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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 May 2016 (26.05.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/079669 A1

(51) International Patent Classification:
C07D 239/47 (2006.01) *A61P 35/00* (2006.01)
A61K 31/506 (2006.01)

(21) International Application Number:
PCT/IB2015/058880

(22) International Filing Date:
17 November 2015 (17.11.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
14193826.6 19 November 2014 (19.11.2014) EP
15169942.8 29 May 2015 (29.05.2015) EP

(71) Applicant *(for all designated States except US)*: **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(72) Inventors; and
(71) Applicants *(for US only)*: **BRIARD, Emmanuelle** [FR/CH]; Novartis Pharma AG, Werk Klybeck, Postfach, CH-4002 Basel (CH). **AUBERSON, Yves** [CH/CH]; Novartis Pharma AG, Werk Klybeck, Postfach, CH-4002 Basel (CH). **CENNI, Bruno** [CH/CH]; Novartis Pharma AG, Postfach, CH-4002 Basel (CH). **PULZ, Robert Alexander** [DE/CH]; Novartis Pharma AG, Novartis Institutes for Biomed. Research, Postfach, CH-4002 Basel (CH). **ANGST, Daniela** [CH/CH]; Novartis Pharma AG, Novartis Institutes for Biomed. Research, Postfach, CH-4002 Basel (CH).

(74) Common Representative: **NOVARTIS AG**; Lichtstrasse 35, CH-4056 Basel (CH).

(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, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, 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, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, 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, 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).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

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

WO 2016/079669 A1

(54) **Title**: LABELED AMINO PYRIMIDINE DERIVATIVES

(57) **Abstract**: The present invention describes novel radioactive amino pyrimidine derivatives, their preparation and their use as radiotracers / radiomarkers for imaging techniques and as diagnostic tools in the field of BTK receptor susceptible diseases and/or disorders. The compounds of the present invention generally exhibit a potent and selective inhibition of Bruton's tyrosine kinase (BTK).

Labeled Amino Pyrimidine Derivatives

The present invention describes novel radioactive amino pyrimidine derivatives, their preparation and their use as radioligand or radiotracers for imaging techniques and as diagnostic tools in the field of BTK receptor associated diseases and/or disorders.

The compounds of the present invention generally exhibit a potent and selective inhibition of Bruton's tyrosine kinase (BTK).

Background of the invention

The essential role of BTK in autoimmune disease is underlined by the observations that Btk-deficient mice are protected in standard preclinical models for rheumatoid arthritis (Jansson & Holmdahl 1993), systemic lupus erythematosus (Steinberg et al. 1982), as well as allergic disease and anaphylaxis (Hata et al. 1998). In addition, many cancers and lymphomas express BTK and appear to be dependent on BTK function (Davis et al. 2010). The role of BTK in diseases including autoimmunity, inflammation and cancer has been recently reviewed (Tan et al. 2013; Rickert 2013).

Moreover, BTK is highly expressed in B cells, and to a certain extent in other cells of the hematopoietic lineage, such as platelets, erythroid and myeloid cells.

Summary of the invention

A selective and covalent (irreversible) BTK-inhibitor being radioactively labeled may be useful for quantifying or visualizing (imaging) BTK protein concentrations, or measuring BTK protein occupancy.

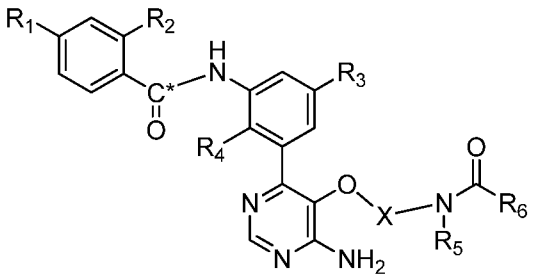
One embodiment of the invention therefore provides the use of a radiolabeled BTK-inhibitor of the invention (e.g. in preclinical and/or clinical studies) to quantify B cell concentration in tissues, to stage or to monitor disease progression, to measure BTK occupancy by a drug candidate, to image tumors related to BTK-expressing cells, e.g. B cell lymphoma, or to measure the effect of a therapeutic treatment on local B cell concentration.

Such radiolabeled BTK-inhibitors may also be used as in vitro or ex vivo diagnostic tools, e.g. in BTK binding assays or receptor occupancy studies.

In another embodiment the invention provides a radiolabeled compound of the present invention for use in the treatment of a wide range of diseases and/or disorders resulting from growth dysregulation of BTK-expressing cells. This may include, but is not limited to autoimmune disorders and cancers of hematopoietic origin or solid tumors, including chronic myelogenous leukemia, myeloid leukemia, non-Hodgkin lymphoma and other B cell lymphomas.

Detailed Description of the Invention

More particularly, in embodiment 1 the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof;



(I)

wherein,

C* means ^{12}C or ^{11}C;

X is a bivalent linker comprising at least one carbon atom and at least one hydrogen atom;

R_1 is C_1-C_6 alkyl or C_3-C_6 cycloakyl;

R_2 is ^{19}F, ^{18}F, ^{124}I, ^{123}I or ^{131}I:

R_3 is hydrogen or ^{19}F, ^{18}F, ^{124}I, ^{123}I or ^{131}I;

R_4 is C_1-C_6 alkyl;

R_5 is C_1-C_6 alkyl optionally substituted by ^{19}F, or ^{18}F; and

R_6 is -CH=CH_2, -C≡CH, -CH=CH-CH_3, -CH_2-CH=CH_2, wherein one or more of the hydrogens are optionally replaced by ^{3}H.

Embodiment 2 of the present invention relates to a compound of formula (I) in accordance to the definition of embodiment 1 or a pharmaceutically acceptable salt thereof, wherein the variables in embodiment 1 are selected such that a compound of formula (I) comprises at least one radioactive atom selected from ^{3}H, ^{11}C, ^{18}F, ^{123}I, ^{124}I and ^{131}I.

Embodiment 3 of the present invention relates to a compound of embodiment 1 - 2 or a pharmaceutically acceptable salt thereof, wherein
the bivalent linker X is C_1-C_6 alkylene optionally substituted by C_1-C_6 alkyl.

Embodiment 4 relates to a compound of embodiment 1 - 2 or a pharmaceutically acceptable salt thereof, wherein
the bivalent linker X is C_3-C_6 cycloalkylene optionally substituted by C_1-C_6 alkyl.

Embodiment 5 relates to a compound of any one of embodiments 1 - 4 or a pharmaceutically acceptable salt thereof, wherein
C* means ^{11}C or ^{12}C.

Embodiment 6 relates to a compound of any one of embodiments 1 - 5 or a pharmaceutically acceptable salt thereof, wherein
R_1 is cyclopropyl.

Embodiment 7 relates to a compound of any one of embodiments 1 - 6 or a pharmaceutically acceptable salt thereof, wherein
R_2 is ^{19}F, ^{18}F, ^{123}I, ^{124}I or ^{131}I.

Embodiment 8 relates to a compound of any one of embodiments 1 - 7 or a pharmaceutically acceptable salt thereof, wherein
R_3 is ^{19}F, ^{18}F, ^{123}I, ^{124}I or ^{131}I.

Embodiment 9 relates to a compound of any one of embodiments 1 - 8 or a pharmaceutically acceptable salt thereof, wherein R_4 is methyl.

Embodiment 10 relates to a compound of any one of embodiments 1 – 3, or 5 - 9 or a pharmaceutically acceptable salt thereof, wherein X is ethylene.

Embodiment 11 relates to a compound of any one of embodiments 1 – 3, or 5 - 9 or a pharmaceutically acceptable salt thereof, wherein X is methylene.

Embodiment 12 relates to a compound of any one of embodiments 1 - 11 or a pharmaceutically acceptable salt thereof, wherein
R_5 is ethyl optionally substituted by ^{19}F or ^{18}F.

Embodiment 13 relates to a compound of any one of embodiments 1 - 12 or a pharmaceutically acceptable salt thereof, wherein
R_6 is -CH=CH_2, wherein one or more hydrogens are optionally replaced by ^{3}H.

With regard to a compound of formula (I) the following significances represent further embodiments of the invention independently, collectively or in any combination or in any sub-combination thereof:

1. R_1 is cyclopropyl;
2. R_2 is ^{19}F, ^{18}F, ^{123}I, ^{124}I or ^{131}I
3. R_3 is ^{19}F, ^{18}F, ^{123}I, ^{124}I or ^{131}I
4. R_4 is methyl;
5. X is ethylene;
6. C* means ^{11}C or ^{12}C;
7. R_5 is ethyl optionally substituted by ^{19}F or ^{18}F;
8. R_6 is -CH=CH_2, wherein the hydrogens are optionally replaced by ^{3}H.

In another embodiment the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as a medical or diagnostic tool incorporating a technique selected from in vitro binding assays, ex vivo binding assays,

autoradiography, positron emission tomography (PET), and single photon emission computed tomography (SPECT).

In another embodiment the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in the treatment of a disease or disorder mediated by BTK, or resulting from BTK-expressing cell growth dysregulation.

In another embodiment the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of embodiments 1 to 13 and further comprising one or more pharmaceutically acceptable carriers.

In another embodiment the present invention provides a combination comprising a therapeutically effective amount of a compound according to any one of embodiments 1 to 13 or a pharmaceutically acceptable salt thereof and one or more therapeutically active co-agents.

In another embodiment the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, which is selected from:
[$^{3}H_{3}$]-N-(3-(6-amino-5-(2-(N-(2-fluoroethyl)acrylamido)ethoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide,
N-(3-(6-amino-5-(2-(N-(2-[^{18}F]fluoroethyl)acrylamido)ethoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide,
N-(3-(6-amino-5-(2-(N-(2-fluoroethyl)acrylamido)ethoxy)pyrimidin-4-yl)-5-[^{18}F]fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide,
N-(3-(6-amino-5-(2-(N-(2-fluoroethyl)acrylamido)ethoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-[^{18}F]fluorobenzamide,
N-(3-(6-amino-5-(2-(N-(2-fluoroethyl)acrylamido)ethoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluoro-benz-[^{11}C]amide,
N-(3-(6-amino-5-(2-(N-(2-fluoroethyl)acrylamido)ethoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-[^{123}I]iodobenzamide,
N-(3-(6-amino-5-(2-(N-(2-fluoroethyl)acrylamido)ethoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-[^{124}I]iodobenzamide,

N-(3-(6-amino-5-(2-(N-(2-fluoroethyl)acrylamido)ethoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-[^{131}I]iodobenzamide,
N-(3-(6-amino-5-(2-(N-(2-fluoroethyl)acrylamido)ethoxy)pyrimidin-4-yl)-5-[^{123}I]iodo-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide,
N-(3-(6-amino-5-(2-(N-(2-fluoroethyl)acrylamido)ethoxy)pyrimidin-4-yl)-5-[^{124}I]iodo-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide, and
N-(3-(6-amino-5-(2-(N-(2-fluoroethyl)acrylamido)ethoxy)pyrimidin-4-yl)-5-[^{131}I]iodo-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide.

Definitions that may be used herein

As used herein, imaging techniques may include in vitro or ex vivo autoradiography, positron emission tomography (PET), single photon emission computed tomography (SPECT) and other techniques known to the skilled artisan.

As used herein, suitable radiolabels (radionuclides), or radioactive atoms, comprised in a compound of the present invention include ^{3}H, ^{11}C, ^{18}F, ^{123}I, ^{124}I, ^{131}I.

As used herein, the bivalent linker X comprising at least one carbon atom and at least one hydrogen atom is typically C_1-C_6 alkylene or C_1-C_2 alkylene or C_3-C_6 cycloalkylene each of which being optionally substituted by C_1-C_6 alkyl.

As used herein, the term "C_1-C_6 alkyl" refers to a fully saturated branched or unbranched hydrocarbon moiety having up to 6 carbon atoms. Unless otherwise provided, it refers to hydrocarbon moieties having 1 to 6 carbon atoms, 1 to 4 carbon atoms or 1 to 2 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl, isopentyl, neopentyl, *n*-hexyl and the like.

As used herein, the term "C_2-C_6 alkenyl" refers to an unsaturated branched or unbranched hydrocarbon moiety having 2 to 6 carbon atoms. Unless otherwise provided, C_2-C_6 alkenyl refers to moieties having 2 to 6 carbon atoms, 2 to 5 carbon atoms, or 2 to 4 carbon atoms. Representative examples of alkenyl include, but are not limited to, ethenyl, *n*-propenyl, *iso*-propenyl, *n*-butenyl, *sec*-butenyl, *iso*-butenyl, *tert*-butenyl, *n*-pentenyl, isopentenyl, neopentenyl, *n*-hexenyl, and the like.

As used herein, the term "C_2-C_6 alkynyl" refers to an unsaturated branched or unbranched hydrocarbon moiety having 2 to 6 carbon atoms, containing at least one triple bond, and which is attached to the rest of the molecule by a single bond. The term "C_{2-4}alkynyl" is to be construed accordingly. Examples of C_{2-6}alkynyl include, but are not limited to, ethynyl, prop-1-ynyl, but-1-ynyl, pent-1-ynyl and penta-1,4-diynyl and the like.

As used herein, the term "C_1-C_6 alkoxy" refers to alkyl-O-, wherein alkyl is defined herein above. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, *tert*-butoxy, pentyloxy, hexyloxy, cyclopropyloxy-, cyclohexyloxy- and the like. Typically, alkoxy groups have about 1 to 6 carbon atoms, 1 to 4 carbon atoms or 1 to 2 carbon atoms.

As used herein, the term "di C_{1-6}alkylamino" refers to a moiety of the formula -N(R_a)-R_a where each R_a is a C_{1-6}alkyl , which may be the same or different, as defined above.

As used herein, the term "C_3-C_6 cycloalkyl" refers to saturated monocyclic hydrocarbon groups of 3-6 carbon atoms. Cycloalkyl may also be referred to as a carbocyclic ring and vice versa additionally referring to the number of carbon atoms present. Unless otherwise provided, cycloalkyl refers to cyclic hydrocarbon groups having between 3 and 6 ring carbon atoms or between 3 and 4 ring carbon atoms. Exemplary monocyclic hydrocarbon groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

As used herein, the term "C_3-C_6 cycloalkylene" refers to saturated monocyclic bivalent hydrocarbon group of 3-6 carbon atoms. Cycloalkylene may also be referred to as a carbocyclic ring and vice versa additionally referring to the number of carbon atoms present. Unless otherwise provided, cycloalkylene refers to bivalent cyclic hydrocarbon groups having between 3 and 6 ring carbon atoms or between 3 and 4 ring carbon atoms. Exemplary monocyclic hydrocarbon groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

As used herein "C_1-C_6 alkylene" refers to a branched or unbranched bivalent hydrocarbon moiety comprising having from 2 to 6 carbon atoms. Representative examples include methylene, ethylene, propylene, iso-proyplene, butylene, iso-butylenye, pentylene, hexylene, and the like

As used herein, the term “halogen” or “halo” refers to fluoro, chloro, bromo, and iodo.

As used herein, the terms “salt” or “salts” refers to an acid addition or base addition salt of a compound of the invention. “Salts” include in particular “pharmaceutically acceptable salts”. The term “pharmaceutically acceptable salts” refers to salts that retain the biological effectiveness and properties of the compounds of this invention and, which typically are not biologically or otherwise undesirable. In many cases, the compounds of the present invention are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids, e.g., acetate, bromide/hydrobromide, chloride/hydrochloride, citrate, fumarate, and the like.

Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like.

Organic acids from which salts can be derived include, for example, acetic acid, fumaric acid, citric acid, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from a basic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting free base forms of these compounds with a stoichiometric amount of the appropriate acid. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two. Generally, use of non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile is desirable, where practicable. Lists of additional suitable salts can be found, e.g., in “Remington's Pharmaceutical Sciences”, 20th ed., Mack Publishing Company, Easton, Pa., (1985); and in “Handbook of Pharmaceutical Salts: Properties, Selection, and Use” by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, *e.g.* D_2O, d_6-acetone, d_6-DMSO.

Compounds of the invention, i.e. compounds of formula (I) that contain groups capable of acting as donors and/or acceptors for hydrogen bonds may be capable of forming co-crystals with suitable co-crystal formers. These co-crystals may be prepared from compounds of formula (I) by known co-crystal forming procedures. Such procedures include grinding, heating, co-subliming, co-melting, or contacting in solution compounds of formula (I) with the co-crystal former under crystallization conditions and isolating co-crystals thereby formed. Suitable co-crystal formers include those described in WO 2004/078163. Hence the invention further provides co-crystals comprising a compound of formula (I).

As used herein, the term "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, surfactants, antioxidants, preservatives (*e.g.*, antibacterial agents, antifungal agents), isotonic agents, absorption delaying agents, salts, preservatives, drug stabilizers, binders, excipients, disintegration agents, lubricants, sweetening agents, flavoring agents, dyes, and the like and combinations thereof, as would be known to those skilled in the art (see, for example, Remington's Pharmaceutical Sciences, 18th Ed. Mack Printing Company, 1990, pp. 1289- 1329). Except insofar as any conventional carrier is incompatible with the active ingredient, its use in the therapeutic or pharmaceutical compositions is contemplated.

The term "a therapeutically effective amount" of a compound of the present invention refers to an amount of the compound of the present invention that will elicit the biological or medical response of a subject, for example, reduction or inhibition of an enzyme or a protein activity, or ameliorate symptoms, alleviate conditions, slow or delay disease progression, or prevent a disease, etc. In one non-limiting embodiment, the term “a therapeutically effective amount” refers to the amount of the compound of the present invention that, when administered to a subject, is effective to (1) at least partially alleviating, inhibiting, preventing and/or ameliorating a condition, or a disorder or a disease (i) mediated by BTK, or (ii) associated with BTK activity, or (iii) characterized by activity (normal or abnormal) of BTK; or (2) reducing or inhibiting the activity of BTK; or

(3) reducing or inhibiting the expression of BTK. In another non-limiting embodiment, the term “a therapeutically effective amount” refers to the amount of the compound of the present invention that, when administered to a cell, or a tissue, or a non-cellular biological material, or a medium, is effective to at least partially reducing or inhibiting the activity of BTK, or reducing or inhibiting the expression of BTK partially or completely.

As used herein, the term “subject” refers to an animal. Typically the animal is a mammal. A subject also refers to for example, primates (*e.g.*, humans, male or female), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, fish, birds and the like. In certain embodiments, the subject is a primate. In yet other embodiments, the subject is a human.

As used herein, the term “inhibit”, "inhibition" or “inhibiting” refers to the reduction or suppression of a given condition, symptom, or disorder, or disease, or a significant decrease in the baseline activity of a biological activity or process.

As used herein, the term “treat”, “treating" or "treatment" of any disease or disorder refers in one embodiment, to ameliorating the disease or disorder (i.e., slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment “treat”, "treating" or "treatment" refers to alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient. In yet another embodiment, “treat”, "treating" or "treatment" refers to modulating the disease or disorder, either physically, (*e.g.*, stabilization of a discernible symptom), physiologically, (*e.g.*, stabilization of a physical parameter), or both. In yet another embodiment, “treat”, "treating" or "treatment" refers to preventing or delaying the onset or development or progression of the disease or disorder.

As used herein, a subject is “in need of” a treatment if such subject would benefit biologically, medically or in quality of life from such treatment.

As used herein, the term "a," "an," "the” and similar terms used in the context of the present invention (especially in the context of the claims) are to be construed to cover both the singular and plural unless otherwise indicated herein or clearly contradicted by the context.

All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (*e.g.* "such as") provided herein is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention otherwise claimed.

Any asymmetric atom (e.g., carbon or the like) of the compound(s) of the present invention can be present in racemic or enantiomerically enriched, for example the (*R*)-, (*S*)- or (*R,S*)- configuration. In certain embodiments, each asymmetric atom has at least 50 % enantiomeric excess, at least 60 % enantiomeric excess, at least 70 % enantiomeric excess, at least 80 % enantiomeric excess, at least 90 % enantiomeric excess, at least 95 % enantiomeric excess, or at least 99 % enantiomeric excess in the (*R*)- or (*S*)- configuration. Substituents at atoms with unsaturated double bonds may, if possible, be present in *cis*- (*Z*)- or *trans*- (*E*)- form.

Accordingly, as used herein a compound of the present invention can be in the form of one of the possible isomers selected from rotamers, tautomers, geometric (*cis* or *trans*) isomers, diastereomers, optical isomers (antipodes), and racemates or mixtures thereof.

Any resulting mixtures of isomers can be separated on the basis of the physicochemical differences of the constituents, into the pure or substantially pure geometric or optical isomers, diastereomers, racemates, for example, by chromatography and/or fractional crystallization.

Any resulting racemates of final products or intermediates can be resolved into the optical antipodes by known methods, *e.g.*, by separation of the diastereomeric salts thereof, obtained with an optically active acid or base, and liberating the optically active acidic or basic compound. In particular, a basic moiety may thus be employed to resolve the compounds of the present invention into their optical antipodes, *e.g.*, by fractional crystallization of a salt formed with an optically active acid, *e.g.*, tartaric acid, dibenzoyl tartaric acid, diacetyl tartaric acid, di-*O,O'-p*-toluoyl tartaric acid, mandelic acid, malic acid or camphor-10-sulfonic acid. Racemic products can also be resolved by chiral chromatography, *e.g.*, high pressure liquid chromatography (HPLC) using a chiral adsorbent.

Furthermore, the compounds of the present invention, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization. The compounds of the present invention may inherently or by design form solvates with pharmaceutically acceptable solvents (including water); therefore, it is intended that the invention embrace both solvated and unsolvated forms. The term "solvate" refers to a molecular complex of a compound of the present invention (including pharmaceutically acceptable salts thereof) with one or more solvent molecules. Such solvent molecules are those commonly used in the pharmaceutical art, which are known to be innocuous to the recipient, e.g., water, ethanol, and the like. The term "hydrate" refers to the complex where the solvent molecule is water.

The compounds of the present invention, including salts, hydrates and solvates thereof, may inherently or by design form polymorphs.

In another aspect, the present invention provides a pharmaceutical composition comprising a compound of the present invention and a pharmaceutically acceptable carrier.

The pharmaceutical composition of the present invention is preferably formulated for intravenous or local administration.

The pharmaceutical composition of the present invention is typically suitable for preclinical, clinical, in vitro, in vivo, diagnostic and other studies.

The pharmaceutical composition may be also formulated for other particular routes of administration such as oral administration, parenteral administration, and rectal administration, etc. In addition, the pharmaceutical compositions of the present invention may be made up in a solid form (including without limitation capsules, tablets, pills, granules, powders or suppositories), or in a liquid form (including without limitation solutions, suspensions or emulsions). The pharmaceutical compositions may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional inert diluents, lubricating agents, or buffering agents, as well as adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers and buffers, etc.

Typically, the pharmaceutical compositions might be tablets or gelatin capsules comprising the active ingredient together with

a) diluents, *e.g.*, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine;

b) lubricants, *e.g.*, silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also

c) binders, *e.g.*, magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone; if desired

d) disintegrants, *e.g.*, starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or

e) absorbents, colorants, flavors and sweeteners.

Tablets may be either film coated or enteric coated according to methods known in the art.

Suitable compositions for oral administration typically include an effective amount of a compound of the invention in the form of tablets, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use are prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets may contain the active ingredient in admixture with nontoxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients are, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example, starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets are uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract

and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed. Formulations for oral use can be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil.

Certain injectable compositions might be aqueous isotonic solutions or suspensions, and suppositories may advantageously be prepared from fatty emulsions or suspensions. Said compositions may be sterilized and/or may contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances. Said compositions may be prepared according to conventional methods, and they typically contain for diagnostic purposes *a*n amount of a compound of the invention sufficient to produce emissions in a range of from 0.1 MBq to about 1000 MBq; and for therapeutic purposes, said compositions typically contain an amount of a compound of the invention sufficient to produce emissions in a range of from 100 MBq to about 10'000 MBq.

Suitable compositions for transdermal application include an effective amount of a compound of the invention with a suitable carrier. Carriers suitable for transdermal delivery include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound of the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

Suitable compositions for topical application, *e.g.*, to the skin and eyes, include aqueous solutions, suspensions, ointments, creams, gels or sprayable formulations, *e.g.*, for delivery by aerosol or the like. Such topical delivery systems will in particular be appropriate for dermal application, *e.g.*, for the treatment of skin cancer, *e.g.*, for prophylactic use in sun creams, lotions, sprays and the like. They are thus particularly suited for use in topical, including cosmetic, formulations well-known in the art. Such

may contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

As used herein a topical application may also pertain to an inhalation or to an intranasal application. They may be conveniently delivered in the form of a dry powder (either alone, as a mixture, for example a dry blend with lactose, or a mixed component particle, for example with phospholipids) from a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray, atomizer or nebuliser, with or without the use of a suitable propellant.

The present invention further provides anhydrous pharmaceutical compositions and dosage forms comprising the compounds of the present invention as active ingredients, since water may facilitate the degradation of certain compounds.

Anhydrous pharmaceutical compositions and dosage forms of the invention can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. An anhydrous pharmaceutical composition may be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions are packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers (*e. g.*, vials), blister packs, and strip packs.

The invention further provides pharmaceutical compositions and dosage forms that comprise one or more agents that reduce the rate by which the compound of the present invention as an active ingredient will decompose. Such agents, which are referred to herein as "stabilizers," include, but are not limited to, antioxidants such as ascorbic acid, pH buffers, or salt buffers, etc.

Utility

The compounds of formula I in free form or in salt form, exhibit *inter alia* valuable pharmacological properties, e.g. BTK binding properties, e.g. as indicated by in vitro and in vivo tests as provided in the next sections and are therefore indicated for therapy

and/or diagnostic purposes; they further exhibit valuable properties with respect to radiolabeling experiments and radioimaging.

Compounds of the invention may be useful in the in vitro or in vivo staging or diagnosis of a disease or disorder typically selected from chronic autoimmune urticaria, allergy (atopic dermatitis, contact dermatitis, allergic rhinitis), atherosclerosis, B-cell lymphoma, type 1 diabetes, type 2 diabetes, inflammatory bowel disease, ulcerative colitis, morbus Crohn, pancreatitis, Sjoegren's disease, glomerolunephritis, Goodpasture's syndrome, Hashimoto's thyroiditis, and/or Grave's disease.

Compounds of the invention may also be useful in the treatment of a wide range of diseases and/or disorders resulting from BTK-expressing cell growth dysregulation.

Compounds of the invention may be useful in the in vitro or in vivo staging or diagnosis of diseases and/or in the therapeutic treatement that are characterized by pathological proliferation and/or tissue infiltration of B lymphocytes, e.g. primary immune deficiency syndromes (e.g. ALPS, APDS/PASLI, X-linked proliferative disease, CVID), neuroinflammatory diseases (e.g. multiple sclerosis), autoimmune connective tissue diseases (e.g. primary and secondary Sjoegren's syndrome, Systemic Lupus erythematodes, Rheumatoid arthritis, Systemic sclerosis, Dermatomyositis, Polymyositis, mixed connective tissue disease, primary biliary cirrhosis, autoimmune hepatitis), type 1 and type 2 diabetes mellitus, celiac's disease, inflammatory bowel diseases (e.g. crohn's disease, ulcerative colitis), primary and secondary vasculitides (e.g. granulomatosis with polyangiitis/Wegener's; Churg-Strauss syndrome; microscopic polyangiitis, panarteriitis nodosa, focal segmental necrotizing glomerulonephritis, HCV associated or essential cryoglobulinaemic vasculitis, giant cell arteriitis), autoimmune skin diseases (e.g. chronic autoimmune urticaria, atopic dermatitis, contact dermatitis), allergic rhinitis, asthma, atherosclerosis, autoimmune thyroid diseases (e.g. Hashimoto thyroiditis, Grave's disease), IgG4-related disease (e.g. Ormond's disease, autoimmune pancreatitis), autoimmune glomerulonephritis syndromes (e.g. Goodpasture's syndrome, IgA nephropathy), autoimmune hemolytic anaemia, idiopathic thrombocytopenic purpura, and B-cell lymphomas.

Diagnostic and Imaging Uses

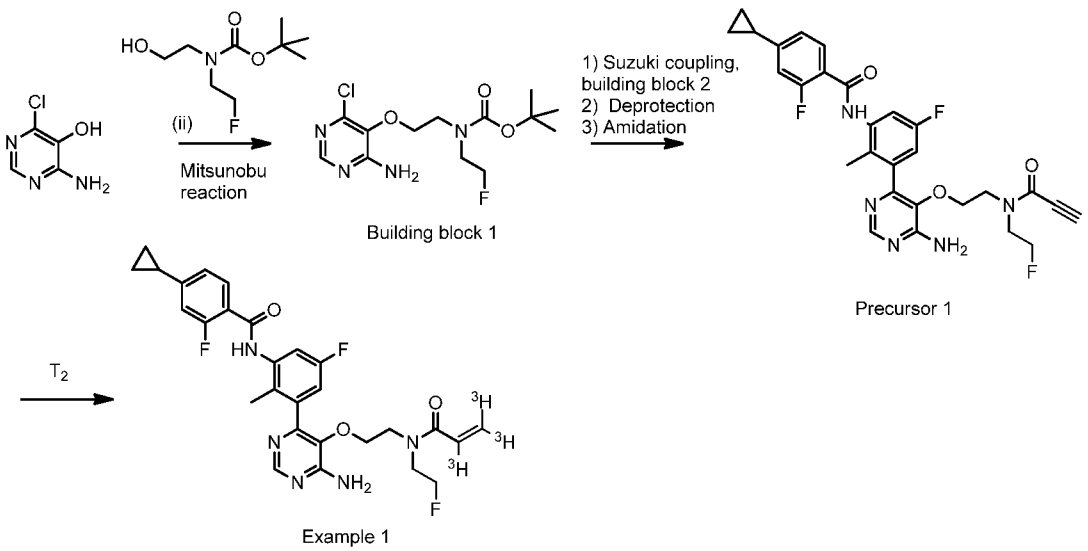
Compounds of the invention may be used to evaluate whether a patient is susceptible to be treated with a drug acting on a disease associated with BTK, e.g. for diagnosing diseases or disorders where BTK is involved, e.g. is being expressed, for example a disease mentioned hereinabove or hereinbelow.

Further provided is herein a method to diagnose the appearance or progression of a diseases or disorders where BTK expression is altered, for example an autoimmune disease, in a subject or in a biological sample from a subject, wherein said method comprises using a radiolabeled compound of the invention as defined hereinabove, e.g. a radiolabeled fluoro derivative as described hereinabove, e.g. a compound of formula I as hereinabove defined.

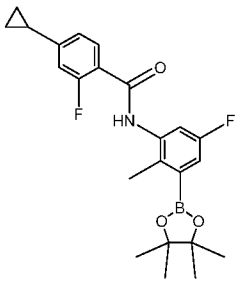
Methods of Synthesizing the Compounds of the Invention

1) Synthesis of N-(3-(6-amino-5-(2-(N-(2-fluoroethyl)[$^3H_3$]acrylamido)ethoxy) pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide

Compounds of the invention may be prepared by a reaction sequence involving Mitsunobu reaction of 4-amino-6-chloropyrimidin-5-ol with an alcohol of formula (ii) using an appropriate azodicarboxylate, such as DIAD, and Smopex-301 or triphenylphosphine; thereupon a Suzuki coupling with a boronic ester (building block 2) using an appropriate catalyst, such as bis(triphenyl-phosphine)-palladium(II) dichloride, deprotection using an appropriate acid, such as TFA or HCl, followed by amide formation of the ammonium salt or the free amine with an acid and using an appropriate coupling reagent, such as T_3P, and an appropriate base, such as DIPEA, or with an acid chloride using an appropriate base, such as DIPEA, and finally by reduction in the presence of tritium gas to yield a compound of the invention as shown below:

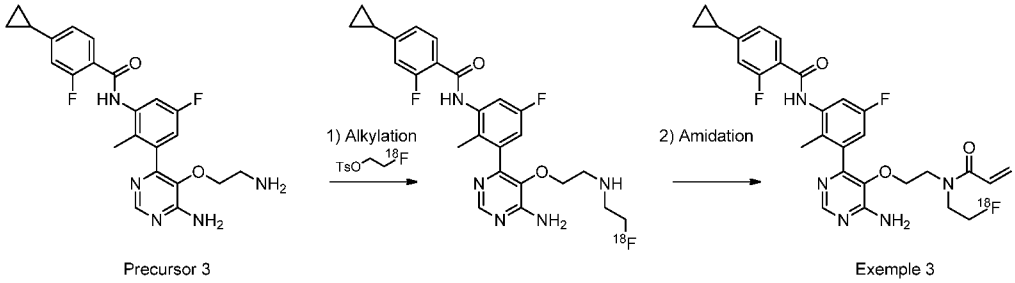


Building block 2 has the following structure:



2) Synthesis of N-(3-(6-amino-5-(2-(N-(2-[^{18}F]fluoroethyl)acrylamido)ethoxy) pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide

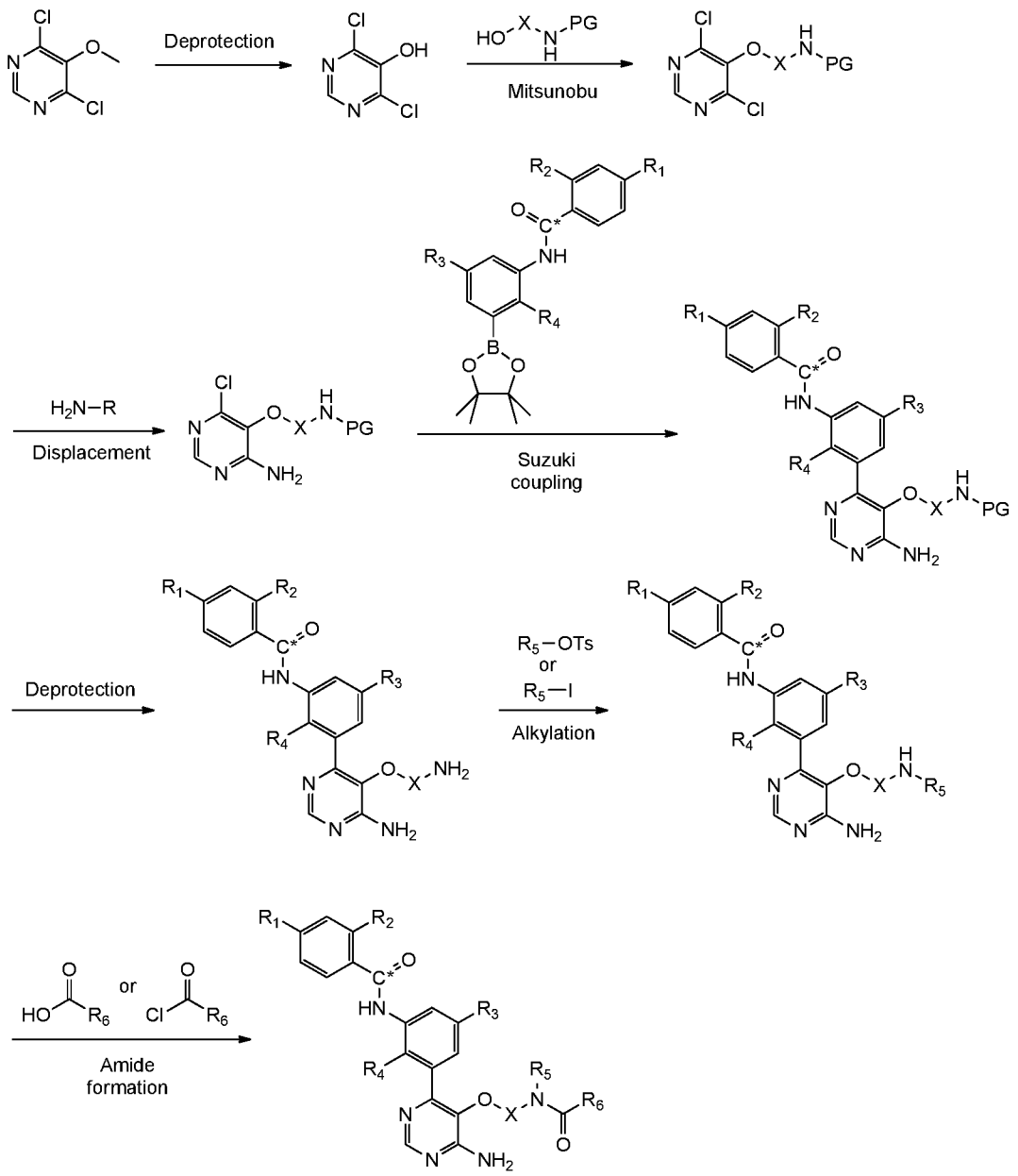
Compounds of the invention may be prepared by a reaction sequence involving N-alkylation of Precursor **3** using [^{18}F]fluoroethyltosylate in the presence of a base. Followed by amide formation with an acid, e.g. acrylic acid, and using an appropriate coupling reagent, such as T_3P, and an appropriate base, such as DIPEA, or with an acid chloride, e.g. acrylic acid chloride using an appropriate base, such as DIPEA.



Precursor 3 Exemple 3

3) Synthesis of N-(3-(6-amino-5-(2-(N-(3-fluoropropyl)acrylamido)ethoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide (Example 4)

Agents of the invention may alternatively be prepared by a reaction sequence starting from 4,6-dichloro-5-methoxypyrimidine involving methoxy cleavage using an appropriate lewis acid, such as aluminum chloride or boron tribromide, Mitsunobu reaction with an appropriate alcohol, e.g. N-tert butoxycarbonyl-2-aminoethanol , triphenylphosphine and an appropriate azadicarboxylate, such as DIAD, followed by displacement with an appropriate amine, such as ammonia, Suzuki coupling with appropriate boronic esters e.g. building block 2, using an appropriate palladium catalyst, such as tetrakis(triphenylphosphine) palladium(0) or bis(triphenyl-phosphine) palladium(II) dichloride, deprotection using an appropriate acid, such as TFA or HCl, alkylation using an appropriate alkyl tosylate or alkyl iodide, such as 2-fluoroethyltosylate, 2-fluoroethyliodide or 3-fluoropropyltosylate, followed by amide formation with an acid, e.g. acrylic acid, using an appropriate coupling reagent, such as T3P, and an appropriate base, such as DIPEA, or with an acid chloride, e.g acrylic acid chloride using an appropriate base, such as triethylamine or DIPEA, as shown in Scheme below:

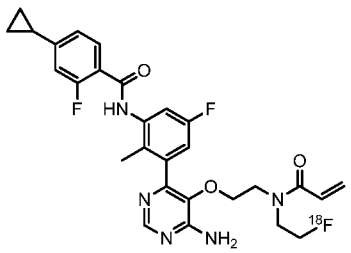


Methods contemplated for synthesizing prophetic compounds

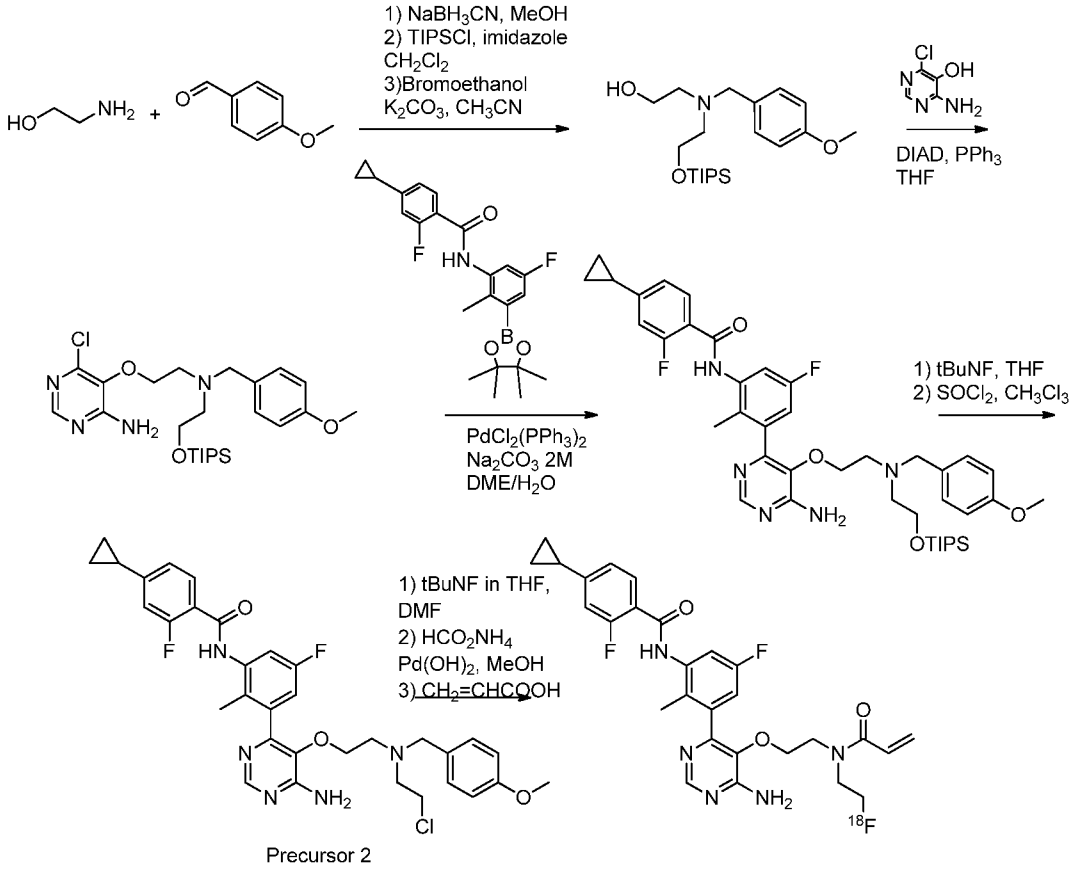
In the following paragraphs, a number of analogous compounds to the compound of Example 1 are being contemplated as valuable compounds within the scope of the present invention. Although these compounds are presently prophetic examples, these may be obtained through synthetic analogy with a reasonable chance of success. In

detail, the following examples and methods for preparing the same are being contemplated:

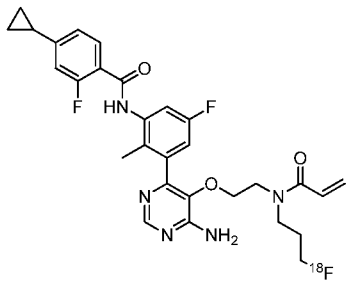
4) Synthesis of N-(3-(6-amino-5-(2-(N-(2-[^{18}F]fluoroethyl)acrylamido) ethoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluoro-benzamide



The synthesis of N-(3-(6-amino-5-(2-(N-(2-[^{18}F]fluoroethyl)acrylamido)ethoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide might be effected by treating Precursor **2** in the presence of [^{18}F]TBAF or [^{18}F]KF/K222 in DMF at 100°C. The removal of the protecting group might be done using ammonium formate or H_2 in presence of a palladium catalyst such as Pd/C or $Pd(OH)_2$ or $Pd(OAc)_2$. Finally, the introduction of the acrylamide group might be achieved by using acrylic acid, DIPEA and T_3P 50% in DMF, thereby yielding the contemplated title compound as shown in the below scheme.

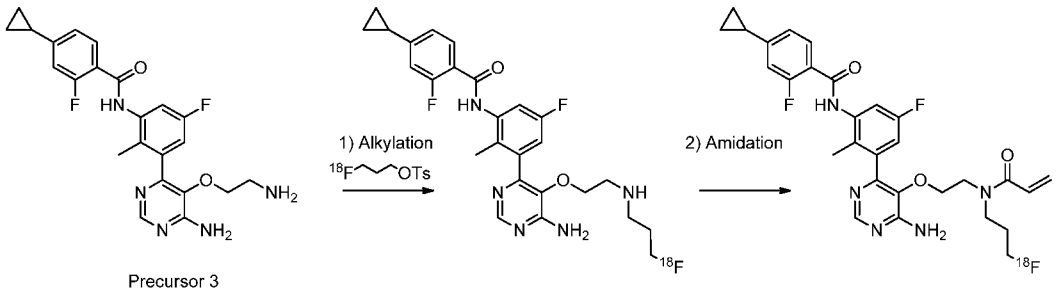


5) Synthesis of N-(3-(6-amino-5-(2-(N-(3-[^{18}F]fluoropropyl)acrylamido)ethoxy) pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide



The contemplated N-(3-(6-amino-5-(2-(N-(3-[^{18}F]fluoropropyl)acrylamido)ethoxy) pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide may be synthesized by a reaction sequence involving N-alkylation of Precursor **3** using [^{18}F]fluoropropyltosylate in the presence of a base, such as Et_3N, DIPEA, K_2CO_3 or Cs_2CO_3. Followed by amide formation with an acid, e.g. acrylic acid, and using

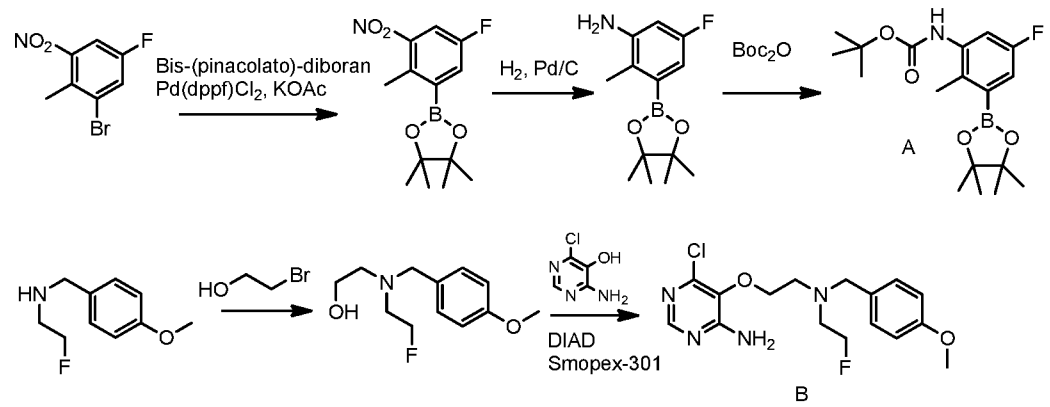
an appropriate coupling reagent, such as T_3P, and an appropriate base, such as DIPEA, or with an acid chloride using an appropriate base, such as DIPEA.

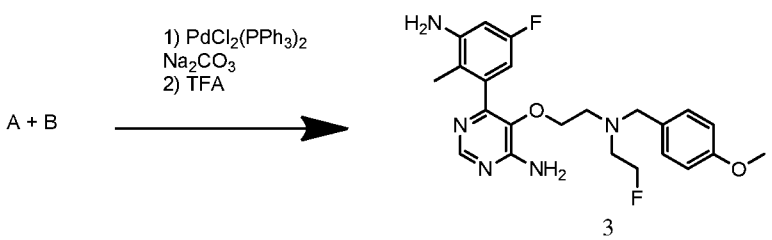


Precursor 3

6) **Synthesis of N-(3-(6-amino-5-(2-(N-(2-fluoroethyl)acrylamido)ethoxy) pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-[^{18}F]fluorobenz-amide**

In a first step, the precursor for radiolabeling might be prepared as shown below:

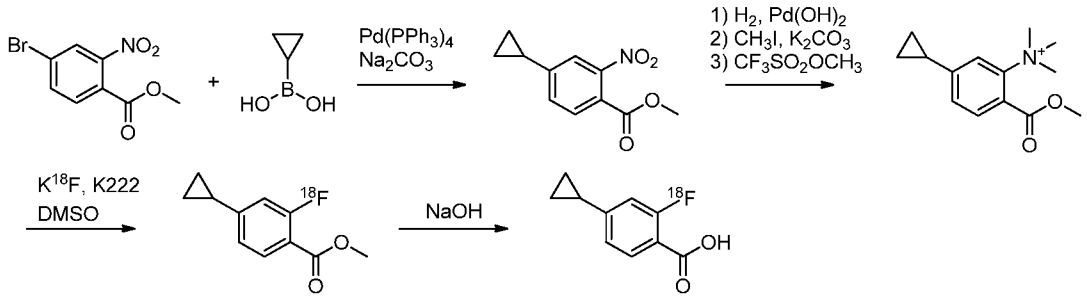




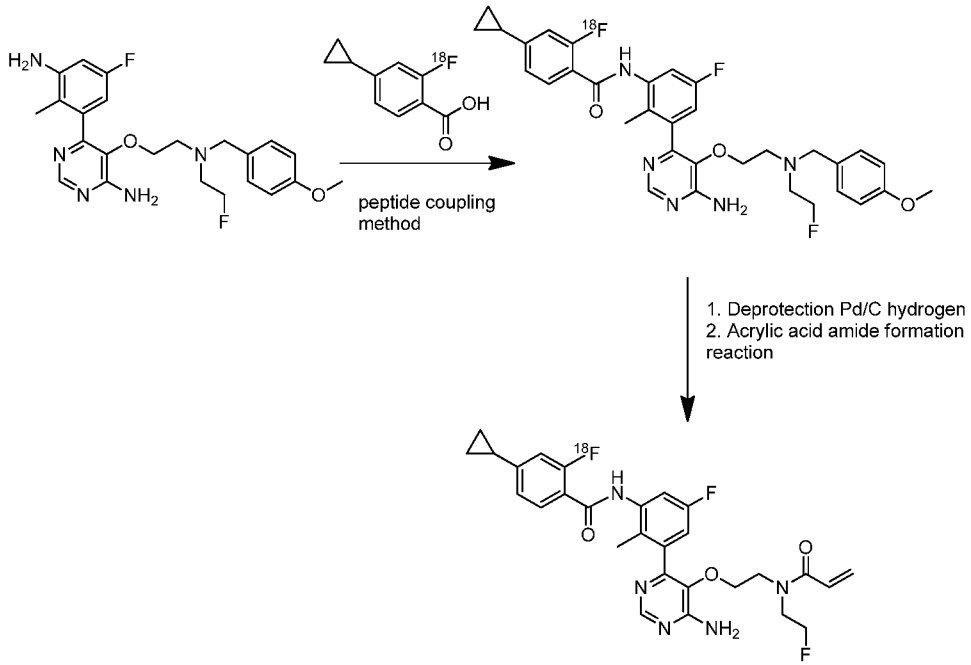
3

The contemplated compound (3) might be obtained by Suzuki coupling of 6-chloro-5-(2-((2-fluoroethyl)(4-methoxybenzyl)amino)ethoxy)pyrimidin-4-amine with tert-butyl (5-fluoro-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)carba-mate. The alkylation of 2-fluoro-N-(4-methoxybenzyl)ethanamine with bromoethanol followed by treatment with 4-amino-6-chloropyrimidin-5-ol under Mitsunobu type conditions may yield the 6-chloro-5-alkoxy-pyrimidin-4-amine. The boronate ester may be prepared starting from 1-bromo-5-fluoro-2-methyl-3-nitrobenzene, which may be first treated with pinacolato boronate followed by reduction and the formation of the protected aniline.

Radiolabeling:



The labeled 4-cyclopropyl-2-[^{18}F]fluorobenzoic acid may be synthesized by treating the 5-cyclopropyl-2-(methoxycarbonyl)-N,N,N-trimethylbenzenaminium with [^{18}F]KF/K222 in DMSO followed by rapid hydrolysis using aq. NaOH. The N,N,N-trimethylbenzammon-ium precursor may be obtained by combining methyl 4-bromo-2-nitrobenzoate with cyclopropylboronic acid under Suzuki type conditions followed by the reduction of the nitro group and the formation of the trimethylaminium salt (see scheme above).



The final labeled compound may be prepared by coupling of 4-cyclopropyl-2-[^{18}F]fluorobenzoic acid with 6-(3-amino-5-fluoro-2-methylphenyl)-5-(2-((2-fluoroethyl)(4-methoxybenzyl)amino)ethoxy)pyrimidin-4-amine using amide formation conditions known to the chemist skilled in the art.

The removal of the protecting group may be done using ammonium formate in presence of a palladium catalyst such as Pd/C or $Pd(OH)_2$ or $Pd(OAc)_2$.

The introduction of the acrylamide group may be done using acrylic acid, DIPEA and T_3P in DMF (see scheme above).

The specific compounds named below are being contemplated as valuable compounds within the scope of the present invention and may be obtained by a similar and/or analogous synthetic procedure as being outlined above:

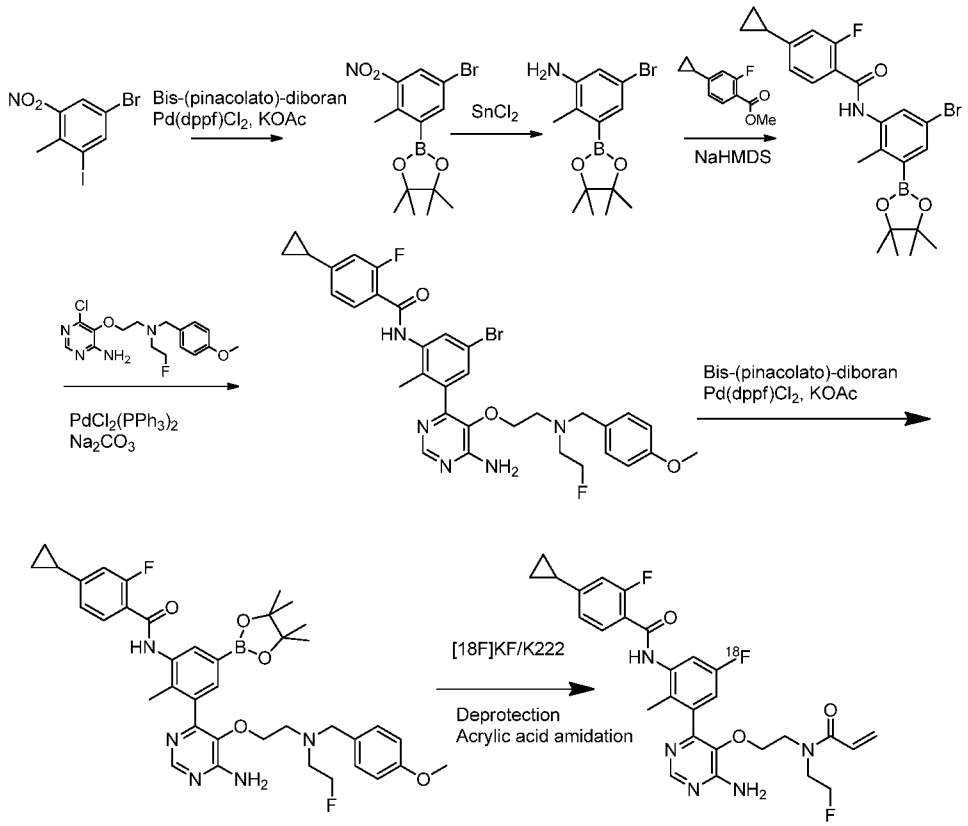
N-(3-(6-amino-5-(2-(N-methylacrylamido)ethoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-[^{18}F]fluorobenzamide,

N-(3-(6-amino-5-(2-(N-ethylacrylamido)ethoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-[^{18}F]fluorobenzamide, and

(E)-N-(3-(6-amino-5-(3-(N-methylacrylamido)prop-1-en-1-yl)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-[^{18}F]fluorobenzamide.

7) Synthesis of N-(3-(6-amino-5-(2-(N-(2-fluoroethyl)acrylamido)ethoxy) pyrimidin-4-yl)-5-[^{18}F]fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenz-amide

The precursor for radiolabeling may be prepared as shown below:



The synthesis of the boronate ester precursor may involve the treatment of 5-bromo-1-iodo-2-methyl-3-nitrobenzene with pinacolato boronate followed by reduction of the nitro group and consecutive formation of the amide using a base such as NaHMDS. The coupling of N-(5-bromo-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4-cyclopropyl-2-fluorobenzamide with 6-chloro-5-(2-((2-fluoroethyl)(4-methoxybenzyl) amino) ethoxy)pyrimidin-4-amine under Suzuki conditions may then yield the intermediate bromophenyl which may be converted into the boronate ester precursor using pinacolato boronate.

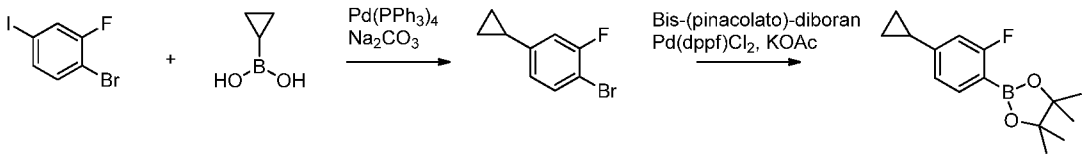
Radiolabeling:

The boronate ester precursor may be treated with [^{18}F]KF/K222 and [Cu(OTf)$_2$(py)$_4$] (OTf=trifluoromethanesulfonate, py=pyridine) to yield the labeled intermediate as described by V. Gouverneur, Angewandte Chemie International Edition, 2014, 53, 7761. Removal of protecting group and amide coupling may be done in analogy to the synthesis of N-(3-(6-amino-5-(2-(N-(2-[^{18}F]fluoroethyl)acrylamido)ethoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide.

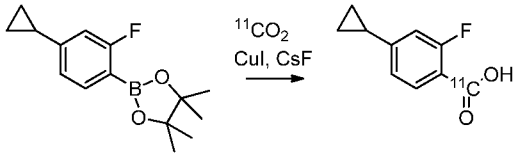
The specific compounds named below are being contemplated as further valuable compounds within the scope of the present invention and may be obtained by a similar and/or analogous synthetic procedure as being outlined above:
N-(3-(6-amino-5-(2-(N-methylacrylamido)ethoxy)pyrimidin-4-yl)-5-[^{18}F]fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide,
N-(3-(6-amino-5-(2-(N-ethylacrylamido)ethoxy)pyrimidin-4-yl)-5-[^{18}F]fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide, and
(E)-N-(3-(6-amino-5-(3-(N-methylacrylamido)prop-1-en-1-yl)pyrimidin-4-yl)-5-[^{18}F]fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide.

8) Synthesis of N-(3-(6-amino-5-(2-(N-(2-fluoroethyl)acrylamido)ethoxy) pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenz-[^{11}C]amide

The precursor for radiolabeling may be synthesized following the synthetic scheme below:



The synthesis of 2-(4-cyclopropyl-2-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane may be carried out by first reacting 1-bromo-2-fluoro-4-iodobenzene and cyclopropylboronic acid in the presence of a palladium catalyst followed by treatment with pinacolato boronate.
Radiolabeling:



The CuI-mediated carboxylation of 2-(4-cyclopropyl-2-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane under subatmospheric partial pressure of [^{11}C]CO_2 in an inert atmosphere, in the presence of TMEDA, KF, and K222 may yield 4-cyclopropyl-2-fluorobenzoic [^{11}C]acid in analogy to the procedure reported by P. Riss, Angew. Chem. Int. Ed. 2012, 51, 2698 –2702.

Coupling, deprotection and amide coupling may be carried outin analogy to the synthesis of N-(3-(6-amino-5-(2-(N-(2-fluoroethyl)acrylamido)ethoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-[^{18}F]fluorobenzamide.

The specific compounds named below are being contemplated as further valuable compounds within the scope of the present invention and may be obtained by a similar and/or analogous synthetic procedure as being outlined above:

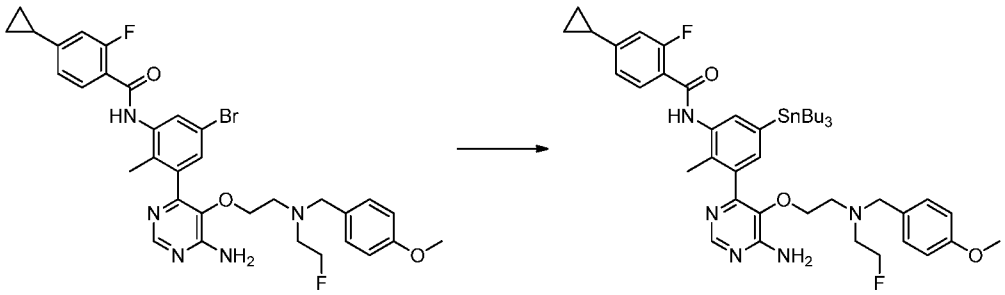
N-(3-(6-amino-5-(2-(N-methylacrylamido)ethoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenz[^{11}C]amide,

N-(3-(6-amino-5-(2-(N-ethylacrylamido)ethoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenz[^{11}C]amide, and

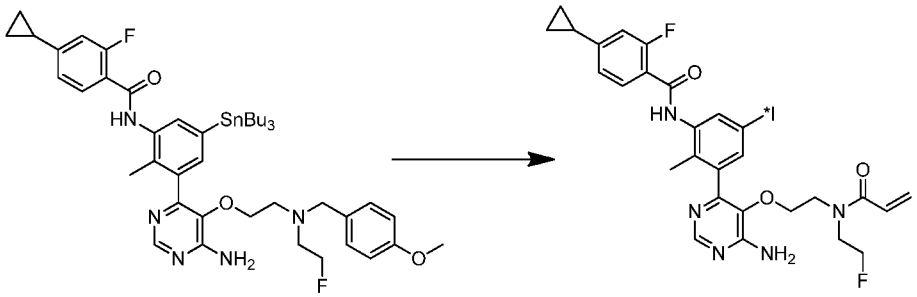
(E)-N-(3-(6-amino-5-(3-(N-methylacrylamido)prop-1-en-1-yl)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenz[^{11}C]amide.

9) Synthesis of N-(3-(6-amino-5-(2-(N-(2-fluoroethyl)acrylamido)ethoxy) pyrimidin-4-yl)-5-[^{123}I]iodo-2-methylphenyl)-4-cyclopropyl-2-fluorobenz-amide and N-(3-(6-amino-5-(2-(N-(2-fluoroethyl)acrylamido)ethoxy) pyrimidin-4-yl)-5-[^{124}I]iodo-2-methylphenyl)-4-cyclopropyl-2-fluoro-benzamide

Preparation of the precursor for radiolabeling:



A stannane precursor (shown above) may be prepared by reacting N-(3-(6-amino-5-(2-((2-fluoroethyl)(4-methoxybenzyl)amino)ethoxy)pyrimidin-4-yl)-5-bromo-2-methyl-phenyl)-4-cyclopropyl-2-fluorobenzamide with bis(tributyltin) in the presence of a palladium catalyst such as $Pd(PPh_3)_4$.



Radiolabeling:

The treatment of N-(3-(6-amino-5-(2-((2-fluoroethyl)(4-methoxybenzyl)amino)ethoxy) pyrimidin-4-yl)-2-methyl-5-(tributylstannyl)phenyl)-4-cyclopropyl-2-fluorobenzamide with [^{123}I]NaI or [^{124}I]NaI in the presence of a oxidizing agent such as chloramine-T may yield the title compounds (*I = [^{123}I], [^{124}I] and [^{131}I]).

The specific compounds named below are being contemplated as further valuable compounds within the scope of the present invention and may be obtained by a similar and/or analogous synthetic procedure as being outlined above:

^{123} I-label:

N-(3-(6-amino-5-(2-(N-methylacrylamido)ethoxy)pyrimidin-4-yl)-5-[^{123}I]iodo-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide,

N-(3-(6-amino-5-(2-(N-ethylacrylamido)ethoxy)pyrimidin-4-yl)-5-[^{123}I]iodo-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide, and

(E)-N-(3-(6-amino-5-(3-(N-methylacrylamido)prop-1-en-1-yl)pyrimidin-4-yl)-5-[^{123}I]iodo-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide.

^{124} I-label:
N-(3-(6-amino-5-(2-(N-methylacrylamido)ethoxy)pyrimidin-4-yl)-5-[^{124}I]iodo-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide ,
N-(3-(6-amino-5-(2-(N-ethylacrylamido)ethoxy)pyrimidin-4-yl)-5-[^{124}I]iodo-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide, and
(E)-N-(3-(6-amino-5-(3-(N-methylacrylamido)prop-1-en-1-yl)pyrimidin-4-yl)-5-[^{124}I]iodo-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide.

^{131} I-label:
N-(3-(6-amino-5-(2-(N-methylacrylamido)ethoxy)pyrimidin-4-yl)-5-[^{131}I]iodo-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide,
N-(3-(6-amino-5-(2-(N-ethylacrylamido)ethoxy)pyrimidin-4-yl)-5-[^{131}I]iodo-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide, and
(E)-N-(3-(6-amino-5-(3-(N-methylacrylamido)prop-1-en-1-yl)pyrimidin-4-yl)-5-[^{131}I]iodo-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide.

EXPERIMENTAL SECTION

Abbreviations:

BISPIN:	Bis(pinacolato)diboron
Boc	t-Butyloxycarbonyl
DCE:	Dichloroethane
DCM:	Dichloromethane
DIAD:	Diisopropyl azodicarboxylate
DIPEA:	*N*-Diisopropylethylamine
DME:	1,2-Dimethoxyethane
DMF:	*N*,*N*-Dimethylformamide

DMSO:	Dimethyl sulfoxide
EtOAc:	Ethyl acetate
EtOH:	Ethanol
hr:	Hour
M:	Molar
MeOH:	Methanol
min:	Minute
NaHMDS:	Sodium bis(trimethylsilyl)amide
rt:	Retention time
RT:	Room temperature
SFC:	Supercritical fluid chromatography
Smopex-301:	Polymer supported triphenylphosphine
SPE:	Solid phase extraction
TBAI:	Tetrabutylammonium iodide
TBAF:	Tetrabutylammonium fluoride
TBDPS:	*tert*-Butyldiphylsilyl
TBHP:	*tert*-Butyl hydroperoxide
TBME:	*tert*-Butyl methyl ether
TEA:	Triethylamine
TFA:	Trifluoroacetic acid
THF:	Tetrahydrofuran
T3P:	Propylphosphonic anhydride
XPhos:	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

^{1}H NMR spectra were recorded on a Bruker 400 MHz NMR spectrometer. Significant peaks are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; v, very) and number of protons. Electron Spray Ionization (ESI) mass spectra were recorded on a Waters Acquity SQD mass spectrometer. Mass spectrometry results are reported as the ratio of mass over charge.

UPLC-MS Method:

Waters Acquity UPLC instrument equipped with PDA detector, Waters Acquity SQD mass spectrometer and Waters Acquity HSS T3 1.8 µm 2.1 x 50 mm column. Peak

detection is reported at full scan 210 - 450 nM. Mass spectrometry results are reported as the ratio of mass over charge.

Eluent A: Water + 0.05% formic acid + 3.75 mM ammonium acetate.

Eluent B: Acetonitrile + 0.04% formic acid.

Flow: 1 mL/min

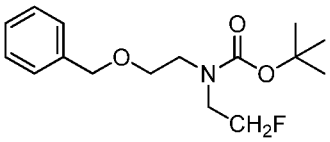
Gradient:

Time [min]	% A (Eluent A)	% B (Eluent B)
0.00	95	5
1.40	2	98
1.80	2	98
1.90	95	5
2.00	95	5

All reagents, starting materials and intermediates utilized in these Examples are available from commercial sources or are readily prepared by methods known to those skilled in the art.

Synthesis of building block 1

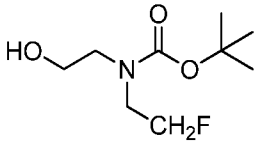
(1) *tert*-Butyl (2-(benzyloxy)ethyl)(2-fluoroethyl)carbamate, **INT 1**



To a solution of 2-fluoroethanamine hydrochloride (4.35 g, 43.71 mmol) and 2-(benzyloxy)-acetaldehyde (6.04 g, 5.65 mL, 40.22 mmol) in MeOH (70 mL) was added sodium triacetoxyborohydride (10.44 g, 49.26 mmol). The reaction mixture was stirred at RT for 4 hr. The mixture was concentrated. The residue was taken up in EtOAc and washed with saturated aqueous sodium hydrogen carbonate solution, water and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated. The residue was taken up in aqueous NaOH solution (2 M, 175 mL, 350 mmol) and di-*tert*-butyl dicarbonate (17.65 g, 80.87 mmol) was added. The reaction mixture was stirred at RT overnight. The mixture was diluted with water and EtOAc. The layers were separated. The aqueous layer was back-extracted with EtOAc. The combined organic

layers were washed with water and brine, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (silica, cyclohexane/EtOAc gradient, 0-10%) to afford **INT 1** as a pale colorless oil. ^{1}H NMR (DMSO-d_6): δ (ppm) 7.41-7.24 (m, 5H), 4.59-4.39 (m, 4H), 3.59-3.45 (m, 4H), 3.44-3.36 (m, 2H), 1.46-1.31 (m, 9H). MS: m/z = 298.3 $[M+H]^+$

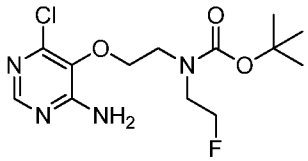
(2) *N*-Boc-*N*-(2-fluoroethyl)-2-hydroxyethylamine, **INT 2**



To a solution of **INT 1** (3.40 g, 11.43 mmol) in THF (115 mL) was added Pd-C 10% (340 mg). The reaction mixture was hydrogenated at RT and normal pressure for 7 hr. Pd-C 10% (340 mg) was added, and the reaction mixture was hydrogenated at RT and normal pressure overnight. More Pd-C 10% (340 mg) was added, and the reaction mixture was hydrogenated at RT and normal pressure for an additional 4 hr. The mixture was diluted with DCM, filtered over a pad of Celite and concentrated to afford crude **INT 2** as a colorless oil.

^{1}H NMR (DMSO-d_6): δ (ppm) 4.70-4.63 (m, 1H), 4.54 (t, 1H), 4.42 (t, 1H), 3.53 (t, 1H), 3.46 (t, 3H), 3.28-3.21 (m, 2H), 1.39 (s, 9H). MS: m/z = 208.2 $[M+H]^+$

(3) *tert*-Butyl (2-((4-amino-6-chloropyrimidin-5-yl)oxy)ethyl)(2-fluoroethyl)carbamate, **building block 1**



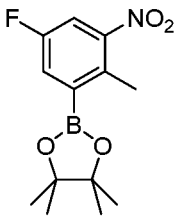
To a solution of 4-amino-6-chloropyrimidin-5-ol (content 90%, 2.00 g, 12.37 mmol) in THF (120 mL) was added *N*-Boc-*N*-2-fluoroethyl-2-hydroxyethylamine (6.5 g), followed by SMOPEX-301 (1 mmol/g, 30.90 g, 30.90 mmol). Then, a solution of DIAD (6.01 mL, 30.52 mmol) in THF (20 mL) was added slowly. The reaction mixture was stirred at 60°C for 3 hr. The mixture was filtered through a pad of Celite. The filtrate was concentrated to afford an oil which was triturated with EtOAc and a white precipitate was formed. The solid was filtered off to afford **building block 1**. The mother liquor was concentrated and

the residue was purified by flash chromatography (silica; DCM/EtOAc gradient, 0-100%) to afford more **building block 1** as a beige solid. The product was used in the next step without further purification.

LC/MS: t_R = 0.90 min, m/z = 335.1 $[M+H]^+$

Synthesis of building block 2

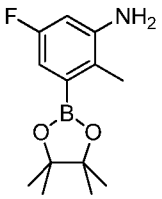
(1) 2-(5-Fluoro-2-methyl-3-nitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, **INT 3**



To a mixture of 1-bromo-5-fluoro-2-methyl-3-nitro-benzene (5.0 g, 21.37 mmol) and bis(diphenylphosphino)ferrocenedichloropalladium(II) (0.78 g, 1.06 mmol) in dioxane (200 mL) was added BISPIN (8.14 g, 32.05 mmol) followed by potassium acetate (7.34 g, 74.79 mmol). The reaction mixture was stirred at 100 °C for 6 hr. After cooling the brownish mixture was diluted with water (200 mL) and extracted with EtOAc. The organic layer was washed with saturated aqueous sodium hydrogen carbonate solution and brine (2x), dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (silica; cyclohexane/EtOAc 9:1) to afford **INT 3** as a yellow oil.

^{1}H NMR (DMSO-d_6): δ (ppm) 7.79 (d, 1H), 7.55 (d, 1H), 2.48 (s, 3H), 1.31 (s, 12H).

(2) 5-Fluoro-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline, **INT 4**

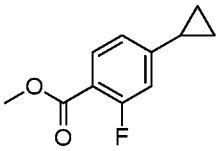


To a solution of **INT 3** (12.4 g, 44.1 mmol) in EtOAc (300 mL) was added Pd/C 10% (4.0 g). The reaction mixture was hydrogenated at room temperature and normal pressure for 18 hr. The mixture was filtered over Kieselgur (Supelco) and the filtrate was

concentrated. The residue was purified by flash chromatography (silica, EtOAc) to afford **INT 4** as a beige solid.

^{1}H NMR (DMSO-d_6): δ (ppm) 6.52-6.46 (m, 2H), 5.13 (br s, 2H), 2.17 (s, 3H), 1.29 (s, 12H). LC/MS: m/z = 252.2 $[M+H]^+$

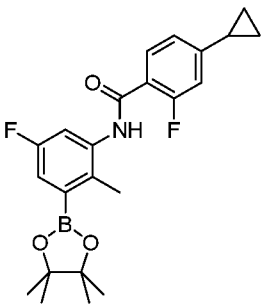
(3) Methyl 4-cyclopropyl-2-fluorobenzoate, **INT 5**



A mixture of methyl 4-bromo-2-fluorobenzoate (20.00 g, 85.82 mmol), cyclopropylboronic acid (9.68 g, 112.69 mmol) and potassium phosphate (35.70 g, 168.00 mmol) in toluene (250 mL) was degassed with argon for 5 min. Then, tricyclohexylphosphine (2.36 g, 8.41 mmol) and water (1.82 mL, 101.00 mmol) were added and the mixture was again degassed with argon for 5 min. Palladium(II) acetate (0.94 g, 4.21 mmol) was added and the reaction mixture was stirred at 100 °C overnight. The mixture was partitioned between EtOAc and water. The suspension was filtered through a pad of Celite. The phases of the filtrate were separated, the aqueous layer was back-extracted with EtOAc. The organic layers were combined, washed with saturated aqueous sodium hydrogen carbonate solution and brine, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (cyclohexane/EtOAc gradient, 0-15%) to afford **INT 5** as an orange oil (13.7 g).

^{1}H NMR ($CDCl_3$): δ (ppm) 7.83 (t, 1H), 6.90 (d, 1H), 6.79 (d, 1H), 3.92 (s, 3H), 2.00-1.96 (m, 1H), 1.15-1.03 (m, 2H), 0.84-0.73 (m, 2H). LC/MS: t_R = 1.11 min, m/z = 195.0 $[M+H]^+$

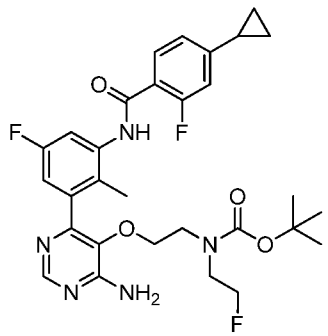
(4) 4-Cyclopropyl-2-fluoro-*N*-(5-fluoro-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)benzamide, **building block 2**



To a solution of **INT 4** (5.88 g, 23.41 mmol) and **INT 5** (5.00 g, 25.70 mmol) in THF (200 mL) at 0°C was added dropwise NaHMDS solution (1 M in THF, 35.1 mL, 35.10 mmol). The reaction mixture was stirred at RT for 2 hr, then additional NaHMDS solution (1 M in THF, 5.0 mL, 5.00 mmol) was added. After stirring for another hour more NaHMDS solution (1 M in THF, 5.0 mL, 5.00 mmol) was added and the mixture was stirred for an additional 2 hr. The mixture was diluted with EtOAc and washed with saturated aqueous sodium hydrogen carbonate solution and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated. The crude was suspended in EtOAc and filtered. The collected solid was washed with EtOAc and dried in vacuum to afford **building block 2** as a beige solid (9.51 g).

^{1}H NMR (DMSO-d_6): δ (ppm) 9.70 (br s, 1H), 7.62 (t, 1H), 7.51 (d, 1H), 7.19 (dd, 1H), 7.10-7.00 (m, 2H), 2.37 (s, 3H), 2.06-1.96 (m, 1H), 1.31 (s, 12H), 1.08-0.99 (m, 2H), 0.82-0.73 (m, 2H). LC/MS: t_R = 1.45 min, m/z = 414.2 $[M+H]^+$

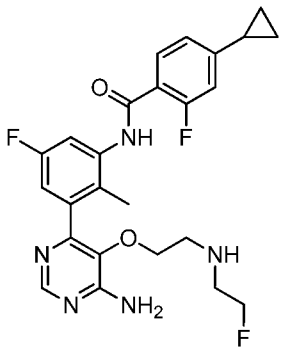
(5) *tert*-Butyl (2-((4-amino-6-(3-(4-cyclopropyl-2-fluorobenzamido)-5-fluoro-2-methylphenyl)pyrimidin-5-yl)oxy)ethyl)(fluoroethyl)carbamate, **INT 6**



To a solution of **building block 1** (1.25 g, 2.24 mmol, content 60%) in DME (10 mL) and water (10 mL) was added **building block 2** (1.02 g, 2.46 mmol) followed by aqueous sodium carbonate solution (2 M, 3.36 mL, 6.72 mmol). The mixture was degassed with argon for 10 min and bis(triphenylphosphine)palladium(II) dichloride (0.08 g, 0.011 mmol) was added. The reaction mixture was stirred at 110 °C for 20 min. The mixture was partitioned between saturated aqueous sodium hydrogen carbonate solution and EtOAc. The organic layer was washed with water and brine, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (silica; DCM/EtOAc gradient, 0-100%) to afford **INT 6** as a beige solid (550 mg).

LC/MS: t_R = 1.12 min, m/z = 586.4 $[M+H]^+$

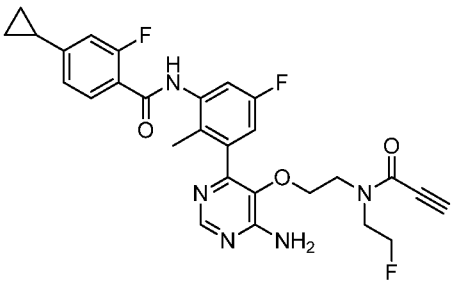
(6) *N*-(3-(6-Amino-5-(2-(fluoroethyl-amino)ethoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide, **INT 7**



To a solution of **INT 6** (550 mg, 0.94 mmol) in DCM (10 mL) was added 2M HCl in Et_2O (4.7 mL, 9.4 mmol). The reaction mixture was stirred at RT for 8 hr. The mixture was concentrated under reduced pressure. The residue was dried in vacuum to afford **INT 7** as a yellow solid (550 mg).
LC/MS: t_R = 0.76 min, m/z = 486.3 $[M+H]^+$

Synthesis of Precursor 1

N-(3-(6-Amino-5-(2-(*N*-fluoroethyl-propiolamido)ethoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide,

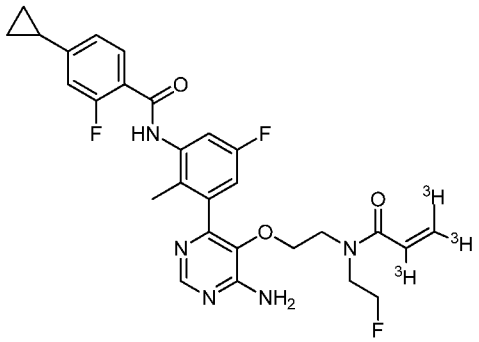


To a solution of propiolic acid (31.5 mg, 0.45 mmol) in DMF (3 mL) was added DIPEA (0.19 mL, 1.12 mmol) followed by T_3P (50% in DMF, 0.240 mL, 0.41 mmol). The mixture was stirred at RT for 15 minutes to form the active ester solution, which was added dropwise to a mixture of **INT 7** (220 mg, 0.37 mmol) with DIPEA (0.2 mL, 1.12 mmol) in

DMF (3 mL). The reaction mixture was stirred at RT for 1 hour. The mixture was diluted with EtOAc and washed with sat. aq. $NaHCO_3$, H_2O and brine. The organic layer was dried over anh. $MgSO_4$, filtered and concentrated. The crude was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH from 100:0 to 90:10) to give the **precursor 1** as a brown oil (19% yield, 82% pure), which was used as such in the next step. LC/MS: t_R = 0.97 min, m/z = 538 $[M+H]^+$

Example 1

[$^3H_3$]-N-(3-(6-amino-5-(2-(N-(2-fluoroethyl)acrylamido)ethoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide



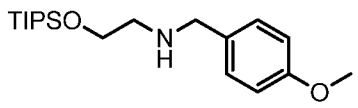
4.19 mg, (7.77 µmol) of **precursor 1** and 4.46 mg of Lindlar catalyst were suspended in DMF (0.8 mL) and quinolin-2(1H)-one (8 µL). This suspension was degassed three times and then charged with tritium gas (8.9 Ci T_2-gas) and then stirred under a sub-atmospheric pressure for 100 min at room temperature. The solvent was removed *in vacuo* and chemically labile tritium was completely re-exchanged by repeated lyophilisation from methanol. The product so obtained was dissolved again in methanol and filtered to yield a solution comprising 273 mCi (10.1 GBq) of crude title product at a radiochemical purity of 27%.

Subsequent purification was performed by preparative HPLC chromatography (column: Macherey + Nagel Nucleodur Gravity C18, 5 mm, 10 x 250 mm; solvents A: water with 0.1% TFA; B: acetonitrile with 0.1% TFA; gradient: 0 min - 11 min: 37.5% B; 11.5 min - 16 min: 95% B; 16.5 min: 37.5% B; UV detection at 254 nm and 230 nm; flow: 4.7 ml/min; temperature: 20°C). The combined fractions of interest were extracted under basic conditions, evaporated and dissolved in oxygen-free ethanol, yielding 36 mCi (1.33 GBq) of the title product, which was obtained at a radiochemical purity of > 98%. Identity

and purity was determined by comparison with unlabeled material (HPLC with RA- and UV-detection, MS-spectroscopy). From the isotopic abundance the specific activity was determined to be 52.2 Ci/mmol (1.93 TBq/mmol) by ESI^+-MS-spectroscopy. The positions of labeling were confirmed by ^3H-NMR spectroscopy (533.42 MHz, d_6-DMSO) δ (ppm) = 5.6 – 5.65, m, CO-CH=CHH; 6.05-6.15, m, CO-CH=CHH; 6.6 - 6.7, m, CO-CH=CHH).

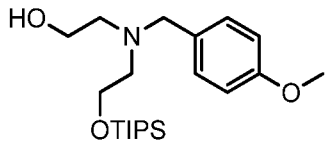
Synthesis of N-(3-(6-Amino-5-(2-((2-chloroethyl)(4-methoxybenzyl)amino)ethoxy) pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide (Precursor 2) and its conversion to N-(3-(6-amino-5-(2-(N-(2-fluoroethyl)acrylamido)ethoxy) pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide (Example 2)

N-(4-Methoxybenzyl)-2-((triisopropylsilyl)oxy)ethanamine, INT 8



Imidazole (3.38 g, 49.7 mmol) and DMAP (0.40 g, 3.31 mmol) were added to a solution of 2-((4-methoxybenzyl)amino)ethanol (6.0 g, 33.1 mmol) in CH_2Cl_2 (50 mL) and CH_3Cl_3 (50 mL) at RT under argon. Then TIPSCl (7.72 mL, 36.4 mmol) was added slowly at 0°C. The reaction mixture was stirred at 0°C for 30 min, allowed to warm to RT and stirred overnight. The resulting mixture was quenched with water and extracted with CH_2Cl_2. The aqueous phase was separated using an isolute® phase separator and the organic phase was concentrated in vacuo to give the crude product, which was then purified by flash chromatography on silica gel (CH_2Cl_2/MeOH/NH_4OH 90:10:1) to afford the title compound as a colorless oil (9 g, 81%).
^1H NMR (400 MHz, $CDCl_3$): δ = 7.27 - 7.19 (m, 2H), 6.90 - 6.81 (m, 2H), 3.85 - 3.73 (m, 4H), 3.79 (s, 3H), 2.74 (t, 2H), 1.16 - 0.98 (m, 21H); LC/MS: t_R = 1.03 min, m/z = 338.5 $[M+H]^+$

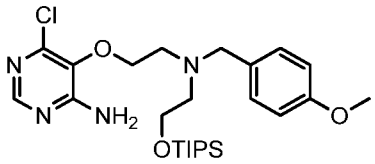
2-((4-Methoxybenzyl)(2-((triisopropylsilyl)oxy)ethyl)amino)ethanol, INT 9



2-bromoethanol (0.39 mL, 5.33 mmol) was added to a stirred solution of **INT 8** (1.5 g, 4.44 mmol) and K_2CO_3 (1.84 g, 13.33 mmol) in dry CH_3CN (30 mL) at RT under argon, and the reaction mixture was stirred at reflux for 1h. After cooling to RT, the precipitate was filtered off and the filtrate concentrated in vacuo to yield the crude product. After addition of water and CH_2Cl_2, the resulting mixture was extracted and the aqueous phase was separated through an isolute® phase separator and the organic phase was concentrated in vacuo. The residue was purified by silica gel chromatography (hexane/EtOAc, from 100:0 to 60:40) to yield the title compound as a colorless oil (950 mg, 55%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, J = 8 Hz, 2H), 6.84 (d, J = 8 Hz, 2H), 3.79 (s, 3H), 3.72 (t, J = 5.8 Hz, 2H), 3.65 (s, 2H), 3.53 (t, J = 5.3 Hz, 2H), 2.69 (dt, J = 8.4, 5.6 Hz, 4H), 1.15 - 0.99 (m, 21H); LC/MS: t_R = 1.02 min, m/z = 382.0 $[M+H]^+$

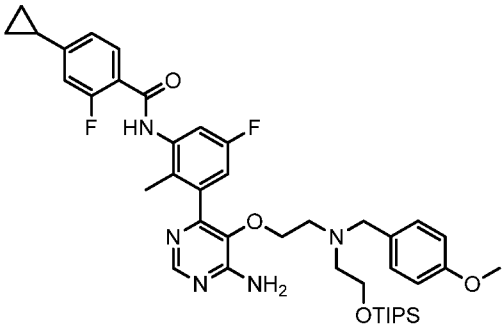
6-Chloro-5-(2-((4-methoxybenzyl)(2-((triisopropylsilyl)oxy)ethyl)amino)ethoxy)pyrimidin-4-amine, INT 10



A mixture of PPh_3 (2027 mg, 7.73 mmol) and DIAD (1.58 mL, 7.73 mmol) was added to a solution of **INT 9** (2360 mg, 6.18 mmol) and 4-amino-6-chloropyrimidin-5-ol (750 mg, 5.15 mmol) in THF (40 mL) at RT under argon. The reaction mixture was stirred at RT for 1h. The organic solvent was removed in vacuo. The crude product was purified by silica gel chromatography (hexane/EtOAc, from 100:0 to 80:20) to afford the title compound as a yellow oil (2.1 g, 73%).

LC/MS: t_R = 1.45 min, m/z = 510.4 $[M+H]^+$

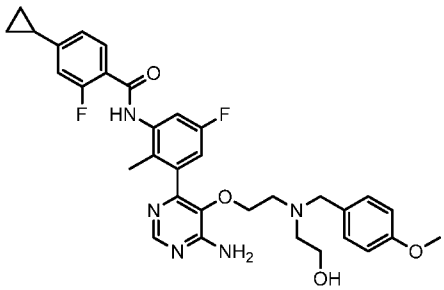
N-(3-(6-Amino-5-(2-((4-methoxybenzyl)(2-((triisopropylsilyl)oxy)ethyl)amino) ethoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide, INT 11



A mixture of 2 M aq. Na_2CO_3 (0.59 mL, 1.18 mmol) and $PdCl_2(PPh_3)_2$ (13.79 mg, 0.020 mmol) was added to a solution of **INT 10** (200 mg, 0.39 mmol) and 4-cyclopropyl-2-fluoro-N-(5-fluoro-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)benzamide (162 mg, 0.39 mmol) in DME (2.5 mL) and water (0.5 mL) at RT. The reaction mixture was irradiated in a microwave reactor at 120°C for 20 min. The resulting mixture was filtered through Celite and the filtrate was extracted with EtOAc and washed with 2M aq. Na_2CO_3. The combined organic layers were dried using an isolute® phase separator and concentrated in vacuo. The residue was purified by silica gel flash chromatography (hexane/EtOAc, from 100:0 to 0:100) to give the title compound as a colorless oil (220 mg, 67%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.55 (d, J = 17.7 Hz, 1H), 8.34 (s, 1H), 8.19 (dd, J = 10.8, 2.7 Hz, 1H), 8.09 (t, J = 8.4 Hz, 1H), 7.72 - 7.63 (m, 1H), 7.59 - 7.41 (m, 2H), 7.21 - 7.13 (d, J = 8 Hz, 2H), 7.02 (dd, J = 8.2, 1.6 Hz, 1H), 6.88 (dd, J = 8.5, 2.8 Hz, 2H), 6.85 - 6.77 (m, 2H), 3.80 – 3.76 (m, 5H), 3.63 (s, 2H), 3.49 (t, J = 4.7 Hz, 2H), 2.70 - 2.64 (m, 4H), 2.10 (s, 3H), 1.97 – 1.93 (m, 1H), 1.15 – 0.95 (m, 23H), 0.86 – 0.69 (m, 2H). LC/MS: t_R = 1.59 min, m/z = 761.4 $[M+H]^+$

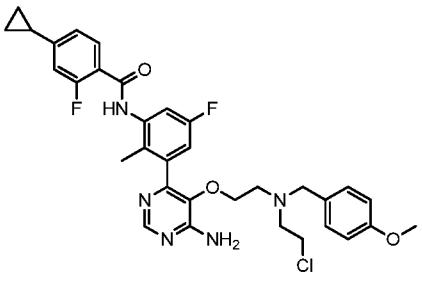
N-(3-(6-Amino-5-(2-((2-hydroxyethyl)(4-methoxybenzyl)amino)ethoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide, INT 12



A solution of 1M TBAF in THF (0.61 mL, 0.61 mmol) was added to a solution of **INT 11** (330 mg, 0.40 mmol) in THF (15 mL). The reaction mixture was stirred at RT and under argon for 20 min. The organic solvent was removed in vacuo at RT. The crude product was purified by silica gel flash chromatography (CH_2Cl_2/MeOH/NH_4OH 90:10:1) to give a white solid (190 mg, 72%).

^1H NMR (600 MHz, DMSO) δ = 9.78 (s, 1H), 8.17 (s, 1H), 7.63 (t, J = 7.9 Hz, 1H), 7.54 (d, J = 9.5 Hz, 1H), 7.18 (s, 2H), 7.10 (d, J = 8.4 Hz, 2H), 7.08 – 7.02 (m, 2H), 6.97 (dd, J = 8.7, 2.4 Hz, 1H), 6.80 (d, J = 8.4 Hz, 2H), 4.35 (t, J = 5.2 Hz, 1H), 3.69 (s, 3H), 3.47 (t, J = 5.1 Hz, 2H), 3.42 (s, 2H), 3.39 (q, J = 6.1 Hz, 2H), 2.53 (t, J = 5.4 Hz, 2H), 2.39 (t, J = 6.4 Hz, 2H), 2.05 – 2.0 (m, 1H), 2.0 (s, 3H), 1.05-1.02 (m, 2H), 0.79-0.76 (m, 2H); LC/MS: t_R = 0.85 min, m/z = 603.6 $[M+H]^+$

N-(3-(6-Amino-5-(2-((2-chloroethyl)(4-methoxybenzyl)amino)ethoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide, precursor 2

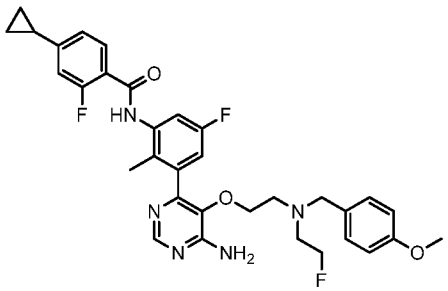


Thionyl chloride (7.25 µl, 0.099 mmol) was added slowly to a solution of **INT 12** (40 mg, 0.066 mmol) in CH_3Cl_3 (5 mL) at RT and under argon. The reaction mixture was stirred at RT for 16 h. The resulting mixture was washed with saturated aq $NaHCO_3$ and extracted with CH_2Cl_2. The aqueous phase was separated through an isolute® phase separator and the organic phase was concentrated in vacuo at RT. The crude product

was purified by silica gel flash chromatography (hexane/EtOAc, from 100:0 to 0:100) to afford the title compound as a white solid (35 mg, 85%)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.55 (d, J = 17.6 Hz, 1H), 8.36 (s, 1H), 8.18 (dd, J = 10.6, 2.8 Hz, 1H), 8.08 (t, J = 8.4 Hz, 1H), 7.18 – 7.11 (m, 2H), 7.02 (dd, J = 8.2, 1.7 Hz, 1H), 6.90 (dd, J = 8.4, 2.8 Hz, 1H), 6.85 - 6.80 (m, 2H), 3.78 (s, 3H), 3.59 (s, 2H), 3.56 - 3.43 (m, 4H), 2.83 (t, J = 6.6 Hz, 2H), 2.65 (t, J = 4.9 Hz, 2H), 2.12 (s, 3H), 1.97 – 1.93 (m, 1H), 1.16 - 1.05 (m, 2H), 0.81 – 0.76 (m, 2H); t_R = 1.24 min, m/z = 622.3 $[M]^+$.

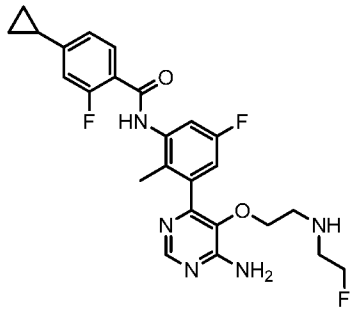
N-(3-(6-Amino-5-(2-((2-fluoroethyl)(4-methoxybenzyl)amino)ethoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide, INT 13



A solution of 1M TBAF in THF (0.11 mL, 0.11 mmol) was added slowly to a solution of **precursor 2** (55 mg, 0.088 mmol) in DMF (1 mL) at RT under argon. The reaction mixture was stirred at 100°C for 20 min. After cooling to RT, a second addition of TBAF (0.05 mL) was performed and the reaction mixture was stirred at 100°C for 10 min under argon. The resulting mixture was concentrated in vacuo at 40°C and the residue purified by preparative HPLC (t_R = 11.3 min) to provide the title compound as a yellow oil (45 mg, 84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.55 (d, J = 17.6 Hz, 1H), 8.35 (s, 1H), 8.18 (dd, J = 10.8, 2.8 Hz, 1H), 8.08 (t, J = 8.4 Hz, 1H), 7.19 – 7.12 (m, 2H), 7.02 (dd, J = 8.3, 1.7 Hz, 1H), 6.90 (dd, J = 8.5, 2.8 Hz, 1H), 6.87 – 6.80 (m, 3H), 4.51 (dt, J = 47.5, 4.8 Hz, 2H), 3.78 (s, 3H), 3.62 (s, 2H), 3.48 (t, J = 4.8 Hz, 2H), 2.80 (dt, J = 28.1, 4.8 Hz, 2H), 2.67 (t, J = 4.8 Hz, 2H), 2.11 (s, 3H), 1.95 (td, J = 8.5, 4.3 Hz, 1H), 1.15 – 1.03 (m, 2H), 0.79 (dt, J = 6.8, 4.8 Hz, 2H). t_R = 1.10 min, m/z = 606.4 $[M]^+$

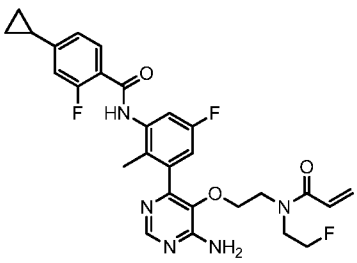
N-(3-(6-Amino-5-(2-((2-fluoroethyl)amino)ethoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide, INT 14



A mixture of $Pd(OH)_2/C$, 20 wt.% (27.8 mg, 0.04 mmol) and ammonium formate (7.5 mg, 0.16 mmol) was added to a solution of **INT 13** (24 mg, 0.04 mmol) in MeOH (4 mL) at RT under argon. The reaction mixture was stirred at reflux for 10 min. The resulting mixture was filtered through Celite and the filtrate was concentrated in vacuo to give the crude product, which was purified by preparative HPLC (t_R = 9.0 min) to yield the title compound as a colorless oil (3.5 mg, 18%).

^{1}H NMR (400 MHz, DMSO) δ = 10.03 (br.s, 1H), 8.97 (br.s, 2H), 8.64 (s, 1H), 7.76 - 7.62 (m, 2H), 7.28 (dd, J = 8.4, 2.8 Hz, 1H), 7.16 - 7.04 (m, 2H), 5.76 (s, 1H), 4.68 (dt, J = 47.2, 4.4 Hz, 2H), 3.83 - 3.67 (m, 2H), 3.3 - 3.14 (m, 4H), 2.12 (s, 3H), 2.04 (dt, J = 8.4, 3.7 Hz, 1H), 1.09 – 1.0 (m, 2H), 0.83 – 0.73 (m, 2H); t_R = 0.73 min, m/z = 485.3 $[M]^+$

N-(3-(6-Amino-5-(2-(N-(2-fluoroethyl)acrylamido)ethoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide, Example 2



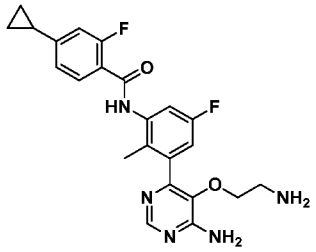
A solution of DIPEA (0.132 mL, 0.037 mmol) and T_3P 50% in DMF (0.065 mL, 0.013 mmol) was added to a solution of acrylic acid (0.9 mg, 0.016 mmol) in DMF (0.1 mL). The mixture was stirred at RT for 30 min to form the active ester, which was slowly added to a solution of **INT 14** (6 mg, 0.012 mmol) and DIPEA (0.065 mL, 0.037 mmol) in DMF (0.1 mL). The reaction mixture was stirred at RT for 3 h, then diluted with EtOAc. The organic layer was washed with saturated aq. $NaHCO_3$, water and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel flash

chromatography (CH_2Cl_2 (A), MeOH + NH_3 2% (B), with a gradient from 0 to 10% B) to provide the title compound as a white solid (3 mg, 45%).

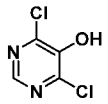
^{1}H NMR (400 MHz, DMSO) δ = 9.79 and 9.63 (br.s, 1H), 8.19 (d, J = 10.8 Hz, 1H), 7.77 – 7.47 (m, 2H), 7.23 - 6.91 (m, 5H), 6.58 (dt, J = 16.4, 11.4 Hz, 1H), 6.16 – 5.99 (m, 1H), 5.60 (dt, J = 10.6, 2.7 Hz, 1H), 4.39 (dt, J = 47.4, 5.1 Hz, 2H), 3.69 - 3.43 (m, 3H), 3.37 – 3.23 (m, 3H), 2.10 – 1.88 (m, 4H), 1.15 – 0.98 (m, 2H), 0.84 – 0.76 (m, 2H); t_R = 0.96 min, m/z = 540.3 $[M+H]^+$

Synthesis of Precursor **3**

N-(3-(6-amino-5-(2-aminoethoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide



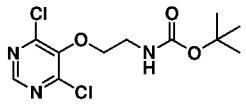
(5) 4,6-Dichloropyrimidin-5-ol, **INT 15**



To a solution of 4,6-dichloro-5-methoxypyrimidine (20.00 g, 112 mmol) in DCE (250 mL) at 0 °C was added aluminum trichloride (22.35 g, 168 mmol) in two portions. The reaction mixture was stirred at 0 °C for 10 min, then at 50 °C for 4 hr. The mixture was cooled to 0 °C and aqueous HCl (1 M, 120 mL) followed by MeOH (50 mL) were added slowly while stirring vigorously. The mixture was poured into water and extracted with Et2O (3x). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue was dried in vacuum to afford **INT 15** as a beige solid.

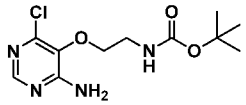
UPLC-MS: MS (ESI): $[M-H]^-$ 163.0, rt = 0.44 min. ^{1}H NMR (DMSO-d_6): δ (ppm) 11.69 (s, br, 1H), 8.38 (s, 1H).

(6) tert-Butyl (2-((4,6-dichloropyrimidin-5-yl)oxy)ethyl)carbamate, **INT 16**



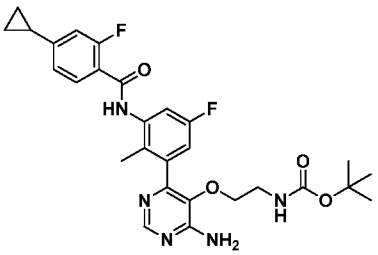
To a solution of **INT 15** (5.80 g, 35.2 mmol) and tert-butyl (2-hydroxyethyl)carbamate (95 %, 8.95 g, 52.7 mmol) in THF (200 mL) was added triphenylphosphine (13.83 g, 52.7 mmol) followed by DIAD (10.25 mL, 52.7 mmol). The reaction mixture was stirred at 60 °C for 1 hr. The mixture was concentrated and the residue was dried in vacuum. The residue was purified by flash chromatography (silica; cyclohexane/EtOAc gradient, 0-50 %) to afford **INT 16** as as white solid.
UPLC-MS: MS (ESI): $[M+H]^+$ 308.0, rt = 1.02 min. ^{1}H NMR (DMSO-d_6): δ (ppm) 8.68 (s, 1H), 7.06 – 6.98 (m, 1H), 4.13 (t, 2H), 3.37 – 3.27 (m, 2H, overlapping with HDO), 1.38 (s, 9H).

(7) tert-Butyl (2-((4-amino-6-chloropyrimidin-5-yl)oxy)ethyl)carbamate, **INT 17**



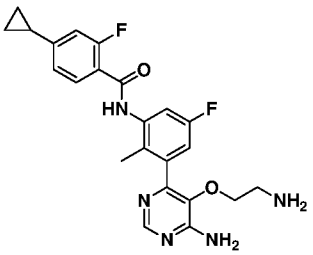
To a solution of **INT 16** (9.00 g, 29.2 mmol) in 2-propanol (80 mL) in an autoclave was added aqueous ammonium hydroxide solution (26 %, 44.2 mL, 292 mmol). The autoclave was sealed and the reaction mixture was stirred at 80 °C for 4 hr. The mixture was concentrated. The residue was partitioned between water and DCM. The organic layer was separated, washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue was dried in vacuum to afford **INT 17** as a white solid.
UPLC-MS: MS (ESI): $[M+H]^+$ 289.1, rt = 0.77 min. ^{1}H NMR (DMSO-d_6): δ (ppm) 7.96 (s, 1H), 7.24 (s, br, 2H), 7.14 – 7.08 (m, 1H), 3.89 (t, 2H), 3.31 – 3.26 (m, 2H, overlapping with HDO), 1.39 (s, 9H).

(8) tert-Butyl (2-((4-amino-6-(3-(4-cyclopropyl-2-fluorobenzamido)-5-fluoro-2-methylphenyl)pyrimidin-5-yl)oxy)ethyl)carbamate, **INT 18**



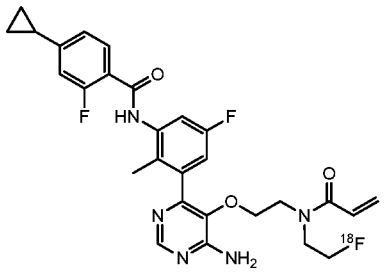
To a solution of **INT 17** (95 %, 1.00 g, 3.29 mmol) and **Building Block 2** (1.50 g, 3.62 mmol) in DME (10 mL) and water (1.43 mL) was added aqueous sodium carbonate solution (2 M, 4.94 mL, 9.87 mmol). The reaction mixture was degassed with argon for 10 min. Then bis(triphenylphosphine)palladium(II) dichloride (0.115 g, 0.165 mmol) was added. The reaction mixture was stirred in a microwave reactor at 120 °C for 60 min. The above reaction was repeated four times. The four batches were combined and the mixture was diluted with saturated aqueous sodium hydrogencarbonate solution and EtOAc. The layers were separated, the aqueous layer was back-extracted with EtOAc. The combined organic layers were washed with water and brine, dried over magnesium sulfate, filtered and concentrated. The residue was triturated with DCM. The solid was filtered off to afford a first batch of **INT 18** as a white solid. The filtrate was concentrated and the residue was triturated with DCM. The beige solid was filtered off and triturated with DCM and EtOAc. The white solid was filtered off to afford a second batch of **INT 18**. The two batches were combined to afford **INT 18** as a white solid.
UPLC-MS: MS (ESI): $[M+H]^+$ 540.2, rt = 1.09 min. ^{1}H NMR (DMSO-d_6): δ (ppm) δ 9.80 (s, br, 1H), 8.17 (s, 1H), 7.69 – 7.62 (m, 1H), 7.59 – 7.51 (m, 1H), 7.10 – 6.93 (m, 5H), 6.86 – 6.77 (m, 1H), 3.40 – 3.35 (m, 2H), 3.02 – 2.95 (m, 2H), 2.07 – 1.98 (m, 4H), 1.33 (s, 9H), 1.09 – 1.01 (m, 2H), 0.82 – 0.75 (m, 2H).

(9) N-(3-(6-Amino-5-(2-aminoethoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide, **Precursor 3**



To a solution of **INT 18** (95 %, 4.20 g, 7.39 mmol) in DCM (50 mL) was added TFA (5.70 mL, 73.9 mmol). The reaction mixture was stirred at RT for 15 hr. The mixture was poured into saturated aqueous sodium hydrogencarbonate solution (200 mL). The mixture was stirred at RT for 20 min. The layers were separated, the organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated. The residue was dried in vacuum to afford **Precursor 3** as a white solid.
UPLC-MS: MS (ESI): $[M+H]^+$ 440.2, rt = 0.69 min. ^{1}H NMR (DMSO-d_6): δ (ppm) 9.82 (s, 1H), 8.17 (s, 1H), 7.69 – 7.61 (m, 1H), 7.55 – 7.47 (m, 1H), 7.37 (s, br, 2H), 7.11 – 6.97 (m, 3H), 3.42 (t, 2H), 2.61 (t, 2H), 2.07 – 1.98 (m, 4H), 1.09 – 1.01 (m, 2H), 0.82 – 0.76 (m, 2H), 2 exchangeable protons not observed.

Synthesis of Example 3
N-(3-(6-amino-5-(2-(N-(2-[^{18}F]fluoroethyl)acrylamido)ethoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide

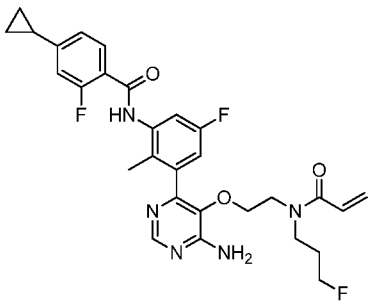


A solution of [^{18}F]fluoroethyl tosylate in CH_3CN was prepared using TRACERlab FX N synthesizer (from GE Healthcare). A solution of **precursor 3** (5 mg, 11.3 μmol) in CH_3CN/*t*-AmylOH and Cs_2CO_3 (3.7 mg, 11.3 μmol) were added and the mixture was stirred at 125 °C for 25 min. The mixture was allowed to cool to RT and the intermediate was purified by semi-preparative HPLC. The purified intermediate was added to a solution of acrylic acid (7 µl, 0.10 mmol), DIPEA (25 µL, 0.14 mmol) and T_3P (50% in

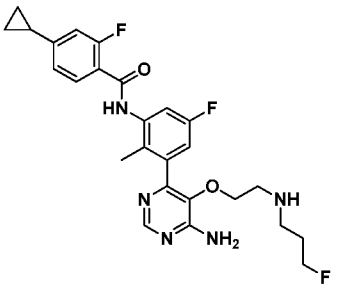
DMF) (50 μL, 0.09 mmol) in DMF (400 μL). The mixture was stirred at RT for 10 min. The reaction mixture was stirred at RT for 10 min and the product purified by semi-preparative HPLC (Luna C18, $CH_3CN/H_2O/Et_3N$ 40/60/0.1). The identity of the final product (rt = 22.17 min) was confirmed by co-injection with the cold material (rt = 21.82 min) onto an analytical HPLC (Waters XBridgeC18, $MeOH/H_2O/H_2PO_4$ (0.1%), 65/35/0.1, 1 mL/min).

Synthesis of **Example 4**

N-(3-(6-amino-5-(2-(N-(3-fluoropropyl)acrylamido)ethoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide



N-(3-(6-Amino-5-(2-((3-fluoropropyl)amino)ethoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide, **INT 19**



To a solution of **Precursor 3** (95 %, 651 mg, 1.408 mmol) and DIPEA (0.492 mL, 2.816 mmol) in DMF (5.5 mL) was added 3-fluoropropyltosylate (98 %, 334 mg, 1.408 mmol) followed by TBAI (520 mg, 1.408 mmol). The reaction mixture was stirred at 100 °C for 1 hr, then more 3-fluoropropyltosylate (98 %, 67 mg, 0.282 mmol) and TBAI (104 mg, 0.282 mmol) were added. The reaction mixture was stirred at 100 °C for an additional 10 min. The mixture was partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with saturated

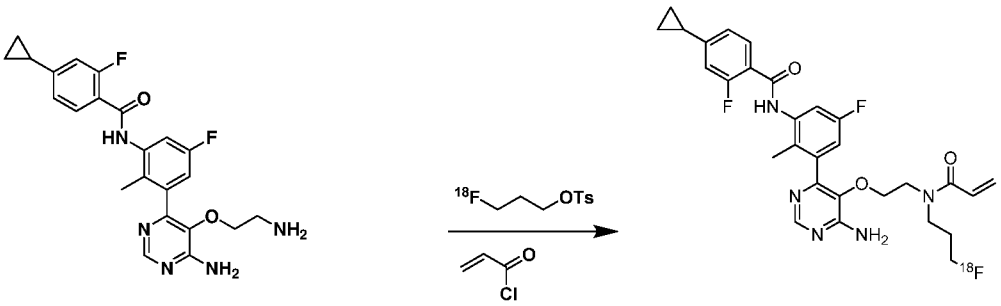
aqueous sodium hydrogen carbonate solution and brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (silica; EtOAc/MeOH gradient, 0-20 %). The isolated solid was re-purified by flash chromatography (silica; DCM/MeOH gradient, 0-10 %) to afford **INT 19** as a white solid.
UPLC-MS: MS (ESI): $[M+H]^+$ 500.3, rt = 0.76 min. ^{1}H NMR (DMSO-d_6): δ (ppm) rotamers δ 9.84 – 9.78 (m, 1H), 8.18 (s, 1H), 7.64 (t, 1H), 7.56 – 7.49 (m, 1H), 7.33 (s, br, 2H), 7.10 – 6.99 (m, 3H), 4.55 – 4.47 (m, 1H), 4.42 – 4.36 (m, 1H), 3.54 – 3.47 (m, 2H), 3.21 – 3.14 (m, 1H), 2.59 (s, br, 2H), 2.52 – 2.45 (m, 2 H, overlapping with DMSO), 2.06 – 1.99 (m, 4H), 1.79 – 1.64 (m, 2H), 1.10 – 0.99 (m, 2H), 0.84 – 0.73 (m, 2H).

(2) N-(3-(6-Amino-5-(2-(N-(3-fluoropropyl)acrylamido)ethoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide, **Example 4**

To a solution of **INT 19** (361.5 mg, 0.724 mmol) and DIPEA (0.260 mL, 1.489 mmol) in DCM (7 mL) at -78 °C was added a solution of acryloyl chloride (0.065 mL, 0.804 mmol) in DCM (0.5 mL) dropwise. The reaction mixture was stirred at -78 °C for 10 min. The mixture was quenched with saturated aqueous sodium hydrogencarbonate solution and extracted with DCM (2x). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (silica; EtOAc/MeOH gradient, 0-5 %). The isolated solid was re-purified by reverse phase flash chromatography (RP C18; water/acetonitrile gradient, 10-60 %) to afford **Example 4** as a white solid.
UPLC-MS: MS (ESI): $[M+H]^+$ 554.3, rt = 0.99 min. ^{1}H NMR (DMSO-d_6): rotamers δ (ppm) 9.80 – 9.57 (m, 1H), 8.25 – 8.11 (m, 1H), 7.74 – 7.62 (m, 1H), 7.61 – 7.49 (m, 1H), 7.15 – 7.01 (m, 4H), 6.99 – 6.93 (m, 1H), 6.62 – 6.48 (m, 1H), 6.11 – 6.03 (m, 1H), 5.64 – 5.53 (m, 1H), 4.46 – 4.36 (m, 1H), 4.34 – 4.23 (m, 1H), 3.63 – 3.56 (m, 1H), 3.56 – 3.46 (m, 2H), 3.46 – 3.40 (m, 1H), 3.29 – 3.21 (m, 1H), 3.09 – 3.03 (m, 1H), 2.09 – 2.01 (m, 1H), 2.01 – 1.97 (m, 3H), 1.79 – 1.60 (m, 2H), 1.09 – 1.01 (m, 2H), 0.83 – 0.77 (m, 2H).

Example 5

Synthesis of N-(3-(6-amino-5-(2-(N-(2-[^{18}F]fluoropropyl)acrylamido)ethoxy)pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-4-cyclopropyl-2-fluorobenzamide



Precursor 3 Example 5

A solution of [^{18}F]fluoropropyl tosylate in CH_3CN was prepared using TRACERlab FX N synthesizer (from GE Healthcare). A solution of **precursor 3** (5 mg, 11.3 mmol) in CH_3CN/*t*-AmylOH and Cs_2CO_3 (3.7 mg, 11.3 mmol) were added and the mixture was stirred at 125°C for 25 min. The mixture was allowed to cool to RT and the intermediate was purified by semi-preparative HPLC. The purified intermediate was diluted into ascorbic acid solution (10 mg/mL, 20 mL), loaded onto an Oasis HLB cartridge and eluted with DMF (0.6 mL). Acryloyl chloride (5 µl, 0.06 mmol) and DIPEA (10 mL, 0.06 mmol) were added consecutively. The reaction mixture was stirred at RT for 10 min and the product purified by semi-preparative HPLC (Luna C18, $CH_3CN/H_2O/Et_3N$ 40/60/0.1, 4 mL/min). The identity of the final product was confirmed by co-injection with the cold material (rt = 12.97 min) onto an analytical HPLC (Waters XBridgeC18, MeOH/H_2O/TFA, 60/40/0.1, 1 mL/min).

Biological Part

Inhibition of Btk enzymatic activity

The inhibitory activity of the present compounds against Btk was assessed in a biochemical enzyme assay. Assay plates in 384 well format were prepared with 8-point serial dilutions for the test compounds on a Thermo CatX workstation equipped with a Innovadyne Nanodrop Express. The assay plates were prepared by addition of 50 nl per well of compound solution in 90 % DMSO. The kinase reactions were started by stepwise addition of 4.5 µl per well of peptide/ATP-solution (4 µM FITC-Ahx-TSELKKVVALYDYMPMNAND-NH2, 164 µM ATP) in kinase buffer (50mM HEPES, pH 7.5, 1mM DTT, 0.02% Tween20, 0.02% BSA, 0.6% DMSO, 10 mM beta-

glycerophosphate, and 10 µM sodium orthovanadate, 18 mM MgCl2, 1 mM MnCl2) and 4.5 µl per well of enzyme solution (6.4nM full-lenght human recombinant BTK) in kinase buffer. Kinase reactions were incubated at 30°C for 60 minutes and subsequently terminated by addition of 16 µl per well of stop solution (100 mM HEPES pH 7.5, 5 % DMSO, 0.1 % Caliper coating reagent, 10 mM EDTA, and 0.015 % Brij35). Kinase reactions were analyzed on a Caliper LC3000 workstation by separating phosphorylated and unphosphorylated peptides and kinase activities were calculated from the amounts of newly formed phospho-peptide. Inhibition data were calculated by comparison to control reactions without enzyme (100 % inhibition) and without inhibitors (0 % inhibition). The concentration of inhibitor required for 50 % inhibition (IC50) was calculated from the inhibition in response to inhibitor concentrations.

Example	Inhibition of Btk enzymatic activity IC_{50} [uM]
Example 1	0.001
Example 4	0.011

Inhibition of Btk activity in blood

Alternatively, the inhibitory activity of the present compounds in blood was assessed in the following in vitro B cell activation assay. Whole blood was collected with written consent from healthy volunteers by venipuncture into sodium heparin vials. Then, 90 µl blood was mixed in 96 well U-bottomed microtiter plates (Thermo Scientific #163320) with 0.5 µl of serial dilutions of test compounds in DMSO. Cultures were incubated at 37°C, 5% CO2 for 1 hour. B cells were then stimulated by adding 10 µl of a dilution containing mouse anti-human IgM antibody (clone CW11) and recombinant human IL-4 (Immunotools) to final concentrations of 30 µg/ml and 5 ng/ml, respectively. The cultures were incubated for 20 hours and activation of B cells was measured by flow cytometry after staining for the B cell subset with APC-labeled anti-human CD19 (Beckton-Dickinson) and for the activation marker CD69 (PE-labeled anti-human CD69, Beckton-Dickinson). All staining procedures were performed at room temperature for 30 min in the dark in 96-deep well V-bottomed microtiter plates (Eppendorf) with FACS Lysing

Solution (Beckton-Dickinson). Cytometric data was acquired on a CyAn cytometer (Beckman Coulter) and the subpopulation of lymphocytes were gated according to size and granularity, then further analyzed for expression of CD19 and the activation marker. Data for the inhibition of B cell activation were calculated from the percentage of cells positively stained for activation markers within the CD19 positive population. Inhibition data were calculated by comparison to control cultures without anti-IgM/IL-4 (100 % inhibition) and without inhibitors (0 % inhibition). The concentration of inhibitor required for 50 % inhibition (IC50) was calculated from the inhibition in response to inhibitor concentrations.

Example	Inhibition of Btk activity in blood IC_{50} [uM]
1	0.029
4	0.025

Selectivity of the compounds of the invention:

Example 1 was also tested in the kinase assays listed below, where it was virtually inactive at a concentration of 10 micromol.

Abelson murine leukemia viral oncogene homolog 1
Activin A receptor, type I
Aurora A Kinase
Bruton's tyrosine kinase
Fibroblast growth factor receptor 2
Fibroblast growth factor receptor 4
Cluster of differentiation antigen 135
Glycogen synthase kinase 3 beta
Interleukin-1 receptor-associated kinase 1
Interleukin-1 receptor-associated kinase 4
Janus kinase 2
Kinase insert domain receptor

Tyrosine-protein kinase Lyn
Mitogen-activated protein kinase kinase kinase 7 - Mitogen-activated protein kinase kinase kinase 7 interacting protein 1
Mitogen-activated protein kinase kinase kinase 8
Mitogen-activated protein kinase kinase kinase kinase 4
Alpha-type platelet-derived growth factor receptor
Protein kinase C alpha
Protein kinase C theta
Rho-associated protein kinase 2
serine/threonine kinase 17b
Serine/threonine-protein kinase 4
Spleen tyrosine kinase
Zeta-chain-associated protein kinase 70

Quantitative Whole-Body Autoradiography QWBA:

A quantitative whole-body autoradiography (QWBA) study was conducted to compare signal intensity in wild-type and B cell knock-out mice, after a single intravenous administration of 12.5 µg/kg [^{3}H] of the compound of example 1. The aim was to measure differences in radioactive signal, comparing the tissues in the presence and absence of B cells.

As illustrated in the below Table, organs which normally do not contain significant amounts of B cells (e.g. heart) also did not show a difference in signal intensity between wild-type and B-cell knock-out mice. In contrast, the signal in B-cell rich lymph nodes was elevated in wild-type as compared to B-cell knock-out mice. This effect was especially marked in the cortex and paracortex of the lymph node, which contain the germinal centers and the highest B cell concentration.

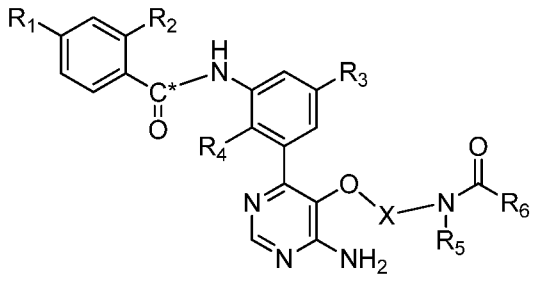
Table: Relative tissue concentration of radioactivity (organ/blood)

	wt mice			B-cell k.o. mice		
	2h	6h	24h	2h	6h	24h
Blood	1	1	1	1	1	1
Heart	0.48	0.44	0.38	0.55	0.59	0.39

Lymph nodes (submandibular)	1.6	2.8	2.8	1.1	1.3	1.1
Lymph nodes (cortex/paracortex)	1.9	5.5	6.1	1.7	1.8	2.2
Lymph nodes (medulla)	1.8	3.1	4.4	1.1	2.1	3.5

CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof;



(I)

wherein,

C* means ^{12}C or ^{11}C;

X is a bivalent linker comprising at least one carbon atom and at least one hydrogen atom;

R_1 is C_1-C_6 alkyl or C_3-C_6cycloakyl;

R_2 is ^{19}F, ^{18}F, ^{124}I, ^{123}I or ^{131}I:

R_3 is hydrogen or ^{19}F, ^{18}F, ^{124}I, ^{123}I or ^{131}I;

R_4 is C_1-C_6 alkyl;

R_5 is C_1-C_6 alkyl optionally substituted by ^{19}F, or ^{18}F; and

R_6 is $-CH=CH_2$, $-C\equiv CH$, $-CH=CH-CH_3$, $-CH_2-CH=CH_2$, wherein one or more of the hydrogens are optionally replaced by ^{3}H.

2. A compound of formula (I) in accordance to the definition of claim 1 or a pharmaceutically acceptable salt thereof, wherein the variables in claim 1 are selected such that a compound of formula (I) comprises at least one radioactive atom selected from ^{3}H, ^{11}C, ^{18}F, ^{123}I, ^{124}I and ^{131}I.

3. A compound according to claim 1 - 2, or a pharmaceutically acceptable salt thereof, wherein the bivalent linker X is C_1-C_6 alkylene optionally substituted by C_1-C_6 alkyl.

4. A compound according to claim 1 - 2, or a pharmaceutically acceptable salt thereof, wherein the bivalent linker X is C_3-C_6 cycloalkylene optionally substituted by C_1-C_6 alkyl.

5. A compound according to any one of claims 1, 2, 3 or 4, or a pharmaceutically acceptable salt thereof wherein C* means ^{11}C or ^{12}C.

6. A compound according to any one of claims 1, 2, 3, 4 or 5, or a pharmaceutically acceptable salt thereof wherein R_1 is cyclopropyl.

7. A compound according to any one of claims 1, 2, 3, 4, 5 or 6, or a pharmaceutically acceptable salt thereof wherein R_2 is ^{19}F, ^{18}F, ^{123}I, ^{124}I or ^{131}I.

8. A compound according to any one of claims 1, 2, 3, 4, 5, 6 or 7, or a pharmaceutically acceptable salt thereof wherein R_3 is ^{19}F, ^{18}F, ^{123}I, ^{124}I or ^{131}I.

9. A compound according to any one of claims 1, 2, 3, 4, 5, 6, 7 or 8, or a pharmaceutically acceptable salt thereof wherein R_4 is methyl.

10. A compound according to any one of claims 1, 2, 3, 5, 6, 7, 8 or 9, or a pharmaceutically acceptable salt thereof wherein X is ethylene.

11. A compound according to any one of claims 1, 2, 3, 5, 6, 7, 8 or 9, or a pharmaceutically acceptable salt thereof wherein X is methylene.

12. A compound according to any one of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or 11, or a pharmaceutically acceptable salt thereof wherein R_5 is ethyl optionally substituted by ^{19}F or ^{18}F.

13. A compound according to any one of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12, or a pharmaceutically acceptable salt thereof wherein R_6 is $-CH=CH_2$, wherein one or more hydrogens are optionally replaced by ^3H.

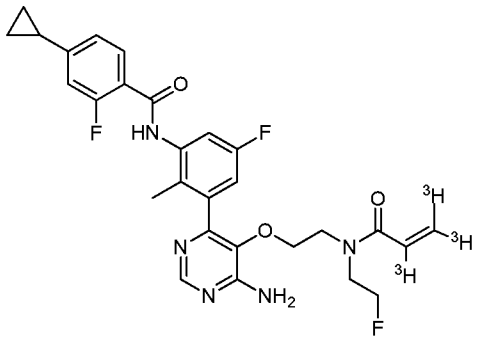
14. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of claims 1 to 13 and further comprising one or more pharmaceutically acceptable carriers.

15. A combination comprising a therapeutically effective amount of a compound according to any one of claims 1 to 13 or a pharmaceutically acceptable salt thereof and one or more therapeutically active co-agents.

16. A method of modulating BTK activity in a subject, wherein the method comprises administering to the subject a therapeutically effective amount of the compound according to any one of claims 1 to 13 or a pharmaceutically acceptable salt thereof.

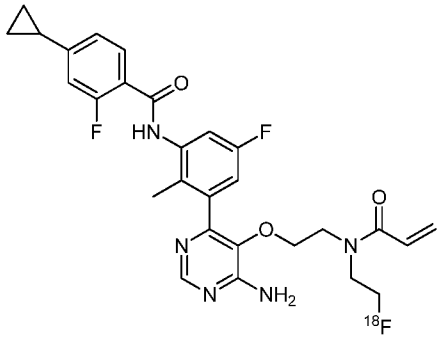
17. A compound according to any one of claims 1 to 13 or a pharmaceutically acceptable salt thereof, for use as a medicament and/or a diagnostic incorporating a technique selected from in vitro binding assays, ex vivo binding assays, autoradiography, positron emission tomography (PET), and single photon emission computed tomography (SPECT).

18. A compound according to claim 1, which is



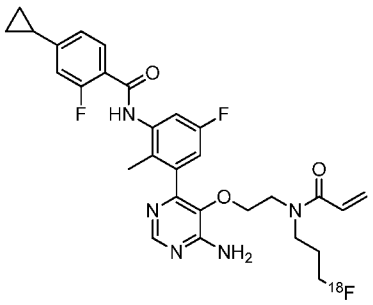
or a pharmaceutically acceptable salt thereof.

19. A compound according to claim 1, which is



or a pharmaceutically acceptable salt thereof.

20. A compound according to claim 1, which is



or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/058880

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D239/47 A61K31/506 A61P35/00
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

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, 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.
X	US 2008/125417 A1 (CURRIE KEVIN S [US] ET AL) 29 May 2008 (2008-05-29)	1,2,4-9, 12-17
A	claims 1, 21, 68	3,10,11, 18-20

X	US 2014/243306 A1 (NOVARTIS AG [CH]; HENG RICHARD [CH]; HOEGENAUER ELIZABETH KATE [CH]; K) 28 August 2014 (2014-08-28)	1,2,4-9, 12-17
A	claims 1, 15	3,10,11, 18-20

X	WO 2008/033857 A2 (CGI PHARMACEUTICALS INC [US]; BLOMGREN PETER A [US]; LEE TONY [US]; MI) 20 March 2008 (2008-03-20)	1,2,4-9, 12-17
A	claims 1, 70	3,10,11, 18-20

☐ Further documents are listed in the continuation of Box C.

☒ 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

"E" earlier application or patent but published on or after the international filing date

"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
21 December 2015	07/01/2016

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	Beligny, Samuel

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2015/058880

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2008125417 A1	29-05-2008	AR 063946 A1	04-03-2009
		AU 2007296550 A1	20-03-2008
		BR PI0716888 A2	22-10-2013
		CA 2661938 A1	20-03-2008
		CL 2007002641 A1	20-06-2008
		CN 101605766 A	16-12-2009
		EP 2069314 A1	17-06-2009
		JP 2010502749 A	28-01-2010
		KR 20090061655 A	16-06-2009
		PE 10592008 A1	22-10-2008
		RU 2009113691 A	20-10-2010
		TW 200829577 A	16-07-2008
		US 2008125417 A1	29-05-2008
		WO 2008033834 A1	20-03-2008
		ZA 200901593 A	31-03-2010
US 2014243306 A1	28-08-2014	AU 2012282229 A1	16-01-2014
		CA 2841111 A1	17-01-2013
		CN 103732596 A	16-04-2014
		EA 201490229 A1	30-05-2014
		EP 2729466 A1	14-05-2014
		ES 2548414 T3	16-10-2015
		JP 2014520793 A	25-08-2014
		KR 20140058543 A	14-05-2014
		US 2014243306 A1	28-08-2014
		WO 2013008095 A1	17-01-2013
WO 2008033857 A2	20-03-2008	AR 063707 A1	11-02-2009
		AT 496909 T	15-02-2011
		AU 2007296563 A1	20-03-2008
		BR PI0716914 A2	05-11-2013
		CA 2661951 A1	20-03-2008
		CL 2007002642 A1	18-07-2008
		CN 101605778 A	16-12-2009
		CO 6180464 A2	19-07-2010
		CR 10709 A	14-07-2009
		EC SP099238 A	31-07-2009
		EP 2079726 A2	22-07-2009
		ES 2363269 T3	28-07-2011
		JP 5563301 B2	30-07-2014
		JP 2010502750 A	28-01-2010
		KR 20090074192 A	06-07-2009
		MA 31276 B1	01-04-2010
		PE 13702008 A1	28-11-2008
		RU 2009113692 A	20-10-2010
		TW 200829567 A	16-07-2008
		WO 2008033857 A2	20-03-2008
		ZA 200901634 A	30-12-2009