyrrolidine-2-carboxylic acid,

(2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-(3-(4-fluorophenyl)-propoxy)pyrrolidine-2-carboxylic acid,

10

(2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-((3-(4-methoxy-3-methylphenyl)prop-2-yn-1-yl)(methyl)amino)pyrrolidine-2-carboxylic acid,

(2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-((3-(4-methoxy-3-methylphenyl)propyl)(methyl)amino)pyrrolidine-2-carboxylic acid,

15

(2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-(4-phenylbutyl)-pyrrolidine-2-carboxylic acid,

(2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-(3-phenylthiophen-2-yl)-pyrrolidine-2-carboxylic acid,

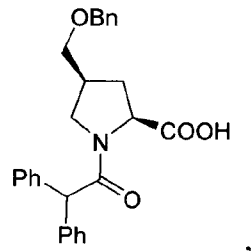
(2*S*,3*S*)-1-(2,2-diphenylacetyl)-3-(3-phenylpropoxy)-azetidine-2-carboxylic acid,

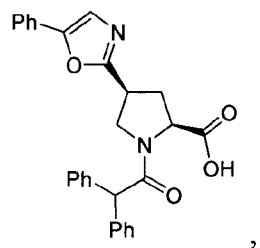
(2*R*,3*R*)-1-(2,2-diphenylacetyl)-3-(3-phenylpropoxy)-azetidine-2-carboxylic acid,

(2*R*,3*R*)-3-(3-phenylpropoxy)-1-(2,2-diphenylacetyl)-azetidine-2-carboxylic acid,

20

(2*S*,3*S*)-3-(3-phenylpropoxy)-1-(2,2-diphenylacetyl)-azetidine-2-carboxylic acid,





(2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-((3-(4-fluorophenyl)propyl)thio)pyrrolidine-2-carboxylic acid,

5

(2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-((3-(4-fluorophenyl)propyl)sulfonyl)pyrrolidine-2-carboxylic acid,

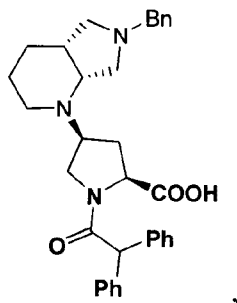
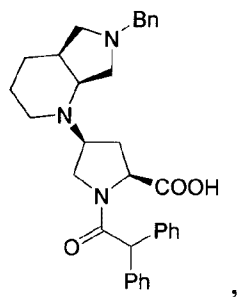
(2*S*,4*S*)-1-(2,2-diphenylacetyl)-*N*-(methylsulfonyl)-4-(phenylpropoxy)pyrrolidine-2-carboxamide,

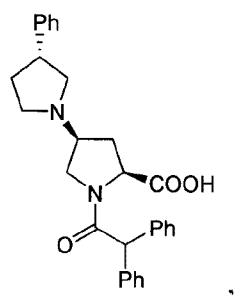
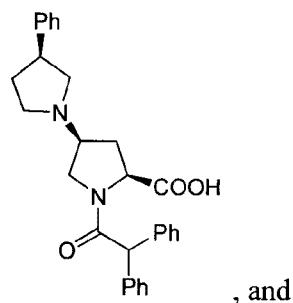
(2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-(phenethylthio)pyrrolidine-2-carboxylic acid,

10

(2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-(((1*R*,2*R*)-2-phenylcyclopropyl)methoxy)pyrrolidine-2-carboxylic acid,

(2*S*,4*S*)-1-(2,2-diphenylacetyl)-4-(((1*S*,2*S*)-2-phenylcyclopropyl)methoxy)pyrrolidine-2-carboxylic acid,





or a pharmaceutically acceptable salt thereof.

- 5 8. A pharmaceutical composition comprising a compound of formula (I) of any one of
claims 1 to 7, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable
carrier.
9. A use of a compound of formula (I) of any one of claims 1 to 7, or a pharmaceutically
- 10 acceptable salt thereof, for treating or preventing neuropathic pain.
10. A use of a compound of formula (I) of any one of claims 1 to 7, or a pharmaceutically
acceptable salt thereof, for treating or preventing a condition characterized by neuronal
hypersensitivity.
- 15 11. A use of a compound of formula (I) of any one of claims 1 to 7, or a pharmaceutically
acceptable salt thereof, for treating or preventing inflammatory pain.
12. A use of a compound of formula (I) of any one of claims 1 to 7, or a pharmaceutically
- 20 acceptable salt thereof, for treating or preventing impaired nerve conduction velocity.
13. A use of a compound of formula (I) of any one of claims 1 to 7, or a pharmaceutically
acceptable salt thereof, as an analgesic.

14. A use of a compound of formula (I) of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, for treating or preventing a cell proliferative disorder.
15. A use of a compound of formula (I) of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, for treating or preventing a disorder associated with an imbalance between bone resorption and bone formation.
16. A use of a formula (I) of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, for treating or preventing a disorder associated with aberrant nerve regeneration.
17. A use of a compound of formula (I) of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, for preparation of a medicament for treating or preventing neuropathic pain.
18. A use of a compound of formula (I) of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, for preparation of a medicament for treating or preventing a condition characterized by neuronal hypersensitivity.
19. A use of a compound of formula (I) of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, for preparation of a medicament for treating or preventing inflammatory pain.
20. A use of a compound of formula (I) of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, for preparation of a medicament for treating or preventing impaired nerve conduction velocity.
21. A use of a compound of formula (I) of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, for preparation of a medicament as an analgesic.
22. A use of a compound of formula (I) of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, for preparation of a medicament for treating or preventing a cell proliferative disorder.

23. A use of a compound of formula (I) of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, for preparation of a medicament for treating or preventing a disorder associated with an imbalance between bone resorption and bone formation.
- 5 24. A use of a formula (I) of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, for preparation of a medicament for treating or preventing a disorder associated with aberrant nerve regeneration.
25. Compound of formula (I) of any one of claims 1 to 7, or a pharmaceutically acceptable
10 salt thereof, for use to treat or prevent neuropathic pain.
26. Compound of formula (I) of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, for use to treat or prevent a condition characterized by neuronal hypersensitivity.
- 15 27. Compound of formula (I) of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, for use to treat or prevent inflammatory pain.
28. Compound of formula (I) of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, for use to treat or prevent impaired nerve conduction velocity.
- 20 29. Compound of formula (I) of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, for use as an analgesic.
30. Compound of formula (I) of any one of claims 1 to 7, or a pharmaceutically acceptable
25 salt thereof, for use to treat or prevent a cell proliferative disorder.
31. Compound of formula (I) of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, for use to treat or prevent a disorder associated with an imbalance between bone resorption and bone formation.
- 30 32. A use of a formula (I) of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, for treating or preventing a disorder associated with aberrant nerve regeneration.

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Figure 1

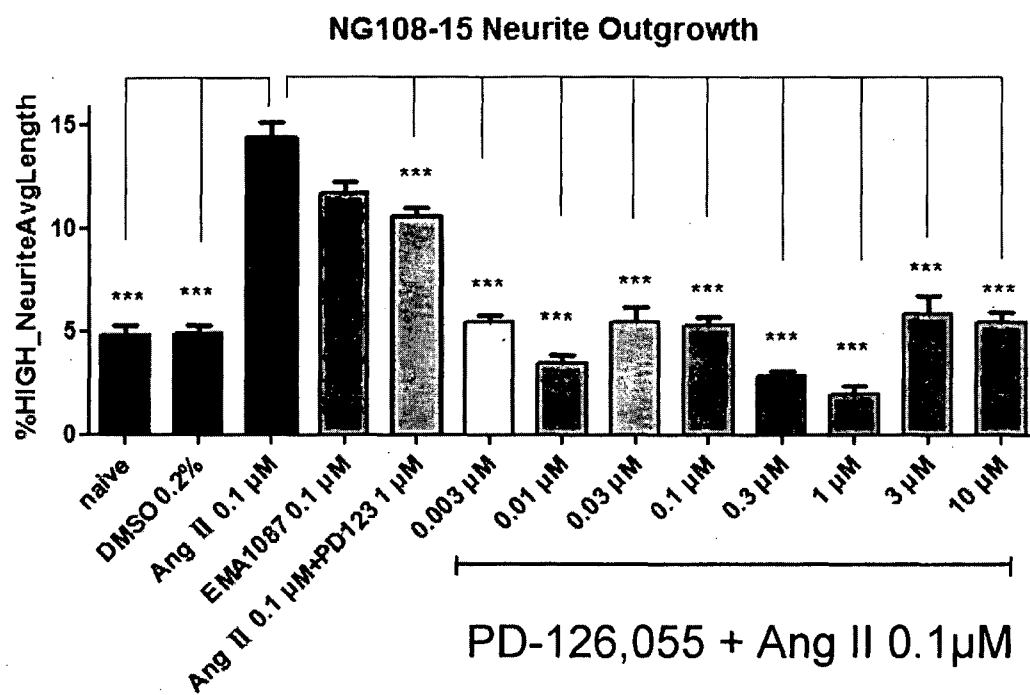
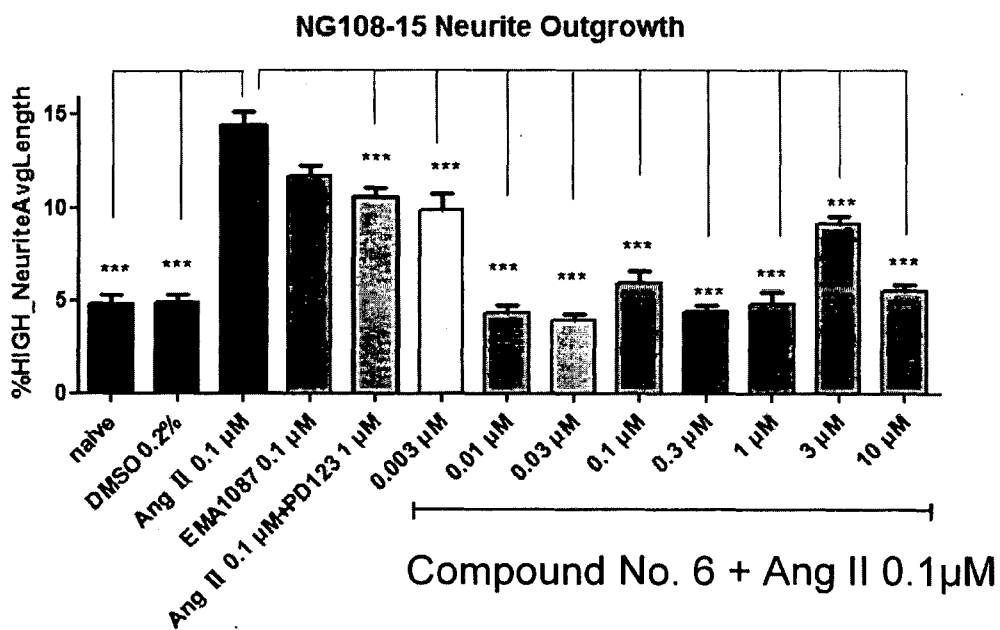


Figure 2



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Figure 3

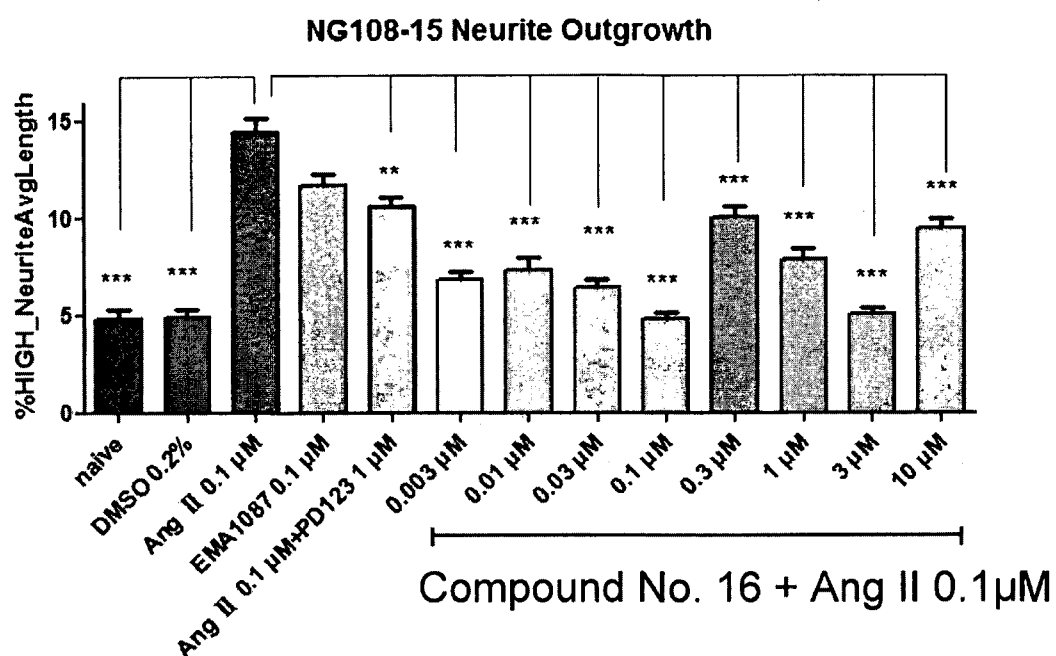
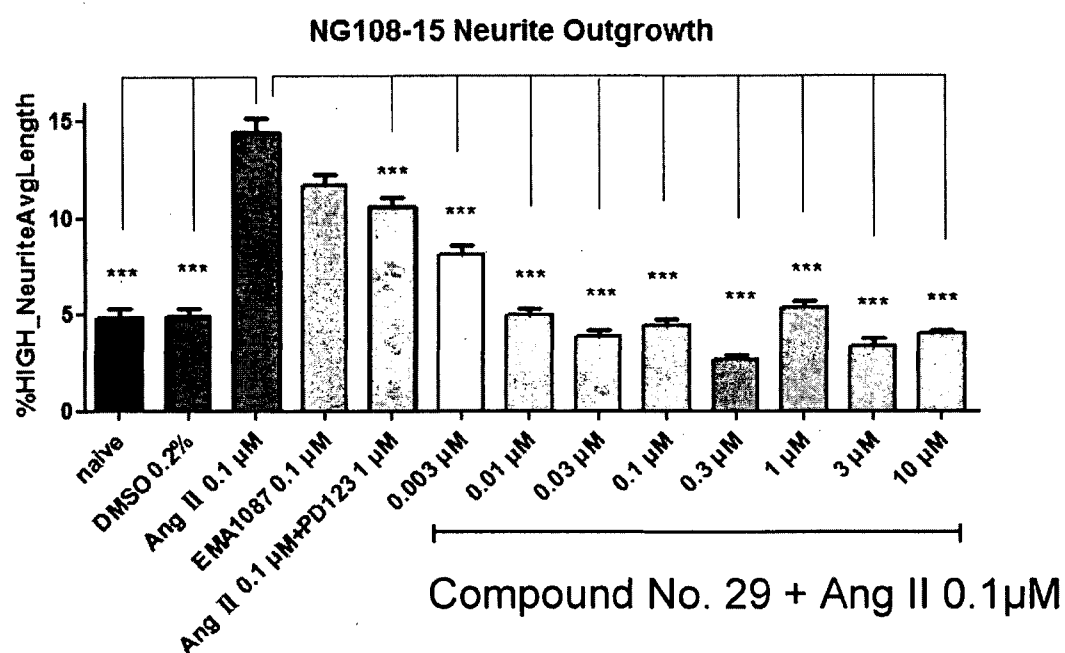


Figure 4



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Figure 5

