

WO2009158369 describes certain heterocyclic antibacterial agents. WO2016183534 describes certain heterocyclic compounds suitable as EBNA1 inhibitors. WO2011128279 describes certain heterocyclic compounds suitable as mGluR5 modulators.

The term "pharmaceutically acceptable salts" refers to those salts which retain the biological effectiveness and properties of the free bases or free acids, which are not biologically or otherwise undesirable. The salts are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, in particular hydrochloric acid, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, N-acetylcystein and the like. In addition, these salts may be prepared by addition of an inorganic base or an organic base to the free acid. Salts derived from an inorganic base include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium salts and the like. Salts derived from organic bases include, but are not limited to salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, lysine, arginine, N-ethylpiperidine, piperidine, polyimine resins and the like. Particular pharmaceutically acceptable salts of compound of formula (I) are the hydrochloride salts, methanesulfonic acid salts and citric acid salts.

The abbreviation uM means microMolar and is equivalent to the symbol μM .

The abbreviation uL means microliter and is equivalent to the symbol μL .

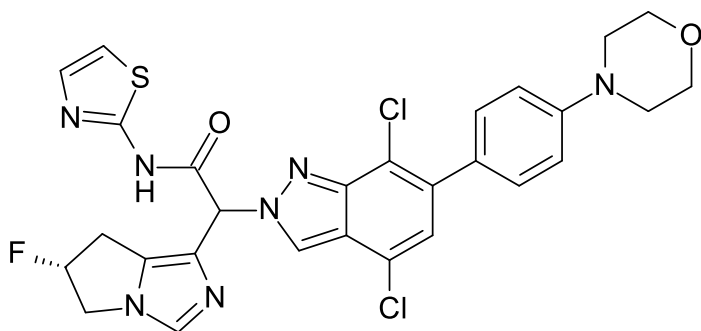
The abbreviation ug means microgram and is equivalent to the symbol μg .

Summary

The compound of formula (I) can contain several asymmetric centers and can be present in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates or mixtures of diastereoisomeric racemates.

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

~~Also an embodiment of the present invention is~~The present disclosure relates to a compound according to formula (I) as described herein and pharmaceutically acceptable salts thereof, more particularly a compound according to formula (I) as described herein. In one aspect, the present disclosure relates to a compound of formula (I)



5 (I)

or pharmaceutically acceptable salts.

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

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

~~A certain embodiment of the invention~~The present 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 embodiment of the invention~~The present 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 or prophylaxis of cancer.

A certain ~~embodiment~~example of the ~~invention~~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 or prophylaxis of non-small cell lung cancer.

~~A certain embodiment of the invention~~The present 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 embodiment of the invention~~The present 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 auxiliary substance. In another aspect, the present disclosure relates to a pharmaceutical composition comprising a compound as described herein and a therapeutically inert carrier.

~~A certain embodiment of the invention~~The present 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.

~~A certain embodiment of the invention~~The present 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 embodiment of the invention~~The present 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 embodiment of the invention~~The present 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 ~~invention~~disclosure includes all substituents in its corresponding deuterated form, 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 compounds are included within this ~~invention~~disclosure. The present ~~invention~~disclosure is meant to encompass all such isomeric forms of the 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 compounds 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 ~~embodiments~~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.

5 Also an embodiment example of the present invention disclosure is a compound of formula (I) as described herein, when manufactured according to any one of the described processes.

Assay procedures

HTRF Phospho EGFR TMLRCS assay (cellular)

Cell line and media

10 BaF3-TMLRCS cell line were obtained from Crownbio (San Diego, CA, USA). Cells were maintained at 37°C, 5% CO₂ in RPMI ATCC (Gibco 31870) + 2mM Glutamine + 0.5µg/ml Puromycin supplemented with 10% fetal bovine serum (FBS) (Gibco).

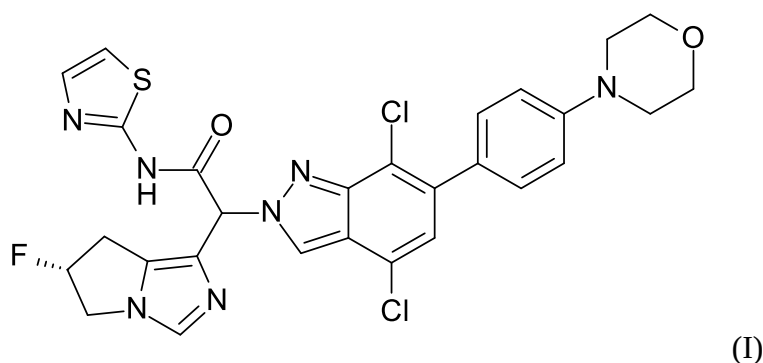
Protocol

Cells are transferred as above to Greiner Bio-One, Nr. 784-08 micro-titerplate at 20000
15 cells/well in 12.5 µl of growth medium/well after the plates had been pre-filled with 12.5 nl of DMSO solutions of the to be tested compounds (in dose response) or DMSO only. After spinning the plates at 300 x g for 30 seconds the cells were incubated for 4 hours at 37C, 5% CO₂, 95% humidity. The cells were lysed by adding to the compound mix 4 µl/well of the supplemented lysis buffer (Cis-bio, Phospho-EGFR HTRF kit, 64EG1PEH), followed by
20 incubation for 30 min at room temperature with shaking (400 rpm). The plates were then frozen and stored overnight at -80C. On the next day and after thawing the plates, 4 µl of a mixture of anti-Phospho-EGFR Cryptate and of anti-Phospho-EGFR-d2 antibody solutions prepared in the supplied detection buffer was added to each well. The lidded plates were then incubated for 4 h at room temperature before reading the fluorescence emission at 616 and 665 nm using an
25 Envision reader (Perkin Elmer). Data was analyzed in similar fashion as above using the normalized ratio of the 665 to 616 signals multiplied by 10000.

The results are shown in Table 1

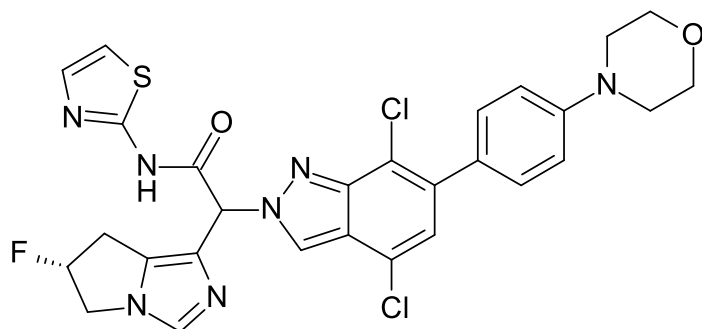
Claims

1. A compound of formula (I)



or pharmaceutically acceptable salts.

2. A compound of formula (I) according to claim 1, wherein the compound is



3. A compound according to any one of claims 1 or 2 for use as therapeutically active substance.

4. A pharmaceutical composition comprising a compound according to any one of claims 1 or 2 and a therapeutically inert carrier.

5. A compound according to any one of claims 1 or 2 for use in the treatment or prophylaxis of cancer.

6. A compound according to any one of claims 1 to 2 for use in the treatment or prophylaxis of non-small cell lung cancer.

7. ~~The use of a compound according to any one of claims 1 to 2 or a pharmaceutically acceptable salt for the treatment or prophylaxis of cancer.~~

8. ~~The use of a compound according to any one of claims 1 to 2 or a pharmaceutically acceptable salt for the treatment or prophylaxis of non-small cell lung cancer.~~

97. The use of a compound according to any one of claims 1 to 2 ~~for~~in the preparation of a medicament for the treatment or prophylaxis of cancer.

108. The use of a compound according to any one of claims 1 to 2 ~~for~~in the preparation of a medicament for the treatment or prophylaxis of non-small cell lung cancer.

5 ~~11.—A method for the treatment or prophylaxis of cancer, which method comprises administering an effective amount of a compound according to any one of claims 1 to 2.~~

~~12.—A method for the treatment or prophylaxis of non-small cell lung cancer, which method comprises administering an effective amount of a compound according to any one of claims 1 to 2.~~