

HYDANTOIN BASED KINASE INHIBITORS

- The present invention relates to hydantoin derivatives and their use as inhibitors of the two protein kinases commonly known as MEK1 and MEK2 for the treatment of human diseases such as cancer. MEK is a commonly used abbreviation for MAP kinase / ERK kinase which is in turn an abbreviation for mitogen activated protein / extracellular signal regulated kinase kinase. MEK is also sometimes referred to as MAPK kinase or MAP kinase kinase.
- Cancer is a disease characterized by the proliferation of malignant cells and tumors which have the potential for unlimited growth, local expansion and systemic metastasis. This uncontrolled growth is derived from abnormalities in the signal transduction pathways and the response to various growth factors, which differ from those found in normal cells. The abnormalities include changes in the intrinsic activity or in the cellular concentration of one or more signaling proteins in the signaling cascade. These changes are frequently caused by genetic mutations or overexpression of intracellular signaling proteins which can lead to spurious mitogenic signals within the cells.
- The mitogen activated protein (MAP) kinase pathway represents one of the best characterized signaling pathways involved in the development and progression of human cancers. This pathway, via the Ras / Raf / MEK / ERK signal cascade, is responsible for transmitting and amplifying mitogenic signals from the cell surface to the nucleus where activated transcription factors regulate gene expression and determine cell fate. The constitutive activation of this pathway is sufficient to induce cellular transformation. Dysregulated activation of the MAP kinase pathway due to aberrant receptor tyrosine kinase activation, Ras mutations or Raf mutations has frequently been found in human cancers, and represents a major factor determining abnormal growth control. In human malignances, Ras mutations are common, having been identified in about 30%

of cancers. The Ras family of GTPase proteins (proteins which convert guanosine triphosphate to guanosine diphosphate) relay signals from activated growth factor receptors to downstream intracellular partners. Prominent among the targets recruited by active membrane-bound Ras are the Raf family of

5 serine/threonine protein kinases. The Raf family is composed of three related kinases (A-, B- and C-Raf) that act as downstream effectors of Ras. Ras-mediated Raf activation in turn triggers activation of MEK1 and MEK2 (MAP / ERK kinases 1 and 2) which in turn phosphorylate ERK1 and ERK2 (extracellular signal-regulated kinases 1 and 2) on both tyrosine-185 and threonine-183.

10 Activated ERK1 and ERK2 translocate and accumulate in the nucleus, where they can phosphorylate a variety of substrates, including transcription factors that control cellular growth and survival. Given the importance of the Ras / Raf / MEK / ERK pathway in the development of human cancers, the kinase components of this signaling cascade are emerging as potentially important targets for the

15 modulation of disease progression in cancer and other proliferative diseases.

MEK1 and MEK2 are members of a larger family of dual-specificity kinases (MEK1-7) that phosphorylate threonine and tyrosine residues of various MAP kinases. MEK1 and MEK2 are encoded by distinct genes, but they share high

20 homology (80%) both within the C-terminal catalytic kinase domains and most of the *N*-terminal regulatory region. Oncogenic forms of MEK1 and MEK2 have not been found in human cancers, but constitutive activation of MEK has been shown to result in cellular transformation. In addition to Raf, MEK can also be activated by other oncogenes as well. So far, the only known substrates of

25 MEK1 and MEK2 are ERK1 and ERK2. This unusual substrate specificity in addition to the unique ability to phosphorylate both tyrosine and threonine residues places MEK1 and MEK2 at a critical point in the signal transduction cascade which allows it to integrate many extracellular signals into the MAPK pathway.

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Previously reported studies with the MEK inhibitor 2-(2-chloro-4-iodo-phenylamino)-*N*-cyclopropylmethoxy-3,4-difluoro-benzamide, also known as CI-1040 (PCT publication No. WO 99/01426) provide further evidence that MEK1 and MEK2 represent an attractive target for pharmacological intervention in

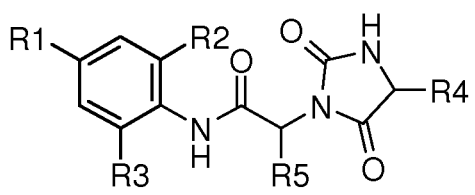
cancer or other human diseases characterized by the hyperactivity of MEK and diseases regulated by the MAPK pathway.

Substituted hydantoins have previously been reported as glucokinase activators
5 (PCT publication No. WO 01/83478).

Summary of the Invention

This invention relates to compounds of formula I:

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or pharmaceutically acceptable salts thereof,

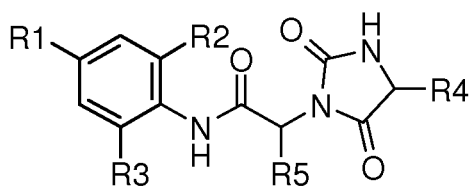
wherein R1, R2, R3, R4, R5, R6, R7, and R8 are described in this application.

15 These compounds inhibit the enzymes MEK 1 and MEK2, protein kinases that are components of the MAP kinase signal transduction pathway and as such the compounds will have anti-hyperproliferative cellular activity.

Detailed Description of the Invention

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The present invention is directed to compounds of formula I:



25 wherein:

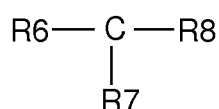
R1 is selected from the group consisting of bromo, iodo, ethynyl, cycloalkyl, alkoxy, azetidiny, acetyl, heterocycyl, cyano, straight-chained alkyl and branched-chain alkyl;

R2 is selected from the group consisting of hydrogen, chlorine, fluorine, and alkyl;

R3 is selected from the group consisting of hydrogen, chlorine, and fluorine;

5 R4 is selected from the group consisting of hydrogen, optionally substituted aryl, alkyl, and cycloalkyl;

R5 is selected from the group consisting of hydrogen and



10 wherein R6 is selected from the group consisting of hydroxyl, alkoxy, cycloalkyl, optionally substituted alkyl, optionally substituted aryl, and optionally substituted heteroaryl;

R7 and R8 are independently selected from the group consisting of hydrogen and optionally substituted alkyl; or

R6 and R7 can together form a cycloalkyl group and R8 is hydrogen; and pharmaceutically acceptable salts or esters thereof.

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In one aspect the invention is directed to compounds of formula I where R1 is iodo, ethynyl, or cyclopropyl.

20 In another aspect the invention is directed to compounds of formula I where R2 is hydrogen, chlorine, or fluorine.

In another aspect the invention is directed to compounds of formula I where R3 is hydrogen.

25 In another aspect the invention is directed to compounds of formula I where R8 is hydrogen or methyl.

In another aspect the invention is directed to compounds of formula I where R4 is substituted aryl.

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In another aspect the invention is directed to compounds of formula I where R1 is iodo, ethynyl, or cyclopropyl, R2 is hydrogen, fluorine, chlorine, or methyl, R3

is hydrogen, R4 is optionally substituted aryl, R5 is
$$\begin{array}{c} \text{R6} - \text{C} - \text{R8} \\ | \\ \text{R7} \end{array},$$

R6 is alkoxy, cycloalkyl, or optionally substituted aryl, R7 is hydrogen, and R8 is hydrogen or methyl.

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In another aspect the invention is directed to compounds of formula I where R1 is iodo, ethynyl, or cyclopropyl, R2 is hydrogen, fluorine, or chlorine, R3 is

hydrogen, R4 is optionally substituted phenyl, R5 is
$$\begin{array}{c} \text{R6} - \text{C} - \text{R8} \\ | \\ \text{R7} \end{array},$$

10 R6 is optionally substituted phenyl, R7 is hydrogen, and R8 is methyl.

In another aspect the invention is directed to compounds of formula 1 where R1 is iodo, R2 is fluorine or chlorine, R3 is hydrogen, R4 is phenyl substituted by

alkoxy, R5 is
$$\begin{array}{c} \text{R6} - \text{C} - \text{R8} \\ | \\ \text{R7} \end{array},$$

15

R6 is phenyl, R7 is hydrogen, and R8 is methyl.

In another aspect the invention is directed to compounds of formula 1 where R1 is iodo, R2 is fluorine or chlorine, R3 is hydrogen, R4 is phenyl substituted by

20 2,3-dihydroxy-propoxy or 2-hydroxy ethoxy, R5 is
$$\begin{array}{c} \text{R6} - \text{C} - \text{R8} \\ | \\ \text{R7} \end{array},$$

R6 is phenyl, R7 is hydrogen, and R8 is methyl.

25 In a preferred embodiment according to the present invention, there is provided the compound of formula I, wherein

R4 is phenyl, which is unsubstituted or 1 or 2 times substituted with a substituent independently selected from

-halogen,

-P(O)(O-CH₃)₂,

5 -P(O)(OH)₂,

-S(O)₂-(C1-C6 alkyl),

-(O-CH₂-CH₂)₂-O-CH₃, and

-O-(C1-C6 alkyl), wherein the alkyl group is unsubstituted or 1 or 2 times substituted with a substituent independently selected from

10 -OH,

-oxo,

-C3-C6 cycloalkyl,

-O-(C1-C6 alkyl), -NH-(C1-C6 alkyl) or -N(C1-C6 alkyl)₂,

wherein the alkyl groups are unsubstituted or substituted by

15 -OH, or

- a 4 to 6-membered heterocycle, wherein the heteroatoms are selected from N, S and O; and

all remaining substituents have the meanings given above.

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In still another preferred embodiment according to the present invention, there is provided the compound of formula I, wherein

25 R4 is phenyl, which is unsubstituted or 1 or 2 times substituted with a substituent independently selected from

-halogen,

-P(O)(O-CH₃)₂,

-P(O)(OH)₂,

30 -S(O)₂-(C1-C6 alkyl),

-(O-CH₂-CH₂)₂-O-CH₃, and

-O-(C1-C6 alkyl), wherein the alkyl group is unsubstituted or 1 or 2 times substituted with a substituent independently selected from

-OH,

5 -oxo,
 -C3-C6 cycloalkyl,
 -O-(C1-C6 alkyl), -NH-(C1-C6 alkyl) or -N(C1-C6 alkyl)₂,
 wherein the alkyl groups are unsubstituted or substituted by
 -OH, or
 - a 4 to 6-membered heterocycle, wherein the heteroatoms
 are selected from N, S and O;

10 R5 is 1-phenyl-ethyl; and

all remaining substituents have the meanings given above.

15 In still another preferred embodiment according to the present invention, there is
provided the compound of formula I, wherein

 R1 is iodo;
 R2 is hydrogen or fluoro;
 R3 is hydrogen or fluoro;
20 R4 is phenyl, which is unsubstituted or 1 or 2 times substituted with a
 substituent independently selected from
 -halogen,
 -P(O)(O-CH₃)₂,
 -P(O)(OH)₂,
25 -S(O)₂-(C1-C6 alkyl),
 -(O-CH₂-CH₂)₂-O-CH₃, and
 -O-(C1-C6 alkyl), wherein the alkyl group is unsubstituted or 1 or 2
 times substituted with a substituent independently selected from
 -OH,
30 -oxo,
 -C3-C6 cycloalkyl,
 -O-(C1-C6 alkyl), -NH-(C1-C6 alkyl) or -N(C1-C6 alkyl)₂,
 wherein the alkyl groups are unsubstituted or substituted by
 -OH, or

- a 4 to 6-membered heterocycle, wherein the heteroatoms are selected from N, S and O; and

R5 is 1-phenyl-ethyl.

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In yet another preferred embodiment according to the present invention, there is provided the compound of formula I, wherein

- 10 R4 is phenyl, which is unsubstituted or 1 or 2 times substituted with a substituent independently selected from
- halogen,
 - P(O)(O-CH₃)₂,
 - P(O)(OH)₂,
 - 15 -S(O)₂-(C1-C6 alkyl),
 - (O-CH₂-CH₂)₂-O-CH₃, and
 - O-(C1-C6 alkyl), wherein the alkyl group is unsubstituted or 1 or 2 times substituted with a substituent independently selected from
 - OH,
 - 20 -oxo,
 - C3-C6 cycloalkyl,
 - O-(C1-C6 alkyl), -NH-(C1-C6 alkyl) or -N(C1-C6 alkyl)₂, wherein the alkyl groups are unsubstituted or substituted by -OH, or
 - 25 - a 4 to 6-membered heterocycle, wherein the heteroatoms are selected from N, S and O;

- R5 is benzyl, which benzyl is unsubstituted or once substituted by
- 30 -(C1-C6) alkyl,
 - flouro or chloro,
 - CN,
 - O-(C1-C6) alkyl, and
 - CF₃; and

all remaining substituents have the meanings given above.

In yet another preferred embodiment according to the present invention, there is
5 provided the compound of formula I, wherein

R4 is phenyl, which is unsubstituted or 1 or 2 times substituted with a
substituent independently selected from

- halogen,
- 10 -P(O)(O-CH₃)₂,
- P(O)(OH)₂,
- S(O)₂-(C1-C6 alkyl),
- (O-CH₂-CH₂)₂-O-CH₃, and
- O-(C1-C6 alkyl), wherein the alkyl group is unsubstituted or 1 or 2
15 times substituted with a substituent independently selected from
- OH,
- oxo,
- C3-C6 cycloalkyl,
- O-(C1-C6 alkyl), -NH-(C1-C6 alkyl) or -N(C1-C6 alkyl)₂,
- 20 wherein the alkyl groups are unsubstituted or substituted by
- OH, or
- a 4 to 6-membered heterocycle, wherein the heteroatoms
are selected from N, S and O;

25 R5 is (C1-C6) alkyl, which is unsubstituted or 1 or 2 times substituted with a
substituent independently selected from

- naphthyl, pyridinyl, thiazolyl, thiophenyl which is optionally
substituted with bromine, imidazolyl which is optionally
- 30 substituted with methyl; or
- (C3-C6) cycloalkyl;
- CF₃;
- O-(C1-C6) alkyl;
- O-CH₂-phenyl;

-S(O)₂-methyl;
 -oxo; or
 -NH₂; and

5 all remaining substituents have the meanings given above.

Preferred compounds of the invention are:

- (2S,3S)-N-(4-Bromo-phenyl)-2-[(R)-4-(4-methoxy-phenyl)-2,5-dioxo-
 10 imidazolidin-1-yl]-3-phenyl-butyramide;
 (2S,3S)-N-(4-Iodo-phenyl)-2-[(R)-4-(4-methoxy-phenyl)-2,5-dioxo-
 imidazolidin-1-yl]-3-phenyl-butyramide;
 (2S,3S)-N-(2-Fluoro-4-iodo-phenyl)-2-[(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-
 2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide;
 15 (2S,3S)-N-(4-Ethynyl-2-fluoro-phenyl)-2-[(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-
 2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide;
 (2R,3S)-N-(4-Ethynyl-2-fluoro-phenyl)-2-[(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-
 2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide;
 (2S,3S)-N-(2-Chloro-4-iodo-phenyl)-2-[(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-
 20 2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide;
 (2S,3S)-2-[(R)-4-[4-(2-Hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-
 N-(4-iodo-2-methyl-phenyl)-3-phenyl-butyramide;
 (2S,3S)-N-(2-Chloro-4-iodo-phenyl)-2-[(R)-4-[4-((R)-2,3-dihydroxy-propoxy)-
 phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide;
 25 (2S,3S)-N-(2-Chloro-4-iodo-phenyl)-2-[(R)-4-[4-((S)-2,3-dihydroxy-propoxy)-
 phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide;
 (2S,3S)-2-[(R)-2,5-Dioxo-4-[4-(2-oxo-2-pyrrolidin-1-yl-ethoxy)-phenyl]-
 imidazolidin-1-yl]-N-(2-fluoro-4-iodo-phenyl)-3-phenyl-butyramide;
 (2S,3S)-2-[(R)-2,5-Dioxo-4-thiophen-3-yl-imidazolidin-1-yl]-N-(4-iodo-phenyl)-
 30 3-phenyl-butyramide;
 (S)-2-[(R)-4-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-2,5-dioxo-imidazolidin-1-yl]-
 N-(2-fluoro-4-iodo-phenyl)-3-phenyl-propionamide;
 (S)-2-[(R)-4-(4-Acetylamino-phenyl)-2,5-dioxo-imidazolidin-1-yl]-N-(2-fluoro-4-
 iodo-phenyl)-3-phenyl-propionamide;

- (4-{(R)-1-[(1S,2S)-1-(2-Fluoro-4-iodo-phenylcarbamoyl)-2-phenyl-propyl]-2,5-dioxo-imidazolidin-4-yl}-phenoxy-methyl)-phosphonic acid dimethyl ester;
- (2S,3S)-N-(2-Fluoro-4-iodo-phenyl)-2-[(R)-4-isopropyl-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide;
- 5 (S)-N-(2-Fluoro-4-iodo-phenyl)-2-[(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-methyl-butyramide;
- (S)-N-(2-Fluoro-4-iodo-phenyl)-2-[(R)-4-(4-methoxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-3-o-tolyl-propionamide;
- (S)-N-(2-Fluoro-4-iodo-phenyl)-2-[(R)-4-(4-methoxy-phenyl)-2,5-dioxo-
- 10 imidazolidin-1-yl]-3-m-tolyl-propionamide;
- (S)-N-(2-Fluoro-4-iodo-phenyl)-2-[(R)-4-(4-methoxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-3-p-tolyl-propionamide; and
- (S)-N-(4-Cyclopropyl-2-fluoro-phenyl)-3-(4-fluoro-phenyl)-2-[(R)-4-[4-(2-hydroxy-1-hydroxymethyl-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-
- 15 propionamide.

"Alkyl" denotes a straight-chained, branched or cyclic saturated aliphatic hydrocarbon. Preferably, alkyl denotes a lower alkyl group i.e., a C1-C6 alkyl group and includes methyl, ethyl, propyl, isopropyl, butyl, *t*-butyl, 2-butyl, pentyl,

20 hexyl, and the like. More preferably lower alkyl is C1-C4 alkyl, and even more preferably C1-C3 alkyl. Examples of "cycloalkyl" groups as used herein are moieties having 3 to 10, preferably 3 to 7 carbon atoms including cyclopropyl, cyclopentyl and cyclohexyl groups.

25 "Halogen" means fluorine, chlorine, bromine and iodine.

"Trihaloalkyl" means an alkyl group in which the three hydrogens of one of the terminal carbon atoms are replaced by halogen, preferably by fluorine. Examples of such groups are trifluoromethyl, trichloromethyl, 1,1,1-trifluoroethyl, 1,1,1-trichloropropyl and the like. "Trihalo lower alkyl" denotes a trihaloalkyl group with

30 one to six carbon atoms, preferably one to three carbon atoms.

"Aryl" means a monovalent, monocyclic or bicyclic, aromatic carbocyclic or heterocyclic radical, preferably a 6-10 member aromatic ring system. An "aryl"

group containing one or several heteroatoms, preferably selected from N, S and O can also be referred to as a "heteroaryl" group. Preferred aryl and heteroaryl groups include, but are not limited to, phenyl, naphthyl, tolyl, xylyl, thienyl, furyl, indolyl, pyrrolyl, pyridinyl, oxy-pyridinyl, pyrazinyl, oxazolyl, thiazolyl, quinolinyl, 5 pyrimidinyl, imidazole and tetrazolyl. Aryl groups can be optionally mono-, di- or tri- substituted by, for example, lower alkyl, cycloalkyl, e.g., cyclopropyl, trihalo-lower alkyl, e.g., trifluoromethyl, hydroxyl, alkoxy, especially lower alkoxy, mono or dihydroxyl-substituted alkoxy, acetamido, methoxyacetamido, dimethylaminoacetamido, halogen, e.g., fluoro, chloro, or bromo, aniline 10 derivatives, amide derivatives of the aniline derivatives and methanesulfonyl. When two or more substituents are present on an aryl or heteroaryl ring they may also be present in the form of a fused ring. Such fused rings include, but are not limited to, 3,4-methylenedioxyphenyl and 3,4-ethylenedioxyphenyl.

15 "Heteroatom" means an atom selected from N, O and S.

"Heterocyclyl" means a monocyclic, non-aromatic hydrocarbon radical having four to six carbon atoms and at least one, preferably one or two, heteroatom(s). Examples of such heterocyclyl group are azetidiny, oxetanyl, pyrrolidinyl, 20 morpholino and the like.

"Alkoxy or lower alkoxy" refers to any of the above lower alkyl groups attached to an oxygen atom. Typical lower alkoxy groups include methoxy, ethoxy, isopropoxy or propoxy, butyloxy, cyclopropyl methoxy, and the like. Further 25 included within the meaning of alkoxy are multiple alkoxy side chains, e.g. ethoxy ethoxy, methoxy ethoxy, methoxy ethoxy ethoxy, methyl oxetanyl methoxy and the like. Also included are substituted alkoxy side chains, e.g., hydroxyethoxy, dihydroxypropoxy, dimethylamino ethoxy, diethylamino ethoxy, phosphoryl methoxy, dimethoxy-phosphoryl methoxy, carbamoyl methoxy, methyl and 30 dimethyl carbamoyl methoxy, carbamoyl ethoxy, methyl and dimethyl carbamoyl ethoxy, azetidiny carbamoyl ethoxy, oxopyrrolidinyl ethoxy, bishydroxyethylcarbamoyl methoxy, morpholinyl methoxy, morpholinyl ethoxy, piperazinyl methoxy, piperazinyl ethoxy, lower-alkyl piperazine ethoxy, oxo-pyrrolidinyl ethoxy, and the like.

“Pharmaceutically acceptable ester” refers to a conventionally esterified compound of formula I having a carboxyl group, which esters retain the biological effectiveness and properties of the compounds of formula I and are cleaved *in vivo* (in the organism) to the corresponding active carboxylic acid.

Information concerning esters and the use of esters for the delivery of pharmaceutical compounds is available in Design of Prodrugs. Bundgaard Hans ed. (Elsevier, 1985). *See also*, Ansel et. al., Pharmaceutical Dosage Forms and Drug Delivery Systems (6th Ed. 1995) at pp. 108-109; Krogsgaard-Larsen, *et al.*, Textbook of Drug Design and Development (2d Ed. 1996) at pp. 152-191.

“Pharmaceutically acceptable salt” refers to conventional acid-addition salts or base-addition salts that retain the biological effectiveness and properties of the compounds of the present invention and are formed from suitable non-toxic organic or inorganic acids or organic or inorganic bases. Sample acid-addition salts include those derived from inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulfamic acid, phosphoric acid and nitric acid, and those derived from organic acids such as p-toluenesulfonic acid, salicylic acid, methanesulfonic acid, oxalic acid, succinic acid, citric acid, malic acid, lactic acid, fumaric acid, trifluoro acetic acid and the like. Sample base-addition salts include those derived from ammonium, potassium, sodium and, quaternary ammonium hydroxides, such as for example, tetramethylammonium hydroxide. Chemical modification of a pharmaceutical compound (i.e. drug) into a salt is a technique well known to pharmaceutical chemists to obtain improved physical and chemical stability, hygroscopicity, flowability and solubility of compounds. *See, e.g.*, Ansel *et al.*, Pharmaceutical Dosage Forms and Drug Delivery Systems (6th Ed. 1995) at pp. 196 and 1456-1457.

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“Pharmaceutically acceptable,” such as pharmaceutically acceptable carrier, excipient, etc., means pharmacologically acceptable and substantially non-toxic to the subject to which the particular compound is administered.

"Substituted," as in substituted aryl or heteroaryl, means that the substitution can occur at one or more positions and, unless otherwise indicated, that the substituents at each substitution site are independently selected from the specified options.

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"Therapeutically effective amount or effective amount" means an amount of at least one designated compound that significantly inhibits proliferation and/or prevents differentiation of a human tumor cell, including human tumor cell lines.

- 10 Compounds of the general formula I may herein also be referred to as compounds of formula 1.

The compounds of the present invention are useful in the treatment or control of cell proliferative disorders such as inflammatory/autoimmune disorders, e.g.,
15 restenosis, cognitive disorders, e.g., dementia and Alzheimer's disease, CNS disorders, e.g., neuropathic pain and, in particular, oncological disorders. These compounds and formulations containing said compounds may be useful in the treatment or control of solid tumors, such as, for example, breast, colon, lung and prostate tumors.

20

Consequently, the present invention also provides a compound of formula I as defined herein before for the use as a medicament.

A further object of the present invention is a compound of formula I as defined
25 above for use as a medicament for the treatment of cancer, in particular solid tumors, more particularly lung, breast, colon and prostate tumors.

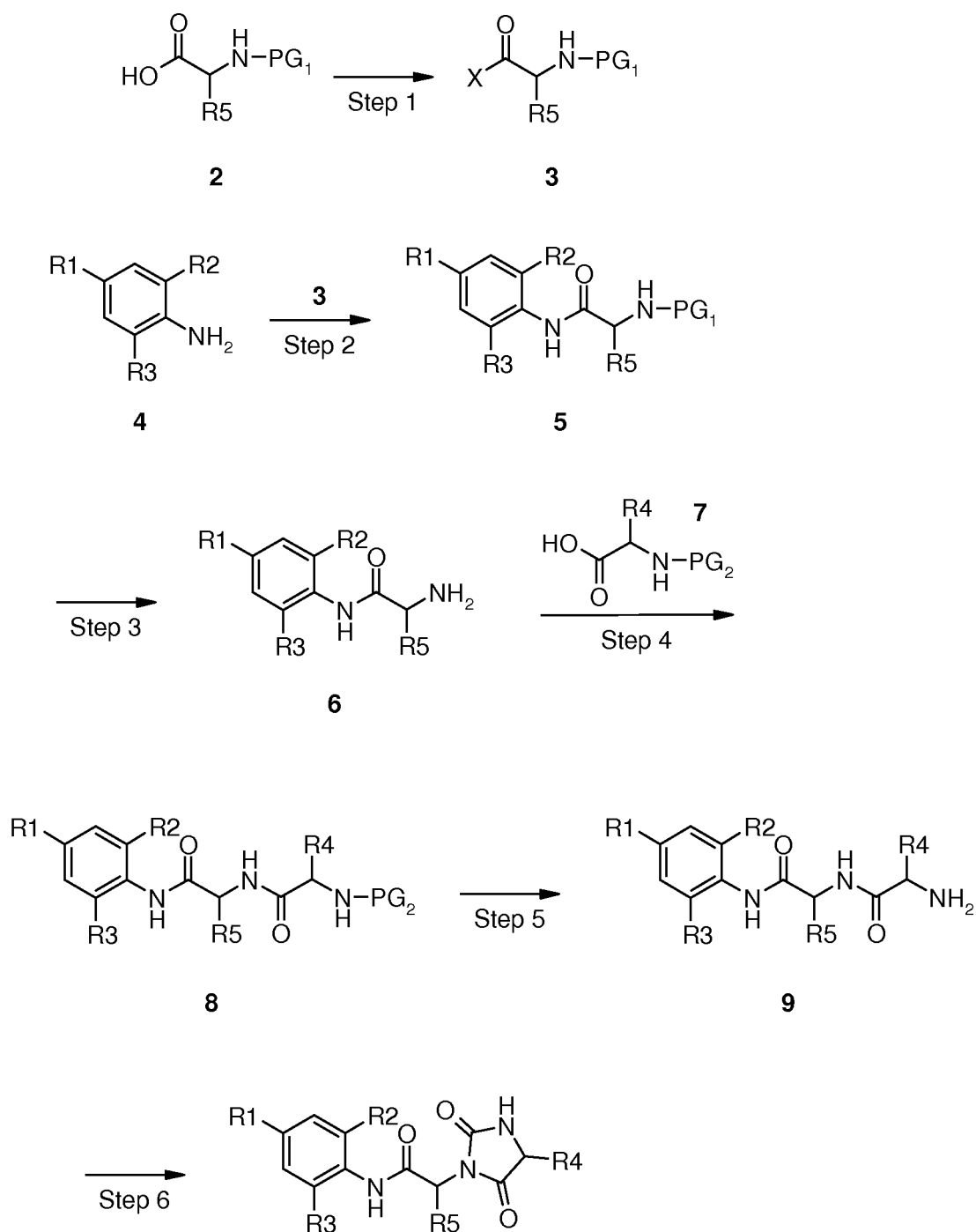
Still another object of the present invention is the use of a compound of formula I as defined above for the manufacture of a medicament for the treatment of
30 cancer, in particular solid tumors, more particularly lung, breast, colon and prostate tumors.

The compounds of formula I as well as their salts have at least two asymmetric carbon atoms and therefore may be present as mixtures of different

stereoisomers. The various isomers can be isolated by known separation methods, e.g., chromatography.

- A therapeutically effective amount of a compound in accordance with this invention means an amount of compound that is effective to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated. Determination of a therapeutically effective amount is within the skill in the art.
- 10 The therapeutically effective amount or dosage of a compound according to this invention can vary within wide limits and may be determined in a manner known in the art. Such dosage will be adjusted to the individual requirements in each particular case including the specific compound(s) being administered, the route of administration, the condition being treated, as well as the patient being treated.
- 15 In general, in the case of oral or parenteral administration to adult humans weighing approximately 70 Kg, a daily dosage of about 10 mg to about 10,000 mg, preferably from about 200 mg to about 1,000 mg, should be appropriate, although the upper limit may be exceeded when indicated. The daily dosage can be administered as a single dose or in divided doses, or for parenteral
- 20 administration, it may be given as one or more bolus injections or as a continuous infusion.

- The compounds claimed in the present invention (compounds of general formula I) can be prepared using the general reaction sequence set out in Scheme 1, wherein all substituents have the meanings as defined herein before, unless explicitly otherwise stated.
- 25



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Scheme 1

Step1: A compound containing an α -amino acid functional group of general formula 2 is converted in to a reactive acylating species of general formula 3 which is suitable for use in step 2 of the synthetic sequence. Step 1 is most conveniently performed on an α -amino acid which bears a protecting group (PG1) on the α -amine nitrogen. A suitable choice for protecting group PG1 is

one which renders the α -amine nitrogen inert to the reaction conditions employed during steps 1 and 2 of the synthetic sequence but which may be removed during step 3 of the synthetic sequence without causing undesired modifications to the rest of the compound when exposed to the conditions required for the removal of the protecting group. Preferred choices for protecting group PG1 may be made by reference to organic chemistry text books (e.g. Protective Groups in Organic Synthesis, Theodora W. Greene et al.), the original chemistry literature, or would be generally known to one knowledgeable in the art of organic synthesis. In particular carbamate-based protecting groups, e.g. tert-butylloxycarbonyl and 9H-fluoren-9-ylmethoxycarbonyl, are preferred but other amine-protecting groups may also be effective.

The choice of which reactive acylating agent of general formula 3 to form is dependent upon both compatibility with potentially reactive functional groups present elsewhere in compounds of general formula 3 and the reactivity and selectivity of the acylating agent of general formula 3 for acylation of the aniline derivative of general formula 4. This reaction yields the desired amide bond present in compounds of general formula 5. Typical reactive acylating agents which may be employed in step 2 are acyl halides (3, X = halogen) and acid anhydrides (3, X = O-C(O)R). Preferred choices for the acylating agents of general formula 3 are the acyl halides, in particular acyl fluorides (3, X = fluorine), acyl chlorides (3, X = chlorine) and acyl bromides (3, X = bromine). Additional choices for acylating agents of general formula 3 may also be suitable for use in step 2 and would be apparent to one knowledgeable in the art of organic synthesis.

In the case where compounds of general formula 2 contain a chiral center at the α -carbon, the preferred stereochemistry is S.

Step 2: An aniline derivative of general formula 4 is combined with a pre-formed acylating agent of general formula 3 to form amide derivatives of general formula 5.

It will be apparent to one skilled in the art of organic synthesis that by use of known peptide coupling reaction techniques it may be possible to prepare compounds of general formula 5 directly from compounds of general formula 2 and general formula 4 without having to pre-form a reactive acylating agent of general formula 3. Typical peptide coupling reagents which may be employed for the direct conversion of compounds of general formula 2 and general formula 4 to compounds of general formula 5 include diimide based reagents e.g. dicyclohexylcarbodiimide, (3-dimethylamino-propyl)-ethyl-carbodiimide hydrochloride; or uronium based reagents, e.g. O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate or O-benzotriazol-1-yl-N,N,N',N'-bis(tetramethylene)uronium hexafluorophosphate. Alternative peptide coupling reagents may also be effective in performing this conversion. Selection of alternative peptide coupling reagents may be made by reference to the original chemistry literature or would be generally known to one knowledgeable in the art of organic synthesis.

Step 3: This step in the synthetic sequence entails the removal of protecting group PG1 from compounds of general formula 5 to form amine-containing compounds of general formula 6 in preparation for subsequent elaboration. As mentioned above the choice of protecting group PG1 and conditions used during step 3 for removal of PG1 is influenced by what other potentially reactive functional groups are present in compounds of general formula 5 and the requirement of avoiding undesired reactions elsewhere in the starting material or product of the reaction, i.e., compounds of general formulae 5 and 6, respectively. In the case where the amine-protecting group PG1 present in compounds of general formula 5 is tert-butyloxycarbonyl, the protecting group can be removed under acidic conditions such as trifluoroacetic acid in dichloromethane or hydrochloric acid in p-dioxane. Removal of the tert-butyloxycarbonyl group under acidic conditions initially liberates the corresponding salt of the compound of general formula 6, from which the free amine of general formula 6 can be liberated after treatment with base. In the case where the amine-protecting group PG1 present in compounds of general formula 5 is 9H-fluoren-9-ylmethoxycarbonyl, the protecting group can be removed under basic conditions such as piperidine in dichloromethane.

Step 4: Compounds of general formula 8 are obtained by combining amines of general formula 6 with a compound containing an α -amino acid functional grouping. Step 4 is most conveniently performed on compounds of general formula 7 which contain an α -amino acid which bears a protecting group (PG2) on the α -amine nitrogen. The criteria for choice of the protecting group PG2 are the same as described for the choice of protecting group PG1 in step 1. In particular carbamate-based protecting groups, e.g. tert-butyloxycarbonyl, are preferred but other amine-protecting groups may also be effective.

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In the case where compounds of general formula 7 contain a chiral center at the α -carbon, the preferred stereochemistry is R.

Step 5: This step in the synthetic sequence entails the removal of protecting group PG2 from compounds of general formula 8 to form amine-containing compounds of general formula 9 prior to completion of the synthetic sequence. The choice of conditions for effecting removal of protecting group PG2 from compounds of general formula 8 is based both upon the chemical reactivity of protecting group PG2 and the nature and reactivity of other functional groups present in the starting material and product of the reaction performed in step 5, i.e., compounds of general formula 8 and 9, respectively. In the case where the amine-protecting group PG2 present in compounds of general formula 8 is tert-butyloxycarbonyl, the protecting group can be removed under acidic conditions such as trifluoroacetic acid in dichloromethane, hydrochloric acid in p-dioxane or in neat formic acid. Removal of the tert-butyloxycarbonyl group under acidic conditions initially liberates the corresponding salt of the compound of general formula 9, from which the free amine of general formula 9 can be liberated after treatment with base.

Step 6: Compounds of general formula I as are claimed in the present invention can be obtained from compounds of general formula 9 by cyclization in the presence of phosgene or an equivalent reagent, i.e. a carbonyl group directly attached to two displaceable groups. A preferred reagent for effecting the cyclization of compounds of general formula 9 to compounds of general formula I

is trichloromethyl chloroformate which functions in the reaction mixture as two equivalents of phosgene. Cyclization of compounds of general formula 9 with trichloromethyl chloroformate is generally rapid and is typically performed at low temperature ($<0\text{ }^{\circ}\text{C}$) and in the presence of a carefully controlled amount of
5 base to neutralize acid formed during the cyclization but to avoid unnecessary isomerization of the potentially labile chiral center on the newly formed hydantoin ring.

It will be apparent to one knowledgeable in the art of organic synthesis that when
10 one or more of the substituents labeled R1 through R5, or substituents included in their definitions, in the compounds shown in Scheme 1 are in and of themselves chemically reactive groups, or contains chemically reactive groups, then additional modification of the compounds of general formula I through 9 which contain those reactive groups may be possible. The point in the synthetic
15 sequence at which modification of the chemically reactive groups takes place may be chosen such that the newly elaborated group is chemically inert to the reagents to be employed during the remaining steps of the synthetic sequence and does not interfere with the remaining steps in the synthetic sequence shown in Scheme 1. Alternatively, if the newly elaborated group is not chemically inert
20 or can interfere with the remaining steps in the synthetic sequence it may be necessary to temporarily mask the reactive functional group with an appropriate protecting group or to derivatize the functional group into a moiety which is stable to the remaining transformations in the synthetic sequence and will be present in the final product of the reaction sequence. If a protecting group is introduced
25 which is not required in the final compound of general structure 1 then it may either be removed under the conditions remaining in the synthetic sequence shown in Scheme 1 or by introduction of an additional deprotection step into the synthetic sequence depending upon the nature of the protecting group employed.

30 The reaction conditions for the above reactions can vary to a certain extent.

Methods to perform the above described reactions and processes would be apparent to those of ordinary skill in the art based on the present disclosure, or can be deduced in analogy from the examples. Starting materials are

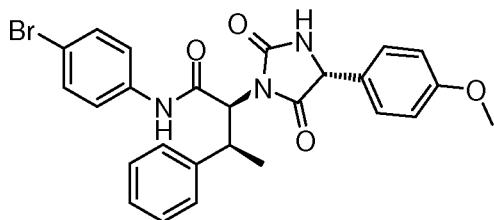
commercially available or can be made by methods analogous to those described in the Examples.

The following examples shall illustrate preferred embodiments of the present
5 invention but are not intended to limit the scope of the invention.

Example 1

(2S,3S)-N-(4-Bromo-phenyl)-2-[(R)-4-(4-methoxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butamide

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Step 1: To a solution of (2S, 3S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid (838 mg, 3.0 mmol) in dichloromethane (10 mL) at -35 °C was added dry pyridine (255 µL, 3.15 mmol) and cyanuric fluoride (375 µL, 4.5 mmol) under an atmosphere of dry argon. The mixture was stirred for 1.5 hours while maintaining the temperature between -35 and -25 °C. A small amount of ice was added to the reaction mixture and the mixture stirred vigorously for 15 minutes. The organic layer was decanted away from the aqueous solution and the aqueous layer extracted with dichloromethane (2 × 10 mL). The combined organic layers were washed with ice cold water (15 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to give (1-fluorocarbonyl-2-phenyl-propyl)-carbamic acid *tert*-butyl ester which was used in the subsequent step without further purification.

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Step 2: To a solution of 4-bromoaniline (97% purity) (177 mg, 1.0 mmol) and *N*-methyl morpholine (220 µL, 2.0 mmol) in dry tetrahydrofuran (3 mL) was added a solution of (1-fluorocarbonyl-2-phenyl-propyl)-carbamic acid *tert*-butyl ester (≈ 1.5 mmol) in dry tetrahydrofuran (2 mL + 1 mL to rinse addition funnel in to reaction mixture) and a catalytic amount of dimethyl-pyridin-4-yl-amine. The mixture was heated to reflux under an atmosphere of dry argon for 3 hours and then cooled to ambient temperature. The reaction mixture was concentrated *in vacuo* and the residue taken up in ethyl acetate. The organic solution was washed sequentially with water (once), 1.5 M aqueous potassium hydrogen sulfate solution (once), water (three times), brine (once), dried over sodium sulfate, filtered and

30

concentrated *in vacuo* to give (1S, 2S)-1-(4-bromo-phenylcarbamoyl)-2-phenyl-propyl]-carbamic acid *tert*-butyl ester which was used in the subsequent step without further purification (530 mg).

LC-MS: Obs Mass ($M+H^+$), 433/435; Calcd. Mass, 433/435 for

5 $C_{21}H_{26}BrN_2O^+$.

Step 3: To a solution of (1S, 2S)-1-(4-bromo-phenylcarbamoyl)-2-phenyl-propyl]-carbamic acid *tert*-butyl ester (530 mg, ≈ 1 mmol) in dichloromethane (12 mL) at 0 °C under an atmosphere of dry argon was added trifluoroacetic acid (8 mL, 108 mmol) and the mixture stirred at 0 °C for 1.5 hours. The reaction mixture was concentrated *in vacuo* and the residue suspended in ice cold water. The aqueous suspension was neutralized with saturated aqueous sodium hydrogen carbonate solution (12 mL) then extracted with dichloromethane (three times). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to give (2S, 3S)-2-amino-*N*-(4-bromo-phenyl)-3-phenyl-butylamide which was used in the subsequent step without further purification (334 mg).

LC-MS: Obs Mass ($M+H^+$) = 333/335; Calcd. Mass, 333/335 for $C_{16}H_{18}BrN_2O^+$.

20

Step 4: To a solution of (2S, 3S)-2-amino-*N*-(4-bromo-phenyl)-3-phenyl-butylamide (167 mg, ≈ 0.5 mol) in *N,N*-dimethylformamide (3 mL) at 0 °C was added (R)-*tert*-butyloxycarbonylamino-4-methoxyphenylglycine (155 mg, 0.55 mmol) (prepared according to the procedure of Hyun, M.H., *et al.*, *J. Liq. Chrom. & Rel. Technol.* **2002**, 25, 573-588), *N,N*-diisopropylethylamine (350 μ L, 2.0 mmol), *N*-hydroxybenzotriazole (82 mg, 0.6 mmol), *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (227 mg, 0.6 mmol) and a catalytic amount of dimethyl-pyridin-4-yl-amine and the mixture stirred under an atmosphere of dry argon and allowed to slowly warm to ambient temperature overnight. The reaction mixture was poured into ice / water (20 mL), extracted with ethyl acetate (2×10 mL), the combined organic extracts washed with water (3×10 mL), brine (10 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by chromatography over silica gel eluted with 2:1 v/v hexanes / ethyl acetate to give [(1S, 2S)-1-(4-bromo-

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phenylcarbamoyl)-2-phenyl-propylcarbamoyl]-((R)-4-methoxy-phenyl)-methyl]-carbamic acid *tert*-butyl ester as a colorless solid (154 mg, 52%).

LC-MS: Obs Mass ($M-H^-$), 594/596; Calcd. Mass, 594/596 for $C_{30}H_{33}BrN_3O_5^-$.

- 5 Step 5: To a solution of [[(1S, 2S)-1-(4-bromo-phenylcarbamoyl)-2-phenyl-propylcarbamoyl]-((R)-4-methoxy-phenyl)-methyl]-carbamic acid *tert*-butyl ester (150 mg, 0.25 mmol) in dichloromethane (10 mL) at 0 °C under an atmosphere of dry argon was added trifluoroacetic acid (6 mL, 81 mmol) and the mixture stirred at 0 °C for 1.5 hours. The reaction mixture was concentrated *in vacuo*
10 and the residue suspended in ice cold water. The aqueous suspension was neutralized with saturated aqueous sodium hydrogen carbonate solution (12 mL) then extracted with dichloromethane (three times). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to give (2S, 3S)-2-[(R)-2-amino-2-(4-methoxy-phenyl)-acetylamino]-*N*-(4-bromo-phenyl)-3-phenyl-butyramide which was used in the subsequent step without
15 further purification (124 mg).

LC-MS: Obs Mass ($M+H^+$), 496/498; Calcd. Mass, 496/498 for $C_{25}H_{26}BrN_3O_3^+$.

- 20 Step 6: To a solution of diphosgene (20 μ L, 0.17 mmol) in 1:1 v/v toluene / tetrahydrofuran (16 mL total) at -35 °C under an atmosphere of dry argon was added a solution of (2S, 3S)-2-[(R)-2-amino-2-(4-methoxy-phenyl)-acetylamino]-*N*-(4-bromo-phenyl)-3-phenyl-butyramide (120 mg, 0.24 mmol) and *N,N*-diisopropylethylamine (210 μ L, 1.2 mmol) in tetrahydrofuran (8 mL) dropwise
25 with stirring over 10 minutes. After an additional 45 minutes ice was added and the reaction mixture stirred vigorously and warmed to ambient temperature. The reaction mixture was poured into water, extracted with ethyl acetate (twice) and the combined organic layers were washed sequentially with water (twice), 0.1 M aqueous hydrochloric acid, water, saturated aqueous sodium hydrogen
30 carbonate, water and brine, then dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by chromatography over silica gel eluted with 2:1 v/v hexanes / ethyl acetate. The isolated product was dissolved in a small volume of dichloromethane and then precipitated by dropwise addition to a vigorously stirred large volume of petroleum ether. The

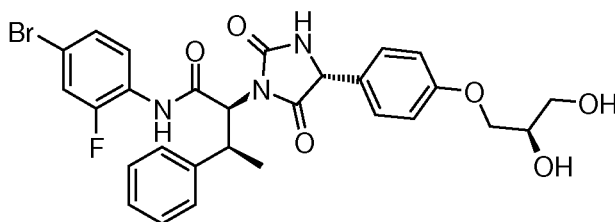
precipitated solid was isolated by filtration and dried *in vacuo* to give (2S,3S)-*N*-(4-bromo-phenyl)-2-[(R)-4-(4-methoxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide as a colorless solid (87 mg, 69%).

HRMS: Obs. Mass ($M+H^+$), 522.1021. Calcd. Mass, 522.1023 for

5 $_{26}H_{25}BrN_3O_4^+$.

Example 2

(2S,3S)-*N*-(4-Bromo-2-fluoro-phenyl)-2-[(R)-4-[4-((R)-2,3-dihydroxy-propoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide



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Prepared by the same method as described in example 1 except that (i) 4-bromo-2-fluoroaniline was used in place of 4-bromoaniline in step 2, and (ii) (R)-*tert*-butoxycarbonylamino-[4-((S)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-4-methoxyphenylglycine in step 4. (R)-*tert*-Butoxycarbonylamino-[4-((S)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-acetic acid was prepared and used as described in example 114.

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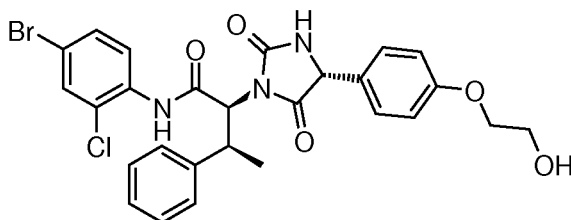
HRMS: Obs Mass ($M+H^+$), 600.1137. Calcd. Mass, 600.1140 for

$C_{28}H_{28}BrFN_3O_6^+$.

20

Example 3

(2S,3S)-*N*-(4-Bromo-2-chloro-phenyl)-2-[(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide



25

Step 1: 4-Bromo-2-chloro-aniline (325 mg, 1.58 mmol) and (S, S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid (440 mg, 1.58 mmol) in pyridine (5 mL) were cooled to -30 °C. Phosphorus oxychloride (0.158 mL, 1.7 mmol) was

added and stirred at -20 °C for 2 hours. The mixture was poured into ice water and extracted with ethyl acetate (3 ×). The combined organic extracts were washed with water, brine, dried over sodium sulfate and concentrated *in vacuo*. The residue was dissolved in dichloromethane (5 mL) at 0 °C and trifluoroacetic acid (3 mol) added. Stirring was continued for 2 hours at 0 °C. The mixture was evaporated and the residue dissolved in ether. The ether solution was basified with saturated aqueous sodium bicarbonate and extracted with ether. The organic extracts were washed with brine, dried over sodium sulfate and evaporated to give (2S, 3S)-2-amino-*N*-(4-bromo-2-chloro-phenyl)-3-phenylbutyramide (325 mg, 55%).

Step 2: To a solution of (2S, 3S)-2-amino-*N*-(4-bromo-2-chloro-phenyl)-3-phenylbutyramide (320 mg, 0.87 mmol) in *N,N*-dimethylformamide (3 mL) at 0 °C was added (*R*)-*tert*-butoxycarbonylamino-[4-(2-*tert*-butoxy-ethoxy)-phenyl]-acetic acid (320 mg, 0.87 mmol) (prepared as described in example 48 for the preparation of (*R*)-*tert*-butoxycarbonylamino-{4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-acetic acid except that 2-(2-bromo-ethoxy)-2-methyl-propane was used in place of 2-(2-bromo-ethoxy)-tetrahydropyran), *N,N*-diisopropylethylamine (0.71 mL, 2.0 mmol), *N*-hydroxybenzotriazole (82 mg, 0.6 mmol), *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (227 mg, 0.6 mmol). After 30 minutes, the reaction mixture was poured into ice / water (20 mL), extracted with ethyl acetate (2 × 10 mL), the combined organic extracts washed with water (3 × 10 mL), brine (10 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to give [(1S, 2S)-1-(4-bromo-2-chloro-phenylcarbamoyl)-2-phenylbutylcarbamoyl]-((*R*)-4-(*tert*-butoxy-ethoxy)-phenyl)-methyl]-carbamic acid *tert*-butyl ester as a white solid (560 mg). The ester was suspended in acetonitrile (5 mL) in a ice bath. 4 M hydrogen chloride in *p*-dioxane (2 mL) was added and the mixture stirred for 1.5 hours. The mixture was evaporated and triturated with ether / hexanes. The solid was filtered and partitioned between saturated aqueous sodium bicarbonate and dichloromethane. The organic layer was separated and washed with brine and dried over sodium sulfate. Evaporation of the solvents gave [(1S, 2S)-1-(4-bromo-2-chloro-phenylcarbamoyl)-2-phenylbutylcarbamoyl]-((*R*)-4-(*tert*-butoxy-ethoxy)-phenyl)-methyl]-carbamic acid as a white solid (346 mg, 72%).

Step3: [[(1S, 2S)-1-(4-Bromo-2-chloro-phenylcarbamoyl)-2-phenyl-butylcarbamoyl]-((R)-4-(*tert*-butoxy-ethox(-phenyl)-methyl]-carbamic acid (344 mg, 0.56 mmol) and diisopropyl ethyl amine (0.40 mL, 2.25 mmol) were added to diphosgene (47 μ L, 0.39 mmol) in tetrahydrofuran (5 mL) and toluene (5 mL) at -78 °C. The mixture was stirred and warmed slowly from -78 to -30 °C over 1.5 hours and then diluted with ethyl acetate and washed with water. The organic layer was washed with brine, dried over sodium sulfate and evaporated. The residue was triturated with hexanes to give *N*-(4-bromo-2-chloro-phenyl)-2-{4-[4-(2-*tert*-butoxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl}-3-phenyl-butylamide (300 mg, 84%).

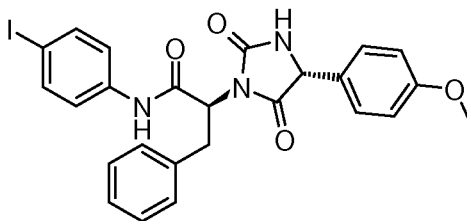
Step4: *N*-(4-Bromo-2-chloro-phenyl)-2-{4-[4-(2-*tert*-butoxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl}-3-phenyl-butylamide (300 mg) was dissolved in dichloromethane (2 mL) and acetonitrile (2 mL) in an ice bath. Trimethylsilyl chloride (0.36 mL, 2.8 mmol) was added followed by sodium iodide (352 mg, 2.35 mmol). The mixture was stirred at 0 °C for 1.5 hours and then diluted with ethyl acetate. The mixture was washed with aqueous sodium bisulfite, washed with brine, dried over sodium sulfate and concentrated *in vacuo*. Trituration of the residue with hexanes gave *N*-(4-bromo-2-chloro-phenyl)-2-{4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl}-3-phenyl-butylamide (210 mg, 76%).

HRMS: Obs Mass ($M+H^+$), 586.0739. Calcd. Mass, 586.0739 for $C_{27}H_{26}BrClN_3O_5^+$.

25

Example 4

(S)-*N*-(4-Iodo-phenyl)-2-[(R)-4-(4-methoxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-propionamide



Prepared by the same method as described in example 1 except that (i) (S)-2-*tert*-butoxycarbonylamino-3-phenyl-propionic acid was used in place of (2S, 3S)-

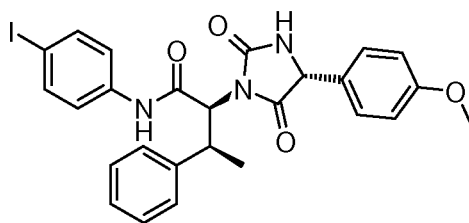
2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid in step 1, (ii) 4-iodoaniline was used in place of 4-bromoaniline in step 2, and (iii) the trifluoroacetic acid salt of (S)-2-amino-*N*-(4-iodo-phenyl)-3-phenyl-propionamide was isolated in step 3 and used directly in step 4 with 1.0 equivalent of triethylamine and (3-dimethylamino-propyl)-ethyl-carbodiimide hydrochloride as the coupling reagent in place of *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate.

HRMS: Obs Mass ($M+H^+$), 556.0726. Calcd. Mass, 556.0728 for $C_{25}H_{23}IN_3O_4^+$.

10

Example 5

(2S,3S)-*N*-(4-iodo-phenyl)-2-[(R)-4-(4-methoxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide



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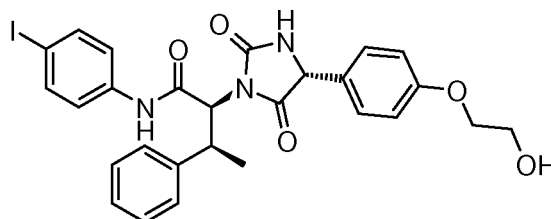
Prepared by the same method as described in example 1 except that 4-iodoaniline was used in place of 4-bromoaniline in step 2 and (3-dimethylamino-propyl)-ethyl-carbodiimide hydrochloride was used as the coupling reagent in place of *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate in step 4.

20

HRMS: Obs. Mass ($M+H^+$), 570.0883. Calcd. Mass, 570.0884 for $C_{26}H_{25}IN_3O_4^+$.

Example 6

(2S,3S)-2-[(R)-4-[4-(2-Hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-*N*-(4-iodo-phenyl)-3-phenyl-butyramide



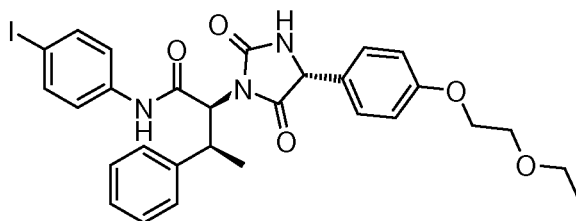
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- Prepared by the same method as described in example 48 except that (i) 4-iodoaniline was used in place of 2-fluoro-4-iodoaniline in step 2, and (ii) (3-dimethylamino-propyl)-ethyl-carbodiimide hydrochloride was used as the coupling reagent in place of *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium
- 5 hexafluorophosphate in step 4.

HRMS: Obs Mass ($M+H^+$), 600.0987 Calcd. Mass, 600.0990 for $C_{27}H_{27}IN_3O_5^+$.

Example 7

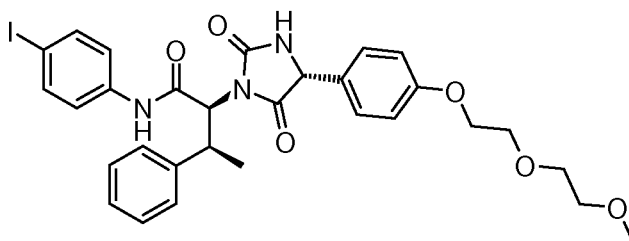
- 10 (2*S*,3*S*)-2-((*R*)-4-[4-(2-Ethoxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl)-*N*-(4-iodo-phenyl)-3-phenyl-butyramide



- Prepared by the same method as described in example 1 except that (i) 4-iodoaniline was used in place of 4-bromoaniline in step 2 and (ii) (*R*)-*tert*-butoxycarbonylamino-{4-ethoxy-ethoxy}-phenyl}-acetic acid was used in place of (*R*)-*tert*-butoxycarbonylamino-4-methoxyphenylglycine in step 4. (*R*)-*tert*-Butoxycarbonylamino-{4-ethoxy-ethoxy}-phenyl}-acetic acid was prepared as described in example 48 except that 1-bromo-2-ethoxy-ethane was used in place of 2-(2-bromo-ethoxy)-tetrahydropyran.
- 20 HRMS: Obs Mass ($M+H^+$), 628.1305. Calcd. Mass, 628.1303 for $C_{29}H_{31}IN_3O_5^+$.

Example 8

- (2*S*,3*S*)-*N*-(4-Iodo-phenyl)-2-((*R*)-4-{4-[2-(2-methoxy-ethoxy)-ethoxy]-phenyl}-2,5-dioxo-imidazolidin-1-yl)-3-phenyl-butyramide
- 25

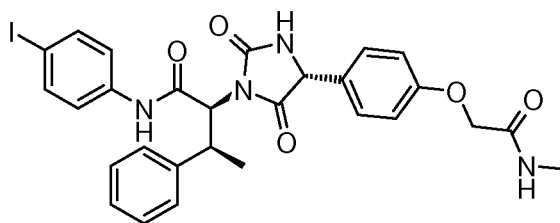


Prepared by the same method as described in example 7 except except that (R)-*tert*-butoxycarbonylamino-{4-[2-(2-methoxy-ethoxy)-ethoxy]-phenyl}-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-{4-ethoxy-ethoxy}-phenyl}-acetic acid. (R)-*tert*-Butoxycarbonylamino-{4-[2-(2-methoxy-ethoxy)-ethoxy]-phenyl}-acetic acid was prepared as described in example 48 except that 1-(2-bromo-ethoxy)-2-methoxy-ethane was used in place of 2-(2-bromo-ethoxy)-tetrahydropyran.

HRMS: Obs Mass ($M+H^+$), 658.1410. Calcd. Mass, 658.1409 for $C_{30}H_{33}IN_3O_6^+$.

Example 9

(2S,3S)-*N*-(4-Iodo-phenyl)-2-[(R)-4-(4-methylcarbamoylmethoxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide



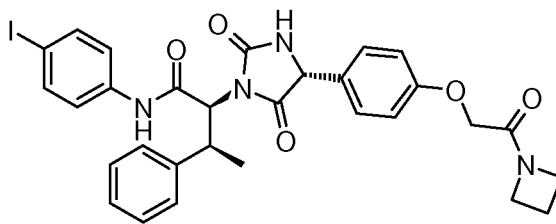
Prepared by the same method as described in example 5 except that (R)-*tert*-butoxycarbonylamino-(4-methylcarbamoylmethoxy-phenyl)-acetic acid was used in place of (R)-*tert*-butyloxycarbonylamino-4-methoxyphenylglycine in step 4. (R)-*tert*-Butoxycarbonylamino-(4-methylcarbamoylmethoxy-phenyl)-acetic acid was prepared by a method similar to that used for the preparation of (R)-*tert*-butyloxycarbonylamino-4-methoxyphenylglycine in example 1 except that 2-chloro-*N*-methyl-acetamide was used in place of iodomethane.

HRMS: Obs Mass ($M+H^+$), 627.1096. Calcd. Mass, 627.1099 for $C_{28}H_{28}IN_4O_5^+$.

Example 10

(2S,3S)-2-[(R)-4-[4-(2-Azetidin-1-yl-2-oxo-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-*N*-(4-iodo-phenyl)-3-phenyl-butyramide

- 31 -

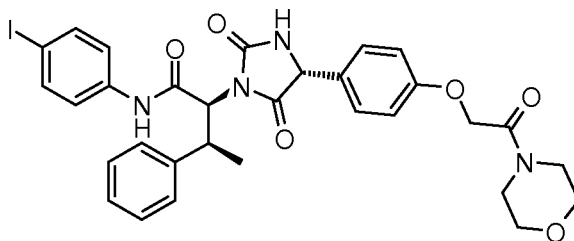


Prepared by the same method as described in example 1 except that (i) 4-iodoaniline was used in place of 4-bromoaniline in step 2 and (ii) (R)-[4-(2-azetidin-1-yl-2-oxo-ethoxy)-phenyl]-*tert*-butoxycarbonylamino-acetic acid was used in place of (R)-*tert*-butyloxycarbonylamino-4-methoxyphenylglycine. (R)-[4-(2-Azetidin-1-yl-2-oxo-ethoxy)-phenyl]-*tert*-butoxycarbonylamino-acetic acid was prepared by a method similar to that used for the preparation of (R)-*tert*-butyloxycarbonylamino-4-methoxyphenylglycine in example 1 except that 1-azetidin-1-yl-2-chloro-ethanone was used in place of iodomethane.

HRMS: Obs Mass ($M+H^+$), 653.1258. Calcd. Mass, 658.1256 for $C_{30}H_{30}IN_4O_5^+$.

Example 11

(2S,3S)-*N*-(4-Iodo-phenyl)-2-[(R)-4-[4-(2-morpholin-4-yl-2-oxo-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide

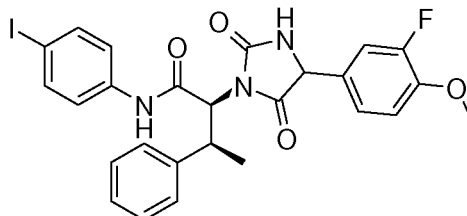


Prepared by the same method as described in example 1 except that (i) 4-iodoaniline was used in place of 4-bromoaniline in step 2 and (ii) (R)-*tert*-butoxycarbonylamino [4-(2-morpholin-4-yl-2-oxo-ethoxy)-phenyl]-acetic acid was used in place of (R)-*tert*-butyloxycarbonylamino-4-methoxyphenylglycine. (R)-*tert*-Butoxycarbonylamino [4-(2-morpholin-4-yl-2-oxo-ethoxy)-phenyl]-acetic acid was prepared by a method similar to that used for the preparation of (R)-*tert*-butyloxycarbonylamino-4-methoxyphenylglycine in example 1 except that 2-chloro-1-morpholin-4-yl-ethanone was used in place of iodomethane.

HRMS: Obs Mass ($M+H^+$), 683.1363. Calcd. Mass, 683.1361 for $C_{31}H_{32}IN_4O_6^+$.

Example 12

(2S,3S)-2-[4-(3-Fluoro-4-methoxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-N-(4-iodo-phenyl)-3-phenyl-butylamide, isomer 1



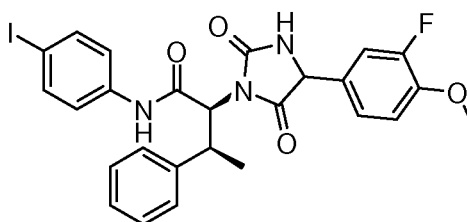
5

Prepared by the same method as described in example 1 except that (i) 4-iodoaniline was used in place of 4-bromoaniline in step 2, (ii) *tert*-butoxycarbonylamino-[3-fluoro-4-methoxy-phenyl]-acetic acid was used in place of (R)-*tert*-butyloxycarbonylamino-4-methoxyphenylglycine in step 4, and (iii) after step 5 the 2 diastereomers were separated by chromatography using silica gradient eluted between 0.2 and 1.5 % v/v methanol in dichloromethane. The fractions containing the second eluted component were collected and taken forward in to step 6. *tert*-Butoxycarbonylamino-[3-fluoro-4-methoxy-phenyl]-acetic acid was prepared as described in WO 2006/029862.

15 HRMS: Obs Mass ($M+H^+$), 588.0790. Calcd. Mass, 588.0790 for $C_{26}H_{24}FIN_3O_4^+$.

Example 13

20 (2S,3S)-2-[4-(3-Fluoro-4-methoxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-N-(4-iodo-phenyl)-3-phenyl-butylamide, isomer 2

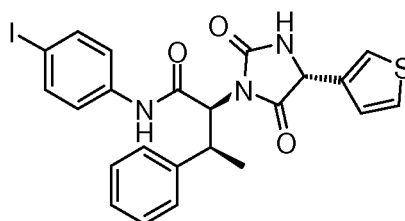


Prepared by the same method as described in example 12 except that during the chromatographic separation of the diastereomers after step 5 the first eluted component was collected and taken forward in to step 6.

25 HRMS: Obs Mass ($M+H^+$), 588.0785. Calcd. Mass, 588.0790 for $C_{26}H_{24}FIN_3O_4^+$.

Example 14

(2S,3S)-2-((R)-2,5-Dioxo-4-thiophen-3-yl-imidazolidin-1-yl)-N-(4-iodo-phenyl)-3-phenyl-butyramide



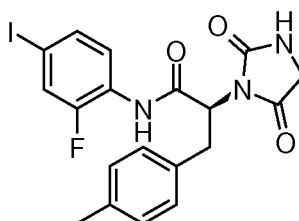
- 5 Prepared by the same method as described in example 5 except that (R)-*tert*-butoxycarbonylamino-thiophen-3-yl-acetic acid was used in place of (R)-*tert*-butyloxycarbonylamino-4-methoxyphenylglycine.

HRMS: Obs. Mass ($M+H^+$), 546.0339. Calcd. Mass, 546.0343 for $C_{23}H_{21}IN_3O_3S^+$.

10

Example 15

(S)-2-(2,5-Dioxo-imidazolidin-1-yl)-N-(2-fluoro-4-iodo-phenyl)-3-*p*-tolyl-propionamide



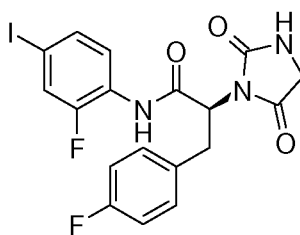
- 15 Prepared by the same method as described in example 1 except that (i) (S)-2-*tert*-butoxycarbonylamino-3-*p*-tolyl-propionic acid was used in place of (2S, 3S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid in step 1, (ii) 2-fluoro-4-iodoaniline was used in place of 4-bromoaniline in step 2, and (iii) *tert*-butyloxycarbonylamino-glycine was used in place of (R)-*tert*-butyloxycarbonylamino-4-methoxyphenylglycine in step 4.

20

HRMS: Obs Mass ($M+H^+$), 482.0372. Calcd. Mass, 482.0372 for $C_{19}H_{18}FIN_3O_3^+$.

Example 16

- 25 (S)-2-(2,5-Dioxo-imidazolidin-1-yl)-N-(2-fluoro-4-iodo-phenyl)-3-(4-fluoro-phenyl)-propionamide



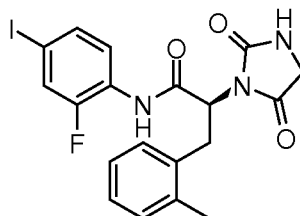
Prepared by the same method as described in example 1 except that (i) (S)-2-*tert*-butoxycarbonylamino-3-(4-fluoro-phenyl)-propionic acid was used in place of (2S, 3S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid in step 1, (ii) 2-fluoro-4-iodoaniline was used in place of 4-bromoaniline in step 2, and (iii) *tert*-butyloxycarbonylamino-glycine was used in place of (R)-*tert*-butyloxycarbonylamino-4-methoxyphenylglycine in step 4.

HRMS: Obs Mass ($M+H^+$), 486.0116. Calcd. Mass, 486.0121 for $C_{18}H_{15}F_2IN_3O_3^+$.

10

Example 17

(S)-2-(2,5-Dioxo-imidazolidin-1-yl)-N-(2-fluoro-4-iodo-phenyl)-3-*o*-tolyl-propionamide



15

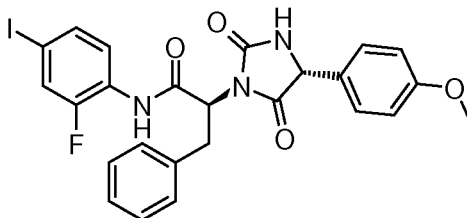
Prepared by the same method as described in example 1 except that (i) (S)-2-*tert*-butoxycarbonylamino-3-*o*-tolyl-propionic acid was used in place of (2S, 3S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid in step 1, (ii) 2-fluoro-4-iodoaniline was used in place of 4-bromoaniline in step 2, and (iii) *tert*-butyloxycarbonylamino-glycine was used in place of (R)-*tert*-butyloxycarbonylamino-4-methoxyphenylglycine in step 4.

20

HRMS: Obs Mass ($M+Na^+$), 504.0190. Calcd. Mass, 504.0191 for $C_{19}H_{17}FIN_3NaO_3^+$.

Example 18

(S)-N-(2-Fluoro-4-iodo-phenyl)-2-[(R)-4-(4-methoxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-propionamide



5

Prepared by the same method as described in example 4 except that 2-fluoro-4-iodoaniline was used in place of 4-iodoaniline in step 2.

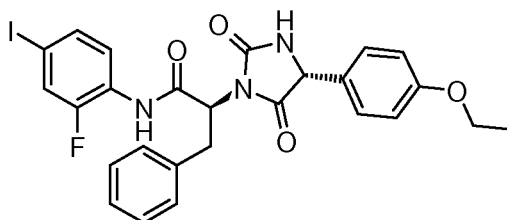
HRMS: Obs Mass ($M+H^+$), 574.0629. Calcd. Mass, 574.0634 for $C_{25}H_{22}FIN_3O_4^+$.

10

Example 19

(S)-2-[(R)-4-(4-Ethoxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-N-(2-fluoro-4-iodo-phenyl)-3-phenyl-propionamide

15



20

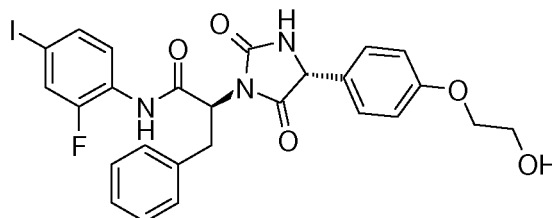
Prepared by the same method as described in example 1 except that (i) (S)-2-*tert*-butoxycarbonylamino-3-phenyl-propionic acid was used in place of (2S, 3S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid in step 1, (ii) 2-fluoro-4-iodoaniline was used in place of 4-bromoaniline in step 2, and (iii) (R)-*tert*-butyloxycarbonylamino-4-ethoxyphenylglycine was used in place of (R)-*tert*-butyloxycarbonylamino-4-methoxyphenylglycine in step 4. (R)-*tert*-Butyloxycarbonylamino-4-ethoxyphenylglycine was prepared as described in example 48 except that ethyl iodide was used in place of 2-(2-bromo-ethoxy)-tetrahydropyran.

25

HRMS: Obs Mass ($M+Na^+$), 610.0605. Calcd. Mass, 610.0609 for $C_{26}H_{23}FIN_3NaO_4^+$.

Example 20

(S)-N-(2-Fluoro-4-iodo-phenyl)-2-{(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-
5 imidazolidin-1-yl}-3-phenyl-propionamide

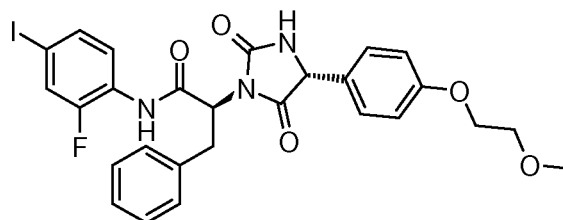


Prepared by the same method as described in example 18 except that (R)-*tert*-
butoxycarbonylamino-{4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-acetic acid
was used in place of (R)-*tert*-butyloxycarbonylamino-4-methoxyphenylglycine in
10 step 4.

HRMS: Obs Mass ($M+H^+$), 604.0738. Calcd. Mass, 604.0739 for $C_{26}H_{24}FIN_3O_5^+$.

Example 21

(S)-N-(2-Fluoro-4-iodo-phenyl)-2-{(R)-4-[4-(2-methoxy-ethoxy)-phenyl]-2,5-dioxo-
15 imidazolidin-1-yl}-3-phenyl-propionamide

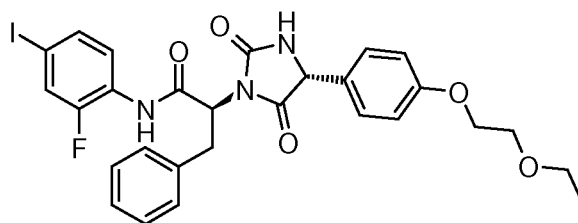


Prepared in a similar way as described in example 1 except that (i) (S)-2-*tert*-
butoxycarbonylamino-3-phenyl-propionic acid was used in place of (2S,3S)-2-
tert-butoxycarbonylamino-3-phenyl-butyric acid in step 1, (ii) 2-fluoro-4-
20 iodoaniline was used in place of 4-bromoaniline in step 2, and (iii) (R)-*tert*-
butoxycarbonylamino-[4-(methoxy-ethoxy)-phenyl]-acetic acid was used in place
of (R)-*tert*-butoxycarbonylamino-[4-methoxy-phenyl]-acetic acid in step 4. (R)-
tert-Butoxycarbonylamino-[4-(methoxy-ethoxy)-phenyl]-acetic acid was prepared
as described in example 80.

25 HRMS: Obs Mass ($M+H^+$), 618.0896. Calcd. Mass, 618.0896 for
 $C_{27}H_{26}FIN_3O_5^+$.

Example 22

(S)-2-[(R)-4-[4-(2-Ethoxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-N-(2-fluoro-4-iodo-phenyl)-3-phenyl-propionamide



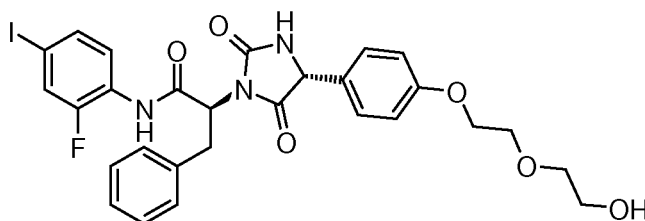
- 5 Prepared by the same method as described in example 18 except that (R)-*tert*-butoxycarbonylamino-[4-(2-ethoxy-ethoxy)-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-4-methoxyphenylglycine in step 4.

HRMS: Obs Mass ($M+Na^+$), 654.0874. Calcd. Mass, 654.0871 for $C_{28}H_{27}FIN_3NaO_5^+$.

10

Example 23

(S)-N-(2-Fluoro-4-iodo-phenyl)-2-[(R)-4-{4-[2-(2-hydroxy-ethoxy)-ethoxy]-phenyl}-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-propionamide



- 15 Prepared by the same method as described in example 18 except that (R)-*tert*-butoxycarbonylamino-(4-{2-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-ethoxy}-phenyl)-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-4-methoxyphenylglycine in step 4.

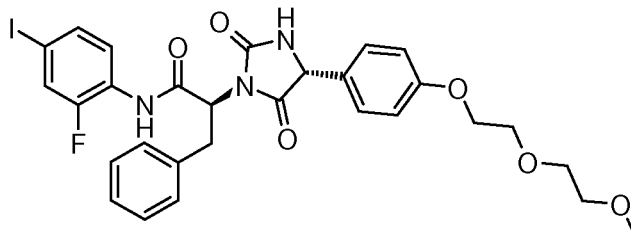
HRMS: Obs Mass ($M+Na^+$), 670.0819. Calcd. Mass, 670.0821 for

20

$C_{28}H_{27}FIN_3NaO_6^+$.

Example 24

(S)-N-(2-Fluoro-4-iodo-phenyl)-2-((R)-4-{4-[2-(2-methoxy-ethoxy)-ethoxy]-phenyl}-2,5-dioxo-imidazolidin-1-yl)-3-phenyl-propionamide



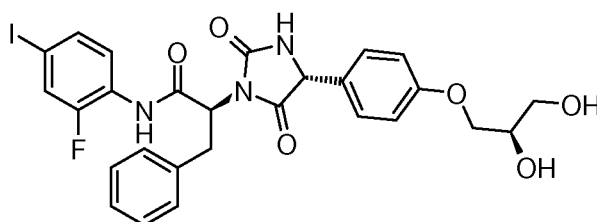
5

Prepared by the same method as described in example 1 except that (i) (S)-2-*tert*-butoxycarbonylamino-3-phenyl-propionic acid was used in place of (2S, 3S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid in step 1, (ii) 2-fluoro-4-iodoaniline was used in place of 4-bromoaniline in step 2, and (iii) (R)-*tert*-butoxycarbonylamino-[4-(methoxy-ethoxy-ethoxy)-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-[4-methoxy-phenyl]-acetic acid in step 4. (R)-*tert*-Butoxycarbonylamino-[4-(methoxy-ethoxy-ethoxy)-phenyl]-acetic acid was prepared as described in example 48 except that 1-(2-bromo-ethoxy)-2-methoxy-ethane was used in place of 2-(2-bromo-ethoxy)-tetrahydropyran.

15 LC-MS: Obs Mass (M+H⁺), 662.13. Calcd. Mass, 662.12 for C₂₉H₃₀FIN₃O₆⁺.

Example 25

(S)-2-((R)-4-[4-((R)-2,3-Dihydroxy-propoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl)-N-(2-fluoro-4-iodo-phenyl)-3-phenyl-propionamide



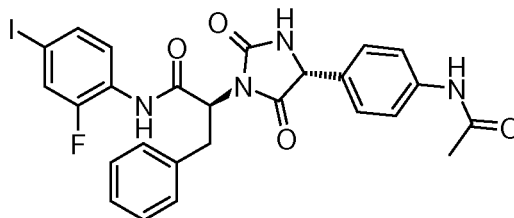
20

Prepared by the same method as described in example 2 except that (i) 2-fluoro-4-iodoaniline was used in place of 4-bromo-2-fluoro-aniline, and (ii) (S)-2-*tert*-butoxycarbonylamino-3-phenyl-propionic acid was used in place of (2S,3S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid.

25 HRMS: Obs Mass (M+H⁺), 634.0839. Calcd. Mass, 634.0845 for C₂₇H₂₆FIN₃O₆⁺.

Example 26

(S)-2-[(R)-4-(4-Acetylamino-phenyl)-2,5-dioxo-imidazolidin-1-yl]-N-(2-fluoro-4-iodo-phenyl)-3-phenyl-propionamide



5

Prepared by the same method as described in example 29 except that (2R)-(4-acetylamino-phenyl)-*tert*-butoxycarbonylamino-acetic acid was used in place of (2R)-*tert*-butoxycarbonylamino-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-acetic acid. (2R)-(4-acetylamino-phenyl)-*tert*-butoxycarbonylamino-acetic acid was prepared as follows:

10

(1) To a suspension of (2R)-amino-phenyl-acetic acid (10.0 g, 66.2 mmol) in water (300 mL) was added sodium hydroxide (2.65 g, 66.3 mmol). After stirring for 2 minutes acetic anhydride (12.5 mL, 132.2 mmol) was added and the mixture stirred at ambient temperature for 15 minutes. The reaction mixture was acidified to pH = 1 with 1M aqueous hydrochloric acid and the colorless precipitate of (2R)-acetylamino-phenyl-acetic acid collected by filtration and dried (10.24 g, 80%).

15

LC-MS: Obs. Mass, 194. Calcd. Mass, 194 for $C_{10}H_{12}NO_3^+$.

20

(2) (2R)-Acetylamino-phenyl-acetic acid (9.7 g, 50.5 mmol) was dissolved in concentrated sulfuric acid (25 mL) at -10 °C and concentrated nitric acid (4.2 mL, 100 mmol) added dropwise with stirring while maintaining the temperature below 0 °C. After stirring for 30 minutes at -10 °C the reaction mixture was poured onto ice (150 g) and after thawing, filtration and drying (2R)-acetylamino-(4-nitro-phenyl)-acetic acid was obtained as a colorless solid (8.75 g, 73%).

25

LC-MS: Obs. Mass, 239. Calcd. Mass, 194 for $C_{10}H_{11}N_2O_5^+$.

(3) (2R)-Acetylamino-(4-nitro-phenyl)-acetic (500 mg, 2.10 mmol) was heated to 100 °C under reflux in 2M aqueous hydrochloric acid for 3.5 hours. The reaction

30

mixture was cooled to ambient temperature and half of the reaction mixture was dried by lyophilization. The residue from lyophilization was suspended in water (2 mL), and treated with saturated aqueous sodium carbonate solution to obtain a solution with pH = 10. *p*-Dioxane (6 mL) was added to the aqueous mixture
5 followed by di-*tert*-butyldicarbonate (368 μ L, 1.6 mmol) and the mixture stirred at ambient temperature for 3 hours. The reaction mixture was acidified with 20% *w/v* aqueous citric acid solution then extracted with ethyl acetate (three times), the combined organic layers dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by chromatography over silica gel gradient
10 eluted using 0 to 10% *v/v* methanol in dichloromethane to afford (2R)-*tert*-butoxycarbonylamino-(4-nitro-phenyl)-acetic acid as a colorless oil (372 mg, >100 %).

LC-MS: Obs. Mass, 297. Calcd. Mass, 297 for $C_{13}H_{17}N_2O_6^+$.

15 To a solution of (2R)-*tert*-butoxycarbonylamino-(4-nitro-phenyl)-acetic acid (350 mg, <1.18 mmol) in absolute ethanol (15 mL) was added a small amount of 10% palladium on carbon and the mixture stirred under an atmosphere of hydrogen for 16 hours. The reaction mixture was filtered through a pad of Celite and the Celite eluted with absolute ethanol. The filtrate was concentrated *in vacuo* then
20 purified by chromatography over silica gel gradient eluted between 0 and 7% *v/v* methanol in dichloromethane. (2R)-(4-Amino-phenyl)-*tert*-butoxycarbonylamino-acetic acid was obtained as a yellow oil (146 mg, 46%).

LC-MS: Obs. Mass, 267. Calcd. Mass, 267 for $C_{13}H_{19}N_2O_4^+$.

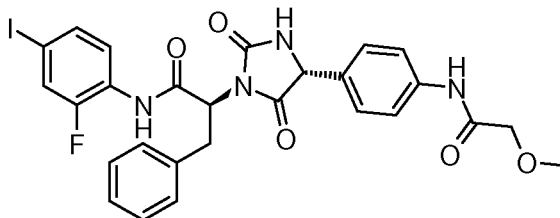
25 (4) To a solution of (2R)-(4-amino-phenyl)-*tert*-butoxycarbonylamino-acetic acid (100 mg, 0.376 mmol) in dichloromethane (2 mL) was added pyridine (36 μ L, 0.45 mmol) and acetic anhydride (42 μ L, 0.44 mmol) and the mixture stirred at ambient temperature for 2 hours. The reaction mixture was diluted with dichloromethane, washed with 1M aqueous citric acid solution, brine, dried over
30 sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by chromatography over silica gel gradient eluted from 0 to 10% *v/v* methanol in dichloromethane to afford (2R)-(4-acetylamino-phenyl)-*tert*-butoxycarbonylamino-acetic acid as a yellow solid (59 mg, 51 %).

LC-MS: Obs. Mass, 307. Calcd. Mass, 307 for $C_{15}H_{19}N_2O_5^-$.

LC-MS: Obs. Mass ($M+H^+$), 601. Calcd. Mass, 601 for $C_{26}H_{23}FIN_4O_4^+$.

Example 27

(S)-N-(2-Fluoro-4-iodo-phenyl)-2-((R)-4-[4-(2-methoxy-acetyl-amino)-phenyl]-2,5-dioxo-imidazolidin-1-yl)-3-phenyl-propionamide



5

Prepared by the same method as described in example 1 except that (i) 2-fluoro-4-iodoaniline was used in place of 4-bromoaniline in step 2, (ii) *O*-benzotriazol-1-yl-*N,N,N',N'*-bis(tetramethylene)uronium hexafluorophosphate was used as the coupling reagent in place of *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate in step 4, and (iii) (*R*)-*tert*-butoxycarbonylamino-[4-(2-methoxy-acetyl-amino)-phenyl]-acetic acid was used in place of (*R*)-*tert*-butoxycarbonylamino-4-methoxyphenyl-glycine in step 4. (*R*)-*tert*-Butoxycarbonylamino-[4-(2-methoxy-acetyl-amino)-phenyl]-acetic acid was prepared by the same method as described for preparation of (*R*)-(4-acetyl-amino-phenyl)-*tert*-butoxycarbonyl-amino-acetic acid in example 26 except that methoxy-acetyl chloride was used in place of acetic anhydride in step 5.

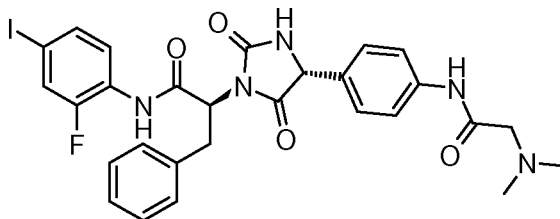
15

LC-MS: Obs. Mass ($M+H^+$), 631. Calcd. Mass, 631 for $C_{27}H_{25}FIN_4O_5^+$.

Example 28

(S)-2-((R)-4-[4-(2-Dimethylamino-acetyl-amino)-phenyl]-2,5-dioxo-imidazolidin-1-yl)-N-(2-fluoro-4-iodo-phenyl)-3-phenyl-propionamide

20



25

Prepared by the same method as described in example 1 except that (i) 2-fluoro-4-iodoaniline was used in place of 4-bromoaniline in step 2, (ii) *O*-benzotriazol-1-yl-*N,N,N',N'*-bis(tetramethylene)uronium hexafluorophosphate was used as the coupling reagent in place of *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate in step 4, and (iii) and (*R*)-*tert*-butoxycarbonylamino-[4-(2-

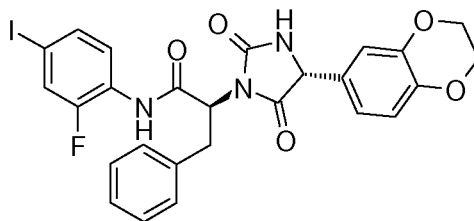
dimethylamino-acetyl-amino)-phenyl]-acetic acid was used in place of (R)-*tert*-butyloxycarbonylamino-4-methoxyphenyl-glycine in step 4. (R)-*tert*-Butoxycarbonylamino-[4-(2-dimethylamino-acetyl-amino)-phenyl]-acetic acid was prepared by the same method as described for preparation of (R)-(4-acetyl-amino-phenyl)-*tert*-butoxycarbonyl-amino-acetic acid in example 26 except that 2-dimethylamino-acetyl chloride was used in place of acetic anhydride in step 5.

LC-MS: Obs. Mass ($M+H^+$), 644. Calcd. Mass, 644 for $C_{28}H_{28}FIN_5O_4^+$.

10

Example 29

(S)-2-[(R)-4-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-2,5-dioxo-imidazolidin-1-yl]-N-(2-fluoro-4-iodo-phenyl)-3-phenyl-propionamide



15

Prepared by the same method as described in example 18 except that (i) (2S)-2-*tert*-butoxycarbonylamino-3-phenyl-propionic acid was used in place of (2S, 3S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid in step 1, and (ii) (2R)-*tert*-butoxycarbonylamino-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-acetic acid (prepared according to the procedure of Bohme, E.H.W. *et al.*, *J. Med. Chem.* **1980**, 23, 405-412), was used in place of (R)-*tert*-butoxycarbonylamino-{4-[2-(tetrahydropyran-2-yloxy)-ethoxy]-phenyl}-acetic acid in step 4.

20

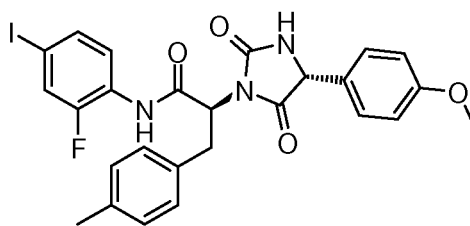
HRMS: Obs. Mass ($M+H^+$), 602.0587. Calcd. Mass, 602.0583 for $C_{26}H_{22}FIN_3O_5^+$.

25

Example 30

(S)-N-(2-Fluoro-4-iodo-phenyl)-2-[(R)-4-(4-methoxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-3-p-tolyl-propionamide

- 43 -

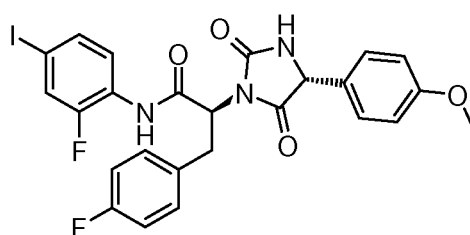


- Prepared by the same method as described in example 1 except that (i) (S)-2-*tert*-butoxycarbonylamino-3-*p*-tolyl-propionic acid was used in place of (2S, 3S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid in step 1, and (ii) 2-fluoro-4-iodoaniline was used in place of 4-bromoaniline in step 2.

HRMS: Obs. Mass ($M+Na^+$), 610.0613. Calcd. Mass, 610.0609 for $C_{26}H_{23}FIN_3NaO_4^+$.

Example 31

- (S)-*N*-(2-Fluoro-4-iodo-phenyl)-3-(4-fluoro-phenyl)-2-[(R)-4-(4-methoxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-propionamide



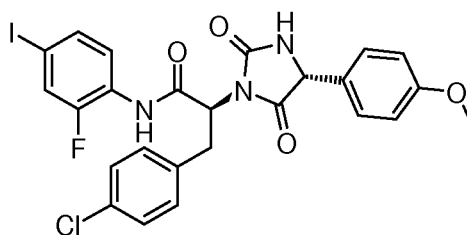
- Prepared by the same method as described in example 4 except that (i) (S)-2-*tert*-butoxycarbonylamino-3-(4-fluoro-phenyl)-propionic acid was used in place of (S)-2-*tert*-butoxycarbonylamino-3-phenyl-propionic acid in step 1, and (ii) 2-fluoro-4-iodoaniline was used in place of 4-iodoaniline in step 2.

HRMS: Obs Mass ($M+H^+$), 592.0539. Calcd. Mass, 592.0540 for $C_{25}H_{21}F_2IN_3O_4^+$.

Example 32

(S)-3-(4-Chloro-phenyl)-*N*-(2-fluoro-4-iodo-phenyl)-2-[(R)-4-(4-methoxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-propionamide

- 44 -

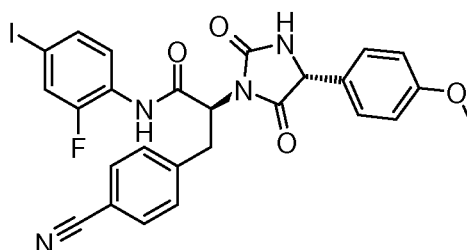


Prepared by the same method as described in example 1 except that (i) (S)-2-*tert*-butoxycarbonylamino-3-*p*-chloro-propionic acid was used in place of (2S, 3S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid in step 1, and (ii) 2-fluoro-4-iodoaniline was used in place of 4-bromoaniline in step 2.

HRMS: Obs Mass ($M+H^+$), 608.0241. Calcd. Mass, 608.0244 for $C_{25}H_{21}ClFIN_3O_4^+$.

Example 33

(S)-3-(4-Cyano-phenyl)-*N*-(2-fluoro-4-iodo-phenyl)-2-[(R)-4-(4-methoxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-propionamide



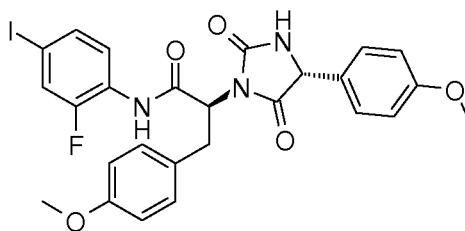
Prepared by the same method as described in example 1 except that (i) (S)-2-*tert*-butoxycarbonylamino-3-(4-cyano-phenyl)-propionic acid was used in place of (2S, 3S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid in step 1, and (ii) 2-fluoro-4-iodoaniline was used in place of 4-bromoaniline in step 2.

HRMS: Obs Mass ($M+H^+$), 599.0575. Calcd. Mass, 599.0586 for $C_{26}H_{21}FIN_4O_4^+$.

Example 34

(S)-*N*-(2-Fluoro-4-iodo-phenyl)-3-(4-methoxy-phenyl)-2-[(R)-4-(4-methoxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-propionamide

- 45 -

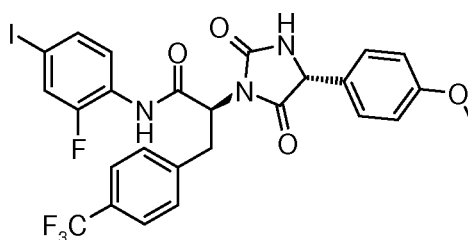


- Prepared by the same method as described in example 1 except that (i) (S)-2-*tert*-butoxycarbonylamino-3-(4-methoxy-phenyl)-propionic acid was used in place of (2S, 3S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid in step 1, and (ii) 2-fluoro-4-iodoaniline was used in place of 4-bromoaniline in step 2.

HRMS: Obs Mass ($M+H^+$), 604.0739. Calcd. Mass, 604.0739 for $C_{26}H_{24}FIN_3O_5^+$.

Example 35

- (S)-N-(2-Fluoro-4-iodo-phenyl)-2-[(R)-4-(4-methoxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-3-(4-trifluoromethyl-phenyl)-propionamide



- Prepared by the same method as described in example 1 except that (i) (S)-2-*tert*-butoxycarbonylamino-3-(4-trifluoromethyl-phenyl)-propionic acid was used in place of (2S, 3S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid in step 1, and (ii) 2-fluoro-4-iodoaniline was used in place of 4-bromoaniline in step 2.

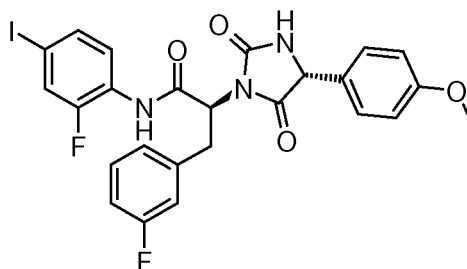
HRMS: Obs Mass ($M+H^+$), 642.0507. Calcd. Mass, 642.0508 for $C_{26}H_{21}F_4IN_3O_4^+$.

20

Example 36

- (S)-N-(2-Fluoro-4-iodo-phenyl)-3-(3-fluoro-phenyl)-2-[(R)-4-(4-methoxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-propionamide

- 46 -

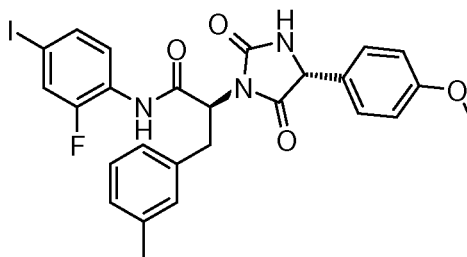


Prepared by the same method as described in example 1 except that (i) (S)-2-*tert*-butoxycarbonylamino-3-(3-fluoro-phenyl)-propionic acid was used in place of (2S, 3S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid in step 1, and (ii) 2-fluoro-4-iodoaniline was used in place of 4-bromoaniline in step 2.

HRMS: Obs Mass ($M+Na^+$), 614.0350. Calcd. Mass, 614.0359 for $C_{25}H_{20}F_2IN_3NaO_4^+$.

Example 37

(S)-N-(2-Fluoro-4-iodo-phenyl)-2-[(R)-4-(4-methoxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-3-*m*-tolyl-propionamide



Prepared by the same method as described in example 1 except that (i) (S)-2-*tert*-butoxycarbonylamino-3-*m*-tolyl-propionic acid was used in place of (2S, 3S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid in step 1, and (ii) 2-fluoro-4-iodoaniline was used in place of 4-bromoaniline in step 2.

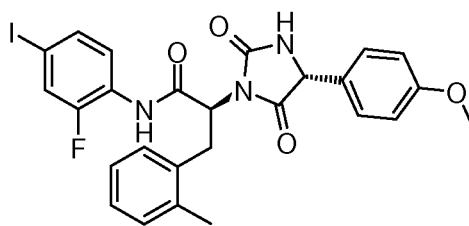
HRMS: Obs. Mass ($M+Na^+$), 610.0607. Calcd. Mass, 610.0609 for $C_{26}H_{23}FIN_3NaO_4^+$.

20

Example 38

(S)-N-(2-Fluoro-4-iodo-phenyl)-2-[(R)-4-(4-methoxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-3-*o*-tolyl-propionamide

- 47 -

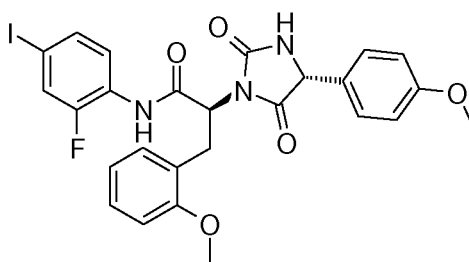


- Prepared by the same method as described in example 1 except that (i) (S)-2-*tert*-butoxycarbonylamino-3-*o*-tolyl-propionic acid was used in place of (2S, 3S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid in step 1, and (ii) 2-fluoro-4-iodoaniline was used in place of 4-bromoaniline in step 2.

HRMS: Obs. Mass ($M+H^+$), 588.0791. Calcd. Mass, 588.0790 for $C_{26}H_{24}FIN_3O_4^+$.

Example 39

- (S)-N-(2-Fluoro-4-iodo-phenyl)-3-(2-methoxy-phenyl)-2-[(R)-4-(4-methoxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-propionamide



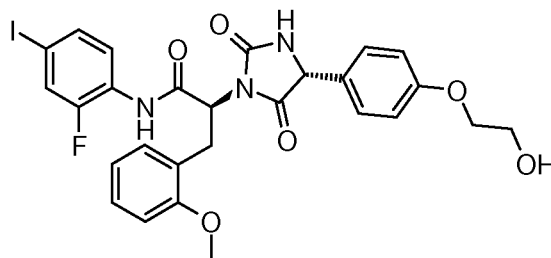
- Prepared by the same method as described in example 4 except that (i) (S)-2-*tert*-butoxycarbonylamino-3-(2-methoxy-phenyl)-propionic acid was used in place of (S)-2-*tert*-butoxycarbonylamino-3-phenyl-propionic acid in step 1, and (ii) 2-fluoro-4-iodoaniline was used in place of 4-iodoaniline in step 2.

HRMS: Obs Mass ($M+H^+$), 604.0745 Calcd. Mass, 604.0739 for $C_{26}H_{24}FIN_3O_5^+$.

Example 40

(S)-N-(2-Fluoro-4-iodo-phenyl)-2-[(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-(2-methoxy-phenyl)-propionamide

- 48 -



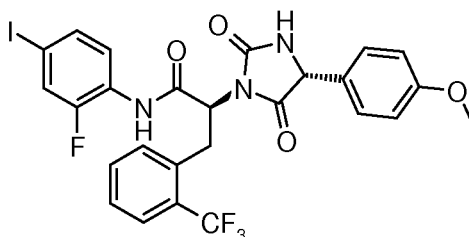
Prepared by the same method as described in example 39 except that (i) (R)-*tert*-butoxycarbonylamino-4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-acetic acid (prepared as described in example 48) was used in place of (R)-*tert*-butyloxycarbonylamino-4-methoxyphenylglycine in step 4, and (ii) step 6 was performed as described in example 48.

HRMS: Obs Mass ($M+H^+$), 634.0842 Calcd. Mass, 634.0845 for $C_{27}H_{26}FIN_3O_6^+$.

10

Example 41

N-(2-Fluoro-4-iodo-phenyl)-2-[(R)-4-(4-methoxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-3-(2-trifluoromethyl-phenyl)-propionamide, isomer 1



Prepared by the same method as described in example 4 except that (i) (S)-2-*tert*-butoxycarbonylamino-3-(2-trifluoromethyl-phenyl)-propionic acid was used in place of (S)-2-*tert*-butoxycarbonylamino-3-phenyl-propionic acid in step 1, (ii) 2-fluoro-4-iodoaniline was used in place of 4-iodoaniline in step 2, (iii) the trifluoroacetic acid salt of (S)-2-amino-*N*-(2-fluoro-4-iodo-phenyl)-3-(2-trifluoromethyl-phenyl)-propionamide was isolated in step 3 and used directly in step 4 with 1.0 equivalent of triethylamine and (3-dimethylamino-propyl)-ethylcarbodiimide hydrochloride as the coupling reagent in place of *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate, and (iv) after performing step 5, the diastereomers (resulting from racemization in step 2) of 2-[(R)-2-amino-2-(4-methoxy-phenyl)-acetylamino]-*N*-(2-fluoro-4-iodo-phenyl)-3-(2-trifluoromethyl-phenyl)-propionamide were separated by chromatography over silica gel gradient eluted between 40 and 60% v/v ethyl acetate in hexane. The

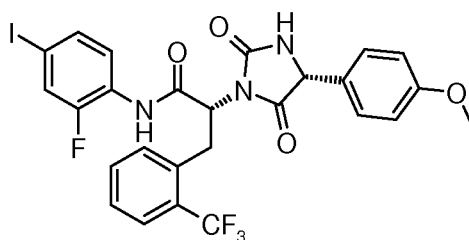
slower moving component was collected and after concentration *in vacuo* carried on to step 6.

HRMS: Obs Mass ($M+H^+$), 642.0502 Calcd. Mass, 642.0508 for $C_{26}H_{21}F_4IN_3O_4^+$.

5

Example 42

N-(2-Fluoro-4-iodo-phenyl)-2-[(*R*)-4-(4-methoxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-3-(2-trifluoromethyl-phenyl)-propionamide, isomer 2

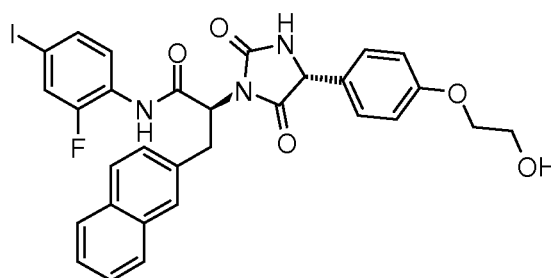


- 10 Prepared by the same method as described in example 41 except that the faster moving component from the chromatographic separation of the diastereomers of 2-[(*R*)-2-amino-2-(4-methoxy-phenyl)-acetylamino]-*N*-(2-fluoro-4-iodo-phenyl)-3-(2-trifluoromethyl-phenyl)-propionamide was collected and after concentration *in vacuo* carried on to step 6.

- 15 HRMS: Obs Mass ($M+Na^+$), 664.0327 Calcd. Mass, 664.0327 for $C_{26}H_{20}F_4IN_3NaO_4^+$.

Example 43

- 20 (*S*)-*N*-(2-Fluoro-4-iodo-phenyl)-2-[(*R*)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-naphthalen-2-yl-propionamide



Prepared by the same method as described in example 48 except that (i) steps 1-2 described below were performed in place of the steps 1-3 described in example 48, and (ii) *O*-benzotriazol-1-yl-*N,N,N',N'*-bis(tetramethylene)uronium

hexafluorophosphate was used as the coupling reagent in place of *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate in step 4.

Step 1: To a solution of (S)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-naphthalen-2-yl-propionic acid (1.0 g, 2.30 mmol) and 2-fluoro-4-iodoaniline (434 mg, 1.84 mmol), triphenylphosphine (0.94 g, 3.45 mmol) and pyridine (0.39 mL, 4.60 mmol) in dichloromethane (10 mL) at 0 °C was added *N*-bromosuccinimide (0.61 mg, 3.45 mmol) in two portions under an atmosphere of dry nitrogen. The mixture was stirred for 2 hours at 0 °C. The reaction mixture was purified by chromatography over silica gel gradient eluted from 100% dichloromethane up to 10% methanol / 90% dichloromethane over 30 minutes. Concentration of the product containing fractions gave [(S)-1-(2-fluoro-4-iodo-phenylcarbamoyl)-2-naphthalen-2-yl-ethyl]-carbamic acid 9*H*-fluoren-9-ylmethyl ester as a yellow solid foam (1.05 g, 70%).

LC-MS: Obs. Mass ($M+H^+$), 657. Calcd. Mass, 657 for $C_{34}H_{27}FIN_2O_3^+$.

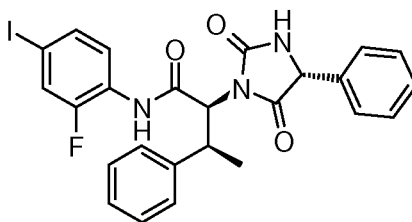
Step 2: To a solution of [(S)-1-(2-fluoro-4-iodo-phenylcarbamoyl)-2-naphthalen-2-yl-ethyl]-carbamic acid 9*H*-fluoren-9-ylmethyl ester (1.05 g, 1.60 mmol) in dichloromethane (24 mL) was added piperidine (6 mL) and the mixture stirred at room temperature for 1 hour. After removal of the solvent, the residue was purified by chromatography over silica gel gradient eluted from 100% hexane up to 40% ethyl acetate / 60% hexane in 30 minutes. Concentration of the product containing fractions gave (S)-2-amino-*N*-(2-fluoro-4-iodo-phenyl)-3-naphthalen-2-yl-propionamide as a yellow solid (390 mg, 56%).

LC-MS: Obs. Mass ($M+H^+$), 435. Calcd. Mass, 435 for $C_{19}H_{17}FIN_2O^+$.

LC-MS: Obs. Mass ($M+H^+$), 654. Calcd. Mass, 654 for $C_{30}H_{26}FIN_3O_5^+$.

Example 44

(2*S*,3*S*)-2-((*R*)-2,5-Dioxo-4-phenyl-imidazolidin-1-yl)-*N*-(2-fluoro-4-iodo-phenyl)-3-phenyl-butyrarnide

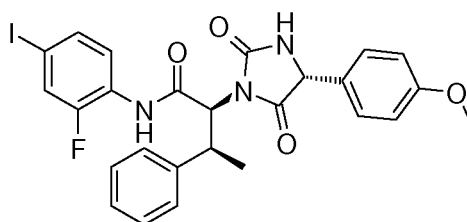


Prepared by the same method as described in example 1 except that (i) 2-fluoro-4-iodoaniline was used in place of 4-bromoaniline in step 2, and (ii) (R)-*tert*-butoxycarbonylamino phenyl-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino [4-methoxy-phenyl]-acetic acid in step 4.

- 5 HRMS: Obs Mass ($M+Na^+$), 580.0492. Calcd. Mass, 580.0504 for $C_{25}H_{21}FIN_3NaO_3^+$.

Example 45

- (2S,3S)-N-(2-Fluoro-4-iodo-phenyl)-2-[(R)-4-(4-methoxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide
- 10

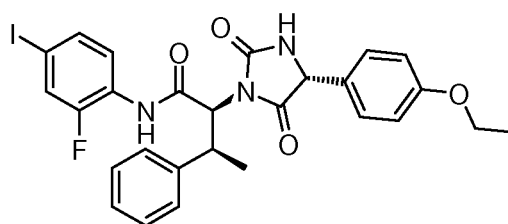


Prepared by the same method as described in example 1 except that 2-fluoro-4-iodoaniline was used in place of 4-bromoaniline in step 2.

- HRMS: Obs Mass ($M+H^+$), 588.0791. Calcd. Mass, 588.0790 for $C_{26}H_{24}FIN_3O_4^+$.
- 15

Example 46

- (2S,3S)-2-[(R)-4-(4-Ethoxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-N-(2-fluoro-4-iodo-phenyl)-3-phenyl-butyramide

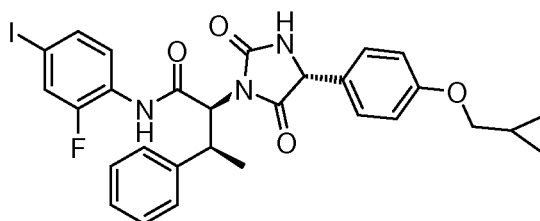


- 20 Prepared by the same method as described in example 44 except that (R)-*tert*-butoxycarbonylamino-(4-ethoxy-phenyl)-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-phenyl-acetic acid in step 4. (R)-*tert*-Butoxycarbonylamino-(4-ethoxy-phenyl)-acetic acid was prepared as described in example 1 step 4 for the preparation of (R)-*tert*-butoxycarbonylamino-(4-methoxy-phenyl)-acetic acid except that ethyl iodide was used in place of methyl iodide.
- 25

HRMS: Obs Mass ($M+H^+$), 602.0944. Calcd. Mass, 602.0947 for $C_{27}H_{26}FIN_3O_4^+$.

Example 47

- 5 (2S,3S)-2-[(R)-4-(4-Cyclopropylmethoxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-N-(2-fluoro-4-iodo-phenyl)-3-phenyl-butyramide

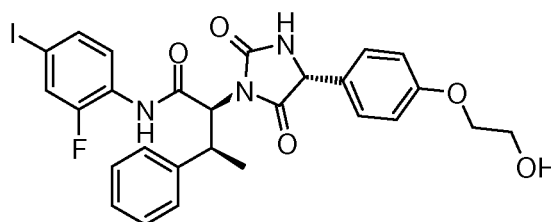


- Prepared by the same method as described in example 46 except that (R)-*tert*-butoxycarbonylamino-(4-cyclopropylmethoxy-phenyl)-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-(4-ethoxy-phenyl)-acetic acid. (R)-*tert*-Butoxycarbonylamino-(4-cyclopropylmethoxy-phenyl)-acetic acid was prepared as described in example 46 except that bromomethylcyclopropane was used in place of ethyl iodide.

- HRMS: Obs Mass ($M+H^+$), 628.1094. Calcd. Mass, 628.1103 for $C_{29}H_{28}FIN_3O_4^+$.

Example 48

(2S,3S)-N-(2-Fluoro-4-iodo-phenyl)-2-{(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl}-3-phenyl-butyramide



- Prepared by the same method as described in example 1 except that (i) 2-fluoro-4-iodoaniline was used in place of 4-bromoaniline in step 2, (ii) (R)-*tert*-butoxycarbonylamino-{4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-acetic acid (prepared as described below) was used in place of (R)-*tert*-butyloxycarbonylamino-4-methoxyphenylglycine in step 4, and (iii) step 6 was performed as described below.

Preparation of (R)-*tert*-butoxycarbonylamino-{4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-acetic acid: (R)-*tert*-butoxycarbonylamino-(4-hydroxy-phenyl)-acetic acid (2.67 g, 10 mmol) (Salituro, G.M.; Townsend, C.A. *J. Am. Chem. Soc.* **1990**, *112*, 760-770) was dissolved in *N,N*-dimethylformamide (70 mL) in
5 an ice bath. Sodium hydride (0.88 g, 60% in mineral oil, 22 mmol) was added in small portions. The mixture was warmed up to 10 °C for 1 hour. 2-(2-Bromo-ethoxy)-tetrahydropyran (1.7 mol, 11 mmol) in *N,N*-dimethylformamide (20 mL) was added drop wise. The reaction mixture was stirred for 24 hours and then diluted with ice/water. The mixture was extracted with ethyl acetate. The
10 aqueous layer was cooled in an ice bath and acidified using 1.5 M aqueous potassium hydrogen sulfate to pH = 2-3. The resulting mixture was extracted with ethyl acetate (5 ×), washed with water (5 ×), brine and dried over sodium sulfate. Filtration and evaporation of the solvents gave (R)-*tert*-butoxycarbonylamino-{4-[2-(tetrahydropyran-2-yloxy)-ethoxy]-phenyl}-acetic acid
15 as a solid white foam (3.2 g, 82%).

Step 6: To a solution of diphosgene (21.1 µL, 0.173 mmol) in 1:1 v/v toluene / tetrahydrofuran (20 mL total) at -40 °C was added a mixture of (2S, 3S)-2-[(R)-2-amino-2-[4-(2-hydroxy-ethoxy)-phenyl]-acetyl-amino]-*N*-(2-fluoro-4-iodo-phenyl)-3-phenyl-butamide (180 mg, 0.289 mmol) and *N,N*-diisopropylethylamine (154 µL, 0.867 mmol) in dry dichloromethane (40 mL) over 5 minutes and the
20 remaining residue washed in to the reaction mixture with a small amount of dry dichloromethane. After 20 minutes at -40 °C the temperature was raised to – 20 °C for an additional 15 minutes to complete reaction. The colorless solution
25 was diluted with ethyl acetate (100 mL) and washed sequentially with 1.5 M aqueous potassium hydrogen sulfate (twice), 5% w/v aqueous sodium hydrogen carbonate solution (once) and brine (once). The aqueous layers were back extracted with ethyl acetate (2 × 50 mL). The combined ethyl acetate extracts were diluted with an equal volume of dichloromethane and passed through a
30 column of sodium sulfate on top of a 4" column of flash silica gel. The eluant was concentrated to afford a pale yellow residue (177 mg). The residue was triturated with dichloromethane (5 × 2 mL) and the combined organic solutions purified by chromatography over silica gel (deactivated prior to use with methanol) gradient eluted in 1% steps from 100% dichloromethane up to 3%

methanol / 97% dichloromethane. Concentration of the product containing fractions gave a glassy residue (98 mg). The residue was dissolved in a small volume of dichloromethane, diluted with diethyl ether (1 mL) and the product was precipitated by the addition of hexanes (10 mL). The product was isolated by
5 filtration, washed with hexanes and dried *in vacuo* to give (2S,3S)-N-(2-fluoro-4-iodo-phenyl)-2-{(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl}-3-phenyl-butyramide as a colorless solid (81 mg).

HRMS: Obs. Mass ($M+Na^+$), 640.0713. Calcd. Mass, 640.0715 for $C_{27}H_{25}FIN_3NaO_5^+$.

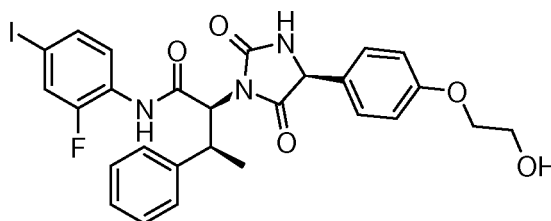
10 LC-MS (reverse phase HPLC, C18 column, water / acetonitrile gradient): R_t = 2.29 minutes, Obs. Mass ($M+Na^+$), 640. Calcd. Mass, 640 for $C_{27}H_{25}FIN_3NaO_5^+$.

1H NMR (DMSO- d_6 , 300 MHz) δ_H 10.11 (s, 1H), 8.53 (s, 1H), 5.02 (d, J = 11.8 Hz, 1H) ppm (characteristic resonances).

15

Example 49

(2S,3S)-N-(2-Fluoro-4-iodo-phenyl)-2-{(S)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl}-3-phenyl-butyramide



20 A solution of (2S,3S)-N-(2-fluoro-4-iodo-phenyl)-2-{(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl}-3-phenyl-butyramide (prepared as described in example 48) (50 mg, 0.081 mmol) was dissolved in methanol (3 mL) and stirred at ambient temperature for 4 days. The resulting mixture of isomers was concentrated *in vacuo* and then purified by super-critical fluid chromatography
25 using a Chiracel OJ column eluted with carbon dioxide at 100 bar and 30 °C modified with 35% v/v ethanol in acetonitrile eluted at 2 mL/minute. The first eluted compound was collected and concentrated *in vacuo* to obtain (2S,3S)-N-(2-fluoro-4-iodo-phenyl)-2-{(S)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl}-3-phenyl-butyramide (9.1 mg, 18%) The compound eluted
30 second was identical with (2S,3S)-N-(2-fluoro-4-iodo-phenyl)-2-{(R)-4-[4-(2-

hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl}-3-phenyl-butylamide (19.9 mg, 40%).

LC-MS (reverse phase HPLC, C18 column, water / acetonitrile gradient): R_t = 2.34 minutes, Obs. Mass ($M+Na^+$), 640. Calcd. Mass, 640 for

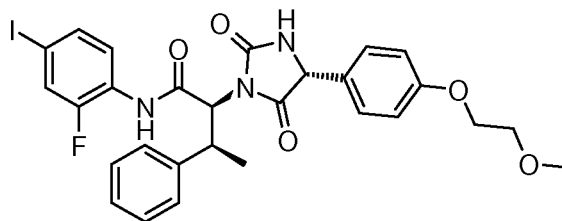
5 $C_{27}H_{25}FIN_3NaO_5^+$.

1H NMR (DMSO- d_6 , 300 MHz) δ_H 10.18 (s, 1H), 8.57 (s, 1H), 4.84 (s, 1H) ppm (characteristic resonances).

10

Example 50

(2S,3S)-N-(2-Fluoro-4-iodo-phenyl)-2-[(R)-4-[4-(2-methoxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butylamide

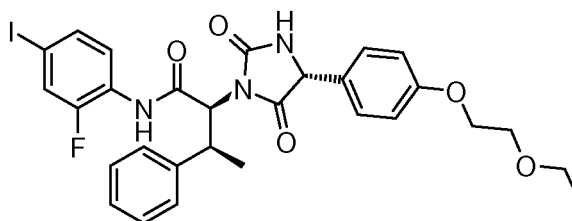


Prepared by the same method as that described in example 1 except that (i) 2-fluoro-4-iodoaniline was used in place of 4-bromoaniline in step 2, and (ii) (R)-*tert*-butoxycarbonylamino-[4-(2-methoxy-ethoxy)-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-[4-methoxy-phenyl]-acetic acid in step 4. (R)-*tert*-Butoxycarbonylamino-[4-(2-methoxy-ethoxy)-phenyl]-acetic acid was prepared as described in example 80.

20 HRMS: Obs Mass ($M+H^+$), 632.1053. Calcd. Mass, 632.1052 for $C_{28}H_{28}FIN_3O_5^+$.

Example 51

25 (2S,3S)-2-[(R)-4-[4-(2-Ethoxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-N-(2-fluoro-4-iodo-phenyl)-3-phenyl-butylamide



Prepared in a manner similar to that described in example 1 except that (i) 2-fluoro-4-iodoaniline was used in place of 4-bromoaniline in step 2, and (ii) (R)-*tert*-butoxycarbonylamino-[4-(2-ethoxy-ethoxy)-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-[4-methoxy-phenyl]-acetic acid in step 4.

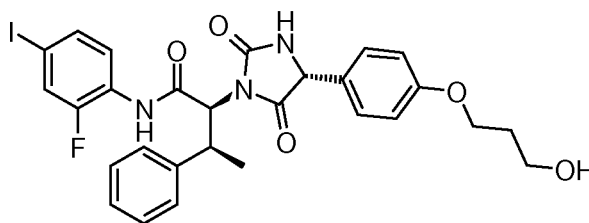
- 5 (R)-*tert*-Butoxycarbonylamino-[4-(2-ethoxy-ethoxy)-phenyl]-acetic acid was prepared as described in example 48 except that 1-bromo-2-ethoxyethane was used in place of 2-(2-bromo-ethoxy)-tetrahydropyran.

HRMS: Obs Mass ($M+H^+$), 646.1192. Calcd. Mass, 646.1209 for $C_{29}H_{30}FIN_3O_5^+$.

10

Example 52

(2S,3S)-*N*-(2-Fluoro-4-iodo-phenyl)-2-[(R)-4-[4-(3-hydroxy-propoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide



- 15 Prepared by the same method as described in example 48 except that (R)-*tert*-butoxycarbonylamino-[4-[3-(tetrahydro-pyran-2-yloxy)-propoxy]-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-[4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl]-acetic acid. (R)-*tert*-Butoxycarbonylamino-[4-[3-(tetrahydro-pyran-2-yloxy)-propoxy]-phenyl]-acetic acid was prepared as described in example 48 except that 2-(3-bromo-propoxy)-tetrahydropyran was used in place of 2-(2-bromo-ethoxy)-tetrahydropyran.

20

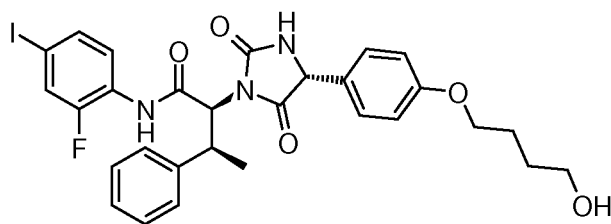
HRMS: Obs Mass ($M+H^+$), 632.1055. Calcd. Mass, 632.1052 for $C_{28}H_{28}FIN_3O_5^+$.

25

Example 53

(2S,3S)-*N*-(2-Fluoro-4-iodo-phenyl)-2-[(R)-4-[4-(4-hydroxy-butoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide

- 57 -



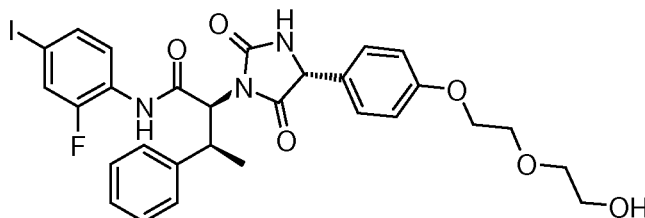
Prepared by the same method as described in example 48 except that (R)-*tert*-butoxycarbonylamino-4-[4-(tetrahydro-pyran-2-yloxy)-butoxy]-phenyl}-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-acetic acid. (R)-*tert*-Butoxycarbonylamino-4-[4-(tetrahydro-pyran-2-yloxy)-butoxy]-phenyl}-acetic acid was prepared as described in example 48 except that 2-(4-bromo-butoxy)-tetrahydropyran was used in place of 2-(2-bromo-ethoxy)-tetrahydropyran.

HRMS: Obs Mass ($M+H^+$), 646.1208. Calcd. Mass, 646.1209 for

$C_{29}H_{30}FIN_3O_5^+$.

Example 54

(2S,3S)-N-(2-Fluoro-4-iodo-phenyl)-2-((R)-4-[4-[2-(2-hydroxy-ethoxy)-ethoxy]-phenyl]-2,5-dioxo-imidazolidin-1-yl)-3-phenyl-butylamide



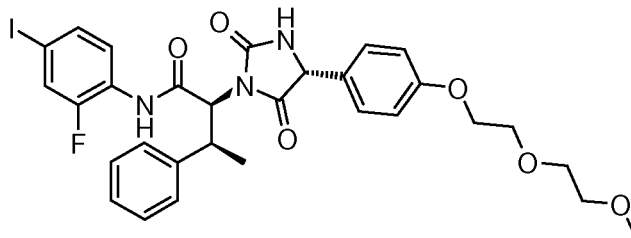
Prepared by the same method as described in example 48 except that (R)-*tert*-butoxycarbonylamino-(4-{2-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-ethoxy}-phenyl)-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-acetic acid. (R)-*tert*-Butoxycarbonylamino-(4-{2-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-ethoxy}-phenyl)-acetic acid was prepared as described in example 48 except that 2-[2-(2-chloro-ethoxy)-ethoxy]-tetrahydro-pyran was used in place of 2-(2-bromo-ethoxy)-tetrahydropyran.

HRMS: Obs Mass ($M+H^+$), 662.1158. Calcd. Mass, 662.1158 for

$C_{29}H_{30}FIN_3O_6^+$.

Example 55

(2S,3S)-N-(2-Fluoro-4-iodo-phenyl)-2-((R)-4-{4-[2-(2-methoxy-ethoxy)-ethoxy]-phenyl}-2,5-dioxo-imidazolidin-1-yl)-3-phenyl-butamide



5

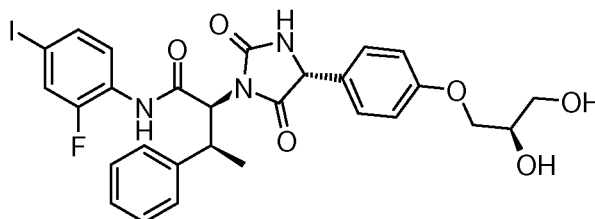
Prepared by the same method as that described in example 1 except that (i) 2-fluoro-4-iodoaniline was used in place of 4-bromoaniline in step 2, and (ii) (R)-*tert*-butoxycarbonylamino-[4-(2-{2-methoxy-ethoxy}-ethoxy)-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-[4-methoxy-phenyl]-acetic acid in step 4. (R)-*tert*-Butoxycarbonylamino-[4-(2-{2-methoxy-ethoxy}-ethoxy)-phenyl]-acetic acid was prepared as described in example 48 except that 1-(2-bromo-ethoxy)-2-methoxy-ethane was used in place of 2-(2-bromo-ethoxy)-tetrahydropyran.

HRMS: Obs Mass ($M+H^+$), 676.1306. Calcd. Mass, 676.1315 for $C_{30}H_{32}FIN_3O_6^+$.

15

Example 56

(2S,3S)-2-((R)-4-{4-((R)-2,3-Dihydroxy-propoxy)-phenyl}-2,5-dioxo-imidazolidin-1-yl)-N-(2-fluoro-4-iodo-phenyl)-3-phenyl-butamide



20

Prepared by the same method as described in example 114 except that 2-fluoro-4-iodoaniline was used in place of 2-chloro-4-iodoaniline in step 2.

HRMS: Obs Mass ($M+H^+$), 648.0995. Calcd. Mass, 648.1002 for $C_{28}H_{28}FIN_3O_6^+$.

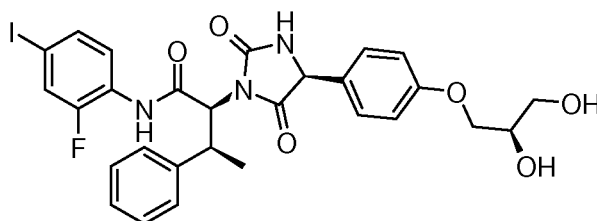
LC-MS (reverse phase HPLC, C18 column, water / acetonitrile gradient): R_t = 3.55 minutes, Obs. Mass ($M+H^+$), 648. Calcd. Mass, 648 for $C_{28}H_{28}FIN_3O_6^+$.

25

^1H NMR (DMSO- d_6 , 300 MHz) δ_{H} 10.11 (s, 1H), 8.52 (s, 1H), 5.02 (d, $J = 11.5$ Hz, 1H) ppm (characteristic resonances).

Example 57

- 5 (2S,3S)-2-[(S)-4-[4-((R)-2,3-Dihydroxy-propoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-N-(2-fluoro-4-iodo-phenyl)-3-phenyl-butyramide



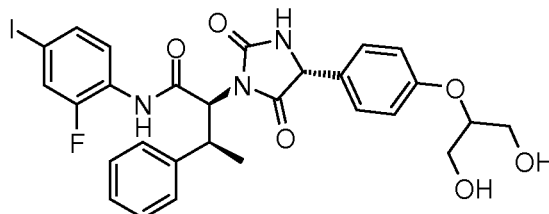
- (2S,3S)-2-[(R)-4-[4-((R)-2,3-Dihydroxy-propoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-N-(2-fluoro-4-iodo-phenyl)-3-phenyl-butyramide (prepared as described in
 10 example 56) (160 mg, 0.25 mmol) was dissolved in methanol (10 ml) and allowed to stir for 48 hours at ambient temperature followed by warming to 50 °C for an additional 6 hours. The solvent was removed *in vacuo* and the residue was then purified by super-critical fluid chromatography using a Chiracel OD column eluted with carbon dioxide at 100 bar and 30 °C containing 35%
 15 methanol in acetonitrile eluted at 2 mL/minute. The second eluted compound was collected and concentrated *in vacuo* to obtain (2S,3S)-2-[(S)-4-[4-((R)-2,3-dihydroxy-propoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-N-(2-fluoro-4-iodo-phenyl)-3-phenyl-butyramide as a colorless solid (35 mg, 44%). The compound eluted first was identical with (2S,3S)-2-[(R)-4-[4-((R)-2,3-dihydroxy-propoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-N-(2-fluoro-4-iodo-phenyl)-3-phenyl-
 20 butyramide.

HRMS: Obs Mass ($M+H^+$), 648.0995. Calcd. Mass, 648.1002 for $C_{28}H_{28}FIN_3O_6^+$.

- LC-MS (reverse phase HPLC, C18 column, water / acetonitrile gradient): $R_t =$
 25 3.13 minutes, Obs. Mass ($M+H^+$), 648. Calcd. Mass, 648 for $C_{28}H_{28}FIN_3O_6^+$.
 ^1H NMR (DMSO- d_6 , 300 MHz) δ_{H} 10.18 (s, 1H), 8.57 (s, 1H), 4.84 (s, 1H) ppm (characteristic resonances).

Example 58

(2S,3S)-N-(2-Fluoro-4-iodo-phenyl)-2-{(R)-4-[4-(2-hydroxy-1-hydroxymethyl-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl}-3-phenyl-butylamide



5

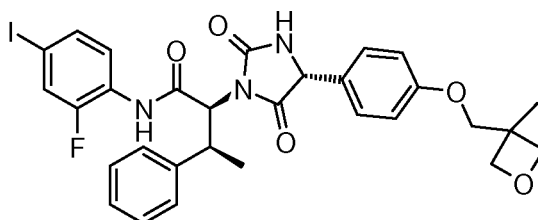
- Prepared by the same method as described in example 1 except that (i) 2-fluoro-4-iodoaniline was used in place of 4-bromoaniline in step 2, (ii) (R)-*tert*-butoxycarbonylamino-[4-(2-hydroxy-1-hydroxymethyl-ethoxy)-phenyl]-acetic acid (prepared as described in example 160) was used in place of (R)-*tert*-butoxycarbonylamino-(4-methoxy-phenyl)-acetic acid in step 4, (iii) the diol functionality contained in (2S,3S)-2-{(R)-2-amino-2-[4-(2-hydroxy-1-hydroxymethyl-ethoxy)-phenyl]-acetyl-amino}-N-(2-fluoro-4-iodo-phenyl)-3-phenyl-butylamide was temporarily protected as the *bis*-trimethylsilyl ether (performed as described in example 114) prior to performing step 6, and (iv) acid catalyzed hydrolysis of (2S,3S)-2-{(R)-2,5-dioxo-4-[4-(2-trimethylsilyloxy-1-trimethylsilyloxymethyl-ethoxy)-phenyl]-imidazolidin-1-yl}-N-(2-fluoro-4-iodo-phenyl)-3-phenyl-butylamide was performed as described in example 114 prior to purification and isolation of (2S,3S)-N-(2-fluoro-4-iodo-phenyl)-2-{(R)-4-[4-(2-hydroxy-1-hydroxymethyl-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl}-3-phenyl-butylamide in step 6.

20

HRMS: Obs Mass ($M+H^+$), 648.0991 Calcd. Mass, 648.1002 for $C_{28}H_{28}FIN_3O_6^+$.

Example 59

- (2S,3S)-N-(2-Fluoro-4-iodo-phenyl)-2-{(R)-4-[4-(3-methyl-oxetan-3-ylmethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl}-3-phenyl-butylamide



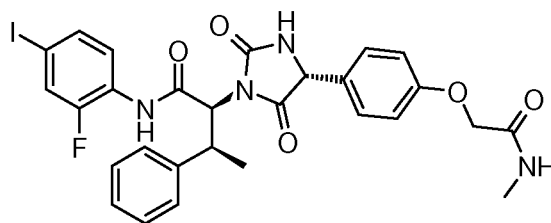
25

Prepared by the same method as described in example 48 except that (R)-*tert*-butoxycarbonylamino-[4-(3-methyl-oxetan-3-ylmethoxy)-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-{4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-acetic acid. (R)-*tert*-Butoxycarbonylamino-[4-(3-methyl-oxetan-3-ylmethoxy)-phenyl]-acetic acid was prepared as described in example 48 except that 3-bromomethyl-3-methyl-oxetane was used in place of 2-(2-bromo-ethoxy)-tetrahydropyran.

HRMS: Obs Mass ($M+H^+$), 658.1202. Calcd. Mass, 658.1209 for $C_{30}H_{30}FIN_3O_5^+$.

Example 60

(2R,3S)-N-(2-Fluoro-4-iodo-phenyl)-2-[(R)-4-(4-methylcarbamoylmethoxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide

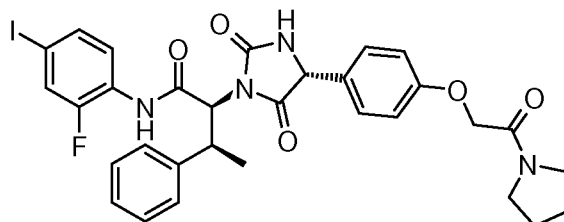


Prepared by the same method as described in example 48 except that (R)-*tert*-butoxycarbonylamino-(4-methylcarbamoylmethoxy-phenyl)-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-{4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-acetic acid. (R)-*tert*-Butoxycarbonylamino-(4-methylcarbamoylmethoxy-phenyl)-acetic acid was prepared as described in example 48 except that 2-chloro-N-methyl-acetamide was used in place of 2-(2-bromo-ethoxy)-tetrahydropyran.

HRMS: Obs Mass ($M+Na^+$), 667.0820. Calcd. Mass, 667.0824 for $C_{28}H_{26}FIN_4NaO_5^+$.

Example 61

(2S,3S)-2-[(R)-2,5-Dioxo-4-[4-(2-oxo-2-pyrrolidin-1-yl-ethoxy)-phenyl]-imidazolidin-1-yl]-N-(2-fluoro-4-iodo-phenyl)-3-phenyl-butyramide



5

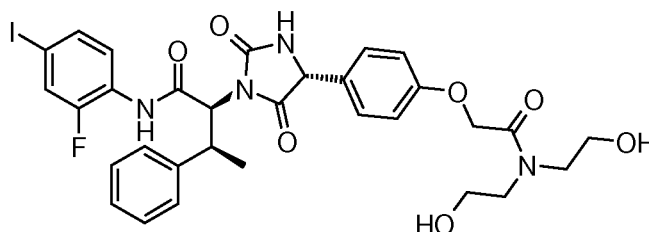
Prepared by the same method as described in example 48 except that (R)-*tert*-butoxycarbonylamino-[4-(2-oxo-2-pyrrolidin-1-yl-ethoxy)-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-{4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-acetic acid. (R)-*tert*-butoxycarbonylamino-[4-(2-oxo-2-pyrrolidin-1-yl-ethoxy)-phenyl]-acetic acid was prepared by a method similar to that used for the preparation of (R)-*tert*-butyloxycarbonylamino-4-methoxyphenylglycine in example 1 except that 2-chloro-1-pyrrolidin-1-yl-ethanone was used in place of iodomethane.

LC-MS: Obs. Mass ($M+H^+$), 685/687. Calcd. Mass, 685/687 for $C_{31}H_{31}FIN_4O_5^+$.

15

Example 62

(2S,3S)-2-[(R)-4-(4-[[Bis-(2-hydroxy-ethyl)-carbamoyl]-methoxy]-phenyl)-2,5-dioxo-imidazolidin-1-yl]-N-(2-fluoro-4-iodo-phenyl)-3-phenyl-butyramide



20

Prepared by the same method as described in example 48 except that (R)-[4-(2-{bis-[2-(*tert*-butyl-dimethyl-silyloxy)-ethyl]-amino}-acetoxy)-phenyl]-*tert*-butoxycarbonylamino-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-[4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl]-acetic acid. (R)-[4-(2-{Bis-[2-(*tert*-butyl-dimethyl-silyloxy)-ethyl]-amino}-acetoxy)-phenyl]-*tert*-butoxycarbonylamino-acetic acid was prepared as described in example 48

25

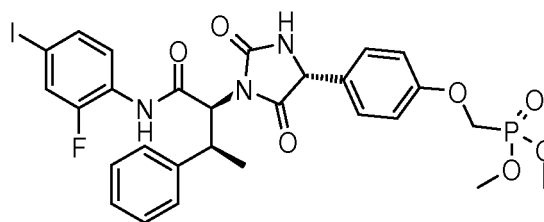
except that *N,N*-bis-[2-(*tert*-butyl-dimethyl-silanyloxy)-ethyl]-2-chloro-acetamide was used in place of 2-(2-bromo-ethoxy)-tetrahydropyran.

HRMS: Obs Mass ($M+Na^+$), 741.1194. Calcd. Mass, 741.1192 for $C_{31}H_{32}FIN_4NaO_7^+$.

5

Example 63

(4-{{(R)-1-[(1*S*,2*S*)-1-(2-Fluoro-4-iodo-phenylcarbamoyl)-2-phenyl-propyl]-2,5-dioxo-imidazolidin-4-yl}-phenoxy)methyl}-phosphonic acid dimethyl ester



10 Prepared by the same method as described in example 48 except that (R)-*tert*-butoxycarbonylamino-[4-(dimethoxy-phosphorylmethoxy)-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-{4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-acetic acid. (R)-*tert*-Butoxycarbonylamino-[4-(dimethoxy-phosphorylmethoxy)-phenyl]-acetic acid was prepared as follows:

15 (1) Dimethyl phosphite (2.0 g, 18.2 mmol), paraformaldehyde (574 mg, 19.1 mmol) and triethylamine (0.25 mL, 1.8 mmol) were combined and heated to 70 °C to give a clear solution. After 1 hour the reaction was cooled and concentrated *in vacuo* overnight to afford the crude hydroxymethyl-phosphonic acid dimethyl ester (2.5 g).

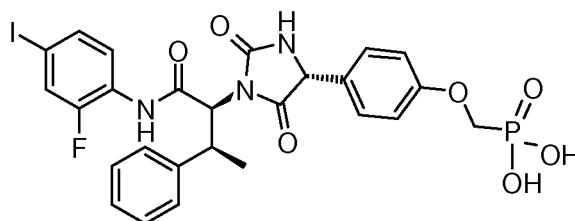
20 (2) To a solution of hydroxymethyl-phosphonic acid dimethyl ester (2.0 g, 14.5 mmol) in anhydrous dichloromethane (50 mL) at -20 °C was added pyridine (1.4 mL, 16.7 mmol) followed by trifluoromethanesulfonic anhydride (2.7 mL, 15.9 mmol). After stirring at 0 °C for 0.5 hours, the mixture was filtered through celite with a thin layer of silica gel. The filtrate was washed
25 with cold 1.0 N aqueous hydrochloric acid, water, saturated aqueous sodium bicarbonate and dried over sodium sulfate. The solvents were removed to give trifluoro-methanesulfonic acid dimethoxy-phosphorylmethyl ester as an oil (2.1 g, 53%).

(3) Sodium hydride (18.9 mg, 0.79 mmol) was added to (R)-*tert*-
30 butoxycarbonylamino-(4-hydroxy-phenyl)-acetic acid (100 mg, 0.37 mmol) in

anhydrous dimethylformamide (2.5 mL) in an ice bath. The mixture was allowed to warm to room temperature followed by the addition of trifluoromethanesulfonic acid dimethoxy-phosphorylmethyl ester (122 mg, 0.45 mmol). Stirring was continued overnight at room temperature. The reaction was poured into 0.2 M aqueous hydrochloric acid (10 mL) and the mixture extracted with ethyl acetate. The combined extracts were washed with saturated aqueous sodium bicarbonate, brine and dried over sodium sulfate. Evaporation of the solvents gave *tert*-butoxycarbonylamino-[(R)-4-(dimethoxy-phosphorylmethoxy)-phenyl]-acetic acid (120 mg, 83% yield). HRMS: Obs. Mass ($M+H^+$), 696.0766. Calcd. Mass, 696.0767 for $C_{28}H_{29}FIN_3O_7P^+$.

Example 64

15 (4-{{(R)-1-[(1S,2S)-1-(2-Fluoro-4-iodo-phenylcarbamoyl)-2-phenyl-propyl]-2,5-dioxo-imidazolidin-4-yl}}-phenoxy)methyl)-phosphonic acid

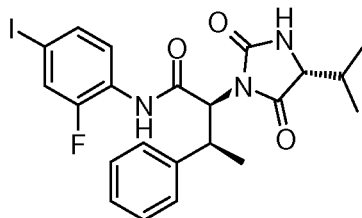


To a solution of (4-((R)-1-[(1S,2S)-1-(2-fluoro-4-iodo-phenylcarbamoyl)-2-phenyl-propyl]-2,5-dioxo-imidazolidin-4-yl)-phenoxy-methyl)-phosphonic acid dimethyl ester (prepared as described in example 63) (79 mg, 0.11 mmol) in dichloromethane (2.0 mL) was added bromotrimethylsilane (0.12 mL, 0.88 mmol) at room temperature. After 4 hours, the reaction was concentrated *in vacuo* and diluted with water (5 mL). The precipitated solids were filtered and dried to give (4-((R)-1-[(1S,2S)-1-(2-fluoro-4-iodo-phenylcarbamoyl)-2-phenyl-propyl]-2,5-dioxo-imidazolidin-4-yl)-phenoxy-methyl)-phosphonic acid (51 mg, 68%).

HRMS: Obs. Mass ($M+H^+$), 668.0453. Calcd. Mass, 668.0454 for $C_{26}H_{25}FIN_3O_7P^+$.

Example 65

(2S,3S)-N-(2-Fluoro-4-iodo-phenyl)-2-((R)-4-isopropyl-2,5-dioxo-imidazolidin-1-yl)-3-phenyl-butyramide



5

Prepared by the same method as described in example 48 except that (R)-2-*tert*-butoxycarbonylamino-3-methyl-butyric acid was used in place of (R)-*tert*-butoxycarbonylamino-{4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-acetic acid.

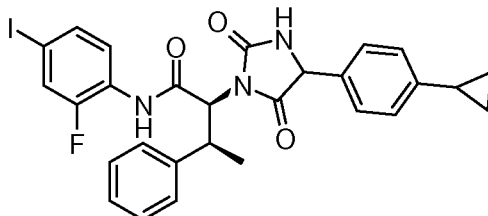
HRMS: Obs. Mass ($M+H^+$), 524.0840. Calcd. Mass, 524.0841 for

10

$C_{22}H_{24}FIN_3O_3^+$.

Example 66

(2S,3S)-2-[4-(4-Cyclopropyl-phenyl)-2,5-dioxo-imidazolidin-1-yl]-N-(2-fluoro-4-iodo-phenyl)-3-phenyl-butyramide, isomer 1



15

Prepared by the same method as described in example 48 except that *tert*-butoxycarbonylamino-(4-cyclopropyl-phenyl)-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-{4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-acetic acid. *tert*-Butoxycarbonylamino-(4-cyclopropyl-phenyl)-acetic acid was prepared as follows:

20

(i) *p*-Cyclopropylbenzaldehyde (840 mg, 5.68 mmol) was dissolved in dry dichloromethane (2.5 mL) and treated with trimethylsilyl cyanide (756 mg, 7.394 mmol) and 5 crystals of zinc iodide and heated to 40 °C for 15 minutes. The reaction mixture was then concentrated *in vacuo*.

25

(ii) The concentrated orange solution from (i) was treated with 7N ammonia in methanol (7.1 mL, 14.22 mmol) and heated in a sealed tube under argon at 40 °C for 20 h. The solution was concentrated to a yellow residue (1.08 g).

- (iii) The yellow residue from (ii) was dissolved in 6 N HCl_(aq) (4.18 mL, 25.08 mmol) and heated at 100 °C for 5 h. The solution was concentrated to a volume of approximately 3 mL and titrated with concentrated NaOH_(aq) to pH 8.0 to give a gummy residue (0.41 g).
- 5 (iv) The residue from (iii) was dissolved in 1N aqueous sodium hydroxide (2.1 mL, 2.1 mmol), water (2.14 mL) and *p*-dioxane (7.1 mL) and cooled in an ice bath. To this mixture was added di-*tert*-butyldicarbonate (661 mg, 3.002 mmol) and the mixture stirred and allowed to warm to ambient temperature for 2 h. The solution was concentrated to remove *p*-dioxane, diluted with
- 10 water (25 mL), washed with diethyl ether (3 × 25 mL) and back extracted with saturated aqueous sodium bicarbonate (25 mL). The combined aqueous layers were acidified to pH 2-3 with 1.5 N aqueous potassium hydrogen sulfate and extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to
- 15 give *tert*-butoxycarbonylamino-(4-cyclopropyl-phenyl)-acetic acid (70 mg, 11 %yield)

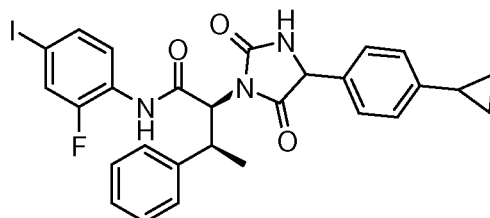
The diastereomers of (2S,3S)-2-[4-(4-cyclopropyl-phenyl)-2,5-dioxo-imidazolidin-1-yl]-*N*-(2-fluoro-4-iodo-phenyl)-3-phenyl-butyramide were separated by

20 chromatography over silica gel gradient eluted from 5 to 20 % v/v ethyl acetate in hexanes. Fractions containing the faster moving component were collected and concentrated *in vacuo*. The residue was precipitated from ether/hexanes to give (2S,3S)-2-[4-(4-cyclopropyl-phenyl)-2,5-dioxo-imidazolidin-1-yl]-*N*-(2-fluoro-4-iodo-phenyl)-3-phenyl-butyramide, isomer 1.

25 HRMS: Obs Mass (M+H⁺), 598.0998. Calcd. Mass, 598.0998 for C₂₈H₂₆FIN₃O₃⁺.

Example 67

(2S,3S)-2-[(S)-4-(4-Cyclopropyl-phenyl)-2,5-dioxo-imidazolidin-1-yl]-N-(2-fluoro-4-iodo-phenyl)-3-phenyl-butyramide, isomer 2



5

Prepared by the same method as described in example 66.

The diastereomers of (2S,3S)-2-[4-(4-cyclopropyl-phenyl)-2,5-dioxo-imidazolidin-1-yl]-N-(2-fluoro-4-iodo-phenyl)-3-phenyl-butyramide were separated by chromatography over silica gel gradient eluted from 5 to 20 % v/v ethyl acetate in hexanes. Fractions containing the slower moving component were collected and concentrated *in vacuo* to give (2S,3S)-2-[4-(4-cyclopropyl-phenyl)-2,5-dioxo-imidazolidin-1-yl]-N-(2-fluoro-4-iodo-phenyl)-3-phenyl-butyramide, isomer 2.

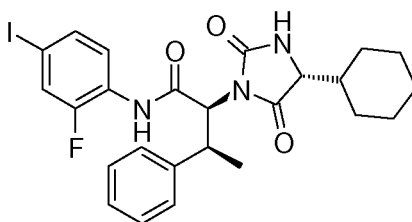
10

HRMS: Obs Mass ($M+H^+$), 598.0994. Calcd. Mass, 598.0998 for $C_{28}H_{26}FIN_3O_3^+$.

15

Example 68

(2S,3S)-2-((R)-4-Cyclohexyl-2,5-dioxo-imidazolidin-1-yl)-N-(2-fluoro-4-iodo-phenyl)-3-phenyl-butyramide



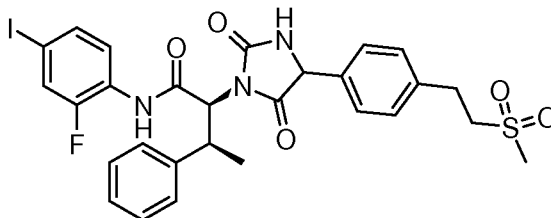
Prepared by the same method as described in example 48 except that (R)-*tert*-butoxycarbonylamino-cyclohexyl-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-{4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-acetic acid.

20

HRMS: Obs Mass ($M+H^+$), 564.1156. Calcd. Mass, 564.1154 for $C_{25}H_{28}FIN_3O_3^+$.

Example 69

(2S,3S)-N-(2-Fluoro-4-iodo-phenyl)-2-{4-[4-(2-methanesulfonyl-ethyl)-phenyl]-2,5-dioxo-imidazolidin-1-yl}-3-phenyl-butylamide, diastereomer 1



5

Prepared by the same method as described in example 1 except that (i) 2-fluoro-4-iodoaniline was used in place of 4-bromoaniline in step 2, (ii) *tert*-butoxycarbonylamino-[4-(2-methanesulfonyl-ethyl)-phenyl]-acetic acid (prepared as described below) was used in place of (R)-*tert*-butyloxycarbonylamino-4-methoxyphenylglycine in step 4, and (iii) super-critical fluid chromatography was used to separate the diastereomers of (2S,3S)-N-(2-fluoro-4-iodo-phenyl)-2-{4-[4-(2-methanesulfonyl-ethyl)-phenyl]-2,5-dioxo-imidazolidin-1-yl}-3-phenyl-butylamide after performing step 6. Super-critical fluid chromatography separation was performed using a Chiracel OJ column eluted with carbon dioxide at 100 bar and 30 °C modified with 25% ethanol in acetonitrile eluted at 2 mL/minute. The first eluted compound was collected and concentrated *in vacuo* to obtain (2S,3S)-N-(2-Fluoro-4-iodo-phenyl)-2-{4-[4-(2-methanesulfonyl-ethyl)-phenyl]-2,5-dioxo-imidazolidin-1-yl}-3-phenyl-butylamide, diastereomer 1.

Preparation of *tert*-butoxycarbonylamino-[4-(2-methanesulfonyl-ethyl)-phenyl]-acetic acid:

(1) To a mixture of amino-(4-bromo-phenyl)-acetic acid (543 mg, 2.4 mmol), triethylamine (822 μ L, 5.9 mmol), 4-(dimethylamino)pyridine (29 mg, 0.24 mmol) in dioxane/water (2:1, 12 mL) was added di-*tert*-butyl dicarbonate (1.1 g, 5.0 mmol) and the resulting solution was allowed to stir for 3 hours. The reaction was diluted with ethyl acetate (50 mL), washed with 0.2 N aqueous hydrochloric acid (10 mL), water (20 mL), brine and the organic layer was dried over sodium sulfate and filtered. The solvent was removed *in vacuo* to give (4-bromo-phenyl)-*tert*-butoxycarbonylamino-acetic acid (780mg, 100%)

25

(2) (4-Bromo-phenyl)-*tert*-butoxycarbonylamino-acetic acid (780mg, 2.4 mmol) was dissolved in *N,N*-dimethylformamide (15 mL) and to this was added potassium hydrogen carbonate (260 mg, 2.6 mmol) followed by benzyl bromide (281 μ L, 2.4 mmol) and stirring continued at ambient temperature for 6 hours.

- 5 The reaction was poured into water (50 mL) and extracted with ethyl acetate (2 x 60 mL). The organic extracts were washed with water (2 x 20 mL), brine, dried over sodium sulfate and filtered through a layer of silica gel. The filtrate was concentrated *in vacuo* and the residue crystallized from 100% hexane to give (4-bromo-phenyl)-*tert*-butoxycarbonylamino-acetic acid benzyl ester (500 mg, 50%).
- 10 (3) (4-Bromo-phenyl)-*tert*-butoxycarbonylamino-acetic acid benzyl ester (1.5 g, 3.6 mmol), methyl vinyl sulfone (406 μ L, 4.6 mmol), palladium(II) acetate (80 mg, 10 mol%), tri-*o*-tolylphosphine (217 mg, 20 mol%) and triethylamine (2.0 ml, 14.3 mmol) were combined in acetonitrile (18 mL), degassed and refluxed for 8 hours. Additional palladium(II) acetate (80 mg, 10 mol%) and tri-*o*-tolylphosphine (217
- 15 mg, 20 mol%) were added and refluxing continued overnight. The reaction was cooled, solvent removed *in vacuo* and the residue was purified by chromatography over silica gel gradient eluted from 20 to 90% *v/v* ethyl acetate in hexane to afford *tert*-butoxycarbonylamino-[4-((E)-2-methanesulfonyl-vinyl)-phenyl]-acetic acid benzyl ester (1.2 g, 75%).

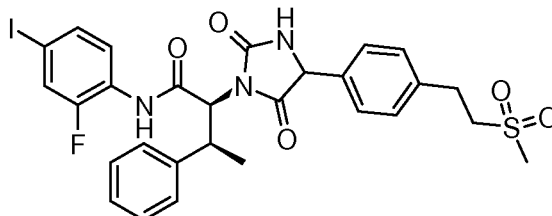
- 20 (4) A hydrogenation vessel containing *tert*-butoxycarbonylamino-[4-((E)-2-methanesulfonyl-vinyl)-phenyl]-acetic acid benzyl ester (1.1 g, 2.5 mmol) in methanol/ethyl acetate (3:1, 50 ml) was purged with nitrogen and 10% palladium on carbon (200 mg) added. The atmosphere above the organic solution was exchanged for hydrogen and the reaction mixture stirred vigorously for 3 hours at
- 25 ambient temperature. The reaction mixture was filtered through a pad of Celite and concentrated *in vacuo* to give *tert*-butoxycarbonylamino-[4-(2-methanesulfonyl-ethyl)-phenyl]-acetic acid (800 mg, 94%).

HRMS: Obs Mass ($M+H^+$), 664.0778. Calcd. Mass, 664.0773 for $C_{28}H_{28}FIN_3O_5S^+$.

- 30 1H NMR (DMSO- d_6 , 300 MHz) δ_H 10.11 (s, 1H), 8.56 (s, 1H), 5.02 (d, $J = 11.7$ Hz, 1H), 4.41 (s, 1H).ppm (characteristic resonances).

Example 70

(2S,3S)-N-(2-Fluoro-4-iodo-phenyl)-2-{4-[4-(2-methanesulfonyl-ethyl)-phenyl]-2,5-dioxo-imidazolidin-1-yl}-3-phenyl-butyramide, diastereomer 2



5

Prepared as described in example 69 except that the second eluted compound was collected and concentrated *in vacuo* to obtain (2S,3S)-N-(2-Fluoro-4-iodo-phenyl)-2-{4-[4-(2-methanesulfonyl-ethyl)-phenyl]-2,5-dioxo-imidazolidin-1-yl}-3-phenyl-butyramide, diastereomer 2.

10 HRMS: Obs Mass ($M+H^+$), 664.0763. Calcd. Mass, 664.0773 for $C_{28}H_{28}FIN_3O_5S^+$.

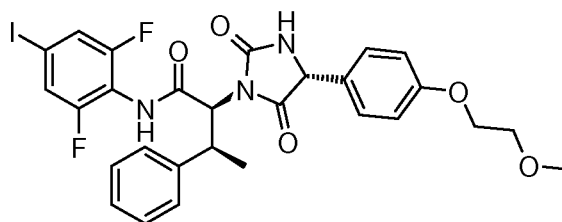
LC-MS:

1H NMR (DMSO- d_6 , 300 MHz) δ_H 10.18 (s, 1H), 8.61 (s, 1H), 4.93 (s, 1H), 4.87 (d, $J = 11.4$ Hz, 1H) ppm (characteristic resonances).

15

Example 71

(2S,3S)-N-(2,6-Difluoro-4-iodo-phenyl)-2-{(R)-4-[4-(2-methoxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl}-3-phenyl-butyramide



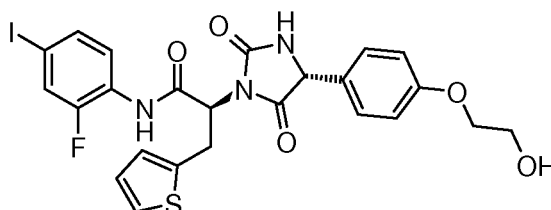
20 Prepared by the same method as described in example 48 except that (i) 2,6-difluoro-4-iodoaniline was used in place of 2-fluoro-4-iodoaniline, and (ii) (R)-*tert*-butoxycarbonylamino-[4-(2-methoxy-ethoxy)-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-[4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl]-acetic acid. (R)-*tert*-Butoxycarbonylamino-[4-(2-methoxy-ethoxy)-

25 phenyl]-acetic acid was prepared as described in example 48 except that 1-bromo-2-methoxyethane was used in place of 2-(2-bromo-ethoxy)-tetrahydropyran.

HRMS: Obs Mass ($M+H^+$), 650.0952. Calcd. Mass, 650.0958 for $C_{28}H_{27}F_2IN_3O_5^+$.

Example 72

- 5 (S)-N-(2-Fluoro-4-iodo-phenyl)-2-[(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-thiophen-2-yl-propionamide



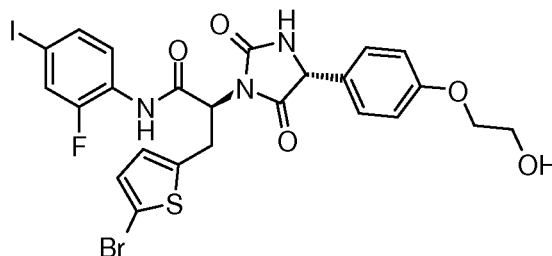
- Prepared by the same method as described in example 48 except that (i) step 1 was performed as described below and (ii) *O*-benzotriazol-1-yl-*N,N,N',N'*-bis(tetramethylene)uronium hexafluorophosphate was used as the coupling reagent in place of *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate in step 4.
- Step 1: To a solution of (S)-2-*tert*-butoxycarbonylamino-3-thiophen-2-yl-propionic acid (1.1 g, 4.06 mmol) and 2-fluoro-4-iodoaniline (800 mg, 3.38 mmol) in pyridine (15 mL) at -10 °C was slowly added phosphorus oxychloride (0.35 mL, 3.72 mmol) under an atmosphere of dry nitrogen. The mixture was stirred for 2 hours at -10 °C. After removal of the solvent and the excess reagent by rotary evaporator, ice water was added. The mixture was extracted with dichloromethane and the organic layer washed with 1 M aqueous citric acid, brine, saturated aqueous sodium carbonate, brine and dried over sodium sulfate. The solvents were removed to give [(S)-1-(2-fluoro-4-iodo-phenylcarbamoyl)-2-thiophen-2-yl-ethyl]-carbamic acid *tert*-butyl ester as a yellow viscous oil for use in the next step (1.52 g, 92%).

LC-MS: Obs Mass ($M+H^+$), 491. Calcd. Mass, 491 for $C_{18}H_{20}FIN_2O_3S^+$.

- 25 LC-MS: Obs Mass ($M+H^+$), 610; Calcd. Mass, 610 for $C_{24}H_{22}FIN_3O_5S^+$.

Example 73

(S)-3-(5-Bromo-thiophen-2-yl)-*N*-(2-fluoro-4-iodo-phenyl)-2-{(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl}-propionamide



5

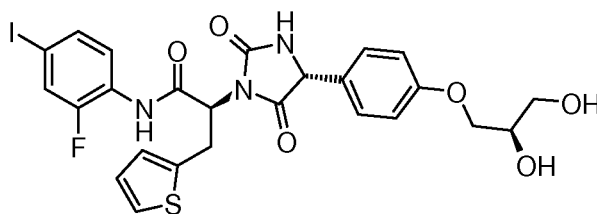
Prepared by the same method as described in example 72 except that (S)-3-(5-bromo-thiophen-2-yl)-2-*tert*-butoxycarbonylamino-propionic acid was used in place of (S)-2-*tert*-butoxycarbonylamino-3-thiophen-2-yl-propionic acid in step 1.

LC-MS: Obs Mass ($M+H^+$), 688; Calcd. Mass, 688 for $C_{24}H_{21}BrFIN_3O_5S^+$.

10

Example 74

(S)-2-{(R)-4-[4-((R)-2,3-Dihydroxy-propoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl}-*N*-(2-fluoro-4-iodo-phenyl)-3-thiophen-2-yl-propionamide

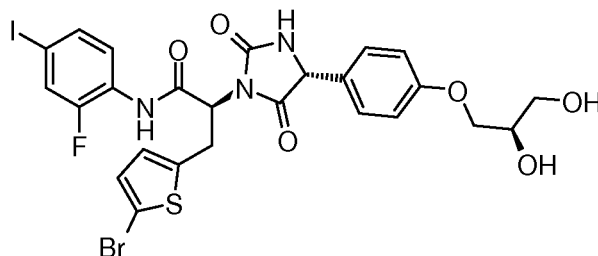


15 Prepared by the same method as described in example 114 except that (i) step 1 was performed as described in example 72 and (ii) *O*-benzotriazol-1-yl-*N,N,N',N'*-bis(tetramethylene)uronium hexafluorophosphate was used as the coupling reagent in place of *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate in step 4.

20 LC-MS: Obs Mass ($M+H^+$), 640; Calcd. Mass, 640 for $C_{25}H_{24}FIN_3O_6S^+$.

Example 75

(S)-3-(5-Bromo-thiophen-2-yl)-2-[(R)-4-[4-((R)-2,3-dihydroxy-propoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-N-(2-fluoro-4-iodo-phenyl)-propionamide



5

Prepared by the same method as described in example 114 except that (i) step 1 was performed as described in example 73 and (ii) *O*-benzotriazol-1-yl-*N,N,N',N'*-bis(tetramethylene)uronium hexafluorophosphate was used as the coupling reagent in place of *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate in step 4.

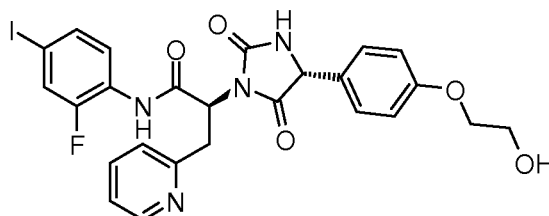
10

LC-MS: Obs Mass ($M+H^+$), 718; Calcd. Mass, 718 for $C_{25}H_{23}BrFIN_3O_6S^+$.

Example 76

(S)-N-(2-Fluoro-4-iodo-phenyl)-2-[(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-pyridin-2-yl-propionamide

15



Prepared by the same method as described in example 43 except that (i) (S)-2-*tert*-butoxycarbonylamino-3-pyridin-2-yl-propionic acid was used in place of (S)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-naphthalen-2-yl-propionic acid in step 1 and (ii) step 3 was performed as described below.

20

Step 3: To a solution of (S)-[1-(2-fluoro-4-iodo-phenylcarbonyl)-2-pyridin-2-yl-ethyl]-carbamic acid *tert*-butyl ester (1.2 g, 2.47 mmol) in dichloromethane (5 mL) at 0 °C was added trifluoroacetic acid (5 mL) and the mixture stirred at 0 °C for 1 hour. The reaction mixture was concentrated *in vacuo* and the residue suspended in ice cold water. The aqueous suspension was neutralized with saturated aqueous sodium carbonate solution to basic then extracted with

25

dichloromethane (three times). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by chromatography over silica gel gradient eluted from 100% hexane up to 100% ethyl acetate in 40 minutes. Concentration of the product containing fractions gave (S)-2-amino-N-(2-fluoro-4-iodo-phenyl)-3-pyridin-2-yl-propionamide as a yellow solid (806 mg, 85%).

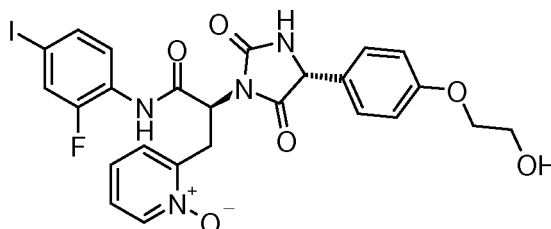
LC-MS: Obs Mass ($M+H^+$), 386; Calcd. Mass, 386 for $C_{14}H_{13}FIN_3O^+$.

LC-MS: Obs Mass ($M+H^+$), 605; Calcd. Mass, 605 for $C_{25}H_{23}FIN_4O_5^+$.

10

Example 77

(S)-N-(2-Fluoro-4-iodo-phenyl)-2-[(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-(1-oxy-pyridin-2-yl)-propionamide



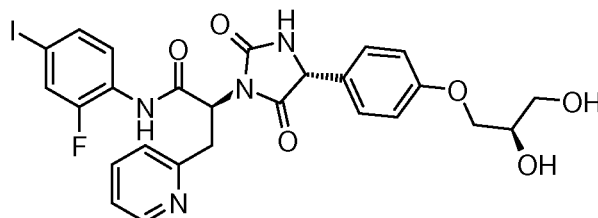
To a solution of (S)-N-(2-fluoro-4-iodo-phenyl)-2-[(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-pyridin-2-yl-propionamide (prepared as described in example 76) (50 mg, 0.083 mmol) in dichloromethane (4 mL) was added 3-chloroperbenzoic acid (77%, 28 mg, 0.12 mmol) and the mixture stirred for 5 hours. The reaction mixture was concentrated *in vacuo* and the residue was purified by chromatography over silica gel gradient eluted from 100% dichloromethane up to 10% methanol / 90% dichloromethane in 30 minutes. Concentration of the product containing fractions gave (S)-N-(2-fluoro-4-iodo-phenyl)-2-[(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-(1-oxy-pyridin-2-yl)-propionamide as a white solid (40 mg, 78%).

LC-MS: Obs Mass ($M+H^+$), 621; Calcd. Mass, 621 for $C_{25}H_{23}FIN_4O_6^+$.

25

Example 78

(S)-2-[(R)-4-[4-[(R)-2,3-Dihydroxy-propoxy]-phenyl]-2,5-dioxo-imidazolidin-1-yl]-N-(2-fluoro-4-iodo-phenyl)-3-pyridin-2-yl-propionamide



5

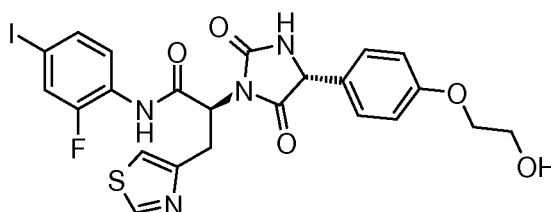
Prepared by the same method as described in example 114 except that (i) steps 1-3 were performed as described in example 76 and (ii) *O*-benzotriazol-1-yl-*N,N,N',N'*-bis(tetramethylene)uronium hexafluorophosphate was used as the coupling reagent in place of *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate in step 4.

10

LC-MS: Obs Mass ($M+H^+$), 635. Calcd. Mass, 635 for $C_{26}H_{25}FIN_4O_6^+$.

Example 79

15 (S)-N-(2-Fluoro-4-iodo-phenyl)-2-[(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-thiazol-4-yl-propionamide



Prepared by the same method as described in example 1 except that 2-fluoro-4-iodoaniline was used in place of 4-bromoaniline and (S)-2-*tert*-

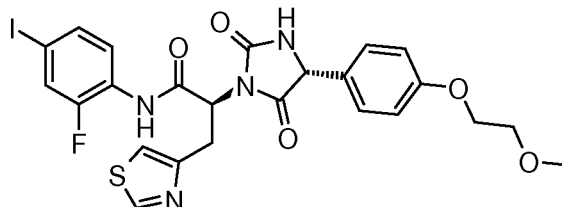
20 *butoxycarbonylamino*-3-thiazol-4-yl-propionic acid was used in place of (2S, 3S)-2-*tert*-*butoxycarbonylamino*-3-phenyl-butyric acid in step 2 and (R)-*tert*-*butoxycarbonylamino*-{4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-acetic acid was used in place of (R)-*tert*-*butoxycarbonylamino* [4-methoxy-phenyl]-acetic acid in step 4. (R)-*tert*-*Butoxycarbonylamino*-{4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-acetic acid was prepared as described in example 48.

25

HRMS: Obs Mass ($M+H^+$), 611.0253. Calcd. Mass, 611.0256 for $C_{23}H_{21}FIN_4O_5S^+$.

Example 80

(S)-N-(2-Fluoro-4-iodo-phenyl)-2-((R)-4-[4-(2-methoxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl)-3-thiazol-4-yl-propionamide



5

Prepared by the same method as described in example 79 except that (R)-*tert*-butoxycarbonylamino-[4-(2-methoxy-ethoxy)-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-{4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-acetic acid. (R)-*tert*-Butoxycarbonylamino-[4-(2-methoxy-ethoxy)-phenyl]-acetic acid was prepared as described in example 48 except that 1-bromo-2-methoxyethane was used in place of 2-(2-bromo-ethoxy)-tetrahydropyran.

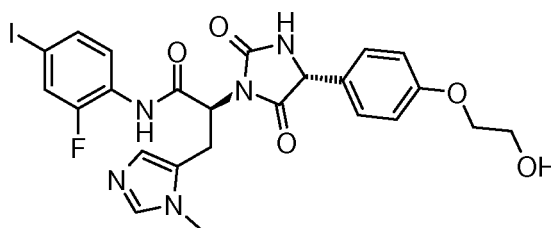
10

HRMS: Obs Mass ($M+H^+$), 625.0403. Calcd. Mass, 625.0413 for $C_{24}H_{23}FIN_4O_5S^+$.

15

Example 81

(S)-N-(2-Fluoro-4-iodo-phenyl)-2-((R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl)-3-(3-methyl-3H-imidazol-4-yl)-propionamide



Prepared by the same method as described in example 3 except that (i) 2-fluoro-4-iodoaniline used in place of 2-chloro-4-bromoaniline, and (ii) (2S)-2-*tert*-butoxycarbonylamino-3-(3-methyl-3H-imidazol-4-yl)-propionic acid used in place of (2S, 3S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid in step 1.

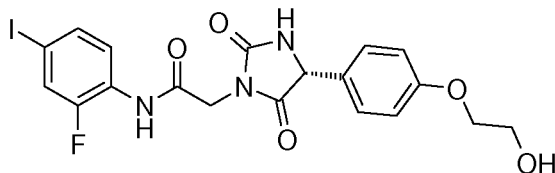
20

HRMS: Obs Mass ($M+H^+$), 608.0798. Calcd. Mass, 608.0801 for $C_{24}H_{24}FIN_5O_5^+$.

25

Example 82

N-(2-Fluoro-4-iodo-phenyl)-2-{(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl}-acetamide



5

Prepared by the same method as described in example 48 except that *tert*-butoxycarbonylamino-acetic acid was used in place of (2*S*, 3*S*)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid.

HRMS: Obs Mass ($M+Na^+$), 536.0088. Calcd. Mass 536.0089 for

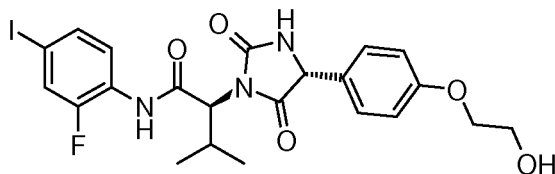
10

$C_{19}H_{17}FIN_3NaO_5^+$.

Example 83

(*S*)-*N*-(2-Fluoro-4-iodo-phenyl)-2-{(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl}-3-methyl-butyramide

15



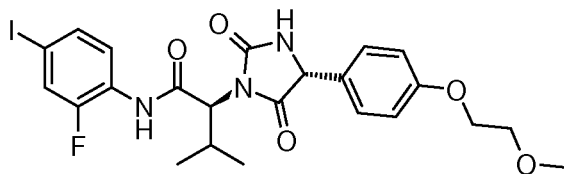
Prepared by the same method as that described in example 48 except that (*S*)-2-*tert*-butoxycarbonylamino-3-methyl-butyric acid was used in place of (2*S*, 3*S*)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid in step 1.

20

LC-MS: Obs. Mass, 556. Calcd. Mass, 556 for $C_{22}H_{24}FIN_3O_5^+$.

Example 84

(*S*)-*N*-(2-Fluoro-4-iodo-phenyl)-2-{(R)-4-[4-(2-methoxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl}-3-methyl-butyramide



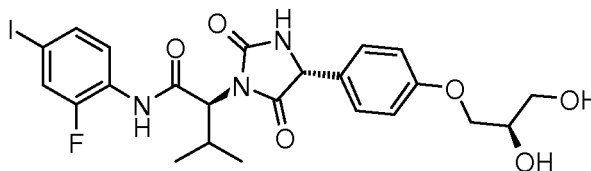
25

Prepared by the same method as described in example 21 except that (i) (S)-2-*tert*-butoxycarbonylamino-3-methyl-butyric acid was used in place of (S)-2-*tert*-butoxycarbonylamino-3-phenyl-propionic acid in step 1, and (ii) *O*-benzotriazol-1-yl-*N,N,N',N'*-bis(tetramethylene)uronium hexafluorophosphate was used as the
 5 coupling reagent in place of *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate in step 4.

LC-MS: Obs Mass ($M+H^+$), 570. Calcd. Mass, 570 for $C_{23}H_{26}FIN_3O_5^+$.

Example 85

10 (S)-2-[(R)-4-[4-[(R)-2,3-Dihydroxy-propoxy]-phenyl]-2,5-dioxo-imidazolidin-1-yl]-*N*-(2-fluoro-4-iodo-phenyl)-3-methyl-butyramide



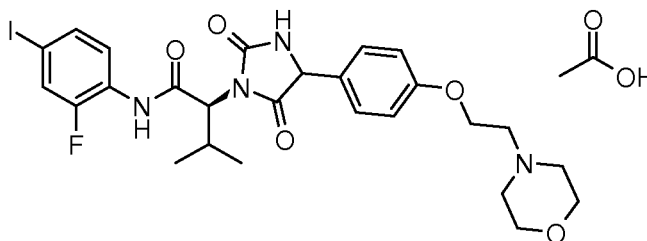
Prepared by the same method as described in example 114 except that (i) step 1 was performed as described in example 83, and (ii) *O*-benzotriazol-1-yl-*N,N,N',N'*-bis(tetramethylene)uronium hexafluorophosphate was used as the
 15 coupling reagent in place of *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate in step 4.

LC-MS: Obs Mass ($M+H^+$), 586. Calcd. Mass, 586 for $C_{23}H_{26}FIN_3O_6^+$.

20

Example 86

(S)-*N*-(2-Fluoro-4-iodo-phenyl)-3-methyl-2-[4-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-butyramide; compound with acetic acid



Prepared by the same method as described in example 1 except that (i) (S)-2-*tert*-butoxycarbonylamino-3-methyl-butyric acid was used in place of (2*S*, 3*S*)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid in step 1, (ii) 2-fluoro-4-iodoaniline was used in place of 4-bromoaniline in step 2, and (iii) (R,*S*)-*tert*-
 25

butoxycarbonylamino-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-4-methoxyphenylglycine in step 4.

(R,S)-*tert*-Butoxycarbonylamino-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-acetic acid was prepared as follows:

5 (1) To a solution of (R)-*tert*-butoxycarbonylamino-[4-(2-hydroxy-ethoxy)-phenyl]-acetic acid (1.0 g, 3.21 mmol) in methanol (10 mL) was added a catalytic amount of concentrated sulfuric acid. The reaction mixture was stirred at reflux for 3 hours. The solvent was evaporated and the crude (R)-*tert*-butoxycarbonylamino-[4-(2-hydroxy-ethoxy)-phenyl]-acetic acid methyl ester (0.836 g, 80% yield) was
10 carried on to the next step without further purification.

(2) To a stirred solution of (R)-*tert*-butoxycarbonylamino-[4-(2-hydroxy-ethoxy)-phenyl]-acetic acid methyl ester (80 mg, 0.25 mmol) in pyridine (1.5 mL) was added methanesulfonyl chloride (0.023 mL, 0.30 mmol) dropwise. The reaction mixture was stirred at room temperature for 3 hours. The solvent was
15 evaporated and the crude product was purified by chromatography over silica gel eluted with 3:1 v/v hexanes / ethyl acetate to give (R)-*tert*-butoxycarbonylamino-[4-(2-methanesulfonyloxy-ethoxy)-phenyl]-acetic acid methyl ester (50 mg, 50% yield) as a colorless oil.

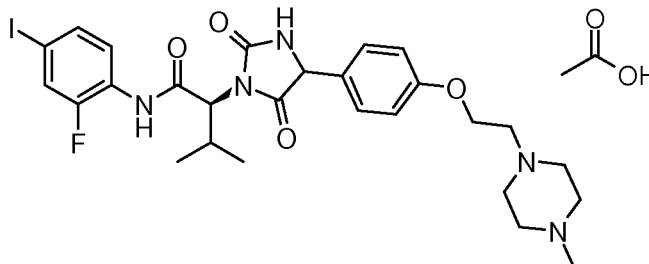
(3) To a stirred solution of (R)-*tert*-butoxycarbonylamino-[4-(2-methanesulfonyloxy-ethoxy)-phenyl]-acetic acid methyl ester (50 mg, 0.12 mmol)
20 in ethanol (1 mL) was added morpholine (0.043 mL, 0.49 mmol) at room temperature. The reaction mixture was refluxed for 1 hour. The solvent was evaporated and the crude product was purified by chromatography over silica gel eluted with 1:1 v/v hexanes / ethyl acetate to give (R)-*tert*-butoxycarbonylamino-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-acetic acid methyl ester (45 mg, 92% yield)
25 as a colorless oil.

(4) To a stirred solution of (R)-*tert*-butoxycarbonylamino-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-acetic acid methyl ester (45 mg, 0.11 mmol) in methanol (0.6 mL) and water (0.2 mL) was added lithium hydroxide monohydrate (14.3 mg, 0.34 mmol) at room temperature. The reaction mixture was stirred at room
30 temperature for 3 hours. The solvent was evaporated and the crude product (R,S)-*tert*-butoxycarbonylamino-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-acetic acid (43 mg, 99% yield) was carried on to the next step without further purification.

HRMS: Obs Mass ($M+H^+$), 625.1318. Calcd. Mass, 625.1318 for $C_{26}H_{31}FIN_4O_5^+$.

Example 87

- 5 (S)-N-(2-Fluoro-4-iodo-phenyl)-3-methyl-2-(4-{4-[2-(4-methyl-piperazin-1-yl)-ethoxy]-phenyl}-2,5-dioxo-imidazolidin-1-yl)-butyramide; compound with acetic acid



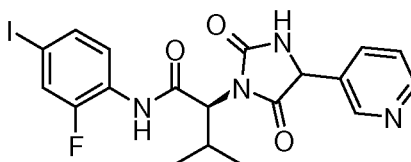
- Prepared by the same method as described in example 86 except that (i) (R,S)-*tert*-butoxycarbonylamino-{4-[2-(4-methyl-piperazin-1-yl)-ethoxy]-phenyl}-acetic acid was used in place of (R,S)-*tert*-butoxycarbonylamino-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-acetic acid in step 4. (R,S)-*tert*-Butoxycarbonylamino-{4-[2-(4-methyl-piperazin-1-yl)-ethoxy]-phenyl}-acetic acid was prepared using the same method as described for (R,S)-*tert*-butoxycarbonylamino-[4-(2-morpholin-4-yl-ethoxy)-phenyl]-acetic acid in example 86 except that 1-methyl-piperazine was used in place of morpholine in step 3.

HRMS: Obs Mass ($M+H^+$), 638.1633. Calcd. Mass, 638.1637 for $C_{27}H_{34}FIN_5O_4^+$.

20

Example 88

(S)-2-(2,5-Dioxo-4-pyridin-3-yl-imidazolidin-1-yl)-N-(2-fluoro-4-iodo-phenyl)-3-methyl-butyramide



- Prepared by the same method as described in example 1 except that (i) (S)-2-*tert*-butoxycarbonylamino-3-methyl-butyric acid was used in place of (2S, 3S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid in step 1, (ii) 2-fluoro-4-iodoaniline was used in place of 4-bromoaniline in step 2, and (iii) (R,S)-*tert*-

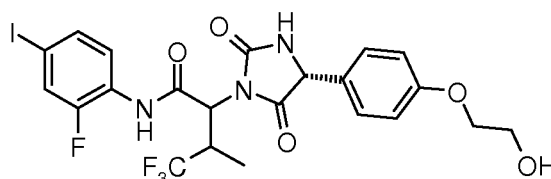
butoxycarbonylamino-pyridin-3-yl-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-4-methoxyphenylglycine in step 4.

HRMS: Obs Mass ($M+H^+$), 497.0476. Calcd. Mass, 497.0481 for $C_{19}H_{19}FIN_4O_3^+$.

5

Example 89

4,4,4-Trifluoro-*N*-(2-fluoro-4-iodo-phenyl)-2-[(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-methyl-butylamide



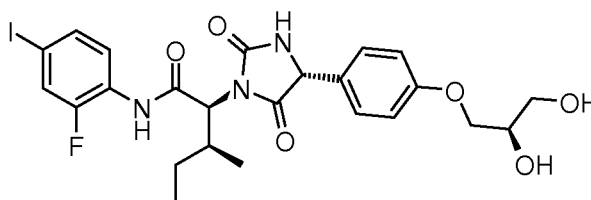
- 10 Prepared by the same method as described in example 72 except that ($\pm$)-2-*tert*-butoxycarbonylamino-4,4,4-trifluoro-3-methyl-butylric was used in place of (S)-2-*tert*-butoxycarbonylamino-3-thiophen-2-yl-propionic acid in step 1.

LC-MS: Obs Mass ($M+H^+$), 610. Calcd. Mass, 610 for $C_{22}H_{21}F_4IN_3O_5^+$.

15

Example 90

(2S,3S)-2-[(R)-4-[4-[(R)-2,3-Dihydroxy-propoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-methyl-pentanoic acid (2-fluoro-4-iodo-phenyl)-amide

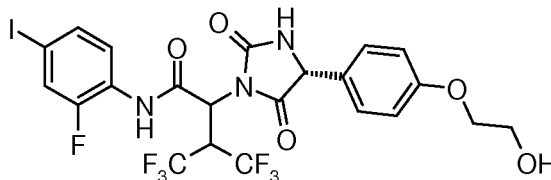


- 20 Prepared by the same method as described in example 74 except (2S, 3S)-2-*tert*-butoxycarbonylamino-3-methyl-propionic acid was used in place of (S)-2-*tert*-butoxycarbonylamino-3-thiophen-2-yl-propionic acid in step 1.

LC-MS: Obs Mass ($M+H^+$), 600. Calcd. Mass, 600 for $C_{24}H_{28}FIN_3O_6^+$.

Example 91

4,4,4-Trifluoro-*N*-(2-fluoro-4-iodo-phenyl)-2-[(*R*)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-trifluoromethyl-butylamide



5

Prepared by the same method as described in example 72 except that ($\pm$)-2-*tert*-butoxycarbonyl-amino-4,4,4-trifluoro-3-trifluoromethyl-butylamide was used in place of (*S*)-2-*tert*-butoxycarbonylamino-3-thiophen-2-yl-propionic acid in step 1. 2-*tert*-Butoxycarbonyl-amino-4,4,4-trifluoro-3-trifluoromethyl-butylamide was prepared as described below.

10

Preparation of 2-*tert*-butoxycarbonyl-amino-4,4,4-trifluoro-3-trifluoromethyl-butylamide:

To a solution of 4,4,4,4',4'-hexafluoro-DL-valine (1.0 g, 4.4 mmol) and sodium carbonate (933 mg, 8.8 mmol) in dioxane (10 mL) and water (10 mL) at 0 °C was slowly added di-*tert*-butyldicarbonate. After addition, the mixture was stirred for 12 hours at room temperature. The reaction mixture was partitioned between water and ethyl acetate and the organic layer was discarded. The organic layer was adjusted to pH > 4 with 1 M aqueous citric acid solution, washed with brine, dried over sodium sulfate and concentrated to give 2-*tert*-butoxycarbonyl-amino-4,4,4-trifluoro-3-trifluoromethyl-butylamide as a yellow solid (1.34 g, 96%).

20

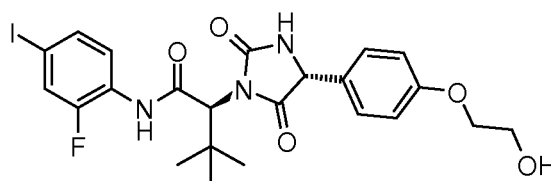
LC-MS: Obs Mass ($M-H^+$) = 324; Calcd. Mass, 324 for $C_{10}H_{12}F_6NO_4^-$.

LC-MS: Obs Mass ($M+H^+$) = 664; Calcd. Mass, 664 for $C_{22}H_{18}F_7IN_3O_5^+$.

25

Example 92

(*S*)-*N*-(2-Fluoro-4-iodo-phenyl)-2-[(*R*)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3,3-dimethyl-butylamide

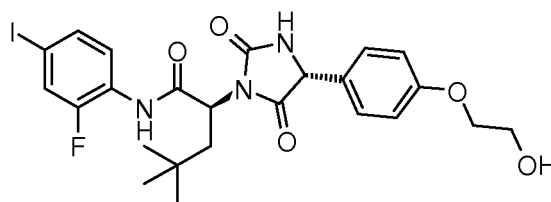


Prepared by the same method as described in example 43 except that (S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-3,3-dimethyl-2-yl-butyric acid was used in place of (S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-3-naphthalen-2-yl-propionic acid in step 1.

LC-MS: Obs Mass ($M+H^+$), 570. Calcd. Mass, 570 for $C_{23}H_{26}FIN_3O_5^+$.

Example 93

(S)-2-[(R)-4-[4-(2-Hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-4,4-dimethyl-pentanoic acid (2-fluoro-4-iodo-phenyl)-amide



Prepared by the same method as described in example 43 except that (i) (S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-4,4-dimethyl-2-yl-pentanoic acid was used in place of (S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-3-naphthalen-2-yl-propanoic acid in step 1, and (ii) steps 4 to 7 were performed as described below:

Step 4: To the solution of 2-amino-4,4-dimethyl-pentanoic acid (2-fluoro-4-iodo-phenyl)-amide (364 mg, 1 mmol), (R)-*tert*-butoxycarbonylamino-[4-(2-*tert*-butoxy-ethoxy)-phenyl]-acetic acid (1 M in DMF, 1.1 mL, 1.1 mmol), 1-

Hydroxybenzotriazole (168 mg, 1.1 mmol) and diisopropylethyl amine (0.53 mL, 3.3 mmol) in *N,N*-dimethylformamide (5 mL) was added dropwise the solution of *O*-benzotriazol-1-yl-*N,N,N',N'*-bis(tetramethylene)uronium hexafluorophosphate (474 mg, 1.1 mmol). The reaction mixture was stirred for 1 hour at room temperature. The reaction mixture was diluted with ethyl acetate and the mixture washed with water and brine. The organic layers were successively washed with 1 M aqueous citric acid solution, brine, saturated aqueous sodium carbonate, brine, dried over sodium sulfate, filtered, and concentrated to give [(R)-[4-(2-*tert*-butoxy-ethoxy)-phenyl]-[(S)-1-(2-fluoro-4-iodo-phenylcarbamoyl)-3,3-dimethyl-butylcarbamoyl]-methyl]-carbamic acid *tert*-butyl ester (652 mg, 91 %) as a white solid.

LC-MS: Obs Mass ($M+H^+$) = 714; Calcd. Mass, 714 for $C_{32}H_{45}FIN_3O_6^+$.

Step 5: To a solution of {(R)-[4-(2-*tert*-butoxy-ethoxy)-phenyl]-[(S)-1-(2-fluoro-4-iodo-phenylcarbamoyl)-3,3-dimethyl-butylcarbamoyl]-methyl}-carbamic acid *tert*-butyl ester (652 mg, 0.91 mmol) in acetonitrile (6 mL) was added 4 N hydrogen chloride in dioxane (1 mL, 4 mmol) and the mixture stirred at 40 °C for 30 minutes. The reaction mixture was concentrated *in vacuo* and the residue suspended in ice cold water. The aqueous suspension was neutralized to basic pH with saturated aqueous sodium carbonate solution then extracted with dichloromethane (three times). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* and the residue purified by chromatography over silica gel gradient eluted from 100% dichloromethane up to 10% methanol / 90% dichloromethane in 30 minutes. Concentration of the product containing fractions gave (S)-2-[(R)-2-amino-2-[4-(2-*tert*-butoxy-ethoxy)-phenyl]-acetylamino]-4,4-dimethyl-pentanoic acid (2-fluoro-4-iodo-phenyl)-amide (490 mg, 87%).

LC-MS: Obs Mass ($M+H^+$) = 614; Calcd. Mass, 614 for $C_{27}H_{38}FIN_3O_4^+$.

Step 6: To a solution of diphosgene (41 μ L, 0.34 mmol) in 1:1 v/v toluene / tetrahydrofuran (18 mL total) at -35 °C under an atmosphere of dry argon was added a solution of (S)-2-[(R)-2-amino-2-[4-(2-*tert*-butoxy-ethoxy)-phenyl]-acetylamino]-4,4-dimethyl-pentanoic acid (2-fluoro-4-iodo-phenyl)-amide (300 mg, 0.49 mmol) and *N,N*-diisopropylethylamine (260 μ L, 1.47 mmol) in tetrahydrofuran (9 mL) dropwise with stirring over 10 minutes. After an additional 45 minutes ice was added and the reaction mixture stirred vigorously and warmed to ambient temperature. The reaction mixture was poured into water, extracted with ethyl acetate (twice) and the combined organic layers washed sequentially with water (twice), 0.1 M aqueous hydrochloric acid, water, saturated aqueous sodium hydrogen carbonate, water and brine, then dried over sodium sulfate, filtered and concentrated *in vacuo* to give (S)-2-[(R)-4-[4-(2-*tert*-butoxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-4,4-dimethyl-pentanoic acid (2-fluoro-4-iodo-phenyl)-amide as yellow sticky solid (295 mg, 95%) which was used in the subsequent step without further purification.

LC-MS: Obs Mass ($M+H^+$), 640; Calcd. Mass, 640 for $C_{28}H_{36}FIN_3O_5^+$.

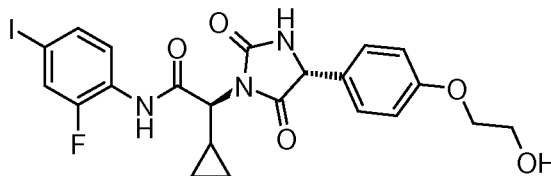
Step 7: To a solution of (S)-2-[(R)-4-[4-(2-*tert*-butoxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-4,4-dimethyl-pentanoic acid (2-fluoro-4-iodo-phenyl)-amide (295 mg, 0.46 mmol) in dichloromethane (3 mL) at 0 °C under an atmosphere of

dry argon was slowly added a solution of trimethylsilyl iodide (183 μ L, 1.3 mmol) in dichloromethane (1 mL). The reaction mixture stirred at ambient temperature for 2 hours. Methanol (0.5 mL) was added to quench the reaction. The reaction mixture extracted with dichloromethane and the organic layer was washed
5 sequentially with saturated aqueous sodium carbonate, 5% aqueous sodium thiosulfate, brine, then dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by chromatography over silica gel gradient eluted from 100% hexane up to 50% ethyl acetate / 50% hexane over 30 minutes. Concentration of the product containing fractions gave (S)-2-[(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-4,4-dimethyl-pentanoic
10 acid (2-fluoro-4-iodo-phenyl)-amide as a white solid (126 mg, 47%).

LC-MS: Obs Mass ($M+H^+$), 584; Calcd. Mass, 584 for $C_{24}H_{28}FIN_3O_5^+$.

Example 94

15 (S)-2-Cyclopropyl-N-(2-fluoro-4-iodo-phenyl)-2-[(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-acetamide

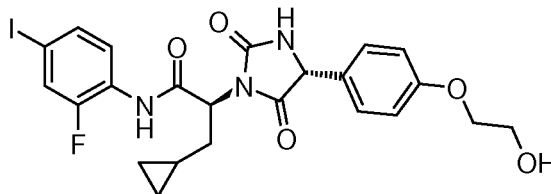


Prepared by the same method as described in example 48 except that (i) (S)-*tert*-butoxycarbonylamino-cyclopropyl-acetic acid was used in place of (2S, 3S)-
20 2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid in step 1, and (ii) *O*-benzotriazol-1-yl-*N,N,N',N'*-bis(tetramethylene)uronium hexafluorophosphate was used as the coupling reagent in place of *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate in step 4.

LC-MS: Obs Mass ($M+H^+$), 554; Calcd. Mass, 554 for $C_{22}H_{22}FIN_3O_5^+$.

Example 95

(S)-3-Cyclopropyl-*N*-(2-fluoro-4-iodo-phenyl)-2-{(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl}-propionamide



5

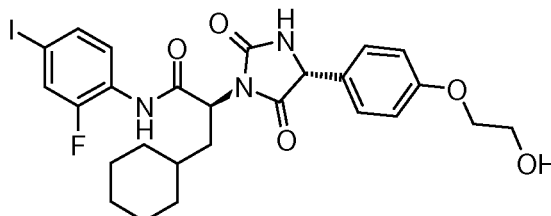
Prepared by the same method as described in example 48 except that (i) (S)-2-*tert*-butoxycarbonylamino-3-cyclopropyl-propionic acid was used in place of (2S, 3S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid in step 1, and (ii) *O*-benzotriazol-1-yl-*N,N,N',N'*-bis(tetramethylene)uronium hexafluorophosphate

10 was used as the coupling reagent in place of *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate in step 4.

LC-MS: Obs Mass ($M+H^+$), 568; Calcd. Mass, 568 for $C_{23}H_{24}FIN_3O_5^+$.

Example 96

15 (S)-3-Cyclohexyl-*N*-(2-fluoro-4-iodo-phenyl)-2-{(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl}-propionamide



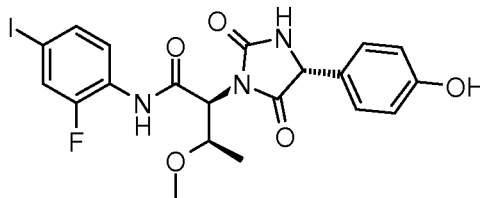
Prepared by the same method as described in example 48 except that (i) (S)-2-*tert*-butoxycarbonylamino-3-cyclohexyl-propionic acid was used in place of (2S, 3S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid in step 1, and (ii) *O*-benzotriazol-1-yl-*N,N,N',N'*-bis(tetramethylene)uronium hexafluorophosphate

20 was used as the coupling reagent in place of *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate in step 4.

LC-MS: Obs Mass ($M+H^+$), 610; Calcd. Mass, 610 for $C_{26}H_{30}FIN_3O_5^+$.

Example 97

(2S,3R)-*N*-(2-Fluoro-4-iodo-phenyl)-2-[(R)-4-(4-hydroxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-3-methoxy-butamide



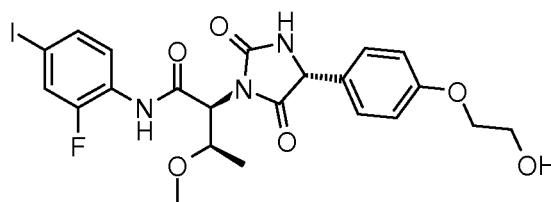
5

Prepared by the same method as described in example 1 except that (i) (2S, 3R)-2-*tert*-butoxycarbonylamino-3-methoxy-butyric acid was used in place of (2S, 3S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid in step 1, (ii) 2-fluoro-4-iodoaniline was used in place of 4-bromoaniline in step 2, (iii) *O*-benzotriazol-1-yl-*N,N,N',N'*-bis(tetramethylene)uronium hexafluorophosphate was used as the coupling reagent in place of *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate in step 4, and (iv) (R)-*tert*-butoxycarbonylamino-4-hydroxyphenylglycine was used in place of (R)-*tert*-butoxycarbonylamino-4-methoxyphenylglycine in step 4.

15 LC-MS: Obs Mass ($M+H^+$), 528; Calcd. Mass, 528 for $C_{20}H_{20}FIN_3O_5^+$.

Example 98

(2S,3R)-*N*-(2-Fluoro-4-iodo-phenyl)-2-[(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-methoxy-butamide



20

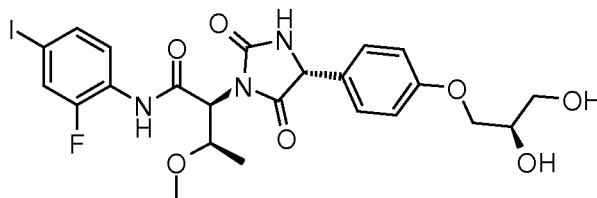
Prepared by the same method as described in example 48 except that (i) (2S, 3R)-2-*tert*-butoxycarbonylamino-3-methoxy-butyric acid was used in place of (2S, 3S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid in step 1, and (ii) *O*-benzotriazol-1-yl-*N,N,N',N'*-bis(tetramethylene)uronium hexafluorophosphate was used as the coupling reagent in place of *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate in step 4.

25

LC-MS: Obs Mass ($M+H^+$), 572; Calcd. Mass, 572 for $C_{22}H_{24}FIN_3O_6^+$.

Example 99

(2S,3R)-2-[(R)-4-[4-[(R)-2,3-dihydroxy-propoxy]-phenyl]-2,5-dioxo-imidazolidin-1-yl]-N-(2-fluoro-4-iodo-phenyl)-3-methoxy-butamide



5

Prepared by the same method as described in example 114 except that (i) (2S, 3R)-2-*tert*-butoxycarbonylamino-3-methoxy-butyrac acid was used in place of (2S, 3S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyrac acid in step 1, (ii) 2-fluoro-4-

10 iodoaniline was used in place of 2-chloro-4-iodoaniline in step 2., and (iii) *O*-

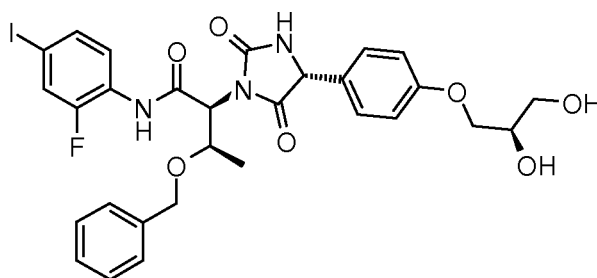
benzotriazol-1-yl-*N,N,N',N'*-bis(tetramethylene)uronium hexafluorophosphate was used as the coupling reagent in place of *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate in step 4.

LC-MS: Obs Mass ($M+H^+$), 602; Calcd. Mass, 602 for $C_{23}H_{26}FIN_3O_7^+$.

15

Example 100

(2S,3R)-3-Benzoyloxy-2-[(R)-4-[4-[(R)-2,3-dihydroxy-propoxy]-phenyl]-2,5-dioxo-imidazolidin-1-yl]-N-(2-fluoro-4-iodo-phenyl)-butamide

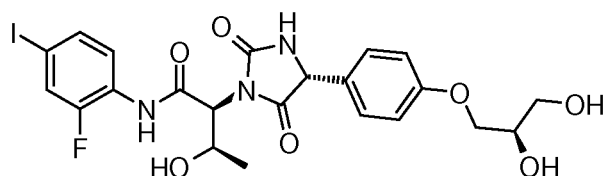


20 Prepared by the same method as described in example 43 except that (i) (2S, 3R)-3-benzoyloxy-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-butyrac acid was used in place of (S)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-naphthalen-2-yl-propionic acid in step 1, and (ii) the steps following step 3 were performed as described in example 114.

25 LC-MS: Obs Mass ($M+H^+$), 678; Calcd. Mass, 678 for $C_{29}H_{30}FIN_3O_7^+$.

Example 101

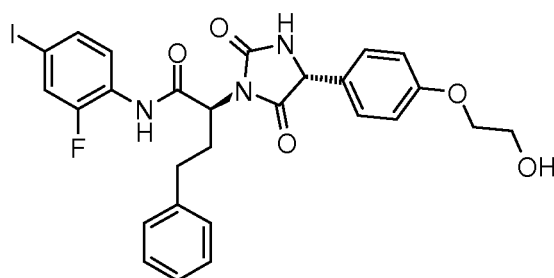
(2S,3R)-2-[(R)-4-[4-[(R)-2,3-Dihydroxy-propoxy]-phenyl]-2,5-dioxo-imidazolidin-1-yl]-N-(2-fluoro-4-iodo-phenyl)-3-hydroxy-butyramide



- 5 Prepared by the same method as described in example 43 except that (i) (2S, 3R)-3-*tert*-butoxy-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-butyric acid was used in place of (S)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-naphthalen-2-yl-propionic acid in step 1, and (ii) the steps following step 4 were performed as described in example 114.
- 10 LC-MS: Obs Mass ($M+H^+$), 588; Calcd. Mass, 588 for $C_{22}H_{24}FIN_3O_7^+$.

Example 102

(S)-N-(2-Fluoro-4-iodo-phenyl)-2-[(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-4-phenyl-butyramide



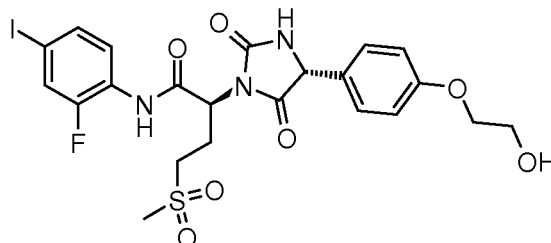
15

Prepared by the same method as described in example 72 except that (S)-2-*tert*-butoxycarbonylamino-4-phenyl-2-yl-butyric acid was used in place of (S)-2-*tert*-butoxycarbonylamino-3-thiophen-2-yl-propionic acid in step 1.

LC-MS: Obs Mass ($M+H^+$), 618; Calcd. Mass, 618 for $C_{27}H_{26}FIN_3O_5^+$.

Example 103

(S)-N-(2-Fluoro-4-iodo-phenyl)-2-((R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl)-4-methanesulfonyl-butylamide



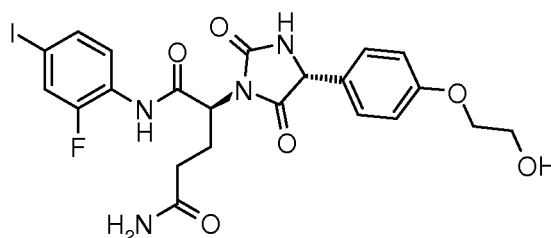
5

Prepared by the same method as described in example 43 except that (S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-4-methanesulfonyl-butylamide was used in place of (S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-3-naphthalen-2-yl-propionic acid in step 1.

10 LC-MS: Obs Mass ($M+H^+$), 620; Calcd. Mass, 620 for $C_{22}H_{24}FIN_3O_7S^+$.

Example 104

(S)-2-((R)-4-[4-(2-Hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl)-pentanedioic acid 5-amide 1-[(2-fluoro-4-iodo-phenyl)-amide]



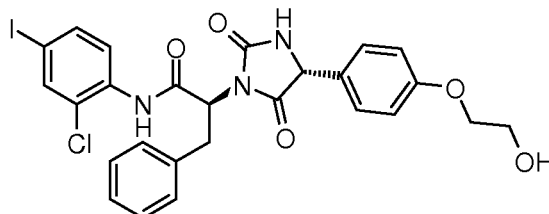
15

Prepared by the same method as described in example 72 except that (S)-2-tert-butoxycarbonylamino-4-carbamoyl-butylamide was used in place of (S)-2-tert-butoxycarbonylamino-3-thiophen-2-yl-propionic acid in step 1.

LC-MS: Obs Mass ($M+H^+$), 585; Calcd. Mass, 585 for $C_{22}H_{23}FIN_4O_6^+$.

Example 105

(S)-N-(2-Chloro-4-iodo-phenyl)-2-[(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-propionamide



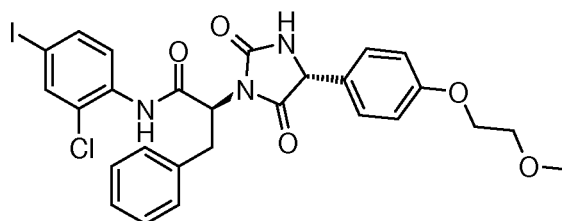
5

Prepared by the same method as described in example 3 except that (i) 2-chloro-4-iodo-aniline was used in place of 4-bromo-2-chloro-aniline in step 1, and (ii) (S)-2-*tert*-butoxycarbonylamino-3-phenyl-propionic acid was used in place of (S,S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid in step 1.

10 HRMS: Obs Mass ($M+H^+$), 620.0442. Calcd. Mass, 620.0444 for $C_{26}H_{24}ClIN_3O_5^+$.

Example 106

15 (S)-N-(2-Chloro-4-iodo-phenyl)-2-[(R)-4-[4-(2-methoxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-propionamide

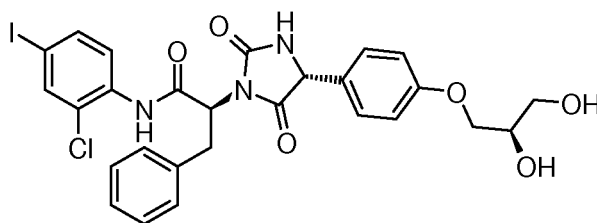


Prepared by the same method as described in example 3 except that (i) 2-chloro-4-iodo-aniline was used in place of 4-bromo-2-chloro-aniline in step 1, (ii) (S)-2-*tert*-butoxycarbonylamino-3-phenyl-propionic acid was used in place of (S,S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid in step 1, and (iii) (R)-*tert*-butoxycarbonylamino-[4-(2-methoxy-ethoxy)-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-[4-(2-*tert*-butoxy-ethoxy)-phenyl]-acetic acid in step 2. (R)-*tert*-butoxycarbonylamino-[4-(2-methoxy-ethoxy)-phenyl]-acetic acid was prepared as described in example 80.

25 HRMS: Obs Mass ($M+H^+$), 634.0602. Calcd. Mass, 634.0600 for $C_{27}H_{26}ClIN_3O_5^+$.

Example 107

(S)-N-(2-Chloro-4-iodo-phenyl)-2-[(R)-4-[4-((R)-2,3-dihydroxy-propoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-propionamide

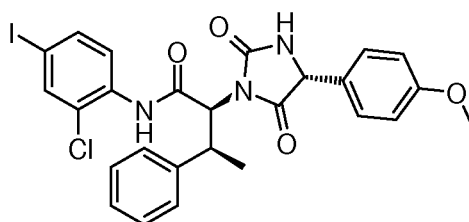


- 5 Prepared by the same method as described in example 3 except that (i) 2-chloro-4-iodo-aniline was used in place of 4-bromo-2-chloro-aniline in step 1, (ii) (S)-2-*tert*-butoxycarbonylamino-3-phenyl-propionic acid was used in place of (S,S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid in step 1, and (iii) (R)-*tert*-butoxycarbonylamino-[4-((S)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-[4-(2-*tert*-butoxyethoxy)-phenyl]-acetic acid in step 2. (R)-*tert*-Butoxycarbonylamino-[4-((S)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-acetic acid was prepared and used as described in example 114.

HRMS: Obs Mass ($M+H^+$), 650.0541. Calcd. Mass, 650.0550 for
 15 $C_{27}H_{26}ClIN_3O_6^+$.

Example 108

(2S,3S)-N-(2-Chloro-4-iodo-phenyl)-2-[(R)-4-(4-methoxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide

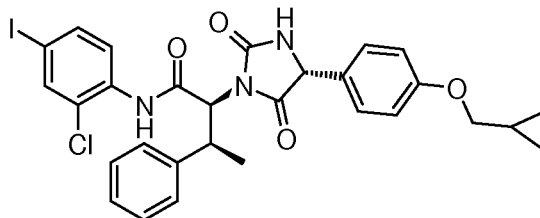


- 20 Prepared by the method as described in example 1 except that (i) 2-chloro-4-iodoaniline was used in place of 4-bromoaniline in step 2, and (ii) (3-dimethylamino-propyl)-ethyl-carbodiimide hydrochloride was used as the coupling reagent in place of *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate in step 4.

HRMS: Obs Mass ($M+H^+$), 604.0496. Calcd. Mass, 604.0495 for
 25 $C_{26}H_{24}ClIN_3O_4^+$.

Example 109

(2S,3S)-N-(2-Chloro-4-iodo-phenyl)-2-[(R)-4-(4-cyclopropylmethoxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butamide



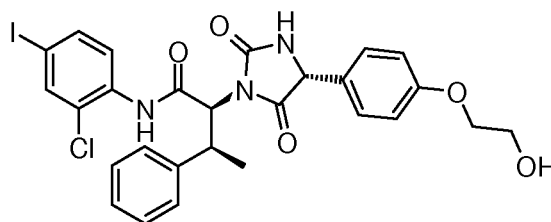
5

Prepared by the same method as described in example 3 except that 2-chloro-4-iodoaniline was used in place of 2-chloro-4-bromoaniline in step 1 and (R)-*tert*-butoxycarbonylamino-(4-cyclopropylmethoxy-phenyl)-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-[4-(2-*tert*-butoxy-ethoxy)-phenyl]-acetic acid in step 2. (R)-*tert*-butoxycarbonylamino-[4-(2-*tert*-butoxy-ethoxy)-phenyl]-acetic acid was prepared by a similar method as described for the preparation of (R)-*tert*-butoxycarbonylamino-{4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-acetic acid in example 48 except that cyclopropylmethyl bromide was used in place of 2-(2-bromo-ethoxy)-tetrahydropyran.

15 HRMS: Obs Mass ($M+H^+$), 644.0799. Calcd. Mass, 644.0808 for $C_{29}H_{28}ClIN_3O_4^+$.

Example 110

(2S,3S)-N-(2-Chloro-4-iodo-phenyl)-2-[(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butamide



25

Prepared by the same method as described in example 48 except that 2-chloro-4-iodoaniline was used in place of 2-fluoro-4-iodoaniline in step 2.

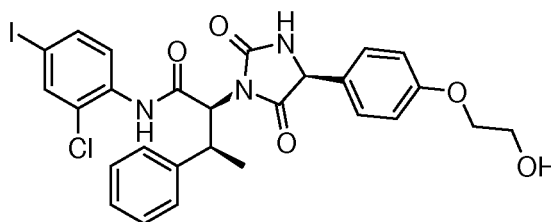
HRMS: Obs. Mass ($M+H^+$), 634.0597. Calcd. Mass, 634.0600 for $C_{27}H_{26}ClIN_3O_5^+$.

LC-MS (reverse phase HPLC, C18 column, water / acetonitrile gradient): R_t = 2.36 minutes, Obs. Mass ($M+Na^+$), 656. Calcd. Mass, 640 for $C_{27}H_{25}ClIN_3NaO_5^+$.

1H NMR (DMSO- d_6 , 300 MHz) δ_H 9.85 (s, 1H), 8.56 (s, 1H), 4.95 (d, J = 11.5 Hz, 1H) ppm (characteristic resonances).

Example 111

(2S,3S)-*N*-(2-Chloro-4-iodo-phenyl)-2-[(S)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butylamide



10

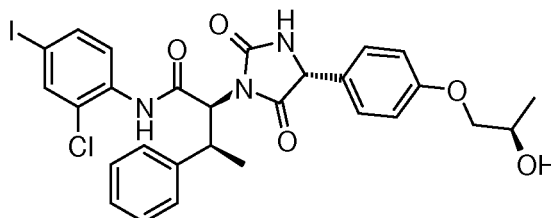
A solution of (2S,3S)-*N*-(2-chloro-4-iodo-phenyl)-2-[(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butylamide (prepared as described in example 110) (50 mg, 0.079 mmol) was dissolved in methanol (3 mL) and stirred at ambient temperature for 4 days. The resulting mixture of isomers was concentrated *in vacuo* and then purified by super-critical fluid chromatography using a Chiracel OJ column eluted with carbon dioxide at 100 bar and 30 °C modified with 35% v/v ethanol in acetonitrile eluted at 2 mL/minute. The first eluted compound was collected and concentrated *in vacuo* to obtain (2S,3S)-*N*-(2-chloro-4-iodo-phenyl)-2-[(S)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butylamide (14.6 mg, 29%) The compound eluted second was identical with (2S,3S)-*N*-(2-chloro-4-iodo-phenyl)-2-[(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butylamide (18.1 mg, 36%).

LC-MS (reverse phase HPLC, C18 column, water / acetonitrile gradient): R_t = 2.40 minutes, Obs. Mass ($M+Na^+$), 656. Calcd. Mass, 640 for $C_{27}H_{25}ClIN_3NaO_5^+$.

1H NMR (DMSO- d_6 , 300 MHz) δ_H 9.98 (s, 1H), 8.61 (s, 1H), 4.81 (d, J = 11.8 Hz, 1H) ppm (characteristic resonances).

Example 112

(2S,3S)-N-(2-Chloro-4-iodo-phenyl)-2-[(R)-4-[4-((R)-2-hydroxy-propoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide



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Prepared by the same method as described in example 3 except that (i) 2-chloro-4-iodo-aniline was used in place of 4-bromo-2-chloro-aniline in step 1, and (ii) (R)-*tert*-butoxycarbonylamino-[4-((R)-2-hydroxy-propoxy)-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-[4-(2-*tert*-butoxy-ethoxy)-phenyl]-acetic acid in step 2. (R)-*tert*-Butoxycarbonylamino-[4-((R)-2-hydroxy-propoxy)-phenyl]-acetic acid was prepared as described in example 48 except that (R)-2-methyl-oxirane was used in place of 2-(2-bromo-ethoxy)-tetrahydropyran.

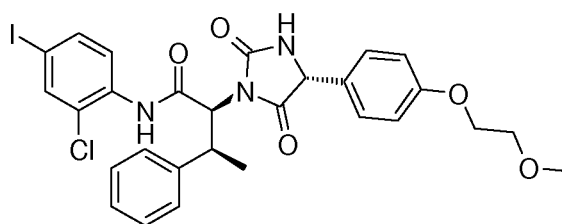
10

HRMS: Obs Mass ($M+H^+$), 648.0755. Calcd. Mass, 648.0757 for $C_{28}H_{28}ClIN_3O_5^+$.

15

Example 113

(2S,3S)-N-(2-Chloro-4-iodo-phenyl)-2-[(R)-4-[4-(2-methoxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide



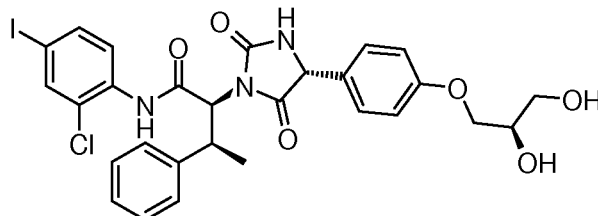
Prepared by the same method as described in example 3 except that (i) 2-chloro-4-iodo-aniline was used in place of 4-bromo-2-chloro-aniline in step 1, and (ii) (R)-*tert*-butoxycarbonylamino-[4-(2-methoxy-ethoxy)-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-[4-(2-*tert*-butoxy-ethoxy)-phenyl]-acetic acid in step 2. (R)-*tert*-Butoxycarbonylamino-[4-(2-methoxy-ethoxy)-phenyl]-acetic acid was prepared as described in example 80.

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HRMS: Obs Mass ($M+H^+$), 648.0746. Calcd. Mass, 648.0757 for $C_{28}H_{28}ClIN_3O_5^+$.

Example 114

(2S,3S)-N-(2-Chloro-4-iodo-phenyl)-2-[(R)-4-[4-((R)-2,3-dihydroxy-propoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide



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Prepared by the same method as described in example 110 except that (i) (R)-*tert*-butoxycarbonylamino-[4-((S)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-acetic acid (prepared as described below) was used in place of (R)-*tert*-butoxycarbonylamino-[4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl]-acetic acid in step 4, (ii) (2S, 3S)-2-[(R)-2-amino-2-[4-((R)-2,3-dihydroxy-propoxy)-phenyl]-acetylamino]-N-(2-chloro-4-iodo-phenyl)-3-phenyl-butyramide was temporarily protected as (2S, 3S)-2-[(R)-2-amino-2-[4-((S)-2,3-*bis*-trimethylsilanyloxy-propoxy)-phenyl]-acetylamino]-N-(2-chloro-4-iodo-phenyl)-3-phenyl-butyramide (performed as described below) prior to performing step 6, and (iii) acid catalyzed hydrolysis of (2S, 3S)-2-[(R)-4-[4-((S)-2,3-*bis*-trimethylsilanyloxy-propoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-N-(2-chloro-4-iodo-phenyl)-3-phenyl-butyramide (performed as described below) was performed prior to purification and isolation of (2S,3S)-N-(2-chloro-4-iodo-phenyl)-2-[(R)-4-[4-((R)-2,3-dihydroxy-propoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide in step 6.

20

Preparation of (R)-*tert*-butoxycarbonylamino-[4-((S)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-acetic acid:

(1) To a solution of (S)-2,2-dimethyl-1,3-dioxolane-4-methanol (5.22 g, 39.5 mmol) in dichloromethane (60 mL) at 0 °C under an atmosphere of dry argon were added triethylamine (11 mL, 79 mmol) and 2,5-dichlorosulfonyl chloride (10.18 g, 41.5 mmol) and the mixture left to stir and warm slowly to ambient temperature overnight. The reaction mixture was diluted with dichloromethane and washed with water. The aqueous layer was separated and washed once with dichloromethane. The combined organic layers were washed with saturated

30

aqueous sodium hydrogen carbonate solution (once), brine (once), dried over sodium sulfate, filtered and concentrated *in vacuo* to leave an oily residue. The residue was purified by chromatography over silica gel gradient eluted from 0 to 40% v/v ethyl acetate in hexanes to give (R)-2,5-dichloro-benzenesulfonic acid (R)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl ester as a colorless solid (11.06 g, 82%).

(2) To a stirred solution of (R)-*tert*-butoxycarbonylamino-(4-hydroxy-phenyl)-acetic acid (1.4 g, 5.24 mmol) in dry *N,N*-dimethylformamide (25 mL) at 0 °C under an atmosphere of dry argon was added sodium hydride (60% suspension in mineral oil) (290 mg, 0.12 mmol) and the mixture stirred at 0 °C for 15 minutes.

2,5-Dichloro-benzenesulfonic acid (R)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl ester (2.14 mmol, 6.29 mmol) was added to the reaction mixture to form a yellow solution which was stirred at ambient temperature for 5 minutes before warming to 100 °C for 10 minutes. The reaction mixture which by now contained a heavy precipitate was cooled to ambient temperature, diluted with ethyl acetate, cooled to 0 °C and treated with an equal volume of water. The stirred mixture was acidified to pH $\approx$ 4 with 1 M aqueous hydrochloric acid. The organic layer was separated and the aqueous layer extracted with ethyl acetate. The combined organic layers were washed with water (three times), dried over sodium sulfate, filtered through a thin pad of silica gel and concentrated *in vacuo* to give (R)-*tert*-butoxycarbonylamino-[4-((S)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-acetic acid as a pale yellow solid foam which was of adequate purity for subsequent use in step 4 without additional purification (1.96 g, 96%).

Preparation of (2S, 3S)-2-((R)-2-amino-2-[4-((S)-2,3-*bis*-trimethylsilyloxy-propoxy)-phenyl]-acetylamino)-*N*-(2-chloro-4-iodo-phenyl)-3-phenyl-butyramide:

To a solution of (2S, 3S)-2-((R)-2-amino-2-[4-((R)-2,3-dihydroxy-propoxy)-phenyl]-acetylamino)-*N*-(2-chloro-4-iodo-phenyl)-3-phenyl-butyramide (330 mg, 0.44 mmol) in dry, degassed tetrahydrofuran (5 mL) were added triethylamine (277 μ L, 1.98 mmol) and chlorotrimethylsilane (230 μ L, 1.76 mmol) and the mixture stirred at ambient temperature for 30 minutes. The resulting suspension was diluted with ethyl acetate (50 mL) and washed with brine (2 $\times$ 50 mL). The combined brine layers were back extracted with ethyl acetate (2 $\times$ 50 mL), the combined organic layers dried over sodium sulfate, filtered and concentrated *in vacuo* to give crude (2S, 3S)-2-((R)-2-amino-2-[4-((S)-2,3-*bis*-trimethylsilyloxy-

propoxy)-phenyl]-acetylamino}-*N*-(2-chloro-4-iodo-phenyl)-3-phenyl-butyramide which was of adequate purity for subsequent use in step 6 without additional purification (330 mg, 96%).

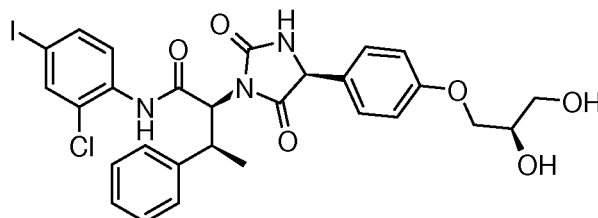
- 5 Hydrolysis of (2*S*, 3*S*)-2-[(*R*)-4-[4-[(*S*)-2,3-*bis*-trimethylsilyloxy-propoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-*N*-(2-chloro-4-iodo-phenyl)-3-phenyl-butyramide:

- Following cyclization of (2*S*, 3*S*)-2-[(*R*)-2-amino-2-[4-[(*S*)-2,3-*bis*-trimethylsilyloxy-propoxy)-phenyl]-acetylamino}-*N*-(2-chloro-4-iodo-phenyl)-3-phenyl-butyramide using a method similar to that described in example 6 crude (2*S*, 3*S*)-2-[(*R*)-4-[4-[(*S*)-2,3-*bis*-trimethylsilyloxy-propoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-*N*-(2-chloro-4-iodo-phenyl)-3-phenyl-butyramide was dissolved in ethyl acetate (50 mL) and mixed vigorously with 1:1 *v/v* 1M aqueous hydrochloric acid / brine at ambient temperature for 15 minutes to effect removal of the trimethylsilyl protecting groups. The layers were separated and the aqueous layer extracted with ethyl acetate (2 × 50 mL). The combined ethyl acetate layers were dried over sodium sulfate, filtered and concentrated *in vacuo* prior to final purification by chromatography over silica gel gradient eluted in 1% *v/v* steps between 100% dichloromethane and 3% methanol in dichloromethane.
- 20 After concentration *in vacuo* of the product containing fractions the glassy residue was dissolved in dichloromethane (0.5 mL), diluted with diethyl ether (2 mL) and hexanes (15 mL) added to precipitate (2*S*,3*S*)-*N*-(2-chloro-4-iodo-phenyl)-2-[(*R*)-4-[4-[(*R*)-2,3-dihydroxy-propoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide which was obtained as a colorless solid after filtration and drying *in vacuo* (72 mg, 25%).

HRMS: Obs. Mass, 664.0703. Calcd. Mass, 664.0706 for C₂₈H₂₈ClIN₃O₆⁺.

Example 115

(2S,3S)-*N*-(2-Chloro-4-iodo-phenyl)-2-{(S)-4-[4-((R)-2,3-dihydroxy-propoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl}-3-phenyl-butylamide



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The filtrate from the final purification step in the preparation of (2S,3S)-*N*-(2-chloro-4-iodo-phenyl)-2-{(R)-4-[4-((R)-2,3-dihydroxy-propoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl}-3-phenyl-butylamide (prepared as described in example 114) was enriched in (2S,3S)-*N*-(2-chloro-4-iodo-phenyl)-2-{(R)-4-[4-((R)-2,3-dihydroxy-propoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl}-3-phenyl-butylamide.

The diastereomers were separated by supercritical fluid chromatography using a Daicel OD column eluted with 45% v/v 1:1 acetonitrile / ethanol in carbon dioxide.

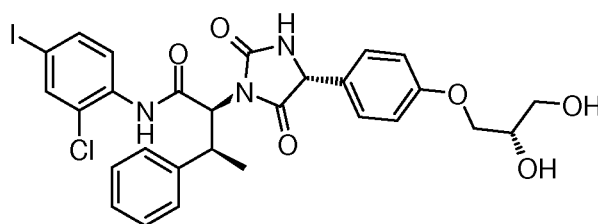
10

HRMS: Obs Mass ($M+H^+$), 664.0706. Calcd. Mass, 664.0706 for $C_{28}H_{28}ClIN_3O_6^+$.

15

Example 116

(2S,3S)-*N*-(2-Chloro-4-iodo-phenyl)-2-{(R)-4-[4-((S)-2,3-dihydroxy-propoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl}-3-phenyl-butylamide



Prepared by the same method as described in example 114 except that (R)-*tert*-butoxycarbonylamino-[4-((R)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-[4-((S)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-acetic acid in step 4. (R)-*tert*-butoxycarbonylamino-[4-((R)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-acetic acid was prepared by the same method as described for the preparation of (R)-*tert*-butoxycarbonylamino-[4-((S)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-

20

25

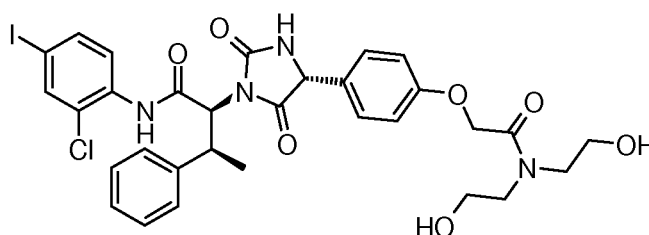
phenyl]-acetic acid in example 114 except that (R)-2,2-dimethyl-1,3-dioxolane-4-methanol was used in place of (S)-2,2-dimethyl-1,3-dioxolane-4-methanol.

HRMS: Obs. Mass ($M+H^+$), 664.0710. Calcd. Mass, 664.0706 for $C_{28}H_{28}ClIN_3O_6^+$.

5

Example 117

(2S,3S)-2-[(R)-4-(4-[[Bis-(2-hydroxy-ethyl)-carbamoyl]-methoxy]-phenyl)-2,5-dioxo-imidazolidin-1-yl]-N-(2-chloro-4-iodo-phenyl)-3-phenyl-butyramide



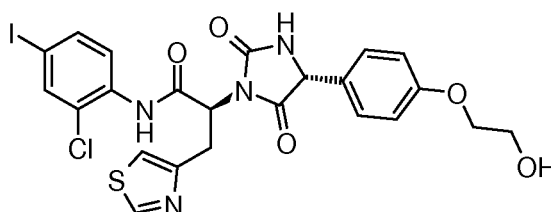
- 10 Prepared by the same method as described in example 109 except that (R)-[4-(2-{bis-[2-(*tert*-butyl-dimethyl-silanyloxy)-ethyl]-amino}-acetoxy)-phenyl]-*tert*-butoxycarbonylamino-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-(4-cyclopropylmethoxy-phenyl)-acetic acid. (R)-[4-(2-{Bis-[2-(*tert*-butyl-dimethyl-silanyloxy)-ethyl]-amino}-acetoxy)-phenyl]-*tert*-
- 15 butoxycarbonylamino-acetic acid was prepared as described in example 48 except that *N,N*-bis-[2-(*tert*-butyl-dimethyl-silanyloxy)-ethyl]-2-chloro-acetamide was used in place of 2-(2-bromo-ethoxy)-tetrahydropyran.

HRMS: Obs Mass ($M+Na^+$), 757.0898. Calcd. Mass, 757.0896 for $C_{31}H_{32}ClIN_4NaO_7^+$.

20

Example 118

(S)-N-(2-Chloro-4-iodo-phenyl)-2-{(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl}-3-thiazol-4-yl-propionamide



- 25 Prepared by the same method as described in example 3 except that (i) 2-chloro-4-iodo-aniline was used in place of 4-bromo-2-chloro-aniline in step 1, and (ii)

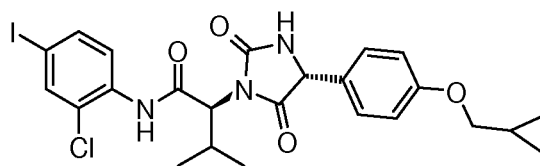
(S)-2-*tert*-butoxycarbonylamino-3-thiazol-4-yl-propionic acid was used in place of (2S, 3S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid in step 1.

HRMS: Obs Mass ($M+H^+$), 626.9964. Calcd. Mass, 626.9961 for $C_{23}H_{21}ClIN_4O_5S^+$.

5

Example 119

(S)-*N*-(2-Chloro-4-iodo-phenyl)-2-[(R)-4-(4-cyclopropylmethoxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-3-methyl-butylamide



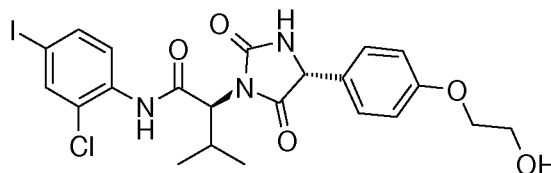
- 10 Prepared by the same method as described in example 3 except that (i) 2-chloro-4-iodo-aniline was used in place of 4-bromo-2-chloro-aniline in step 1, (ii) (S)-2-*tert*-butoxycarbonylamino-3-methyl-butyric acid was used in place of (S, S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid in step 1, and (iii) (R)-*tert*-butoxycarbonylamino-(4-cyclopropylmethoxy-phenyl)-acetic acid (prepared as
15 described in example 109) was used in place of (R)-*tert*-butoxycarbonylamino-[4-(2-*tert*-butoxy-ethoxy)-phenyl]-acetic acid in step 2.

HRMS: Obs Mass ($M+H^+$), 582.0655. Calcd. Mass, 582.0651 for $C_{24}H_{26}ClIN_3O_4^+$.

20

Example 120

(S)-*N*-(2-Chloro-4-iodo-phenyl)-2-[(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-methyl-butylamide

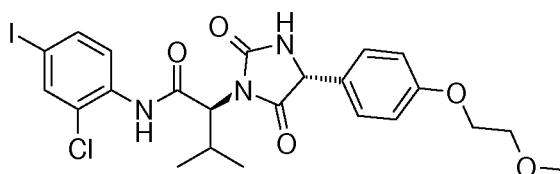


- Prepared by the same method as described in example 119 except that (R)-*tert*-
25 butoxycarbonylamino-{4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-(4-cyclopropylmethoxy-phenyl)-acetic acid. (R)-*tert*-butoxycarbonylamino-{4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-acetic acid was prepared as described in example 48.

HRMS: Obs Mass ($M+H^+$), 572.0433. Calcd. Mass, 572.0444 for $C_{22}H_{24}ClIN_3O_5^+$.

Example 121

- 5 (S)-N-(2-Chloro-4-iodo-phenyl)-2-((R)-4-[4-(2-methoxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl)-3-methyl-butylamide



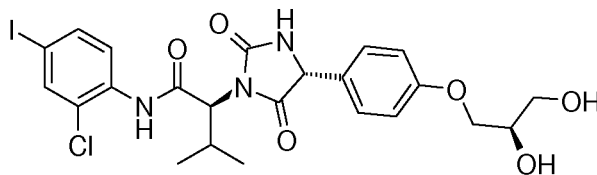
- Prepared by the same method as described in example 119 except that (R)-*tert*-butoxycarbonylamino-[4-(2-methoxy-ethoxy)-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-(4-cyclopropylmethoxy-phenyl)-acetic acid. (R)-*tert*-butoxycarbonylamino-[4-(2-methoxy-ethoxy)-phenyl]-acetic acid was prepared as described in example 80.

HRMS: Obs Mass ($M+H^+$), 586.0586. Calcd. Mass, 586.0600 for $C_{23}H_{26}ClIN_3O_5^+$.

15

Example 122

- (S)-N-(2-Chloro-4-iodo-phenyl)-2-((R)-4-[4-((R)-2,3-dihydroxy-propoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl)-3-methyl-butylamide

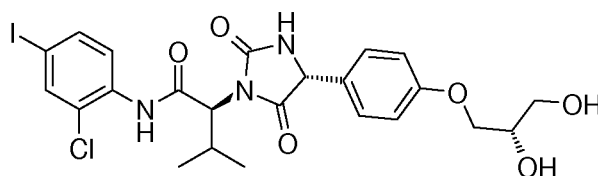


- Prepared by the same method as described in example 3 except that (i) 2-chloro-4-iodoaniline was used in place of 4-bromo-2-chloroaniline in step 1, (ii) (S)-2-*tert*-butoxycarbonylamino-3-methyl-butylamide was used in place of (2S, 3S)-2-*tert*-butoxycarbonylamino-3-phenyl-butylamide in step 1, and (iii) (R)-*tert*-butoxycarbonylamino-[4-((S)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-[4-(2-*tert*-butoxy-ethoxy)-phenyl]-acetic acid in step 2. (R)-*tert*-Butoxycarbonylamino-[4-((S)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-acetic acid was prepared and used as described in example 114.

HRMS: Obs Mass ($M+Na^+$), 624.0367. Calcd. Mass, 624.0369 for $C_{23}H_{25}ClIN_3NaO_6^+$.

Example 123

- 5 (S)-N-(2-Chloro-4-iodo-phenyl)-2-[(R)-4-[4-((S)-2,3-dihydroxy-propoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-methyl-butylamide



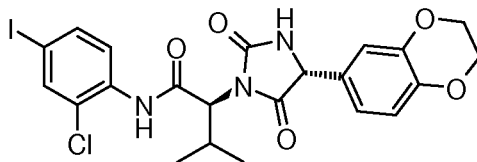
- Prepared by the same method as described in example 3 except that (i) 2-chloro-4-iodoaniline was used in place of 4-bromo-2-chloroaniline in step 1, (ii) (S)-2-*tert*-butoxycarbonylamino-3-methyl-butyl acid was used in place (2S, 3S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyl acid in step 1, and (iii) (R)-*tert*-butoxycarbonylamino-[4-((R)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-[4-(2-*tert*-butoxyethoxy)-phenyl]-acetic acid in step 2. (R)-*tert*-Butoxycarbonylamino-[4-((R)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-acetic acid was prepared and used as described in example 116.

HRMS: Obs Mass ($M+H^+$), 602.0541. Calcd. Mass, 602.0550 for $C_{23}H_{26}ClIN_3O_6^+$.

20

Example 124

- (S)-N-(2-Chloro-4-iodo-phenyl)-2-[(R)-4-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-2,5-dioxo-imidazolidin-1-yl]-3-methyl-butylamide

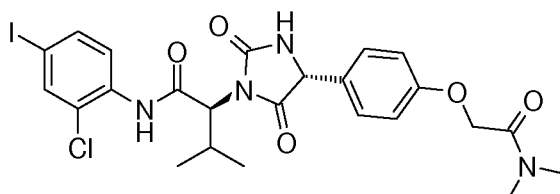


- Prepared by the same method as described in example 119 except that (R)-*tert*-butoxycarbonylamino-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-(4-cyclopropylmethoxy-phenyl)-acetic acid. (R)-*tert*-Butoxycarbonylamino-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-acetic acid was prepared as described in example 29.

HRMS: Obs Mass ($M+H^+$), 570.0277. Calcd. Mass, 570.0287 for $C_{22}H_{22}ClIN_3O_5^+$.

Example 125

- 5 (S)-N-(2-Chloro-4-iodo-phenyl)-2-[(R)-4-(4-dimethylcarbamoylmethoxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-3-methyl-butamide

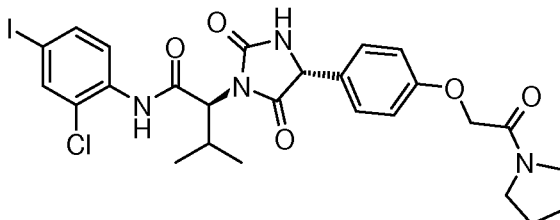


- Prepared by the same method as described in example 119 except that (R)-*tert*-butoxycarbonylamino-(4-dimethylcarbamoylmethoxy-phenyl)-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-(4-cyclopropylmethoxy-phenyl)-acetic acid. (R)-*tert*-Butoxycarbonylamino-(4-dimethylcarbamoylmethoxy-phenyl)-acetic acid was prepared by the same method as used for the preparation of (R)-*tert*-butyloxycarbonylamino-4-methoxyphenylglycine in example 1 except that 2-chloro-*N,N*-dimethyl-acetamide was used in place of iodomethane.

HRMS: Obs Mass ($M+H^+$), 613.0703. Calcd. Mass, 613.0709 for $C_{24}H_{27}ClIN_4O_5^+$.

Example 126

- 20 (S)-N-(2-Chloro-4-iodo-phenyl)-2-[(R)-2,5-dioxo-4-[4-(2-oxo-2-pyrrolidin-1-yl-ethoxy)-phenyl]-imidazolidin-1-yl]-3-methyl-butamide



- Prepared by the same method as described in example 119 except that (R)-*tert*-butoxycarbonylamino-[4-(2-oxo-2-pyrrolidin-1-yl-ethoxy)-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-(4-cyclopropylmethoxy-phenyl)-acetic acid. (R)-*tert*-Butoxycarbonylamino-[4-(2-oxo-2-pyrrolidin-1-yl-ethoxy)-phenyl]-acetic acid was prepared by the same method as used for the

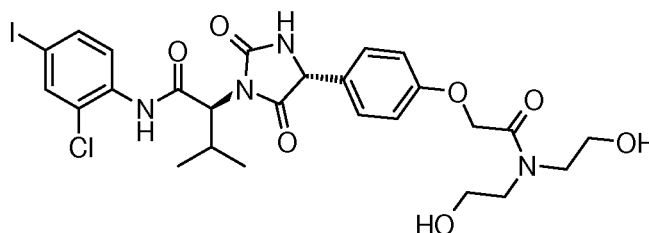
preparation of (R)-*tert*-butoxycarbonylamino-4-methoxyphenylglycine in example 1 except that 2-chloro-1-pyrrolidin-1-yl-ethanone was used in place of iodomethane.

HRMS: Obs Mass ($M+H^+$), 639.0864. Calcd. Mass, 639.0866 for

5 $C_{26}H_{29}ClIN_4O_5^+$.

Example 127

(S)-2-[(R)-4-(4-{[*Bis*-(2-hydroxy-ethyl)-carbamoyl]-methoxy}-phenyl)-2,5-dioxo-imidazolidin-1-yl]-*N*-(2-chloro-4-iodo-phenyl)-3-methyl-butylamide



10

Prepared by the same method as described in example 119 except that (R)-[4-(2-{*bis*-[2-(*tert*-butyl-dimethyl-silanyloxy)-ethyl]-amino}-acetoxo)-phenyl]-*tert*-butoxycarbonylamino-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-(4-cyclopropylmethoxy-phenyl)-acetic acid. (R)-[4-(2-{*Bis*-

15 [2-(*tert*-butyl-dimethyl-silanyloxy)-ethyl]-amino}-acetoxo)-phenyl]-*tert*-butoxycarbonylamino-acetic acid was prepared as described in example 62.

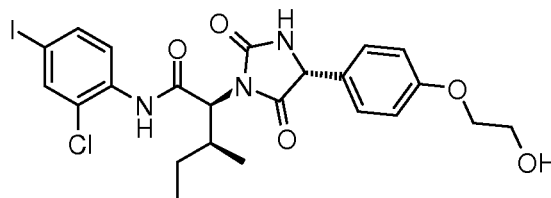
HRMS: Obs Mass ($M+Na^+$), 695.0739. Calcd. Mass, 695.0740 for

$C_{26}H_{30}ClIN_4NaO_7^+$.

20

Example 128

(2S,3S)-2-{(R)-4-[4-(2-Hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl}-3-methyl-pentanoic acid (2-chloro-4-iodo-phenyl)-amide



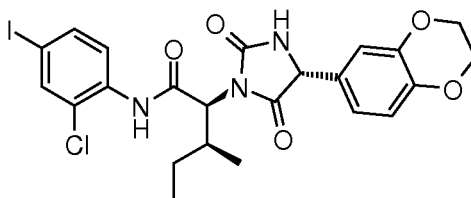
Prepared by the same method as described in example 3 except that 2-chloro-4-iodoaniline was used in place of 4-bromo-2-chloroaniline and (2S, 3S)-2-*tert*-butoxycarbonylamino-3-methyl-pentanoic acid was used in place of (2S, 3S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid in step 1.

25

HRMS: Obs Mass ($M+H^+$), 586.0603. Calcd. Mass, 586.0600 for $C_{23}H_{26}ClIN_3O_5^+$.

Example 129

- 5 (2S,3S)-2-[(R)-4-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-2,5-dioxo-imidazolidin-1-yl]-3-methyl-pentanoic acid (2-chloro-4-iodo-phenyl)-amide



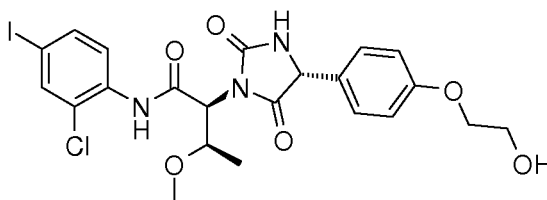
- Prepared by the same method as described in example 128 except that (R)-*tert*-butoxycarbonylamino-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-acetic acid was used in
10 place of (R)-*tert*-butoxycarbonylamino-[4-(2-*tert*-butoxy-ethoxy)-phenyl]-acetic acid. (R)-*tert*-Butoxycarbonylamino-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-acetic acid was prepared as described in example 29.

HRMS: Obs Mass ($M+H^+$), 584.0438. Calcd. Mass, 584.0444 for $C_{23}H_{24}ClIN_3O_5^+$.

15

Example 130

- (2S,3R)-N-(2-Chloro-4-iodo-phenyl)-2-[(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-methoxy-butamide

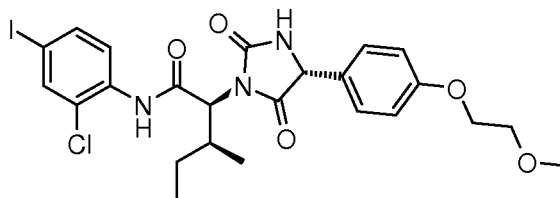


- 20 Prepared by the same method as described in example 72 except that 2-fluoro-4-iodoaniline was used in place of 2-chloro-4-iodoaniline and (2S, 3R)-2-*tert*-butoxycarbonylamino-3-methoxy-butyric acid was used in place of (S)-2-*tert*-butoxycarbonylamino-3-thiophen-2-yl-propionic acid in step 1.

LC-MS: Obs Mass ($M+H^+$), 588; Calcd. Mass, 588 for $C_{22}H_{24}ClIN_3O_6^+$.

Example 131

(2S,3S)-2-[(R)-4-[4-(2-Methoxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-methyl-pentanoic acid (2-chloro-4-iodo-phenyl)-amide



5

Prepared by the same method as described in example 3 except that (i) 2-chloro-4-iodoaniline was used in place of 4-bromo-2-chloroaniline in step 1, (ii) (2S, 3S)-2-*tert*-butoxycarbonylamino-3-methyl-pentanoic acid was used in place (2S, 3S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid in step 1, and (iii) (R)-*tert*-butoxycarbonylamino-[4-(2-methoxy-ethoxy)-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-[4-(2-*tert*-butoxy-ethoxy)-phenyl]-acetic acid in step 2. (R)-*tert*-Butoxycarbonylamino-[4-(2-methoxy-ethoxy)-phenyl]-acetic acid was prepared as described in example 80.

10

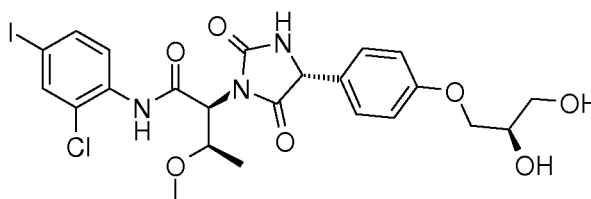
HRMS: Obs Mass ($M+H^+$), 600.0758. Calcd. Mass, 600.0757 for

15

$C_{24}H_{28}ClIN_3O_5^+$.

Example 132

(2S,3R)-N-(2-Chloro-4-iodo-phenyl)-2-[(R)-4-[4-((R)-2,3-dihydroxy-propoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-methoxy-butyramide



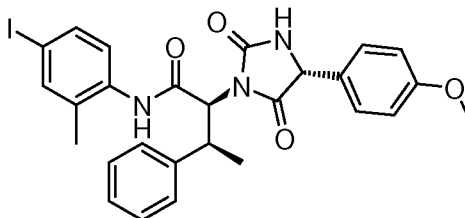
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Prepared by the same method as described in example 114 except that (i) (2S, 3R)-2-*tert*-butoxycarbonylamino-3-methoxy-butyric acid was used in place (2S, 3S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid.

LC-MS: Obs Mass ($M+H^+$), 618; Calcd. Mass, 618 for $C_{23}H_{26}ClIN_3O_7^+$.

Example 133

(2S,3S)-N-(4-Iodo-2-methyl-phenyl)-2-[(R)-4-(4-methoxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide



5

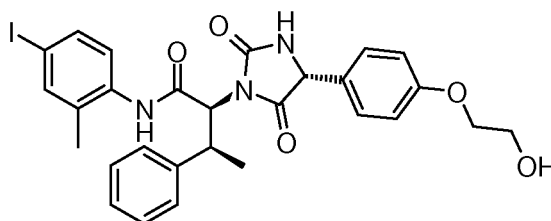
Prepared by the same method as described in example 1 except that 4-iodo-2-methyl-aniline was used in place of 4-bromoaniline in step 2.

HRMS: Obs Mass ($M+H^+$), 584.1042. Calcd. Mass, 584.1041 for $C_{27}H_{27}IN_3O_4^+$.

10

Example 134

(2S,3S)-2-[(R)-4-[4-(2-Hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-N-(4-iodo-2-methyl-phenyl)-3-phenyl-butyramide



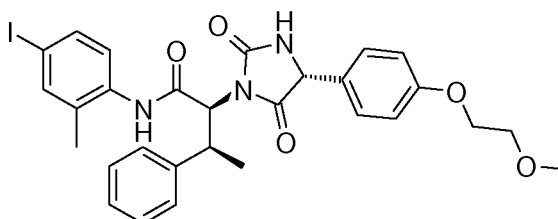
15 Prepared by the same method as described in example 48 except that 4-iodo-2-methylaniline was used in place of 2-fluoro-4-iodoaniline in step 2.

HRMS: Obs. Mass ($M+H^+$), 614.1135. Calcd. Mass, 614.1147 for $C_{28}H_{29}IN_3O_5^+$.

20

Example 135

(2S,3S)-N-(4-Iodo-2-methyl-phenyl)-2-[(R)-4-[4-(2-methoxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide



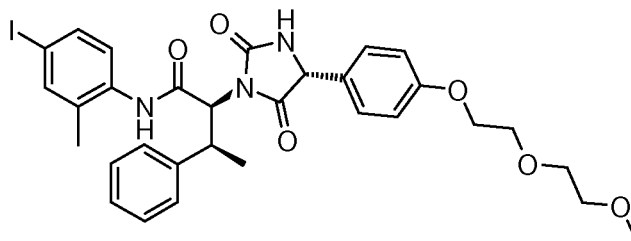
Prepared by the same method as described in example 48 except that (i) 4-iodo-2-methylaniline was used in place of 2-fluoro-4-iodoaniline in step 2, and (ii) (R)-*tert*-butoxycarbonylamino-[4-(2-methoxy-ethoxy)-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-{4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-acetic acid. (R)-*tert*-Butoxycarbonylamino-[4-(2-methoxy-ethoxy)-phenyl]-acetic acid was prepared as described in example 80.

HRMS: Obs Mass ($M+H^+$), 628.1293. Calcd. Mass, 628.1303 for $C_{29}H_{31}IN_3O_5^+$.

10

Example 136

(2S,3S)-N-(4-iodo-2-methyl-phenyl)-2-((R)-4-{4-[2-(2-methoxy-ethoxy)-ethoxy]-phenyl}-2,5-dioxo-imidazolidin-1-yl)-3-phenyl-butylamide



15

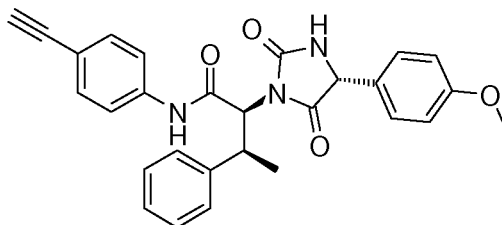
Prepared by the same method as described in example 48 except that (i) 4-iodo-2-methylaniline was used in place of 2-fluoro-4-iodoaniline in step 2, and (ii) (R)-*tert*-butoxycarbonylamino-[4-(2-{2-methoxy-ethoxy}-ethoxy)-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-{4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-acetic acid. (R)-*tert*-Butoxycarbonylamino-[4-(2-{2-methoxy-ethoxy}-ethoxy)-phenyl]-acetic acid was prepared as described in example 48 except that 1-(2-bromo-ethoxy)-2-methoxy-ethane was used in place of 2-(2-bromo-ethoxy)-tetrahydropyran.

20

HRMS: Obs Mass ($M+H^+$), 672.1556. Calcd. Mass, 672.1565 for $C_{31}H_{35}IN_3O_6^+$.

Example 137

(2S,3S)-N-(4-Ethynyl-phenyl)-2-[(R)-4-(4-methoxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butamide



5

Prepared by the same method as described in example 1 except that (i) 4-ethynylaniline was used in place of 4-bromoaniline in step 2, (ii) (3-dimethylamino-propyl)-ethyl-carbodiimide hydrochloride was used as the coupling reagent in place of *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate in step 4, and (iii) formic acid was used to cleave the tert-butylloxycarbonyl protecting group in steps 3 and 5 as described below.

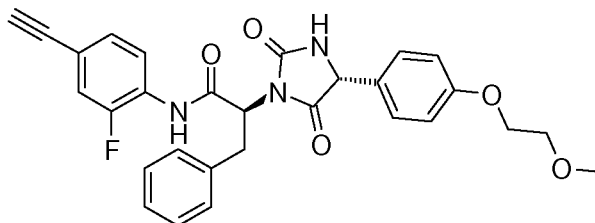
Preparation of (2S,3S)-2-amino-*N*-(4-ethynyl-phenyl)-3-phenyl-butamide:
A suspension of [(1S,2S)-1-(4-ethynyl-phenylcarbonyl)-2-phenyl-propyl]-carbamic acid *tert*-butyl ester (300 mg, 0.79 mmol) in formic acid (5 mL) was heated to 50 °C for 1 hour. The reaction was concentrated *in vacuo*, basified with saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were washed with water, brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to give (2S,3S)-2-amino-*N*-(4-ethynyl-phenyl)-3-phenyl-butamide as a foam (214 mg, 92%).

20

HRMS: Obs Mass ($M+Na^+$), 490.1731. Calcd. Mass, 490.1737 for $C_{28}H_{25}N_3NaO_4^+$.

Example 138

(S)-N-(4-Ethynyl-2-fluoro-phenyl)-2-((R)-4-[4-(2-methoxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl)-3-phenyl-propionamide



5

Prepared by the same method as described in example 140 except that (2S)-2-*tert*-butoxycarbonylamino-3-phenyl-propanoic acid was used in place of (2S, 3S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid and (R)-*tert*-butoxycarbonylamino-[4-(2-methoxy-ethoxy)-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-{4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-acetic acid. (R)-*tert*-Butoxycarbonylamino-[4-(2-methoxy-ethoxy)-phenyl]-acetic acid was prepared as described in example 80.

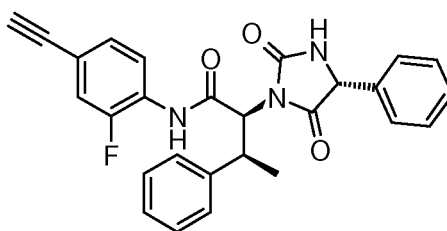
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HRMS: Obs Mass ($M+H^+$), 516.1932. Calcd. Mass, 516.1929 for $C_{29}H_{27}FN_3O_5^+$.

15

Example 139

(2S,3S)-2-((R)-2,5-Dioxo-4-phenyl-imidazolidin-1-yl)-N-(4-ethynyl-2-fluoro-phenyl)-3-phenyl-butyramide



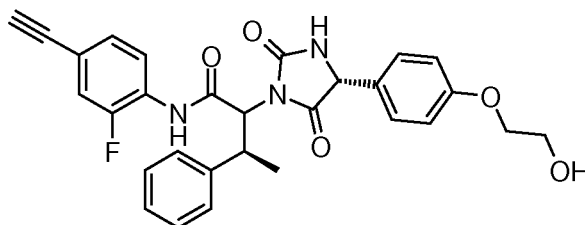
20

Prepared by the same method as described in example 140 except that (R)-*tert*-butoxycarbonylamino-phenyl-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-{4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-acetic acid.

HRMS: Obs Mass ($M+Na^+$), 478.1529. Calcd. Mass, 478.1537 for $C_{27}H_{22}FN_3NaO_3^+$.

Example 140

(3S)-N-(4-Ethynyl-2-fluoro-phenyl)-2-[(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide, isomer 1



5

Prepared by the same method as described in example 48 except that (i) after step 3, and prior to step 4, (2S, 3S)-2-amino-N-(2-fluoro-4-iodo-phenyl)-3-phenyl-butyramide was converted to (2S, 3S)-2-amino-N-(2-fluoro-4-trimethylsilanylethynyl-phenyl)-3-phenyl-butyramide under the conditions described below, and (ii) after initial purification in step 6 the product was subjected to chiral HPLC separation as described below. The trimethylsilyl group introduced in step 3 was subsequently removed during step 5 of the synthesis, concomitant with removal of the *tert*-butoxycarbonyl protecting group.

15 Preparation of (2S, 3S)-2-amino-N-(4-ethynyl-2-fluoro-phenyl)-3-phenyl-butyramide:

A solution of (2S, 3S)-2-amino-N-(2-fluoro-4-iodo-phenyl)-3-phenyl-butyramide (1.00 g, 2.51 mmol) in triethylamine (1.5 mL, 10.8 mmol) was thoroughly degassed with argon, *bis*-dichlorotriphenylphosphine palladium(II) (20.3 mg, 0.05 mmol) added followed by copper iodide (9.8 mg, 0.05 mmol) and trimethylsilylacetylene (277 mg, 2.77 mmol) and the mixture stirred under argon at ambient temperature for 3 hours. Additional triethylamine (1.5 mL, 10.8 mmol) was added to form a stirrable reaction mixture and stirring continued for an additional 20 hours. The reaction mixture was diluted with diethyl ether and a small amount of Celite added prior to filtration through Celite. The Celite was eluted with diethyl ether (4 × 20 mL) and the combined organic filtrates concentrated *in vacuo*. The resulting green oil was dissolved in a small amount of diethyl ether and diluted with hexanes (10 mL) to induce crystallization. The product was isolated by filtration, washed with hexanes and dried *in vacuo* to afford (2S, 3S)-2-amino-N-(2-fluoro-4-trimethylsilanylethynyl-phenyl)-3-phenyl-

30

butyramide as a grey solid (610 mg, 66%). A second crop of product was obtained by reprocessing of the mother liquors from the initial crystallization (168 mg, 18%).

HRMS: Obs. Mass, 369.1793. Calcd. Mass, 369.1793 for $C_{21}H_{26}FN_2OSi^+$.

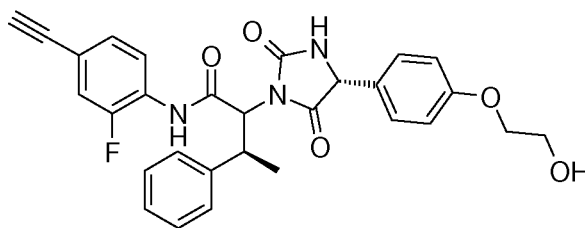
5 Chiral HPLC separation:

A sample of (3S)-N-(4-ethynyl-2-fluoro-phenyl)-2-[(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butylamide (22 mg, 0.43 mmol) was purified by chiral HPLC using a 2.0 cm $\times$ 25 cm Daicel OD column eluted with 1:1 v/v hexanes in absolute ethanol at 5 mL per minute using UV detection at 260 nm to monitor the eluant for presence of product. The first eluted product was collected and concentrated *in vacuo* to afford (3S)-N-(4-ethynyl-2-fluoro-phenyl)-2-[(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butylamide, isomer 1 as a white solid (6.1 mg, 28%).

15 HRMS: Obs. Mass ($M+H^+$), 516.1926. Calcd. Mass, 516.1929 for $C_{29}H_{27}FN_3O_5^+$.

Example 141

(3S)-N-(4-Ethynyl-2-fluoro-phenyl)-2-[(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butylamide, isomer 2

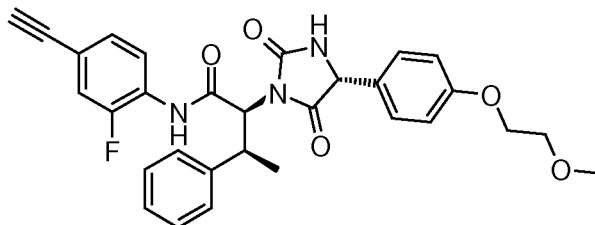


Prepared by the same method as described in example 140 except that the second eluted product from the chiral HPLC purification step was collected and concentrated *in vacuo* to afford (3S)-N-(4-ethynyl-2-fluoro-phenyl)-2-[(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butylamide, isomer 2 as a colorless solid (7 mg, 32%).

HRMS: Obs. Mass ($M+H^+$), 516.1931. Calcd. Mass, 516.1929 for $C_{29}H_{27}FN_3O_5^+$.

Example 142

(3S)-N-(4-Ethynyl-2-fluoro-phenyl)-2-[(R)-4-[4-(2-methoxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide, isomer 1



5

Prepared by the same method as described in example 140 except that (R)-*tert*-butoxycarbonylamino-[4-(2-methoxy-ethoxy)-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-{4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-acetic acid. (R)-*tert*-Butoxycarbonylamino-[4-(2-methoxy-ethoxy)-phenyl]-acetic acid was prepared as described in example 80. Purification of the final product was performed by chromatography over silica gel gradient eluted with 0 to 30% v/v ethyl acetate in hexanes. The first eluted product was collected and concentrated *in vacuo*, then precipitated from ethyl ether (1 mL) containing a small amount of dichloromethane with hexanes (10 mL). The precipitated solid was collected by filtration and dried to afford (3S)-N-(4-ethynyl-2-fluoro-phenyl)-2-[(R)-4-[4-(2-methoxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide, isomer 1 as a colorless solid (19%).

10

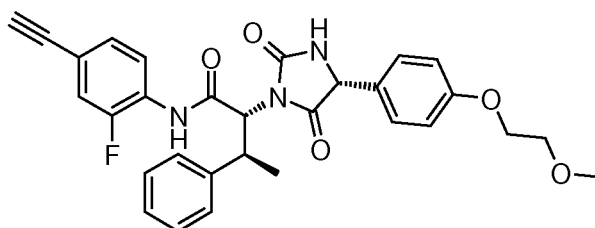
15

HRMS: Obs Mass ($M+Na^+$), 552.1905. Calcd. Mass, 552.1905 for $C_{30}H_{28}FN_3NaO_5^+$.

20

Example 143

(3S)-N-(4-Ethynyl-2-fluoro-phenyl)-2-[(R)-4-[4-(2-methoxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide, isomer 2



25

Prepared by the same method as described in example 142 except that the second eluted product from the chromatographic purification of the final reaction

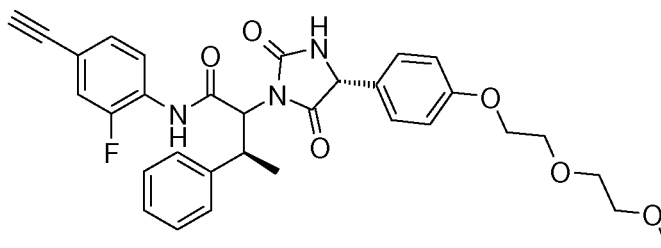
product was collected. The second eluted product was collected and concentrated *in vacuo*, then precipitated from ethyl ether (1 mL) containing a small amount of dichloromethane with hexanes (10 mL). The precipitated solid was collected by filtration and dried to afford (3S)-N-(4-ethynyl-2-fluoro-phenyl)-2-((R)-4-[4-(2-methoxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl)-3-phenyl-butylamide, isomer 2 as a colorless solid (10%).

HRMS: Obs Mass ($M+Na^+$), 552.1906. Calcd. Mass, 552.1905 for $C_{30}H_{28}FN_3NaO_5^+$.

10

Example 144

(S)-N-(4-Ethynyl-2-fluoro-phenyl)-2-((R)-4-{4-[2-(2-methoxy-ethoxy)-ethoxy]-phenyl}-2,5-dioxo-imidazolidin-1-yl)-3-phenyl-butylamide

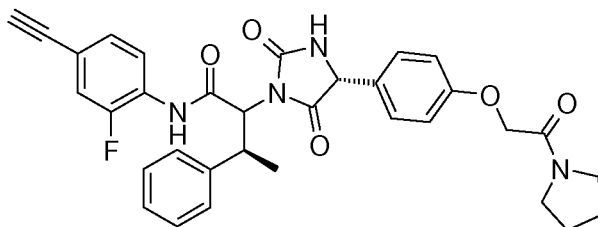


Prepared by the same method as described in example 140 except that (R)-*tert*-butoxycarbonylamino-{4-[2-(2-methoxy-ethoxy)-ethoxy]-phenyl}-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-{4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-acetic acid. (R)-*tert*-Butoxycarbonylamino-{4-[2-(2-methoxy-ethoxy)-ethoxy]-phenyl}-acetic acid was prepared as described in example 48 except that 1-(2-bromo-ethoxy)-2-methoxy-ethane was used in place of 2-(2-bromo-ethoxy)-tetrahydropyran.

HRMS: Obs Mass ($M+Na^+$), 596.2168. Calcd. Mass, 596.2167 for $C_{32}H_{32}FN_3NaO_6^+$.

Example 145

(2S,3S)-2-[(R)-2,5-Dioxo-4-[4-(2-oxo-2-pyrrolidin-1-yl-ethoxy)-phenyl]-imidazolidin-1-yl]-N-(4-ethynyl-2-fluoro-phenyl)-3-phenyl-butyramide



5

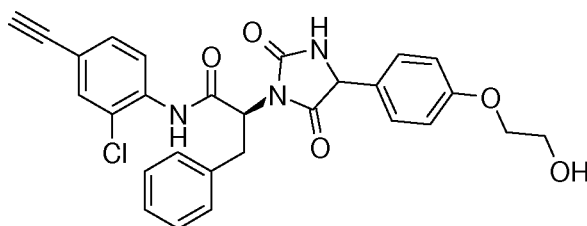
Prepared by the same method as described in example 140 except that (R)-*tert*-butoxycarbonylamino-[4-(2-oxo-2-pyrrolidin-1-yl-ethoxy)-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-{4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-acetic acid. (R)-*tert*-Butoxycarbonylamino-[4-(2-oxo-2-pyrrolidin-1-yl-ethoxy)-phenyl]-acetic acid was prepared as described in example 126.

10

HRMS: Obs Mass ($M+H^+$), 583.2352. Calcd. Mass, 583.2351 for $C_{33}H_{32}FN_4O_5^+$.

Example 146

(S)-N-(2-Chloro-4-ethynyl-phenyl)-2-{4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl}-3-phenyl-propionamide, isomer 1



15

20

Prepared as described below starting from (S)-2-amino-(2-chloro-4-iodo-phenyl)-3-phenyl-propionamide. (S)-2-Amino-(2-chloro-4-iodo-phenyl)-3-phenyl-propionamide was prepared by the same method as described in step 1 of example 3 except that 2-chloro-4-iodo-aniline was used in place of 4-bromo-2-chloro-aniline and (S)-2-*tert*-butoxycarbonylamino-3-phenyl-propionic acid was used in place of (S, S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid.

25

Step 2: To a dry flask were added (S)-2-amino-(2-chloro-4-iodo-phenyl)-3-phenyl-propionamide (980 mg, 2.44 mmol), *bis*-dichlorotriphenylphosphine palladium (19.8 mg, 0.0489 mmol), and copper iodide (9.5 mg, 0.049 mmol). To

this mixture was added trimethylsilylacetylene (269.7 mg, 2.69 mmol) in dry triethylamine (1.46 mL). Dry dichloromethane (1 mL) was added after 30 minutes. After 3 hours additional *bis*-dichlorotriphenylphosphine palladium (40 mg, 0.099 mmol) and copper iodide (20 mg, 0.099 mmol) were added. After 1
5 hour the reaction mixture was diluted with a 1:1 v/v mixture of diethyl ether / dichloromethane and passed through a bed of silica gel and the silica gel then eluted with a 2:3 v/v mixture of diethyl ether / dichloromethane. The eluant was concentrated *in vacuo* and the crude residue was purified by chromatography over silica gel gradient eluted with 5 to 30% v/v diethyl ether in hexanes. The
10 pooled fractions containing product were concentrated to give (S)-2-amino-*N*-(2-chloro-4-trimethylsilanylethynyl-phenyl)-3-phenyl-propionamide as a white solid (820 mg 90% yield).

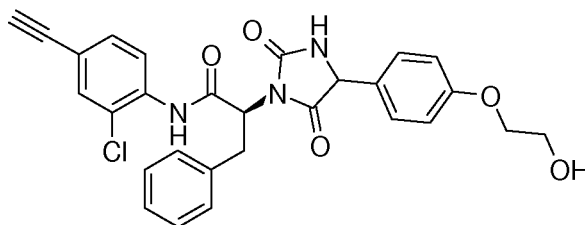
Step 3: (S)-2-Amino-*N*-(2-chloro-4-trimethylsilanylethynyl-phenyl)-3-phenyl-propionamide was coupled to (R)-*tert*-butoxycarbonylamino-{4-[2-(tetrahydro-
15 pyran-2-yloxy)-ethoxy]-phenyl}-acetic acid (prepared as described in example 48) using the same method as described in step 4 of example 1 to give ((S)-[(S)-1-(2-chloro-4-trimethylsilanylethynyl-phenylcarbamoyl)-2-phenyl-ethylcarbamoyl]-
{4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-methyl)-carbamic acid *tert*-butyl ester.

20 Step 4: ((S)-[(S)-1-(2-Chloro-4-trimethylsilanylethynyl-phenylcarbamoyl)-2-phenyl-ethylcarbamoyl]-{4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-methyl)-carbamic acid *tert*-butyl ester. (491 mg, 0.656 mmol) was dissolved into formic acid (7.1 mL) and heated for 30 minutes at 40 °C. The temperature was then increased to between 50 and 55 °C for 3 hours. The reaction mixture was then
25 concentrated *in vacuo*, the residue taken into dichloromethane, carefully neutralized with saturated aqueous sodium bicarbonate and then extracted into dichloromethane. The combined organic extracts were dried over sodium sulfate, concentrated *in vacuo* and the crude product purified by chromatography over silica gel gradient eluted with between 0.5 and 5% v/v methanol in
30 dichloromethane. The fractions containing the product were concentrated to give a white residue that was triturated in 1:1 ether / hexanes (20 mL), filtered and dried to give (S)-2-[(S)-2-amino-2-[4-(2-hydroxy-ethoxy)-phenyl]-acetyl-amino]-*N*-[2-chloro-4-(3-oxo-prop-1-ynyl)-phenyl]-3-phenyl-propionamide (240 mg, 70 %).

- Step 5: Cyclization with diphosgene was performed using the same method as described in step 6 of example 1 except that after work up the crude material (250 mg) was dissolved in methanol (11.3 mL), cooled in an ice bath and treated with sodium borohydride (123 mg, 3.28 mmol). After 15 minutes the reaction was treated with 1.5 N aqueous potassium hydrogen sulfate solution and extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with 1.5 N aqueous potassium hydrogen sulfate solution (2 × 50 mL) and water (2 × 50 mL). The organic solution was dried over sodium sulfate, filtered and concentrated and gave the crude mixture of diastereomers.
- Step 6: The crude mixture of diastereomers was purified by chromatography using a Daicel OD column eluted with 50% v/v methanol in 10 mmol aqueous ammonium acetate. The faster running component was concentrated *in vacuo*, dissolved in ethyl acetate (100 mL), the organic solution was washed with 5% w/v aqueous sodium bicarbonate solution (3 × 50 mL) and then the aqueous layers were combined and back extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were dried over sodium sulfate and concentrated to give (S)-N-(2-Chloro-4-ethynyl-phenyl)-2-{4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl}-3-phenyl-propionamide, isomer 1 (64 mg, 25.5 % yield).
- HRMS: Obs Mass (M+H⁺), 518.1477. Calcd. Mass, 518.1477 for C₂₈H₂₅ClN₃O₅⁺.

Example 147

(S)-N-(2-Chloro-4-ethynyl-phenyl)-2-{4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl}-3-phenyl-propionamide, isomer 2



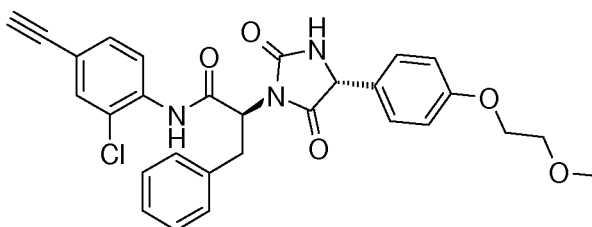
25

Prepared by the same procedure as described in example 146 except that in step 6 the slower running component was collected to give after washing and drying (S)-N-(2-chloro-4-ethynyl-phenyl)-2-{4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl}-3-phenyl-propionamide, isomer 2 (42 mg, 18.5 % yield).

HRMS: Obs Mass ($M+H^+$), 518.1472. Calcd. Mass, 518.1477 for $C_{28}H_{25}ClN_3O_5^+$.

Example 148

- 5 (S)-N-(2-Chloro-4-ethynyl-phenyl)-2-[(R)-4-[4-(2-methoxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-propionamide



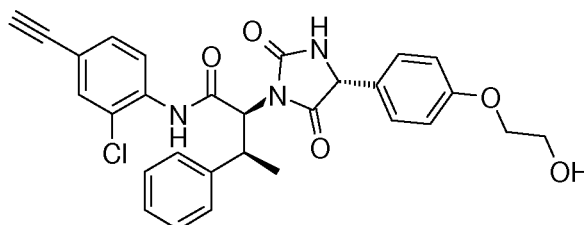
- Prepared by the same method as described in example 146 except that: (i) in step 3 (R)-*tert*-butoxycarbonylamino-[4-(2-methoxy-ethoxy)-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-{4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-acetic acid. (R)-*tert*-Butoxycarbonylamino-[4-(2-methoxy-ethoxy)-phenyl]-acetic acid was prepared as described in example 80, (ii) no formyl group was present after treatment with diphosgene in step 5 and so treatment with sodium borohydride was not required, and (iii) no diastereomer was observed after step 5 and so separation of diastereomers by super critical fluid chromatography was not required (step 6 in example 146).

HRMS: Obs Mass ($M+H^+$), 532.1634. Calcd. Mass, 532.1634 for $C_{29}H_{27}ClN_3O_5^+$.

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Example 149

- (2S,3S)-N-(2-Chloro-4-ethynyl-phenyl)-2-[(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide)

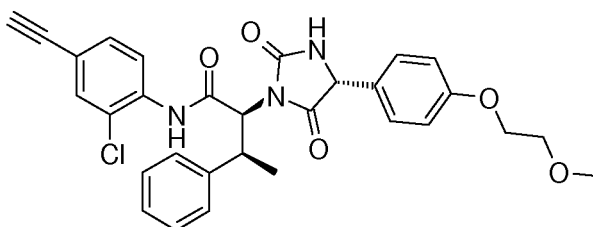


- Prepared by the same method as described in example 146 except that (2S,3S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid was used in place of (S)-2-*tert*-butoxycarbonylamino-3-phenyl-propionic acid.

HRMS: Obs Mass ($M+H^+$), 532.1637. Calcd. Mass, 532.1634 for $C_{29}H_{27}ClN_3O_5^+$.

Example 150

- 5 (2S,3S)-N-(2-Chloro-4-ethynyl-phenyl)-2-((R)-4-[4-(2-methoxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl)-3-phenyl-butyramide



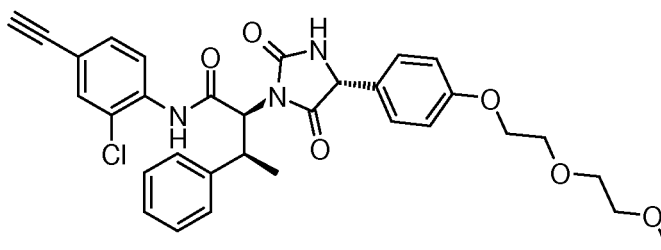
- Prepared by the same method as described in example 149 except that (R)-*tert*-butoxycarbonylamino-[4-(2-methoxy-ethoxy)-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-{4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-acetic acid. (R)-*tert*-Butoxycarbonylamino-[4-(2-methoxy-ethoxy)-phenyl]-acetic acid was prepared as described in example 80.

HRMS: Obs Mass ($M+H^+$), 546.1785. Calcd. Mass, 546.1790 for $C_{30}H_{29}ClN_3O_5^+$.

15

Example 151

- (2S,3S)-N-(2-Chloro-4-ethynyl-phenyl)-2-((R)-4-{4-[2-(2-methoxy-ethoxy)-ethoxy]-phenyl}-2,5-dioxo-imidazolidin-1-yl)-3-phenyl-butyramide

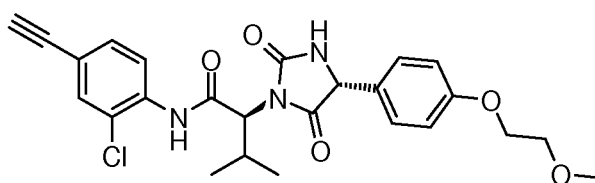


- 20 Prepared by the same method as described in example 150 except that (R)-*tert*-butoxycarbonylamino-{4-[2-(2-methoxy-ethoxy)-ethoxy]-phenyl}-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-[4-(2-methoxy-ethoxy)-phenyl]-acetic acid. (R)-*tert*-Butoxycarbonylamino-{4-[2-(2-methoxy-ethoxy)-ethoxy]-phenyl}-acetic acid was prepared as described in example 48 except that 1-(2-bromo-ethoxy)-2-methoxy-ethane was used in place of 2-(2-bromo-ethoxy)-tetrahydropyran.
- 25

HRMS: Obs Mass ($M+H^+$), 590.2053. Calcd. Mass, 590.2053 for $C_{32}H_{33}ClN_3O_6^+$.

Example 152

- 5 (S)-N-(2-Chloro-4-ethynyl-phenyl)-2-[(R)-4-[4-(2-methoxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-methyl-butylamide

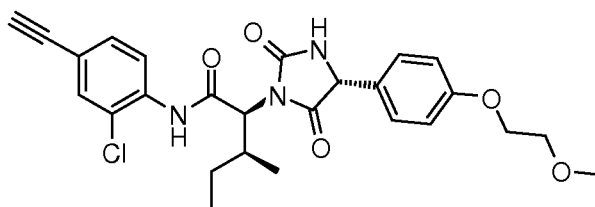


- Prepared by the same method as described in example 150 except that (S)-2-*tert*-butoxycarbonylamino-3-methyl-butyl acid was used in place (2S, 3S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyl acid.

HRMS: Obs Mass ($M+Na^+$), 506.1455. Calcd. Mass, 506.1453 for $C_{25}H_{26}ClN_3NaO_5^+$.

Example 153

- 15 (2S,3S)-2-[(R)-4-[4-(2-Methoxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-methyl-pentanoic acid (2-chloro-4-ethynyl-phenyl)-amide

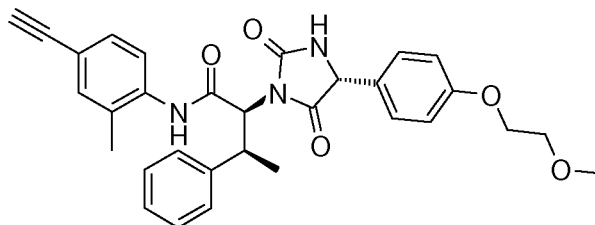


- Prepared by the same method as described in example 150 except that (2S, 3S)-2-*tert*-butoxycarbonylamino-3-methyl-pentanoic acid was used in place (2S, 3S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyl acid.

HRMS: Obs Mass ($M+Na^+$), 520.1612. Calcd. Mass, 520.1609 for $C_{26}H_{28}ClN_3NaO_5^+$.

Example 154

(2S,3S)-N-(4-Ethynyl-2-methyl-phenyl)-2-((R)-4-[4-(2-methoxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl)-3-phenyl-butyramide



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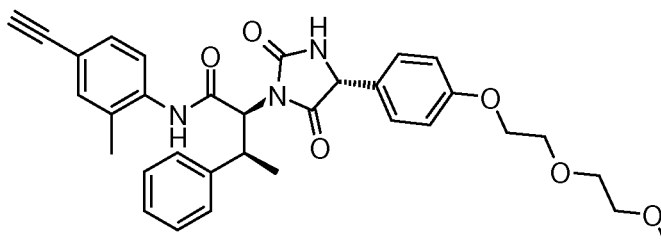
Prepared by the same method as described in example 150 except that 4-iodo-2-methylaniline was used in place of 2-chloro-4-iodomethylaniline.

HRMS: Obs Mass ($M+Na^+$), 548.2154. Calcd. Mass, 548.2156 for $C_{31}H_{31}N_3NaO_5^+$.

10

Example 155

(2S,3S)-N-(4-Ethynyl-2-methyl-phenyl)-2-((R)-4-{4-[2-(2-methoxy-ethoxy)-ethoxy]-phenyl}-2,5-dioxo-imidazolidin-1-yl)-3-phenyl-butyramide

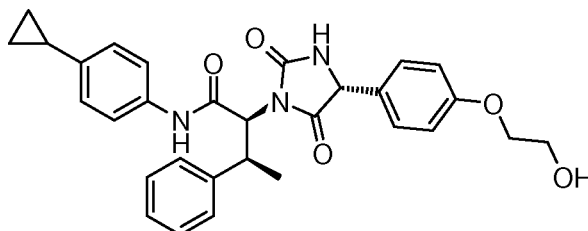


15 Prepared by the same method as described in example 151 except that 4-iodo-2-methylaniline was used in place of 2-chloro-4-iodomethylaniline.

HRMS: Obs Mass ($M+Na^+$), 592.2411. Calcd. Mass, 592.2418 for $C_{33}H_{35}N_3NaO_6^+$.

Example 156

(2S,3S)-*N*-(4-Cyclopropyl-phenyl)-2-{(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl}-3-phenyl-butyramide



5

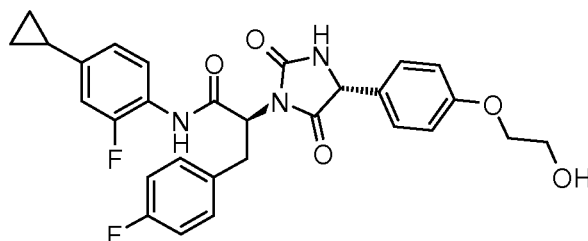
Prepared by the same method as described in example 48 except that 4-cyclopropyl-aniline was used in place of 2-fluoro-4-iodoaniline.

HRMS: Obs Mass ($M+H^+$), 514.2333. Calcd. Mass, 514.2337 for $C_{30}H_{32}N_3O_5^+$.

10 HRMS: Obs Mass ($M+Na^+$), 536.2153. Calcd. Mass, 536.2156 for $C_{30}H_{31}N_3NaO_5^+$.

Example 157

15 (S)-*N*-(4-Cyclopropyl-2-fluoro-phenyl)-3-(4-fluoro-phenyl)-2-{(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl}-propionamide



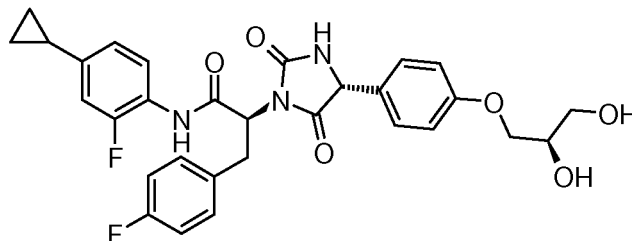
Prepared by the same method as described in example 160 except that (R)-*tert*-butoxycarbonylamino-{4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-acetic was used in place of (R)-*tert*-butoxycarbonylamino-[4-(2-hydroxy-1-hydroxymethyl-ethoxy)-phenyl]-acetic acid. (R)-*tert*-Butoxycarbonylamino-{4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-acetic acid was prepared as described in example 48.

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HRMS: Obs Mass ($M+H^+$), 536.1986. Calcd. Mass, 536.1992 for $C_{29}H_{28}F_2N_3O_5^+$.

Example 158

(S)-N-(4-Cyclopropyl-2-fluoro-phenyl)-2-((R)-4-[4-((R)-2,3-dihydroxy-propoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl)-3-(4-fluoro-phenyl)-propionamide



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Prepared by the same method as described in example 160 except that (R)-*tert*-butoxycarbonylamino-[4-((R)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-[4-(2-hydroxy-1-hydroxymethyl-ethoxy)-phenyl]-acetic acid. (R)-*tert*-Butoxycarbonylamino-[4-((R)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-acetic acid was prepared and used as described in example 114.

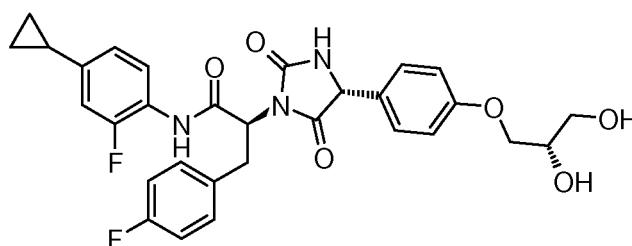
10

HRMS: Obs Mass ($M+H^+$), 566.2099. Calcd. Mass, 566.2097 for $C_{30}H_{30}F_2N_3O_6^+$.

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Example 159

(S)-N-(4-Cyclopropyl-2-fluoro-phenyl)-2-((R)-4-[4-((S)-2,3-dihydroxy-propoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl)-3-(4-fluoro-phenyl)-propionamide



Prepared by the same method as described in example 160 except that (R)-*tert*-butoxycarbonylamino-[4-((S)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-[4-((R)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-acetic acid. (R)-*tert*-Butoxycarbonylamino-[4-((S)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-acetic acid was prepared and used as described in example 116.

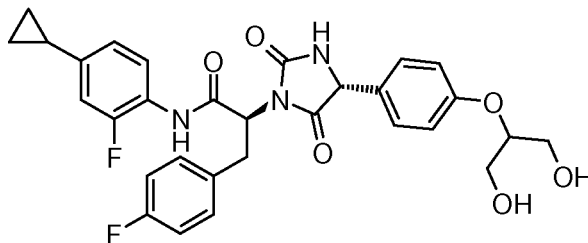
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25

HRMS: Obs Mass ($M+Na^+$), 588.1912. Calcd. Mass, 588.1916 for $C_{30}H_{29}F_2N_3NaO_6^+$.

Example 160

(S)-N-(4-Cyclopropyl-2-fluoro-phenyl)-3-(4-fluoro-phenyl)-2-[(R)-4-[4-(2-hydroxy-1-hydroxymethyl-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-propionamide



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Prepared by the same method as described in example 3 except that (i) (S)-2-*tert*-butoxycarbonylamino-3-(4-fluoro-phenyl)-propionic acid was used in place of (2S, 3S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid in step 1, (ii) (S)-[1-(2-fluoro-4-iodo-phenylcarbamoyl)-2-(4-fluoro-phenyl)-ethyl]-carbamic acid *tert*-butyl ester was converted in to (S)-[1-(4-cyclopropyl-2-fluoro-phenylcarbamoyl)-2-(4-fluoro-phenyl)-ethyl]-carbamic acid *tert*-butyl ester after step 2 and prior to step 3 (using the conditions described below), (iii) (R)-*tert*-butoxycarbonylamino-[4-(2-hydroxy-1-hydroxymethyl-ethoxy)-phenyl]-acetic acid (prepared as described below) was used in place of (R)-*tert*-butoxycarbonylamino-[4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl]-acetic acid in step 4, and (iv) the diol functionality contained in (S)-2-{2-amino-2-[4-(2-hydroxy-1-hydroxymethyl-ethoxy)-phenyl]-acetyl-amino}-N-(4-cyclopropyl-2-fluoro-phenyl)-3-(4-fluoro-phenyl)-propionamide was temporarily protected as the *bis*-trimethylsilyl ether during step 6 by the same method as described in example 114.

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Preparation of (S)-[1-(4-cyclopropyl-2-fluoro-phenylcarbamoyl)-2-(4-fluoro-phenyl)-ethyl]-carbamic acid *tert*-butyl ester:

To (S)-[1-(2-fluoro-4-iodo-phenylcarbamoyl)-2-(4-fluoro-phenyl)-ethyl]-carbamic acid *tert*-butyl ester (4.5 g, 9.0 mmol) and cyclopropylboronic acid (1.0 g, 11.7 mmol) in a mixture of toluene (40 mL) and water (2 mL) were added potassium phosphate tribasic (6.68 g, 31.5 mmol), tricyclohexylphosphine (0.50 g, 1.8 mmol) and palladium acetate (0.20 g, 0.89 mmol). The mixture was heated to 100 °C for 3 hours then additional tricyclohexylphosphine (0.25 g, 0.89 mmol) and palladium acetate (0.10 g, 0.45 mmol) were added. Heating at 100 °C was continued for an additional 3 hours before adding cyclopropylboronic acid (0.2 g,

30

2.33 mmol) and heating at 100 °C for a final period of 3 hours. The reaction mixture was diluted with ethyl acetate, washed with water (twice), brine (once), dried over sodium sulphate, filtered and concentrated *in vacuo*. The residue was purified by chromatography over silica gel eluted with 9:1 v/v dichloromethane in hexanes to afford (S)-[1-(4-cyclopropyl-2-fluoro-phenylcarbamoyl)-2-(4-fluoro-phenyl)-ethyl]-carbamic acid *tert*-butyl ester as a colorless solid (2.0 g, 53%).

LC-MS: Obs. Mass, 417. Calcd. Mass, 417 for C₂₃H₂₇F₂N₂O₃⁺.

Preparation of (R)-*tert*-butoxycarbonylamino-[4-(2-hydroxy-1-hydroxymethyl-ethoxy)-phenyl]-acetic acid:

(1) 2,5-Dichloro-benzenesulfonic acid 2-benzyloxy-1-benzyloxymethyl-ethyl ester was obtained from 1,3-*bis*-benzyloxy-propan-2-ol according to the procedure of Shimizu, M. *et al.* (*J. Chem. Soc. Chem. Commun.* **1986**, 867).

(2) To a solution of (R)-*tert*-butoxycarbonylamino-(4-hydroxy-phenyl)-acetic (1.0 g, 3.74 mmol) in dry *N,N*-dimethylformamide (50 mL) was added sodium hydride (60% suspension in mineral oil) (328 mg, 8.2 mmol) and the mixture was stirred at ambient temperature under an atmosphere of dry argon for 15 minutes. 2,5-Dichloro-benzenesulfonic acid 2-benzyloxy-1-benzyloxymethyl-ethyl ester (2.2 g, 4.57 mmol) dissolved in dry *N,N*-dimethylformamide (25 mL) was added and the stirred mixture placed in a 110 °C oil bath for 10 minutes. The reaction mixture was cooled to ambient temperature and 0.5 M aqueous hydrochloric acid (16.5 mL, 8.3 mmol) added. The reaction mixture was extracted with ethyl acetate (2 × 250 mL), the combined organic layers washed with water (2 × 250 mL), brine (250 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by chromatography over silica gel eluted with 49:1 v/v dichloromethane / methanol containing 0.2 % v/v acetic acid to afford (R)-[4-(2-benzyloxy-1-benzyloxymethyl-ethoxy)-phenyl]-*tert*-butoxycarbonylamino-acetic acid as a colorless solid (1.2 g, 80%).

HRMS: Obs. Mass, 544.2307. Calcd. Mass, 544.2306 for C₃₀H₃₅NNaO₇⁺.

(3) A hydrogenation vessel containing a solution of (R)-[4-(2-benzyloxy-1-benzyloxymethyl-ethoxy)-phenyl]-*tert*-butoxycarbonylamino-acetic acid (1.86 g, 3.57 mmol) in methanol (50 mL) was purged with nitrogen and 10% palladium on carbon (100 mg) added. The atmosphere above the methanol solution was exchanged for hydrogen and the reaction mixture stirred vigorously for 30

minutes at ambient temperature. The reaction mixture was filtered through a pad of Celite and concentrated *in vacuo* to give (R)-*tert*-butoxycarbonylamino-[4-(2-hydroxy-1-hydroxymethyl-ethoxy)-phenyl]-acetic acid which was of sufficient purity for subsequent use without additional purification (0.88 g, 73%).

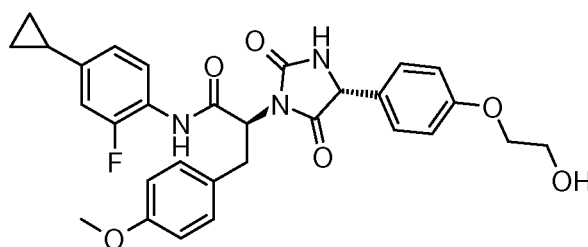
5

HRMS: Obs. Mass, 364.1368. Calcd. Mass, 364.1367 for $C_{16}H_{23}NNaO_7^+$.

HRMS: Obs. Mass, 566.2100. Calcd. Mass, 566.2097 for $C_{30}H_{30}F_2N_3O_6^+$.

Example 161

- 10 (S)-*N*-(4-Cyclopropyl-2-fluoro-phenyl)-2-[(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-(4-methoxy-phenyl)-propionamide

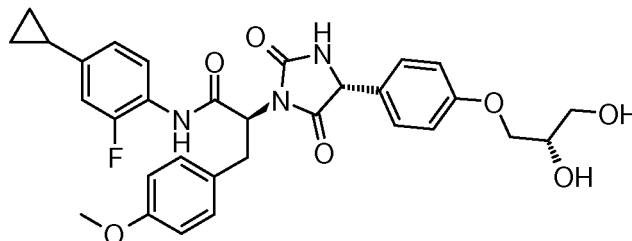


- Prepared by the same method as described in example 160 except that (i) (S)-2-*tert*-butoxycarbonylamino-3-(4-methoxy-phenyl)-propionic acid was used in place of (S)-2-*tert*-butoxycarbonylamino-3-(4-fluoro-phenyl)-propionic acid, and (ii) (R)-*tert*-butoxycarbonylamino-{4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-acetic was used in place of (R)-*tert*-butoxycarbonylamino-[4-(2-hydroxy-1-hydroxymethyl-ethoxy)-phenyl]-acetic acid. (R)-*tert*-Butoxycarbonylamino-{4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl}-acetic acid was prepared as described in example 48.
- 20

HRMS: Obs Mass ($M+H^+$), 548.2180. Calcd. Mass, 548.2192 for $C_{30}H_{31}FN_3O_6^+$.

Example 162

(S)-N-(4-Cyclopropyl-2-fluoro-phenyl)-2-((R)-4-[4-((S)-2,3-dihydroxy-propoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl)-3-(4-methoxy-phenyl)-propionamide



5

Prepared by the same method as described in example 160 except that (i) (S)-2-*tert*-butoxycarbonylamino-3-(4-methoxy-phenyl)-propionic acid was used in place of (S)-2-*tert*-butoxycarbonylamino-3-(4-fluoro-phenyl)-propionic acid, and (ii) (R)-*tert*-butoxycarbonylamino-[4-((S)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-acetic acid (prepared as described in example 116) was used in place of (R)-*tert*-butoxycarbonylamino-[4-(2-hydroxy-1-hydroxymethyl-ethoxy)-phenyl]-acetic acid.

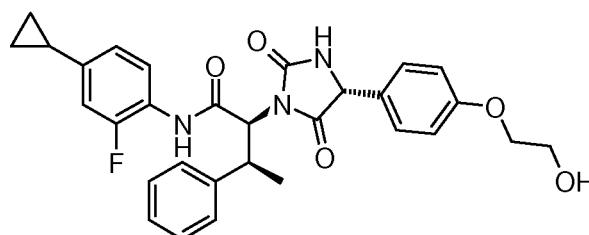
10

HRMS: Obs Mass ($M+Na^+$), 600.2112. Calcd. Mass, 600.2116 for $C_{31}H_{32}FN_3NaO_7^+$.

15

Example 163

(2S,3S)-N-(4-Cyclopropyl-2-fluoro-phenyl)-2-((R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl)-3-phenyl-butyramide



20

Prepared by the same method as described in example 48 except that (i) 4-cyclopropyl-2-fluoroaniline (prepared as described below) was used in place of 2-fluoro-4-iodoaniline, and (ii) the modified procedure shown below was used to perform step 6.

Preparation of 4-cyclopropyl-2-fluoroaniline:

(According to the procedure of D. Wallace and C. Chen, Tetrahedron Lett., 43, 6987 (2002)) 4-Bromo-2-fluoroaniline (19.0g, 100 mmol) was reacted with
5 cyclopropyl boronic acid (11.3 g, 131 mmol), palladium(II) acetate (1.12 g, 4.79 mmol), tricyclohexyl phosphine (2.80 g, 13.2 mmol), and potassium phosphate (74.2 g, 265 mmol) in toluene (400 mL) and water (30 mL). The mixture was heated in an oil bath at 100 °C for 2 days, cooled, and the liquid was filtered through a pad of celite. The residual solid in the reaction vessel was triturated
10 with water (200 mL), and the suspension was filtered through celite. The aqueous filtrate was extracted once with hexanes (100 mL), the combined organic layers were dried over anhydrous magnesium sulfate. The dried organic layers were filtered through a silica gel pad, and the pad was washed with 80% v/v dichloromethane in hexanes (250 mL). The filtrates were concentrated *in*
15 *vacuo* to give a red oil that was fractionally distilled (Vigreux column, 6 plates). The fraction distilling between 65-73 °C at 6-7 mbar was collected to give 6.8 g (45 mmol, 45%) of 4-cyclopropyl-2-fluoroaniline as a pale yellow liquid.

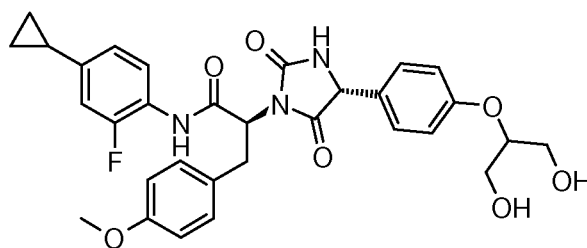
¹H-NMR (300MHz, CDCl₃) δ: 6.69 (m, 3H), 3.57 (br.s., 2H), 1.79 (m, 1H), 0.87 (m, 2H), 0.57 (m, 2H).

20 Step 6: 2-{2-Amino-2-[4-(2-trimethylsilanyloxy-ethoxy)-phenyl]-acetylamino}-*N*-(4-cyclopropyl-2-fluorophenyl)-3-phenyl-butyramide (680 mg, 1.2 mmol) and pyridine (3 mL) were dissolved in dichloromethane (60 mL) at -78 °C. To this mixture was added a solution of triphosgene (296 mg, 1 mmol) in dichloromethane (15 mL) dropwise. The mixture was allowed to slowly warm to
25 room temperature and stirred overnight at room temperature. The mixture was cooled in an ice bath and 3 M HCl (60 mL) was added slowly and stirring was continued at 0 °C for 30 minutes. The organic layer was separated and dried over anhydrous sodium sulfate. Concentration gave 150 mg of a oily solid that was chromatographed over silica gel (65% v/v ethyl acetate in hexanes) to give
30 *N*-(4-cyclopropyl-2-fluoro-phenyl)-2-{4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxoimidazolidin-1-yl}-3-phenyl-butyramide as a yellow solid (70 mg, 0.13 mmol, 13%).

HRMS: Obs Mass (M+H⁺), 532.2244. Calcd. Mass, 532.2242 for C₃₀H₃₁FN₃O₅⁺.

Example 164

(S)-N-(4-Cyclopropyl-2-fluoro-phenyl)-2-[(R)-4-[4-(2-hydroxy-1-hydroxymethylethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-(4-methoxy-phenyl)-propionamide

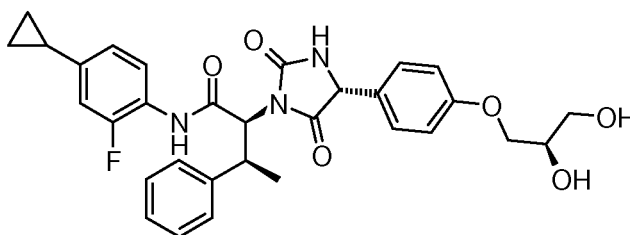


- 5 Prepared by the same method as described in example 160 except that (i) (S)-2-*tert*-butoxycarbonylamino-3-(4-methoxy-phenyl)-propionic acid was used in place of (S)-2-*tert*-butoxycarbonylamino-3-(4-fluoro-phenyl)-propionic acid in step 1, and (ii) (3-dimethylamino-propyl)-ethyl-carbodiimide hydrochloride was used as the coupling reagent in place of *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate in step 4.

HRMS: Obs Mass ($M+H^+$), 578.2295 Calcd. Mass, 578.2297 for $C_{31}H_{33}FN_3O_7^+$.

Example 165

- 15 (2S,3S)-N-(4-Cyclopropyl-2-fluoro-phenyl)-2-[(R)-4-[4-((R)-2,3-dihydroxypropoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide

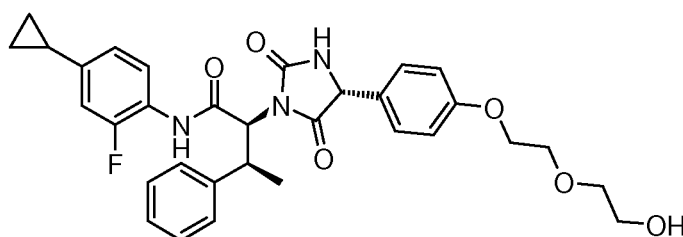


- Prepared by the same method as described in example 160 except that (i) (2S,3S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid was used in place of (S)-2-*tert*-butoxycarbonylamino-3-(4-fluoro-phenyl)-propionic acid in step 1, and (ii) (R)-*tert*-butoxycarbonylamino-[4-((R)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-[4-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-phenyl]-acetic acid in step 4. (R)-*tert*-Butoxycarbonylamino-[4-((R)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-acetic acid was prepared and used as described in example 114.

HRMS: Obs Mass ($M+H^+$), 562.2349. Calcd. Mass, 562.2348 for $C_{31}H_{33}FN_3O_6^+$.

Example 166

- 5 (2S,3S)-N-(4-Cyclopropyl-2-fluoro-phenyl)-2-((R)-4-{4-[2-(2-hydroxy-ethoxy)-ethoxy]-phenyl}-2,5-dioxo-imidazolidin-1-yl)-3-phenyl-butamide



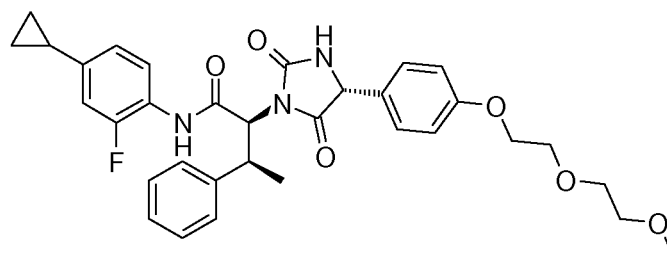
- Prepared by the same method as described in example 165 except that (R)-*tert*-butoxycarbonylamino-(4-{2-[2-(tetrahydro-pyran-2-yloxy)-ethoxy]-ethoxy}-phenyl)-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-[4-((S)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-acetic acid.

HRMS: Obs Mass ($M+H^+$), 576.2504. Calcd. Mass, 576.2505 for $C_{32}H_{35}FN_3O_6^+$.

15

Example 167

- (2S,3S)-N-(4-Cyclopropyl-2-fluoro-phenyl)-2-((R)-4-{4-[2-(2-methoxy-ethoxy)-ethoxy]-phenyl}-2,5-dioxo-imidazolidin-1-yl)-3-phenyl-butamide



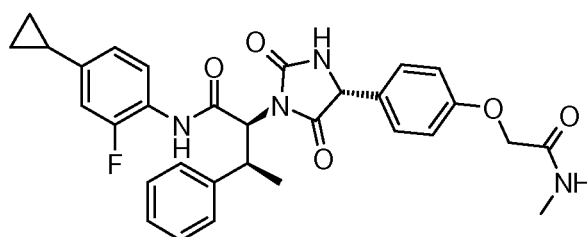
- Prepared by the same method as described in example 165 except that (R)-*tert*-butoxycarbonylamino-[4-[2-(2-methoxy-ethoxy)-ethoxy]-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-[4-((S)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-acetic acid.

HRMS: Obs Mass ($M+H^+$), 590.2656. Calcd. Mass, 590.2661 for $C_{33}H_{37}FN_3O_6^+$.

HRMS: Obs Mass ($M+Na^+$), 612.2475. Calcd. Mass, 612.2480 for $C_{33}H_{36}FN_3NaO_6^+$.

Example 168

- 5 (2S,3S)-N-(4-Cyclopropyl-2-fluoro-phenyl)-2-[(R)-4-(4-methylcarbamoylmethoxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide

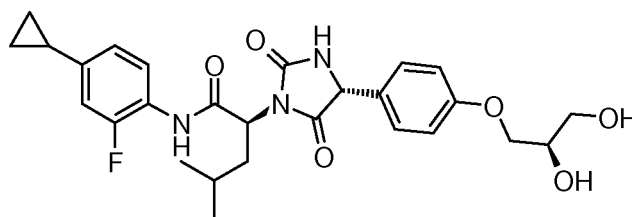


- Prepared by the same method as described in example 165 except that (R)-*tert*-butoxycarbonylamino-(4-methylcarbamoylmethoxy-phenyl)-acetic acid was used
 10 in place of (R)-*tert*-butoxycarbonylamino-[4-((S)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-acetic acid. (R)-*tert*-Butoxycarbonylamino-(4-methylcarbamoylmethoxy-phenyl)-acetic acid was prepared as described in example 9.

- HRMS: Obs Mass ($M+H^+$), 559.2354. Calcd. Mass, 559.2351 for
 15 $C_{31}H_{32}FN_4O_5^+$.

Example 169

- (S)-2-[(R)-4-[4-((R)-2,3-Dihydroxy-propoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-4-methyl-pentanoic acid (4-cyclopropyl-2-fluoro-phenyl)-amide

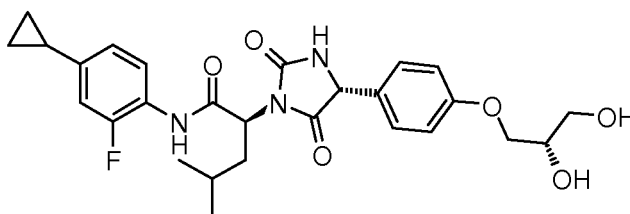


- 20 Prepared by the same method as described in example 165 except that (S)-2-*tert*-butoxycarbonylamino-4-methyl-pentanoic acid was used in place of (2S, 3S)-2-*tert*-butoxycarbonylamino-3-phenyl-butyric acid.

- HRMS: Obs Mass ($M+H^+$), 514.2349. Calcd. Mass, 514.2348 for
 25 $C_{27}H_{33}FN_3O_6^+$.

Example 170

(S)-2-[(R)-4-[4-[(S)-2,3-Dihydroxy-propoxy]-phenyl]-2,5-dioxo-imidazolidin-1-yl]-4-methyl-pentanoic acid (4-cyclopropyl-2-fluoro-phenyl)-amide



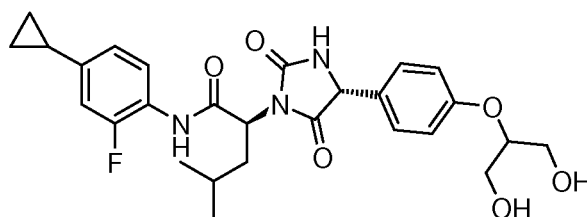
- 5 Prepared using the same method as described in example 169 except that (R)-*tert*-butoxycarbonylamino-[4-((R)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-[4-((S)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-acetic acid in step 4. (R)-*tert*-butoxycarbonylamino-[4-((R)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-
10 acetic acid was prepared by the same method as described for the preparation of (R)-*tert*-butoxycarbonylamino-[4-((S)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-phenyl]-acetic acid in example 114 except that (R)-2,2-dimethyl-1,3-dioxolane-4-methanol was used in place of (S)-2,2-dimethyl-1,3-dioxolane-4-methanol.

HRMS: Obs Mass ($M+Na^+$), 536.2164. Calcd. Mass, 536.2167 for

- 15 $C_{27}H_{32}FN_3NaO_6^+$.

Example 171

(S)-2-[(R)-4-[4-(2-Hydroxy-1-hydroxymethyl-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-4-methyl-pentanoic acid (4-cyclopropyl-2-fluoro-phenyl)-amide



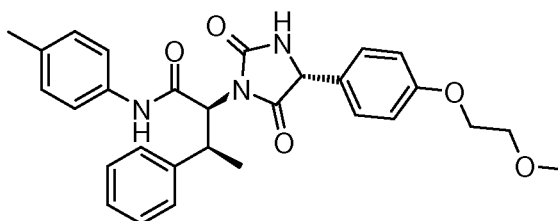
20

- Prepared by the same method as described in example 160 except that (i) (S)-2-*tert*-butoxycarbonylamino-4-methyl-pentanoic acid was used in place of (S)-2-*tert*-butoxycarbonylamino-3-(4-fluoro-phenyl)-propionic acid in step 1, and (ii) (3-dimethylamino-propyl)-ethyl-carbodiimide hydrochloride was used as the
25 coupling reagent in place of *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate in step 4.

HRMS: Obs Mass ($M+H^+$), 514.2347 Calcd. Mass, 514.2348 for $C_{27}H_{33}FN_3O_6^+$.

Example 172

- 5 (2S,3S)-2-{(R)-4-[4-(2-Methoxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl}-3-phenyl-*N*-p-tolyl-butamide

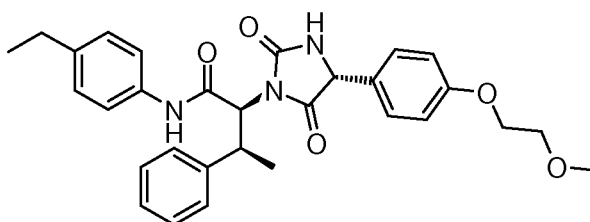


- Prepared by the same method as described in example 1 except that (i) 4-methyl-aniline was used in place of 4-bromoaniline in step 2, and (ii) (R)-*tert*-butoxycarbonylamino-[4-(2-methoxy-ethoxy)-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-(4-methoxy-phenyl)-acetic acid in step 4. (R)-*tert*-Butoxycarbonylamino-[4-(2-methoxy-ethoxy)-phenyl]-acetic acid was prepared as described in example 80.

- HRMS: Obs Mass ($M+H^+$), 502.2332. Calcd. Mass, 502.2337 for $C_{29}H_{32}N_3O_5^+$.

Example 173

(2S,3S)-*N*-(4-Ethyl-phenyl)-2-{(R)-4-[4-(2-methoxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl}-3-phenyl-butamide

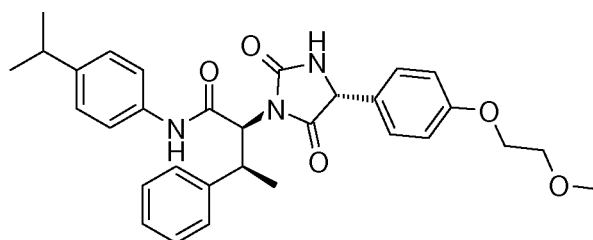


- Prepared using the same method as described in example 1 except that (i) 4-ethyl-aniline was used in place of 4-bromoaniline in step 2, and (ii) (R)-*tert*-butoxycarbonylamino-[4-(2-methoxy-ethoxy)-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-(4-methoxy-phenyl)-acetic acid in step 4. (R)-*tert*-Butoxycarbonylamino-[4-(2-methoxy-ethoxy)-phenyl]-acetic acid was prepared as described in example 80.

HRMS: Obs Mass ($M+H^+$), 516.2489. Calcd. Mass, 516.2493 for $C_{30}H_{34}N_3O_5^+$.

Example 174

- 5 (2S,3S)-N-(4-Isopropyl-phenyl)-2-[(R)-4-[4-(2-methoxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide

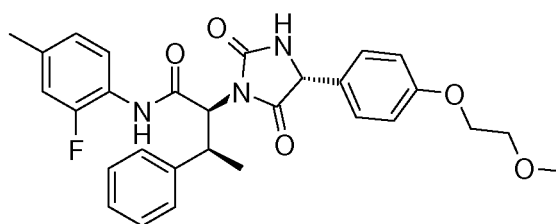


- Prepared using the same method as described in example 1 except that (i) 4-isopropyl-aniline was used in place of 4-bromoaniline in step 2, and (ii) (R)-*tert*-butoxycarbonylamino-[4-(2-methoxy-ethoxy)-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-(4-methoxy-phenyl)-acetic acid in step 4. (R)-*tert*-Butoxycarbonylamino-[4-(2-methoxy-ethoxy)-phenyl]-acetic acid was prepared as described in example 80.

- HRMS: Obs Mass ($M+H^+$), 530.2646. Calcd. Mass, 530.2650 for $C_{31}H_{36}N_3O_5^+$.

Example 175

- (2S,3S)-N-(2-Fluoro-4-methyl-phenyl)-2-[(R)-4-[4-(2-methoxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide

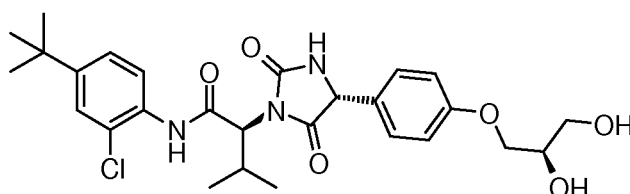


- Prepared using the same method as described in example 1 except that (i) 2-fluoro-4-methyl-aniline was used in place of 4-bromoaniline in step 2, and (ii) (R)-*tert*-butoxycarbonylamino-[4-(2-methoxy-ethoxy)-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-(4-methoxy-phenyl)-acetic acid in step 4. (R)-*tert*-Butoxycarbonylamino-[4-(2-methoxy-ethoxy)-phenyl]-acetic acid was prepared as described in example 80.

HRMS: Obs Mass ($M+Na^+$), 542.2056. Calcd. Mass, 542.2061 for $C_{29}H_{30}FN_3NaO_5^+$.

Example 176

- 5 (S)-N-(4-*tert*-Butyl-2-chloro-phenyl)-2-((R)-4-[4-((R)-2,3-dihydroxy-propoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl)-3-methyl-butylamide



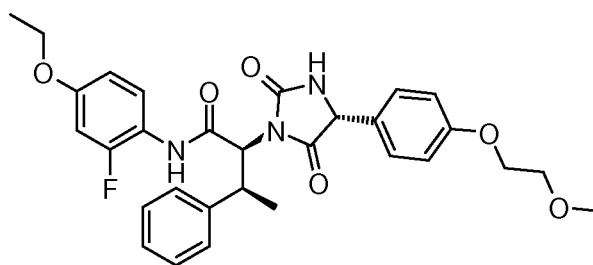
- Prepared by the same method as described in example 43 except that (i) (S)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-methyl-butylamide was used in place of (S)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-naphthalen-2-yl-propionic acid in step 1, (ii) 4-*tert*-butyl-2-chloro-phenylamine was used in place of 2-fluoro-4-iodoaniline in step 1, and (iii) the steps following step 3 were performed as described in example 114.

LC-MS: Obs Mass ($M+H^+$), 532; Calcd. Mass, 532 for $C_{27}H_{35}ClN_3O_6^+$.

15

Example 177

- (2*S*,3*S*)-N-(4-Ethoxy-2-fluoro-phenyl)-2-((R)-4-[4-(2-methoxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl)-3-phenyl-butylamide

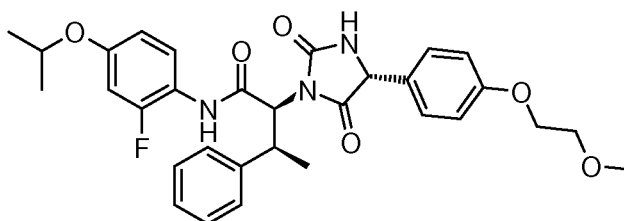


- 20 Prepared using the same method as described in example 1 except that (i) 4-ethoxy-2-fluoro-aniline was used in place of 4-bromoaniline in step 2, and (ii) (R)-*tert*-butoxycarbonylamino-[4-(2-methoxy-ethoxy)-phenyl]-acetic acid was used in place of (R)-*tert*-butoxycarbonylamino-(4-methoxy-phenyl)-acetic acid in step 4. (R)-*tert*-Butoxycarbonylamino-[4-(2-methoxy-ethoxy)-phenyl]-acetic acid was prepared as described in example 80.
- 25

HRMS: Obs Mass ($M+H^+$), 550.2352. Calcd. Mass, 550.2348 for $C_{30}H_{33}FN_3O_6^+$.

Example 178

- 5 (2S,3S)-*N*-(2-Fluoro-4-isopropoxy-phenyl)-2-[(R)-4-[4-(2-methoxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide

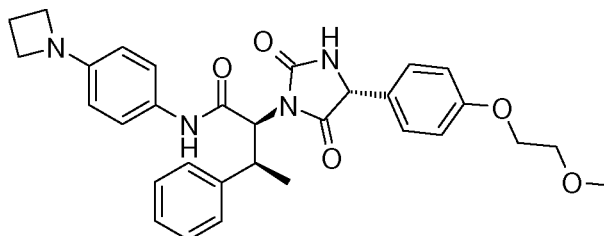


Prepared by the same method as described in example 50 except that 2-fluoro-4-isopropoxyaniline hydrochloride was used in place of 2-fluoro-4-iodoaniline.

- 10 HRMS: Obs Mass ($M+H^+$), 564.2498. Calcd. Mass, 564.2505 for $C_{31}H_{35}FN_3O_6^+$.

Example 179

- 15 (2S,3S)-*N*-(4-Azetidin-1-yl-2-fluoro-phenyl)-2-[(R)-4-[4-(2-methoxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide



Prepared by the same method as described in example 50 except that 4-azetidin-1-yl-2-fluoro-phenylamine was used in place of 2-fluoro-4-iodoaniline. 4-Azetidin-1-yl-2-fluoro-phenylamine was prepared in the following way:

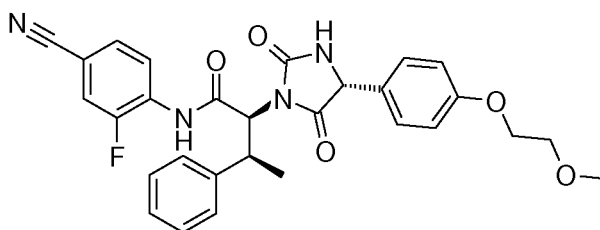
- 20 To a mixture of 2-fluoro-4-iodoaniline (1 g, 4.14 mmol), copper iodide (304 mg, 0.21 mmol) and potassium phosphate (1.75g, 8.27 mmol) in ethylene glycol (465 μ l, 8.27 mmol) and isopropanol (4 mL) in a bomb flask was added azetidine (304 mg, 5.17 mmol). The flask was sealed and heated to 80 °C for 24 hours. The reaction mixture was dissolved in ethyl acetate (50 mL), washed with water (3 $\times$ 50 mL), brine (50 mL), and the brine layer back extracted with ethyl acetate (2 $\times$ 50 mL). The combined organic extracts were dried over sodium sulfate, filtered

and concentrated *in vacuo* to a brown oil. The oil was purified by chromatography over silica gel eluted with 40% v/v ethyl acetate in hexanes. The product containing fractions were combined and concentrated to give 4-azetidin-1-yl-2-fluoro-phenylamine as an orange oil (555 mg, 81% yield).

- 5 HRMS: Obs Mass ($M+H^+$), 561.2501. Calcd. Mass, 561.2508 for $C_{31}H_{34}FN_4O_5^+$.

Example 180

- 10 (2S,3S)-N-(4-Cyano-2-fluoro-phenyl)-2-[(R)-4-[4-(2-methoxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide



Prepared by the same method as that described in example 50 except that prior to performing step 4 in the reaction sequence the transformation detailed below (step 3a) was performed.

- 15 Step 3a: To an argon degassed and dried flask was added (2S,3S)-2-amino-N-(2-fluoro-4-iodo-phenyl)-3-phenyl-butyramide (796 mg, 1.99mmol), zinc cyanide (352 mg, 2.99 mmol), *tetrakis*-triphenylphosphine palladium (0) (116 mg, 0.1 mmol) and dry tetrahydrofuran (4 mL). After heating at 80 °C for 8 hours there was no reaction. To the cooled mixture was added 2-dicyclohexylphosphino-2'-6'-
- 20 dimethoxybiphenyl (42 mg, 0.1 mmol) and the reaction mixture heated again to 80 °C for 90 minutes, again no reaction occurred. To the cooled mix was added triethylamine (840 µl, 5.99 mmol) and the reaction mixture heated at 80 °C for 2 hours, again no reaction occurred. To the cooled mix was added 2-
- 25 dicyclohexylphosphino-2'-6'-dimethoxybiphenyl (84 mg, 0.2 mmol) and still no reaction occurred after 2 hours at 85 °C. To the cooled mix was added *rac*-2-2'-*bis*(diphenylphosphino)-1-1'-binaphthyl (125.6 mg, 0.2 mmol) and dry toluene (2 mL). After heating at 85 °C for 40 hours the reaction mix was dissolved in ethyl acetate (50 mL) and washed with 1.5 N aqueous potassium hydrogen sulfate solution, saturated aqueous sodium bicarbonate solution and the aqueous layers
- 30 were back extracted with ethyl acetate (2 × 50 mL). The combined organic

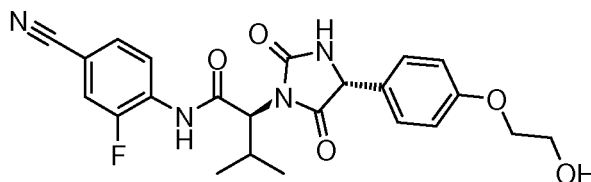
layers were dried over sodium sulfate and concentrated. The crude residue was purified by chromatography over silica gel gradient eluted from 5 to 15% v/v ethyl acetate in hexanes to give (2S,3S)-2-amino-*N*-(4-cyano-2-fluoro-phenyl)-3-phenyl-butyramide as a yellow residue after concentration of the product

5 containing fractions (120 mg, 20.2 % yield).

HRMS: Obs Mass ($M+H^+$), 531.2035. Calcd. Mass, 531.2038 for $C_{29}H_{28}FN_4O_5^+$.

Example 181

10 (S)-*N*-(4-Cyano-2-fluoro-phenyl)-2-[(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-methyl-butyramide



Prepared by the same method as described in example 43 except that step 1 was performed as described below.

15 Step 1: To a solution of (S)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-methyl-butyric acid (2.5 g, 7.37 mmol) and a few drops of *N,N*-dimethylformamide in dichloromethane (20 mL) was slowly added oxalyl chloride (1.3 mL, 14.74 mmol) at 0 °C under an atmosphere of dry nitrogen. The mixture was stirred for 15 minutes at 0 °C and 2 hours at room temperature. After removal of the solvent,

20 the residue was dissolved in dichloromethane (20 mL) and to the resulting solution was added 4-amino-3-fluoro-benzonitrile (840 mg, 6.14 mmol), 4-dimethylaminopyridine (150 mg, 1.2 mmol) and pyridine (0.78 mL, 9.21 mmol) at 0 °C. The mixture was stirred for 2 hrs at 0 °C and overnight at room temperature. The reaction was quenched with 1 M aqueous citric acid solution

25 and then extracted with dichloromethane (three times). The combined organic extracts were washed with 1 M aqueous citric acid solution, brine, saturated aqueous sodium carbonate, brine, dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by chromatography over silica gel gradient eluted from 100% dichloromethane up to 10% methanol / 90%

30 dichloromethane over 30 minutes. Concentration of the product containing

fractions gave [(S)-1-(4-cyano-2-fluoro-phenylcarbamoyl)-2-methyl-propyl]-carbamic acid 9H-fluoren-9-ylmethyl ester as a white solid (2.15 mg, 77%).

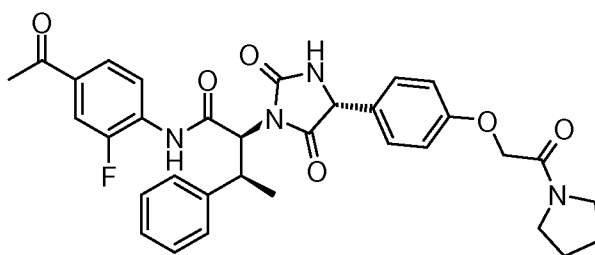
LC-MS: Obs Mass ($M+H^+$), 458; Calcd. Mass, 548 for $C_{27}H_{25}FN_3O_3^+$.

LC-MS: Obs Mass ($M+H^+$), 455; Calcd. Mass, 455 for $C_{23}H_{24}FN_4O_5^+$.

5

Example 182

(2S,3S)-N-(4-Acetyl-2-fluoro-phenyl)-2-[(R)-2,5-dioxo-4-[4-(2-oxo-2-pyrrolidin-1-yl-ethoxy)-phenyl]-imidazolidin-1-yl]-3-phenyl-butyramide



- 10 Prepared by the same method as described in example 145 with this compound being obtained as a by-product during the purification in step 6.

HRMS: Obs Mass ($M+H^+$), 601.2454. Calcd. Mass, 601.2457 for $C_{33}H_{34}FN_4O_6^+$.

15

Example 183

Compound IC₅₀ determination in MEK cascade assay

- The evaluation of the compounds as MEK inhibitor was performed in a bead-based FP assay termed IMAP assay with MEK cascade components. In brief, the assay was performed in a reaction solution containing 10 mM HEPES, pH 7.0, 10 mM $MgCl_2$, 50 mM NaCl, 0.1 mM $NaVO_4$, and 1m M DTT in the presence of 50 μ M ATP, 0.45 nM c-RAF, 11.25 nM MEK, 90.5 nM ERK, and 0.5 μ M FITC-labeled ERK (FITC-Aca-Ala-Ala-Ala-Thr-Gly-Pro-Leu-Ser-Pro-Gly-Pro-Phe-Ala-NH₂). C-RAF, MEK, ERK and the ERK peptide substrates were added sequentially into the reaction buffer. Activated c-Raf phosphorylates MEK, activated MEK phosphorylates ERK, and subsequently activated ERK phosphorylates its peptide substrate. The FITC-labeled peptide substrates, when phosphorylated by the kinase, bind to nanoparticles derivatized with trivalent metal cations through a metal-phospholigand interaction. The result of this
- 20
- 25
- 30

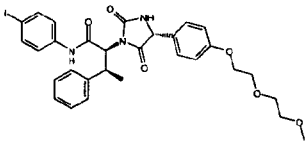
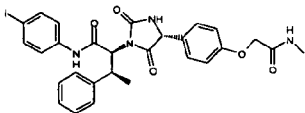
- 141 -

bound fluoresceinated phosphorylated product is an increase in polarization signal caused by a decrease in the molecular mobility of the bound product. Ten-point serial dilutions of the compounds were added into the MEK cascade assays before mixing with ERK and ERK peptide substrates. The reaction was incubated at 37 °C for 20 minutes for MEK activation, 20 minutes for ERK activation, 30 minutes for ERK peptide substrate phosphorylation, then was incubated overnight at room temperature for binding of IMAP beads. The IMAP assay was performed in a 384-well plate format. The changes in fluorescence polarization were measured by LJI instrument at 485 nm for excitation and 530 nm for emission. Polarization value (MP) was calculated as the following:

$$(MP) = 1000 \times (\text{intensity}_{\text{vertical}} - \text{intensity}_{\text{horizontal}}) / (\text{intensity}_{\text{vertical}} + \text{intensity}_{\text{horizontal}}).$$

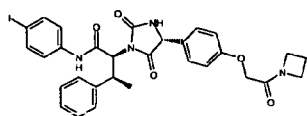
The IC₅₀ values were generated using Excel XLfit3 wizard. Percent activity and percent inhibition of reactions in the presence of a compound were calculated by comparing their MP values to those without a compound (as 100% activity).

The compounds of formula I in the above assay exhibit IC₅₀ values of less than 10 micromolar, as can be seen from the following specific data:

Example No.	Chemical Structure	IC ₅₀ / μM
8		0.113
9		0.063

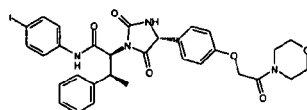
- 142 -

10



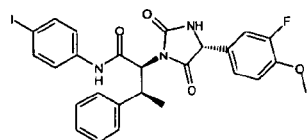
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11



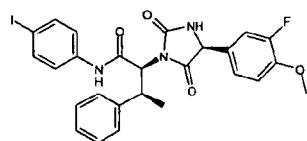
0.071

12



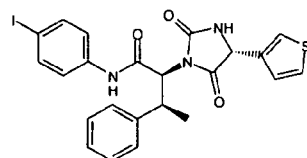
0.027

13



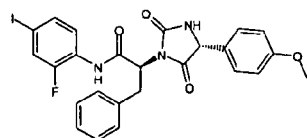
0.765

14



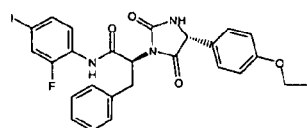
0.089

18



0.063

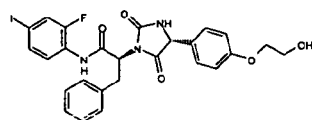
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0.106

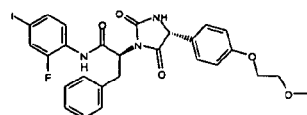
- 143 -

20



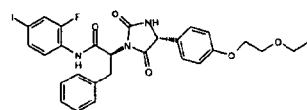
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21



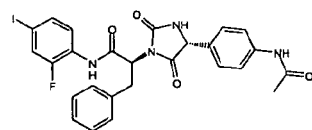
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22



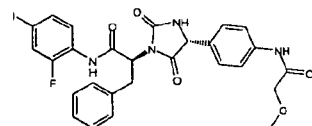
0.085

26



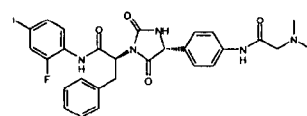
0.062

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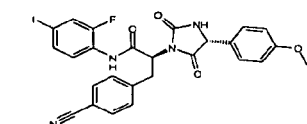
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28



0.055

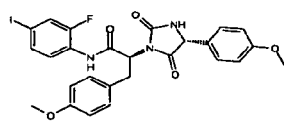
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0.336

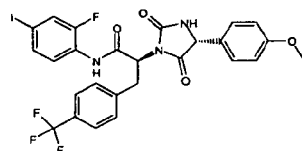
- 144 -

34



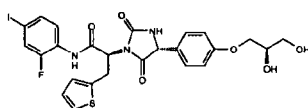
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35



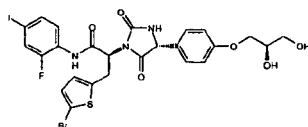
0.306

74



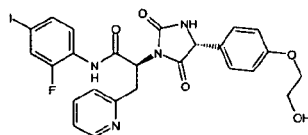
0.023

75



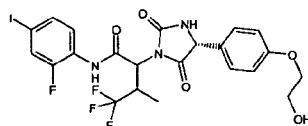
0.158

76



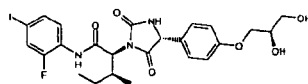
0.058

89



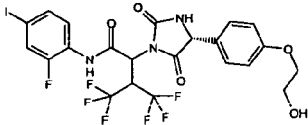
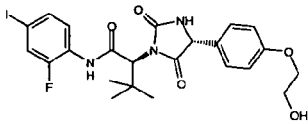
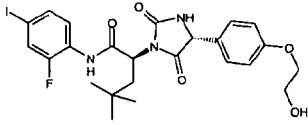
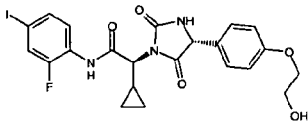
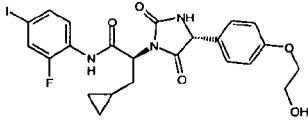
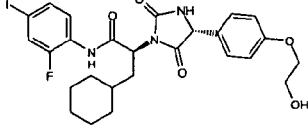
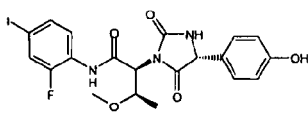
0.191

90



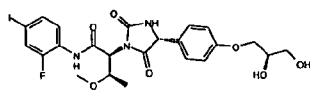
0.045

- 145 -

91		0.435
92		0.278
93		0.608
94		0.370
95		0.082
96		0.089
97		0.047

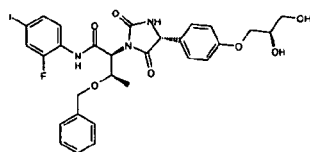
- 146 -

99



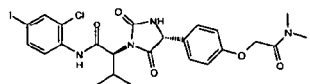
0.157

100



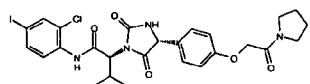
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125



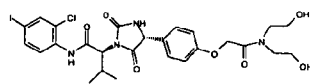
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126



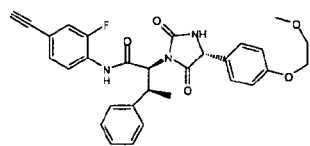
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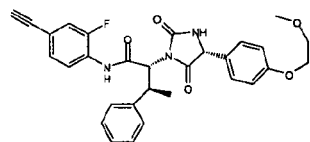
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142



0.040

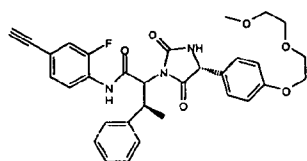
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0.385

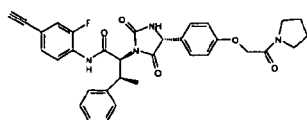
- 147 -

144



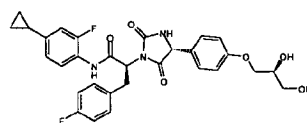
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145



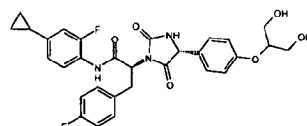
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159



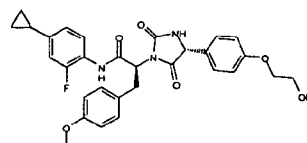
0.110

160



0.084

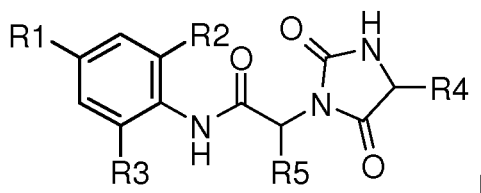
161



0.026

Claims:

1. A compound of formula I:

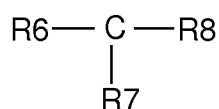


5

wherein:

- R1 is selected from the group consisting of bromo, iodo, ethynyl, cycloalkyl, alkoxy, azetidiny, acetyl, heterocycyl, cyano, straight-chained alkyl and branched-chain alkyl;
- R2 is selected from the group consisting of hydrogen, chloro, fluoro, and alkyl;
- R3 is selected from the group consisting of hydrogen and fluoro;
- R4 is selected from the group consisting of hydrogen, optionally substituted aryl, alkyl, and cycloalkyl;
- R5 is selected from the group consisting of hydrogen and

15



20

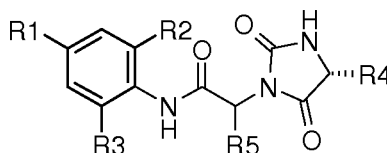
wherein R6 is selected from the group consisting of hydroxyl, alkoxy, cycloalkyl, trihaloalkyl, alkyl, optionally substituted aryl, and optionally substituted heteroaryl;

R7 and R8 are independently selected from the group consisting of hydrogen, alkyl, and trihaloalkyl; or

R6 and R7 can together form a cycloalkyl group and R8 is hydrogen;

and pharmaceutically acceptable salts or esters thereof.

2. The compound of claim 1 with the formula:



25

wherein:

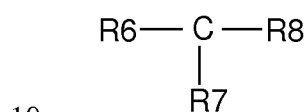
R1 is selected from the group consisting of bromo, iodo, ethynyl, cycloalkyl, alkoxy, acetyl, alkylthio, heterocycyl, cyano, straight-chained lower alkyl and branched-chain lower alkyl;

5 R2 is selected from the group consisting of hydrogen, chloro, fluoro, and lower alkyl;

R3 is selected from the group consisting of hydrogen and fluoro;

R4 is selected from the group consisting of optionally substituted aryl, lower alkyl, and cycloalkyl;

R5 is selected from the group consisting of hydrogen and



wherein R6 is selected from the group consisting of hydroxyl, alkoxy, cycloalkyl, trihalo lower alkyl, lower alkyl, optionally substituted aryl, and optionally substituted heteroaryl;

15 R7 and R8 are independently selected from the group consisting of hydrogen, lower alkyl, and trihalo lower alkyl; or

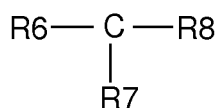
R6 and R7 can together form a cycloalkyl group and R8 is hydrogen; and pharmaceutically acceptable salts or esters thereof.

20 3. The compound of claim 2 wherein R1 is selected from the group consisting of iodo, ethynyl, and cyclopropyl.

4. The compound of claim 3 wherein R2 is selected from the group consisting of hydrogen, chloro, and fluoro.

25 5. The compound of claim 4 wherein R3 is hydrogen.

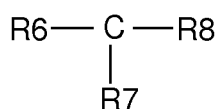
6. The compound of claim 5 wherein R5 is



30 and R7 and R8 are independently selected from the group consisting of hydrogen and methyl.

7. The compound of claim 6 wherein R4 is optionally substituted aryl.

8. The compound of claim 7 wherein R1 is selected from the group consisting of iodo, ethynyl, and cyclopropyl, R2 is selected from the group consisting of hydrogen, fluoro, and chloro, R3 is hydrogen, R4 is optionally substituted phenyl, R5 is



R6 is optionally substituted phenyl, R7 is methyl, and R8 is hydrogen.

9. The compound of claim 8 wherein R4 is phenyl substituted with alkoxy.

10. The compound of claim 9 wherein R1 is iodo and R2 is selected from the group consisting of chloro and fluoro.

11. The compound of claim 10, wherein R6 is phenyl and R4 is phenyl substituted with a member selected from a 2,3-dihydroxy-propoxy group and a 2-hydroxy-ethoxy group.

12. The compound according to claim 1 or 2, wherein

R4 is phenyl, which is unsubstituted or 1 or 2 times substituted with a substituent independently selected from

-halogen,

-P(O)(O-CH₃)₂,

-P(O)(OH)₂,

-S(O)₂-(C1-C6 alkyl),

-(O-CH₂-CH₂)₂-O-CH₃, and

-O-(C1-C6 alkyl), wherein the alkyl group is unsubstituted or 1 or 2 times substituted with a substituent independently selected from

-OH,

-oxo,

-C3-C6 cycloalkyl,

-O-(C1-C6 alkyl), -NH-(C1-C6 alkyl) or -N(C1-C6 alkyl)₂,
wherein the alkyl groups are unsubstituted or substituted by
-OH, or
- a 4 to 6-membered heterocycle, wherein the heteroatoms
are selected from N, S and O.

5

13. The compound of claim 12, wherein R5 is 1-phenyl-ethyl.

14. The compound of claim 13, wherein

10

R1 is iodo;

R2 is hydrogen or fluoro; and

R3 is hydrogen or fluoro.

15. The compound of claim 12, wherein R5 is benzyl, which benzyl is

15

unsubstituted or once substituted by

-(C1-C6) alkyl,

-fluoro or chloro,

-CN,

-O-(C1-C6) alkyl, and

20

-CF₃.

16. The compound of claim 12, wherein R5 is (C1-C6) alkyl, which is
unsubstituted or 1 or 2 times substituted with a substituent independently
selected from

25

-naphthyl, pyridinyl, thiazolyl, thiophenyl which is optionally
substituted with bromine, imidazolyl which is optionally
substituted with methyl; or

-(C3-C6) cycloalkyl;

30

-CF₃;

-O-(C1-C6) alkyl;

-O-CH₂-phenyl;

-S(O)₂-methyl;

-oxo; or

-NH₂.

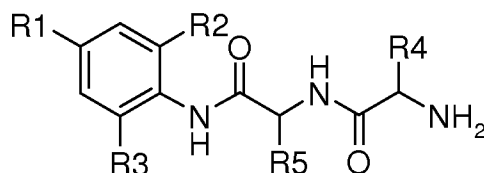
17. A compound according to claim 1 or 2, selected from the group consisting of:
- 5 (2S,3S)-N-(4-Bromo-phenyl)-2-[(R)-4-(4-methoxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide;
 - (2S,3S)-N-(4-Iodo-phenyl)-2-[(R)-4-(4-methoxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide;
 - (2S,3S)-N-(4-Ethynyl-2-fluoro-phenyl)-2-[(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-
 - 10 dioxo-imidazolidin-1-yl]-3-phenyl-butyramide;
 - (2R,3S)-N-(4-Ethynyl-2-fluoro-phenyl)-2-[(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide;
 - (2S,3S)-N-(2-Chloro-4-iodo-phenyl)-2-[(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide;
 - 15 (2S,3S)-2-[(R)-4-[4-(2-Hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-N-(4-iodo-2-methyl-phenyl)-3-phenyl-butyramide;
 - (2S,3S)-N-(2-Chloro-4-iodo-phenyl)-2-[(R)-4-[4-((R)-2,3-dihydroxy-propoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide;
 - (2S,3S)-N-(2-Chloro-4-iodo-phenyl)-2-[(R)-4-[4-((S)-2,3-dihydroxy-propoxy)-
 - 20 phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide;
 - (2S,3S)-2-[(R)-2,5-Dioxo-4-[4-(2-oxo-2-pyrrolidin-1-yl-ethoxy)-phenyl]-imidazolidin-1-yl]-N-(2-fluoro-4-iodo-phenyl)-3-phenyl-butyramide;
 - (2S,3S)-2-[(R)-2,5-Dioxo-4-thiophen-3-yl-imidazolidin-1-yl]-N-(4-iodo-phenyl)-3-phenyl-butyramide;
 - 25 (S)-2-[(R)-4-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-2,5-dioxo-imidazolidin-1-yl]-N-(2-fluoro-4-iodo-phenyl)-3-phenyl-propionamide;
 - (S)-2-[(R)-4-(4-Acetyl-amino-phenyl)-2,5-dioxo-imidazolidin-1-yl]-N-(2-fluoro-4-iodo-phenyl)-3-phenyl-propionamide;
 - (4-[(R)-1-[(1S,2S)-1-(2-Fluoro-4-iodo-phenyl-carbamoyl)-2-phenyl-propyl]-2,5-
 - 30 dioxo-imidazolidin-4-yl]-phenoxy-methyl)-phosphonic acid dimethyl ester;
 - (2S,3S)-N-(2-Fluoro-4-iodo-phenyl)-2-[(R)-4-isopropyl-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide;
 - (S)-N-(2-Fluoro-4-iodo-phenyl)-2-[(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-methyl-butyramide;

- (S)-N-(2-Fluoro-4-iodo-phenyl)-2-[(R)-4-(4-methoxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-3-o-tolyl-propionamide;
- (S)-N-(2-Fluoro-4-iodo-phenyl)-2-[(R)-4-(4-methoxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-3-m-tolyl-propionamide;
- 5 (S)-N-(2-Fluoro-4-iodo-phenyl)-2-[(R)-4-(4-methoxy-phenyl)-2,5-dioxo-imidazolidin-1-yl]-3-p-tolyl-propionamide; and
- (S)-N-(4-Cyclopropyl-2-fluoro-phenyl)-3-(4-fluoro-phenyl)-2-[(R)-4-[4-(2-hydroxy-1-hydroxymethyl-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-propionamide.
- 10 18. A compound according to claim 1 or 2, selected from the group consisting of:
- (2S,3S)-N-(2-Fluoro-4-iodo-phenyl)-2-[(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide;
- (2S,3S)-2-[(R)-4-[4-((R)-2,3-dihydroxy-propoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-N-(2-fluoro-4-iodo-phenyl)-3-phenyl-butyramide;
- 15 (2S,3S)-N-(2-Chloro-4-iodo-phenyl)-2-[(R)-4-[4-((R)-2,3-dihydroxy-propoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide;
- (2S,3S)-N-(2-Chloro-4-iodo-phenyl)-2-[(R)-4-[4-((S)-2,3-dihydroxy-propoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide; and
- 20 (2S,3S)-N-(4-Cyclopropyl-2-fluoro-phenyl)-2-[(R)-4-[4-(2-hydroxy-ethoxy)-phenyl]-2,5-dioxo-imidazolidin-1-yl]-3-phenyl-butyramide.
19. A pharmaceutical composition comprising a compound of claim 1 or 2, and a pharmaceutically acceptable diluent, excipient, or adjuvant.
- 25 20. A pharmaceutical composition comprising a compound of claim 11 or 14, and a pharmaceutically acceptable diluent, excipient, or adjuvant.
21. A pharmaceutical composition comprising a compound of claim 18, and a pharmaceutically acceptable diluent, excipient, or adjuvant.
- 30 22. A compound of claim 1 or 2 for the use as a medicament.

23. A compound according to claim 1 or 2 for use as a medicament for the treatment of cancer, in particular solid tumors, more particularly lung, breast, colon and prostate tumors.

5 24. The use of a compound according to claim 1 or 2 for the manufacture of a medicament for the treatment of cancer, in particular solid tumors, more particularly lung, breast, colon and prostate tumors.

10 25. A process for the synthesis of the compounds of formula I according to claim 1 or 2, comprising reacting a compound of formula 9



9

15 in the presence of phosgene or trichloromethyl chloroformate at temperatures below 0 °C and in the presence of a base, to give the corresponding compounds of formula I, wherein all substituents R1 to R5 have the meanings given in claim 1.

26. The novel compounds, intermediates, processes and uses substantially as described herein before.

20
