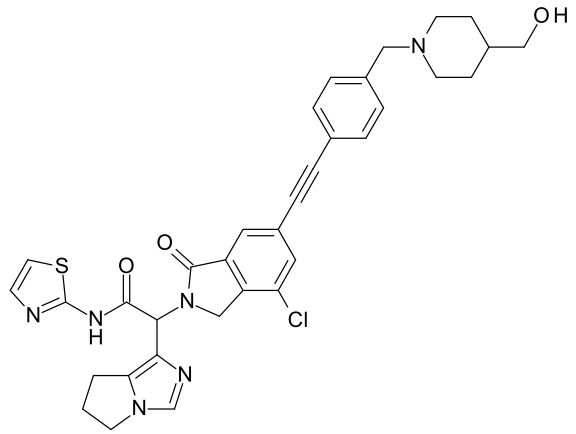
According to the Cahn-Ingold-Prelog Convention the asymmetric carbon atom can be of the "R" or "S" configuration.

The present disclosure provides a compound according to formula (I) as described herein and pharmaceutically acceptable salts thereof, in particular a compound according to formula (I) as described herein.

In one aspect, the present disclosure relates to a compound of formula (I)



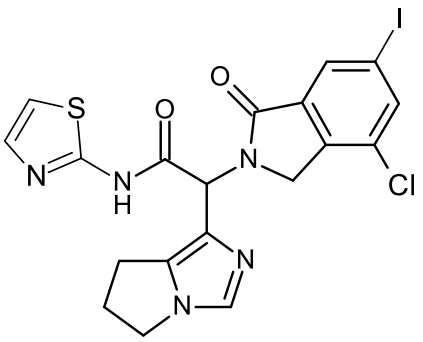
(I)

or a pharmaceutically acceptable salt thereof.

Also an example of the present disclosure is a compound according to formula (I) as described herein.

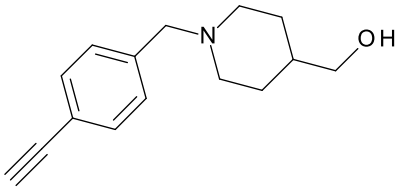
Also an example of the present disclosure is a compound according to formula (I) as described herein, wherein the compound is 2-[4-chloro-6-[2-[4-[[4-(hydroxymethyl)-1-piperidyl]methyl]phenyl]ethynyl]-1-oxo-isoindolin-2-yl]-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-thiazol-2-yl-acetamide.

In another aspect, the present disclosure relates to a process for the preparation of a compound according to the disclosure, comprising the coupling of a compound of formula (B1)



(B1)

with a compound of formula (B2)



(B2)

in the presence of a base and a catalyst.

The coupling can conveniently be carried out in a solvent. The solvent can be for example DMF.

In the coupling the base can be for example trimethylamine, triethylamine, dimethylamine, diethylamine or diisopropylethylamine. Conveniently the base is triethylamine.

In the coupling the catalyst is Pd(II) with suitable ligands and Cu(I). A convenient ligand is TPP.

Convenient conditions for the coupling can be between around 20°C to around 120°C, particularly between around 40°C to around 100°C, more particularly between around 60°C to around 90°C.

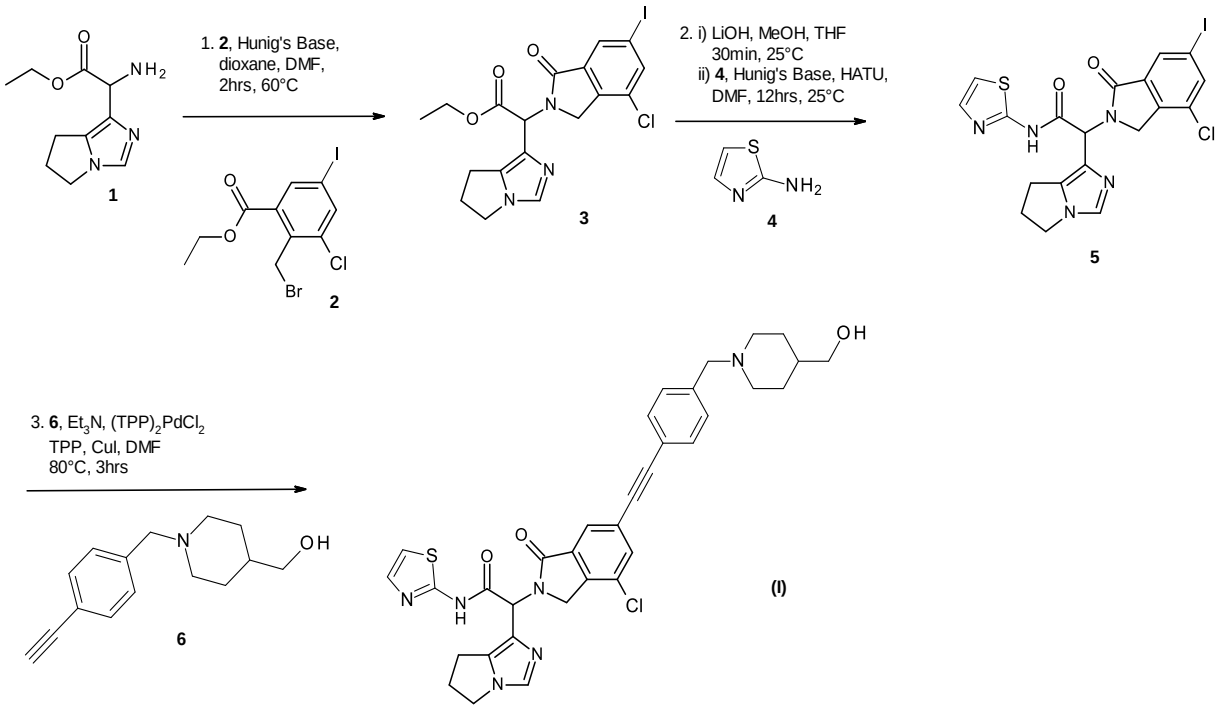
Preferred conditions for the coupling are the use of triethylamine in DMF at around 80°C for between around 1 h to around 24 hrs, in particular between around 2 hrs to around 5 hrs.

Processes for the manufacture of a compound of formula (I) as described herein are also an object of the disclosure.

The preparation of compound of formula (I) of the present disclosure may be carried out in sequential or convergent synthetic routes. Syntheses of the disclosure are shown in the following general scheme. The skills required for carrying out the reactions and purifications of the resulting products are known to those skilled in the art.

In more detail, the compound of formula (I) can be manufactured by the methods given below, by the methods given in the examples or by analogous methods. Appropriate reaction conditions for the individual reaction steps are known to a person skilled in the art. The reaction sequence is not limited to the one displayed in scheme 1, however, depending on the starting materials and their respective reactivity the sequence of reaction steps can be freely altered. Starting materials are either commercially available or can be prepared by methods analogous to the methods given below, by methods described in references cited in the description or in the examples, or by methods known in the art.

Scheme 1



The compound of formula (I) can be obtained for example by ring cyclization of a previously prepared aminoester **1** with an appropriately substituted methyl 2-(bromomethyl)benzoate of formula **2** to yield the desired isoindoline ester **3**. Saponification and amide coupling with an appropriately substituted amine of formula **4** with a coupling agent such as HATU yields the desired amide compound of formula **5**. Sonogashira coupling of **5** with an appropriately substituted acetylene of formula **6** yields the desired isoindoline compound of formula (I) (scheme 1).

Generally speaking, the sequence of steps used to synthesize the compound of formula (I) and further functionalization can also be modified in certain cases.

Insofar as its preparation is not described in the examples, the compound of formula (I) as well as all intermediate products can be prepared according to analogous methods or according to the methods set forth herein. Starting materials are commercially available, known in the art or can be prepared by methods known in the art or in analogy thereto.

It will be appreciated that the compound of general formula (I) in this disclosure may be derivatised at functional groups to provide derivatives which are capable of conversion back to the parent compound *in vivo*.

A certain example of the disclosure relates to the compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, for use as therapeutically active substance. In another aspect, the present disclosure relates to a compound as described herein for use as therapeutically active substance.

A certain example of the disclosure relates to the compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, for the use in the therapeutic and/or prophylactic treatment of cancer, in particular non-small-cell lung cancer. In another aspect, the present disclosure relates to a compound as described herein for use in the treatment of prophylaxis of cancer.

A certain example of the disclosure relates to the compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, for the use in the therapeutic and/or prophylactic treatment of non-small-cell lung cancer. In another aspect, the present disclosure relates to a compound as described herein for use in the treatment of prophylaxis of non-small cell lung cancer.

A certain example of the disclosure relates to the compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the therapeutic and/or prophylactic treatment of cancer, in particular non-small-cell lung cancer. In another aspect, the present disclosure relates to the use of a compound as described herein in the preparation of a medicament for the treatment or prophylaxis of cancer. In another aspect, the present disclosure relates to the use of a compound as described herein in the preparation of a medicament for the treatment or prophylaxis of non-small cell lung cancer.

A certain example of the disclosure relates to a pharmaceutical composition comprising the compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient. In another aspect, the present disclosure relates to a pharmaceutical composition comprising a compound as described herein and a therapeutically inert carrier.

A certain example of the disclosure relates to a method for the therapeutic and/or prophylactic treatment of cancer, in particular non-small-cell lung cancer by administering the compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, to a patient.

The disclosure also relates in particular to:

A compound of formula (I) for use as therapeutically active substance;

A pharmaceutical composition comprising a compound of formula (I) and a therapeutically inert carrier;

A compound of formula (I) for use in the treatment or prophylaxis of cancer;

A compound of formula (I) for use in the treatment or prophylaxis of non-small cell lung cancer;

The use of a compound of formula (I) for the treatment or prophylaxis of cancer;

The use of a compound of formula (I) for the treatment or prophylaxis of cancer for the treatment or prophylaxis of non-small cell lung cancer;

The use of a compound of formula (I) for the preparation of a medicament for the treatment or prophylaxis of cancer;

The use of a compound of formula (I) for the preparation of a medicament for the treatment or prophylaxis of non-small cell lung cancer;

A method for the treatment or prophylaxis of cancer, which method comprises administering an effective amount of a compound of formula (I) to a patient in need thereof; and

A method for the treatment or prophylaxis of non-small cell lung cancer, which method comprises administering an effective amount of a compound of formula (I) to a patient in need thereof.

A certain example of the disclosure relates to the compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, for the use as a medicament in therapeutic and/or prophylactic treatment of a patient with EGFR activating mutations suffering from cancer, in particular non-small-cell lung cancer, comprising determining the EGFR activating mutations status in said patient and then administering the compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, to said patient.

A certain example of the disclosure relates to the compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, for the use as a medicament in therapeutic and/or prophylactic treatment of a patient with EGFR mutations T790M/L858R, T790M/L858R/C797S, L858R and/or L858R/C797S suffering from cancer, in particular non-small-cell lung cancer, comprising determining the EGFR activating mutations status in said patient and then administering the compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, to said patient.

A certain example of the disclosure relates to the compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, for the use as a medicament in therapeutic and/or prophylactic treatment of a patient with EGFR activating mutations as determined with a cobas® EGFR Mutation Test v2 suffering from cancer, in particular non-small-cell lung cancer, comprising determining the EGFR activating mutations status in said patient and then administering the compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, to said patient.

Furthermore, the disclosure includes all substituents in its corresponding deuterated form, wherever applicable, of the compound of formula (I).

Furthermore, the disclosure includes all optical isomers, i.e. diastereoisomers, diastereomeric mixtures, racemic mixtures, all their corresponding enantiomers and/or tautomers as well as their solvates, wherever applicable, of the compound of formula (I).

The compound of formula (I) may contain one or more asymmetric centers and can therefore occur as racemates, racemic mixtures, single enantiomers, diastereomeric mixtures and

individual diastereomers. Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Each such asymmetric center will independently produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in mixtures and as pure or partially purified compound are included within this disclosure. The present disclosure is meant to encompass all such isomeric forms of these compound. The independent syntheses of these diastereomers or their chromatographic separations may be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration. If desired, racemic mixtures of the compound may be separated so that the individual enantiomers are isolated. The separation can be carried out by methods well known in the art, such as the coupling of a racemic mixture of compound to an enantiomerically pure compound to form a diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography.

In the examples, where optically pure enantiomers are provided, optically pure enantiomer means that the compound contains > 90 % of the desired isomer by weight, particularly > 95 % of the desired isomer by weight, or more particularly > 99 % of the desired isomer by weight, said weight percent based upon the total weight of the isomer(s) of the compound. Chirally pure or chirally enriched compound may be prepared by chirally selective synthesis or by separation of enantiomers. The separation of enantiomers may be carried out on the final product or alternatively on a suitable intermediate.

Also an example of the present disclosure are compound of formula (I) as described herein, when manufactured according to any one of the described processes. In another aspect, the present disclosure relates to a compound as described herein, when manufactured according to a process as described herein.

Assay procedures

The compound of formula (I) and pharmaceutically acceptable salts thereof possess valuable pharmacological properties. The compound was investigated in accordance with the test given hereinafter.

HTRF Phospho EGFR TMLRCS assay (cellular)

Cell line and media