(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 November 2023 (16.11.2023)

WIPO | PCT

(10) International Publication Number
WO 2023/217923 A1

(51) International Patent Classification:
C07D 487/04 (2006.01) *A61K 31/5377* (2006.01)
A61P 35/00 (2006.01) *A61K 9/00* (2006.01)

(21) International Application Number:
PCT/EP2023/062529

(22) International Filing Date:
11 May 2023 (11.05.2023)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
22173211.8 13 May 2022 (13.05.2022) EP
22175324.7 25 May 2022 (25.05.2022) EP

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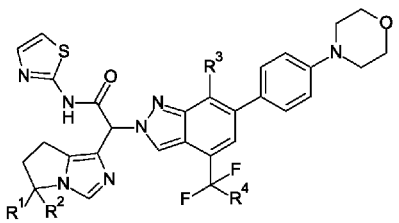
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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

(54) Title: NEW INDAZOLE DERIVATIVES



(I)

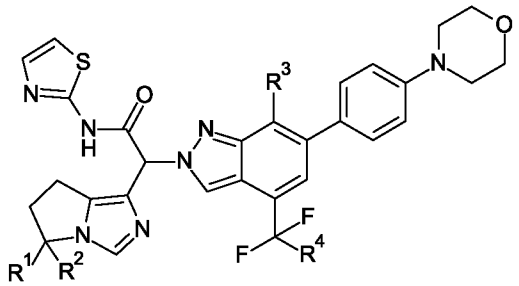
(57) Abstract: The invention provides novel compounds having the general formula (I) or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3 and R^4 are as described herein. The compound of formula (I) can be used as a medicament.

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New indazole derivatives

The present invention relates to compounds that are selective allosteric inhibitors of T790M/L858R, T790M/L858R/C797S, L858R, and/or L858R/C797S containing EGFR mutants, their manufacture, pharmaceutical compositions containing it and their use as therapeutically active substances.

The invention relates in particular to a novel compound of formula (I)



(I)

wherein

R^1 and R^2 are independently selected from alkyl, or R^1 and R^2 together with the carbon they are attached to form cycloalkyl;

R^3 is alkyl or haloalkyl; and

R^4 is hydrogen or halogen;

or a pharmaceutically acceptable salt thereof.

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 inhibitors, June 2016, Nature 534, 129-132)

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

The compound of formula (I) as described herein does have improved EGFR potency and selectivity for T790M/L858R, T790M/L858R/C797S, L858R and/or L858R/C797S containing EGFR mutants, in particular T790M and C797S containing EGFR mutants as well as improved physico-chemical properties.

In the present description the term “alkyl”, alone or in combination, signifies a straight-chain or branched-chain alkyl group with 1 to 8 carbon atoms, particularly a straight or branched-chain alkyl group with 1 to 6 carbon atoms and more particularly a straight or branched-chain alkyl group with 1 to 4 carbon atoms. Examples of straight-chain and branched-chain C1-C8 alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, sec.-butyl, the isomeric pentyls, the isomeric hexyls, the isomeric heptyls and the isomeric octyls, particularly methyl, ethyl, propyl, butyl and pentyl. Particular examples of alkyl are methyl, ethyl, propyl, isopropyl, and tert.-butyl. Methyl and ethyl are particular examples of “alkyl” in the compound of formula (I).

The term “cycloalkyl”, alone or in combination, signifies a cyclic ring system one or more rings comprising 3 to 8 carbon atoms and particularly comprising 3 to 6 carbon atoms. Examples of “cycloalkyl” are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, cycloheptyl, cyclooctanyl, bicyclo[1.1.1]pentanyl, bicyclo[1.1.1]hexanyl and bicyclo[1.1.1]heptanyl. A particular example of “cycloalkyl” is bicyclo[1.1.1]pentanyl.

The terms “halogen” or “halo”, alone or in combination, signifies fluorine, chlorine, bromine or iodine and particularly fluorine or chlorine. A particular “halogen” or “halo” is fluorine. The term “halo”, in combination with another group, denotes the substitution of said group with at least one halogen, particularly substituted with one to five halogens, particularly one to four halogens, i.e. one, two, three or four halogens.

The term “haloalkyl”, alone or in combination, denotes an alkyl group substituted with at least one halogen, particularly substituted with one to five halogens, particularly one to three halogens. Particular examples of “haloalkyl” are fluoromethyl, difluoromethyl and trifluoromethyl.

The term "pharmaceutically acceptable salt" refers to those salts of the compound of formula (I) 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.

If one of the starting materials or a compound of formula (I) contains one or more functional groups which are not stable or are reactive under the reaction conditions of one or more reaction steps, appropriate protecting groups (as described *e.g.* in “Protective Groups in Organic Chemistry” by T. W. Greene and P. G. M. Wuts, 3rd Ed., 1999, Wiley, New York) can be introduced before the critical step applying methods well known in the art. Such protecting groups can be removed at a

later stage of the synthesis using standard methods described in the literature. Examples of protecting groups are tert-butoxycarbonyl (Boc), 9-fluorenylmethyl carbamate (Fmoc), 2-trimethylsilylethyl carbamate (Teoc), carbobenzyloxy (Cbz) and p-methoxybenzyloxycarbonyl (Moz).

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.

The term “asymmetric carbon atom” means a carbon atom with four different substituents. According to the Cahn-Ingold-Prelog Convention the asymmetric carbon atom can be of the "R" or "S" configuration.

The invention thus relates to:

A compound according to the invention, wherein R^1 and R^2 are methyl, or R^1 and R^2 together with the carbon they are attached to form cyclopropyl;

A compound according to the invention, wherein R^1 and R^2 together with the carbon they are attached to form cyclopropyl;

A compound according to the invention, wherein R^1 and R^2 are methyl;

A compound according to the invention, wherein R^3 is alkyl;

A compound according to the invention, wherein R^3 is methyl or fluoromethyl;

A compound according to the invention, wherein R^3 is methyl;

A compound according to the invention, wherein R^4 is hydrogen or fluoro;

A compound according to the invention, wherein R^4 is hydrogen; and

A compound according to the invention, wherein R^4 is fluoro.

The invention further relates to a compound selected from

2-[4-(Difluoromethyl)-7-methyl-6-(4-morpholinophenyl)indazol-2-yl]-2-spiro[6,7-dihydropyrrolo[1,2-c]imidazole-5,1'-cyclopropane]-1-yl-N-thiazol-2-yl-acetamide;

2-[7-Methyl-6-(4-morpholinophenyl)-4-(trifluoromethyl)indazol-2-yl]-2-spiro[6,7-dihydropyrrolo[1,2-c]imidazole-5,1'-cyclopropane]-1-yl-N-thiazol-2-yl-acetamide; and

2-(5,5-Dimethyl-6,7-dihydropyrrolo[1,2-c]imidazol-1-yl)-2-[7-methyl-6-(4-morpholinophenyl)-4-(trifluoromethyl)indazol-2-yl]-N-thiazol-2-yl-acetamide;

or a pharmaceutically acceptable salt thereof.

The invention further relates to a compound selected from

2-[7-Methyl-6-(4-morpholinophenyl)-4-(trifluoromethyl)indazol-2-yl]-2-spiro[6,7-dihydropyrrolo[1,2-c]imidazole-5,1'-cyclopropane]-1-yl-N-thiazol-2-yl-acetamide; and

2-(5,5-Dimethyl-6,7-dihydropyrrolo[1,2-c]imidazol-1-yl)-2-[7-methyl-6-(4-morpholinophenyl)-4-(trifluoromethyl)indazol-2-yl]-N-thiazol-2-yl-acetamide;

or a pharmaceutically acceptable salt thereof.

The invention further relates to

2-[4-(Difluoromethyl)-7-methyl-6-(4-morpholinophenyl)indazol-2-yl]-2-spiro[6,7-dihydropyrrolo[1,2-c]imidazole-5,1'-cyclopropane]-1-yl-N-thiazol-2-yl-acetamide;

or a pharmaceutically acceptable salt thereof.

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

The preparation of a compound of formula (I) of the present invention may be carried out in sequential or convergent synthetic routes. Exemplary syntheses of the compounds of the invention are shown in the description of specific examples. The skills required for carrying out the reactions and purifications of the resulting products are known to those skilled in the art. The substituents and indices used in the following description of the processes have the significance given herein before unless indicated to the contrary. The reaction sequence is not limited to the one displayed in the specific example, however, depending on the starting materials and their respective reactivity the sequence of reaction steps can be freely altered. Starting materials are either commercially

available or can be prepared by methods analogous to the methods given below, by methods described in references cited in the description or in the examples, or by methods known in the art.

The invention also relates to a compound according to the invention when manufactured according to a process of the invention.

Another embodiment of the invention provides a pharmaceutical composition or medicament containing a compound of the invention and a therapeutically inert carrier, diluent or excipient, as well as a method of using the compounds of the invention to prepare such composition and medicament. In one example, the compound of formula (I) may be formulated by mixing at ambient temperature at the appropriate pH, and at the desired degree of purity, with physiologically acceptable carriers, i.e., carriers that are non-toxic to recipients at the dosages and concentrations employed into a galenical administration form. The pH of the formulation depends mainly on the particular use and the concentration of compound, but preferably ranges anywhere from about 3 to about 8. In one example, a compound of formula (I) is formulated in an acetate buffer, at pH 5. In another embodiment, the compound of formula (I) is sterile. The compound may be stored, for example, as a solid or amorphous composition, as a lyophilized formulation or as an aqueous solution.

Compositions are formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners.

The compound of the invention may be administered by any suitable means, including oral, topical (including buccal and sublingual), rectal, vaginal, transdermal, parenteral, subcutaneous, intraperitoneal, intrapulmonary, intradermal, intrathecal and epidural and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration.

The compound of the present invention may be administered in any convenient administrative form, e.g., tablets, powders, capsules, solutions, dispersions, suspensions, syrups,

sprays, suppositories, gels, emulsions, patches, etc. Such compositions may contain components conventional in pharmaceutical preparations, e.g., diluents, carriers, pH modifiers, sweeteners, bulking agents, and further active agents.

A typical formulation is prepared by mixing a compound of the present invention and a carrier or excipient. Suitable carriers and excipients are well known to those skilled in the art and are described in detail in, e.g., Ansel, Howard C., et al., Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. Philadelphia: Lippincott, Williams & Wilkins, 2004; Gennaro, Alfonso R., et al. Remington: The Science and Practice of Pharmacy. Philadelphia: Lippincott, Williams & Wilkins, 2000; and Rowe, Raymond C. Handbook of Pharmaceutical Excipients. Chicago, Pharmaceutical Press, 2005. The formulations may also include one or more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents, diluents and other known additives to provide an elegant presentation of the drug (i.e., a compound of the present invention or pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (i.e., medicament).

The invention thus also relates in particular to:

A compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as therapeutically active substance;

A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a therapeutically inert carrier;

A compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment or prophylaxis of cancer;

A compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment or prophylaxis of non-small cell lung cancer;

A compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in the treatment or prophylaxis of cancer, in particular non-small cell lung cancer;

The use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, for the treatment or prophylaxis of cancer, in particular non-small cell lung cancer;

The use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment or prophylaxis of cancer, in particular non-small cell lung cancer; and

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

A certain embodiment of the invention 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.

A certain embodiment of the invention relates to the compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, for the use in the treatment or prophylaxis of cancer, in particular non-small cell lung cancer, characterized by at least one EGFR mutation selected from T790M/L858R, T790M/L858R/C797S, L858R and L858R/C797S.

A certain embodiment of the invention relates to a method for the treatment or prophylaxis of cancer, in particular non-small cell lung cancer, wherein at least one EGFR mutation selected from T790M/L858R, T790M/L858R/C797S, L858R and L858R/C797S is present in the cancer, which method comprises administering an effective amount of a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, to a patient in need thereof.

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

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 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. 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 is a compounds of formula (I) as described herein, when manufactured according to any one of the described processes.

The compound of formula (I) or a pharmaceutically acceptable salt thereof can be used as a medicament (e.g. in the form of a pharmaceutical preparation). The pharmaceutical preparation 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 compound of formula (I) or a pharmaceutically acceptable salt thereof 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 preparation 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. The pharmaceutical preparation can also contain still other therapeutically valuable substances.

The dosage can vary in wide limits and will, 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.

Pharmaceutical Compositions

The compound of formula (I) or a pharmaceutically acceptable salt thereof can be used as a therapeutically active substance, e.g. in the form of a pharmaceutical preparation. The pharmaceutical preparation can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatin capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The compound of formula (I) or a pharmaceutically acceptable salt thereof can be processed with pharmaceutically inert, inorganic or organic carriers for the production of a pharmaceutical preparation. Lactose, corn starch or derivatives thereof, talc, stearic acids or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatin capsules. Suitable carriers for soft gelatin capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Depending on the nature of the active substance no carriers are however usually required in the case of soft gelatin capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, glycerol, vegetable oil and the like. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

The pharmaceutical preparation can, moreover, contain pharmaceutically acceptable auxiliary substances such as preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. The pharmaceutical preparation can also contain still other therapeutically valuable substances.

Medicaments containing a compound of formula (I) or a pharmaceutically acceptable salt thereof and a therapeutically inert carrier are also provided by the present invention, as is a process for their production, which comprises bringing a compound of formula (I) and/or pharmaceutically

acceptable salts thereof and, if desired, one or more other therapeutically valuable substances into a galenical administration form together with one or more therapeutically inert carriers.

The dosage can vary within wide limits and will, have to be adjusted to the individual requirements in each particular case. In the case of oral administration the dosage for adults can vary from about 0.01 mg to about 1000 mg per day of a compound of general formula (I) or of the corresponding amount of a pharmaceutically acceptable salt thereof. The daily dosage may be administered as single dose or in divided doses and, in addition, the upper limit can also be exceeded when this is found to be indicated.

The following examples illustrate the present invention without limiting it, but serve merely as representative thereof. The pharmaceutical preparations conveniently contain about 1-500 mg, particularly 1-100 mg, of a compound of formula (I). Examples of compositions according to the invention are:

Example A

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

ingredient	mg/tablet			
	5	25	100	500
(1) Compound of formula (I)	5	25	100	500
(2) Lactose Anhydrous DTG	125	105	30	150
(3) Sta-Rx 1500	6	6	6	60
(4) Microcrystalline Cellulose	30	30	30	450
(5) Magnesium Stearate	1	1	1	1
Total	167	167	167	831

Table 1: possible tablet composition

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.

Example B-1

Capsules of the following composition are manufactured:

ingredient	mg/capsule			
	5	25	100	500
(1) Compound of formula (I)	5	25	100	500
(2) Hydrous Lactose	159	123	148	-
(3) Corn Starch	25	35	40	70
(4) Talk	10	15	10	25
(5) Magnesium Stearate	1	2	2	5
Total	200	200	300	600

Table 2: possible capsule ingredient composition

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.

The compound of formula (I), 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 thoroughly. The mixture is filled by machine into suitable capsules, e.g. hard gelatin capsules.

Example B-2

Soft Gelatin Capsules of the following composition are manufactured:

ingredient	mg/capsule
Compound of formula (I)	5
Yellow wax	8
Hydrogenated Soya bean oil	8
Partially hydrogenated plant oils	34
Soya bean oil	110
Total	165

Table 3: possible soft gelatin capsule ingredient composition

ingredient	mg/capsule
Gelatin	75
Glycerol 85 %	32
Karion 83	8 (dry matter)
Titan dioxide	0.4
Iron oxide yellow	1.1
Total	116.5

Table 4: possible soft gelatin capsule composition

Manufacturing Procedure

The compound of formula (I) is dissolved in a warm melting of the other ingredients and the mixture is filled into soft gelatin capsules of appropriate size. The filled soft gelatin capsules are treated according to the usual procedures.

Example C

Suppositories of the following composition are manufactured:

ingredient	mg/supp.
Compound of formula (I)	15
Suppository mass	1285
Total	1300

Table 5: possible suppository composition

Manufacturing Procedure

The suppository mass is melted in a glass or steel vessel, mixed thoroughly and cooled to 45°C. Thereupon, the finely powdered compound of formula (I) is added thereto and stirred until it has dispersed completely. The mixture is poured into suppository moulds of suitable size, left to cool; the suppositories are then removed from the moulds and packed individually in wax paper or metal foil.

Example D

Injection solutions of the following composition are manufactured:

ingredient	mg/injection solution.
Compound of formula (I)	3
Polyethylene Glycol 400	150
acetic acid	q.s. ad pH 5.0
water for injection solutions	ad 1.0 ml

Table 6: possible injection solution composition

Manufacturing Procedure

The compound of formula (I) is dissolved in a mixture of Polyethylene Glycol 400 and water for injection (part). The pH is adjusted to 5.0 by acetic acid. The volume is adjusted to 1.0 ml by

addition of the residual amount of water. The solution is filtered, filled into vials using an appropriate overage and sterilized.

Example E

Sachets of the following composition are manufactured:

ingredient	mg/sachet
Compound of formula (I)	50
Lactose, fine powder	1015
Microcrystalline cellulose (AVICEL PH 102)	1400
Sodium carboxymethyl cellulose	14
Polyvinylpyrrolidon K 30	10
Magnesium stearate	10
Flavoring additives	1
Total	2500

Table 7: possible sachet composition

Manufacturing Procedure

The compound of formula (I) is mixed with lactose, microcrystalline cellulose and sodium carboxymethyl cellulose and granulated with a mixture of polyvinylpyrrolidone in water. The granulate is mixed with magnesium stearate and the flavoring additives and filled into sachets.

Examples

Abbreviations

AcOH = acetic acid; ATP = adenosine triphosphate; BOC = *tert*-butyloxycarbonyl; BPR = back pressure regulator; CAS = chemical abstract service; CDI = 1,1'-carbonyldiimidazole; DCM = dichloromethane; DIPEA = diisopropylethylamine; DME = dimethoxyethane; DMF = dimethylformamide; DMSO = diemethyl sulfoxide; dppf = 1,1'-Bis(diphenylphosphino)ferrocene; EtOAc = ethyl acetate; EtOH = ethanol; HATU = hexafluorophosphate azabenzotriazole tetramethyl uronium; LDA = lithium diisopropylamide; MeOH = methanol; MS = mass spectrometry; NMR = nuclear magnetic resonance; rt = room temperature; THF = tetrahydrofuran.

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-7-methyl-4-(trifluoromethyl)-1H-indazole

Step 1: 1-Bromo-3-fluoro-2-methyl-5-(trifluoromethyl)benzene

1-Bromo-3-fluoro-5-(trifluoromethyl)benzene (12.7 g) was dissolved in Tetrahydrofuran (60 ml) and cooled to -75 °C. LDA, 2.1mol/l in THF (27.4 ml) was added dropwise. After stirring for 30 min at -75°C, iodomethane (8.16 g) was added dropwise. The mixture was allowed to warm to room temperature overnight. After addition of half saturated ammonium chloride solution and ethyl acetate the layers were separated, once more extracted with ethyl acetate. The org layers were washed with water, combined, dried over sodium sulphate and concentrated. The residual brown liquid (15.42g) was bulb-to-bulb distilled at ~10 mbar and 60-80°C oven tempertaure to give the title compound as colorless liquid (11.91 g) containing 8 mol% of ethylbenzene.

Step 2: 4-Bromo-2-fluoro-3-methyl-6-(trifluoromethyl)benzaldehyde

In analogy to the synthesis of 4-bromo-3,6-dichloro-2-fluorobenzaldehyde, 1-bromo-3-fluoro-2-methyl-5-(trifluoromethyl)benzene 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 brown liquid.

Step 3: 6-Bromo-7-methyl-4-(trifluoromethyl)-1H-indazole

In analogy to the synthesis of 6-bromo-4-chloro-7-methoxy-2H-indazole, a solution of 4-bromo-2-fluoro-3-methyl-6-(trifluoromethyl)benzaldehyde was heated with an excess of hydrazine hydrate to give the title compound as light yellow solid. MS: m/e= 278.9 ($[M+H]^+$, 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-7-methyl-4-(trifluoromethyl)-2H-indazol-2-yl)acetate	6-bromo-7-methyl-4-(trifluoromethyl)-1H-indazole	ethyl 2-bromoacetate	365.0 ($[M+H]^+$, Br)

ethyl 2-(6-bromo-7-(difluoromethyl)-4-(trifluoromethyl)-2H-indazol-2-yl)acetate	6-bromo-7-(difluoromethyl)-4-(trifluoromethyl)-2H-indazole	ethyl 2-bromoacetate	403.2 ([M+H]+, Br)

Boronic acid derivatives are known or can be prepared in analogy to known methods or using the methods described below.

[4-[(3S,4S)-1-Ethyl-3-fluoro-4-piperidyl]phenyl]boronic acid OR [4-[(3R,4R)-1-ethyl-3-fluoro-4-piperidyl]phenyl]boronic acid

Step 1: tert-butyl (3S,4S)-4-(4-bromophenyl)-3-hydroxy-piperidine-1-carboxylate and tert-butyl (3R,4R)-4-(4-bromophenyl)-3-hydroxy-piperidine-1-carboxylate

A solution of tert-butyl 4-(4-bromophenyl)-3,6-dihydro-2H-pyridine-1-carboxylate (CAS 273727-44-9, 30 g, 79.8 mmol, Eq: 1.0, 90% purity) in THF (275 mL) was cooled to 0 °C. Borane tetrahydrofuran complex (1.0 M solution in THF, CAS 14044-65-6, 87.8 mL, 87.8 mmol, Eq: 1.1) was added dropwise at 0 °C. After the addition was complete, the ice bath was removed and the reaction mixture was stirred for 16 h at rt. The reaction mixture was cooled to 0 °C. NaOH (5 M in water, 40 mL, 200 mmol, Eq: 2.51) was added dropwise and the reaction mixture was stirred for 30 min at 0 °C. Hydrogen peroxide (35 wt.% solution in water, 19.4 g, 17.5 mL, 200 mmol, Eq: 2.5) was added and the reaction mixture was stirred for 2.5 h at 50 °C. The reaction mixture was cooled to rt and the excess of peroxide was quenched by addition of 2 M aq. $Na_2S_2O_3$. The mixture was diluted with ethyl acetate and water. The aqueous layer was back-extracted twice with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was suspended in diisopropyl ether and filtered. The solids were washed with diisopropyl ether and dried in vacuo to give the title compound as a white solid (26.74 g, 92 % yield). *m/z* 258.1 $[M\text{-}BOC+H]^+$, ESI pos.

Step 2: tert-Butyl (3S,4S)-4-(4-bromophenyl)-3-fluoro-piperidine-1-carboxylate and tert-butyl (3R,4R)-4-(4-bromophenyl)-3-fluoro-piperidine-1-carboxylate

A solution of tert-butyl (3S,4S)-4-(4-bromophenyl)-3-hydroxy-piperidine-1-carboxylate and tert-butyl (3R,4R)-4-(4-bromophenyl)-3-hydroxy-piperidine-1-carboxylate (37.2g, 99.2 mmol, Eq: 1) in dichlormethane (500 mL) was cooled to −78 °C. Deoxofluor® (50% solution in THF, CAS 202289-38-1, 79 g, 65.8 mL, 179 mmol, Eq: 1.8) was added dropwise at −78 °C. The reaction mixture was allowed to slowly warm to rt and stirred for 16 h at rt. The reaction mixture was quenched with sat. aq. $NaHCO_3$. The mixture was stirred for 30 min (pH 7). The organic layer was separated. The aqueous layer was back-extracted with DCM. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude material was adsorbed on Isolute HM-N and purified by flash chromatography (silica gel, 330 g, 0% to 40% EtOAc in heptane) to give the title compound as a light yellow oil (31.7 g, 85% yield)). *m/z* 304.1 $[M\text{-}tBu+H]^+$, ESI pos.

Step 3: tert-Butyl (3S,4S)-4-(4-bromophenyl)-3-fluoro-piperidine-1-carboxylate OR tert-butyl (3R,4R)-4-(4-bromophenyl)-3-fluoro-piperidine-1-carboxylate

Chiral separation of tert-butyl (3S,4S)-4-(4-bromophenyl)-3-fluoro-piperidine-1-carboxylate and tert-butyl (3R,4R)-4-(4-bromophenyl)-3-fluoro-piperidine-1-carboxylate (31.8 g, 88.8 mmol, Eq: 1.0) by SFC (column: IG, 12 nm, 5 µm, 250 x 30 mm, eluent: isocratic 5% isopropanol – BPR at 120 bar to 80 g/min) to give the title compound as a colorless oil (13.27 g, 40% yield). *m/z* 304.0 $[M\text{-}tBu+H]^+$, ESI pos. The absolute stereochemistry was not determined.

Step 4: (3S,4S)-4-(4-Bromophenyl)-3-fluoro-piperidine hydrochloride OR (3R,4R)-4-(4-bromophenyl)-3-fluoro-piperidine hydrochloride

To a solution of tert-butyl (3S,4S)-4-(4-bromophenyl)-3-fluoro-piperidine-1-carboxylate or tert-butyl (3R,4R)-4-(4-bromophenyl)-3-fluoro-piperidine-1-carboxylate (10.5 g, 29.3 mmol, Eq: 1.0) in DCM (100 mL) was added HCl (4 M in 1,4-dioxane, 73.3 mL, 293 mmol, Eq: 10). The reaction mixture was stirred for 3 h at rt. The reaction mixture was concentrated in vacuo. The residue was taken up in 40 mL Et_2O and the mixture was stirred for 10 min. The reaction mixture was filtered through sintered glass and washed with Et_2O. The white solid was dried in vacuo to give the title compound (9.5 g, 90% purity, 99 % yield). *m/z* 260.0 $[M+H]^+$, ESI pos.

Step 5: (3S,4S)-4-(4-Bromophenyl)-1-ethyl-3-fluoro-piperidine OR (3R,4R)-4-(4-bromophenyl)-1-ethyl-3-fluoro-piperidine

To a suspension of (3S,4S)-4-(4-bromophenyl)-3-fluoro-piperidine hydrochloride or (3R,4R)-4-(4-bromophenyl)-3-fluoro-piperidine hydrochloride (9.50 g, 32.2 mmol, Eq: 1.0) in THF (148 mL) was added NEt_3 (6.53 g, 8.99 mL, 64.5 mmol, Eq: 2.0). Diethyl sulfate (CAS 64-67-5, 5.97 g, 5.07 mL, 38.7 mmol, Eq: 1.2) was added dropwise at rt. The reaction mixture was stirred for 30 min at 35 °C and for 3 h at 55 °C. The reaction mixture was poured into EtOAc and washed with Na_2CO_3/water and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel, 40 g, 1% MeOH in DCM) to give the title compound as a yellow oil (7.20 g, 74% yield). *m/z* 287.9 $[M+H]^+$, ESI pos.

Step 6: [4-[(3S,4S)-1-Ethyl-3-fluoro-4-piperidyl]phenyl]boronic acid OR [4-[(3R,4R)-1-ethyl-3-fluoro-4-piperidyl]phenyl]boronic acid

A solution of (3S,4S)-4-(4-bromophenyl)-1-ethyl-3-fluoro-piperidine or (3R,4R)-4-(4-bromophenyl)-1-ethyl-3-fluoro-piperidine (1.000 g, 3.49 mmol, Eq: 1.0) in THF (8.0 mL) was cooled to -76 °C. n-Butyllithium (1.6 M in hexanes, 2.4 mL, 3.84 mmol, Eq: 1.1) was added dropwise and the reaction mixture was stirred for 2 h at −76 °C. Triethyl borate (618 mg, 0.72 mL, 4.23 mmol, Eq: 1.21) was added at −76 °C and the reaction mixture was stirred for 15 min at −76 °C. Then, the dry ice bath was removed and the reaction mixture was stirred at rt (1.5 h). The reaction mixture was quenched with sat. aq. NH_4Cl (10 mL) and stirred for 15 min at rt. The mixture was extracted with EtOAc. The aqueous layer was back-extracted with EtOAc. The organic layers were washed with water and brine. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel, 24 g, 0% to 10% MeOH in DCM) to give the title compound as an off-white solid (744 mg, 90% purity, 76% yield). *m/z* 252.2 $[M+H]^+$, ESI pos.

(1-(2-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)ethyl)piperidin-4-yl)methanol

To a mixture of [1-[2-(4-bromophenoxy)ethyl]-4-piperidyl]methanol (CAS 1226008-23-6, 1.3 g, 4.14 mmol, Eq: 1.0), bis(pinacolato)diboron (1.16 g, 4.55 mmol, Eq: 1.1), potassium acetate (1.22 g, 12.4 mmol, Eq: 3.0) in 1,4-dioxane (15 mL) was added $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (303 mg, 414 µmol, Eq: 0.1). The reaction mixture was flushed with argon and stirred for 3 h at 90 °C. The reaction mixture was concentrated in vacuo and purified by flash chromatography (silica gel, 50

g, 0% to 20% MeOH in DCM) to give the title compound as a dark brown oil (1.45 g, 80% purity, 77% yield). *m/z* 362.2 $[M+H]^+$, ESI pos.

(1-((3-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)bicyclo[1.1.1]pentan-1-yl)methyl)piperidin-4-yl)methanol

In a flame-dried flask, (1-((3-(4-bromophenyl)bicyclo[1.1.1]pentan-1-yl)methyl)piperidin-4-yl)methanol(295 mg), descripted Example 50 step 3, was dissolved in 1,4-Dioxane (6.58 ml) under inert atmosphere. bis(pinacolato)diboron (235 mg) and potassium acetate (248 mg) were added. The mixture was degassed under sonication and then1,1'-bis(diphenylphosphino)ferrocene-palladium(ii)dichloride dichloromethane complex (75.6 mg) was added. The flask was placed on a preheated heatblock at 90 °C with reflux condenser. The reaction was stirred for 40 min. The reaction mixture was transferred to a 150 mL round-bottom flask and isolute added. The solvent was removed and the residue loaded for flash column chromatography on amine modified gel (0-10% DCM:MeOH, 40 g). All fractions containing product were combined and concentrated to give the title compound (286mg) as a brown solid. MS: m/e= 398.3 ([M+H]+)

1-(2-Methoxyethyl)-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine

Step 1: 4-(4-Bromophenyl)-1-(2-methoxyethyl)piperidine

To a solution of 4-(4-bromophenyl)piperidine (7 g, 29.1 mmol, Eq: 1.0, CAS 80980-89-8) was added DIPEA (7.53 g, 10.2 ml, 58.3 mmol, Eq: 2.0) and 1-bromo-2-methoxyethane (4.86 g, 3.29 ml, 35 mmol, Eq: 1.2). The reaction mixture was stirred for 3 h at rt and 16 h at 50 °C. The reaction mixture was poured into H_2O and extracted with AcOEt (2 x). The organic layers were combined, dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel, 80 g, 0% to 10% MeOH in DCM) to give the title compound as a yellow semisolid (5.08g, 58% yield). *m/z* 300.1 [M+H]+, ESI pos.

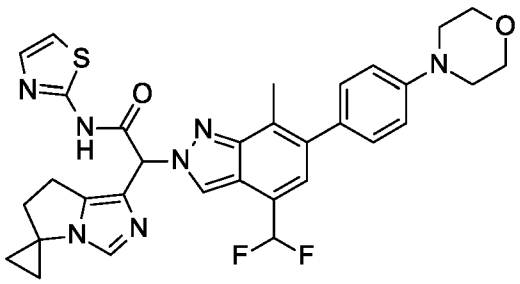
Step 2: 1-(2-Methoxyethyl)-4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperidine

To a solution of 4-(4-bromophenyl)-1-(2-methoxyethyl)piperidine (5 g, 16.8 mmol, Eq: 1.0) in 1,4-dioxane (100 ml) were added bis(pinacolato)diboron (5.53 g, 21.8 mmol, Eq: 1.3), KOAc (4.94 g, 50.3 mmol, Eq: 3.0) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (859 mg, 1.17 mmol, Eq: 0.07). The reaction mixture was flushed with argon and stirred for 3 h at 90 °C. The crude material was

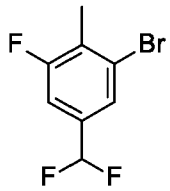
purified by flash chromatography (Si-amine, 40 g, 0% to 10% MeOH in EtOAc) to give the title compound as brown liquid (1.98g, 24% yield, 70% purity). *m/z* 346.2 [M+H]+, ESI pos.

Example 1

2-[4-(Difluoromethyl)-7-methyl-6-(4-morpholinophenyl)indazol-2-yl]-2-spiro[6,7-dihydropyrrolo[1,2-*c*]imidazole-5,1'-cyclopropane]-1-yl-*N*-thiazol-2-yl-acetamide

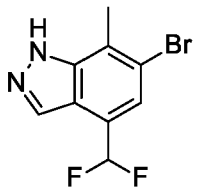


Step 1: 1-Bromo-5-(difluoromethyl)-3-fluoro-2-methyl-benzene



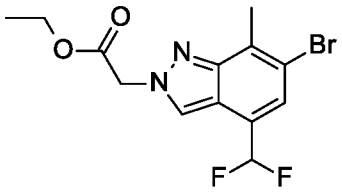
To a cooled solution of 3-bromo-5-fluoro-4-methylbenzaldehyde (CAS # 1370411-47-4, 20.5 g, 89.7 mmol, 1.0 equiv) in dichloromethane (98 mL) was added morpholinosulfur trifluoride (CAS # 51010-74-3, 24.8 g, 17.3 mL, 135 mmol, 1.5 equiv) in portions. The reaction mixture was stirred at 0-5 °C for 20 minutes, then at room temperature for 16 hours. Saturated aqueous $NaHCO_3$-solution (300 mL) was added carefully under ice cooling. The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into dichloromethane and washed with water. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel, 120 g, 100% pentane) to afford the title compound (18.6 g, 87% yield) as a colourless oil. ^{1}H NMR (300 MHz, chloroform-*d*) δ = 7.50 (s, 1H), 7.16 (d, J = 9.1 Hz, 1H), 6.57 (t, J = 56.0 Hz, 1H), 2.50 - 2.22 (m, 3H)

Step 2: 6-Bromo-4-(difluoromethyl)-7-methyl-1H-indazole



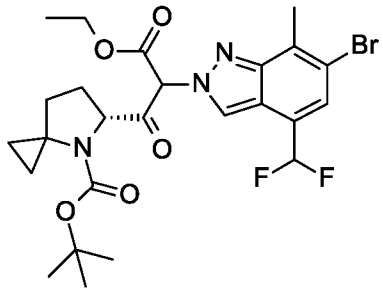
A solution of 1-bromo-5-(difluoromethyl)-3-fluoro-2-methyl-benzene (*Example 1, step 1*) (26.4 g, 110 mmol, 1.0 equiv) in tetrahydrofuran (240 mL) was cooled to -75 °C. Lithium diisopropylamide solution (2 M in tetrahydrofuran/heptane/ethylbenzene, 66.3 mL, 133 mmol, 1.2 equiv) was added dropwise maintaining the temperature below -70 °C. The reaction mixture was stirred at -75 °C for 30 minutes. Ethyl formate (16.4 g, 17.7 mL, 220 mmol, 2.0 equiv) was added below -70 °C. The reaction mixture was stirred at -75 °C for 30 minutes. Acetic acid (16.6 g, 15.8 mL, 277 mmol, 2.5 equiv) was added below -55 °C. The reaction mixture was allowed to warm up to room temperature, poured into ethyl acetate and washed with diluted aqueous HCl-solution, water and brine. The organic layer was dried over sodium sulfate and concentrated in vacuo to give presumed 4-bromo-6-(difluoromethyl)-2-fluoro-3-methyl-benzaldehyde as a yellow oil (29.5 g) which was used without further purification. The crude presumed 4-bromo-6-(difluoromethyl)-2-fluoro-3-methyl-benzaldehyde (29.5 g) was dissolved in dimethoxyethane (150 mL). *O*-Methylhydroxylamine hydrochloride (10.2 g, 122 mmol, 1.1 equiv) and potassium carbonate (30.6 g, 221 mmol, 2.0 equiv) were added. The reaction mixture was stirred at 45 °C for 2.5 hours then filtered through sintered glass and washed with dimethoxyethane (2 x). The filtrate was concentrated in vacuo. The oxime ether intermediate was dissolved in dimethylsulfoxide (150 mL). Hydrazine hydrate (83 g, 80.5 mL, 1.66 mol, 15 equiv) was added. The reaction mixture was stirred at 110 °C for for 3 hours. The reaction mixture was poured into a mixture of ethyl acetate/tetrahydrofuran 5:1. The organic layer was washed with water and brine, dried over sodium sulfate and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel, 2 x 120 g, gradient 0% to 30% ethyl acetate in heptane) to afford the title compound (13.5 g, 45% yield) as a white solid (13.5 g, 45% yield). LCMS: *m/z* 260.9/262.8 $[M+H]^+$, ESI pos, Br isotopes.

Step 3: Ethyl 2-[6-bromo-4-(difluoromethyl)-7-methyl-indazol-2-yl]acetate

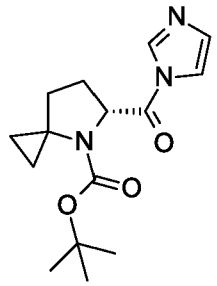


To a solution of 6-bromo-4-(difluoromethyl)-7-methyl-1H-indazole (*Example 1, step 2*) (19 g, 72.8 mmol, 1.0 equiv) in *N*,*N*-dimethylformamide (75 mL) was added ethyl 2-bromoacetate (CAS # 105-36-2, 18.2 g, 12.2 mL, 109 mmol, 1.5 equiv). The reaction mixture was stirred at 100 °C for 16 hours. The reaction mixture was poured into ethyl acetate and washed with water and brine. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel, 2 x 120g, gradient 0% to 20% ethyl acetate in heptane) to afford the title compound (21.2 g, 80% yield) as a yellow solid. LCMS: *m/z* 346.9/348.8 $[M+H]^+$, ESI pos, Br isotopes.

Step 4: tert-Butyl (5*R*)-5-[2-[6-bromo-4-(difluoromethyl)-7-methyl-indazol-2-yl]-3-ethoxy-3-oxo-propanoyl]-4-azaspiro[2.4]heptane-4-carboxylate



Preparation of tert-butyl (5*R*)-5-(imidazole-1-carbonyl)-4-azaspiro[2.4]heptane-4-carboxylate

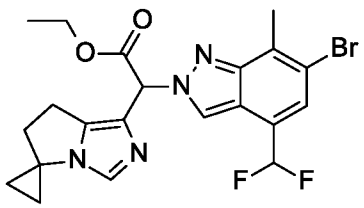


To a solution of (5*R*)-4-tert-butoxycarbonyl-4-azaspiro[2.4]heptane-5-carboxylic acid (CAS # 2007916-06-3, 1.02 g, 4.21 mmol, 1.0 equiv) in dichloromethane (17 mL) was added 1,1'-carbonyldiimidazole (818 mg, 5.04 mmol, 1.2 eq) in three portions and the reaction mixture was

stirred at room temperature for 2.5 hours. The reaction mixture was poured into saturated aqueous $NaHCO_3$-solution and extracted three times with dichloromethane. The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo to afford tert-butyl (5*R*)-5-(imidazole-1-carbonyl)-4-azaspiro[2.4]heptane-4-carboxylate (1.30 g, 95% yield, 90% purity) as an off-white solid, which was used directly in the next step.

A solution of ethyl 2-[6-bromo-4-(difluoromethyl)-7-methyl-indazol-2-yl]acetate (*Example 1, step 3*) (1.2 g, 3.46 mmol, 1.0 equiv) in tetrahydrofuran (16 mL) was cooled to -50 °C. NaHMDS (1 M in tetrahydrofuran) (4 mL, 4 mmol, 1.16 equiv) was added and the reaction mixture was stirred at -50 °C for 45 minutes. A solution of aforementioned tert-butyl (5*R*)-5-(imidazole-1-carbonyl)-4-azaspiro[2.4]heptane-4-carboxylate (1.29 g, 3.98 mmol, 1.15 equiv) in tetrahydrofuran (16 mL) was added dropwise at -50 °C. The reaction mixture was stirred at -50 °C for 30 minutes. Then, the cooling bath was removed and the reaction mixture was allowed to warm up to room temperature. The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was cooled and quenched with saturated aqueous NH_4Cl-solution, diluted with water and extracted with ethyl acetate. The aqueous layer was backextracted with ethyl acetate. The organic layers were washed with saturated aqueous $NaHCO_3$-solution then brine. The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo to afford the title compound (2.37 g, 96% yield, 80% purity) as a light brown foam, which was used without further purification. LCMS: *m/z* 570.3/572.3 $[M+H]^+$, ESI pos, Br isotopes.

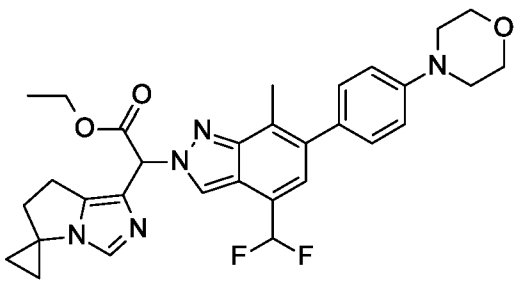
Step 5: Ethyl 2-[6-bromo-4-(difluoromethyl)-7-methyl-indazol-2-yl]-2-spiro[6,7-dihydropyrrolo[1,2-*c*]imidazole-5,1'-cyclopropane]-1-yl-acetate



A mixture of tert-butyl (5*R*)-5-[2-[6-bromo-4-(difluoromethyl)-7-methyl-indazol-2-yl]-3-ethoxy-3-oxo-propanoyl]-4-azaspiro[2.4]heptane-4-carboxylate (*Example 1, step 4*) (2.36 g, 3.31 mmol, 1.0 equiv, 80% purity) and HCl (4 M in 1,4-dioxane, 4.2 mL, 16.8 mmol, 5.07 equiv). The reaction mixture was stirred at room temperature for 1 hour. HCl (4 M in 1,4-dioxane, 1 mL, 4.0 mmol, 1.21 equiv) was added and the reaction mixture was stirred at room temperature for 30 minutes.

HCl (4 M in 1,4-dioxane, 1 mL, 4.0 mmol, 1.21 equiv) was added and the reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with ethanol (7.6 mL) and water (2.0 mL). Potassium thiocyanate (419 mg, 4.31 mmol, 1.3 equiv) was added and the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was cooled and pyridine (3.91 g, 4 mL, 49.46 mmol, 14.9 equiv) was added slowly. The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into 1 N $KHSO_4$ + water and extracted three times with ethyl acetate. The organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo. The crude material was dissolved in acetic acid (7.6 mL) and cooled to 0 °C. Hydrogen peroxide (35 wt.% solution in water, 0.580 mL, 6.62 mmol, 2.0 equiv) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 1 hour. The excess of hydrogen peroxide was destroyed with a 1 M aqueous solution of $Na_2S_2O_3$. The mixture was carefully basified with solid Na_2CO_3 and extracted twice with ethyl acetate. The organic layers were washed with brine, combined, dried over sodium sulfate, filtered and concentrated in vacuo. The crude material was adsorbed on ISOLUTE HM-N and purified by flash chromatography (silica gel, 24 g, gradient 0% to 100% ethyl acetate in heptane). All fractions containing product were combined and concentrated in vacuo to afford the title compound (882 mg, 53% yield) as a light yellow solid. LCMS: *m/z* 479.3/481.3 $[M+H]^+$, ESI pos, Br isotopes.

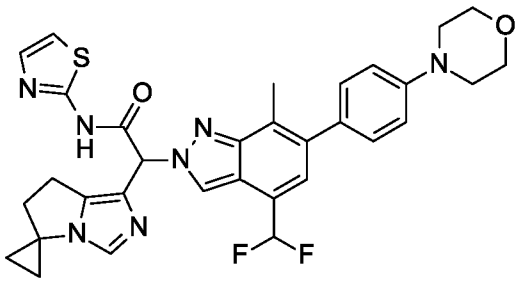
Step 6: Ethyl 2-[4-(difluoromethyl)-7-methyl-6-(4-morpholinophenyl)indazol-2-yl]-2-spiro[6,7-dihydropyrrolo[1,2-*c*]imidazole-5,1'-cyclopropane]-1-yl-acetate



A mixture of ethyl 2-[6-bromo-4-(difluoromethyl)-7-methyl-indazol-2-yl]-2-spiro[6,7-dihydropyrrolo[1,2-*c*]imidazole-5,1'-cyclopropane]-1-yl-acetate (*Example 1, step 5*) (350 mg, 0.69 mmol, 1.00 equiv), (4-morpholinophenyl)boronic acid (CAS # 186498-02-2, 187 mg, 0.90 mmol, 1.30 equiv), cesium carbonate (679 mg, 2.08 mmol, 3.00 equiv) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (82 mg, 0.10 mmol, 0.14 equiv) in 1,4-dioxane (6.0 mL) was flushed with argon and stirred at 100 °C for

2 hours. The reaction mixture was cooled to room temperature and then extracted with ethyl acetate and water. The aqueous layer was back-extracted with ethyl acetate. The organic layers were washed with water and brine. The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The crude material was adsorbed on ISOLUTE HM-N and purified by flash chromatography (silica gel, 24 g, gradient 0% to 90% ethyl acetate in heptane). All fractions containing product were combined and concentrated to afford the title compound (352 mg, 81% yield, 90% purity) as an off-white foam. LCMS: *m/z* 562.5 $[M+H]^+$, ESI pos.

Step 7: 2-[4-(Difluoromethyl)-7-methyl-6-(4-morpholinophenyl)indazol-2-yl]-2-spiro[6,7-dihydropyrrolo[1,2-*c*]imidazole-5,1'-cyclopropane]-1-yl-*N*-thiazol-2-yl-acetamide

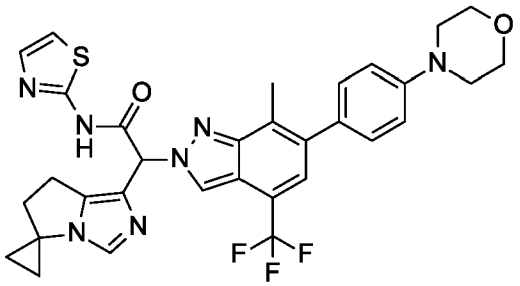


To a solution of ethyl 2-[4-(difluoromethyl)-7-methyl-6-(4-morpholinophenyl)indazol-2-yl]-2-spiro[6,7-dihydropyrrolo[1,2-c]imidazole-5,1'-cyclopropane]-1-yl-acetate (*Example 1, step 6*) (346 mg, 0.55 mmol, 1.0 equiv) in ethanol (1.8 mL) and tetrahydrofuran (1.8 mL) was added lithium hydroxide (1 M aqueous solution, 0.64 mL, 0.64 mmol, 1.15 equiv). The reaction mixture was stirred at room temperature for 1.5 hours. The reaction mixture was evaporated and co-evaporated with toluene twice. The residue was suspended in *N*,*N*-dimethylformamide (1.8 mL) and *N*,*N*-diisopropylethylamine (0.30 mL, 1.72 mmol, 3.1 equiv), thiazol-2-amine (72 mg, 0.72 mmol, 1.3 equiv) and HATU (274 mg, 0.72 mmol, 1.3 equiv) were added. The reaction mixture was stirred at room temperature for 45 minutes. The reaction mixture was extracted with ethyl acetate and water. The aqueous layer was backextracted with ethyl acetate. The organic layers were washed three times with water and once with brine. The combined organic layers were dried over sodium sulfate, filtered and concentrated in vacuo. The crude product was adsorbed on ISOLUTE HM-N and purified by flash chromatography (silica gel, 25 g, gradient 0% to 5% methanol in dichloromethane). All fractions containing product were combined and concentrated in vacuo. The residue was adsorbed on ISOLUTE HM-N and repurified by flash chromatography (Si-amine, 12

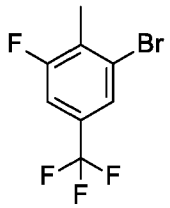
g, gradient 0% to 10% methanol in ethyl acetate). All fractions containing product were combined and concentrated to afford the title compound (183 mg, 53% yield) as an off-white foam. LCMS: *m/z* 616.4 $[M+H]^+$, ESI pos.

Example 2

2-[7-Methyl-6-(4-morpholinophenyl)-4-(trifluoromethyl)indazol-2-yl]-2-spiro[6,7-dihydropyrrolo[1,2-*c*]imidazole-5,1'-cyclopropane]-1-yl-*N*-thiazol-2-yl-acetamide

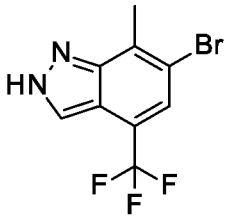


Step 1: 1-Bromo-3-fluoro-2-methyl-5-(trifluoromethyl)benzene



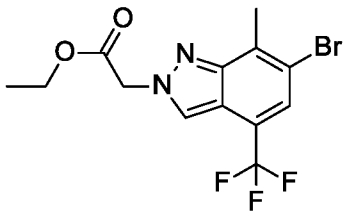
1-Bromo-3-fluoro-5-(trifluoromethyl)benzene (12.7 g, 52.2 mmol, 1.0 equiv) was dissolved in tetrahydrofuran (60 ml) and cooled to -75 °C. LDA (2.1 M in tetrahydrofuran, 27.4 ml, 57.5 mmol, 1.1 equiv) was added dropwise. After stirring for 30 minutes at -75 °C, iodomethane (8.16 g, 3.6 ml, 57.4 mmol, 1.1 equiv) was added dropwise. The mixture was allowed to warm to room temperature overnight. After addition of half saturated ammonium chloride solution and ethyl acetate the layers were separated, once more extracted with ethyl acetate. The organic layers were washed with water, combined, dried over sodium sulfate and concentrated in vacuo. The residual brown liquid (15.42 g) was bulb-to-bulb distilled at ~10 mbar and 60-80 °C oven temperature to give the title compound as colorless liquid (11.9 g, 89% yield).

Step 2: 6-Bromo-7-methyl-4-(trifluoromethyl)-1H-indazole



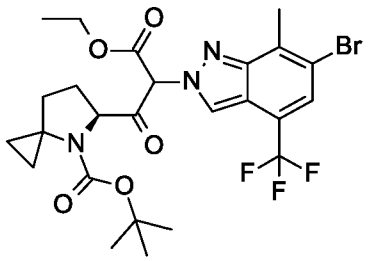
The title compound was obtained as a light yellow solid, LCMS: *m/z* 278.9 $[M+H]^+$, ESI pos, using chemistry similar to that described in Example 1, step 2 starting from 1-bromo-3-fluoro-2-methyl-5-(trifluoromethyl)benzene *(Example 2, step 1)*.

Step 3: Ethyl 2-(6-bromo-7-methyl-4-(trifluoromethyl)-2H-indazol-2-yl)acetate



The title compound was obtained as a light yellow solid, LCMS: *m/z* 365.1/367.1 $[M+H]^+$, ESI pos, Br isotopes, using chemistry similar to that described in Example 1, step 3 starting from 6-bromo-7-methyl-4-(trifluoromethyl)-1H-indazole *(Example 2, step 2)*.

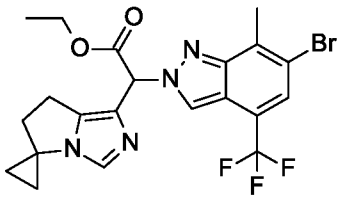
Step 4: tert-Butyl (5*S*)-5-[2-[6-bromo-7-methyl-4-(trifluoromethyl)indazol-2-yl]-3-ethoxy-3-oxo-propanoyl]-4-azaspiro[2.4]heptane-4-carboxylate



In analogy to *Example 1, step 4*, (5*S*)-4-tert-butoxycarbonyl-4-azaspiro[2.4]heptane-5-carboxylic acid was treated with carbonyldiimidazole to give solution A. Ethyl 2-(6-bromo-7-methyl-4-(trifluoromethyl)-2H-indazol-2-yl)acetate *(Example 2, step 3)* was deprotonated with LDA and treated with solution A at -78 °C. After stirring at room temperature for 16 hours and workup in

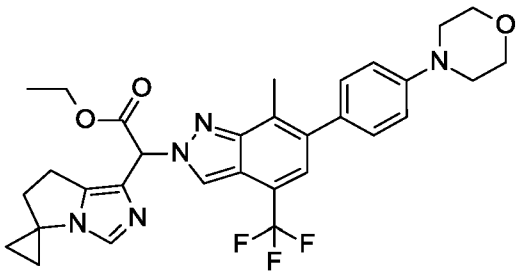
analogy to *Example 1, step 4*, the crude title compound was obtained as a light brown foam, which was used for the next step without further purification. LCMS: *m/z* 590.3 $[M+H]^+$, ESI pos.

Step 5: Ethyl 2-[6-bromo-7-methyl-4-(trifluoromethyl)indazol-2-yl]-2-spiro[6,7-dihydropyrrolo[1,2-*c*]imidazole-5,1'-cyclopropane]-1-yl-acetate



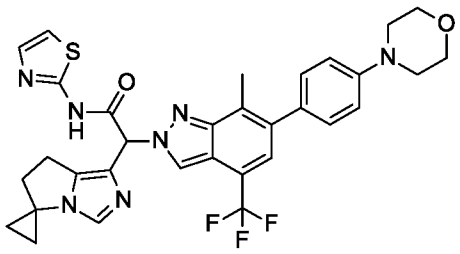
In analogy to *Example 1, step 5*, tert-butyl (5*S*)-5-[2-[6-bromo-7-methyl-4-(trifluoromethyl)indazol-2-yl]-3-ethoxy-3-oxo-propanoyl]-4-azaspiro[2.4]heptane-4-carboxylate *(Example 2, step 4)* was deprotected using HCl in dioxane followed by reaction with potassium thiocyanate and hydrogen peroxide in acetic acid to give the title compound as a white foam. LCMS: *m/z* 499.2 $[M+H]^+$, ESI pos.

Step 6: Ethyl 2-[7-methyl-6-(4-morpholinophenyl)-4-(trifluoromethyl)indazol-2-yl]-2-spiro[6,7-dihydropyrrolo[1,2-*c*]imidazole-5,1'-cyclopropane]-1-yl-acetate



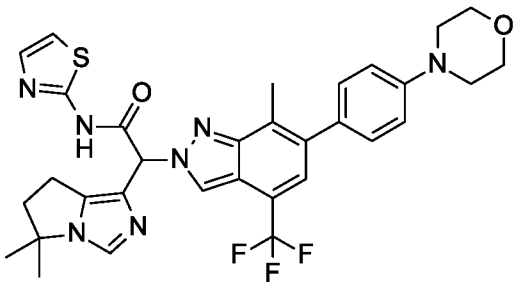
The title compound was obtained as a light brown foam, LCMS: *m/z* 580.4 $[M+H]^+$, ESI pos, using chemistry similar to that described in Example 1, step 6 starting from ethyl 2-[6-bromo-7-methyl-4-(trifluoromethyl)indazol-2-yl]-2-spiro[6,7-dihydropyrrolo[1,2-*c*]imidazole-5,1'-cyclopropane]-1-yl-acetate *(Example 2, step 5)* and (4-morpholinophenyl)boronic acid.

Step 7: 2-[7-Methyl-6-(4-morpholinophenyl)-4-(trifluoromethyl)indazol-2-yl]-2-spiro[6,7-dihydropyrrolo[1,2-*c*]imidazole-5,1'-cyclopropane]-1-yl-*N*-thiazol-2-yl-acetamide

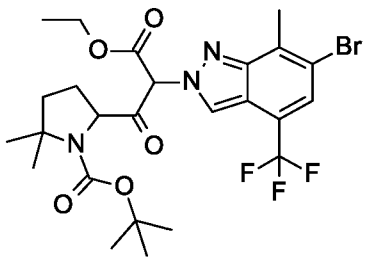


The title compound was obtained as a light red solid, LCMS: *m/z* 634.4 $[M+H]^+$, ESI pos, using chemistry similar to that described in Example 1, step 7 starting from ethyl 2-[7-methyl-6-(4-morpholinophenyl)-4-(trifluoromethyl)indazol-2-yl]-2-spiro[6,7-dihydropyrrolo[1,2-*c*]imidazole-5,1'-cyclopropane]-1-yl-acetate *(Example 2, step 6)* and thiazol-2-amine.

Example 3
2-(5,5-Dimethyl-6,7-dihydropyrrolo[1,2-*c*]imidazol-1-yl)-2-[7-methyl-6-(4-morpholinophenyl)-4-(trifluoromethyl)indazol-2-yl]-*N*-thiazol-2-yl-acetamide



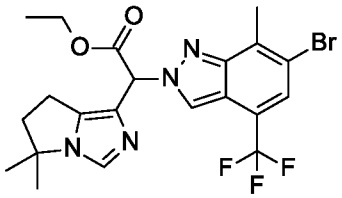
Step 1: tert-Butyl 5-[2-[6-bromo-7-methyl-4-(trifluoromethyl)indazol-2-yl]-3-ethoxy-3-oxo-propanoyl]-2,2-dimethyl-pyrrolidine-1-carboxylate



In analogy to *Example 1, step 4*, 1-tert-butoxycarbonyl-5,5-dimethyl-proline was treated with carbonyldiimidazole to give solution A. Ethyl 2-(6-bromo-7-methyl-4-(trifluoromethyl)-2H-indazol-2-yl)acetate *(Example 2, step 3)* was deprotonated with LDA and treated with solution A

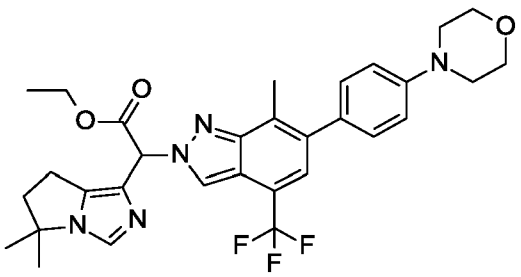
at -78 °C. After stirring at room temperature for 16 hours and workup in analogy to *Example 1, step 4*, the crude title compound was obtained as a light brown foam, which was used for the next step without further purification. LCMS: *m/z* 590.3 $[M+H]^+$, ESI pos.

Step 2: Ethyl 2-[6-bromo-7-methyl-4-(trifluoromethyl)indazol-2-yl]-2-(5,5-dimethyl-6,7-dihydropyrrolo[1,2-*c*]imidazol-1-yl)acetate



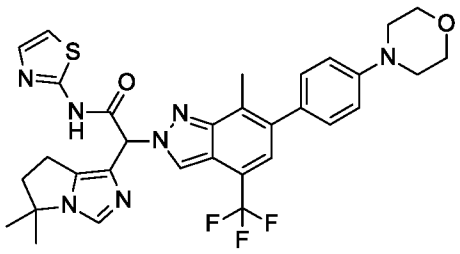
In analogy to *Example 1, step 5*, tert-butyl 5-[2-[6-bromo-7-methyl-4-(trifluoromethyl)indazol-2-yl]-3-ethoxy-3-oxo-propanoyl]-2,2-dimethyl-pyrrolidine-1-carboxylate *(Example 3, step 1)* was deprotected using HCl in dioxane followed by reaction with potassium thiocyanate and hydrogen peroxide in acetic acid to give the title compound as a light yellow foam. LCMS: *m/z* 501.2 $[M+H]^+$, ESI pos.

Step 3: Ethyl 2-(5,5-dimethyl-6,7-dihydropyrrolo[1,2-*c*]imidazol-1-yl)-2-[7-methyl-6-(4-morpholinophenyl)-4-(trifluoromethyl)indazol-2-yl]acetate



The title compound was obtained as a light brown foam, LCMS: *m/z* 582.5 $[M+H]^+$, ESI pos, using chemistry similar to that described in Example 1, step 6 starting from ethyl 2-[6-bromo-7-methyl-4-(trifluoromethyl)indazol-2-yl]-2-(5,5-dimethyl-6,7-dihydropyrrolo[1,2-*c*]imidazol-1-yl)acetate *(Example 3, step 2)* and (4-morpholinophenyl)boronic acid.

Step 4: 2-(5,5-Dimethyl-6,7-dihydropyrrolo[1,2-*c*]imidazol-1-yl)-2-[7-methyl-6-(4-morpholinophenyl)-4-(trifluoromethyl)indazol-2-yl]-*N*-thiazol-2-yl-acetamide



The title compound was obtained as a white solid, LCMS: *m/z* 636.4 $[M+H]^+$, ESI pos, using chemistry similar to that described in Example 1, step 7 starting from ethyl 2-(5,5-dimethyl-6,7-dihydropyrrolo[1,2-*c*]imidazol-1-yl)-2-[7-methyl-6-(4-morpholinophenyl)-4-(trifluoromethyl)indazol-2-yl]acetate *(Example 3, step 3)* and thiazol-2-amine.

Example 4

HTRF Phospho EGFR LRCS assay (cellular)

Cell line and media

BaF3-LRCS 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).

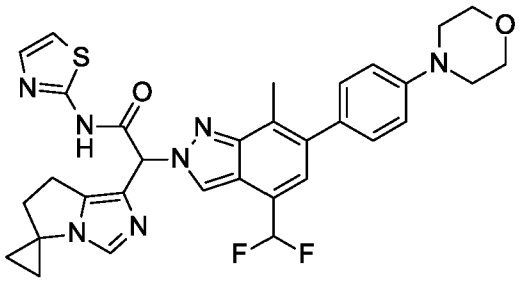
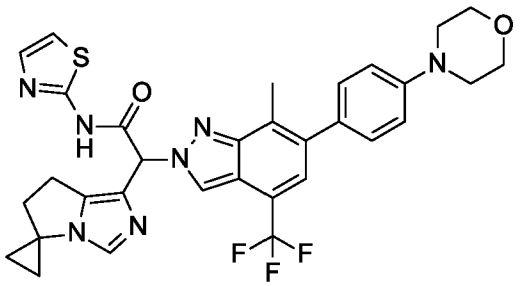
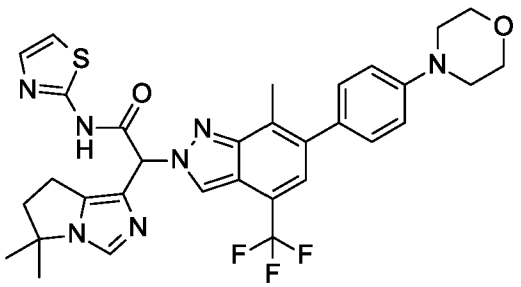
Protocol

Cells are transferred as above to Greiner Bio-One, Nr. 784-08 micro-titerplate at 20000 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 -80°C. 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.

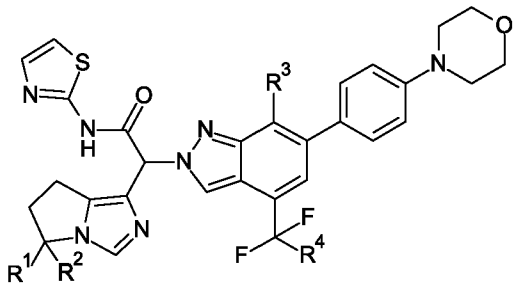
The results are shown in Table 8.

Table 8: BaF3 cellular HTRF Phospho EGFR LRCS assay data

Exam.	Structure	IC_{50} (BaF3 LRCS)
1		20nM
2		45nM
3		45nM

Claims

1. A compound of formula (I)



(I)

wherein

R^1 and R^2 are independently selected from alkyl, or R^1 and R^2 together with the carbon they are attached to form cycloalkyl;

R^3 is alkyl or haloalkyl; and

R^4 is hydrogen or halogen;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein R^1 and R^2 are methyl, or R^1 and R^2 together with the carbon they are attached to form cyclopropyl.

3. A compound according to claim 1 or 2 wherein R^1 and R^2 together with the carbon they are attached to form cyclopropyl.

4. A compound according to claim 1 or 2 wherein R^1 and R^2 are methyl.

5. A compound according to any one of claims 1 to 4 wherein R^3 is methyl.

6. A compound according to any one of claims 1 to 5 wherein R^4 is hydrogen or fluoro.

7. A compound according to any one of claims 1 to 6 wherein R^4 is hydrogen.

8. A compound according to any one of claims 1 to 6 wherein R^4 is fluoro.

9. A compound according to any one of claims 1 to 8 selected from

2-[4-(Difluoromethyl)-7-methyl-6-(4-morpholinophenyl)indazol-2-yl]-2-spiro[6,7-dihydropyrrolo[1,2-c]imidazole-5,1'-cyclopropane]-1-yl-N-thiazol-2-yl-acetamide;

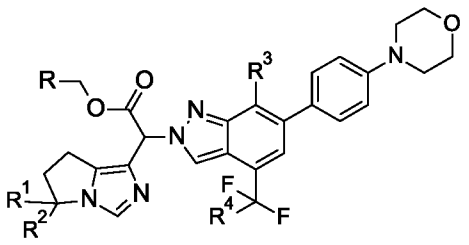
2-[7-Methyl-6-(4-morpholinophenyl)-4-(trifluoromethyl)indazol-2-yl]-2-spiro[6,7-dihydropyrrolo[1,2-c]imidazole-5,1'-cyclopropane]-1-yl-N-thiazol-2-yl-acetamide; and

2-(5,5-Dimethyl-6,7-dihydropyrrolo[1,2-c]imidazol-1-yl)-2-[7-methyl-6-(4-morpholinophenyl)-4-(trifluoromethyl)indazol-2-yl]-N-thiazol-2-yl-acetamide;

or a pharmaceutically acceptable salt thereof.

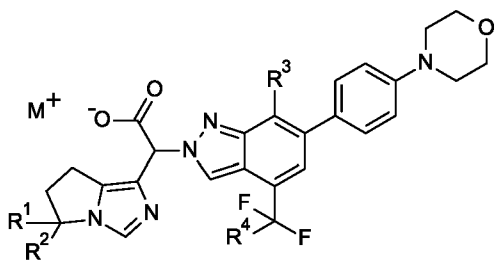
10. A process for the preparation of a compound according to any one of claims 1 to 9, comprising at least one of the following steps:

(a) the reaction of a compound of formula (B1)



(B1)

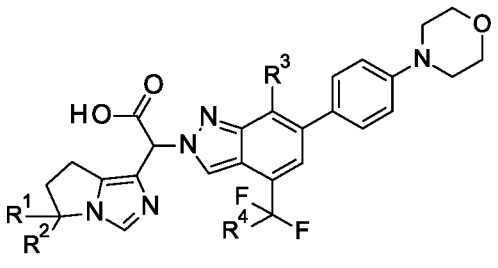
in a suitable solvent and in presence of a base, to arrive at a compound of formula (B2)



(B2)

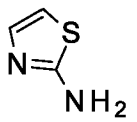
wherein M^+ is Na^+, Li^+ or a protonated base;

(b) the reaction of the compound of formula (B2) in a suitable solvent and in presence of an acid to yield a compound of formula (B3)



(B3); and

(c) the reaction of a compound of formula (B3) with a compound of formula (B4)



(B4)

in the presence of a suitable coupling agent and a base;

wherein R^1, R^2, R^3 and R^4 are as defined in any one of claims 1 to 9; and wherein R is H or alkyl.

11. A compound according to any one of claims 1 to 9, when manufactured according to a process of claim 10.

12. A compound according to any one of claims 1 to 9 for use as therapeutically active substance.

13. A pharmaceutical composition comprising a compound according to any one of claims 1 to 9 and a therapeutically inert carrier.

14. A compound according to any one of claims 1 to 9 for use in the treatment or prophylaxis of cancer, in particular non-small cell lung cancer.

15. The use of a compound according to any one of claims 1 to 9 for use in the treatment or prophylaxis of cancer, in particular non-small cell lung cancer.

16. The use of a compound according to any one of claims 1 to 9 for the preparation of a medicament for the treatment or prophylaxis of cancer, in particular non-small cell lung cancer.

17. A method for the treatment or prophylaxis of cancer, in particular non-small cell lung cancer, which method comprises administering an effective amount of a compound as defined in any one of claims 1 to 9 to a patient in need thereof.

18. The invention as hereinbefore described.

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