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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 August 2017 (24.08.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/140758 A1

(51) International Patent Classification:
C07D 487/04 (2006.01) *A61K 31/519* (2006.01)
C07D 495/04 (2006.01) *A61P 35/00* (2006.01)

(21) International Application Number:
PCT/EP2017/053464

(22) International Filing Date:
16 February 2017 (16.02.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PCT/IB2016/000171
19 February 2016 (19.02.2016) IB

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, 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, KH, KN, KP, KR, KW, 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.

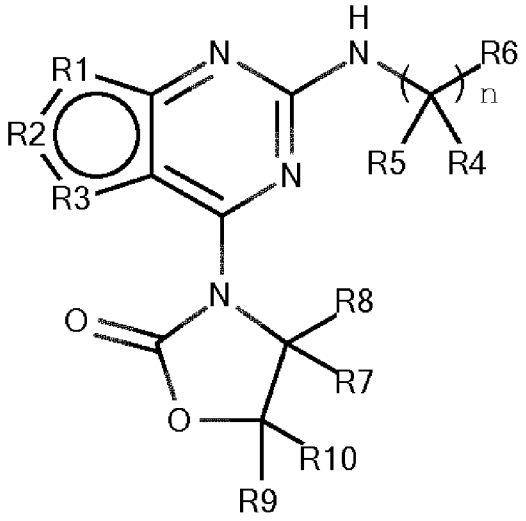
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, 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).

Published:

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

[Continued on next page]

(54) Title: DERIVATIVES OF 2-AMINO-4-(2-OXAZOLIDINON-3-YL)-PYRIMIDINE FUSED WITH A FIVE-MEMBERED HETEROAROMATIC RING IN 5,6-POSITION WHICH ARE USEFUL FOR THE TREATMENT OF VARIOUS CANCERS



(I)

(57) Abstract: The present invention relates to compounds of general Formula (I), uses of the compound of general Formula (I) for use in the treatment or prophylaxis of a disorder of the human or animal body, and pharmaceutical compositions comprising a therapeutically effective amount of the compounds of general Formula (I) as active ingredients.

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— *with sequence listing part of description (Rule 5.2(a))*

DERIVATIVES OF 2-AMINO-4-(2-OXAZOLIDINON-3-YL)-PYRIMIDINE FUSED WITH A FIVE-MEMBERED HETEROAROMATIC RING IN 5,6-POSITION WHICH ARE USEFUL FOR THE TREATMENT OF VARIOUS CANCERS

Background of the Invention

Isocitrate dehydrogenases (IDH) represent a family of cellular enzymes catalyzing $NADP^+$ / NAD^+ dependent oxidative decarboxylation of isocitrate, whereby α-ketoglutarate is produced and CO_2 and NADPH / NADH are liberated.

Human IDHs exist in several forms; the isoforms IDH1 (cytosolic and peroxisomal) and IDH2 (mitochondrial) catalyze the reaction outside the context of the citric acid cycle and use $NADP^+$ as a cofactor. Mutant forms of IDH often exhibit a neomorphic activity as a result of a "gain of function" mutation, whereby α-ketoglutarate is reduced to 2-hydroxyglutarate (2-HG) (P.S. Ward et al., *Cancer Cell* 2010, 17, 225). Regular cells have 2-HG levels, while cells and tumors with mutated IDH1 or IDH2 (referred herein as mIDH1 and mIDH2) show increased 2-HG levels (See S. Gross et al., *J. Exp. Med.* 2010, 207(2), 339). The dysregulation caused by the altered levels of 2-HG and α-ketoglutarate in cells bearing mIDH1 and/or mIDH2 may contribute to an alteration in a number of cellular activities, e.g. signaling and gene expression, and give raise to increased angiogenesis in human cancers. Accordingly, elevated levels of 2-HG are highly associated with tumorigenesis (J.R. Prensner et al., *Nature Med.* 2011, 17, 291-293).

Malignant gliomas, including primary and secondary glioblastomas, are among the most lethal and also the most prevalent of brain tumors. Genomic analyses of glioma genomes have revealed recurrent mutations of IDH in up to 70% of grade II-IV gliomas, in about 10% of acute myeloid leukemia

(AML) cases, and in several other cancer types. In particular, IDH1 R132 and IDH2 R172 mutations have been shown to have neomorphic activity (reducing α-ketoglutarate to 2-HG), as disclosed by L. Dang et al., Nature 2009, 462 and in WO 2011/123618 A1 and WO 2015/003641 A1.

Mutant IDH1 and IDH2 have been further identified in multiple cancer types, in particular brain cancers, such as glioma, glioblastoma multiforme, paraganglioma, and supratentorial primordial neuroectodermal tumors (pNET); leukemia, such as acute myeloid leukemia (AML), myelodysplasia syndrome, and chronic myelogenous leukemia (CML), skin cancer such as melanoma, prostate cancer, thyroid cancer, colon cancer, lung cancer, sarcoma, including central chondrosarcoma, central and periosteal chondroma, and fibrosarcoma.

To date, only a few inhibitors of mIDH1 and/or mIDH2 have been identified.

WO 2015/003355 A2 and WO 2015/003641 A1 disclose compounds based on a 2,4-diamino-1,3,5-triazine core as inhibitors of the neomorphic activity of mIDH2 R140Q and IDH2 R172K.

WO 2012/171506 A1 discloses compounds based on a pyridine or a pyrimidine core fused to a saturated 6-membered ring as inhibitors of the neomorphic activity of mIDH1 R132H.

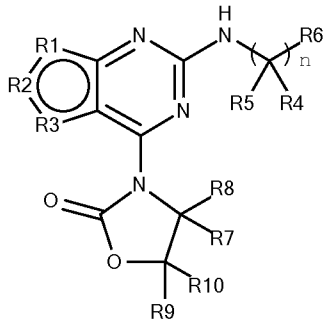
WO 2013/046136 A1, WO 2014/141104 A1, WO 2014/141153 A1 and WO 2014/147586 A1 disclose inhibitors of the neomorphic activity of mIDH1 R132H.

There is however still a need for small molecule inhibitors of mutant IDH proteins having a neomorphic activity, in particular for dual mIDH1/mIDH2 inhibitors, as well as for selective mIDH1 and/or selective mIDH2 inhibitors, for use in the treatment of diseases and disorders associated with these mutant proteins.

IDH related compounds are also described in WO 2015/017821 A2, WO 2015/003640 A1, WO 2015/003360 A2, WO 2015/006591 A1, WO 2015/006592 A1, WO 2012/171337 A1, WO 2012/171506 A1, WO 2014/062511 A1, WO 2013/107291 A1, WO 2013/107405 A1 and WO 2013/102431 A1.

Summary of the Invention

The present invention relates to a compound of general Formula (I)



(I)

or a salt or solvate thereof, wherein

n is 0 or 1;

R^1 is $N(R^{11})$ or CH;
R^2 is N or $C(R^{12})$;
R^3 is S or $C(R^{13})$;
provided that
R^1 is CH and R^2 is CR^{12} when R^3 is S; and
R^1 is $N(R^{11})$ when R^3 is $C(R^{13})$;

R^{11} is a hydrogen atom or CH_3;
R^{12} is a hydrogen atom, a cyano group or CH_3;
R^{13} is a hydrogen atom or a halogen atom;

R^4, R^5 are independently selected from a hydrogen atom; CH_2OH; CH_2OCH_3; a C_{1-6} alkyl group, wherein the C_{1-6} alkyl group is unsubstituted or substituted with at least one halogen atom;
or
R^4, R^5 may be joined together to form a C_{3-6} cycloalkyl group;

R^6 is an aromatic group, a heteroaromatic group or a C_{3-6} cycloalkyl group, wherein R^6 is unsubstituted or substituted with one or two R^{6a}, which are the same or different;
R^{6a} is a halogen atom, a C_{1-6} alkyl group, a C_{1-6} alkoxy group, a $S(O)_2$-C_{1-6} alkyl group, or R^{6aa};
R^{6aa} is an aromatic group, a heteroaromatic group, or a heteroalicyclylalkyl group, wherein R^{6aa} is unsubstituted or substituted with one or two R^{6b}, which are the same or different;
R^{6b} is a halogen atom; a C_{1-6} alkyl group, which is unsubstituted or substituted with at least one halogen atom; cyclopropyl or benzyloxycarbonyl;

R^7, R^8 are independently selected from a hydrogen atom, or R^{7a}, or R^7 and R^8 may be joined together to form a C_{3-6} cycloalkyl group or a heteroalicyclic group;
R^{7a} is a C_{1-6} alkyl group, an aromatic group, a heteroaromatic group, or a heteroalicyclic group, wherein R^{7a} is unsubstituted or substituted with a substituent selected from a halogen atom, CH_3, or OH;

R^9, R^{10} are independently selected from a hydrogen atom, or R^{9a}, or R^9 and R^{10} may be joined together to form a C_{3-6} cycloalkyl group or a heteroalicyclic group;
R^{9a} is a C_{1-6} alkyl group, an aromatic group, a heteroaromatic group, or a heteroalicyclic group, wherein R^{9a} is unsubstituted or substituted with a substituent selected from a halogen atom, CH_3, or OH.

A further aspect of the present invention relates to the compound of general Formula (I) or a salt or solvate thereof as a medicament and may be used in the treatment of a human or animal body. In particular, the present invention relates

to the compound of the general Formula (I) or a salt or a solvate thereof for use in the treatment or prophylaxis of a disease or disorder associated with a mutant isocitrate dehydrogenase having a neomorphic activity, preferably a cell proliferation disorder.

Yet a further aspect of the present invention relates to a pharmaceutical composition comprising a therapeutically effective amount of the compound of general Formula (I), or a salt or solvate thereof as active ingredient. In a particular embodiment, said pharmaceutical composition may be an oral dosage form.

Yet a further aspect of the present invention relates to the use of a compound of the general Formula (I) or a salt or a solvate thereof for the preparation of a medicament for the treatment or prophylaxis of a disease or disorder associated with a mutant isocitrate dehydrogenase having a neomorphic activity, preferably a cell proliferation disorder.

Yet a further aspect of the present invention is a method of treating, controlling, delaying or preventing in a mammalian patient in need of the treatment of one or more diseases or disorders associated with a mutant isocitrate dehydrogenase having a neomorphic activity, preferably a cell proliferation disorder, wherein the method comprises the administration to said patient a therapeutically effective amount of a compound of the present invention or a salt or a solvate thereof.

Detailed Description of the Invention

Compounds of the Present Invention

The term "substituted" means that one or more hydrogen atoms of a molecule or residue are replaced by a substituent. Suitable substituents are further described herein. Generally -but not limited to-, "one or more substituents" means one, two or three, preferably one or two substituents and more preferably one substituent unless specifically defined herein. Generally these substituents can be the same or different.

The term "alkyl" or "alkyl group" means a straight-chain or branched hydrocarbon chain.

The term "C_{1-4} alkyl" or "C_{1-4} alkyl group" means an alkyl chain having 1 - 4 carbon atoms, e.g. if present at the end of a molecule: methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, or e.g. $-CH_2-$, $-CH_2-CH_2-$, $-CH(CH_3)-$, $-CH_2-CH_2-CH_2-$, $-CH(C_2H_5)-$, $-C(CH_3)_2-$, when two moieties of a molecule are linked by the alkyl group.

The term "C_{1-6} alkyl" or "C_{1-6} alkyl group" means an alkyl chain having 1 - 6 carbon atoms, e.g. if present at the end of a molecule: C_{1-4} alkyl, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl; tert-butyl, n-pentyl, n-hexyl, or e.g. $-CH_2-$, $-CH_2-CH_2-$, $-CH(CH_3)-$, $-CH_2-CH_2-CH_2-$, $-CH(C_2H_5)-$, $-C(CH_3)_2-$, when two moieties of a molecule are linked by the alkyl group.

The term "C_{1-6} alkoxy group" (O-C_{1-6} alkyl) means a C_{1-6} alkyl group, which is attached to the rest of the molecule via oxygen atom. Examples are OCH_3 and OCH_2CH_3.

The term "*aromatic group*" means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "*aromatic group*" embraces aromatic substituents such as phenyl, naphthyl, and biphenyl. In a preferred embodiment, the term "*aromatic group*" refers to a phenyl group.

The term "C_{3-6} cycloalkyl" or "C_{3-6} cycloalkyl ring" or "C_{3-6} cycloalkyl group" means a cyclic alkyl chain having 3 - 6 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl. Preferably, cyloalkyl refers to cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

The term "3 to 7 membered heterocyclyl" or "3 to 7 membered heterocycle" means a ring with 3, 4, 5, 6 or 7 ring atoms that may contain up to the maximum number of double bonds (aromatic or non-aromatic ring which is fully, partially or unsaturated) wherein at least one ring atom up to 4 ring atoms are replaced by a heteroatom selected from the group consisting of sulfur (including -S(O)-, -$S(O)_2$-), oxygen and nitrogen (including =N(O)-) and wherein the ring is linked to the rest of the molecule via a carbon or nitrogen atom. Examples for a 3 to 7 membered heterocycles are aziridine, azetidine, oxetane, thietane, furan, thiophene, pyrrole, pyrroline, imidazole, imidazoline, pyrazole, pyrazoline, oxazole, oxazoline, isoxazole, isoxazoline, thiazole, thiazoline, isothiazole, isothiazoline, thiadiazole, thiadiazoline, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, imidazolidine, pyrazolidine, oxazolidine,

isoxazolidine, thiazolidine, isothiazolidine, thiadiazolidine, sulfolane, pyran, dihydropyran, tetrahydropyran, imidazolidine, pyridine, pyridazine, pyrazine, pyrimidine, piperazine, piperidine, morpholine, tetrazole, triazole, triazolidine, tetrazolidine, diazepane, azepine or homopiperazine. The term "4 to 7 membered heterocyclyl" or "4 to 7 membered heterocycle" is defined accordingly. The term "5 to 6 membered heterocyclyl" or "5 to 6 membered heterocycle" is defined accordingly.

"Saturated 4 to 7 membered heterocyclyl" or "saturated 4 to 7 membered heterocycle" means fully saturated "4 to 7 membered heterocyclyl" or "4 to 7 membered heterocycle".

"4 to 7 membered at least partly saturated heterocyclyl" or "4 to 7 membered at least partly saturated heterocycle" means an at least partly saturated "4 to 7 membered heterocyclyl" or "4 to 7 membered heterocycle".

"5 to 6 membered aromatic heterocyclyl" or "5 to 6 membered aromatic heterocycle" means a heterocycle derived from cyclopentadienyl or benzene, where at least one carbon atom is replaced by a heteroatom selected from the group consisting of sulfur (including -S(O)-, $-S(O)_2-$), oxygen and nitrogen (including =N(O)-). Examples for such heterocycles are furan, thiophene, pyrrole, imidazole, pyrazole, oxazole, isoxazole, thiazole, isothiazole, thiadiazole, triazole, tetrazole, pyridine, pyrimidine, pyridazine, pyrazine, triazine.

The term "heteroaromatic group" means a 5 to 6 membered aromatic heterocyclyl or 5 to 6 membered aromatic heterocycle.

The term "heteroalicyclic group" means a 4 to 7 membered at least partly saturated heterocyclyl or 4 to 7 membered at least partly saturated heterocycle or a saturated 4 to 7 membered heterocyclyl or saturated 4 to 7 membered heterocycle. Preferably the term "heteroalicyclic group" means a saturated 4 to 7 membered heterocyclyl or saturated 4 to 7 membered heterocycle.

The term "heteroalicyclylalkyl group" means a heteroalicyclyl group, which is attached to the rest of the molecule via a C_{1-6} alkyl group.

The term "halogen" or "halogen atom" means fluoro, chloro, bromo or iodo. It is generally preferred that halogen is fluoro or chloro.

The term "cyano group" means -CN.

The term "benzyl" means Ph-CH_2- (phenylmethyl), wherein "Ph" means phenyl.

The compounds of the present invention may also exist as several tautomeric forms. For instance, when the substituent R^{9a} is a pyridyl group substituted with a hydroxyl group, R^{9a} and the corresponding compound of the Formula (I) may exist in a corresponding pyridone form.

The compound of the present invention or a salt or solvate thereof is preferably the compound of general Formula (I) as defined in the summary of the invention or a salt or solvate thereof, wherein

(i) R^1 is NH, R^2 is CH, R^3 is CH; or

(ii) R^1 is NH, R^2 is N, R^3 is CH; or
(iii)R^1 is CH, R^2 is CH, R^3 is S; or
(iv) R^1 is NH, R^2 is CH, R^3 is CF; or
(v) R^1 is NH, R^2 is CCN, R^3 is CH; or
(vi) R^1 is NH, R^2 is CCH_3, R^3 is CH; or
(vii)R^1 is NCH_3, R^2 is CH, R^3 is CH.

The compound of the present invention or a salt or solvate thereof is preferably the compound of general Formula (I) as defined in the summary of the invention or a salt or solvate thereof, wherein one of R^4, R^5 is a hydrogen atom or CH_3 and the other is a hydrogen atom, CH_3, CH_2CH_3, CH_2OH, CH_2OCH_3, CH_2F or CF_3; or R^4, R^5 are joined together to form a cyclopropyl group.

The compound of the present invention or a salt or solvate thereof is preferably the compound of general Formula (I) as defined in the summary of the invention or a salt or solvate thereof, wherein R^6 is an aromatic group or a heteroaromatic group and wherein R^6 is unsubstituted or substituted with one or two R^{6a}, which are the same or different.

The compound of the present invention or a salt or solvate thereof is preferably the compound of general Formula (I) as defined in the summary of the invention or a salt or solvate thereof, wherein R^6 is imidazolyl, pyridyl, thiazolyl, pyrazolyl, phenyl, oxadiazolyl, oxazolyl, cyclohexyl, thiophenyl or furanyl and wherein R^6 is unsubstituted or substituted with one or two R^{6a}, which are the same or different.

The compound of the present invention or a salt or solvate thereof is preferably the compound of general Formula (I) as

defined in the summary of the invention or a salt or solvate thereof, wherein R^{6a} is CH_3, OCH_3, F, Cl, $S(O)_2CH_3$ or R^{6aa}.

The compound of the present invention or a salt or solvate thereof is preferably the compound of general Formula (I) as defined in the summary of the invention or a salt or solvate thereof, wherein R^{6aa} is phenyl, pyridyl, thiophenyl or piperazinylmethyl and wherein R^{6aa} is unsubstituted or substituted with one or two R^{6b}, which are the same or different.

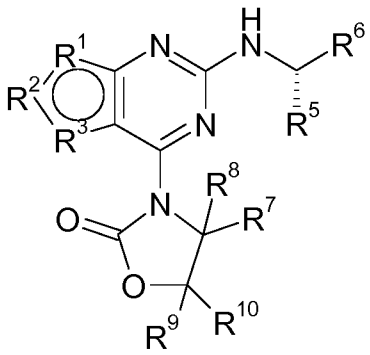
The compound of the present invention or a salt or solvate thereof is preferably the compound of general Formula (I) as defined in the summary of the invention or a salt or solvate thereof, wherein R^{6b} is Cl, F, CF_3, cyclopropyl or benzyloxycarbonyl.

The compound of the present invention or a salt or solvate thereof is preferably the compound of general Formula (I) as defined in the summary of the invention or a salt or solvate thereof, wherein one of R^7, R^8 is a hydrogen atom or CH_3 and the other is CH_2F, a fluoroethyl, methyl, ethyl, isopropyl, tert.-butyl, 1-methyl-propyl, a hydroxyethyl, phenyl, pyridyl or methylimidazolyl; or R^7 and R^8 are joined together to form a cyclopropyl, tetrahydrofuranyl or tetrahydropyranyl group.

The compound of the present invention or a salt or solvate thereof is preferably the compound of general Formula (I) as defined in the summary of the invention or a salt or solvate thereof, wherein R^9 and R^{10} are hydrogen atoms, and at least one of R^7 and R^8 is other than a hydrogen atom.

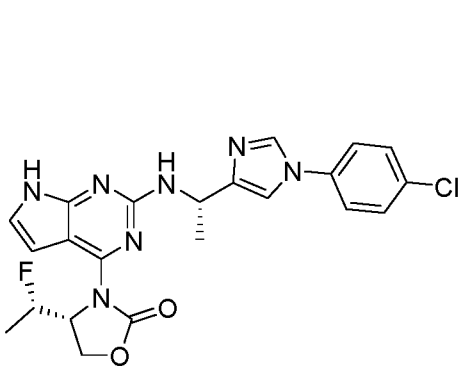
The compound of the present invention or a salt or solvate thereof is preferably the compound of general Formula (I) as defined in the summary of the invention or a salt or solvate thereof, wherein n is 1.

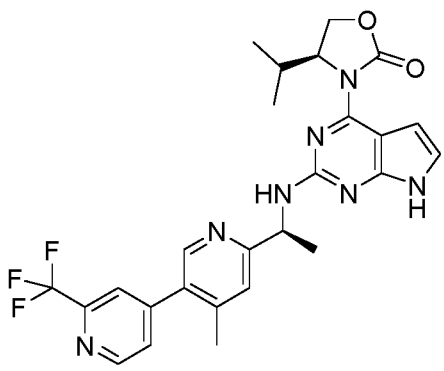
The compound of the present invention or a salt or solvate thereof is preferably the compound of general Formula (I) as defined in the summary of the invention or a salt or solvate thereof, wherein n is 1, R^4 is a hydrogen atom and R^5 is other than a hydrogen atom to give Formula (Ia)

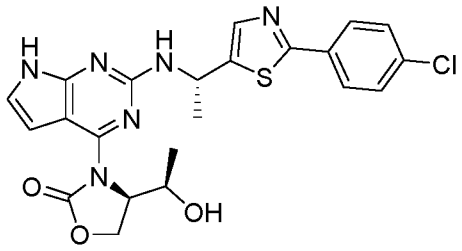


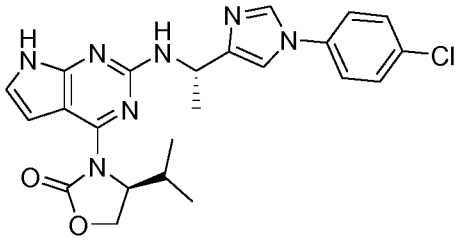
(Ia).

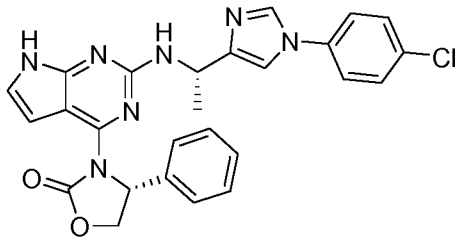
Finally, the compound of the present invention or a salt or solvate thereof is preferably selected from Table 1 herein or more preferably one of the following:

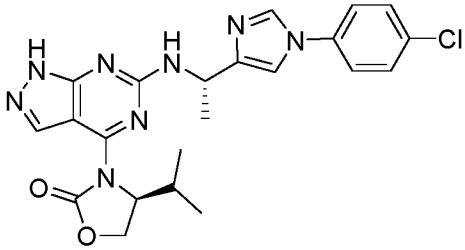


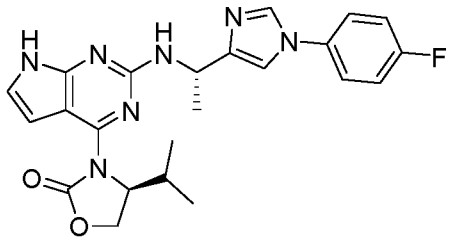


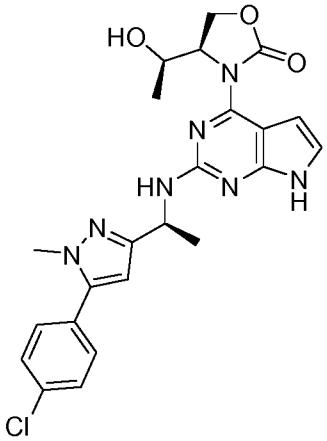


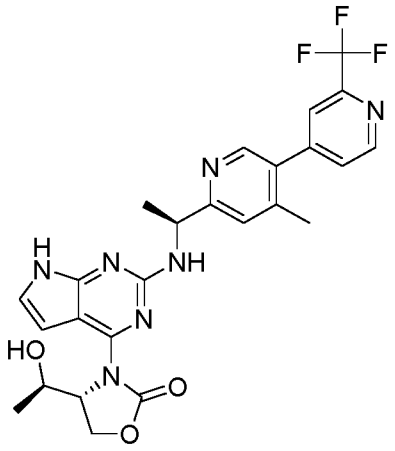












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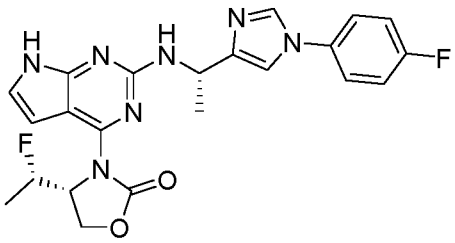

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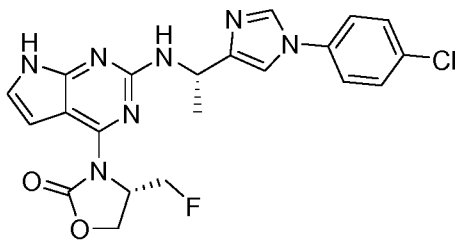

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A further aspect of the present invention is a solvent or salt of a compound of formula (I).

Accordingly, in case the compounds according to formula (I) contain one or more acidic or basic groups, the invention also comprises their corresponding salt, preferably pharmaceutically acceptable salts. Thus, the compounds of the formula (I) which contain acidic groups can be used according to the invention, for example, as alkali metal salts, alkaline earth metal salts or as ammonium salts. More precise examples of such salts include sodium salts, potassium salts, calcium salts, magnesium salts or salts with ammonia or organic amines such as, for example, ethylamine, ethanolamine, triethanolamine or amino acids. Compounds of the formula (I) which contain one or more basic groups, i.e. groups which can be protonated, can be present and can be used according to the invention in the form of their addition salts with inorganic or organic acids. Examples for suitable acids include hydrogen chloride, hydrogen bromide, phosphoric acid, sulfuric acid, nitric acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acids, oxalic acid, acetic acid, tartaric acid, lactic acid, salicylic acid, benzoic acid, formic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, malic acid, sulfaminic acid, phenylpropionic acid, gluconic acid,

ascorbic acid, isonicotinic acid, citric acid, adipic acid, and other acids known to the person skilled in the art. If the compounds of the formula (I) simultaneously contain acidic and basic groups in the molecule, the invention also includes, in addition to the salt forms mentioned, inner salts or betaines (zwitterions). The respective salts according to the formula (I) can be obtained by customary methods which are known to the person skilled in the art like, for example by contacting these with an organic or inorganic acid or base in a solvent or dispersant, or by anion exchange or cation exchange with other salts. The present invention also includes all salts of the compounds of the formula (I) which, owing to low physiological compatibility, are not directly suitable for use in pharmaceuticals but which can be used, for example, as intermediates for chemical reactions or for the preparation of pharmaceutically acceptable salts.

Use of the Compounds of the Invention in Methods for Treatment

A compound of general Formula (I) according to the present invention or a salt or solvate thereof can be used in the treatment or prophylaxis of a human or animal body.

The use may be in the treatment or prophylaxis of a disorder associated with a mutant isocitrate dehydrogenase having a neomorphic activity. The disorder associated with a mutant isocitrate dehydrogenase having a neomorphic activity may be a cell proliferation disorder. The disorder may be one of the following: brain cancer, such as glioma, glioblastoma multiforme, paraganglioma, and supratentorial primordial neuroectodermal tumors (pNET), leukemia, such as acute myeloid leukemia (AML), myelodysplasia syndrome, and chronic myelogenous leukemia (CML), skin cancer such as melanoma, prostate cancer, thyroid cancer, colon cancer, lung cancer, sarcoma, including central chondrosarcoma, central and periosteal chondroma, and fibrosarcoma.

Pharmaceutical Compositions of the Invention

The present invention also provides pharmaceutical compositions comprising the compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, as active ingredient, and a pharmaceutically acceptable carrier. The term "*pharmaceutically acceptable salt*" includes an ammonium salt, a calcium salt, a magnesium salt, a potassium salt or a sodium salt of compound of Formula (I).

The pharmaceutical compositions of the present invention may comprise the compound of Formula (I), or a pharmaceutically

acceptable salt or solvate thereof in form of one or several polymorphs.

The term "*composition*", as in pharmaceutical composition, is intended to encompass a product comprising the active ingredient, and the inert ingredient(s) (such as pharmaceutically acceptable excipients) that make up the pharmaceutically acceptable carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing the compound of Formula (I) and pharmaceutically acceptable excipients.

Any suitable route of administration may be employed for providing a patient, with an effective dosage of a compound of the present invention, including without limitation oral and parenteral (such as intravenous bolus or infusion, injection, intraperitoneal, subcutaneous or intramuscular administration).

Pharmaceutical compositions of the present invention that are suitable for oral administration (oral dosage forms) may be presented in solid or liquid form. Suitable solid oral dosage forms include discrete units such as capsules, pills, cachets, powders (such as effervescent), granules or tablets, and the like, each containing a predetermined amount of the compound of Formula (I) as active ingredient. Suitable liquid oral dosage forms include solutions or suspensions in an aqueous liquid, a non-aqueous liquid, an oil-in-water

emulsion or a water-in-oil liquid emulsion, including elixirs, tinctures, solutions, suspensions, syrups and emulsions. Pharmaceutical compositions of the present invention may also be in the form of sustained release formulations.

Any inert ingredient that is commonly used as a carrier or diluent may be used in the formulations of the present invention, such as for example, a gum, a starch, a sugar, a cellulosic material, an acrylate, or mixtures thereof. A preferred diluent is microcrystalline cellulose. The compositions may further comprise a disintegrating agent (*e.g.*, croscarmellose sodium) and a lubricant (*e.g.*, magnesium stearate), and may additionally comprise one or more additives selected from a binder, a buffer, a protease inhibitor, a surfactant, a solubilizing agent, a plasticizer, an emulsifier, a stabilizing agent, a viscosity increasing agent, a sweetener, a film forming agent, or any combination thereof.

The pharmaceutical compositions of the present invention may be prepared by any of the methods of pharmacy but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet may be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine, the active ingredient in a free-flowing form such as powder or granules,

optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Desirably, each tablet, cachet or capsule contains from about 0.1 to 1,000 mg, particularly 0.1, 0.2, 0.5, 1.0, 5, 10, 25, 50, 75, 100, 110, 115, 120, 125, 130, 135, 140, 145, 150, 175, 180, 200, 225, 250, 300, 350, 400, 450, 500, 750 and 1,000 milligrams of the active ingredient, for the symptomatic adjustment of the dosage to the patient to be treated.

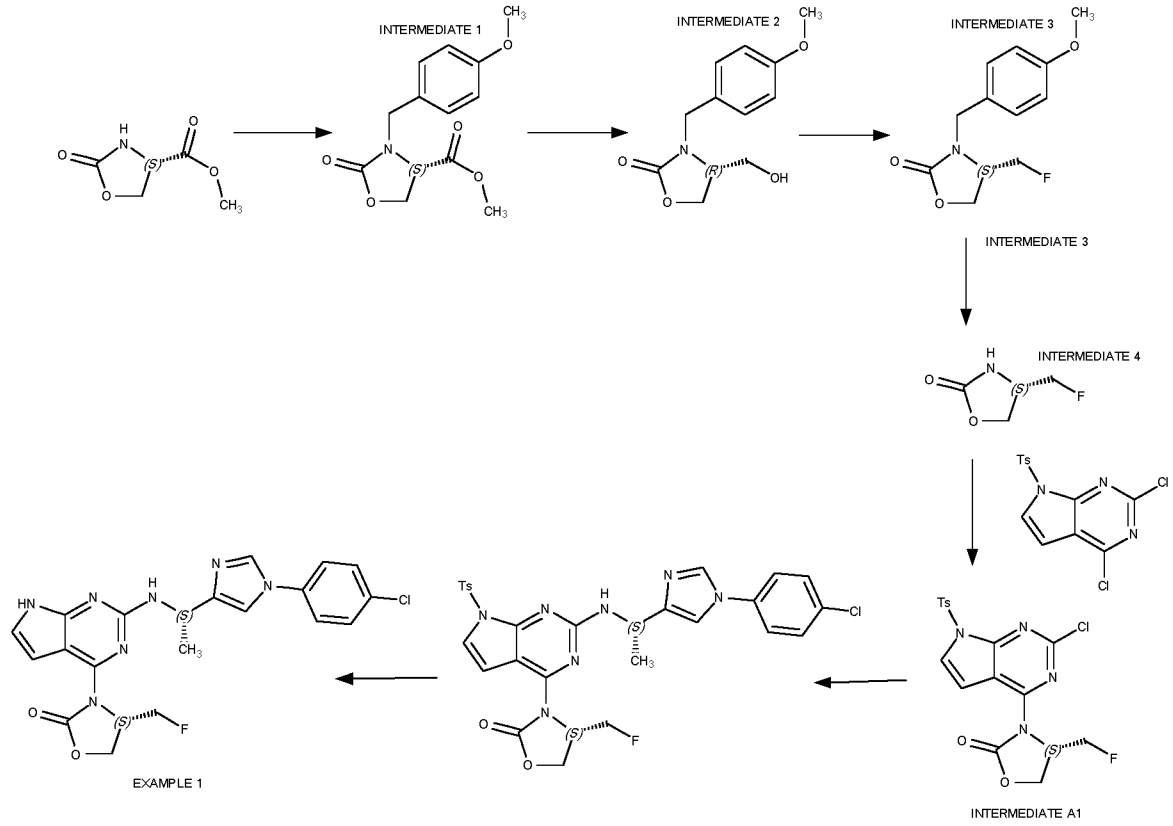
Examples

Methods of preparation of compound of Formula (I)

The following general methods described hereinafter in the schemes and in examples may be used to prepare compounds of Formula (I) using appropriate materials. If such starting materials are not commercially available, they may be prepared by standard synthetic techniques. Methods for extraction, isolation, purification, treatment known by one skilled in the art may be applied. Moreover, by utilizing the procedure described below, one of ordinary skilled in the art can readily prepare additional compounds of the present invention claimed herein.

Where typical or preferred experimental conditions are given (*i.e.* solvent, temperature, reaction time, stoichiometry of reagents, *etc.*), other experimental conditions may also be used unless otherwise stated. Compounds of the general Formula (I) might be synthesised by several processes using both solid and/or solution phase chemistry protocols.

Examples of synthetic pathways for the preparation of compounds of general Formula (I) are described here below. Optimal reaction conditions may vary with particular reactants or solvent, but such conditions can be determined by the person skilled in the art using routine optimization procedures. Compound numbers refer to the numbering in Table 1 below. A synthetic scheme for the preparation of Compound 12 is shown below. The exemplary synthetic procedures can be easily modified for the preparation of further compounds of the present invention by substituting the corresponding intermediates as described in detail below.



Scheme 1: Synthesis of Compound 12 (for reaction conditions details, see the experimental procedures below).

Abbreviations

aq Aqueous

Brine	Saturated solution of sodium chloride in water
DIPEA	N,N-Diisopropylethylamine
DMF	N,N-Dimethylformamide
EtOAc	Ethyl acetate
EtOH	Ethanol
EtO_2	Diethyl ether
FCC	Flash column chromatography
g	Gram (s)
h	Hour (s)
HPLC	High-performance liquid chromatography
IPC	In process check
LDA	Lithium diisopropylamide
MeCN	Acetonitrile
MeOH	Methanol
Min (s)	Minute (s)
mg	Milligram (s)
ml	Millilitre (s)
mm	Millimetre (s)
mM	Millimolar
$NaHCO_3$	Sodium hydrogen carbonate
NaOH	Sodium hydroxide
$Na_2S_2O_3$	Sodium thiosulfate
NH_3	Ammonia
NH_4Cl	Ammonium chloride
NMR	Nuclear Magnetic Resonance
RT	Room temperature
SCX	Cation-exchange columns with propylsulfonic acid-tailed silica
THF	Tetrahydrofuran
TBME	Methyl tert-butyl ether
t_R	Time of retention
µl	Microlitre (s)

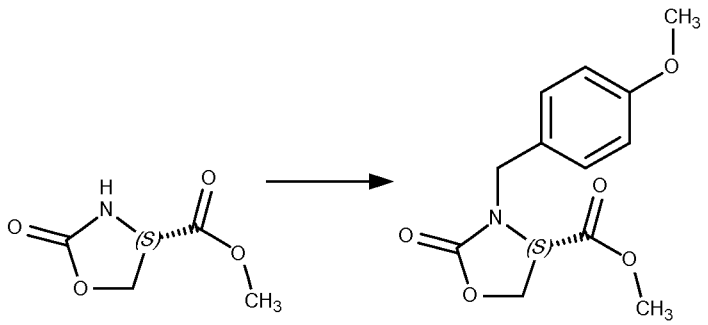
µm Micrometre (s)

Analytical LCMS conditions are as follows:

System 1: ACIDIC IPC 2 min METHOD: Linear gradient 5-100 % solvent B in 1.5 mins + 0.1 mins 100 % solvent B, flow rate 1ml/min. Column Supelco Ascentis Express Part No. 53802-U (30 X 2.1 mm, 1.7 µm). Solvent A = 0.1 % Formic acid in water, Solvent B = 0.1 % Formic acid in Acetonitrile.

System 2: ACIDIC FINAL 7 min METHOD: Linear gradient 5-100 % solvent B in 5.3 mins + 0.5 mins 100 % solvent B, flow rate 0.6ml/min. Column Phenomenex Kinetix-XB C18 Part No. 00D-4498-AN (100 X 2.1 mm, 1.7 µm). Solvent A = 0.1 % Formic acid in water, Solvent B = 0.1 % Formic acid in Acetonitrile.

Synthesis of methyl (4S)-3-[(4-methoxyphenyl)methyl]-2-oxo-1,3-oxazolidine-4-carboxylate: INTERMEDIATE 1

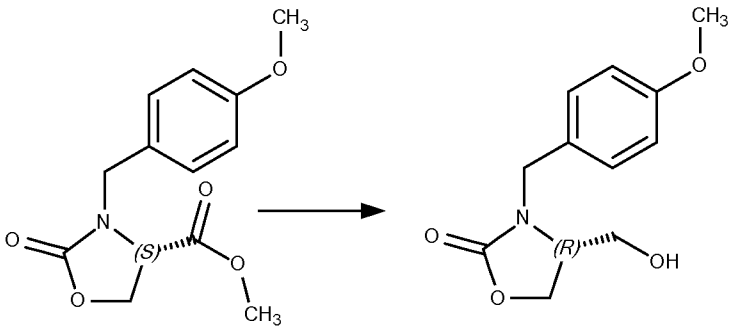


Sodium hydride (60%, 8.77g, 219 mmol) was added to a cooled (-10 °C) solution of methyl (4S)-2-oxo-1,3-oxazolidine-4-carboxylate (30 g, 208.8 mmol) in dry DMF (1500 ml) under nitrogen and the mixture stirred at -10 °C for 5 min. 1-(chloromethyl)-4-methoxybenzene (31.9 ml, 230 mmol) was added and the mixture stirred at -10 °C to 0 °C over 1 hr and at RT for 2 hr. The mixture was poured into an ice cold mixture of EtOAc (1 l) and 0.5M citric acid (100 ml) in water (1 l) in 1 portion. The organic layer was separated and the aqueous re-extracted with EtOAc (500 ml). The combined organic extracts were washed with water (4 x 1 l), sat brine (1 l), dried over sodium sulfate and concentrated in vacuo to give the crude product as a pale yellow oil which was purified by chromatography on silica eluting with heptane-5% to 50% EtOAc to give methyl (4S)-3-[(4-methoxyphenyl)methyl]-2-oxo-1,3-oxazolidine-4-carboxylate (18.51 g) as a yellow oil.

^{1}H NMR (500 MHz, Chloroform-d) δ 7.18 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 4.82 (d, J = 14.8 Hz, 1H), 4.41 - 4.35 (m, 1H), 4.32 (dd, J = 9.0, 5.1 Hz, 1H), 4.17 (d, J = 14.8 Hz,1H), 4.08 (dd, J = 9.5, 5.1 Hz, 1H), 3.80 (s, 3H), 3.75 (s, 3H).

LCMS MH+ 265.9 RT 1.00 System 1

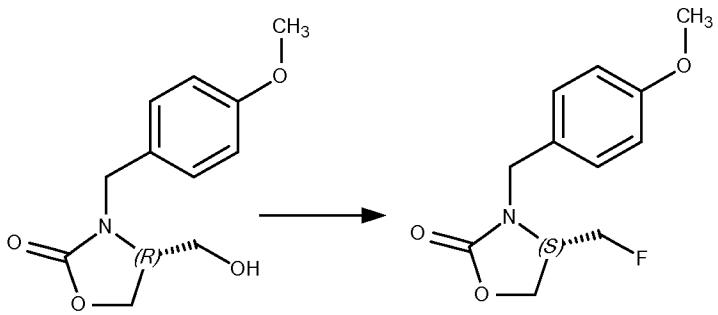
Synthesis of (4R)-4-(hydroxymethyl)-3-[(4-methoxyphenyl)methyl]-1,3-oxazolidin-2-one: INTERMEDIATE 2



$NaBH_4$ (365 mg, 9.65 mmol) was added to a cooled (ice bath) solution of methyl (4*S*)-3-[(4-methoxyphenyl)methyl]-2-oxo-1,3-oxazolidine-4-carboxylate (2.45 g, 8.77 mmol) in EtOH (50 ml). The reaction mixture was allowed to warm to RT then stirred at RT. The reaction mixture was cooled in ice then acetone (5 ml) added to quench excess borohydride. The reaction mixture was allowed to warm to RT then concentrated *in vacuo*. The resultant mixture was partitioned between EtOAc (50 ml) and 1 M aq. HCl (50 ml). The phases were separated then the aqueous phase was extracted with EtOAc (50 ml). The combined organic phases were washed with water (50 ml) and brine (50 ml) then dried over Na_2SO_4 and evaporated to an amber gum which crystallised on standing to yield the crude product as an amber solid. Purification by flash column chromatography on a silica column (50 g) eluting with EtOAc:heptane, increasing the gradient linearly from 50:50 to 100:0 afforded a colourless gum which crystallised on standing to yield (4R)-4-(hydroxymethyl)-3-[(4-methoxyphenyl)methyl]-1,3-oxazolidin-2-one (1.45 g) as a white solid.

^{1}H NMR (500 MHz, Chloroform-d) δ 7.28 – 7.22 (m, 2H), 6.90 – 6.85 (m, 2H), 4.58 (d, J = 15.1 Hz, 1H), 4.34 – 4.20 (m, 3H), 3.80 (s, 3H), 3.76 – 3.67 (m, 2H), 3.57 – 3.49 (m, 1H)
LCMS MH+ 238.0 RT 0.85 System 1

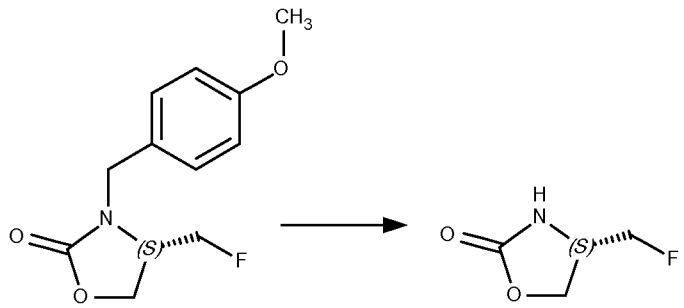
Synthesis of (4S)-4-(fluoromethyl)-3-[(4-methoxyphenyl)methyl]-1,3-oxazolidin-2-one: INTERMEDIATE 3



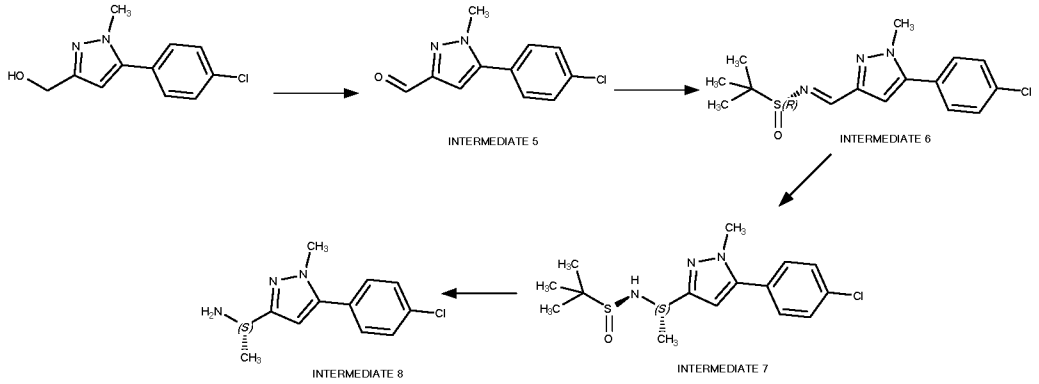
PBSF (3.3 ml, 19 mmol) was added drop-wise to a cooled (0 °C, ice bath) solution of (4R)-4-(hydroxymethyl)-3-[(4-methoxyphenyl)methyl]-1,3-oxazolidin-2-one (1.45 g, 6.11 mmol) and triethylamine (7.7 ml, 55 mmol) in MeCN (30 ml). The reaction solution was stirred at 0 °C for 5 min then TREAT-HF (3.0 ml, 19 mmol) was added drop-wise. The resultant solution was left to stir at 0 °C for one hour then the reaction mixture was partitioned between EtOAc (60 ml) and water (60 ml). The phases were separated and the aqueous phase was extracted with EtOAc (60 ml). The combined organic phases were washed with brine (60 ml) then dried over Na_2SO_4 and evaporated to give the crude product which was purified by flash column chromatography on a silica column (50 g). The column was eluted with EtOAc:heptane, increasing the gradient linearly from 0:100 to 70:30 over 10 column volumes. The desired fractions were combined and evaporated to yield the required product as colourless oil (887 mg)

^{1}H NMR (500 MHz, Chloroform-d) δ 7.23 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 4.77 (d, J = 15.1 Hz, 1H), 4.51 - 4.29 (m, 3H), 4.17 (d, J = 15.1 Hz, 1H), 4.11 (dd, J = 8.9, 6.0 Hz, 1H), 3.90 - 3.79 (m, 4H).
LCMS MH+ 239.9 RT 0.98 System 1

Synthesis of (4S)-4-(fluoromethyl)-1,3-oxazolidin-2-one: INTERMEDIATE 4



A solution of (4S)-4-(fluoromethyl)-3-[(4-methoxyphenyl)methyl]-1,3-oxazolidin-2-one (8.91 g, 37.2 mmol) in TFA (200 ml) was heated at 65 °C for 16 hours to give an orange/brown solution. The reaction mixture was concentrated in vacuo then azeotroped with EtOAc (3 x 100 ml) to yield a green mixture. Purification by flash chromatography on a silica column (100 g) eluting with DCM:EtOAc 0 to 100% afforded the required product (4.25 g, 95%) as a green oil. Further purification by chromatography on silica eluting with heptane-25% EtOAc to 100% EtOAc to give (4S)-4-(fluoromethyl)-1,3-oxazolidin-2-one (4.01g, 90%) as a pale green oil (3.76 g, 85%).
^{1}H NMR (250 MHz, Chloroform-d) δ 6.52 (s, 1H), 4.57 - 4.43 (m, 2H), 4.38 - 4.04 (m, 3H).



Scheme 2: Synthesis of Intermediate 8 (for reaction conditions details, see the experimental procedures below).

Synthesis of 5-(4-chlorophenyl)-1-methyl-1H-pyrazole-3-carbaldehyde: INTERMEDIATE 5

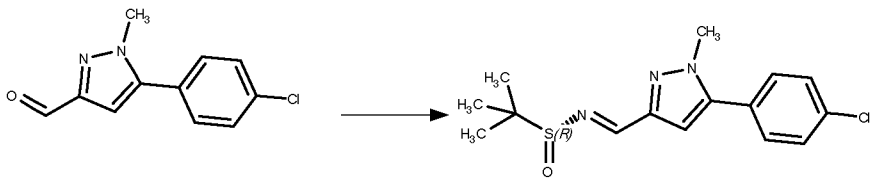
Dimethyl sulfoxide (2.17 ml, 30.48 mmol) in dichloromethane (5 ml) was added dropwise to a cooled (-78 °C) solution of oxalyl chloride (1.08 ml, 12.8 mmol) in dichloromethane (10 ml) under nitrogen and stirred for 15 minutes. A solution of 5-(4-chlorophenyl)-1-methyl-1H-pyrazol-3-yl]methanol (2.72 g, 12.19 mmol) in 1:1 dichloromethane/THF (50ml) was added dropwise and the reaction stirred for a further 60 minutes at -78 °C. Triethylamine (8.5 ml, 60.96 mmol) in dichloromethane (10 ml) was then added slowly and the reaction was allowed to warm to ambient temperature overnight. The reaction was diluted with water (75.0 ml) and $NaHCO_3$(sat aq) (50.0 ml) along with further DCM (50.0 ml) and the organic layer was separated, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was retreated in a similar manner. Oxalyl

chloride (1.62 ml, 19.4 mmol) was dissolved in dichloromethane (10 ml) under nitrogen and cooled to -78°C then dimethyl sulfoxide (2.17 ml, 30.48 mmol) in dichloromethane (5 ml) was added dropwise and stirred for 15 minutes. The recovered residue was dissolved in tetrahydrofuran (25.0 ml) and added slowly to the reaction washing in with DCM (25.0 ml) then the reaction was stirred for 1.5 hr at -78 °C before the slow addition of triethylamine (8.5 ml, 60.96 mmol) in dichloromethane (10 ml). After a further 10 minutes the reaction was allowed to warm to 0 °C and stirred for 30 mins. Reaction diluted with DCM (50.0 ml), water (75.0 ml) and NaHCO3(sat aq) (50.0 ml) then the organic layer was separated, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was treated with TBME (30.0 ml) and the resultant suspension was filtered, washing with further TBME and dried in vacuo to give 1.637g of 5-(4-chlorophenyl)-1-methyl-1H-pyrazole-3-carbaldehyde as a pale yellow powdery solid.

^{1}H NMR (500 MHz, DMSO-d6) 9.94 (s, 1H), 7.90 - 7.87 (m, 2H), 7.54 (s, 1H), 7.52 - 7.48 (m, 2H), 4.16 (s, 3H)

LCMS MH+ 220.8 RT 1.17 System 1

Synthesis of (R)-N-[(1E)-[5-(4-chlorophenyl)-1-methyl-1H-pyrazol-3-yl]methylidene]-2-methylpropane-2-sulfinamide: INTERMEDIATE 6

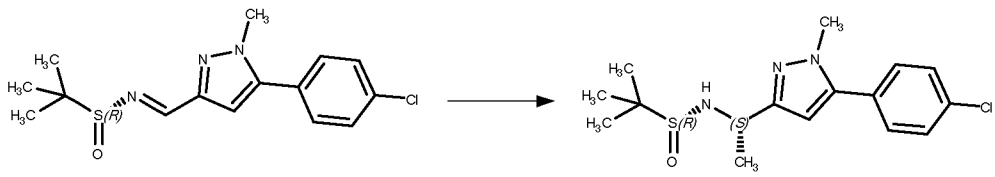


Titanium tetraethoxide (3.11 ml, 14.84 mmol) was added to a solution of 5-(4-chlorophenyl)-1-methyl-1H-pyrazole-3-carbaldehyde (1.64 g, 7.42 mmol) and (R)-2-methylpropane-2-sulfinamide (0.99 g, 8.16 mmol) in tetrahydrofuran (25 ml) and the reaction heated to 55 °C under nitrogen for 4 hours. The reaction was cooled, diluted with EtOAc (50.0 ml) and water (30.0 ml) then stirred for 10 minutes. The biphasic suspension was filtered through celite, washing with further EtOAc then the organic layer was separated, dried over Na_2SO_4, filtered and concentrated in vacuo to give (R)-N-[(1E)-[5-(4-chlorophenyl)-1-methyl-1H-pyrazol-3-yl]methylidene]-2-methylpropane-2-sulfinamide (2.189g) as a pale tan viscous oil which crystallised on standing.

^{1}H NMR (500 MHz, DMSO-d6) 8.52 (s, 1H), 7.88 - 7.84 (m, 2H), 7.52 - 7.47 (m, 2H), 7.47 (s, 1H), 4.16 (s, 3H), 1.21 (s, 9H).

LCMS MH+ 423.9 RT 1.31 System 1

Synthesis of (R)-N-[(1S)-1-[5-(4-chlorophenyl)-1-methyl-1H-pyrazol-3-yl]ethyl]-2-methylpropane-2-sulfinamide: INTERMEDIATE 7



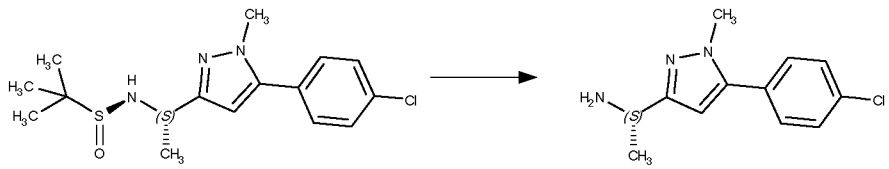
Methyl magnesium bromide [3M in hexanes] (6.42 ml) was added slowly to a cooled (0 °C) solution of (R)-N-[(1E)-[5-(4-chlorophenyl)-1-methyl-1H-pyrazol-3-yl]methylidene]-2-methylpropane-2-sulfinamide (2.19 g) in tetrahydrofuran (35

ml) and the reaction was stirred for 30 mins. The reaction was quenched via the slow addition of water (10 ml) then the reaction was further diluted with EtOAc (50.0 ml) and water (30.0 ml) and the organic layer separated, dried over Na2SO4, filtered and concentrated in vacuo to give a viscous oil. Purification via neutral reverse phase Biotage (Water/MeCN) followed by further purification via column chromatography [100% DCM to 20% MeOH in DCM] afforded 1.438g of a 7:3 mixture of the required product and (R)-N-[(1R)-1-[5-(4-chlorophenyl)-1-methyl-1H-pyrazol-3-yl]ethyl]-2-methylpropane-2-sulfinamide as a clear oil.

^{1}H NMR (500 MHz, DMSO-d6) 7.80 – 7.75 (m, 2H), 7.43 (dt, J = 9.2, 1.9 Hz, 2H), 6.73 (s, 0H), 6.68 (s, 1H), 5.67 (d, J = 5.7 Hz, 0H), 5.48 (d, J = 7.3 Hz, 1H), 4.57 (h, J = 6.9 Hz, 1H), 3.84 (s, 1H), 3.82 (s, 2H), 1.57 (d, J = 6.8 Hz, 2H), 1.53 (d, J = 6.8 Hz, 1H), 1.12 (s, 6H), 1.09 (s, 3H).

LCMS MH+ 339.9 RT 1.13 System 1

Synthesis of (1S)-1-[5-(4-chlorophenyl)-1-methylpyrazol-3-yl]ethanamine: INTERMEDIATE 8



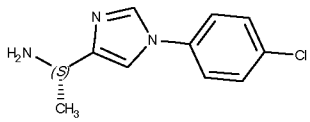
Hydrogen chloride [4M in 1,4-dioxane] (0.74 ml) was added to a solution of (R)-N-[(1S)-1-[5-(4-chlorophenyl)-1-methyl-1H-pyrazol-3-yl]ethyl]-2-methylpropane-2-sulfinamide (500 mg, 1.47 mmol) in 1,4-dioxane (5 ml) to give a white precipitate.

The reaction was agitated at ambient temperature for 60 mins to form a thick cake. The reaction was diluted with dioxane (20.0 ml) and triturated to give a mobile suspension which was filtered. The residual solid was washed with TBME and dried under vacuum to give 447mg of a mixture of (1S)-1-[5-(4-chlorophenyl)-1-methylpyrazol-3-yl]ethanamine hydrochloride and (1R)-1-[5-(4-chlorophenyl)-1-methylpyrazol-3-yl]ethanamine hydrochloride as a white powdery solid.

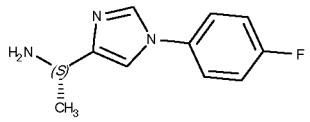
^{1}H NMR (500 MHz, DMSO-d6) 8.36 (s, 3H), 7.77 (d, J = 8.5 Hz, 2H), 7.48 (d, J = 8.5 Hz, 2H), 6.90 (s, 1H), 4.68 (s, 1H), 3.92 (s, 3H), 1.57 (d, J = 6.7 Hz, 3H)

LCMS MH+ 236.9 RT 0.81 System 1

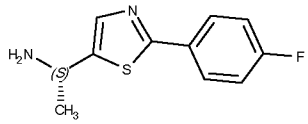
(1S)-1-[1-(4-chlorophenyl)-1H-imidazol-4-yl]ethan-1-amine was synthesized according to a literature method



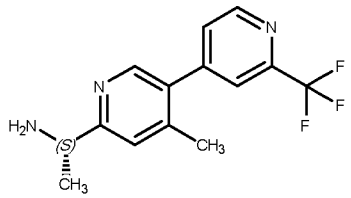
(1S)-1-[1-(4-fluorophenyl)-1H-imidazol-4-yl]ethan-1-amine was synthesized according to a literature method

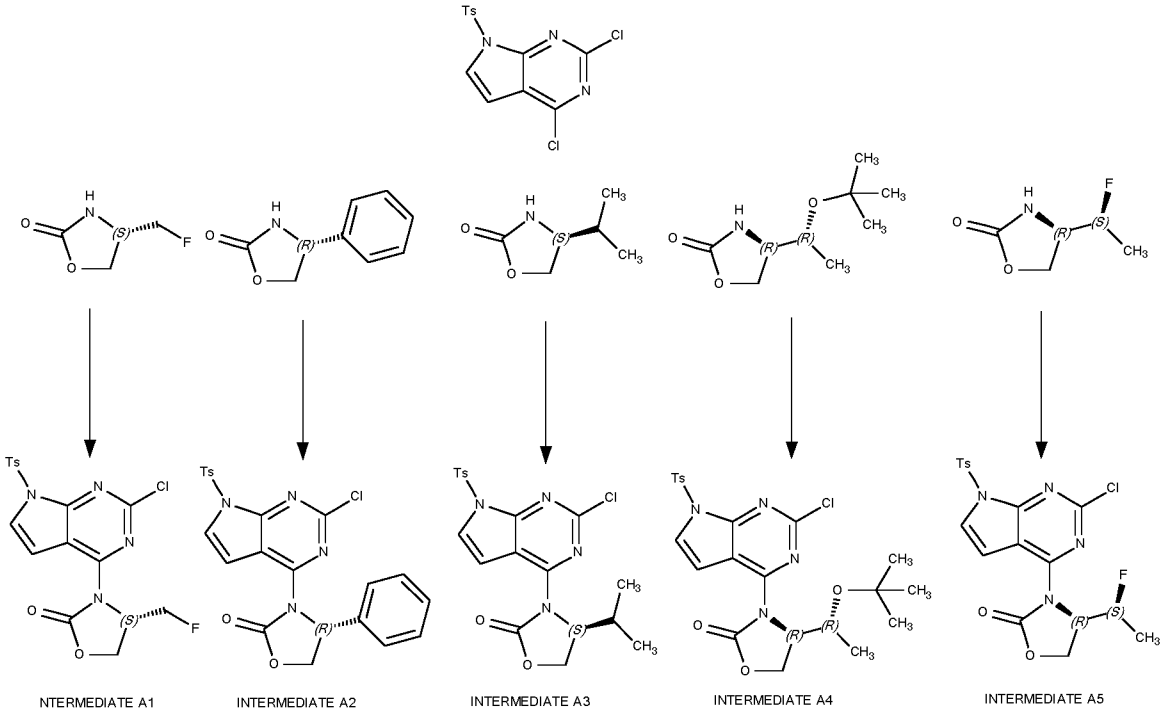


(1S)-1-[2-(4-fluorophenyl)-1,3-thiazol-5-yl]ethan-1-amine was synthesized according to a literature method



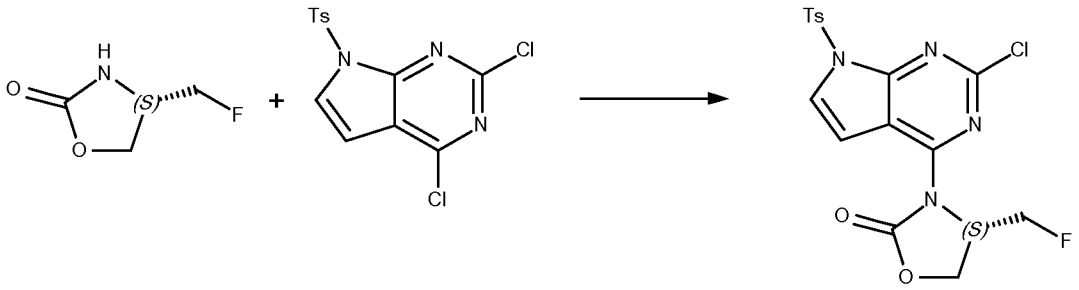
(1S)-1-{4-methyl-5-[2-(trifluoromethyl)pyridin-4-yl]pyridin-2-yl}ethan-1-amine was synthesized according to a literature method





Scheme 3: Synthesis of Intermediates A1-A5 (for reaction conditions details, see the experimental procedures below).

Synthesis of (4S)-3-[2-chloro-7-(4-methylbenzenesulfonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-(fluoromethyl)-1,3-oxazolidin-2-one; Intermediate A1

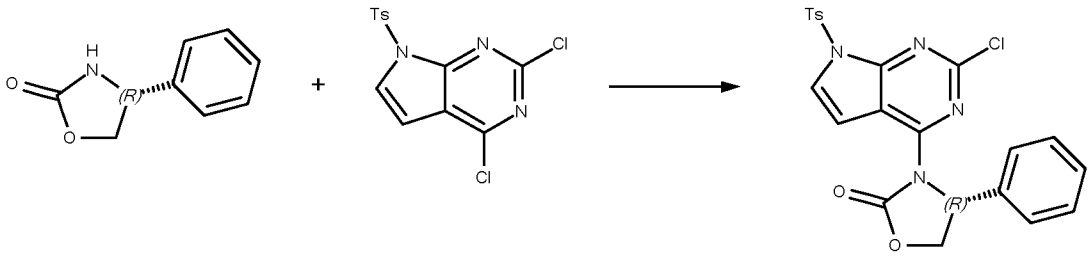


2,4-dichloro-7-(4-methylbenzenesulfonyl)-7H-pyrrolo[2,3-d]pyrimidine (3200 mg, 9.35 mmol), K3PO4 (3.97 g, 18.7 mmol), (4S)-4-(fluoromethyl)-1,3-oxazolidin-2-one (1.114g, 9.35 mmol) and Xantphos **Pd-G3** (221 mg, 0.23 mmol) were added to dry toluene (90 ml) that had been degassed by bubbling a stream of nitrogen through it for 5 minutes and the mixture was heated at 80 °C for 3.5 hr. The reaction mixture was taken up in EtOAc (200 ml), washed with water (2 x 200 ml) dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by flash column chromatography on a silica column (100 g) eluting with heptane-EtOAc 0-60% to give (4S)-3-[2-chloro-7-(4-methylbenzenesulfonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-(fluoromethyl)-1,3-oxazolidin-2-one (1.65 g, 39%) as a white solid.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.11 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 4.1 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 4.1 Hz, 1H), 5.15 – 5.04 (m, 1H), 4.85 (ddd, *J* = 47.9, 10.1, 3.9 Hz, 1H), 4.73 – 4.56 (m, 3H), 2.42 (s, 3H).

LCMS MH+ 424.9 RT 1.28 System 1

Synthesis of (4R)-3-[2-chloro-7-(4-methylbenzenesulfonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-phenyl-1,3-oxazolidin-2-one; Intermediate A2

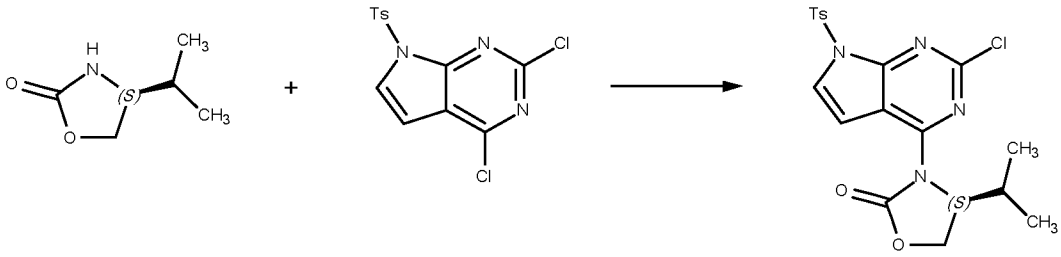


By proceeding in a similar manner to INTERMEDIATE A1 but using (4R)-4-phenyl-1,3-oxazolidin-2-one instead of (4S)-4-(fluoromethyl)-1,3-oxazolidin-2-one, (4R)-3-[2-chloro-7-(4-methylbenzenesulfonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-phenyl-1,3-oxazolidin-2-one was obtained as a white solid.

^{1}H NMR (250 MHz, Chloroform-d) δ 8.10 (d, J = 8.5 Hz, 2H), 7.64 (d, J = 4.0 Hz, 1H), 7.46 – 7.24 (m, 7H), 7.16 (d, J = 4.0 Hz, 1H), 5.97 (dd, J = 9.0, 6.5 Hz, 1H), 4.88 (t, J = 9.0 Hz, 1H), 4.46 (dd, J = 9.0, 6.5 Hz,1H), 2.42 (s, 3H).

LCMS MH+ 468.9 RT 1.56 System 1

Synthesis of (4S)-3-[2-chloro-7-(4-methylbenzenesulfonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-(propan-2-yl)-1,3-oxazolidin-2-one; Intermediate A3

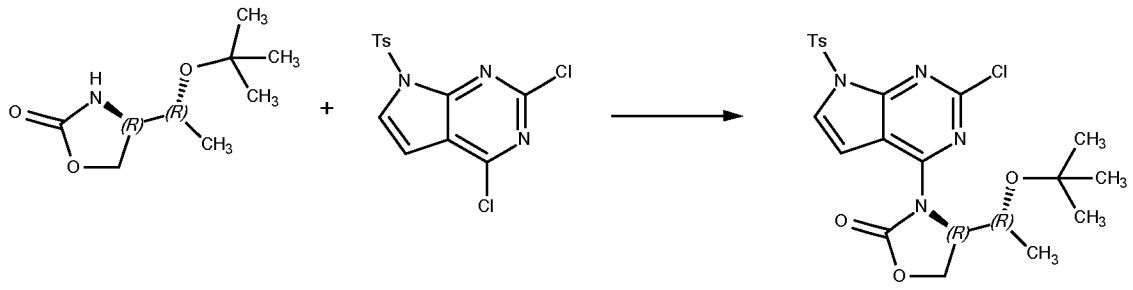


By proceeding in a similar manner but using (4S)-4-(propan-2-yl)-1,3-oxazolidin-2-one instead of (4S)-4-(fluoromethyl)-1,3-oxazolidin-2-one, (4S)-3-[2-chloro-7-(4-methylbenzenesulfonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-(propan-2-yl)-1,3-oxazolidin-2-one was obtained as an off white solid.

^{1}H NMR (500 MHz, DMSO-d6) 8.03 (d, J = 8.4 Hz, 2H), 7.89 (d, J = 4.1 Hz, 1H), 7.50 (d, J = 8.2 Hz, 2H), 7.08 (d, J = 4.1 Hz, 1H), 4.83 (dt, J = 8.5, 4.2 Hz, 1H), 4.52 (t, J = 8.8 Hz, 1H), 4.42 (dd, J = 9.0, 4.5 Hz,1H), 2.39 (s, 3H), 2.36 – 2.30 (m, 1H), 0.86 (d, J = 7.0 Hz, 3H), 0.74 (d, J = 6.9 Hz, 3H)

LCMS MH+ 434.8 RT 1.36 System 1

Synthesis of (4R)-4-[(1R)-1-(tert-butoxy)ethyl]-3-[2-chloro-7-(4-methylbenzenesulfonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-1,3-oxazolidin-2-one; Intermediate A4

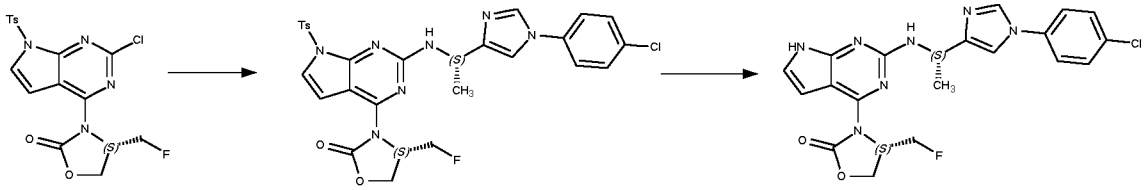


By proceeding in a similar manner but using (4R)-4-[(1R)-1-(tert-butoxy)ethyl]-1,3-oxazolidin-2-one instead of (4S)-4-(fluoromethyl)-1,3-oxazolidin-2-one, (4R)-4-[(1R)-1-(tert-butoxy)ethyl]-3-[2-chloro-7-(4-methylbenzenesulfonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-1,3-oxazolidin-2-one was obtained as a colourless gum.

^{1}H NMR (500 MHz, Chloroform-d) δ 8.12 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 4.0 Hz, 1H), 7.39 - 7.32 (m, 3H), 7.21 (d, J = 4.0 Hz, 1H), 4.83 (dt, J = 9.0, 4.0 Hz, 1H), 4.64 (dd, J = 9.0, 4.0 Hz, 1H), 4.50 - 4.41 (m, 2H),2.42 (s, 3H), 1.22 (s, 9H), 1.01 (d, J = 6.5 Hz, 3H).

LCMS MH+ 492.9 RT 1.82 System 1

EXAMPLE 1 Synthesis of (4S)-3-(2-{[(1S)-1-[1-(4-chlorophenyl)-1H-imidazol-4-yl]ethyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-(fluoromethyl)-1,3-oxazolidin-2-one (Compound 12)



A solution of (1S)-1-[1-(4-chlorophenyl)-1H-imidazol-4-yl]ethan-1-amine (2.58 g, 11.65 mmol), (4S)-3-[2-chloro-7-(4-methylbenzenesulfonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-(fluoromethyl)-1,3-oxazolidin-2-one (1.65 g, 3.88 mmol) and DIPEA (744 µl, 4.27 mmol) in DMSO (15 ml) was sealed in a nitrogen flushed pressure tube and heated at 110 °C for 16 hours. The reaction was allowed to cool then partitioned between water (60 ml) and EtOAc (60 ml). The phases were

separated and the aqueous phase extracted with more EtOAc (60 ml). The combined organic phases were washed with water (4 x 60 ml), dried over sodium sulfate and concentrated in vacuo to yield the crude (4S)-3-(2-{[(1S)-1-[1-(4-chlorophenyl)-1H-imidazol-4-yl]ethyl]amino}-7-(4-methylbenzenesulfonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-(fluoromethyl)-1,3-oxazolidin-2-one as an orange foam. 1M TBAF in THF (39 ml, 39 mmol) was added to a solution of the crude intermediate in THF (20 ml) under nitrogen and the mixture heated at 50 °C for 3 hr. The reaction mixture was taken up in EtOAc (100 ml) and washed with saturated NH_4Cl (2 x100 ml), water (100 ml) and then dried over sodium sulfate to give the crude product as a brown gum.

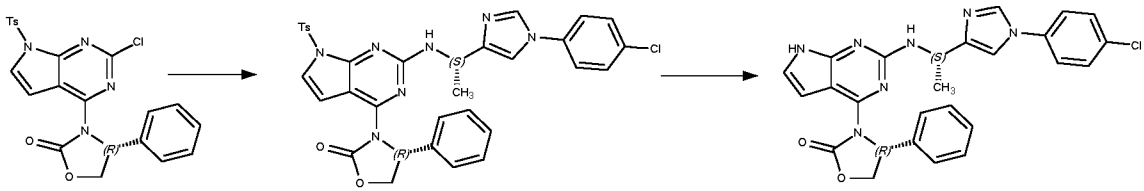
Purification by C18 RP chromatography on silica eluting with water, 0.1% ammonia-15% to 100% MeCN to followed by further purification by chromatography on silica eluting with heptane-30% to 100% EtOAc, and then DCM-1% to 5% MeOH afforded (4S)-3-(2-{[(1S)-1-[1-(4-chlorophenyl)-1H-imidazol-4-yl]ethyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-(fluoromethyl)-1,3-oxazolidin-2-one (602 mg, 31%) as a colourless solid. The sample was sonicated in hexane-ether 1:1 (2 x 5 ml), the supernatent removed by pipette and the sample dried in vacuo at 60 °C for 18hr. NMR shows 1% ether, 4% hexane w/w (402 mg, 95% w/w purity). The sample was dried further in vacuo at 60C for 18 hr to give (4S)-3-(2-{[(1S)-1-[1-(4-chlorophenyl)-1H-imidazol-4-yl]ethyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-(fluoromethyl)-1,3-oxazolidin-2-one (373 mg, 20%) as a colourless solid.

^1H NMR (500 MHz, Chloroform-*d*) δ 7.86 – 7.77 (m, 1H), 7.47 – 7.39 (m, 2H), 7.32 – 7.27 (m, 2H), 7.15 – 7.10 (m, 1H), 6.90

(d, *J* = 2.4 Hz, 1H), 6.80 - 6.75 (m, 1H), 5.34 - 4.38 (m, 7H), 1.62 (d, *J* = 6.9 Hz, 3H).

LCMS MH+ 455.0 RT 2.06 System 2

EXAMPLE 2: Synthesis of (4R)-3-(2-{[(1S)-1-[1-(4-chlorophenyl)-1H-imidazol-4-yl]ethyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-phenyl-1,3-oxazolidin-2-one (Compound 5)



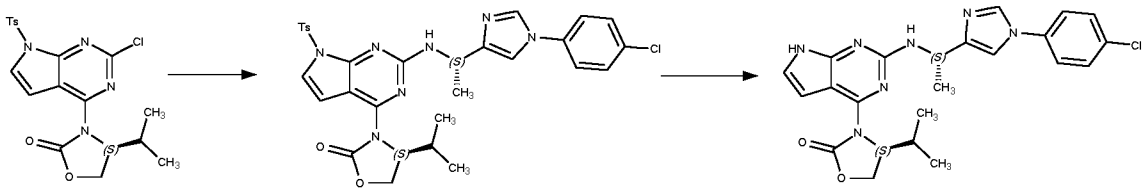
By proceeding in a similar manner to Example 1 but replacing (4S)-3-[2-chloro-7-(4-methylbenzenesulfonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-(fluoromethyl)-1,3-oxazolidin-2-one (Intermediate A1) by (4R)-3-[2-chloro-7-(4-methylbenzenesulfonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-phenyl-1,3-oxazolidin-2-one; (Intermediate A2), (4R)-3-(2-{[(1S)-1-[1-(4-chlorophenyl)-1H-imidazol-4-yl]ethyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-phenyl-1,3-oxazolidin-2-one was obtained as a beige solid.

^{1}H NMR (500 MHz, DMSO-d6) δ 11.16 (s, 1H), 8.18 (d, J = 1.4 Hz, 1H), 7.64 - 7.54 (m, 4H), 7.43 - 7.37 (m, 3H), 7.35 - 7.28 (m, 2H), 7.27 - 7.20 (m, 1H), 6.92 (dd, J = 3.6, 2.2 Hz, 1H), 6.55 (dd, J = 3.6, 2.0 Hz,1H), 6.33 (d, J = 8.7 Hz, 1H), 5.95 (dd, J = 8.7, 6.6 Hz, 1H), 4.98 (p, J = 6.6 Hz, 1H),

4.90 (t, J = 8.7 Hz, 1H), 4.22 (dd, J = 8.4, 6.7 Hz, 1H), 1.31 - 1.09 (m, 3H).

LCMS MH+ 499.2 RT 2.47 System 2

Example 3: Synthesis of (4S)-3-(2-{[(1S)-1-[1-(4-chlorophenyl)-1H-imidazol-4-yl]ethyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-(propan-2-yl)-1,3-oxazolidin-2-one (Compound 4)

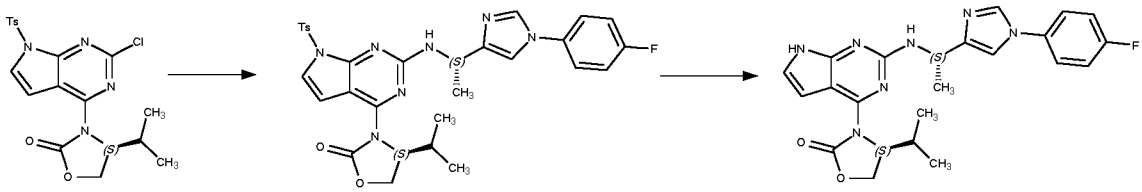


By proceeding in a similar manner to Example 1 but replacing (4S)-3-[2-chloro-7-(4-methylbenzenesulfonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-(fluoromethyl)-1,3-oxazolidin-2-one (Intermediate A1) by (4S)-3-[2-chloro-7-(4-methylbenzenesulfonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-(propan-2-yl)-1,3-oxazolidin-2-one (Intermediate A3), (4S)-3-(2-{[(1S)-1-[1-(4-chlorophenyl)-1H-imidazol-4-yl]ethyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-(propan-2-yl)-1,3-oxazolidin-2-one was obtained as an off white solid beige solid.

^{1}H NMR (500 MHz, Chloroform-d) 9.97 (br. s, 1H), 7.81 (s, 1H), 7.47 - 7.40 (m, 2H), 7.29 (d, J = 8.7 Hz, 2H), 7.14 (s, 1H), 6.89 (d, J = 2.5 Hz, 1H), 6.74 (d, J = 2.4 Hz, 1H), 6.37 (br. s, 1H), 5.31 (s, 1H), 4.94 (dt,J = 8.9, 4.8 Hz, 1H), 4.44 (t, J = 8.9 Hz, 1H), 4.31 (dd, J = 8.8, 5.3 Hz, 1H), 2.56 - 2.45 (m, 1H), 1.63 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 7.1 Hz, 3H), 0.87 (d, J = 6.9 Hz, 3H)

LCMS MH+ 466.2 RT 2.39 System 2

Example 4: Synthesis of (4S)-3-(2-{[(1S)-1-[1-(4-fluorophenyl)-1H-imidazol-4-yl]ethyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-(propan-2-yl)-1,3-oxazolidin-2-one (Compound 7)

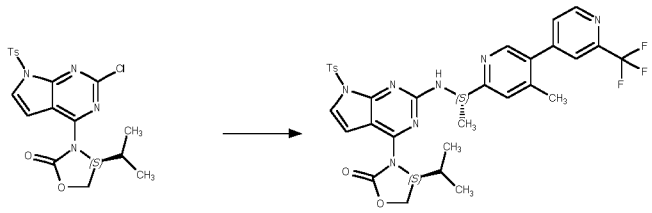


By proceeding in a similar manner to Example 3 but replacing (1S)-1-[1-(4-chlorophenyl)-1H-imidazol-4-yl]ethan-1-amine by (1S)-1-[1-(4-fluorophenyl)-1H-imidazol-4-yl]ethan-1-amine), (4S)-3-(2-{[(1S)-1-[1-(4-fluorophenyl)-1H-imidazol-4-yl]ethyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-(propan-2-yl)-1,3-oxazolidin-2-one was obtained as the formate salt.

^{1}H NMR (500 MHz, Methanol-d4) δ 8.07 – 8.01 (m, 1H), 7.54 – 7.45 (m, 2H), 7.30 (s, 1H), 7.26 – 7.17 (m, 2H), 6.91 (d, J = 3.7 Hz, 1H), 6.53 (d, J = 3.7 Hz, 1H), 5.20 (q, J = 6.9 Hz, 1H), 4.93 – 4.86 (m, 1H), 4.48(t, J = 9.0 Hz, 1H), 4.32 (dd, J = 8.9, 5.6 Hz, 1H), 2.16 – 2.05 (m, 1H), 1.60 (d, J = 6.9 Hz, 3H), 0.72 (dd, J = 19.3, 6.9 Hz, 6H)

LCMS MH+ 450.3 RT 2.09 System 2

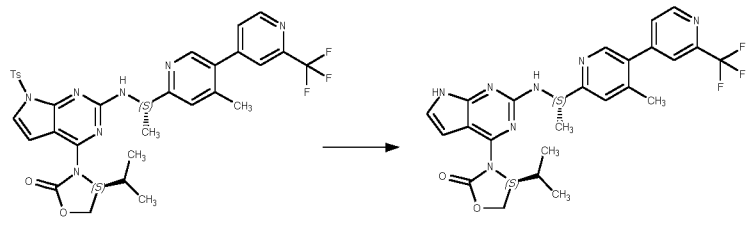
Synthesis of (4S)-3-(2-{[(1S)-1-{4-methyl-5-[2-(trifluoromethyl)pyridin-4-yl]pyridin-2-yl}ethyl]amino}-7-(4-methylbenzenesulfonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-(propan-2-yl)-1,3-oxazolidin-2-one



(4S)-3-[2-chloro-7-(4-methylbenzenesulfonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-(propan-2-yl)-1,3-oxazolidin-2-one (150 mg, 0.34 mmol) and (1S)-1-{4-methyl-5-[2-(trifluoromethyl)pyridin-4-yl]pyridin-2-yl}ethan-1-amine (242.54 mg, 0.86 mmol) were dissolved in DMSO (1.5 ml) and the sealed reaction heated to 105°C for 18 hours. The reaction was cooled then purified by column chromatography to give 480mg of the required product as a brown oil containing ~50% residual DMSO.

LCMS MH+ 680 RT 1.37mins System 1

Example 5: Synthesis of (4S)-3-(2-{[(1S)-1-{4-methyl-5-[2-(trifluoromethyl)pyridin-4-yl]pyridin-2-yl}ethyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-(propan-2-yl)-1,3-oxazolidin-2-one (Compound 2)



(4S)-3-(2-{[(1S)-1-{4-methyl-5-[2-(trifluoromethyl)pyridin-4-yl]pyridin-2-yl}ethyl]amino}-7-(4-methylbenzenesulfonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-(propan-2-yl)-1,3-oxazolidin-2-one (49%, 480 mg, 0.35 mmol) was dissolved in TBAF [1M in THF] (1.5 ml) then the sealed reaction was heated at 50 °C for 18 hours. Reaction partitioned between DCM (10.0 ml) and

water (5.0 ml) then the organic layer was separated, dried over Na_2SO_4, filtered and concentrated in vacuo.

The residue was purified via reverse phase Biotage to afford the required product.

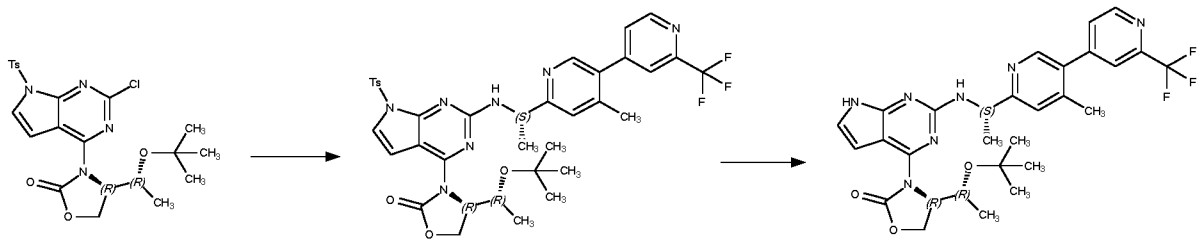
^{1}H NMR (500 MHz, DMSO-d6) 11.23 (s, 1H), 8.84 (d, J = 5.0 Hz, 1H), 8.42 (s, 1H), 7.93 (s, 1H), 7.77 (d, J = 5.0 Hz, 1H), 7.36 (s, 1H), 7.15 (d, J = 7.8 Hz, 1H), 6.92 (s, 1H), 6.39 (dd, J = 3.6, 1.9 Hz, 1H), 5.16 -5.07 (m, 1H), 4.71 (s, 1H), 4.46 (s, 1H), 4.27 (s, 1H), 2.24 (s, 3H), 1.50 (d, J = 7.1 Hz, 3H), 0.82 - 0.35 (m, 6H).

LCMS MH+ 526.2 RT 2.67 System 2

Synthesis of (4R)-4-[(1R)-1-(tert-butoxy)ethyl]-3-(2-{[(1S)-1-{4-methyl-5-[2-(trifluoromethyl)pyridin-4-yl]pyridin-2-yl}ethyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1,3-oxazolidin-2-one: Intermediate B1

By proceeding in a similar manner to Example 1 but replacing (4S)-3-[2-chloro-7-(4-methylbenzenesulfonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-(fluoromethyl)-1,3-oxazolidin-2-one by (4R)-4-[(1R)-1-(tert-butoxy)ethyl]-3-[2-chloro-7-(4-methylbenzenesulfonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-1,3-oxazolidin-2-one (Intermediate A4) and (1S)-1-[1-(4-chlorophenyl)-1H-imidazol-4-yl]ethan-1-amine by (1S)-1-{4-methyl-5-[2-(trifluoromethyl)pyridin-4-yl]pyridin-2-yl}ethan-1-amine , (4R)-4-[(1R)-1-(tert-butoxy)ethyl]-3-(2-{[(1S)-1-{4-methyl-5-[2-(trifluoromethyl)pyridin-4-yl]pyridin-2-

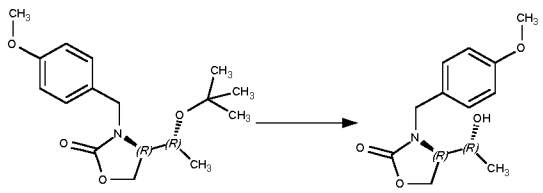
yl}ethyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1,3-oxazolidin-2-one is obtained as a pale amber gum.



^{1}H NMR (500 MHz, Chloroform-d) δ 8.82 (d, J = 5.0 Hz, 1H), 8.61 (s, 1H), 8.38 (s, 1H), 7.65 (s, 1H), 7.45 (dd, J = 5.0, 1.0 Hz, 1H), 6.87 (t, J = 3.5, 2.0 Hz, 1H), 6.78 (t, J = 3.5, 2.0 Hz, 1H), 5.84 (d, J = 7.0 Hz,1H), 5.35 – 5.25 (m, 1H), 4.91 (dt, J = 9.0, 4.5 Hz, 1H), 4.61 (dd, J = 9.0, 4.5 Hz, 1H), 4.45 (t, J = 9.0 Hz, 1H), 4.43 – 4.35 (m, 1H), 2.28 (s, 3H), 1.62 (d, J = 7.0 Hz, 3H), 1.23 (s, 9H), 1.06 (d, J = 6.5 Hz, 3H)

LCMS MH+ 584.4 RT 1.26 System 2

Synthesis of (4R)-4-[(1R)-1-hydroxyethyl]-3-[(4-methoxyphenyl)methyl]-1,3-oxazolidin-2-one (described in WO 2014/141104 A1)



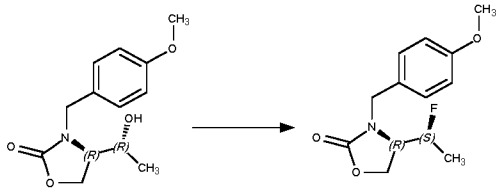
Trifluoroacetic acid (20 ml) was added to a solution of (4R)-4-[(1R)-1-(tert-butoxy)ethyl]-3-[(4-methoxyphenyl)methyl]-1,3-oxazolidin-2-one (2.75 g, 8.95 mmol) in DCM (20 ml). The reaction was stirred for 10 min. The reaction mixture was

concentrated in vacuo then partitioned between saturated aq. NaHCO3 (20 ml) and EtOAc (20 ml). The aqueous phase was extracted with more EtOAc (20 ml) then the organic phases were combined, dried over Na_2SO_4 and evaporated to yield the product as a colourless oil which crystallised on standing to a give a white solid (2.255 g)

^{1}H NMR (500 MHz, Chloroform-d) δ 7.26 - 7.22 (m, 2H), 6.90 - 6.85 (m, 2H), 4.70 (d, J = 15.0 Hz, 1H), 4.28 (d, J = 15.0 Hz, 1H), 4.21 (t, J = 9.0 Hz, 1H), 4.11 (dd, J = 9.0, 6.5 Hz, 1H), 3.96 (p, J = 6.5 Hz, 1H),3.80 (s, 3H), 3.61 (dt, J = 9.0, 6.5 Hz, 1H), 1.14 (d, J = 6.5 Hz, 3H).

LCMS MH+ 251.9 RT 0.90 System 1

Synthesis of (4R)-4-[(1S)-1-fluoroethyl]-3-[(4-methoxyphenyl)methyl]-1,3-oxazolidin-2-one (described in WO 2014/141104 A1)



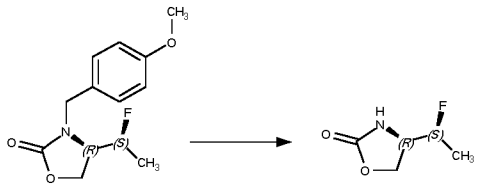
PBSF (4.71 ml, 26.3 mmol) was added drop-wise to a cooled (0 °C, ice bath) solution of (4R)-4-[(1R)-1-hydroxyethyl]-3-[(4-methoxyphenyl)methyl]-1,3-oxazolidin-2-one (2.18 g, 8.69 mmol) and triethylamine (11 ml, 79 mmol) in MeCN (50 ml). The reaction solution was stirred at 0 °C for 5 min then TREAT-HF (4.3 ml, 27 mmol) was added drop-wise. The resultant solution was left to stir at 0 °C. After 1.5 h at 0 °C, the reaction mixture was partitioned between EtOAc (100 ml) and water (100 ml). The phases were separated and the organic phase washed

with brine (100 ml), dried over Na_2SO_4 and evaporated. The crude material was pre-adsorbed onto silica then purified by flash column chromatography on a silica column (50 g). The column was eluted with EtOAc:heptane, increasing the gradient linearly from 10:90 to 50:50 over 10 column volumes then isocratic at 50:50 for 2 CVs to afford the required product as colourless oil which solidified on standing to an off-white solid.

^{1}H NMR (500 MHz, Chloroform-d) δ 7.26 - 7.19 (m, 2H), 6.90 - 6.85 (m, 2H), 4.87 (d, J = 15.0 Hz, 1H), 4.75 (dqd, J = 47.5, 6.5, 2.0 Hz, 1H), 4.25 (td, J = 9.5, 1.0 Hz, 1H), 4.13 (dd, J = 9.5, 6.0 Hz, 1H), 4.10 (d, J= 15.0 Hz, 1H), 3.80 (s, 3H), 3.71 (dddd, J = 20.0, 9.5, 6.0, 2.0 Hz, 1H), 1.29 (dd, J = 23.5, 6.5 Hz, 3H)

LCMS MH+ 253.9 RT 1.03 System 1

Synthesis of (4R)-4-[(1S)-1-fluoroethyl]-1,3-oxazolidin-2-one (described in WO 2014/141104 A1)



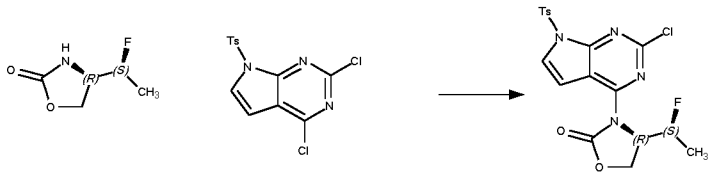
A solution of (4R)-4-[(1S)-1-fluoroethyl]-3-[(4-methoxyphenyl)methyl]-1,3-oxazolidin-2-one (1.77 g, 6.99 mmol) in TFA (35 ml) was heated at 65 °C for 4 hours. The reaction mixture was concentrated in vacuo then azeotroped with EtOAc to yield a green mixture. The crude material was purified by flash column chromatography on a silica column

(50 g), eluting with EtOAc:DCM, increasing the gradient linearly from 0:100 to 100:0. to yield the required product as a pale-green solid.

^{1}H NMR (500 MHz, Chloroform-d) δ 6.46 (s, 1H), 4.60 (dp, J = 47.3, 6.2 Hz, 1H), 4.50 (t, J = 8.9 Hz, 1H), 4.34 (dd, J = 9.1, 4.9 Hz, 1H), 3.97 - 3.87 (m, 1H), 1.37 (dd, J = 24.1, 6.3 Hz, 3H)

LCMS MH+ 133.9 RT 0.25 System 1

Synthesis of (4R)-3-[2-chloro-7-(4-methylbenzenesulfonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-[(1S)-1-fluoroethyl]-1,3-oxazolidin-2-one: Intermediate A5

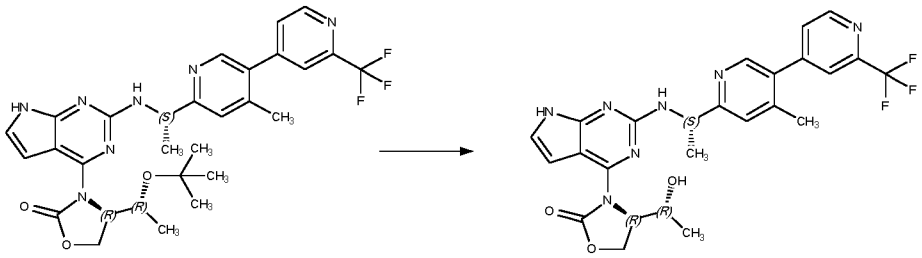


By proceeding in a similar manner to INTERMEDIATE A1 but using (4R)-4-[(1S)-1-fluoroethyl]-1,3-oxazolidin-2-one instead of (4S)-4-(fluoromethyl)-1,3-oxazolidin-2-one, (4R)-3-[2-chloro-7-(4-methylbenzenesulfonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-[(1S)-1-fluoroethyl]-1,3-oxazolidin-2-one was obtained as a pale yellow foam.

1H NMR (500 MHz, Chloroform-d) δ 8.11 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 4.1 Hz, 1H), 7.34 (d, J = 8.3 Hz, 2H), 7.17 (d, J = 4.1 Hz, 1H), 5.28 - 5.10 (m, 1H), 4.95 (dddd, J = 25.1, 9.1, 5.3, 1.5 Hz, 1H), 4.62 (dd, J= 8.8, 5.3 Hz, 1H), 4.55 (td, J = 9.0, 1.1 Hz, 1H), 2.42 (s, 3H), 1.38 (dd, J = 23.2, 6.6 Hz, 3H).

LCMS MH+ 438.9 RT 1.30 System 1

Example 6: Synthesis of (4R)-4-[(1R)-1-hydroxyethyl]-3-(2-{[(1S)-1-{4-methyl-5-[2-(trifluoromethyl)pyridin-4-yl]pyridin-2-yl}ethyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1,3-oxazolidin-2-one (Compound 9)



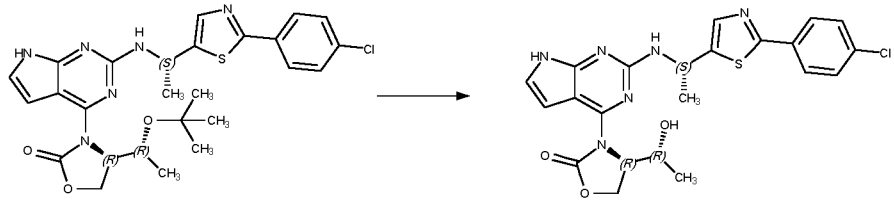
Trifluoroacetic acid (0.5 ml) was added to a solution of (4R)-4-[(1R)-1-(tert-butoxy)ethyl]-3-(2-{[(1S)-1-{4-methyl-5-[2-(trifluoromethyl)pyridin-4-yl]pyridin-2-yl}ethyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1,3-oxazolidin-2-one (94%, 46 mg, 0.074 mmol) in DCM (0.5 ml). The reaction solution was left to stir at RT for 1 h. The mixture was concentrated in vacuo, partitioned between DCM (2 ml) and saturated $NaHCO_3$ (2 ml). The organic phase was collected using a hydrophobic frit then evaporated. The crude material was purified by basic HPLC to afford (4R)-4-[(1R)-1-hydroxyethyl]-3-(2-{[(1S)-1-{4-methyl-5-[2-(trifluoromethyl)pyridin-4-yl]pyridin-2-yl}ethyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1,3-oxazolidin-2-one as an off white solid.

^1H NMR (500 MHz, DMSO-d6) δ 11.23 (s, 1H), 8.84 (d, J = 5.0 Hz, 1H), 8.42 (s, 1H), 7.97 (s, 1H), 7.79 (d, J = 4.9 Hz, 1H), 7.40 (s, 1H), 7.07 (d, J = 7.9 Hz, 1H), 6.91 (t, J = 3.5, 2.3 Hz, 1H), 6.42 (dd, J = 3.5, 2.0Hz, 1H), 5.13 (q, J =

7.3 Hz, 1H), 5.04 - 4.91 (m, 1H), 4.91 - 4.76 (m, 1H), 4.51 - 4.44 (m, 2H), 4.21 - 3.86 (m, 1H), 2.25 (s, 3H), 1.51 (d, J = 7.0 Hz, 3H), 0.91 - 0.61 (m, 3H)

LCMS MH+ 528.2 RT 2.24 System 2

Example 7: Synthesis of (4R)-3-(2-{[(1S)-1-[2-(4-chlorophenyl)-1,3-thiazol-5-yl]ethyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-[(1R)-1-hydroxyethyl]-1,3-oxazolidin-2-one (Compound 3)

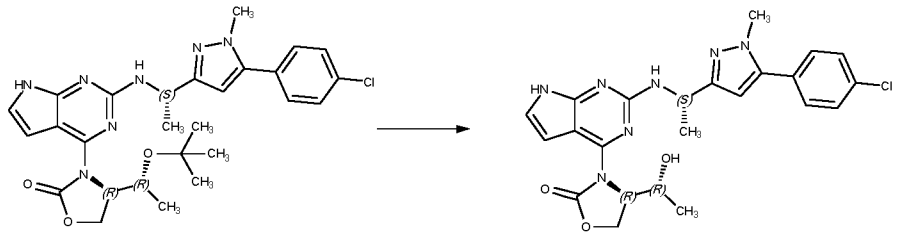


By proceeding in a similar manner but replacing (4R)-4-[(1R)-1-(tert-butoxy)ethyl]-3-(2-{[(1S)-1-{4-methyl-5-[2-(trifluoromethyl)pyridin-4-yl]pyridin-2-yl}ethyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1,3-oxazolidin-2-one with (4R)-4-[(1R)-1-(tert-butoxy)ethyl]-3-(2-{[(1S)-1-[2-(4-chlorophenyl)-1,3-thiazol-5-yl]ethyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1,3-oxazolidin-2-one, (4R)-3-(2-{[(1S)-1-[2-(4-chlorophenyl)-1,3-thiazol-5-yl]ethyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-[(1R)-1-hydroxyethyl]-1,3-oxazolidin-2-one was obtained as a white solid.

^{1}H NMR (500 MHz, DMSO-d6) δ 11.27 (s, 1H), 7.89 - 7.83 (m, 2H), 7.77 (s, 1H), 7.53 - 7.48 (m, 2H), 7.29 (d, J = 8.4 Hz, 1H), 6.94 (dd, J = 3.5, 2.3 Hz, 1H), 6.47 (dd, J = 3.6, 2.0 Hz, 1H), 5.45 (p, J = 7.2 Hz, 1H),5.05 (d, J = 4.5 Hz, 1H), 4.90 - 4.83 (m, 1H), 4.48 (m, 2H), 4.29 - 4.18 (m, 1H), 1.63 (d, J = 6.9 Hz, 3H), 0.87 (d, J = 6.0 Hz, 3H)

LCMS MH+ 485.1 RT 3.03 System 2

Example 8: Synthesis of (4R)-3-(2-{[(1S)-1-[5-(4-chlorophenyl)-1-methyl-1H-pyrazol-3-yl]ethyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-[(1R)-1-hydroxyethyl]-1,3-oxazolidin-2-one (Compound 8)



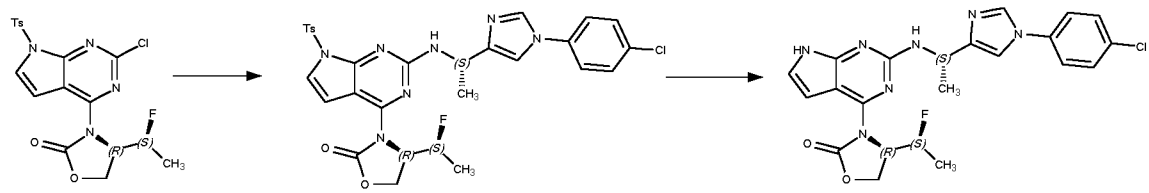
By proceeding in a similar manner to Example 7 but replacing (4R)-4-[(1R)-1-(tert-butoxy)ethyl]-3-(2-{[(1S)-1-[2-(4-chlorophenyl)-1,3-thiazol-5-yl]ethyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1,3-oxazolidin-2-one with a 7:3 mixture of (4R)-4-[(1R)-1-(tert-butoxy)ethyl]-3-(2-{[(1S)-1-[5-(4-chlorophenyl)-1-methyl-1H-pyrazol-3-yl]ethyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1,3-oxazolidin-2-one and (4R)-4-[(1R)-1-(tert-butoxy)ethyl]-3-(2-{[(1R)-1-[5-(4-chlorophenyl)-1-methyl-1H-pyrazol-3-yl]ethyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1,3-oxazolidin-2-one, a 7:3 mixture of (4R)-3-(2-{[(1S)-1-[5-(4-chlorophenyl)-1-methyl-1H-pyrazol-3-yl]ethyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-[(1R)-1-hydroxyethyl]-1,3-oxazolidin-2-one and (4R)-3-(2-{[(1R)-1-[5-(4-chlorophenyl)-1-methyl-1H-pyrazol-3-yl]ethyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-[(1R)-1-hydroxyethyl]-1,3-oxazolidin-2-one was obtained.

^{1}H NMR (500 MHz, DMSO-d6) 11.25 (s, 1H), 7.78 – 7.68 (m, 2H), 7.45 – 7.36 (m, 2H), 7.04 (d, J = 8.4 Hz, 1H), 6.96 – 6.90 (m, 1H), 6.65 (s, 1H), 6.51 – 6.44 (m, 1H), 5.34 – 5.20 (m,1H), 5.04 (d, J = 4.6 Hz, 1H), 4.92 – 4.82 (m, 1H), 4.52 –

4.43 (m, 2H), 4.19 (br. s, 1H), 3.86 (s, 3H), 1.53 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 5.3 Hz, 3H).

LCMS MH+ 482.2 RT 2.89 System 2

Example 9: Synthesis of (4R)-3-(2-{[(1S)-1-[1-(4-chlorophenyl)-1H-imidazol-4-yl]ethyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-[(1S)-1-fluoroethyl]-1,3-oxazolidin-2-one (Compound 1)

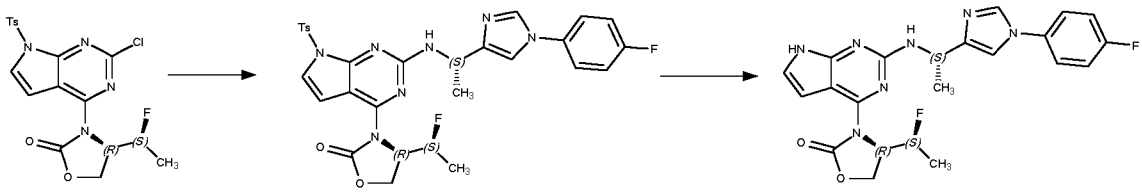


By proceeding in a similar manner to Example 1 but replacing (4S)-3-[2-chloro-7-(4-methylbenzenesulfonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-(fluoromethyl)-1,3-oxazolidin-2-one (Intermediate A1) by ((4R)-3-[2-chloro-7-(4-methylbenzenesulfonyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]-4-[(1S)-1-fluoroethyl]-1,3-oxazolidin-2-one; ((4R)-3-(2-{[(1S)-1-[1-(4-chlorophenyl)-1H-imidazol-4-yl]ethyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-[(1S)-1-fluoroethyl]-1,3-oxazolidin-2-one was obtained.

^{1}H NMR (500 MHz, DMSO-d6) δ 11.21 (s, 1H), 8.19 (d, J = 1.3 Hz, 1H), 7.66 – 7.60 (m, 2H), 7.56 – 7.50 (m, 2H), 7.45 (s, 1H), 6.90 (d, J = 3.6 Hz, 1H), 6.69 (d, J = 8.0 Hz, 1H), 6.55 (d, J = 3.6 Hz, 1H), 5.28 – 5.01(m, 2H), 4.87 (ddd, J = 27.9, 8.9, 4.3 Hz, 1H), 4.54 (t, J = 8.9 Hz, 1H), 4.46 (dd, J = 8.8, 4.4 Hz, 1H), 1.49 (d, J = 6.9 Hz, 3H), 1.25 – 1.03 (m, 3H)

LCMS MH+ 470.1 RT 2.20 System 2

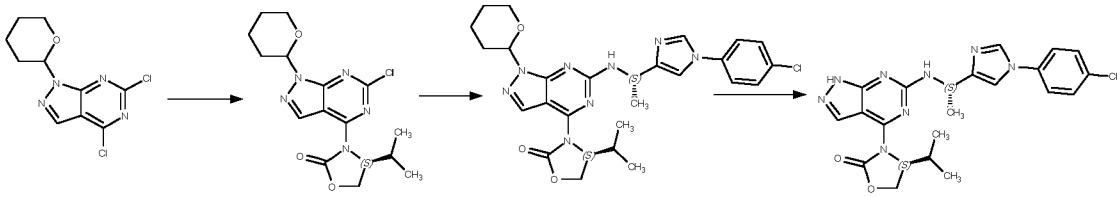
Example 10: Synthesis of (4R)-3-(2-{[(1S)-1-[1-(4-fluorophenyl)-1H-imidazol-4-yl]ethyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-[(1S)-1-fluoroethyl]-1,3-oxazolidin-2-one (Compound 10)



By proceeding in a similar manner to Example 9 but replacing (1S)-1-[1-(4-chlorophenyl)-1H-imidazol-4-yl]ethan-1-amine by (1S)-1-[1-(4-fluorophenyl)-1H-imidazol-4-yl]ethan-1-amine), (4R)-3-(2-{[(1S)-1-[1-(4-fluorophenyl)-1H-imidazol-4-yl]ethyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-4-[(1S)-1-fluoroethyl]-1,3-oxazolidin-2-one was obtained.

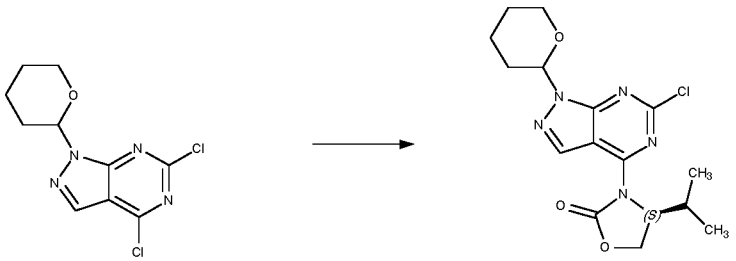
^{1}H NMR (500 MHz, DMSO-d6) δ 11.22 (s, 1H), 8.12 (d, J = 1.3 Hz, 1H), 7.66 – 7.59 (m, 2H), 7.41 (s, 1H), 7.36 – 7.29 (m, 2H), 6.91 (d, J = 2.0 Hz, 1H), 6.69 (d, J = 8.0 Hz, 1H), 6.55 (d, J = 2.6 Hz, 1H), 5.32 – 5.02(m, 2H), 4.88 (ddd, J = 28.0, 9.1, 4.3 Hz, 1H), 4.55 (t, J = 8.9 Hz, 1H), 4.47 (dd, J = 8.8, 4.4 Hz, 1H), 1.50 (d, J = 6.9 Hz, 3H), 1.25 – 1.09 (m, 3H).

LCMS MH+ 454.1 RT 1.94 System 2



Scheme 4: Synthesis of Compound 6 (for reaction conditions details, see the experimental procedures below).

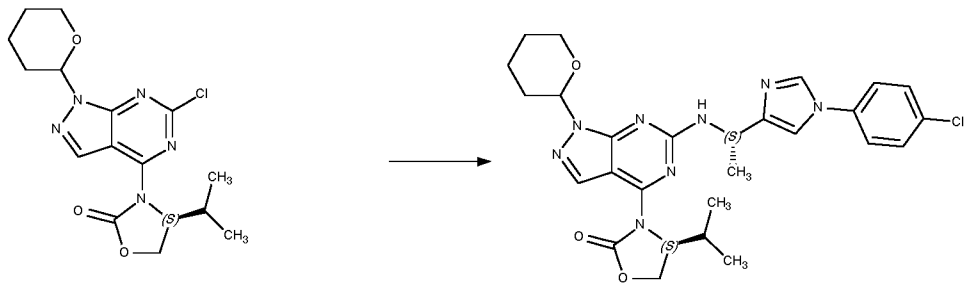
Synthesis of (4S)-3-[6-chloro-1-(oxan-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-4-(propan-2-yl)-1,3-oxazolidin-2-one



4,6-dichloro-1-(oxan-2-yl)-1H-pyrazolo[3,4-d]pyrimidine (500 mg, 1.83 mmol), (4S)-4-(propan-2-yl)-1,3-oxazolidin-2-one (260.09 mg, 2.01 mmol), Pd2(dba)3 (50.29 mg, 0.05 mmol), Xantphos (31.78 mg, 0.05 mmol), K3PO4 (777.19 mg, 3.66 mmol) were weighed out in an Ace pressure tube. Toluene (5 ml) was added and the mixture was "degassed" by bubbling a stream of nitrogen through it for 10 minutes. The mixture was then heated at 80 °C for 16 h. The reaction mixture was cooled to room temperature, then partitioned between DCM (10 ml) and water (10 ml). The aqueous phase was further extracted with DCM (10 x 2ml) and the combined organic layers dried (Na_2SO_4) and concentrated. The crude material was purified by Biotage Isolera flash column chromatography (SiO_2; 25 g) eluting with 10-50% EtOAc in heptane gradient to give 320 mg of required product as a mixture of diastereoisomers.

LCMS MH+ 281.9 RT 1.26 System 1

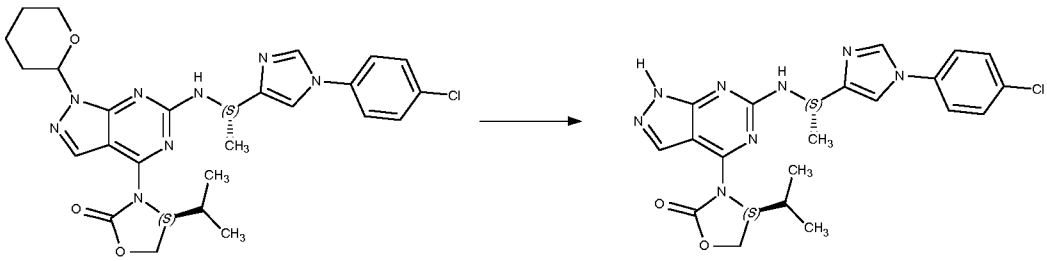
Synthesis of (4S)-3-(6-{[(1S)-1-[1-(4-chlorophenyl)-1H-imidazol-4-yl]ethyl]amino}-1-(oxan-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-4-(propan-2-yl)-1,3-oxazolidin-2-one



To a solution of (4S)-3-[6-chloro-1-(oxan-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-4-(propan-2-yl)-1,3-oxazolidin-2-one (160 mg, 0.44 mmol) in DMSO (1.5 ml) was added DIPEA (84.03 µl, 0.48 mmol) and (1S)-1-[1-(4-chlorophenyl)-1H-imidazol-4-yl]ethan-1-amine (193.92 mg, 0.87 mmol). The mixture was heated at 110 °C for 16 h. Water (5 ml) was added and the mixture extracted with DCM (3 x 5 ml), the combined organic layer was dried (Na_2SO_4) and concentrated in vacuo. The crude material was purified by Biotage Isolera FCC (SiO_2;10 g) eluting with 25-100% EtOAc in Heptane gradient to give 80 mg of required product as a mixture of diastereoisomers.

LCMS MH+ 551.7 RT 1.16 System 1

Example 11: Synthesis of (4S)-3-(6-{[(1S)-1-[1-(4-chlorophenyl)-1H-imidazol-4-yl]ethyl]amino}-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-4-(propan-2-yl)-1,3-oxazolidin-2-one (Compound 6)

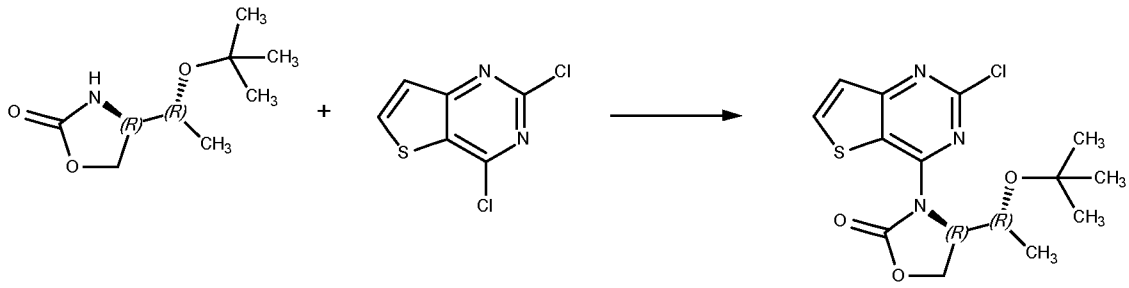


TFA (0.3 ml) was added to a solution of (4S)-3-(6-{[(1S)-1-[1-(4-chlorophenyl)-1H-imidazol-4-yl]ethyl]amino}-1-(oxan-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-4-(propan-2-yl)-1,3-oxazolidin-2-one (99%, 80 mg, 0.14 mmol) in DCM (0.5 ml) and the reaction stirred at 40 °C for 3 h. The reaction mixture was concentrated in vacuo then partitioned between saturated NaHCO3 (5 ml) and DCM (5 ml). The organic phase was collected using a hydrophobic frit then evaporated to give the crude product which was purified by high pH preparative HPLC to give 46 mg of (4S)-3-(6-{[(1S)-1-[1-(4-chlorophenyl)-1H-imidazol-4-yl]ethyl]amino}-1H-pyrazolo[3,4-d]pyrimidin-4-yl)-4-(propan-2-yl)-1,3-oxazolidin-2-one.

^{1}H NMR (500 MHz, DMSO-d6) δ 12.93 (s, 1H), 8.16 (d, J = 27.4 Hz, 2H), 7.78 - 7.33 (m, 5H), 7.27 (d, J = 7.9 Hz, 1H), 5.11 (s, 1H), 4.79 (s, 1H), 4.47 (t, J = 8.7 Hz, 1H), 4.38 (s, 1H), 2.53 - 2.51 (m, 1H), 1.52 (d, J = 6.9 Hz, 3H), 1.10 - 0.22 (m, 6H).

LCMS MH+ 467.1 RT 2.30 System 2

Synthesis of (4R)-4-[(1R)-1-(tert-butoxy)ethyl]-3-{2-chlorothieno[3,2-d]pyrimidin-4-yl}-1,3-oxazolidin-2-one; (Intermediate A6)

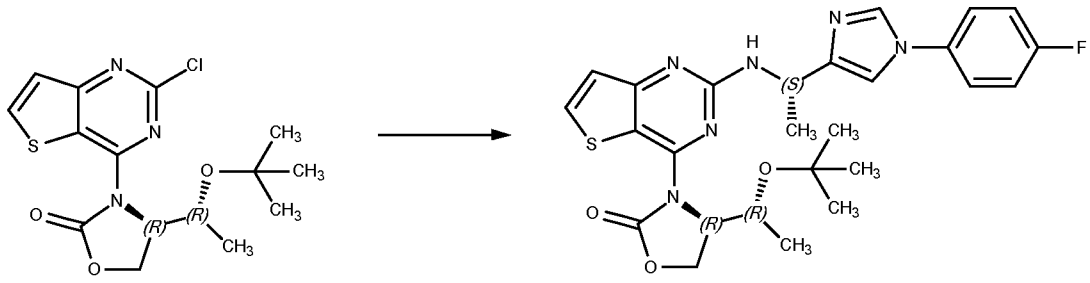


2,4-dichlorothieno[3,2-d]pyrimidine (5 g, 24.38 mmol), (4R)-4-[(1R)-1-(tert-butoxy)ethyl]-1,3-oxazolidin-2-one (5.48 g, 29.26 mmol) and Caesium carbonate (9.53 g, 29.26 mmol) were added to a nitrogen flushed round bottomed flask. Acetonitrile (100 ml) was added and the reaction was heated to 60°C overnight. The reaction mixture was diluted with EtOAc (150ml) and filtered. The solvent was then removed in vacuo to give the crude product as an orange/yellow solid which was purified by column chromatography (Biotage SNAP 50g cartridge) eluting with 0-25% EtOAc in heptane to afford 2.65 g of (4R)-4-[(1R)-1-(tert-butoxy)ethyl]-3-{2-chlorothieno[3,2-d]pyrimidin-4-yl}-1,3-oxazolidin-2-one.

^{1}H NMR (500 MHz, Chloroform-d) δ 8.04 (d, J = 5.6 Hz, 1H), 7.45 (d, J = 5.6 Hz, 1H), 4.93 (dt, J = 8.4, 4.0 Hz, 1H), 4.72 (dd, J = 9.4, 3.7 Hz, 1H), 4.59 - 4.54 (m, 1H), 4.54 - 4.49 (m, 1H), 1.26 (s, 9H), 1.07 (d, J= 6.5 Hz, 3H).

LCMS MH+ 355.8 RT 1.30 System 1

Synthesis of (4R)-4-[(1R)-1-(tert-butoxy)ethyl]-3-(2-{[(1S)-1-[1-(4-fluorophenyl)-1H-imidazol-4-yl]ethyl]amino}thieno[3,2-d]pyrimidin-4-yl)-1,3-oxazolidin-2-one

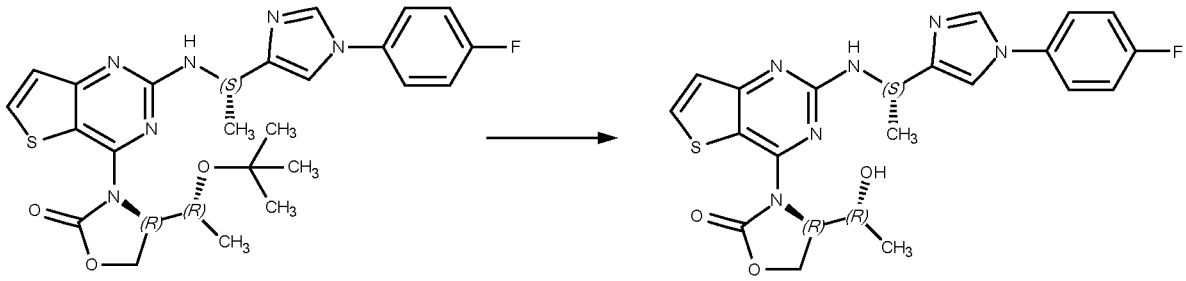


(4R)-4-[(1R)-1-(tert-butoxy)ethyl]-3-{2-chlorothieno[3,2-d]pyrimidin-4-yl}-1,3-oxazolidin-2-one (150 mg, 0.42 mmol) was suspended in DMSO (2 mL), to this DIPEA (441.74 µl, 2.53 mmol) and (1S)-1-[1-(4-fluorophenyl)-1H-imidazol-4-yl]ethan-1-amine hydrochloride (305.65 mg, 1.26 mmol) were added and the reaction mixture heated to 110°C for 24 hours. The reaction mixture was cooled to room temperature and retreated with (1S)-1-[1-(4-fluorophenyl)-1H-imidazol-4-yl]ethan-1-amine hydrochloride (152.82 mg, 0.63 mmol) and DIPEA (220.87 µl, 1.26 mmol). The reaction mixture was heated to 110°C overnight. After cooling, the reaction mixture was diluted with EtOAc (5 ml) and water (5 ml) and the phases separated. The aqueous layer was adjusted to pH 9 and extracted with EtOAc (2 x 5 ml). The combined organic layers were then washed with brine (5 ml) and dried over Na2SO4. The solvent was removed under reduced pressure. The crude material was purified by Reverse Phase column chromatography (Biotage C18 12g cartridge). Elution with 0-100% MeCN (0.1% Ammonium Hydroxide) in water (0.1% Ammonium Hydroxide) afforded 172.3 mg of (4R)-4-[(1R)-1-(tert-butoxy)ethyl]-3-(2-{[(1S)-1-[1-(4-fluorophenyl)-1H-imidazol-4-

yl]ethyl]amino}thieno[3,2-d]pyrimidin-4-yl)-1,3-oxazolidin-2-one.

LCMS MH+ 263.3 RT 1.03 System 1

Example 12: synthesis of (4R)-3-(2-{[(1S)-1-[1-(4-fluorophenyl)-1H-imidazol-4-yl]ethyl]amino}thieno[3,2-d]pyrimidin-4-yl)-4-[(1R)-1-hydroxyethyl]-1,3-oxazolidin-2-one (Compound 24)



By proceeding in a similar manner to Example 7 but replacing (4R)-4-[(1R)-1-(tert-butoxy)ethyl]-3-(2-{[(1S)-1-[2-(4-chlorophenyl)-1,3-thiazol-5-yl]ethyl]amino}-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1,3-oxazolidin-2-one with (4R)-4-[(1R)-1-(tert-butoxy)ethyl]-3-(2-{[(1S)-1-[1-(4-fluorophenyl)-1H-imidazol-4-yl]ethyl]amino}thieno[3,2-d]pyrimidin-4-yl)-1,3-oxazolidin-2-one, synthesis of (4R)-3-(2-{[(1S)-1-[1-(4-fluorophenyl)-1H-imidazol-4-yl]ethyl]amino}thieno[3,2-d]pyrimidin-4-yl)-4-[(1R)-1-hydroxyethyl]-1,3-oxazolidin-2-one was obtained.

^{1}H NMR (500 MHz, DMSO-d6) δ 8.15 – 8.10 (m, 2H), 7.68 – 7.61 (m, 2H), 7.50 (s, 1H), 7.38 – 7.30 (m, 2H), 7.13 (d, J = 5.2 Hz, 1H), 7.05 (s, 1H), 5.22 – 5.14 (m, 1H), 5.14 – 5.07 (m, 1H), 4.94 (dt, J = 8.4, 4.1 Hz,1H), 4.57 – 4.47 (m, 2H), 4.21 (s, 1H), 1.52 (d, J = 6.9 Hz, 3H), 0.86 (s, 3H).

LCMS MH+ 469.2 RT 1.77 System 2

Mutant IDH Proteins and Assays

Human IDH1 R132H

Cloning

The IDH1 R132H mutant residues M1-L414 was directionally cloned via restriction sites NdeI and BamHI into pET9a vector to yield the full length protein carrying a non-cleavable C-terminal His_8-tag.
The protein was expressed from *Escherichia coli* Rosetta 2 (DE3) cells transformed with the plasmid in the presence of 50 µg/ml kanamycin and after induction by 1 mM IPTG.

Protein Sequence Recombinant HsIDH1 R132H carrying a non-cleavable C-terminal His_8-tag

MSKKISGGSVVEMQGDEMTRIIWELIKEKLIFPYVELDLHSYDLGIENRDATNDQVTKDAA
EAIKKHNVGVKCATITPDEKRVEEFKLKQMWKSPNGTIRNILGGTVFREAIICKNIPRLVS
GWVKPIIIGHHAYGDQYRATDFVVPGPGKVEITYTPSDGTQKVTYLVHNFEEGGGVAMGMY
NQDKSIEDFAHSSFQMALSKGWPLYLSTKNTILKKYDGRFKDIFQEIYDKQYKSQFEAQKI
WYEHRLIDDMVAQAMKSEGGFIWACKNYDGDVQSDSVAQGYGSLGMMTSVLVCPDGKTVEA
EAAHGTVTRHYRMYQKGQETSTNPIASIFAWTRGLAHRAKLDNNKELAFFANALEEVSIET
IEAGFMTKDLAACIKGLPNVQRSDYLNTFEFMDKLGENLKIKLAQAKLSLEHHHHHHHH

Purification

On average 5 g of wet pellet weight were resuspended in 50 ml of lysis buffer (20 mM Tris/HCl pH 7.5, 500 mM NaCl, 5 mM β mercaptoethanol , 0.1% Triton X-100, 10% glycerol, 1 mM PMSF). Cells were lysed by sonication (40% amplitude, 2 min 30 sec, 30 sec on/off clycle). The lysate was cleared from debris by centrifugation (45 min at 25000g).
The IDH protein was isolated by affinity chromatography, desalting and size exclusion chromatography.

Protein was loaded onto a 5 ml HisTrap Crude FF column. The column was washed with 100 ml of wash buffer (20 mM Tris/HCl pH 7.4, 500 mM NaCl, 5 mM β mercaptoethanol, 10% glycerol). The protein was eluted in a linear gradient from wash buffer to elution buffer (20 mM Tris/HCl pH 7.4, 500 mM NaCl, 5 mM β mercaptoethanol, 10% glycerol, 500 mM imidazol pH 8.0) over 20 column volumes.
Positive elution fractions were buffer exchanged using a PD-10 column to 50 mM Tris/HCl pH 7.5, 200 mM NaCl, 10% glycerol, 5 mM β mercaptoethanol, 2 mM MnSO4. The protein was concentrated using 30 K Amicon Ultra centrifugal filters and then subjected to size exclusion chromatography on Superdex S200 16/60pg columns equilibrated in 50 mM Tris/HCl pH 7.5, 200 mM NaCl, 10% glycerol, 5 mM β mercaptoethanol, 2 mM MnSO4.
Positive fractions were combined and the protein concentration adjusted to the required concentration using centrifugal filters. The protein was then aliquoted and after plunge-freezing in liquid nitrogen stored at -80°C.

Human IDH2 R172K

Cloning

The IDH2 R172K mutant residues M1-L414 was directionally cloned via restriction sites BamHI and XhoI into pTriIJ-HV vector to yield the full length protein carrying a non-cleavable C-terminal His_6-tag.

This plasmid was used to produce baculovirus for infecting Sf21 insect cells. These cells were stored as BIICs (baculovirus infected insect cells) and used to infect large scale Sf21 cell cultures. Expression was carried out at MOI-1 in Sf900 II media supplemented with 5 µg/mL Gentamicin for 72 h at 27°C. Sf21 cells were prepared at a cell density of ~0.5 $x10^6$ cell/mL 24 hours prior to infection. Cell parameters

were measured using a Cell Countess (Invitrogen) at time of infection and prior to harvest. Ideal cell density at time of infection (0 hours) is ~1.2x10^6 cell/mL, cell viability ~99%. Set cell parameters for harvest are viability ~80-90% and cell size increase >2.5µm. Usually at harvest, cell density has reached ~2 x10^6 cell/mL.

Protein Sequence Recombinant HsIDH2 R172K carrying a non-cleavable C-terminal His_6-tag

MAGYLRVVRSLCRASGSRPAWAPAALTAPTSQEQPRRHYADKRIKVAKPVVEMDGDEMTRI
IWQFIKEKLILPHVDIQLKYFDLGLPNRDQTDDQVTIDSALATQKYSVAVKCATITPDEAR
VEEFKLKKMWKSPNGTIRNILGGTVFREPIICKNIPRLVPGWTKPITIGKHAHGDQYKATD
FVADRAGTFKMVFTPKDGSGVKEWEVYNFPAGGVGMGMYNTDESISGFAHSCFQYAIQKKW
PLYMSTKNTILKAYDGRFKDIFQEIFDKHYKTDFDKNKIWYEHRLIDDMVAQVLKSSGGFV
WACKNYDGDVQSDILAQGFGSLGLMTSVLVCPDGKTIEAEAAHGTVTRHYREHQKGRPTST
NPIASIFAWTRGLEHRGKLDGNQDLIRFAQMLEKVCVETVESGAMTKDLAGCIHGLSNVKL
NEHFLNTTDFLDTIKSNLDRALGRQHHHHHH

Purification

Approximately 70g of cells (wet weight) were obtained from a 10 l insect cell expression culture. Cell pellet was resuspended in 360 ml of lysis buffer (25 mM HEPES/NaOH pH 7.5, 200 mM NaCl, 5% glycerol) with 1 Roche Complete protease inhibitor cocktail tablet added per 50 ml. Cells were lysed by sonication (40% amplitude, 2 min 30 sec of sonication time, 30 sec on/off cycles) in batches of 120 ml. The lysate was cleared by centrifugation for 60 min at 16500g.
The protein was purified by affinity chromatography, hydrophobic interaction chromatography and size exclusion chromatography.
Protein was loaded onto a 5 ml HisTrap Crude FF column equilibrated in lysis buffer (25 mM HEPES pH 7.5, 200 mM NaCl, 5% glycerol). The column was washed with 10 column volumes of lysis buffer. The protein was eluted in a linear gradient from 0% to 100% elution buffer (25 mM HEPES pH 7.5, 200 mM NaCl, 5% glycerol, 250 mM imidazole pH 8.0) over 10 column volumes.
Positive elution fractions were pooled. Ammonium sulphate salt was slowly added to the stirred and cooled protein

solution until a final concentration of 2 M. The sample was cleared from precipitated protein by short centrifugation at 12000 rpm.
The protein was then loaded onto a 5 ml HiTrap Butyl Sepharose column equilibrated in HIC loading buffer (25 mM HEPES/NaOH pH 7.5, 2 M Ammonium Sulfate, 1 mM DTT, 5% glycerol). After washing of the column with 10 volumes of HIC loading buffer the protein was eluted in a linear gradient from 0 to 100% HIC elution buffer (25 mM HEPES/NaOH pH 7.5, 1 mM DTT, 5% Glycerol) over 20 column volumes.
The protein in the positive elution fractions was pooled and concentrated using 30 K Amicon ultra centrifugal filters and then subjected to size exclusion chromatography on Superdex S75 26/60pg columns equilibrated in 25 mM HEPES/NaOH pH 7.5, 100 mM NaCl, 1 mM DTT, 10% glycerol.
Positive fractions were combined and the protein concentration adjusted to the required concentration using centrifugal filters. The protein was then aliquoted and after plunge-freezing in liquid nitrogen stored at -80°C.

Mutant IDH1 biochemical assay

The enzymatic reaction was performed at room temperature in 384-well plates using a final reaction volume of 16 µL containing 20 mM Tris pH 7.5, 150 mM NaCI, 10 mM $MgCI_2$ and 0.03% BSA. A final concentration 0.5µg/mL IDH1(R132H) was pre-incubated with compound for 90 minutes, followed by addition of substrate solution (20 µM NADPH and 1mM α-ketoglutarate). The reaction was incubated for a further 90 minutes at room temperature, and then 48 µL 100% methanol was added to quench the reaction. After termination, plates were sealed and stored at 4°C until analysis.
IDH1(R132H) catalytic activity was measured using the RapidFire™ mass spectrometry (RF/MS) platform. Plates were analysed on the Agilent RF300 integrated autosampler/solid-phase extraction (SPE) system coupled to an Agilent QQQ 6460 mass spectrometer for the conversion of substrate (α-

ketoglutarate) to product (2-hydroxyglutarate). Solvent A was water containing 0.1% (v/v) acetic acid. Solvent B was methanol/0.1% ammonium acetate (9:1, v/v). More specifically, plates were centrifuged at 4350 rpm for 10 min, samples were aspirated under vacuum for 600 ms, then loaded onto a graphite solid-phase extraction cartridge and washed for 3 s with solvent A at a flow rate of 1 mL/min. Retained substrate and product were eluted with solvent B at a flow rate of 0.8 mL/min for 6 s and finally the cartridge was reequilibrated with solvent A for 500 ms. The mass transition for 2-HG and α-ketoglutarate were 146.9/128.9 and 144.9/100.9, respectively. The relative responses 2-HG/(2-HG+α–KG) were measured at varied inhibitor concentrations and used to calculate inhibitory IC_{50} values (normalized IC_{50} regression curves).

Mutant IDH2 biochemical assay

The enzymatic reaction was performed at room temperature in 384-well plates using a final reaction volume of 16 µL containing 20 mM Tris pH 7.5, 150 mM NaCI, 10 mM $MgCI_2$ and 0.03% BSA. A final concentration 0.5µg/mL IDH2(R172K) was pre-incubated with compound for 90 minutes, followed by addition of substrate solution (20 µM NADPH and 1mM α-ketoglutarate). The reaction was incubated for a further 90 minutes at room temperature, and then 48 µL 100% methanol was added to quench the reaction. After termination, plates were sealed and stored at 4°C until analysis.

IDH2(R172K) catalytic activity was measured using the RapidFire™ mass spectrometry (RF/MS) platform. Plates were analysed on the Agilent RF300 integrated autosampler/solid-phase extraction (SPE) system coupled to an Agilent QQQ 6460 mass spectrometer for the conversion of substrate (α-ketoglutarate) to product (2-hydroxyglutarate). Solvent A was water containing 0.1% (v/v) acetic acid. Solvent B was methanol/0.1% ammonium acetate (9:1, v/v). More specifically, plates were centrifuged at 4350 rpm for 10 min, samples were aspirated under vacuum for 600 ms, then loaded onto a

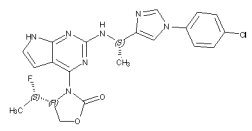
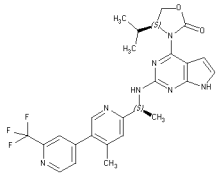
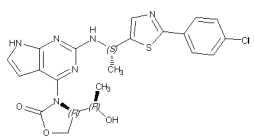
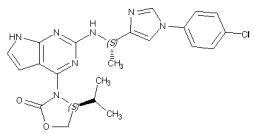
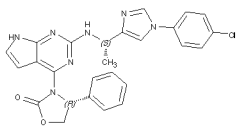
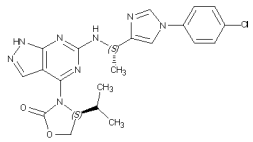
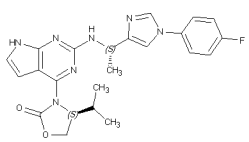
graphite solid-phase extraction cartridge and washed for 3 s with solvent A at a flow rate of 1 mL/min. Retained substrate and product were eluted with solvent B at a flow rate of 0.8 mL/min for 6 s and finally the cartridge was reequilibrated with solvent A for 500 ms. The mass transition for 2-HG and α-ketoglutarate were 146.9/128.9 and 144.9/100.9, respectively. The relative responses 2-HG/(2-HG+α–KG) were measured at varied inhibitor concentrations and used to calculate inhibitory IC_{50} values (normalized IC_{50} regression curves).

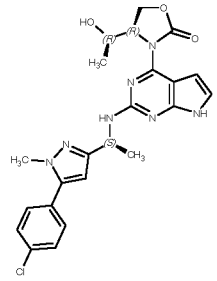
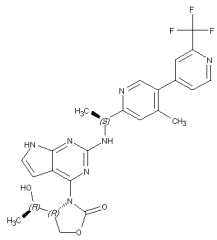
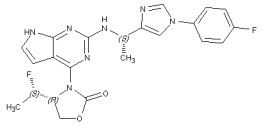
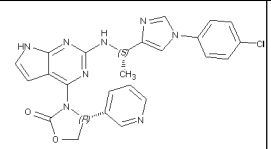
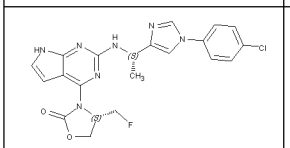
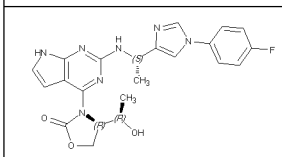
Results

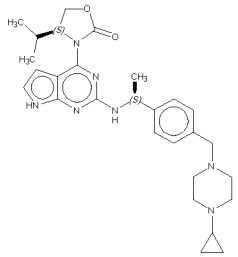
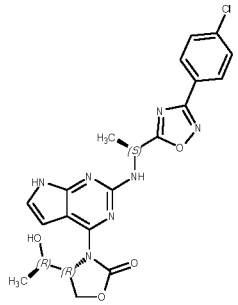
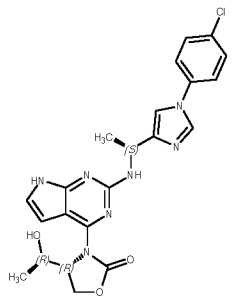
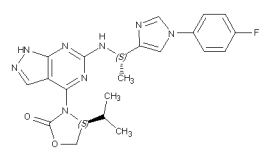
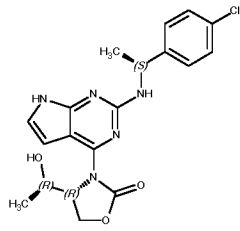
The results of the mIDH1 R132H and mIDH2 R172K biochemical inhibition assays with exemplary compounds of the present invention are summarized in Table 1.

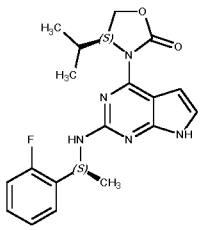
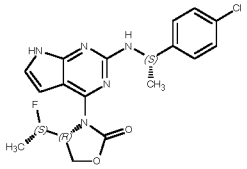
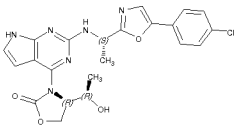
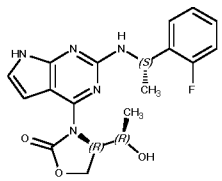
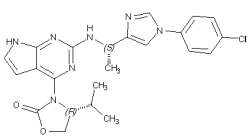
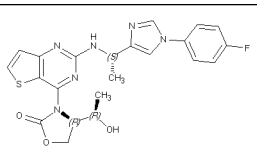
The compounds according to the present invention were active inhibitors in the employed assays. For example, Compounds 1 and 4 of the present invention are particularly efficient dual mIDH1/mIDH2 inhibitors, whereas compounds 2, 3, 5-10 of the present invention are specific mIDH1 inhibitors with considerable mIDH2 inhibitory activity.

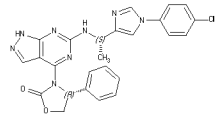
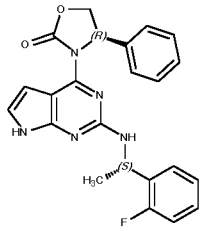
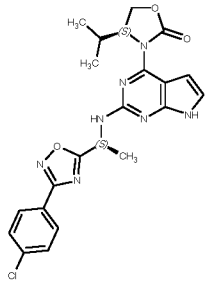
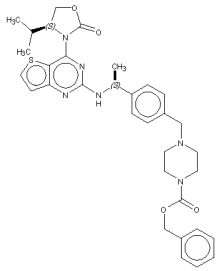
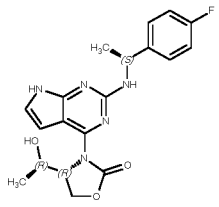
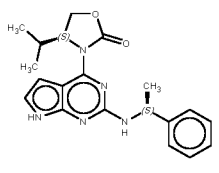
Table 1. IC_{50} values (μM) for the inhibition of neomorphic activity of mIDH1 and mIDH2 calculated from the biochemical assay data for different compounds with mIDH1 and mIDH2.

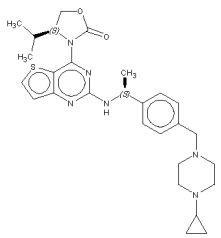
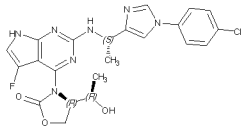
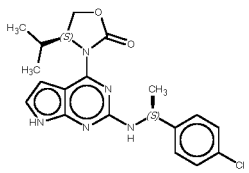
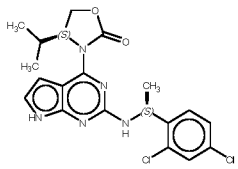
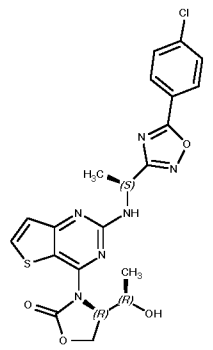
Structure	Example	**Rf Idh1 R132 H Ic50 (μM)**	**Rf Idh2 R172 K Ic50 (μM)**	**NMR**	**LCMS Retention Time MH+**
	1	0.002	0.006		
	2	0.004	0.247		
	3	0.004	0.056		
	4	0.004	0.009		
	5	0.005	0.023		
	6	0.005	0.043		
	7	0.006	0.059		

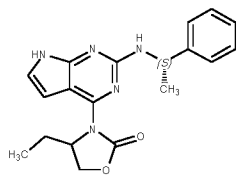
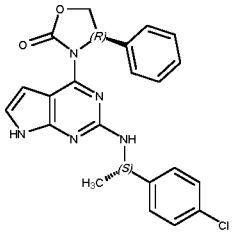
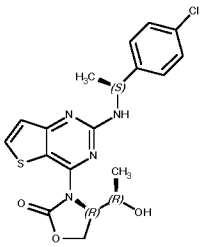
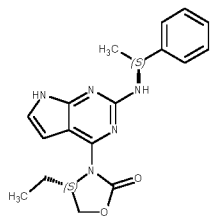
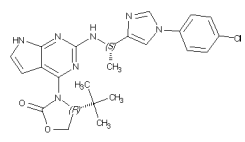
	8	0.006	0.084		
	9	0.007	0.819		
	10	0.008	0.045		
	11	0.01	0.162	(500 MHz, DMSO-d6) δ : 11.17 (s, 1H), 8.72 (s, 1H), 8.45 (dd, J = 4.7, 1.4 Hz, 1H), 8.18 (d, J = 1.3 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.65 – 7.61 (m, 2H), 7.59 – 7.55 (m, 2H), 7.40 – 7.32 (m, 2H), 6.91 (dd, J = 3.6, 2.2 Hz, 1H), 6.54 (dd, J = 3.6, 2.0 Hz, 1H), 6.45 (d, J = 8.1 Hz, 1H), 5.98 (dd, J = 8.7, 6.9 Hz, 1H), 5.00 – 4.88 (m, 2H), 4.34 (t, J = 7.6 Hz, 1H), 1.30 – 1.15 (m, 3H).	2.63 501/503
	12	0.013	0.246		
	13	0.012	0.18	(500 MHz, DMSO-d6) δ 11.23 (s, 1H), 8.32 (s, 1H), 7.70 - 7.62 (m, 2H), 7.56 (s, 1H), 7.36 (m, 2H), 6.92 (dd, J = 3.6, 2.3 Hz, 1H), 6.59 (d, J = 7.1 Hz, 1H), 6.48 (dd, J = 3.6, 2.0 Hz, 1H), 5.18-5.00 (m, 2H), 4.91 - 4.85 (m, 1H), 4.49 - 4.45 (m, 2H), 4.26 - 4.17 (m, 1H), 1.52 (d, J = 6.8 Hz, 3H), 0.89 (d, J = 6.3 Hz, 3H).	1.58 452/453

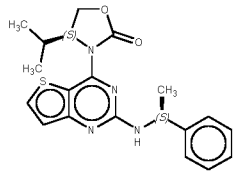
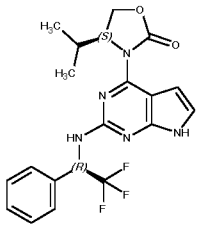
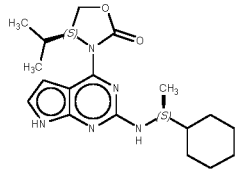
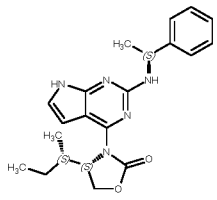
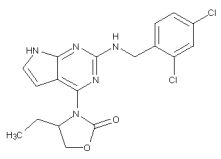
	14	0.013	12.3	(500 MHz, Methanol-*d4*) δ 8.33 (s, 1H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 6.89 (d, *J* = 3.7 Hz, 1H), 6.47 (d, *J* = 3.7 Hz, 1H), 5.14 (q, *J* = 7.0 Hz, 1H), 4.56 (s, 1H), 4.47 (t, *J* = 9.0 Hz, 1H),4.31 (dd, *J* = 8.9, 5.6 Hz, 1H), 3.89 (s, 2H), 3.06 – 2.64 (m, 8H), 1.90 (s, 1H), 1.81 (s, 1H), 1.51 (d, *J* = 7.1 Hz, 3H), 0.69 (d, *J* = 6.7 Hz, 3H), 0.63 (d, *J* = 6.7 Hz, 3H), 0.53 (d, *J* = 4.7 Hz, 2H), 0.44 (d, *J* = 2.9 Hz, 2H).	1.84 504
	15	0.014	0.925	(500 MHz, DMSO-d6) δ 11.31 (s, 1H), 8.02 – 7.94 (m, 2H), 7.62 (ddd, J = 8.6, 4.4, 2.2 Hz, 2H), 7.48 (t, J = 8.0 Hz, 1H), 6.95 (s, 1H), 6.52 – 6.45 (m, 1H), 5.41 (p, J = 7.4 Hz, 1H), 5.14 – 4.93 (m, 1H), 4.82 (s, 1H), 4.45 (d, J = 5.8 Hz, 2H), 4.22 (d, J = 67.6 Hz, 1H), 1.67 (dd, J = 7.1, 2.2 Hz, 3H), 0.94 (d, J = 6.4 Hz, 3H).	3.04 470
	16	0.014	0.129	(500 MHz, DMSO-*d6*) _ 11.22 (s, 1H), 8.24 (br. s, 1H), 7.65 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 8.9 Hz, 3H), 6.91 (dd, *J* = 3.5, 2.3 Hz, 1H), 6.54 (d, *J* = 7.7 Hz, 1H), 6.47 (dd, *J* = 3.5, 2.0 Hz, 1H), 5.19 – 4.98 (m, 2H), 4.95 – 4.81 (m, 1H), 4.53 – 4.40 (m, 2H), 4.23 (s, 1H), 1.51 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.3 Hz, 3H).	1.82 468
	17	0.019	0.21	(500 MHz, DMSO-d6) δ 12.95 (s, 1H), 8.13 (d, J = 7.8 Hz, 2H), 7.62 (s, 2H), 7.55 – 7.17 (m, 4H), 5.11 (s, 1H), 4.79 (s, 1H), 4.47 (t, J = 8.8 Hz, 1H), 4.38 (s, 1H), 2.53 – 2.51 (m, 1H), 1.52 (d, J = 6.9 Hz, 3H), 0.80 (d, J = 68.4 Hz, 6H).	2.03 451
	18	0.02	0.16	(500 MHz, Chloroform-d) δ : 8.23 (s, 1H), 7.34 – 7.26 (m, 4H), 6.86 (t, J = 3.5, 2.0 Hz, 1H), 6.69 (t, J = 3.5, 2.0 Hz, 1H), 5.11 (d, J = 7.0 Hz, 1H), 5.03 (p, J = 7.0 Hz, 1H), 4.63 – 4.56 (m, 1H), 4.45 (t, J = 9.0 Hz, 1H), 4.37 (dd, J = 9.0, 4.0 Hz, 1H), 3.94 – 3.78 (m, 1H), 1.52 (d, J = 7.0 Hz, 3H), 1.06 (d, J = 6.5 Hz, 3H).	2.71 402

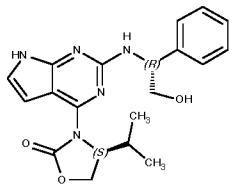
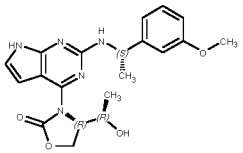
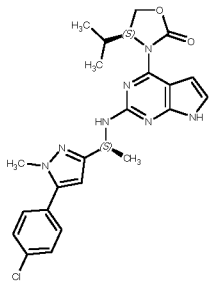
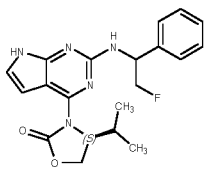
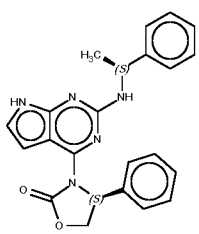
	19	0.021	0.118	(500 MHz, DMSO-*d*6) _ 11.18 (s, 1H), 7.40 (t, *J* = 7.1 Hz, 1H), 7.27 – 7.16 (m, 2H), 7.13 – 7.04 (m, 2H), 6.90 (d, *J* = 3.4 Hz, 1H), 6.34 (d, *J* = 3.6 Hz, 1H), 5.32 (p, *J* = 6.8 Hz, 1H), 4.69 (s, 1H), 4.45 (t, *J* = 8.9 Hz, 1H), 4.29 – 4.20 (m, 1H), 1.42 (d, *J* = 7.0 Hz, 3H), 0.58 (d, *J* = 51.8 Hz, 6H).	3.39 384
	20	0.021	0.068	(500 MHz, DMSO-*d*6) δ 11.19 (s, 1H), 7.39 – 7.29 (m, 4H), 7.20 (d, *J* = 7.9 Hz, 1H), 6.90 (d, *J* = 3.5 Hz, 1H), 6.47 (d, *J* = 3.6 Hz, 1H), 5.07 – 4.96 (m, 1H), 4.78 (d, *J* = 27.6 Hz, 1H), 4.53 (t, *J* = 8.9 Hz, 1H), 4.45 (d, *J* = 4.2 Hz, 1H), 1.43 (d, *J* = 7.0 Hz, 3H), 1.11 (s, 3H).	3.26 404
	21	0.021	0.402	(500 MHz, DMSO-d6) δ 11.25 (s, 1H), 7.64 (d, J = 8.6 Hz, 2H), 7.57 (s, 1H), 7.50 (d, J = 8.6 Hz, 2H), 7.18 (d, J = 8.2 Hz, 1H), 6.94 (d, J = 3.6 Hz, 1H), 6.48 (d, J = 3.6 Hz, 1H), 5.31 (p, J = 7.1 Hz, 1H), 5.07 (s, 1H), 4.88 - 4.82 (m, 1H), 4.48 - 4.43 (m, 2H), 4.19 (s, 1H), 1.60 (d, J = 7.1 Hz, 3H), 0.80 (s, 3H).	2.86 469/471
	22	0.022	0.221	(500 MHz, Methanol-d4) δ 7.41 (td, J = 7.9, 1.7 Hz, 1H), 7.23 - 7.16 (m, 1H), 7.10 - 7.01 (m, 2H), 6.87 (d, J = 3.7 Hz, 1H), 6.54 (d, J = 3.7 Hz, 1H), 5.40 (q, J = 6.9 Hz, 1H), 4.92 (dt, J = 8.5, 4.2 Hz, 1H), 4.57 - 4.46 (m, 2H), 4.05 (s, 1H), 1.53 (d, J = 7.0 Hz, 3H), 0.80 (d, J = 5.4 Hz, 3H).	2.41 386
	23	0.023	0.067	(500 MHz, DMSO-d6) δ : 11.23 (s, 1H), 8.21 (d, J = 1.2 Hz, 1H), 7.69 – 7.62 (m, 2H), 7.59 – 7.52 (m, 3H), 6.92 (dd, J = 3.5, 2.2 Hz, 1H), 6.54 (d, J = 8.2 Hz, 1H), 6.45 (dd, J = 3.5, 1.9 Hz, 1H), 5.11 (p, J = 6.9 Hz, 1H), 4.84 (dt, J = 8.8, 4.7 Hz, 1H), 4.48 (t, J = 8.9 Hz, 1H), 4.33 (dd, J = 8.9, 4.9 Hz, 1H), 2.38 – 2.28 (m, 1H), 1.48 (d, J = 6.8 Hz, 3H), 0.86 (d, J = 7.0 Hz, 3H), 0.76 (d, J = 6.9 Hz, 3H).	2.36 466
	24	0.028	0.563		

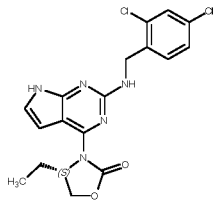
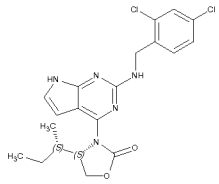
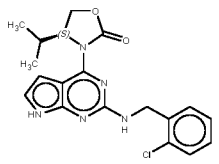
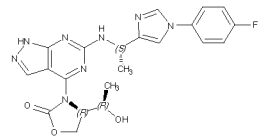
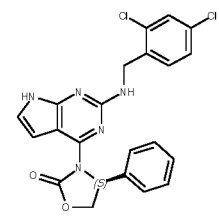
	25	0.029	0.714	(500 MHz, DMSO-*d*6) _ 12.92 (br. s, 1H), 8.43 – 8.12 (m, 2H), 7.80 – 7.54 (m, 5H), 7.49 – 7.24 (m, 6H), 7.14 – 6.96 (m, 1H), 5.92 (s, 1H), 5.15 – 4.80 (m, 2H), 4.27 (s, 1H), 1.71– 0.74 (m, 3H).	
	26	0.03	0.047	(500 MHz, DMSO-d6) δ : 11.15 (s, 1H), 7.46 – 7.41 (m, 2H), 7.37 – 7.31 (m, 2H), 7.31 – 7.24 (m, 2H), 7.23 – 7.18 (m, 1H), 7.16 – 7.09 (m, 1H), 7.06 – 7.02 (m, 1H), 6.96 (d, *J* = 9.0 Hz, 1H), 6.91 – 6.87 (m, 1H), 6.52 – 6.48 (m, 1H), 5.84 (s, 1H), 5.25 – 5.17 (m, 1H), 4.90 (t, *J* = 8.5 Hz, 1H), 4.30 – 4.22 (m, 1H), 1.32 – 1.24 (m, 3H).	3.46 418
	27	0.03	1.109	(500 MHz, DMSO-d6) δ 11.32 (s, 1H), 8.02 – 7.93 (m, 2H), 7.65 – 7.58 (m, 2H), 7.52 (dd, J = 23.0, 7.2 Hz, 1H), 6.97 (d, J = 11.1 Hz, 1H), 6.50 – 6.39 (m, 1H), 5.41 – 5.26 (m, 1H), 4.69 (s, 1H), 4.42 (s, 1H), 4.35 – 4.20 (m, 1H), 2.32 (s, 1H), 1.66 (dd, J = 7.1, 5.1 Hz, 3H), 0.80 (dd, J = 56.9, 6.9 Hz, 6H).	3.79 468
	28	0.031	16.9	(500 MHz, Methanol-d4) δ 8.00 (d, J = 5.6 Hz, 1H), 7.39 (d, J = 8.0 Hz, 2H), 7.36 – 7.26 (m, 7H), 7.11 (d, J = 5.6 Hz, 1H), 5.20 – 5.12 (m, 1H), 5.11 (s, 2H), 4.85 – 4.79 (m, 1H), 4.51 (t, J = 9.0 Hz, 1H), 4.38 – 4.30 (m, 1H), 3.60 (s, 2H), 3.51 (br. s, 4H), 2.56 – 2.46 (m, 4H), 1.54 (d, J = 7.0 Hz, 3H), 1.36 – 1.32 (m, 1H), 0.65 (br. s, 3H), 0.59 (br. s, 3H).	2.42 615
	29	0.033	0.366	(500 MHz, DMSO-d6) δ : 11.15 (s, 1H), 7.45 – 7.38 (m, 2H), 7.12 (d, J = 8.5 Hz, 1H), 7.11 – 7.04 (m, 2H), 6.88 (dd, J = 3.5, 2.2 Hz, 1H), 6.40 (dd, J = 3.6, 1.9 Hz, 1H), 5.08 (p, J = 7.1 Hz, 1H), 5.02 – 4.98 (m, 1H), 4.84 (dt, J = 7.5, 4.6 Hz, 1H), 4.51 – 4.42 (m, 2H), 4.19 – 4.01 (m, 1H), 1.43 (d, J = 7.0 Hz, 3H), 0.77 (s, 3H).	2.40 386
	30	0.035	0.262	(500 MHz, Methanol-d4) δ 7.37 (d, J = 7.4 Hz, 2H), 7.27 (t, J = 7.7 Hz, 2H), 7.16 (t, J = 7.3 Hz, 1H), 6.90 (d, J = 3.7 Hz, 1H), 6.47 (d, J = 3.7 Hz, 1H), 5.10 (q, J = 6.9 Hz, 1H), 4.80 – 4.72 (m, 1H), 4.46 (t, J = 9.0 Hz, 1H), 4.33 – 4.26 (m, 1H), 1.77 (br. s, 1H), 1.52 (d,	3.23 366

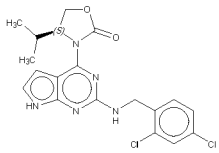
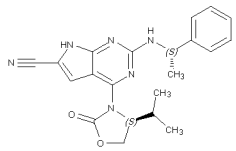
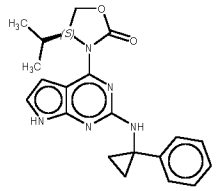
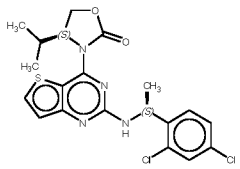
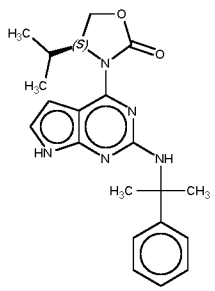
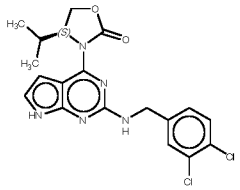
				J = 7.0 Hz, 3H), 0.64 (d, J = 7.0 Hz, 3H), 0.60 (d, J = 6.8 Hz, 3H).	
	31	0.042	30	(500 MHz, Methanol-d4) δ 8.29 (s, 1H), 8.00 (d, J = 5.6 Hz, 1H), 7.48 (d, J = 8.1 Hz, 2H), 7.38 (d, J = 8.1 Hz, 2H), 7.09 (d, J = 5.6 Hz, 1H), 5.18 (q, J = 7.0 Hz, 1H), 4.51 (t, J = 9.0 Hz, 1H), 4.35 (dd, J =8.8, 5.6 Hz, 1H), 4.03 (s, 2H), 2.92 (d, J = 48.2 Hz, 8H), 1.87 (tt, J = 6.8, 3.6 Hz, 2H), 1.54 (d, J = 7.1 Hz, 3H), 0.98 - 0.39 (m, 11H).	1.90 521
	32	0.044	0.727	(500 MHz, Chloroform-d) δ 8.11 (s, 1H), 7.81 (s, 1H), 7.46 - 7.40 (m, 2H), 7.36 - 7.28 (m, 3H), 6.68 (s, 1H), 5.34 - 5.24 (m, 1H), 4.66 - 4.59 (m, 1H), 4.56 (q, J = 8.5 Hz, 1H), 4.34 (dd, J = 8.7, 4.6 Hz, 1H), 4.09 (dq, J = 12.6, 6.3 Hz, 1H), 2.98 (s, 2H), 1.62 (d, J = 7.0 Hz, 3H), 1.21 (d, J = 6.3 Hz, 3H).	4.09 486/488
	33	0.045	0.096	(500 MHz, DMSO-d6) δ 11.16 (s, 1H), 7.36 (d, J = 8.5 Hz, 2H), 7.32 – 7.28 (m, 2H), 7.20 (d, J = 7.8 Hz, 1H), 6.90 (d, J = 3.4 Hz, 1H), 6.33 (d, J = 3.5 Hz, 1H), 5.04 – 4.96 (m, 1H), 4.67 (s, 1H), 4.43 (t, J = 8.9 Hz, 1H), 4.29 – 4.21 (m, 1H), 1.41 (d, J = 7.1 Hz, 3H), 0.59 (d, J = 35.4 Hz, 6H).	3.58 400/402
	34	0.06	0.094	(500 MHz, DMSO-*d*6) _ δ 11.20 (s, 1H), 7.54 (d, *J* = 2.1 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.34 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.94 (s, 1H), 6.31 (s, 1H), 5.26 (t, *J* = 7.4 Hz, 1H), 4.64 (s, 1H), 4.46 (t, *J* = 8.9 Hz, 1H), 4.24 (s, 1H), 1.41 (d, *J* = 7.0 Hz, 3H), 0.49 (s, 6H).	3.95 434/436
	35	0.065	3.587	(500 MHz, DMSO-d6) δ 8.17 (d, J = 5.0 Hz, 1H), 7.99 (t, J = 8.4 Hz, 2H), 7.92 (dd, J = 11.6, 7.5 Hz, 1H), 7.64 – 7.60 (m, 2H), 7.13 (d, J = 5.3 Hz, 1H), 5.53 – 5.47 (m, 1H), 5.16 (s, 0H), 4.88 (s, 1H), 4.51 (s, 2H), 4.27 (s, 1/2H), 1.68 (dd, J = 7.1, 2.6 Hz, 3H), 0.94 (m, 3H).	3.36 487

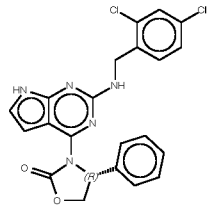
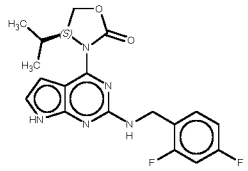
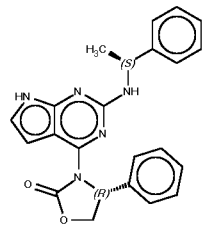
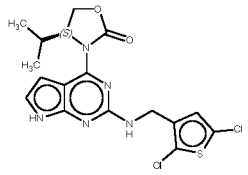
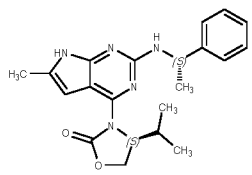
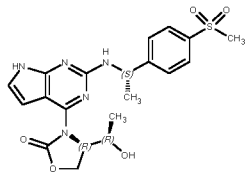
	36	0.071	0.202	(500 MHz, DMSO-d6) δ 11.13 (s, 1H), 7.38 (dd, J = 15.4, 7.3 Hz, 2H), 7.27 (dt, J = 12.9, 7.6 Hz, 2H), 7.20 – 7.02 (m, 2H), 6.87 (t, J = 3.9 Hz, 1H), 6.40 (dd, J = 24.6, 3.6 Hz, 1H), 5.11 – 5.00 (m, 1H), 4.69 (d, J = 32.6 Hz, 1H), 4.54 (td, J = 8.5, 2.9 Hz, 1H), 4.25 – 4.12 (m, 1H), 1.94 – 1.69 (m, 1H), 1.44 (dd, J = 7.0, 3.1 Hz, 3H), 0.87 – 0.54 (m, 3H).	3.09 351
	37	0.074	0.048	(500 MHz, DMSO-*d*6) δ : 11.12 (s, 1H), 7.43 (d, *J* = 7.4 Hz, 2H), 7.39 – 7.25 (m, 7H), 6.94 (d, *J* = 8.5 Hz, 1H), 6.90 (t, *J* = 3.5, 2.0 Hz, 1H), 6.51 (t, *J* = 3.5, 2.0 Hz, 1H), 5.88 – 5.78 (m, 1H), 4.89 (t, *J* = 8.5 Hz, 1H), 4.86 – 4.76 (m, 1H), 4.36 – 4.19 (m, 1H), 1.34 – 1.15 (m, 3H).	3.65 434/436
	38	0.094	0.687	(500 MHz, DMSO-*d*6) δ :1H NMR (500 MHz, DMSO-d6) δ 8.12 (d, J = 5.5 Hz, 1H), 7.66 (s, 1H), 7.43 (d, J = 8.5 Hz, 2H), 7.35 – 7.31 (m, 2H), 7.07 (d, J = 5.6 Hz, 1H), 5.07 (d, J = 30.3 Hz, 2H), 4.88 (s, 1H), 4.57 – 4.47 (m, 2H), 3.99 (s, 1H), 1.44 (d, J = 7.0 Hz, 3H), 0.66 (s, 3H).	2.91 419
	39	0.096	0.362	(500 MHz, Chloroform-*d*) δ : 8.25 (s, 1H), 7.34 (d, J = 7.5 Hz, 2H), 7.29 (t, J = 7.5 Hz, 2H), 7.19 (t, J = 7.5 Hz, 1H), 6.83 (d, J = 3.5 Hz, 1H), 6.71 (d, J = 3.5 Hz, 1H), 5.16 – 5.05 (m, 2H), 4.76 – 4.69 (m, 1H), 4.50 (t, J = 8.5 Hz, 1H), 4.13 (dd, J = 8.5, 6.0 Hz, 1H), 1.58 – 1.45 (m, 4H), 1.42 – 1.30 (m, 1H), 0.68 (t, J = 7.5 Hz, 3H).	3.08 352
	40	0.099	0.086	(500 MHz, DMSO-*d*6) δ : 11.26 (s, 1H), 8.20 (d, J = 1.4 Hz, 1H), 7.65 – 7.59 (m, 2H), 7.59 – 7.53 (m, 2H), 7.51 (s, 1H), 6.97 (d, J = 3.6 Hz, 1H), 6.58 (d, J = 8.4 Hz, 1H), 6.37 (d, J = 3.6 Hz, 1H), 5.14 (p, J = 6.8 Hz, 1H), 4.88 (dd, J = 8.5, 3.2 Hz, 1H), 4.51 (t, J = 8.9 Hz, 1H), 4.47 (dd, J = 9.3, 3.2 Hz, 1H), 1.49 (d, J = 6.8 Hz, 3H), 0.78 (s, 9H).	2.47 480/482

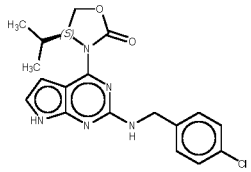
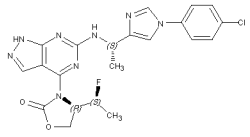
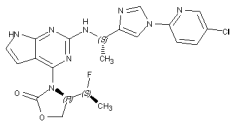
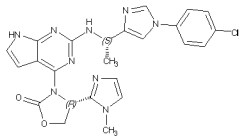
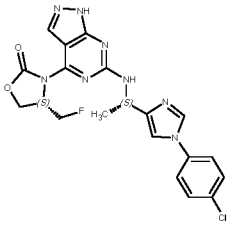
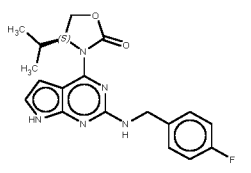
	41	0.12	0.915	(500 MHz, Methanol-d4) δ 8.01 (d, J = 5.6 Hz, 1H), 7.38 (d, J = 7.4 Hz, 2H), 7.29 (t, J = 7.7 Hz, 2H), 7.18 (t, J = 7.3 Hz, 1H), 7.11 (d, J = 5.6 Hz, 1H), 5.12 (q, J = 6.9 Hz, 1H), 4.83 (br. s, J = 7.3 Hz, 1H), 4.50 (t, J = 9.0 Hz, 1H), 4.36 – 4.28 (m, 1H), 1.69 (br. s, J = 7.1 Hz, 1H), 1.55 (d, J = 7.0 Hz, 3H), 0.62 (br. s, 3H), 0.58 (br. s, 3H).	3.36 383
	42	0.135	0.206	(500 MHz, DMSO-*d*6) _ δ 11.35 (s, 1H), 8.03 (d, *J* = 10.3 Hz, 1H), 7.63 (d, *J* = 7.3 Hz, 2H), 7.49 – 7.31 (m, 4H), 7.00 (d, *J* = 3.6 Hz, 1H), 6.45 (d, *J* = 3.5 Hz, 1H), 6.00 (t, *J* = 9.4 Hz, 1H), 4.95 (s, 1H), 4.51 (t, *J* = 9.0 Hz, 1H), 4.33 (dd, *J* = 9.0, 5.1 Hz, 1H), 0.80 (d, *J* = 6.9 Hz, 3H), 0.63 (s, 3H).	3.60 420
	43	0.142	3.99	(500 MHz, DMSO-*d*6) δ 11.09 (s, 1H), 6.88 (dd, *J* = 3.6, 2.2 Hz, 1H), 6.39 (dd, *J* = 3.5, 1.9 Hz, 1H), 6.34 (d, *J* = 9.0 Hz, 1H), 4.83 (dt, *J* = 8.9, 4.9 Hz, 1H), 4.49 (t, *J* = 8.9 Hz, 1H), 4.32 (dd, *J* = 8.9, 5.1 Hz, 1H), 3.94 – 3.81 (m, 1H), 2.33 – 2.22 (m, 1H), 1.77 – 1.64 (m, 4H), 1.60 (m, 1H), 1.49 – 1.35 (m, 1H), 1.24 – 1.10 (m, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 1.02 – 0.90 (m, 2H), 0.85 (d, *J* = 7.1 Hz, 3H), 0.76 (d, *J* = 6.9 Hz, 3H).	3.78 372
	44	0.148	0.405	(500 MHz, Chloroform-*d*) δ : 8.20 (s, 1H), 7.38 – 7.32 (m, 2H), 7.32 – 7.27 (m, 2H), 7.24 – 7.17 (m, 1H), 6.84 (dd, J = 3.5, 2.0 Hz, 1H), 6.68 (dd, J = 3.5, 2.0 Hz, 1H), 5.18 – 5.07 (m, 2H), 4.91 – 4.83 (m, 1H), 4.40 (t, J = 9.0 Hz, 1H), 4.23 (dd, J = 9.0, 5.5 Hz, 1H), 1.87 – 1.77 (m, 1H), 1.56 (d, J = 6.5 Hz, 3H), 1.16 – 1.06 (m, 1H), 1.03 – 0.90 (m, 1H), 0.79 (t, J = 7.5 Hz, 3H), 0.71 (d, J = 7.0 Hz, 3H).	3.55 380
	45	0.172	0.589	(500 MHz, DMSO-d6) δ 11.26 (s, 1H), 7.59 (d, J = 2.1 Hz, 1H), 7.36 (dd, J = 8.4, 2.1 Hz, 1H), 7.29 (dd, J = 13.3, 7.3 Hz, 2H), 6.93 (d, J = 3.5 Hz, 1H), 6.46 (d, J = 3.6 Hz, 1H), 4.59 (dq, J = 22.9, 8.4, 7.4 Hz, 3H), 4.43 (dd, J = 17.0, 5.8 Hz, 1H), 4.22 – 4.13 (m, 1H), 1.57 (m, 2H), 0.67 (s, 3H).	3.63 406

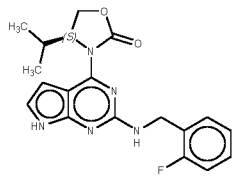
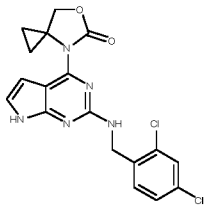
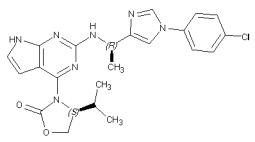
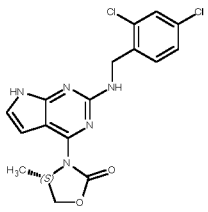
	46	0.174	5.25	(500 MHz, DMSO-d6) δ 11.18 (s, 1H), 7.36 (d, J = 7.4 Hz, 2H), 7.26 (t, J = 7.6 Hz, 2H), 7.17 (t, J = 7.3 Hz, 1H), 6.95 – 6.86 (m, 2H), 6.36 (d, J = 2.3 Hz, 1H), 5.76 (s, 1H), 4.97 (q, J = 6.5 Hz, 1H), 4.88 (d, J = 8.7 Hz, 1H), 4.73 (s, 1H), 4.46 (t, J = 8.8 Hz, 1H), 4.28 (s, 1H), 3.66 (s, 2H), 3.21 – 3.13 (m, 1H), 1.59 (d, J = 12.4 Hz, 1H), 0.61 (d, J = 42.3 Hz, 6H).	2.71 382
	47	0.176	1.453	(500 MHz, DMSO-d6) δ 11.13 (s, 1H), 7.17 (t, J = 7.9 Hz, 1H), 7.06 (d, J = 8.6 Hz, 1H), 6.98 - 6.93 (m, 2H), 6.87 (dd, J = 3.5, 1.8 Hz, 1H), 6.74 - 6.69 (m, 1H), 6.40 (dd, J = 3.6, 1.5 Hz, 1H), 5.10 - 4.95 (m, 2H), 4.86 - 4.79 (m, 1H), 4.49 - 4.42 (m, 2H), 4.20 - 4.08 (m, 1H), 3.70 (s, 3H), 1.42 (d, J = 7.0 Hz, 3H), 0.76 (s, 3H).	2.33 397
	48	0.193	4.053	(500 MHz, Chloroform-*d*) _ δ 8.53 (br. s, 1H), 7.70 – 7.64 (m, 2H), 7.36 – 7.30 (m, 2H), 6.91 (d, *J* = 3.7 Hz, 1H), 6.77 (d, *J* = 3.7 Hz, 1H), 6.47 (s, 1H), 5.32 – 5.25 (m, 1H), 4.83 (dt, *J* = 9.0, 4.8 Hz, 1H), 4.44 (t, *J* = 8.9 Hz, 1H), 4.28 (dd, *J* = 8.9, 5.4 Hz, 1H), 3.90 (s, 3H), 2.20 (br. s, 1H), 1.65 (d, *J* = 6.6 Hz, 3H), 0.80 (dd, *J* = 22.9, 7.0 Hz, 6H).	3.55 480
	49	0.205	0.696	(500 MHz, Chloroform-d) δ 8.28 (s, 2H), 7.36 – 7.20 (m, 10H), 6.79 (q, J = 3.3 Hz, 2H), 6.70 (dd, J = 3.7, 2.2 Hz, 1H), 6.64 (dd, J = 3.6, 2.2 Hz, 1H), 5.48 (d, J = 6.4 Hz, 1H), 5.38 (d, J = 7.0 Hz, 1H), 5.28 – 5.17 (m, 2H), 4.68 (dddd, J = 34.7, 20.1, 10.2, 5.0 Hz, 6H), 4.55 (td, J = 9.3, 5.7 Hz, 1H), 4.32 (q, J = 8.9 Hz, 2H), 4.20 (dd, J = 8.8, 5.2 Hz, 1H), 4.16 (dd, J = 8.8, 5.5 Hz, 1H), 2.45 – 2.35 (m, 1H), 1.90 (s, 1H), 0.86 (d, J = 7.1 Hz, 3H), 0.79 (d, J = 6.9 Hz, 3H), 0.61 (d, J = 6.9 Hz, 6H).	3.24 384
	50	0.206	0.288	(500 MHz, Chloroform-d) δ : 8.26 (s, 1H), 7.22 – 7.03 (m, 10H), 6.74 (d, *J* = 3.5 Hz, 1H), 6.70 (d, *J* = 3.5 Hz, 1H), 5.80 (dd, *J* = 9.0, 6.5 Hz, 1H), 4.95 – 4.80 (m, 2H), 4.74 (t, *J* = 9.0 Hz, 1H), 4.22 (dd, *J* = 9.0, 6.5 Hz, 1H), 1.42 (d, *J* = 6.5 Hz, 3H)	3.36 400

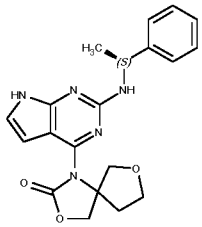
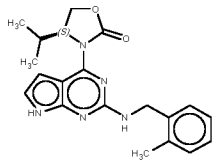
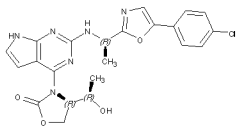
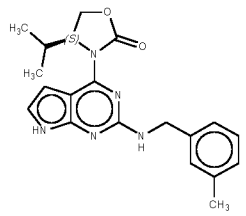
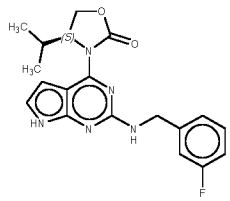
	51	0.219	0.237	(500 MHz, Chloroform-d) δ: 8.31 (s, 1H), 7.38 (d, J = 2.0 Hz, 1H), 7.32 (d, J = 8.5 Hz, 1H), 7.17 (dd, J = 8.5, 2.0 Hz, 1H), 6.87 (t, J = 3.5, 2.0 Hz, 1H), 6.78 (t, J = 3.5, 2.0 Hz, 1H), 5.28 (t, J = 6.5 Hz, 1H), 4.78 – 4.68 (m, 2H), 4.60 (dd, J = 16.5, 6.0 Hz, 1H), 4.52 (t, J = 8.5 Hz, 1H), 4.17 (dd, J = 8.5, 5.5 Hz, 1H), 1.87 – 1.75 (m, 1H), 1.70 – 1.56 (m, 1H), 0.79 (t, J = 7.5 Hz, 3H).	3.63 406
	52	0.221	0.411	(500 MHz, Chloroform-d) δ: 8.39 (s, 1H), 7.39 (d, J = 2.0 Hz, 1H), 7.32 (d, J = 8.5 Hz, 1H), 7.17 (dd, J = 8.5, 2.0 Hz, 1H), 6.88 (t, J = 3.5, 2.0 Hz, 1H), 6.77 (t, J = 3.5, 2.0 Hz, 1H), 5.29 (t, J = 6.0 Hz, 1H), 4.95 – 4.87 (m, 1H), 4.75 (dd, J = 16.5, 6.0 Hz, 1H), 4.61 (dd, J = 16.5, 6.0 Hz, 1H), 4.40 (t, J = 9.0 Hz, 1H), 4.26 (dd, J = 9.0, 5.5 Hz, 1H), 2.10 – 1.98 (m, 1H), 1.25 – 1.13 (m, 1H), 1.13 – 1.02 (m, 1H), 0.85 (t, J = 7.5 Hz, 3H), 0.79 (d, J = 7.0 Hz, 3H).	4.03 434
	53	0.24	0.212	(500 MHz, DMSO-*d*6) δ 11.26 (s, 1H), 7.45 – 7.38 (m, 1H), 7.31 – 7.27 (m, 1H), 7.27 – 7.21 (m, 3H), 6.96 – 6.90 (m, 1H), 6.44 (dd, *J* = 3.5, 2.0 Hz, 1H), 4.65 (dd, *J* = 16.9, 6.5 Hz, 2H), 4.51 – 4.38 (m, 2H), 4.33 – 4.22 (m, 1H), 2.08 (m, 1H), 0.88 – 0.39 (m, 6H).	3.46 386
	54	0.277	0.551	(500 MHz, Methanol-d4) δ 8.33 (s, 1H), 8.03 (d, J = 1.2 Hz, 1H), 7.59 – 7.49 (m, 2H), 7.38 (s, 1H), 7.24 (t, J = 8.6 Hz, 2H), 5.31 (q, J = 6.9 Hz, 1H), 5.04 (dt, J = 8.0, 3.4 Hz, 1H), 4.61 (dd, J = 9.1, 3.0 Hz, 1H), 4.55 – 4.29 (m, 2H), 1.61 (d, J = 6.9 Hz, 3H), 1.01 (s, 3H).	1.52 453
	55	0.278	0.421	(500 MHz, Chloroform-d) δ: 8.37 (s, 1H), 7.37 (d, *J* = 2.0 Hz, 1H), 7.28 – 7.17 (m, 6H), 7.04 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.98 (d, *J* = 8.5 Hz, 1H), 6.92 – 6.87 (m, 1H), 6.90 – 6.84 (m, 1H), 5.80 (dd, *J* = 8.5, 7.0 Hz, 1H), 5.06 (t, *J* = 6.5 Hz, 1H), 4.79 (t, *J* = 8.5 Hz, 1H), 4.52 (dd, *J* = 16.5, 6.5 Hz, 1H), 4.41 (dd, *J* = 16.5, 6.5 Hz, 1H), 4.25 (dd, *J* = 8.5, 7.0 Hz, 1H).	3.85 454/456

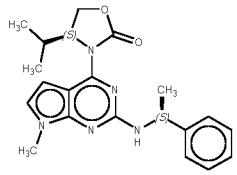
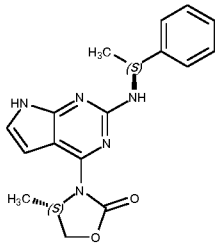
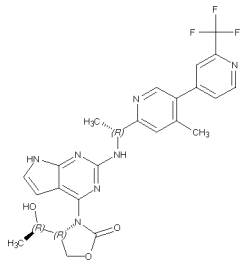
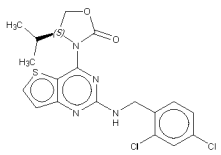
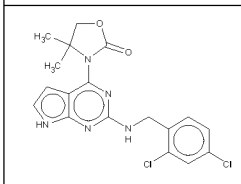
	56	0.311	0.066	(500 MHz, DMSO-*d*6) δ 11.27 (s, 1H), 7.57 (d, *J* = 2.1 Hz, 1H), 7.34 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.32 – 7.26 (m, 2H), 6.96 – 6.90 (m, 1H), 6.44 (dd, *J* = 3.6, 2.0 Hz, 1H), 4.61 (m, 2H), 4.50 – 4.34 (m, 2H), 4.31 – 4.23 (m, 1H), 2.18 – 1.88 (m, 1H), 0.65 (s, 6H).	3.79 420
	57	0.314	0.671	(500 MHz, DMSO-d6) δ 12.29 (s, 1H), 7.75 (s, 1H), 7.33 (d, J = 6.6 Hz, 3H), 7.27 (t, J = 7.6 Hz, 2H), 7.16 (t, J = 7.2 Hz, 1H), 5.08 (p, J = 7.1 Hz, 1H), 4.75 (s, 1H), 4.47 (s, 1H), 4.32 (s, 1H), 1.64 (s, 1H), 1.45 (d, J = 6.3 Hz, 3H), 0.96 – 0.36 (m, 6H).	3.69 390
	58	0.328	0.204	(500 MHz, DMSO-*d*6) δ 11.25 (s, 1H), 7.51 (s, 1H), 7.20 (t, *J* = 7.6 Hz, 2H), 7.13 (d, *J* = 7.3 Hz, 2H), 7.07 (t, *J* = 7.2 Hz, 1H), 6.90 (s, 1H), 6.43 (s, 1H), 4.60 (m, 1H), 4.40 (m, 1H), 4.25 (m, 1H), 2.08 (m, 1H), 1.34 – 1.15 (m, 4H), 0.60 (d, *J* = 7.4 Hz, 6H).	3.33 378
	59	0.345	0.454	(500 MHz, Chloroform-d) δ 7.78 (d, J = 5.6 Hz, 1H), 7.32 (d, J = 8.4 Hz, 1H), 7.29 (d, J = 2.1 Hz, 1H), 7.10 (dd, J = 8.4, 2.1 Hz, 1H), 7.05 (d, J = 5.6 Hz, 1H), 5.27 (p, J = 6.8 Hz, 1H), 4.66 (dt, J = 10.2, 5.7 Hz, 1H), 4.36 (t, J = 9.0 Hz, 1H), 4.15 (dd, J = 8.9, 6.0 Hz, 1H), 1.46 (d, J = 6.9 Hz, 3H), 0.49 (d, J = 6.7 Hz, 6H).	4.23 450
	60	0.424	0.29	(500 MHz, DMSO-*d*6) δ 11.08 (s, 1H), 7.37 (d, *J* = 7.5 Hz, 2H), 7.22 (t, *J* = 7.7 Hz, 2H), 7.10 (t, *J* = 7.3 Hz, 1H), 6.92 – 6.87 (m, 1H), 6.84 (s, 1H), 6.32 (dd, *J* = 3.4, 1.9 Hz, 1H), 4.32 (t, *J* = 8.5 Hz, 2H), 4.19 (dd, *J* = 8.2, 4.6 Hz, 1H), 1.78 (s, 3H), 1.65 (m, 1H), 1.58 (s, 3H), 0.59 (d, *J* = 6.4 Hz, 3H), 0.53 (d, *J* = 6.7 Hz, 3H).	3.51 380
	61	0.511	0.282	(500 MHz, DMSO-*d*6) δ 11.24 (s, 1H), 7.58 – 7.48 (m, 2H), 7.37 – 7.24 (m, 2H), 6.98 – 6.89 (m, 1H), 6.42 (dd, *J* = 3.5, 2.0 Hz, 1H), 4.69 (m, 1H), 4.56 (dd, *J* = 16.3, 6.4 Hz, 1H), 4.49 – 4.34 (m, 2H), 4.28 (dd, *J* = 8.8, 5.2 Hz, 1H), 2.20 – 1.81 (m, 1H), 0.81 – 0.55 (m, 6H).	3.69 420

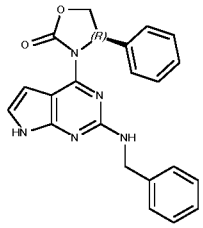
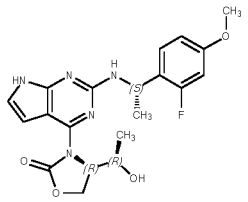
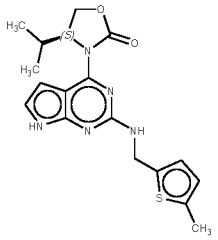
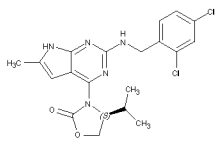
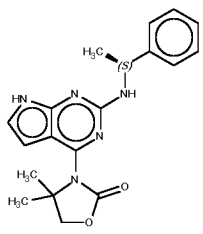
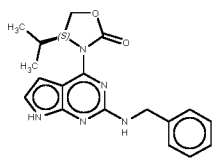
	62	0.518	0.012	(500 MHz, Chloroform-d) δ : 8.25 (s, 1H), 7.29 (d, J = 2.0 Hz, 1H), 7.21 – 7.05 (m, 6H), 6.96 (dd, J = 8.5, 2.0 Hz, 1H), 6.90 (d, J = 8.5 Hz, 1H), 6.84 – 6.75 (m, 2H), 5.72 (dd J = 8.5, 7.0 Hz, 1H), 4.98 (t, J = 6.5 Hz, 1H), 4.71 (d, J = 8.5 Hz, 1H), 4.44 (dd, J = 16.5, 6.5 Hz, 1H), 4.33 (dd, J = 16.5, 6.5 Hz, 1H), 4.17 (dd, J = 8.5, 7.0 Hz, 1H).	3.85 454/456
	63	0.524	0.195	(500 MHz, DMSO-d6) δ 11.24 (s, 1H), 7.34 (q, J = 8.3 Hz, 1H), 7.25 – 7.14 (m, 2H), 7.02 – 6.96 (m, 1H), 6.95 – 6.90 (m, 1H), 6.43 (dd, J = 3.4, 1.9 Hz, 1H), 4.72 (m, 1H), 4.59 (dd, J = 16.1, 6.4 Hz, 1H), 4.50 – 4.36 (m, 2H), 4.29 (dd, J = 8.8, 5.1 Hz, 1H), 2.11 (m, 1H), 0.82 – 0.57 (m, 6H).	3.36 388
	64	0.552	0.209	(500 MHz, Chloroform-d) δ :8.35 (s, 1H), 7.30 – 7.11 (m, 10H), 6.79 – 6.72 (m, 2H), 5.66 (dd, J = 8.5, 7.0 Hz, 1H), 4.90 (d, J = 7.0 Hz, 1H), 4.75 (p, J = 7.0 Hz, 1H), 4.67 (t, J = 8.5 Hz, 3H), 4.17 (t, J = 8.5, 7.0 Hz, 1H), 1.21 (d, J = 7.0 Hz, 2H).	3.36 400
	65	0.682	1.488	(500 MHz, DMSO-*d*6) δ 11.27 (s, 1H), 7.19 (t, *J* = 6.2 Hz, 1H), 6.95 (m, 2H), 6.43 (dd, *J* = 3.6, 1.9 Hz, 1H), 4.79 (dt, *J* = 8.9, 4.8 Hz, 1H), 4.48 (t, *J* = 8.9 Hz, 1H), 4.42 – 4.29 (m, 2H), 4.09 (q, *J* = 5.2 Hz,1H), 2.19 (m, 1H), 0.80 (d, *J* = 7.0 Hz, 3H), 0.71 (d, *J* = 6.9 Hz, 3H).	3.87 426
	66	0.902	1.29	(500 MHz, Chloroform-d) δ 7.32 (d, J = 7.3 Hz, 2H), 7.28 (d, J = 7.4 Hz, 2H), 7.19 (d, J = 7.1 Hz, 1H), 6.29 (s, 1H), 5.06 (p, J = 7.0 Hz, 1H), 4.69 (dt, J = 9.5, 5.4 Hz, 1H), 4.37 (t, J = 8.9 Hz, 1H), 4.19 (dd, J = 8.8, 5.7 Hz, 1H), 2.31 (d, J = 1.0 Hz, 3H), 1.81 (s, 1H), 1.54 (d, J = 6.9 Hz, 3H), 0.62 (dd, J = 9.5, 7.1 Hz, 6H).	3.40 379
	67	0.966	17.493	(500 MHz, DMSO-d6) δ 11.19 (s, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.0 Hz, 1H), 6.89 (s, 1H), 6.40 (dd, J = 3.6, 1.9 Hz, 1H), 5.13 (p, J = 7.1 Hz, 1H), 4.99 (s, 1H), 4.81 (s, 1H), 4.50 - 4.41 (m, 2H), 3.95 (s, 1H), 3.14 (s, 3H), 1.47 (d, J = 7.1 Hz, 3H), 0.70 (s, 3H).	1.89 446

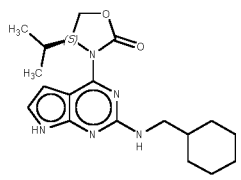
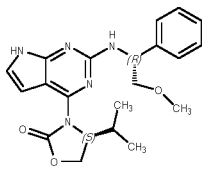
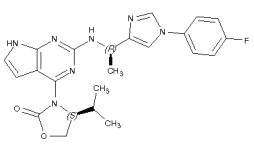
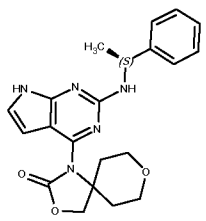
	68	0.968	0.369	(500 MHz, DMSO-d6) δ 11.21 (s, 1H), 7.35 – 7.29 (m, 4H), 7.26 (t, J = 6.3 Hz, 1H), 6.96 – 6.89 (m, 1H), 6.41 (dd, J = 3.5, 1.9 Hz, 1H), 4.71 (m, 1H), 4.55 (dd, J = 16.0, 6.5 Hz, 1H), 4.49 – 4.35 (m, 2H), 4.28 (dd, J = 8.8, 5.2 Hz, 1H), 2.07 (m, 1H), 0.80 – 0.55 (m, 6H).	3.45 386
	69	0.008	0.125	(500 MHz, DMSO-d6) δ 12.97 (s, 1H), 8.27 - 8.08 (m, 2H), 7.75 - 7.22 (m, 6H), 5.63 - 4.76 (m, 3H), 4.69 - 4.39 (m, 2H), 1.60 - 1.46 (m, 3H), 1.42 - 0.90 (m, 3H).	2.17 471/473
	70	0.009	1.133	(500 MHz, DMSO-*d*6) δ : 11.22 (s, 1H), 8.50 (d, J = 2.5 Hz, 1H), 8.46 (d, J = 1.3 Hz, 1H), 8.10 (dd, J = 8.8, 2.6 Hz, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.62 (s, 1H), 6.91 (dd, J = 3.5, 2.3 Hz, 1H), 6.83 (d, J = 8.2 Hz, 1H), 6.55 (dd, J = 3.6, 2.0 Hz, 1H), 5.28 – 4.96 (m, 2H), 4.88 (ddd, J = 27.4, 9.1, 4.6 Hz, 1H), 4.55 (t, J = 9.0 Hz, 1H), 4.46 (dd, J = 8.7, 4.4 Hz, 1H), 1.50 (d, J = 6.9 Hz, 3H), 1.15 (d, J = 15.7 Hz, 3H).	2.25 471/473
	71	0.015	0.608	(500 MHz, DMSO-*d*6) δ 11.19 (s, 1H), 8.20 (d, *J* = 1.4 Hz, 1H), 7.66 – 7.61 (m, 2H), 7.59 – 7.54 (m, 2H), 7.43 (s, 1H), 7.03 (d, *J* = 0.9 Hz, 1H), 6.90 (dd, *J* = 3.6, 2.2 Hz, 1H), 6.74 (d, *J* = 1.0 Hz, 1H), 6.53 (dd, *J* = 3.5, 2.0 Hz, 1H), 6.27 (d, *J* = 8.6 Hz, 1H), 6.05 (dd, *J* = 8.5, 5.4 Hz, 1H), 5.02 (p, *J* = 7.4, 6.9 Hz, 1H), 4.80 (t, *J* = 8.5 Hz, 1H), 4.40 (dd, *J* = 8.2, 5.4 Hz, 1H), 3.80 (s, 3H), 1.33 (d, *J* = 5.4 Hz, 3H).	1.37 504/506
	72	0.083	1.62	(500 MHz, DMSO-d6) δ 12.99 (s, 1H), 8.21 (s, 1H), 8.16 (s, 1H), 7.66 (dd, J = 8.7, 6.4 Hz, 2H), 7.59 – 7.47 (m, 3H), 7.35 (d, J = 8.0 Hz, 1H), 5.22 – 4.91 (m, 3H), 4.78 (dd, J = 45.6, 7.9 Hz, 1H), 4.70 – 4.60 (m, 1H), 4.49 (dd, J = 8.7, 3.4 Hz, 1H), 1.51 (dd, J = 6.7, 3.1 Hz, 3H).	2.01 457/459
	73	1.06	1.03	(500 MHz, DMSO-d6) δ 11.20 (s, 1H), 7.33 (dd, J = 8.2, 5.9 Hz, 2H), 7.23 (t, J = 6.3 Hz, 1H), 7.09 (t, J = 8.9 Hz, 2H), 6.95 – 6.88 (m, 1H), 6.41 (dd, J = 3.4, 1.8 Hz, 1H),	3.23 370

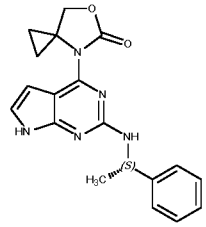
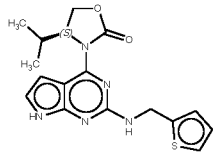
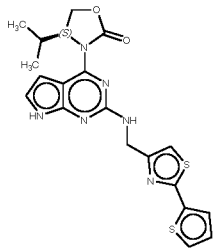
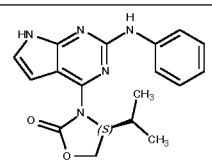
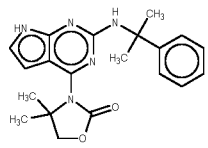
				4.73 (m, 1H), 4.54 (dd, J = 15.7, 6.5 Hz, 1H), 4.46 (t, J = 8.9 Hz, 1H), 4.39 (dd, J = 15.7, 5.8 Hz, 1H), 4.29 (dd, J = 8.9, 5.1 Hz, 1H), 2.11 (m, 1H), 0.70 (m, 6H).	
	74	1.083	0.772	(500 MHz, DMSO-*d*6) δ 11.24 (s, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.27 – 7.22 (m, 1H), 7.20 (m, 1H), 7.16 – 7.12 (m, 1H), 7.10 (t, *J* = 7.4 Hz, 1H), 6.96 – 6.89 (m, 1H), 6.43 (dd, *J* = 3.5, 2.0 Hz, 1H), 4.72 (m, 1H), 4.64 (dd, *J* = 16.2, 5.2 Hz, 1H), 4.50 – 4.40 (m, 2H), 4.28 (dd, *J* = 8.8, 5.1 Hz, 1H), 2.78 – 2.52 (m, 1H), 0.76 – 0.59 (m, 6H).	3.22 370
	75	1.092	0.512	(500 MHz, Chloroform-d) δ : 8.24 (s, 1H), 7.42 (d, J = 2.0 Hz, 1H), 7.32 (d, J = 8.5 Hz, 1H), 7.20 (dd, J = 8.5, 2.0 Hz, 1H), 6.91 (t, J = 3.5, 2.0 Hz, 1H), 6.50 (t, J = 3.5, 2.0 Hz, 1H), 5.21 (t, J = 6.5 Hz, 1H), 4.64 (d, J = 6.5 Hz, 2H), 4.38 (s, 2H), 1.85 – 1.78 (m, 2H), 0.67 – 0.61 (m, 2H).	3.51 404
	76	1.155	7.243	(500 MHz, Chloroform-d) δ 9.97 (br. s, 1H), 7.81 (s, 1H), 7.47 – 7.40 (m, 2H), 7.29 (d, J = 8.7 Hz, 2H), 7.14 (s, 1H), 6.89 (d, J = 2.5 Hz, 1H), 6.74 (d, J = 2.4 Hz, 1H), 6.37 (br. s, 1H), 5.31 (s, 1H), 4.94 (dt, J = 8.9, 4.8 Hz, 1H), 4.44 (t, J = 8.9 Hz, 1H), 4.31 (dd, J = 8.8, 5.3 Hz, 1H), 2.56 – 2.45 (m, 1H), 1.63 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 7.1 Hz, 3H), 0.87 (d, J = 6.9 Hz, 3H).	2.39 466
	77	1.32	2.49	(500 MHz, Chloroform-d) δ : 8.57 (s, 1H), 7.39 (d, J = 2.1 Hz, 1H), 7.33 (d, J = 8.3 Hz, 1H), 7.17 (dd, J = 8.3, 2.1 Hz, 1H), 6.87 (d, J = 3.7 Hz, 1H), 6.79 (d, J = 3.6 Hz, 1H), 5.51 – 5.40 (m, 1H), 4.87 – 4.79 (m, 1H), 4.73 (dd, J = 16.5, 6.5 Hz, 1H), 4.62 (dd, J = 16.5, 6.0 Hz, 1H), 4.56 (t, J = 8.5 Hz, 1H), 4.05 (dd, J = 8.5, 6.0 Hz, 1H), 1.32 (d, J = 6.0 Hz, 3H).	3.40 392/394

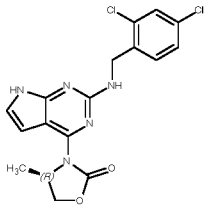
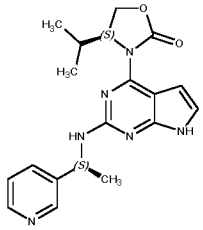
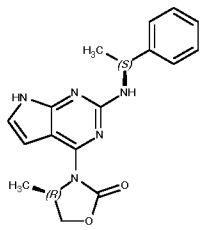
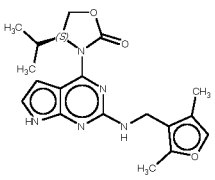
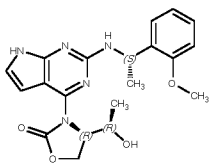
	78	1.43	0.265	(500 MHz, DMSO-d6) δ : 11.22 (s, 1H), 7.38 (d, J = 7.5 Hz, 2H), 7.31 – 7.22 (m, 2H), 7.22 – 7.09 (m, 2H), 6.97 – 6.87 (m, 1H), 6.19 – 6.08 (m, 1H), 5.09 (p, J = 7.5 Hz, 1H), 4.49 – 4.35 (m, 2H), 4.35 – 4.12 (m, 1H), 3.94 – 3.64 (m, 3H), 2.69 – 2.57 (m, 1H), 2.04 – 1.80 (m, 1H), 1.45 (d, J = 7.0 Hz, 3H).	2.72 380
	79	1.52	2.071	(500 MHz, DMSO-d6) δ 11.20 (s, 1H), 7.22 – 7.16 (m, 1H), 7.15 – 7.11 (m, 1H), 7.11 – 7.04 (m, 3H), 6.90 (d, J = 2.7 Hz, 1H), 6.42 (d, J = 3.0 Hz, 1H), 4.71 (s, 1H), 4.53 (dd, J = 16.1, 6.4 Hz, 1H), 4.45 (t, J = 8.9 Hz, 1H), 4.36 (dd, J = 16.1, 5.7 Hz, 1H), 4.27 (dd, J = 8.8, 5.1 Hz, 1H), 2.31 (s, 3H), 2.12 (s, 1H), 0.66 (d, J = 6.2 Hz, 6H).	3.35 366
	80	1.578	11.659	(500 MHz, DMSO-d6) δ 11.28 (s, 1H), 7.67 (d, J = 8.6 Hz, 2H), 7.61 (s, 1H), 7.51 (d, J = 8.6 Hz, 2H), 7.20 (d, J = 8.2 Hz, 1H), 6.93 (d, J = 3.6 Hz, 1H), 6.50 (d, J = 3.6 Hz, 1H), 5.29 (p, J = 7.1 Hz, 1H), 5.13 (s, 1H), 4.89 - 4.82 (m, 1H), 4.51 - 4.37 (m, 2H), 4.37 - 4.27 (m, 1H), 1.59 (d, J = 7.0 Hz, 3H), 0.95 (d, J = 6.5 Hz, 3H).	2.88 469/471
	81	1.589	2.49	(500 MHz, DMSO-d6) 11.20 (s, 1H), 7.20 – 7.14 (m, 2H), 7.13 – 7.06 (m, 2H), 7.00 (d, J = 7.3 Hz, 1H), 6.91 (dd, J = 3.6, 2.2 Hz, 1H), 6.42 (dd, J = 3.6, 1.9 Hz, 1H), 4.75 (s, 1H), 4.55 (dd, J = 15.9, 6.6 Hz, 1H), 4.47 (t, J = 8.9 Hz, 1H), 4.39 (dd, J = 15.6, 6.1 Hz, 1H), 4.30 (dd, J = 8.9, 5.1 Hz, 1H), 2.26 (s, 3H), 2.17 (s, 1H), 0.85 – 0.60 (m, 6H).	3.36 366
	82	1.898	1.837	(500 MHz, DMSO-d6) δ 11.23 (s, 1H), 7.35 – 7.26 (m, 2H), 7.14 (d, J = 7.6 Hz, 1H), 7.09 (d, J = 10.4 Hz, 1H), 7.00 (td, J = 8.6, 2.3 Hz, 1H), 6.92 (dd, J = 3.4, 2.3 Hz, 1H), 6.43 (dd, J = 3.5, 2.0 Hz, 1H), 4.73 (m, 1H), 4.59 (m, 1H), 4.52 – 4.38 (m, 2H), 4.28 (dd, J = 8.9, 5.1 Hz, 1H), 2.08 (m, 1H), 0.82 – 0.55 (m, 6H).	3.20 370

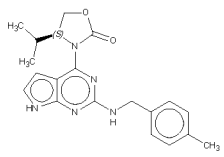
	83	2.025	30	(500 MHz, Chloroform-d) δ 7.35 (d, J = 7.4 Hz, 2H), 7.30 - 7.27 (m, 2H), 7.18 (t, J = 7.3 Hz, 1H), 6.73 (d, J = 3.6 Hz, 1H), 6.62 (d, J = 3.6 Hz, 1H), 5.19 (d, J = 6.7 Hz, 1H), 5.16 - 5.04 (m, 1H), 4.70 (dd, J= 8.9, 4.5 Hz, 1H), 4.37 (t, J = 8.9 Hz, 1H), 4.19 (dd, J = 8.8, 5.7 Hz, 1H), 3.64 (s, 3H), 1.84 (s, 1H), 1.54 (s, 3H), 0.62 (dd, J = 11.1, 7.0 Hz, 6H).	3.80 380.3
	84	2.11	1.36	(500 MHz, Chloroform-d) δ : 8.53 (s, 1H), 7.38 – 7.32 (m, 2H), 7.32 – 7.26 (m, 2H), 7.23 – 7.16 (m, 1H), 6.83 (d, J = 3.5 Hz, 1H), 6.72 (d, J = 3.5 Hz, 1H), 5.27 (d, J = 7.0 Hz, 1H), 5.06 (p, J = 7.0 Hz, 1H), 4.84 – 4.76 (m, 1H), 4.54 (t, J = 8.5 Hz, 1H), 3.99 (dd, J = 8.5, 6.5 Hz, 1H), 1.55 (d, J = 7.0 Hz, 3H), 0.98 (d, J = 4.0 Hz, 3H).	2.84 338
	85	2.117	30	(500 MHz, DMSO-*d*6) δ : 11.24 (s, 1H), 8.84 (d, J = 5.0 Hz, 1H), 8.43 (s, 1H), 8.00 (s, 1H), 7.81 (dd, J = 5.0, 1.0 Hz, 1H), 7.45 (s, 1H), 7.03 (d, J = 8.1 Hz, 1H), 6.91 (dd, J = 3.3, 1.6 Hz, 1H), 6.47 (dd, J = 3.3, 2.0 Hz, 1H), 5.21 – 5.11 (m, 2H), 4.94 – 4.76 (m, 1H), 4.50 – 4.42 (m, 2H), 4.41 – 4.24 (m, 1H), 2.27 (s, 3H), 1.51 (d, J = 7.0 Hz, 3H), 0.96 (d, J = 6.5 Hz, 3H).	2.30 528
	86	2.349	1.066	(500 MHz, MeOH-d4) δ 8.05 (d,J=5.6Hz, 1H), 7.48 (d, J=2.0Hz, 1H), 7.36 (d, J=8.4Hz, 1H), 7.27 (dd, J=8.4, 2.1 Hz), 7.15 (d, J=5.6Hz, 2H), 4.80 (d, J=16.9Hz, 2H), 4.46-4.58 (m, broad, 2H), 4.34-4.39 (m, broad, 1H), 2.04 (d, J=10.57Hz, 1H), 0.73 (d, J=6.0Hz, 6H)	4.03 437
	87	2.521	0.097	(500 MHz, DMSO-*d*6) δ 11.24 (s, 1H), 7.58 (d, *J* = 2.0 Hz, 1H), 7.40 – 7.27 (m, 3H), 7.00 – 6.86 (m, 1H), 6.16 (dd, *J* = 3.5, 1.9 Hz, 1H), 4.51 (d, *J* = 6.1 Hz, 2H), 4.13 (s, 2H), 1.40 (s, 6H).	3.70 406

	88	2.547	0.284	(500 MHz, DMSO-d6) δ : 11.15 (s, 1H), 7.36 – 7.21 (m, 7H), 7.20 – 7.15 (m, 3H), 6.97 (t, *J* = 6.5 Hz, 1H), 6.90 (t, *J* = 3.5, 2.0 Hz, 1H), 6.52 (dd, *J* = 3.5, 2.0 Hz, 1H), 5.93 – 5.86 (m, 1H), 4.89 (t, *J* = 8.5 Hz,1H), 4.39 (dd, *J* = 15.5, 6.5 Hz, 1H), 4.31 (dd, *J* = 15.5, 6.5 Hz, 1H), 4.27 – 4.20 (m, 1H).	3.22 386
	89	2.608	30	(250 MHz, DMSO-d6) δ 11.09 (s, 1H), 7.09 (t, J = 8.8 Hz, 1H), 6.83 - 6.68 (m, 2H), 6.12 (s, 1H), 5.98 (s, 2H), 5.11 (s, 1H), 4.85 - 4.74 (m, 1H), 4.45 (d, J = 7.1 Hz, 2H), 4.36 - 4.16 (m, 2H), 3.74 (s, 3H), 1.51 (d, J = 7.0 Hz, 3H), 0.93 (d, J = 5.5 Hz, 3H).	3.38 416
	90	2.719	4.109	(500 MHz, DMSO-d6) δ 11.26 (s, 1H), 7.19 (t, J = 6.3 Hz, 1H), 6.93 (dd, J = 3.5, 2.2 Hz, 1H), 6.73 (d, J = 3.3 Hz, 1H), 6.61 – 6.53 (m, 1H), 6.42 (dd, J = 3.5, 1.9 Hz, 1H), 4.81 (dt, J = 8.9, 4.7 Hz, 1H), 4.59 (dd, J = 15.6, 6.5 Hz, 1H), 4.53 – 4.43 (m, 2H), 4.32 (dd, J = 8.9, 5.1 Hz, 1H), 2.33 (s, 3H), 2.29 – 2.18 (m, 1H), 0.80 (d, J = 7.0 Hz, 3H), 0.72 (d, J = 6.9 Hz, 3H).	3.31 372
	91	2.75	0.78	(500 MHz, Chloroform-d) δ 7.93 (s, 1H), 7.38 (d, J = 2.0 Hz, 1H), 7.30 (d, J = 8.3 Hz, 1H), 7.15 (dd, J = 8.3, 2.0 Hz, 1H), 6.37 (s, 1H), 5.19 (t, J = 6.1 Hz, 1H), 4.78 – 4.68 (m, 2H), 4.55 (dd, J = 16.5, 6.2 Hz, 1H), 4.39 (t, J = 8.9 Hz, 1H), 4.24 (dd, J = 8.8, 5.5 Hz, 1H), 2.34 (d, J = 0.9 Hz, 3H), 2.16 (d, J = 7.1 Hz, 1H), 0.76 (dd, J = 6.9, 4.8 Hz, 6H).	3.92 434.2
	92	2.795	0.243	(500 MHz, DMSO-d6) δ 11.12 (s, 1H), 7.37 (d, J = 7.3 Hz, 2H), 7.27 (t, J = 7.7 Hz, 2H), 7.15 (dd, J = 13.2, 7.6 Hz, 2H), 6.88 (dd, J = 3.4, 2.3 Hz, 1H), 6.11 (dd, J = 3.5, 1.9 Hz, 1H), 5.04 (p, J = 7.1 Hz,1H), 4.12 (q, J = 8.3 Hz, 2H), 1.57 (s, 3H), 1.45 (d, J = 7.0 Hz, 3H), 1.40 – 1.04 (m, 3H).	3.06 352
	93	3.61	6.8	(500 MHz, DMSO-*d*6) δ 11.19 (s, 1H), 7.32 – 7.28 (m, 3H), 7.26 (d, *J* = 7.9 Hz, 1H), 7.19 (dt, *J* = 13.8, 6.7 Hz, 2H), 6.90 (dd, *J* = 3.6, 2.2 Hz, 1H), 6.41 (dd, *J* = 3.6, 2.0 Hz, 1H), 4.74 (m, 1H), 4.57 (dd, *J* =	3.14 352

				15.8, 6.7 Hz, 1H), 4.50 – 4.38 (m, 2H), 4.28 (dd, *J* = 8.9, 5.1 Hz, 1H), 2.11 (m, 1H), 0.79 – 0.62 (m, 6H).	
	94	3.89	30	(500 MHz, DMSO-d6) δ 11.12 (s, 1H), 6.88 (dd, J = 3.6, 2.2 Hz, 1H), 6.62 (t, J = 6.0 Hz, 1H), 6.40 (s, 1H), 4.81 (dt, J = 8.8, 4.8 Hz, 1H), 4.49 (t, J = 8.9 Hz, 1H), 4.32 (dd, J = 8.9, 5.0 Hz, 1H), 3.24 – 3.18 (m, 1H), 3.03 – 2.94 (m, 1H), 1.82 – 1.41 (m, 7H), 1.15 (s, 3H), 0.89 (d, J = 12.4 Hz, 2H), 0.85 (d, J = 7.0 Hz, 3H), 0.76 (d, J = 6.9 Hz, 3H).	3.55 358
	95	3.94	3.7	(500 MHz, DMSO-d6) δ 11.18 (s, 1H), 7.39 (d, J = 7.4 Hz, 2H), 7.28 (t, J = 7.6 Hz, 2H), 7.18 (q, J = 7.7 Hz, 2H), 7.06 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 3.6 Hz, 1H), 6.36 (d, J = 3.6 Hz, 1H), 5.18 (q, J = 8.0 Hz, 1H), 4.77 (s, 1H), 4.47 (t, J = 8.9 Hz, 1H), 4.28 (dd, J = 8.6, 5.4 Hz, 1H), 3.71 – 3.61 (m, 1H), 3.53 (dd, J = 9.9, 5.4 Hz, 1H), 3.28 (s, 3H), 0.94 (t, J = 7.3 Hz, 1H), 0.69 (s, 3H), 0.59 (s, 3H).	3.19 395
	96	4.302	30	(500 MHz, Methanol-d4) δ 8.05 (d, J = 1.4 Hz, 1H), 7.61 – 7.49 (m, 2H), 7.41 (s, 1H), 7.29 – 7.17 (m, 2H), 6.91 (d, J = 3.7 Hz, 1H), 6.55 (d, J = 3.7 Hz, 1H), 5.25 (q, J = 6.8 Hz, 1H), 5.00 – 4.92 (m, 1H), 4.50 (t, J = 9.0 Hz, 1H), 4.38 (dd, J = 9.0, 5.3 Hz, 1H), 2.52 – 2.28 (m, 1H), 1.59 (d, J = 6.9 Hz, 3H), 0.89 (dd, J = 39.2, 7.0 Hz, 6H)	2.14 450
	97	4.5	0.637	(500 MHz, Chloroform-d) δ 8.27 (s, 1H), 7.42 – 7.36 (m, 2H), 7.34 – 7.28 (m, 2H), 7.25 – 7.17 (m, 1H), 6.84 (dd, J = 3.5, 1.5 Hz, 1H), 6.37 (t, J = 3.5, 1.5 Hz, 1H), 5.23 (d, J = 7.0 Hz, 1H), 5.14 (h, J = 7.0 Hz, 1H), 4.35 (s, 2H), 4.03 (dd, J = 12.0, 5.0 Hz, 1H), 3.91 (dd, J = 12.0, 5.0 Hz, 1H), 3.42 – 3.30 (m, 2H), 3.07 (td, J = 13.0, 5.0 Hz, 1H), 2.83 – 2.74 (m, 1H), 1.67 – 1.62 (m, 1H), 1.58 (d, J = 7.0 Hz, 3H), 1.48 (d, J = 13.5 Hz, 1H).	2.71 394

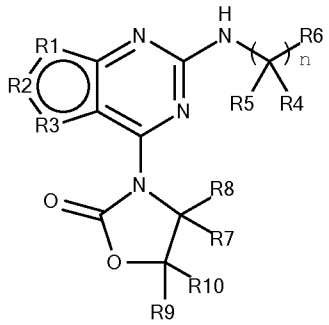
	98	4.995	0.547	(500 MHz, Chloroform-d) δ: 8.18 (s, 1H), 7.38 – 7.33 (m, 2H), 7.34 – 7.27 (m, 2H), 7.26 – 7.19 (m, 1H), 6.85 (t, J = 3.5, 2.0 Hz, 1H), 6.43 (dd, J = 3.5, 2.0 Hz, 1H), 5.08 – 5.01 (m, 2H), 4.38 – 4.30 (m, 2H), 1.94 – 1.86 (m, 1H), 1.65 – 1.52 (m, 4H+water), 0.68 – 0.59 (m, 1H), 0.57 – 0.48 (m, 1H).	3.04 350
	99	5.01	2.59	(500 MHz, DMSO-d6) δ 11.22 (s, 1H), 7.30 (dd, J = 5.0, 1.3 Hz, 1H), 7.24 (t, J = 6.3 Hz, 1H), 6.97 (d, J = 2.4 Hz, 1H), 6.95 – 6.91 (m, 2H), 6.44 (d, J = 3.6 Hz, 1H), 4.84 – 4.79 (m, 1H), 4.70 (dd, J = 15.9, 6.5 Hz, 1H), 4.58 (dd, J = 15.7, 6.0 Hz, 1H), 4.48 (t, J = 8.9 Hz, 1H), 4.32 (dd, J = 9.0, 5.1 Hz, 1H), 0.79 (d, J = 7.0 Hz, 3H), 0.72 (d, J = 6.9 Hz, 3H).	3.16 358
	100	5.09	30	(500 MHz, DMSO-d6) δ 11.25 (s, 1H), 7.68 (d, J = 4.0 Hz, 1H), 7.61 (d, J = 3.6 Hz, 1H), 7.21 (dd, J = 13.1, 6.8 Hz, 2H), 7.17 – 7.12 (m, 1H), 6.93 (d, J = 3.5 Hz, 1H), 6.45 (d, J = 3.6 Hz, 1H), 5.75 (s, 1H), 4.76 (s, 1H), 4.66 (d, J = 16.3 Hz, 1H), 4.54 – 4.40 (m, 2H), 4.28 (s, 1H), 0.75 – 0.63 (m, 6H).	3.27 441
	101	6.06	1.68	(500 MHz, DMSO-d6) δ 11.50 (s, 1H), 9.16 (s, 1H), 7.77 (d, J = 7.8 Hz, 2H), 7.26 (t, J = 7.9 Hz, 2H), 7.08 (d, J = 3.6 Hz, 1H), 6.90 (t, J = 7.3 Hz, 1H), 6.56 (d, J = 3.6 Hz, 1H), 4.93 (dt, J = 8.9, 4.8 Hz, 1H), 4.55 (t, J = 8.9 Hz, 1H), 4.38 (dd, J = 8.9, 5.1 Hz, 1H), 2.36 (tt, J = 10.8, 5.4 Hz, 1H), 0.89 (d, J = 7.0 Hz, 3H), 0.77 (d, J = 6.9 Hz, 3H).	3.30 338
	102	6.956	5.561	(500 MHz, DMSO-d6) δ 11.05 (s, 1H), 7.40 (d, J = 7.4 Hz, 2H), 7.23 (t, J = 7.7 Hz, 2H), 7.10 (t, J = 7.3 Hz, 1H), 6.90 – 6.83 (m, 2H), 6.04 (dd, J = 3.5, 1.9 Hz, 1H), 4.04 (s, 2H), 1.68 (s, 6H), 1.15 (s, 6H).	3.42 366

	103	7.17	1.87	(500 MHz, Chloroform-d) δ: 8.25 (s, 1H), 7.39 (d, J = 2.0 Hz, 1H), 7.34 (d, J = 8.5 Hz, 1H), 7.17 (dd, J = 8.5, 2.0 Hz, 1H), 6.87 (t, J = 3.5, 2.0 Hz, 1H), 6.77 (t, J = 3.5, 2.0 Hz, 1H), 5.27 (t, J = 6.0 Hz, 1H), 4.89 – 4.78 (m, 1H), 4.73 (dd, J = 16.5, 6.5 Hz, 1H), 4.62 (dd, J = 16.5, 6.5 Hz, 1H), 4.56 (t, J = 8.5 Hz, 1H), 4.05 (dd, J = 8.5, 6.0 Hz, 1H), 1.33 (d, J = 6.0 Hz, 3H).	3.41 392
	104	7.89	12.8	(500 MHz, DMSO-d6) δ 11.19 (s, 1H), 8.59 (s, 1H), 8.37 (d, J = 4.7 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.29 (dd, 1H), 7.26 (d, J = 8.1 Hz, 1H), 6.92 (s, 1H), 6.36 (d, J = 2.9 Hz, 1H), 5.08 (p, J = 7.4 Hz, 1H), 4.76 – 4.68 (m, 1H), 4.46 (t, J = 9.1 Hz, 1H), 4.32 – 4.22 (m, 1H), 1.47 (d, J = 7.2 Hz, 3H), 0.61 (d, J = 40.3 Hz, 6H).	1.56 367
	105	8.96	1.51	(500 MHz, Chloroform-d) δ: 8.24 (s, 1H), 7.40 – 7.34 (m, 2H), 7.35 – 7.28 (m, 2H), 7.26 – 7.19 (m, 3H), 6.82 (dd, J = 3.5, 2.0 Hz, 1H), 6.75 (t, J = 3.5, 2.0 Hz, 1H), 5.13 – 5.05 (m, 2H), 4.73 – 4.62 (m, 1H), 4.50 (t, J = 8.5 Hz, 1H), 4.04 (dd, J = 8.5, 6.0 Hz, 1H), 1.56 (d, J = 6.5 Hz, 3H), 1.49 (d, J = 6.0 Hz, 3H).	2.82 338
	106	10.8	19.9	(500 MHz, DMSO-d6) δ 11.18 (s, 1H), 7.20 – 7.15 (m, 1H), 6.91 (dd, J = 3.6, 2.2 Hz, 1H), 6.68 (t, J = 5.6 Hz, 1H), 6.41 (dd, J = 3.6, 2.0 Hz, 1H), 4.85 – 4.80 (m, 1H), 4.48 (t, J = 8.9 Hz, 1H), 4.31 (dd, J = 8.9, 5.2 Hz, 1H), 4.23 (qd, J = 14.6, 5.7 Hz, 2H), 2.30 – 2.26 (m, 1H), 2.25 (s, 3H), 1.92 (d, J = 1.1 Hz, 3H), 0.82 (d, J = 7.0 Hz, 3H), 0.73 (d, J = 6.9 Hz, 3H).	3.25 370
	107	18.615	6.364	(500 MHz, Chloroform-d) δ 8.58 (s, 1H), 7.23 - 7.18 (m, 1H), 7.16 - 7.10 (m, 1H), 6.95 - 6.87 (m, 2H), 6.49 (d, J = 5.7 Hz, 1H), 4.73 (s, 2H), 4.62 - 4.53 (m, 2H), 4.52 - 4.47 (m, 2H), 4.40 - 4.33 (m, 1H), 4.28 - 4.21 (m, 1H), 3.91 (d, J = 2.9 Hz, 3H), 1.65 (dd, J = 7.2, 1.0 Hz, 3H), 1.24 (t, J = 6.6 Hz, 3H).	2.41 398

	108	19.222	3.72	(500 MHz, DMSO-*d*6) _ 11.19 (s, 1H), 7.19 (d, *J* = 7.9 Hz, 2H), 7.16 (t, *J* = 6.5 Hz, 1H), 7.08 (d, *J* = 7.8 Hz, 2H), 6.91 (dd, *J* = 3.6, 2.0 Hz, 1H), 6.41 (dd, *J* = 3.6, 1.7 Hz, 1H), 4.75 (s, 1H), 4.52 (dd, *J* = 15.5, 6.5 Hz, 1H), 4.47 (t, *J* = 8.9 Hz, 1H), 4.38 (dd, *J* = 15.5, 6.1 Hz, 1H), 4.30 (dd, *J* = 8.9, 5.2 Hz, 1H), 2.25 (s, 3H), 2.12 (d, *J* = 31.5 Hz, 1H), 0.75 (s, 3H), 0.69 (d, *J* = 6.7 Hz, 3H).	3.37 366

Claims

1. A compound of general Formula (I)



(I)

or a salt or solvate thereof, wherein

n is 0 or 1;

R^1 is $N(R^{11})$ or CH;
R^2 is N or $C(R^{12})$;
R^3 is S or $C(R^{13})$;
provided that
R^1 is CH and R^2 is CR^{12} when R^3 is S; and
R^1 is $N(R^{11})$ when R^3 is $C(R^{13})$;

R^{11} is a hydrogen atom or CH_3;
R^{12} is a hydrogen atom, a cyano group or CH_3;
R^{13} is a hydrogen atom or a halogen atom;

R^4, R^5 are independently selected from a hydrogen atom; CH_2OH; CH_2OCH_3; a C_{1-6} alkyl group, wherein the C_{1-6} alkyl group is unsubstituted or substituted with at least one halogen atom; or

R^4, R^5 may be joined together to form a C_{3-6} cycloalkyl group;

R^6 is an aromatic group, a heteroaromatic group or a C_{3-6} cycloalkyl group, wherein R^6 is unsubstituted or substituted with one or two R^{6a}, which are the same or different;
R^{6a} is a halogen atom, a C_{1-6} alkyl group, a C_{1-6} alkoxy group, a $S(O)_2$-C_{1-6} alkyl group, or R^{6aa};
R^{6aa} is an aromatic group, a heteroaromatic group, or a heteroalicyclylalkyl group, wherein R^{6aa} is unsubstituted or substituted with one or two R^{6b}, which are the same or different;
R^{6b} is a halogen atom; a C_{1-6} alkyl group, which is unsubstituted or substituted with at least one halogen atom; cyclopropyl or benzyloxycarbonyl;

R^7, R^8 are independently selected from a hydrogen atom, or R^{7a}, or R^7 and R^8 may be joined together to form a C_{3-6} cycloalkyl group or a heteroalicyclic group;
R^{7a} is a C_{1-6} alkyl group, an aromatic group, a heteroaromatic group, or a heteroalicyclic group, wherein R^{7a} is unsubstituted or substituted with a substituent selected from a halogen atom, CH_3, or OH;

R^9, R^{10} are independently selected from a hydrogen atom, or R^{9a}, or R^9 and R^{10} may be joined together to form a C_{3-6} cycloalkyl group or a heteroalicyclic group;
R^{9a} is a C_{1-6} alkyl group, an aromatic group, a heteroaromatic group, or a heteroalicyclic group, wherein R^{9a} is unsubstituted or substituted with a substituent selected from a halogen atom, CH_3, or OH.

2. The compound according to claim 1 or a salt or solvate thereof, wherein

(i) R^1 is NH, R^2 is CH, R^3 is CH; or

(ii) R^1 is NH, R^2 is N, R^3 is CH; or

(iii) R^1 is CH, R^2 is CH, R^3 is S; or

(iv) R^1 is NH, R^2 is CH, R^3 is CF; or

(v) R^1 is NH, R^2 is CCN, R^3 is CH; or

(vi) R^1 is NH, R^2 is CCH_3, R^3 is CH; or

(vii) R^1 is NCH_3, R^2 is CH, R^3 is CH.

3. The compound according to claim 1 or 2 or a salt or solvate thereof, wherein one of R^4, R^5 is a hydrogen atom or CH_3 and the other is a hydrogen atom, CH_3, CH_2CH_3, CH_2OH, CH_2OCH_3, CH_2F or CF_3; or R^4, R^5 are joined together to form a cyclopropyl group.

4. The compound according to any of claims 1 to 3 or a salt or solvate thereof, wherein R^6 is an aromatic group or a heteroaromatic group and wherein R^6 is unsubstituted or substituted with one or two R^{6a}, which are the same or different.

5. The compound according to any of claims 1 to 4 or a salt or solvate thereof, wherein R^6 is imidazolyl, pyridyl, thiazolyl, pyrazolyl, phenyl, oxadiazolyl, oxazolyl, cyclohexyl, thiophenyl or furanyl and wherein R^6 is unsubstituted or substituted with one or two R^{6a}, which are the same or different.

6. The compound according to any of claims 1 to 5 or a salt or solvate thereof, wherein R^{6a} is CH_3, OCH_3, F, Cl, $S(O)_2CH_3$ or R^{6aa}.

7. The compound of any of claims 1 to 6 or a salt or solvate thereof, wherein R^{6aa} is phenyl, pyridyl, thiophenyl or piperazinylmethyl and wherein R^{6aa} is unsubstituted or substituted with one or two R^{6b}, which are the same or different.

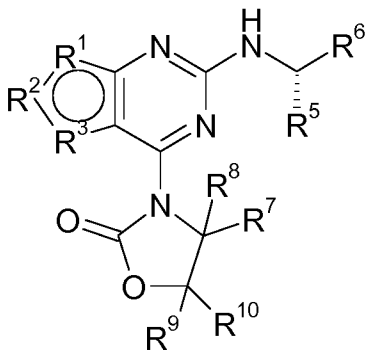
8. The compound according to any of claims 1 to 7 or a salt or solvate thereof, wherein R^{6b} is Cl, F, CF_3, cyclopropyl or benzyloxycarbonyl.

9. The compound according to any of claims 1 to 8 or a salt or solvate thereof, wherein one of R^7, R^8 is a hydrogen atom or CH_3 and the other is CH_2F, a fluoroethyl, methyl, ethyl, isopropyl, tert.-butyl, 1-methyl-propyl, a hydroxyethyl, phenyl, pyridyl or methylimidazolyl; or R^7 and R^8 are joined together to form a cyclopropyl, tetrahydrofuranyl or tetrahydropyranyl group.

10. The compound according to any of claims 1 to 9 or a salt or solvate thereof, wherein R^9 and R^{10} are hydrogen atoms, and at least one of R^7 and R^8 is other than a hydrogen atom.

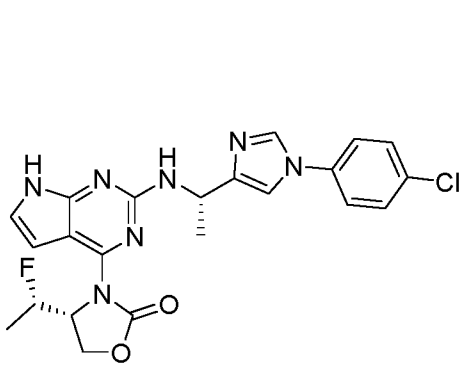
11. The compound according to any of claims 1 to 10 or a salt or solvate thereof, wherein n is 1.

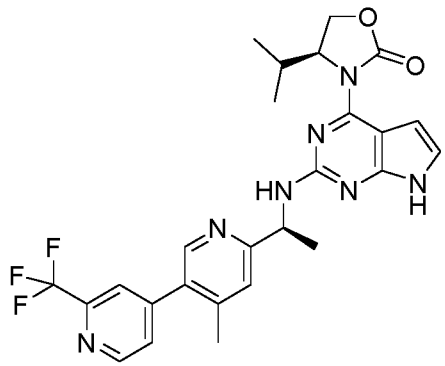
12. The compound according to any of claims 1 to 11 or a salt or solvate thereof of Formula (I), wherein n is 1, R^4 is a hydrogen atom and R^5 is other than a hydrogen atom to give Formula (Ia)

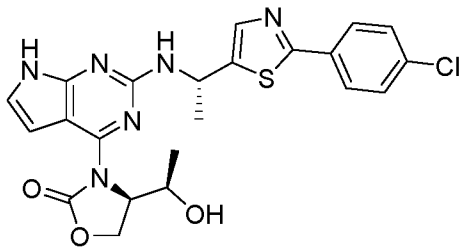


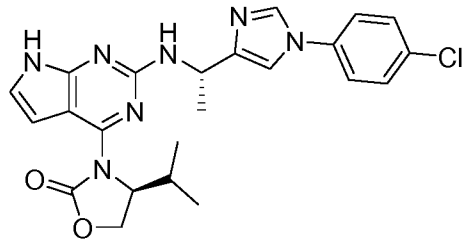
(Ia).

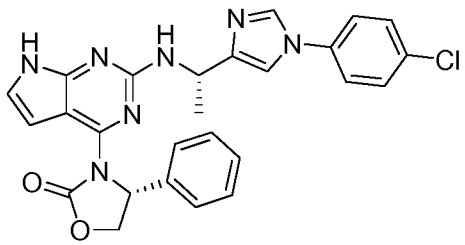
13. The compound according to any of claims 1 to 12 or a salt or solvate thereof, wherein the compound is selected from one of the following:

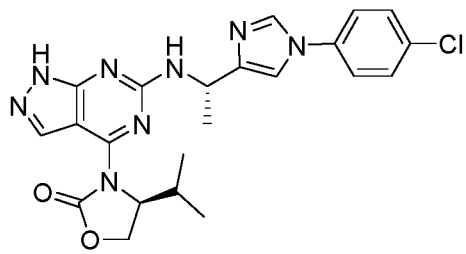


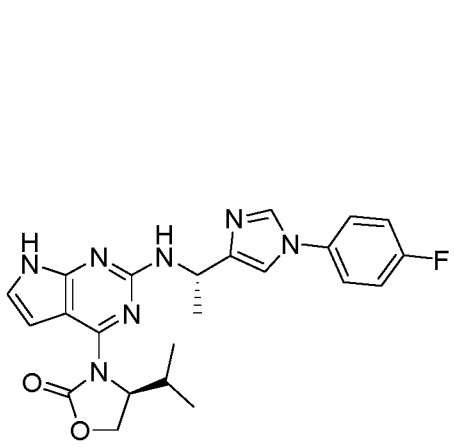


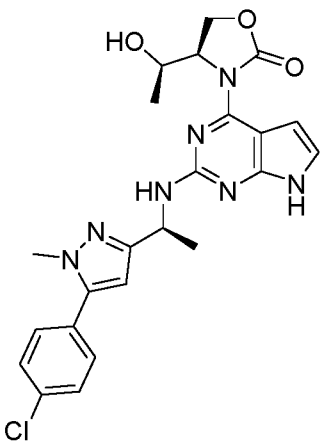


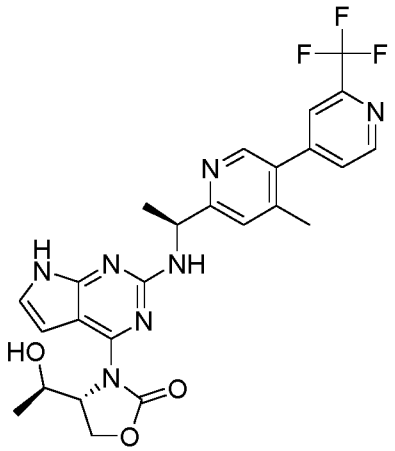


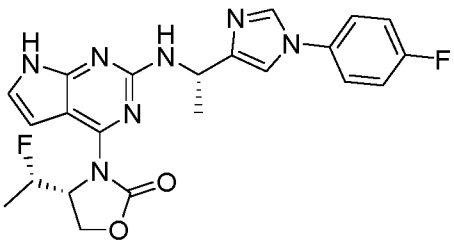


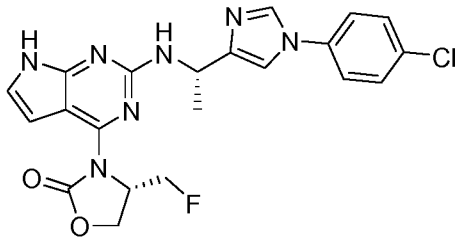












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14. A compound according to any of claims 1 to 13 or a salt or solvate thereof for use in the treatment or prophylaxis of a disorder of a human or animal body.

15. A compound according to any of claims 1 to 13 or a salt or solvate thereof for use in the treatment or prophylaxis of a disorder associated with a mutant isocitrate dehydrogenase having a neomorphic activity.

16. The compound according to any of claims 1 to 13 or a salt or solvate thereof for use according to Claim 15, wherein the disorder associated with a mutant isocitrate dehydrogenase having a neomorphic activity is a cell proliferation disorder.

17. The compound according to any of claims 1 to 13 or a salt or solvate thereof for use according to Claim 15 or 16, wherein the disorder associated with a mutant isocitrate dehydrogenase having a neomorphic activity is one of the following: brain cancer, such as glioma, glioblastoma multiforme, paraganglioma, and supratentorial primordial neuroectodermal tumors (pNET), leukemia, such as acute myeloid leukemia (AML), myelodysplasia syndrome, and chronic myelogenous leukemia (CML), skin cancer such as melanoma, prostate cancer, thyroid cancer, colon cancer, lung cancer, sarcoma, including central chondrosarcoma, central and periosteal chondroma, and fibrosarcoma.

18. A pharmaceutical composition comprising the compound of general Formula (I) according to any of Claims 1 to 13 or of a salt or solvate thereof as active ingredient.

19. The pharmaceutical composition according to Claim 18, wherein said pharmaceutical composition is an oral dosage form.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/053464

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 C07D495/04 A61K31/519 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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2013/046136 A1 (NOVARTIS AG [CH]; CHO YOUNG SHIN [US]; LEVELL JULIAN ROY [US]; TOURE B) 4 April 2013 (2013-04-04) cited in the application page 1, line 4 - line 8 page 2, line 10 - line 12 page 3; compound (I) page 33, line 12 - line 23 tables 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 26, 28, 30	1-19
A	CN 104 177 363 A (JIANGSU SIMCERE PHARMACEUTICAL; JIANGSU SIMCERE PHARMACEUTICAL) 3 December 2014 (2014-12-03) examples 27-30 claims 9, 10	1-19

☐ 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

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Date of the actual completion of the international search	Date of mailing of the international search report
28 March 2017	06/04/2017

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