

Prodrug derivatives of substituted triazolopyridines

The present invention relates to prodrug derivatives of Mps-1 kinase inhibitors, processes for their preparation, and their use for the treatment and/or prophylaxis of diseases.

BACKGROUND OF THE INVENTION

Mps-1 (Monopolar Spindle 1) kinase (also known as Tyrosine Threonine Kinase, TTK) is a dual specificity Ser/Thr kinase which plays a key role in the activation of the mitotic checkpoint (also known as spindle checkpoint, spindle assembly checkpoint) thereby ensuring proper chromosome segregation during mitosis [Abrieu A *et al.*, Cell, 2001, 106, 83-93]. Every dividing cell has to ensure equal separation of the replicated chromosomes into the two daughter cells. Upon entry into mitosis, chromosomes are attached at their kinetochores to the microtubules of the spindle apparatus. The mitotic checkpoint is a surveillance mechanism that is active as long as unattached kinetochores are present and prevents mitotic cells from entering anaphase and thereby completing cell division with unattached chromosomes [Suijkerbuijk SJ and Kops GJ, Biochemica et Biophysica Acta, 2008, 1786, 24-31; Musacchio A and Salmon ED, Nat Rev Mol Cell Biol., 2007, 8, 379-93]. Once all kinetochores are attached in a correct amphitelic, *i.e.* bipolar, fashion with the mitotic spindle, the checkpoint is satisfied and the cell enters anaphase and proceeds through mitosis. The mitotic checkpoint consists of a complex network of a number of essential proteins, including members of the MAD (mitotic arrest deficient, MAD 1-3) and Bub (Budding uninhibited by benzimidazole, Bub 1-3) families, the motor protein CENP-E, Mps-1 kinase as well as other components, many of these being over-expressed in proliferating cells (*e.g.* cancer cells) and tissues [Yuan B *et al.*, Clinical Cancer Research, 2006, 12, 405-10]. The essential role of Mps-1 kinase activity in mitotic checkpoint signalling has been shown by

shRNA-silencing, chemical genetics as well as chemical inhibitors of Mps-1 kinase [Jelluma N *et al.*, PLoS ONE, 2008, 3, e2415; Jones MH *et al.*, Current Biology, 2005, 15, 160-65; Dorer RK *et al.*, Current Biology, 2005, 15, 1070-76; Schmidt M *et al.*, EMBO Reports, 2005, 6, 866-72].

- 5 There is ample evidence linking reduced but incomplete mitotic checkpoint function with aneuploidy and tumorigenesis [Weaver BA and Cleveland DW, Cancer Research, 2007, 67, 10103-5; King RW, Biochimica et Biophysica Acta, 2008, 1786, 4-14]. In contrast, complete inhibition of the mitotic checkpoint has been recognised to result in severe chromosome missegregation and
- 10 induction of apoptosis in tumour cells [Kops GJ *et al.*, Nature Reviews Cancer, 2005, 5, 773-85; Schmidt M and Medema RH, Cell Cycle, 2006, 5, 159-63; Schmidt M and Bastians H, Drug Resistance Updates, 2007, 10, 162-81].

Therefore, mitotic checkpoint abrogation through pharmacological inhibition

15 of Mps-1 kinase or other components of the mitotic checkpoint represents a new approach for the treatment of proliferative disorders including solid tumours such as carcinomas and sarcomas and leukaemias and lymphoid malignancies or other disorders associated with uncontrolled cellular proliferation.

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Different compounds have been disclosed in prior art which show an inhibitory effect on Mps-1 kinase: WO 2009/024824 A1 discloses 2-Anilinopurin-8-ones as inhibitors of Mps-1 for the treatment of proliferate disorders. WO 2010/124826 A1 discloses substituted imidazoquinoxaline compounds as inhibitors of Mps-1

25 kinase. WO 2011/026579 A1 discloses substituted aminoquinoxalines as Mps-1 inhibitors. WO 2011/064328 A1, WO 2011/063907 A1, WO 2011/063908 A1, and WO 2012/143329 A1 relate to [1,2,4]-triazolo-[1,5-*a*]-pyridines and their use for inhibition of Mps-1 kinase.

The above mentioned patent applications which are related to [1,2,4]-triazolo-[1,5-*a*]-pyridines mainly focus on the effectiveness of the compounds in inhibiting Mps-1 kinase, expressed by the half maximal inhibitory concentration (IC₅₀) of the compounds. For example, in WO 2011/063908 A1 the effectiveness in inhibiting Mps-1 kinase was measured in an Mps-1 kinase assay with a concentration of 10 μ M adenosine triphosphate (ATP). The cellular concentration of ATP in mammals is in the millimolar range. Therefore it is important that a drug substance is also effective in inhibiting Mps-1 kinase in a kinase assay with a concentration of ATP in the millimolar range, e.g. 2 mM ATP, in order to potentially achieve an antiproliferative effect in a cellular assay.

In addition, as one of ordinary skill in the art knows, there are many more factors determining the druglikeness of a compound. The objective of a pre-clinical development is to assess e.g. safety, toxicity, pharmacokinetics and metabolism parameters prior to human clinical trials. One important factor for assessing the druglikeness of a compound is the metabolic stability. The metabolic stability of a compound can be determined e.g. by incubating the compound with a suspension of liver microsomes from e.g. a rat, a dog and/or a human (for details see experimental section).

Another important factor for assessing the druglikeness of a compound for the treatment of cancer is the inhibition of cell proliferation which can be determined e.g. in a HeLa cell proliferation assay (for details see experimental section).

The successful delivery of a pharmaceutical to a patient is of critical importance in the treatment of disorders as well. The use of many clinical drugs with known bioactive properties is limited by the drugs' very low water

solubility, making for example intravenous administration of the active ingredient difficult.

Intravenous (i.v.) medication administration refers to the process of giving
5 medication directly into a patient's vein. Methods of administering i.v. medication may include giving the medication by rapid injection (push) into the vein using a syringe, giving the medication intermittently over a specific amount of time using an i.v. secondary line, or giving the medication continuously mixed in the main i.v. solution.

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The primary purpose of giving i.v. medications is to initiate a rapid systemic response to medication. It is one of the fastest ways to deliver medication. The drug is immediately available to the body. It is easier to control the actual amount of drug delivered to the body by using the i.v. method and it is also
15 easier to maintain drug levels in the blood for therapeutic response.

As a result of low water solubility, many drugs often are formulated in co-solvent pharmaceutical vehicles or as prodrugs.

20 A prodrug is an active drug chemically transformed into a derivative which by virtue of chemical or enzymatic attack is converted to the parent drug within the body before or after reaching the site of action. The process of converting an active drug into inactive form is called drug latentiation. Prodrugs can be carrier-linked-prodrugs and bioprecursors. The carrier-linked prodrug results
25 from a temporary linkage of the active molecule with a transport moiety. Such prodrugs are less active or inactive compared to the parent active drug. The transport moiety will be chosen for its non-toxicity and its ability to ensure the release of the active principle with efficient kinetics. Whereas the bioprecursors result from a molecular modification of the active principle itself

by generation of a new molecule that is capable of being a substrate to the metabolizing enzymes releasing the active principle as a metabolite.

Prodrugs are prepared to alter the drug pharmacokinetics, improve stability
5 and solubility, decrease toxicity, increase specificity, and/or increase duration of the pharmacological effect of the drug. By altering pharmacokinetics the drug bioavailability is increased by increasing absorption, distribution, biotransformation, and/or excretion of the drug.

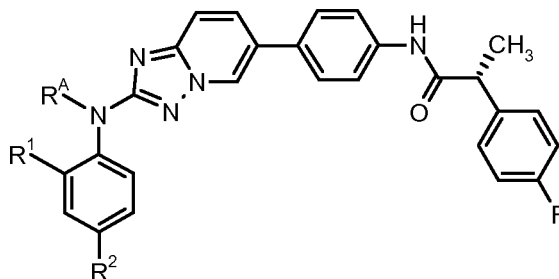
10 In designing the prodrugs, it is important to consider the following factors: a) the linkage between the carrier and the drug is usually a covalent bond, b) the prodrug is inactive or less active than the active principle, c) the prodrug synthesis should not be expensive, d) the prodrug has to be reversible or bioreversible derivative of the drug, and e) the carrier moiety must be non-
15 toxic and inactive when released.

Prodrugs are usually prepared by: a) formation of ester, hemiesters, carbonate esters, nitrate esters, amides, hydroxamic acids, carbamates, imines, mannich bases, and enamines of the active drug, b) functionalizing the drug with azo,
20 glycoside, peptide, and ether functional groups, c) use of polymers, salts, complexes, phosphoramides, acetals, hemiacetals, and ketal forms of the drug (for example, see Andrejus Korolkovas's, "Essentials of Medicinal Chemistry", pp. 97-118).

25 It was therefore an object of the present invention to identify an Mps-1 kinase inhibiting compound or a prodrug derivative thereof which is characterized by a high druglikeness and which can be administered intravenously.

SUMMARY of the INVENTION

The present invention relates to compounds of general formula (I) :



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(I)

in which :

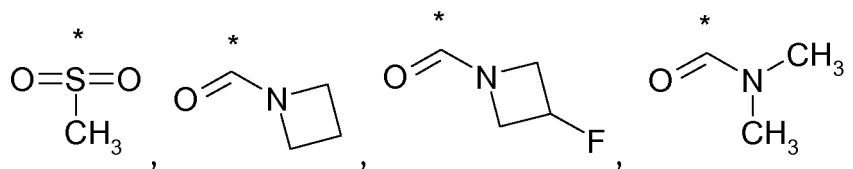
R^A represents a group selected from:

- C(=O)-(CH₂)₃-N(H)R³,
- C(=O)-(CR⁴R⁵)-N(R⁶)R⁷,
- C(=O)-O-(CH₂)₂-N(H)R³,
- C(=O)-O-(CR⁴R⁵)-O-P(=O)(OH)₂,
- C(=O)-O-(CR⁴R⁵)-O-C(=O)-R⁸,
- C(=O)-O-(CR⁴R⁵)-O-C(=O)-CH(R⁶)-NH-C(=O)-R⁹;

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R^1 represents a group selected from methoxy- and 2,2,2-trifluoroethoxy-;

R^2 represents a group selected from:



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wherein "*" indicates the point of attachment to the phenyl ring R^2 is attached to;

R^3 represents a group selected from:

C₁-C₆-alkyl, C₃-C₆-cycloalkyl-,

4- to 7-membered heterocycloalkyl-;

said group being optionally substituted, one or more times, identically or differently, with a group selected from:

-OH, -NH₂, -N(H)R¹⁰, -N(R¹⁰)R¹¹, -O-P(=O)(OH)₂;

5

R⁴ and R⁵, independently from each other, represent a group selected from a hydrogen atom and a C₁-C₃-alkyl- group,

or

10 R⁴ and R⁵, together with the carbon atom to which they are attached, form a C₃-C₆-cycloalkyl ring;

R⁶ represents a hydrogen atom or a C₁-C₃-alkyl- group;

15 R⁷ represents a hydrogen atom or a group -C(=O)R⁹;

R⁸ represents a group selected from:

C₁-C₆-alkyl, C₃-C₆-cycloalkyl-,

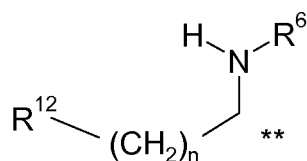
4- to 7-membered heterocycloalkyl-;

20 said group being optionally substituted, one or more times, identically or differently, with a group selected from:

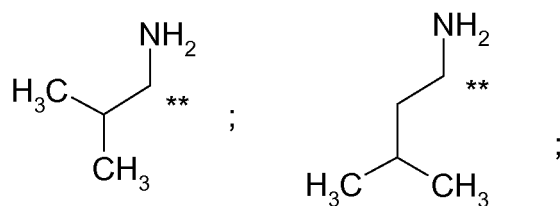
-OH, -NH₂, -N(H)R¹⁰, -N(R¹⁰)R¹¹, -O-P(=O)(OH)₂;

R⁹ represents a group

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or R⁹ represents a group selected from:



wherein "*" indicates the point of attachment to the carbonyl group R⁹
 5 is attached to;

R¹⁰ and R¹¹, independently from each other, represent a group selected from a
 hydrogen atom and a C₁-C₃-alkyl- group, or

10 R¹⁰ and R¹¹, together with the nitrogen atom to which they are attached form a
 4- to 7-membered heterocycloalkyl ring;

R¹² represents a group selected from a hydrogen atom, -OH, -NR¹⁰R¹¹,
 -NH-C(=NH)-NH₂;

15

n is an integer of 0, 1, 2, 3 or 4;

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture
 of same.

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DETAILED DESCRIPTION of the INVENTION

The terms as mentioned in the present text have preferably the following
 25 meanings :

The term “halogen atom” or “halo-” is to be understood as meaning a fluorine, chlorine, bromine or iodine atom.

The term “C₁-C₆-alkyl” is to be understood as preferably meaning a linear or
5 branched, saturated, monovalent hydrocarbon group having 1, 2, 3, 4, 5 or 6
carbon atoms, *e.g.* a methyl, ethyl, propyl, butyl, pentyl, hexyl, *iso*-propyl,
iso-butyl, *sec*-butyl, *tert*-butyl, *iso*-pentyl, 2-methylbutyl, 1-methylbutyl, 1-
ethylpropyl, 1,2-dimethylpropyl, *neo*-pentyl, 1,1-dimethylpropyl, 4-
methylpentyl, 3-methylpentyl, 2-methylpentyl, 1-methylpentyl, 2-ethylbutyl,
10 1-ethylbutyl, 3,3-dimethylbutyl, 2,2-dimethylbutyl, 1,1-dimethylbutyl, 2,3-
dimethylbutyl, 1,3-dimethylbutyl, or 1,2-dimethylbutyl group, or an isomer
thereof. Particularly, said group has 1, 2, 3 or 4 carbon atoms (“C₁-C₄-alkyl”),
e.g. a methyl, ethyl, propyl, butyl, *iso*-propyl, *iso*-butyl, *sec*-butyl, *tert*-butyl
group, more particularly 1, 2 or 3 carbon atoms (“C₁-C₃-alkyl”), *e.g.* a methyl,
15 ethyl, *n*-propyl- or *iso*-propyl group.

The term “C₁-C₆-alkylene” is to be understood as preferably meaning a linear
or branched, saturated, bivalent hydrocarbon group having 1, 2, 3, 4, 5 or 6
carbon atoms, *e.g.* a methylene, ethylene, propylene, butylene, pentylene,
20 hexylene, *iso*-propylene, *iso*-butylene, *sec*-butylene, *tert*-butylene, *iso*-
pentylene, 2-methylbutylene, 1-methylbutylene, 1-ethylpropylene, 1,2-
dimethylpropylene, *neo*-pentylene, 1,1-dimethylpropylene, 4-
methylpentylene, 3-methylpentylene, 2-methylpentylene, 1-methylpentylene,
2-ethylbutylene, 1-ethylbutylene, 3,3-dimethylbutylene, 2,2-
25 dimethylbutylene, 1,1-dimethylbutylene, 2,3-dimethylbutylene, 1,3-
dimethylbutylene, or 1,2-dimethylbutylene group, or an isomer thereof.
Particularly, said group has 2, 3, 4, 5 or 6 carbon atoms (“C₂-C₆-alkylene”),
e.g. a methylene, ethylene, propylene, butylene, *iso*-propylene, *iso*-butylene,
sec-butylene, *tert*-butylene group, more particularly 2, 3 or 4 carbon atoms

("C₂-C₄-alkylene"), e.g. an ethylene, propylene-, *iso*-propylene, butylene, or *iso*-butylene group.

The term "halo-C₁-C₆-alkyl" is to be understood as preferably meaning a linear or branched, saturated, monovalent hydrocarbon group in which the term "C₁-C₆-alkyl" is defined *supra*, and in which one or more of the hydrogen atoms is replaced, in identically or differently, by a halogen atom. Particularly, said halogen atom is F. Said halo-C₁-C₆-alkyl group is, for example, -CF₃, -CHF₂, -CH₂F, -CF₂CF₃, or -CH₂CF₃.

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The term "C₁-C₆-alkoxy" is to be understood as preferably meaning a linear or branched, saturated, monovalent group of formula -O-(C₁-C₆-alkyl), in which the term "C₁-C₆-alkyl" is defined *supra*, e.g. a methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *iso*-butoxy, *tert*-butoxy, *sec*-butoxy, pentoxy, *iso*-pentoxy, or *n*-hexoxy group, or an isomer thereof.

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The term "halo-C₁-C₆-alkoxy" is to be understood as preferably meaning a linear or branched, saturated, monovalent C₁-C₆-alkoxy group, as defined *supra*, in which one or more of the hydrogen atoms is replaced, in identically or differently, by a halogen atom. Particularly, said halogen atom is F. Said halo-C₁-C₆-alkoxy group is, for example, -OCF₃, -OCHF₂, -OCH₂F, -OCF₂CF₃, or -OCH₂CF₃.

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The term "C₁-C₆-alkoxy-C₁-C₆-alkyl" is to be understood as preferably meaning a linear or branched, saturated, monovalent C₁-C₆-alkyl group, as defined *supra*, in which one or more of the hydrogen atoms is replaced, in identically or differently, by a C₁-C₆-alkoxy group, as defined *supra*, e.g. methoxyalkyl, ethoxyalkyl, propyloxyalkyl, *iso*-propoxyalkyl, butoxyalkyl, *iso*-butoxyalkyl, *tert*-butoxyalkyl, *sec*-butoxyalkyl, pentyloxyalkyl, *iso*-pentyloxyalkyl, hexyloxyalkyl group, or an isomer thereof.

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- The term “halo-C₁-C₆-alkoxy-C₁-C₆-alkyl” is to be understood as preferably meaning a linear or branched, saturated, monovalent C₁-C₆-alkoxy-C₁-C₆-alkyl group, as defined *supra*, in which one or more of the hydrogen atoms is replaced, in identically or differently, by a halogen atom. Particularly, said halogen atom is F. Said halo-C₁-C₆-alkoxy-C₁-C₆-alkyl group is, for example, -CH₂CH₂OCF₃, -CH₂CH₂OCHF₂, -CH₂CH₂OCH₂F, -CH₂CH₂OCF₂CF₃, or -CH₂CH₂OCH₂CF₃.
- 10 The term “C₂-C₆-alkenyl” is to be understood as preferably meaning a linear or branched, monovalent hydrocarbon group, which contains one or more double bonds, and which has 2, 3, 4, 5 or 6 carbon atoms, particularly 2 or 3 carbon atoms (“C₂-C₃-alkenyl”), it being understood that in the case in which said alkenyl group contains more than one double bond, then said double bonds may be isolated from, or conjugated with, each other. Said alkenyl group is, for example, a vinyl, allyl, (*E*)-2-methylvinyl, (*Z*)-2-methylvinyl, homoallyl, (*E*)-but-2-enyl, (*Z*)-but-2-enyl, (*E*)-but-1-enyl, (*Z*)-but-1-enyl, pent-4-enyl, (*E*)-pent-3-enyl, (*Z*)-pent-3-enyl, (*E*)-pent-2-enyl, (*Z*)-pent-2-enyl, (*E*)-pent-1-enyl, (*Z*)-pent-1-enyl, hex-5-enyl, (*E*)-hex-4-enyl, (*Z*)-hex-4-enyl, (*E*)-hex-3-enyl, (*Z*)-hex-3-enyl, (*E*)-hex-2-enyl, (*Z*)-hex-2-enyl, (*E*)-hex-1-enyl, (*Z*)-hex-1-enyl, *iso*-propenyl, 2-methylprop-2-enyl, 1-methylprop-2-enyl, 2-methylprop-1-enyl, (*E*)-1-methylprop-1-enyl, (*Z*)-1-methylprop-1-enyl, 3-methylbut-3-enyl, 2-methylbut-3-enyl, 1-methylbut-3-enyl, 3-methylbut-2-enyl, (*E*)-2-methylbut-2-enyl, (*Z*)-2-methylbut-2-enyl, (*E*)-1-methylbut-2-enyl, (*Z*)-1-methylbut-2-enyl, (*E*)-3-methylbut-1-enyl, (*Z*)-3-methylbut-1-enyl, (*E*)-2-methylbut-1-enyl, (*Z*)-2-methylbut-1-enyl, (*E*)-1-methylbut-1-enyl, (*Z*)-1-methylbut-1-enyl, 1,1-dimethylprop-2-enyl, 1-ethylprop-1-enyl, 1-propylvinyl, 1-isopropylvinyl, 4-methylpent-4-enyl, 3-methylpent-4-enyl, 2-methylpent-4-enyl, 1-methylpent-4-enyl, 4-methylpent-3-enyl, (*E*)-3-methylpent-3-enyl, (*Z*)-3-methylpent-3-enyl,

(E)-2-methylpent-3-enyl, (Z)-2-methylpent-3-enyl, (E)-1-methylpent-3-enyl,
 (Z)-1-methylpent-3-enyl, (E)-4-methylpent-2-enyl, (Z)-4-methylpent-2-enyl,
 (E)-3-methylpent-2-enyl, (Z)-3-methylpent-2-enyl, (E)-2-methylpent-2-enyl,
 (Z)-2-methylpent-2-enyl, (E)-1-methylpent-2-enyl, (Z)-1-methylpent-2-enyl,
 5 (E)-4-methylpent-1-enyl, (Z)-4-methylpent-1-enyl, (E)-3-methylpent-1-enyl,
 (Z)-3-methylpent-1-enyl, (E)-2-methylpent-1-enyl, (Z)-2-methylpent-1-enyl,
 (E)-1-methylpent-1-enyl, (Z)-1-methylpent-1-enyl, 3-ethylbut-3-enyl,
 2-ethylbut-3-enyl, 1-ethylbut-3-enyl, (E)-3-ethylbut-2-enyl,
 (Z)-3-ethylbut-2-enyl, (E)-2-ethylbut-2-enyl, (Z)-2-ethylbut-2-enyl,
 10 (E)-1-ethylbut-2-enyl, (Z)-1-ethylbut-2-enyl, (E)-3-ethylbut-1-enyl,
 (Z)-3-ethylbut-1-enyl, 2-ethylbut-1-enyl, (E)-1-ethylbut-1-enyl,
 (Z)-1-ethylbut-1-enyl, 2-propylprop-2-enyl, 1-propylprop-2-enyl,
 2-isopropylprop-2-enyl, 1-isopropylprop-2-enyl, (E)-2-propylprop-1-enyl,
 (Z)-2-propylprop-1-enyl, (E)-1-propylprop-1-enyl, (Z)-1-propylprop-1-enyl,
 15 (E)-2-isopropylprop-1-enyl, (Z)-2-isopropylprop-1-enyl,
 (E)-1-isopropylprop-1-enyl, (Z)-1-isopropylprop-1-enyl,
 (E)-3,3-dimethylprop-1-enyl, (Z)-3,3-dimethylprop-1-enyl,
 1-(1,1-dimethylethyl)ethenyl, buta-1,3-dienyl, penta-1,4-dienyl,
 hexa-1,5-dienyl, or methylhexadienyl group. Particularly, said group is vinyl or
 20 allyl.

The term “C₂-C₆-alkynyl” is to be understood as preferably meaning a linear or
 branched, monovalent hydrocarbon group which contains one or more triple
 bonds, and which contains 2, 3, 4, 5 or 6 carbon atoms, particularly 2 or 3
 25 carbon atoms (“C₂-C₃-alkynyl”). Said C₂-C₆-alkynyl group is, for example,
 ethynyl, prop-1-ynyl, prop-2-ynyl, but-1-ynyl, but-2-ynyl, but-3-ynyl,
 pent-1-ynyl, pent-2-ynyl, pent-3-ynyl, pent-4-ynyl, hex-1-ynyl, hex-2-ynyl,
 hex-3-ynyl, hex-4-ynyl, hex-5-ynyl, 1-methylprop-2-ynyl, 2-methylbut-3-ynyl,
 1-methylbut-3-ynyl, 1-methylbut-2-ynyl, 3-methylbut-1-ynyl,
 30 1-ethylprop-2-ynyl, 3-methylpent-4-ynyl, 2-methylpent-4-ynyl, 1-methyl-

pent-4-ynyl, 2-methylpent-3-ynyl, 1-methylpent-3-ynyl, 4-methylpent-2-ynyl, 1-methylpent-2-ynyl, 4-methylpent-1-ynyl, 3-methylpent-1-ynyl, 2-ethylbut-3-ynyl, 1-ethylbut-3-ynyl, 1-ethylbut-2-ynyl, 1-propylprop-2-ynyl, 1-isopropylprop-2-ynyl, 2,2-dimethylbut-3-ynyl, 1,1-dimethylbut-3-ynyl, 1,1-dimethylbut-2-ynyl, or 3,3-dimethylbut-1-ynyl group. Particularly, said alkynyl group is ethynyl, prop-1-ynyl, or prop-2-ynyl.

The term “C₃-C₇-cycloalkyl” is to be understood as meaning a saturated, monovalent, monocyclic hydrocarbon ring which contains 3, 4, 5, 6 or 7 carbon atoms. Said C₃-C₇-cycloalkyl group is for example a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl ring. Particularly, said ring contains 3, 4, 5 or 6 carbon atoms (“C₃-C₆-cycloalkyl”).

The term “C₄-C₈-cycloalkenyl” is to be understood as preferably meaning a monovalent, monocyclic hydrocarbon ring which contains 4, 5, 6, 7 or 8 carbon atoms and one or two double bonds, in conjugation or not, as the size of said cycloalkenyl ring allows. Particularly, said ring contains 4, 5 or 6 carbon atoms (“C₄-C₆-cycloalkenyl”). Said C₄-C₈-cycloalkenyl group is for example a cyclobutenyl, cyclopentenyl, or cyclohexenyl group.

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The term “3- to 10-membered heterocycloalkyl”, is to be understood as meaning a saturated, monovalent, mono- or bicyclic hydrocarbon ring which contains 2, 3, 4, 5, 6, 7, 8 or 9 carbon atoms, and one or more heteroatom-containing groups selected from C(=O), O, S, S(=O), S(=O)₂, NR^a, in which R^a represents a hydrogen atom, or a C₁-C₆-alkyl- group ; it being possible for said heterocycloalkyl group to be attached to the rest of the molecule via any one of the carbon atoms or, if present, the nitrogen atom.

Particularly, said 3- to 10-membered heterocycloalkyl can contain 2, 3, 4, 5 or 6 carbon atoms, and one or more of the above-mentioned

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heteroatom-containing groups (a “3- to 7-membered heterocycloalkyl”), more particularly said heterocycloalkyl can contain 4, 5 or 6 carbon atoms, and one or more of the above-mentioned heteroatom-containing groups (a “4- to 6-membered heterocycloalkyl”).

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Particularly, without being limited thereto, said heterocycloalkyl can be a 4-membered ring, such as an azetidiny, oxetanyl, or a 5-membered ring, such as tetrahydrofuranyl, dioxolinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, or a 6-membered ring, such as tetrahydropyranyl, piperidinyl, morpholinyl, 10 dithianyl, thiomorpholinyl, piperazinyl, or trithianyl, or a 7-membered ring, such as a diazepanyl ring, for example.

The term “4- to 10-membered heterocycloalkenyl”, is to be understood as meaning an unsaturated, monovalent, mono- or bicyclic hydrocarbon ring 15 which contains 3, 4, 5, 6, 7, 8 or 9 carbon atoms, and one or more heteroatom-containing groups selected from C(=O), O, S, S(=O), S(=O)₂, NR^a, in which R^a represents a hydrogen atom or a C₁-C₆-alkyl- group ; it being possible for said heterocycloalkenyl group to be attached to the rest of the molecule via any one of the carbon atoms or, if present, the nitrogen atom. Examples of 20 said heterocycloalkenyl may contain one or more double bonds, e.g. 4H-pyranyl, 2H-pyranyl, 3H-diaziriny, 2,5-dihydro-1H-pyrrolyl, [1,3]dioxolyl, 4H-[1,3,4]thiadiazinyl, 2,5-dihydrofuranyl, 2,3-dihydrofuranyl, 2,5-dihydrothiophenyl, 2,3-dihydrothiophenyl, 4,5-dihydrooxazolyl, or 4H-[1,4]thiazinyl group.

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The term “aryl” is to be understood as preferably meaning a monovalent, aromatic, mono-, or bi- or tricyclic hydrocarbon ring having 6, 7, 8, 9, 10, 11, 12, 13 or 14 carbon atoms (a “C₆-C₁₄-aryl” group), particularly a ring having 6 carbon atoms (a “C₆-aryl” group), e.g. a phenyl group; or a ring having 9 30 carbon atoms (a “C₉-aryl” group), e.g. an indanyl or indenyl group, or a ring

having 10 carbon atoms (a “C₁₀-aryl” group), e.g. a tetralinyl, dihydronaphthyl, or naphthyl group, or a biphenyl group (a “C₁₂-aryl” group), or a ring having 13 carbon atoms, (a “C₁₃-aryl” group), e.g. a fluorenyl group, or a ring having 14 carbon atoms, (a “C₁₄-aryl” group), e.g. an anthracenyl group. Preferably, the aryl group is a phenyl group.

The term “heteroaryl” is understood as preferably meaning a monovalent, monocyclic-, bicyclic- or tricyclic aromatic ring system having 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 ring atoms (a “5- to 14-membered heteroaryl” group), particularly 5 or 6 or 9 or 10 atoms, and which contains at least one heteroatom which may be identical or different, said heteroatom being such as oxygen, nitrogen or sulfur, and in addition in each case can be benzocondensed. Particularly, heteroaryl is selected from thienyl, furanyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, thia-4H-pyrazolyl *etc.*, and benzo derivatives thereof, such as, for example, benzofuranyl, benzothienyl, benzoxazolyl, benzisoxazolyl, benzimidazolyl, benzotriazolyl, indazolyl, indolyl, isoindolyl, *etc.*; or pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, *etc.*, and benzo derivatives thereof, such as, for example, quinolinyl, quinazolinyl, isoquinolinyl, *etc.*; or azocinyl, indolizinyl, purinyl, *etc.*, and benzo derivatives thereof; or cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthpyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, xanthenyl, or oxepinyl, *etc.*.

In general, and unless otherwise mentioned, the heteroaryl or heteroarylenic radicals include all the possible isomeric forms thereof, e.g. the positional isomers thereof. Thus, for some illustrative non-restricting example, the term pyridyl includes pyridin-2-yl, pyridin-3-yl, and pyridin-4-yl; or the term thienyl includes thien-2-yl and thien-3-yl. Preferably, the heteroaryl group is a pyridinyl group.

The term "C₁-C₆", as used throughout this text, *e.g.* in the context of the definition of "C₁-C₆-alkyl", "C₁-C₆-haloalkyl", "C₁-C₆-alkoxy", or "C₁-C₆-haloalkoxy" is to be understood as meaning an alkyl group having a finite
5 number of carbon atoms of 1 to 6, *i.e.* 1, 2, 3, 4, 5, or 6 carbon atoms. It is to be understood further that said term "C₁-C₆" is to be interpreted as any sub-range comprised therein, *e.g.* C₁-C₆, C₂-C₅, C₃-C₄, C₁-C₂, C₁-C₃, C₁-C₄, C₁-C₅, C₁-C₆; particularly C₁-C₂, C₁-C₃, C₁-C₄, C₁-C₅, C₁-C₆; more particularly C₁-C₄; in the case of "C₁-C₆-haloalkyl" or "C₁-C₆-haloalkoxy" even more particularly C₁-C₂.

10

Similarly, as used herein, the term "C₂-C₆", as used throughout this text, *e.g.* in the context of the definitions of "C₂-C₆-alkenyl" and "C₂-C₆-alkynyl", is to be understood as meaning an alkenyl group or an alkynyl group having a finite number of carbon atoms of 2 to 6, *i.e.* 2, 3, 4, 5, or 6 carbon atoms. It is to be
15 understood further that said term "C₂-C₆" is to be interpreted as any sub-range comprised therein, *e.g.* C₂-C₆, C₃-C₅, C₃-C₄, C₂-C₃, C₂-C₄, C₂-C₅; particularly C₂-C₃.

Further, as used herein, the term "C₃-C₇", as used throughout this text, *e.g.* in
20 the context of the definition of "C₃-C₇-cycloalkyl", is to be understood as meaning a cycloalkyl group having a finite number of carbon atoms of 3 to 7, *i.e.* 3, 4, 5, 6 or 7 carbon atoms. It is to be understood further that said term "C₃-C₇" is to be interpreted as any sub-range comprised therein, *e.g.* C₃-C₆, C₄-C₅, C₃-C₅, C₃-C₄, C₄-C₆, C₅-C₇; particularly C₃-C₆.

25

As used herein, the term "leaving group" refers to an atom or a group of atoms that is displaced in a chemical reaction as stable species taking with it the bonding electrons. Preferably, a leaving group is selected from the group comprising: halo, in particular chloro, bromo or iodo, methanesulfonyloxy,
30 p-toluenesulfonyloxy, trifluoromethanesulfonyloxy,

nonafluorobutanesulfonyloxy, (4-bromo-benzene)sulfonyloxy, (4-nitro-benzene)sulfonyloxy, (2-nitro-benzene)-sulfonyloxy, (4-isopropyl-benzene)sulfonyloxy, (2,4,6-tri-isopropyl-benzene)-sulfonyloxy, (2,4,6-trimethyl-benzene)sulfonyloxy, (4-tertbutyl-benzene)sulfonyloxy, 5 benzenesulfonyloxy, and (4-methoxy-benzene)sulfonyloxy.

As used herein, the term "PG¹" refers to a protecting group for hydroxy groups e.g. a TMS group or TBDPS group as described for example in T.W. Greene and P.G.M. Wuts in *Protective Groups in Organic Synthesis*, 3rd edition, Wiley 1999 10 (TMS = trimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl).

As used herein, the term "PG²" refers to a protecting group for amino groups e.g. a Boc group as described for example in T.W. Greene and P.G.M. Wuts in *Protective Groups in Organic Synthesis*, 3rd edition, Wiley 1999 (Boc = *tert*- 15 butyloxycarbonyl).

As used herein, the term "one or more times", e.g. in the definition of the substituents of the compounds of the general formulae of the present invention, is understood as meaning "one, two, three, four or five times, 20 particularly one, two, three or four times, more particularly one, two or three times, even more particularly one or two times".

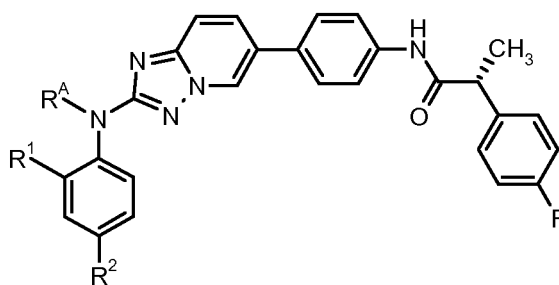
Compounds A1, A2, A3, A4, and A5, as defined in the Experimental Section, are very effective Mps-1 inhibitors. Surprisingly it was found, that these 25 compounds are characterized by :

- an IC₅₀ lower than or equal to 1 nM (more potent than 1 nM) in an Mps-1 kinase assay with a concentration of 10 μM ATP, and
- an IC₅₀ lower than 2 nM (more potent than 2 nM) in an Mps-1 kinase assay with a concentration of 2 mM ATP, and

- a maximum oral bioavailability ($F_{\max}$) in rat that is higher than 70 % determined by means of rat liver microsomes as described below, and
 - a maximum oral bioavailability ($F_{\max}$) in dog that is higher than 50 % determined by means of dog liver microsomes as described below, and
 - 5 - a maximum oral bioavailability ($F_{\max}$) in human that is higher than 60 %, determined by means of human liver microsomes as described below, and
 - an IC_{50} lower than 400 nM in a HeLa cell proliferation assay as described below.
- 10 However, these compounds have only limited solubility in water and physiological media, making intravenous administration difficult.

In accordance with a first aspect, the present invention relates to prodrug derivatives which show a higher solubility in water and physiological media than
 15 the compounds A1, A2, A3, A4, and A5, making them suitable for therapeutic use, especially on intravenous administration.

The prodrug derivatives are defined by general formula (I)

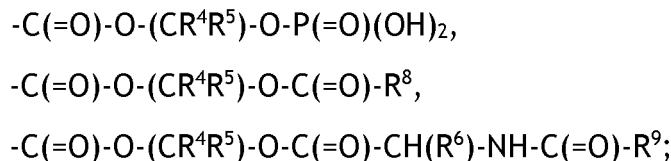


20 (I)

in which :

R^A represents a group selected from:

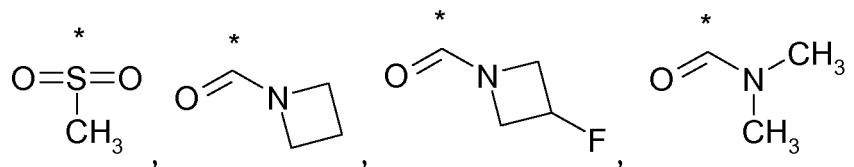
- C(=O)-(CH₂)₃-N(H)R³,
- 25 -C(=O)-(CR⁴R⁵)-N(R⁶)R⁷,
- C(=O)-O-(CH₂)₂-N(H)R³,



R^1 represents a group selected from methoxy- and 2,2,2-trifluoroethoxy-;

5

R^2 represents a group selected from:



wherein "*" indicates the point of attachment to the phenyl ring R^2 is attached to;

10

R^3 represents a group selected from:

C_1 - C_6 -alkyl, C_3 - C_6 -cycloalkyl-,

4- to 7-membered heterocycloalkyl-;

said group being optionally substituted, one or more times, identically

15

or differently, with a group selected from:

$-\text{OH}$, $-\text{NH}_2$, $-\text{N}(\text{H})\text{R}^{10}$, $-\text{N}(\text{R}^{10})\text{R}^{11}$, $-\text{O}-\text{P}(=\text{O})(\text{OH})_2$;

R^4 and R^5 , independently from each other, represent a group selected from a hydrogen atom and a C_1 - C_3 -alkyl- group,

20 or

R^4 and R^5 , together with the carbon atom to which they are attached, form a C_3 - C_6 -cycloalkyl ring;

R^6 represents a hydrogen atom or a C_1 - C_3 -alkyl- group;

25

R^7 represents a hydrogen atom or a group $-\text{C}(=\text{O})\text{R}^9$;

R^8 represents a group selected from:

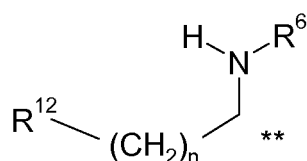
C₁-C₆-alkyl, C₃-C₆-cycloalkyl-,

4- to 7-membered heterocycloalkyl-;

said group being optionally substituted, one or more times, identically or differently, with a group selected from:

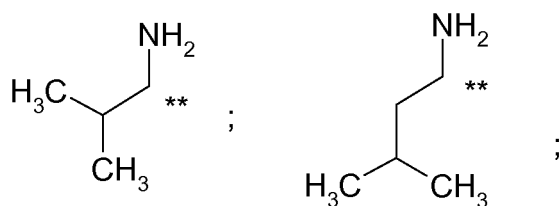
5 -OH, -NH₂, -N(H)R¹⁰, -N(R¹⁰)R¹¹, -O-P(=O)(OH)₂;

R⁹ represents a group



10

or R⁹ represents a group selected from:



15 wherein "***" indicates the point of attachment to the carbonyl group R⁹ is attached to;

R¹⁰ and R¹¹, independently from each other, represent a group selected from a hydrogen atom and a C₁-C₃-alkyl- group, or

20

R¹⁰ and R¹¹, together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocycloalkyl ring;

R¹² represents a group selected from a hydrogen atom, -OH, -NR¹⁰R¹¹,
25 -NH-C(=NH)-NH₂;

n is an integer of 0, 1, 2, 3 or 4;

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture
5 of same.

In a preferred embodiment,

R^A represents a group selected from:

10 -C(=O)-(CH₂)₃-N(H)R³,
-C(=O)-O-(CH₂)₂-N(H)R³,
-C(=O)-O-(CR⁴R⁵)-O-P(=O)(OH)₂,
-C(=O)-O-(CR⁴R⁵)-O-C(=O)-R⁸,
-C(=O)-O-(CR⁴R⁵)-O-C(=O)-CH(R⁶)-NH-C(=O)-R⁹.

15

In another preferred embodiment, R^A represents a group selected from

-C(=O)-(CH₂)₃-N(H)R³,
-C(=O)-O-(CR⁴R⁵)-O-P(=O)(OH)₂,
-C(=O)-O-(CR⁴R⁵)-O-C(=O)-R⁸,
20 -C(=O)-O-(CR⁴R⁵)-O-C(=O)-CH(R⁶)-NH-C(=O)-R⁹.

In another preferred embodiment, R^A represents a group selected from

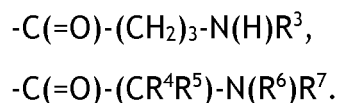
-C(=O)-O-(CR⁴R⁵)-O-P(=O)(OH)₂,
-C(=O)-O-(CR⁴R⁵)-O-C(=O)-R⁸,
25 -C(=O)-O-(CR⁴R⁵)-O-C(=O)-CH(R⁶)-NH-C(=O)-R⁹.

In another preferred embodiment, R^A represents a group selected from

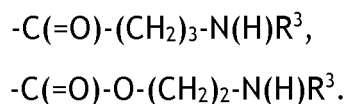
-C(=O)-O-(CR⁴R⁵)-O-C(=O)-R⁸,
-C(=O)-O-(CR⁴R⁵)-O-C(=O)-CH(R⁶)-NH-C(=O)-R⁹.

30

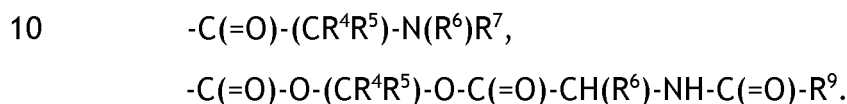
In another preferred embodiment, R^A represents a group selected from



5 In another preferred embodiment, R^A represents a group selected from



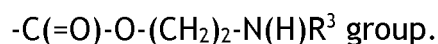
In another preferred embodiment, R^A represents a group selected from



In another preferred embodiment, R^A represents a $-C(=O)-(CH_2)_3-N(H)R^3$ group.

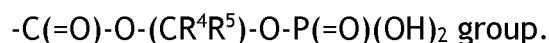
15 In another preferred embodiment, R^A represents a $-C(=O)-(CR^4R^5)-N(R^6)R^7$ group.

In another preferred embodiment, R^A represents a



20

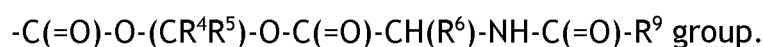
In another preferred embodiment, R^A represents a



In another preferred embodiment, R^A represents a

25 $-C(=O)-O-(CR^4R^5)-O-C(=O)-R^8$ group.

In another preferred embodiment, R^A represents a



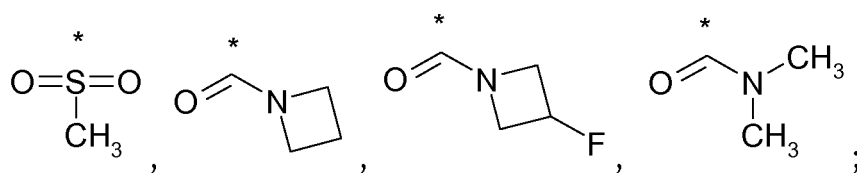
In another preferred embodiment, R^1 represents a group selected from methoxy- and 2,2,2-trifluoroethoxy-.

In another preferred embodiment, R^1 represents a 2,2,2-trifluoroethoxy- group.

5

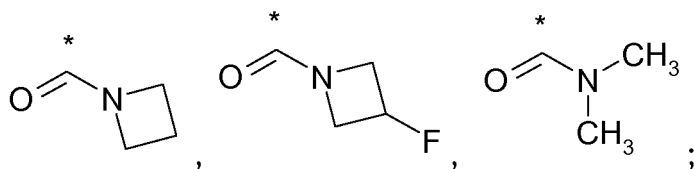
In a more preferred embodiment, R^1 represents a methoxy- group.

In another preferred embodiment, R^2 represents a group selected from:



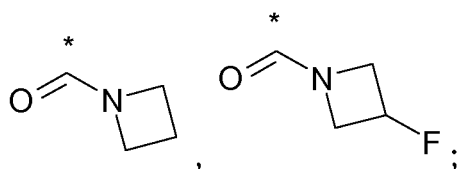
10 wherein "*" indicates the point of attachment to the phenyl ring R^2 is attached to.

In another preferred embodiment, R^2 represents a group selected from



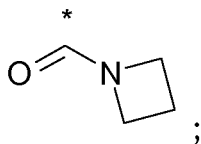
15 wherein "*" indicates the point of attachment to the phenyl ring R^2 is attached to.

In another preferred embodiment, R^2 represents a group selected from



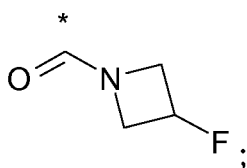
20 wherein "*" indicates the point of attachment to the phenyl ring R^2 is attached to.

In another preferred embodiment, R^2 represents



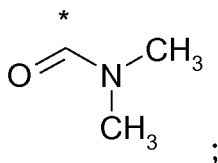
wherein "*" indicates the point of attachment to the phenyl ring R^2 is attached to.

- 5 In another preferred embodiment, R^2 represents



wherein "*" indicates the point of attachment to the phenyl ring R^2 is attached to.

- 10 In another preferred embodiment, R^2 represents



wherein "*" indicates the point of attachment to the phenyl ring R^2 is attached to.

- 15 In a particularly preferred embodiment, R^2 represents a $-S(=O)_2CH_3$ group.

In another embodiment, R^3 represents a group selected from:

C_1 - C_6 -alkyl, C_3 - C_6 -cycloalkyl-, 4- to 7-membered heterocycloalkyl-;

said group being optionally substituted, one or more times, identically or

- 20 differently, with a group selected from:

$-OH$, $-NH_2$, $-N(H)R^{10}$, $-N(R^{10})R^{11}$, $-O-P(=O)(OH)_2$.

In a preferred embodiment, R^3 represents a C_1 - C_6 -alkyl group, said group being optionally substituted, one or more times, identically or differently, with a group selected from: $-OH$, $-NH_2$, $-N(H)R^{10}$, $-N(R^{10})R^{11}$, $-O-P(=O)(OH)_2$.

- 5 In another preferred embodiment, R^3 represents a C_3 - C_6 -cycloalkyl- group, said group being optionally substituted, one or more times, identically or differently, with a group selected from:

$-OH$, $-NH_2$, $-N(H)R^{10}$, $-N(R^{10})R^{11}$, $-O-P(=O)(OH)_2$.

- 10 In another preferred embodiment, R^3 represents a 4- to 7-membered heterocycloalkyl- group, said group being optionally substituted, one or more times, identically or differently, with a group selected from:

$-OH$, $-NH_2$, $-N(H)R^{10}$, $-N(R^{10})R^{11}$, $-O-P(=O)(OH)_2$.

- 15 In another preferred embodiment, R^3 represents a C_1 - C_3 -alkyl- group.

In another preferred embodiment, R^3 represents a C_1 - C_2 -alkyl- group.

In another preferred embodiment, R^3 represents an ethyl- group.

20

In a particularly preferred embodiment, R^3 represents a methyl- group.

In another embodiment, R^4 and R^5 , independently from each other, represent a group selected from a hydrogen atom and a C_1 - C_3 -alkyl- group, or

- 25 R^4 and R^5 , together with the carbon atom to which they are attached, form a C_3 - C_6 -cycloalkyl ring.

In another embodiment, R^4 and R^5 , independently from each other, represent a group selected from a hydrogen atom and a C_1 - C_3 -alkyl- group.

30

In another embodiment, R^4 and R^5 , together with the carbon atom to which they are attached, form a C_3 - C_6 -cycloalkyl ring.

5 In a preferred embodiment, R^4 represents a hydrogen atom or a C_1 - C_3 -alkyl-group, and R^5 represents a hydrogen atom.

In another preferred embodiment, R^4 represents a hydrogen atom or a methyl- or *iso*-propyl- group, and R^5 represents a hydrogen atom.

10 In another preferred embodiment, R^4 and R^5 each represent a hydrogen atom.

In a particularly preferred embodiment, R^4 represents a methyl- group, and R^5 represents a hydrogen atom.

15 In another particularly preferred embodiment, R^4 represents an *iso*-propyl-group, and R^5 represents a hydrogen atom.

In a preferred embodiment, R^4 represents a hydrogen atom or a C_1 - C_3 -alkyl-group.

20

In a particularly preferred embodiment, R^4 represents a hydrogen atom or a methyl- group.

In another particularly preferred embodiment, R^4 represents a hydrogen atom.

25

In another particularly preferred embodiment, R^4 represents a methyl- group.

In another preferred embodiment, R^5 represents a hydrogen atom.

30 In another embodiment, R^6 represents a hydrogen atom or a C_1 - C_3 -alkyl- group.

In a preferred embodiment, R^6 represents a hydrogen atom or a methyl- group.

In another preferred embodiment, R^6 represents a hydrogen atom.

5

In a particularly preferred embodiment, R^6 represents a methyl- group.

In another embodiment, R^7 represents a hydrogen atom or a group $-C(=O)R^9$.

10 In a preferred embodiment, R^7 represents a group $-C(=O)R^9$.

In another preferred embodiment, R^7 represents a hydrogen atom.

In another embodiment, R^8 represents a group selected from:

15 C_1 - C_6 -alkyl, C_3 - C_6 -cycloalkyl-,

4- to 7-membered heterocycloalkyl-;

said group being optionally substituted, one or more times, identically or differently, with a group selected from:

$-OH$, $-NH_2$, $-N(H)R^{10}$, $-N(R^{10})R^{11}$, $-O-P(=O)(OH)_2$.

20

In a preferred embodiment, R^8 represents a C_1 - C_6 -alkyl group, said group being optionally substituted, one or more times, identically or differently, with a group selected from: $-OH$, $-NH_2$, $-N(H)R^{10}$, $-N(R^{10})R^{11}$, $-O-P(=O)(OH)_2$.

25 In another preferred embodiment, R^8 represents a C_3 - C_6 -cycloalkyl- group, said group being optionally substituted, one or more times, identically or differently, with a group selected from:

$-OH$, $-NH_2$, $-N(H)R^{10}$, $-N(R^{10})R^{11}$, $-O-P(=O)(OH)_2$.

In another preferred embodiment, R^8 represents a 4- to 7-membered heterocycloalkyl- group, said group being optionally substituted, one or more times, identically or differently, with a group selected from:

-OH, -NH₂, -N(H)R¹⁰, -N(R¹⁰)R¹¹, -O-P(=O)(OH)₂.

5

In another preferred embodiment, R^8 represents a group selected from:

C₁-C₆-alkyl, substituted one or more times, identically or differently, with a group selected from: -NH₂, -N(H)R¹⁰, -N(R¹⁰)R¹¹,

4- to 7-membered heterocycloalkyl-, optionally substituted, one or more times, identically or differently, with a group selected from:

10

-NH₂, -N(H)R¹⁰, -N(R¹⁰)R¹¹.

In another preferred embodiment, R^8 represents a C₁-C₆-alkyl group, substituted one or more times, identically or differently, with a group selected from: -NH₂, -N(H)R¹⁰, -N(R¹⁰)R¹¹.

15

In another preferred embodiment, R^8 represents a 4- to 7-membered heterocycloalkyl- group, optionally substituted, one or more times, identically or differently, with a group selected from: -NH₂, -N(H)R¹⁰, -N(R¹⁰)R¹¹.

20

In another preferred embodiment, R^8 represents a group selected from:

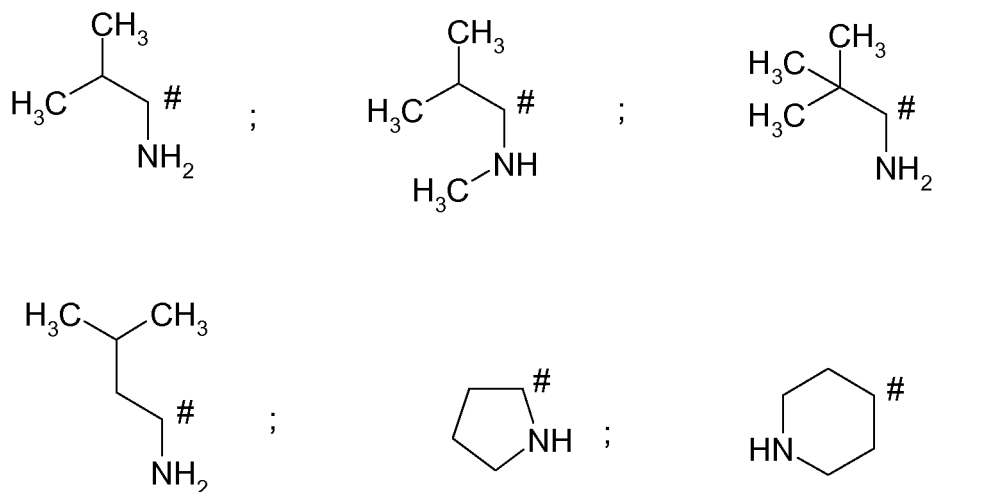
C₁-C₆-alkyl, substituted one or more times, identically or differently, with a group selected from -NH₂, -N(H)R¹⁰, -N(R¹⁰)R¹¹,

a heterocycloalkyl group selected from pyrrolidinyl-, piperidinyl-, morpholinyl-, and piperazinyl-.

25

In another preferred embodiment, R^8 represents a heterocycloalkyl group selected from pyrrolidinyl-, piperidinyl-, morpholinyl-, and piperazinyl-.

In a particularly preferred embodiment, R⁸ represents a heterocycloalkyl group selected from:

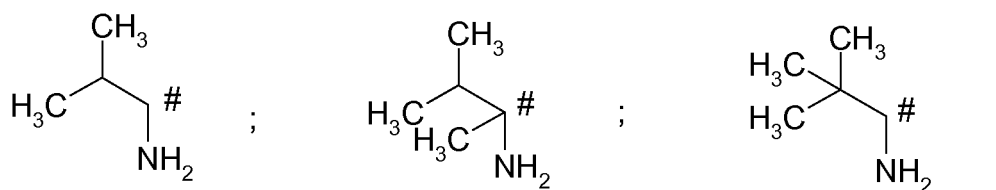


5

wherein "#" represents the point of attachment to the carbonyl group R⁸ is attached to.

In another particularly preferred embodiment, R⁸ represents a heterocycloalkyl group selected from:

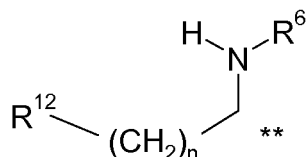
10



wherein "#" represents the point of attachment to the carbonyl group R⁸ is attached to.

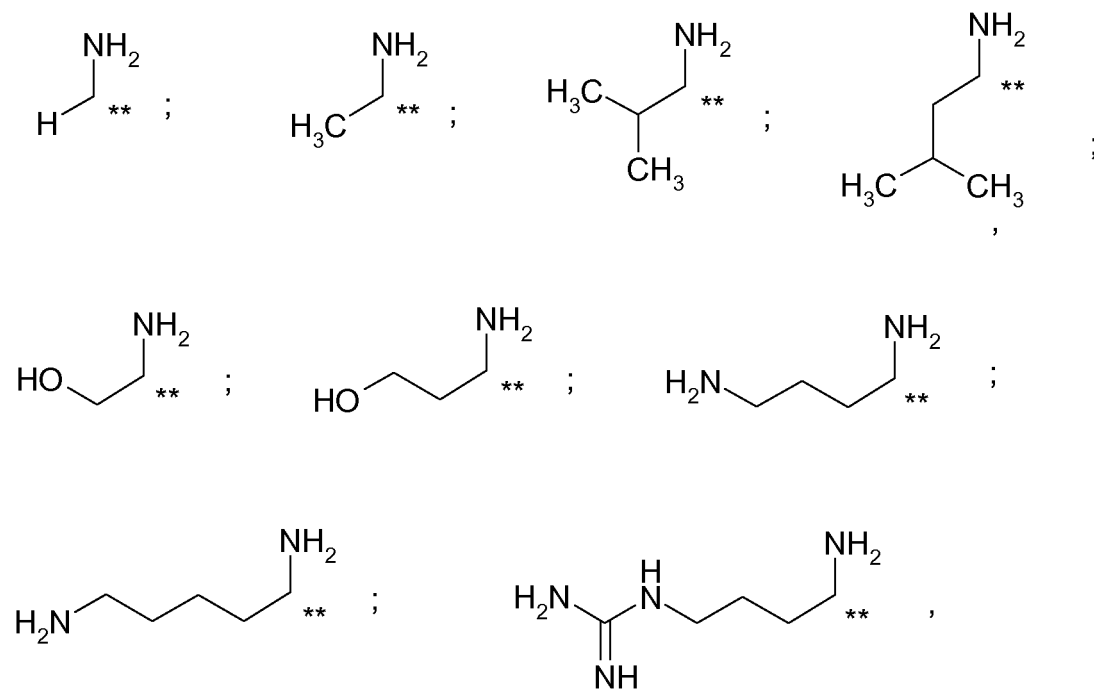
15

In a preferred embodiment, R⁹ represents



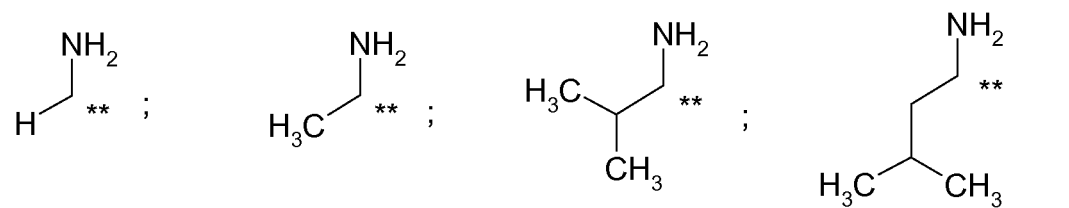
wherein "***" indicates the point of attachment to the carbonyl group R⁹ is attached to.

In another preferred embodiment, R⁹ represents a group selected from:



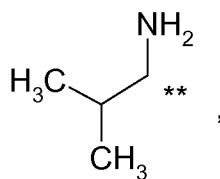
wherein "***" indicates the point of attachment to the carbonyl group R⁹ is attached to.

In another preferred embodiment, R⁹ represents a group selected from:



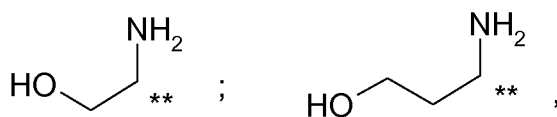
wherein "***" indicates the point of attachment to the carbonyl group R⁹ is attached to.

In another preferred embodiment, R⁹ represents a group:



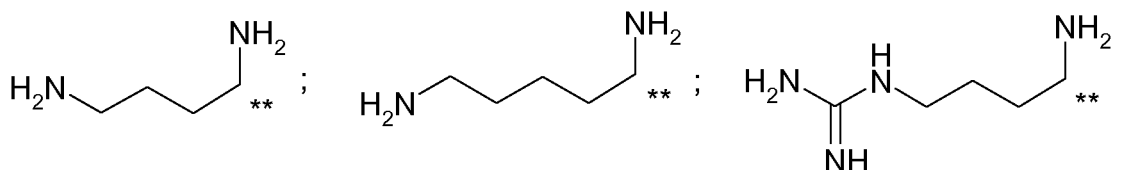
wherein "*" indicates the point of attachment to the carbonyl group R^9 is attached to.

- 5 In another preferred embodiment, R^9 represents a group selected from:



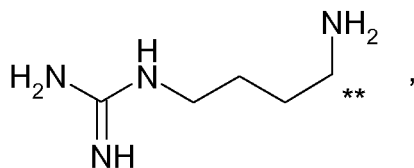
wherein "*" indicates the point of attachment to the carbonyl group R^9 is attached to.

- 10 In another preferred embodiment, R^9 represents a group selected from:



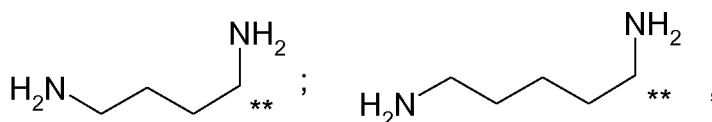
wherein "*" indicates the point of attachment to the carbonyl group R^9 is attached to.

- 15 In another preferred embodiment, R^9 represents



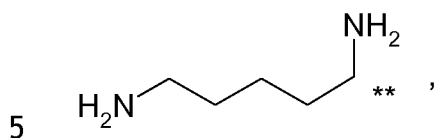
wherein "*" indicates the point of attachment to the carbonyl group R^9 is attached to.

- 20 In another preferred embodiment, R^9 represents a group selected from:



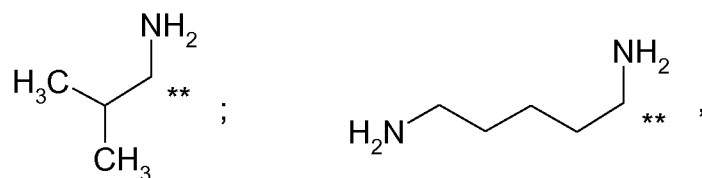
wherein "*" indicates the point of attachment to the carbonyl group R^9 is attached to.

In a particularly preferred embodiment, R^9 represents



wherein "*" indicates the point of attachment to the carbonyl group R^9 is attached to.

10 In another particularly preferred embodiment, R^9 represents a group selected from:



wherein "*" indicates the point of attachment to the carbonyl group R^9 is attached to.

15 In another embodiment, R^{10} and R^{11} , independently from each other, represent a group selected from a hydrogen atom and a C_1 - C_3 -alkyl- group, or R^{10} and R^{11} , together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocycloalkyl ring.

20 In a preferred embodiment, R^{10} and R^{11} , independently from each other, represent a group selected from a hydrogen atom and a C_1 - C_3 -alkyl- group.

In another preferred embodiment, R^{10} and R^{11} , together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocycloalkyl ring.

25

In a preferred embodiment, R^{10} and R^{11} , independently from each other, represent a group selected from a hydrogen atom and a C_1 - C_2 -alkyl- group.

In another preferred embodiment, R^{10} and R^{11} , independently from each other,
5 represent a group selected from a hydrogen atom and a methyl- group.

In another embodiment, R^{12} represents a group selected from a hydrogen atom, -OH, $-NR^{10}R^{11}$, $-NH-C(=NH)-NH_2$.

10 In another embodiment, R^{12} represents a group selected from a hydrogen atom, -OH.

In another embodiment, R^{12} represents a -OH group.

15 In another embodiment, R^{12} represents a hydrogen atom.

In a preferred embodiment, R^{12} represents a group selected from $-NR^{10}R^{11}$, $-NH-C(=NH)-NH_2$.

20 In another preferred embodiment, R^{12} represents a group selected from $-N(H)R^{10}$, $-NH-C(=NH)-NH_2$.

In another preferred embodiment, R^{12} represents a group selected from $-NH_2$, $-NH-C(=NH)-NH_2$.

25

In another preferred embodiment, R^{12} represents $-NH-C(=NH)-NH_2$.

In another preferred embodiment, R^{12} represents $-NR^{10}R^{11}$.

30 In another preferred embodiment, R^{12} represents $-N(H)R^{10}$.

In a particularly preferred embodiment, R¹² represents -NH₂.

In a further embodiment of the above-mentioned aspect, the invention relates
 5 to compounds of formula (I), according to any of the above-mentioned
 embodiments, in the form of or a tautomer, an N-oxide, a hydrate, a solvate,
 or a salt thereof, or a mixture of same.

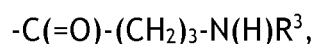
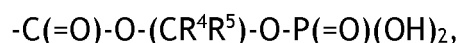
It is to be understood that the present invention relates also to any
 10 combination of the preferred embodiments described above.

Some examples of combinations are given hereinafter. However, the invention
 is not limited to these combinations.

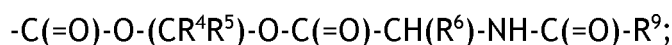
15 In a preferred embodiment, the invention relates to compounds of the formula
 (I), *supra*,

wherein

20 R^A represents a group selected from:

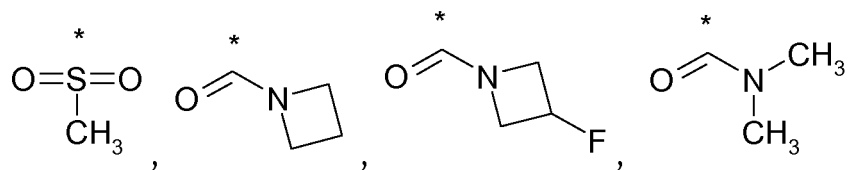


25 -C(=O)-O-(CR⁴R⁵)-O-C(=O)-R⁸,



R¹ represents a group selected from methoxy- and 2,2,2-trifluoroethoxy-;

30 R² represents a group selected from:



wherein "*" indicates the point of attachment to the phenyl ring R^2 is attached to;

5 R^3 represents a C_1 - C_3 -alkyl- group;

R^4 and R^5 , independently from each other, represent a group selected from a hydrogen atom and a C_1 - C_3 -alkyl- group, or

10 R^4 and R^5 , together with the carbon atom to which they are attached, form a C_3 - C_6 -cycloalkyl ring;

R^6 represents a hydrogen atom or a C_1 - C_3 -alkyl- group;

15 R^7 represents a hydrogen atom or a group $-C(=O)R^9$;

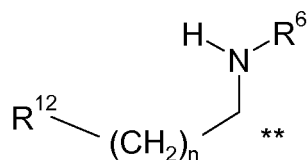
R^8 represents a group selected from:

C_1 - C_6 -alkyl, C_3 - C_6 -cycloalkyl-,
4- to 7-membered heterocycloalkyl-;

20 said group being optionally substituted, one or more times, identically or differently, with a group selected from:
-OH, -NH₂, -N(H) R^{10} , -N(R^{10}) R^{11} , -O-P(=O)(OH)₂;

R^9 represents a group

25



wherein "***" indicates the point of attachment to the carbonyl group R⁹ is attached to;

5 R¹⁰ and R¹¹, independently from each other, represent a group selected from a hydrogen atom and a C₁-C₃-alkyl- group, or

R¹⁰ and R¹¹, together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocycloalkyl ring;

10

R¹² represents a group selected from a hydrogen atom, -OH, -NR¹⁰R¹¹, -NH-C(=NH)-NH₂;

n is an integer of 0, 1, 2, 3 or 4;

15

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

20 In another preferred embodiment,

R^A represents a group selected from:

-C(=O)-(CH₂)₃-N(H)R³,

-C(=O)-(CR⁴R⁵)-N(R⁶)R⁷,

25 -C(=O)-O-(CH₂)₂-N(H)R³,

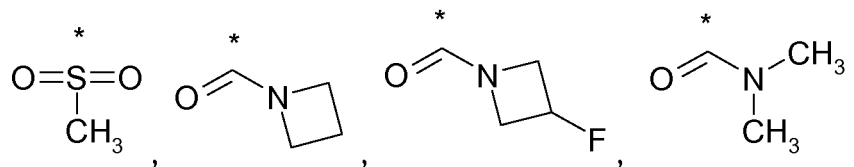
-C(=O)-O-(CR⁴R⁵)-O-P(=O)(OH)₂,

-C(=O)-O-(CR⁴R⁵)-O-C(=O)-R⁸,

-C(=O)-O-(CR⁴R⁵)-O-C(=O)-CH(R⁶)-NH-C(=O)-R⁹;

30 R¹ represents a group selected from methoxy- and 2,2,2-trifluoroethoxy-;

R² represents a group selected from:



wherein "*" indicates the point of attachment to the phenyl ring R² is attached to;

R³ represents a methyl- group;

R⁴ represents a hydrogen atom or a C₁-C₃-alkyl- group;

R⁵ represents a hydrogen atom;

R⁶ represents a hydrogen atom or a methyl- group;

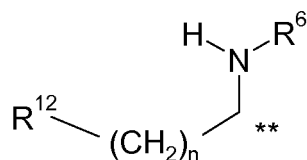
R⁷ represents a hydrogen atom or a group -C(=O)R⁹;

R⁸ represents a group selected from:

C₁-C₆-alkyl, substituted one or more times, identically or differently, with a group selected from: -NH₂, -N(H)R¹⁰, -N(R¹⁰)R¹¹;

4- to 7-membered heterocycloalkyl-, optionally substituted, one or more times, identically or differently, with a group selected from: -NH₂, -N(H)R¹⁰, -N(R¹⁰)R¹¹;

R⁹ represents a group



wherein "***" indicates the point of attachment to the carbonyl group R⁹ is attached to;

5 R¹⁰ and R¹¹, independently from each other, represent a group selected from a hydrogen atom and a methyl- group;

R¹² represents a group selected from a hydrogen atom, -OH, -NR¹⁰R¹¹,
-NH-C(=NH)-NH₂;

10

n is an integer of 0, 1, 2, 3 or 4;

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

15

In yet another preferred embodiment,

R^A represents a group selected from:

20

-C(=O)-(CH₂)₃-N(H)R³,

-C(=O)-(CR⁴R⁵)-N(R⁶)R⁷,

-C(=O)-O-(CH₂)₂-N(H)R³,

-C(=O)-O-(CR⁴R⁵)-O-P(=O)(OH)₂,

-C(=O)-O-(CR⁴R⁵)-O-C(=O)-R⁸,

25

-C(=O)-O-(CR⁴R⁵)-O-C(=O)-CH(R⁶)-NH-C(=O)-R⁹;

R¹ represents methoxy-;

R² represents a -S(=O)₂CH₃ group;

30

R^3 represents a methyl- group;

R^4 represents a hydrogen atom or a methyl- group;

5 R^5 represents a hydrogen atom;

R^6 represents a hydrogen atom or a methyl- group;

R^7 represents a hydrogen atom or a group $-C(=O)R^9$;

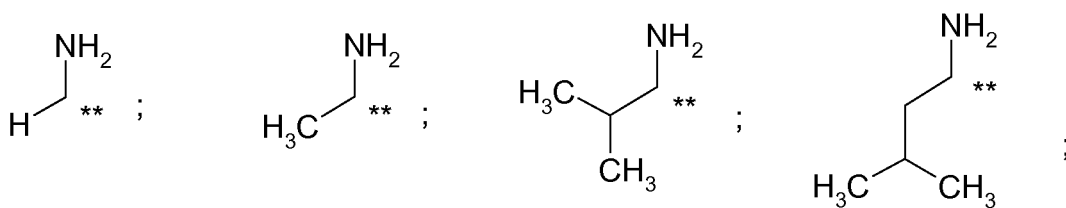
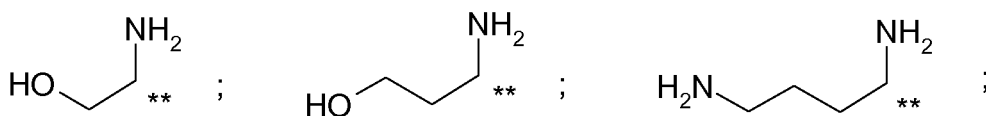
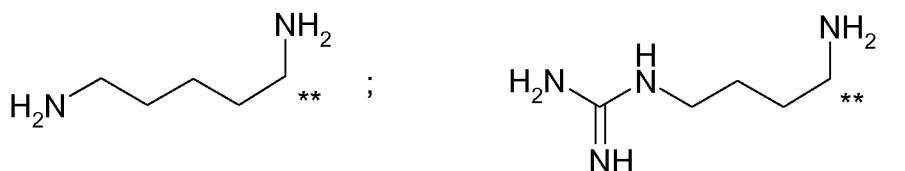
10

R^8 represents a group selected from:

C_1 - C_6 -alkyl, substituted one or more times, identically or differently,
with a group selected from $-NH_2$, $-N(H)R^{10}$, $-N(R^{10})R^{11}$,

a heterocycloalkyl group selected from pyrrolidinyl-, piperidinyl-,
15 morpholinyl-, and piperazinyl-;

R^9 represents a group selected from



20

wherein "*" indicates the point of attachment to the carbonyl group R⁹ is attached to;

R¹⁰ and R¹¹, independently from each other, represent a group selected from a
5 hydrogen atom and a methyl- group;

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

10

In a particularly preferred embodiment,

R^A represents a group selected from:

-C(=O)-(CH₂)₃-N(H)R³,
15 -C(=O)-(CR⁴R⁵)-N(R⁶)R⁷,
-C(=O)-O-(CH₂)₂-N(H)R³,
-C(=O)-O-(CR⁴R⁵)-O-P(=O)(OH)₂,
-C(=O)-O-(CR⁴R⁵)-O-C(=O)-R⁸,
-C(=O)-O-(CR⁴R⁵)-O-C(=O)-CH(R⁶)-NH-C(=O)-R⁹;

20

R¹ represents methoxy-;

R² represents a -S(=O)₂CH₃ group;

25 R³ represents a methyl- group;

R⁴ represents a hydrogen atom or a methyl- group;

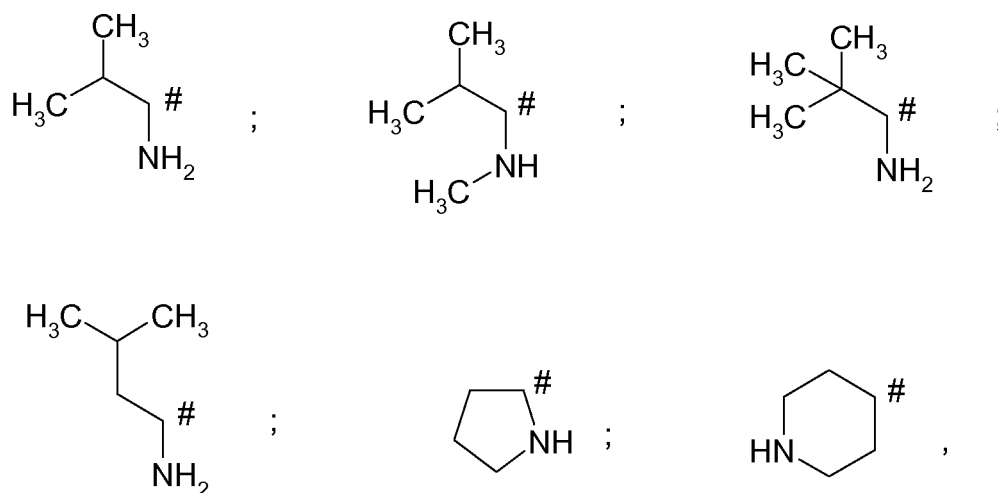
R⁵ represents a hydrogen atom;

30

R^6 represents a methyl- group;

R^7 represents a hydrogen atom or a group $-C(=O)R^9$;

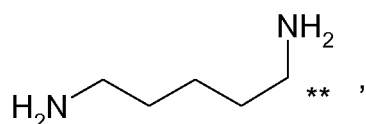
5 R^8 represents a group selected from:



wherein "#" represents the point of attachment to the carbonyl group R^8 is attached to;

10

R^9 represents a group



wherein "**" indicates the point of attachment to the carbonyl group R^9 is attached to;

15

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

In another particularly preferred embodiment,

20

R^A represents a group:



R¹ represents methoxy-;

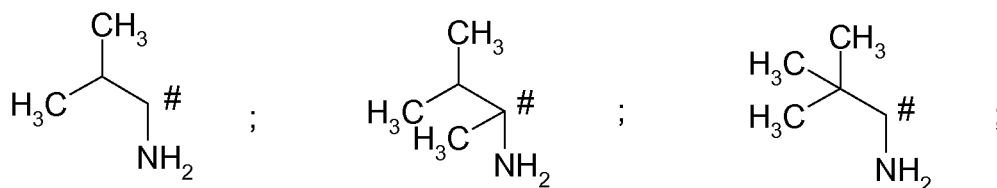
5 R² represents a -S(=O)₂CH₃ group;

R⁴ represents a hydrogen atom or a C₁-C₃-alkyl- group;

R⁵ represents a hydrogen atom;

10

R⁸ represents a group selected from:



wherein "#" represents the point of attachment to the carbonyl group R⁸

15

is attached to;

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

20

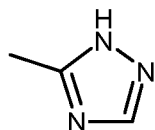
It is to be understood that the present invention relates to any sub-combination within any embodiment or aspect of the present invention of compounds of general formula (I), *supra*.

25

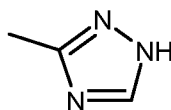
More particularly still, the present invention covers compounds of general formula (I) which are disclosed in the Examples section of this text, *infra*.

The invention also includes all suitable isotopic variations of a compound of the invention. An isotopic variation of a compound of the invention is defined as one in which at least one atom is replaced by an atom having the same atomic number but an atomic mass different from the atomic mass usually or predominantly found in nature. Examples of isotopes that can be incorporated into a compound of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulphur, fluorine, chlorine, bromine and iodine, such as ^2H (deuterium), ^3H (tritium), ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{17}O , ^{18}O , ^{32}P , ^{33}P , ^{33}S , ^{34}S , ^{35}S , ^{36}S , ^{18}F , ^{36}Cl , ^{82}Br , ^{123}I , ^{124}I , ^{129}I and ^{131}I , respectively. Certain isotopic variations of a compound of the invention, for example, those in which one or more radioactive isotopes such as ^3H or ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution studies. Tritiated and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements and hence may be preferred in some circumstances. Isotopic variations of a compound of the invention can generally be prepared by conventional procedures known by a person skilled in the art such as by the illustrative methods or by the preparations described in the examples hereafter using appropriate isotopic variations of suitable reagents.

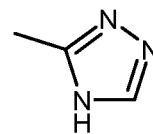
The compounds of the present invention may exist as tautomers. For example, any compound of the present invention which contains a pyrazole moiety as a heteroaryl group for example can exist as a 1H tautomer, or a 2H tautomer, or even a mixture in any amount of the two tautomers, or a triazole moiety for example can exist as a 1H tautomer, a 2H tautomer, or a 4H tautomer, or even a mixture in any amount of said 1H, 2H and 4H tautomers, viz. :



1H-tautomer



2H-tautomer



4H-tautomer.

The present invention includes all possible tautomers of the compounds of the present invention as single tautomers, or as any mixture of said tautomers, in any ratio.

Further, the compounds of the present invention can exist as N-oxides, which are defined in that at least one nitrogen of the compounds of the present invention is oxidised. The present invention includes all such possible N-oxides.

10

The present invention also relates to useful forms of the compounds as disclosed herein, such as hydrates, solvates, salts, in particular pharmaceutically acceptable salts, and co-precipitates.

The compounds of the present invention can exist as a hydrate, or as a solvate, wherein the compounds of the present invention contain polar solvents, in particular water, methanol or ethanol for example as structural element of the crystal lattice of the compounds. The amount of polar solvents, in particular water, may exist in a stoichiometric or non-stoichiometric ratio. In the case of stoichiometric solvates, e.g. a hydrate, hemi-, (semi-), mono-, sesqui-, di-, tri-, tetra-, penta- etc. solvates or hydrates, respectively, are possible. The present invention includes all such hydrates or solvates.

Further, the compounds of the present invention can exist in free form, e.g. as a free base, or as a free acid, or as a zwitterion, or can exist in the form of a salt. Said salt may be any salt, either an organic or inorganic addition salt, particularly any pharmaceutically acceptable organic or inorganic addition salt, customarily used in pharmacy.

The term "pharmaceutically acceptable salt" refers to a relatively non-toxic, inorganic or organic acid addition salt of a compound of the present invention. For example, see S. M. Berge, *et al.* "Pharmaceutical Salts," J. Pharm. Sci. 1977, 66, 1-19.

A suitable pharmaceutically acceptable salt of the compounds of the present invention may be, for example, an acid-addition salt of a compound of the present invention bearing a nitrogen atom, in a chain or in a ring, for example, which is sufficiently basic, such as an acid-addition salt with an inorganic acid, such as hydrochloric, hydrobromic, hydroiodic, sulfuric, bisulfuric, phosphoric, or nitric acid, for example, or with an organic acid, such as formic, acetic, acetoacetic, pyruvic, trifluoroacetic, propionic, butyric, hexanoic, heptanoic, undecanoic, lauric, benzoic, salicylic, 2-(4-hydroxybenzoyl)-benzoic, camphoric, cinnamic, cyclopentanepropionic, digluconic, 3-hydroxy-2-naphthoic, nicotinic, pamoic, pectinic, persulfuric, 3-phenylpropionic, picric, pivalic, 2-hydroxyethanesulfonate, itaconic, sulfamic, trifluoromethanesulfonic, dodecylsulfuric, ethansulfonic, benzenesulfonic, para-toluenesulfonic, methansulfonic, 2-naphthalenesulfonic, naphthalenedisulfonic, camphorsulfonic acid, citric, tartaric, stearic, lactic, oxalic, malonic, succinic, malic, adipic, alginic, maleic, fumaric, D-gluconic, mandelic, ascorbic, glucoheptanoic, glycerophosphoric, aspartic, sulfosalicylic, hemisulfuric, or thiocyanic acid, for example.

Further, another suitably pharmaceutically acceptable salt of a compound of the present invention which is sufficiently acidic, is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically acceptable cation, for example a salt with N-methyl-glucamine, dimethyl-glucamine, ethyl-glucamine, lysine, dicyclohexylamine, 1,6-hexadamine, ethanolamine, glucosamine, sarcosine,

serinol, tris-hydroxy-methyl-aminomethane, aminopropandiol, sovak-base, 1-amino-2,3,4-butantriol. Additionally, the compounds according to the invention may form salts with a quarternary ammonium ion obtainable e.g. by quarternisation of a basic nitrogen containing group with agents like lower
5 alkylhalides such as methyl-, ethyl-, propyl-, and butylchlorides, -bromides and -iodides ; dialkylsulfates like dimethyl-, diethyl-, dibutyl- and diamylsulfates, long chain halides such as decyl-, lauryl-, myristyl- and stearylchlorides, -bromides and -iodides, aralkylhalides like benzyl- and phenethylbromides and others. Examples of suitable quarternary ammonium ions are
10 tetramethylammonium, tetraethylammonium, tetra(*n*-propyl)ammonium, tetra(*n*-butyl)ammonium, or *N*-benzyl-*N,N,N*-trimethylammonium.

Those skilled in the art will further recognise that acid addition salts of the claimed compounds may be prepared by reaction of the compounds with the appropriate inorganic or organic acid via any of a number of known methods.
15 Alternatively, alkali and alkaline earth metal salts of acidic compounds of the invention are prepared by reacting the compounds of the invention with the appropriate base via a variety of known methods.

The present invention includes all possible salts of the compounds of the present invention as single salts, or as any mixture of said salts, in any ratio.

20

Furthermore, the present invention includes all possible crystalline forms, or polymorphs, of the compounds of the present invention, either as single polymorphs, or as a mixture of more than one polymorphs, in any ratio.

25 More particularly still, the present invention covers compounds of general formula (I) which are disclosed in the Example section of this text, *infra*.

In accordance with another aspect, the present invention covers methods of preparing compounds of the present invention, said methods comprising the steps as described in the Experimental Section herein.

5 This invention also relates to pharmaceutical compositions containing one or more compounds of the present invention. These compositions can be utilised to achieve the desired pharmacological effect by administration to a patient in need thereof. A patient, for the purpose of this invention, is a mammal, including a human, in need of treatment for the particular condition or
10 disease. Therefore, the present invention includes pharmaceutical compositions that are comprised of a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound, or salt thereof, of the present invention. A pharmaceutically acceptable carrier is preferably a carrier that is relatively non-toxic and innocuous to a patient at concentrations
15 consistent with effective activity of the active ingredient so that any side effects ascribable to the carrier do not vitiate the beneficial effects of the active ingredient. A pharmaceutically effective amount of compound is preferably that amount which produces a result or exerts an influence on the particular condition being treated.

20

The compounds of this invention may also be administered parenterally, that is, subcutaneously, intravenously, intraocularly, intrasynovially, intramuscularly, or interperitoneally, as injectable dosages of the compound in preferably a physiologically acceptable diluent with a pharmaceutical carrier
25 which can be a sterile liquid or mixture of liquids such as water, saline, aqueous dextrose and related sugar solutions, an alcohol such as ethanol, isopropanol, or hexadecyl alcohol, glycols such as propylene glycol or polyethylene glycol, glycerol ketals such as 2,2-dimethyl-1,1-dioxolane-4-methanol, ethers such as poly(ethylene glycol) 400, an oil, a fatty acid, a fatty
30 acid ester or, a fatty acid glyceride, or an acetylated fatty acid glyceride, with

or without the addition of a pharmaceutically acceptable surfactant such as a soap or a detergent, suspending agent such as pectin, carbomers, methycellulose, hydroxypropylmethylcellulose, or carboxymethylcellulose, or emulsifying agent and other pharmaceutical adjuvants.

5

The parenteral compositions of this invention will typically contain from about 0.5% to about 25% by weight of the active ingredient in solution. Preservatives and buffers may also be used advantageously. In order to minimise or eliminate irritation at the site of injection, such compositions may contain a non-ionic surfactant having a hydrophile-lipophile balance (HLB) preferably of from about 12 to about 17. The quantity of surfactant in such formulation preferably ranges from about 5% to about 15% by weight. The surfactant can be a single component having the above HLB or can be a mixture of two or more components having the desired HLB.

10

15

Illustrative of surfactants used in parenteral formulations are the class of polyethylene sorbitan fatty acid esters, for example, sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol.

20

The pharmaceutical compositions may be in the form of sterile injectable aqueous suspensions. Such suspensions may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents such as, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia ; dispersing or wetting agents which may be a naturally occurring phosphatide such as lecithin, a condensation product of an alkylene oxide with a fatty acid, for example, polyoxyethylene stearate, a condensation product of ethylene oxide with a long chain aliphatic alcohol, for example, heptadeca-ethyleneoxycetanol, a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol such as

25

polyoxyethylene sorbitol monooleate, or a condensation product of an ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride, for example polyoxyethylene sorbitan monooleate.

5 The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent. Diluents and solvents that may be employed are, for example, water, Ringer's solution, isotonic sodium chloride solutions and isotonic glucose solutions.

10 Pharmaceutical compositions according to the present invention can be illustrated as follows:

Sterile i.v. Solution: A 5 mg/mL solution of the desired compound of this invention can be made using sterile, injectable water, and the pH is adjusted if necessary. The solution is diluted for administration to 1 - 2 mg/mL with sterile 5% dextrose and is administered as an i.v. infusion over about 60
15 minutes.

As mentioned *supra*, compound A has been found to effectively inhibit Mps-1 and may therefore be used for the treatment or prophylaxis of diseases of uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses, or
20 diseases which are accompanied with uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses, particularly in which the uncontrolled cell growth, proliferation and/or survival, inappropriate cellular immune responses, or inappropriate cellular inflammatory responses is mediated by Mps-1, such
25 as, for example, haematological tumours, solid tumours, and/or metastases thereof, e.g. leukaemias and myelodysplastic syndrome, malignant lymphomas, head and neck tumours including brain tumours and brain metastases, tumours of the thorax including non-small cell and small cell lung tumours, gastrointestinal tumours, endocrine tumours, mammary and other

gynaecological tumours, urological tumours including renal, bladder and prostate tumours, skin tumours, and sarcomas, and/or metastases thereof.

In accordance with another aspect therefore, the present invention covers a
5 compound of general formula (I), or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, as described and defined herein, for use in the treatment or prophylaxis of a disease, as mentioned *supra*.

10 Another particular aspect of the present invention is therefore the use of a compound of general formula (I), described *supra*, or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, for the prophylaxis or treatment of a disease.

15 Another particular aspect of the present invention is therefore the use of a compound of general formula (I) described *supra* for manufacturing a pharmaceutical composition for the treatment or prophylaxis of a disease.

20 The term “inappropriate” within the context of the present invention, in particular in the context of “inappropriate cellular immune responses, or inappropriate cellular inflammatory responses”, as used herein, is to be understood as preferably meaning a response which is less than, or greater than normal, and which is associated with, responsible for, or results in, the
25 pathology of said diseases.

The present invention relates to a method for using the compounds of the present invention and compositions thereof, to treat mammalian hyper-proliferative disorders. Compounds can be utilized to inhibit, block, reduce,
30 decrease, etc., cell proliferation and/or cell division, and/or produce

apoptosis. This method comprises administering to a mammal in need thereof, including a human, an amount of a compound of this invention, or a pharmaceutically acceptable salt, isomer, polymorph, metabolite, hydrate, solvate or ester thereof ; etc. which is effective to treat the disorder. Hyper-
5 proliferative disorders include but are not limited, e.g., psoriasis, keloids, and other hyperplasias affecting the skin, benign prostate hyperplasia (BPH), solid tumors, such as cancers of the breast, respiratory tract, brain, reproductive organs, digestive tract, urinary tract, eye, liver, skin, head and neck, thyroid, parathyroid and their distant metastases. Those disorders also include
10 lymphomas, sarcomas, and leukemias.

Examples of breast cancer include, but are not limited to invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma in situ, and lobular carcinoma in situ.

Examples of cancers of the respiratory tract include, but are not limited to
15 small-cell and non-small-cell lung carcinoma, as well as bronchial adenoma and pleuropulmonary blastoma.

Examples of brain cancers include, but are not limited to brain stem and hypophtalmic glioma, cerebellar and cerebral astrocytoma, medulloblastoma, ependymoma, as well as neuroectodermal and pineal tumor.

20 Tumors of the male reproductive organs include, but are not limited to prostate and testicular cancer. Tumors of the female reproductive organs include, but are not limited to endometrial, cervical, ovarian, vaginal, and vulvar cancer, as well as sarcoma of the uterus.

Tumors of the digestive tract include, but are not limited to anal, colon,
25 colorectal, esophageal, gallbladder, gastric, pancreatic, rectal, small-intestine, and salivary gland cancers.

Tumors of the urinary tract include, but are not limited to bladder, penile, kidney, renal pelvis, ureter, urethral and human papillary renal cancers.

Eye cancers include, but are not limited to intraocular melanoma and retinoblastoma.

- 5 Examples of liver cancers include, but are not limited to hepatocellular carcinoma (liver cell carcinomas with or without fibrolamellar variant), cholangiocarcinoma (intrahepatic bile duct carcinoma), and mixed hepatocellular cholangiocarcinoma.

- 10 Skin cancers include, but are not limited to squamous cell carcinoma, Kaposi's sarcoma, malignant melanoma, Merkel cell skin cancer, and non-melanoma skin cancer.

- Head-and-neck cancers include, but are not limited to laryngeal, hypopharyngeal, nasopharyngeal, oropharyngeal cancer, lip and oral cavity cancer and squamous cell. Lymphomas include, but are not limited to AIDS-
15 related lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, Burkitt lymphoma, Hodgkin's disease, and lymphoma of the central nervous system.

- Sarcomas include, but are not limited to sarcoma of the soft tissue, osteosarcoma, malignant fibrous histiocytoma, lymphosarcoma, and
20 rhabdomyosarcoma.

Leukemias include, but are not limited to acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and hairy cell leukemia.

- These disorders have been well characterized in humans, but also exist with a
25 similar etiology in other mammals, and can be treated by administering pharmaceutical compositions of the present invention.

The term “treating” or “treatment” as stated throughout this document is used conventionally, *e.g.*, the management or care of a subject for the purpose of combating, alleviating, reducing, relieving, improving the condition of, *etc.*, of a disease or disorder, such as a carcinoma.

- 5 The present invention also provides methods for the treatment of disorders associated with aberrant mitogen extracellular kinase activity, including, but not limited to stroke, heart failure, hepatomegaly, cardiomegaly, diabetes, Alzheimer's disease, cystic fibrosis, symptoms of xenograft rejections, septic shock or asthma.
- 10 Effective amounts of compounds of the present invention can be used to treat such disorders, including those diseases (*e.g.*, cancer) mentioned in the Background section above. Nonetheless, such cancers and other diseases can be treated with compounds of the present invention, regardless of the mechanism of action and/or the relationship between the kinase and the
- 15 disorder.

The phrase “aberrant kinase activity” or “aberrant serine-threonine kinase activity,” includes any abnormal expression or activity of the gene encoding the kinase or of the polypeptide it encodes. Examples of such aberrant activity, include, but are not limited to, over-expression of the gene or

20 polypeptide ; gene amplification ; mutations which produce constitutively-active or hyperactive kinase activity ; gene mutations, deletions, substitutions, additions, *etc.*

The present invention also provides for methods of inhibiting a kinase activity, especially of mitogen extracellular kinase, comprising administering an

25 effective amount of a compound of the present invention, including salts, polymorphs, metabolites, hydrates, solvates, prodrugs (*e.g.*: esters) thereof, and diastereoisomeric forms thereof. Kinase activity can be inhibited in cells

(e.g., *in vitro*), or in the cells of a mammalian subject, especially a human patient in need of treatment.

GENERAL SYNTHESIS OF PRODRUG COMPOUNDS OF FORMULA (I)

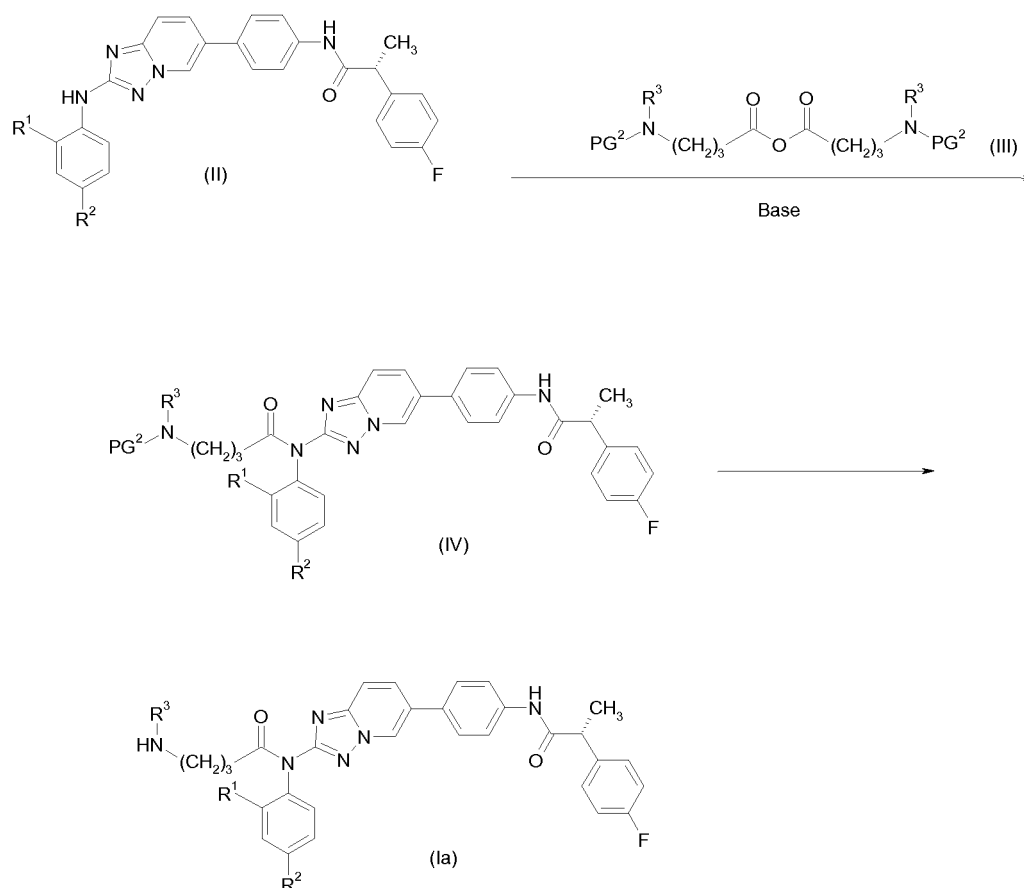
The following paragraphs outline a variety of synthetic approaches suitable to
5 prepare compounds of formulae (Ia), (Ib), (Ic), (Id) and (Ie) as shown in the following schemes, all constituting subsets of formula (I) in that they feature different embodiments of the group R^A.

In addition to the routes described below, also other routes may be used to synthesise the target compounds, in accordance with common general
10 knowledge of a person skilled in the art of organic synthesis. The order of transformations exemplified in the following Schemes is therefore not intended to be limiting, and suitable synthesis steps from various schemes can be combined to form additional synthesis sequences. In addition, interconversion of any of the substituents shown can be achieved before and/or after the
15 exemplified transformations. These modifications can be such as reduction or oxidation of functional groups, halogenation, metallation, metal catalysed coupling reactions, substitution or other reactions known to a person skilled in the art. These transformations include those which introduce a functionality allowing for further interconversion of substituents. In particular, the synthetic
20 routes below encompass the introduction and cleavage of protective groups. Appropriate protective groups and their introduction and cleavage are well-known to a person skilled in the art (see for example T.W. Greene and P.G.M. Wuts in *Protective Groups in Organic Synthesis*, 3rd edition, Wiley 1999); more specifically, protective groups include groups such as PG¹ (protecting group for hydroxy as defined *supra*), and PG² (protecting group for amino as defined
25 *supra*). Where appropriate, this is indicated by the inclusion of " ' " in the respective denomination of the respective residue, e.g. R⁸ for a protected equivalent of R⁸, and *vice versa* in R⁹ and R⁹, respectively, in the schemes shown below.

Specific examples are described in the subsequent paragraphs. Further, it is possible that two or more successive steps may be performed without work-up being performed between said steps, e.g. a “one-pot” reaction, as it is well-known to a person skilled in the art.

- 5 As outlined in scheme 1, compounds of the general formula (Ia), in which R^1 , R^2 and R^3 are as defined for the general formula (I) can be prepared by reacting of starting materials of the formula (II), in which R^1 and R^2 are as defined for the general formula (I), with anhydrides of the formula (III), in which R^3 is as defined for the general formula (I), and in which PG^2 represents a protecting
10 group for amino groups, as defined *supra*, such as *tert*-butoxycarbonyl (Boc), benzyloxycarbonyl (Z) or *p*-methoxybenzyl (PMB), in the presence of a suitable base, to give intermediates of the formula (IV). Said intermediates can be converted into compounds of the formula (Ia) by removal of PG^2 using deprotection methods known to the person skilled in the art (see e.g. T.W.
15 Greene and P.G.M. Wuts in *Protective Groups in Organic Synthesis*, 3rd edition, Wiley 1999). Protective groups PG^2 , if occurring more than once in one molecule, can be identical or different. Prodrug compounds of formula (Ia) are typically isolated as salts, preferably as HCl salts or as TFA-salts.

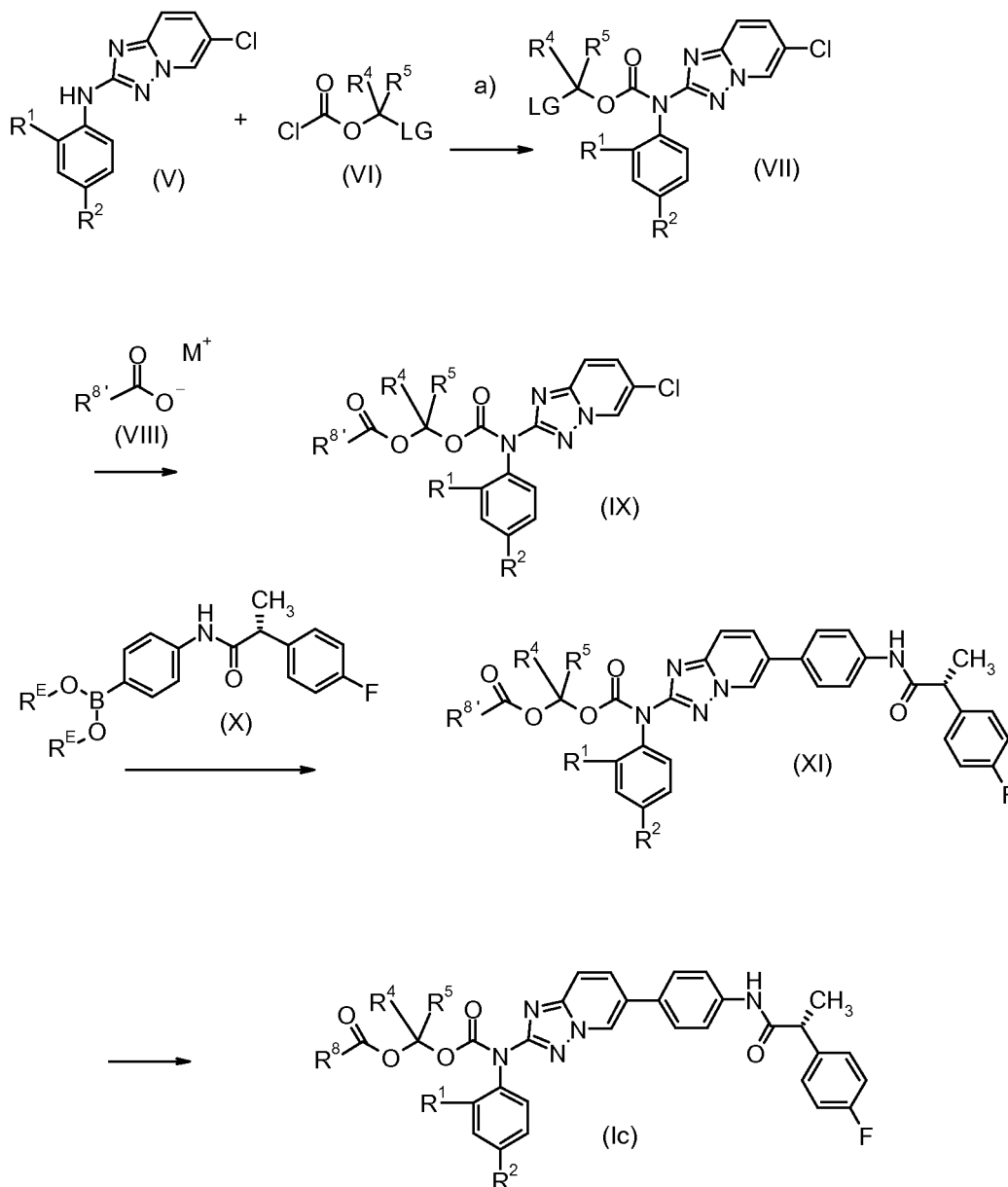
The preparation of starting materials (II) is described in the Experimental
20 Section in several instances, and can be alternatively performed e.g. according to WO2012/143329(A1). Anhydrides such as (III) can be approached by methods known to the person skilled in the art and are also described in the literature (see e.g. Y. Armaki et al., *Chem. Pharm. Bull.* 52, 258 (2004)).



Scheme 1: Synthesis of prodrug compounds of formula (Ia) from intermediates (II)

Scheme 2 outlines the synthesis of prodrug derivatives (Ic), in which R¹, R², R⁴,
 5 R⁵ and R⁸ are as defined for compounds of general formula (I), from
 intermediates of the formula (V), in which R¹ and R² are as defined for
 compounds of general formula (I). The preparation of intermediates (V) can be
 performed as described in the Experimental Section. Intermediates (V) are
 deprotonated by a suitable base, such as sodium hydride, in a suitable solvent,
 10 such as an ether, e.g. tetrahydrofuran, and subsequently reacted with a
 chloroformate of formula (VI), in which R⁴ and R⁵ are as defined for
 compounds of the general formula (I), and LG stands for a leaving group, as
 defined *supra*, preferably chloro, to give carbamates (VII). Chloroformates of
 formula (VI) are well known to the person skilled in the art, and are
 15 commercially available in several cases. Said carbamates (VII) are reacted with

a carboxylate salt of the formula (VIII), in which M^+ stands for a monovalent cation such as an alkali cation or an ammonium salt, preferably cesium, and in which $R^{8'}$ represents an equivalent of R^8 featuring an additional protective group if needed, as described *supra*, in a suitable solvent, such as *N,N*-dimethylformamide, to give intermediates of the formula (IX). This substitution can also be performed in the presence of a catalytic amount of an iodide salt like sodium iodide or potassium iodide whereby the leaving group LG is in situ transformed to iodide. Alternatively, the leaving group LG can be transformed to iodide prior to the substitution reaction. Intermediates (IX) are then subjected to a Suzuki coupling involving boronic acid derivatives (X), in which R^E stand for hydrogen or independently from each other stand for C_1 - C_6 -alkyl-, or together form a C_2 - C_6 -alkylene- group. Suzuki couplings are well known to the person skilled in the art, the coupling as shown in Scheme 2 employs S-Phos as a ligand, $Pd(OAc)_2$ or $Pd_2(dba)_3$ as palladium source, potassium phosphate monohydrate or potassium phosphate as a base, and toluene or *N*-methylpyrrolidine or mixtures of toluene and *N*-methylpyrrolidine as a solvent. The coupling products (XI) are subsequently deprotected (if needed), e.g. by treatment with hydrochloric acid to remove a Boc group, to give prodrug compounds of formula (Ic). Prodrug compounds of formula (Ic) are typically isolated as salts, preferably as HCl salts or as TFA-salts.



Scheme 2: Synthesis of prodrug compounds of formula (Ic) from intermediates (V)

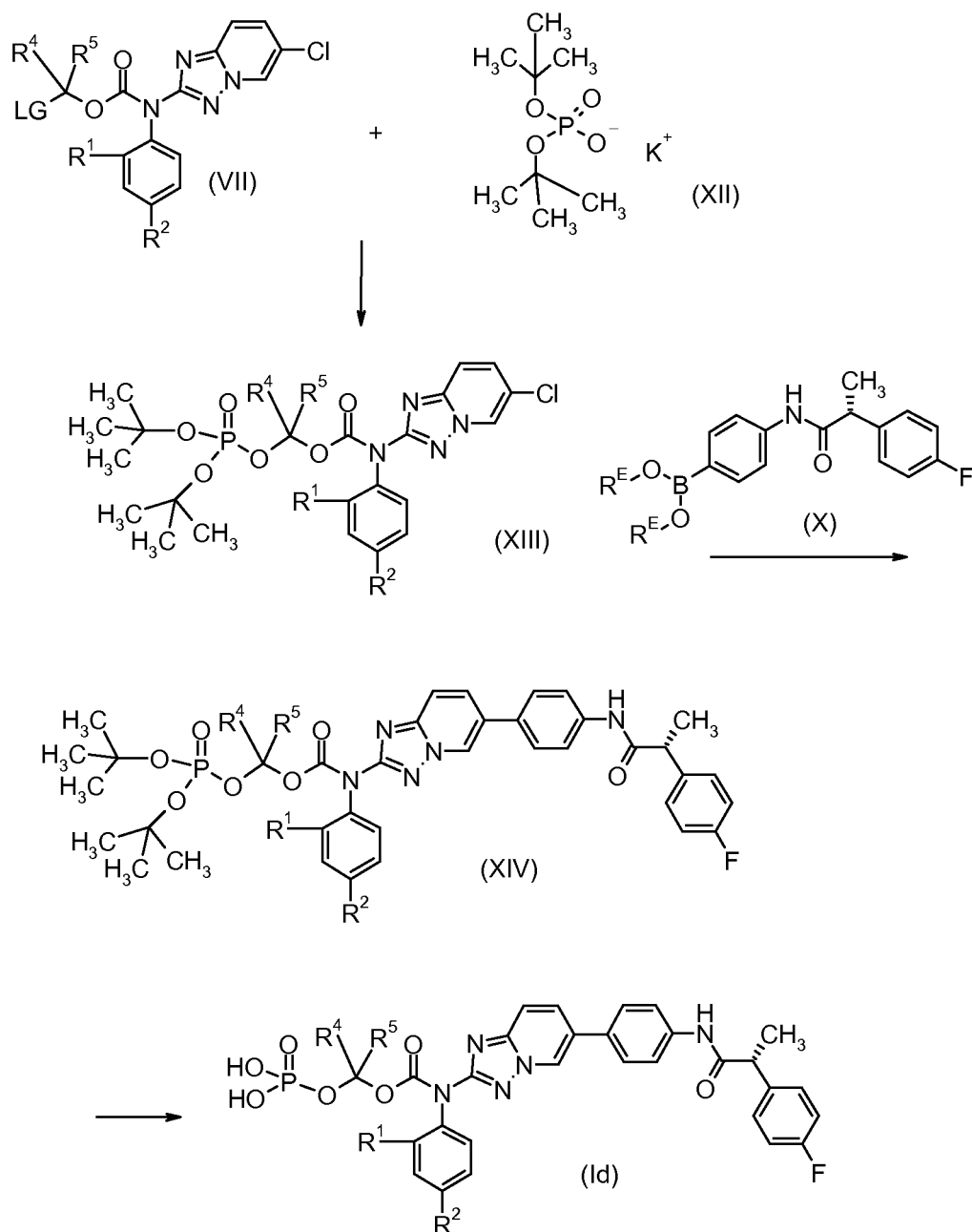
Prodrug compounds of the formula (Id), featuring a phosphate unit, can be synthesised from carbamates of formula (VII), in which R^1 , R^2 , R^4 and R^5 are as defined for compounds of the general formula (I), and LG stands for a leaving group, as defined *supra*, preferably chloro. Said carbamates can be prepared as described in Scheme 2. Carbamates (VII) are reacted with an alkali salt of di-*tert*-butyl phosphate, e.g. the commercially available potassium salt (XII), to give phosphate intermediates (XIII). This substitution can also be performed

in the presence of a catalytic amount of an iodide salt like sodium iodide or potassium iodide whereby the leaving group LG is in situ transformed to iodide. Alternatively, the leaving group LG can be transformed to iodide prior to the substitution reaction. Phosphate intermediates (XIII) are in turn subjected to a

5 Suzuki coupling with boronic acid derivatives (X) in which R^E stand for hydrogen or independently from each other stand for C₁-C₆-alkyl-, or together form a C₂-C₆-alkylene- group. Suzuki couplings are well known to the person skilled in the art, the coupling as shown in Scheme 3 employs S-Phos as a ligand, Pd(OAc)₂ or Pd₂(dba)₃ as palladium source, potassium phosphate monohydrate or potassium

10 phosphate as a base, and toluene or *N*-methylpyrrolidine as a solvent. The coupling products (XIV) are then subjected to an acidic cleavage, e.g. with a solution of hydrogen chloride in dioxane and dichloromethane, of the *tert*-butyl phosphate ester groups, to give phosphate prodrug compounds of the formula (Id).

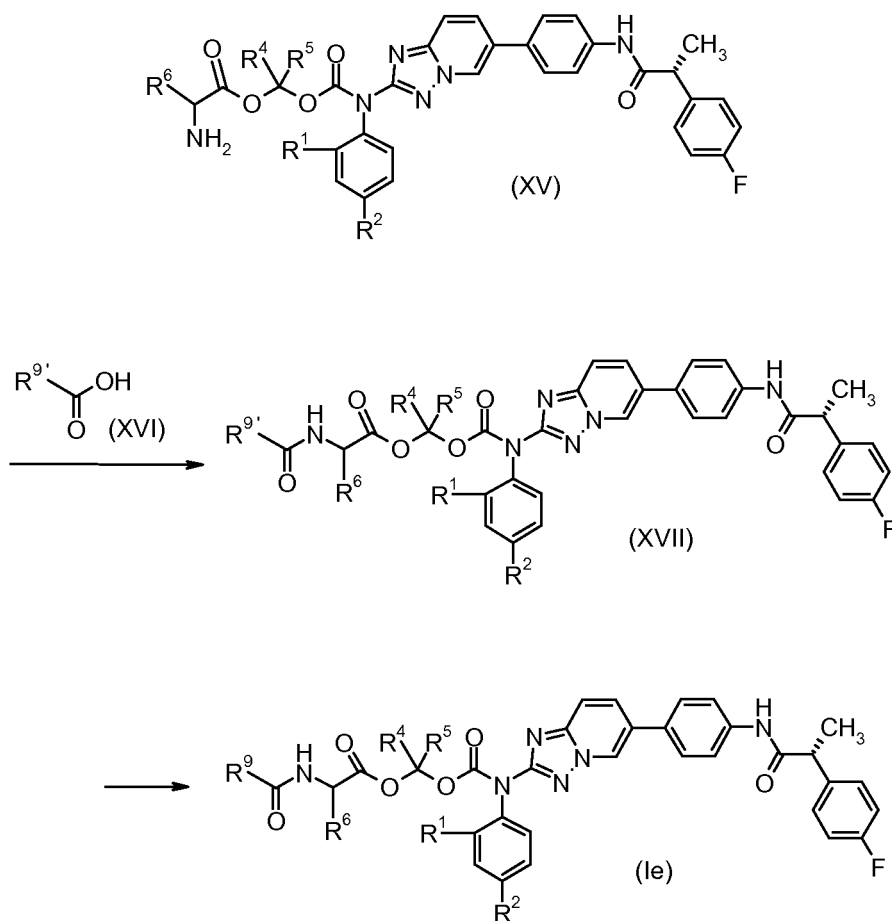
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Scheme 3: Synthesis of phosphate prodrug compounds of formula (Id) from carbamates (VII)

Prodrug compounds of the general formula (Ie), featuring a dipeptide or dipeptide-like group, can be prepared from amines (XV), in which R^1 , R^2 , R^4 , R^5 , and R^6 are as defined for compounds of the general formula (I), by coupling with an optionally protected amino acid (XVI), in which R^9 represents an equivalent of R^9 featuring an additional protective group if needed, as described *supra*. The coupling can be performed with a variety of standard

peptide coupling reagents well known to the person skilled in the art, such as HATU; optionally protected amino acids of the formula (XVI) are commercially available in many instances. Amines of the formula (XV) can be approached with the methods described in scheme 2 (compounds of formula (XV) can be understood as compounds of formula (Ic), in which R^8 stands for $-CH(R^6)-NH_2$), and in the Experimental Section to give intermediates of formula (XVII), which are subsequently deprotected (if needed), e.g. by treatment with hydrochloric acid to remove a Boc group, to give prodrug compounds of formula (Ie). Prodrug compounds of formula (Ie) are typically isolated as salts, preferably as HCl salts or as TFA-salts.



Scheme 4: Synthesis of prodrug compounds of formula (Ie) from amines (XV)

EXPERIMENTAL SECTION

The following Table lists the abbreviations used in this paragraph, and in the Examples section. NMR peak forms are stated as they appear in the spectra, possible higher order effects have not been considered.

Abbreviation	Meaning
Ac	acetyl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Boc	<i>tert</i> -butyloxycarbonyl
br	broad
Brett-Phos	2-(dicyclohexylphosphino)-3,6-dimethoxy-2'-4'-6'-tri- <i>i</i> -propyl-1,1'-biphenyl
c-	cyclo-
1-Chloroethyl chloroformate	1-chloroethyl carbonochloridate
Chloromethyl chloroformate	chloromethyl carbonochloridate
d	doublet
dd	doublet of doublets
DCM	dichloromethane
DME	1,2-dimethoxyethane
DIPE	diisopropylether

DIPEA	<i>N,N</i> -diisopropylethylamine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
Dppf	1,1'-bis(diphenylphosphino)ferrocene
Eq	equivalent
ESI	electrospray ionisation
HATU	<i>N</i> -[(dimethylamino)(3 <i>H</i> -[1,2,3]triazolo[4,5- <i>b</i>]pyridin-3-yloxy)-methylene]- <i>N</i> -methylethaniminium hexafluorophosphate
Hünig Base	<i>N,N</i> -diisopropylethylamine
m	multiplet
m.p.	melting point in °C
MS	mass spectrometry
MW	molecular weight
NaOtBu	sodium <i>tert</i> -butoxide; sodium 2-methylpropan-2-olate
NMP	<i>N</i> -methylpyrrolidinone
NMR	nuclear magnetic resonance spectroscopy: chemical shifts (δ) are given in ppm.
PdCl ₂ (PPh ₃) ₂	dichlorobis(triphenylphosphine)palladium(II)
Pd(dba) ₂	bis-(dibenzylideneacetone)palladium(0) complex
Pd ₂ (dba) ₃	tris-(dibenzylideneacetone)dipalladium(0) complex chloroform

Pd(dppf)Cl ₂	dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II)
Pd(dppf)Cl ₂ . CH ₂ Cl ₂	dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloromethane adduct
Pd-Brett-Phos- pre-cat	chloro[2-(dicyclohexylphosphino)-3,6-dimethoxy-2'-4'-6'-tri- iso-propyl-1,1'-biphenyl][2-(2- aminoethyl)phenyl]palladium(II)
Pd- <i>t</i> Bu-X-Phos- pre-cat	chloro(2-di- <i>tert</i> -butylphosphino-2',4',6'-tri-isopropyl-1,1'- biphenyl)[2-(2-aminoethyl)phenyl] palladium(II),
Pd-X-Phos-pre- cat	chloro(2-dicyclohexylphosphino-2',4',6'-tri-isopropyl-1,1'- biphenyl)[2-(2-aminoethyl)phenyl] palladium(II) methyl- <i>tert</i> - butylether adduct
PPh ₃	triphenylphosphine
P(<i>o</i> Tol) ₃	tri- <i>o</i> -tolylphosphine
q	quartet
quin	quintett
Rac	racemic
Rt	room temperature
r.t.	room temperature
RT	retention time in minutes
s	singlet
S-Phos	dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine
t	triplet

TBAF	tetrabutylammoniumfluoride
tBu-X-Phos	2-di- <i>tert</i> -butylphosphino-2',4',6'-tri-isopropyl-1,1'-biphenyl
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBTU	<i>N</i> -[(1 <i>H</i> -benzotriazol-1-yloxy)(dimethylamino)methylene]- <i>N</i> -methylmethanaminium tetrafluoroborate
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
Ts	para toluenesulfonyl; (tosyl)
UPLC	ultra performance liquid chromatography
X-Phos	2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

The compounds and intermediates produced according to the methods of the invention may require purification. Purification of organic compounds is well known to the person skilled in the art and there may be several ways of purifying the same compound. In some cases, no purification may be necessary. In some cases, the compounds may be purified by crystallisation. In some cases, impurities may be stirred out using a suitable solvent. In some cases, the compounds may be purified by chromatography, particularly flash chromatography, using for example pre-packed silica gel cartridges, e.g. from Separtis such as Isolute® Flash silica gel (silica gel chromatography) or Isolute® Flash NH₂ silica gel (aminophase-silica-gel chromatography) in combination with a suitable chromatographic system such as a Flashmaster II (Separtis) or

- an Isolera system (Biotage) and eluents such as, for example, gradients of hexane/ethyl acetate or DCM/methanol. In some cases, the compounds may be purified by preparative HPLC using, for example, a Waters autopurifier equipped with a diode array detector and/or on-line electrospray ionisation
- 5 mass spectrometer in combination with a suitable pre-packed reverse phase column and eluants such as, for example, gradients of water and acetonitrile which may contain additives such as trifluoroacetic acid, formic acid or aqueous ammonia.
- 10 Optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example, by the formation of diastereoisomeric salts using an optically active acid or base or formation of covalent diastereomers. Examples of appropriate acids are tartaric, diacetyltartaric, ditoluoyltartaric and camphorsulfonic acid. Mixtures of
- 15 diastereoisomers can be separated into their individual diastereomers on the basis of their physical and/or chemical differences by methods known in the art, for example, by chromatography or fractional crystallisation. The optically active bases or acids are then liberated from the separated diastereomeric salts. A different process for separation of optical isomers
- 20 involves the use of chiral chromatography (e.g., chiral HPLC columns), with or without conventional derivatisation, optimally chosen to maximise the separation of the enantiomers. Suitable chiral HPLC columns are manufactured by Diacel, e.g., Chiracel OD and Chiracel OJ among many others, all routinely selectable. Enzymatic separations, with or without
- 25 derivatisation, are also useful. The optically active compounds of this invention can likewise be obtained by chiral syntheses utilizing optically active starting materials.

In the present text, in particular in the Experimental Section, for the synthesis

30 of intermediates and of examples of the present invention, when a compound

is mentioned as a salt form with the corresponding base or acid, the exact stoichiometric composition of said salt form, as obtained by the respective preparation and/or purification process, is, in most cases, unknown.

- 5 Unless specified otherwise, suffixes to chemical names or structural formulae such as "hydrochloride", "trifluoroacetate", "sodium salt", or "x HCl", "x CF₃COOH", "x Na⁺", for example, are to be understood as not a stoichiometric specification, but solely as a salt form.
- 10 This applies analogously to cases in which synthesis intermediates or example compounds or salts thereof have been obtained, by the preparation and/or purification processes described, as solvates, such as hydrates with (if defined) unknown stoichiometric composition.
- 15 Analytical UPLC-MS was performed as follows:
Method A: System: UPLC Acquity (Waters) with PDA Detector und Waters ZQ mass spectrometer; Column: Acquity BEH C18 1.7µm 2.1x50mm; Temperature: 60°C; Solvent A: Water + 0.1% formic acid; Solvent B: acetonitrile; Gradient: 99 % A → 1 % A (1.6 min) → 1 % A (0.4 min) ; Flow: 0.8 mL/min; Injection
20 Volume: 1.0 µl (0.1mg-1mg/mL sample concentration); Detection: PDA scan range 210-400 nm - Fixed and ESI (+), scan range 170-800 m/z

LC-MS methods:

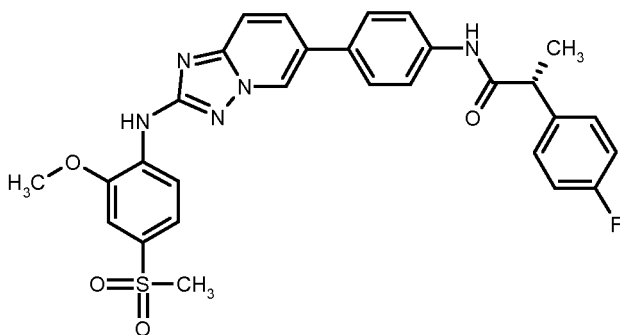
Method 1:

- 25 Instrument: Waters ACQUITY SQD UPLC System; Column: Waters Acquity UPLC HSS T3 1.8 µ 50 x 1 mm; Eluent A: 1 l Wasser + 0.25 ml 99%ige Formic acid, Eluent B: 1 l Acetonitril + 0.25 ml 99%ige Formic acid; Gradient: 0.0 min 90% A → 1.2 min 5% A → 2.0 min 5% A Ofen: 50°C; Flow: 0.40 ml/min; UV-Detection: 208 - 400 nm.

30

Preparation of compound A1Route I

(2R)-2-(4-fluorophenyl)-N-[4-(2-{[2-methoxy-4-(methylsulfonyl)phenyl]-amino}[1,2,4]triazolo[1,5- α]pyridin-6-yl)phenyl]propanamide



To a stirred suspension of Int08.011 (6.0 g) in DMF (48 mL) and dichloromethane (96 mL) was added sodium bicarbonate (3.69 g), (2R)-2-(4-fluorophenyl)propanoic acid (2.71 g) and HATU (8.36 g). The mixture was stirred at room temperature for 4 h. Water was added, and the mixture was stirred for 30 minutes. A half-saturated solution of sodium bicarbonate was added and the mixture was extracted with ethyl acetate. The organic phase was washed with saturated sodium chloride solution, dried (sodium sulfate) and the solvent was removed in vacuum. Silicagel chromatography gave a solid that was triturated with ethyl acetate to give 7.44 g of the title compound.

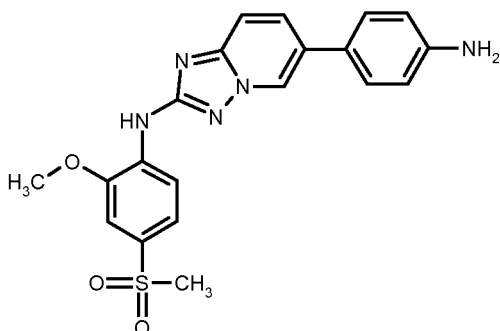
$^1\text{H-NMR}$ (400MHz, DMSO- d_6): δ [ppm] = 1.40 (d, 3H), 3.16 (s, 3H), 3.84 (q, 1H), 3.96 (s, 3H), 7.09 - 7.18 (m, 2H), 7.36 - 7.44 (m, 3H), 7.51 (dd, 1H), 7.63 - 7.76 (m, 5H), 7.92 (dd, 1H), 8.48 (d, 1H), 8.60 (s, 1H), 9.10 (d, 1H), 10.16 (s, 1H).
 $[\alpha]_D^{20}$: -77.0° (in DMSO).

Determination of enantiomeric purity by analytical chiral HPLC:

Column: Chiralcel OD-RH 150x4.6; Flow: 1.00 mL/min; Solvent: A: Water with 0.1 % formic acid, B: Acetonitrile; Solvent mixture: 40% A + 60% B. Run Time: 30 min. Retention Time: 12.83 min; UV 254 nm; Enantiomeric Ratio: <1% : > 99%.

Intermediate Int08.011

6-(4-aminophenyl)-N-[2-methoxy-4-(methylsulfonyl)phenyl][1,2,4]-
 triazolo[1,5- α]pyridin-2-amine



5

To a stirred suspension of Int08.010 (12.3 g) in dichloromethane (40 mL) was added TFA (46 mL). The mixture was stirred at room temperature for 16 h. Further TFA was added (1 mL) and the mixture was stirred at room temperature for 5 h. A saturated solution of potassium carbonate was added until pH 9 was reached. The mixture was extracted with dichloromethane and methanol (10:1 mixture). The solution was dried (sodium sulfate) and the solvent was removed in vacuum. The residue was triturated with ethanol to give 9.2 g of the title compound.

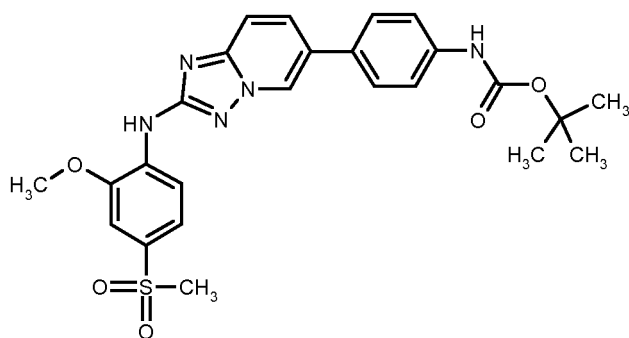
¹H-NMR (300MHz, DMSO-*d*₆): δ [ppm]= 3.16 (s, 3H), 3.95 (s, 3H), 5.30 (s, 2H), 6.63 (d, 2H), 7.38 - 7.46 (m, 3H), 7.51 (dd, 1H), 7.61 (d, 1H), 7.84 (dd, 1H), 8.48 (d, 1H), 8.55 (s, 1H), 8.93 (d, 1H).

15

Intermediate Int08.010

tert-butyl [4-(2-{[2-methoxy-4-(methylsulfonyl)phenyl]amino}[1,2,4]-
 triazolo[1,5- α]pyridin-6-yl)phenyl]carbamate

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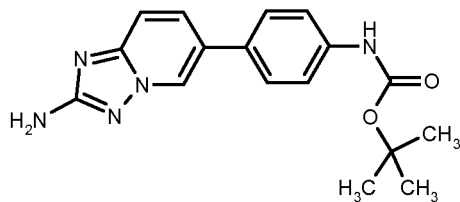
To a stirred suspension of Int01.03 (4.0 g) in toluene (250 mL) and NMP (25 mL) was added Int03.02 (8.31 g), chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl] palladium(II) methyl-*tert*-butylether adduct (1.08 g), X-Phos (0.64 g) and powdered potassium phosphate (16.6 g). The flask was degassed twice and backfilled with argon. The mixture was heated to reflux for 16 h.

The reaction mixture was filtered through a microfilter and the solvent was removed in vacuum. The residue was triturated with dichloromethane to give 12.3 g of the title compound.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm] = 1.46 (s, 9H), 3.16 (s, 3H), 3.96 (s, 3H), 7.43 (d, 1H), 7.48 - 7.59 (m, 3H), 7.63 - 7.72 (m, 3H), 7.92 (dd, 1H), 8.48 (d, 1H), 8.58 (s, 1H), 9.06 - 9.12 (m, 1H), 9.46 (s, 1H).

15 Intermediate Int01.03.

tert-butyl [4-(2-amino[1,2,4]triazolo[1,5-*a*]pyridin-6-yl)phenyl]carbamate



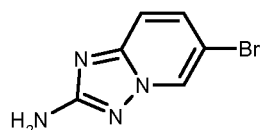
To a stirred solution of Int01.02 (5.82 g) in 1-propanol (400 mL) was added 2M potassium carbonate solution (41 mL), {4-[(*tert*-butoxycarbonyl) amino] phenyl} boronic acid (8.6 g), triphenylphosphine (150 mg) and PdCl₂(PPh₃)₂ (1.9 g). The mixture was heated to reflux for 4 h, the solvent was removed in vacuum, water (150 mL) was added and the mixture was extracted with ethyl

acetate (500 mL). The organic phase was dried (sodium sulfate), filtered through Celite and the solvent was removed in vacuum. The residue was triturated with DCM to give the title compound as a white solid. Yield: 7.2 g.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm] = 1.37 - 1.55 (m, 9H), 5.99 (s, 2H), 7.36 (dd, 1H), 7.48 - 7.55 (m, 2H), 7.55 - 7.62 (m, 2H), 7.69 (dd, 1H), 8.78 (dd, 1H), 9.44 (s, 1H).

Intermediate Int01.02

6-Bromo[1,2,4]triazolo[1,5-α]pyridin-2-amine



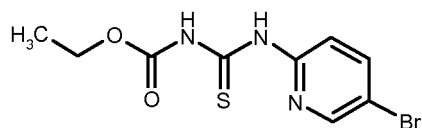
Hydroxylammonium chloride (39.8 g) was suspended in methanol (200 mL) and ethanol (190 mL) and Hünig Base (59 mL) was added at r.t. The mixture was heated to 60°C, Int01.01 (30 g) was added portionwise, and the mixture was stirred at 60°C for 2h. The solvent was removed in vacuum and water (150 mL) was added. A solid was collected by filtration and was washed with water and dried in vacuum.

Yield: 19.3 g of the title compound.

¹H-NMR (300MHz, DMSO-d₆): δ [ppm] = 6.10 (s, 2H), 7.28 (dd, 1H), 7.51 (dd, 1H), 8.88 (dd, 1H).

Intermediate Int01.01

Ethyl [(5-bromopyridin-2-yl)carbamothioyl]carbamate



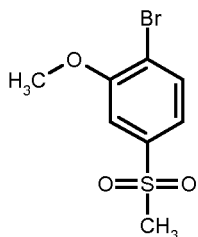
Ethoxycarbonylisothiocyanate (16.7 g) was added to a stirred solution of 2-amino-5-bromopyridine (20 g) in dioxane (200 mL). The mixture was stirred for 2h at r.t. A white solid precipitated. Hexane (20 mL) was added and the white solid was collected by filtration.

Yield: 30.4 g of the title compound.

$^1\text{H-NMR}$ (300MHz, DMSO-d_6): δ [ppm] = 1.22 (t, 3H), 4.19 (q, 2H), 8.08 (dd, 1H), 8.49 (d, 1H), 8.57 (br. d, 1H), 11.37 - 12.35 (m, 2H).

5 Intermediate Int03.02

1-bromo-2-methoxy-4-(methylsulfonyl)benzene

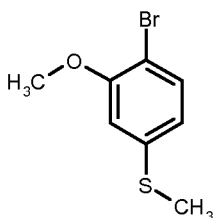


To a stirred solution of Int03.01 (265 mg) in chloroform (10 mL) was added 3-chlorobenzenecarboperoxoic acid (mCPBA) (890 mg). The mixture was stirred at room temperature for 1 h. A half-saturated solution of sodium bicarbonate was added and the mixture was extracted with dichloromethane. The organic phase was washed with saturated sodium chloride solution, dried (sodium sulfate) and the solvent was removed in vacuum. Silica gel chromatography gave 252 mg of the title compound.

$^1\text{H-NMR}$ (300MHz, DMSO-d_6): δ [ppm] = 3.22 (s, 3H), 3.93 (s, 3H), 7.39 (dd, 1H), 7.50 (d, 1H), 7.84 (d, 1H).

Intermediate Int03.01

1-bromo-2-methoxy-4-(methylsulfanyl)benzene



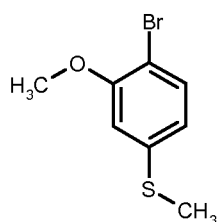
To a stirred solution of 1-bromo-4-fluoro-2-methoxybenzene (4.0 g) in DMF (40 mL) was added sodium methanethiolate (2.76 g). The mixture was stirred at room temperature for 30 minutes and at 85°C for 2 h. Water was added and the mixture was extracted with ethyl acetate. The organic phase was washed

with saturated sodium chloride solution, dried (sodium sulfate) and the solvent was removed in vacuum. Silica gel chromatography gave 280 mg of the title compound.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm] = 2.46 (s, 3H), 3.82 (s, 3H), 6.74 (dd, 1H),
5 6.91 (d, 1H), 7.44 (d, 1H).

Intermediate Int03.00

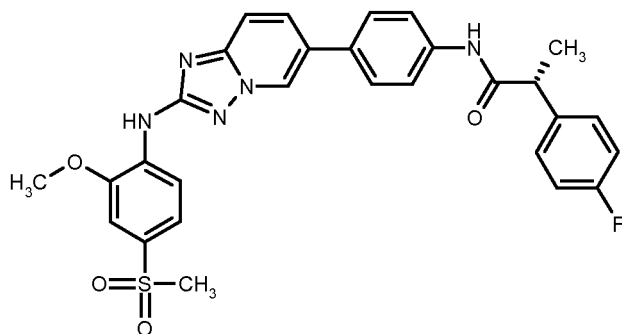
1-bromo-2-methoxy-4-(methylsulfanyl)benzene (alternative procedure)



- 10 To a stirred solution of 1-bromo-4-fluoro-2-methoxybenzene (10.0 g) in DMF (100 mL) was added sodium methanethiolate (4.44 g). The mixture was stirred at 65°C for 2 h. The mixture was cooled to 0°C and methyl iodide (4.55 mL) was added. The mixture was stirred at room temperature for 1 h and further sodium methanethiolate (4.44 g) was added. The mixture was stirred at 65°C
15 for 1 h. The mixture was cooled to 0°C and methyl iodide (4.55 mL) was added. The mixture was stirred at room temperature for 1 h. Water was added and the mixture was extracted with ethyl acetate. The organic phase was washed with saturated sodium chloride solution, dried (sodium sulfate) and the solvent was removed in vacuum. Silica gel chromatography gave 6.2 g of the
20 title compound as a 2:1 mixture with the starting material. The mixture was used for the next step without purification.

Route II

- (2R)-2-(4-fluorophenyl)-N-[4-(2-{[2-methoxy-4-(methylsulfonyl)phenyl]-
25 amino}[1,2,4]triazolo[1,5-α]pyridin-6-yl)phenyl]propanamide



To a stirred suspension of Int21.06 (550 mg) in toluene (18 mL) was added potassium fluoride (260 mg) and powdered potassium phosphate (842 mg) and the flask was degassed twice and backfilled with argon. The mixture was stirred for 15 minutes at r.t.. Int21.03 (350 mg), dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (81 mg) and palladium acetate (22 mg) were added and the flask was degassed twice and backfilled with argon. The mixture was heated to 85 °C for 3 h. Water was added and the reaction mixture was extracted with ethyl acetate. The organic phase was washed with saturated sodium chloride solution, dried (sodium sulfate) and the solvent was removed in vacuum. Aminophase-silica-gel chromatography gave a solid that was triturated with a mixture of dichloromethane and hexane to give 452 mg of the title compound.

¹H-NMR (300 MHz, DMSO-d₆), δ [ppm] = 1.39 (3H), 3.16 (3H), 3.83 (1H), 3.95 (3H), 7.08-7.20 (2H), 7.34-7.45 (3H), 7.51 (1H), 7.63-7.77 (5H), 7.92 (1H), 8.48 (1H), 8.64 (1H), 9.11 (1H), 10.19 (1H).

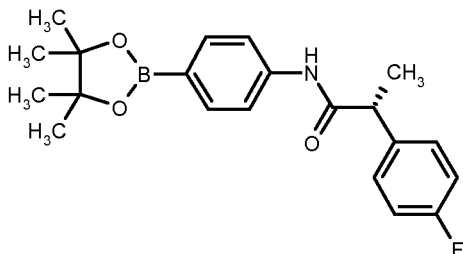
[α]_D²⁰ : -78.9° (in DMSO).

Determination of enantiomeric purity by analytical chiral HPLC:

Column: Chiralcel OD-RH 150x4.6; Flow: 1.00 mL/min; Solvent: A: Water with 0.1 % formic acid, B: Acetonitrile; Solvent mixture: 40% A + 60% B. Run Time: 30 min. Retention Time: 12.83 min; UV 254 nm; Enantiomeric Ratio: <1% : > 99%.

Intermediate Int21.06

(2R)-2-(4-fluorophenyl)-N-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]propanamide



- 5 To a stirred solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.0 g) in DMF (45 mL) and dichloromethane (90 mL) was added sodium bicarbonate (766 mg), Int09.03 (844 mg) and HATU (2.6 g). The mixture was stirred at room temperature for 4 h. Water was added, and the mixture was stirred for 30 minutes. A half-saturated solution of sodium bicarbonate was
- 10 added and the mixture was extracted with ethyl acetate. The organic phase was washed with saturated sodium chloride solution, dried (sodium sulfate) and the solvent was removed in vacuum. Silica-gel chromatography gave 1.53 g of the title compound.

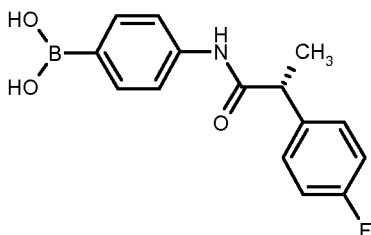
¹H-NMR (400 MHz, DMSO-d₆), δ [ppm] = 1.23 (12H), 1.37 (3H), 3.74-3.87 (1H),

15 7.06-7.16 (2H), 7.31-7.42 (2H), 7.51-7.61 (4H), 10.12 (1H).

Intermediate Example Int21.05

(4-[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)boronic acid

20



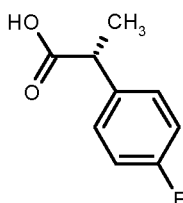
To a stirred solution of (4-aminophenyl)boronic acid hydrochloride (2.00 g) in DMF (42 mL) was added sodium bicarbonate (2.9 g), (2R)-2-(4-

fluorophenyl)propanoic acid (2.04 g) and HATU (6.58 g). The mixture was stirred at room temperature for 72 h. Water (140 mL) was added, and the mixture was stirred for 2 h. The white precipitate was collected by filtration and was washed with water and was dried in vacuum to give 2.86 g of the title compound.

$^1\text{H-NMR}$ (300 MHz, DMSO- d_6), δ [ppm] = 1.39 (3H), 3.84 (1H), 7.08-7.21 (2H), 7.35-7.44 (2H), 7.52 (2H), 7.69 (2H), 7.88 (2H), 10.07 (1H).

Intermediate Int09.03

10 (2R)-2-(4-fluorophenyl)propanoic acid



To a stirred solution of Int09.02 (23.6 g) in refluxing ethyl acetate (250mL) was added a solution of (1S)-1-phenylethanamine (17.35 g) in ethyl acetate. The mixture was allowed to cool down to room temperature within 1 h. A white solid was collected by filtration, was washed with ethyl acetate and dried in vacuum to give 27.5 g of a solid. The solid was recrystallized from 400 mL refluxing ethyl acetate. The mixture was allowed to cool down to room temperature. A white solid was collected by filtration, was washed with ethyl acetate and dried in vacuum to give 18.3 g of a solid. The solid was twice recrystallized from refluxing ethyl acetate (350 mL; 300 mL). A white solid was collected by filtration, was washed with ethyl acetate and dried in vacuum to give 10.51 g of a solid. The solid was dissolved in water, hydrochloric acid (c=2.0 M) was added until pH 5 was reached and the reaction mixture was extracted with dichloromethane. The organic phase was dried (sodium sulfate) and the solvent was removed in vacuum to give 5.6 g of the title product. The crude product was used without further purification.

$^1\text{H-NMR}$ (300MHz, DMSO-d_6): δ [ppm] = 1.31 (d, 3H), 3.66 (q, 1H), 7.05 - 7.16 (m, 2H), 7.24 - 7.33 (m, 2H), 12.28 (br. s., 1H).

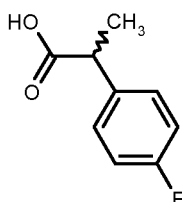
$[\alpha]_{\text{D}}^{20}$: -79.3° (in DMSO)

5 Determination of enantiomeric purity by analytical chiral HPLC:

Column: Chiralcel OJ-H 150x4.6; Flow: 1.00 mL/min; Solvent: A: Hexane, B: 2-propanol with 0.1 % formic acid; Solvent mixture: 80% A + 20% B. Run Time: 30 min. Retention Time: 3.41 min; UV 254 nm; Enantiomeric Ratio: 99.8% : 0.2%.

10 Intermediate Int09.02

Rac-2-(4-fluorophenyl)propanoic acid

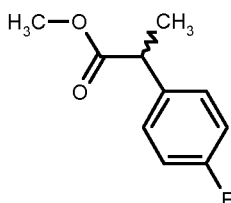


To a stirred solution of Int09.01 (18.9 g) in ethanol (200 mL) was added a solution of potassium hydroxide (35 g), dissolved in water (200 mL). The mixture was stirred at 0°C for 4 h. Hydrochloric acid ($c=4.0\text{ M}$) was added until pH 5 was reached and the reaction mixture was extracted with ethyl acetate. The organic phase was separated and the solvent was removed in vacuum to give 15.64 g of the title product. The crude product was used without further purification.

20 $^1\text{H-NMR}$ (300MHz, DMSO-d_6): δ [ppm] = 1.31 (d, 3H), 3.66 (q, 1H), 7.05 - 7.15 (m, 2H), 7.24 - 7.33 (m, 2H), 12.30 (s, 1H).

Intermediate Int09.01

Rac-methyl 2-(4-fluorophenyl)propanoate



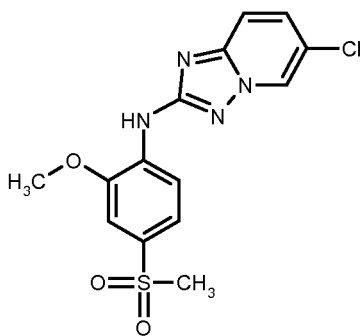
25

To a stirred solution of diisopropylamine (13.0 g) in tetrahydrofuran (160 mL) was added a solution of n-butyllithium in hexane (51.4 mL; c= 2.5 M) at -78 °C. The solution was stirred at 0 °C for 15 minutes. The solution was cooled to -78 °C and a solution of methyl (4-fluorophenyl)acetate (18.0 g), dissolved in tetrahydrofuran (40 mL) was added. The solution was stirred at -78 °C for 30 minutes. Methyl iodide (10.0 mL) was added at -78 °C, and the solution was allowed to warm up to 0 °C within 1 h. Water was added and the reaction mixture was extracted with ethyl acetate. The organic phase was dried (sodium sulfate) and the solvent was removed in vacuum. Silicagel chromatography gave 18.9 g of the title compound.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm] = 1.34 (d, 3H), 3.55 (s, 3H), 3.79 (q, 1H), 7.08 - 7.15 (m, 2H), 7.25 - 7.32 (m, 2H).

Intermediate Int21.03

6-chloro-N-[2-methoxy-4-(methylsulfonyl)phenyl][1,2,4]triazolo[1,5- α]pyridin-2-amine



To a stirred suspension of Int21.02 (0.7 g) in toluene (28 mL) was added Int03.02 (1.27 g), chloro(2-dicyclohexylphosphino-2',4',6'-tri-isopropyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl] palladium(II) methyl-*tert*-butylether adduct (343 mg), X-Phos (202 mg) and powdered potassium phosphate (3.09 g). The flask was degassed twice and backfilled with argon. The mixture was heated to reflux for 3 h. Further chloro(2-dicyclohexylphosphino-2',4',6'-tri-isopropyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl] palladium(II) methyl-*tert*-butylether adduct (30 mg) and X-Phos (19 mg) were added and the mixture was heated to reflux

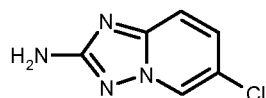
for 15 h. The solvent was removed in vacuum. Silicagel chromatography gave a solid that was triturated ethyl acetate to give 1.0 g of the title compound.

¹H-NMR (400 MHz, DMSO-d₆): δ [ppm] = 3.16 (3H), 3.95 (3H), 7.42 (1H), 7.50 (1H), 7.62-7.69 (2H), 8.41 (1H), 8.70 (1H), 9.17 (1H).

5

Intermediate Int21.02

6-chloro[1,2,4]triazolo[1,5-α]pyridin-2-amine



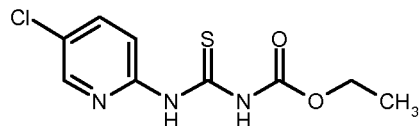
Hydroxylammonium chloride (4.4 g) was suspended in methanol (35 mL) and ethanol (35 mL) and Hünig Base (10.2 mL) was added at r.t. The mixture was heated to 60°C, Int21.01 (4.4 g) was added portionwise, and the mixture was stirred at 60°C for 2h. The solvent was removed in vacuum and water (150 mL) was added. A solid was collected by filtration and was washed with water and dried in vacuum.

15 Yield: 2.0 g of the title compound.

¹H-NMR (300 MHz, DMSO-d₆): δ [ppm] = 6.09 (2H), 7.28-7.37 (1H), 7.39-7.49 (1H), 8.84 (1H).

Intermediate Int21.01

20 Ethyl [(5-chloropyridin-2-yl)carbamothioyl]carbamate

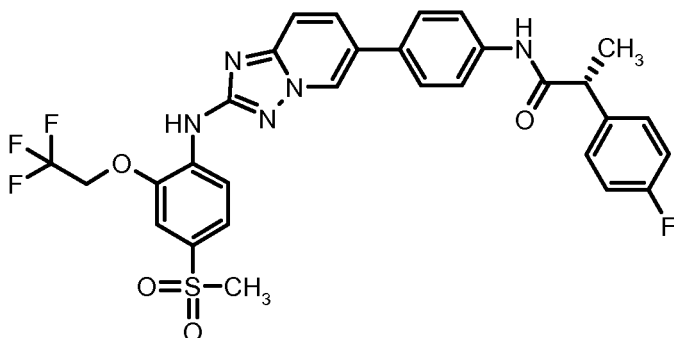


Ethoxycarbonylthiocyanate (3.37 g) was added to a stirred solution of 2-amino-5-chloropyridine (3.0 g) in dioxane (100 mL). The mixture was stirred at r.t. for 14 h. The solvent was removed in vacuum. The solid was dissolved in dichloromethane and methanol (100 : 1), filtered and the solvent was removed in vacuum to give a solid that was recrystallized from ethyl acetate to give 4.4 g of the title compound.

¹H-NMR (400 MHz, CHLOROFORM-d): δ [ppm] = 1.35 (3H), 4.31 (2H), 7.71 (1H), 8.03 (1H), 8.34 (1H), 8.83 (1H), 12.09 (1H).

Preparation of Compound A2

- 5 (2*R*)-2-(4-fluorophenyl)-*N*-[4-(2-{[4-(methylsulfonyl)-2-(2,2,2-trifluoroethoxy)phenyl]amino}[1,2,4]triazolo[1,5- α]pyridin-6-yl)phenyl]-propanamide



- To a stirred suspension of Int08.021 (5.6 g) in DMF (45 mL) and
 10 dichloromethane (90 mL) was added sodium bicarbonate (1.97 g), (2*R*)-2-(4-fluorophenyl)propanoic acid (2.17 g) and HATU (6.69 g). The mixture was stirred at room temperature for 4 h. Water was added, and the mixture was stirred for 30 minutes. A half-saturated solution of sodium bicarbonate was added and the mixture was extracted with ethyl acetate. The organic phase
 15 was washed with saturated sodium chloride solution, dried (sodium sulfate) and the solvent was removed in vacuum. Aminophase-silica-gel chromatography gave a solid that was triturated with a mixture of ethyl acetate and cyclohexane to give 6.60 g of the title compound.

- ¹H-NMR (300MHz, DMSO-d₆): δ [ppm] = 1.39 (d, 3H), 3.17 (s, 3H), 3.83 (q, 1H),
 20 5.00 (q, 2H), 7.08 - 7.19 (m, 2H), 7.35 - 7.45 (m, 2H), 7.58 - 7.76 (m, 7H), 7.93 (dd, 1H), 8.50 (d, 1H), 8.59 (s, 1H), 9.11 (d, 1H), 10.19 (s, 1H).

[α]_D²⁰ : -69.3° (in DMSO).

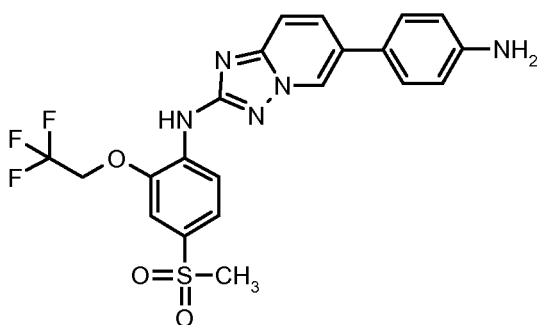
Determination of enantiomeric purity by analytical chiral HPLC:

Column: Chiralcel OD-RH 150x4.6; Flow: 1.00 mL/min; Solvent: A: Water with 0.1 % formic acid, B: Acetonitrile; Solvent mixture: 40% A + 60% B. Run Time: 20 min. Retention Time: 12.28 min; UV 254 nm; Enantiomeric Ratio: <1% : > 99%.

5

Intermediate Example Int08.021

6-(4-aminophenyl)-N-[4-(methanesulfonyl)-2-(2,2,2-trifluoroethoxy)phenyl]-[1,2,4]triazolo[1,5- α]pyridin-2-amine

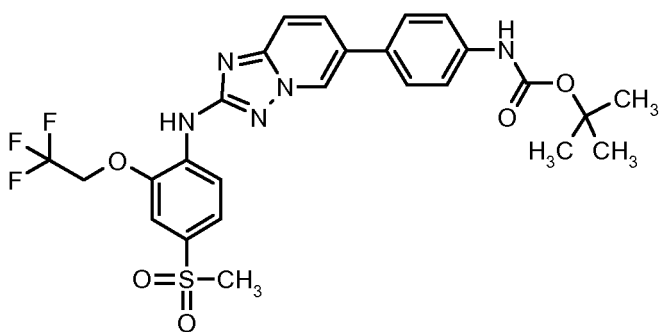


- 10 To a stirred suspension of Int08.020 (11.9 g) in dichloromethane (80 mL) was added TFA (40 mL). The mixture was stirred at room temperature for 24 h. The solvent was removed in vacuum, and the residue was dissolved in ethyl acetate. A half-saturated solution of sodium bicarbonate was added until pH 9 was reached. The precipitated solid was collected by filtration to give 9.7 g of
- 15 the title compound.

¹H-NMR (400MHz, DMSO-*d*₆): δ [ppm] = 3.16 (s, 3H), 5.00 (q, 2H), 5.34 (br. s., 2H), 6.60 - 6.68 (m, 2H), 7.39 - 7.48 (m, 2H), 7.57 - 7.66 (m, 3H), 7.85 (dd, 1H), 8.48 (s, 1H), 8.51 (d, 1H), 8.89 - 8.96 (m, 1H).

20 Intermediate Example Int08.020

***tert*-butyl [4-(2-{[4-(methanesulfonyl)-2-(2,2,2-trifluoroethoxy)phenyl]-amino}[1,2,4]triazolo[1,5- α]pyridin-6-yl)phenyl]carbamate**

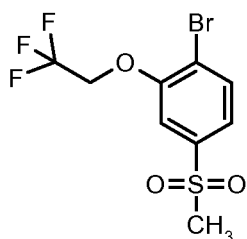


To a stirred suspension of Int01.03 (4.0 g) in toluene (77 mL) and NMP (7.7 mL) was added Int05.03 (4.91 g), chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl] palladium(II) methyl-*tert*-butylether adduct (254 mg) and X-Phos (150 mg) and the flask was degassed twice and backfilled with argon. The mixture was stirred for 5 minutes at room temperature. Powdered potassium phosphate (9.13 g) was added and the flask was degassed twice and backfilled with argon. The mixture was heated to reflux for 1 h. The reaction mixture was filtered through an aminophase-silica-gel column and the solvent was removed in vacuum. Aminophase-silica-gel chromatography gave a solid that was triturated with a mixture of hexane and dichloromethane to give 6.05 g of the title compound.

¹H-NMR (400MHz, DMSO-*d*₆): δ [ppm] = 1.46 (s, 9H), 3.17 (s, 3H), 5.00 (q, 2H), 7.55 (d, 2H), 7.60 - 7.71 (m, 5H), 7.93 (dd, 1H), 8.50 (d, 1H), 8.54 (s, 1H), 9.09 (dd, 1H), 9.46 (s, 1H).

Intermediate Example Int05.03

1-bromo-4-(methylsulfonyl)-2-(2,2,2-trifluoroethoxy)benzene

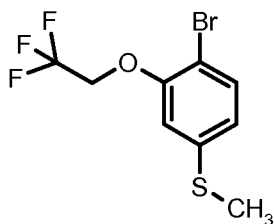


20

To a stirred solution of Int05.02 (3.8 g) in chloroform (100 mL) was added 3-chlorobenzenecarboxylic acid (mCPBA) (8.48 g). The mixture was stirred at

room temperature for 16 h. With ice bath cooling, a half-saturated solution of sodium bicarbonate and a 0.2 M solution of sodium thiosulfate was added, the mixture was stirred for 30 minutes and the mixture was extracted with dichloromethane. The organic phase was washed with a 0.2 M solution of sodium thiosulfate and a saturated sodium chloride solution, dried (sodium sulfate) and the solvent was removed in vacuum. Silica gel chromatography gave a solid that was triturated with ether to give 2.1 g of the title compound. $^1\text{H-NMR}$ (400MHz, CHLOROFORM- d): δ [ppm] = 3.06 (s, 3H), 4.50 (q, 2H), 7.45 (d, 1H), 7.52 (dd, 1H), 7.81 (d, 1H).

10

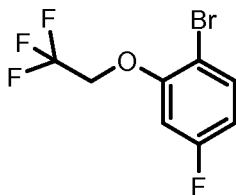
Intermediate Example Int05.02**1-bromo-4-(methylsulfonyl)-2-(2,2,2-trifluoroethoxy)benzene**

To a stirred solution of Int05.01 (4.0 g) in DMF (15 mL) was added sodium methanethiolate (1.0 g). The mixture was stirred for 2 h at 60 °C. The mixture was cooled to room temperature. Water was added and the mixture was extracted with ethyl acetate. The organic phase was washed with saturated sodium chloride solution, dried (sodium sulfate) and the solvent was removed in vacuum to give 3.8 g of the crude title compound, that was used for the next step without purification.

20

$^1\text{H-NMR}$ (300MHz, CHLOROFORM- d): δ [ppm] = 2.48 (s, 3H), 4.39 (q, 2H), 6.78 - 6.88 (m, 2H), 7.46 (d, 1H).

Intermediate Example Int05.01**25 1-bromo-4-fluoro-2-(2,2,2-trifluoroethoxy)benzene**

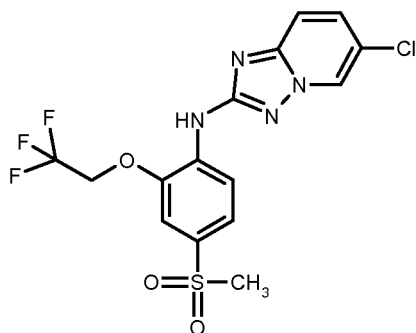


To a stirred solution of 2-bromo-5-fluorophenol (1.5 g) in acetonitrile (0.5 mL) and DMF (8.5 mL) in a microwave tube was added potassium carbonate (2.1 g) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (2.37 g). The mixture was
 5 heated to 150°C in a microwave oven for 30 minutes. In a second microwave tube the same reaction was repeated. Both mixtures were combined. The solvent was removed in vacuum, ethyl acetate and hexane (1:1) was added and the mixture was washed with water. The organic phase was washed with saturated sodium chloride solution, dried (sodium sulfate) and the solvent was
 10 removed in vacuum. Silica gel chromatography gave 4.0 g of the title compound.

¹H-NMR (300MHz, CHLOROFORM-d): δ [ppm] = 4.39 (q, 2H), 6.62 - 6.78 (m, 2H), 7.53 (dd, 1H).

15 Intermediate Example Int05.04.

6-chloro-N-[4-(methanesulfonyl)-2-(2,2,2-trifluoroethoxy)phenyl][1,2,4]triazolo[1,5-α]pyridin-2-amine

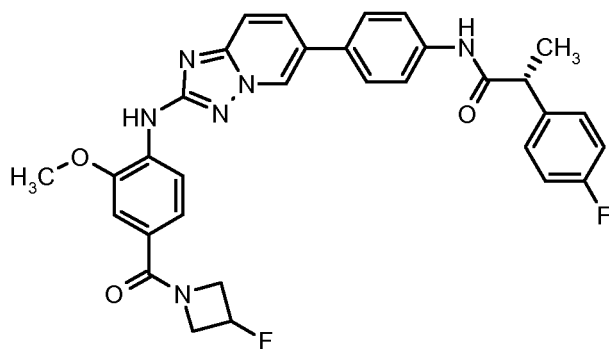


Starting with Intermediate Int21.02 (1.4 g) and Intermediate Example
 20 Int05.03 (3.18 g) Intermediate Example Int05.04 was prepared analogously to the procedure for the preparation of Intermediate Int21.03.

Yield: 3.49 g of the title compound.

Preparation of Compound A3

(2R)-N-{4-[2-({4-[(3-fluoroazetidin-1-yl)carbonyl]-2-methoxyphenyl}amino)-
 5 [1,2,4]triazolo[1,5- α]pyridin-6-yl]phenyl]-2-(4-fluorophenyl)propanamide



To a stirred suspension of Int08.061 (1.10 g) in DMF (8.5 mL) and dichloromethane (17 mL) was added sodium bicarbonate (427 mg), (2R)-2-(4-fluorophenyl)propanoic acid (470 mg) and HATU (1.45 g). The mixture was stirred at room temperature for 4 h. Water was added, and the mixture was stirred for 30 minutes. A half-saturated solution of sodium bicarbonate was added and the mixture was extracted with ethyl acetate. The organic phase was washed with saturated sodium chloride solution, dried (sodium sulfate) and the solvent was removed in vacuum. Aminophase-silica-gel chromatography gave 1.13 g of the title compound.

¹H-NMR (400MHz, DMSO-*d*₆): δ [ppm] = 1.42 (d, 3H), 3.86 (q, 1H), 3.93 (s, 3H), 3.98 - 4.80 (m, 4H), 5.44 (m, 1H, *J*=57.5 Hz), 7.12 - 7.20 (m, 2H), 7.26 (d, 1H), 7.30 (dd, 1H), 7.40 - 7.46 (m, 2H), 7.63 - 7.76 (m, 5H), 7.93 (dd, 1H), 8.31 - 8.39 (m, 2H), 9.11 (d, 1H), 10.19 (s, 1H)..

$[\alpha]_D^{20}$: -70.0° (in DMSO).

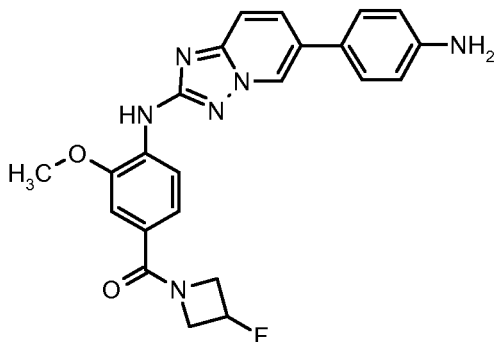
Determination of enantiomeric purity by analytical chiral HPLC:

Column: Chiralcel OD-RH 150x4.6; Flow: 1.00 mL/min; Solvent: A: Water with 0.1 % formic acid, B: Acetonitrile; Solvent mixture: 40% A + 60% B. Run Time:

20 min. Retention Time: 13.88 min; UV 254 nm; Enantiomeric Ratio: <1% : > 99%.

Intermediate Example Int08.061

- 5 (4-{[6-(4-aminophenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl]amino}-3-methoxyphenyl)(3-fluoroazetidin-1-yl)methanone

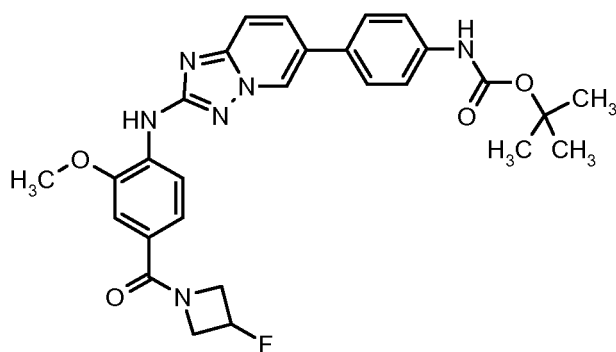


To a stirred suspension of Int08.060 (7.8 g) in dichloromethane (55 mL) was added TFA (28 mL). The mixture was stirred at room temperature for 16 h. The solvent was removed in vacuum and the residue was dissolved in ethyl acetate. A saturated solution of sodium bicarbonate was added until pH 9 was reached. The precipitated solid was collected by filtration to give 5.2 g of the title compound. The crude product was used for the next step without further purification.

- 15 ¹H-NMR (300MHz, DMSO-d₆): δ [ppm] = 3.90 (s, 3H), 4.45 (br. s., 4H), 5.20 - 5.58 (m, 3H), 6.63 (d, 2H), 7.23 (d, 1H), 7.27 (dd, 1H), 7.42 (d, 2H), 7.52 - 7.61 (m, 1H), 7.81 (dd, 1H), 8.23 (s, 1H), 8.34 (d, 1H), 8.86 - 8.94 (m, 1H).

Intermediate Example Int08.060

- 20 *tert*-butyl {4-[2-({4-[(3-fluoroazetidin-1-yl)carbonyl]-2-methoxyphenyl}-amino)[1,2,4]triazolo[1,5- α]pyridin-6-yl]phenyl}carbamate

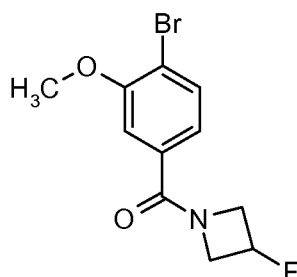


To a stirred suspension of Int01.03 (6.0 g) in toluene (350 mL) and NMP (29 mL) was added Int02.05 (6.91 g), chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl] palladium(II) methyl-*tert*-butylether adduct (610 mg) and X-Phos (359 mg) and the flask was degassed twice and backfilled with argon. The mixture was stirred for 5 minutes at room temperature. Powdered potassium phosphate (13.7 g) was added and the flask was degassed twice and backfilled with argon. The mixture was heated to reflux for 1 h. The reaction mixture was filtered through an aminophase-silica-gel column and the solvent was removed in vacuum. Aminophase-silica-gel chromatography gave 7.9 g of the title compound.

¹H-NMR (300MHz, DMSO-*d*₆): δ [ppm] = 1.46 (s, 9H), 3.90 (s, 3H), 4.04 - 4.80 (m, 4H), 5.27 - 5.57 (m, 1H), 7.23 (d, 1H), 7.27 (dd, 1H), 7.54 (d, 2H), 7.59 - 7.71 (m, 3H), 7.89 (dd, 1H), 8.29 (s, 1H), 8.34 (d, 1H), 9.06 (d, 1H), 9.45 (s, 1H).

Intermediate Example Int02.05

(4-Bromo-3-methoxyphenyl)(3-fluoroazetidin-1-yl)methanone



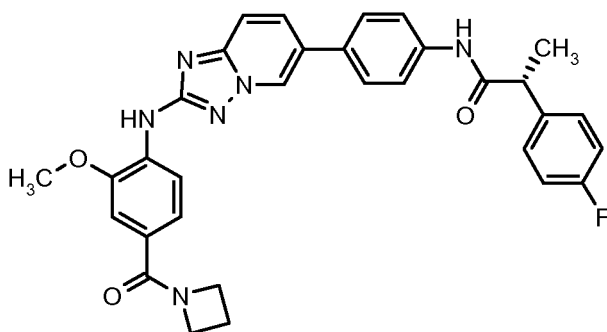
To a stirred solution of 4-bromo-3-methoxybenzoic acid (1.4 g) in DMF (15 mL) was added potassium carbonate (2.51 g), 3-fluoroazetidine hydrochloride (1.01

g) and HATU (3.69 g). The mixture was stirred at room temperature for 18 h. Water was added, the mixture was stirred for 15 minutes and the solvent was removed in vacuum. Water was added and the mixture was extracted with ethyl acetate. The organic phase was washed with water, saturated sodium chloride solution, dried (sodium sulfate) and the solvent was removed in vacuum, to give 1.25 g of the title compound.

¹H-NMR (400 MHz, DMSO-d₆): δ [ppm] = 3.90 (s, 3H), 3.99 - 4.16 (m, 1H), 4.31 - 4.65 (m, 3H), 5.36 (tt, 0.5H), 5.50 (tt, 0.5H), 7.14 (dd, 1H), 7.26 (d, 1H), 7.66 (d, 1H).

Preparation of Compound A4

(2R)-N-[4-(2-[[4-(azetidin-1-ylcarbonyl)-2-methoxyphenyl]amino}[1,2,4]-triazolo[1,5-α]pyridin-6-yl)phenyl]-2-(4-fluorophenyl)propanamide



To a stirred suspension of Int08.071 (200 mg) in DMF (1.6 mL) and dichloromethane (3.2 mL) was added sodium bicarbonate (122 mg), (2R)-2-(4-fluorophenyl)propanoic acid (89 mg) and HATU (275 mg). The mixture was stirred at room temperature for 4 h. Water was added, and the mixture was stirred for 30 minutes. A half-saturated solution of sodium bicarbonate was added and the mixture was extracted with a mixture of dichloromethane and methanol (100:1). The organic phase was washed with saturated sodium chloride solution, dried (sodium sulfate) and the solvent was removed in vacuum. Aminophase-silica-gel chromatography followed by silica gel

chromatography gave a solid that was triturated with ether to give 250 mg of the title compound.

¹H-NMR (300MHz, DMSO-d₆): δ [ppm] = 1.39 (d, 3H), 2.22 (quin, 2H), 3.78 - 3.92 (m, 4H), 4.00 (br. s., 2H), 4.32 (br. s, 2H), 7.09 - 7.17 (m, 2H), 7.20 - 7.26 (m, 2H), 7.36 - 7.44 (m, 2H), 7.59 - 7.75 (m, 5H), 7.89 (dd, 1H), 8.24 - 8.36 (m, 2H), 9.08 (d, 1H), 10.18 (s, 1H).

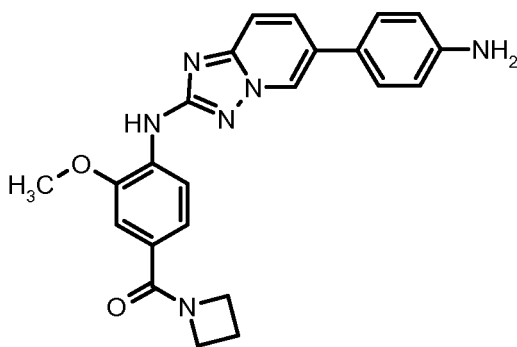
[α]_D²⁰ : -63.5° (in DMSO).

Determination of enantiomeric purity by analytical chiral HPLC:

10 Column: Chiralcel OD-RH 150x4.6; Flow: 1.00 mL/min; Solvent: A: Water with 0.1 % formic acid, B: Acetonitrile; Solvent mixture: 40% A + 60% B. Run Time: 30 min. Retention Time: 14.22 min; UV 254 nm; Enantiomeric Ratio: <2% : > 98%.

15 **Intermediate Example Int08.071**

(4-{[6-(4-aminophenyl)[1,2,4]triazolo[1,5-α]pyridin-2-yl]amino}-3-methoxyphenyl)(azetidin-1-yl)methanone

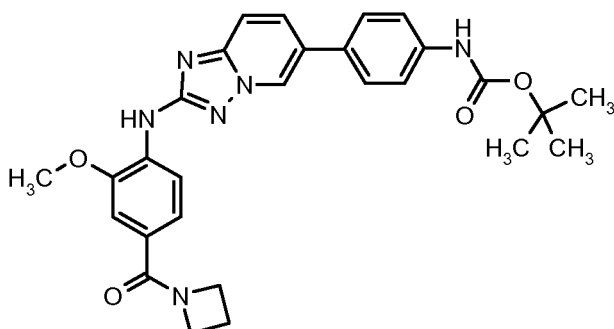


To a stirred suspension of Int08.070 (600 mg) in dichloromethane (12 mL) was added TFA (2.2 mL). The mixture was stirred at room temperature for 16 h. A saturated solution of potassium carbonate was added until pH 9 was reached. The mixture was extracted with dichloromethane and methanol (10:1 mixture). The reaction mixture was filtered through an aminophase-silica-gel column and the solvent was removed in vacuum. The residue was triturated with ethanol to give 475 mg of the title compound.

¹H-NMR (300MHz, DMSO-d₆): δ [ppm] = 2.23 (quin, 2H), 3.88 (s, 3H), 4.00 (br. s., 2H), 4.33 (br. s., 2H), 5.30 (s, 2H), 6.62 (d, 2H), 7.18 - 7.28 (m, 2H), 7.42 (d, 2H), 7.57 (d, 1H), 7.81 (dd, 1H), 8.23 (s, 1H), 8.32 (d, 1H), 8.90 (d, 1H).

5 Intermediate Example Int08.070

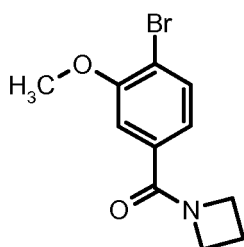
***tert*-butyl [4-(2-{[4-(azetidin-1-ylcarbonyl)-2-methoxyphenyl]amino}-[1,2,4]triazolo[1,5-α]pyridin-6-yl)phenyl]carbamate**



To a stirred suspension of Int01.03 (672 mg) in toluene (13 mL) and NMP (1.3
10 mL) was added Int02.04 (670 mg), chloro(2-dicyclohexylphosphino-2',4',6'-tri-
isopropyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl] palladium(II) methyl-*tert*-
butylether adduct (85 g), X-Phos (50 mg) and powdered potassium phosphate
(1.32 g). The flask was degassed twice and backfilled with argon. The mixture
was heated to reflux for 16 h. Aminophase-silica-gel chromatography of the
15 crude mixture gave 600 mg of the title compound, which contained a small
ammount of Int08.071. The crude product was used for the next step without
further purification.

Intermediate Example Int02.04

20 **azetidin-1-yl(4-bromo-3-methoxyphenyl)methanone**

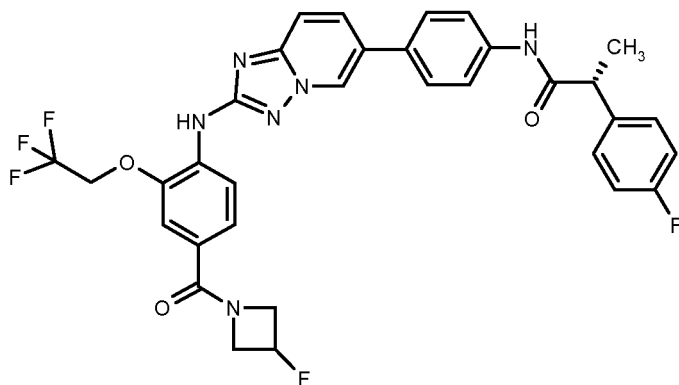


To a stirred solution of 4-bromo-3-methoxybenzoic acid (400 mg) in DMF (4.0 mL) was added potassium carbonate (720 mg), azetidine (148 mg) and TBTU (890 mg). The mixture was stirred at room temperature for 60 h. Water was added, the mixture was stirred for 15 minutes and the solvent was removed in vacuum. Water was added and the mixture was extracted with ethyl acetate. The organic phase was washed with saturated sodium chloride solution, dried (sodium sulfate) and the solvent was removed in vacuum. Silica gel chromatography gave 370 mg of the title compound.

¹H-NMR (400MHz, DMSO-d₆): δ [ppm] = 2.15 - 2.27 (m, 2H), 3.85 (s, 3H), 4.00 (t, 2H), 4.26 (t, 2H), 7.07 (dd, 1H), 7.21 (d, 1H), 7.61 (d, 1H).

Preparation of Compound A5

(2R)-N-{4-[2-({4-[(3-fluoroazetidin-1-yl)carbonyl]-2-(2,2,2-trifluoroethoxy)phenyl}amino)[1,2,4]triazolo[1,5-a]pyridin-6-yl]phenyl}-2-(4-fluorophenyl)propanamide



To a stirred suspension of Int08.111 (300 mg) in DMF (6.0 mL) and dichloromethane (12 mL) was added sodium bicarbonate (151 mg), (2R)-2-(4-fluorophenyl)propanoic acid (111 mg) and HATU (296 mg). The mixture was stirred at room temperature for 4 h. Water was added, and the mixture was stirred for 30 minutes. A half-saturated solution of sodium bicarbonate was added and the mixture was extracted with a mixture of dichloromethane and methanol (100:1). The organic phase was washed with saturated sodium

chloride solution, dried (sodium sulfate) and the solvent was removed in vacuum. Aminophase-silica-gel chromatography followed by silica-gel chromatography gave a solid that was triturated with ethanol to give 240 mg of the title compound.

5

¹H-NMR (300MHz, DMSO-d₆): δ [ppm] = 1.39 (d, 3H), 3.83 (q, 1H), 3.91 - 4.73 (m, 4H), 4.92 (d, 2H), 5.25 - 5.58 (m, 1H), 7.13 (t, 2H), 7.33 - 7.46 (m, 4H), 7.59 - 7.76 (m, 5H), 7.91 (dd, 1H), 8.27 (s, 1H), 8.32 - 8.40 (m, 1H), 9.10 (s, 1H), 10.18 (s, 1H).

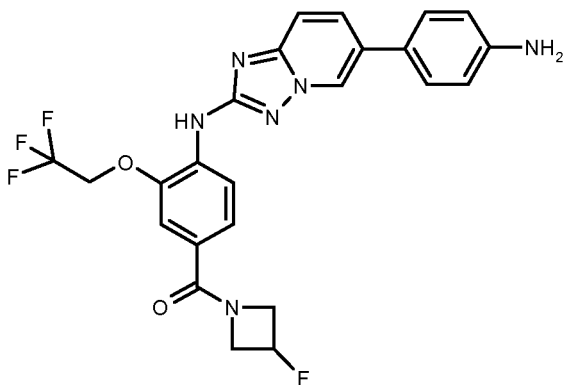
10 Determination of enantiomeric purity by analytical chiral HPLC:

Column: Chiralcel OD-RH 150x4.6; Flow: 1.00 mL/min; Solvent: A: Water with 0.1 % formic acid, B: Acetonitrile; Solvent mixture: 40% A + 60% B. Run Time: 30 min. Retention Time: 12.44 min; UV 254 nm; Enantiomeric Ratio: <2% : > 98%.

15

Intermediate Example Int08.111

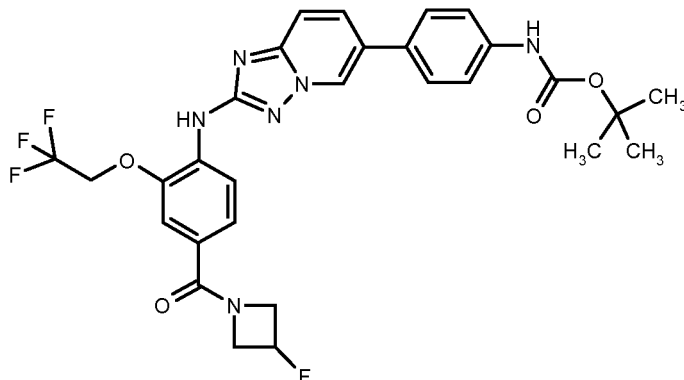
[4-{[6-(4-aminophenyl)[1,2,4]triazolo[1,5-α]pyridin-2-yl]amino}-3-(2,2,2-trifluoroethoxy)phenyl](3-fluoroazetidin-1-yl)methanone



20 Starting with Int08.110, Int08.111 was prepared analogously to the procedure for the preparation of Int08.071.

Intermediate Example Int08.110

tert-butyl {4-[2-({4-[(3-fluoroazetidin-1-yl)carbonyl]-2-(2,2,2-trifluoroethoxy)phenyl}amino)[1,2,4]triazolo[1,5- α]pyridin-6-yl]phenyl}carbamate

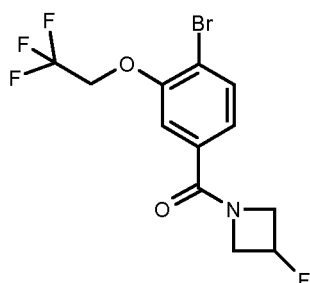


5

To a stirred suspension of Int01.03 in toluene (12 mL) and NMP (0.6 mL) was added Int06.04, chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2-aminoethyl)phenyl] palladium(II) methyl-*tert*-butylether adduct, X-Phos and powdered potassium phosphate. The flask was degassed
10 twice and backfilled with argon. The mixture was heated to reflux for 16 h. The solvent was removed in vacuum. Aminophase-silica-gel chromatography gave a solid that was triturated with ether.

15 Intermediate Example Int06.04

[4-bromo-3-(2,2,2-trifluoroethoxy)phenyl](3-fluoroazetidin-1-yl)methanone

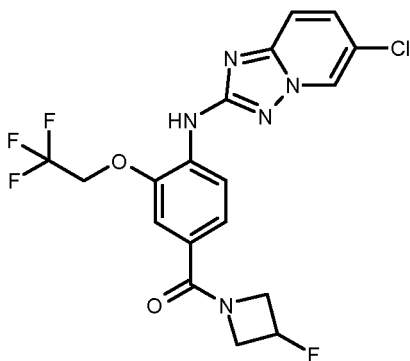


To a stirred solution of 4-bromo-3-(2,2,2-trifluoroethoxy)benzoic acid in DMF
20 (15 mL) was added potassium carbonate (2.51 g), 3-fluoroazetidine

hydrochloride and HATU (3.69 g). The mixture was stirred at room temperature for 18 h. Water was added, the mixture was stirred for 15 minutes and the solvent was removed in vacuum. Water was added and the mixture was extracted with ethyl acetate. The organic phase was washed with water, 5 saturated sodium chloride solution, dried (sodium sulfate) and the solvent was removed in vacuum.

Intermediate Example Int06.05.

10 {4-[(6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)amino]-3-(2,2,2-trifluoroethoxy)phenyl}(3-fluoroazetidin-1-yl)methanone

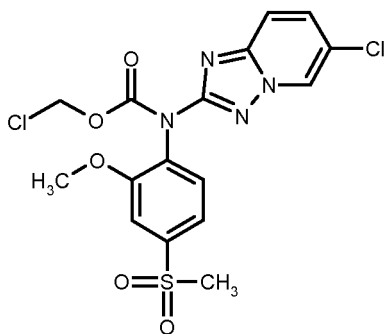


Starting with Intermediate Int21.02 (280 g) and Intermediate Example Int06.04 (680 mg), Intermediate Example Int06.05 was prepared analogously to the procedure for the preparation of Intermediate Int21.03.

15 Yield: 548 mg of the title compound.

Intermediate Example IntP01.01

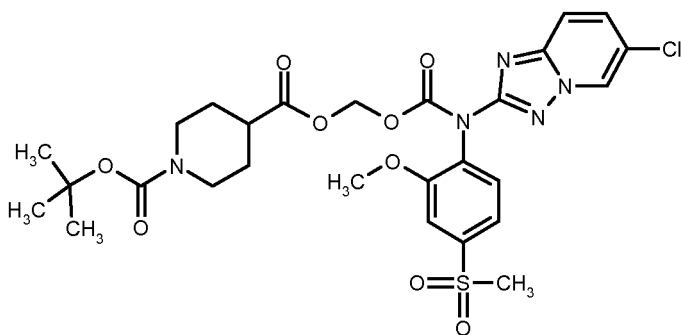
20 chloromethyl (6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-methoxy-4-(methylsulfonyl)phenyl]carbamate



To a stirred solution of 6-chloro-N-[2-methoxy-4-(methylsulfonyl)phenyl][1,2,4]triazolo[1,5- α]pyridin-2-amine (Int21.03) (2.00 g) in THF (100 mL) was added sodium hydride (55%w/w in oil; 1.24 g) at room temperature and the mixture was stirred at 0 °C for 15 minutes. Chloromethyl chloroformate (1.29 mL) was added and the mixture was stirred at room temperature for 2 hours. A half-saturated solution of sodium chloride was added and the mixture was extracted with ethyl acetate. The organic phase was dried (sodium sulfate) and the solvent was removed in vacuum. Silicagel chromatography gave 1.66 g of the title compound.

Intermediate Example IntP01.02

1-tert-butyl 4-[(6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-methoxy-4-(methylsulfonyl)phenyl]carbonyloxy)methyl]piperidine-1,4-dicarboxylate

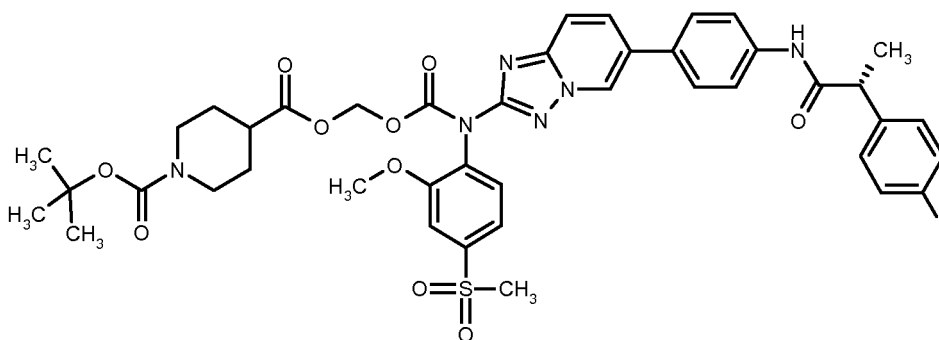


To a stirred solution of chloromethyl (6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-methoxy-4-(methylsulfonyl)phenyl]carbamate (200 mg) in DMF (10 mL) was added 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (257 mg)

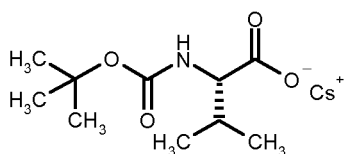
and cesium carbonate (731 mg). The mixture was stirred at room temperature for 3 h. Water was added, the mixture was extracted with ethyl acetate. The organic phase was washed with saturated sodium chloride solution, dried (sodium sulfate) and the solvent was removed in vacuum. Silicagel
5 chromatography gave 250 mg of the title compound.

Intermediate Example IntP01.03

(2R)-2-(4-fluorophenyl)-N-[4-(2-{[2-methoxy-4-(
(methylsulfonyl)phenyl]amino}[1,2,4]triazolo[1,5- α]pyridin-6-
10 yl)phenyl]propanamide



To a stirred suspension of 1-tert-butyl 4-[(6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-methoxy-4-(
15 (methylsulfonyl)phenyl]carbamoyl]oxy)methyl] piperidine-1,4-dicarboxylate (250 mg) in toluene (10 mL) and NMP (0.5 mL) was added (4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)boronic acid (167 mg), powdered potassium phosphate monohydrate (329 mg), dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (31.8 mg) and palladium acetate (8.7 mg)
20 and the flask was degassed twice and backfilled with argon. The mixture was heated to reflux for 30 minutes. The reaction mixture was filtered and the solvent was removed in vacuum. Silicagel chromatography followed by preparative reverse phase HPLC gave 90 mg of the title compound.

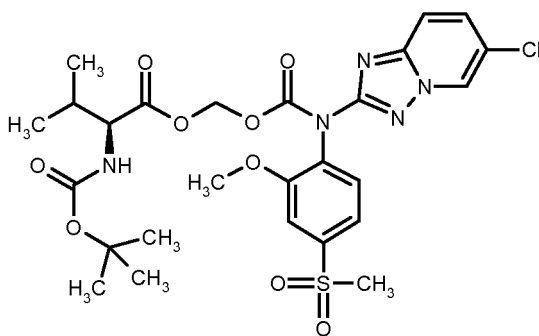
Intermediate Example IntP02.01**caesium (2S)-2-[(tert-butoxycarbonyl)amino]-3-methylbutanoate**

To a stirred solution of N-(tert-butoxycarbonyl)-L-valine (400 mg) in methanol
 5 (7.6 mL) was added a solution of caesium carbonate in water until pH 7 was
 reached (approx. 300 mg caesium carbonate in 1.52 mL water) and the solution
 was stirred for 30 minutes. The solvent was removed in vacuum, toluene was
 added and the solvent was again removed in vacuum to give 644 mg of the title
 compound.

10

Intermediate Example IntP02.02

**((6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-methoxy-4-
 (methylsulfonyl)phenyl]carbamoyl}oxy)methyl N-(tert-butoxycarbonyl)-L-
 valinate**



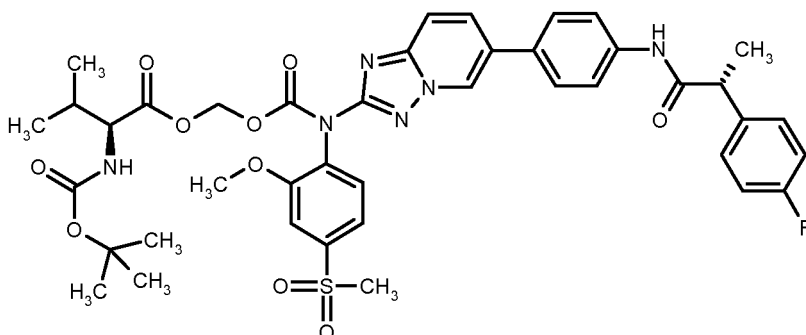
15

To a stirred solution of chloromethyl (6-chloro[1,2,4]triazolo[1,5- α]pyridin-
 2-yl)[2-methoxy-4-(methylsulfonyl)phenyl]carbamate (500 mg) in DMF (25
 mL) was added caesium (2S)-2-[(tert-butoxycarbonyl)amino]-3-
 methylbutanoate (627 mg) and the mixture was stirred at room temperature
 20 for 16 h. Water was added, the mixture was extracted with ethyl acetate. The
 organic phase was washed with saturated sodium chloride solution, dried
 (sodium sulfate) and the solvent was removed in vacuum. Silicagel
 chromatography gave 568 mg of the title compound.

Intermediate Example IntP02.03

(([6-(4-{[(2R)-2-(4-

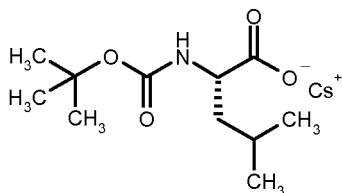
- 5 fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)methyl N-(tert-butoxycarbonyl)-L-valinate



- To a stirred suspension of ((6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)methyl N-(tert-butoxycarbonyl)-L-valinate (580 mg) in toluene (20.5 mL) and NMP (2.0 mL) was added (4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)boronic acid (399 mg), powdered potassium phosphate monohydrate (787 mg), dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (76 mg) and palladium acetate (20.8 mg) and the flask was degassed twice and backfilled with argon. The mixture was heated to reflux for 20 minutes. The reaction mixture was filtered through a silica-gel column and the solvent was removed in vacuum. Silicagel chromatography gave 284 mg of the title compound.

20 Intermediate Example IntP03.01

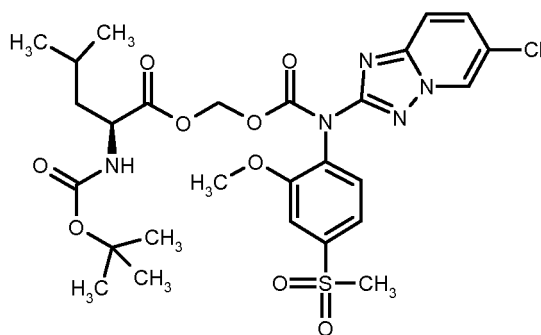
caesium (2S)-2-[(tert-butoxycarbonyl)amino]-4-methylpentanoate



To a stirred solution of N-(tert-butoxycarbonyl)-L-leucine (1.0 g) in methanol (18.0 mL) was added a solution of caesium carbonate in water until pH 7 was reached (approx. 704 mg caesium carbonate in 3.6 mL water) and the solution was stirred for 30 minutes. The solvent was removed in vacuum, toluene was added and the solvent was again removed in vacuum to give 1.59 g of the title compound.

Intermediate Example IntP03.02

({(6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)methyl N-(tert-butoxycarbonyl)-L-leucinate



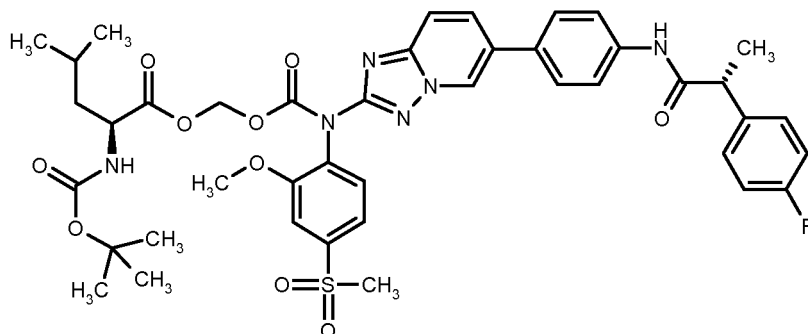
To a stirred solution of chloromethyl (6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-methoxy-4-(methylsulfonyl)phenyl]carbamate (150 mg) in DMF (7.5 mL) was added caesium (2S)-2-[(tert-butoxycarbonyl)amino]-4-methylpentanoate (196 mg) and the mixture was stirred at room temperature for 16 h. Water was added, the mixture was extracted with ethyl acetate. The organic phase was washed with saturated sodium chloride solution, dried (sodium sulfate) and the solvent was removed in vacuum. Silicagel chromatography gave 179 mg of the title compound.

Intermediate Example IntP03.03

({[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-

methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)methyl
 N-(tert-butoxycarbonyl)-L-leucinate

N-(tert-

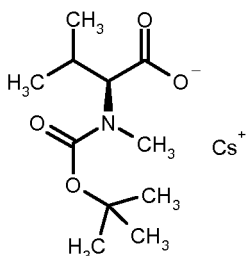


- 5 To a stirred suspension of ((6-chloro[1,2,4]triazolo[1,5-a]pyridin-2-yl)[2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)methyl N-(tert-butoxycarbonyl)-L-leucinate (170 mg) in toluene (6.0 mL) and NMP (0.6 mL) was added (4-[[2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)boronic acid (114 mg), powdered potassium phosphate monohydrate (225 mg),
 10 dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (21.8 mg) and palladium acetate (6.0 mg) and the flask was degassed twice and backfilled with argon. The mixture was heated to reflux for 20 minutes. The reaction mixture was filtered through a silica-gel column and the solvent was removed in vacuum. Silicagel chromatography gave 76 mg of the title compound.

15

Intermediate Example IntP04.01

caesium (2S)-2-[(tert-butoxycarbonyl)(methyl)amino]-3-methylbutanoate



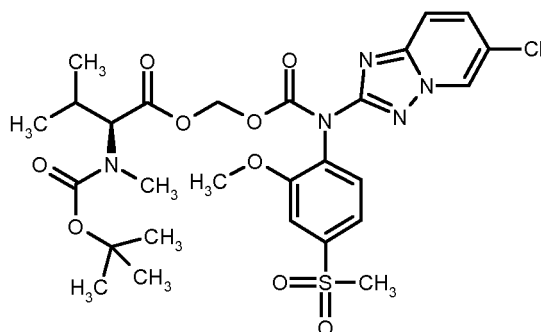
- To a stirred solution of N-(tert-butoxycarbonyl)-N-methyl-L-valine (1.0 g) in
 20 methanol (18.0 mL) was added a solution of caesium carbonate in water until pH 7 was reached (approx. 704 mg caesium carbonate in 3.5 mL water) and the

solution was stirred for 30 minutes. The solvent was removed in vacuum, toluene was added and the solvent was again removed in vacuum to give 1.55 g of the title compound.

5

Intermediate Example IntP04.02

({(6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)methyl N-(tert-butoxycarbonyl)-N-methyl-L-valinate



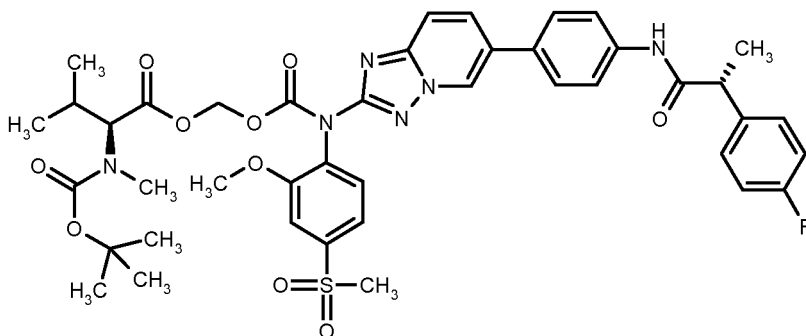
10

To a stirred solution of chloromethyl (6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-methoxy-4-(methylsulfonyl)phenyl]carbamate (220 mg) in DMF (11 mL) was added caesium (2S)-2-[(tert-butoxycarbonyl)(methyl)amino]-3-methylbutanoate (278 mg) and the mixture was stirred at room temperature for 16 h. Water was added, the mixture was extracted with ethyl acetate. The organic phase was washed with saturated sodium chloride solution, dried (sodium sulfate) and the solvent was removed in vacuum. Silicagel chromatography gave 298 mg of the title compound.

15

20 Intermediate Example IntP04.03

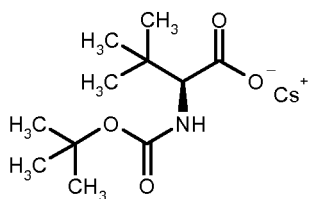
({[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)methyl N-(tert-butoxycarbonyl)-N-methyl-L-valinate



To a stirred suspension of ((6-chloro[1,2,4]triazolo[1,5-a]pyridin-2-yl)[2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)methyl N-(tert-butoxycarbonyl)-N-methyl-L-valinate (292 mg) in toluene (10 mL) and NMP (1.0 mL) was added (4-[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl) boronic acid (196 mg), powdered potassium phosphate monohydrate (387 mg), dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (37.5 mg) and palladium acetate (10.2 mg) and the flask was degassed twice and backfilled with argon. The mixture was heated to reflux for 20 minutes. The reaction mixture was filtered through a silica-gel column and the solvent was removed in vacuum. Silicagel chromatography gave 110 mg of the title compound.

Intermediate Example IntP05.01

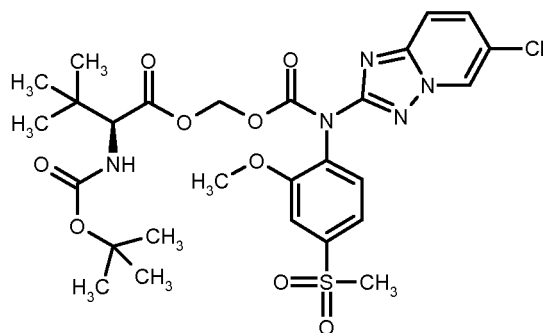
caesium (2S)-2-[(tert-butoxycarbonyl)amino]-3,3-dimethylbutanoate



To a stirred solution of N-(tert-butoxycarbonyl)-N-methyl-L-valine (4.08 g) in methanol (36 mL) was added a solution of caesium carbonate in water until pH 7 was reached (approx. 2.85 g caesium carbonate in 36 mL water) and the solution was stirred for 30 minutes. The solvent was removed in vacuum, toluene was added and the solvent was again removed in vacuum to give 6.34 g of the title compound.

Intermediate Example IntP05.02

5 {[(6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)methyl N-(tert-butoxycarbonyl)-3-methyl-L-valinate

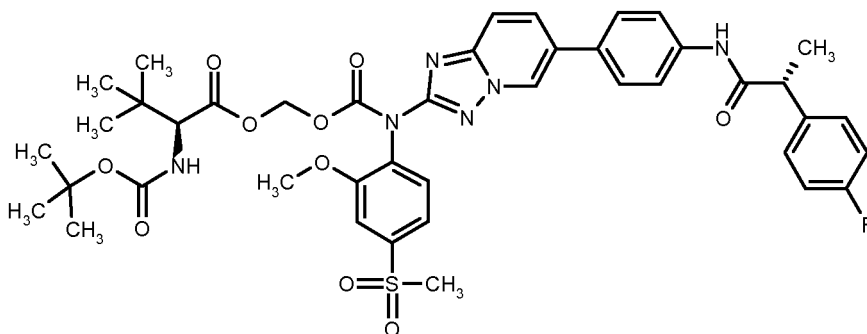


To a stirred solution of chloromethyl (6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-methoxy-4-(methylsulfonyl)phenyl]carbamate (1.66 g) in DMF (83 mL) was added caesium (2S)-2-[(tert-butoxycarbonyl)amino]-3,3-dimethylbutanoate (2.17 g) and the mixture was stirred at room temperature for 16 h. Water was added, the mixture was extracted with ethyl acetate. The organic phase was washed with saturated sodium chloride solution, dried (sodium sulfate) and the solvent was removed in vacuum. Silicagel chromatography gave 2.30 g of the title compound.

15

Intermediate Example IntP05.03

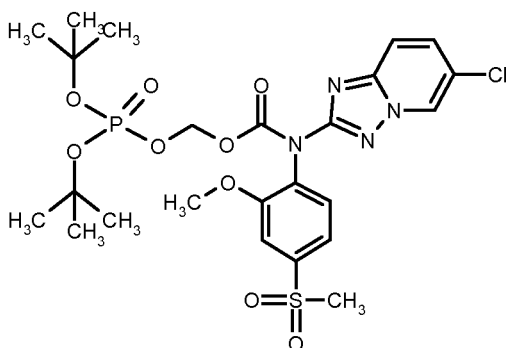
20 {[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)methyl N-(tert-butoxycarbonyl)-3-methyl-L-valinate



To a stirred suspension of ((6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-methoxy-4-(methylsulfonyl)phenyl]carbamoyloxy)methyl N-(tert-butoxycarbonyl)-3-methyl-L-valinate (404 mg) in toluene (11.5 mL) was added (4-[[2-(4-fluorophenyl)propanoyl]amino]phenyl) boronic acid (245 mg), powdered potassium phosphate monohydrate (482 mg), dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (46.6 mg) and palladium acetate (12.8 mg) and the flask was degassed twice and backfilled with argon. The mixture was heated to 100 °C for 20 minutes. The reaction mixture was filtered through a silica-gel column and the solvent was removed in vacuum. Silicagel chromatography gave a solid that was triturated with a mixture of hexane and dichloromethane to give 223 mg of the title compound.

Intermediate Example IntP06.01

[(di-tert-butoxyphosphoryl)oxy]methyl (6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-methoxy-4-(methylsulfonyl)phenyl]carbamate



To a stirred solution of chloromethyl (6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-methoxy-4-(methylsulfonyl)phenyl]carbamate (200 mg) in DMF (6.0 mL) was added potassium di-tert-butyl phosphate (278 mg) and the mixture

was heated to 75 °C for 75 minutes in a microwave oven. Water was added, the mixture was extracted with ethyl acetate. The organic phase was washed with saturated sodium chloride solution, dried (sodium sulfate) and the solvent was removed in vacuum. Silicagel chromatography gave 80 mg of the title compound.

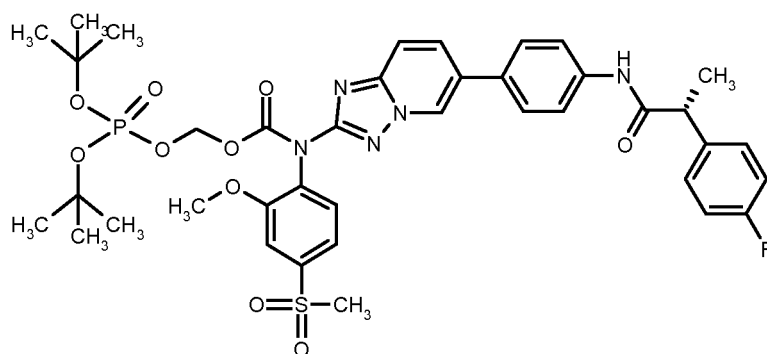
Intermediate Example IntP06.02

[(di-tert-butoxyphosphoryl)oxy]methyl

[6-(4-[(2R)-2-(4-

fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-

10 methoxy-4-(methylsulfonyl)phenyl]carbamate

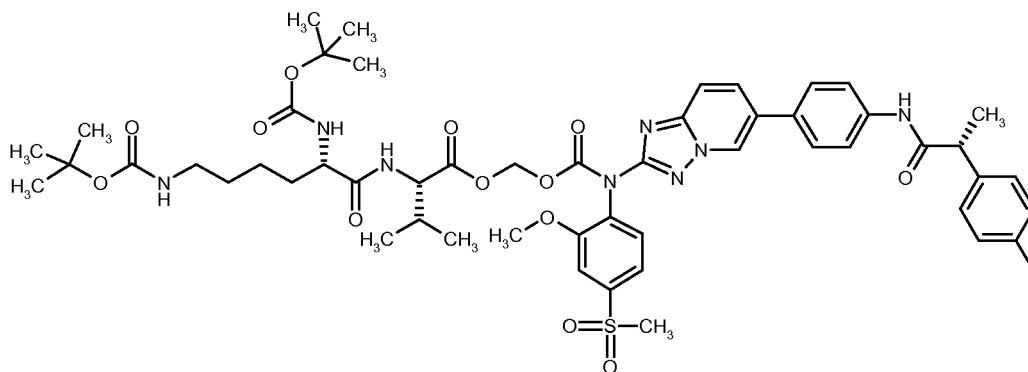


To a stirred suspension of [(di-tert-butoxyphosphoryl)oxy]methyl (6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-methoxy-4-

15 (methylsulfonyl)phenyl]carbamate (77 mg) in toluene (3.0 mL) and NMP (0.3 mL) was added (4-[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl) boronic acid (53.6 mg), powdered potassium phosphate monohydrate (106 mg), dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (10.2 mg) and palladium acetate (2.8 mg) and the flask was degassed twice and backfilled with argon. The mixture was heated to 100 °C for 20 minutes. The reaction mixture was filtered through a silica-gel column and the solvent was removed in vacuum. Silicagel chromatography gave a solid that was triturated with a mixture of hexane and dichloromethane to give 35 mg of the title compound.

Intermediate Example IntP07.01

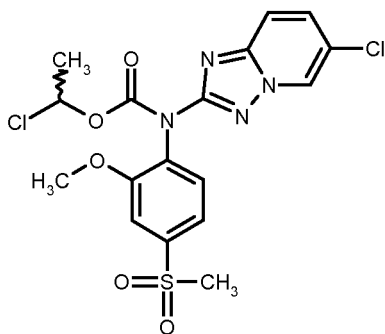
({[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)methyl N²,N⁶-bis(tert-butoxycarbonyl)-L-lysyl-L-valinate



To a stirred suspension of ({[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)methyl L-valinate hydrochloride (122 mg) in DMF (2.6 mL) and dichloromethane (1.3 mL) was added sodium bicarbonate (37 mg), N²,N⁶-bis(tert-butoxycarbonyl)-L-lysine (56 mg) and HATU (84 mg). The mixture was stirred at room temperature for 3 h. Water was added, and the mixture was stirred for 2 h. Water was added and the mixture was extracted with ethyl acetate. The organic phase was washed with saturated sodium chloride solution, dried (sodium sulfate) and the solvent was removed in vacuum to give 61 mg of the title product as a crude product that was used for the next step without purification.

20 Intermediate Example IntP08.01

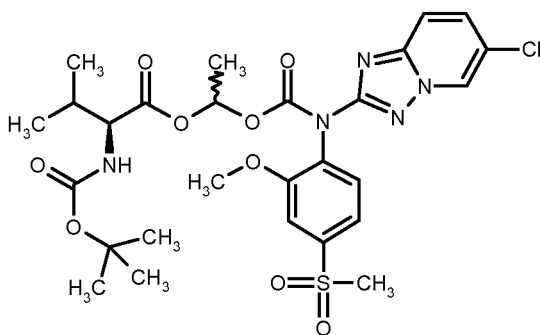
1-chloroethyl (6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-methoxy-4-(methylsulfonyl)phenyl]carbamate



To a stirred solution of **6-chloro-N-[2-methoxy-4-(methylsulfonyl)phenyl][1,2,4]triazolo[1,5- α]pyridin-2-amine (Int21.03)** (1.00 g) in THF (100 mL) was added sodium hydride (55%w/w in oil; 618 mg) at
 5 room temperature and the mixture was stirred at 0 °C for 15 minutes. **1-Chloroethyl chloroformate**(0.78 mL) was added and the mixture was stirred at room temperature for 1 h. A half-saturated solution of sodium chloride was added and the mixture was extracted with ethyl acetate. The organic phase was dried (sodium sulfate) and the solvent was removed in vacuum. Silicagel
 10 chromatography gave 1.03 g of the title compound.

Intermediate Example IntP08.02

(1RS)-1-(({6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl}[2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)ethyl N-(tert-butoxycarbonyl)-L-
 15 **valinate (mixture of 2 epimers)**



To a stirred solution of **1-chloroethyl (6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-methoxy-4-(methylsulfonyl)phenyl]carbamate** (500 mg) in DMF (24 mL) was added caesium **(2S)-2-[(tert-butoxycarbonyl)amino]-3-methylbutanoate** (608 mg) and the mixture was heated to 50°C for 16 h.
 20

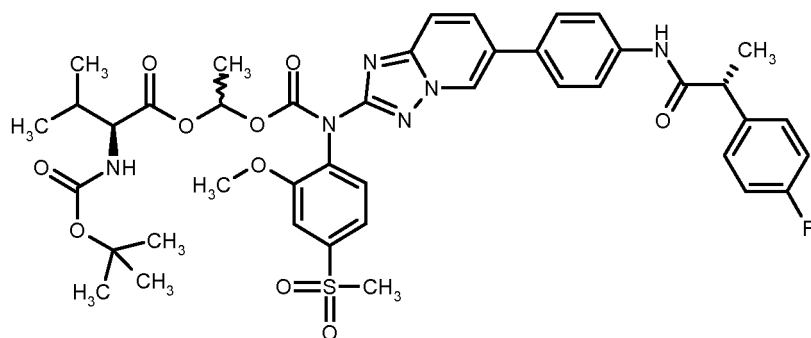
Water was added, the mixture was extracted with ethyl acetate. The organic phase was washed with saturated sodium chloride solution, dried (sodium sulfate) and the solvent was removed in vacuum. Silicagel chromatography gave 626 mg of the title compound.

5

Intermediate Example IntP08.03

(1RS)-1-({[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)ethyl N-(tert-butoxycarbonyl)-L-valinate (mixture of 2 epimers)

10



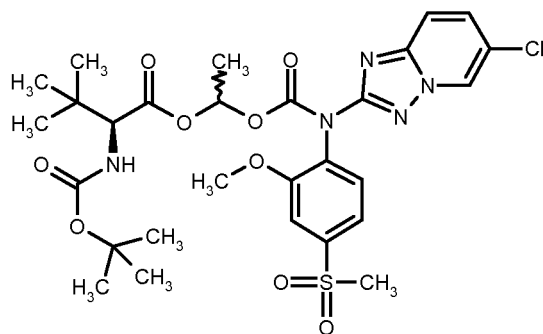
To a stirred suspension of 1-({[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)ethyl N-(tert-butoxycarbonyl)-L-valinate (595 mg) in toluene (20 mL) and NMP (2.0 mL) was added (4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl) boronic acid (400 mg), powdered potassium phosphate monohydrate (789 mg), dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (76.3 mg) and palladium acetate (20.9 mg) and the flask was degassed twice and backfilled with argon. The mixture was heated to 100 °C for 20 minutes. The reaction mixture was filtered through a silica-gel column and the solvent was removed in vacuum. Silicagel chromatography gave 341 mg of the title compound.

15

20

Intermediate Example IntP09.01

(1RS)-1-({(6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)ethyl N-(tert-butoxycarbonyl)-3-methyl-L-valinate (mixture of 2 epimers)



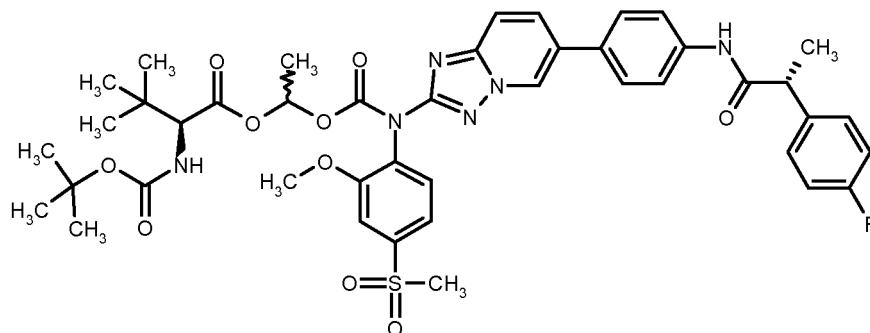
5

To a stirred solution of 1-chloroethyl (6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-methoxy-4-(methylsulfonyl)phenyl]carbamate (500 mg) in DMF (24 mL) was added caesium (2S)-2-[(tert-butoxycarbonyl)amino]-3,3-dimethylbutanoate (633 mg) and the mixture was heated to 50°C for 16 h.

10 Water was added, the mixture was extracted with ethyl acetate. The organic phase was washed with saturated sodium chloride solution, dried (sodium sulfate) and the solvent was removed in vacuum. Silicagel chromatography gave 548 mg of the title compound.

15 Intermediate Example IntP09.02

(1RS)-1-({[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)ethyl N-(tert-butoxycarbonyl)-3-methyl-L-valinate (mixture of 2 epimers)



20

To a stirred suspension of (1R)-1-({(6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)ethyl N-(tert-butoxycarbonyl)-3-methyl-L-valinate (mixture of 2 epimers) (100 mg) in
5 toluene (3.4 mL) and NMP (0.34 mL) was added (4-{{(2R)-2-(4-fluorophenyl)propanoyl}amino}phenyl) boronic acid (65.8 mg), powdered potassium phosphate monohydrate (130 mg), dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (12.6 mg) and palladium acetate (3.4 mg) and the flask was degassed twice and backfilled with argon. The mixture was
10 heated to reflux for 20 minutes. The reaction mixture was filtered through a silica-gel column and the solvent was removed in vacuum. Silicagel chromatography gave 42 mg of the title compound as a mixture of 2 epimers.

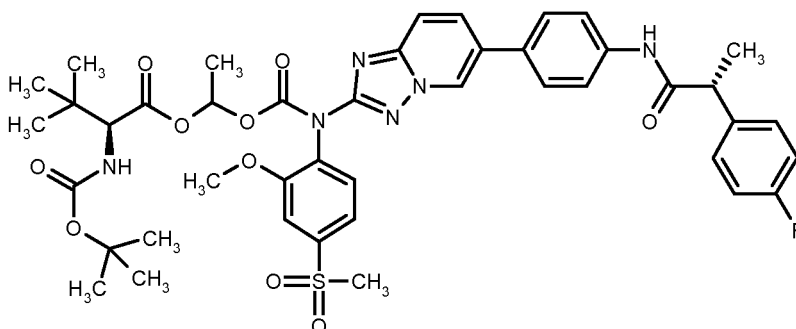
Large scale procedure:

15 To a stirred suspension of 1-({(6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)ethyl N-(tert-butoxycarbonyl)-3-methyl-L-valinate (8830 mg) in toluene (250 mL) and NMP (12 mL) was added (4-{{(2R)-2-(4-fluorophenyl)propanoyl}amino}phenyl) boronic acid (4558 mg), powdered potassium phosphate monohydrate (9627
20 mg), dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (931 mg) and palladium acetate (255 mg) and the flask was degassed twice and backfilled with argon. The mixture was heated to reflux for 20 minutes. The reaction mixture was twice filtered through a silica-gel column and the solvent was removed in vacuum. Silicagel chromatography gave 5035 mg of the title
25 compound as a mixture of 2 epimers.

Intermediate Example IntP09.03

(1R or 1S)-1-({[6-(4-{{(2R)-2-(4-
30 fluorophenyl)propanoyl}amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-

methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)ethyl -N-(tert-butoxycarbonyl)-3-methyl-L-valinate (single stereoisomer A)

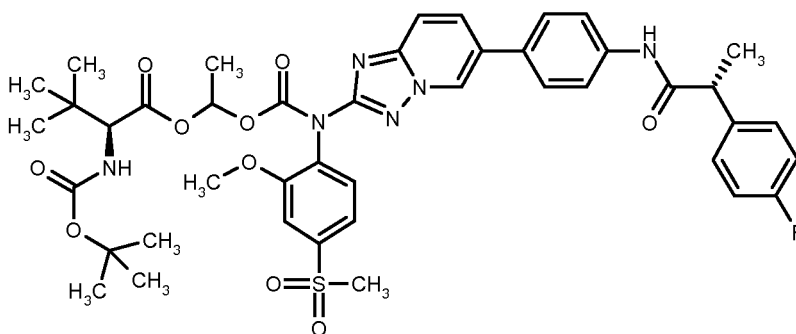


5

Intermediate Example IntP09.04

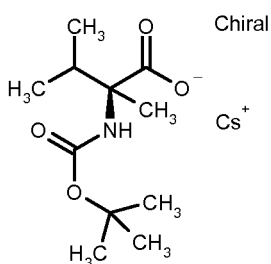
(1S or 1R)-1-({[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)ethyl -N-(tert-butoxycarbonyl)-3-methyl-L-valinate (single stereoisomer B)

10



15 7.96g of (1RS)-1-({[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)ethyl N-(tert-butoxycarbonyl)-3-methyl-L-valinate (mixture of 2 epimers) was separated into the single stereoisomers (Intermediate Example IntP09.03 and Intermediate Example IntP09.04) via preparative,
20 chiral HPLC.

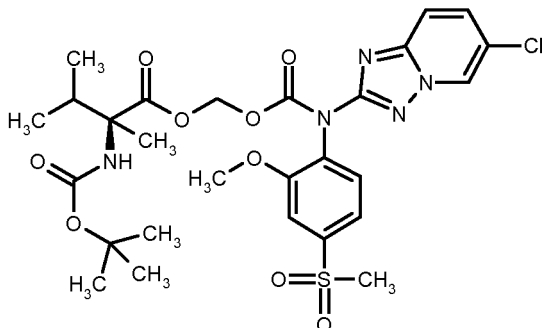
<i>System:</i>	Agilent: Prep 1200, 2xPrep Pump, DLA, MWD, Gilson: Liquid Handler 215		
<i>Column:</i>	Chiralpak IB 5µm 250x30 mm		
<i>Solvent:</i>	Hexane / ethanol 70:30 (v/v)		
<i>Flow:</i>	50 mL/min		
<i>Temperature:</i>	RT		
<i>Solution:</i>	7960 mg / 29.6 mL DCM/MeOH		
<i>Injection:</i>	47 x 0.63 mL		
<i>Detection:</i>	UV 280 nm		
	Retention time in min	purity in %	yield
Intermediate Example IntP09.03 Stereoisomer A	10.2 - 13.2	> 99.9%	2997 mg
Intermediate Example IntP09.04 Stereoisomer B	13.7 - 20.6	99.1%	3386 mg

Intermediate Example IntP10.01**Caesium (2S)-2-[(tert-butoxycarbonyl)amino]-2,3-dimethylbutanoate**

Intermediate Example IntP10.01. was prepared analogously to the procedure
 5 for the preparation of Intermediate Example IntP02.01.

Intermediate Example IntP10.02

({(6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-methoxy-4-
 10 (methylsulfonyl)phenyl]carbamoyl}oxy)methyl N-(tert-butoxycarbonyl)-3-
 methyl-L-isovalinate



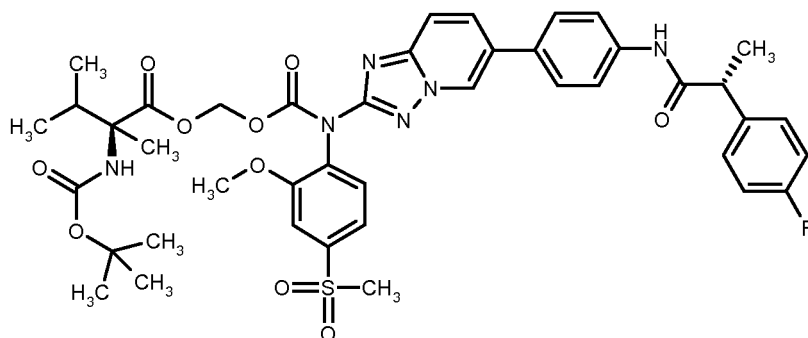
Starting with chloromethyl (6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-
 methoxy-4-(methylsulfonyl)phenyl]carbamate and caesium (2S)-2-[(tert-
 15 butoxycarbonyl)amino]-2,3-dimethylbutanoate, Intermediate Example
 IntP10.02. was prepared analogously to the procedure for the preparation of
 Intermediate Example IntP02.02.

Intermediate Example IntP10.03

({[6-(4-{[(2R)-2-(4-
 20 fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-

methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)methyl
butoxycarbonyl)-3-methyl-L-isovalinate

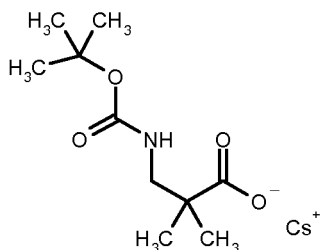
N-(tert-



Starting with Intermediate Example IntP10.02 and (4-{{[(2R)-2-(4-
5 fluorophenyl)propanoyl]amino}phenyl}boronic acid, Intermediate Example
IntP10.03. was prepared analogously to the procedure for the preparation of
Intermediate Example IntP02.03.

10 Intermediate Example IntP11.01

Caesium 3-[(tert-butoxycarbonyl)amino]-2,2-dimethylpropanoate



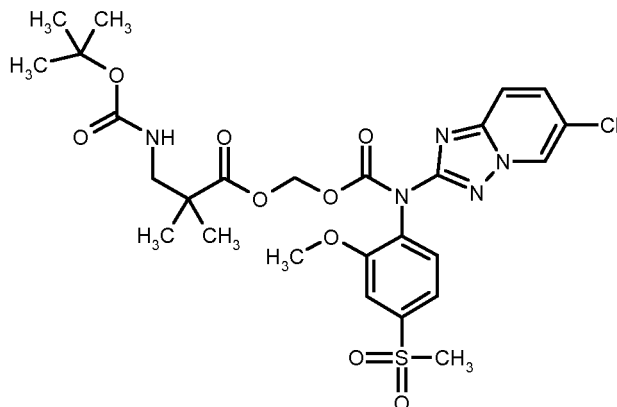
Intermediate Example IntP11.01. was prepared analogously to the procedure
for the preparation of Intermediate Example IntP02.01.

15

Intermediate Example IntP11.02

{{(6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-methoxy-4-
(methylsulfonyl)phenyl]carbamoyl}oxy)methyl 3-[(tert-

20 butoxycarbonyl)amino]-2,2-dimethylpropanoate



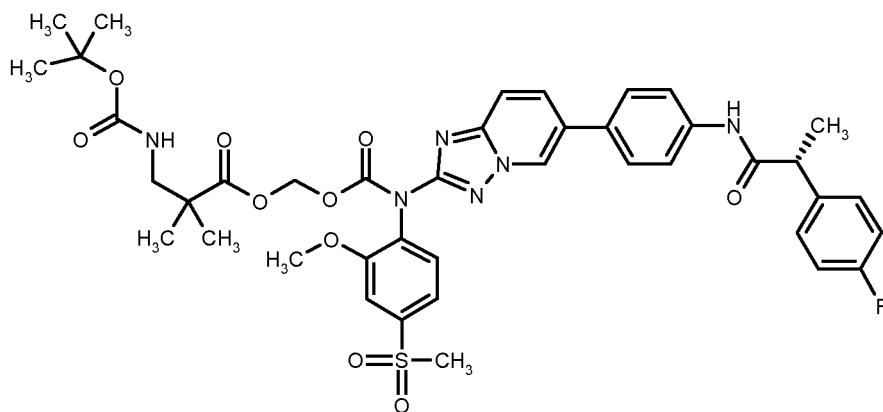
Intermediate Example IntP11.02. was prepared analogously to the procedure for the preparation of Intermediate Example IntP02.02.

5

Intermediate Example IntP11.03

({[6-(4-{[(2R)-2-(4-

10 fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoylethyl 3-[(tert-butoxycarbonyl)amino]-2,2-dimethylpropanoate

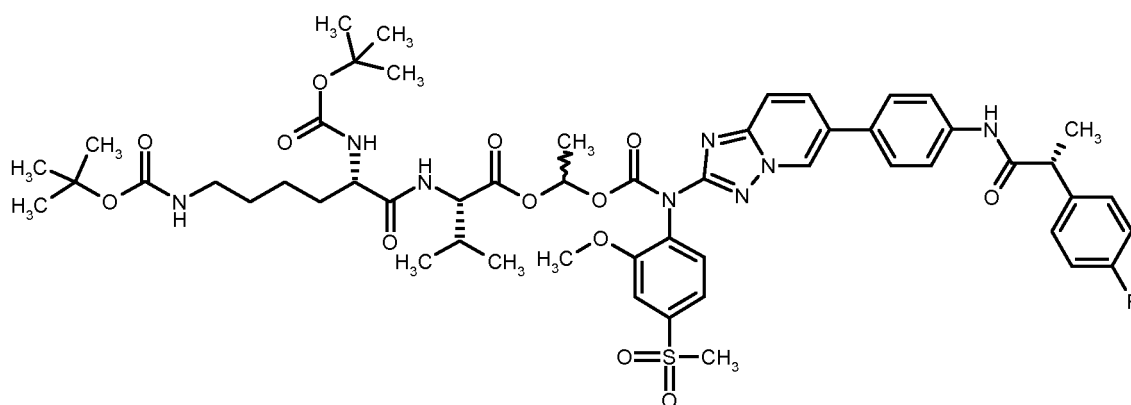


Starting with Intermediate Example IntP11.02 and (4-{[(2R)-2-(4-
15 fluorophenyl)propanoyl]amino}phenyl)boronic acid, Intermediate Example IntP11.03. was prepared analogously to the procedure for the preparation of Intermediate Example IntP02.03.

Intermediate Example IntP12.01

(1RS)-1-({[6-(4-{[(2R)-2-(4-

- 5 fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)ethyl N²,N⁶-bis(tert-butoxycarbonyl)-L-lysyl-L-valinate (mixture of 2 epimers)



- 10 To a stirred suspension of (1RS)-1-({[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)ethyl L-valinate hydrochloride (mixture of 2 epimers) (150 mg) in DMF (3.2 mL) and dichloromethane (3.2 mL) was added N²,N⁶-bis(tert-butoxycarbonyl)-L-lysine
- 15 (93 mg) and HATU (115 mg). Then sodium bicarbonate (75 mg) was added in small portions and the mixture was stirred at room temperature for 4 h. Water was added, and the mixture was stirred for 2 h. Water was added and the mixture was extracted with ethyl acetate. The organic phase was washed with saturated sodium chloride solution, dried (sodium sulfate) and the solvent was
- 20 removed in vacuum. Silicagel chromatography followed by preparative reverse phase HPLC gave 76 mg of the title compound.

Intermediate Example IntP13.01

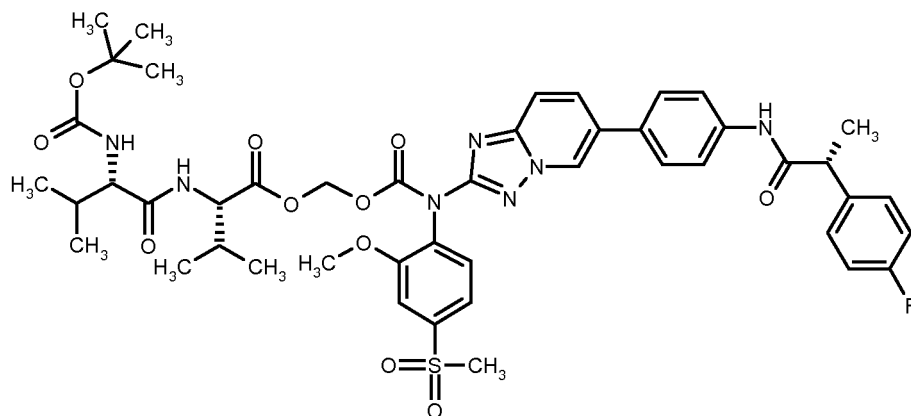
({[6-(4-{[(2R)-2-(4-

fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-

methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)methyl

N-(tert-

5 butoxycarbonyl)-L-valyl-L-valinate



Intermediate Example IntP13.01. was prepared analogously to the procedure for the preparation of Intermediate Example IntP12.01.

10

Intermediate Example IntP14.01

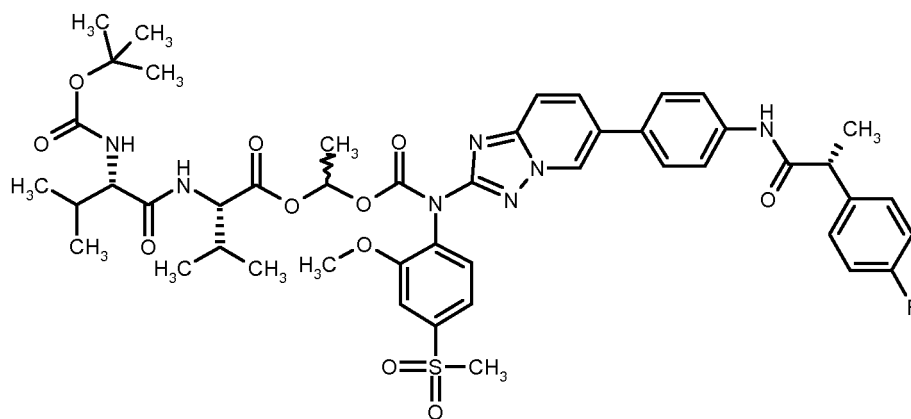
(1RS)-1-({[6-(4-{[(2R)-2-(4-

fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-

methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)ethyl

N-(tert-

15 butoxycarbonyl)-L-valyl-L-valinate (mixture of 2 epimers)

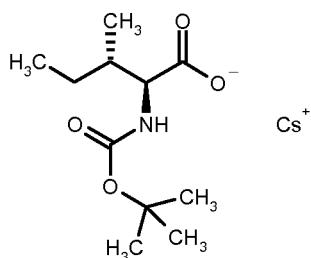


Intermediate Example IntP14.01. was prepared analogously to the procedure for the preparation of Intermediate Example IntP12.01.

5

Intermediate Example IntP15.01

Caesium (2S,3S)-2-[(tert-butoxycarbonyl)amino]-3-methylpentanoate



Intermediate Example IntP15.01. was prepared analogously to the procedure for the preparation of Intermediate Example IntP02.01.

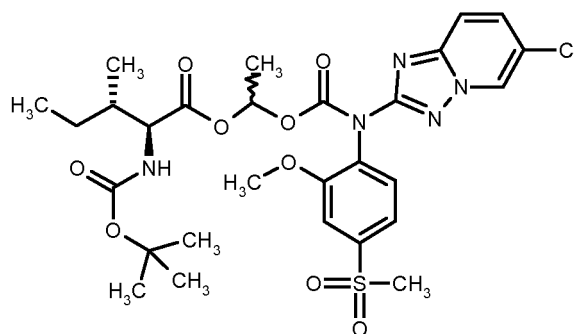
10

Intermediate Example IntP15.02

(1RS)-1-({(6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-methoxy-4-

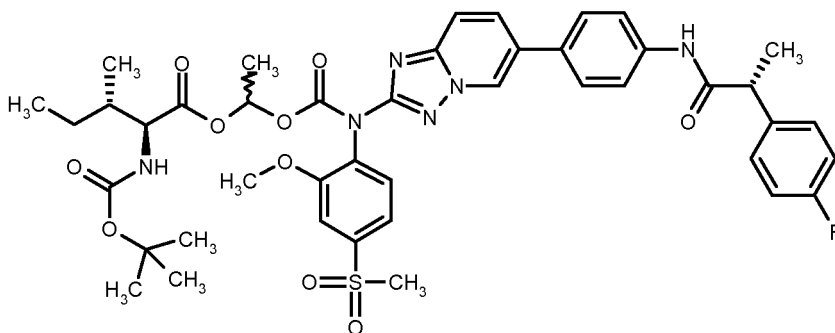
(methylsulfonyl)phenyl]carbamoyl}oxy)ethyl N-(tert-butoxycarbonyl)-L-isoleucinate (mixture of 2 epimers)

15

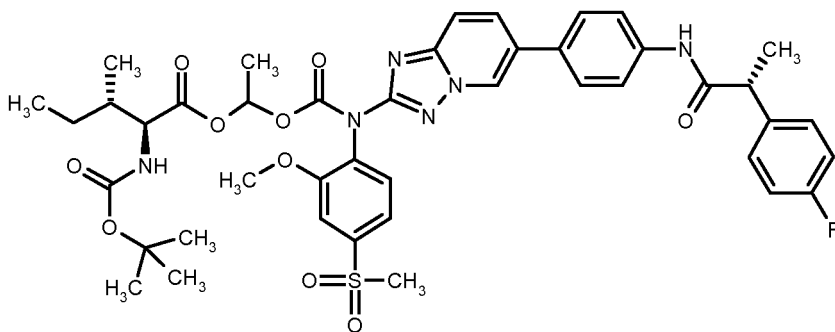


Intermediate Example IntP15.02. was prepared analogously to the procedure for the preparation of Intermediate Example IntP09.01.

20

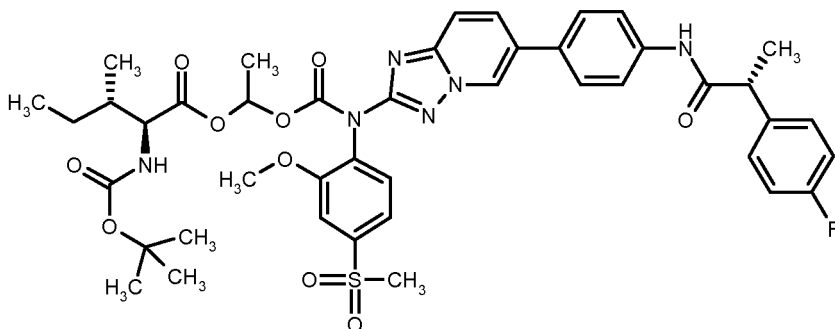
Intermediate Example IntP15.03**(1RS)-1-({[6-(4-{[(2R)-2-(4-****fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-****methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)ethyl **N**-(tert-****5 butoxycarbonyl)-L-isoleucinate (mixture of 2 epimers)**

Starting with **Intermediate Example IntP15.02 (1.37 g)** **Intermediate Example IntP15.03.** was prepared analogously to the procedure for the preparation of **Intermediate Example IntP09.02.** Yield: 623 mg of the title compound.

Intermediate Example IntP15.04**(1S or 1R)-1-({[6-(4-{[(2R)-2-(4-****15 fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-****methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)ethyl -N-(tert-****butoxycarbonyl)-L-isoleucinate (single stereoisomer A)**

Intermediate Example IntP15.05

(1R or 1S)-1-({[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)ethyl -N-(tert-butoxycarbonyl)-L-isoleucinate (single stereoisomer B)



10 (1*RS*)-1-({[6-(4-{[(2*R*)-2-(4-fluorophenyl)propanoyl]amino}phenyl)
[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]
carbamoyl]oxy)ethyl N-(tert-butoxycarbonyl)-L-isoleucinate (mixture of 2
epimers) (523 mg) was separated into the single stereoisomers (Intermediate
Example IntP15.04 and Intermediate Example IntP15.05) via preparative,
15 chiral HPLC.

<i>System:</i>	Agilent: Prep 1200, 2xPrep Pump, DLA, MWD, Gilson: Liquid Handler 215			
<i>Column:</i>	Chiralpak IB 5µm 250x30 mm			
<i>Solvent:</i>	Hexane / ethanol 70:30 (v/v)			
<i>Flow:</i>	50 mL/min			
<i>Temperature:</i>	RT			
<i>Solution:</i>	523 mg / 4 mL DCM/MeOH			
<i>Injection:</i>	8 x 0.5 mL			
<i>Detection:</i>	UV 254 nm			
	Retention	purity in %	yield	

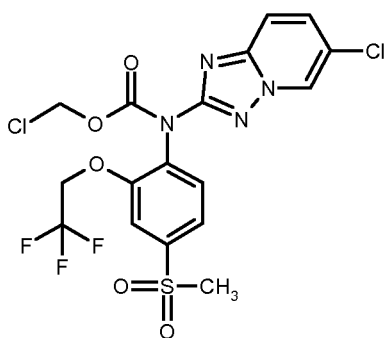
	time in min		
Intermediate Example IntP15.04 Stereoisomer A	10 - 12,5	> 99.2%	210 mg
Intermediate Example IntP15.05 Stereoisomer B	15-20	98.45%	235 mg

5

Intermediate Example IntP16.01

chloromethyl (6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[4-(methylsulfonyl)-2-(2,2,2-trifluoroethoxy)phenyl]carbamate

10

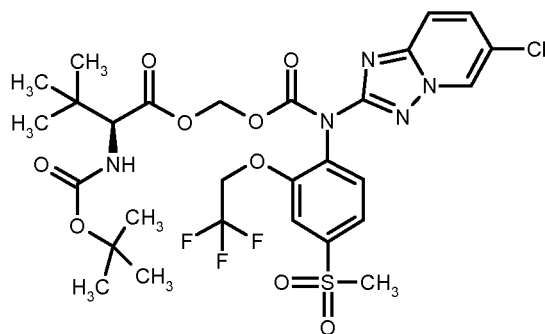


Starting with Intermediate Example Int05.04., IntP16.01. was prepared analogously to the procedure for the preparation of Intermediate Example IntP01.01.

15

Intermediate Example IntP16.02

{(6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[4-(methylsulfonyl)-2-(2,2,2-trifluoroethoxy)phenyl]carbamoyl}oxy)methyl N-(tert-butoxycarbonyl)-3-methyl-L-valinate



5

To a stirred solution of chloromethyl (6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[4-(methylsulfonyl)-2-(2,2,2-trifluoroethoxy)phenyl]carbamate (220 mg) in DMF (8.3 mL) was added caesium (2S)-2-[(tert-butoxycarbonyl)amino]-3,3-dimethylbutanoate (249 mg) and the mixture was stirred at room temperature for 16 h. Water was added, the mixture was extracted with ethyl acetate. The organic phase was washed with saturated sodium chloride solution, dried (sodium sulfate) and the solvent was removed in vacuum. Silicagel chromatography gave 260 mg of the title compound.

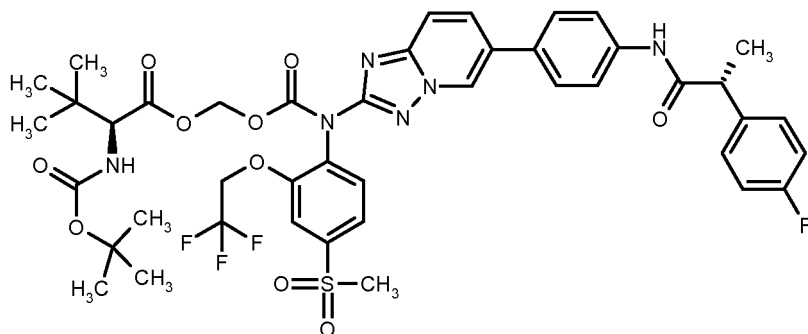
10

15

Intermediate Example IntP16.03.

{[6-(4-[(2R)-2-(4-fluorophenyl)propanoyl]amino)phenyl][1,2,4]triazolo[1,5- α]pyridin-2-yl][4-(methylsulfonyl)-2-(2,2,2-trifluoroethoxy)phenyl]carbamoyl}oxy)methyl N-(tert-butoxycarbonyl)-3-methyl-L-valinate

20



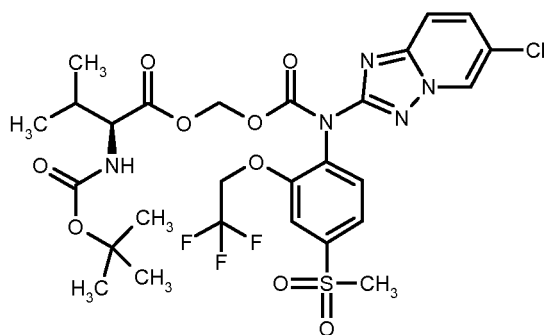
Starting with Intermediate Example IntP16.02 and (4-{{(2R)-2-(4-fluorophenyl)propanoyl}amino}phenyl)boronic acid, Intermediate Example IntP16.03. was prepared analogously to the procedure for the preparation of

5 Intermediate Example IntP02.03.

Intermediate Example IntP17.01

{{(6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[4-(methanesulfonyl)-2-(2,2,2-trifluoroethoxy)phenyl]carbamoyl}oxy)methyl N-(tert-butoxycarbonyl)-L-valinate

10



Starting with Intermediate Example IntP16.01 (230 mg) and IntP02.01 (250 mg) Intermediate Example IntP17.01. was prepared analogously to the

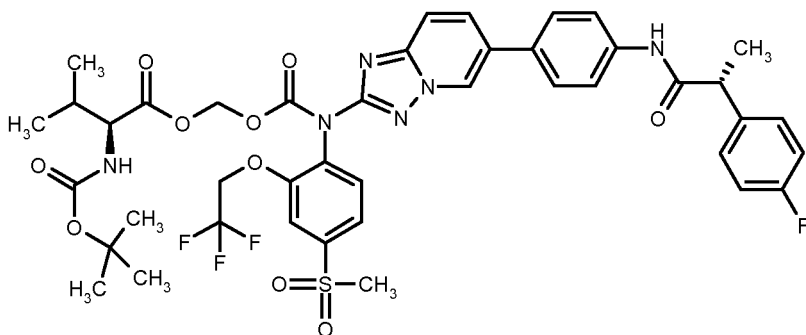
15 procedure for the preparation of Intermediate Example IntP16.02.

Yield: 240 mg of the title compound.

Intermediate Example IntP17.02

{[6-(4-{[(2R)-2-(4-

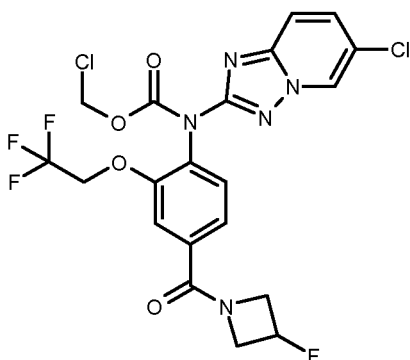
fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl)[4-(methylsulfonyl)-2-(2,2,2-trifluoroethoxy)phenyl]carbamoyl}oxy)methyl N-(tert-butoxycarbonyl)-L-valinate



Starting with Intermediate Example IntP17.01 and (4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)boronic acid, Intermediate Example IntP17.02. was prepared analogously to the procedure for the preparation of Intermediate Example IntP02.03.

Intermediate Example IntP18.01

chloromethyl (6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl){4-[(3-fluoroazetidin-1-yl)carbonyl]-2-(2,2,2-trifluoroethoxy)phenyl}carbamate

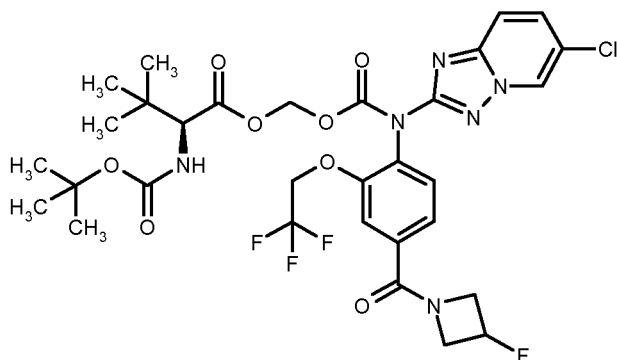


To a stirred solution of Intermediate Example Int06.05. (200 mg) in THF (10 mL) and NMP (2.0 mL) was added sodium hydride (55%w/w in oil; 98 mg) at room temperature and the mixture was stirred at room temperature for 15

minutes. Chloromethyl chloroformate (0.12 mL) was added and the mixture was stirred at room temperature for 1 hour. A half-saturated solution of ammonium chloride was added and the mixture was extracted with ethyl acetate. The organic phase was dried (sodium sulfate) and the solvent was removed in vacuum. Silicagel chromatography gave 153 mg of the title compound.

Intermediate Example IntP18.02

10 {[(6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl){4-[(3-fluoroazetidin-1-yl)carbonyl]-2-(2,2,2-trifluoroethoxy)phenyl}carbamoyl]oxy}methyl N-(tert-butoxycarbonyl)-3-methyl-L-valinate

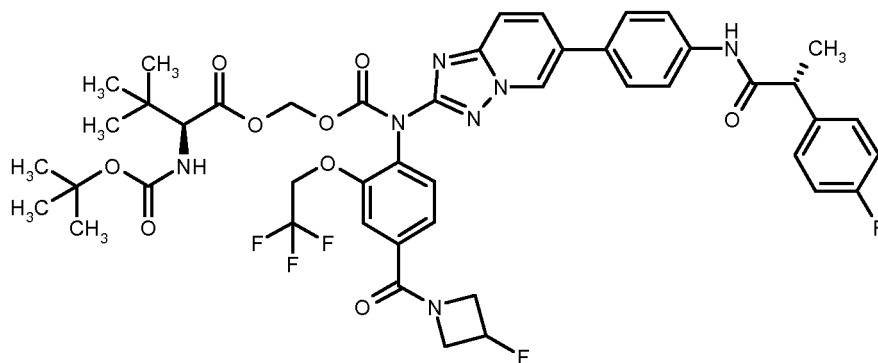


Starting with Intermediate Example IntP18.01 (150 mg) and caesium (2S)-2-
 15 [((tert-butoxycarbonyl)amino)-3,3-dimethylbutanoate (234 mg), Intermediate Example IntP18.02. was prepared analogously to the procedure for the preparation of Intermediate Example IntP16.02.
 Yield: 153 mg of the title compound.

20

Intermediate Example IntP18.03

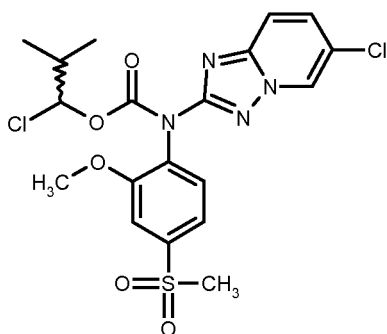
[({4-[(3-fluoroazetidin-1-yl)carbonyl]-2-(2,2,2-trifluoroethoxy)phenyl}[6-(4-[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl]carbamoyl]oxy}methyl N-(tert-butoxycarbonyl)-3-methyl-L-
 25 valinate



Starting with Intermediate Example IntP18.02 and (4-{{(2R)-2-(4-fluorophenyl)propanoyl}amino}phenyl)boronic acid, Intermediate Example IntP18.03. was prepared analogously to the procedure for the preparation of
5 Intermediate Example IntP02.03.

Intermediate Example IntP19.01

10 1-chloro-2-methylpropyl (6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-
methoxy-4-(methylsulfonyl)phenyl]carbamate

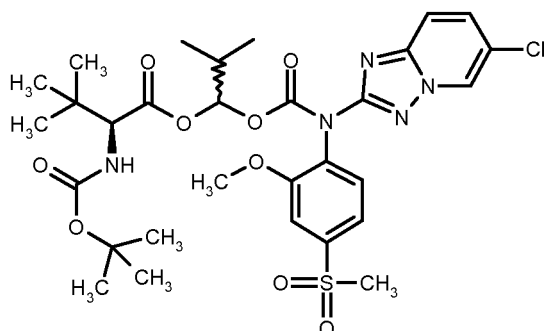


To a stirred solution of 6-chloro-N-[2-methoxy-4-(methylsulfonyl)phenyl][1,2,4]triazolo[1,5-a]pyridin-2-amine (Int21.03) (4.00 g) in THF (200 mL) was added sodium hydride (55%w/w in oil; 2.47 g) at room temperature and the mixture was stirred at 0 °C for 15 minutes. 1-chloro-2-methylpropyl carbonochloridate (4.13 mL) was added and the mixture was stirred at room temperature for 4 hours. A half-saturated solution of sodium chloride was added and the mixture was extracted with ethyl acetate. The organic phase was dried (sodium sulfate) and the solvent was

removed in vacuum. Silicagel chromatography gave 3.00 g of the title compound.

Intermediate Example IntP19.02

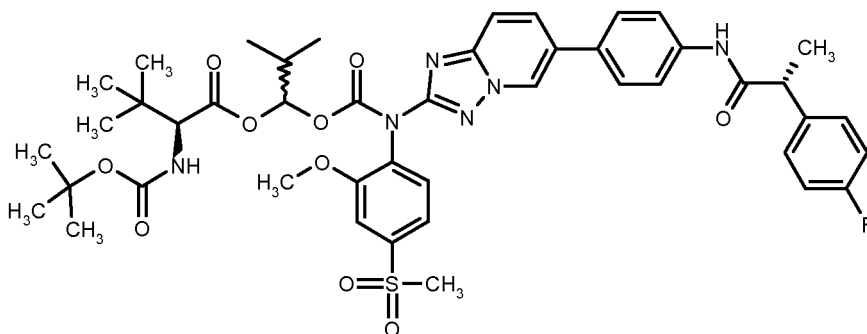
- 5 (1RS)-1-({(6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)-2-methylpropyl-N-(tert-butoxycarbonyl)-3-methyl-L-valinate



- To a stirred solution of 1-chloro-2-methylpropyl (6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-methoxy-4-(methylsulfonyl)phenyl]carbamate (2500 mg) in DMF (125 mL) was added caesium (2S)-2-[(tert-butoxycarbonyl)amino]-3,3-dimethylbutanoate (2981 mg) and the mixture was heated to 70°C for 16 h. The mixture was added to a half-saturated solution of sodium chloride and the mixture was extracted with ethyl acetate. The organic phase was washed with saturated sodium chloride solution, dried (sodium sulfate), filtered and the solvent was removed in vacuum. Silicagel chromatography gave 2240 mg of the title compound.

20 Intermediate Example IntP19.03

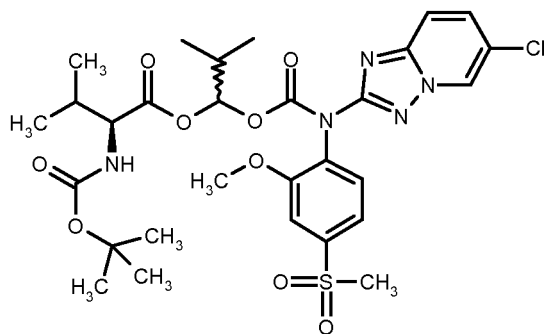
- (1RS)-1-({[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)-2-methylpropyl N-(tert-butoxycarbonyl)-3-methyl-L-valinate (mixture of 2 epimers)



To a stirred suspension of (1*RS*)-1-({(6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)-2-methylpropyl N-
 5 (tert-butoxycarbonyl)-3-methyl-L-valinate (2200 mg) in toluene (64.6 mL) and NMP (10.8 mL) was added (4-[(2*R*)-2-(4-fluorophenyl)propanoyl]amino}phenyl) boronic acid (1389 mg), powdered potassium phosphate monohydrate (2738 mg), dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (265 mg) and palladium acetate (72 mg) and
 10 the flask was degassed twice and backfilled with argon. The mixture was heated to reflux for 30 minutes. After cooling, the reaction mixture was diluted with water and extracted with ethyl acetate (3x). The combined organic phases were dried (sodium sulfate), filtered and the solvent was removed in vacuum. Silicagel chromatography gave 2200 mg of the title
 15 compound.

Intermediate Example IntP20.01

(1*RS*)-1-({(6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)-2-methylpropyl-N-(tert-
 20 butoxycarbonyl)-L-valinate (mixture of 2 epimers)

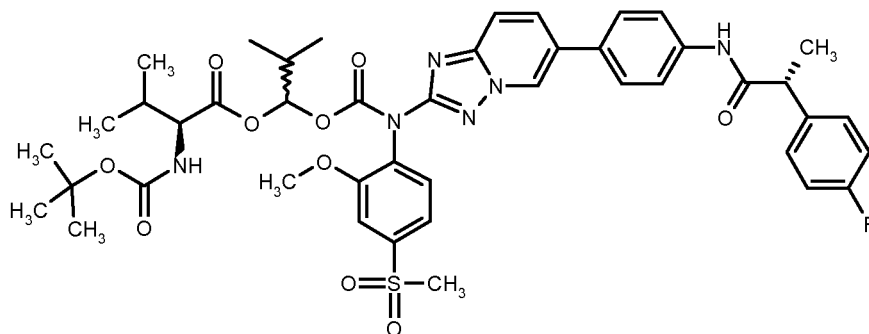


To a stirred solution of 1-chloro-2-methylpropyl (6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-methoxy-4-(methylsulfonyl)phenyl]carbamate (5000 mg) in DMF (150 mL) was added caesium (2S)-2-[(tert-butoxycarbonyl)amino]-3-methylbutanoate (5373 mg) and the mixture was heated to 70°C for 16 h. The mixture was added to water and extracted with ethyl acetate. The organic phase was washed with a half-saturated solution of sodium chloride, dried (sodium sulfate), filtered and the solvent was removed in vacuum. Preparative HPLC separation gave 4300 mg of the title compound.

10

Intermediate Example IntP20.02

(1RS)-1-({[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)-2-methylpropyl-N-(tert-butoxycarbonyl)-L-valinate (mixture of 2 epimers)
and single stereoisomers Intermediate Example IntP20.03 and Intermediate Example IntP20.04.



20

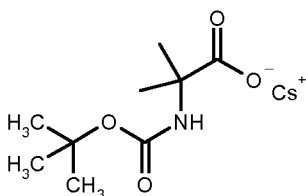
- To a stirred suspension of (1R)-1-({(6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-methoxy-4-(methylsulfonyl)phenyl]carbonyl}oxy)-2-methylpropyl-N-(tert-butoxycarbonyl)-L-valinate (2000 mg) in toluene (60.0 mL) and NMP (10.0 mL) was added (4-{{(2R)-2-(4-fluorophenyl)propanoyl}amino}phenyl) boronic acid (1289 mg), powdered potassium phosphate monohydrate (2541 mg), dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (246 mg) and palladium acetate (67 mg) and the flask was degassed twice and backfilled with argon. The mixture was heated to reflux for 45 minutes. After cooling, the reaction mixture was diluted with water and extracted with ethyl acetate (3x).
- 10 The combined organic phases were dried (sodium sulfate), filtered and the solvent was removed in vacuum. Silicagel chromatography gave 1500 mg of the title compound as a mixture of 2 stereoisomers (IntP20.02).
- The mixture was separated into the single stereoisomers (Intermediate Example IntP20.03 and Intermediate Example IntP20.04.) via preparative, 15 chiral HPLC.

<i>System:</i>	Agilent: Prep 1200, 2xPrep Pump, DLA, MWD, Gilson: Liquid Handler 215		
<i>Column:</i>	Chiralpak IB 5 μ m 250x30 mm		
<i>Solvent:</i>	Hexane / ethanol 70:30 (v/v)		
<i>Flow:</i>	50 mL/min		
<i>Temperature:</i>	RT		
<i>Solution:</i>	1500 mg / 19 mL DCM/MeOH		
<i>Injection:</i>	55 x 0.35 mL		
<i>Detection:</i>	UV 280 nm		
	Retention time in min	purity in %	yield
Intermediate Example IntP20.03 Stereoisomer	9.5 - 10.7	> 99.9%	700 mg

A			
Intermediate Example IntP20.04 Stereoisomer B	10.9 - 12.4	97.1	725 mg

Intermediate Example IntP21.01

caesium 2-[(tert-butoxycarbonyl)amino]-2-methylpropanoate



5

To a stirred solution of N-(tert-butoxycarbonyl)-2-methylalanine (4.00 g) in methanol (76 mL) was added a solution of caesium carbonate in water until pH 7 was reached (approx. 3.21 g caesium carbonate in 15 mL water) and the solution was stirred for 30 minutes. The solvent was removed in vacuum, toluene was added and the solvent was again removed in vacuum to give 7.00 g of the title compound.

10

Intermediate Example IntP21.02

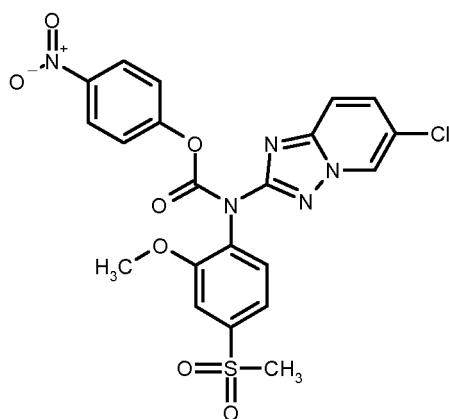
(rac)-1-({(6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-methoxy-4-(methylsulfonyl)phenyl]carbonyloxy)-2-methylpropyl N-(tert-butoxycarbonyl)-2-methylalaninate

15

butoxycarbonyl)-2-methylalaninate (600 mg) in toluene (18.4 mL) and NMP (3.1 mL) was added (4-[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl) boronic acid (395 mg), powdered potassium phosphate monohydrate (779 mg), dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (75 mg) and palladium acetate (21 mg) and the flask was degassed twice and backfilled with argon. The mixture was heated to reflux for 30 minutes. After cooling, the reaction mixture was diluted with water and extracted with ethyl acetate (3x). The combined organic phases were dried (sodium sulfate), filtered and the solvent was removed in vacuum. Silicagel chromatography gave 30 mg of the title compound as a mixture of 2 epimers.

Intermediate Example IntP22.01

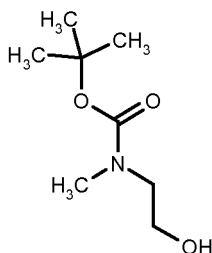
4-nitrophenyl (6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-methoxy-4-(methylsulfonyl)phenyl]carbamate



To a stirred solution of 6-chloro-N-[2-methoxy-4-(methylsulfonyl)phenyl][1,2,4]triazolo[1,5- α]pyridin-2-amine (Int21.03) (500 mg) in THF (50 mL) was added sodium hydride (55%w/w in oil; 1.24 g) at room temperature and the mixture was stirred at room temperature for 15 minutes. 4-Nitrophenyl chloroformate (0.29 mL) was added at 0 °C and the mixture was stirred at room temperature for 15 minutes. Aqueous hydrochloric acid (c = 2M) was added until acidic pH was reached and the mixture was

extracted with ethyl acetate. The organic phase was dried (sodium sulfate) and the solvent was removed in vacuum. Silicagel chromatography gave 725 mg of the title compound.

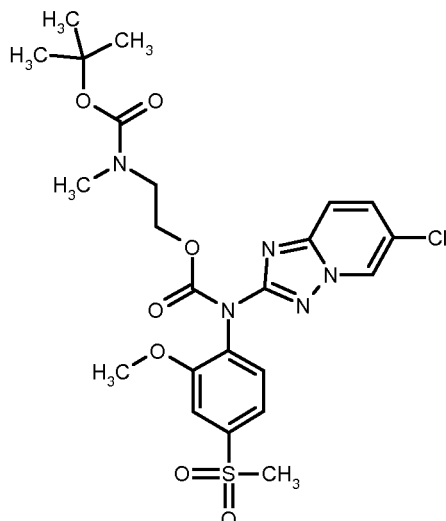
5

Intermediate Example IntP22.02**tert-butyl (2-hydroxyethyl)methylcarbamate**

To a stirred suspension of 2-(methylamino)ethanol (5.0 g) in water (75 mL)
10 was added potassium carbonate (15.3 g) and di-tert-butyl dicarbonate (12.1 g)
and the mixture was stirred at room temperature for 16 hours. The mixture
was extracted with dichloromethane. The organic phase was washed with
saturated sodium chloride solution, dried (sodium sulfate) and the solvent was
removed in vacuum. Aminophase-silica-gel chromatography gave 6.6 g of the
15 title compound.

Intermediate Example IntP22.03

2-[(tert-butoxycarbonyl)(methyl)amino]ethyl (6-chloro[1,2,4]triazolo[1,5-
20 α]pyridin-2-yl)[2-methoxy-4-(methylsulfonyl)phenyl]carbamate



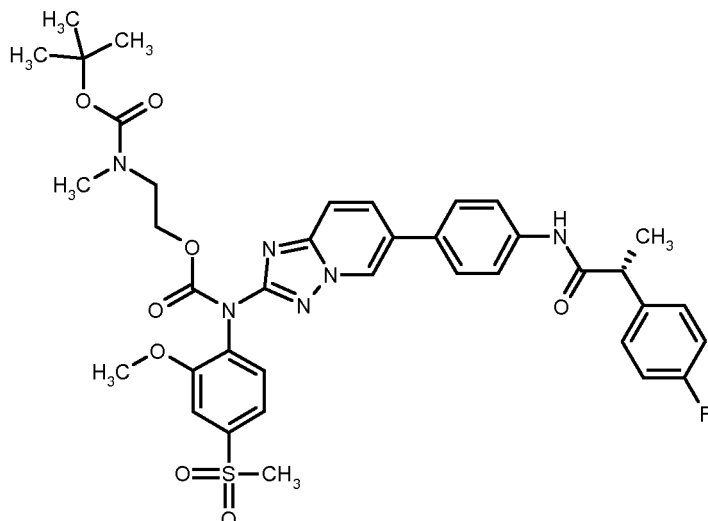
To a stirred solution of 4-nitrophenyl (6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-methoxy-4-(methylsulfonyl)phenyl]carbamate (720 mg) in DMF (40 mL) was added caesium carbonate (4.53 g), and tert-butyl(2-hydroxyethyl)methylcarbamate (487 mg). The mixture was stirred at room temperature for 1 h. Water was added, and the mixture was extracted with ethyl acetate. The organic phase was washed with saturated sodium chloride solution, dried (sodium sulfate) and the solvent was removed in vacuum. Silicagel chromatography gave 425 mg of the title compound.

10

Intermediate Example IntP22.04

2-[(tert-butoxycarbonyl)(methyl)amino]ethyl [6-(4-[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamate

15



To a stirred suspension of 2-[(tert-butoxycarbonyl)(methyl)amino]ethyl (6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-methoxy-4-

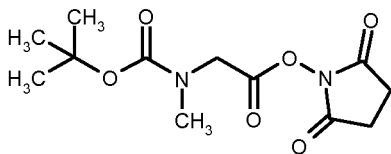
5 (methylsulfonyl)phenyl]carbamate (100 mg) in toluene (3.2 mL) was added potassium fluoride (47.2 mg) and powdered potassium phosphate (153 mg) and the flask was twice degased and backfilled with argon. The mixture was stirred at room temperature for 15 minutes. (2R)-2-(4-fluorophenyl)-N-[4-(4,4,5,5-

10 tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]propanamide (100 mg), dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (14.8 mg) and palladium acetate (4.1 mg) were added and the flask was twice degased and backfilled with argon. The mixture was heated to 85 °C for 5 h. Water was added and the reaction mixture was extracted with ethyl acetate. The organic phase was washed with saturated sodium chloride solution, dried (sodium sulfate) and the

15 solvent was removed in vacuum. Silicagel chromatography followed by preparative reverse phase HPLC (gradient of water and acetonitrile containing conc. ammonium hydroxide as additiv) gave 28 mg of the title compound.

20 Intermediate Example IntP23.01

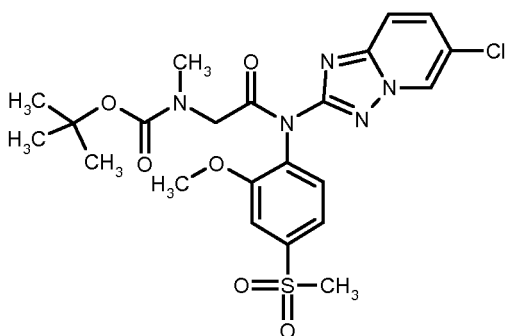
2,5-dioxopyrrolidin-1-yl N-(tert-butoxycarbonyl)-N-methylglycinate



To a stirred solution of N,N'-dicyclohexylcarbodiimide (6.0 g) in THF (100 mL) at -5 °C was added N-(tert-butoxycarbonyl)-N-methylglycine (5.0 g) and 1-hydroxypyrrolidine-2,5-dione (4.7 g) and the mixture was allowed to warm up to room temperature over night. A solid was removed by filtration and the solution was concentrated in vacuum. Silicagel chromatography gave 5.0 g of the title compound.

10 Intermediate Example IntP23.02

tert-butyl (2-((6-chloro[1,2,4]triazolo[1,5- α]pyridin-2-yl)[2-methoxy-4-(methylsulfonyl)phenyl]amino)-2-oxoethyl)methylcarbamate



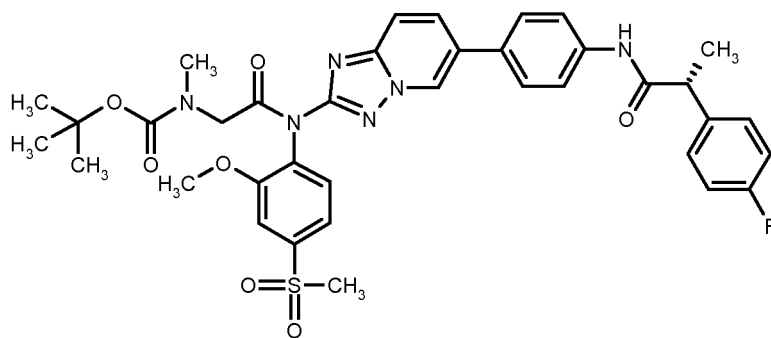
To a stirred solution of 6-chloro-N-[2-methoxy-4-(methylsulfonyl)phenyl][1,2,4]triazolo[1,5- α]pyridin-2-amine (Int21.03) (1.0 g) in THF (140 mL) was added sodium hydride (55%w/w in oil; 1.36 g) at room temperature and the mixture was stirred at room temperature for 15 minutes. 2,5-dioxopyrrolidin-1-yl N-(tert-butoxycarbonyl)-N-methylglycinate (1.62 g) was added and the mixture was stirred at room temperature for 10 minutes. A half-saturated aqueous solution of ammonium chloride was added and the mixture was extracted with ethyl acetate. The organic phase was dried (sodium sulfate) and the solvent was removed in vacuum. The residue was dissolved in dichloromethane and filtered through

silicagel, and eluted with a mixture of dichloromethane and methanol (95:5) to give the crude product as a solid. The solid was triturated with warm ethanol, undissolved material was removed by filtration and the solution was concentrated in vacuum. Silicagel chromatography gave 1.2 g of the title compound.

Intermediate Example IntP23.03

tert-butyl (2-{[6-(4-{[(2R)-2-(4-

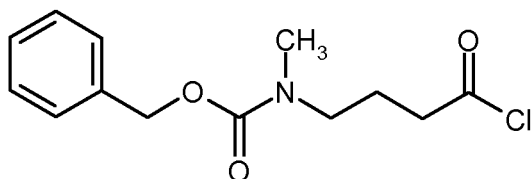
10 fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]amino}-2-oxoethyl)methylcarbamate



To a stirred suspension of tert-butyl (2-{[6-chloro[1,2,4]triazolo[1,5-
15 α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]amino}-2-oxoethyl)methylcarbamate (350 mg) in toluene (11.7 mL) and NMP (0.58 mL) was added (4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)boronic acid (249 mg), powdered potassium phosphate monohydrate (567 mg), dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine (54.8 mg) and Pd₂(dba)₃
20 (30.6 mg) and the flask was degassed twice and backfilled with argon. The mixture was heated to 90 °C for 60 minutes. The reaction mixture was filtered, water was added and the mixture was extracted with ethyl acetate. The organic phase was washed with saturated sodium chloride solution, dried (sodium sulfate) and the solvent was removed in vacuum. Silicagel

chromatography followed by aminophase-silica-gel chromatography gave 170 mg of the title compound.

5

Intermediate Example 4.01A**Benzyl (4-chloro-4-oxobutyl)methylcarbamate**

The starting material, 4-[[[(benzyloxy)carbonyl](methyl)amino]butyric acid, was prepared by a literature procedure [Y. Aramaki et al., *Chem. Pharm. Bull.* 52, 258 (2004)] from commercially available 4-[[[(benzyloxy)carbonyl]amino]butyric acid. An alternative preparation was also to introduce the benzyloxycarbonyl protective group into ω -N-methylaminoalkylcarboxylic acids which were obtainable according to P. Quitt et al. [*Helv. Chim. Acta* 46, 327 (1963)].

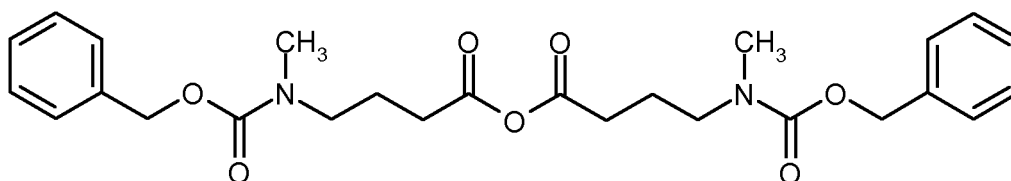
15

1.74 g (6.92 mmol) of 4-[[[(benzyloxy)carbonyl](methyl)amino]butyric acid were dissolved in 35 ml of dichloromethane and 3.5 ml (48 mmol) of thionyl chloride were added. The mixture was heated under reflux for 1 h. It was then concentrated in vacuo, and the residue was again mixed with dichloromethane and concentrated once again. A viscous oil remained and was dried under high vacuum. 1.8 g (96% of theory) of the target compound were obtained and were reacted further without further purification and characterization.

20

Intermediate Example 4.02A

4-[[[(benzyloxy)carbonyl](methyl)amino]butanoic
anhydride



The starting material, 4-[[[(benzyloxy)carbonyl](methyl)amino]butyric acid, was
5 prepared by a literature procedure [Y. Aramaki et al., *Chem. Pharm. Bull.* 52,
258 (2004)] from commercially available 4-[[[(benzyloxy)carbonyl]amino]butyric
acid. An alternative preparation was also to introduce the benzyloxycarbonyl
protective group into ω -N-methylaminoalkylcarboxylic acids which were
obtainable according to P. Quitt et al. [*Helv. Chim. Acta* 46, 327 (1963)].

10

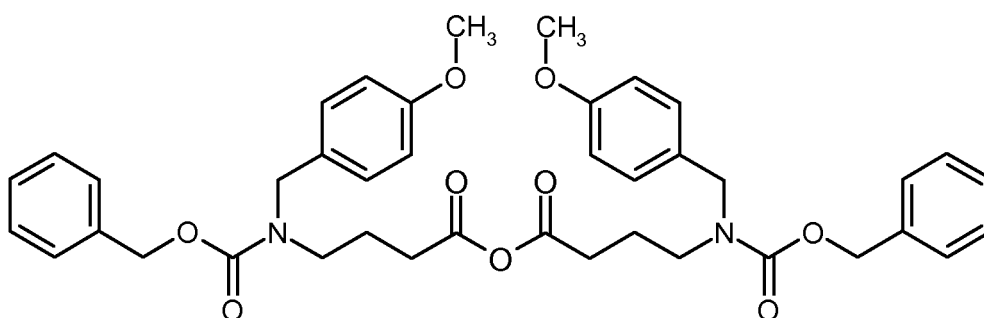
2.36 g (9.39 mmol) of 4-[[[(benzyloxy)carbonyl](methyl)amino]butyric acid
were dissolved in 30 ml of dichloromethane and 0.969 g (4.7 mmol) of
dicyclohexyl carbodiimide were added. The mixture was treated in ultrasonic
equipment for 2 h. It was then concentrated in vacuo to about half of the
15 original volume and the precipitate was filtered off. The remaining solution
was concentrated in vacuo to dryness and the residue was dried under high
vacuum. 2.33 g (84% of theory) of the target compound were obtained and
reacted further without further purification.

LC-MS (method 1): $R_t = 1.2$ min; $m/z = 485$ ($M+H$)⁺.

20

Intermediate Example 4.03A

5-[[[(benzyloxy)carbonyl](4-methoxybenzyl)amino]butanoic anhydride



Step a): 4-[(4-methoxybenzyl)amino]butanoic acid:

20 g (194 mmol) of 4-aminobutanoic acid, 39.6 g (291 mmol) of p-anisaldehyde
5 and 14 g (116 mmol) of magnesium sulphate were taken up in 300 ml of
ethanol and heated under reflux overnight. The solid was filtered off and
washed with ethanol. Subsequently a total of 4.4 g (116 mmol) of sodium
borohydride were added in portions to the filtrate over the course of 15 min.
The mixture was concentrated in vacuo and then 582 ml of a 2 M sodium
10 hydroxide solution were added. After 5 min the mixture was extracted with
500 ml dichloromethane and twice with 200 ml of ethyl acetate each time. The
aqueous phase was concentrated in vacuo. The residue was dried under high
vacuum and reacted in the next step without further purification.

15 Step b): 4-[[[(benzyloxy)carbonyl](4-methoxybenzyl)amino]butanoic acid:

43 g of the crude p-methoxybenzyl protected 4-aminobutanoic acid derivative
obtained in this way was taken up in dioxane/2M NaOH (1:1). 49 g (288 mmol)
of benzyl chlorocarbonate were added dropwise and the pH was kept at 11-12
20 by adding 2M NaOH. After stirring at RT for 30 min, the dioxane was removed
in vacuo and the remaining solution was adjusted to pH 2 with 2 M hydrochloric
acid. The solution was extracted twice with 500 ml ethyl acetate. The organic
phase was washed with a saturated solution of ammonium chloride and then
concentrated in vacuo. The residue was dried under high vacuum and reacted
25 in the next step without further purification.

Step c): 5-[[[(benzyloxy)carbonyl](4-methoxybenzyl)amino]butanoic anhydride

1920 mg (5.372 mmol) of crude 4-[[[(benzyloxy)carbonyl](4-
30 methoxybenzyl)amino] butanoic acid were dissolved in 20 ml of

dichloromethane and 554 mg (2.69 mmol) of dicyclohexyl carbodiimide were added. The mixture was stirred at RT for 1 h. It was then concentrated in vacuo to half of the original volume and the precipitate was filtered off. The remaining solution was concentrated in vacuo to dryness and the residue was
 5 dried under high vacuum. 1900 mg (97% of theory) of the target compound were obtained and reacted further without further purification.

LC-MS (method 1): R_t = 1.43 min; m/z = 697 ($M+H$)⁺.

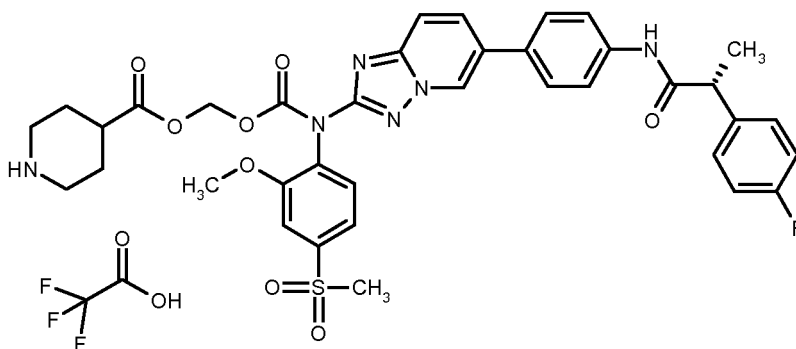
Compounds of the present invention

10

Example 1.1

({[6-(4-[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbonyl}oxy)methyl piperidine-4-carboxylate trifluoroacetate

15



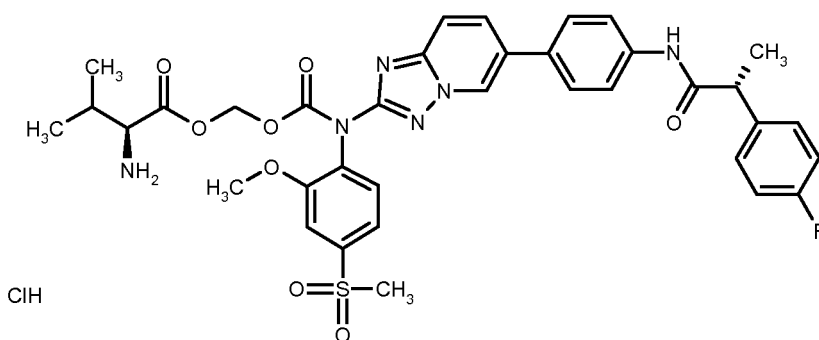
To a stirred solution of Intermediate Example IntP01.03 (90 mg) in dichloromethane (5 mL) and methanol (0.5 mL) was added a solution of hydrochloric acid in dioxane (2.66 mL; c = 4.0 M). The mixture was stirred at
 20 room temperature for 10 minutes. The solvent was removed in vacuum. Preparative reverse phase HPLC followed by lyophilisation gave 14 mg of the title compound.

¹H-NMR (300 MHz, DMSO- d_6 , detected signals), δ [ppm] = 1.41 (3H), 1.61-1.78 (2H), 1.94-2.06 (2H), 2.74-2.85 (1H), 2.88-3.03 (2H), 3.19-3.29 (2H), 3.80-3.90

(4H), 5.72-5.83 (2H), 7.12-7.20 (2H), 7.42 (2H), 7.55 (2H), 7.64 (1H), 7.66-7.75 (4H), 7.79 (1H), 8.01 (1H), 8.24 (1H), 8.49 (1H), 9.19 (1H), 10.23 (1H).

Example1.2

5 ([6-(4-((2R)-2-(4-fluorophenyl)propanoyl)amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)methyl L-valinate hydrochloride



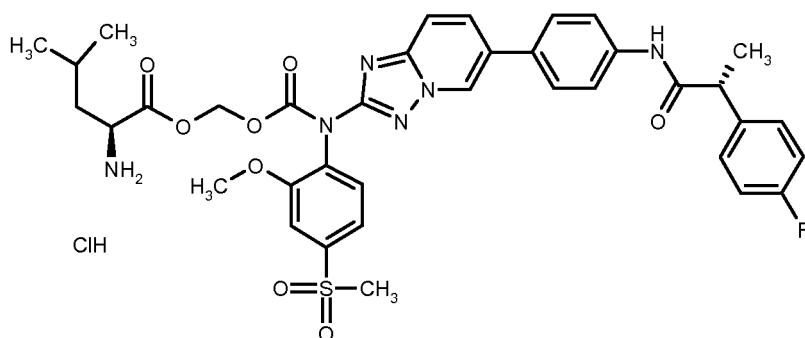
To a stirred solution of **Intermediate Example IntP02.03** (284 mg) in dichloromethane (3.5 mL) and methanol (0.35 mL) was added a solution of hydrochloric acid in dioxane (1.1 mL; c = 4.0 M). The mixture was stirred at room temperature for 20 minutes. The solvent was removed in vacuum. The solid residue was triturated with dichloromethane for three times, the solvent was removed each time and the solid was dried in vacuum to give 255 mg of the title compound.

¹H-NMR (300 MHz, DMSO-d₆), δ [ppm] = 0.92 (3H), 0.96 (3H), 1.41 (3H), 2.18 (1H), 3.32 (3H), 3.84-3.96 (4H), 4.03 (1H), 5.85 (1H), 5.97 (1H), 7.10-7.20 (2H), 7.44 (2H), 7.52-7.61 (2H), 7.65 (1H), 7.72 (4H), 7.79 (1H), 8.01 (1H), 8.52 (3H), 9.20 (1H), 10.38 (1H).

Example1.3

([6-(4-((2R)-2-(4-fluorophenyl)propanoylamino)phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-

methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)methyl L-leucinate hydrochloride



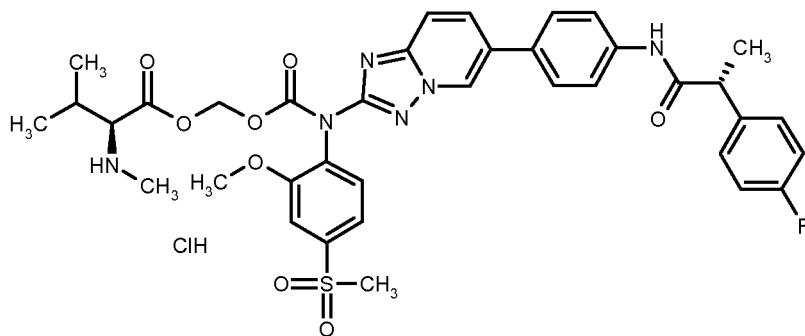
To a stirred solution of Intermediate Example IntP03.03 (69 mg) in
 5 dichloromethane (0.8 mL) was added a solution of hydrochloric acid in dioxane
 (0.41 mL; c = 4.0 M). The mixture was stirred at room temperature for 20
 minutes. A solid precipitated. The solvent was removed by decantation. The
 solid residue was triturated with dichloromethane for three times, the solvent
 was removed each time and the solid was dried in vacuum to give 56 mg of the
 10 title compound.

¹H-NMR (300 MHz, DMSO-d₆), δ [ppm] = 0.89 (6H), 1.41 (3H), 1.59-1.68 (2H),
 1.74 (1H), 3.32 (3H), 3.81-3.97 (4H), 4.03-4.14 (1H), 5.86 (1H), 5.93 (1H), 7.15
 (2H), 7.44 (2H), 7.53-7.61 (2H), 7.65 (1H), 7.72 (4H), 7.79 (1H), 8.02 (1H), 8.54
 (3H), 9.20 (1H), 10.39 (1H).

15

Example 1.4

**({[6-(4-{{(2R)-2-(4-
 fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5-α]pyridin-2-yl][2-
 methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)methyl N-methyl-L-
 20 valinate hydrochloride**

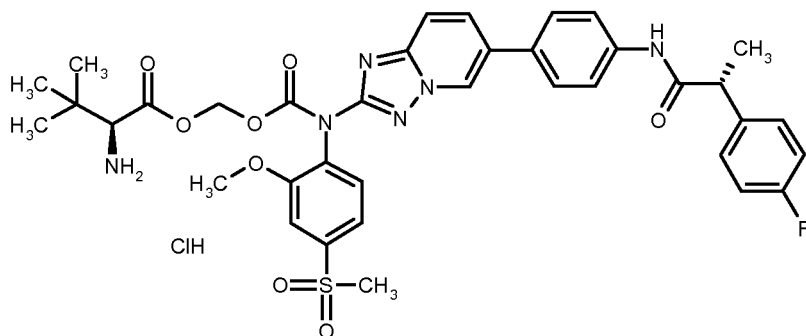


To a stirred solution of **Intermediate Example IntP04.03** (108 mg) in dichloromethane (2.5 mL) and methanol (0.76 mL) was added a solution of hydrochloric acid in dioxane (1.28 mL; $c = 4.0$ M). The mixture was stirred at room temperature for 30 minutes. The solvent was removed in vacuum. The solid residue was triturated with dichloromethane for three times, the solvent was removed each time and the solid was dried in vacuum to give the title compound with some remaining starting material. Dichloromethane (0.5 mL) and a solution of hydrochloric acid in dioxane (0.25 mL; $c = 4.0$ M) were added and the mixture was stirred at room temperature for 30 minutes. The solvent was removed in vacuum. The solid residue was triturated with dichloromethane for three times, the solvent was removed each time and the solid was dried in vacuum to give 58 mg of the title compound.

$^1\text{H-NMR}$ (300 MHz, DMSO-d_6 , detected signals), δ [ppm] = 0.88 (3H), 1.01 (3H), 1.41 (3H), 2.21-2.34 (1H), 2.54-2.60 (3H), 3.32 (3H), 3.91 (3H), 4.11 (1H), 5.86 (1H), 6.00 (1H), 7.15 (2H), 7.43 (2H), 7.52-7.61 (2H), 7.65 (1H), 7.72 (4H), 7.79 (1H), 8.02 (1H), 9.14-9.44 (3H), 10.34 (1H).

Example 1.5

({[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5-a]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbonyloxy)methyl 3-methyl-L-valinate hydrochloride

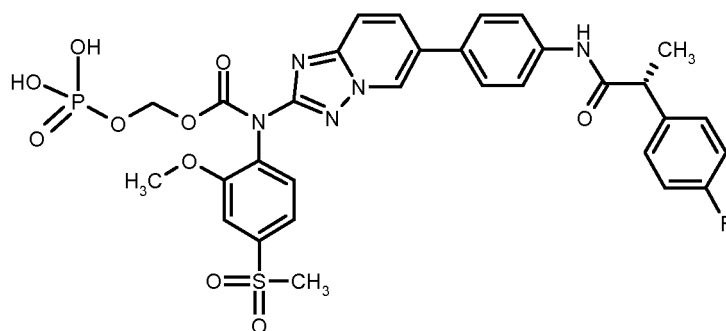


To a stirred solution of Intermediate Example IntP05.03 (218 mg) in dichloromethane (4.0 mL) and methanol (0.4 mL) was added a solution of hydrochloric acid in dioxane (1.3 mL; c = 4.0 M). The mixture was stirred at room temperature for 20 minutes. The solvent was removed in vacuum. The solid residue was triturated with dichloromethane for three times, the solvent was removed each time and the solid was dried in vacuum to give 170 mg of the title compound.

¹H-NMR (400 MHz, DMSO-d₆, detected signals), δ [ppm] = 0.98 (9H), 1.41 (3H), 3.31 (3H), 3.84-3.94 (4H), 5.85 (1H), 5.97 (1H), 7.10-7.20 (2H), 7.40-7.46 (2H), 7.53-7.61 (2H), 7.64 (1H), 7.72 (4H), 7.78 (1H), 8.01 (1H), 8.44 (3H), 9.18 (1H), 10.33 (1H).

Example 1.6

(phosphonoxy)methyl [6-(4-[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5-a]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamate



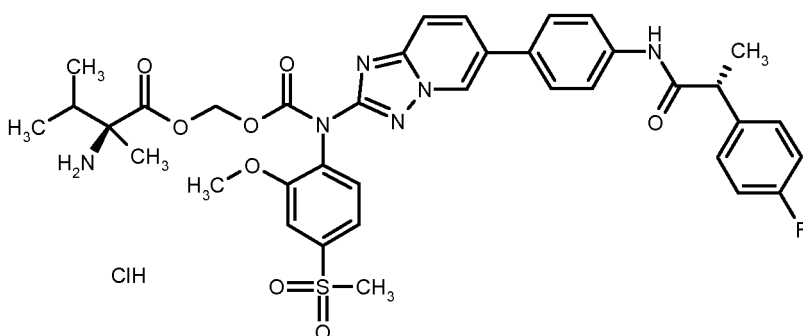
To a stirred solution of Intermediate Example IntP06.02 (33 mg) in dichloromethane (250 μL) was added a solution of hydrochloric acid in dioxane

(30 μ L; c = 4.0 M). The mixture was stirred at room temperature for 40 minutes. A solid precipitated. The solvent was removed by decantation. The solid residue was triturated with dichloromethane for two times, the solvent was removed each time and the solid was dried in vacuum to give 22 mg of the title compound.

$^1\text{H-NMR}$ (400 MHz, DMSO- d_6 , detected signals), δ [ppm] = 1.41 (3H), 3.31 (3H), 3.82-3.91 (4H), 5.52 (1H), 5.55 (1H), 7.11-7.19 (2H), 7.39-7.46 (2H), 7.52-7.64 (3H), 7.66-7.74 (4H), 7.78 (1H), 8.00 (1H), 9.20 (1H), 10.24 (1H).

10 Example 1.7

({[6-(4-[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)methyl 3-methyl-L-isovalinate hydrochloride

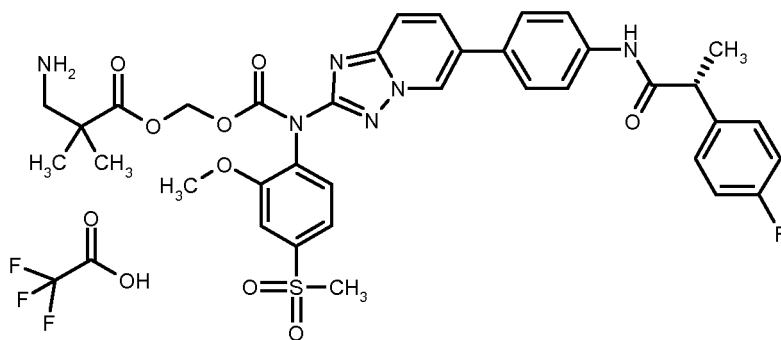


Starting with Intermediate Example IntP10.03, Example 1.7. was prepared analogously to the procedure for the preparation of Example 1.5.

$^1\text{H-NMR}$ (300 MHz, DMSO- d_6), δ [ppm] = 0.90 (6H), 1.35-1.51 (6H), 2.01-2.17 (1H), 3.32 (3H), 3.81-3.97 (4H), 5.83-5.97 (2H), 7.15 (2H), 7.44 (2H), 7.53-7.61 (2H), 7.65 (1H), 7.72 (4H), 7.79 (1H), 8.01 (1H), 8.59 (3H), 9.20 (1H), 10.38 (1H).

Example 1.8

({[6-(4-[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)methyl 3-amino-2,2-dimethylpropanoate trifluoroacetate

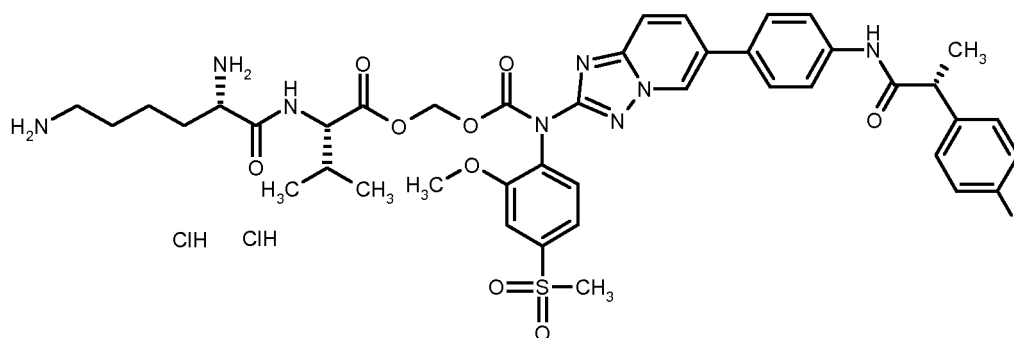


Starting with Intermediate Example IntP11.03, Example 1.8. was prepared analogously to the procedure for the preparation of Example 1.5. Final purification by preparative reverse phase HPLC (gradient of water and acetonitrile containing trifluoroacetic acid as additive) gave the title compound after lyophilisation.

$^1\text{H-NMR}$ (300 MHz, DMSO-d_6), δ [ppm] = 1.22 (6H), 1.41 (3H), 3.00 (2H), 3.32 (3H), 3.78-3.91 (4H), 5.80 (2H), 7.16 (2H), 7.42 (2H), 7.56 (2H), 7.62-7.92 (9H), 8.01 (1H), 9.20 (1H), 10.23 (1H).

Example 2.1

({[6-(4-[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)methyl L-lysyl-L-valinate dihydrochloride



To a stirred solution of **Intermediate Example IntP07.01** (57 mg) in dichloromethane (1.1 mL) and methanol (0.3 mL) was added a solution of hydrochloric acid in dioxane (0.36 mL; c = 4.0 M). The mixture was stirred at room temperature for 40 minutes. The solvent was removed in vacuum. The solid residue was triturated with dichloromethane for three times, the solvent was removed each time and the solid was dried in vacuum to give 27 mg of the title compound.

10 ¹H-NMR (300 MHz, DMSO-d₆, detected signals), δ [ppm] = 0.90 (6H), 1.41 (5H), 1.48-1.63 (2H), 1.73 (2H), 2.11 (1H), 2.72 (2H), 3.32 (3H), 3.84-3.95 (4H), 4.27 (1H), 5.72-5.79 (1H), 5.86 (1H), 7.15 (2H), 7.43 (2H), 7.56 (2H), 7.64 (1H), 7.72 (4H), 7.79 (1H), 7.91 (3H), 8.02 (1H), 8.27 (3H), 8.84 (1H), 9.20 (1H), 10.37 (1H).

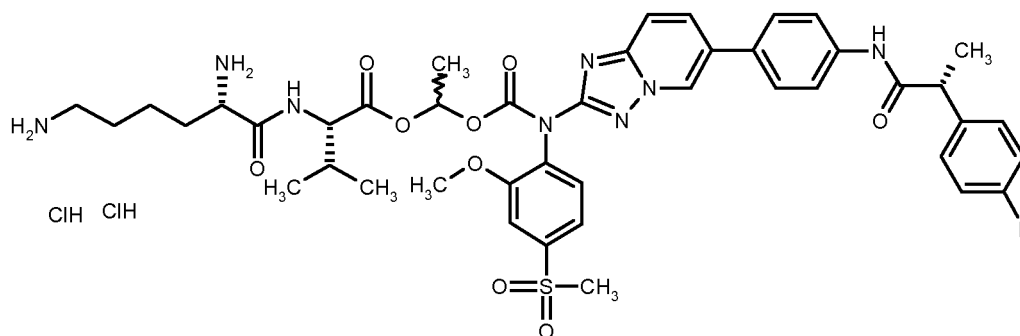
15

Example 2.2.

(1RS)-1-({[6-(4-{[(2R)-2-(4-

fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-

20 methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)ethyl L-lysyl-L-valinate
dihydrochloride (mixture of 2 epimers)



Starting with Intermediate Example IntP12.01, Example2.2. was prepared analogously to the procedure for the preparation of Example2.1.

- 5 ¹H-NMR (400 MHz, DMSO-d₆), δ [ppm] = 0.77-0.91 (6H), 1.32-1.47 (8H), 1.57 (2H), 1.67-1.79 (2H), 1.97-2.14 (1H), 2.73 (2H), 3.31 (3H), 3.88 (3H), 3.90-3.96 (2H), 4.18-4.27 (1H), 6.81 (1H), 7.09-7.19 (2H), 7.44 (2H), 7.49-7.59 (2H), 7.63 (1H), 7.72 (4H), 7.78 (1H), 7.88-8.05 (4H), 8.28 (3H), 8.80 (1H), 9.18 (1H), 10.38 (1H).

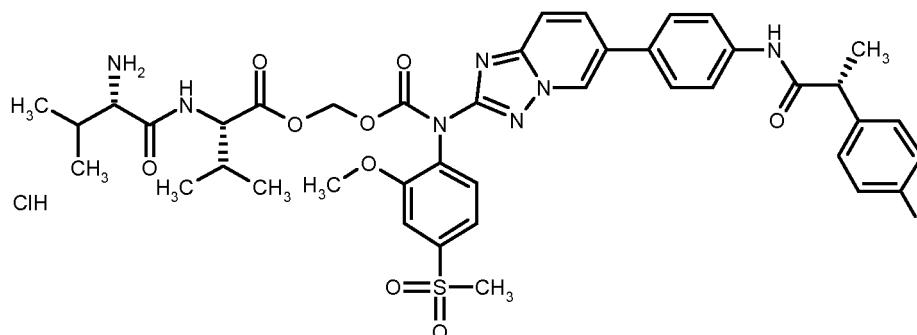
10

Example2.3.

({[6-(4-{[(2R)-2-(4-

fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5-α]pyridin-2-yl][2-

- 15 methoxy-4-(methylsulfonyl)phenyl]carbamoylethyl L-valyl-L-valinate hydrochloride



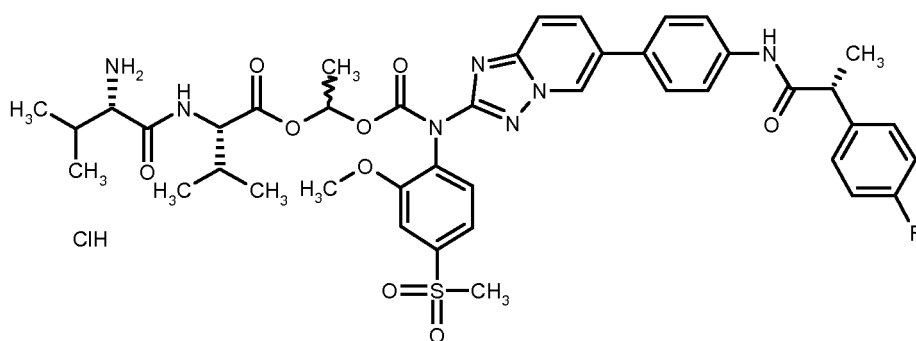
Starting with Intermediate Example IntP13.01, Example2.3. was prepared analogously to the procedure for the preparation of Example2.1.

¹H-NMR (400 MHz, DMSO-d₆), δ [ppm] = 0.85-0.98 (12H), 1.41 (3H), 2.02-2.16 (2H), 3.31 (3H), 3.70-3.75 (1H), 3.86 (3H), 3.89-3.93 (1H), 4.27 (1H), 5.76 (1H), 5.86 (1H), 7.15 (2H), 7.38-7.47 (2H), 7.55 (2H), 7.63 (1H), 7.72 (4H), 7.75-7.80 (1H), 8.00 (1H), 8.14 (3H), 8.66 (1H), 9.15-9.22 (1H), 10.32 (1H).

5

Example 2.4.

(1*RS*)-1-({[6-(4-{[(2*R*)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)ethyl L-valyl-L-valinate hydrochloride (mixture of 2 epimers)



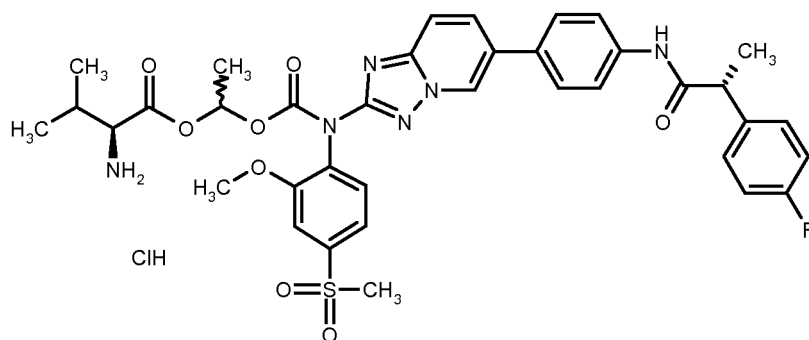
Starting with Intermediate Example IntP14.01, Example 2.4. was prepared analogously to the procedure for the preparation of Example 2.1.

¹H-NMR (400 MHz, DMSO-d₆), δ [ppm] = 0.78-0.98 (12H), 1.33-1.45 (6H), 2.06 (2H), 3.30 (3H), 3.68-3.78 (1H), 3.83-3.95 (4H), 4.15-4.26 (1H), 6.81 (1H), 7.10-7.20 (2H), 7.40-7.47 (2H), 7.49-7.57 (2H), 7.62 (1H), 7.68-7.74 (4H), 7.77 (1H), 8.00 (1H), 8.16 (3H), 8.65 (1H), 9.18 (1H), 10.37 (1H).

20

Example 3.1

(1*RS*)-1-({[6-(4-{[(2*R*)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)ethyl L-valinate hydrochloride (mixture of 2 epimers)

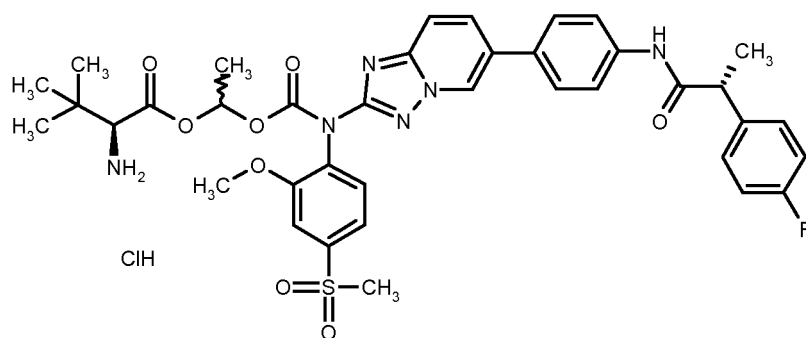


To a stirred solution of **Intermediate Example IntP08.03** (337 mg) in dichloromethane (4.0 mL) and methanol (0.4 mL) was added a solution of hydrochloric acid in dioxane (1.3 mL; c = 4.0 M). The mixture was stirred at
 5 room temperature for 20 minutes. The solvent was removed in vacuum. The solid residue was triturated with dichloromethane for three times, the solvent was removed each time and the solid was dried in vacuum to give 309 mg of the title compound.

¹H-NMR (300 MHz, DMSO-d₆), δ [ppm] = 0.77-1.01 (6H), 1.41 (3H), 1.43-1.51
 10 (3H), 2.03-2.24 (1H), 3.31 (3H), 3.84-4.03 (5H), 6.81-7.00 (1H), 7.10-7.20 (2H), 7.39-7.48 (2H), 7.55 (2H), 7.63 (1H), 7.68-7.82 (5H), 8.01 (1H), 8.54 (3H), 9.19 (1H), 10.42 (1H).

Example 3.2

15 **(1R)-1-({[6-(4-{{(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5-a]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)ethyl 3-methyl-L-valinate hydrochloride (mixture of 2 epimers)**

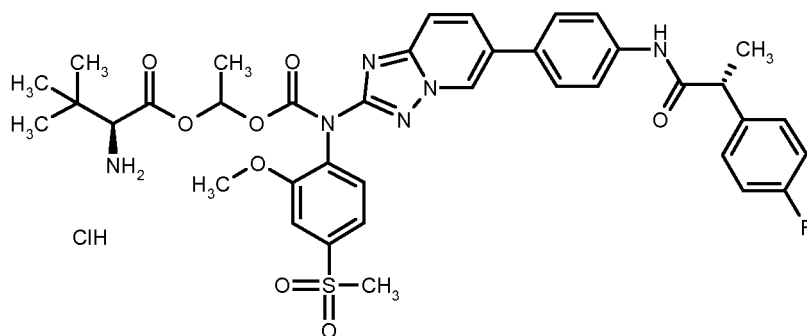


To a stirred solution of **Intermediate Example IntP09.02** (39 mg) in dichloromethane (0.45 mL) and methanol (0.045 mL) was added a solution of hydrochloric acid in dioxane (0.15 mL; c = 4.0 M). The mixture was stirred at room temperature for 3 h. The solvent was removed in vacuum. The solid residue was triturated with dichloromethane for three times, the solvent was removed each time and the solid was dried in vacuum to give 36 mg of the title compound.

¹H-NMR (400 MHz, DMSO-d₆), δ [ppm] = 0.86-1.01 (9H), 1.41 (3H), 1.45-1.51 (3H), 3.27-3.34 (3H), 3.74-3.93 (5H), 6.82-6.98 (1H), 7.15 (2H), 7.43 (2H), 7.52-7.58 (2H), 7.63 (1H), 7.72 (4H), 7.78 (1H), 8.01 (1H), 8.42 (3H), 9.18 (1H), 10.32 (1H).

Example 3.3.

(1R or 1S)-1-({[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5-α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbonyl}oxy)ethyl -3-methyl-L-valinate hydrochloride (single stereoisomer A)



Starting with **Intermediate Example IntP09.03** (2.99 g) **Example 3.3.** was prepared analogously to the procedure for the preparation of **Example 3.2.**

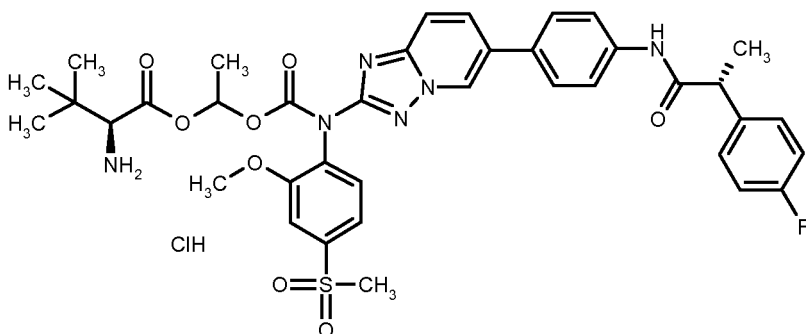
Yield: 2.76 g of the title compound.

¹H-NMR (400 MHz, DMSO-d₆), δ [ppm] = 0.91 (9H), 1.41 (3H), 1.48 (3H), 3.30 (3H), 3.76 (1H), 3.88 (3H), 3.93 (1H), 6.81-6.91 (1H), 7.11-7.19 (2H), 7.39-7.48

(2H), 7.55 (2H), 7.63 (1H), 7.68-7.81 (5H), 8.00 (1H), 8.49 (3H), 9.18 (1H), 10.41 (1H).

5 Example3.4.

(1S or 1R)-1-({[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)ethyl -3-methyl-L-valinate hydrochloride (single stereoisomer B)



10

Starting with Intermediate Example IntP09.04 (3.38 g) Example3.4. was prepared analogously to the procedure for the preparation of Example3.2.

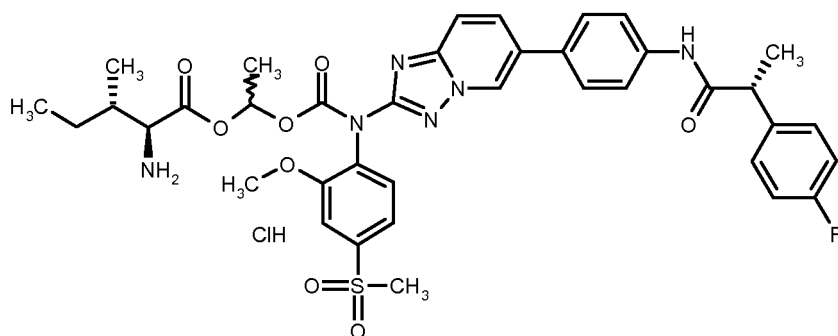
Yield: 3.13 g of the title compound.

¹H-NMR (400 MHz, DMSO-d₆), δ [ppm] = 0.96 (9H), 1.41 (3H), 1.48 (3H), 3.31 (3H), 3.80 (1H), 3.85-3.98 (4H), 6.87-6.96 (1H), 7.09-7.19 (2H), 7.40-7.48 (2H), 7.52-7.60 (2H), 7.63 (1H), 7.67-7.81 (5H), 8.00 (1H), 8.53 (3H), 9.14-9.23 (1H), 10.42 (1H).

15

20 Example3.5.

(1RS)-1-({[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)ethyl-L-isoleucinate hydrochloride (mixture of 2 epimers)



Starting with Intermediate Example IntP15.03 (100 mg) Example 3.5. was prepared analogously to the procedure for the preparation of Example 3.2.

Yield: 55 mg of the title compound.

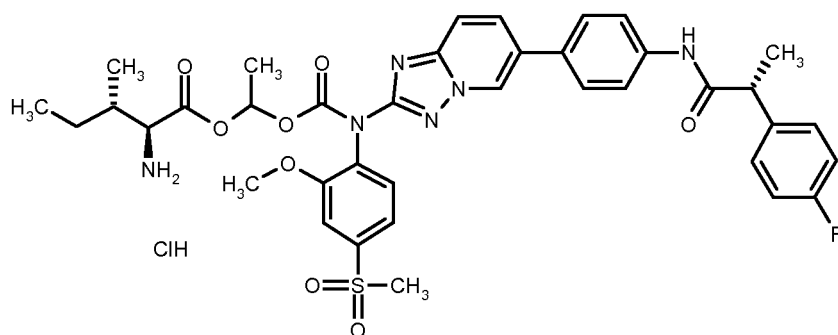
- 5 ¹H-NMR (400 MHz, DMSO-d₆), δ [ppm] = 0.79 (3H), 0.85-0.93 (3H), 1.08-1.31 (2H), 1.39-1.51 (6H), 1.77-1.94 (1H), 3.33 (3H), 3.85-3.96 (4H), 3.98-4.10 (1H), 6.85-7.00 (1H), 7.12-7.21 (2H), 7.40-7.49 (2H), 7.53-7.60 (2H), 7.65 (1H), 7.74 (4H), 7.77-7.83 (1H), 8.03 (1H), 8.39-8.59 (3H), 9.20 (1H), 10.37 (1H).

10

Example 3.6.

(1S or 1R)-1-({[6-(4-{{(2R)-2-(4-fluorophenyl)propanoyl}amino}phenyl)[1,2,4]triazolo[1,5-a]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)ethyl-L-isoleucinate

- 15 hydrochloride (single stereoisomer B)



Starting with Intermediate Example IntP15.04 (205 mg) Example 3.6. was prepared analogously to the procedure for the preparation of Example 3.2.

Yield: 145 mg of the title compound.

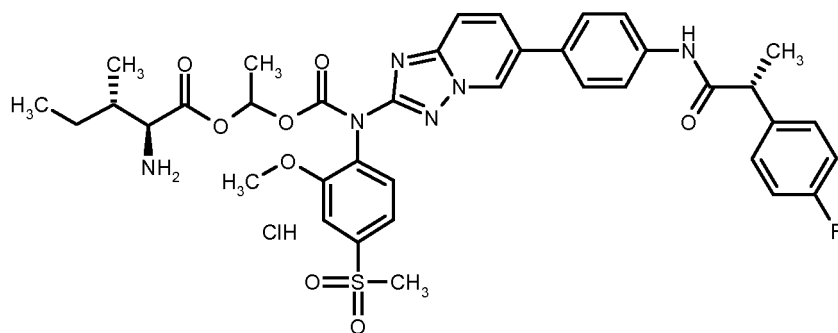
¹H-NMR (300 MHz, DMSO-d₆, detected signals), δ [ppm] = 0.77 (6H), 1.01-1.53 (8H), 1.83 (1H), 3.31 (3H), 3.86-3.94 (4H), 6.82-6.92 (1H), 7.10-7.21 (2H), 7.38-7.48 (2H), 7.51-7.59 (2H), 7.63 (1H), 7.68-7.82 (5H), 8.01 (1H), 8.50 (3H), 9.19 (1H), 10.39 (1H).

5

Example 3.7.

(1R or 1S)-1-({[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5-α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbonyl}oxy)ethyl-L-isoleucinate hydrochloride (single stereoisomer A)

10



Starting with Intermediate Example IntP15.05 (230 mg) Example 3.7. was prepared analogously to the procedure for the preparation of Example 3.2.

15

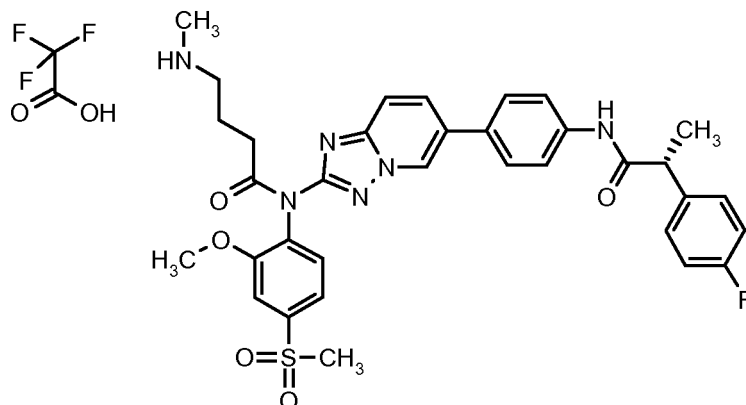
Yield: 155 mg of the title compound.

¹H-NMR (300 MHz, DMSO-d₆), δ [ppm] = 0.80-0.93 (6H), 1.17-1.50 (8H), 1.90 (1H), 3.32 (3H), 3.85-3.95 (4H), 4.05 (1H), 6.94 (1H), 7.15 (2H), 7.38-7.47 (2H), 7.56 (2H), 7.64 (1H), 7.72 (4H), 7.79 (1H), 8.01 (1H), 8.50 (3H), 9.19 (1H), 10.36 (1H).

20

Example 4.1

N-[6-(4-[[*(2R)*-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl]-N-[2-methoxy-4-(methylsulfonyl)phenyl]-4-(methylamino)butanamide trifluoroacetate



- 5 400 mg (0.715 mmol) of (*2R*)-2-(4-fluorophenyl)-N-[4-(2-[[2-methoxy-4-(methylsulfonyl)phenyl]amino][1,2,4]triazolo[1,5- α]pyridin-6-yl)phenyl]propanamide (see compound A1) and 4156 mg (8.58 mmol) 4-[[*(benzyloxy)*carbonyl](methyl) amino]butanoic anhydride were dissolved in 35 ml pyridine and 12 mg (0.071 mmol) DMAP were added. In 2 portions the
- 10 mixture was heated in the microwave to 85°C for 18 h. Both portions were unified and another 20 mg of DMAP were added and the mixture was stirred for additional 20 h at 90°C. The mixture was concentrated in vacuo and the remaining residue was dissolved in 300 ml dichloromethane. It was washed twice with 50 ml of 5% citric acid each, dried upon magnesium sulfate and
- 15 concentrated in vacuo. The remaining residue was washed twice with 100 ml diethyl ether and dried in vacuo. 50 ml trifluoro acetic acid were added and the mixture was treated in ultrasonic equipment for 18 h. Trifluoro acetic acid was removed in vacuo and the remaining residue was washed twice with 100 ml diethyl ether and subsequently purified by HPLC (Reprosil C18-10/ 250-30
- 20 (Flow 16ml/min; solvent A: water (0, 1% TFA); solvent B: acetonitrile). Relevant fractions were collected, 10 ml DMF were added and subsequently the solvents were removed in vacuo. The remaining residue was washed twice with 100 ml diethyl ether and dried in vacuo.

Yield: 273 mg (49%)

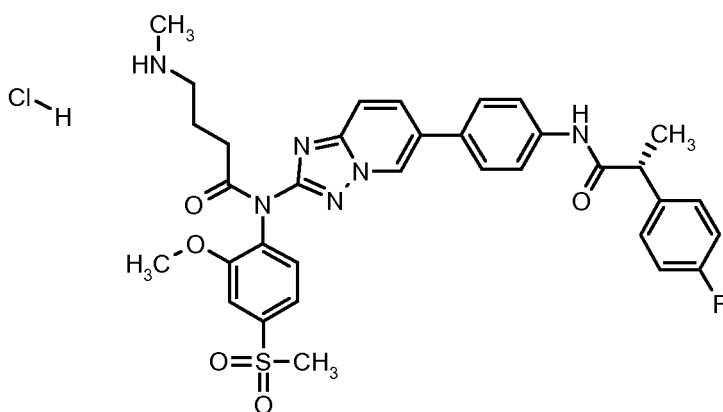
LC-MS (method 1): $R_t = 0.82$ min; $m/z = 659$ ($M+H$)⁺.

¹H-NMR (400 MHz, DMSO-d₆), δ [ppm] = 1.45 (3H), 1.95 (2H), 2.6 (3H), 2.95 (4H), 3.3 (3H), 3.85 (3H), 3.9 (1H), 7.15 (2H), 7.43 (2H), 7.58 (2H), 7.62 (1H), 7.72 (4H), 7.81 (1H), 8.02 (1H), 8.35 (2H), 9.2 (1H), 10.25 (1H).

5

Example 4.1.1

N-[6-(4-[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl]-N-[2-methoxy-4-(methylsulfonyl)phenyl]-4-(methylamino)butanamide hydrochloride



10

273 mg (0.353 mmol) of N-[6-(4-[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl]-N-[2-methoxy-4-(methylsulfonyl)phenyl]-4-(methylamino)butanamide trifluoroacetate were dissolved in 100 ml of a 0.1 M aqueous HCl solution and the solution was lyophilized. The procedure was repeated with another 100 ml of 0.1 M aqueous HCl solution. The remaining residue was solved in 100 ml of a mixture of acetonitrile and water and again lyophilized. 192 mg (78%) of the target compound were obtained as a white powder.

15

LC-MS (method 1): $R_t = 0.8$ min; $m/z = 659$ ($M+H$)⁺.

20

¹H-NMR (400 MHz, DMSO-d₆), δ [ppm] = 1.43 (3H), 1.95 (2H), 2.95 (4H), 3.3 (3H), 3.85 (3H), 3.9 (1H), 7.15 (2H), 7.43 (2H), 7.55 (2H), 7.62 (1H), 7.72 (4H), 7.81 (1H), 8.02 (1H), 8.5 (2H), 9.2 (1H), 10.3 (1H).

washed twice with 50 ml diethyl ether and dried in vacuo. After purification by HPLC (Chromatorex C18-10/ 125-40 (Flow 16ml/min; solvent A: water (0, 1% TFA); solvent B: acetonitrile) and drying in high vacuum 61 mg (10%) of the protected intermediate of the target compound was obtained.

5 LC-MS (method 1): $R_t = 1.31$ min; $m/z = 899$ ($M+H$)⁺.

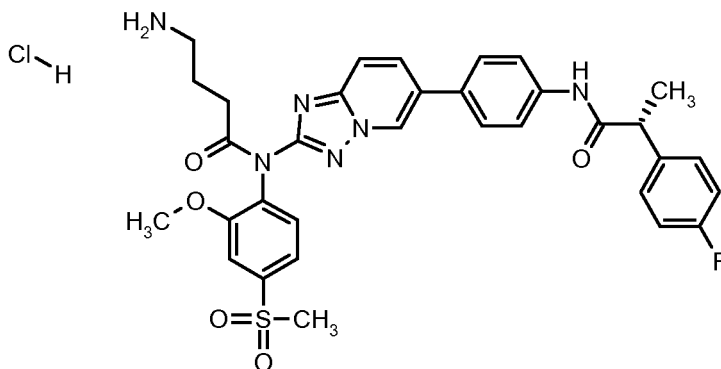
Step b) 4-amino-N-[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4] triazolo[1,5- α]pyridin-2-yl]-N-[2-methoxy-4-(methylsulfonyl)phenyl] butanamide trifluoroacetate :

10 35 mg (0.039 mmol) of the product obtained in step a) were dissolved in 7 ml trifluoro acetic acid and the mixture was treated in ultrasonic equipment for 6 h. Trifluoro acetic acid was removed in vacuo and the remaining residue purified by HPLC (Chromatorex C18-10/ 125-40 (Flow 16ml/min; solvent A: water (0.1% TFA); solvent B: acetonitrile). Relevant fractions were collected
15 and the solvents were removed in vacuo. The remaining residue was lyophilized from a 1:1 mixture of acetonitrile and water and 23 mg (77%) of a white powder were obtained.

LC-MS (method 1): $R_t = 0.81$ min; $m/z = 645$ ($M+H$)⁺.

20 Reference Example R4.2.1

4-amino-N-[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4] triazolo[1,5- α]pyridin-2-yl]-N-[2-methoxy-4-(methylsulfonyl)phenyl] butanamide hydrochloride



22 mg (0.024 mmol) of 4-amino-N-[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4] triazolo[1,5- α]pyridin-2-yl]-N-[2-methoxy-4-(methylsulfonyl)phenyl] butanamide trifluoroacetate were dissolved in 2 ml of a 0.1 M aqueous HCl solution and the solution was lyophilized. The procedure
 5 was repeated with another 2 ml of 0.1 M aqueous HCl solution. The remaining residue was dissolved in 5 ml of a mixture of acetonitrile and water and again lyophilized. 17 mg (99%) of the target compound were obtained as a white powder.

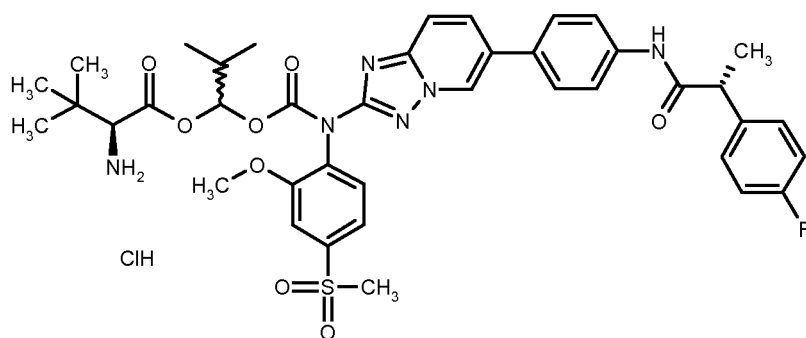
10 LC-MS (method 1): R_t = 0.81 min; m/z = 645 ($M+H$)⁺.

¹H-NMR (400 MHz, DMSO- d_6), δ [ppm] = 1.42 (3H), 1.92 (2H), 2.87 (2H), 2.95 (2H), 3.3 (3H), 3.85 (3H), 3.9 (1H), 7.15 (2H), 7.45 (2H), 7.58 (2H), 7.62 (1H), 7.72 (4H), 7.81 (4H), 8.02 (1H), 9.2 (1H), 10.25 (1H).

15

Example 5.1

(1R)-1-({[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)-2-methylpropyl 3-methyl-L-valinate hydrochloride (mixture of 2 epimers)
 20



To a stirred solution of Intermediate Example IntP19.03 (250 mg) in dichloromethane (2.80 mL) and methanol (0.28 mL) was added a solution of hydrochloric acid in dioxane (0.94 mL; c = 4.0 M). The mixture was stirred at
 25 room temperature for 30 minutes. The solvent was removed in vacuum. The

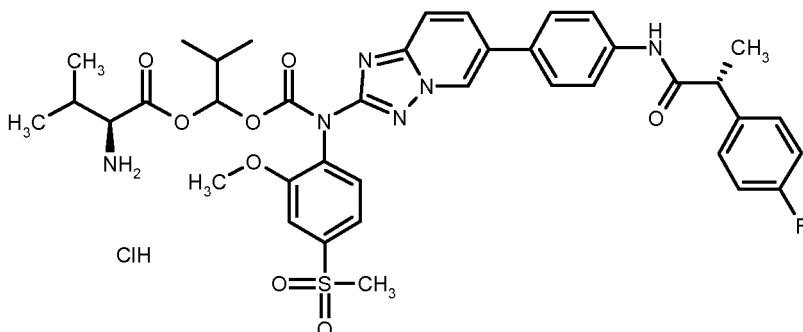
solid residue was triturated with dichloromethane for three times, the solvent was removed each time and the solid was dried in vacuum to give 230 mg of the title compound.

¹H-NMR (400 MHz, DMSO-d₆), δ [ppm] = 0.80-1.00 (15H), 1.41 (3H), 2.02 (1H),
 5 3.30 (3H), 3.74-3.98 (5H), 6.63-6.72 (1H), 7.15 (2H), 7.43 (2H), 7.55 (1H), 7.57 (1H), 7.64 (1H), 7.72 (4H), 7.78 (1H), 8.01 (1H), 8.49 (3H), 9.18 (1H), 10.38 (1H).

10 Example 5.2

(1R or S)-1-({[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5-α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbonyl}oxy)-2-methylpropyl-L-valinate hydrochloride (single stereoisomer A)

15



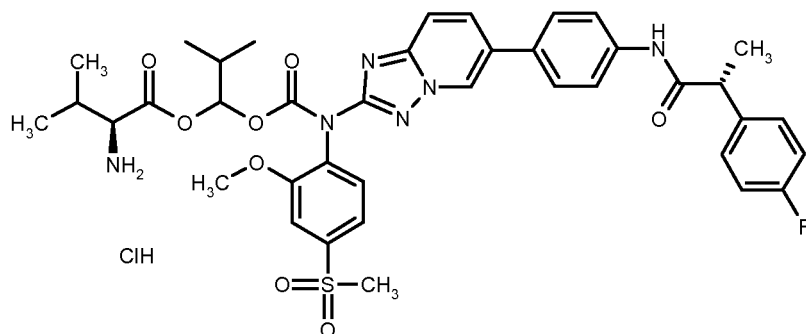
To a stirred solution of Intermediate Example IntP20.03 (100 mg) in dichloromethane (2.00 mL) and methanol (0.17 mL) was added a solution of hydrochloric acid in dioxane (0.38 mL; c = 4.0 M). The mixture was stirred at
 20 room temperature for 90 minutes. The solvent was removed in vacuum. The solid residue was triturated with dichloromethane for three times, the solvent was removed each time and the solid was dried in vacuum to give 90 mg of the title compound.

¹H-NMR (400 MHz, DMSO-d₆), δ [ppm] = 0.75-1.00 (12H), 1.41 (3H), 1.99 (1H),
 25 2.13 (1H), 3.30 (3H), 3.84-3.94 (4H), 4.01 (1H), 6.66 (1H), 7.15 (2H), 7.43 (2H),

7.55 (2H), 7.64 (1H), 7.72 (4H), 7.77 (1H), 8.00 (1H), 8.48 (3H), 9.18 (1H), 10.36 (1H).

Example 5.3

- 5 (1S or R)-1-({[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbonyl}oxy)-2-methylpropyl-L-valinate hydrochloride (single stereoisomer B)



10

To a stirred solution of **Intermediate Example IntP20.04**. (100 mg) in dichloromethane (2.00 mL) and methanol (0.17 mL) was added a solution of hydrochloric acid in dioxane (0.38 mL; c = 4.0 M). The mixture was stirred at room temperature for 90 minutes. The solvent was removed in vacuum. The solid residue was triturated with dichloromethane for three times, the solvent was removed each time and the solid was dried in vacuum to give 93 mg of the title compound.

15

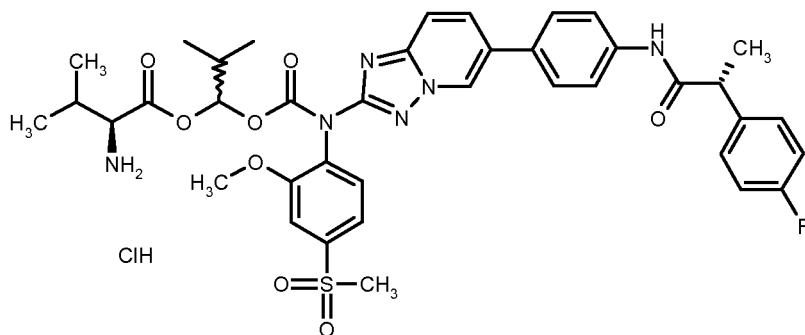
¹H-NMR (400 MHz, DMSO-d₆), δ [ppm] = 0.75-1.00 (12H), 1.41 (3H), 1.99 (1H), 2.22 (1H), 3.31 (3H), 3.84-3.94 (4H), 4.05 (1H), 6.71 (1H), 7.15 (2H), 7.43 (2H), 7.58 (2H), 7.65 (1H), 7.72 (4H), 7.77 (1H), 8.00 (1H), 8.50 (3H), 9.18 (1H), 10.37 (1H).

20

Example 5.4

(1RS)-1-({[6-(4-[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)-2-methylpropyl-L-valinate hydrochloride (mixture of 2 epimers)

5



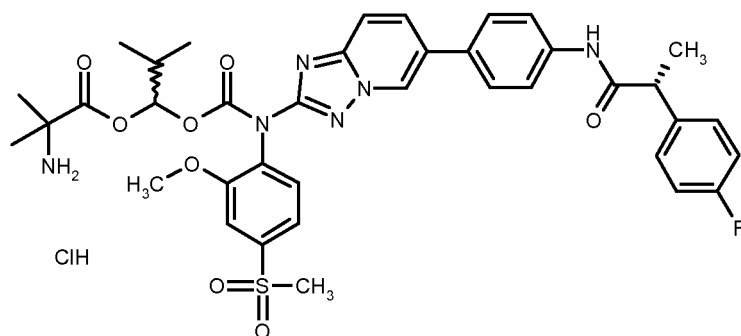
To a stirred solution of **Intermediate Example IntP20.02** (25 mg) in dichloromethane (0.28 mL) and methanol (0.03 mL) was added a solution of hydrochloric acid in dioxane (0.10 mL; c = 4.0 M). The mixture was stirred at room temperature for 30 minutes. The solvent was removed in vacuum. The solid residue was triturated with dichloromethane for three times, the solvent was removed each time and the solid was dried in vacuum to give 22 mg of the title compound.

¹H-NMR (400 MHz, DMSO-d₆), δ [ppm] = 0.75-1.00 (12H), 1.41 (3H), 1.99 (1H), 2.06-2.25 (1H), 3.30 (3H), 3.84-3.94 (4H), 3.99-4.07 (1H), 6.65-6.73 (1H), 7.15 (2H), 7.42 (2H), 7.55 (1H), 7.57 (1H), 7.64 (1H), 7.71 (4H), 7.77 (1H), 8.01 (1H), 8.40 (3H), 9.17 (1H), 10.28 (1H).

20 Example 5.5

(1RS)-1-({[6-(4-[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)-2-methylpropyl-2-methylalaninate hydrochloride (mixture of 2 epimers)

25

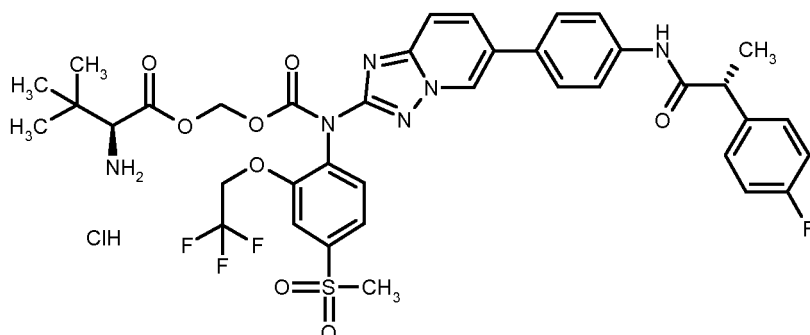


To a stirred solution of **Intermediate Example IntP21.03** (30 mg) in dichloromethane (1.00 mL) and methanol (0.05 mL) was added a solution of hydrochloric acid in dioxane (0.13 mL; c = 4.0 M). The mixture was stirred at room temperature for 2 hours. The solvent was removed in vacuum. The solid residue was triturated with dichloromethane for three times, the solvent was removed each time and the solid was dried in vacuum to give 14 mg of the title compound.

¹H-NMR (400 MHz, DMSO-d₆), δ [ppm] = 0.82 (6H), 1.40 (3H), 1.49 (6H), 1.95 (1H), 3.31 (3H), 3.82-3.96 (4H), 6.60 (1H), 7.15 (2H), 7.43 (2H), 7.57 (2H), 7.65 (1H), 7.72 (4H), 7.77 (1H), 8.00 (1H), 8.70 (3H), 9.18 (1H), 10.38 (1H).

15 **Example6.1.**

({[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][4-(methylsulfonyl)-2-(2,2,2-trifluoroethoxy)phenyl]carbamoyl}oxy)methyl 3-methyl-L-valinate hydrochloride



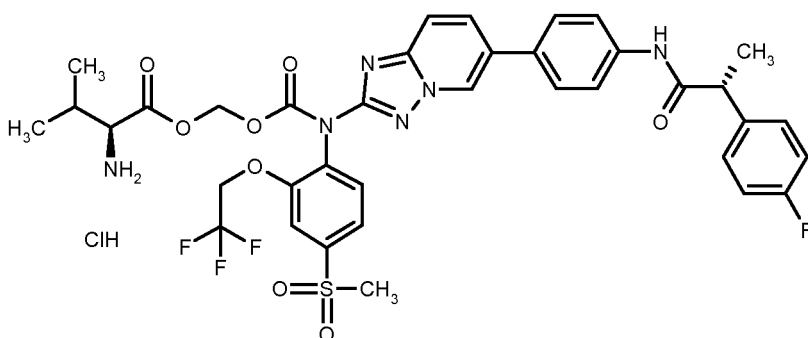
Starting with Intermediate Example IntP16.03. (80 mg) Example6.1. was prepared analogously to the procedure for the preparation of Example1.5.

Yield: 25 mg of the title compound.

¹H-NMR (400 MHz, DMSO-d₆), δ [ppm] = 0.97 (9H), 1.41 (3H), 3.83-3.94 (2H),
 5 4.92 (2H), 5.87 (1H), 5.96 (1H), 7.10-7.19 (2H), 7.39-7.46 (2H), 7.64-7.83 (8H),
 8.01 (1H), 8.41 (3H), 9.18 (1H), 10.29 (1H).

10 Example6.2.

(([6-(4-[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5-α]pyridin-2-yl][4-(methylsulfonyl)-2-(2,2,2-trifluoroethoxy)phenyl]carbamoyl}oxy)methyl L-valinate hydrochloride



15

Starting with Intermediate Example IntP17.02. (140 mg) Example6.2. was prepared analogously to the procedure for the preparation of Example1.5.

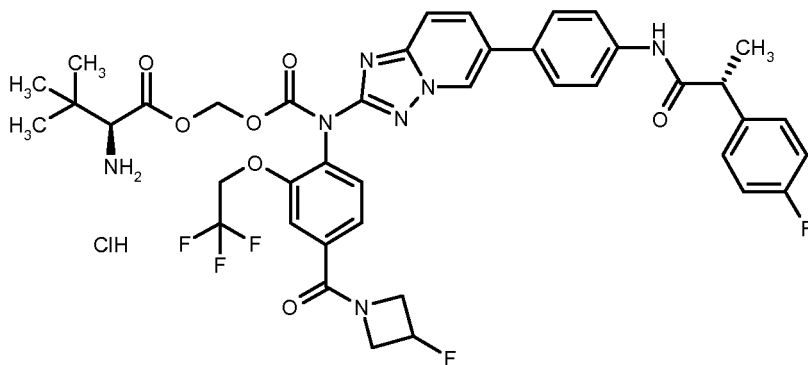
Yield: 50 mg of the title compound.

¹H-NMR (400 MHz, DMSO-d₆), δ [ppm] = 0.93 (6H), 1.41 (3H), 2.18 (1H), 3.32
 20 (3H), 3.91 (1H), 3.98-4.05 (1H), 4.93 (2H), 5.86 (1H), 5.96 (1H), 7.10-7.20 (2H),
 7.39-7.47 (2H), 7.66-7.68 (2H), 7.70-7.74 (4H), 7.77 (1H), 7.81 (1H), 8.01 (1H),
 8.52 (3H), 9.19 (1H), 10.36 (1H).

25

Example 6.3.

[(4-[(3-fluoroazetidin-1-yl)carbonyl]-2-(2,2,2-trifluoroethoxy)phenyl)[6-(4-[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl]carbamoyl]oxy]methyl 3-methyl-L-valinate hydrochloride



5

Starting with Intermediate Example IntP18.03 (160 mg) Example 6.3. was prepared analogously to the procedure for the preparation of Example 1.5.

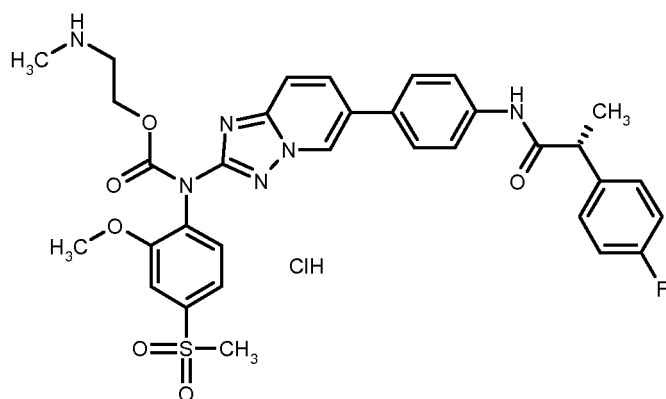
Yield: 130 mg of the title compound.

- 10 $^1\text{H-NMR}$ (300 MHz, DMSO- d_6), δ [ppm] = 0.92-1.03 (9H), 1.37-1.44 (3H), 3.81-3.96 (2H), 3.97-4.24 (1H), 4.25-4.70 (3H), 4.83 (2H), 5.28-5.62 (1H), 5.85 (1H), 5.95 (1H), 7.08-7.22 (2H), 7.33-7.51 (5H), 7.67-7.82 (5H), 8.01 (1H), 8.47 (3H), 9.18 (1H), 10.38 (1H).

15

Example 7.1.

2-(methylanino)ethyl [6-(4-[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamate hydrochloride



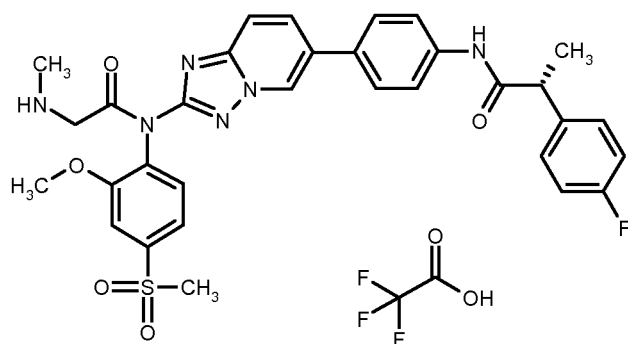
Starting with Intermediate Example IntP22.04. (25 mg) Example7.1. was prepared analogously to the procedure for the preparation of Example1.5.

Yield: 25 mg of the title compound.

- 5 $^1\text{H-NMR}$ (300 MHz, DMSO- d_6 , detected signals), δ [ppm] = 1.41 (3H), 3.13-3.26 (2H), 3.32 (3H), 3.86 (3H), 3.89-3.98 (1H), 4.46 (2H), 7.15 (2H), 7.44 (2H), 7.53-7.67 (3H), 7.68-7.83 (5H), 8.01 (1H), 8.99 (2H), 9.19 (1H), 10.44 (1H).

Example8.1.

- 10 **(2R)-2-(4-fluorophenyl)-N-[4-(2-{[2-methoxy-4-(methylsulfonyl)phenyl](N-methylglycyl)amino}[1,2,4]triazolo[1,5- α]pyridin-6-yl)phenyl]propanamide trifluoroacetate**



- 15 To a stirred solution of Intermediate Example IntP23.03 (500 mg) in dichloromethane (20 mL) was added trifluoroacetic acid (2.6 mL). The mixture was stirred at room temperature for 2 h. The solvent was removed in vacuum. Silicagel chromatography followed by preparative reverse phase HPLC (gradient of water and acetonitrile containing trifluoroacetic acid as additive) gave 110 mg of the title compound after lyophilisation.

¹H-NMR (300 MHz, DMSO-d₆), δ [ppm] = 1.41 (3H), 2.64 (3H), 3.35 (3H), 3.79-3.91 (4H), 4.64 (2H), 7.11-7.20 (2H), 7.42 (3H), 7.61-7.76 (7H), 7.85 (1H), 8.07 (1H), 8.93 (2H), 9.22 (1H), 10.24 (1H).

5

Solubility

The solubility of compound A1 at 25°C in different solvents is shown in Table 1:

Table 1: *Solubility of compound A1 at 25°C*

solvent	dissolved amount in mg / 100 mL solution
water	< 0.1
aqueous solution, phopshate buffer pH 8	< 0.1
aqueous solution, phopshate buffer pH 7	< 0.1
aqueous solution, acetate buffer pH 4.5	< 0.1
0.1 M HCl in water	< 0.1
ethanol	45.7
acetonitrile	350.2
acetone	1518.3

10

Biological assay: Proliferation Assay

Cultivated tumor cells (MCF7, hormone dependent human mammary carcinoma cells, ATCC HTB22; NCI-H460, human non-small cell lung carcinoma cells, ATCC
 15 HTB-177; DU 145, hormone-independent human prostate carcinoma cells, ATCC HTB-81; HeLa-MaTu, human cervical carcinoma cells, EPO-GmbH, Berlin; HeLa-MaTu-ADR, multidrug-resistant human cervical carcinoma cells, EPO-GmbH,

Berlin; HeLa human cervical tumor cells, ATCC CCL-2; B16F10 mouse melanoma cells, ATCC CRL-6475) were plated at a density of 5000 cells/well (MCF7, DU145, HeLa-MaTu-ADR), 3000 cells/well (NCI-H460, HeLa-MaTu, HeLa), or 1000 cells/well (B16F10) in a 96-well multititer plate in 200 μ l of their
5 respective growth medium supplemented 10% fetal calf serum. After 24 hours, the cells of one plate (zero-point plate) were stained with crystal violet (see below), while the medium of the other plates was replaced by fresh culture medium (200 μ l), to which the test substances were added in various concentrations (0 μ M, as well as in the range of 0.01-30 μ M; the final
10 concentration of the solvent dimethyl sulfoxide was 0.5%). The cells were incubated for 4 days in the presence of test substances. Cell proliferation was determined by staining the cells with crystal violet: the cells were fixed by adding 20 μ l/measuring point of an 11% glutaric aldehyde solution for 15 minutes at room temperature. After three washing cycles of the fixed cells
15 with water, the plates were dried at room temperature. The cells were stained by adding 100 μ l/measuring point of a 0.1% crystal violet solution (pH 3.0). After three washing cycles of the stained cells with water, the plates were dried at room temperature. The dye was dissolved by adding 100 μ l/measuring point of a 10% acetic acid solution. The extinction was determined by
20 photometry at a wavelength of 595 nm. The change of cell number, in percent, was calculated by normalization of the measured values to the extinction values of the zero-point plate (=0%) and the extinction of the untreated (0 μ M) cells (=100%). The IC₅₀ values were determined by means of a 4 parameter fit. The compounds A1, A2, A3, A4 and A5 are characterized by an IC₅₀ determined
25 in a HeLa-MaTu-ADR cell proliferation assay (as described above) that is lower than 10 μ M. The IC₅₀ of preferred compounds is even lower than 2.0 μ M. The IC₅₀ of more preferred compounds is even lower than 500 nM. The IC₅₀ of even more preferred compounds is even lower than 250 nM. The IC₅₀ of most preferred compounds is even lower than 200 nM.

The compounds A1, A2, A3, A4 and A5 are characterized by the following IC₅₀ values, determined in a HeLa cell proliferation assay (as described above):

Compound	Inhibition of cell proliferation, cell Line: HeLa IC ₅₀
A1	< 400 nM
A2	< 200 nM
A3	< 100 nM
A4	< 100 nM
A5	< 100 nM

5

Mps-1 kinase assay

The human kinase Mps-1 phosphorylates a biotinylated substrate peptide. Detection of the phosphorylated product is achieved by time-resolved fluorescence resonance energy transfer (TR-FRET) from Europium-labelled anti-phospho-Serine/Threonine antibody as donor to streptavidin labelled with cross-linked allophycocyanin (SA-XLent) as acceptor. Compounds are tested for their inhibition of the kinase activity.

N-terminally GST-tagged human full length recombinant Mps-1 kinase (purchased from Invitrogen, Karlsruhe, Germany, cat. no PV4071) was used. As substrate for the kinase reaction a biotinylated peptide of the amino-acid sequence PWDPDDADITEILG (C-terminus in amide form, purchased from Biosynthan GmbH, Berlin) was used.

For the assay 50 nl of a 100-fold concentrated solution of the test compound in DMSO was pipetted into a black low volume 384well microtiter plate (Greiner Bio-One, Frickenhausen, Germany), 2 µl of a solution of Mps-1 in assay buffer [0.1 mM sodium-ortho-vanadate, 10 mM MgCl₂, 2 mM DTT, 25 mM Hepes pH 7.7, 0.05% BSA, 0.001% Pluronic F-127] were added and the mixture was incubated for 15 min at 22°C to allow pre-binding of the test compounds to Mps-1 before the start of the kinase reaction. Then the kinase reaction was started by the addition of 3 µl of a solution of 16.7 adenosine-tri-phosphate (ATP, 16.7 µM => final conc. in the 5 µl assay volume is 10 µM) and peptide substrate (1.67 µM => final conc. in the 5 µl assay volume is 1 µM) in assay buffer and the resulting mixture was incubated for a reaction time of 60 min at 22°C. The concentration of Mps-1 in the assay was adjusted to the activity of the enzyme lot and was chosen appropriate to have the assay in the linear range, typical enzyme concentrations were in the range of about 1 nM (final conc. in the 5 µl assay volume). The reaction was stopped by the addition of 3 µl of a solution of HTRF detection reagents (100 mM Hepes pH 7.4, 0.1% BSA, 40 mM EDTA, 140 nM Streptavidin-XLent [# 61GSTXLB, Fa. Cis Biointernational, Marcoule, France], 1.5 nM anti-phospho(Ser/Thr)-Europium-antibody [#AD0180, PerkinElmer LAS, Rodgau-Jügesheim, Germany].

20

The resulting mixture was incubated 1 h at 22°C to allow the binding of the phosphorylated peptide to the anti-phospho(Ser/Thr)-Europium-antibody. Subsequently the amount of phosphorylated substrate was evaluated by measurement of the resonance energy transfer from the Europium-labelled anti-phospho(Ser/Thr) antibody to the Streptavidin-XLent. Therefore, the fluorescence emissions at 620 nm and 665 nm after excitation at 350 nm was measured in a Viewlux TR-FRET reader (PerkinElmer LAS, Rodgau-Jügesheim, Germany). The “blank-corrected normalized ratio” (a Viewlux specific readout, similar to the traditional ratio of the emissions at 665 nm and at 622 nm, in which blank and Eu-donor crosstalk are subtracted from the 665 nm

30

signal before the ratio is calculated) was taken as the measure for the amount of phosphorylated substrate. The data were normalised (enzyme reaction without inhibitor = 0 % inhibition, all other assay components but no enzyme = 100 % inhibition). Test compounds were tested on the same microtiter plate at 10 different concentrations in the range of 20 μ M to 1 nM (20 μ M, 6.7 μ M, 2.2 μ M, 0.74 μ M, 0.25 μ M, 82 nM, 27 nM, 9.2 nM, 3.1 nM and 1 nM, dilution series prepared before the assay at the level of the 100fold conc. stock solutions by serial 1:3 dilutions) in duplicate values for each concentration and IC_{50} values were calculated by a 4 parameter fit.

10

The compounds A1, A2, A3, A4 and A5 are characterized by the following IC_{50} values, determined in Mps-1 kinase assays (as described above):

Compound	Mps-1 Inhibition, IC_{50} in M (Assay with 10 μ M ATP)	Mps-1 Inhibition, IC_{50} in M (Assay with 2 mM ATP)
A1	< 1 nM	1.9 nM
A2	< 1 nM	< 1 nM
A3	< 1 nM	< 1 nM
A4	< 1 nM	< 1 nM
A5	< 1 nM	< 1 nM

15

Spindle Assembly Checkpoint Assay

The spindle assembly checkpoint assures the proper segregation of chromosomes during mitosis. Upon entry into mitosis, chromosomes begin to condensate which is accompanied by the phosphorylation of histone H3 on

serine 10. Dephosphorylation of histone H3 on serine 10 begins in anaphase and ends at early telophase. Accordingly, phosphorylation of histone H3 on serine 10 can be utilized as a marker of cells in mitosis. Nocodazole is a microtubule destabilizing substance. Thus, nocodazole interferes with microtubule dynamics and mobilises the spindle assembly checkpoint. The cells arrest in mitosis at G2/M transition and exhibit phosphorylated histone H3 on serine 10. An inhibition of the spindle assembly checkpoint by Mps-1 inhibitors overrides the mitotic blockage in the presence of nocodazole, and the cells complete mitosis prematurely. This alteration is detected by the decrease of cells with phosphorylation of histone H3 on serine 10. This decline is used as a marker to determine the capability of compounds of the present invention to induce a mitotic breakthrough.

Cultivated cells of the human cervical tumor cell line HeLa (ATCC CCL-2) were plated at a density of 2500 cells/well in a 384-well microtiter plate in 20 μ l Dulbecco's Medium (w/o phenol red, w/o sodium pyruvate, w 1000 mg/ml glucose, w pyridoxine) supplemented with 1% (v/v) glutamine, 1% (v/v) penicillin, 1% (v/v) streptomycin and 10% (v/v) fetal calf serum. After incubation overnight at 37°C, 10 μ l/well nocodazole at a final concentration of 0.1 μ g/ml were added to cells. After 24 h incubation, cells were arrested at G2/M phase of the cell cycle progression. Test compounds solubilised in dimethyl sulfoxide (DMSO) were added at various concentrations (0 μ M, as well as in the range of 0.005 μ M - 10 μ M; the final concentration of the solvent DMSO was 0.5% (v/v)). Cells were incubated for 4 h at 37°C in the presence of test compounds. Thereafter, cells were fixed in 4% (v/v) paraformaldehyde in phosphate buffered saline (PBS) at 4°C overnight then permeabilised in 0.1% (v/v) Triton XTM 100 in PBS at room temperature for 20 min and blocked in 0.5% (v/v) bovine serum albumin (BSA) in PBS at room temperature for 15 min. After washing with PBS, 20 μ l/well antibody solution (anti-phospho-histone H3 clone 3H10, FITC; Upstate, Cat# 16-222; 1:200 dilution) was added to cells, which

were incubated for 2 h at room temperature. Afterwards, cells were washed with PBS and 20 µl/well HOECHST 33342 dye solution (5 µg/ml) was added to cells and cells were incubated 12 min at room temperature in the dark. Cells were washed twice with PBS then covered with PBS and stored at 4°C until
5 analysis. Images were acquired with a Perkin Elmer OPERA™ High-Content Analysis reader. Images were analyzed with image analysis software MetaXpress™ from Molecular devices utilizing the Cell Cycle application module. In this assay both labels HOECHST 33342 and phosphorylated Histone H3 on serine 10 were measured. HOECHST 33342 labels DNA and is used to
10 count cell number. The staining of phosphorylated Histone H3 on serine 10 determines the number of mitotic cells. Inhibition of Mps-1 decreases the number of mitotic cells in the presence of nocodazole indicating an inappropriate mitotic progression. The raw assay data were further analysed by four parameter logistic regression analysis to determine the IC₅₀ value for each
15 tested compound.

Stability in buffer at pH 7.4

0.3 mg of the test compound are solved in 0.1 ml dimethylsulfoxide and 0.4 ml
20 acetonitrile. For complete dissolution the HPLC vial with the sample solution is sonified for about 20 seconds. Then 1.0 ml of the buffer solution is added, and the sample is again treated in the ultrasonic bath.

Preparation of the buffer solution:

90 g of sodium chloride, 13.61 g of potassium dihydrogen phosphate and 83.35
25 g of 1 M sodium hydroxide solution are made up to 1 litre with Millipore water and then diluted 1:10.

10 µl portions of the sample solution are analysed by HPLC to determine the amount of the test compound over a period of 24 hours at 37°C. The peak areas in percentage are used for quantification.

30 HPLC method:

Agilent 1100 with DAD (G1315B), binary pump (G1312A), autosampler (G1329A), column oven (G1316A), thermostat (G1330B); column: Kromasil 100 C18, 250 mm x 4 mm, 5 µm; column temperature: 37°C; eluent A: water + 5 ml of perchloric acid/litre, eluent B: acetonitrile.

5 *Gradient:*

0 min 98% A, 2% B → 0-3.0 min 85% A, 15% B → 3.0-8.0 min 50% A, 50% B → 8.0-16.0 min 50% A, 50% B → 16.0-20.0 min 10% A, 90% B → 20.0-21.0 min 10% A, 90% B → 21.0-24.0 min 98% A, 2% B → 24.0-25.0 min 98% A, 2% B; flow rate: 1.5 ml/min; UV detection: 210 nm.

10

The ratio of the peak areas (F) at different time points in relation to the peak areas at the starting time are shown in Table 2 for representative examples:

Table 2: Stability in buffer at pH 7.4

15

Example No.	% Test Compound after 24 h [F(t=24h)x100/F(t=0h)]
1.1.	35.0 *)
1.2	0.0
1.4	0.0
1.5	0.0
1.7	0.0
1.8	0.0
2.1	0.0
2.2	0.0
2.3	16
2.4	48
3.1	0.0
3.2	0.0

3.3	0.0
3.4	0.0
3.6	0.0
3.7	0.0
4.1	23
4.1.1	21
5.1	21
5.2	48
5.3	11
5.4	17
6.1.	0.0
6.3.	0.0
7.1	48

*) measured for formic acid salt

***In vitro* stability in rat and human plasma (HPLC detection)**

- 5 1 mg of test compound is dissolved in 1.25 ml dimethylsulfoxide. Then 1.25 ml water are added. 0.5 ml of this sample solution are mixed with 0.5 ml heparinized and 37°C warm plasma (wistar rat plasma or human plasma). A first sample (10 µl) is immediately taken for HPLC analysis. In the period up to 4 h after the start of incubation further 10 µl aliquots are taken after 30, 60, 10 90, 120 and 240 minutes and the amount of the test compound is determined.

HPLC method:

- Agilent 1100 with DAD (G1315A), binary pump (G1312A), autosampler (G1329A), column oven (G1316A), thermostat (G1330B); column: Kromasil 100 C18, 250 mm x 4 mm, 5 µm; column temperature: 45°C; eluent A: water + 5 15 ml of perchloric acid/litre, eluent B: acetonitrile.

Gradient:

0 min 98% A, 2% B → 0-3.0 min 85% A, 15% B → 3.0-8.0 min 55% A, 45% B → 8.0-16.0 min 55% A, 45% B → 16.0-20.0 min 10% A, 90% B → 20.0-21.0 min 10% A, 90% B → 21.0-24.0 min 98% A, 2% B → 24.0-25.0 min 98% A, 2% B; flow rate: 1.5 ml/min; UV detection: 222 nm.

- 5 The ratio of the peak areas (F) at the respective time points in relation to the peak areas at the starting time indicates the remaining parent compound, hence indicating stability under the experimental conditions described.

Table 3: In vitro stability in rat plasma

10

Example No.	% Test Compound after 4 h [F(t=24h)x100/F(t=0h)]
1.2	0.0
1.3	0.0
1.4	14
1.5	0.0
1.6	0.0
1.7	36
1.8	3
2.1	0.0
2.2	5
2.3	37
2.4	45
3.1	0.0
3.2	0.0
3.3	22
3.4	29
3.5	19
4.1	12

Example No.	% Test Compound after 4 h [F(t=24h)x100/F(t=0h)]
4.1.1	32
5.1	19
5.2	44
5.3	45
5.4	44
5.5	33
6.1.	4
6.2.	6
6.3.	0.0
7.1	80
8.1	57

Determination of metabolic stability *in vitro*

(including calculation of hepatic *in vivo* blood clearance (CL) and of maximal oral bioavailability ($F_{\max}$))

The metabolic stability of test compounds *in vitro* was determined by incubating them at 1 μ M with a suspension liver microsomes in 100 mM phosphate buffer, pH7.4 ($\text{NaH}_2\text{PO}_4 \times \text{H}_2\text{O} + \text{Na}_2\text{HPO}_4 \times 2\text{H}_2\text{O}$) at a protein concentration of 0.5 mg/mL and at 37° C. The reaction was activated by adding a co-factor mix containing 1.2 mg NADP, 3 IU glucose-6-phosphate dehydrogenase, 14.6 mg glucose-6-phosphate and 4.9 mg MgCl_2 in phosphate buffer, pH 7.4. Organic solvent in the incubations was limited to <0.2 % dimethylsulfoxide (DMSO) and <1% methanol. During incubation, the microsomal suspensions were continuously shaken and aliquots were taken at 2, 8, 16, 30, 45 and 60 min, to which equal volumes of cold methanol were

immediately added. Samples were frozen at -20° C over night, subsequently centrifuged for 15 minutes at 3000 rpm and the supernatant was analyzed with an Agilent 1200 HPLC-system with LCMS/MS detection.

5 The half-life of a test compound was determined from the concentration-time plot. From the half-life the intrinsic clearances were calculated. Together with the additional parameters liver blood flow, specific liver weight and microsomal protein content the hepatic *in vivo* blood clearance (CL) and the maximal oral bioavailability ($F_{\max}$) were calculated for the different species. The following parameter values were used: Liver blood flow - 1.3 L/h/kg
10 (human), 2.1 L/h/kg (dog), 4.2 L/h/kg (rat); specific liver weight - 21 g/kg (human), 39 g/kg (dog), 32 g/kg (rat); microsomal protein content - 40 mg/g.

With the described assay only phase-I metabolism of microsomes is reflected, e.g. typically oxidoreductive reactions by cytochrome P450 enzymes and flavin mono-oxygenases (FMO) and hydrolytic reactions by esterases (esters and
15 amides).

The compounds A1, A2, A3 and A4 are characterized by the values of maximum oral bioavailability ($F_{\max}$) in rat, dog and humans (determined by means of liver microsomes as described above) shown in the table below:

20

Compound	Rat liver microsomes; Fmax [%]	Human liver microsomes; Fmax [%]	Dog liver microsomes; Fmax [%]
A1	92	92	64
A2	93	> 95	55
A3	83	> 95	86
A4	74	62	75
A5	89	69	57

Surprisingly it was found, that compounds A1, A2, A3, A4 and A5 show superior properties over compounds of the state of the art.

5

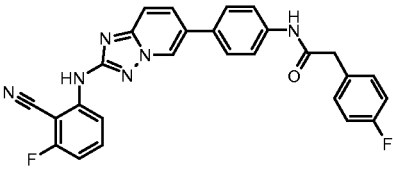
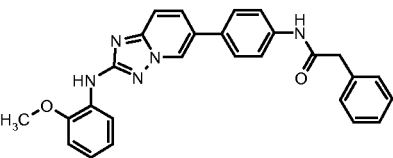
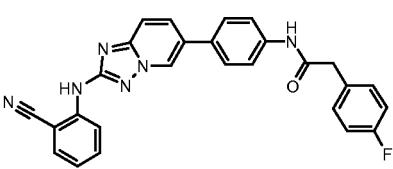
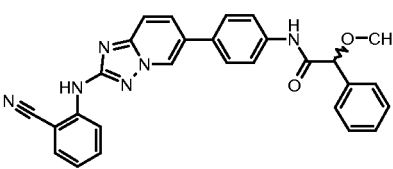
Compounds A1, A2, A3, A4 and A5 are characterized by the following attributes:

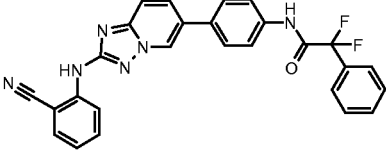
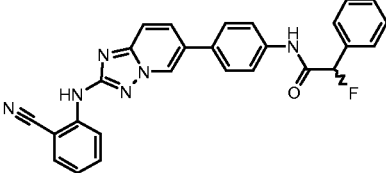
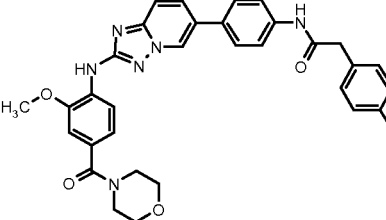
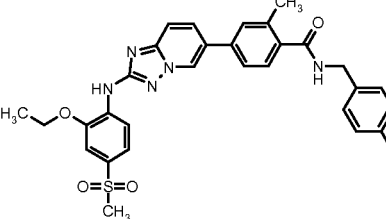
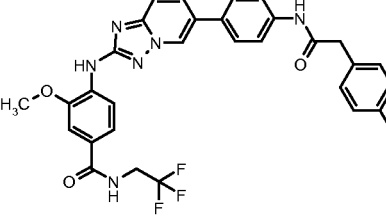
- 10 - The IC₅₀ determined in an Mps-1 kinase assay with a concentration of 10 μ M ATP (as described above) is lower than or equal to 1 nM.
- The IC₅₀ determined in an Mps-1 kinase assay with a concentration of 2 mM ATP (as described above) is lower than 2 nM.
- 15 - The maximum oral bioavailability (F_{max}) in rat (determined by means of rat liver microsomes as described above) is higher than 70 %.
- The maximum oral bioavailability (F_{max}) in dog (determined by means of dog liver microsomes as described above) is higher than 50 %.

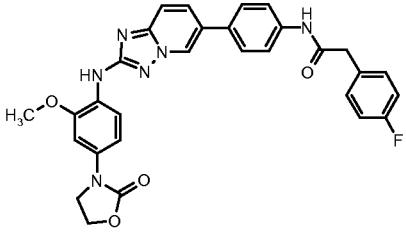
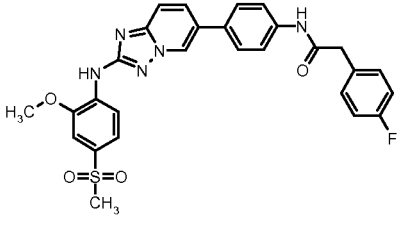
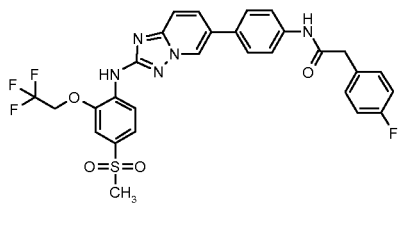
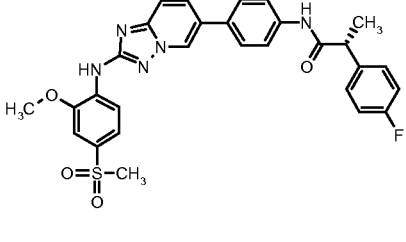
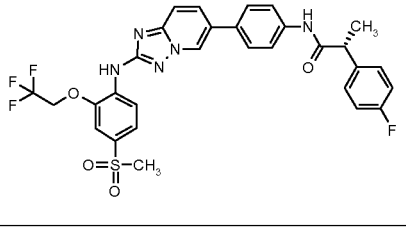
- The maximum oral bioavailability ($F_{\max}$) in human (determined by means of human liver microsomes as described above) is higher than 60 %.
- 5 - The IC_{50} determined in a HeLa cell proliferation assay (as described above) is lower than 400 nM.

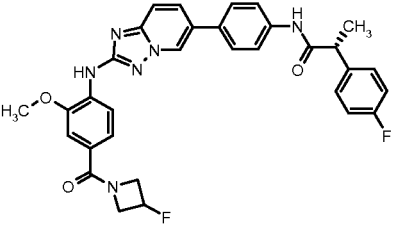
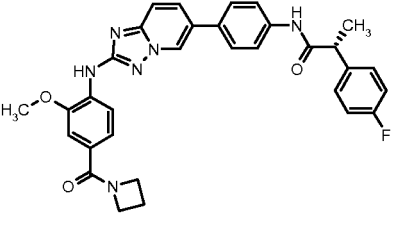
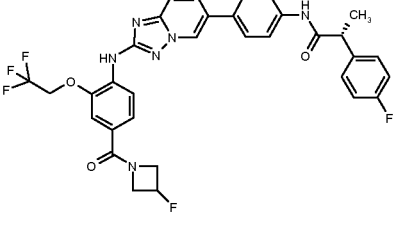
The following table demonstrates the superiority of compounds A1, A2, A3, A4 and A5 by way of comparison with compounds from prior art as well as with

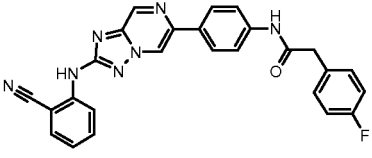
10 compounds which are structurally similar to said compounds.

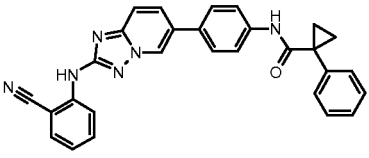
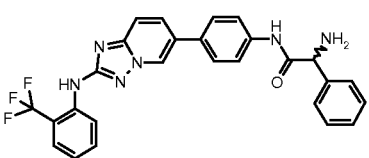
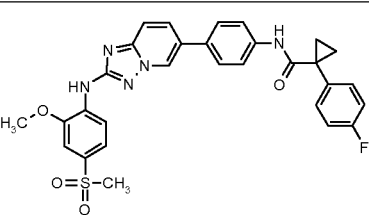
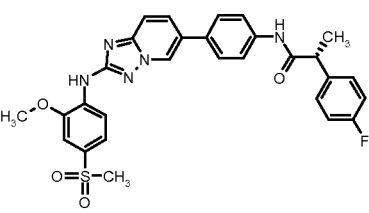
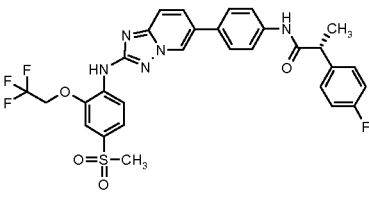
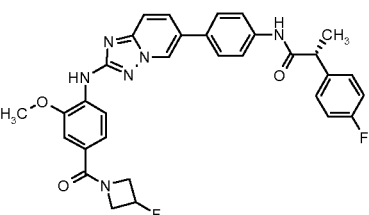
Formula	Specification of Example	Rat liver microsomes; $F_{\max}$ [%]	Dog liver microsomes; $F_{\max}$ [%]
	comparative example		15
	comparative example disclosed in WO 2011/063908	40	
	comparative example disclosed in WO2011/063908	40	
	comparative example disclosed in	19	

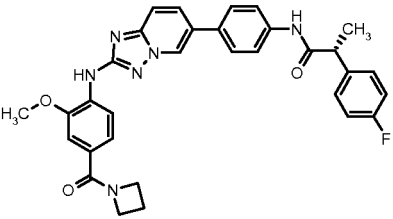
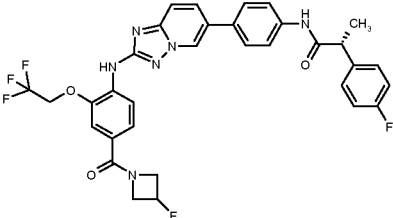
Formula	Specification of Example	Rat liver microsomes; Fmax [%]	Dog liver microsomes; Fmax [%]
	WO2011/063908		
	comparative example	27	
	comparative example	26	
	comparative example disclosed in WO2011/157688	48	
	comparative example		12
	comparative example		40

Formula	Specification of Example	Rat liver microsomes; Fmax [%]	Dog liver microsomes; Fmax [%]
	comparative example disclosed in WO2011/157688		17
	comparative example disclosed in WO2012/143329		10
	comparative example disclosed in WO2012/143329		25
	Compound A1	92	64
	Compound A2	93	55

Formula	Specification of Example	Rat liver microsomes; Fmax [%]	Dog liver microsomes; Fmax [%]
	Compound A3	83	86
	Compound A4	74	75
	Compound A5	89	57

Structure	Specification of Example	Mps-1 Inhibition, IC ₅₀ (Assay with 10 μM ATP)	Inhibition of cell proliferation, cell Line: HeLa; IC ₅₀
	comparative example		1500 nM

Structure	Specification of Example	Mps-1 Inhibition, IC ₅₀ (Assay with 10 μ M ATP)	Inhibition of cell proliferation, cell Line: HeLa; IC ₅₀
	comparative example	11 nM	1400 nM
	comparative example disclosed in WO2011/063908	13 nM	
	comparative example	15 nM	
	Compound A1	< 1 nM	< 400 nM
	Compound A2	< 1 nM	< 200 nM
	Compound A3	< 1 nM	< 100 nM

Structure	Specification of Example	Mps-1 Inhibition, IC ₅₀ (Assay with 10 μ M ATP)	Inhibition of cell proliferation, cell Line: HeLa; IC ₅₀
	Compound A4	< 1 nM	< 100 nM
	Compound A5	< 1 nM	< 100 nM

Prior Art Document	Example No.	Mps-1 Inhibition, IC ₅₀ (Assay with 10 μ M ATP)	Inhibition of cell proliferation, cell Line: HeLa; IC ₅₀
WO 2011/064328 A1	11.001	20 nM	
WO 2011/064328 A1	11.002	21 nM	
WO 2011/064328 A1	11.005	27 nM	
WO 2011/064328 A1	11.006	28 nM	
WO 2011/064328 A1	11.007	66 nM	
WO 2011/064328 A1	11.018	58 nM	
WO 2011/064328 A1	11.028		1100 nM
WO 2011/064328 A1	11.029		630 nM

Prior Art Document	Example No.	Mps-1 Inhibition, IC ₅₀ (Assay with 10 μ M ATP)	Inhibition of cell proliferation, cell Line: HeLa; IC ₅₀
WO 2011/064328 A1	11.030	16 nM	
WO 2011/064328 A1	11.031	18 nM	
WO 2011/064328 A1	11.032	20 nM	
WO 2011/064328 A1	11.033	23 nM	
WO 2011/064328 A1	11.037		1100 nM
WO 2011/064328 A1	11.042	53 nM	
WO 2011/064328 A1	11.043	60 nM	
WO 2011/064328 A1	11.076		730 nM
WO 2011/064328 A1	11.077	16 nM	
WO 2011/064328 A1	11.078	23 nM	
WO 2011/064328 A1	11.079	24 nM	
WO 2011/064328 A1	11.080	25 nM	
WO 2011/064328 A1	11.081	28 nM	
WO 2011/064328 A1	11.083	32 nM	
WO 2011/064328 A1	11.084	40 nM	
WO 2011/064328 A1	11.085		1800 nM
WO 2011/064328 A1	11.086		2200 nM
WO 2011/064328 A1	11.087		870 nM
WO 2011/064328 A1	11.088	15 nM	
WO 2011/064328 A1	11.089	25 nM	
WO 2011/064328 A1	11.091		1300 nM
WO 2011/064328 A1	11.092		820 nM
WO 2011/064328 A1	11.093		2400 nM
WO 2011/064328 A1	11.094		1400 nM

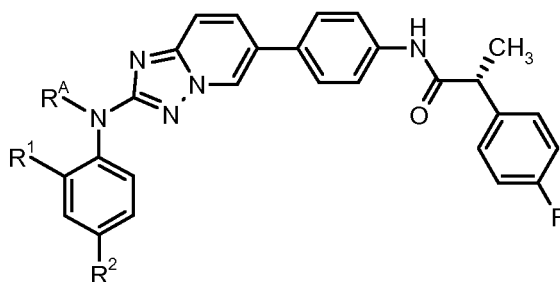
Prior Art Document	Example No.	Mps-1 Inhibition, IC ₅₀ (Assay with 10 µM ATP)	Inhibition of cell proliferation, cell Line: HeLa; IC ₅₀
WO 2011/064328 A1	11.095		2000 nM
WO 2011/064328 A1	11.096		1900 nM

Prior Art Document	Example No.	Inhibition of cell proliferation, cell Line: HeLa; IC ₅₀	Rat liver microsomes; Fmax [%]
WO 2011/063908 A1	3.3	1500 nM	
WO 2011/063908 A1	3.4	1300 nM	
WO 2011/063908 A1	3.5		27
WO 2011/063908 A1	3.6		40
WO 2011/063908 A1	3.9		21
WO 2011/063908 A1	3.10	930 nM	
WO 2011/063908 A1	3.11		25
WO 2011/063908 A1	4.1		40
WO 2011/063908 A1	7.1		29

CLAIMS

1. A compound of general formula (I) :

5



(I)

in which :

10 R^A represents a group selected from:

-C(=O)-(CH₂)₃-N(H)R³,

-C(=O)-(CR⁴R⁵)-N(R⁶)R⁷,

-C(=O)-O-(CH₂)₂-N(H)R³,

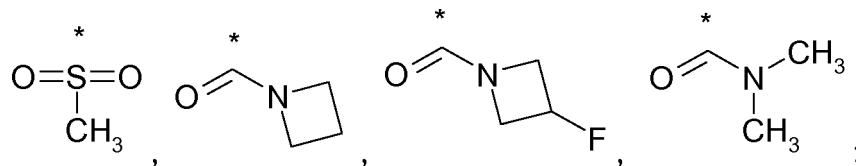
-C(=O)-O-(CR⁴R⁵)-O-P(=O)(OH)₂,

15 -C(=O)-O-(CR⁴R⁵)-O-C(=O)-R⁸,

-C(=O)-O-(CR⁴R⁵)-O-C(=O)-CH(R⁶)-NH-C(=O)-R⁹;

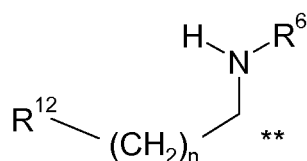
R^1 represents a group selected from methoxy- and 2,2,2-trifluoroethoxy-;

20 R^2 represents a group selected from:

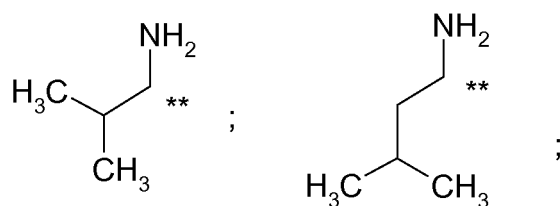


wherein "*" indicates the point of attachment to the phenyl ring R^2 is attached to;

- R^3 represents a group selected from:
 C_1 - C_6 -alkyl, C_3 - C_6 -cycloalkyl-,
 4- to 7-membered heterocycloalkyl-;
 said group being optionally substituted, one or more times, identically
 5 or differently, with a group selected from:
 $-OH$, $-NH_2$, $-N(H)R^{10}$, $-N(R^{10})R^{11}$, $-O-P(=O)(OH)_2$;
- R^4 and R^5 , independently from each other, represent a group selected from a
 hydrogen atom and a C_1 - C_3 -alkyl- group,
 10 or
 R^4 and R^5 , together with the carbon atom to which they are attached, form a
 C_3 - C_6 -cycloalkyl ring;
- R^6 represents a hydrogen atom or a C_1 - C_3 -alkyl- group;
 15
- R^7 represents a hydrogen atom or a group $-C(=O)R^9$;
- R^8 represents a group selected from:
 C_1 - C_6 -alkyl, C_3 - C_6 -cycloalkyl-,
 20 4- to 7-membered heterocycloalkyl-;
 said group being optionally substituted, one or more times, identically
 or differently, with a group selected from:
 $-OH$, $-NH_2$, $-N(H)R^{10}$, $-N(R^{10})R^{11}$, $-O-P(=O)(OH)_2$;
- 25 R^9 represents a group



or R⁹ represents a group selected from:



5 wherein "*" indicates the point of attachment to the carbonyl group R⁹ is attached to;

R¹⁰ and R¹¹, independently from each other, represent a group selected from a hydrogen atom and a C₁-C₃-alkyl- group, or

10

R¹⁰ and R¹¹, together with the nitrogen atom to which they are attached form a 4- to 7-membered heterocycloalkyl ring;

15 R¹² represents a group selected from a hydrogen atom, -OH, -NR¹⁰R¹¹, -NH-C(=NH)-NH₂;

n is an integer of 0, 1, 2, 3 or 4;

20 or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

2. A compound according to claim 1, wherein :

25 R^A represents a group selected from:

- C(=O)-(CH₂)₃-N(H)R³,
- C(=O)-O-(CR⁴R⁵)-O-C(=O)-R⁸,
- C(=O)-O-(CR⁴R⁵)-O-C(=O)-CH(R⁶)-NH-C(=O)-R⁹.

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

3. A compound according to claim 1, wherein :

5 R^A represents a group:



or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

10 4. A compound according to claim 1,2 or 3, wherein :

R^1 represents a methoxy- group,

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

15 5. A compound according to any one of claims 1 to 4, wherein :

R^2 represents a $-S(=O)_2CH_3$ group,

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

20 6. A compound according to any one of claims 1 to 5, wherein :

R^3 represents a C_1 - C_3 -alkyl- group,

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

25 7. A compound according to any one of claims 1 to 6, wherein :

R^4 represents a hydrogen atom or a C_1 - C_3 -alkyl- group, and

R^5 represents a hydrogen atom,

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

30

8. A compound according to any one of claims 1 to 7, wherein :

R^6 represents a hydrogen atom or a methyl- group,
or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture
of same.

5

9. A compound according to any one of claims 1 to 8, wherein :

R^8 represents a group selected from:

C_1 - C_6 -alkyl, substituted one or more times, identically or differently,
with a group selected from: $-NH_2$, $-N(H)R^{10}$, $-N(R^{10})R^{11}$,

10 4- to 7-membered heterocycloalkyl-, optionally substituted, one or more
times, identically or differently, with a group selected from:

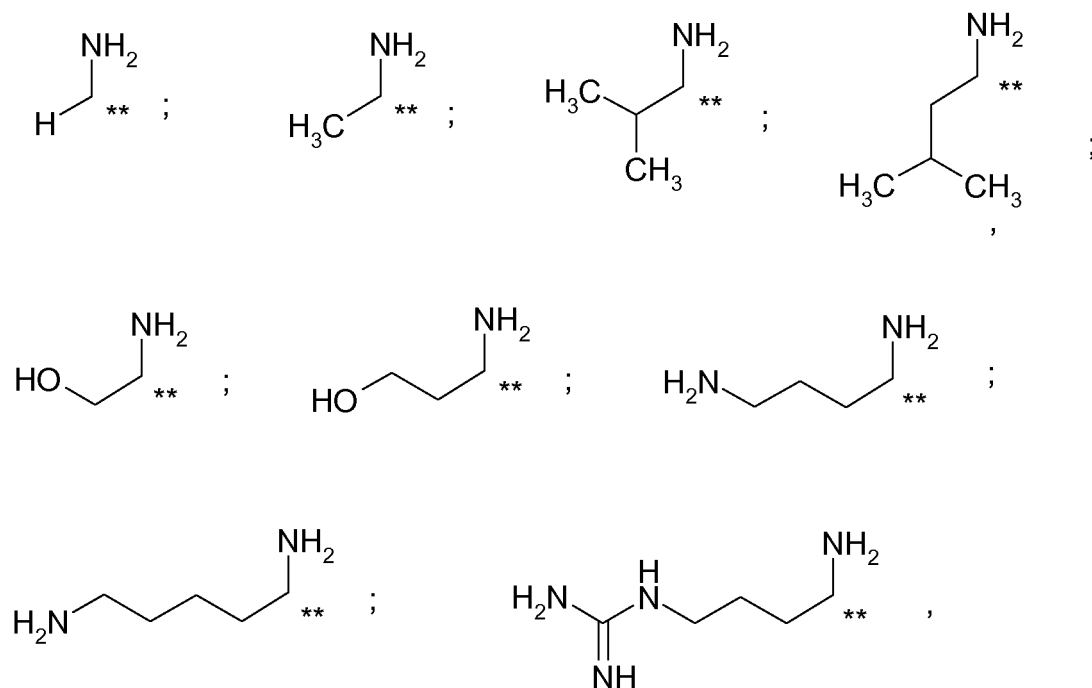
$-NH_2$, $-N(H)R^{10}$, $-N(R^{10})R^{11}$,

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture
of same.

15

10. A compound according to any one of claims 1 to 9, wherein :

R^9 represents a group selected from:



wherein "*" indicates the point of attachment to the carbonyl group R^9 is
20 attached to,

or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

11. A compound according to any one of claims 1 to 10, wherein :

- 5 R^{10} and R^{11} , independently from each other, represent a group selected from a hydrogen atom and a C_1 - C_3 -alkyl- group,
or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

- 10 12. A compound according to any one of claims 1 to 11, wherein :

R^{12} represents a group $-NR^{10}R^{11}$,
or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

- 15 13. A compound according to claim 1, which is selected from the group consisting of:

({[6-(4-{{(2R)-2-(4-fluorophenyl)propanoyl}amino}phenyl)[1,2,4]triazolo[1,5-
 α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)methyl
20 piperidine-4-carboxylate trifluoroacetate,

({[6-(4-{{(2R)-2-(4-fluorophenyl)propanoyl}amino}phenyl)[1,2,4]triazolo[1,5-
 α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)methyl L-
valinate hydrochloride,

25

({[6-(4-{{(2R)-2-(4-fluorophenyl)propanoyl}amino}phenyl)[1,2,4]triazolo[1,5-
 α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)methyl L-
leucinate hydrochloride,

({[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)methyl N-methyl-L-valinate hydrochloride,

- 5 ({[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)methyl 3-methyl-L-valinate hydrochloride,

- (phosphonooxy)methyl [6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamate,
- 10

- ({[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)methyl 3-methyl-L-isovalinate hydrochloride,
- 15

- ({[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)methyl 3-amino-2,2-dimethylpropanoate trifluoroacetate,
- 20

- ({[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)methyl L-lysyl-L-valinate dihydrochloride,

- 25 (1RS)-1-({[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)ethyl L-lysyl-L-valinate dihydrochloride (mixture of 2 epimers),

{[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)methyl L-valyl-L-valinate hydrochloride,

- 5 (1RS)-1-({[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)ethyl L-valyl-L-valinate hydrochloride (mixture of 2 epimers),
- 10 (1RS)-1-({[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)ethyl L-valinate hydrochloride (mixture of 2 epimers),
- 15 (1RS)-1-({[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)ethyl 3-methyl-L-valinate hydrochloride (mixture of 2 epimers),
- 20 (1R or 1S)-1-({[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)ethyl -3-methyl-L-valinate hydrochloride (single stereoisomer A),
- 25 (1S or 1R)-1-({[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)ethyl -3-methyl-L-valinate hydrochloride (single stereoisomer B),

(1RS)-1-({[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)ethyl-L-isoleucinate hydrochloride (mixture of 2 epimers),

5

(1S or 1R)-1-({[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)ethyl-L-isoleucinate hydrochloride (single stereoisomer B),

10

(1R or 1S)-1-({[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)ethyl-L-isoleucinate hydrochloride (single stereoisomer A),

15

N-[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4] triazolo[1,5- α]pyridin-2-yl]-N-[2-methoxy-4-(methylsulfonyl)phenyl]-4-(methylamino)butanamide trifluoroacetate,

20 N-[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4] triazolo[1,5- α]pyridin-2-yl]-N-[2-methoxy-4-(methylsulfonyl)phenyl]-4-(methylamino)butanamide hydrochloride,

(1RS)-1-({[6-(4-{[(2R)-2-(4-

25 fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)-2-methylpropyl 3-methyl-L-valinate hydrochloride (mixture of 2 epimers),

(1R or S)-1-({[6-(4-{[(2R)-2-(4-

30 fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-

methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)-2-methylpropyl-L-valinate hydrochloride (single stereoisomer A),

(1S or R)-1-({[6-(4-{[(2R)-2-(4-

- 5 fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)-2-methylpropyl-L-valinate hydrochloride (single stereoisomer B),

(1RS)-1-({[6-(4-{[(2R)-2-(4-

- 10 fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)-2-methylpropyl-L-valinate hydrochloride (mixture of 2 epimers),

(1RS)-1-({[6-(4-{[(2R)-2-(4-

- 15 fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamoyl}oxy)-2-methylpropyl-2-methylalaninate hydrochloride (mixture of 2 epimers),

({[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5-

- 20 α]pyridin-2-yl][4-(methylsulfonyl)-2-(2,2,2-trifluoroethoxy)phenyl]carbamoyl}oxy)methyl 3-methyl-L-valinate hydrochloride,

({[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5-

- 25 α]pyridin-2-yl][4-(methylsulfonyl)-2-(2,2,2-trifluoroethoxy)phenyl]carbamoyl}oxy)methyl L-valinate hydrochloride,

[({4-[(3-fluoroazetidin-1-yl)carbonyl]-2-(2,2,2-trifluoroethoxy)phenyl}[6-(4-

- 30 {[6-(4-{[(2R)-2-(4-fluorophenyl)propanoyl]amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl]carbamoyl}oxy)methyl 3-methyl-L-valinate hydrochloride,

2-(methylamino)ethyl [6-(4-{{(2R)-2-(4-fluorophenyl)propanoyl}amino}phenyl)[1,2,4]triazolo[1,5- α]pyridin-2-yl][2-methoxy-4-(methylsulfonyl)phenyl]carbamate hydrochloride,

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(2R)-2-(4-fluorophenyl)-N-[4-(2-{{2-methoxy-4-(methylsulfonyl)phenyl}(N-methylglycyl)amino}[1,2,4]triazolo[1,5- α]pyridin-6-yl)phenyl]propanamide trifluoroacetate;

10 or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, or a mixture of same.

14. A compound according to any one of claims 1 to 13, or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, for use in the treatment or prophylaxis of a disease.

15. A pharmaceutical composition comprising a compound according to any one of claims 1 to 13, or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, and a pharmaceutically acceptable diluent or carrier.

16. Use of a compound of any one of claims 1 to 13, or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically acceptable salt thereof, or a mixture of same, for the prophylaxis or treatment of a disease.

17. Use of a compound of any one of claims 1 to 13, or a tautomer, an N-oxide, a hydrate, a solvate, or a salt thereof, particularly a pharmaceutically

acceptable salt thereof, or a mixture of same, for the preparation of a medicament for the prophylaxis or treatment of a disease.

18. Use according to claim 14, 16 or 17, wherein said disease is a disease of
5 uncontrolled cell growth, proliferation and/or survival, an inappropriate
cellular immune response, or an inappropriate cellular inflammatory response,
particularly in which the uncontrolled cell growth, proliferation and/or
survival, inappropriate cellular immune response, or inappropriate cellular
inflammatory response is mediated by Mps-1, more particularly in which the
10 disease of uncontrolled cell growth, proliferation and/or survival,
inappropriate cellular immune response, or inappropriate cellular
inflammatory response is a haematological tumour, a solid tumour and/or
metastases thereof, e.g. leukaemias and myelodysplastic syndrome, malignant
lymphomas, head and neck tumours including brain tumours and brain
15 metastases, tumours of the thorax including non-small cell and small cell lung
tumours, gastrointestinal tumours, endocrine tumours, mammary and other
gynaecological tumours, urological tumours including renal, bladder and
prostate tumours, skin tumours, and sarcomas, and/or metastases thereof.

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