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(71) Applicant *(for all designated States except US)*: **F. HOFFMANN-LA ROCHE AG** [CH/CH]; Grenzacherstrasse 124, 4070 Basel (CH).

(71) Applicant *(for US only)*: **HOFFMANN-LA ROCHE INC.** [US/US]; Overlook at Great Notch, 150 Clove Road 8th Floor, Suite 8 - Legal Department, Little Falls, New Jersey 07424 (US).

(72) Inventors: **DOLENTE, Cosimo**; c/o F. Hoffmann-La Roche AG Grenzacherstrasse 124, 4070 BASEL (CH). **GOERGLER, Annick**; c/o F. Hoffmann-La Roche AG Grenzacherstrasse 124, 4070 Basel (CH). **HEWINGS, David**; c/o F. Hoffmann-La Roche AG Grenzacherstrasse 124, 4070 Basel (CH). **JAESCHKE, Georg**; c/o F. Hoffmann-La Roche AG Grenzacherstrasse 124, 4070 Basel (CH). **KUHN, Bernd**; c/o F. Hoffmann-La Roche AG Grenzacherstrasse 124, 4070 Basel (CH). **NAGEL, Yvonne Alice**; c/o F. Hoffmann-La Roche AG Grenzacherstrasse 124, 4070 Basel (CH). **OBST SANDER, Ulrike**; c/o F. Hoffmann-La Roche AG Grenzacherstrasse 124, 4070 Basel (CH). **RICCI, Antonio**; c/o F. Hoffmann-La Roche AG Grenzacherstrasse 124, 4070 Basel (CH). **RUEHER, Daniel**; c/o F. Hoffmann-La Roche AG Grenzacherstrasse 124, 4070 Basel (CH). **STEINER, Sandra**; c/o F. Hoffmann-La Roche AG Grenzacherstrasse 124, 4070 Basel (CH).

(74) Agent: **BERNARD, Guillaume**; Grenzacherstrasse 124, 4070 Basel (CH).

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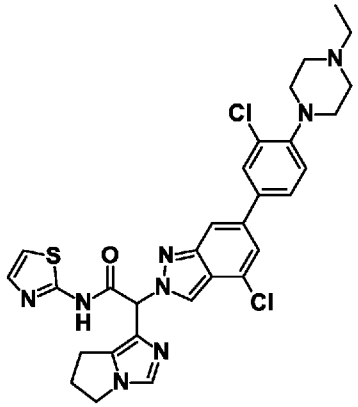
(54) Title: EGFR INHIBITORS FOR THE TREATMENT OF CANCER

(57) Abstract: The application relates to 17 specific compounds containing a thiazole ring, an indazol ring and a 6,7-dihydro-5H-pyrrolo[l,2-c]imidazole ring system, to pharmaceutical compositions containing them and their medical use. The compounds are described as selective allosteric inhibitors of T790M/L858R, T790M/L858R/C797S, L858R, L858R/C797S containing EGFR mutants and thus useful for the treatment of cancer, in particular non-small cell lung cancer. (Formula)



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EGFR INHIBITORS FOR THE TREATMENT OF CANCER

The present invention provides compounds which are selective allosteric inhibitors of T790M/L858R, T790M/L858R/C797S, L858R, L858R/C797S containing EGFR mutants, their manufacture, pharmaceutical compositions containing them and their use as therapeutically active substances.

The present invention provides a novel compounds selected from

2-(4-chloro-6-(4-(piperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide hydrochloride;

2-(6-(4-(4-acetylpiperazin-1-yl)phenyl)-4-chloro-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide;

2-(4-chloro-6-(3-chloro-4-(piperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide hydrochloride;

2-(4-chloro-6-(3-chloro-4-(4-ethylpiperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide;

2-(6-(3-chloro-4-(piperazin-1-yl)phenyl)-4-fluoro-2H-indazol-2-yl)-2-((R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide hydrochloride;

2-(6-(4-(4-acetylpiperazin-1-yl)-3-chlorophenyl)-4-fluoro-2H-indazol-2-yl)-2-((R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide;

2-(6-(3-chloro-4-(4-ethylpiperazin-1-yl)phenyl)-4-fluoro-2H-indazol-2-yl)-2-((R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide;

2-(4,7-dichloro-6-(4-(piperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide hydrochloride;

2-(6-(4-(4-acetylpiperazin-1-yl)phenyl)-4,7-dichloro-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide;

2-(4,7-dichloro-6-(4-(4-ethylpiperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide;

2-(4-chloro-7-fluoro-6-(4-(piperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide hydrochloride;

2-(4-chloro-6-(4-(4-ethylpiperazin-1-yl)phenyl)-7-fluoro-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide;

2-(4-chloro-7-fluoro-6-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide;

2-[4-chloro-7-methoxy-6-(1-methyl-2-oxo-3,4-dihydroquinolin-6-yl)indazol-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-(1,3-thiazol-2-yl)acetamide;

2-[4-chloro-6-[4-(4-ethylpiperazin-1-yl)phenyl]-7-methoxyindazol-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-(1,3-thiazol-2-yl)acetamide;

2-[4-chloro-6-[4-(1-cyclopropylpiperidin-4-yl)phenyl]-7-methoxyindazol-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-(1,3-thiazol-2-yl)acetamide;

2-(4-chloro-7-fluoro-6-(1-isopropyl-2-oxo-1,2-dihydropyridin-4-yl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide

or pharmaceutically acceptable salts.

The HER family receptor tyrosine kinases are mediators of cell growth, differentiation and survival. The receptor family includes four distinct members, i.e. epidermal growth factor receptor (EGFR, ErbBl, or HER1) HER2 (ErbB2), HER3 (ErbB3) and HER4 (ErbB4). Upon ligand binding the receptors form homo and heterodimers and subsequent activation of the intrinsic tyrosine kinase activity leads to receptor auto-phosphorylation and the activation of downstream signaling molecules (Yarden, Y., Sliwkowski, MX. Untangling the ErbB signalling network. Nature Review Mol Cell Biol. 2001 Feb;2(2): 127-37). De-regulation of EGFR by overexpression or mutation has been implicated in many types of human cancer including colorectal, pancreatic, gliomas, head and neck and lung cancer, in particular non-small cell lung cancer (NSCLC) and several EGFR targeting agents have been developed over the years (Ciardiello, F., and Tortora, G. (2008). EGFR antagonists in cancer treatment. The New England journal of medicine 358, 1160-1174). Erlotinib (Tarceva®), a reversible inhibitor of the EGFR tyrosine kinase was approved in numerous countries for the treatment of recurrent NSCLC.

An impressive single agent activity of EGFR tyrosine kinase inhibitors is observed in a subset of NSCLC patients whose tumors harbor somatic kinase domain mutations, whereas clinical benefit in wild-type EGFR patients is greatly diminished (Paez, J. *et al.* (2004). EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science (New York, NY 304, 1497-1500). The most common somatic mutations of EGFR are exon 19 deletions with delta 746-750 the most prevalent mutation and the exon 21 amino acid substitutions with L858R the

most frequent mutation (Sharma SV, Bell DW, Settleman J, Haber DA. Epidermal growth factor receptor mutations in lung cancer. Nat Rev Cancer. 2007 Mar;7(3): 169-81).

Treatment resistance arises frequently, often due to the secondary T790M mutation within the ATP site of the receptor. Some developed mutant-selective irreversible inhibitors are highly active against the T790M mutant, but their efficacy can be compromised by acquired mutation of C797S, that is the cysteine residue with which they form a key covalent bond (Thress, K. S. et al. Acquired EGFR C797S mutation mediates resistance to AZD9291 in non-small cell lung cancer harboring EGFR T790M. Nat. Med. 21, 560–562 (2015)). C797S mutation was further reported by Wang to be a major mechanism for resistance to T790M-targeting EGFR inhibitors (Wang *et al.* ***EGFR*** C797S mutation mediates resistance to third-generation inhibitors in T790M-positive non-small cell lung cancer, J Hematol Oncol. 2016; 9: 59). Additional mutations that cause resistance to Osimertinib are described by Yang, for example L718Q.(Yang *et al*, Investigating Novel Resistance Mechanisms to Third-Generation EGFR Tyrosine Kinase Inhibitor Osimertinib in Non–Small Cell Lung Cancer Patients, Clinical Cancer Research, DOI: 10.1158/1078-0432.CCR-17-2310) Lu *et al.*(Targeting $EGFR^{L858R/T790M}$ and $EGFR^{L858R/T790M/C797S}$ resistance mutations in NSCLC: Current developments in medicinal chemistry, Med Res Rev 2018; 1-32) report in a review article on Targeting $EGFR^{L858R/T790M}$ and $EGFR^{L858R/T790M/C797S}$ resistance mutations in NSCLC treatment.

As most available EGFR tyrosine kinase inhibitors target the ATP-site of the kinase, there is a need for new therapeutic agents that work differently, for example through targeting drug-resistant EGFR mutants.

Recent studies suggest that purposefully targeting allosteric sites might lead to mutant-selective inhibitors (Jia *et al.* Overcoming EGFR(T790M) and EGFR(C797S) resistance with mutant-selective allosteric inhibito*RS*, June 2016, Nature 534, 129-132)

There is just a need in the generation of selective molecules that specifically inhibit T790M/L858R, T790M/L858R/C797S, L858R, L858R/C797S containing EGFR mutants useful for the therapeutic and/or prophylactic treatment of cancer, in particular T790M and C797S containing EGFR mutants.

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 compounds of the present invention 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.

The compounds of the present invention 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 a compound as described herein and pharmaceutically acceptable salts thereof, more particularly a compound as described herein.

In another embodiment a compound as described herein is selected from

2-(4-chloro-6-(4-(piperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide hydrochloride;

2-(6-(4-(4-acetylpiperazin-1-yl)phenyl)-4-chloro-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide;

2-(4-chloro-6-(3-chloro-4-(piperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide hydrochloride;

2-(4-chloro-6-(3-chloro-4-(4-ethylpiperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide;

2-(6-(3-chloro-4-(piperazin-1-yl)phenyl)-4-fluoro-2H-indazol-2-yl)-2-((R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide hydrochloride;

2-(6-(4-(4-acetylpiperazin-1-yl)-3-chlorophenyl)-4-fluoro-2H-indazol-2-yl)-2-((R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide;

2-(6-(3-chloro-4-(4-ethylpiperazin-1-yl)phenyl)-4-fluoro-2H-indazol-2-yl)-2-((R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide;

2-(4,7-dichloro-6-(4-(piperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide hydrochloride;

2-(6-(4-(4-acetylpiperazin-1-yl)phenyl)-4,7-dichloro-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide;

2-(4,7-dichloro-6-(4-(4-ethylpiperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide;

2-(4-chloro-7-fluoro-6-(4-(piperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide hydrochloride;

2-(4-chloro-6-(4-(4-ethylpiperazin-1-yl)phenyl)-7-fluoro-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide;

2-(4-chloro-7-fluoro-6-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide;

2-[4-chloro-7-methoxy-6-(1-methyl-2-oxo-3,4-dihydroquinolin-6-yl)indazol-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-(1,3-thiazol-2-yl)acetamide;

2-[4-chloro-6-[4-(4-ethylpiperazin-1-yl)phenyl]-7-methoxyindazol-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-(1,3-thiazol-2-yl)acetamide;

2-[4-chloro-6-[4-(1-cyclopropylpiperidin-4-yl)phenyl]-7-methoxyindazol-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-(1,3-thiazol-2-yl)acetamide;

2-(4-chloro-7-fluoro-6-(1-isopropyl-2-oxo-1,2-dihydropyridin-4-yl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide.

Processes for the manufacture of a compound of the present invention as described herein are also an object of the invention.

The corresponding pharmaceutically acceptable salts with acids can be obtained by standard methods known to the person skilled in the art, e.g. by dissolving the compound of the present invention in a suitable solvent such as e.g. dioxane or tetrahydrofuran and adding an appropriate amount of the corresponding acid. The products can usually be isolated by filtration or by chromatography. The conversion of a compound of the present invention into a pharmaceutically acceptable salt with a base can be carried out by treatment of such a compound with such a base. One possible method to form such a salt is e.g. by addition of 1/n equivalents of a basic salt such as e.g. $M(OH)_n$, wherein M = metal or ammonium cation and n = number of hydroxide anions, to a solution of the compound in a suitable solvent (e.g. ethanol, ethanol-water mixture, tetrahydrofuran-water mixture) and to remove the solvent by evaporation or lyophilisation. Particular salts are hydrochloride, formate and trifluoroacetate.

Insofar as their preparation is not described in the examples, the compounds of the present invention 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 compounds of the present invention 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 relates to the compound of the present invention as described herein, or a pharmaceutically acceptable salt thereof, for use as therapeutically active substance.

A certain embodiment of the invention relates to the compound of the present invention 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.

A certain embodiment of the invention relates to the compound of the present invention 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.

A certain embodiment of the invention relates to the compound of the present invention 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.

A certain embodiment of the invention relates to a pharmaceutical composition comprising the compound of the present invention as described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable auxiliary substance.

A certain embodiment of the invention 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 the present invention as described herein, or a pharmaceutically acceptable salt thereof, to a patient.

A certain embodiment of the invention relates to the compound of the present invention 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 the present invention as described herein, or a pharmaceutically acceptable salt thereof, to said patient.

A certain embodiment of the invention relates to the compound of the present invention 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 the present invention as described herein, or a pharmaceutically acceptable salt thereof, to said patient.

A certain embodiment of the invention relates to the compound of the present invention 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 the present invention as described herein, or a pharmaceutically acceptable salt thereof, to said patient.

Furthermore, the invention includes all substituents in its corresponding deuterated form, wherever applicable, of the compounds of the present invention.

Furthermore, the invention 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 compounds of the present invention.

The compounds of the present invention 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. The present invention is meant to encompass all such isomeric forms of these compounds. 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 compounds 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, 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 compounds 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 embodiment of the present invention are compounds of the present invention as described herein, when manufactured according to any one of the described processes.

Assay procedures

HTRF Phospho EGFR TMLR assay (cellular)

Cell line and media

H1975 cell line (CRL-5908; Lot BA70803) was obtained from American Type Culture Collection (Manassas, VA, USA). Cells were maintained at 37°C, 5% CO_2 in complete Media RPMI 1640 without phenol red containing 0.3 mg/ml glutamine, 100 IU/ml penicillin, and 100 mg/ml streptomycin (Gibco, 15140-122) supplemented with 10% fetal bovine serum (FBS, Gibco, 10091-148). Compounds were diluted into starving medium RPMI 1640 Media (Gibco, 11835-030) without phenol red containing 0.3 mg/ml glutamine, 100 IU/ml penicillin, and 100 mg/ml streptomycin (Gibco).

Protocol

Cells were cultured for 24 h in a 384-well plate (Greiner Bio-One, Nr. 784-080; 5000 cells/well) using 8 µl of complete medium/well. Then 4 µl/well of the 3× compound solution, containing a factor 3 dilution series of the compound or DMSO in starving medium, were added to the cells (final DMSO 0.33%). After 16 hours at 37°C, 5% CO2, 95% rel. humidity 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 incubation for 30 min at room temperature with shaking (400 rpm). Then 4 µl of a mixture of anti-Phospho-EGFR Cryptate and of anti-Phospho-EGFR-d2 antibody solutions prepared in the detection buffer was added. The plates were then incubated for 4 h at room temperature before reading the fluorescence emission at 620 and 665 nm using an Envision reader (Perkin Elmer).

HTRF Phospho EGFR TMLRCS assay (cellular)

Cell line and media

BaF3-TMLRCS cell line were obtained from Crownbio (San Diego, CA, USA). Cells were maintained at 37°C, 5% CO_2 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 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

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 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

Example	IC_{50} (H1975) µM	IC_{50} (BaF3) µM
1	0.003	0.007
2	0.0004	0.005
3	0.009	
4	0.011	0.014
6	0.003	
7	0.001	
8	0.005	
9	0.002	
12	0.001	
13	0.001	0.011
15	0.002	
16	0.002	
18	0.001	
20	0.001	
21	0.003	
22	0.005	
23	0.001	

The compounds of the present invention and their pharmaceutically acceptable salts can be used as medicaments (e.g. in the form of pharmaceutical preparations). The pharmaceutical preparations can be administered internally, such as orally (e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatin capsules, solutions, emulsions or suspensions), nasally (e.g. in the form of nasal sprays), rectally (e.g. in the form of suppositories) or topical ocularly (e.g. in the form of solutions, ointments, gels or water soluble polymeric inserts). However, the administration can also be effected parenterally, such as intramuscularly, intravenously, or intraocularly (e.g. in the form of sterile injection solutions).

The compounds of the present invention and their pharmaceutically acceptable salts can be processed with pharmaceutically inert, inorganic or organic adjuvants for the production of tablets, coated tablets, dragées, hard gelatin capsules, injection solutions or topical formulations Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc. can be used, for example, as such adjuvants for tablets, dragées and hard gelatin capsules.

Suitable adjuvants for soft gelatin capsules, are, for example, vegetable oils, waxes, fats, semi-solid substances and liquid polyols, etc.

Suitable adjuvants for the production of solutions and syrups are, for example, water, polyols, saccharose, invert sugar, glucose, etc.

Suitable adjuvants for injection solutions are, for example, water, alcohols, polyols, glycerol, vegetable oils, etc.

Suitable adjuvants for suppositories are, for example, natural or hardened oils, waxes, fats, semi-solid or liquid polyols, etc.

Suitable adjuvants for topical ocular formulations are, for example, cyclodextrins, mannitol or many other carriers and excipients known in the art.

Moreover, the pharmaceutical preparations can contain preservatives, solubilizers, viscosity-increasing substances, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

The dosage can vary in wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of oral administration a daily dosage of about 0.1 mg to 20 mg per kg body weight, preferably about 0.5 mg to 4 mg per kg body weight (e.g. about 300 mg per person), divided into preferably 1-3 individual doses, which can consist, for example, of the same amounts, should it be appropriate. In the case of topical administration, the formulation can contain 0.001% to 15% by weight of medicament and the required dose, which can be between 0.1 and 25 mg in can be administered either by single dose per day or per week, or by multiple doses (2 to 4) per day, or by multiple doses per week It will, however, be clear that the upper or lower limit given herein can be exceeded when this is shown to be indicated.

Preparation of pharmaceutical compositions comprising compounds of the invention:

Tablets of the following composition are manufactured in the usual manner:

Ingredient	mg/tablet			
	5	25	100	500
Compound	5	25	100	500
Lactose Anhydrous DTG	125	105	30	150
Sta-Rx 1500	6	6	6	60
Microcrystalline Cellulose	30	30	30	450
Magnesium Stearate	1	1	1	1
Total	167	167	167	831

Manufacturing Procedure

1. Mix ingredients 1, 2, 3 and 4 and granulate with purified water.
2. Dry the granules at 50°C.
3. Pass the granules through suitable milling equipment.
4. Add ingredient 5 and mix for three minutes; compress on a suitable press.

Capsules of the following composition are manufactured:

Ingredient	mg/capsule			
	5	25	100	500
Compound	5	25	100	500
Hydrous Lactose	159	123	148	-
Corn Starch	25	35	40	70
Talk	10	15	10	25
Magnesium Stearate	1	2	2	5
Total	200	200	300	600

Manufacturing Procedure

1. Mix ingredients 1, 2 and 3 in a suitable mixer for 30 minutes.
2. Add ingredients 4 and 5 and mix for 3 minutes.
3. Fill into a suitable capsule.

A compound of the present invention, lactose and corn starch are firstly mixed in a mixer and then in a comminuting machine. The mixture is returned to the mixer; the talc is added thereto

and mixed thoapproximatively. The mixture is filled by machine into suitable capsules, e.g. hard gelatin capsules.

Injection solutions of the following composition are manufactured:

Ingredient	**mg/injection solution.**
Compound	3
Polyethylene Glycol 400	150
acetic acid	q.s. ad pH 5.0
water for injection solutions	ad 1.0 ml

The invention is illustrated hereinafter by Examples, which have no limiting character.

In case the preparative examples are obtained as a mixture of enantiomers, the pure enantiomers can be obtained by methods described herein or by methods known to those skilled in the art, such as e.g. chiral chromatography or crystallization.

Examples

The following examples are provided for illustration of the invention. They should not be considered as limiting the scope of the invention, but merely as being representative thereof.

Synthesis of Intermediates

Substituted indazoles (II) are known or can be prepared in analogy to known methods or using the methods described below.

6-Bromo-4,7-dichloro-1H-indazole

Step 1: 4-Bromo-3,6-dichloro-2-fluorobenzaldehyde

A solution of 1-bromo-2,5-dichloro-3-fluorobenzene (9.414 g) in tetrahydrofuran (70 ml) was cooled in a dry ice / acetone bath. LDA, 2mol/l in THF (21.2 ml) was added and the mixture was stirred at -75 °C for 20 min. N,N-dimethylformamide (2.82 g) was added dropwise and stirred for 1 h. A solution of AcOH in Et2O (1:1, 10 ml) was added. The mixture was allowed to warm to room temperature. Water was added and the mixture was extracted with EtOAc. The organic layers were washed with water, dried ($MgSO_4$), filtered and concentrated in vacuo to give the crude title compound (11.323 g) as light yellow solid. The compound was used for the next step without further purification.

Step 2: 6-Bromo-4,7-dichloro-1H-indazole

To a solution of 4-bromo-3,6-dichloro-2-fluorobenzaldehyde (10.5 g) in Dioxane (50 ml) was added hydrazine hydrate (3.86 g). The mixture was stirred at room temperature for 3 days. Hydrazine hydrate (386 mg) was added and the mixture was warmed to 70 °C for 7 h. After cooling to room temperature water was added and the precipitated solid was collected by filtration. To the solid was added a small amount of acetonitrile and stirred for 2 h. The solid was collected by filtration, washed with a small amount of acetonitrile and dried to give the title compound (7.842 g) as off-white solid. MS: m/e= 267.0 ($[M+H]^+$, Br)

6-Bromo-4-chloro-7-fluoro-2H-indazole

Step 1: 4-Bromo-6-chloro-2,3-difluorobenzaldehyde

In analogy to the synthesis of 4-bromo-3,6-dichloro-2-fluorobenzaldehyde, 1-bromo-5-chloro-2,3-difluorobenzene was first treated with LDA in tetrahydrofuran at -75 °C followed by treatment with N,N-dimethylformamide. Workup in analogy to the synthesis of 4-bromo-3,6-dichloro-2-fluorobenzaldehyde gave the crude title compound as light brown solid.

Step 2: 6-Bromo-4-chloro-7-fluoro-2H-indazole

4-Bromo-6-chloro-2,3-difluorobenzaldehyde (5 g) was combined under argon with 1,4-dioxane (19.6 ml) and hydrazine hydrate (1.18 g) and stirred overnight. Hunig's base (2.53 g) was added and stirred for 18 h at 60°C, for 3 h at 80°C and overnight at 100°C. The mixture was cooled down to room temperature and concentrated. After addition of CH_2Cl_2 a solid precipitated. The solid was collected by filtration, washed with CH_2Cl_2 and dried to give the title compound (3.9 g) as off-white solid. MS: m/e= 251.0 ($[M+H]^+$, Br)

6-Bromo-4-chloro-7-methoxy-2H-indazole

Step 1: 4-Bromo-6-chloro-2-fluoro-3-methoxybenzaldehyde

In analogy to the synthesis of 4-bromo-3,6-dichloro-2-fluorobenzaldehyde, 1-bromo-5-chloro-3-fluoro-2-methoxybenzene was first treated with LDA in Tetrahydrofuran at -75 °C followed by treatment with N,N-dimethylformamide. Workup in analogy to the synthesis of 4-bromo-3,6-dichloro-2-fluorobenzaldehyde gave the crude title compound as light brown solid.

Step 2: 6-Bromo-4-chloro-7-methoxy-2H-indazole

Crude 4-bromo-6-chloro-2-fluoro-3-methoxybenzaldehyde (11.75 g) was dissolved in

THF (50 ml). After addition of hydrazine hydrate (3.83 g) the mixture was stirred at room temperature for 42 h.The temperature was increased to 70 °C and the mixture was stirred for 36 h. The temperature was increased to 90 °C and the mixture was stirred for 7 days. After addition of hydrazine hydrate (15.3 g) the mixture was stirred for 18h at 90°C. After cooling to room temperature, the mixture was diluted with water and stirred for 30 min. The sticky solid was collected by filtration, washed with water and dried to give the slightly impure title compound (6.88 g) as a light brown solid which was used for the next step without further purification.

MS: m/e= 261.0 ($[M+H]^+$, Br)

General Method A: Alkylation of Indazoles

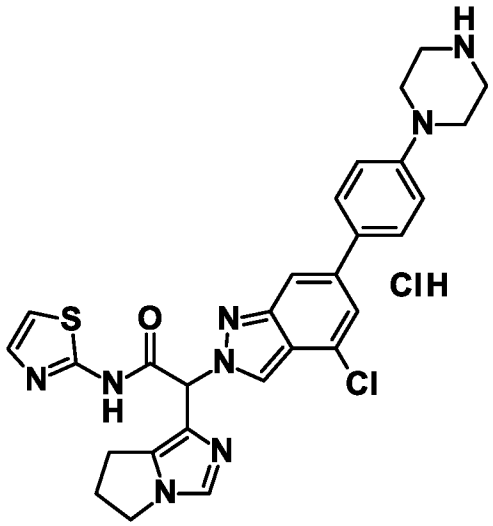
A mixture of indazole (**II**, 1 eq), ethyl 2-bromoacetate (2 eq) and N,N-dimethylacetamide (small amount to produce a solution) is heated to 100°C until completion of the reaction (usually 5-48 h). After cooling to room temperature, ice is added and the precipitated solid is collected by filtration and washed with water. Purification of the desired regioisomer can be accomplished by chromatography or in certain cases by re-crystallization from solvents such as EtOH, acetonitrile or dichloromethane.

Using General Method A, the following intermediates (**III**) were prepared:

Intermediate (III)	**Indazole (II)**	**Alkylating agent**	**MS m/e**
ethyl 2-(6-bromo-4-chloro-2H-indazol-2-yl)acetate	6-bromo-4-chloro-1H-indazole (CAS 885518-99-0)	ethyl 2-bromoacetate	319.0 ($[M+H]^+$, Br)
ethyl 2-(4-fluoro-6-iodo-2H-indazol-2-yl)acetate	4-fluoro-6-iodo-1H-indazole (CAS 887568-03-8)	ethyl 2-bromoacetate	349.1 ($[M+H]^+$)
ethyl 2-(6-bromo-4,7-dichloro-2H-indazol-2-yl)acetate	6-bromo-4,7-dichloro-1H-indazole	ethyl 2-bromoacetate	353.0 ($[M+H]^+$, Br)
ethyl 2-(6-bromo-4-chloro-7-fluoro-2H-indazol-2-yl)acetate	6-bromo-4-chloro-7-fluoro-2H-indazole	ethyl 2-bromoacetate	336.96 ($[M+H]^+$, Br)
ethyl 2-(6-bromo-4-chloro-7-methoxy-2H-indazol-2-yl)acetate	6-bromo-4-chloro-7-methoxy-2H-indazole	ethyl 2-bromoacetate	348.98 ($[M+H]^+$, Br)

Synthesis of Examples

Example 1



2-(4-Chloro-6-(4-(piperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide hydrochloride

Step 1: tert-Butyl (2S)-2-(2-(6-bromo-4-chloro-2H-indazol-2-yl)-3-ethoxy-3-oxopropanoyl)pyrrolidine-1-carboxylate

A solution of (tert-butoxycarbonyl)-L-proline (1.58 g) in Tetrahydrofuran (7.5 ml) was cooled in an ice bath. Carbonyldiimidazole (1.19 g) was added. The cooling bath was removed and the mixture was stirred for 3h to give solution A. A solution of ethyl 2-(6-bromo-4-chloro-2H-indazol-2-yl)acetate (1.5 g) in tetrahydrofuran (7.5 ml) was cooled to -75°C. LDA, 2mol/l in THF (3.66 ml) was added dropwise within 5 min. The mixture was stirred for 30 min at -75°C. Solution A was added dropwise within 5 min. The mixture was allowed to warm to room temperature in the cooling bath overnight. After addition of sat. aqueous NH_4Cl-solution, the mixture was extracted twice with EtOAc.The organic layers were washed with water, combined, dried over sodium sulphate and concentrated to dryness to give the crude title compound (2.2 g) which was used for the next step without further purification. MS: m/e= 516.2 ($[M+H]^+$, Br)

Step 2: Ethyl 2-(6-bromo-4-chloro-2H-indazol-2-yl)-2-(3-thioxo-2,5,6,7-tetrahydro-3H-pyrrolo[1,2-c]imidazol-1-yl)acetate

A solution of tert-butyl (2S)-2-(2-(6-bromo-4-chloro-2H-indazol-2-yl)-3-ethoxy-3-oxopropanoyl)pyrrolidine-1-carboxylate (2.2 g) in HCl, 4M in dioxane (10.7 ml) was stirred for 1h at room temperature. The mixture was concentrated to dryness. The residue was dissolved in Ethanol (25 ml), potassium thiocyanate (558 mg) and HCl, 1 M in EtOH (4.27 ml) were added and

stirred over night. Water was added and the mixture was extracted with EtOAc. The organic layers were washed with water, dried over $MgSO_4$, filtered, concentrated and dried to give the crude title compound (2.1 g) which was used for the next step without further purification. MS: m/e= 457.1 ($[M+H]^+$, Br)

5 Step 3: Ethyl 2-(6-bromo-4-chloro-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate

A solution of ethyl 2-(6-bromo-4-chloro-2H-indazol-2-yl)-2-(3-thioxo-2,5,6,7-tetrahydro-3H-pyrrolo[1,2-c]imidazol-1-yl)acetate (2.13 g) in AcOH (10.ml) was cooled to 10°C. Hydrogen peroxide, 35% (2.78 g) was added dropwise. The reaction mixture was stirred for 45 min at room 10 temperature. The excess of hydrogen peroxide was destroyed by addition of saturated sodium sulfit solution. After addition of some water (just enough to dissolve all salts) and EtOAc the mixture was brought to pH 9 by careful addition of solid sodium carbonate. The mixture was extracted with EtOAc. The organic layers were washed with water, dried over sodium sulphate and concentrated. The product was purified by chromatography (SiO_2, 0-20% EtOH in EtOAc) to 15 give the title compound (0.64 g) as light brown solid. MS: m/e= 425.2 ($[M+H]^+$, Br)

Step 4: tert-Butyl 4-(4-(4-chloro-2-(1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-ethoxy-2-oxoethyl)-2H-indazol-6-yl)phenyl)piperazine-1-carboxylate

Ethyl 2-(6-bromo-4-chloro-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate (100 mg), (4-(4-(tert-butoxycarbonyl)piperazin-1-yl)phenyl)boronic acid (217 mg) and 20 cesium carbonate (231 mg) were mixed with toluene (3.08 ml), degassed by bubbling argon through the mixture under ultra sonic treatment. [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (18 mg) was added and the mixture was stirred for 30 min at 115°C in a sealed tube. The mixture was cooled to room temperature, diluted with EtOAc, washed with half concentrated sodium carbonate solution, dried over sodium sulphate 25 and concentrated. The crude material was purified by flash chromatography (SiO_2, 0% to 100% EtOAc in n-heptane) to give the title compound (83 mg) as light brown solid. MS: m/e= 605.6 ($[M+H]^+$)

Step 5: tert-Butyl 4-(4-(4-chloro-2-(1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-oxo-2-(thiazol-2-ylamino)ethyl)-2H-indazol-6-yl)phenyl)piperazine-1-carboxylate

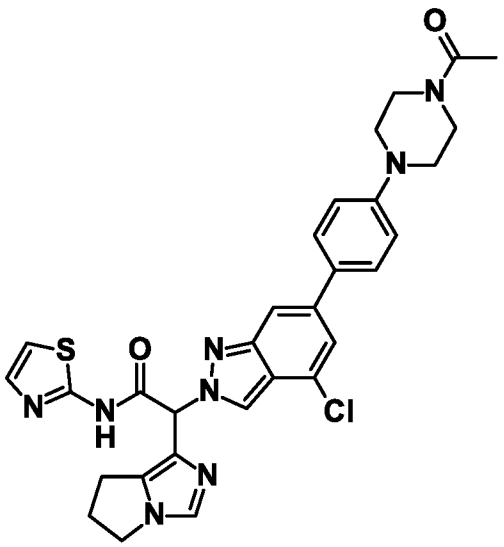
30 To a solution of tert-butyl 4-(4-(4-chloro-2-(1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-ethoxy-2-oxoethyl)-2H-indazol-6-yl)phenyl)piperazine-1-carboxylate (80.9 mg) in THF (1.81 ml) were added LiOH 1M (201 µl) and Water (722 µl). The mixture was stirred for 30 min at room temperature. The mixture was concentrated and dried. The residue was dissolved in DMF

(1.81 ml). After addition of thiazol-2-amine (16.1 mg), HATU (61 mg) and Hunig's base (51.8 mg) the mixture was stirred for 45 min at room temperature. Water was added and the mixture was extracted with EtOAc. The org layers were combined, dried, filtered and concentrated. The crude material was purified by flash chromatography (SiO_2, 0% to 40% MeOH in AcOEt) followed by another chromatography (SiO_2, 0% to 20% MeOH in dichloromethane)to give the title compound (49 mg) as off-white solid. MS: m/e= 659.5 ($[M+H]^+$)

Step 6: 2-(4-Chloro-6-(4-(piperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide hydrochloride

To a solution of tert-butyl 4-(4-(4-chloro-2-(1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-oxo-2-(thiazol-2-ylamino)ethyl)-2H-indazol-6-yl)phenyl)piperazine-1-carboxylate (47.4 mg) in dichloromethane (1.69 ml) and methanol (967 µl) was added HCl, 4M in dioxan (899 µl). The mixture was stirred for 45 min at room temperature. The mixture was concentrated, once suspended in dichloromethane and concentrated and dried to give the title compound (47 mg) as light yellow solid. MS: m/e= 559.4 ($[M+H]^+$)

Example 2

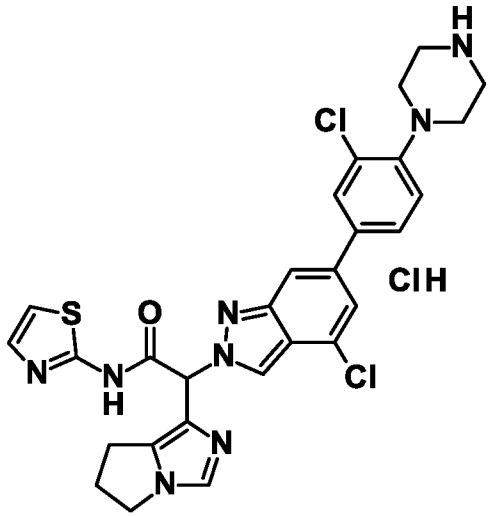


2-(6-(4-(4-Acetylpiperazin-1-yl)phenyl)-4-chloro-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide

To a suspension of 2-(4-chloro-6-(4-(piperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide hydrochloride (*Example 1*, 40 mg) in dichloromethane (5 ml) were added triethylamine (20.4 mg) and acetyl chloride (5.8 mg) and the mixture was stirred over night. Acetyl chloride (5.8 mg) was added and the mixture was stirred

for 1 h. The mixture was diluted with dichloromethane, washed with sat. sodium carbonate solution and with water. The organic layers were dried over sodium sulphate, filtered, concentrated, and dried under high vacuum at 60 °C to give the title compound (37 mg) as a grey solid. MS: m/e= 599.5 ($[M-H]^-$)

Example 3



2-(4-Chloro-6-(3-chloro-4-(piperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide hydrochloride

Step 1: tert-Butyl 4-(2-chloro-4-(4-chloro-2-(1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-ethoxy-2-oxoethyl)-2H-indazol-6-yl)phenyl)piperazine-1-carboxylate

In analogy to *Example 1, step 4*, ethyl 2-(6-bromo-4-chloro-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate (*Example 1, step 3)* was treated with (4-(4-(tert-butoxycarbonyl)piperazin-1-yl)-3-chlorophenyl)boronic acid in toluene in the presence of cesium carbonate and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) to give the title compound as off-white solid. MS: m/e= 639.5 ($[M+H]^+$)

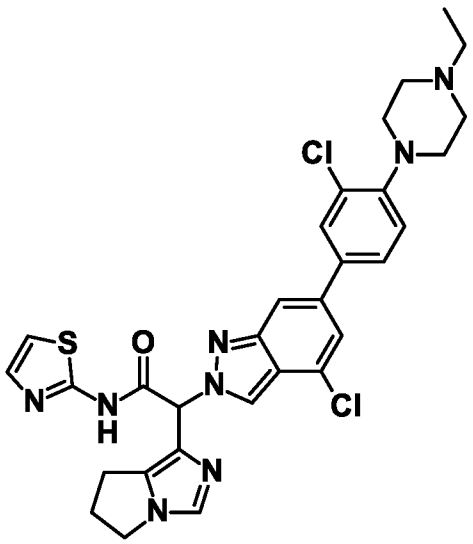
Step 2: tert-Butyl 4-(2-chloro-4-(4-chloro-2-(1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-oxo-2-(thiazol-2-ylamino)ethyl)-2H-indazol-6-yl)phenyl)piperazine-1-carboxylate

In analogy to *Example 1, step 5*, tert-butyl 4-(2-chloro-4-(4-chloro-2-(1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-ethoxy-2-oxoethyl)-2H-indazol-6-yl)phenyl)piperazine-1-carboxylate was first treated with LiOH and the resulting acid salt was reacted with thiazol-2-amine in the presence of HATU and Hunig's base to give the title compound as off-white solid. MS: m/e= 693.4 ($[M+H]^+$)

Step 2: 2-(4-Chloro-6-(3-chloro-4-(piperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide hydrochloride

In analogy to *Example 1, step 6*, a solution of tert-butyl 4-(2-chloro-4-(4-chloro-2-(1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-oxo-2-(thiazol-2-ylamino)ethyl)-2H-indazol-6-yl)phenyl)piperazine-1-carboxylate in dichloromethane and methanol was treated with HCl in dioxane to give the title compound as off-white solid. MS: m/e= 591.5 ($[M-H]^-$)

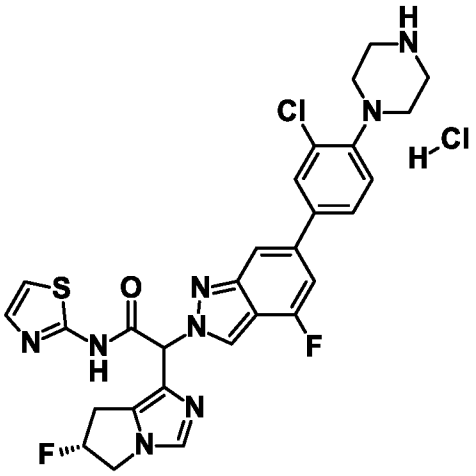
Example 4



2-(4-Chloro-6-(3-chloro-4-(4-ethylpiperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide

To a solution of 2-(4-chloro-6-(3-chloro-4-(piperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide hydrochloride (58.0 mg) in N,N-dimethylformamide (2.14 ml) were added iodoethane (15.8 mg) and Hunig's base (35.7 mg) and the mixture was stirred overnight.The reaction mixture was poured into H2O (25 ml) and extracted with EtOAc, dried, filtered and concentrated. The crude material was purified by preparative TLC (SiO_2, 2.0 mm, 9:1 dichloromethane/MeOH) to give the title compound (17 mg) as off-white solid. MS: m/e= 619.6 ($[M-H]^-$)

Example 6



2-(6-(3-Chloro-4-(piperazin-1-yl)phenyl)-4-fluoro-2H-indazol-2-yl)-2-((R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide hydrochloride

Step 1: tert-Butyl (2S,4R)-2-(3-ethoxy-2-(4-fluoro-6-iodo-2H-indazol-2-yl)-3-oxopropanoyl)-4-fluoropyrrolidine-1-carboxylate

In analogy to *Example 1, step 1*, (2S,4R)-1-(tert-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid was treated with carbonyldiimidazole to give solution A. Ethyl 2-(4-fluoro-6-iodo-2H-indazol-2-yl)acetate was deprotonated with LDA and treated with solution A at -78 °C. After stirring at room temperature overnight and workup in analogy to *Example 1, step 1*, the crude title compound was obtained which was used for the next step without further purification. MS: m/e= 564.3 ($[M+H]^+$)

Step 2: Ethyl 2-((R)-6-fluoro-3-thioxo-2,5,6,7-tetrahydro-3H-pyrrolo[1,2-c]imidazol-1-yl)-2-(4-fluoro-6-iodo-2H-indazol-2-yl)acetate

In analogy to *Example 1, step 2*, tert-butyl (2S,4R)-2-(3-ethoxy-2-(4-fluoro-6-iodo-2H-indazol-2-yl)-3-oxopropanoyl)-4-fluoropyrrolidine-1-carboxylate was deprotected using HCl in dioxane followed by reaction with potassium thiocyanate to give the crude title compound which was used for the next step without further purification. MS: m/e= 505.2 ($[M+H]^+$)

Step 3: Ethyl 2-((R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-(4-fluoro-6-iodo-2H-indazol-2-yl)acetate

In analogy to *Example 1, step 3*, ethyl 2-((R)-6-fluoro-3-thioxo-2,5,6,7-tetrahydro-3H-pyrrolo[1,2-c]imidazol-1-yl)-2-(4-fluoro-6-iodo-2H-indazol-2-yl)acetate was treated with

hydrogen peroxide in AcOH to give the title compound as light brown solid. MS: m/e= 473.3 ([M+H]$^+$)

Step 4: tert-butyl 4-(2-chloro-4-(2-(2-ethoxy-1-((R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-oxoethyl)-4-fluoro-2H-indazol-6-yl)phenyl)piperazine-1-carboxylate

In analogy to *Example 1, step 4*, ethyl 2-((R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-(4-fluoro-6-iodo-2H-indazol-2-yl)acetate was reacted with (4-(4-(tert-butoxycarbonyl)piperazin-1-yl)-3-chlorophenyl)boronic acid in toluene in the presence of [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) and cesium carbonate to give the title compound as light brown solid. MS: m/e= 641.5 ([M+H]$^+$)

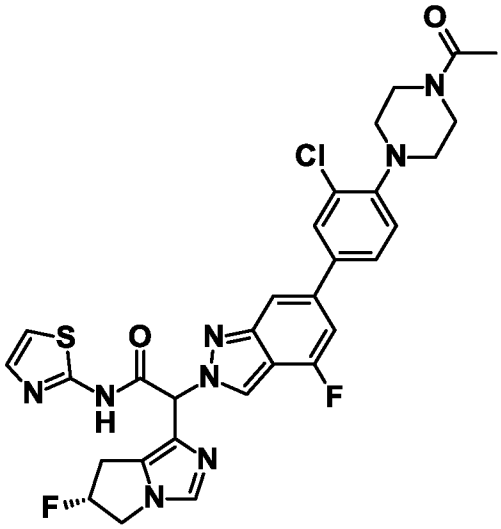
Step 5: tert-Butyl 4-(2-chloro-4-(4-fluoro-2-(1-((R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-oxo-2-(thiazol-2-ylamino)ethyl)-2H-indazol-6-yl)phenyl)piperazine-1-carboxylate

In analogy to *Example 1, step 5*, tert-butyl 4-(2-chloro-4-(2-(2-ethoxy-1-((R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-oxoethyl)-4-fluoro-2H-indazol-6-yl)phenyl)piperazine-1-carboxylate was first treated with LiOH and the resulting acid salt was reacted with thiazol-2-amine in the presence of HATU and Hunig's base to give the title compound as off-white solid. MS: m/e= 695.5 ([M+H]+)

Step 6: 2-(6-(3-Chloro-4-(piperazin-1-yl)phenyl)-4-fluoro-2H-indazol-2-yl)-2-((R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide hydrochloride

In analogy to *Example 1, step 6*, a solution of tert-butyl 4-(2-chloro-4-(4-fluoro-2-(1-((R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-oxo-2-(thiazol-2-ylamino)ethyl)-2H-indazol-6-yl)phenyl)piperazine-1-carboxylate in dichloromethane and methanol was treated with HCl in dioxane to give the title compound as off-white solid. MS: m/e= 595.4 ([M+H]$^+$)

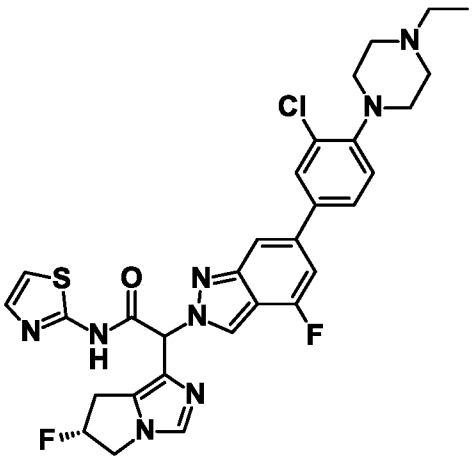
Example 7



2-(6-(4-(4-Acetylpiperazin-1-yl)-3-chlorophenyl)-4-fluoro-2H-indazol-2-yl)-2-((R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide

In analogy to *Example 2*, 2-(6-(3-chloro-4-(piperazin-1-yl)phenyl)-4-fluoro-2H-indazol-2-yl)-2-((R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide hydrochloride (*Example 6*) was treated with acetyl chloride in the presence of triethylamine to give the title compound as off-white solid. MS: m/e= 637.4 ($[M+H]^+$)

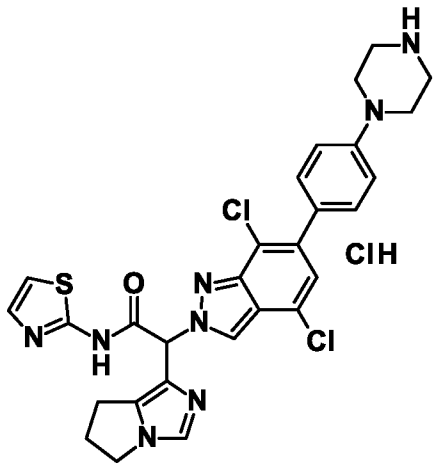
Example 8



2-(6-(3-Chloro-4-(4-ethylpiperazin-1-yl)phenyl)-4-fluoro-2H-indazol-2-yl)-2-((R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide

In analogy to *Example 4*, 2-(6-(3-chloro-4-(piperazin-1-yl)phenyl)-4-fluoro-2H-indazol-2-yl)-2-((R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide hydrochloride (*Example 6*) was treated with iodoethane in the presence of triethylamine to give the title compound as off-white solid. MS: m/e= 623.4 ($[M+H]^+$)

Example 9



2-(4,7-Dichloro-6-(4-(piperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide hydrochloride

Step 1: tert-Butyl (2S)-2-(2-(6-bromo-4,7-dichloro-2H-indazol-2-yl)-3-ethoxy-3-oxopropanoyl)pyrrolidine-1-carboxylate

In analogy to *Example 1, step 1*, (tert-butoxycarbonyl)-L-proline was treated with carbonyldiimidazole to give solution A. Ethyl 2-(6-bromo-4,7-dichloro-2H-indazol-2-yl)acetate was deprotonated with LDA and treated with solution A at -78 °C. After stirring at room temperature overnight and workup in analogy to *Example 1, step 1*, the crude title compound was obtained which was used for the next step without further purification. MS: m/e= 550.2 ($[M+H]^+$)

Step 2: Ethyl 2-(6-bromo-4,7-dichloro-2H-indazol-2-yl)-2-(3-thioxo-2,5,6,7-tetrahydro-3H-pyrrolo[1,2-c]imidazol-1-yl)acetate

In analogy to *Example 1, step 2*, tert-butyl (2S)-2-(2-(6-bromo-4,7-dichloro-2H-indazol-2-yl)-3-ethoxy-3-oxopropanoyl)pyrrolidine-1-carboxylate was deprotected using HCl in dioxane followed by reaction with potassium thiocyanate to give the crude title compound which was used for the next step without further purification. MS: m/e= 491.1 ($[M+H]^+$, Br)

Step 3: Ethyl 2-(6-bromo-4,7-dichloro-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate

In analogy to *Example 1, step 3*, ethyl 2-(6-bromo-4,7-dichloro-2H-indazol-2-yl)-2-(3-thioxo-2,5,6,7-tetrahydro-3H-pyrrolo[1,2-c]imidazol-1-yl)acetate was treated with hydrogen peroxide in AcOH to give the title compound as light yellow solid. MS: m/e= 457.1 ($[M+H]^+$, Br)

Step 4: tert-Butyl 4-(4-(4,7-dichloro-2-(1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-ethoxy-2-oxoethyl)-2H-indazol-6-yl)phenyl)piperazine-1-carboxylate

In analogy to *Example 1, step 4*, ethyl 2-(6-bromo-4,7-dichloro-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate was treated with (4-(4-(tert-butoxycarbonyl)piperazin-1-yl)phenyl)boronic acid in toluene in the presence of cesium carbonate and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) to give the title compound as light brown solid. MS: m/e= 639.5 ($[M+H]^+$)

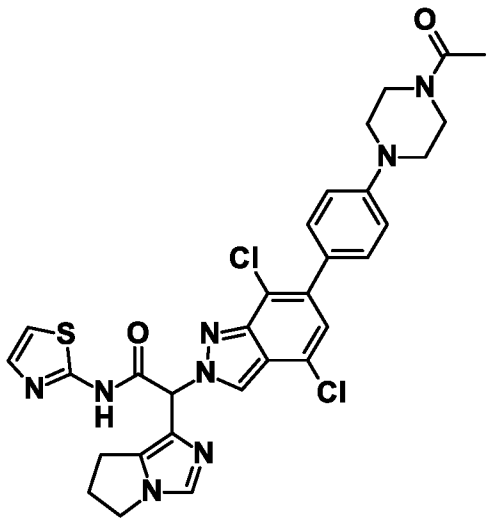
Step 5: tert-Butyl 4-(4-(4,7-dichloro-2-(1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-oxo-2-(thiazol-2-ylamino)ethyl)-2H-indazol-6-yl)phenyl)piperazine-1-carboxylate

In analogy to *Example 1, step 5*, tert-butyl 4-(4-(4,7-dichloro-2-(1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-ethoxy-2-oxoethyl)-2H-indazol-6-yl)phenyl)piperazine-1-carboxylate was first treated with LiOH and the resulting acid salt was reacted with thiazol-2-amine in the presence of HATU and Hunig's base to give the title compound as light brown solid. MS: m/e= 691.5 ($[M-H]^-$)

Step 6: 2-(4,7-Dichloro-6-(4-(piperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide hydrochloride

In analogy to *Example 1, step 6*, a solution of tert-butyl 4-(4-(4,7-dichloro-2-(1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-oxo-2-(thiazol-2-ylamino)ethyl)-2H-indazol-6-yl)phenyl)piperazine-1-carboxylate in dichloromethane and methanol was treated with HCl in dioxane to give the title compound as light yellow solid. MS: m/e= 591.4 ($[M-H]^-$)

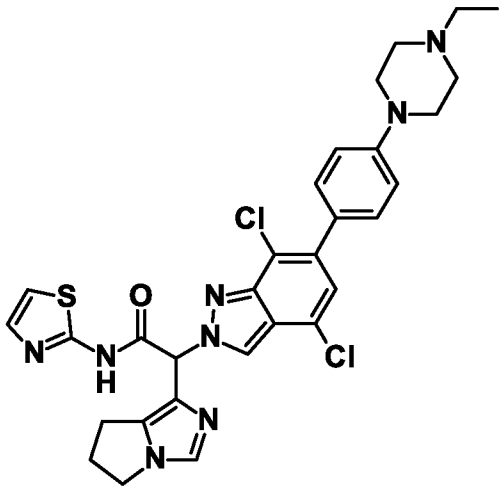
Example 12



2-(6-(4-(4-Acetylpiperazin-1-yl)phenyl)-4,7-dichloro-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide

In analogy to *Example 2*, 2-(4,7-dichloro-6-(4-(piperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide hydrochloride (*Example 9*) was treated with acetyl chloride in the presence of triethylamine to give the title compound as light brown solid. MS: m/e= 635.3 ($[M+H]^+$)

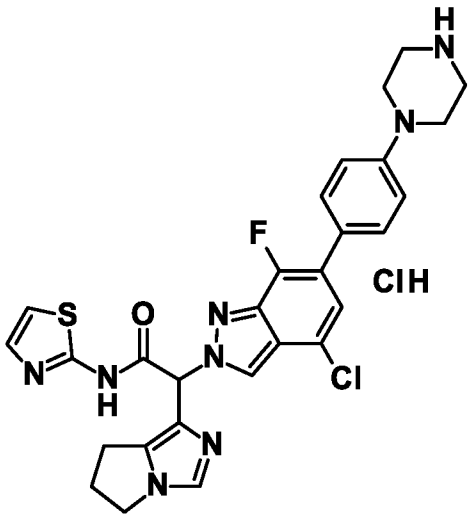
Example 13



2-(4,7-Dichloro-6-(4-(4-ethylpiperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide

In analogy to *Example 4*, 2-(4,7-dichloro-6-(4-(piperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide hydrochloride (*Example 9*) was treated with iodoethane in the presence of triethylamine to give the title compound as light brown solid. MS: m/e= 621.3 ($[M+H]^+$)

Example 15



2-(4-Chloro-7-fluoro-6-(4-(piperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide hydrochloride

Step 1: tert-Butyl (2S)-2-(2-(6-bromo-4-chloro-7-fluoro-2H-indazol-2-yl)-3-ethoxy-3-oxopropanoyl)pyrrolidine-1-carboxylate

In analogy to *Example 1, step 1*, (tert-butoxycarbonyl)-L-proline was treated with carbonyldiimidazole to give solution A. Ethyl 2-(6-bromo-4-chloro-7-fluoro-2H-indazol-2-yl)acetate was deprotonated with LDA and treated with solution A at -78 °C. After stirring at room temperature overnight and workup in analogy to *Example 1, step 1*, the crude title compound was obtained which was used for the next step without further purification.

Step 2: Ethyl 2-(6-bromo-4-chloro-7-fluoro-2H-indazol-2-yl)-2-(3-thioxo-2,5,6,7-tetrahydro-3H-pyrrolo[1,2-c]imidazol-1-yl)acetate

In analogy to *Example 1, step 2*, tert-butyl (2S)-2-(2-(6-bromo-4-chloro-7-fluoro-2H-indazol-2-yl)-3-ethoxy-3-oxopropanoyl)pyrrolidine-1-carboxylate was deprotected using HCl in dioxane followed by reaction with potassium thiocyanate to give the crude title compound which was used for the next step without further purification. MS: m/e= 475.1 ($[M+H]^+$)

Step 3: Ethyl 2-(6-bromo-4-chloro-7-fluoro-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate

In analogy to *Example 1, step 3*, ethyl 2-(6-bromo-4-chloro-7-fluoro-2H-indazol-2-yl)-2-(3-thioxo-2,5,6,7-tetrahydro-3H-pyrrolo[1,2-c]imidazol-1-yl)acetate was treated with hydrogen peroxide in AcOH to give the title compound as light yellow solid. MS: m/e= 443.2 ($[M+H]^+$, Br)

Step 4: tert-Butyl 4-(4-(4-chloro-2-(1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-ethoxy-2-oxoethyl)-7-fluoro-2H-indazol-6-yl)phenyl)piperazine-1-carboxylate

In analogy to *Example 1, step 4*, ethyl 2-(6-bromo-4-chloro-7-fluoro-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate was treated with (4-(4-(tert-butoxycarbonyl)piperazin-1-yl)phenyl)boronic acid in toluene in the presence of cesium carbonate and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) to give the title compound as off-white solid. MS: m/e= 623.4 ($[M+H]^+$)

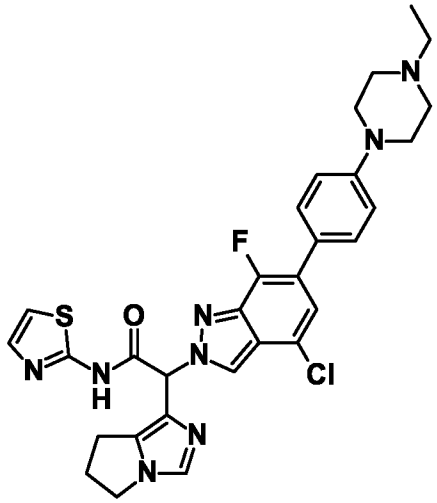
Step 5: tert-Butyl 4-(4-(4-chloro-2-(1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-oxo-2-(thiazol-2-ylamino)ethyl)-7-fluoro-2H-indazol-6-yl)phenyl)piperazine-1-carboxylate

In analogy to *Example 1, step 5*, tert-butyl 4-(4-(4-chloro-2-(1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-ethoxy-2-oxoethyl)-7-fluoro-2H-indazol-6-yl)phenyl)piperazine-1-carboxylate was first treated with LiOH and the resulting acid salt was reacted with thiazol-2-amine in the presence of HATU and Hunig's base to give the title compound as off-white solid. MS: m/e= 675.5 ($[M-H]^-$)

Step 6: 2-(4-Chloro-7-fluoro-6-(4-(piperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide hydrochloride

In analogy to *Example 1, step 6*, a solution of tert-butyl 4-(4-(4-chloro-2-(1-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-oxo-2-(thiazol-2-ylamino)ethyl)-7-fluoro-2H-indazol-6-yl)phenyl)piperazine-1-carboxylate in dichloromethane and methanol was treated with HCl in dioxane to give the title compound as off-white solid. MS: m/e= 575.4 ($[M-H]^-$)

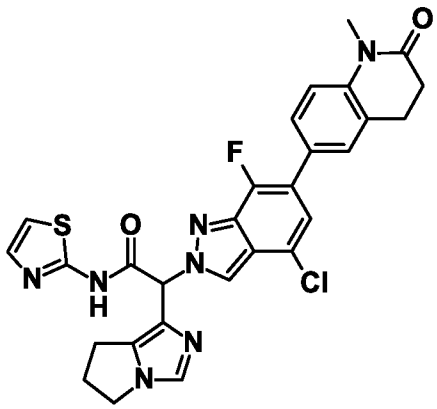
Example 16



2-(4-Chloro-6-(4-(4-ethylpiperazin-1-yl)phenyl)-7-fluoro-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide

In analogy to *Example 4*, 2-(4-chloro-7-fluoro-6-(4-(piperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide hydrochloride (*Example 15*) was treated with iodoethane in the presence of triethylamine to give the title compound as colorless solid. MS: m/e= 603.5 ([M-H]$^-$)

Example 18



2-(4-Chloro-7-fluoro-6-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide

Step 1: Ethyl 2-(4-chloro-7-fluoro-6-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate

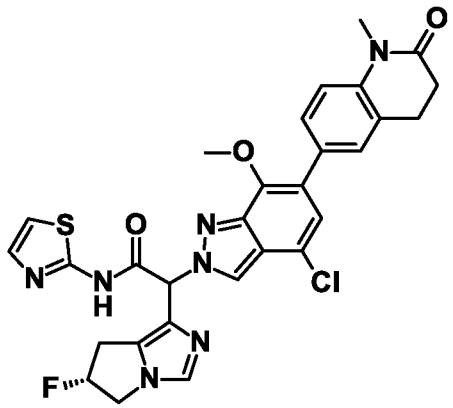
In analogy to *Example 1, step 4*, ethyl 2-(6-bromo-4-chloro-7-fluoro-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate (*Example 15, step 3*) was reacted with 1-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroquinolin-2(1H)-one in toluene in the presence of [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), cesium

carbonate and 10 equivalents of water to give the title compound as off-white solid. MS: m/e= 522.3 ([M+H]$^+$)

Step 2: 2-(4-Chloro-7-fluoro-6-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide

In analogy to *Example 1, step 5*, ethyl 2-(4-chloro-7-fluoro-6-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate was first treated with LiOH and the resulting acid salt was reacted with thiazol-2-amine in the presence of HATU and Hunig's base to give the title compound as off-white solid. MS: m/e= 576.2 ([M+H]$^+$)

Example 20



2-[4-Chloro-7-methoxy-6-(1-methyl-2-oxo-3,4-dihydroquinolin-6-yl)indazol-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-(1,3-thiazol-2-yl)acetamide

Step 1: tert-Butyl (2S,4R)-2-(2-(6-bromo-4-chloro-7-methoxy-2H-indazol-2-yl)-3-ethoxy-3-oxopropanoyl)-4-fluoropyrrolidine-1-carboxylate

In analogy to *Example 1, step 1*, (2S,4R)-1-(tert-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid was treated with carbonyldiimidazole to give solution A. Ethyl 2-(6-bromo-4-chloro-7-methoxy-2H-indazol-2-yl)acetate was deprotonated with LDA and treated with solution A at -78 °C. After stirring at room temperature for 90 min and workup in analogy to *Example 1, step 1*, the crude title compound was obtained which was used for the next step without further purification. MS: m/e= 564.2 ([M+H]$^+$, Br)

Step 2: Ethyl 2-(6-bromo-4-chloro-7-methoxy-2H-indazol-2-yl)-2-((R)-6-fluoro-3-thioxo-2,5,6,7-tetrahydro-3H-pyrrolo[1,2-c]imidazol-1-yl)acetate

In analogy to *Example 1, step 2*, tert-butyl (2S,4R)-2-(2-(6-bromo-4-chloro-7-methoxy-2H-indazol-2-yl)-3-ethoxy-3-oxopropanoyl)-4-fluoropyrrolidine-1-carboxylate was deprotected using HCl in dioxane followed by reaction with potassium thiocyanate to give the crude title compound which was used for the next step without further purification. MS: m/e= 505.1 ($[M+H]^+$, Br)

Step 3: Ethyl 2-(6-bromo-4-chloro-7-methoxy-2H-indazol-2-yl)-2-((R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate

In analogy to *Example 1, step 3*, ethyl 2-(6-bromo-4-chloro-7-methoxy-2H-indazol-2-yl)-2-((R)-6-fluoro-3-thioxo-2,5,6,7-tetrahydro-3H-pyrrolo[1,2-c]imidazol-1-yl)acetate was treated with hydrogen peroxide in AcOH to give the title compound as light brown solid. MS: m/e= 472.9 ($[M+H]^+$, Br)

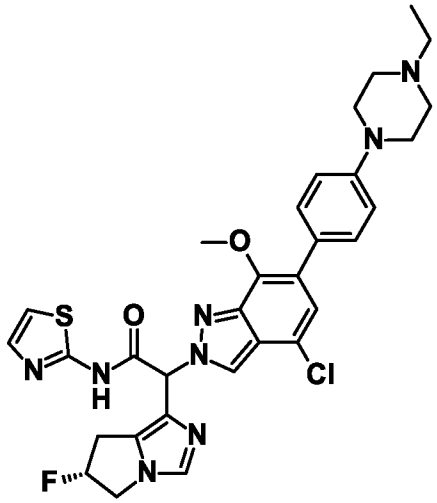
Step 4: Ethyl 2-(4-chloro-7-methoxy-6-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-2H-indazol-2-yl)-2-((R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate

In analogy to *Example 1, step 4*, ethyl 2-(6-bromo-4-chloro-7-methoxy-2H-indazol-2-yl)-2-((R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate (*Example 19, step 3*) was reacted with 1-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroquinolin-2(1H)-one in toluene in the presence of [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), cesium carbonate and 10 equivalents of water to give the title compound as off-white solid. MS: m/e= 552.3 ($[M+H]^+$)

Step 5: 2-[4-Chloro-7-methoxy-6-(1-methyl-2-oxo-3,4-dihydroquinolin-6-yl)indazol-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-(1,3-thiazol-2-yl)acetamide

In analogy to *Example 1, step 5*, ethyl 2-(4-chloro-7-methoxy-6-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-2H-indazol-2-yl)-2-((R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate was first treated with LiOH and the resulting acid salt was reacted with thiazol-2-amine in the presence of HATU and Hunig's base to give the title compound as off-white solid. MS: m/e= 606.2 ($[M+H]^+$)

Example 21



2-[4-Chloro-6-[4-(4-ethylpiperazin-1-yl)phenyl]-7-methoxyindazol-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-(1,3-thiazol-2-yl)acetamide

5 Step 1: tert-Butyl 4-(4-(4-chloro-2-(2-ethoxy-1-((R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-oxoethyl)-7-methoxy-2H-indazol-6-yl)phenyl)piperazine-1-carboxylate

In analogy to *Example 1, step 4*, ethyl 2-(6-bromo-4-chloro-7-methoxy-2H-indazol-2-yl)-2-((R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate (*Example 20, step 3*) was reacted with (4-(4-(tert-butoxycarbonyl)piperazin-1-yl)phenyl)boronic acid in toluene in the
10 presence of [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) and cesium carbonate to give the title compound as off-white solid. MS: m/e= 653.4 ($[M+H]^+$)

Step 2: tert-Butyl 4-(4-(4-chloro-2-(1-((R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-oxo-2-(thiazol-2-ylamino)ethyl)-7-methoxy-2H-indazol-6-yl)phenyl)piperazine-1-
15 carboxylate

In analogy to *Example 1, step 5*, tert-butyl 4-(4-(4-chloro-2-(2-ethoxy-1-((R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-oxoethyl)-7-methoxy-2H-indazol-6-yl)phenyl)piperazine-1-carboxylate was first treated with LiOH and the resulting acid salt was reacted with thiazol-2-amine in the presence of HATU and Hunig's base to give the title compound
20 as off-white solid. MS: m/e= 705.5 ($[M-H]^-$)

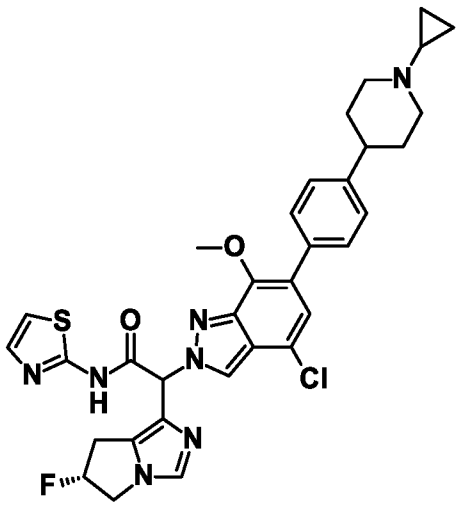
Step 3: 2-(4-Chloro-7-methoxy-6-(4-(piperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-((R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide hydrochloride

In analogy to *Example 1, step 6*, a solution of tert-butyl 4-(4-(4-chloro-2-(1-((R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-2-oxo-2-(thiazol-2-ylamino)ethyl)-7-methoxy-2H-indazol-6-yl)phenyl)piperazine-1-carboxylate in dichloromethane and methanol was treated with HCl in dioxane to give the title compound as off-white solid. MS: m/e= 605.5 ($[M-H]^-$)

Step 4: 2-[4-Chloro-6-[4-(4-ethylpiperazin-1-yl)phenyl]-7-methoxyindazol-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-(1,3-thiazol-2-yl)acetamide

In analogy to *Example 4*, 2-(4-chloro-7-methoxy-6-(4-(piperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-((R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide hydrochloride was treated with iodoethane in the presence of triethylamine to give the title compound as off-white solid. MS: m/e= 633.4 ($[M-H]^-$)

Example 22



2-[4-Chloro-6-[4-(1-cyclopropylpiperidin-4-yl)phenyl]-7-methoxyindazol-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-(1,3-thiazol-2-yl)acetamide

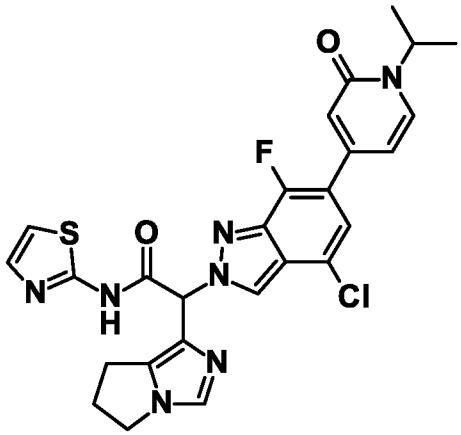
Step 1: Ethyl 2-(4-chloro-6-(4-(1-cyclopropylpiperidin-4-yl)phenyl)-7-methoxy-2H-indazol-2-yl)-2-((R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate

In analogy to *Example 1, step 4*, ethyl 2-(6-bromo-4-chloro-7-methoxy-2H-indazol-2-yl)-2-((R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate (*Example 20, step 3*) was reacted with 1-cyclopropyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidine (CAS# 2244702-81-4) in THF and water in the presence of [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) and cesium carbonate to give the title compound as light brown solid. MS: m/e= 592.4 ($[M+H]^+$)

Step 2: 2-[4-Chloro-6-[4-(1-cyclopropylpiperidin-4-yl)phenyl]-7-methoxyindazol-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-(1,3-thiazol-2-yl)acetamide

In analogy to *Example 1, step 5*, ethyl 2-(4-chloro-6-(4-(1-cyclopropylpiperidin-4-yl)phenyl)-7-methoxy-2H-indazol-2-yl)-2-((R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate was first treated with LiOH and the resulting acid salt was reacted with thiazol-2-amine in the presence of HATU and Hunig's base to give the title compound as off-white solid. MS: m/e= 644.4 ($[M-H]^-$)

Example 23



2-(4-Chloro-7-fluoro-6-(1-isopropyl-2-oxo-1,2-dihydropyridin-4-yl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide

Step 1: Ethyl 2-(4-chloro-7-fluoro-6-(1-isopropyl-2-oxo-1,2-dihydropyridin-4-yl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate

In analogy to *Example 1, step 4*, ethyl 2-(6-bromo-4-chloro-7-fluoro-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate (*Example 15, step 3*) was reacted with 1-isopropyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1H)-one in toluene in the presence of [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), cesium carbonate and 10 equivalents of water to give the title compound as off-white solid. MS: m/e= 498.4 ($[M+H]^+$)

Step 2: 2-(4-Chloro-7-fluoro-6-(1-isopropyl-2-oxo-1,2-dihydropyridin-4-yl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide

In analogy to *Example 1, step 5*, ethyl 2-(4-chloro-7-fluoro-6-(1-isopropyl-2-oxo-1,2-dihydropyridin-4-yl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)acetate

was first treated with LiOH and the resulting acid salt was reacted with thiazol-2-amine in the presence of HATU and Hunig's base to give the title compound as off-white solid. MS: m/e= 550.4 ($[M-H]^-$).

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Claims

1. A compound selected from

2-(4-chloro-6-(4-(piperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide hydrochloride;

2-(6-(4-(4-acetylpiperazin-1-yl)phenyl)-4-chloro-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide;

2-(4-chloro-6-(3-chloro-4-(piperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide hydrochloride;

2-(4-chloro-6-(3-chloro-4-(4-ethylpiperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide;

2-(6-(3-chloro-4-(piperazin-1-yl)phenyl)-4-fluoro-2H-indazol-2-yl)-2-((R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide hydrochloride;

2-(6-(4-(4-acetylpiperazin-1-yl)-3-chlorophenyl)-4-fluoro-2H-indazol-2-yl)-2-((R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide;

2-(6-(3-chloro-4-(4-ethylpiperazin-1-yl)phenyl)-4-fluoro-2H-indazol-2-yl)-2-((R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide;

2-(4,7-dichloro-6-(4-(piperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide hydrochloride;

2-(6-(4-(4-acetylpiperazin-1-yl)phenyl)-4,7-dichloro-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide;

2-(4,7-dichloro-6-(4-(4-ethylpiperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide;

2-(4-chloro-7-fluoro-6-(4-(piperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide hydrochloride;

2-(4-chloro-6-(4-(4-ethylpiperazin-1-yl)phenyl)-7-fluoro-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide;

2-(4-chloro-7-fluoro-6-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide;

2-[4-chloro-7-methoxy-6-(1-methyl-2-oxo-3,4-dihydroquinolin-6-yl)indazol-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-(1,3-thiazol-2-yl)acetamide;

2-[4-chloro-6-[4-(4-ethylpiperazin-1-yl)phenyl]-7-methoxyindazol-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-(1,3-thiazol-2-yl)acetamide;

2-[4-chloro-6-[4-(1-cyclopropylpiperidin-4-yl)phenyl]-7-methoxyindazol-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-(1,3-thiazol-2-yl)acetamide;

2-(4-chloro-7-fluoro-6-(1-isopropyl-2-oxo-1,2-dihydropyridin-4-yl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide;

or pharmaceutically acceptable salts.

2. A compound according to claim 1 selected from

2-(4-chloro-6-(4-(piperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide hydrochloride;

2-(6-(4-(4-acetylpiperazin-1-yl)phenyl)-4-chloro-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide;

2-(4-chloro-6-(3-chloro-4-(piperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide hydrochloride;

2-(4-chloro-6-(3-chloro-4-(4-ethylpiperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide;

2-(6-(3-chloro-4-(piperazin-1-yl)phenyl)-4-fluoro-2H-indazol-2-yl)-2-((R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide hydrochloride;

2-(6-(4-(4-acetylpiperazin-1-yl)-3-chlorophenyl)-4-fluoro-2H-indazol-2-yl)-2-((R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide;

2-(6-(3-chloro-4-(4-ethylpiperazin-1-yl)phenyl)-4-fluoro-2H-indazol-2-yl)-2-((R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide;

2-(4,7-dichloro-6-(4-(piperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide hydrochloride;

2-(6-(4-(4-acetylpiperazin-1-yl)phenyl)-4,7-dichloro-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide;

2-(4,7-dichloro-6-(4-(4-ethylpiperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide;

2-(4-chloro-7-fluoro-6-(4-(piperazin-1-yl)phenyl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide hydrochloride;

2-(4-chloro-6-(4-(4-ethylpiperazin-1-yl)phenyl)-7-fluoro-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide;

2-(4-chloro-7-fluoro-6-(1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide;

2-[4-chloro-7-methoxy-6-(1-methyl-2-oxo-3,4-dihydroquinolin-6-yl)indazol-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-(1,3-thiazol-2-yl)acetamide;

2-[4-chloro-6-[4-(4-ethylpiperazin-1-yl)phenyl]-7-methoxyindazol-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-(1,3-thiazol-2-yl)acetamide;

2-[4-chloro-6-[4-(1-cyclopropylpiperidin-4-yl)phenyl]-7-methoxyindazol-2-yl]-2-[rac-(6R)-6-fluoro-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl]-N-(1,3-thiazol-2-yl)acetamide;

2-(4-chloro-7-fluoro-6-(1-isopropyl-2-oxo-1,2-dihydropyridin-4-yl)-2H-indazol-2-yl)-2-(6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-1-yl)-N-(thiazol-2-yl)acetamide.

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.

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

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

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.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2020/067082

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D487/04 A61P35/00 A61K31/496 A61K31/5377 A61K31/4709
A61K31/454 A61K31/4439
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, EMBASE, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2018/115218 A1 (F. HOFFMANN-LA ROCHE AG; HOFFMANN-LA ROCHE INC.; C4 THERAPEUTICS, INC.) 28 June 2018 (2018-06-28) abstract; claims pages 18-23; examples 2-6,8,10-20 -----	1-12
A	JIA, Y. ET AL.: "Overcoming EGFR(T790M) and EGFR(C797S) resistance with mutant-selective allosteric inhibitors", NATURE, vol. 534, no. 7605, 2016, pages 129-132, XP055342543, ISSN: 0028-0836, DOI: 10.1038/nature17960 cited in the application abstract page 130; figure 1 -----	1-12

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 July 2020	28/07/2020

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Kiernan, Andrea

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2020/067082

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2018/220149 A1 (F. HOFFMANN-LA ROCHE AG; HOFFMANN-LA ROCHE INC.; C4 THERAPEUTICS, INC.) 6 December 2018 (2018-12-06) abstract page 20; example 8 -----	1-12

1

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2020/067082

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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