

HETEROCONDENSED PYRIDONES COMPOUNDS AND THEIR USE AS IDH INHIBITORS

The present invention relates to certain substituted heterocondensed pyridone analogues, which modulate the activity of Isocitrate Dehydrogenase (IDH). The compounds of this invention are therefore useful in treating diseases caused by mutated IDH1 and/or mutated IDH2 enzyme and/or IDH1 wild type enzyme. The present invention also provides methods for preparing these compounds, pharmaceutical compositions comprising these compounds, and methods of treating diseases utilizing pharmaceutical compositions comprising these compounds.

Background of the invention

Isocitrate dehydrogenases (IDHs) represent a family of metal dependent oxidoreductases involved in cellular metabolism. These enzymes catalyze the oxidative decarboxylation of isocitrate to alpha-ketoglutarate generating carbon dioxide and NADH or NADPH in the process.

Three different members of this family have been identified: IDH1 and IDH2 that are structurally related homodimers and use NADP⁺ as electron acceptor, and IDH3 that is a heterotrimeric complex and uses instead NAD⁺ as electron acceptor.

IDH1 is localized in the cytoplasm and peroxisomes and represent a major source of NADPH production for cells, while IDH2 is localized in the mitochondria as an integral part of the tricarboxylic acid cycle (TCA). The human IDH1 gene encodes a protein of 414 amino acids whose amino acid sequence can be found as UniProtKB accession no. O75874. The human IDH2 gene encodes a protein of 452 amino acid whose amino acid sequence can be found as UniProtKB accession no. P48735.

Somatic heterozygous mutations in isocitrate dehydrogenase 1 (IDH1) were identified in approximately 80% of grade II–III gliomas and in secondary glioblastomas (see Balss, J. Acta Neuropathol, 2008, 116, 597–602, Watanabe, T., Am. J. Pathol, 2009, 174, 1149–1153, Yan, H. N. Engl. J. Med. 2009, 360, 765–773). IDH1 mutations were also found in 50 % of chondrosarcoma (see Amary MF, J. Pathol 2011, 224, 334–43), in 15%–20% of intrahepatic cholangiocarcinoma (see Borger DR, Oncol. 2012, 17, 72–9), and at lower frequency (< 5%) in other solid tumors (e.g. glioblastomas, colorectal cancer, esophageal cancer, bladder cancer, melanoma, prostate carcinoma, breast adenocarcinoma (see Cerami E, Cancer Discov. 2012, 2, 401–4).

IDH1 and IDH2 mutations were also observed in a number of hematopoietic neoplasms, most commonly in 10%–15% acute myeloid leukemia (AML) (see, e.g. Mardis ER, N Engl J. Med. 2009, 361, 1058–66, Gross S, J. Exp. Med. 2010, 207, 339–44, Marcucci G, J. Clin. Oncol. 2010, 28, 2348–55) and 20% of angio-immunoblastic T-cell lymphoma (see Cairns RA, Blood 2012, 119, 1901–3).

Interestingly the same mutations in IDH1 or IDH2 were identified in the majority of enchondromas and spindle cell hemangiomas in patients with the Ollier disease and Maffucci syndrome, nonhereditary skeletal disorders (see Amary et al., Nature Genetics, 2011, 1261–1265; and Pansuriya TC, Nat. Genet. 2011, 43, 1256–61).

All mutations have been found in heterozygosity in a mutual exclusive way and in specific tissues. These mutations reside in the catalytic domain of the enzyme responsible for 2-oxoglutarate coordination, and involve mainly Arg 132 (R132) in IDH1 and Arg 140 (R140) or Arg 172 (R172) in IDH2, that can mutate to different aminoacids. Other mutations were also identified in IDH1 although with very low frequency (e.g. Arg 100, and Gly 97; Dang L, Nature, 2009, 462, 739–44). In all cases these points of mutation of Arg to Cys, His, Lys, Leu or Ser abolish magnesium

binding and prevent the conversion of isocitrate to alpha-ketoglutarate. Instead, the mutated enzymes acquired a neomorphic activity that converts the alpha-ketoglutarate into R(-)-2-hydroxyglutarate (R-2-HG) (See P.S. Ward et al., Cancer Cell, 2010, 17, 225). In general, the production of 2-HG is enantiospecific, resulting in generation of the D-enantiomer (also known as R enantiomer or R-2-HG). R(-)-2-hydroxyglutarate was shown to act as an oncometabolite, mainly through the inhibition of several DNA and histone demethylases. The consequence at cellular level is an epigenetic reprogramming, leading to a different transcriptional asset, that induce dedifferentiation and tumorigenesis.

IDH1 over-expression was shown to sustain a less differentiated tumor cell state, to promote growth, to accelerate tumor progression and to reduce susceptibility to RTK-targeting therapies in glioblasoma (GBM) and other solid and systemic cancer models. At molecular level, diminished IDH1 activity results in reduced α -ketoglutarate (α -KG) and NADPH production, exhaustion of reduced glutathione, increased levels of reactive oxygen species (ROS), and enhanced histone methylation and differentiation markers expression. Pharmacological inhibition of IDH1 with a small molecule reduces GBM tumor burden and increases the survival of PDX mice. These data suggest also that cancer-associated IDH1 upregulation represents an actionable ("druggable") cancer-promoting mechanism and provide the rationale for the evaluation of wild-type IDH1 inhibitors as anti-neoplastic agents (see Calvert et al., 2017, Cell Reports 19, 1858–1873).

The inhibition of activity of IDH enzymes is therefore a potential therapeutic treatment option for tumors and other IDH related disorders.

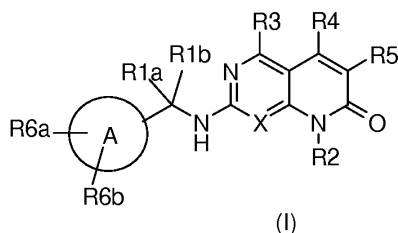
Accordingly, there is a strong medical need for therapeutic agents active against diseases caused by and/or associated with mutated IDH enzymes, and /or IDH wt over-functions, and several efforts are ongoing to develop inhibitors, in particular small molecule inhibitors, of their alpha hydroxyl neomorphic activity.

Certain pyrido-pyridin-7-one derivatives having biological activity as kinase inhibitors are disclosed in WO2005/047284 in the name of Hoffmann La Roche.

Other pyrido-pyrimidin-7-one compounds useful as kinase inhibitors are disclosed in WO2007044813, in the name of Exelixis Inc., and in WO2008/034008 in the name of Deciphera Pharmaceuticals Lcc.

The inventors have now found that compounds of formula (I), described below, are inhibitors of mutated IDH1 and/or mutated IDH2 and/or IDH1 wild type enzymes and are thus useful to treat diseases caused by high level of 2-HG, or caused by IDH wt over-functions.

Accordingly, a first object of the present invention is a substituted heterocondensed pyridone derivative of formula (I):



wherein:

X is nitrogen or -CH-

R1a is hydrogen or an optionally substituted straight or branched (C₁-C₆)alkyl;

- R1b** is an optionally substituted (C₁-C₆)alkyl, or together with the atom to which they are bound, **R1a** and **R1b** may form a (C₃-C₆)cycloalkyl;
- A** is a (C₃-C₆)cycloalkyl, aryl or heteroaryl;
- R6a** and **R6b** are each independently selected from hydrogen, halogen, cyano, an optionally substituted straight or branched (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, cycloalkyl-alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, aryl, heteroaryl, heterocyclyl, -OR7, NR7R8, -COOR7, -SO₂R7, -CONR7R8, -CH(R14)OR7 and -CH(R14)NR7R8;
- wherein:
- R14 is hydrogen or an optionally substituted straight or branched (C₁-C₆)alkyl;
- R7 and R8 are each independently hydrogen or a group selected from an optionally substituted straight or branched (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, aryl, heteroaryl, heterocyclyl, aryl-alkyl, heteroaryl-alkyl, heterocyclyl-alkyl, heterocyclyl-C(O)-alkyl, heterocyclyl-C(O)-alkenyl, heterocyclyl-C(O)-alkynyl or, together with the nitrogen atom to which they are bound, R7 and R8 form a 5- to 7-membered heteroaryl or heterocyclyl group optionally containing one additional heteroatom selected from O, S and NR9;
- wherein:
- R9 is hydrogen, an optionally substituted straight or branched (C₁-C₆)alkyl, -COOR10 or -COR11;
- wherein:
- R10 is hydrogen or an optionally substituted straight or branched (C₁-C₆)alkyl;
- R11 is an optionally substituted straight or branched (C₁-C₆)alkyl, (C₂-C₆)alkenyl or (C₂-C₆)alkynyl;
- R2** is an optionally substituted group selected from straight or branched (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl-(C₁-C₆)alkyl, aryl-(C₁-C₆)alkyl, and heterocyclyl-(C₁-C₆)alkyl;
- R3** is hydrogen, chloro, cyano, CONH₂, NH₂, NR13R13a, OR12, or an optionally substituted group selected from straight or branched (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl-(C₁-C₆)alkyl, aryl and heteroaryl;
- wherein:
- R12 is an optionally substituted straight or branched (C₁-C₆)alkyl;
- R13, R13a are each independently selected from hydrogen or optionally substituted straight or branched (C₁-C₆)alkyl;
- R4** is hydrogen or an optionally substituted straight or branched (C₁-C₆)alkyl;
- R5** is hydrogen, fluoro, cyano, an optionally substituted straight or branched (C₁-C₆)alkyl or -OR12,
- wherein:
- R12 is as described above;
- or a pharmaceutically acceptable salt thereof.
- Preferred compounds of formula (I) are the compounds wherein:
- R3** is hydrogen, chloro, cyano, CONH₂, NH₂, NR13R13a, OR12, or an optionally substituted straight or branched (C₁-C₆)alkyl;
- wherein:
- R12 is an optionally substituted straight or branched (C₁-C₆)alkyl;

R13, R13a are each independently selected from hydrogen or optionally substituted straight or branched (C₁-C₆)alkyl;

R5 is hydrogen, fluoro or -OR12,
wherein:

5 R12 is as described above; and

R1a, R1b, A, X, R6a, R6b, R2 and **R4** are as defined above.

More preferred compounds of formula (I) are the compounds wherein:

R6a and **R6b** are each independently selected from hydrogen, halogen, cyano, an optionally substituted straight or branched (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, aryl, heteroaryl, heterocyclyl, -OR7, NR7R8, -COOR7, -
10 SO₂R7, -CONR7R8, -CH(R14)OR7 and -CH(R14)NR7R8;
wherein:

R7, R8 and R14 are as defined above;

R5 is hydrogen or fluoro; and

R1a, R1b, A, X, R2, R3 and **R4** are as defined above.

15 Most preferred compounds of formula (I) are the compounds wherein:

A is aryl or heteroaryl;

R3 is hydrogen, cyano, CONH₂, NH₂, NR13R13a, or an optionally substituted straight or branched (C₁-C₆)alkyl;
wherein:

20 R13, R13a are each independently selected from hydrogen or optionally substituted straight or branched (C₁-C₆)alkyl; and

R1a, R1b, R6a, R6b, X, R2, R4 and **R5** are as defined above.

Preferred specific compounds of formula (I), or a pharmaceutically acceptable salt thereof, are the compounds listed below:

- methyl 4-((1S)-1-[(8-benzyl-7-oxo-pyrido[2,3-d]pyrimidin-2-yl)amino]ethyl)benzoate (cpd 1);
25 methyl 4-((1S)-1-[(8-ethyl-7-oxo-pyrido[2,3-d]pyrimidin-2-yl)amino]ethyl)benzoate (cpd 2);
methyl 4-((1S)-1-[(8-(methoxymethyl)-7-oxo-pyrido[2,3-d]pyrimidin-2-yl)amino]ethyl)benzoate (cpd 3);
methyl 4-((1S)-1-[(8-methyl-7-oxo-pyrido[2,3-d]pyrimidin-2-yl)amino]ethyl)benzoate (cpd 4);
methyl 4-((1S)-1-[(8-(2-methylpropyl)-7-oxo-pyrido[2,3-d]pyrimidin-2-yl)amino]ethyl)benzoate (cpd 5);
methyl 4-((1S)-1-[(8-(4-fluorobenzyl)-7-oxo-pyrido[2,3-d]pyrimidin-2-yl)amino]ethyl)benzoate (cpd 6);
30 methyl 4-((1S)-1-[(8-(3,5-difluorobenzyl)-7-oxo-pyrido[2,3-d]pyrimidin-2-yl)amino]ethyl)benzoate (cpd 7);
methyl 4-((1S)-1-[(8-[4-fluoro-2-(trifluoromethyl)benzyl]-7-oxo-pyrido[2,3-d]pyrimidin-2-yl)amino]ethyl)benzoate (cpd 8);
methyl 4-((1S)-1-[(7-oxo-8-(propan-2-yl)-pyrido[2,3-d]pyrimidin-2-yl)amino]ethyl)benzoate (cpd 9);
methyl 4-((1S)-1-[(8-[(3-methyloxetan-3-yl)methyl]-7-oxo-pyrido[2,3-d]pyrimidin-2-yl)amino]ethyl)benzoate (cpd 10);
35 methyl 4-((1S)-1-[(8-(2,2-dimethylpropyl)-7-oxo-pyrido[2,3-d]pyrimidin-2-yl)amino]ethyl)benzoate (cpd 11);
2-(((1S)-1-cyclohexylethyl)amino)-8-ethylpyrido[2,3-d]pyrimidin-7(8H)-one (cpd 12);
8-ethyl-2-(((1S)-1-(4-methoxyphenyl)ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 13);
2-(((1S)-1-(4-chlorophenyl)ethyl)amino)-8-ethylpyrido[2,3-d]pyrimidin-7(8H)-one (cpd 14);

- 2-(((1S)-1-(4-chlorophenyl)ethyl)amino)-8-(pentan-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 15);
8-benzyl-2-(((1S)-1-(4-chlorophenyl)ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 16);
2-(((1S)-1-(4-chlorophenyl)ethyl)amino)-8-(2-fluoroethyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 17);
2-(((1S)-1-(4-chlorophenyl)ethyl)amino)-8-(2,2,2-trifluoroethyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 18);
5 2-(((1S)-1-(4-chlorophenyl)ethyl)amino)-8-(2-methylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 19);
2-(((1S)-1-(4-chlorophenyl)ethyl)amino)-8-(cyclopropylmethyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 20);
2-(((1S)-1-(4-chlorophenyl)ethyl)amino)-8-(4-methoxybenzyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 21);
2-(((1S)-1-(4-chlorophenyl)ethyl)amino)-8-(2-fluorobenzyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 22);
2-(((1S)-1-(4-chlorophenyl)ethyl)amino)-8-(3,4-difluorobenzyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 23);
10 2-(((1S)-1-(4-chlorophenyl)ethyl)amino)-8-[3-(trifluoromethyl)benzyl]pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 24);
2-(((1S)-1-(4-chlorophenyl)ethyl)amino)-8-(2,4-difluorobenzyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 25);
2-(((1S)-1-(4-chlorophenyl)ethyl)amino)-8-[4-(trifluoromethoxy)benzyl]pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 26);
4-[[2-(((1S)-1-(4-chlorophenyl)ethyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl]methyl]benzonitrile (cpd 27);
2-(((1S)-1-(4-chlorophenyl)ethyl)amino)-8-(4-fluorobenzyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 28);
15 2-(((1S)-1-(4-chlorophenyl)ethyl)amino)-8-(3,5-difluorobenzyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 29);
2-(((1S)-1-(4-chlorophenyl)ethyl)amino)-8-(3-methoxybenzyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 30);
2-(((1S)-1-(4-chlorophenyl)ethyl)amino)-8-(2,6-difluorobenzyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 31);
2-(((1S)-1-(4-chlorophenyl)ethyl)amino)-4-methyl-8-(2-methylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 32);
8-(2,2-dimethylpropyl)-2-(((1S)-1-(4-methoxyphenyl)ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 33);
20 2-(((1S)-1-(4-bromophenyl)ethyl)amino)-8-(2,2-dimethylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 34);
2-(((1S)-1-(4-bromophenyl)ethyl)amino)-8-(3-hydroxy-2,2-dimethylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 35);
8-(2,2-dimethylpropyl)-2-(((1S)-1-(naphthalen-2-yl)ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 36);
methyl 2,2-dimethyl-3-[2-(((1S)-1-(naphthalen-2-yl)ethyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl]propanoate (cpd 37);
25 8-(3-hydroxy-2,2-dimethylpropyl)-2-(((1S)-1-(naphthalen-2-yl)ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 38);
8-(2,2-dimethylpropyl)-2-(((1R)-1-phenylethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 39);
8-(2,2-dimethylpropyl)-2-(((1S)-1-phenylethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 40);
8-(2,2-dimethylpropyl)-2-[(2-phenylpropan-2-yl)amino]pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 41);
8-(2,2-dimethylpropyl)-2-[(1-phenylcyclopropyl)amino]pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 42);
30 8-(2,2-dimethylpropyl)-2-[(1-phenylcyclobutyl)amino]pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 43);
8-(2,2-dimethylpropyl)-2-[[1-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)ethyl]amino]pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 44);
8-[(3-methyloxetan-3-yl)methyl]-2-(((1S)-1-(naphthalen-2-yl)ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 45);
8-(2-hydroxy-2-methylpropyl)-2-(((1S)-1-phenylethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 46);
8-(2,2-Dimethyl-propyl)-6-fluoro-2-((S)-1-phenyl-ethylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (cpd 47);
35 Methyl 4-(((1S)-1-[[8-(2-hydroxy-2-methylpropyl)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl]amino]ethyl]benzoate (cpd 48);
8-(2,2-dimethylpropyl)-2-(((1S)-1-(4-phenoxyphenyl)ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 49);
2-(((1S)-1-(6-chloro-2-oxo-quinolin-3-yl)ethyl)amino)-8-(2,2-dimethylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 50);

- 8-benzyl-2-(((1S)-1-(5-chloro-1H-benzimidazol-2-yl)ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 51);
8-benzyl-2-(((1S)-1-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl]ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 52);
2-(((1S)-1-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl]ethyl)amino)-8-(2,2-dimethylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 53);
- 5 8-(2,2-dimethylpropyl)-2-(((1S)-1-(4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 54);
2-(((1S)-1-[4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl]ethyl)amino)-8-(3-hydroxy-2,2-dimethylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 55);
4-[4-((S)-1-[8-(3-Hydroxy-2,2-dimethyl-propyl)-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino]-ethyl)-benzyl]-piperazine-1-carboxylic acid tert-butyl ester (cpd 56);
- 10 2-((S)-1-[4-(3,3-Difluoro-piperidin-1-ylmethyl)-phenyl]-ethylamino)-8-(2,2-dimethyl-propyl)-6-fluoro-8H-pyrido[2,3-d]pyrimidin-7-one (cpd 57);
2-((S)-1-[4-(3,3-Difluoro-piperidin-1-ylmethyl)-phenyl]-ethylamino)-8-(2,2-dimethyl-propyl)-6-methoxy-8H-pyrido[2,3-d]pyrimidin-7-one (cpd 58);
- 15 4-[4-((S)-1-[8-(2,2-Dimethyl-propyl)-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino]-ethyl)-benzyl]-piperazine-1-carboxylic acid tert-butyl ester (cpd 59);
2-(((1S)-1-[4-[(3,3-difluoropiperidin-1-yl)methyl]phenyl]ethyl)amino)-8-(2,2-dimethylpropyl)-5-methylpyrido[2,3-d]pyrimidin-7(8H)-one (cpd 60);
8-(butan-2-yl)-2-(((1S)-1-[4-[(3,3-difluoropiperidin-1-yl)methyl]phenyl]ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 61);
- 20 8-[(2S)-butan-2-yl]-2-(((1S)-1-[4-[(3,3-difluoropiperidin-1-yl)methyl]phenyl]ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 62);
ethyl 2-[2-(((1S)-1-[4-[(3,3-difluoropiperidin-1-yl)methyl]phenyl]ethyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl]propanoate (cpd 63);
- 25 2-[2-(((1S)-1-[4-[(3,3-difluoropiperidin-1-yl)methyl]phenyl]ethyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl]propanenitrile (cpd 64);
2-(((1S)-1-[4-[(3,3-difluoropiperidin-1-yl)methyl]phenyl]ethyl)amino)-8-[(2S)-3-methylbutan-2-yl]pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 65);
8-[(1S)-1-cyclohexylethyl]-2-(((1S)-1-[4-[(3,3-difluoropiperidin-1-yl)methyl]phenyl]ethyl)amino)-pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 66);
- 30 2-(((1S)-1-[4-[(4,4-difluoropiperidin-1-yl)methyl]-3-fluorophenyl]ethyl)amino)-8-[(2S)-3-methylbutan-2-yl]pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 67);
2-(((1S)-1-[3-fluoro-4-(morpholin-4-ylmethyl)phenyl]ethyl)amino)-8-[(2S)-3-methylbutan-2-yl]pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 68);
- 35 2-(((1S)-1-[4-[(3,3-difluoropiperidin-1-yl)methyl]phenyl]ethyl)amino)-8-[(2S)-3,3-dimethylbutan-2-yl]pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 69);
8-(2,2-dimethylpropyl)-2-(((1S)-1-phenylpropyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 70);
2-(((1S)-1-(4-chlorophenyl)ethyl)amino)-8-(3-hydroxybenzyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 71);

- 2-(((1S)-1-(4-chlorophenyl)ethyl)amino)-8-(4-hydroxybenzyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 72);
4-(((1S)-1-[[8-(2,6-difluorobenzyl)-7-oxo-pyrido[2,3-d]pyrimidin-2-yl]amino}ethyl]benzoic acid (cpd 73);
4-(((1S)-1-[[8-(2-fluorobenzyl)-7-oxo-pyrido[2,3-d]pyrimidin-2-yl]amino}ethyl]benzoic acid (cpd 74);
4-(((1S)-1-[[8-(2,6-difluorobenzyl)-7-oxo-pyrido[2,3-d]pyrimidin-2-yl]amino}ethyl)-N-(4,4-difluorocyclohexyl)benzamide
5 (cpd 75);
4-(((1S)-1-[[8-(2,6-difluorobenzyl)-7-oxo-pyrido[2,3-d]pyrimidin-2-yl]amino}ethyl)-N-(1-methylpiperidin-4-yl)benzamide
(cpd 76);
8-(2,6-difluorobenzyl)-2-(((1S)-1-{4-[(4,4-difluoropiperidin-1-yl)carbonyl]phenyl}ethyl)amino)pyrido[2,3-d]pyrimidin-7
(8H)-one (cpd 77);
10 4-(((1S)-1-[[8-(2,6-difluorobenzyl)-7-oxo-pyrido[2,3-d]pyrimidin-2-yl]amino}ethyl)-N-(tetrahydro-2H-pyran-4-yl)
benzamide (cpd 78);
N-(4,4-difluorocyclohexyl)-4-(((1S)-1-[[8-(2,2-dimethylpropyl)-7-oxo-pyrido[2,3-d]pyrimidin-2-yl]amino}ethyl)benzamide
(cpd 79);
N-cyclopentyl-4-(((1S)-1-[[8-(2,2-dimethylpropyl)-7-oxo-pyrido[2,3-d]pyrimidin-2-yl]amino}ethyl)benzamide (cpd 80),
15 N-cyclohexyl-4-(((1S)-1-[[8-(2,2-dimethylpropyl)-7-oxo-pyrido[2,3-d]pyrimidin-2-yl]amino}ethyl)benzamide (cpd 81);
2-chloro-N-(4,4-difluorocyclohexyl)-4-(1-[[8-(2,2-dimethylpropyl)-7-oxo-pyrido[2,3-d]pyrimidin-2-yl]amino} ethyl)
benzamide (cpd 82);
2-(((1S)-1-{4-[(4,4-difluoropiperidin-1-yl)carbonyl]phenyl}ethyl)amino)-8-(2,2-dimethylpropyl)pyrido[2,3-d]pyrimidin-
7(8H)-one (cpd 83);
20 N-(4,4-difluorocyclohexyl)-4-(1-[[8-(2,2-dimethylpropyl)-7-oxo-pyrido[2,3-d]pyrimidin-2-yl]amino}ethyl)-2-
fluorobenzamide (cpd 84);
N-(3,3-difluorocyclobutyl)-4-(((1S)-1-[[8-(2,2-dimethylpropyl)-7-oxo-pyrido[2,3-d]pyrimidin-2-yl]amino}ethyl)benzamide
(cpd 85);
4-(((1S)-1-[[8-(2,2-dimethylpropyl)-7-oxo-pyrido[2,3-d]pyrimidin-2-yl]amino}ethyl)benzamide (cpd 86);
25 8-(2,2-dimethylpropyl)-2-(((1S)-1-{4-[(4-hydroxypiperidin-1-yl)carbonyl]phenyl}ethyl)amino)pyrido[2,3-d]pyrimidin-
7(8H)-one (cpd 87);
2-chloro-N-(4,4-difluorocyclohexyl)-4-(((1S)-1-[[8-(2,2-dimethylpropyl)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-
yl]amino}ethyl)benzamide (cpd 88);
N-(4,4-difluorocyclohexyl)-4-(((1S)-1-[[8-(2,2-dimethylpropyl)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl]amino}
30 ethyl)-2-fluorobenzamide (cpd 89);
8-(2,2-dimethylpropyl)-2-(((1S)-1-[3-fluoro-4-(hydroxymethyl)phenyl]ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one
(cpd 90);
2-(((1S)-1-[4-(hydroxymethyl)phenyl]ethyl)amino)-8-(2-methylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 91);
8-(2,6-difluorobenzyl)-2-(((1S)-1-[4-(hydroxymethyl)phenyl]ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 92);
35 2-(((1S)-1-[4-(hydroxymethyl)phenyl]ethyl)amino)-8-(2-hydroxy-2-methylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd
93);
2-(((1S)-1-{4-[(4,4-difluoropiperidin-1-yl)methyl]-3-fluorophenyl}ethyl)amino)-8-(2,2-dimethylpropyl)pyrido[2,3-d]
pyrimidin-7(8H)-one (cpd 94);

- 2-(((1S)-1-{4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl}ethyl)amino)-8-(2-methylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 95);
- 8-benzyl-2-[(1-{4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl}ethyl)amino]pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 96);
- 2-[(1-{4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl}ethyl)amino]-8-(2-fluorobenzyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 97);
- 8-(2,6-difluorobenzyl)-2-[(1-{4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl}ethyl)amino]pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 98);
- 8-(2,6-difluorobenzyl)-2-(((1S)-1-{4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl}ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 99);
- 2-[(1-{4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl}ethyl)amino]-8-(2-fluoroethyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 100);
- 2-(((1S)-1-{4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl}ethyl)amino)-8-propylpyrido[2,3-d]pyrimidin-7(8H)-one (cpd 101);
- 2-(((1S)-1-{4-(azepan-1-ylmethyl)phenyl}ethyl)amino)-8-propylpyrido[2,3-d]pyrimidin-7(8H)-one (cpd 102);
- 2-(((1S)-1-{4-[(4-acetypiperazin-1-yl)methyl]phenyl}ethyl)amino)-8-propylpyrido[2,3-d]pyrimidin-7(8H)-one (cpd 103);
- 2-(((1S)-1-{4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl}ethyl)amino)-8-(2-methylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 104);
- 2-(((1S)-1-{4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl}ethyl)amino)-8-(2,2-dimethylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 105);
- 2-(((1S)-1-{4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl}ethyl)amino)-8-(2,2,2-trifluoroethyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 106);
- 8-[2,3-difluoro-2-(fluoromethyl)propyl]-2-(((1S)-1-{4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl}ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 107);
- 2-(((1S)-1-{4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl}ethyl)amino)-8-[3,3,3-trifluoro-2-(trifluoromethyl)propyl]pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 108);
- 8-(cyclobutylmethyl)-2-(((1S)-1-{4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl}ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 109);
- 8-(2,2-dimethylpropyl)-2-(((1S)-1-{4-(morpholin-4-ylmethyl)phenyl}ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 110);
- 8-(2,2-dimethylpropyl)-2-(((1S)-1-{4-(pyrrolidin-1-ylmethyl)phenyl}ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 111);
- 2-(((1S)-1-{4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl}ethyl)amino)-8-(2-methylbenzyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 112);
- 8-(cyclohexylmethyl)-2-(((1S)-1-{4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl}ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 113);
- 2-(((1S)-1-{4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl}ethyl)amino)-8-(2-methoxyethyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 114);

- 2-(((1S)-1-{4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl}ethyl)amino)-8-[4-fluoro-2-(trifluoromethyl)benzyl]pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 115);
- 2-(((1S)-1-{4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl}ethyl)amino)-8-(3,3,3-trifluoro-2,2-dimethylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 116);
- 5 2-(((1S)-1-{4-[(3,3-difluoropiperidin-1-yl)methyl]phenyl}ethyl)amino)-8-(2,2-dimethylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 117);
- 2-(((1S)-1-{4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl}ethyl)amino)-4-methyl-8-(2-methylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 118);
- 2-(((1S)-1-{4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl}ethyl)amino)-8-(2-hydroxy-2-methylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 119);
- 10 2-(((1S)-1-{4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl}ethyl)amino)-8-[2-(hydroxymethyl)-2-methylpentyl]pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 120);
- 2,2-dimethyl-3-[2-(((1S)-1-(naphthalen-2-yl)ethyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl]propanoic acid (cpd 121);
- 15 2,2-dimethyl-3-[2-(((1S)-1-(naphthalen-2-yl)ethyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl]propanamide (cpd 122);
- N,2,2-trimethyl-3-[7-oxo-2-(((1S)-1-phenylethyl)amino)pyrido[2,3-d]pyrimidin-8(7H)-yl]propanamide (cpd 123);
- N,N,2,2-tetramethyl-3-[7-oxo-2-(((1S)-1-phenylethyl)amino)pyrido[2,3-d]pyrimidin-8(7H)-yl]propanamide (cpd 124);
- 2,2-dimethyl-N-(3-methylphenyl)-3-[7-oxo-2-(((1S)-1-phenylethyl)amino)pyrido[2,3-d]pyrimidin-8(7H)-yl]propanamide (cpd 125);
- 20 N-(2-hydroxyethyl)-2,2-dimethyl-3-[7-oxo-2-(((1S)-1-phenylethyl)amino)pyrido[2,3-d]pyrimidin-8(7H)-yl]propanamide (cpd 126);
- N-(3-hydroxypropyl)-2,2-dimethyl-3-[7-oxo-2-(((1S)-1-phenylethyl)amino)pyrido[2,3-d]pyrimidin-8(7H)-yl]propanamide (cpd 127);
- N-[3-(1-hydroxyethyl)phenyl]-2,2-dimethyl-3-[7-oxo-2-(((1S)-1-phenylethyl)amino)pyrido[2,3-d]pyrimidin-8(7H)-yl]propanamide (cpd 128);
- 25 2,2-dimethyl-3-[2-(((1S)-1-(naphthalen-2-yl)ethyl)amino)-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl]propanenitrile (cpd 129);
- 8-(2,2-dimethylpropyl)-2-(((1S)-1-{4-(1-methyl-1H-pyrazol-4-yl)phenyl}ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 130);
- 30 8-(2,2-dimethylpropyl)-2-(((1S)-1-{4-(pyridin-4-yl)phenyl}ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 131);
- 8-(2,2-dimethylpropyl)-2-(((1S)-1-{4-(2-fluoropyridin-4-yl)phenyl}ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 132)
- 8-(2,2-dimethylpropyl)-2-(((1S)-1-{4-(thiophen-3-yl)phenyl}ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 133);
- 4'-(((1S)-1-{8-(2,2-dimethylpropyl)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl}amino)ethyl)biphenyl-2-carbonitrile (cpd 134);
- 35 8-(3-hydroxy-2,2-dimethylpropyl)-2-(((1S)-1-{4-(1-methyl-1H-pyrazol-4-yl)phenyl}ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 135);

- 8-(3-hydroxy-2,2-dimethylpropyl)-2-(((1S)-1-[4-(thiophen-3-yl)phenyl]ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 136);
- 8-(2,2-dimethylpropyl)-2-(((1S)-1-[4-(methylsulfonyl)phenyl]ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 137);
- 8-(2,2-dimethylpropyl)-2-(((1S)-1-[4-(piperazin-1-ylmethyl)phenyl]ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one
- 5 dihydrochloride (cpd 138);
- 2-(((1S)-1-[4-[(4-acryloylpiperazin-1-yl)methyl]phenyl]ethyl)amino)-8-(2,2-dimethylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 139);
- 2-(((1S)-1-[4-[(4-acryloylpiperazin-1-yl)methyl]phenyl]ethyl)amino)-8-(3-hydroxy-2,2-dimethylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 140);
- 10 2-(((1S)-1-[4-[(4-acryloylpiperazin-1-yl)methyl]-3-fluorophenyl]ethyl)amino)-8-(2,2-dimethylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 141);
- 2-(((1S)-1-[4-[(4-acryloylpiperazin-1-yl)carbonyl]phenyl]ethyl)amino)-8-(2,2-dimethylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 142);
- 2-(((1S)-1-[4-[(4-[(2E)-but-2-enoyl]piperazin-1-yl)methyl]phenyl]ethyl)amino)-8-(2,2-dimethylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 143);
- 15 8-(2,2-dimethylpropyl)-2-(((1S)-1-[4-[(4-(2-methylacryloyl)piperazin-1-yl)methyl]phenyl]ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 144);
- 8-(2,2-Dimethyl-propyl)-2-((S)-1-(4-hydroxy-phenyl)-ethylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (cpd 145);
- 4-(4-((S)-1-[8-((S)-1,2-Dimethyl-propyl)-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino]-ethyl)-phenoxy)-piperidine-1-carboxylic acid benzyl ester (cpd 146);
- 20 2-(((1S)-1-[4-[(3,3-difluoroazetidin-1-yl)methyl]phenyl]ethyl)amino)-8-(2,2-dimethylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 147);
- 2-(((1S)-1-[4-[(3,3-difluoropyrrolidin-1-yl)methyl]phenyl]ethyl)amino)-8-(2,2-dimethylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 148);
- 25 8-[(2R)-butan-2-yl]-2-(((1S)-1-[4-[(3,3-difluoropiperidin-1-yl)methyl]phenyl]ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 149);
- 2-(((1S)-1-[4-[(2R,6S)-2,6-dimethylmorpholin-4-yl)methyl]-3-fluorophenyl]ethyl)amino)-8-[(2S)-3-methylbutan-2-yl]pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 150);
- 2-(((1S)-1-[4-[(2R,6S)-2,6-dimethylmorpholin-4-yl)methyl]-2-fluorophenyl]ethyl)amino)-8-(2,2-dimethyl propyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 151);
- 30 2-(((1S)-1-[4-[(4,4-difluoropiperidin-1-yl)methyl]-2-fluorophenyl]ethyl)amino)-8-(2,2-dimethylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 152);
- 8-(2,2-dimethylpropyl)-2-(((1S)-1-[2-fluoro-4-(morpholin-4-ylmethyl)phenyl]ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 153);
- 35 4-(4-((S)-1-[8-(2,2-Dimethyl-propyl)-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino]-ethyl)-phenoxy)-piperidine-1-carboxylic acid tert-butyl ester (cpd 154);
- 8-((S)-1,2-Dimethyl-propyl)-2-((S)-1-[4-(piperidin-4-yloxy)-phenyl]-ethylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (cpd 155);

- 2-((S)-1-[4-(1-Acryloyl-piperidin-4-yloxy)-phenyl]-ethylamino)-8-(2,2-dimethyl-propyl)-8H-pyrido[2,3-d]pyrimidin-7-one (cpd 156);
- 8-(2,2-dimethylpropyl)-2-(((1S)-1-(4-[(2-methylpropanoyl)piperazin-1-yl]methyl)phenyl)ethyl)amino} pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 157);
- 5 2-(((1S)-1-(4-[(4-(cyclopropylcarbonyl)piperazin-1-yl]methyl)phenyl)ethyl)amino)-8-(2,2-dimethylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 158);
- 2-((S)-1-[4-(1-Acryloyl-piperidin-4-yloxy)-phenyl]-ethylamino)-8-((S)-1,2-dimethyl-propyl)-8H-pyrido[2,3-d]pyrimidin-7-one (cpd 159);
- 8-((S)-1,2-Dimethyl-propyl)-2-((S)-1-[4-(1-isobutyryl-piperidin-4-yloxy)-phenyl]-ethylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (cpd 160);
- 10 2-((S)-1-[4-(4-Acryloyl-piperazin-1-ylmethyl)-phenyl]-ethylamino)-8-((S)-1,2-dimethyl-propyl)-8H-pyrido[2,3-d]pyrimidin-7-one (cpd 161);
- 8-((S)-1,2-Dimethyl-propyl)-2-((S)-1-[4-(2-methyl-acryloyl)-piperazin-1-ylmethyl]-phenyl)-ethylamino)-8H-pyrido[2,3-d]pyrimidin-7-one (cpd 162);
- 15 2-(((1S)-1-(4-bromophenyl)ethyl)amino)-8-[(2S)-3-methylbutan-2-yl]pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 163);
- 2-(((1S)-1-(4-[(2R,6S)-2,6-dimethylmorpholin-4-yl]methyl)phenyl)ethyl)amino)-8-[(2S)-1,1,1-trifluoropropan-2-yl]pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 164);
- 4'-[(1S)-1-((8-[(2S)-3-methylbutan-2-yl]-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl)amino)ethyl]biphenyl-2-carbonitrile (cpd 165);
- 20 2-(((1S)-1-[4-(2-fluoropyridin-4-yl)phenyl]ethyl)amino)-8-[(2S)-3-methylbutan-2-yl]pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 166);
- tert-butyl 4-{4-[(1S)-1-((8-[(2S)-3-methylbutan-2-yl]-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl)amino)ethyl]phenyl}-3,6-dihydropyridine-1(2H)-carboxylate (cpd 167);
- 2-(((1S)-1-[4-(1-acryloyl-1,2,3,6-tetrahydropyridin-4-yl)phenyl]ethyl)amino)-8-[(2S)-3-methylbutan-2-yl]pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 168);
- 25 2-(((1S)-1-[4-[(4-acryloylpiperazin-1-yl)methyl]phenyl)ethyl)amino)-8-[(2S)-1,1,1-trifluoropropan-2-yl]pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 169);
- 2-(((1S)-1-[4-[(3,3-difluoropiperidin-1-yl)methyl]phenyl)ethyl)amino)-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 170);
- 30 8-[(1S)-1-cyclopropylethyl]-2-(((1S)-1-(4-[(2R,6S)-2,6-dimethylmorpholin-4-yl]methyl)-3-fluorophenyl)ethyl)amino} pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 171);
- 2-(((1S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)amino)-8-[(2S)-3-methylbutan-2-yl]pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 172);
- 8-[(2S)-3-methylbutan-2-yl]-2-(((1S)-1-[4-(morpholin-4-yl)phenyl]ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 173);
- 35 benzyl 4-{4-[(1S)-1-((8-[(2S)-3-methylbutan-2-yl]-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl)amino)ethyl]phenyl}piperazine-1-carboxylate (cpd 174);

- 2-(((1S)-1-[4-(4-acryloylpiperazin-1-yl)phenyl]ethyl)amino)-8-[(2S)-3-methylbutan-2-yl]pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 175);
- 8-[(2S)-3-methylbutan-2-yl]-2-(((1S)-1-[4-(piperazin-1-yl)phenyl]ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 176);
- 5 2-(((1S)-1-[4-(4-ethylpiperazin-1-yl)phenyl]ethyl)amino)-8-[(2S)-3-methylbutan-2-yl]pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 177);
- benzyl 4-{2-fluoro-4-[(1S)-1-({8-[(2S)-3-methylbutan-2-yl]-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl)amino}ethyl]phenyl}piperazine-1-carboxylate (cpd 178);
- 2-(((1S)-1-[4-(4-acryloylpiperazin-1-yl)-3-fluorophenyl]ethyl)amino)-8-[(2S)-3-methylbutan-2-yl]pyrido[2,3-d]pyrimidin-
- 10 7(8H)-one (cpd 179);
- 8-[(2S)-3-methylbutan-2-yl]-2-(((1S)-1-[6-(piperazin-1-yl)pyridin-3-yl]ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 180);
- 2-(((1S)-1-[6-(4-acryloylpiperazin-1-yl)pyridin-3-yl]ethyl)amino)-8-[(2S)-3-methylbutan-2-yl]pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 181);
- 15 2-(((1S)-1-[4-[(4-acryloylpiperazin-1-yl)methyl]phenyl]ethyl)amino)-8-(2-azidoethyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 182);
- 2-(((1S)-1-[4-[(4-acryloylpiperazin-1-yl)methyl]-3-fluorophenyl]ethyl)amino)-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 183);
- 2-(((1S)-1-[4-[(4-acryloylpiperazin-1-yl)methyl]phenyl]ethyl)amino)-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one
- 20 (cpd 184);
- tert-butyl 4-{4-((1S)-1-[(8-ethyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl)amino]ethyl)benzyl}piperazine-1-carboxylate (cpd 185);
- 2-(((1S)-1-[4-[(4-acryloylpiperazin-1-yl)methyl]phenyl]ethyl)amino)-8-ethylpyrido[2,3-d]pyrimidin-7(8H)-one (cpd 186);
- 2-(((1S)-1-[4-[1-(4-acryloylpiperazin-1-yl)propyl]phenyl]ethyl)amino)-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one
- 25 (cpd 187);
- 8-[(2S)-3-methylbutan-2-yl]-2-(((1S)-1-[4-[(4-methyl-3-oxopiperazin-1-yl)methyl]phenyl]ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 188);
- tert-butyl 4-{4-((1S)-1-[(8-ethyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl)amino]ethyl)benzoyl}piperazine-1-carboxylate (cpd 189);
- 30 2-(((1S)-1-[4-[(4-acryloylpiperazin-1-yl)carbonyl]phenyl]ethyl)amino)-8-ethylpyrido[2,3-d]pyrimidin-7(8H)-one (cpd 190);
- 2-(((1S)-1-[4-[(4-acryloylpiperazin-1-yl)carbonyl]-3-fluorophenyl]ethyl)amino)-8-[(2S)-3-methylbutan-2-yl]pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 191);
- N-(1-acryloylpiperidin-4-yl)-2-fluoro-4-[(1S)-1-[[7-oxo-8-(propan-2-yl)-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl]amino]ethyl]benzamide (cpd 192);
- 35 tert-butyl 6-[(1S)-1-({8-[(2S)-3-methylbutan-2-yl]-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl)amino}ethyl]-3',6'-dihydro-3,4'-bipyridine-1'(2'H)-carboxylate (cps 193);

- 2-(((1S)-1-(1'-acryloyl-1',2',3',6'-tetrahydro-3,4'-bipyridin-6-yl)ethyl)amino)-8-((2S)-3-methylbutan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 194);
- 2-(((1S)-1-(1'-(cyclopropylcarbonyl)-1',2',3',6'-tetrahydro-3,4'-bipyridin-6-yl)ethyl)amino)-8-((2S)-3-methylbutan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 195);
- 5 8-((2S)-3-methylbutan-2-yl)-2-(((1S)-1-[2'-(trifluoromethyl)-3,4'-bipyridin-6-yl]ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 196);
- 2-(((1S)-1-(2'-fluoro-3,4'-bipyridin-6-yl)ethyl)amino)-8-((2S)-3-methylbutan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 197);
- 2-(((1S)-1-{4-[(4-acryloylpiperazin-1-yl)methyl]phenyl}ethyl)amino)-8-((2S)-1-fluoropropan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 198);
- 10 2-(((1S)-1-{4-[(4-acryloylpiperazin-1-yl)methyl]phenyl}ethyl)amino)-8-((2S)-1-hydroxypropan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 199);
- tert-butyl 4-{4-[(1S)-1-{4-cyano-8-(2,2-dimethylpropyl)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl}amino}ethyl}benzyl}piperazine-1-carboxylate (cpd 200);
- 15 2-(((1S)-1-{4-[(4-acryloylpiperazin-1-yl)methyl]phenyl}ethyl)amino)-8-(2,2-dimethylpropyl)-4-ethoxypyrido[2,3-d]pyrimidin-7(8H)-one (cpd 201);
- 2-(((1S)-1-{4-[(4-acryloylpiperazin-1-yl)methyl]phenyl}ethyl)amino)-8-(2,2-dimethylpropyl)-4-(methylamino)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 202);
- 2-(((1S)-1-{4-[(4-acryloylpiperazin-1-yl)methyl]phenyl}ethyl)amino)-4-(dimethylamino)-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 203);
- 20 2-(((1S)-1-{4-[(4-acryloylpiperazin-1-yl)methyl]phenyl}ethyl)amino)-7-oxo-8-(propan-2-yl)-7,8-dihydropyrido[2,3-d]pyrimidine-4-carbonitrile (cpd 204);
- 2-(((1S)-1-{4-[(4-acryloylpiperazin-1-yl)methyl]phenyl}ethyl)amino)-4-[(2,4-dimethoxybenzyl)amino]-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 205);
- 25 2-(((1S)-1-{4-[(4-acryloylpiperazin-1-yl)methyl]phenyl}ethyl)amino)-4-amino-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 206);
- 2-(((1S)-1-{4-[(2R)-4-acryloyl-2-methylpiperazin-1-yl]methyl}phenyl)ethyl)amino)-8-ethylpyrido[2,3-d]pyrimidin-7(8H)-one (cpd 207);
- 2-(((1S)-1-{4-[(3R)-4-acryloyl-3-methylpiperazin-1-yl]methyl}phenyl)ethyl)amino)-8-ethylpyrido[2,3-d]pyrimidin-7(8H)-one (cpd 208);
- 30 2-(((1S)-1-{4-[(2R)-4-acryloyl-2-(propan-2-yl)piperazin-1-yl]methyl}phenyl)ethyl)amino)-8-ethylpyrido[2,3-d]pyrimidin-7(8H)-one (cpd 209);
- 2-(((1S)-1-{4-[(2S)-4-acryloyl-2-methylpiperazin-1-yl]methyl}phenyl)ethyl)amino)-8-ethylpyrido[2,3-d]pyrimidin-7(8H)-one (cpd 210);
- 35 2-(((1S)-1-{4-[(3S)-4-acryloyl-3-methylpiperazin-1-yl]methyl}phenyl)ethyl)amino)-8-ethylpyrido[2,3-d]pyrimidin-7(8H)-one (cpd 211);
- 2-(((1S)-1-{4-[(2S)-4-acryloyl-2-(propan-2-yl)piperazin-1-yl]methyl}phenyl)ethyl)amino)-8-ethylpyrido[2,3-d]pyrimidin-7(8H)-one (cpd 212);

- 2-(((1S)-1-{6-[[4-(4-acryloylpiperazin-1-yl)methyl]pyridin-3-yl]ethyl}amino)-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 213);
- 2-(((1S)-1-{4-[1-(4-acryloylpiperazin-1-yl)propyl]phenyl}ethyl}amino)-8-ethylpyrido[2,3-d]pyrimidin-7(8H)-one (cpd 214);
- 5 2-(((1S)-1-{4-[1-(4-acryloylpiperazin-1-yl)propyl]phenyl}ethyl}amino)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (cpd 215);
- 2-(((1S)-1-{4-[1-(4-acryloylpiperazin-1-yl)propyl]phenyl}ethyl}amino)-8-(2,6-difluorobenzyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 216);
- 2-(((1S)-1-{4-[1-(4-acryloylpiperazin-1-yl)methyl]phenyl}ethyl}amino)-8-(4-ethynyl-2-fluorobenzyl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 217);
- 10 2-(((1S)-1-{4-[1-(4-acryloylpiperazin-1-yl)propyl]phenyl}ethyl}amino)-8-cyclopropylpyrido[2,3-d]pyrimidin-7(8H)-one (cpd 218);
- 2-(((1S)-1-{4-[1-(4-acryloylpiperazin-1-yl)-2-cyclopropylethyl]phenyl}ethyl}amino)-8-ethylpyrido[2,3-d]pyrimidin-7(8H)-one (cpd 219);
- 15 2-(((1S)-1-{4-[1-(4-acryloylpiperazin-1-yl)-2-cyclopropylethyl]phenyl}ethyl}amino)-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 220);
- 2-(((1S)-1-{4-[1-(4-(2-methylacryloyl)piperazin-1-yl)propyl]phenyl}ethyl}amino)-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 221);
- 2-(((1S)-1-{4-[1-(4-(2E)-but-2-enoyl)piperazin-1-yl]propyl]phenyl}ethyl}amino)-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 222);
- 20 2-(((1S)-1-{4-[(3R)-1-acryloylpyrrolidin-3-yl]oxy}phenyl}ethyl}amino)-8-ethylpyrido[2,3-d]pyrimidin-7(8H)-one (cpd 223);
- 2-(((1S)-1-{4-[(3S)-1-acryloylpyrrolidin-3-yl]oxy}phenyl}ethyl}amino)-8-ethylpyrido[2,3-d]pyrimidin-7(8H)-one (cpd 224);
- 25 phenyl 4-(((1S)-1-{4-[(1S)-1-[[7-oxo-8-(propan-2-yl)-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl]amino]ethyl}phenyl}propyl)piperazine-1-carboxylate (cpd 225);
- phenyl 4-(((1R)-1-{4-[(1S)-1-[[7-oxo-8-(propan-2-yl)-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl]amino]ethyl}phenyl}propyl)piperazine-1-carboxylate (cpd 226);
- 2-(((1S)-1-{4-[(1S)-1-(4-acryloylpiperazin-1-yl)propyl]phenyl}ethyl}amino)-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 227);
- 30 2-(((1S)-1-{4-[(1R)-1-(4-acryloylpiperazin-1-yl)propyl]phenyl}ethyl}amino)-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 228);
- 2-(((1R)-1-{4-[(1R)-1-(4-acryloylpiperazin-1-yl)propyl]phenyl}ethyl}amino)-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 229);
- 35 2-(((1S)-1-{4-[(1S)-1-(4-acryloylpiperazin-1-yl)-2-cyclopropylethyl]phenyl}ethyl}amino)-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 230);
- 2-(((1S)-1-{4-[(1R)-1-(4-acryloylpiperazin-1-yl)-2-cyclopropylethyl]phenyl}ethyl}amino)-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 231);

- 4-{4-[(S)-1-(1-Ethyl-2-oxo-1,2-dihydro-[1,6]naphthyridin-7-ylamino)-ethyl]-benzyl}-piperazine-1-carboxylic acid tert-butyl ester (cpd 232);
- 4-{1-{4-[(S)-1-(1-Ethyl-2-oxo-1,2-dihydro-[1,6]naphthyridin-7-ylamino)-ethyl]-phenyl}-propyl}-piperazine-1-carboxylic acid tert-butyl ester (cpd 233);
- 5 4-{(S)-1-{4-[(S)-1-(1-Ethyl-2-oxo-1,2-dihydro-[1,6]naphthyridin-7-ylamino)-ethyl]-phenyl}-propyl}-piperazine-1-carboxylic acid phenyl ester (cpd 234);
- 7-{(S)-1-[4-(3,3-Difluoro-piperidin-1-ylmethyl)-phenyl]-ethylamino}-1-(2,2-dimethyl-propyl)-1H-[1,6]naphthyridin-2-one (cpd 235);
- 7-{(S)-1-[4-(4-Acryloyl-piperazin-1-ylmethyl)-phenyl]-ethylamino}-1-ethyl-1H-[1,6]naphthyridin-2-one (cpd 236);
- 10 7-{(S)-1-{4-[1-(4-Acryloyl-piperazin-1-yl)-propyl]-phenyl}-ethylamino}-1-ethyl-1H-[1,6]naphthyridin-2-one (cpd 237);
- 7-{(S)-1-{4-[(S)-1-(4-Acryloyl-piperazin-1-yl)-propyl]-phenyl}-ethylamino}-1-ethyl-1H-[1,6]naphthyridin-2-one (cpd 238);
- 7-{[(1S)-1-{4-[(1S)-1-(4-acryloylpiperazin-1-yl)propyl]phenyl}ethyl]amino}-1-(propan-2-yl)-1,6-naphthyridin-2(1H)-one (cpd 239);
- 15 2-{[(1S)-1-{4-[1-(4-propanoylpiperazin-1-yl)propyl]phenyl}ethyl]amino}-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 240);
- 1-acryloyl-4-{4-[(1S)-1-[[7-oxo-8-(propan-2-yl)-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl]amino]ethyl]phenyl}piperidine-4-carbonitrile (cpd 241);
- 2-{[(1S)-1-{4-[(1S)-1-[4-(3-chloropropanoyl)piperazin-1-yl]-2-cyclopropylethyl]phenyl}ethyl]amino}-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 242);
- 20 2-{[(1S)-1-{4-[(1R)-1-[4-(3-hydroxypropanoyl)piperazin-1-yl]propyl]phenyl}ethyl]amino}-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 243);
- 2-{[(1-4-[1-(4-acryloylpiperazin-1-yl)-2-cyclopropylethyl]phenyl)cyclopropyl]amino}-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 244);
- 25 2-{[(1-4-[(1R)-1-(4-acryloylpiperazin-1-yl)-2-cyclopropylethyl]phenyl)cyclopropyl]amino}-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 245);
- 2-{[(1-4-[(1S)-1-(4-acryloylpiperazin-1-yl)-2-cyclopropylethyl]phenyl)cyclopropyl]amino}-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 246);
- 2-{[(1-4-[1-(4-acryloylpiperazin-1-yl)propyl]phenyl)cyclopropyl]amino}-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 247);
- 30 2-{[(1-4-[(1R)-1-(4-acryloylpiperazin-1-yl)propyl]phenyl)cyclopropyl]amino}-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 248);
- 2-{[(1-4-[(1S)-1-(4-acryloylpiperazin-1-yl)propyl]phenyl)cyclopropyl]amino}-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 249);
- 35 2-{[(1S)-1-{4-[(2E)-pent-2-en-3-yl]phenyl}ethyl]amino}-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one (cpd 250); and
- 7-{[(1S)-1-{4-[(1S)-1-(4-acryloylpiperazin-1-yl)-2-cyclopropylethyl]phenyl}ethyl]amino}-1-(propan-2-yl)-1,6-naphthyridin-2(1H)-one (cpd 251).

If a stereogenic center or another form of an asymmetric center is present in a compound of the present invention, all forms of such optical isomer or isomers, including enantiomers and diastereomers, are intended to be covered herein. Compounds containing a stereogenic center may be used as a racemic mixture, an enantiomerically enriched mixture, or the racemic mixture may be separated using well-known techniques and an individual enantiomer may be used. In cases in which compounds have unsaturated carbon-carbon double bonds, both the cis (Z) and trans (E) isomers are within the scope of this invention.

In cases wherein compounds may exist in tautomeric forms, such as keto-enol tautomers, each tautomeric form is contemplated as being included within this invention whether existing in equilibrium or predominantly in one form.

Pharmaceutically acceptable salts of the compounds of formula (I) include the salts with inorganic or organic acids, e.g. nitric, hydrochloric, hydrobromic, sulfuric, perchloric, phosphoric, acetic, trifluoroacetic, propionic, glycolic, lactic, oxalic, fumaric, malonic, malic, maleic, tartaric, citric, benzoic, cinnamic, mandelic, methanesulphonic, isethionic and salicylic acid.

Pharmaceutically acceptable salts of the compounds of formula (I) also include the salts with inorganic or organic bases, e.g. alkali or alkaline-earth metals, especially sodium, potassium, calcium, ammonium or magnesium hydroxides, carbonates or bicarbonates, acyclic or cyclic amines.

With the term "(C₁-C₆)alkyl", we intend an aliphatic (C₁-C₆) hydrocarbon chain, containing carbon-carbon single bonds only, which can be straight or branched. Representative examples include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, n-pentyl, n-hexyl, and the like.

With the term "(C₃-C₆)cycloalkyl", we intend, unless otherwise provided, 3- to 6-membered all-carbon monocyclic ring, which may contain one or more double bonds, but does not have a completely conjugated π -electron system.

Examples of (C₃-C₆)cycloalkyl groups, without limitation, are cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexanyl, cyclohexenyl and cyclohexadienyl. The (C₃-C₆)cycloalkyl ring can be optionally further fused or linked to aromatic and non-aromatic carbocyclic or heterocyclic rings.

With the term "heterocyclyl", we intend a 3- to 7-membered, saturated or partially unsaturated carbocyclic ring where one or more carbon atoms are replaced by heteroatoms such as nitrogen, oxygen and sulfur. Non limiting examples of heterocyclyl groups are, for instance, pyranyl, tetrahydropyranyl, pyrrolidinyl, pyrrolinyl, imidazolynyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, thiazolinyl, thiazolidinyl, dihydrofuranyl, tetrahydrofuranyl, tetrahydropyridinyl, 1,3-dioxolanyl, piperidinyl, piperazinyl, morpholinyl and the like. The heterocyclyl ring can be optionally further fused or linked to aromatic and non-aromatic carbocyclic or heterocyclic rings.

With the term "(C₂-C₆)alkenyl", we intend an aliphatic straight or branched (C₂-C₆) hydrocarbon chain containing at least one carbon-carbon double bond. Representative examples include, but are not limited to, ethenyl, 1-propenyl, 2-propenyl, 1- or 2-butenyl, and the like.

With the term "(C₂-C₆)alkynyl", we intend an aliphatic straight or branched (C₂-C₆) hydrocarbon chain containing at least one carbon-carbon triple bond. Representative examples include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, 1- or 2-butyne, and the like.

With the term "(C₁-C₆)alkoxy", we intend any of the above defined (C₁-C₆)alkyl linked to the rest of the molecule through an oxygen atom (-O-).

The term "aryl" refers to a mono-, bi- or poly-carbocyclic hydrocarbon with from 1 to 4 ring systems, optionally further fused or linked to each other by single bonds, wherein at least one of the carbocyclic rings is "aromatic", wherein the term "aromatic" refers to completely conjugated π -electron bond system. Non limiting examples of such aryl groups are phenyl, α - or β -naphthyl, α - or β -tetrahydronaphthalenyl, biphenyl, and indanyl groups.

- 5 The term "heteroaryl" refers to aromatic heterocyclic rings, typically 5- to 7-membered heterocycles with from 1 to 3 heteroatoms selected among N, O or S; the heteroaryl ring can be optionally further fused or linked to aromatic and non-aromatic carbocyclic and heterocyclic rings. Not limiting examples of such heteroaryl groups are, for instance, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, imidazolyl, thiazolyl, isothiazolyl, pyrrolyl, furanyl, oxazolyl, isoxazolyl, pyrazolyl, thiophenyl, thiadiazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, indazolyl, cinnolyl, benzo[1,3]dioxolyl, benzo[1,4]dioxinyl, benzothiazolyl, benzothiophenyl, benzofuranyl, isoindolyl, benzoimidazolyl, benzoxazolyl, quinolyl, isoquinolyl, 1,2,3-triazolyl, 1-phenyl-1,2,3-triazolyl, 2,3-dihydroindolyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothiophenyl, benzopyranyl, 2,3-dihydrobenzoxazinyl, 2,3-dihydroquinoxalyl and the like.

With the term "halogen", we intend fluoro, chloro, bromo or iodo.

- 15 With the term "polyfluorinated (C₁-C₆)alkyl" or "polyfluorinated (C₁-C₆)alkoxy", we intend any of the above defined (C₁-C₆)alkyl or (C₁-C₆)alkoxy groups which are substituted by more than one fluoro atom such as, for instance, trifluoromethyl, trifluoroethyl, 1,1,1,3,3,3-hexafluoropropyl, trifluoromethoxy and the like.

With the term "hydroxy(C₁-C₆)alkyl" we intend any of the above defined (C₁-C₆)alkyl groups, bearing a hydroxyl group such as, for instance, hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl and the like.

- 20 According to the present invention and unless otherwise provided, **A**, **R1**, **R2**, **R3**, **R4**, **R5** and **R6** may be optionally substituted, in any of their free positions, by one or more groups, for instance 1 to 6 groups, independently selected from: hydroxyl, hydroxy(C₁-C₆)alkyl, halogen, nitro, oxo group (=O), cyano, (C₁-C₆)alkyl, polyfluorinated (C₁-C₆)alkyl, polyfluorinated (C₁-C₆)alkoxy, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, aryl, aryl(C₁-C₆)alkyl, (C₁-C₆)alkylaryl, aryl(C₁-C₆)alkoxy, heteroaryl, heteroaryl(C₁-C₆)alkyl, (C₁-C₆)alkylheteroaryl, heterocyclyl, heterocyclyl(C₁-C₆)alkyl, (C₁-C₆)alkylheterocyclyl, (C₁-C₆)alkylheterocyclyl(C₁-C₆)alkyl, tri(C₁-C₆)alkylsilyl, (C₃-C₇)cycloalkyl, (C₁-C₆)alkoxy, aryloxy, heterocyclyloxy, methylenedioxy, (C₁-C₆)alkylcarbonyloxy, arylcarbonyloxy, di(C₁-C₆)alkylaminoheterocyclyl(C₁-C₆)alkyl, (C₃-C₇)cycloalkenyloxy, heterocyclylcarbonyloxy, (C₁-C₆)alkylideneaminoxy, carboxy, (C₁-C₆)alkoxycarbonyl, aryloxy carbonyl, (C₃-C₇)cycloalkyloxy carbonyl, amino, heterocyclyl(C₁-C₆)alkoxycarbonylamino, ureido, (C₁-C₆)alkylamino, amino(C₁-C₆)alkyl, di(C₁-C₆)alkylamino, arylamino, diarylamino, heterocyclylamino, formylamino, (C₁-C₆)alkylcarbonylamino, arylcarbonylamino, heterocyclylcarbonylamino, aminocarbonyl, (C₁-C₆)alkylaminocarbonyl, di(C₁-C₆)alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl, arylaminocarbonyl(C₁-C₆)alkyl, (C₃-C₇)cycloalkylaminocarbonyl, heterocyclylaminocarbonyl, (C₁-C₆)alkoxycarbonylamino, hydroxyaminocarbonyl, (C₁-C₆)alkoxyimino, (C₁-C₆)alkylsulfonylamino, arylsulfonylamino, heterocyclylsulfonylamino, formyl, (C₁-C₆)alkylcarbonyl, arylcarbonyl, (C₃-C₇)cycloalkylcarbonyl, heterocyclylcarbonyl, heterocyclylcarbonyl(C₁-C₆)alkyl, (C₁-C₆)alkylsulfonyl, polyfluorinated (C₁-C₆)alkylsulfonyl, arylsulfonyl, aminosulfonyl, (C₁-C₆)alkylaminosulfonyl, di(C₁-C₆)alkylaminosulfonyl, arylaminosulfonyl, heterocyclylaminosulfonyl, arylthio, (C₁-C₆)alkylthio; in their turn, whenever appropriate, each of the above substituents may be further substituted by one or more of the aforementioned groups.

From all of the above, it is clear to the skilled person that any group which name is a composite name such as, for instance, "arylamino" has to be intended as conventionally construed by the parts from which it derives, e.g. by an amino group which is substituted by aryl, wherein aryl is as above defined.

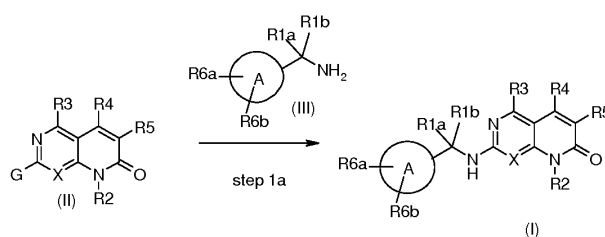
Likewise, any of the terms such as, for instance, (C₁-C₆)alkylthio, (C₁-C₆)alkylamino, di(C₁-C₆)alkylamino, (C₁-C₆)alkoxycarbonyl, (C₁-C₆)alkoxycarbonylamino, heterocyclylcarbonyl, heterocyclylcarbonylamino, (C₃-C₇)cycloalkyloxycarbonyl and the like, include groups wherein the (C₁-C₆)alkyl, (C₁-C₆)alkoxy, aryl, (C₃-C₇)cycloalkyl and heterocyclyl moieties are as above defined.

The present invention also provides processes for the preparation of the compound of general formula (I) as defined above, by using the reaction routes and synthetic schemes described below, employing the techniques available in the art and starting materials readily available. The preparation of certain embodiments of the present invention is described in the examples that follow, but those of ordinary skill in the art will recognize that the preparations described may be readily adapted to prepare other embodiments of the present invention. For example, the synthesis of non-exemplified compounds according to the invention may be performed by apparent modifications to those skilled in the art, for instance by appropriately protecting interfering groups, by suitably replacing reagents with others known in the art, or by making routine modifications of reaction conditions. Alternatively, other reactions referred to herein or known in the art will be recognized as having adaptability for preparing other compounds of the invention.

The compounds of this invention can be prepared from readily available starting materials using the following general methods and procedures. Unless otherwise indicated, the starting materials are known compounds or may be prepared from known compounds according to well known procedures. It will be appreciated that, where typical or preferred process conditions (*i.e.*, reaction temperatures, times, mole ratios of reactants, solvents, pressures) are described, different process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

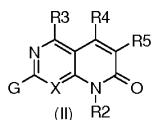
The compound of general formula (I), as defined above, can be prepared according to the general synthetic processes described in Scheme 1, starting from an intermediate compound of formula (II):

Scheme 1



Accordingly, a process of the present invention comprises the following steps:

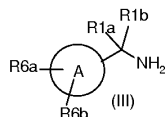
Step 1a) reacting a compound of formula (II):



30

wherein G is chloro, MeS(O)₂-, or MeS(O)-; R₂ is an optionally substituted group selected from straight or branched (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl-(C₁-C₆)alkyl, aryl-(C₁-C₆)alkyl, and heterocyclyl-(C₁-C₆)alkyl; X is nitrogen or -CH-, R₃

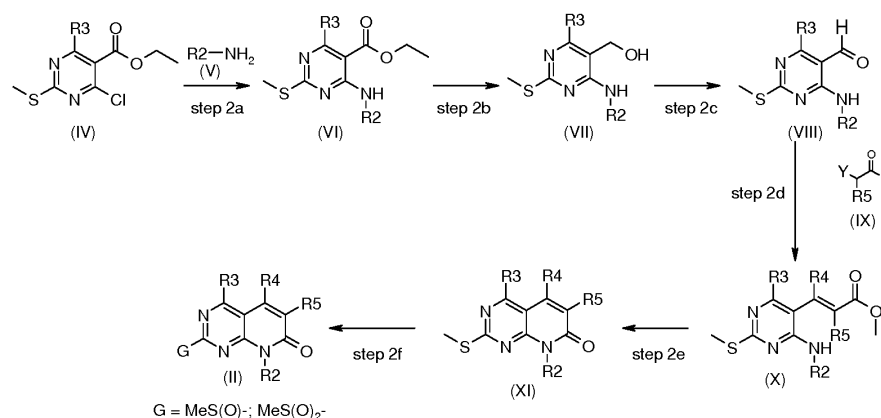
is hydrogen, chloro, cyano, CONH_2 , NH_2 , NR13R13a, OR12, or an optionally substituted group selected from straight or branched (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl-(C₁-C₆)alkyl, aryl and heteroaryl; R₄ is hydrogen or an optionally substituted straight or branched (C₁-C₆)alkyl; R₅ is hydrogen, fluoro, cyano, an optionally substituted straight or branched (C₁-C₆)alkyl or OR12, wherein R₁₂ is an optionally substituted straight or branched (C₁-C₆)alkyl and R₁₃, R13a are each independently selected from hydrogen or optionally substituted straight or branched (C₁-C₆)alkyl; with an compound of formula (III):



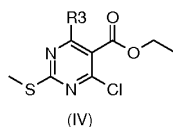
wherein R_{1a} is hydrogen or an optionally substituted straight or branched (C₁-C₆)alkyl; R_{1b} is an optionally substituted (C₁-C₆)alkyl, or together with the atom to which they are bound, R_{1a} and R_{1b} may form a (C₃-C₆)cycloalkyl; A is a (C₃-C₆) cycloalkyl, aryl or heteroaryl; R_{6a} and R_{6b} are each independently selected from hydrogen, halogen, cyano, an optionally substituted straight or branched (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, cycloalkyl-alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, aryl, heteroaryl, heterocyclyl, -OR₇, NR₇R₈, -COOR₇, -SO₂R₇, -CONR₇R₈, -CH(R₁₄)OR₇, and -CH(R₁₄)NR₇R₈ wherein R₁₄ is hydrogen or an optionally substituted straight or branched (C₁-C₆)alkyl and R₇ and R₈ are each independently hydrogen or a group selected from an optionally substituted straight or branched (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl, aryl, heteroaryl, heterocyclyl, aryl-alkyl, heteroaryl-alkyl, heterocyclyl-alkyl, heterocyclyl-C(O)-alkyl, heterocyclyl-C(O)-alkenyl, heterocyclyl-C(O)-alkynyl or, together with the nitrogen atom to which they are bound, R₇ and R₈ form a 5- to 7-membered heteroaryl or heterocyclyl group optionally containing one additional heteroatom selected from O, S and NR₉; wherein R₉ is hydrogen, an optionally substituted straight or branched (C₁-C₆)alkyl, -COOR₁₀ or -COR₁₁; wherein R₁₀ is hydrogen or an optionally substituted straight or branched (C₁-C₆)alkyl; R₁₁ is an optionally substituted straight or branched (C₁-C₆)alkyl, (C₂-C₆)alkenyl or (C₂-C₆)alkynyl; to yield a compound of general formula (I), wherein A, R_{1a}, R_{1b}, R₂, R₃, R₄, R₅, R_{6a} and R_{6b} are as defined above.

The compound of formula (II) can be prepared following the synthetic Scheme 2 or Scheme 4 reported below:
compound of formula (II) wherein G is MeS(O)_2^- or MeS(O)^- can be prepared following the Scheme 2:

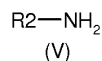
Scheme 2



Step 2a) substituting the chlorine of an intermediate compound of formula (IV):



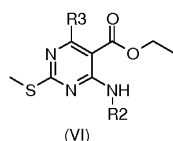
wherein R3 is hydrogen, or an optionally substituted straight or branched (C₁-C₆)alkyl, with an amine intermediate compound of formula (V):



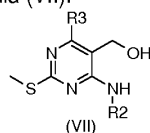
5

wherein R2 is as defined above;

Step 2b) reacting a compound of formula (VI):

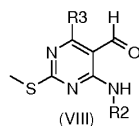


wherein R2 and R3 are as defined above, with a reducing agent;

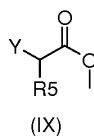
10 **Step 2c)** reacting the resultant compound of formula (VII):

wherein R2 and R3 are as defined above, with an appropriate oxydant reagent;

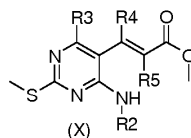
Step 2d) reacting the resultant compound of formula (VIII):



15 wherein R2 and R3 are as defined above, with an compound of formula (IX):

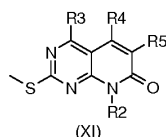


wherein Y is a suitable leaving group for Wittig or Horner–Wadsworth–Emmons reaction (or HWE reaction) such as triphenylphosphorane or diethylphosphonate, and R5 is is hydrogen or fluoro, or an optionally substituted straight or branched (C₁-C₆)alkyl;

20 **Step 2e)** cyclize an intermediate compound of formula (X):

wherein R2, R3, R4 and R5 are as defined above under basic conditions, to obtained the intermediate compound of formula (XI);

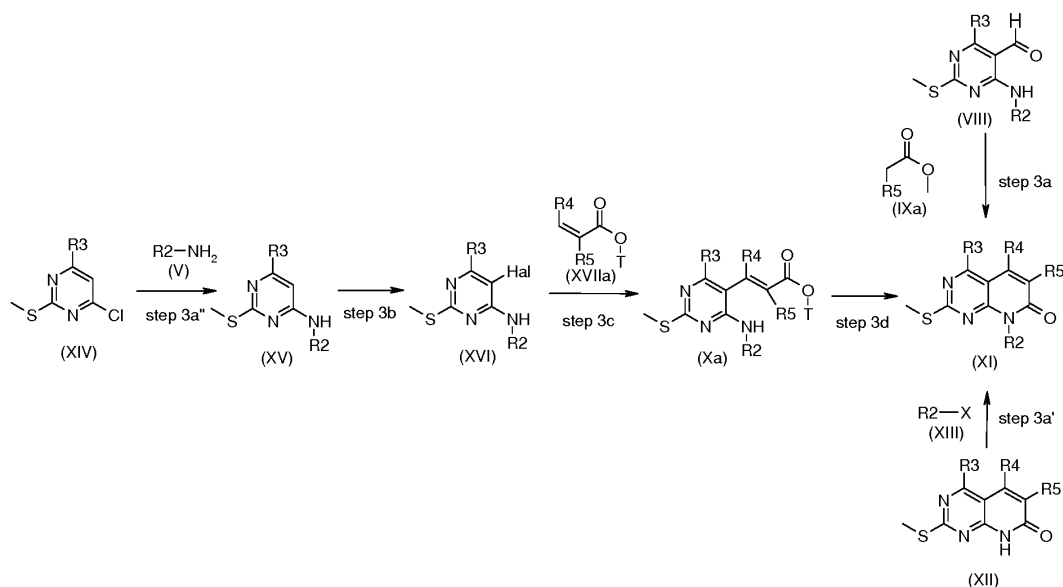
Step 2f) mixing the resultant intermediate compound of formula (XI):



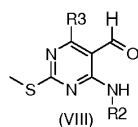
wherein R2, R3, R4 and R5 are as defined above, with a oxydant reagent, to give a compound of formula (II) wherein G is MeS(O)₂-, or MeS(O)- and R2, R3, R4 and R5 are as defined above;

alternatively compounds of formula (XI) can be prepared following Scheme 3 below:

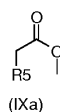
5 Scheme 3



Step 3a) reacting a compound of formula (VIII):



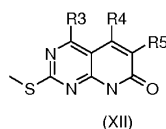
wherein R2, is as defined above, and R3 is hydrogen, chloro or an optionally substituted straight or branched (C₁-C₆)alkyl; with an compound of formula (IXa):



wherein R5 is hydrogen or OR₁₂, wherein R₁₂ is an optionally substituted straight or branched (C₁-C₆)alkyl, to yield a compound of formula (XI) wherein R2, R3 and R4 are as defined above and R5 is hydrogen or OR₁₂ wherein R₁₂ is an optionally substituted straight or branched (C₁-C₆)alkyl;

15 or

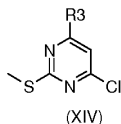
Step 3a') alkylating the intermediate compound of formula (XII):



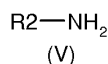
wherein, R3 and R4 are as defined above and R5 is hydrogen, fluoro, cyano, an optionally substituted straight or branched (C₁-C₆)alkyl or OR₁₂, wherein R₁₂ is an optionally substituted straight or branched (C₁-C₆)alkyl, with an alkylating agent of formula R₂-X (XIII), wherein X is bromine, iodine, -OMs -OTs or hydroxy and R₂ is as defined above, to give a compound of formula (XI) wherein R₂, R₃, R₅ and R₅ are as defined above;

5 or

Step 3a'') reacting a compound of formula (XIV):

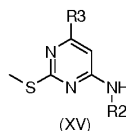


wherein R₃ is as defined above, with a compound of formula (V):



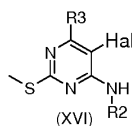
10 wherein R₂ is as defined above;

Step3b) reacting the resultant intermediate compound of formula (XV):



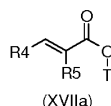
wherein R₃ and R₂ are as defined above, with a halogenation reagent;

Step 3c) reacting the intermediate compound of formula (XVI):



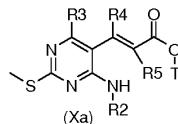
15

with a compound of formula (XVIIa):



wherein R₄ is hydrogen or an optionally substituted straight or branched (C₁-C₆)alkyl, R₅ is hydrogen and T is a straight or branched (C₁-C₆)alkyl;

20 **Step 3d)** cyclize an intermediate compound of formula (Xa):

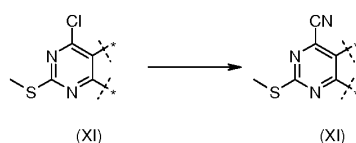


wherein R₂, R₃, R₄, R₅ and T are as defined above under basic conditions, so to obtain the intermediate compound of formula (XI), wherein R₄ is hydrogen or an optionally substituted straight or branched (C₁-C₆)alkyl, R₅ is hydrogen and R₂ and R₃ are as defined above.

25 If desired, converting a first compound of formula (XI) into a second compound of formula (XI) by operating according to well-known synthetic conditions.

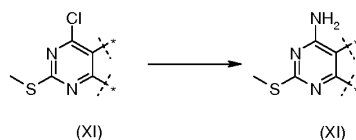
Examples of possible conversions are those reported below:

conv. A) converting a compound of formula (XI):



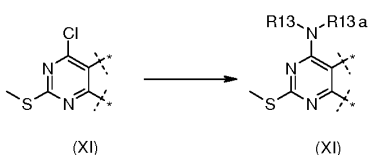
wherein R3 is chloro, into a compound of formula (XI) wherein R3 is CN, by reacting with a source of cyanide, following the condition known in the art for palladium-catalyzed cyanation of aryl halides;

5 **conv. B)** converting a compound of formula (XI):



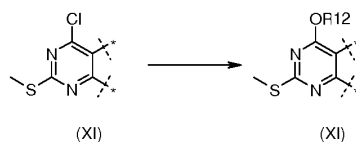
wherein R3 is chloro, into a compound of formula (XI) wherein R3 is NH₂, by reacting with ammonia;

conv. C) converting a compound of formula (XI):



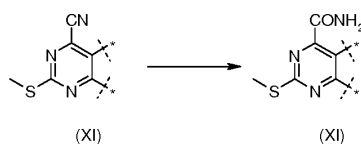
10 wherein R3 is chloro, into a compound of formula (XI) wherein R3 is NR₁₃R_{13a}, by reacting with an amine NR₁₃R_{13a} wherein R₁₃ and R_{13a} are each independently selected from hydrogen or optionally substituted straight or branched (C₁-C₆)alkyl;

conv. D) converting a compound of formula (XI):



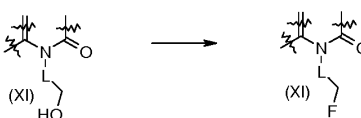
15 wherein R3 is chloro, into a compound of formula (XI) wherein R3 is OR₁₂, by reacting with an alcohol R₁₂-OH wherein R₁₂ is an optionally substituted straight or branched (C₁-C₆)alkyl;

conv. E) converting a compound of formula (XI):



wherein R3 is cyano, into a compound of formula (XI) wherein R3 is CONH₂, by hydrolysis with a suitable agent;

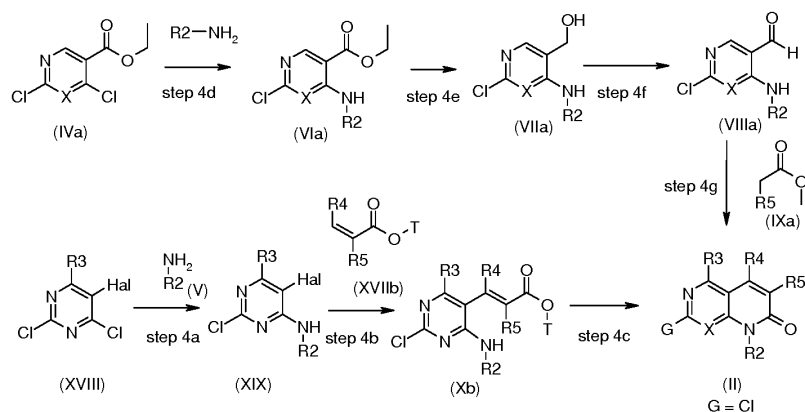
20 **conv. F)** converting a compound of formula (XI):



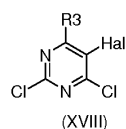
wherein R₂ is a group of formula L-CH₂OH, into a compound of formula (XI), wherein R₂ is a group of formula L-CH₂F wherein L is an optionally substituted group selected straight or branched (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl-(C₁-C₆)alkyl, aryl-(C₁-C₆)alkyl, and heterocyclyl-(C₁-C₆)alkyl, by reacting with a fluorination agent.

The compound of formula (II) wherein G is chloro and X is nitrogen or -CH-, can be prepared following the Scheme 4 below:

Scheme 4



Step 4a) reacting a compound of formula (XVIII):

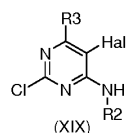


wherein R₃ is hydrogen or an optionally substituted straight or branched (C₁-C₆)alkyl, and Hal is preferably bromo or iodo, with an intermediate compound of formula (V):



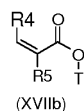
wherein R₂ is as defined above;

Step 4b) mixing the obtained intermediate compound of formula (XIX):



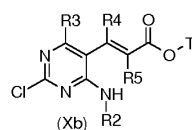
15

wherein R₂, R₃ and Hal are as defined above, with a reagent of formula (XVIIb):



wherein R₄ is hydrogen or an optionally substituted straight or branched (C₁-C₆) alkyl, R₅ and T are hydrogen;

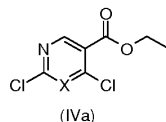
Step 4c) cyclize an intermediate compound of formula (Xb):



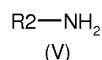
20

wherein R2, R3, R4, R5 and T are as defined above, with addition of acetic anhydride, to obtain the intermediate compound of formula (II) wherein G is chloro, R4 is hydrogen or an optionally substituted straight or branched (C₁-C₆) alkyl, R5 is hydrogen and R2 and R3 are as defined above;

Step 4d) substituting the chlorine of an intermediate compound of formula (IVa):

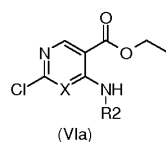


wherein X is N, or -CH, with an amine intermediate compound of formula (V):



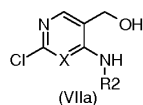
wherein R2 is as defined above;

Step 4e) reacting a compound of formula (VIa):



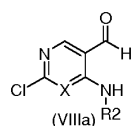
wherein X is N, or -CH and R2 is as defined above, with a reducing agent;

Step 4f) reacting the resultant compound of formula (VIIa):

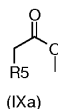


wherein X is N, or -CH and R2 is as defined above, with an appropriate oxydant reagent;

Step 4g) reacting the resultant compound of formula (VIIIa):



wherein R2 is as defined above, with an compound of formula (IXa):



wherein R5 is hydrogen or OR12, wherein R12 is an optionally substituted straight or branched (C₁-C₆)alkyl, to yield a compound of formula (II) wherein G is chloro and X is nitrogen or -CH-, R2 is as defined above, R3 and R4 are hydrogen and R5 is hydrogen or OR12 wherein R12 is an optionally substituted straight or branched (C₁-C₆)alkyl;

According to **step 1a**, the replacement of a leaving group such as methylsulphone, methylsulphoxide or chloro intermediate of formula (II) with an intermediate of formula (III) is carried out using an organic base such as DIPEA, CsF as reaction accelaretor, in a suitable solvent such as ACN, DMSO, and a temperature ranging from 60 to 120°C under conventional heating or microwave irradiation, for a time ranging from 1 to 24 h;

- alternatively, and more in particular when G is chloro the reaction can be accomplished under conditions well known by one skilled in the art. For example, the halide can be displaced by a Buchwald-Hartwig amination reaction with the a suitable palladium source such as PEPPSI precatalyst and a base such as Cs_2CO_3 , in a solvent such as toluene or ACN, a temperature ranging from 60 to 110°C under conventional heating or microwave irradiation, and for a time ranging from 1 to 24 h
- 5 According to **step 2a**, substitution of chlorine of compound of formula (IV) with an amine of formula $\text{R}_2\text{-NH}_2$ (V) can be carried out neat or in the presence of a suitable base, such as Na_2CO_3 , K_2CO_3 , Cs_2CO_3 , TEA, DIPEA and the like, in a suitable solvent, such as DMF, DMA, ACN, DMSO and the like, at a temperature ranging from room temperature to reflux. .
- 10 According to **step 2b**, of the process the reduction of an ester of formula (VI), to obtain a compound of formula (VII) can be performed in different ways and experimental conditions well known in the art. A reducing agent such as lithium aluminium hydride or the like, in a suitable solvent such as THF at a temperature ranging from 0°C to room temperature from 2 to about 24 h can be used. Preferably, the reaction is conveniently performed with lithium aluminium hydride in THF at room temperature.
- 15 According to **step 2c** of the process, the oxidation of an intermediate of formula (VII) to aldehyde of formula (VIII) can be carried out in the presence of Manganese(II)dioxide, Pyridinium chlorochromate, o-Iodoxybenzoic acid (IBX), Tetrapropylammonium perruthenate (TPAP) , 4-Methylmorpholine N-oxide or Sodium hypochlorite/TEMPO/ Bu_4NHSO_4 , in a solvent such as DCM, ACN, THF, EtOAc, Acetone or chloroform at room temperature.
- 20 According to **step 2d** of the process, the aldehyde of formula (VIII) is reacted with a phosphorane of formula (IX) in the Wittig reaction conditions such as, in the presence of a base as TEA, LiHMDS, KHMDS, NaH, KOtBu, and the like, in a suitable solvent such as THF, Et₂O and the like, at a temperature ranging from -20°C to room temperature, or alternatively the aldehyde of formula (VIII) is reacted with a phosphonate of formula (IX) in the *Homer–Wadsworth–Emmons* reaction (or *HWE* reaction) conditions such as in the presence of a base as LiOH, NaOH, TEA, NaH, and the like, in a suitable solvent such as THF, at room temperature temperature.
- 25 According to **step 2e** of the process, the cyclization of an intermediate of formula (X) to give a compound of formula (XI), can be carried out in the presence of a suitable base, such as TEA, DBU, DABCO and the like, in a suitable solvent, such as DMF, DMA, DIPEA and the like, at a temperature approximately to reflux for a time ranging from 1 to 24 h.
- 30 According to **step 2f**, the oxidation of methylthio group of an intermediate of formula (XI) to yield a compound of formula (II) wherein G is MeS(O)_2 - or MeS(O) , can be carried out in the presence of an oxidant agent well-known to those skilled in the art, such as for instance, oxone or m-chloroperbenzoic acid and the like, in a suitable solvent such as DCM, or at room temperature for a time ranging from 1 to 4 h.
- 35 According to **step 3a**, the Knoevenagel-type condensation of an intermediate of formula (VIII) with an intermediate of formula (IXa), can be carried out in the presence of a suitable base, such as Na_2CO_3 , K_2CO_3 , LiOH, Cs_2CO_3 , Potassium t-butoxide, LiHMDS, KHMDS and the like, in a suitable solvent, such as THF, DMF, DMA, and the like, at a temperature ranging from 0°C to reflux for a time ranging from 1 to 24 h in classical thermal conditions or in a microwave apparatus.

- According to **step 3a'**, the alkylation of an intermediate of formula (XII) with an intermediate of formula (XIII), wherein X is bromine, iodine, -OMs or -OTs, can be carried out in the presence of a suitable base, such as Na₂CO₃, K₂CO₃, Cs₂CO₃, NaH, KH and the like, in a suitable solvent, such as DMF, DMA, ACN, acetone, THF and the like, at a temperature ranging from 0 °C to reflux. When is used an intermediate of formula (XIII), wherein X is hydroxy, the reaction is preferentially carried out under Mitsunobu alkylation conditions in the presence of a suitable reagent such as, for instance, diethylazodicarboxylate (DEAD), diisopropylazodicarboxylate (DIAD), di-tert-butylazodicarboxylate (DBAD), 1,1'-(azodicarbonyl)dipiperidine (ADDP), and a phosphine reagent such as, for instance, trimethylphosphine, tri-tert-butylphosphine, triphenylphosphine and the like, in a suitable solvent, such as THF, DMF, DCM, toluene, benzene and the like, at a temperature ranging from 0° C to 65 °C.
- According to **step 3a''**, substitution of chlorine of compound of formula (XIV) with an amine of formula (V) can be carried out as described above in **step 2a** to obtain a compound of formula (XV).
- According to **step 3b**, the intermediate of formula (XV) is reacted with a halogenating agent. The said reaction is performed with halogenating reagent such as NBS or NIS, in a suitable solvent such as DCM or DMF, from -10°C to room temperature in a period of time varying from 2 hours to about 18 hours. Preferably, the reaction is carried out under neutral conditions in the presence of iodine and silver trifluoroacetate, in DCM at a temperature ranging from 0° C to room temperature and for a time varying from 2 hours to overnight.
- According to **step 3c**, the intermediate of formula (XVI) is reacted with a derivative of formula (XVIIa) in Heck type reaction, in the presence of a catalyst such as Pd(OAc)₂ and (+) BINAP, and in the presence of a base such as TEA, in a suitable solvent, such as DMF, DMA and the like. The reaction is heated at 100°C for approximately overnight or less as needed for the reaction to go to completion in classical thermal conditions or in a microwave apparatus.
- According to **step 3d**, the compound of formula (Xa) is cyclized under condition reported in **step 2f** so to afford the compound of formula (XI).
- According to **conv. A** of the process an heteroaryl chloride of formula (XI) can be reacted in different ways and experimental conditions known in the art as nucleophilic aromatic substitution with a source of cyanide such as sodium cyanide, potassium cyanide or alternatively by using ZnCN, CuCN or potassium hexacyanoferrate(II) as a source of cyanide in the presence of palladium(II) acetate as catalyst, sodium carbonate, potassium carbonate or cesium carbonate as base, in a suitable solvent such as DMF, N-methylpyrrolidone, or DMA, from 80°C to reflux, for a time ranging from 4 to about 24 hours (J. Org. Chem. 2005, 70, 1508-1510, *Org. Lett.*, 2011, 13 (4), pp 648–651).
- According to **conv. B** of the process a heteroaryl chloride of formula (XI) can be reacted in different ways and experimental conditions with ammonium hydroxide (30%) in acetonitrile at reflux for a time ranging from 4 to about 24 hours.
- According to **conv. C** of the process an heteroaryl chloride of formula (XI) can be reacted in different ways and experimental conditions with amines of formula NR₁₃R_{13a} in suitable solvent such as acetonitrile, DMF, DMA from rt to reflux for a time ranging from 2 to about 24 hours.
- According to **conv. D** of the process an heteroaryl chloride of formula (XI) can be reacted in different ways and experimental conditions with alcohol of formula OR₁₂ in suitable solvent such as acetonitrile, THF, in the presence of potassium carbonate, cesium carbonate, from rt to reflux for a time ranging from 2 to about 24 hours.

According to **conv. E** of the process a heteroaryl nitrile of formula (XI) can be reacted with acetamide in the presence of 1,4-dioxane, in the presence of Pd(OAc)₂, at reflux for a time ranging from 4 to about 24 hours.

According to **conv. F** of the process conversion of an alcohol of formula (XI) into the corresponding fluoro devivative, can be accomplished in different ways, and experimental conditions known in the art. Preferably the transformation of an alcohol into a aliphatic fluoro derivative is obtained by reaction with perfluoro-1-butanesulfonyl fluoride and NEt₃(HF)₃ in acetonitrile at 0°C for 2h (see, e.g. Yin, J.; *et al.* Org. Lett. 2004, 1465-1468).

According to **step 4a**, substitution of chlorine of compound of formula (XVIII) with an amine of formula (V) can be carried out as described above in **step 2a**.

According to **step 4b**, the intermediate of formula (XIX) is reacted with a acrylic or crotonic acid of formula (XVIIb) in Heck type reaction, in the presence of a catalyst such as dichlorobis(benzonitrile)palladium (II) and tri-o-tolylphosphine, and in the presence of a base such as TEA, in a suitable solvent, such as THF, DMF, DMA and the like. The reaction is heated to approximately 100°C for approximately overnight or less as needed for the reaction to go to completion in classical thermal conditions or in a microwave apparatus.

According to **step 4c** of the process the cyclization of an intermediate of formula (Xb) can be carried out in the presence of acetic anhydride and the like, in a suitable solvent, such as THF, DMF, DMA and the like, at a temperature approximately to reflux for a time ranging from 1 to 24 h to give a compound of formula (II), as defined above.

According to **step 4d** of the process the substitution of chlorine of compound of formula (IVa) with an amine of formula (V) to obtain a compound of formula (VIa) can be carried out as described above in **step 2a**.

According to **step 4e**, of the process the reduction of an ester of formula (VIa), to obtain a compound of formula (VIIa) can be performed as described above in **step 2b**.

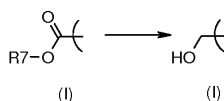
According to **step 4f** of the process, the oxidation of an intermediate of formula (VIIa) to aldehyde of formula (VIIIa) can be carried out as described above in **step 2b**.

According to **Step 4g**, the compound of formula (VIIIa) is cyclized under condition reported in **step 3a** so to afford the compound of formula (II) wherein G is chloro and X is nitrogen or -CH-.

A first compound of general formula (I) can be conveniently converted into a second compound of general formula (I) by operating according to well-known synthetic conditions.

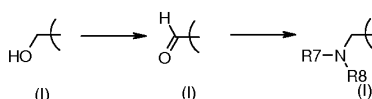
Examples of possible conversions are those reported below:

conv. 1) converting a compound of formula (I):



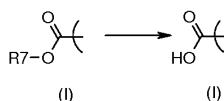
wherein R6a is a group of formula -COOR7, R7 is an optionally substituted straight or branched (C₁-C₆) alkyl, into a compound of formula (I) wherein R6a is a group of formula -CH₂OH, by reacting with a suitable reducing reagent;

conv. 2) converting a compound of formula (I):



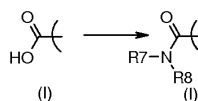
wherein R6a is a group of formula $-\text{CH}_2\text{OH}$, into a compound of formula (I) wherein R6a is a group $-\text{CH}(\text{R14})\text{NR7R8}$ wherein R14 is hydrogen, by first converting the group $-\text{CH}_2\text{OH}$ into the corresponding aldehyde $-\text{CHO}$ then, reacting the resulting derivative with a compound of formula R7R8NH (XX), wherein R6 and R7 are as defined above, under reductive amination conditions in the presence of a suitable reducing agents;

5 **conv. 3)** converting a compound of formula (I):



wherein R6a is a group of formula $-\text{COOR7}$, wherein R7 is an optionally substituted straight or branched ($\text{C}_1\text{-C}_6$) alkyl, into a compound of formula (I), wherein R6a is a group of formula $-\text{COOH}$ under acidic or basic conditions;

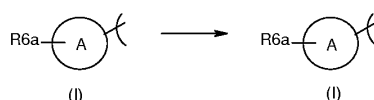
conv. 4) converting a compound of the formula (I):



10

wherein R6a is a group of formula $-\text{COOH}$, into a compound of formula (I), wherein R6a is a group of formula a group $-\text{CONR7R8}$, wherein R7 and R8 are as defined above by reaction with a compound of formula R7R8NH (XX), in the presence of suitable amide coupling agents;

conv. 5) converting a compound of formula (I):

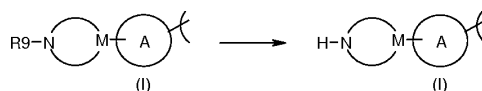


15

wherein A is aryl or heteroaryl and R6a is chloro, bromo or iodo, into a compound of formula (I), wherein R6a is an optionally substituted group selected from ($\text{C}_1\text{-C}_6$)alkyl, ($\text{C}_2\text{-C}_6$)alkenyl, ($\text{C}_2\text{-C}_6$)alkynyl, ($\text{C}_3\text{-C}_7$)cycloalkyl, heterocyclyl, aryl, heteroaryl, by reaction with a reagent of formula R6aQ (XXI), wherein R6a is as defined above and Q is a group selected from boronic acid, boronic ester, and $-\text{Sn}[(\text{C}_1\text{-C}_6)\text{alkyl}]_3$, under Pd-based catalyzed cross-coupling conditions;

20

conv. 6) converting a compound of formula (I):



25

wherein R6a is a linker group M of formula $-\text{CH}(\text{R14})\text{NR7R8}$ or $-\text{CONR7R8}$ or NR7R8 wherein R14 is hydrogen or an optionally substituted straight or branched ($\text{C}_1\text{-C}_6$)alkyl, R7 and R8 together with the nitrogen atom to which they are bound, may form a 5 to 7 membered heterocyclyl group optionally containing one additional group such as N-R9, wherein R9 is a suitable protecting group, into a compound of formula (I), wherein A is as defined above and R9 is hydrogen, under basic or acid hydrogenation conditions;

conv. 7) converting a compound of formula (I):

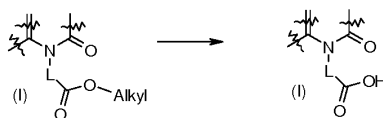


30

wherein R6a is a linker group M of formula $-\text{CH}(\text{R14})\text{NR7R8}$, or $-\text{CONR7R8}$ or NR7R8 wherein R14 is hydrogen or an optionally substituted straight or branched ($\text{C}_1\text{-C}_6$)alkyl, R7 and R8 together with the nitrogen atom to which they

are bound, may form a 5 to 7 membered heterocyclyl group optionally containing one additional group such as N-R9, wherein R9 is hydrogen, into a compound of formula (I) wherein A is as defined above and R9 is -COR11, wherein R11 is an optionally substituted straight or branched (C₁-C₆)alkyl, (C₂-C₆) alkenyl or (C₂-C₆) alkynyl, by reaction with a reagent of formula R11COW (XXII), wherein R11 is as defined above and W is OH or Cl;

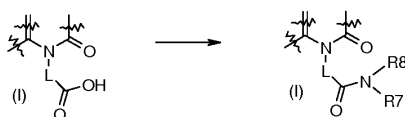
- 5 **conv. 8)** converting a compound of formula (I):



wherein R2 is a group of formula L-COOAlkyl wherein L is an optionally substituted group selected straight or branched (C₁-C₆)alkyl, (C₃-C₆)cycloalkyl-(C₁-C₆)alkyl, aryl-(C₁-C₆)alkyl, and heterocyclyl-(C₁-C₆)alkyl, into a compound of formula (I) wherein R2 is a group of formula L-COOH, wherein L is as defined above; under acidic or basic conditions;

10

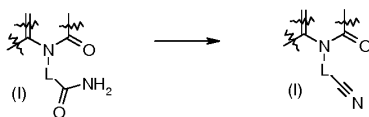
- conv. 9)** converting a compound of formula (I):



wherein R2 is a group of formula L-COOH, wherein L is as defined above, into a compound of formula (I), wherein R2 is a group of formula L-CONR7R8, wherein L, R7 and R8 are as defined above, by reaction with a compound of formula R7R8NH (XX), in the presence of a amide coupling agents;

15

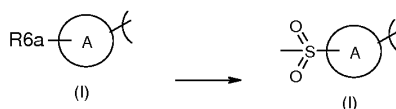
- conv. 10)** converting a compound of formula (I):



wherein R2 is a group of formula L-CONH₂ wherein L is as defined above, into a compound of formula (I), wherein R2 is a group of formula L-CN, wherein L is as defined above, by reaction with a dehydration agent;

20

- conv. 11)** converting a compound of formula (I):



wherein A is aryl or heteroaryl and R6a is chloro, bromo or iodo, into a compound of formula (I), wherein R6a is methylsulphonyl group, under cross-coupling reaction conditions;

- conv. 12)** converting a compound of formula (I):



25

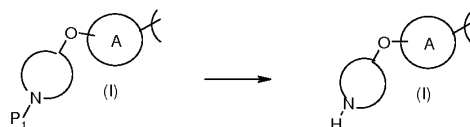
wherein L is a group selected from aryl(C₁-C₆)alkyl, and heterocyclyl-(C₁-C₆) alkyl, into a compound of formula (I) wherein L is defined above, under strong Lewis acid conditions;

- conv. 13)** converting a compound of formula (I):



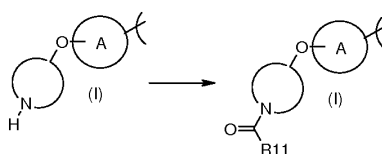
wherein R6a is a phenolic group, into a compound of formula (I) wherein R6a is a group OR7 wherein R7 is as defined above, by reaction with a reagent of formula R7-X (XXIII), wherein R7 is as defined above and X is hydroxy, bromine, iodine, -OMs or -OTs;

- 5 **conv. 14)** converting a compound of formula (I):



wherein A is as defined above and R6a is a group -OR7 wherein R7 is heterocyclyl group and P1 is a suitable protecting group, into a compound of formula (I), wherein A is as defined above and R7 is heterocyclyl, according to procedure well known in the art (see e.g. Green, Theodora W. and Wuts, Peter G.M. – Protective Groups in Organic Synthesis, Third Edition) such as, e.g. under basic or acid hydrogenation;

- 10 **conv. 15)** converting a compound of formula (I):



wherein A is as defined above and R6a is a group -OR7 wherein R7 is a heterocyclyl group, into a compound of formula (I), wherein A and R11 are as defined above, by reaction with a reagent of formula R11COW, (XXII) wherein R11 is as defined above and W is OH or Cl.

- 15 **conv. 16)** converting a compound of formula (I):



wherein L is a group selected from aryl(C₁-C₆)alkyl, and heterocyclyl-(C₁-C₆)-alkyl, into a compound of formula (I) wherein L is defined above, under Sonogashira reaction.

- 20 According to **conv. 1** of the process an ester of formula (I) can be reacted in different ways and experimental conditions known in the art with a reducing agent to obtain the corresponding alcohol compound of formula (I). For example, lithium aluminium hydride or the like, in a suitable solvent such as THF at a temperature ranging from 0°C to room temperature from 2 to about 24 h. Preferably, the reaction is conveniently performed with lithium aluminium hydride in THF at room temperature.
- 25 According to **conv. 2** of the process at first the oxidation of an intermediate of formula (I) can be carried out in the presence of Manganese (II) dioxide, Pyridinium chlorochromate, o-Iodoxybenzoic acid (IBX), Tetrapropylammonium perruthenate (TPAP), 4-Methylmorpholine N-oxide (NMO), Sodium hypochlorite/TEMPO/Bu₄NHSO₄, in a solvent such as methylene chloride, ACN, THF, EtOAc, acetone or chloroform at room temperature to provide the aldehyde of formula (I). Then, the aldehyde intermediate is further reacted in reductive amination conditions with a reagent of

formula (XX), in the presence of a reductive agent such as NaBH_4 , NaCNBH_3 , $\text{NaBH}(\text{OAc})_3$ and the like, in a solvent such as MeOH, EtOH, 2,2,2-trifluoroethanol and the like, at a temperature ranging from rt to 40 °C and for a time ranging from 1 to about 12 h. Said reducing reaction can be optionally carried out in the presence of a suitable catalyst such as AcOH, TFA and the like.

- 5 According to **conv. 3**, the reaction is carried out with aqueous alkaline solutions, such as aqueous LiOH, NaOH or KOH, or in acidic conditions, for instance with AcOH, TFA or HCl, in an organic solvent, such as a lower alcohol, THF, DMF, DCM or 1,4-dioxane or mixtures thereof, at a temperature ranging from rt to about 80 °C and for a time ranging from about 1 to about 12 h.

- According to **conv. 4**, the amidation of a compound of formula (I), is carried out in the presence of a suitable primary
10 or secondary amine of formula (XX), under basic conditions, preferably with DIPEA or TEA, in a suitable solvent such as DCM, DMF, THF, 1,4-dioxane or DMA, in the presence of a suitable condensing agent, for instance dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide (EDC), 3,4-dihydro-3-hydroxy-4-oxo-1,2,3-benzotriazine (DHBT), O-benzotriazolyltetramethylisouronium tetrafluoroborate (TBTU), benzotriazol-1-yl-xyloxytripyrrolidinophosphonium hexafluorophosphate (PyBOP), or 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) at a temperature ranging from about -10 °C to reflux and for a
15 suitable time, for instance from about 30 minutes to about 96 h. Said reaction is optionally carried out in the presence of a suitable catalyst such as DMAP, or in the presence of a further coupling reagent such as N-hydroxybenzotriazole (HOBT); or

- alternatively, conversion can be also carried out, for example through a mixed anhydride method, by using an alkyl
20 chloroformate such as ethyl, isopropyl, benzyl chloroformate, in the presence of a tertiary amine, such as TEA, DIPEA or pyridine, in a suitable solvent, such as, for instance toluene, DCM, THF, DMF and the like, at rt; or alternatively the carboxylic acid is converted first into the corresponding acyl chloride by reaction with an activating agent such as thionyl chloride, oxalyl chloride, cyanuric chloride or 1-chloro-N,N,2-trimethylpropenylamine (Ghosez's reagent) neat or in a suitable solvent, such as toluene or DCM, optionally in the presence of a catalytic amount of
25 DMF, at a temperature ranging from about -10 °C to reflux and for a suitable time, for instance from about 30 minutes to about 4 h. Then, said acyl chloride is reacted with a suitable primary or secondary amine of formula (XX), in a suitable solvent such as DCM, chloroform, THF, diethyl ether, 1,4-dioxane, ACN, toluene, or DMF and the like at a temperature ranging from about -10 °C to reflux and for a suitable time, for instance from about 30 minutes to about 96 h, in the presence of a suitable base such as TEA, DIPEA or pyridine.

- 30 According to **conv. 5**, reaction of a compound of the formula (I) with a compound of general formula (XXI), is performed under standard Suzuki coupling conditions using a Pd-based catalyst, such as $\text{Pd}(\text{dppf})\text{Cl}_2$, $\text{PdCl}_2(\text{PPh}_3)_2$ and $\text{Pd}(\text{PPh}_3)_4$, with a suitable base such as Na_2CO_3 , Cs_2CO_3 , K_3PO_4 , in a suitable solvent such as 1,4-dioxane, 1,4-dioxane/water, THF, DMF, toluene and the like, at temperatures ranging from rt to 130 °C, in classical thermal conditions, or in a microwave apparatus for a time period ranging from 1 hour to 48 h.

- 35 According to **conv. 6**, deprotection of a compound of formula (I) is performed under acidic conditions, such as for instance TFA, HCl and the like in a solvent such as DCM, 1,4-dioxane, or with a catalytic amount of CuCl in a suitable solvent such as MeOH, EtOH or a mixture EtOH/water at a temperature ranging from rt to reflux and for a time ranging from 1 to about 12 h.

- According to **conv. 7**, converting a compound of the formula (I), wherein an amine group is present, into the corresponding carboxamide derivative, by reaction with a compound of formula (XXII). It is clear to the skilled person that this reaction can be accomplished in a variety of ways and operative conditions, which are widely known in the art for the preparation of carboxamides (see e.g. Scott, C.J. et al. J. Med. Chem. 2005, 48, 1344-1358; Amino Acids, Peptides and Proteins in Organic Chemistry: Building Blocks, Catalysis and Coupling Chemistry, Volume 3; Andrew B. Hughes, Ayman El- Faham, Fernando Albericio). As an example, when an acyl chloride is used, the reaction is performed in a suitable solvent such as for instance, DCM, THF, 1,4-dioxane, ACN, or DMF or the like at a temperature ranging from about -10°C to reflux and for a suitable time, for instance from about 30 minutes to about 96 hours. The reaction is carried out in the presence of an opportune proton scavenger such as triethylamine, N,N-diisopropylethylamine or pyridine; or
- when a carboxylic acid is involved, the reaction is carried out in the presence of a coupling agent such as, for instance, 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU), 1,3-dicyclohexylcarbodiimide, 1,3-diisopropylcarbodiimide, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, N-cyclohexylcarbodiimide-N'-propylmethyl polystyrene or N-cyclohexylcarbodiimide-N'-methyl polystyrene, in a suitable solvent such as, for instance, dichloromethane, tetrahydrofuran, 1,4-dioxane, acetonitrile, N,N-dimethylformamide at a temperature ranging from about -10°C to reflux and for a time from about 30 minutes to about 48 hours. The said reaction is optionally carried out in the presence of a suitable catalyst, for instance 4-dimethylaminopyridine, or in the presence of a further coupling agent such as N-hydroxybenzotriazole.
- According to **conv. 8**, the reaction is performed as described as for **conv. 3**.
- According to **conv. 9**, the reaction is performed as described as for **conv. 4**.
- According to **conv. 10** converting the amide of formula (I) into the corresponding nitrile by reaction with a dehydrating agent such as trifluoroacetic anhydride, used as solvent, at a temperature ranging from rt to reflux for a time period ranging from 1 to 4h.
- According to **conv. 11**, conversion of a compound of formula (I) into the corresponding methylsulphonyl compound of formula (I) is performed, through any of the cross-coupling reactions suitable for the formation of C-S bonds (*Org. Lett.*, 2002, 4, pp 4423-4425). Said reactions, imply a coupling with sodium methansulphinate in the presence of CuI in a suitable solvent such as DMSO and the like, at a temperature ranging from 90°C to 130°C for a time ranging from 6 to 24h.
- According to **conv. 12** of the process, conversion of compound of formula (I) into the corresponding hydroxy derivative of formula (I) is carried out by reaction with a Lewis acid such as BBr₃, AlCl₃ or the like in a suitable solvent such as DCM, at a temperature of 0°C for a time ranging from 1 to 4h.
- According to **conv. 13** of the process, a reaction of a compound of the formula (I) with a reagent of formula (XXIII), wherein X is bromine, iodine, -OMs or -OTs, can be carried out in the presence of a suitable base, such as Na₂CO₃, K₂CO₃, Cs₂CO₃, NaH, KH and the like, in a suitable solvent, such as DMF, DMA, ACN, acetone, THF and the like, at a temperature ranging from 0 °C to reflux. When an intermediate of formula (XXIII), wherein X is hydroxy is used, the reaction is preferentially carried out under Mitsunobu alkylation conditions in the presence of a suitable reagent such as, for instance, diethylazodicarboxylate (DEAD), diisopropylazodicarboxylate (DIAD), di-tert-butylazodicarboxylate (DBAD), 1,1'-(azodicarbonyl)dipiperidine (ADDP), and a phosphine reagent such as, for instance,

trimethylphosphine, tritertbutylphosphine, triphenylphosphine and the like, in a suitable solvent, such as THF, DMF, DCM, toluene, benzene and the like, at a temperature ranging from 0° C to 65 °C.

According to **conv. 14**, the reaction is performed as described as for **conv. 6**.

According to **conv. 15**, the reaction is performed as described as for **conv. 7**.

- 5 From all of the above it is clear to the skilled person that any compound of formula (I) bearing a functional group which can be further derivatized to another functional group, by working according to methods well known in the art thus leading to other compounds of the formula (I), is intended to be comprised within the scope of the present invention.

- 10 When preparing the compounds of general formula (I) according to any of the above variants of the process, optional functional groups within the starting materials, the reagents or the intermediates thereof, and which could give rise to unwanted side reactions, need to be properly protected according to conventional techniques (see e.g., Green, Theodora W. and Wuts, Peter G.M. – Protective Groups in Organic Synthesis, Third Edition, John Wiley & Sons Inc., New York (NY), 1999). Likewise, the conversion of these latter into the free deprotected compounds may be carried out according to known procedures.

- 15 The compounds of every general formula can be further transformed in other compounds of the same general formula according to methods well known in the literature, as reported in the experimental section.

According to any variant of the process for preparing the compounds of the formula (I), the starting materials and any other reactants are known or easily prepared according to known methods.

The compounds of the formula (III) can be prepared as described in WO2014141104A1 and WO2017/019429.

- 20 The compounds of the formula (IV), (V), (VIIIa), (IX), (IXa), (IXb), (XII), (XIII), (XIV), (XVIIa), (XVIIb) and (XVIII), are either commercially available or can be prepared with known methods.

The final compounds may be isolated and purified using conventional procedures, for example chromatography and/or crystallization and salt formation.

The compounds of general formula (I) as defined above can be converted into pharmaceutically acceptable salts.

- 25 The compounds of general formula (I) as defined above, or the pharmaceutically acceptable salts thereof, can be subsequently formulated with a pharmaceutically acceptable carrier or diluent to provide a pharmaceutical composition.

- The synthesis of a compound of general formula (I), according to the synthetic processes described above, can be conducted in a stepwise manner, whereby each intermediate is isolated and purified if needed by standard purification techniques, like, for example, column chromatography, before carrying out the subsequent reaction. Alternatively, two or more steps of the synthetic sequence can be carried out in a so-called "one-pot" procedure, as known in the art, whereby only the compound resultant from the two or more steps is isolated and purified.

- 30 In cases where a compound of general formula (I) contains one or more asymmetric centers, said compound can be separated into the single stereoisomers by procedures known to those skilled in the art. Such procedures comprise standard chromatographic techniques, including chromatography using a chiral stationary phase, or crystallization. General methods for separation of compounds containing one or more asymmetric centers are reported, for instance, in Jacques, Jean; Collet, André; Wilen, Samuel H., Enantiomers, Racemates, and Resolutions, John Wiley & Sons Inc., New York (NY), 1981.

The present invention also provides a method of treating a disease caused by and/or associated with increased 2-hydroxyglutarate level, which comprises administering to a mammal, preferably a human, in need thereof, an effective amount of a compound of formula (I) as defined above.

Furthermore the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined above, for use in a method of treating a disease caused by and/or associated with increased 2-hydroxyglutarate level, which comprises administering to a mammal, preferably a human, in need thereof, an effective amount of a compound of formula (I) as defined above.

Additionally, the present invention provides a method of treating a disease caused by and/or associated with mutated IDH enzymes or with IDH wt over-functions, which comprises administering to a mammal, preferably a human, in need thereof, an effective amount of a compound of formula (I) as defined above.

Moreover the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined above, for use in a method of treating a disease caused by and/or associated with mutated IDH enzymes or with IDH wt over-functions, which comprises administering to a mammal, preferably a human, in need thereof, an effective amount of a compound of formula (I) as defined above.

Preferably the disease is selected from the group consisting of cancer, cell proliferative disorders, immune-related disorders. More preferably, the disease is cancer.

According to a most preferred embodiment of the present invention the cancer is selected from the group consisting of: carcinomas, such as bladder, breast, kidney, liver, colon, lung, including small cell lung cancer, esophagus, gall-bladder, ovary, pancreas, stomach, cervix, prostate, and skin, including squamous cell carcinoma; hematopoietic tumors of lymphoid lineage including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, angioimmunoblastic T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkitt's lymphoma; hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia; tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma; tumors of the central and peripheral nervous system, including glioma, glioblastoma, glioblastoma multiforme, astrocytoma, oligodendroglioma, paraglioma, neuroblastoma, and schwannomas; and other tumors, including melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoxanthoma, thyroid cancers, such as papillary thyroid carcinoma and medullary thyroid carcinoma, Kaposi's sarcoma, chondrosarcoma, and cholangiocarcinoma.

Other preferred diseases caused by and/or associated with mutated IDH enzymes or IDH wt over-functions, are cellular proliferation disorders such as, for example, benign prostate hyperplasia, familial adenomatosis, polyposis, neurofibromatosis, psoriasis, vascular smooth cell proliferation associated with atherosclerosis, pulmonary fibrosis, arthritis, glomerulonephritis and post-surgical stenosis and restenosis.

Further preferred diseases caused by and/or associated with mutated IDH enzymes with increased 2-hydroxyglutarate level are for example, Ollier disease or Mafucci syndrome..

Additional preferred diseases caused by and/or associated with mutated IDH enzymes or IDH wt over-functions, are immune-related disorders including but not limited to: transplant rejection, skin disorders like psoriasis, allergies, asthma and autoimmune-mediated diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE),

Crohn's disease and amyotrophic lateral sclerosis. Optionally, the methods of the present invention further comprise treating a mammal in need thereof in combination with radiation therapy or chemotherapy regimen.

Moreover, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, as defined above, for use in a method of treating a mammal in need thereof in combination with radiation therapy or in
5 combination with a chemotherapy regimen.

In one embodiment the chemotherapy regimen comprises at least one cytostatic or cytotoxic agent.

Cytostatic or cytotoxic agents include, but are not limited to, antibiotic-type agents, alkylating agents, antimetabolite agents, hormonal agents, immunological agents, interferon-type agents, cyclooxygenase inhibitors (e.g. COX-2 inhibitors), matrixmetalloprotease inhibitors, telomerase inhibitors, tyrosine kinase inhibitors, anti-growth factor
10 receptor agents, anti-HER agents, anti-EGFR agents, anti-angiogenesis agents (e.g. angiogenesis inhibitors), farnesyl transferase inhibitors, ras-raf signal transduction pathway inhibitors, cell cycle inhibitors, other cdk inhibitors, tubulin binding agents, topoisomerase I inhibitors, topoisomerase II inhibitors, aromatase inhibitors, inhibitors of kinesins, therapeutic monoclonal antibodies, inhibitors of mTOR, histone deacetylase inhibitors, inhibitors of hypoxic response, PD-1 antagonists, or antigen binding fragment thereof, which specifically binds to PD-1 or PD-
15 L1.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described below and the other pharmaceutically active agent within the approved dosage range.

Compounds of formula (I) may be used sequentially with known anticancer agents when a combination formulation is inappropriate.

20 The compounds of formula (I) of the present invention, suitable for administration to a mammal, e.g. to humans, can be administered by the usual routes and the dosage level depends upon the age, weight, and conditions of the patient and administration route.

For example, a suitable dosage adopted for oral administration of a compound of formula (I) may range from about 10 to about 1000 mg per dose, from 1 to 5 times daily. The compounds of the invention can be administered in a
25 variety of dosage forms, e.g. orally, in the form of tablets, capsules, sugar or film coated tablets, liquid solutions or suspensions; rectally in the form of suppositories; parenterally, e.g. intramuscularly, or through intravenous and/or intrathecal and/or intraspinal injection or infusion.

The pharmaceutical compositions containing the compounds of the invention are usually prepared following conventional methods and are administered in a suitable pharmaceutical form.

30 For example, the solid oral forms may contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, sucrose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents, e.g. starches, arabic gum, gelatine methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disintegrating agents, e.g. starch, alginic acid, alginates or sodium starch glycolate; effervescent mixtures; dyestuffs; sweeteners; wetting agents, such as lecithin, polysorbates,
35 laurylsulphates; and, in general, non-toxic and pharmacologically inactive substances used in pharmaceutical formulations. These pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tableting, sugar-coating, or film-coating processes.

The liquid dispersions for oral administration may be, e.g. syrups, emulsions and suspensions.

As an example the syrups may contain, as a carrier, saccharose or saccharose with glycerine and/or mannitol and sorbitol.

The suspensions and the emulsions may contain, as examples of carriers, natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose or polyvinyl alcohol.

- 5 The suspension or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol and, if desired, a suitable amount of lidocaine hydrochloride.

The solutions for intravenous injections or infusions may contain, as a carrier, sterile water or preferably they may be in the form of sterile, aqueous, isotonic, saline solutions or they may contain propylene glycol as a carrier.

- 10 The suppositories may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. cocoa butter, polyethylene glycol, a polyoxyethylene sorbitan fatty acid ester surfactant or lecithin.

The present invention also provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined above, and at least one pharmaceutically acceptable excipient, carrier or diluent.

- 15 The present invention further provides a pharmaceutical composition of a compound of formula (I) further comprising one or more chemotherapeutic agents. Chemotherapeutic agents included, but are not limited to, cytostatic or cytotoxic agents, antibiotic-type agents, alkylating agents, antimetabolite agents, hormonal agents, immunological agents, interferon-type agents, cyclooxygenase inhibitors (e.g. COX-2 inhibitors), matrixmetalloprotease inhibitors, telomerase inhibitors, tyrosine kinase inhibitors, anti-growth factor receptor agents, anti-HER agents, anti-EGFR agents, anti-angiogenesis agents (e.g. angiogenesis inhibitors), farnesyl transferase inhibitors, ras-raf signal transduction pathway inhibitors, cell cycle inhibitors, other cdks inhibitors, tubulin binding agents, topoisomerase I inhibitors, topoisomerase II inhibitors, aromatase inhibitors, inhibitors of kinesins, therapeutic monoclonal antibodies, inhibitors of mTOR, histone deacetylase inhibitors, inhibitors of hypoxic response, PD-1 antagonists, or antigen binding fragment thereof, which specifically binds to PD-1 or PD-L1 and the like.

- 20 Moreover the invention provides an *in vitro* method for inhibiting mutated IDH protein activity which comprises contacting the said protein with an effective amount of a compound of formula (I) as defined above.

Additionally, the invention provides a product comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined above, and one or more chemotherapeutic agents, as a combined preparation for simultaneous, separate or sequential use in anticancer therapy.

- 30 In yet another aspect the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined above, for use as a medicament.

Finally, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, as defined above, in the manufacture of a medicament with anticancer activity.

35 EXPERIMENTAL PART

The short forms and abbreviations used herein have the following meaning:

g gram	mg milligram
mL milliliter	μL microliter

	mM millimolar	mmol millimole
	μ M (micromolar)	MHz (Mega-Hertz)
	h hour(s)	Hz (Hertz)
	mm (millimetres)	min (minutes)
5	μ m (micron)	M (molar)
	BSA bovine serum albumine	DTT dithiothreitol
	NADPH Nicotinamide adenine dinucleotide phosphate	Rt retention time
	2-HG 2-Hydroxy glutaric acid	KOtBu (potassium <i>tert</i> -butoxide)
	rt (room temperature)	TEA (triethylamine)
10	DMAP (4-dimethylaminopyridine)	DME (1,2-dimethoxyethane)
	TFA (trifluoroacetic acid)	Na ₂ SO ₄ (sodium sulphate)
	AcOH (acetic acid)	ESI (electrospray ionization)
	Na ₂ CO ₃ (sodium carbonate)	K ₂ CO ₃ (potassium carbonate)
	Cs ₂ CO ₃ (caesium carbonate)	K ₃ PO ₄ (potassium phosphate)
15	LiOH (lithium hydroxide)	NaOH (sodium hydroxide)
	KOH (potassium hydroxide)	<i>p</i> -TsOH (<i>p</i> -toluensulfonic acid)
	EtOAc (ethyl acetate)	LiHMDS (lithium bis(trimethylsilyl)amide)
	NMP (N-methyl-2-pyrrolidone)	NaH (sodium hydride)
	DMA (N,N-dimethylacetamide)	KH (potassium hydride)
20	DMF (N,N-dimethylformamide)	DCM (dichloromethane)
	DIPEA (N,N-diisopropyl-N-ethylamine)	hex (hexane)
	THF (tetrahydrofuran)	DMSO (dimethylsulfoxide)
	MeOH (methanol)	ACN (acetonitrile)
	EtOH (ethanol)	Bn (benzyl)
25	-OMs (mesylate)	-OTs (tosylate)
	HOBT (N-hydroxy-benzotriazole)	DCC (1,3-dicyclohexylcarbodiimide)
	NMR Nuclear magnetic resonance	MS Mass spectroscopy
	m/z mass to charge ratio	LC Liquid chromatography
	MgCl ₂ Magnesium chloride	
30	EDCI (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride)	
	TBTU (N,N,N',N'-tetramethyl-O-(benzotriazol-1-yl)uronium-tetrafluoroborate)	
	RP-HPLC (reverse phase high performance liquid chromatography)	

Biochemical assay

35 In Vitro Assays for IDH1m (R132H or R132C) and IDH2^{R172K} Inhibitors

IDH mutated enzyme activity converting alpha-ketoglutarate to 2-hydroxyglutaric acid is measured using a NADPH depletion assay. In the assay the remaining cofactor is measured at the end of the reaction with the addition of a catalytic excess of diaphorase and resazurin, to generate a fluorescent signal in proportion to the amount of NADPH

remaining. IDH1 WT enzyme as well as mutated isoforms IDH1^{R132H}, IDH1^{R132C}, and IDH2^{R172K} enzymes are commercially available proteins (see e.g. Sino Biological, Abcam, Active Motif or Creative BioMart).

IDH1^{R132H} homodimer enzyme are diluted to 8nM, in 10 μ L of Assay Buffer (150 mM NaCl, 50 mM Tris-HCl pH 7.6, 10 mM MgCl₂, 0.001% Triton X-100, 4 mM β -mercaptoethanol); 0.2 μ L of test compound, previously serially diluted 1 to 3, >10 experimental points from 1mM in DMSO, is added and the mixture is incubated for 15 minutes at room temperature. The reaction is started with the addition of 10 μ L of Substrate Mix (12 μ M NADPH, 3.4mM alpha-ketoglutarate in Assay Buffer) and the mixture is incubated for 60 minutes at room temperature. The reaction is terminated with the addition of 5 μ L of Detection Buffer (100 μ g/mL diaphorase, 30 μ M resazurin, in IX Assay Buffer), and is incubated for 15 minute before reading on a ViewLux as platereader at Ex544/Em590.

Compounds are assayed for their activity against IDH1^{R132C} following the same assay as above with the following modifications: IDH1^{R132C} and alpha-ketoglutarate final concentrations in the Assay Buffer is 2nM and 0.14 mM, respectively.

Compounds are assayed for their activity against IDH2^{R172K} following the same assay as above with the following modifications: IDH2^{R172K} and alpha-ketoglutarate final concentrations in the Assay Buffer is 16nM and 0.55 mM, respectively.

Enzymatic Assay for IDH1 wild-type (WT)

IDH1WT enzymatic activity converting isocitric acid to alpha-ketoglutarate is measured using a NADPH forming assay. In the assay the forming cofactor is measured in continuous with the addition of a catalytic excess of diaphorase and resazurin, to generate a fluorescent signal in proportion to the amount of NADPH forming.

Compounds were preincubated with the enzyme, then the reaction was started by the addition of NADP⁺, isocitrate, diaphorase and a corresponding substrate, resazurin. Diaphorase reduces resazurin to the highly fluorescent resorufin with the concomitant oxidation of NADPH to NADP. Specifically, 0.2 μ L of test compound, previously serially diluted 1 to 3, 10 experimental points from 1mM in DMSO, was added to 0.016nM IDH1WT enzyme in 10 μ L of Assay Buffer (150 mM NaCl, 50 mM Tris-HCl pH 7.6, 10 mM MgCl₂, 0.001% Triton X-100, 4 mM β -mercaptoethanol); the mixture is incubated for 15 minutes at room temperature. The reaction is started with the addition of 10 μ L of Substrate Mix (400 μ M NADP⁺, 40 μ M iso-citrate, 5 μ g/mL Diaphorase and 7 μ M resazurin in Assay Buffer), the mixture is incubated at room temperature and the reaction is reading on a ViewLux as platereader at Ex544/Em590 in continuous.

Biochemical activity

Biochemical potencies on mutants IDH1^{R132H}, IDH1^{R132C} and IDH2^{R172K} of representative compounds, which were determined according to the above described assays, are reported in Table 1 as IC₅₀ values (μ M), while biochemical potencies on IDH1 wild type enzyme, determined according to the above described assays, are reported in Table 2 as IC₅₀ values (μ M).

Table 1

Cpd. number	IDH1 ^{R132H} IC50(μM)	IDH1 ^{R132C} IC50(μM)	IDH2 ^{R172K} IC50(μM)
1	1.829	0.622	
5	1.128	0.45	
6	3.335	1.336	6.645
7	2.963	1.41	
8	2.436	1.385	
9	1.53	0.604	
10	3.852	1.923	
11	0.362	0.181	6.1
12	3.481	1.775	5.02
14	1.742	0.85	5.733
16	1.003	0.46	2.696
17	4.907	1.893	
18	4.07	1.551	
19	0.41	0.203	6.68
20	0.74	0.332	5.02
21	2.491	0.586	
22	0.451	0.195	2.986
23	2.088	0.891	3.494
24	3.527	1.722	2.96
25	1.943	0.524	
26	2.361	1.257	2.204
27	1.071	0.336	2.595
28	1.476	0.59	2.514
30	1.343	0.406	2.523
31	0.323	0.147	2.2
32	3.769	1.151	
33	0.461	0.19	
34	0.219	0.135	3.35
35	0.211	0.>106	5.053
36	0.178	0.>105	6.543
37	1.481	0.805	4.847
38	0.137	0.067	7.51
40	0.16	0.071	
41	2.464	1.408	
42	1.383	0.951	
43	1.642	1.047	
44	1.09	0.811	
45	0.554	0.206	
47	1.811	0.597	
49	0.118	0.067	4.355
50	0.068	0.038	2.509
52	1.758	0.786	
53	0.941	0.529	
55	0.137	0.065	
57	0.543	0.208	
60	0.341	0.139	
61	0.071	0.038	5.023
62	0.082	0.044	5.7
63	0.29	0.123	
64	0.21	0.133	
65	0.02	0.011	

Cpd_ number	IDH1 ^{R132H} IC50(μM)	IDH1 ^{R132C} IC50(μM)	IDH2 ^{R172K} IC50(μM)
66	0.161	0.094	4.537
67	0.037	0.015	7.36
68	0.078	0.029	
69	0.036	0.022	
70	0.478	0.177	
71	2.479	0.964	4.833
72	2.589	1.236	
75	0.407	0.431	
76	2.38	3.635	
77	0.207	0.209	
78	0.896	1.381	
79	0.529	0.357	
80	0.444	0.282	
81	0.288	0.172	
82	0.146	0.134	
83	0.347	0.196	4.261
84	0.19	0.15	
85	1.767	1.462	
88	0.138	0.097	
89	0.112	0.075	
90	0.697	0.391	
92	0.713	0.715	
94	0.071	0.03	5.568
95	0.425	0.162	5.156
96	0.801	0.42	5.02
97	0.524	0.323	5.03
98	0.366	0.217	5.344
99	0.201	0.132	3.626
100	3.064	1.595	
101	0.575	0.271	2.667
102	4.325	2.803	
103	1.593	0.634	
104	0.276	0.121	5.132
105	0.105	0.055	4.727
106	1.227	0.667	2.91
107	0.722	0.459	
108	0.459	0.307	
109	0.334	0.218	5.681
110	0.238	0.104	
111	4.038	1.423	
112	0.19	0.178	
113	0.367	0.282	5.508
114	2.371	1.913	
115	0.672	0.825	
116	0.176	0.101	5.02
117	0.055	0.029	5.509
118	1.296	0.923	
119	2.232	1.164	
120	0.221	0.108	
121	3.904	1.635	
122	0.717	0.386	
129	0.197	0.098	6.68
130	0.18	0.093	5.03

Cpd_ number	IDH1 ^{R132H} IC50(μM)	IDH1 ^{R132C} IC50(μM)	IDH2 ^{R172K} IC50(μM)
131	0.284	0.17	
132	0.194	0.124	6.114
133	0.218	0.141	5.051
134	0.152	0.061	6.115
135	0.4	0.202	
136	0.122	0.054	
137	3.468	1.299	
138	2.258	0.777	
139	0.042	0.021	0.264
140	0.249	0.115	3.226
141	0.038	0.031	0.213
142	0.176	0.214	0.552
143	0.236	0.066	
144	0.078	0.025	
145	3.561	1.322	
146	0.059	0.016	1.417
147	0.473	0.173	
148	0.187	0.109	5.828
149	0.085	0.048	3.326
150	0.02	0.008	
151	0.095	0.02	
152	0.158	0.065	5.617
153	0.226	0.041	
154	0.199	0.079	5.383
155	0.455	0.147	
156	0.139	0.091	0.476
157	0.162	0.051	
158	0.126	0.04	
159	0.077	0.037	0.51
160	0.068	0.031	
161	0.022	0.013	0.299
162	0.084	0.03	
163	0.163	0.087	6.6
164	0.759	0.406	
165	0.157	0.085	5.663
166	0.179	0.093	7.569
167	0.03	0.023	2.562
168	0.029	0.016	0.137
169	0.193	0.179	0.414
170	0.167	0.09	3.111
171	0.169	0.055	
172	0.179	0.056	3.586
173	0.575	0.144	
174	0.042	0.032	
175	0.065	0.066	0.442
176	3.51	1.909	
177	0.978	0.401	
178	0.046	0.03	5.02
179	0.123	0.063	2.355
180	999	3.541	
181	0.175	0.351	0.878
182	0.103	0.061	
183	0.052	0.039	

Cpd_ number	IDH1 ^{R132H} IC50(μM)	IDH1 ^{R132C} IC50(μM)	IDH2 ^{R172K} IC50(μM)
184	0.126	0.227	0.201
185	2.373	1.271	
186	0.392	0.811	0.431
187	0.002	0.002	0.018
188	0.33	0.12	
189	3.769	0.811	
190	1.938	3.598	0.679
191	0.07	0.116	0.902
192	0.227	0.252	0.645
193	0.126	0.089	
194	0.338	0.2	1.791
195	0.593	0.184	
196	0.955	0.141	
197	2.343	0.405	
198	0.132	0.401	0.248
199	1.403	1.529	0.717
201	0.42	0.173	
202	0.666	0.104	
206	0.013	0.015	0.098
207		0.624	
208		0.213	
209		0.046	
210		0.183	
211		0.525	
212		0.061	
214	0.004	0.002	0.015
215		0.004	
216		0.001	
217		0.015	
218		0.013	
219	0.001	0.001	0.006
220	0.001	0.001	0.015
221		0.068	
222		0.147	
223		1.673	
224		1.697	
227	0.007	0.005	0.049
228	0.002	0.002	0.025
229	0.083	0.044	0.386
230	0.001	0.001	0.011
231	0.001	0.001	0.014
232		0.330	
235	0.128	0.048	5.11
236		0.105	
237	0.004	0.004	0.027
238	0.004	0.004	0.025
239	0.002	0.002	0.020
240		0.068	
241	0.272	0.196	0.146
242		0.010	
243		0.020	
244	0.002	0.003	0.021
245	0.002	0.002	0.020

Cpd_ number	IDH1 ^{R132H} IC50(μM)	IDH1 ^{R132C} IC50(μM)	IDH2 ^{R172K} IC50(μM)
246	0.002	0.001	0.019
247	0.005	0.004	0.035
248	0.004	0.002	0.030
249	0.005	0.003	0.033
251		0.002	

Table 2

Cpd_ number	IDH1wt IC50 (μM)
67	1.709
94	1.326
105	2.045
117	1.583
139	0.720
140	4.848
141	1.825
144	6.798
156	2.540
159	1.731
161	0.908
162	3.896
168	0.758
169	2.847
175	1.171
181	2.137
183	0.899
184	2.869
186	5.460
187	0.541
191	2.986
206	0.221
213	4.286
214	0.064
219	0.052
220	0.053
227	0.109
228	0.0273
229	0.839
230	0.039
231	0.122
237	0.091
241	0.117
244	0.220
245	0.224
246	0.231
247	0.215
248	0.216
249	0.215

Cellular Assay for IDHm Inhibitors

Cell lines HT-1080 (commercially available) and U87-MG-IDH1^{R132H} (obtained in analogy to the procedure reported in *J. Mol. Neurosci* 2013, 50, 165-71) are maintained in E-MEM 10% FCS and incubated at 37°C in a humidified 5% CO₂ atmosphere. Stably transfected U87-MG cell lines are also supplemented with 500 µg/mL G418.

Cells are seeded into 96 well black flat bottom plates at a density of 500 cells/well in 100 µL complete medium. After 24 hr the medium is replaced with 200 µL of fresh medium and compounds (dissolved into DMSO) are administered to the cells using D300E Digital Dispenser (Tecan).

After 72 hr of incubation 100 µL from each well are collected and used for 2HG (R(-)-2-hydroxyglutarate) quantification.

Levels of 2-HG in cell culture media are determined by LC-MS/MS. Cell supernatants (100 µL/well) are treated with 1 M aqueous trichloroacetic acid containing 130 µM of the internal standard 2-HG-d3 (20 µL/well) in a 96-well plate. The plates are sealed, mildly vortexed for 60 minutes, centrifuged at 4,000 RPM for 15 minutes, placed in a refrigerated autosampler taking care not to shake them, and aliquots of the upper part of the samples are directly injected in the chromatographic system. Calibration standards are obtained by ten fold dilution of aqueous 2-HG stock solutions with blank cell culture medium and denatured exactly in the same way as described above for samples. Samples and standards are assayed for 2-HG by reversed phase chromatography on a C18 column eluted with aqueous 0.15% formic acid and briefly washed with 90% methanol at the end of the run. 2-HG is determined by negative ion electrospray ionization with the internal standard method on a triple quadrupole mass spectrometer monitoring the MRM transitions 147 > 129 (2-HG) and 150 > 132 (2-HG-d3).

2-HG inhibition was calculated by comparing treated versus control data using Assay Explore (Symyx) software, with IC₅₀ determined using a sigmoidal fitting algorithm.

Table 3 and Table 4 report the IC₅₀ values (µM) of representative compounds on the inhibition of 2HG production in two cell lines U87MG_IDH1 R132H and HT-1080 (IDH1^{R132C}), determined according to the above described assay.

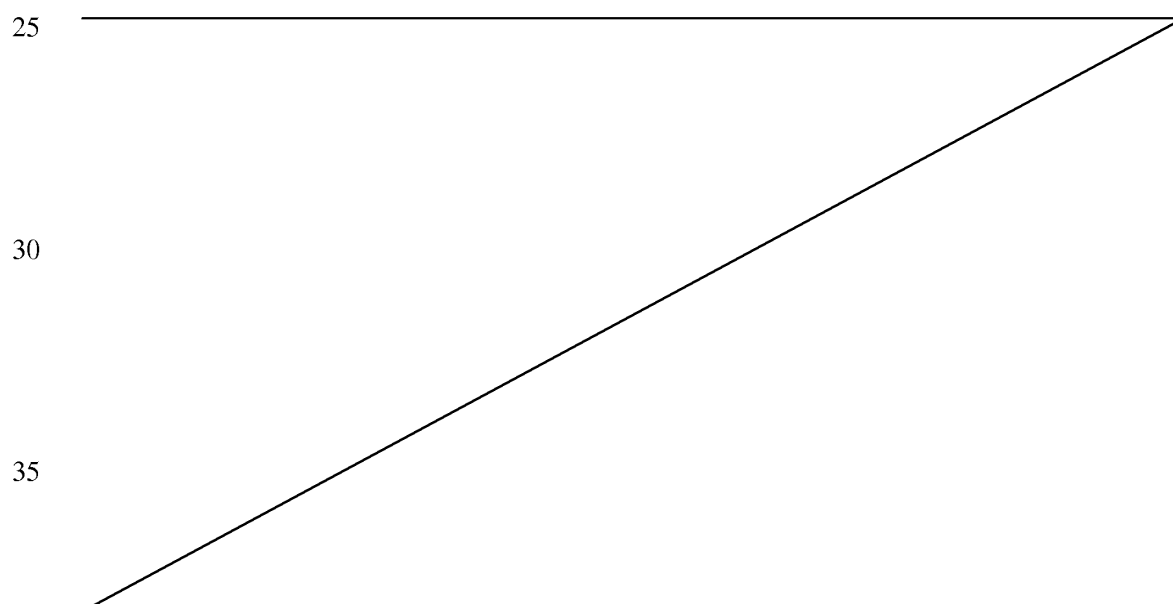


Table 3

Cpd_ number	U87MG_IDH1R132H 2-HG IC50 (μ M)
36	4.042
38	2.642
49	0.507
50	2.531
62	0.462
65	0.179
66	0.691
67	0.2
68	0.646
69	0.078
75	1.189
77	3.034
82	1.323
83	2.064
89	0.501
94	0.370
99	1.385
104	1.770
105	0.417
109	1.813
110	2.61
112	1.610
113	2.538
116	0.612
117	0.177
129	3.841
130	4.839
132	3.220
134	0.874
136	2.909
139	0.008
140	0.010
141	0.024
150	0.127
151	0.321
156	0.289
159	0.081
170	0.637
175	0.021
219	0.0004
220	0.0005
227	0.0004
228	0.0006
229	0.013
230	0.0004
237	0.0010

Table 4

Cpd_ number	HT1080 2-HG IC ₅₀ (μM)
49	0.307
62	0.169
65	0.082
66	0.353
67	0.067
68	0.315
89	0.505
94	0.203
105	0.116
110	0.590
116	0.311
117	0.155
139	0.022
140	0.108
142	0.075
143	0.517
170	0.442
183	0.021
184	0.028
187	<0.001
191	0.040
206	0.0101
209	0.0302
212	0.0531
214	0.0021
215	0.0023
216	0.0011
217	0.0082
218	0.0021
219	0.0004
220	0.0003
221	0.1424
222	0.1680
224	1.0668
227	0.0014
228	0.0008
229	0.0200
230	0.0004
231	0.0003
237	0.0004
238	0.0009
239	0.0009
241	0.0647
242	0.0045
243	0.038
244	0.0016
245	0.0010
246	0.0021
247	0.0030
248	0.0031

Cpd_ number	HT1080 2-HG IC50 (μM)
249	0.0029
251	0.0023

Representative compounds of the invention when tested in cell lines having the mutated form of IDH1 as reported in table 3 and Table 4, showed dose dependent inhibition of cellular production of 2-HG with potency lower than 5 μM. As expected the compounds showed any effect on the cellular proliferation even at the highest dose (10 μM).

5

PREPARATION OF COMPOUNDS OF FORMULA (I)

For a reference to any specific compound of formula (I) of the invention, optionally in the form of a pharmaceutically acceptable salt, see the experimental section and claims. Referring to the examples that follow, compounds of the present invention were synthesized using the methods described herein, or other methods, which are well known in the art.

10

With the aim at better illustrating the present invention, without posing any limitation to it, the following examples are given.

As used herein the symbols and conventions used in the processes, schemes and examples are consistent with those used in the contemporary scientific literature, for example, the *Journal of the American Chemical Society* or the *Journal of Biological Chemistry*.

15

Compound names are IUPAC names, generated by using ACD Name (by Advanced Chemistry Development, Inc.). Unless otherwise noted, all materials, including anhydrous solvent such as DMF, THF, DCM, were obtained from commercial suppliers, of the best grade and used without further purification. All reactions involving air- or moisture-sensitive compounds were performed under nitrogen or argon atmosphere.

20

General purification and analytical methods

Flash Chromatography was performed on silica gel (Merck grade 9395, 60A).

The HPLC equipment consisted of a Waters Alliance™ HT 2795 system equipped with a Waters 996 PDA detector and Waters mod. ZQ 2000 single quadrupole mass spectrometer, equipped with an electrospray (ESI) ion source. Instrument control, data acquisition and data processing were provided by Empower 2 and MassLynx 4.1 softwares.

25

HPLC was carried out at 25 °C at a flow rate of 1.2 mL/min using a YMC-Triart C18 (4,6 x 50mm, 3 μm) column. Mobile phase B was ammonium acetate 5mM pH=5.2 buffer with acetonitrile (95:5), and mobile phase C was H₂O/acetonitrile (5:95); the gradient was from 10 to 90% C in 5 minutes then ramp to 100% C in 0.1 minutes. The injection volume was 10 μL. The mass spectrometer operated in positive and in negative ion mode, the capillary voltage was set up at 3.5 kV (ES⁺) and 2.8 kV (ES⁻); cone voltage was 14 V (ES⁺) and 28 V (ES⁻); the source temperature was 120 °C; full scan, mass range from 100 to 800 amu was set up.

30

The preparative HPLC equipment consisted of a Shimadzu HPLC system equipped with SCL-8A System Controller, two LC-8A Pumps, SPD-6A UV Spectrophotometric Detector and manual Rheodyne injection system. Data acquisition (analogic signal) and data processing were provided by Empower 2 software. Purification was carried out at 25 °C at a flow rate of 15mL/min using a Waters X-Terra MS RP18 (150 x 30 mm, 10 μm) column. Mobile phase A was 0.1% TFA in water/acetonitrile (95:5) or, alternatively, Mobile phase A was 0.05% NH₃ in water/acetonitrile

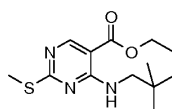
35

(95:5) and mobile phase B was H₂O/acetonitrile (5:95); the gradient was from 10 to 90% B in 15 minutes then ramp to 100% B in 0.1 minutes. Injection volume max 500 µL.

- ¹H-NMR spectra were recorded at a constant temperature of 28 °C on a Varian INOVA 400 spectrometer operating at 400.5 MHz and equipped with a 5 mm ¹H{¹⁵N-³¹P} z-axis PFG Indirect Detection probe and on a Varian INOVA 500 spectrometer operating at 499.7 MHz and equipped with a 5 mm ¹H{¹³C-¹⁵N} triple resonance Indirect Detection probe. Chemical shifts were referenced with respect to the residual solvent signals (DMSO-*d*₆: 2.50 ppm for ¹H). Data are reported as follows: chemical shift (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br. s = broad singlet, dd = doublet of doublets, ddd = doublet of doublets of doublets, m = multiplet), coupling constants (*J*, Hz) and number of protons.
- As formerly reported (M. Colombo, F. R. Sirtori, V. Rizzo, Rapid Commun Mass Spectrom 2004, 18(4), 511-517), ESI(+) high-resolution mass spectra (HRMS) were obtained on a Q-ToF Ultima (Waters, Manchester, UK) mass spectrometer directly connected with an Agilent 1100 micro-HPLC system (Palo Alto, US).

Preparation 1

- Step 1: 4-(2,2-Dimethyl-propylamino)-2-methylsulfanyl-pyrimidine-5-carboxylic acid ethyl ester [(VI), R2 = 2,2-Dimethyl-propyl, R3 = H] step2a**

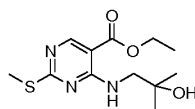


- 4-chloro-2-(methylsulfanyl)pyrimidine-5-carboxylic acid ethyl ester (2.0 g, 8.59 mmol) was dissolved in THF (20.0 mL) to which triethylamine (1.8 mL, 12.89 mmol) and neopentylamine (1.1 mL, 9.45 mmol) was added and stirred for 1 hour at reflux. The precipitated salts were filtered and the solvent evaporated under reduced pressure. The resulting oil was dissolved in Et₂O, washed with sodium water, and then dried over Na₂SO₄. The salts were filtered, and the solvent was evaporated under vacuum to give the product (1.50g, 62% yield) which is carried on without further purification.

- ¹H NMR (500MHz, DMSO-*d*₆) δ = 8.55 (s, 1 H), 8.39 (t, *J* = 5.9 Hz, 1 H), 4.29 (q, *J* = 7.2 Hz, 2 H), 3.38 (d, *J* = 6.1 Hz, 2 H), 2.47 (s, 3 H), 1.30 (t, *J* = 7.1 Hz, 3 H), 0.93 (s, 9 H). LCMS : *m/z* 284 [M+H]⁺ @ r.t. 7.86 min. HRMS (ESI) calcd for C₁₃H₂₁N₃O₂S [M +H]⁺ 284.1427 found 284.1429.

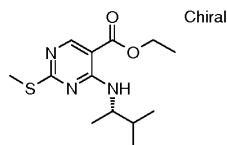
According to the same method, but employing 1-amino-2-methylpropan-2-ol, the following compound was prepared:

4-(2-Hydroxy-2-methyl-propylamino)-2-methylsulfanyl-pyrimidine-5-carboxylic acid ethyl ester [(VI), R2 = 2-Hydroxy-2-methyl-propylamino, R3 = H]



- The title compound was obtained as a colourless oil (64% yield);
- ¹H NMR (500MHz, DMSO-*d*₆) δ = 8.55 (s, 1 H), 8.48 (t, *J* = 5.3 Hz, 1 H), 4.76 (s, 1 H), 4.28 (q, *J* = 7.0 Hz, 2 H), 3.45 (d, *J* = 5.5 Hz, 2 H), 2.47 (s, 3 H), 1.30 (t, *J* = 7.1 Hz, 3 H), 1.13 (s, 6 H). LCMS : *m/z* 286 [M+H]⁺ @ r.t. 5.64 min.
- HRMS (ESI) calcd for C₁₂H₁₉N₃O₃S [M +H]⁺ 286.1220 found 286.1225;

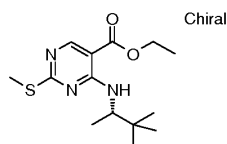
ethyl 4-[(2S)-3-methylbutan-2-yl]amino)-2-(methylsulfanyl)pyrimidine-5-carboxylate [(VI), R2 = (2S)-3-methylbutan-2-yl, R3 = H]



The title compound was obtained as a colourless oil (71% yield);

- 5 ¹H NMR (500MHz, DMSO-d₆) δ = 8.55 (s, 1H), 8.20 (d, J = 8.39 Hz, 1H), 4.28 (dq, J = 1.14, 7.09 Hz, 2H), 4.18 (dq, J = 5.11, 6.76, 8.30 Hz, 1H), 2.47 (s, 3H), 1.79 - 1.92 (m, 1H), 1.30 (t, J = 7.09 Hz, 3H), 1.14 (d, J = 6.71 Hz, 3H), 0.91 (d, J = 6.86 Hz, 3H), 0.89 (d, J = 6.71 Hz, 3H). LCMS : m/z 284 [M+H]⁺ @ r.t. 7.89 min. HRMS (ESI) calcd for C₁₃H₂₂N₃O₂S [M +H]⁺ 284.1427 found 284.1430;

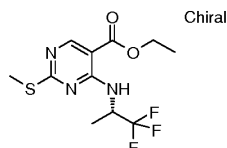
- 10 ethyl 4-[(2S)-3,3-dimethylbutan-2-yl]amino)-2-(methylsulfanyl)pyrimidine-5-carboxylate [(VI), R2 = (2S)-3-methylbutan-2-yl, R3 = H]



The title compound was obtained as a light yellow oil (56% yield);

- ¹H NMR (500MHz, DMSO-d₆) δ = 8.55 (s, 1H), 8.32 (d, J = 9.00 Hz, 1H), 4.23 - 4.34 (m, 2H), 4.19 (qd, J = 6.77, 9.13 Hz, 1H), 2.47 (s, 3H), 1.30 (t, J = 7.09 Hz, 3H), 1.11 (d, J = 6.86 Hz, 3H), 0.92 (s, 9H). LCMS : m/z 298 [M+H]⁺ @ r.t. 8.14 min. HRMS (ESI) calcd for C₁₄H₂₄N₃O₂S [M +H]⁺ 298.1584 found 298.1583.

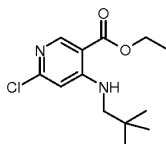
Ethyl 2-(methylsulfanyl)-4-[(2S)-1,1,1-trifluoropropan-2-yl]amino)pyrimidine-5-carboxylate [(VI), R2 = (2S)-3-methylbutan-2-yl, R3 = H]



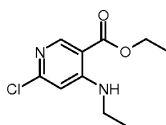
The title compound was obtained as a light yellow oil (56 % yield).

- 20 ¹H NMR (500MHz, DMSO-d₆) δ = 8.66 (s, 1H), 8.35 (d, J = 9.00 Hz, 1H), 5.17 - 5.36 (m, J = 7.27, 8.75 Hz, 1H), 4.31 (q, J = 7.02 Hz, 2H), 1.41 (d, J = 7.02 Hz, 3H), 1.31 (t, J = 7.09 Hz, 3H). LCMS : m/z 310 [M+H]⁺ @ r.t. 7.22 min. HRMS (ESI) calcd for C₁₁H₁₅F₃N₃O₂S [M +H]⁺ 310.0832 found 310.0832.

6-Chloro-4-(2,2-dimethyl-propylamino)-nicotinic acid ethyl ester [(VIa), R2 = 2,2-Dimethyl-propyl, X = CH]

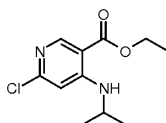


- 25 ¹H NMR (DMSO-d₆) δ = 8.53 (s, 1H), 8.25 (t, J = 5.6 Hz, 1H), 6.92 (s, 1H), 4.31 (q, J = 7.2 Hz, 2H), 3.09 (d, J = 5.6 Hz, 2H), 1.31 (t, J = 7.1 Hz, 3H), 0.95 (s, 9H). LCMS: m/z 271 [M+H]⁺ @ r.t. 7.55 min. HRMS (ESI) calcd for C₁₃H₂₀ClN₂O₂ [M +H]⁺ 271.1208 found 271.1208.

6-Chloro-4-ethylamino-nicotinic acid ethyl ester [(VIa), R2 = Ethyl, X = CH]

The title compound was obtained as a light yellow oil (80 % yield).

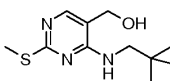
- 1H NMR (DMSO-d₆) δ 8.52 (s, 1H), 8.05 (t, J = 5.2 Hz, 1H), 6.80 (s, 1H), 4.29 (q, J = 7.2 Hz, 2H), 3.25 - 3.32 (m, 2H), 1.31 (t, J = 7.1 Hz, 3H), 1.17 (t, J = 7.2 Hz, 3H). LCMS: m/z 229 [M+H]⁺ @ r.t. 6.27 min.
 HRMS (ESI) calcd for C₁₀H₁₄ClN₂O₂ [M + H]⁺ 229.0739 found 229.0745.

6-Chloro-4-isopropylamino-nicotinic acid ethyl ester [(VIa), R2 = propan-2-yl, X = CH]

- 1H NMR (DMSO-d₆) δ = 8.53 (s, 1H), 7.98 (d, J = 7.9 Hz, 1H), 6.84 (s, 1H), 4.29 (q, J = 7.1 Hz, 2H), 3.80 - 3.93 (m, 1H), 1.31 (t, J = 7.1 Hz, 3H), 1.19 (d, J = 6.4 Hz, 6H). LCMS: m/z 243 [M+H]⁺ @ r.t. 6.72 min.
 HRMS (ESI) calcd for C₁₁H₁₆ClN₂O₂ [M + H]⁺ 243.0895 found 243.0901.

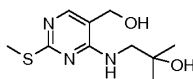
Preparation 2

- [4-(2,2-Dimethyl-propylamino)-2-methylsulfanyl-pyrimidin-5-yl]-methanol [(VII), R2 = 2,2-Dimethyl-propyl, R3 = H] Step 2b**



- LiAlH₄ (11.1 mL, 10.58 mmol, 4% in THF) is added to a solution of 4-(2,2-Dimethyl-propylamino)-2-methylsulfanyl-pyrimidine-5-carboxylic acid ethyl ester (1.5 g, 5.29 mmol) in THF (15 mL) at ~5 °C over 15 minutes. After stirring for 1 hour, ice water (0.40 mL) and 15% aqueous NaOH (0.40 mL) are added, followed by additional ice water (1.2 mL).
 After 30 minutes the quenched reaction mixture is filtered and the filter cake is washed with AcOEt. The combined organic washes are dried over Na₂SO₄ and filtered. The solvent was evaporated under vacuum to give the product (1.25g, 98% yield) which is used without further purification.
 1H NMR (500MHz, DMSO-d₆) δ = 7.80 (s, 1 H), 6.61 (t, J = 6.0 Hz, 1 H), 5.27 (t, J = 5.3 Hz, 1 H), 4.36 (d, J = 5.0 Hz, 2 H), 3.28 (d, J = 6.3 Hz, 2 H), 2.40 (s, 3 H), 0.89 (s, 9 H). LCMS : m/z 242 [M+H]⁺ @ r.t. 5.64 min. HRMS (ESI) calcd for C₁₁H₁₉N₃OS [M + H]⁺ 242.1322 found 242.1319.

The following compound is prepared essentially by the same method of preparation:

1-(5-Hydroxymethyl-2-methylsulfanyl-pyrimidin-4-ylamino)-2-methyl-propan-2-ol [(VII), R2 = methyl-propan-2-ol, R3 = H]

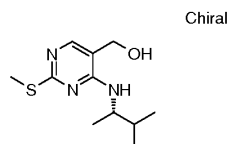
- The title compound was obtained as a white solid (77% yield);

¹H NMR (500MHz, DMSO-d₆) δ = 7.81 (s, 1 H), 6.61 (t, *J* = 5.7 Hz, 1 H), 5.27 (t, *J* = 5.2 Hz, 1 H), 4.66 (s, 1 H), 4.36 (d, *J* = 5.2 Hz, 2 H), 3.36 (d, *J* = 5.8 Hz, 2 H), 2.40 (s, 3 H), 1.11 (s, 6 H). LCMS : *m/z* 244 [M+H]⁺ @ r.t. 3.83 min.

HRMS (ESI) calcd for C₁₀H₁₇N₃O₂S [M +H]⁺ 244.1114 found 244.1111;

[4-[(2S)-3-methylbutan-2-yl]amino]-2-(methylsulfanyl)pyrimidin-5-yl]methanol [(VII), R2 = (2S)-3-

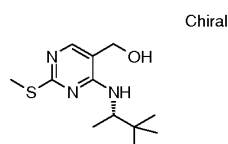
5 methylbutan-2-yl, R3 = H]



The title compound was obtained as a colourless oil (65 % yield);

¹H NMR (500MHz, DMSO-d₆) δ = 7.79 (s, 1H), 6.37 (d, *J* = 8.08 Hz, 1H), 5.21 (t, *J* = 5.49 Hz, 1H), 4.33 (d, *J* = 5.49 Hz, 2H), 4.00 - 4.11 (m, 1H), 2.40 (s, 3H), 1.82 (qd, *J* = 6.71, 13.27 Hz, 1H), 1.10 (d, *J* = 6.71 Hz, 3H), 0.88 (d, *J* = 6.71 Hz, 3H), 0.87 (d, *J* = 6.86 Hz, 3H). LCMS : *m/z* 242 [M+H]⁺ @ r.t. 5.63 min. HRMS (ESI) calcd for C₁₁H₂₀N₃OS [M +H]⁺ 242.1322 found 242.1320;

[4-[(2S)-3,3-dimethylbutan-2-yl]amino]-2-(methylsulfanyl)pyrimidin-5-yl]methanol [(VII), R2 = (2S)-3,3-
dimethylbutan-2-yl, R3 = H]

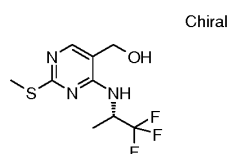


15 The title compound was obtained as a colourless oil (65 % yield);

¹H NMR (500MHz, DMSO-d₆) δ = 7.79 (s, 1H), 6.28 (d, *J* = 9.00 Hz, 1H), 5.35 (t, *J* = 5.26 Hz, 1H), 4.32 - 4.42 (m, 2H), 4.16 (qd, *J* = 6.84, 9.07 Hz, 1H), 2.40 (s, 3H), 1.08 (d, *J* = 6.71 Hz, 3H), 0.90 (s, 9H). LCMS : *m/z* 256 [M+H]⁺ @ r.t. 6.0 min. HRMS (ESI) calcd for C₁₂H₂₂N₃OS [M +H]⁺ 256.1478 found 256.1475;

[2-(methylsulfanyl)-4-[(2S)-1,1,1-trifluoropropan-2-yl]amino]pyrimidin-5-yl]methanol

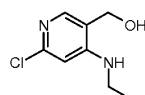
20 [(VII), R2 = (2S)-1,1,1-trifluoropropan-2-yl, R3 = H]



The title compound was obtained as a colourless oil (60 % yield).

LCMS : *m/z* 268 [M+H]⁺ @ r.t. 5.45 min.

(6-Chloro-4-ethylamino-pyridin-3-yl)-methanol [(VIIa), R2 = Ethyl, X = CH]

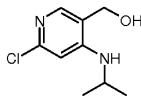


25

¹H NMR (DMSO-d₆) δ = 7.77 (s, 1H), 6.49 (s, 1H), 6.11 (t, *J* = 5.1 Hz, 1H), 5.18 (t, *J* = 5.4 Hz, 1H), 4.37 (d, *J* = 5.3 Hz, 2H), 3.17 (qd, *J* = 7.1, 5.7 Hz, 2H), 1.15 (t, *J* = 7.2 Hz, 3H). LCMS: *m/z* 187 [M+H]⁺ @ r.t. 4.06 min.

HRMS (ESI) calcd for C₈H₁₂N₂OCl [M +H]⁺ 187.0633 found 187.0638.

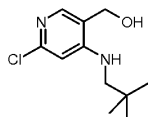
[6-Chloro-4-isopropylamino-pyridin-3-yl]-methanol [(VIIa), R2 = propan-2-yl, X = CH]



¹H NMR (DMSO-d₆) δ = 7.76 (s, 1H), 6.53 (s, 1H), 5.81 (d, *J* = 7.8 Hz, 1H), 5.24 (t, *J* = 5.4 Hz, 1H), 4.38 (d, *J* = 5.2 Hz, 2H), 3.65 - 3.77 (m, 1H), 1.16 (d, *J* = 6.4 Hz, 6H). LCMS: *m/z* 201 [M+H]⁺ @ r.t. 2.74 min.

- 5 HRMS (ESI) calcd for C₉H₁₄ClN₂O [M + H]⁺ 201.0789 found 201.0787.

[6-Chloro-4-(2,2-dimethyl-propylamino)-pyridin-3-yl]-methanol [(VIIa), R2 = 2,2-Dimethyl-propyl, X = CH]

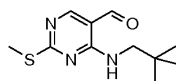


¹H NMR (DMSO-d₆) δ = 7.73 (s, 1H), 6.62 (s, 1H), 6.08 (t, *J* = 5.9 Hz, 1H), 5.40 (t, *J* = 5.3 Hz, 1H), 4.45 (d, *J* = 5.2 Hz, 2H), 2.98 (d, *J* = 5.9 Hz, 2H), 0.93 (s, 9H). LCMS: *m/z* 229 [M+H]⁺ @ r.t. 5.59 min.

- 10 HRMS (ESI) calcd for C₁₁H₁₈ClN₂O [M + H]⁺ 229.1102 found 229.1105.

Preparation 3

4-(2,2-Dimethyl-propylamino)-2-methylsulfanyl-pyrimidine-5-carbaldehyde [(VIII), R2 = 2,2-Dimethyl-propyl, R3 = H] Step 2c



- 15 [4-(2,2-Dimethyl-propylamino)-2-methylsulfanyl-pyrimidin-5-yl]-methanol (1.25 g, 5.17 mmol) was dissolved in DCM (30 mL) to which MnO₂ (3.15 g, 36.19 mmol) was added. The resulting suspension was stirred overnight. The solids were removed by filtration through a celite pad, which was washed with further DCM. The solvent was evaporated in vacuo to obtain the product (1.17 g, 95% yield).

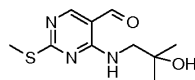
¹H NMR (500MHz, DMSO-d₆) δ = 9.77 (s, 1 H), 8.78 (t, *J* = 5.6 Hz, 1 H), 8.54 (s, 1 H), 3.40 (d, *J* = 6.3 Hz, 2 H), 2.50 (s, 3 H), 0.92 (s, 9 H). LCMS: *m/z* 240 [M+H]⁺ @ r.t. 6.74 min.

- 20

HRMS (ESI) calcd for C₁₁H₁₇N₃OS [M + H]⁺ 240.1165 found 240.1166.

According to the same method the following compound was prepared:

4-(2-Hydroxy-2-methyl-propylamino)-2-methylsulfanyl-pyrimidine-5-carbaldehyde [(VIII), R2 = 2-Hydroxy-2-methyl-propyl, R3 = H]



- 25

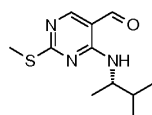
The title compound was obtained in quantitative yield;

¹H NMR (500MHz, DMSO-d₆) δ = 9.76 (s, 1 H), 8.84 (t, *J* = 5.3 Hz, 1 H), 8.54 (s, 1 H), 4.79 (s, 1 H), 3.47 (d, *J* = 5.6 Hz, 2 H), 1.13 (s, 6 H). LCMS: *m/z* 242 [M+H]⁺ @ r.t. 4.53 min.

HRMS (ESI) calcd for C₁₀H₁₅N₃O₂S [M + H]⁺ 242.0958 found 242.0957;

- 30 **4-([(2S)-3-methylbutan-2-yl]amino)-2-(methylsulfanyl)pyrimidine-5-carbaldehyde [(VIII), R2 = (2S)-3-methylbutan-2-yl, R3 = H]**

Chiral

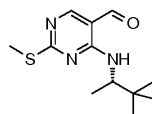


The title compound was obtained as a colourless oil (90 % yield);

- 1H NMR (500MHz ,DMSO-d₆) δ = 9.75 (s, 1H), 8.57 (d, *J* = 8.69 Hz, 1H), 8.54 (s, 1H), 4.15 - 4.26 (m, 1H), 2.50 (s, 3H), 1.79 - 1.93 (m, 1H), 1.15 (d, *J* = 6.71 Hz, 3H), 0.91 (d, *J* = 6.86 Hz, 3H), 0.89 (d, *J* = 6.86 Hz, 3H). LCMS : *m/z* 240 [M+H]⁺ @ r.t. 6.77 min. HRMS (ESI) calcd for C₁₁H₁₈N₃OS [M +H]⁺ 240.1165 found 240.1168;

4-{[(2S)-3,3-dimethylbutan-2-yl]amino}-2-(methylsulfanyl)pyrimidine-5-carbaldehyde [(VIII), R₂ = (2S)- 3,3-dimethylbutan-2-yl, R₃ = H]

Chiral

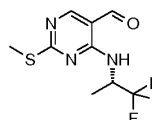


The title compound was obtained as a colourless oil (92 % yield);

- 1H NMR (500MHz ,DMSO-d₆) δ = 9.76 (s, 1H), 8.70 (d, *J* = 9.00 Hz, 1H), 8.54 (s, 1H), 4.21 (qd, *J* = 6.77, 9.28 Hz, 1H), 2.50 (s, 3H), 1.13 (d, *J* = 6.86 Hz, 3H), 0.92 (s, 9H). LCMS : *m/z* 254 [M+H]⁺ @ r.t. 7.07 min. HRMS (ESI) calcd for C₁₂H₂₀N₃OS [M +H]⁺ 254.1322 found 254.1324;

2-(methylsulfanyl)-4-{[(2S)-1,1,1-trifluoropropan-2-yl]amino}pyrimidine-5-carbaldehyde [(VIII), R₂ = (2S)- 1,1,1-trifluoropropan-2-yl, R₃ = H]

Chiral

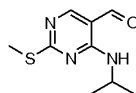


15

The title compound was obtained as a colourless oil (90 % yield).

1H NMR (500MHz ,DMSO-d₆) δ = 9.82 (s, 1H), 8.69 (s, 1H), 8.66 (d, *J* = 9.15 Hz, 1H), 5.19 - 5.39 (m, 1H), 2.53 (s, 3H), 1.43 (d, *J* = 7.02 Hz, 3H). LCMS : *m/z* 266 [M+H]⁺ @ r.t. 6.13 min. HRMS (ESI) calcd for C₉H₁₁F₃N₃OS [M +H]⁺ 266.0570 found 266.0572.

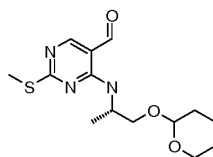
- 2-(methylsulfanyl)-4-(propan-2-ylamino)pyrimidine-5-carbaldehyde [(VIII), R₂ = propan-2-yl, R₃ = H]**



The title compound was obtained as a colourless oil (92 % yield).

- 1H NMR (500MHz ,DMSO-d₆) δ = 9.74 (s, 1H), 8.53 (s, 1H), 8.45 (d, *J* = 7.32 Hz, 1H), 4.28 - 4.44 (m, 1H), 2.50 (s, 3H), 1.24 (d, *J* = 6.56 Hz, 6H). LCMS : *m/z* 212 [M+H]⁺ @ r.t. 5.9 min. HRMS (ESI) calcd for C₉H₁₄N₃OS [M +H]⁺ 212.0852 found 212.0856.

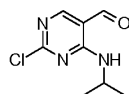
2-(methylsulfanyl)-4-{[(2S)-1-(tetrahydro-2H-pyran-2-yloxy)propan-2-yl]amino}pyrimidine-5-carbaldehyde [(VIII), R₂ = (2S)-1-(tetrahydro-2H-pyran-2-yloxy), R₃ = H]



The title compound was obtained as a colourless oil (89 % yield).

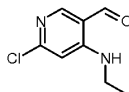
¹H NMR (500MHz, DMSO-d₆) δ = 9.75 (s, 1H), 8.53 (s, 1H), (d, J = 7.78 Hz, 1H), 8.55 (s, 1H), 4.65 (dd, J = 2.9, 4.27 Hz, 1H), 4.45 - 4.56 (m, 1H), 2.50 (s, 3H), 3.69 - 3.77 (m, 2H), 3.39 - 3.50 (m, 2H), 2.49 (s, 3H), 1.40 - 1.73 (m, 6H), 1.25 (d, J = 6.56 Hz, 6H). LCMS : m/z 312 [M+H]⁺ @ r.t. 10.47 min. HRMS (ESI) calcd for C₁₄H₂₂N₃O₃S [M +H]⁺ 312.1377 found 312.1375.

2-chloro-4-(propan-2-ylamino)pyrimidine-5-carbaldehyde [(VIIIa), R2 = propan-2-yl, R3 = H]



LCMS : m/z 200 [M+H]⁺ @ r.t. 4.87 min.

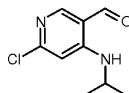
10 **6-Chloro-4-ethylamino-pyridine-3-carbaldehyde [(VIIIa), R2 = propan-2-yl, X = CH]**



¹H NMR (DMSO-d₆) δ = 9.86 (d, J = 0.6 Hz, 1H), 8.56 (t, J = 4.7 Hz, 1H), 8.44 (s, 1H), 6.85 (s, 1H), 3.34 (s, 2H), 1.17 (t, J = 7.2 Hz, 3H). LCMS: m/z 185 [M+H]⁺ @ r.t. 4.89 min.

HRMS (ESI) calcd for C₈H₁₀ClN₂O [M +H]⁺ 185.0476 found 185.0481.

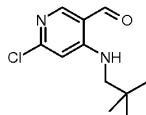
15 **6-Chloro-4-isopropylamino-pyridine-3-carbaldehyde [(VIIIa), R2 = propan-2-yl, X = CH]**



¹H NMR (DMSO-d₆) δ = 9.85 (d, J = 0.5 Hz, 1H), 8.40 - 8.49 (m, 2H), 6.90 (s, 1H), 3.90 (dt, J = 7.9, 6.5 Hz, 1H), 1.20 (d, J = 6.4 Hz, 6H). LCMS: m/z 199 [M+H]⁺ @ r.t. 7.84 min. HRMS (ESI) calcd for C₉H₁₂ClN₂O [M +H]⁺ 199.0633 found 199.0632.

20

6-Chloro-4-(2,2-dimethyl-propylamino)-pyridine-3-carbaldehyde [(VIIIa), R2 = 2,2-Dimethyl-propyl, X = CH]

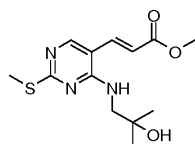


¹H NMR (DMSO-d₆) δ = 9.88 (s, 1H), 8.76 (t, J = 5.6 Hz, 1H), 8.45 (s, 1H), 7.00 (s, 1H), 3.14 (d, J = 6.1 Hz, 2H), 0.94 (s, 9H). LCMS: m/z 279 [M+H]⁺ @ r.t. 6.46 min. HRMS (ESI) calcd for C₁₁H₁₆ClN₂O [M +H]⁺ 227.0946 found 227.0949.

25

Preparation 4

(E)-3-[4-(2-Hydroxy-2-methyl-propylamino)-2-methylsulfanyl-pyrimidin-5-yl]-acrylic acid methyl ester [(X), R2 = 2-Hydroxy-2-methyl-propyl, R3 = R4 = R5= H] step 2d



4-(2-Hydroxy-2-methyl-propylamino)-2-methylsulfanyl-pyrimidine-5-carbaldehyde (500.0 mg, 2.07 mmol) was dissolved in THF (7 mL) to which methyl (triphenylphosphoranylidene)acetate (831.3 mg, 2.49 mmol) was added. The resulting suspension was stirred at reflux for 1 hour. The reaction mixture was allowed to cool to room temperature, then was diluted with AcOEt, and washed with water followed by brine. The organic phases were separated and dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude material was purified through silica gel column chromatography (50 to 70% AcOEt/hexane) to give the title product (498.7 mg, 81% yield).

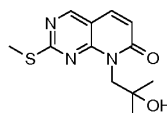
¹H NMR (500MHz, DMSO-d₆) δ = 8.37 (s, 1 H), 7.79 (d, *J* = 16.0 Hz, 1 H), 7.49 - 7.45 (m, 1 H), 6.52 (d, *J* = 15.7 Hz, 1 H), 4.62 (s, 1 H), 3.72 (s, 3 H), 3.44 (d, *J* = 6.1 Hz, 2 H), 2.44 (s, 3 H), 1.13 - 1.01 (m, 6 H).

LCMS : *m/z* 298 [M+H]⁺ @ r.t. 5.06 min.

HRMS (ESI) calcd for C₁₃H₁₉N₃O₃S [M +H]⁺ 298.1220 found 298.1217.

Preparation 5

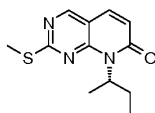
8-(2-Hydroxy-2-methyl-propyl)-2-methylsulfanyl-8H-pyrido[2,3-d]pyrimidin-7-one [(XI), R₂ = 2-Hydroxy-2-methyl-propyl, R₃ = R₄ = R₅ = H] Step 2e



(E)-3-[4-(2-Hydroxy-2-methyl-propylamino)-2-methylsulfanyl-pyrimidin-5-yl]-acrylic acid methyl ester (495.0 mg, 1.66 mmol) was dissolved in DIPEA (7.0 mL) to which DBU (0.25 mL, 1.66 mmol) was added and stirred at reflux overnight. The reaction mixture was allowed to cool to room temperature, then was diluted with DCM, and washed with water followed by saturated NH₄Cl. The organic phases were separated and dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude material was purified through silica gel column chromatography (1 to 10% MeOH/DCM) to give the title product (350.7 mg, 79% yield).

¹H NMR (500MHz, DMSO-d₆) δ = 8.88 (s, 1 H), 7.94 (d, *J* = 9.5 Hz, 1 H), 6.65 (d, *J* = 9.5 Hz, 1 H), 4.53 (s, 1 H), 4.44 (s, 2 H), 2.60 (s, 3 H), 1.10 (s, 6 H). LCMS : *m/z* 266 [M+H]⁺ @ r.t. 4.50 min. HRMS (ESI) calcd for C₁₂H₁₅N₃O₂S [M +H]⁺ 266.0958 found 266.0965;

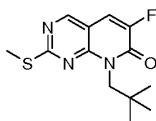
8-[(2S)-butan-2-yl]-2-(methylsulfanyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(XI), R₂ = (2S)-butan-2-yl, R₃ = R₄ = R₅ = H]



¹H NMR (500MHz, DMSO-d₆) δ = 8.86 (s, 1H), 7.90 (d, *J* = 9.46 Hz, 1H), 6.59 (br. s., 1H), 5.39 (br. s., 1H), 2.59 (s, 3H), 2.23 (br. s., 1H), 1.90 (br. s., 1H), 1.52 (br. s., 3H), 0.73 (t, *J* = 7.47 Hz, 3H).

Preparation 6

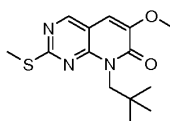
8-(2,2-Dimethyl-propyl)-6-fluoro-2-methylsulfanyl-8H-pyrido[2,3-d]pyrimidin-7-one [(XI), R2 = 2,2-Dimethyl-propyl, R3 = R4 = H, R5= F] step 3a



- 5 Lithium hydroxide monohydrate (26.1 mg, 0.62 mmol) was added to a solution of ethyl (diethoxyphosphoryl)(fluoro)acetate (0.10 mL, 0.50 mmol) and 4-(2,2-Dimethyl-propylamino)-2-methylsulfanyl-pyrimidine-5-carbaldehyde (100.0 mg, 0.41 mmol) in THF (5.0 mL). The solution was stirred overnight at room temperature, in this condition there is a spontaneous cyclization of the acrylic ester intermediate to the title compound.
- 10 The reaction mixture was diluted with DCM, and washed with water followed by brine. The organic phases were separated and dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude material was purified through silica gel column chromatography (10 to 30% AcOEt\hexane) to give the product (50.2 mg, 43% yield). ¹H NMR (500MHz, DMSO-d₆) δ = 8.88 (s, 1 H), 7.92 (d, J = 9.0 Hz, 1 H), 4.33 (br. s., 2 H), 2.61 (s, 3 H), 0.93 (s, 9 H). LCMS : m/z 282 [M+H]⁺ @ r.t. 6.59 min. HRMS (ESI) calcd for C₁₃H₁₆FN₃OS [M +H]⁺ 282.1071 found 282.1069.

15 Preparation 7

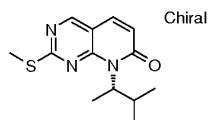
8-(2,2-Dimethyl-propyl)-6-methoxy-2-methylsulfanyl-8H-pyrido[2,3-d]pyrimidin-7-one [(XI), R2 = 2,2-Dimethyl-propyl, R3 = R4 = H, R5= OMe] step 3a



- 4-(2,2-Dimethyl-propylamino)-2-methylsulfanyl-pyrimidine-5-carbaldehyde (120.0 g, 0.50 mmol) and ethyl methoxyacetate (0.062 mL, 0.62 mmol) were stirred in toluene (4.0 mL) at 0°C under nitrogen. Potassium t-butoxide (61.4 mg, 0.55 mmol) was added gradually. The mixture was stirred to room temperature, and then to 65°C for 48 hours. The reaction mixture was concentrated in vacuo and triturated with AcOEt to remove the remaining starting aldehyde. The remaining solid was further purified through silica gel column chromatography (30 to 90% AcOEt\hexane) to give the title product (38.8 mg, 24% yield).
- 20 ¹H NMR (500MHz, DMSO-d₆) δ = 8.80 (s, 1 H), 7.27 (s, 1 H), 4.33 (br. s., 2 H), 3.84 (s, 3 H), 2.58 (s, 3 H), 0.90 (s, 9 H). LCMS : m/z 294 [M+H]⁺ @ r.t. 6.24 min. HRMS (ESI) calcd for C₁₄H₁₉N₃O₂S [M +H]⁺ 294.1271 found 294.1273.

Preparation 8

8-[(2S)-3-methylbutan-2-yl]-2-(methylsulfanyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(XI), R2 = (2S)-3-methylbutan-2-yl, R3 = R4 = R5= H] step 3a



- 30 LiHMDS (4 mL of 1 M in THF solution, 4 mmol) was added to THF (15 mL) at -78°C and treated with EtOAc (0.5 mL, 4.64 mmol). The solution was stirred at -78°C for 10 min, then solid 4-[(2S)-3-methylbutan-2-yl]amino)-2-

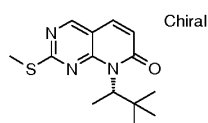
(methylsulfanyl)pyrimidine-5-carbaldehyde (280mg, 1.16 mmol) was added in one portion and the solution was stirred at -78°C for 10 min then removed from the cooling bath warmed to RT for 3 h. The reaction was cooled in an ice bath and quenched with saturated solution of NH₄Cl and extracted with EtOAc (2 x 1mL), dried over Na₂SO₄, filtered and concentrated. Purification with chromatographic column eluent Hex/EtOAc 8:2 to give an off-white solid

5 of the title compound (250 mg, 80% yield).

¹H NMR (500MHz, DMSO-d₆) δ = 8.87 (s, 1H), 7.91 (d, *J* = 9.30 Hz, 1H), 6.45 - 6.72 (m, 1H), 4.86 - 5.45 (m, 1H), 2.58 (s, 3H), 1.37 - 1.65 (m, 3H), 1.03 (br. s., 3H), 0.59 (d, *J* = 13.42 Hz, 3H). LCMS : *m/z* 264 [M+H]⁺ @ r.t. 6.26 min. HRMS (ESI) calcd for C₁₃H₁₈N₃OS [M +H]⁺ 264.1165 found 264.1174

According to the same method the following compounds were prepared:

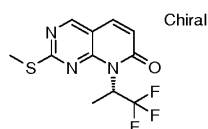
10 **8-[(2S)-3,3-dimethylbutan-2-yl]-2-(methylsulfanyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(XI), R2 = (2S)- 3,3-dimethylbutan -2-yl, R3 = R4 = R5= H]**



LCMS : *m/z* 278 [M+H]⁺ @ r.t. 7.02 min;

2-(methylsulfanyl)-8-[(2S)-1,1,1-trifluoropropan-2-yl]pyrido[2,3-d]pyrimidin-7(8H)-one [(XI), R2 = (2S)- 1,1,1-trifluoropropan-2-yl, R3 = R4 = R5= H]

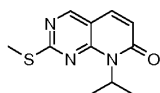
15



¹H NMR (500MHz, DMSO-d₆) δ = 8.95 (s, 1H), 8.92 (s, 1H), 8.00 (d, *J* = 9.46 Hz, 1H), 7.98 (d, *J* = 9.61 Hz, 1H), 6.73 (d, *J* = 9.46 Hz, 1H), 6.61 (d, *J* = 9.46 Hz, 1H), 6.32 - 6.46 (m, 1H), 6.05 - 6.19 (m, 1H), 2.59 (s, 3H), 2.58 (s, 3H), 1.88 (d, *J* = 7.32 Hz, 3H), 1.75 (d, *J* = 7.02 Hz, 3H). LCMS : *m/z* 290 [M+H]⁺ @ r.t. 5.91 min. HRMS (ESI) calcd for C₁₁H₁₁F₃N₃OS [M +H]⁺ 290.0570 found 290.0569.

20

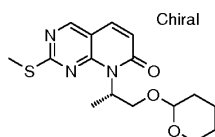
2-(methylsulfanyl)-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one [(XI), R2 = propan-2-yl, R3 = R4 = R5= H]



¹H NMR (500MHz, DMSO-d₆) δ = 8.86 (s, 1H), 7.88 (d, *J* = 9.46 Hz, 1H), 6.57 (d, *J* = 9.46 Hz, 1H), 5.68 (br. s., 1H), 2.60 (s, 3H), 1.54 (d, *J* = 7.02 Hz, 6H). LCMS : *m/z* 236 [M+H]⁺ @ r.t. 9.10 min. HRMS (ESI) calcd for C₁₁H₁₄N₃OS [M +H]⁺ 236.0852 found 236.0861.

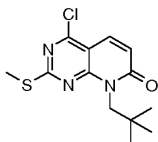
25

2-(methylsulfanyl)-8-[(2S)-1-(tetrahydro-2H-pyran-2-yloxy)propan-2-yl]pyrido[2,3-d]pyrimidin-7(8H)-one [(XI), R2 = (2S)-1-(tetrahydro-2H-pyran-2-yloxy)propan-2-yl, R3 = R4 = R5= H]



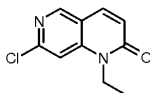
¹H NMR (500MHz, DMSO-d₆) δ = 8.87 (s, 1H), 7.90 (d, *J* = 9.46 Hz, 1H), 6.59 (br. s., 1H), 5.40 - 6.04 (m, 1H), 4.60 (s, 1H), 4.00 (m, 2H), 3.73 (m, 2H), 3.41 (br. s, 2H), 2.59 (s, 3H), 1.07 - 1.73 (m, 9H). LCMS : m/z 336 [M+H]⁺ @ r.t. 9.82 min. HRMS (ESI) calcd for C₁₆H₂₂N₃O₃S [M +H]⁺ 336.1377 found 336.1372.

- 5 **4-chloro-8-(2,2-dimethylpropyl)-2-(methylsulfanyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(XI), R₂ = 2,2-dimethylpropyl, R₃ = Cl, R₄ = R₅ = H]**



¹H NMR (500MHz, DMSO-d₆) δ = 7.99 (d, *J* = 9.76 Hz, 1H), 6.72 (d, *J* = 9.76 Hz, 1H), 4.30 (br. s., 2H), 2.62 (s, 3H), 0.91 (s, 9H). LCMS : m/z 298 [M+H]⁺ @ r.t. 7.13 min. HRMS (ESI) calcd for C₁₃H₁₇ClN₃OS [M +H]⁺ 298.0776 found 298.0783.

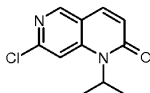
- 10 **7-Chloro-1-ethyl-1H-[1,6]naphthyridin-2-one [(II), G = Cl, X = CH, R₂ = Ethyl, R₃ = R₄ = R₅ = H]**



¹H NMR (DMSO-d₆) δ = 8.74 (s, 1H), 8.02 (d, *J* = 9.6 Hz, 1H), 7.69 (s, 1H), 6.71 (d, *J* = 9.6 Hz, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 1.17 (t, *J* = 7.2 Hz, 3H). LCMS: m/z 209 [M+H]⁺ @ r.t. 4.28 min.
HRMS (ESI) calcd for C₁₀H₁₀ClN₂O [M +H]⁺ 209.0476 found 209.0485.

15

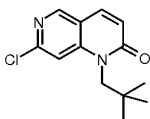
- 7-Chloro-1-isopropyl-1H-[1,6]naphthyridin-2-one [(II), G = Cl, X = CH, R₂ = propan-2-yl, R₃ = R₄ = R₅ = H]**



¹H NMR (DMSO-d₆) δ = 8.71 (s, 1H), 7.96 (d, *J* = 9.5 Hz, 1H), 7.79 (br. s., 1H), 6.63 (d, *J* = 9.5 Hz, 1H), 5.14 (br. s., 1H), 1.50 (d, *J* = 6.9 Hz, 6H). LCMS: m/z 223 [M+H]⁺ @ r.t. 7.11 min.

- 20 HRMS (ESI) calcd for C₁₁H₁₂ClN₂O [M +H]⁺ 223.0633 found 223.0633.

- 7-Chloro-1-(2,2-dimethyl-propyl)-1H-[1,6]naphthyridin-2-one [(II), G = Cl, X = CH, R₂ = Ethyl, R₃ = R₄ = R₅ = H]**



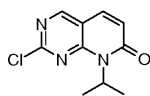
¹H NMR (DMSO-d₆) δ = 8.71 (s, 1H), 8.01 (d, *J* = 9.5 Hz, 1H), 7.84 (s, 1H), 6.72 (d, *J* = 9.5 Hz, 1H), 4.18 (br. s., 2H), 0.91 (s, 9H). LCMS: m/z 251 [M+H]⁺ @ r.t. 5.79 min.

- 25 HRMS (ESI) calcd for C₁₃H₁₆ClN₂O [M +H]⁺ 251.0946 found 251.0949.

Preparation 9

2-chloro-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one [(XI), R₂ = (2S)-3-methylbutan-2-yl, R₃ = R₄ = R₅ = H]

Step 4g



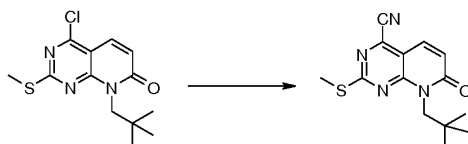
LiHMDS (8 mL of 1 M in THF solution, 18 mmol) was added to THF (20 mL) at -78°C and treated with EtOAc (1.6 mL, 18.1 mmol). The solution was stirred at -78°C for 10 min, then a THF solution (10 mL) of 2-chloro-4-(propan-2-ylamino)pyrimidine-5-carbaldehyde (0.9 g, 4.5 mmol) was added dropwise and the solution was stirred at -78°C for 10 min then removed from the cooling bath and warmed to RT for 3 h. The reaction was cooled in an ice bath and quenched with saturated solution of NH₄Cl and extracted with EtOAc (2 x 1 mL), dried over Na₂SO₄, filtered and concentrated. Purification with chromatographic column eluent Hex/EtOAc 8:2 to give a off-white solid of the title compound (100 mg, 10% yield).

LCMS : m/z 224 [M+H]⁺ @ r.t. 4.26 min.

10

Preparation 10

2-(methylsulfanyl)-7-oxo-8-(2,2 dimethylpropyl)-7,8-dihydropyrido[2,3-d]pyrimidine-4-carbonitrile [(XI), R₂ = 2,2-dimethylpropyl, R₃ = CN, R₄ = R₅ = H] conv. A

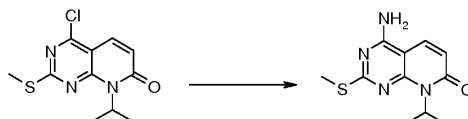


4-Chloro-8-(2,2-dimethyl-propyl)-2-methylsulfanyl-8H-pyrido[2,3-d]pyrimidin-7-one (60 mg, 0.2mmol) was dissolved in DMSO (4.5 mL) to which triethylamine (300 µL) and NaCN (18 mg, 0.2 mmol) was added and stirred for 1 hour at 50°C. Water was then added 10 mL and extracted with AcOEt two times. The organic phases were washed with brine, and then dried over Na₂SO₄. The salts were filtered, and the solvent was evaporated in vacuo. The crude product was purified on SiO₂ chromatographic column eluent Exane/AcOEt 8/2 to give the product (12 mg, 20 % yield).

¹H NMR (500MHz, DMSO-d₆) δ = 7.94 (d, J = 9.61 Hz, 1H), 6.83 (d, J = 9.61 Hz, 1H), 4.28 (br. s., 2H), 2.63 (s, 3H), 0.91 (s, 3H). LCMS : m/z 289 [M+H]⁺ @ r.t. 7.09 min. HRMS (ESI) calcd for C₁₄H₁₇N₄OS [M +H]⁺ 289.1118 found 289.1122.

Preparation 11

4-amino-2-(methylsulfanyl)-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one [(XI), R₂ = propan-2-yl, R₃ = NH₂, R₄ = R₅ = H] conv. B



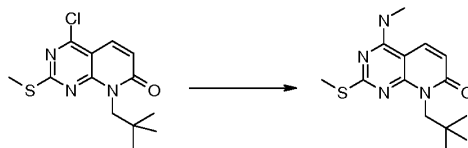
4-Chloro-8-isopropyl-2-methylsulfanyl-8H-pyrido[2,3-d]pyrimidin-7-one (50 mg, 0.15 mmol) in NH₄OH 30% was heated to 60°C for 3 hours. The product precipitate and was filtered off in quantitative yield. No further purification was made.

LCMS : m/z 251 [M+H]⁺ @ r.t. 9.33 min. HRMS (ESI) calcd for C₁₁H₁₅N₄OS [M +H]⁺ 251.0961 found 251.0961.

30

Preparation 12

4-(methylamino)-2-(methylsulfanyl)-8-(2,2-dimethylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(XI), R2 = 2,2-dimethylpropyl, R3 = N(H)Me, R4 = R5= H] conv. C

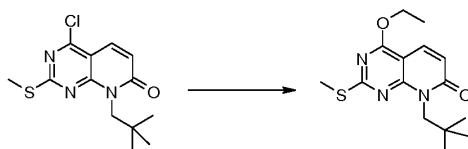


4-Chloro-8-(2,2-dimethyl-propyl)-2-methylsulfanyl-8H-pyrido[2,3-d]pyrimidin-7-one (40 mg, 0.13mmol) was dissolved in THF (4 mL) to which methylamine 1.0 M in EtOH (100 μ L) was added and stirred for 12 hour at room temperature. Water was then added 10 mL and extracted with AcOEt two times. The organic phases were washed with brine, and then dried over Na_2SO_4 . The salts were filtered, and the solvent was evaporated in vacuo. The crude product was purified on SiO_2 chromatographic column DCM/MeOH 98/2 to give the product (33mg, 85 % yield).

^1H NMR (500MHz, DMSO-d_6) δ = 8.11 (q, J = 4.02 Hz, 1H), 8.01 (d, J = 9.61 Hz, 1H), 6.39 (d, J = 9.61 Hz, 1H), 4.27 (br. s., 2H), 2.93 (d, J = 4.42 Hz, 3H), 2.52 (s, 3H), 0.89 (s, 9H). LCMS : m/z 293 $[\text{M}+\text{H}]^+$ @ r.t. 6.63 min. HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{21}\text{N}_4\text{OS}$ $[\text{M}+\text{H}]^+$ 293.1431 found 293.1436.

Preparation 13

4-ethoxy-2-(methylsulfanyl)-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one [(XI), R2 = 2,2-dimethylpropyl, R3 = OEt, R4 = R5= H] conv. D

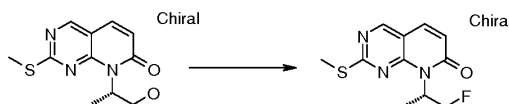


4-Chloro-8-(2,2-dimethyl-propyl)-2-methylsulfanyl-8H-pyrido[2,3-d]pyrimidin-7-one (50 mg, 0.17 mmol) was dissolved in EtOH (4 mL) in the presence of K_2CO_3 (46 mg, 0.34 mmol) was added and stirred for 12 hour at room temperature. Water was then added 10 mL and extracted with AcOEt two times. The organic phases were washed with brine, and then dried over Na_2SO_4 . The salts were filtered, and the solvent was evaporated in vacuo. The crude product was purified on SiO_2 chromatographic column DCM/MeOH 98/2 to give the product (40mg, 76 % yield).

^1H NMR (500MHz, DMSO-d_6) δ = 7.86 (d, J = 9.61 Hz, 1H), 6.51 (d, J = 9.61 Hz, 1H), 4.50 (q, J = 7.07 Hz, 2H), 4.29 (br. s., 2H), 2.59 (s, 3H), 1.38 (t, J = 7.09 Hz, 3H), 0.90 (s, 9H). LCMS : m/z 308 $[\text{M}+\text{H}]^+$ @ r.t. 7.09 min. HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{22}\text{N}_3\text{O}_2\text{S}$ $[\text{M}+\text{H}]^+$ 308.1427 found 308.1428.

Preparation 14

8-[(2S)-1-fluoropropan-2-yl]-2-(methylsulfanyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(XI), R2 = (2S)-1-fluoropropan-2-yl, R3 = R4 = R5= H] conv. F



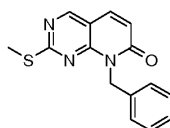
To a solution of 8-[(2S)-1-hydroxypropan-2-yl]-2-(methylsulfanyl)pyrido[2,3-d]pyrimidin-7(8H)-one (100 mg, 0.40 mmol) in MeCN (1.5 mL) were added triethylamine (509 μ L, 3.66 mmol) and perfluoro-1-butanefluoride

(214.4 μ L, 1.194 mmol) followed by $\text{NEt}_3(\text{HF})_3$ (198 μ L, 1.213 mmol) and the resulting mixture was stirred at room temperature for 12 hours. The reaction mixture was diluted with water (6 mL) and extracted with DCM (3 x 6 mL). Combined organics fractions were washed with brine (6 mL), dried over Na_2SO_4 , filtered and concentrated to dryness to give the crude product. Flash column chromatography (diethyl ether) gave 86.7 mg (86%) of the desired product.

^1H NMR (500MHz, $\text{DMSO}-d_6$) δ = 8.90 (s, 1H), 7.94 (d, J = 9.46 Hz, 1H), 6.61 (d, J = 9.46 Hz, 1H), 5.85 (br. s., 1H), 5.11 (td, J = 8.00, 48.00 Hz, 1H), 4.84 (ddd, J = 5.60, 8.70, 46.20 Hz, 1H), 2.59 (s, 3H), 1.49 (d, J = 6.86 Hz, 3H). LCMS : m/z 254 $[\text{M}+\text{H}]^+$ @ r.t. 8.06 min. HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{17}\text{FN}_3\text{OS}$ $[\text{M} + \text{H}]^+$ 254.0758 found 254.0762.

Preparation 15

10 8-benzyl-2-(methylsulfanyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(XI), R2 = benzyl, R3 = R4 = R5= H] step 3a'



A mixture of 2-(methylsulfanyl)pyrido[2,3-d]pyrimidin-7(8H)-one (100 mg, 0.52 mmol), cesium carbonate (337 mg, 1.04 mmol), and benzyl bromide (133 mg, 0.78 mmol) in anhydrous DMF (2 mL) was purged with nitrogen and heated in a sealed tube at 90 $^{\circ}\text{C}$ for 1h. The reaction mixture was allowed to cool to room temperature and diluted with water. The product precipitated, filtered and washed with water. To afford 8-benzyl-2-(methylsulfanyl)pyrido[2,3-d]pyrimidin-7(8H)-one as a yellow solid (117 mg, 80% yield).

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ = 8.91 (s, 1H), 8.00 (d, J = 9.46 Hz, 1H), 7.17 - 7.35 (m, 5H), 6.71 (d, J = 9.46 Hz, 1H), 5.50 (s, 2H), 2.50 (s, 3H). LCMS : m/z 284 $[\text{M}+\text{H}]^+$ r.t. 5.92 min. HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{14}\text{N}_3\text{OS}$ $[\text{M} + \text{H}]^+$ 284.0852 found 284.0865.

20 According to the same method, but employing the appropriate alkylating reagent, the following compounds were prepared:

8-ethyl-2-(methylsulfanyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(XI), R2 = ethyl, R3 = R4 = R5= H]:

The title compound was obtained as a yellow oil (65% yield).

25 ^1H NMR (401 MHz, $\text{DMSO}-d_6$) δ 8.88 (s, 1H), 7.93 (d, J = 9.40 Hz, 1H), 6.62 (d, J = 9.52 Hz, 1H), 4.32 (q, J = 7.04 Hz, 2H), 2.60 (s, 3H), 1.22 (t, J = 7.02 Hz, 3H). LCMS : m/z 222 $[\text{M}+\text{H}]^+$ r.t. 4.95 min. HRMS (ESI) calcd for $\text{C}_{10}\text{H}_{12}\text{N}_3\text{OS}$ $[\text{M} + \text{H}]^+$ 222.0696 found 222.07;

2-(methylsulfanyl)-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one [(XI), R2 = iso-propyl, R3 = R4 = R5= H]:

The title compound was obtained as a light yellow foam (70% yield).

30 ^1H NMR (401 MHz, $\text{DMSO}-d_6$) δ 8.85 (s, 1H), 7.87 (d, J = 9.52 Hz, 1H), 6.57 (d, J = 9.40 Hz, 1H), 5.69 (td, J = 6.93, 13.73 Hz, 1H), 2.60 (s, 3H), 1.54 (d, J = 6.96 Hz, 6H). LCMS : m/z 236 $[\text{M}+\text{H}]^+$ r.t. 5.53 min. HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{14}\text{N}_3\text{OS}$ $[\text{M} + \text{H}]^+$ 236.0852 found 236.0861.

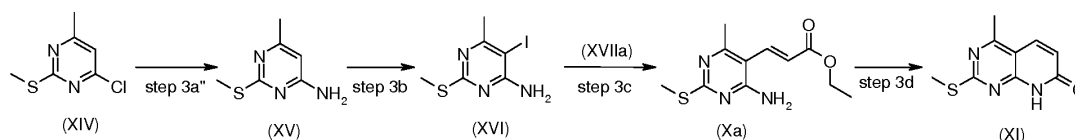
8-(4-bromo-2-fluorobenzyl)-2-(methylsulfanyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(XI), R2 = 4-bromo-2-fluorobenzyl, R3 = R4 = R5= H]:

The title compound was obtained as a off-white foam (75% yield).

¹H NMR (500 MHz, DMSO-d₆) δ = 8.93 (s, 1H), 8.02 (d, *J* = 9.46 Hz, 1H), 7.57 (dd, *J* = 1.83, 9.91 Hz, 1H), 7.29 (dd, *J* = 1.68, 8.39 Hz, 1H), 6.96 (t, *J* = 8.24 Hz, 1H), 6.71 (d, *J* = 9.61 Hz, 1H), 5.48 (s, 2H), 2.44 (s, 3H). LCMS : *m/z* 379 [M+H]⁺ r.t. 6.71 min. HRMS (ESI) calcd for C₁₅H₁₂BrFN₃OS [M + H]⁺ 379.9863 found 379.9872.

5

Preparation 16

4-methyl-2-(methylsulfanyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(XI), R₂ = H, R₃ = Me, R₄ = R₅ = H]

- 10 **Step 3a'':** To a mixture of 4-chloro-6-methyl-2-(methylthio)pyrimidine (1 g, 5.7 mmol) in 5 mL of acetonitrile was added 2 mL of a solution of ammonium hydroxide 28% in water. The reaction was heated to 120°C for 72 h. After completion, the mixture was cooled down to r.t. and diluted with water and a precipitate was observed. The solid was filtered and dried under vacuum to afford 6-methyl-2-(methylsulfanyl)pyrimidin-4-amine (0.76 g, 86% yield).
¹H NMR (401 MHz, DMSO-d₆) δ = 6.75 (br. s., 2H), 5.96 (d, *J* = 0.46 Hz, 1H), 2.36 - 2.38 (m, 3H), 2.13 (s, 3H)

- 15 **Step 3b:** To the solution of 6-methyl-2-(methylsulfanyl)pyrimidin-4-amine (1.1 g, 7.06 mmol) in 7 mL of methanol was added iodine monochloride (1.5 g, 9.24 mmol) in small portions at 0°C. Then the reaction mixture was stirred overnight. After evaporation of solvent, the residue was triturated with acetone, and the product 5-iodo-6-methyl-2-(methylsulfanyl)pyrimidin-4-amine was collected by filtration (1.32 g 66% yield).
LCMS : *m/z* 282 [M+H]⁺ r.t. 5.65 min.

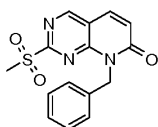
- 20 **Step 3c:** To the solution of 5-iodo-6-methyl-2-(methylsulfanyl)pyrimidin-4-amine (1.49g, 4.9 mmol), in DMA (10mL) were added ethylacrylate (1.06 mL, 9.8 mmol), Pd(OAc)₂ (0.22 g, 0.98 mmol), (+) BINAP (0.61 g, 0.98 mmol), and TEA (2 mL, 14.7 mmol). Then the reaction mixture was heated to 100°C and reacted overnight. After evaporation of solvent, the residue was diluted with water and the aqueous layer was extracted with ethyl acetate. The solvent was evaporated in vacuo, yielding the desired intermediate ethyl (2E)-3-[4-amino-6-methyl-2-(methylsulfanyl)pyrimidin-5-yl]prop-2-enoate (0.5 g, 21% yield).
LCMS : *m/z* 254 [M+H]⁺ r.t. 6.53 min.

- 25 **Step 3d:** To a solution of ethyl (2E)-3-[4-amino-6-methyl-2-(methylsulfanyl)pyrimidin-5-yl]prop-2-enoate (0.5 g, 1.9 mmol), in DIPEA (2 mL), was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1 mL) at reflux for 15 h. After evaporation of volatiles, the residue was triturated with acetone to afford the desired product 4-methyl-2-(methylsulfanyl)pyrido[2,3-d]pyrimidin-7(8H)-one (0.14 g 35% yield).
30 ¹H NMR (401 MHz, DMSO-d₆) δ = 12.30 (br. s., 1H), 8.05 (d, *J* = 9.76 Hz, 1H), 6.47 (d, *J* = 9.76 Hz, 1H), 2.61 (s, 3H), 2.54 (s, 3H). LCMS: *m/z* 208 [M+H]⁺ @ r.t. 3.84 min. HRMS (ESI) calcd for C₁₃H₂₁N₃O₂S [M + H]⁺ 208.0539 found 208.0545.

Preparation 17

8-benzyl-2-(methylsulfonyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(II), G = Me-S(O)₂-, R₂ = benzyl, R₃ = R₄ = R₅ = H]

- 35 **H] Step 2f**

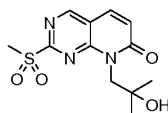


8-benzyl-2-(methylsulfonyl)pyrido[2,3-d]pyrimidin-7(8H)-one (110 mg, 0.388 mmol) was dissolved in 5 mL DCM. To the stirring solution, m-CPBA (251 mg, 1.55 mmol) was added. The reaction was allowed to stir for 2 h at room temperature. LCMS indicated reaction had gone to completion. Sample was diluted with 10 mL of DCM, and washed
 5 twice with saturated NaHCO_3 , followed by brine. The organic phase was separated and dried over Na_2SO_4 , filtered, and concentrated in vacuo. The solvent was evaporated to provide 8-benzyl-2-(methylsulfonyl)pyrido[2,3-d]pyrimidin-7(8H)-one (105 mg, 86% yield) as a yellow solid.

^1H NMR (401 MHz, $\text{DMSO}-d_6$) δ = 9.32 (s, 1H), 8.17 (d, J = 9.64 Hz, 1H), 7.36 - 7.42 (m, 2H), 7.19 - 7.34 (m, 3H), 6.99 (d, J = 9.52 Hz, 1H), 5.52 (s, 2H), 3.39 (s, 3H), 8.91 (s, 1H), 8.00 (d, J = 9.46 Hz, 1H), 7.17 - 7.35 (m, 5H), 6.71
 10 (d, J = 9.46 Hz, 1H), 5.50 (s, 2H). LCMS : m/z 316 $[\text{M}+\text{H}]^+$ r.t. 4.80 min. HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{14}\text{N}_3\text{O}_3\text{S}$ $[\text{M} + \text{H}]^+$ 316.0751 found 316.0760.

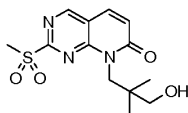
According to the same method the following compounds were prepared:

8-(2-Hydroxy-2-methyl-propyl)-2-methanesulfonyl-8H-pyrido[2,3-d]pyrimidin-7-one [(II), G = Me-S(O) $_2$ -, R $_2$ = 2-Hydroxy-2-methyl-propyl, R $_3$ = R $_4$ = R $_5$ = H]



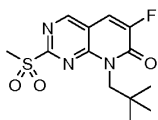
^1H NMR (500MHz, $\text{DMSO}-d_6$) δ = 9.29 (s, 1 H), 8.12 (d, J = 9.6 Hz, 1 H), 6.94 (d, J = 9.5 Hz, 1 H), 4.50 (s, 1 H), 4.44
 15 (s, 2 H), 3.47 (s, 3 H), 1.12 (s, 6 H). LCMS : m/z 320 $[\text{M}+\text{H}]^+$ @ r.t. 3.35 min
 HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{15}\text{N}_3\text{O}_4\text{S}$ $[\text{M} + \text{H}]^+$ 320.0675 found 320.0677;

8-(3-Hydroxy-2,2-dimethyl-propyl)-2-methanesulfonyl-8H-pyrido[2,3-d]pyrimidin-7-one [(II), G = Me-S(O) $_2$ -, R $_2$ = 3-Hydroxy-2,2-dimethyl-propyl, R $_3$ = R $_4$ = R $_5$ = H]



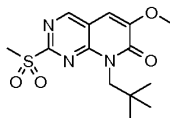
^1H NMR (500MHz, $\text{DMSO}-d_6$) δ = 9.29 (s, 1 H), 8.12 (d, J = 9.6 Hz, 1 H), 6.94 (d, J = 9.5 Hz, 1 H), 4.57 (t, J = 5.8
 20 Hz, 1 H), 4.35 (br. s., 2 H), 3.47 (s, 3 H), 3.20 (d, J = 5.8 Hz, 2 H), 0.83 (s, 6 H). LCMS : m/z 312 $[\text{M}+\text{H}]^+$ @ r.t. 3.76 min. HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{17}\text{N}_3\text{O}_4\text{S}$ $[\text{M} + \text{H}]^+$ 312.1013 found 312.1016;

8-(2,2-Dimethyl-propyl)-6-fluoro-2-methanesulfonyl-8H-pyrido[2,3-d]pyrimidin-7-one [(II), G = Me-S(O) $_2$ -, R $_2$ = 2,2-Dimethyl-propyl, R $_3$ = R $_4$ = H, R $_5$ = F]



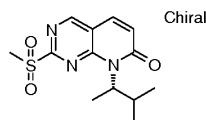
^1H NMR (500MHz, $\text{DMSO}-d_6$) δ = 9.29 (s, 1 H), 8.11 (d, J = 8.7 Hz, 1 H), 4.34 (br. s., 2 H), 3.47 (s, 3 H), 0.94 (s, 9
 H). LCMS : m/z 314 $[\text{M}+\text{H}]^+$ @ r.t. 5.21 min. HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{16}\text{N}_3\text{O}_3\text{FS}$ $[\text{M} + \text{H}]^+$ 314.0969 found 314.0967;

8-(2,2-Dimethyl-propyl)-2-methanesulfonyl-6-methoxy-8H-pyrido[2,3-d]pyrimidin-7-one [(II)], G = Me-S(O)₂-, R₂ = 2,2-Dimethyl-propyl, R₃ = R₄ = H, R₅ = OMe]



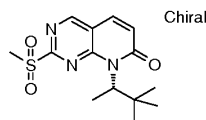
- ¹H NMR (500MHz, DMSO-d₆) δ = 9.17 (s, 1 H), 7.45 (s, 1 H), 4.35 (br. s., 2 H), 3.92 (s, 3 H), 3.43 (s, 3 H), 1.16 (s, 0 H), 0.92 (s, 9 H). LCMS : m/z 326 [M+H]⁺ @ r.t. 4.91 min. HRMS (ESI) calcd for C₁₄H₁₉N₃O₄S [M +H]⁺ 326.1169 found 326.1164;

8-[(2S)-3-methylbutan-2-yl]-2-(methylsulfonyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(II)], G = Me-S(O)₂-, R₂ = (2S)-3-methylbutan-2-yl, R₃ = R₄ = R₅ = H]

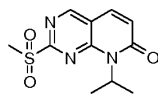


- Purification with chromatographic column eluent Hex/EtOAc 8:2 to give a off-white solid of the title compound (250 mg 95% Yield).
¹H NMR (500MHz, DMSO-d₆) δ = 9.29 (s, 1H), 8.10 (d, J = 9.46 Hz, 1H), 6.71 - 7.06 (m, 1H), 4.83 - 5.43 (m, 1H), 3.45 (s, 3H), 1.41 - 1.68 (m, 3H), 1.05 (d, J = 6.56 Hz, 3H), 0.59 (br. s., 3H). LCMS : m/z 296 [M+H]⁺ @ r.t. 4.92 min. HRMS (ESI) calcd for C₁₃H₁₈N₃O₃S [M +H]⁺ 296.1064 found 296.1065;

- 8-[(2S)-3,3-dimethylbutan-2-yl]-2-(methylsulfonyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(II)], G = Me-S(O)₂-, R₂ = (2S)-3,3-dimethylbutan-2-yl, R₃ = R₄ = R₅ = H]**

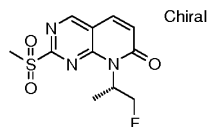


- Purification with chromatographic column eluent Hex/EtOAc 8:2 to give a off-white solid of the title compound (50 mg 95% Yield). LCMS : m/z 310 [M+H]⁺ @ r.t. 5.07 min.
- 2-(methylsulfonyl)-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one [(II)], G = Me-S(O)₂-, R₂ = propan-2-yl, R₃ = R₄ = R₅ = H]**



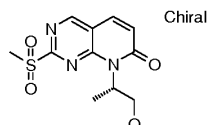
- Purification with chromatographic column eluent Hex/EtOAc 8:2 to give a off-white solid of the title compound (479 mg 69% Yield).
¹H NMR (500MHz, DMSO-d₆) δ = 9.27 (s, 1H), 8.07 (d, J = 9.46 Hz, 1H), 6.88 (d, J = 9.46 Hz, 1H), 5.65 (spt, J = 6.80 Hz, 1H), 3.46 (s, 3H), 1.56 (d, J = 7.02 Hz, 6H). LCMS : m/z 268 [M+H]⁺ @ r.t. 4.48 min. HRMS (ESI) calcd for C₁₁H₁₃N₃O₃S [M +H]⁺ 268.0751 found 268.0746;

8-[(2S)-1-fluoropropan-2-yl]-2-(methylsulfonyl)pyrido[2,3-d]pyrimidin-7(8H)-one one [(II)], G = Me-S(O)₂-, R₂ = (2S)-1-fluoropropan-2-yl, R₃ = R₄ = R₅ = H]



^1H NMR (500MHz, DMSO- d_6) δ = 9.31 (s, 1H), 8.13 (d, J = 9.61 Hz, 1H), 6.92 (d, J = 9.61 Hz, 1H), 5.81 (br. s., 1H), 5.12 (td, J = 8.50, 47.90 Hz, 1H), 4.87 (ddd, J = 5.80, 9.30, 46.20 Hz, 1H), 3.47 (s, 3H), 1.52 (d, J = 7.02 Hz, 3H). LCMS : m/z 286 $[\text{M}+\text{H}]^+$ @ r.t. 3.74 min. HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{13}\text{FN}_3\text{O}_3\text{S}$ $[\text{M}+\text{H}]^+$ 286.0656 found 286.0654;

- 5 **8-[(2S)-1-hydroxypropan-2-yl]-2-(methylsulfonyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(II), G = Me-S(O) $_2$ -, R $_2$ = (2S)-1-hydroxypropan-2-yl, R $_3$ = R $_4$ = R $_5$ = H]**

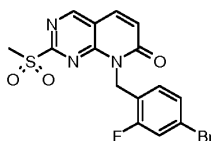


^1H NMR (500MHz, DMSO- d_6) δ = 9.27 (s, 1H), 8.08 (d, J = 9.46 Hz, 1H), 6.88 (d, J = 9.46 Hz, 1H), 5.54 (br. s., 1H), 4.83 (t, J = 5.95 Hz, 1H), 4.02 - 4.23 (m, 1H), 3.70 - 3.87 (m, 1H), 3.45 (s, 3H), 1.47 (d, J = 6.86 Hz, 3H). LCMS : m/z 284 $[\text{M}+\text{H}]^+$ @ r.t. 3.74 min. HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{14}\text{N}_3\text{O}_4\text{S}$ $[\text{M}+\text{H}]^+$ 284.07 found 284.0702.

- 10 **8-(4-bromo-2-fluorobenzyl)-2-(methylsulfonyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(II), G = Me-S(O) $_2$ -, R $_2$ = 4-bromo-2-fluorobenzyl, R $_3$ = R $_4$ = R $_5$ = H]**

Purification with chromatographic column eluent Hex/EtOAc 7:3 to give a off-white solid of the title compound (90% Yield).

15

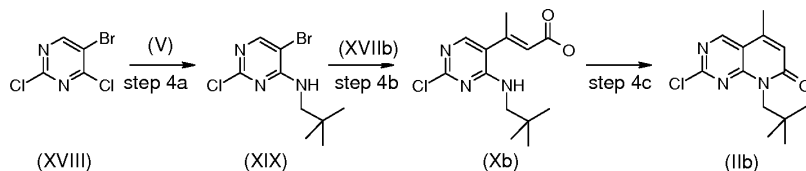


^1H NMR (500 MHz, DMSO- d_6) δ = 9.34 (s, 1H), 8.19 (d, J = 9.61 Hz, 1H), 7.57 (dd, J = 1.83, 9.91 Hz, 1H), 7.29 (dd, J = 1.75, 8.31 Hz, 1H), 7.12 (t, J = 8.31 Hz, 1H), 6.99 (d, J = 9.61 Hz, 1H), 5.51 (s, 2H), 3.37 (s, 3H). LCMS : m/z 411 $[\text{M}+\text{H}]^+$ @ r.t. 5.52 min. HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{12}\text{BrFN}_3\text{O}_3\text{S}$ $[\text{M}+\text{H}]^+$ 411.9762 found 411.9763.

20

Preparation 18

2-Chloro-8-(2,2-dimethyl-propyl)-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one [(II), G = Cl, R $_2$ = 2,2-dimethyl-propyl, R $_3$ = H, R $_4$ = Me, R $_5$ = H] Steps 4a, 4b and 4c



25

Step 4a: 5-bromo-2,4-dichloropyrimidine (1.0 g, 4.38 mmol) was dissolved in THF (20.0 mL) to which triethylamine (0.94 mL, 6.57 mmol) and neopentylamine (0.45 mL, 5.25 mmol) was added and stirred for 2 hour at room

temperature. The precipitated salts were filtered and the solvent evaporated under reduced pressure. The resulting oil was dissolved in Et₂O, washed with brine, and then dried over Na₂SO₄. The salts were filtered, and the solvent was evaporated under vacuum to give the product (1.13g, 70% yield) which is carried on without further purification.

¹H NMR (500MHz, DMSO-d₆) δ = 8.24 (s, 1H), 7.46 (t, *J* = 6.25 Hz, 1H), 3.26 (d, *J* = 6.41 Hz, 2H), 0.88 (s, 9H).

- 5 LCMS : *m/z* 278 [M+H]⁺ @ r.t. 6.98 min. HRMS (ESI) calcd for C₉H₁₄BrClN₃O [M +H]⁺ 278.0054 found 278.0058;

Step 4b: A 3-necked round bottom flask was charged with (5-Bromo-2-chloro-pyrimidin-4-yl)-(2,2-dimethyl-propyl)-amine (200.0 mg, 0.72 mmol), crotonic acid (154.4 mg, 1.79 mmol), DIPEA (0.50 mL, 2.94 mmol) and THF (2.5 mL).

The mixture was degassed by applying 3 vacuum/argon cycles then tri-*o*-tolyl-phosphine (4.4 mg, 0.014 mmol) and dichlorobis(benzonitrile)palladium(II) (5.5 mg, 0.014 mmol) were added. The mixture was degassed again by

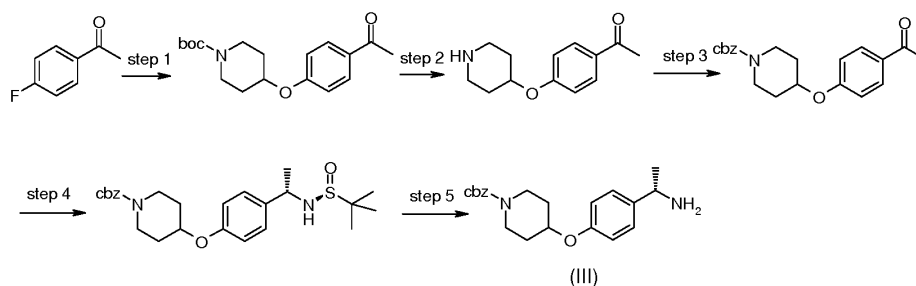
- 10 applying 3 vacuum/argon cycles then heated to 75°C and stirred under argon for 20 h;

Step 4c: Then, acetic anhydride (0.17 mL, 1.79 mmol) was added and the mixture further stirred at 75°C for 2 h. The reaction was quenched with water and the mixture allowed to cool down at room temperature. The reaction mixture was diluted with Et₂O, and washed with water followed by brine. The organic phases were separated and dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude material was purified through silica gel column chromatography (10 to 30% AcOEt/hexane) to give the title product (90.8 mg, 48% yield). ¹H NMR (500MHz, DMSO-d₆) δ = 9.04 (s, 1 H), 6.66 (q, *J* = 1.2 Hz, 1 H), 4.20 (s, 2 H), 2.47 (d, *J* = 1.2 Hz, 3 H), 0.90 (s, 9 H). LCMS : *m/z* 266 [M+H]⁺ @ r.t. 6.50 min. HRMS (ESI) calcd for C₁₃H₁₆N₃OCl [M +H]⁺ 266.1055 found 266.1065.

Preparation 19

Preparation of 4-[4-((S)-1-Amino-ethyl)-phenoxy]-piperidine-1-carboxylic acid benzyl ester hydrochloride [(III), A = phenyl, R1a= H, R1b = Me, R6a= O-R7, R6b = H, R7 = 4- piperidine-1-carboxylic acid benzyl ester]

20



- 25 **Step 1:** 4-fluoroacetophenone (0.691 g, 5.0 mmol) was dissolved in DMF (10.0 mL) to which cesium carbonate (3.26 g, 10.0 mmol) and 1-(tert-butoxycarbonyl)-4-hydroxypiperidine (2.01 g, 10.0 mmol) was added and stirred for 2 days at 100 °C. The cesium carbonate was filtered off and the solution was diluted with ether and washed with water (3x10mL), and then dried over Na₂SO₄. The crude material was purified through silica gel column chromatography (10 to 70% AcOEt/hexane) to give 4-(4-Acetyl-phenoxy)-piperidine-1-carboxylic acid tert-butyl ester (547.5 mg, 34% yield).

- 30 ¹H NMR (500 MHz, DMSO-d₆) δ = 7.86 - 7.95 (m, 2H), 7.02 - 7.12 (m, 2H), 4.71 (tt, *J* = 8.1, 3.8 Hz, 1H), 3.61 - 3.71 (m, 2H), 3.19 (br. s., 2H), 1.87 - 1.98 (m, 2H), 1.46 - 1.60 (m, 2H), 1.40 (s, 9H). LCMS: *m/z* 342 [M+Na]⁺ @ r.t. 6.68 min. HRMS (ESI) calcd for C₁₈H₂₅NNaO₄ [M +Na]⁺ 342.1676 found 342.1677.

Step 2: To a solution of 4-(4-acetyl-phenoxy)-piperidine-1-carboxylic acid tert-butyl ester (250.0 mg) in dioxane (4.0 mL) is added HCl (4 M in dioxane, 1.0 mL). The mixture is stirred overnight at room temperature and it is then concentrated to dryness to provide a white solid which is dried under vacuum to give the compound 1-[4-(Piperidin-4-yloxy)-phenyl]-ethanone hydrochloride as a white solid (220.0 mg).

- 5 ¹H NMR (500 MHz, DMSO-d₆) δ = 8.63 (br. s., 2H), 7.86 - 8.01 (m, 2H), 7.04 - 7.17 (m, 2H), 4.80 (tt, *J* = 7.6, 3.6 Hz, 1H), 3.21 - 3.28 (m, 2H), 3.09 (ddd, *J* = 12.7, 8.8, 3.5 Hz, 2H), 2.52 (s, 3H), 2.12 (ddq, *J* = 10.2, 7.1, 3.5 Hz, 2H), 1.76 - 1.90 (m, 2H). LCMS: *m/z* 220 [M+H]⁺ @ r.t. 3.32 min.

HRMS (ESI) calcd for C₁₃H₁₈ClNO₂ [M +H]⁺ 220.1332 found 220.1338.

- Step 3:** 1-[4-(Piperidin-4-yloxy)-phenyl]-ethanone (215.0 mg, 0.841 mmol) was dissolved in DCM (5.0 mL) to which
10 TEA (0.35 mL, 2.522 mmol) and benzyl chloroformate (0.27 mL, 1.009 mmol) were added. The resulting solution was stirred overnight at room temperature. The reaction mixture was washed with water followed by brine. The organic phases were separated and dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude material was purified through silica gel column chromatography (10 to 70% AcOEt/hexane) to give 4-(4-Acetyl-phenoxy)-piperidine-1-carboxylic acid benzyl ester (210.1 mg, 70% yield).

- 15 ¹H NMR (500 MHz, DMSO-d₆) δ = 7.86 - 7.95 (m, 2H), 7.27 - 7.42 (m, 5H), 7.03 - 7.12 (m, 2H), 5.08 (s, 2H), 4.69 - 4.79 (m, 1H), 3.65 - 3.83 (m, 2H), 3.20 - 3.41 (m, 2H), 2.51 (br. s., 3H), 1.96 (ddd, *J* = 9.4, 6.1, 2.8 Hz, 2H), 1.50 - 1.65 (m, 2H). LCMS: *m/z* 376 [M+Na]⁺ @ r.t. 6.66 min.

HRMS (ESI) calcd for C₂₁H₂₃NaO₄ [M +Na]⁺ 376.1519 found 376.1526.

- Step 4:** A mixture of tetraethoxytitanium (0.237 mL, 1.132 mmol), (S)-2-methylpropane-2- sulfonamide (68.2 mg, 0.566 mmol), and 4-(4-Acetyl-phenoxy)-piperidine-1-carboxylic acid benzyl ester (200.0 mg, 0.566 mmol) in THF
20 (15.0 mL) was heated to 80 °C overnight and then cooled to room temperature. To this mixture was added NaBH₄ (107.0 mg, 2.829 mmol) at 0 °C. The mixture was then slowly warmed up to room temperature in about 5 hours. MeOH (3 mL) was added to quench excess NaBH₄ and was followed by the addition of water. The resulting mixture was filtered to remove solids and the aqueous phase was extracted with EtOAc twice, dried over Na₂SO₄ and concentrated. The crude material was purified through silica gel column chromatography (0 to 10% MeOH/DCM) to
25 give 4-{4-[(S)-1-((S)-2-Methyl-propane-2-sulfinylamino)-ethyl]-phenoxy}-piperidine-1-carboxylic acid benzyl ester (185.6 mg, 72% yield). ¹H NMR (500 MHz, DMSO-d₆) δ = 7.30 - 7.42 (m, 5H), 7.28 (d, *J* = 8.5 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 5.49 (d, *J* = 6.7 Hz, 1H), 5.08 (s, 2H), 4.55 (tt, *J* = 7.8, 3.9 Hz, 1H), 4.30 (quin, *J* = 6.8 Hz, 1H), 3.61 - 3.84 (m, 2H), 3.22 - 3.32 (m, 2H), 1.91 (ddd, *J* = 9.5, 6.2, 2.9 Hz, 2H), 1.46 - 1.61 (m, 2H), 1.36 (d, *J* = 6.9 Hz, 3H),
30 1.10 (s, 9H). LCMS: *m/z* 459 [M+H]⁺ @ r.t. 6.93 min. HRMS (ESI) calcd for C₂₅H₃₄N₂O₄S [M +H]⁺ 459.2312 found 459.2305

- Step 5:** To a solution of 4-{4-[(S)-1-((S)-2-Methyl-propane-2-sulfinylamino)-ethyl]-phenoxy}-piperidine-1-carboxylic acid benzyl ester (150 mg) in MeOH (5 mL) was added HCl (2 mL, 8.0 mmol, 4M in 1,4-dioxane). The mixture was stirred at room temperature overnight. To this mixture was added 6 mL of ethyl ether and the resulting precipitate
35 was collected by filtration, washed with ethyl ether (2x10mL), and then dried to title product (quantitative yield).

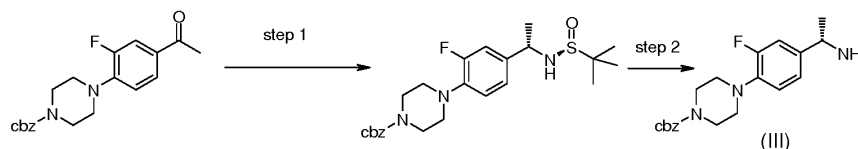
¹H NMR (500 MHz, DMSO-d₆) δ = 8.18 (br. s., 3H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.28 - 7.45 (m, 5H), 7.03 (d, *J* = 8.8 Hz, 2H), 5.08 (s, 2H), 4.61 (tt, *J* = 7.8, 3.7 Hz, 1H), 4.34 (spt, *J* = 6.1 Hz, 1H), 1.74 - 1.98 (m, 2H), 1.54 (dtd, *J* = 12.8, 8.6, 3.9 Hz, 2H), 1.46 (d, *J* = 6.9 Hz, 3H). LCMS: *m/z* 377 [M+Na]⁺ @ r.t. 5.36 min.

HRMS (ESI) calcd for $C_{21}H_{27}Cl NaN_2O_3 [M + Na]^+$ 377.1835 found 377.1835

5

Preparation 20

Preparation of benzyl 4-{4-[(1S)-1-aminoethyl]-2-fluorophenyl}piperazine-1-carboxylate hydrochloride [(III), A = phenyl, R1a= H, R1b = Me, R6a= NR7R8, R6b = H, R7 = 4- piperazine-1-carboxylic acid benzyl ester]



10

Step 1 A mixture of tetraethoxytitanium (0.456 mL, 2 mmol), (S)-2-methylpropane-2-sulfonamide (131 mg, 1 mmol), and benzyl 4-(4-acetyl-2-fluorophenyl)piperazine-1-carboxylate (356.0 mg, 1 mmol) in THF (15.0 mL) was heated to 80°C overnight and then cooled to room temperature. To this mixture was added $NaBH_4$ (185.0 mg, 4 mmol) at 0°C. The mixture was then slowly warmed up to room temperature in about 5 hours. MeOH (3 mL) was added to quench excess $NaBH_4$ and was followed by the addition of water. The resulting mixture was filtered to remove solids and the aqueous phase was extracted with EtOAc twice, dried over Na_2SO_4 and concentrated. The crude material was purified through silica gel column chromatography (0 to 10% MeOH/DCM) to give benzyl 4-{4-[(1S)-1-[(S)-*tert*-butylsulfinyl]amino]ethyl-2-fluorophenyl}piperazine-1-carboxylate (256 mg, 55% yield). ^1H NMR (500 MHz, DMSO- d_6) δ = 7.29 - 7.42 (m, 5H), 7.20 (dd, J = 1.83, 13.88 Hz, 1H), 7.11 (dd, J = 1.75, 8.31 Hz, 1H), 6.99 (t, J = 8.69 Hz, 1H), 5.61 (d, J = 7.47 Hz, 1H), 5.10 (s, 2H), 4.31 (quin, J = 6.83 Hz, 1H), 3.55 (br. s., 4H), 2.96 (t, J = 4.58 Hz, 4H), 1.35 (d, J = 6.71 Hz, 3H), 1.10 (s, 9H). LCMS: m/z 462 $[M+H]^+$ @ r.t. 6.85 min. HRMS (ESI) calcd for $C_{24}H_{33}FN_3O_3S [M + H]^+$ 462.2221 found 462.2232.

Step 2: To a solution of benzyl 4-{4-[(1S)-1-[(S)-*tert*-butylsulfinyl]amino]ethyl-2-fluorophenyl}piperazine-1-carboxylate (250 mg) in MeOH (5 mL) was added HCl (2 mL, 8.0 mmol, 4M in 1,4-dioxane). The mixture was stirred at room temperature overnight. To this mixture was added 6 mL of ethyl ether and the resulting precipitate was collected by filtration, washed with ethyl ether (2x10mL), and then dried to title product (quantitative yield).

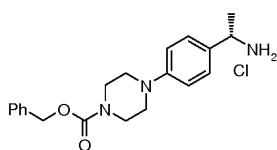
^1H NMR (500 MHz, DMSO- d_6) δ = 8.29 (br. s., 3H), 7.28 - 7.43 (m, 6H), 7.23 (dd, J = 1.98, 8.39 Hz, 1H), 7.09 (t, J = 8.85 Hz, 1H), 5.11 (s, 2H), 4.36 (quin, J = 5.91 Hz, 1H), 3.56 (br. s., 4H), 2.89 - 3.07 (m, J = 4.58 Hz, 4H), 1.46 (d, J = 6.71 Hz, 3H). LCMS: m/z 341 $[M(-NH_3)+H]^+$ @ r.t. 5.4 min.

HRMS (ESI) calcd for $C_{20}H_{26}FN_3O_2 [M(-NH_3)+H]^+$ 341.1160 found 341.1164.

According to the same method, the following compounds were prepared:

Preparation of benzyl 4-{4-[(1S)-1-aminoethyl]-2-fluorophenyl}piperazine-1-carboxylate hydrochloride [(III), A = phenyl, R1a= H, R1b = Me, R6a= NR7R8, R6b = H, R7 = 4- piperazine-1-carboxylic acid benzyl ester]

30

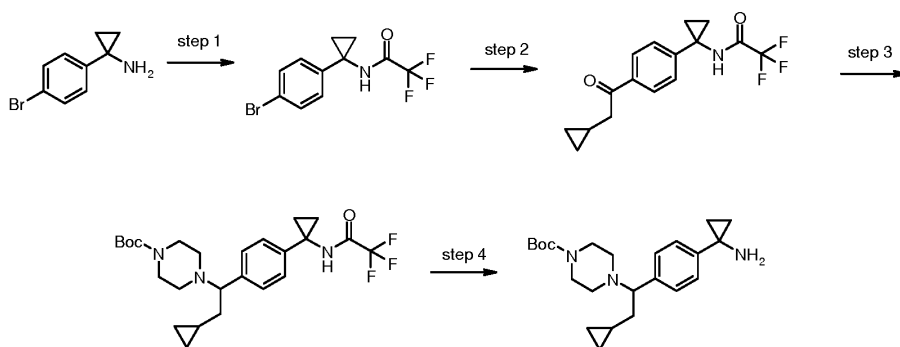


^1H NMR (500 MHz, DMSO- d_6) δ = 8.19 (br. s., 3H), 7.36 - 7.42 (m, 4H), 7.34 (d, J = 8.69 Hz, 3H), 7.00 (d, J = 8.85 Hz, 2H), 5.10 (s, 2H), 4.30 (spt, J = 6.30 Hz, 1H), 3.54 (br. s., 4H), 3.15 (d, J = 4.88 Hz, 4H), 1.46 (d, J = 6.71 Hz, 3H). LCMS: m/z 340 $[\text{M}+\text{H}]^+$ @ r.t. 5.06 min. HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{26}\text{N}_3\text{O}_2$ $[\text{M}+\text{H}]^+$ 340.2020 found 340.2018.

5

Preparation 21

tert-butyl 4-{1-[4-(1-aminocyclopropyl)phenyl]-2-cyclopropylethyl}piperazine-1-carboxylate [(III), A = phenyl, R1a and R1b = cyclopropyl, R6a= 4-CH(R14)NR7R8, R6b = H, R7-R8 = 4- piperazine-1-carboxylic acid benzyl ester, R14 = cyclopropylmethyl]



10

Step 1. To a solution of 1-(4-bromophenyl)cyclopropanamine (1.0 g, 4.71 mmol), in ACN (6.5 ml) at 0°C was slowly added trifluoroacetic anhydride (0.72 ml, 5.26 mmol, 1.1 eq.) in the presence of TEA (1.31 ml, 9.42 mmol, 2 eq.). The mixture is stirred at the same temperature for 15 min. then the cool bath was removed and left warmup at r.t. for 1 h. A mixture of water (10 ml) and brine (5 ml) was added and the slurry was stirred for 15 min. The precipitate was filtered under vacuum and the solid washed with n-Hexane, and dried in oven under vacuum, to obtain *N*-[1-(4-bromophenyl)cyclopropyl]-2,2,2-trifluoroacetamide as a white solid (1.4 g 96%).

15

^1H NMR (500 MHz, DMSO- d_6) δ = 10.22 (s, 1H), 7.47 - 7.56 (m, 2H), 7.08 - 7.17 (m, 2H), 1.20 - 1.31 (m, 4H).

20

Step 2. *n*-Butyl lithium 1.6 M in hexane, (5.67 ml, 9.07 mmol, 2 eq.) was added dropwise to a solution of *N*-[1-(4-bromophenyl)cyclopropyl]-2,2,2-trifluoroacetamide (1.4 g, 4.54 mmol), in THF dry (45 ml) at -78°C and then stirred for additional 40 min. under Argon. To the solution was added *N*-Methoxy-*N*-methylcyclopropaneacetamide (0.845 g 5.90 mmol, 1.3 eq.) dissolved in THF (1 ml). The mixture was stirred at -78°C for 45 min, saturated aqueous ammonium chloride (50 ml) was added, and the mixture was warmed to r.t.. The layers were separated and the organic phase was washed with brine and dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The solid was dissolved in a small amount of DCM and then hexane (25 ml) was added dropwise with vigorous stirring to give a white solid. The solid was collected via filtration, washed with a small amount of hexane, and dried in vacuo to give *N*-[1-(4-{1-[2-(2-cyclopropylacetyl)phenyl]cyclopropyl}-2,2,2-trifluoroacetyl)phenyl]cyclopropyl]-2,2,2-trifluoroacetamide (0.915 g, 65%).

25

^1H NMR (500 MHz, DMSO- d_6) δ = 10.27 (s, 1H), 7.89 (d, J = 8.69 Hz, 2H), 7.24 (d, J = 8.54 Hz, 2H), 2.90 (d, J = 6.71 Hz, 2H), 1.29 - 1.41 (m, 3H), 0.96 - 1.09 (m, 1H), 0.44 - 0.53 (m, 2H), 0.11 - 0.17 (m, 2H).

Step 3 Titanium (IV) isopropoxide (2.14 ml, 7.2 mmol, 5 eq.) was added to a solution of N-{1-[4-(cyclopropylacetyl)phenyl]cyclopropyl}-2,2,2-trifluoroacetamide (0.45 g, 1.44 mmol) and *tert*-butyl piperazine-1-carboxylate (0.644 g, 3.45 mmol, 2.4 eq.), in THF (8 ml) and stirred at 60°C overnight. The mixture was cooled to room temperature and MeOH (3 ml) was added followed by the portion-wise addition of sodium cyanoborohydride (0.18 g, 2.88 mmol, 2 eq.). The mixture was stirred at room temperature for 8 hours and then water (15 ml) and MeOH (4 ml) were added and the mixture was stirred at r.t. overnight. The mixture was filtered to remove solids and the solids were rinsed with MeOH and water. Most of volatiles were removed and the residue was extracted with EtOAc (2x). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated. The crude was purified via column chromatography eluting with a gradient DCM/hexane/EtOAc from 300/300/0 to 300/300/100 to afford *tert*-butyl 4-[2-cyclopropyl-1-(4-{1-[(trifluoroacetyl)amino]cyclopropyl}phenyl)ethyl]piperazine-1-carboxylate as white foam (0.46 g, 66%).

¹H NMR (500 MHz, DMSO-*d*₆) δ = 10.15 (s, 1H), 7.19 (d, *J* = 8.39 Hz, 2H), 7.08 (d, *J* = 8.39 Hz, 2H), 3.42 (dd, *J* = 5.72, 9.07 Hz, 1H), 3.16 - 3.31 (m, 4H), 2.22 (br. s., 4H), 1.69 - 1.81 (m, 1H), 1.50 - 1.60 (m, 1H), 1.34 (s, 9H), 1.21 - 1.29 (m, 4H), 0.25 - 0.44 (m, 3H), -0.11 - 0.03 (m, 2H).

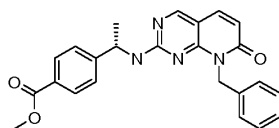
Step 4 Aqueous KOH (2M, 8 ml), was added to a solution of *tert*-butyl 4-[2-cyclopropyl-1-(4-{1-[(trifluoroacetyl)amino]cyclopropyl}phenyl)ethyl]piperazine-1-carboxylate (0.46 g), in EtOH (15 ml) and the resulting mixture was stirred at room temperature for 48 hours. The volatiles were removed under reduced pressure and to the residue was added sat. aqueous NaHCO₃ and partitioned with DCM. The combined organic extracts were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo, to give *tert*-butyl 4-{1-[4-(1-aminocyclopropyl)phenyl]-2-cyclopropylethyl}piperazine-1-carboxylate as light yellow viscous oil (0.358 g, 97%).

¹H NMR (500 MHz, DMSO-*d*₆) δ = 7.23 (d, *J* = 8.24 Hz, 2H), 7.13 (d, *J* = 8.24 Hz, 2H), 3.42 (dd, *J* = 5.49, 9.00 Hz, 1H), 3.25 (d, *J* = 4.27 Hz, 4H), 2.22 (br. s., 5H), 1.73 - 1.83 (m, 1H), 1.55 (s, 1H), 1.33 (s, 9H), 0.85 - 0.97 (m, 4H), 0.34 - 0.45 (m, 1H), 0.25 - 0.32 (m, 2H), -0.02 (d, *J* = 18.76 Hz, 2H).

25

Example 1

Methyl 4-[(1*S*)-1-[(8-benzyl-7-oxo-pyrido[2,3-*d*]pyrimidin-2-yl)amino]ethyl]benzoate [(I), X = N, R₂ = Benzyl, A = Phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = -COOMe, R_{6b} = H, R₃ = R₄ = R₅ = H] step 1a, cpd 1



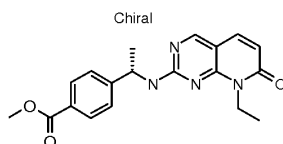
To a solution of compound 8-benzyl-2-(methylsulfonyl)pyrido[2,3-*d*]pyrimidin-7(8H)-one (100mg, 0.32 mmol) in ACN (2 mL) was added (S)-methyl 4-(1-aminoethyl)benzoate (86 mg, 0.48 mmol). The reaction was heated to 90 °C for 2 hours. The reaction mixture was diluted with EtOAc (4 mL) and washed with water (5 mL) and brine (5 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated. The crude material was purified on silica gel column chromatography (DCM/EtOAc 8/2) provided the title compound as a light yellow foam (100 mg, 76% yield).

¹H NMR (401 MHz, DMSO-*d*₆) δ = 8.63 (s, 1H), 8.50 (d, *J* = 7.20 Hz, 1H), 7.79 (d, *J* = 8.18 Hz, 2H), 7.75 (d, *J* = 9.52 Hz, 1H), 7.41 (d, *J* = 8.06 Hz, 2H), 7.08 - 7.19 (m, 3H), 7.04 (d, *J* = 5.61 Hz, 2H), 6.28 (d, *J* = 9.52 Hz, 1H), 5.44 (d, *J*

= 14.04 Hz, 1H), 5.11 (d, J = 14.40 Hz, 1H), 5.07 (quin, J = 7.00 Hz, 1H), 3.83 (s, 3H), 1.44 (d, J = 6.96 Hz, 3H).
LCMS : m/z 415 $[M+H]^+$ r.t. 6.21 min. HRMS (ESI) calcd for $C_{24}H_{23}N_4O_3$ $[M+H]^+$ 415.1765 found 415.177.

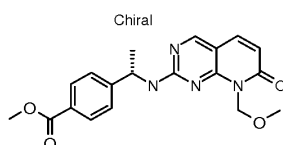
According to the same method, the following compounds were prepared:

- Methyl 4-[(1S)-1-[(8-ethyl-7-oxo-pyrido[2,3-d]pyrimidin-2-yl)amino]ethyl]benzoate [(I), X = N, R2 = Ethyl, A = Phenyl, R1a= H, R1b = Me, R6a= -COOMe, R6b = H, R3 = R4 = R5= H] cpd 2**



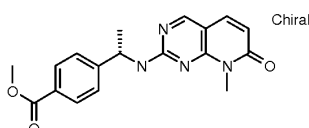
- ^1H NMR (401 MHz, DMSO- d_6) δ = 8.59 (s, 1H), 8.49 (d, J =6.6 Hz, 1H), 7.85 - 7.94 (m, 2H), 7.67 (d, J =9.3 Hz, 1H), 7.54 (d, J =8.3 Hz, 1H), 6.21 (d, J =9.2 Hz, 1H), 5.08 (quin, J =6.9 Hz, 1H), 4.15 (dq, J =12.7, 6.6 Hz, 1H), 3.90 - 4.06 (m, 1H), 3.82 (s, 3H), 1.49 (d, J =7.2 Hz, 3H), 0.87 (t, J =6.8 Hz, 3H). LCMS : m/z 353 $[M+H]^+$ r.t. 5.61 min. HRMS (ESI) calcd for $C_{19}H_{21}N_4O_3$ $[M+H]^+$ 353.1608 found 353.1602;

- Methyl 4-[(1S)-1-[(8-(methoxymethyl)-7-oxo-pyrido[2,3-d]pyrimidin-2-yl)amino]ethyl]benzoate [(I), X = N, R2 = methoxymethyl, A = Phenyl, R1a= H, R1b = Me, R6a= -COOMe, R6b = H, R3 = R4 = R5= H] cpd 3**



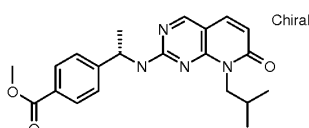
- ^1H NMR (401 MHz, DMSO- d_6) δ = 8.61 (s, 1H), 8.57 (d, J = 7.63 Hz, 1H), 7.91 (d, J = 8.24 Hz, 2H), 7.73 (d, J = 9.30 Hz, 1H), 7.55 (d, J = 8.24 Hz, 2H), 6.23 (d, J = 9.46 Hz, 1H), 5.50 (d, J = 9.00 Hz, 1H), 5.36 (d, J = 9.15 Hz, 1H), 5.14 (quin, J = 7.09 Hz, 1H), 3.82 (s, 3H), 3.11 (s, 3H), 1.49 (d, J = 7.02 Hz, 3H).
LCMS : m/z 369 $[M+H]^+$ r.t. 5.24 min. HRMS (ESI) calcd for $C_{19}H_{21}N_4O_4$ $[M+H]^+$ 369.1558 found 369.1567;

- methyl 4-[(1S)-1-[(8-methyl-7-oxo-pyrido[2,3-d]pyrimidin-2-yl)amino]ethyl]benzoate [(I), X = N, R2 = methyl, A = Phenyl, R1a= H, R1b = Me, R6a= -COOMe, R6b = H, R3 = R4 = R5= H] cpd 4**



- ^1H NMR (401 MHz, DMSO- d_6) δ = 8.96 (br. s., 1H), 8.05 (d, J = 8.54 Hz, 1H), 7.91 (d, J = 7.93 Hz, 2H), 7.58 (d, J = 7.02 Hz, 2H), 6.68 (d, J = 8.54 Hz, 1H), 5.25 - 5.46 (m, 1H), 3.92 (br. s., 3H), 3.82 (s, 3H), 1.50 (d, J = 7.02 Hz, 3H).
LCMS : m/z 339 $[M+H]^+$ r.t. 5.67 min. HRMS (ESI) calcd for $C_{18}H_{19}N_4O_3$ $[M+H]^+$ 339.1452 found 339.1443;

- methyl 4-[(1S)-1-[(8-(2-methylpropyl)-7-oxo-pyrido[2,3-d]pyrimidin-2-yl)amino]ethyl]benzoate [(I), X = N, R2 = 2-methylpropyl, A = Phenyl, R1a= H, R1b = Me, R6a= -COOMe, R6b = H, R3 = R4 = R5= H] cpd 5**

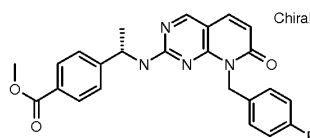


- ¹H NMR (401 MHz, DMSO- *d*₆) δ = 8.60 (s, 1H), 8.47 (d, *J* = 6.47 Hz, 1H), 7.91 (d, *J* = 8.30 Hz, 2H), 7.69 (d, *J* = 9.15 Hz, 1H), 7.51 (d, *J* = 8.18 Hz, 2H), 6.22 (d, *J* = 9.15 Hz, 1H), 5.07 (quin, *J* = 6.87 Hz, 1H), 3.92 (dd, *J* = 7.81, 12.08 Hz, 1H), 3.82 (s, 3H), 3.77 (dd, *J* = 7.60, 12.00 Hz, 1H), 1.88 (tt, *J* = 6.74, 13.64 Hz, 1H), 1.49 (d, *J* = 7.08 Hz, 3H), 0.72 (d, *J* = 6.71 Hz, 3H), 0.57 (d, *J* = 6.47 Hz, 3H). LCMS : *m/z* 381 [M+H]⁺ r.t. 6.2 min. HRMS (ESI) calcd for C₂₁H₂₅N₄O₃ [M + H]⁺ 381.1921 found 381.1915;

methyl 4-[(1S)-1-[[8-(4-fluorobenzyl)-7-oxo-pyrido[2,3-d]pyrimidin-2-yl]amino]ethyl]benzoate

[(I), X = N, R₂ = 4-fluorobenzyl, A = Phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = -COOMe, R_{6b} = H, R₃ = R₄ = R₅ = H] cpd

6

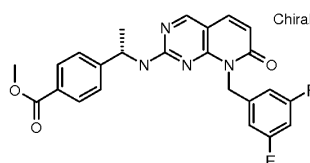


- ¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.60 (s, 1H), 8.47 (d, *J* = 6.47 Hz, 1H), 7.91 (d, *J* = 8.30 Hz, 2H), 7.69 (d, *J* = 9.15 Hz, 1H), 7.51 (d, *J* = 8.18 Hz, 2H), 6.22 (d, *J* = 9.15 Hz, 1H), 5.07 (quin, *J* = 6.87 Hz, 1H), 3.92 (dd, *J* = 7.81, 12.08 Hz, 1H), 3.82 (s, 3H), 3.77 (dd, *J* = 7.60, 12.00 Hz, 1H), 1.88 (tt, *J* = 6.74, 13.64 Hz, 1H), 1.49 (d, *J* = 7.08 Hz, 3H), 0.72 (d, *J* = 6.71 Hz, 3H), 0.57 (d, *J* = 6.47 Hz, 3H). LCMS : *m/z* 433 [M+H]⁺ r.t. 6.29 min. HRMS (ESI) calcd for C₂₄H₂₂FN₄O₃ [M + H]⁺ 433.1671 found 433.1685;

- methyl 4-[(1S)-1-[[8-(3,5-difluorobenzyl)-7-oxo-pyrido[2,3-d]pyrimidin-2-yl]amino]ethyl]benzoate**

[(I), X = N, R₂ = 3,5-difluorobenzyl, A = Phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = -COOMe, R_{6b} = H, R₃ = R₄ = R₅ = H]

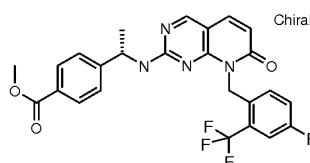
cpd 7



- ¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.60 (s, 1H), 8.47 (d, *J* = 6.47 Hz, 1H), 7.91 (d, *J* = 8.30 Hz, 2H), 7.69 (d, *J* = 9.15 Hz, 1H), 7.51 (d, *J* = 8.18 Hz, 2H), 6.22 (d, *J* = 9.15 Hz, 1H), 5.07 (quin, *J* = 6.87 Hz, 1H), 3.92 (dd, *J* = 7.81, 12.08 Hz, 1H), 3.82 (s, 3H), 3.77 (dd, *J* = 7.60, 12.00 Hz, 1H), 1.88 (tt, *J* = 6.74, 13.64 Hz, 1H), 1.49 (d, *J* = 7.08 Hz, 3H), 0.72 (d, *J* = 6.71 Hz, 3H), 0.57 (d, *J* = 6.47 Hz, 3H). LCMS : *m/z* 451 [M+H]⁺ r.t. 6.36 min. HRMS (ESI) calcd for C₂₄H₂₁F₂N₄O₃ [M + H]⁺ 451.1576 found 451.1584;

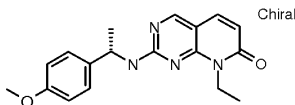
methyl-4-[(1S)-1-[[8-[4-fluoro-2-(trifluoromethyl)benzyl]-7-oxo-pyrido[2,3-d]pyrimidin-2-yl]amino]

- ethyl]benzoate [(I), X = N, R₂ = 4-fluoro-2-(trifluoromethyl)benzyl, A = Phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = -COOMe, R_{6b} = H, R₃ = R₄ = R₅ = H] cpd 8**



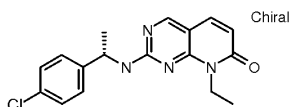
- ¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.70 (s, 1H), 8.55 (d, *J* = 6.71 Hz, 1H), 7.85 (d, *J* = 9.30 Hz, 1H), 7.57 (dd, *J* = 2.44, 9.15 Hz, 1H), 7.52 (d, *J* = 8.24 Hz, 2H), 7.11 (d, *J* = 8.39 Hz, 2H), 7.05 (dt, *J* = 2.29, 8.39 Hz, 1H), 6.24 - 6.35

8-ethyl-2-[[[(1S)-1-(4-methoxyphenyl)ethyl]amino]pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = Ethyl, A = phenyl, R1a= H, R1b = Me, R6a= 4- methoxy, R6b = H, R3 = R4 = R5= H] cpd 13



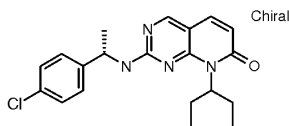
¹H NMR (401 MHz, DMSO- *d*₆) δ = 8.56 (s, 1H), 8.33 (d, *J* = 7.45 Hz, 1H), 7.67 (d, *J* = 9.28 Hz, 1H), 7.26 - 7.38 (m, 2H), 6.79 - 6.92 (m, 2H), 6.21 (d, *J* = 9.40 Hz, 1H), 5.01 (quin, *J* = 7.42 Hz, 1H), 4.15 - 4.34 (m, 1H), 4.02 - 4.15 (m, 1H), 3.70 (s, 3H), 1.46 (d, *J* = 6.96 Hz, 3H), 1.02 (t, *J* = 6.71 Hz, 3H). LCMS : *m/z* 325 [M+H]⁺ r.t. 5.73 min. HRMS (ESI) calcd for C₁₈H₂₁N₄O₂ [M + H]⁺ 325.1659 found 325.1663;

2-[[[(1S)-1-(4-chlorophenyl)ethyl]amino]-8-ethylpyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = Ethyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-Cl, R6b = H, R3 = R4 = R5= H] cpd 14



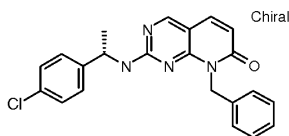
¹H NMR (401 MHz, DMSO- *d*₆) δ = 8.58 (s, 1H), 8.43 (d, *J* = 7.32 Hz, 1H), 7.67 (d, *J* = 9.40 Hz, 1H), 7.39 - 7.45 (m, 2H), 7.33 - 7.38 (m, 2H), 6.22 (d, *J* = 9.52 Hz, 1H), 4.87 - 5.14 (m, 2H), 4.14-4.26 (m, 1H), 3.99-4.07 (m, 1H), 1.47 (d, *J* = 7.08 Hz, 3H), 0.94 (t, *J* = 6.77 Hz, 3H). LCMS : *m/z* 329 [M+H]⁺ r.t. 6.24 min. HRMS (ESI) calcd for C₁₇H₁₈ClN₄O [M + H]⁺ 329.1164 found 329.1167;

2-[[[(1S)-1-(4-chlorophenyl)ethyl]amino]-8-(pentan-3-yl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = pentan-3-yl, A = phenyl, R1a= H, R1b = Me, R6a= 4-Cl, R6b = H, R3 = R4 = R5= H] cpd 15



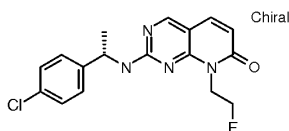
¹H NMR (401 MHz, DMSO- *d*₆) δ = 8.89 (s, 1H), 8.09 (d, *J* = 8.67 Hz, 1H), 8.01 (d, *J* = 8.67 Hz, 1H), 7.33-7.48 (m, 4H), 6.63 (d, *J* = 8.54 Hz, 1H), 5.11 - 5.47 (m, 2H), 1.57 - 1.78 (m, 4H), 1.43 - 1.51 (m, 3H), 0.77 - 0.96 (m, 6H). LCMS : *m/z* 371 [M+H]⁺ r.t. 7.78 min. HRMS (ESI) calcd for C₂₀H₂₄ClN₄O [M + H]⁺ 371.1633 found 371.1642;

8-benzyl-2-[[[(1S)-1-(4-chlorophenyl)ethyl]amino]pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = benzyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-Cl, R6b = H, R3 = R4 = R5= H] cpd 16



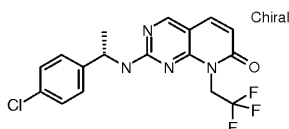
¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.62 (s, 1H), 8.47 (d, *J* = 7.63 Hz, 1H), 7.75 (d, *J* = 9.30 Hz, 1H), 7.26 - 7.30 (m, 2H), 7.22 - 7.26 (m, 2H), 7.15 - 7.20 (m, 3H), 7.08 (d, *J* = 6.10 Hz, 2H), 6.28 (d, *J* = 9.46 Hz, 1H), 5.46 (d, *J* = 14.18 Hz, 1H), 5.17 (d, *J* = 14.03 Hz, 1H), 4.99 - 5.07 (m, 1H), 1.41 (d, *J* = 7.02 Hz, 3H). LCMS : *m/z* 391 [M+H]⁺ r.t. 6.86 min. HRMS (ESI) calcd for C₂₂H₂₀ClN₄O [M + H]⁺ 391.132 found 391.1324;

2-[[[(1S)-1-(4-chlorophenyl)ethyl]amino]-8-(2-fluoroethyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = 2-fluoroethyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-Cl, R6b = H, R3 = R4 = R5= H] cpd 17

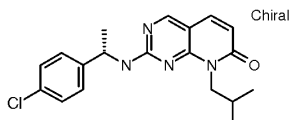


^1H NMR (500 MHz, DMSO- d_6) δ = 8.61 (s, 1H), 8.52 (d, J = 6.86 Hz, 1H), 7.72 (d, J = 9.30 Hz, 1H), 7.38 - 7.43 (m, 2H), 7.33 - 7.38 (m, 2H), 6.24 (d, J = 9.30 Hz, 1H), 4.96 - 5.04 (m, 1H), 4.26-4.75 (m 4H), 1.45 (d, J = 7.02 Hz, 3H). LCMS : m/z 347 $[\text{M}+\text{H}]^+$ r.t. 6.03 min. HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{17}\text{ClF}_3\text{N}_4\text{O}$ $[\text{M} + \text{H}]^+$ 347.107 found 347.1069;

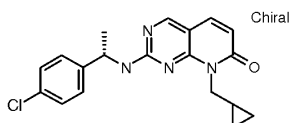
- 5 **2-(((1S)-1-(4-chlorophenyl)ethyl)amino)-8-(2,2,2-trifluoroethyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = 2,2,2-trifluoroethyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-Cl, R6b = H, R3 = R4 = R5= H] cpd 18**



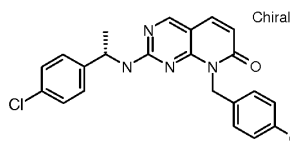
- ^1H NMR (500 MHz, DMSO- d_6) δ = 8.65 (s, 1H), 8.63 (m, 1H), 7.79 (d, J = 9.46 Hz, 1H), 7.38 - 7.42 (m, 2H), 7.33 - 7.38 (m, 2H), 6.29 (d, J = 9.46 Hz, 1H), 5.14 - 5.24 (m, 1H), 4.99-5.07 (m, 1H), 4.74 - 4.87 (m, 1H), 1.41 - 1.52 (m, 3H). LCMS : m/z 383 $[\text{M}+\text{H}]^+$ r.t. 6.61 min. HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{15}\text{ClF}_3\text{N}_4\text{O}$ $[\text{M} + \text{H}]^+$ 383.0881 found 383.0893;
- 10 **2-(((1S)-1-(4-chlorophenyl)ethyl)amino)-8-(2-methylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = 2-methylpropyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-Cl, R6b = H, R3 = R4 = R5= H] cpd 19**



- ^1H NMR (500 MHz, DMSO- d_6) δ = 8.59 (s, 1H), 8.41 (d, J = 7.45 Hz, 1H), 7.69 (d, J = 9.28 Hz, 1H), 7.27 - 7.46 (m, 4H), 6.23 (d, J = 9.28 Hz, 1H), 5.01 (quin, J = 6.87 Hz, 1H), 3.95 (dd, J = 7.51, 12.14 Hz, 1H), 3.68 - 3.89 (m, 1H), 1.92 (spt, J = 6.60 Hz, 1H), 1.46 (d, J = 7.08 Hz, 3H), 0.75 (d, J = 6.59 Hz, 3H), 0.62 (d, J = 6.59 Hz, 3H). LCMS : m/z 357 $[\text{M}+\text{H}]^+$ r.t. 6.86 min. HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{22}\text{ClN}_4\text{O}$ $[\text{M} + \text{H}]^+$ 357.1477 found 357.148;
- 15 **2-(((1S)-1-(4-chlorophenyl)ethyl)amino)-8-(cyclopropylmethyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = cyclopropylmethyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-Cl, R6b = H, R3 = R4 = R5= H] cpd 20**

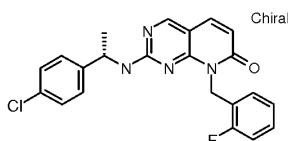


- ^1H NMR (500 MHz, DMSO- d_6) δ = 8.60 (s, 1H), 8.46 (d, J = 6.86 Hz, 1H), 7.70 (d, J = 9.30 Hz, 1H), 7.18 - 7.44 (m, 4H), 6.24 (d, J = 9.15 Hz, 1H), 4.82 - 5.06 (m, 1H), 4.04 (dd, J = 6.86, 12.66 Hz, 1H), 3.76 - 3.89 (m, 1H), 1.46 (d, J = 7.02 Hz, 3H), 0.89 - 1.03 (m, 1H), 0.24 - 0.35 (m, 4H). LCMS : m/z 355 $[\text{M}+\text{H}]^+$ r.t. 6.67 min. HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{20}\text{ClN}_4\text{O}$ $[\text{M} + \text{H}]^+$ 355.132 found 357.1424;
- 25 **2-(((1S)-1-(4-chlorophenyl)ethyl)amino)-8-(4-methoxybenzyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = 4-methoxybenzyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-Cl, R6b = H, R3 = R4 = R5= H] cpd 21**



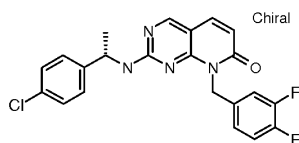
- ¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.62 (s, 1H), 8.48 (d, *J* = 7.47 Hz, 1H), 7.72 (d, *J* = 9.30 Hz, 1H), 7.26 - 7.35 (m, 4H), 7.01 (d, *J* = 8.39 Hz, 2H), 6.67 (d, *J* = 8.54 Hz, 2H), 6.26 (d, *J* = 9.30 Hz, 1H), 5.37 (d, *J* = 13.88 Hz, 1H), 5.05 - 5.14 (m, 2H), 3.68 (s, 3H), 1.45 (d, *J* = 7.02 Hz, 3H). LCMS : *m/z* 421 [M+H]⁺ r.t. 6.75 min. HRMS (ESI) calcd for C₂₃H₂₂ClN₄O₂ [M + H]⁺ 421.1426 found 357.1442;

2-([(1S)-1-(4-chlorophenyl)ethyl]amino)-8-(2-fluorobenzyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = 2-fluorobenzyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-Cl, R_{6b} = H, R₃ = R₄ = R₅ = H] cpd 22



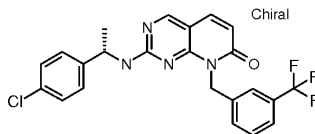
- ¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.64 (s, 1H), 8.13 - 8.52 (m, 1H), 7.80 (d, *J* = 9.30 Hz, 1H), 7.24 - 7.41 (m, 2H), 7.11 - 7.24 (m, 4H), 6.90 - 7.09 (m, 1H), 6.52 - 6.84 (m, 1H), 6.31 (d, *J* = 9.30 Hz, 1H), 5.49 (d, *J* = 15.10 Hz, 1H), 5.20 - 5.32 (m, 1H), 4.82 - 4.95 (m, 1H), 1.32 - 1.49 (m, 3H). LCMS : *m/z* 409 [M+H]⁺ r.t. 6.9 min. HRMS (ESI) calcd for C₂₂H₁₉ClF₂N₄O [M + H]⁺ 409.1226 found 409.123;

2-([(1S)-1-(4-chlorophenyl)ethyl]amino)-8-(3,4-difluorobenzyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = 3,4-difluorobenzyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-Cl, R_{6b} = H, R₃ = R₄ = R₅ = H] cpd 23



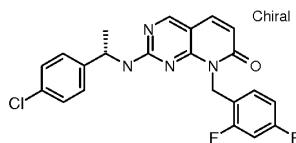
- ¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.56 - 8.70 (m, 1H), 8.52 (d, *J* = 7.47 Hz, 1H), 7.76 (d, *J* = 9.30 Hz, 1H), 7.32 - 7.44 (m, 1H), 7.13 - 7.30 (m, 4H), 6.97 - 7.08 (m, 1H), 6.71 - 6.87 (m, *J* = 5.03 Hz, 1H), 6.28 (d, *J* = 9.30 Hz, 1H), 5.34 - 5.50 (m, 1H), 4.88 - 5.28 (m, 2H), 1.38 - 1.51 (m, 3H). LCMS : *m/z* 427 [M+H]⁺ r.t. 6.9 min. HRMS (ESI) calcd for C₂₂H₁₈ClF₂N₄O [M + H]⁺ 427.1132 found 427.1137;

- 2-([(1S)-1-(4-chlorophenyl)ethyl]amino)-8-[3-(trifluoromethyl)benzyl]pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = 3-(trifluoromethyl)benzyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-Cl, R_{6b} = H, R₃ = R₄ = R₅ = H] cpd 24**



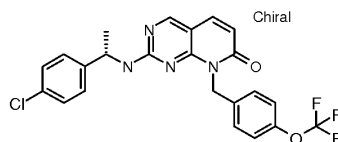
- ¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.56 - 8.72 (m, 1H), 8.31 - 8.53 (m, 1H), 7.70 - 7.80 (m, 1H), 7.51 - 7.66 (m, 2H), 7.39 (t, *J* = 7.63 Hz, 1H), 7.21 - 7.28 (m, 3H), 7.17 (d, *J* = 8.39 Hz, 2H), 6.30 (d, *J* = 9.30 Hz, 1H), 5.58 (d, *J* = 14.49 Hz, 1H), 5.22 (d, *J* = 14.95 Hz, 1H), 4.89 - 5.05 (m, 1H), 1.32 - 1.49 (m, 3H). LCMS : *m/z* 459 [M+H]⁺ r.t. 7.34 min. HRMS (ESI) calcd for C₂₂H₁₉ClF₃N₄O [M + H]⁺ 459.1194 found 459.1192;

2-[[[(1S)-1-(4-chlorophenyl)ethyl]amino]-8-(2,4-difluorobenzyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = 2,4-difluorobenzyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-Cl, R6b = H, R3 = R4 = R5= H] cpd 25



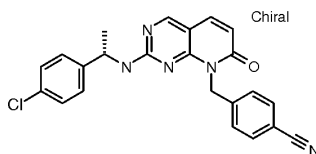
¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.57 - 8.73 (m, 1H), 8.49 (d, *J* = 7.63 Hz, 1H), 7.79 (d, *J* = 9.30 Hz, 1H), 7.31 - 7.42 (m, 1H), 7.13 - 7.28 (m, 4H), 6.53 - 7.00 (m, 2H), 6.30 (d, *J* = 9.46 Hz, 1H), 5.42 (d, *J* = 14.64 Hz, 1H), 5.20 (d, *J* = 14.95 Hz, 1H), 4.80 - 4.99 (m, 1H), 1.33 - 1.47 (m, 3H). LCMS : *m/z* 427 [M+H]⁺ r.t. 6.97 min. HRMS (ESI) calcd for C₂₂H₁₈ClF₂N₄O [M + H]⁺ 427.1132 found 427.1136;

2-[[[(1S)-1-(4-chlorophenyl)ethyl]amino]-8-[4-(trifluoromethoxy)benzyl]pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = 4-(trifluoromethoxy)benzyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-Cl, R6b = H, R3 = R4 = R5= H] cpd 26



¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.57 - 8.68 (m, 1H), 8.27 - 8.54 (m, 1H), 7.64 - 7.80 (m, 1H), 7.33 - 7.48 (m, 1H), 7.30 (d, *J* = 8.39 Hz, 2H), 7.21 - 7.25 (m, 2H), 7.08 - 7.19 (m, 3H), 6.28 (d, *J* = 9.30 Hz, 1H), 5.40 - 5.55 (m, 1H), 4.99 - 5.28 (m, 2H), 1.38 - 1.49 (m, 3H). LCMS : *m/z* 475 [M+H]⁺ r.t. 7.46 min. HRMS (ESI) calcd for C₂₂H₁₉ClF₃N₄O₂ [M + H]⁺ 475.1143 found 475.114;

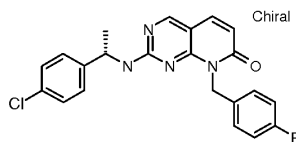
4-[[2-[[[(1S)-1-(4-chlorophenyl)ethyl]amino]-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl]methyl]benzonitrile [(I), X = N, R2 = 4-cyanobenzyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-Cl, R6b = H, R3 = R4 = R5= H] cpd 27



¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.65 (s, 1H), 8.51 (d, *J* = 7.32 Hz, 1H), 7.79 (d, *J* = 9.46 Hz, 1H), 7.62 (d, *J* = 8.08 Hz, 2H), 7.17 - 7.25 (m, 2H), 7.14 (d, *J* = 7.63 Hz, 4H), 6.29 (d, *J* = 9.30 Hz, 1H), 5.54 (d, *J* = 15.10 Hz, 1H), 5.20 (d, *J* = 15.10 Hz, 1H), 4.92 (quin, *J* = 7.28 Hz, 1H), 1.38 (d, *J* = 7.02 Hz, 3H).

LCMS : *m/z* 416 [M+H]⁺ r.t. 6.4 min. HRMS (ESI) calcd for C₂₃H₁₉ClN₄O [M + H]⁺ 416.1273 found 416.129;

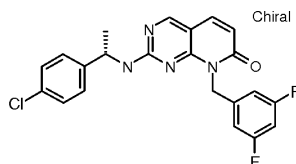
2-[[[(1S)-1-(4-chlorophenyl)ethyl]amino]-8-(4-fluorobenzyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = 4-fluorobenzyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-Cl, R6b = H, R3 = R4 = R5= H] cpd 28



¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.63 (s, 1H), 8.50 (d, *J* = 7.47 Hz, 1H), 7.75 (d, *J* = 9.30 Hz, 1H), 7.28 - 7.33 (m, 2H), 7.22 - 7.28 (m, 2H), 7.08 (dd, *J* = 5.80, 7.93 Hz, 2H), 6.95 (t, *J* = 8.85 Hz, 2H), 6.27 (d, *J* = 9.30 Hz, 1H), 5.42

(d, $J = 14.34$ Hz, 1H), 5.12 (d, $J = 14.18$ Hz, 1H), 5.04 (quin, $J = 6.98$ Hz, 1H), 1.43 (d, $J = 6.86$ Hz, 3H). LCMS : m/z 409 $[M+H]^+$ r.t. 6.4 min. HRMS (ESI) calcd for $C_{22}H_{19}ClFN_4O$ $[M + H]^+$ 409.1226 found 409.1228;

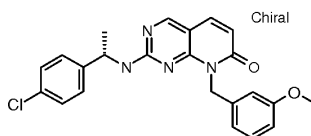
2-[[[(1S)-1-(4-chlorophenyl)ethyl]amino]-8-(3,5-difluorobenzyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = 3,5-difluorobenzyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-Cl, R6b = H, R3 = R4 = R5= H] cpd 29



5

^1H NMR (500 MHz, DMSO- d_6) δ = 8.65 (s, 1H), 8.53 (d, $J = 7.78$ Hz, 1H), 7.78 (d, $J = 9.30$ Hz, 1H), 7.25 (d, $J = 8.24$ Hz, 2H), 7.17 (d, $J = 8.39$ Hz, 2H), 7.05 (tt, $J = 2.30, 9.50$ Hz, 1H), 6.69 (d, $J = 6.71$ Hz, 2H), 6.29 (d, $J = 9.46$ Hz, 1H), 5.50 (d, $J = 14.79$ Hz, 1H), 5.16 (d, $J = 15.10$ Hz, 1H), 4.98 (quin, $J = 7.10$ Hz, 1H), 1.39 (d, $J = 7.02$ Hz, 3H). LCMS : m/z 427 $[M+H]^+$ r.t. 6.99 min. HRMS (ESI) calcd for $C_{22}H_{18}ClF_2N_4O$ $[M + H]^+$ 427.1132 found 427.1139;

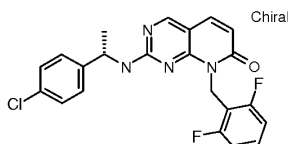
10 2-[[[(1S)-1-(4-chlorophenyl)ethyl]amino]-8-(3-methoxybenzyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = 3-methoxybenzyl A = phenyl, R1a= H, R1b = Me, R6a= 4-Cl, R6b = H, R3 = R4 = R5= H] cpd 30



15

^1H NMR (500 MHz, DMSO- d_6) δ = 8.56 - 8.69 (m, 1H), 8.47 (d, $J = 7.78$ Hz, 1H), 7.76 (d, $J = 9.46$ Hz, 1H), 7.24 - 7.30 (m, 2H), 7.20 (d, $J = 8.24$ Hz, 2H), 7.10 (t, $J = 7.85$ Hz, 1H), 6.79 (dd, $J = 2.13, 7.93$ Hz, 1H), 6.70 (br. s., 1H), 6.61 (d, $J = 7.47$ Hz, 1H), 6.29 (d, $J = 9.30$ Hz, 1H), 5.45 (d, $J = 14.34$ Hz, 1H), 5.16 (d, $J = 14.49$ Hz, 1H), 4.96 - 5.07 (m, 1H), 3.64 - 3.73 (m, 3H), 1.37 - 1.49 (m, 3H). LCMS : m/z 421 $[M+H]^+$ r.t. 6.79 min. HRMS (ESI) calcd for $C_{23}H_{22}ClN_4O_2$ $[M + H]^+$ 421.1426 found 421.1436;

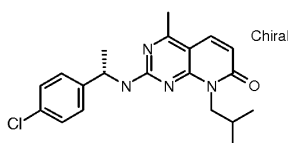
2-[[[(1S)-1-(4-chlorophenyl)ethyl]amino]-8-(2,6-difluorobenzyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = 2,6-difluorobenzyl A = phenyl, R1a= H, R1b = Me, R6a= 4-Cl, R6b = H, R3 = R4 = R5= H] cpd 31



20

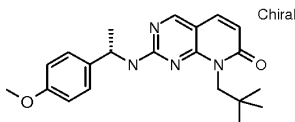
^1H NMR (500 MHz, DMSO- d_6) δ = 8.60 (s, 1H), 8.09 - 8.47 (m, $J = 8.08$ Hz, 1H), 7.74 (d, $J = 9.30$ Hz, 1H), 7.26 - 7.43 (m, 3H), 7.21 (d, $J = 8.24$ Hz, 2H), 6.87 - 7.05 (m, 2H), 6.24 (d, $J = 9.30$ Hz, 1H), 5.56 (d, $J = 14.95$ Hz, 1H), 5.30 (d, $J = 14.95$ Hz, 1H), 4.98 - 5.05 (m, 1H), 1.32 - 1.48 (m, 3H). LCMS : m/z 427 $[M+H]^+$ r.t. 6.84 min. HRMS (ESI) calcd for $C_{22}H_{18}ClF_2N_4O$ $[M + H]^+$ 427.1132 found 427.1135;

25 2-[[[(1S)-1-(4-chlorophenyl)ethyl]amino]-4-methyl-8-(2-methylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = 2-methylpropyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-Cl, R6b = H, R3 = Me, R4 = R5= H] cpd 32



¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.36 (d, *J* = 7.02 Hz, 1H), 7.87 (d, *J* = 9.61 Hz, 1H), 7.28 - 7.43 (m, 4H), 6.20 (d, *J* = 9.61 Hz, 1H), 4.98 (d, *J* = 10.83 Hz, 1H), 3.96 (dd, *J* = 7.40, 11.97 Hz, 1H), 3.79 - 3.87 (m, *J* = 11.74 Hz, 1H), 1.79 - 1.97 (m, 1H), 1.43 (d, *J* = 7.02 Hz, 3H), 1.23 (s, 3H), 0.73 (d, *J* = 6.86 Hz, 3H), 0.60 (d, *J* = 6.71 Hz, 3H). LCMS : *m/z* 371 [M+H]⁺ r.t. 7.11 min. HRMS (ESI) calcd for C₂₀H₂₄ClN₄O [M + H]⁺ 371.1633 found 371.1633;

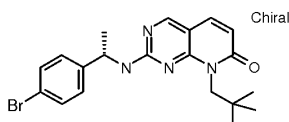
- 5 **8-(2,2-dimethylpropyl)-2-[[[(1*S*)-1-(4-methoxyphenyl)ethyl]amino]pyrido[2,3-*d*]pyrimidin-7(8*H*)-one [(I), X = N, R₂ = 2,2-dimethylpropyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-MeO, R_{6b} = H, R₃ = R₄ = R₅ = H] cpd 33**



- 10 ¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.52 - 8.57 (m, 1H), 8.32 (d, *J* = 7.63 Hz, 1H), 7.67 (d, *J* = 9.15 Hz, 1H), 7.29 (d, *J* = 8.54 Hz, 2H), 6.86 (d, *J* = 8.54 Hz, 2H), 6.22 (d, *J* = 9.30 Hz, 1H), 5.01 - 5.36 (dq, *J* = 7.6, 6.90, Hz, 1H), 3.87 - 4.44 (m, 2H), 3.70 (s, 3H), 1.44 (d, *J* = 7.02 Hz, 3H), 0.58 - 1.02 (m, 9H).

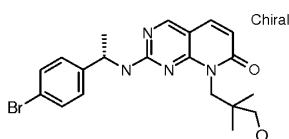
LCMS : *m/z* 367 [M+H]⁺ r.t. 6.6 min. HRMS (ESI) calcd for C₂₁H₂₇N₄O₂ [M + H]⁺ 367.2129 found 367.2132;

- 2-[[[(1*S*)-1-(4-bromophenyl)ethyl]amino]-8-(2,2-dimethylpropyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one [(I), X = N, R₂ = 2,2-dimethylpropyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-Br, R_{6b} = H, R₃ = R₄ = R₅ = H] cpd 34**



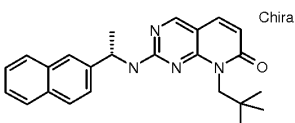
- 15 ¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.58 (s, 1H), 8.40 (d, *J* = 7.47 Hz, 1H), 7.68 (d, *J* = 9.30 Hz, 1H), 7.50 (d, *J* = 8.40 Hz, 2H), 7.34 (d, *J* = 8.39 Hz, 2H), 6.23 (d, *J* = 9.30 Hz, 1H), 5.04 (quin, *J* = 6.90 Hz, 1H), 3.96-4.25 (m, 2H), 1.45 (d, *J* = 7.02 Hz, 3H), 0.75 (br. s., 9H). LCMS : *m/z* 415 [M+H]⁺ r.t. 7.21 min. HRMS (ESI) calcd for C₂₀H₂₄BrN₄O [M + H]⁺ 415.1128 found 415.1135;

- 20 **2-[[[(1*S*)-1-(4-bromophenyl)ethyl]amino]-8-(3-hydroxy-2,2-dimethylpropyl)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one [(I), X = N, R₂ = 3-hydroxy-2,2-dimethylpropyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-Br, R_{6b} = H, R₃ = R₄ = R₅ = H] cpd 35**



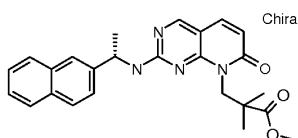
- 25 ¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.52 - 8.67 (m, 1H), 8.47 (d, *J* = 7.63 Hz, 1H), 7.72 (d, *J* = 9.30 Hz, 1H), 7.46 - 7.53 (m, 2H), 7.37 (d, *J* = 8.24 Hz, 2H), 6.26 (d, *J* = 9.15 Hz, 1H), 4.94 - 5.35 (m, *J* = 6.94, 6.94 Hz, 1H), 4.60 (br. s., 1H), 4.01 - 4.28 (m, 2H), 3.06 (br. s., 2H), 1.45 (d, *J* = 7.02 Hz, 3H), 0.62 (br. s., 6H). LCMS : *m/z* 431 [M+H]⁺ r.t. 6.25 min. HRMS (ESI) calcd for C₂₀H₂₄BrN₄O₂ [M + H]⁺ 431.1077 found 431.1085;

- 8-(2,2-dimethylpropyl)-2-[[[(1*S*)-1-(naphthalen-2-yl)ethyl]amino]pyrido[2,3-*d*]pyrimidin-7(8*H*)-one [(I), X = N, R₂ = 2,2-dimethylpropyl, A = 2-naphthalenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = R_{6b} = H, R₃ = R₄ = R₅ = H] cpd 36**



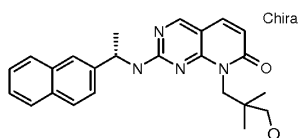
¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.59 (s, 1H), 8.49 (d, *J* = 7.47 Hz, 1H), 7.76 - 7.92 (m, 4H), 7.66 (d, *J* = 9.30 Hz, 1H), 7.58 (dd, *J* = 1.45, 8.46 Hz, 1H), 7.41 - 7.48 (m, 2H), 6.20 (d, *J* = 9.30 Hz, 1H), 5.25 (quin, *J* = 7.32 Hz, 1H), 3.90 - 4.36 (m, 2H), 1.56 (d, *J* = 7.02 Hz, 3H), 0.50 - 1.04 (m, 9H). LCMS : *m/z* 387 [M+H]⁺ r.t. 7.27 min. HRMS (ESI) calcd for C₂₄H₂₇N₄O [M + H]⁺ 387.218 found 387.2178;

- 5 **methyl 2,2-dimethyl-3-[2-[[[(1S)-1-(naphthalen-2-yl)ethyl]amino]-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl]propanoate [(I), X = N, R₂ = methyl-2,2-dimethyl-3-propanoate, A = 2-naphthalenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = R_{6b} = H, R₃ = R₄ = R₅ = H] cpd 37**



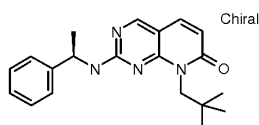
- ¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.60 (s, 1H), 8.55 (d, *J* = 7.47 Hz, 1H), 7.80 - 7.92 (m, 4H), 7.68 (d, *J* = 9.30 Hz, 1H), 7.58 (dd, *J* = 1.45, 8.46 Hz, 1H), 7.38 - 7.50 (m, 2H), 6.18 (d, *J* = 9.30 Hz, 1H), 5.12 - 5.32 (m, *J* = 7.17 Hz, 1H), 4.21 - 4.28 (m, 2H), 3.42 (s, 3H), 1.56 (d, *J* = 7.02 Hz, 3H), 1.07 - 1.11 (m, 3H), 0.83 (s, 3H). LCMS : *m/z* 431 [M+H]⁺ r.t. 6.63 min. HRMS (ESI) calcd for C₂₅H₂₇N₄O₃ [M + H]⁺ 431.2078 found 431.2076;

- 8-(3-hydroxy-2,2-dimethylpropyl)-2-[[[(1S)-1-(naphthalen-2-yl)ethyl]amino]pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = 3-hydroxy-2,2-dimethyl-propyl, A = 2-naphthalenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = R_{6b} = H, R₃ = R₄ = R₅ = H] cpd 38**



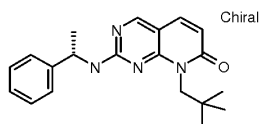
- ¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.61 (s, 1H), 8.55 (d, *J* = 7.32 Hz, 1H), 7.79 - 7.92 (m, 4H), 7.71 (d, *J* = 9.30 Hz, 1H), 7.60 (d, *J* = 8.54 Hz, 1H), 7.37 - 7.52 (m, 2H), 6.23 (d, *J* = 9.30 Hz, 1H), 5.08 - 5.47 (m, *J* = 7.32, 7.32 Hz, 1H), 4.50 - 4.69 (m, 1H), 3.96 - 4.40 (m, 2H), 3.00 - 3.16 (m, 2H), 1.56 (s, 3H), 0.80-0.86 (m, 3H), 0.68-0.74 (m, 3H). LCMS : *m/z* 403 [M+H]⁺ r.t. 6.34 min. HRMS (ESI) calcd for C₂₄H₂₇N₄O₂ [M + H]⁺ 403.2129 found 403.214;

- 8-(2,2-dimethylpropyl)-2-[[[(1R)-1-phenylethyl]amino]pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = 2,2-dimethyl-propyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = R_{6b} = H, R₃ = R₄ = R₅ = H] cpd 39**



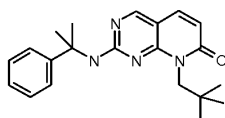
- ¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.50 - 8.60 (m, 1H), 8.05 - 8.43 (m, 1H), 7.67 (d, *J* = 9.30 Hz, 1H), 7.36 - 7.42 (m, 2H), 7.26 - 7.33 (m, 2H), 7.15 - 7.22 (m, 1H), 6.22 (d, *J* = 9.30 Hz, 1H), 5.01 - 5.30 (m, 1H), 3.79 - 4.33 (m, 2H), 1.46 (d, *J* = 7.02 Hz, 3H), 0.66 - 0.99 (m, 9H). LCMS : *m/z* 337 [M+H]⁺ r.t. 6.73 min. HRMS (ESI) calcd for C₂₀H₂₅N₄O [M + H]⁺ 337.2023 found 337.2025;

- 8-(2,2-dimethylpropyl)-2-[[[(1S)-1-phenylethyl]amino]pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = 2,2-dimethyl-propyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = R_{6b} = H, R₃ = R₄ = R₅ = H] cpd 40**



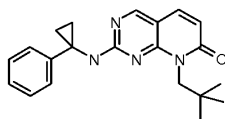
- ¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.57 (s, 1H), 8.39 (d, *J* = 7.63 Hz, 1H), 7.67 (d, *J* = 9.15 Hz, 1H), 7.38 (d, *J* = 7.63 Hz, 2H), 7.30 (t, *J* = 7.55 Hz, 2H), 7.16 - 7.21 (m, 1H), 6.22 (d, *J* = 9.30 Hz, 1H), 5.08 (t, *J* = 7.09 Hz, 1H), 3.98-4.28 (m, 2H), 1.46 (d, *J* = 7.02 Hz, 3H), 0.77 (br. s., 9H). LCMS : *m/z* 337 [M+H]⁺ r.t. 6.73 min. HRMS (ESI) calcd for C₂₀H₂₅N₄O [M + H]⁺ 337.2023 found 337.2024;

8-(2,2-dimethylpropyl)-2-[(2-phenylpropan-2-yl)amino]pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = 2,2-dimethyl-propyl, A = phenyl, R_{1a}= R_{1b} = Me, R_{6a}= R_{6b} = H, R₃ = R₄ = R₅= H] cpd 41



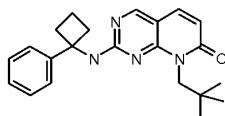
- ¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.57 (br. s., 1H), 8.15 (br. s., 1H), 7.64 (d, *J* = 8.85 Hz, 1H), 7.38 (d, *J* = 6.71 Hz, 2H), 7.25 (t, *J* = 7.63 Hz, 2H), 7.11 - 7.16 (m, 1H), 6.20 (d, *J* = 9.30 Hz, 1H), 3.73 (br. s., 2H), 1.71 (s, 6H), 0.54 (br. s., 9H). LCMS : *m/z* 351 [M+H]⁺ r.t. 7.02 min. HRMS (ESI) calcd for C₂₁H₂₇N₄O [M + H]⁺ 351.218 found 351.2176;

8-(2,2-dimethylpropyl)-2-[(1-phenylcyclopropyl)amino]pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = 2,2-dimethyl-propyl, A = phenyl, R_{1a}- R_{1b} = cyclopropyl, R_{6a}= R_{6b} = H, R₃ = R₄ = R₅= H] cpd 42



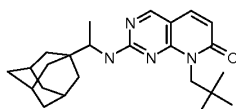
- ¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.64 (s, 1H), 8.60 (s, 1H), 7.68 - 7.72 (m, 1H), 7.22 (d, *J* = 7.32 Hz, 2H), 7.16 - 7.19 (m, 2H), 7.06 - 7.13 (m, 1H), 6.25 (d, *J* = 9.30 Hz, 1H), 3.87 - 4.29 (m, 2H), 1.23-1.38 (m, 2H), 0.90-0.95 (m, 2H), 0.61 (s, 9H). LCMS : *m/z* 349 [M+H]⁺ r.t. 6.71 min. HRMS (ESI) calcd for C₂₁H₂₅N₄O [M + H]⁺ 349.2023 found 349.2021;

- 8-(2,2-dimethylpropyl)-2-[(1-phenylcyclobutyl)amino]pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = 2,2-dimethyl-propyl, A = phenyl, R_{1a}- R_{1b} = cyclobutyl, R_{6a}= R_{6b} = H, R₃ = R₄ = R₅= H] cpd 43**



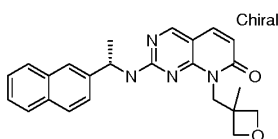
- ¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.69 (s, 1H), 8.58 (s, 1H), 7.65 (d, *J* = 9.00 Hz, 1H), 7.45 - 7.52 (m, 2H), 7.29 (t, *J* = 8.01 Hz, 2H), 7.10 - 7.18 (m, 1H), 6.20 (d, *J* = 9.30 Hz, 1H), 3.88 (br. s., 2H), 1.90 - 2.13 (m, 4H), 0.9-0.94 (m, 2H), 0.57 (s, 9H). LCMS : *m/z* 363 [M+H]⁺ r.t. 7.16 min. HRMS (ESI) calcd for C₂₂H₂₇N₄O [M + H]⁺ 363.218 found 363.2187;

8-(2,2-dimethylpropyl)-2-[[1-(tricyclo[3.3.1.1.3.7]dec-1-yl)ethyl]amino]pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = 2,2-dimethyl-propyl, A = adamantanyl, R_{1a}= H, R_{1b} = Me, R_{6a}= R_{6b} = H, R₃ = R₄ = R₅= H] cpd 44



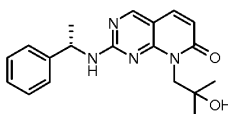
¹H NMR (500 MHz, DMSO- *d*₆) δ 8.53 (s, 1H), 7.57 - 7.72 (m, 1H), 7.17 - 7.56 (m, 1H), 6.07 - 6.29 (m, 1H), 4.20 (br. s., 2H), 3.84 - 4.05 (m, 1H), 1.94 (br. s., 3H), 1.39 - 1.71 (m, 12H), 1.05 (d, *J* = 6.86 Hz, 3H), 0.86 - 0.96 (m, 9H). LCMS : *m/z* 395 [M+H]⁺ r.t. 8.81 min. HRMS (ESI) calcd for C₂₄H₃₄N₄O [M + H]⁺ 395.2806 found 395.2813;

- 5 **8-[(3-methyloxetan-3-yl)methyl]-2-[[1S)-1-(naphthalen-2-yl)ethyl]amino]pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = (3-methyloxetan-3-yl)methyl, A = 2-naphthalenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = R_{6b} = H, R₃ = R₄ = R₅ = H] cpd 45**



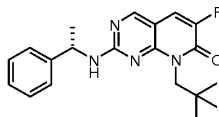
- 10 ¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.65 (s, 1H), 8.60 (d, *J* = 7.02 Hz, 1H), 7.78 - 7.91 (m, 3H), 7.74 (d, *J* = 9.30 Hz, 1H), 7.54 (d, *J* = 8.39 Hz, 1H), 7.39 - 7.52 (m, 3H), 6.23 (d, *J* = 9.30 Hz, 1H), 4.99 - 5.46 (m, *J* = 6.63, Hz, 1H), 4.66-4.69 (m, 1H), 4.56 (d, *J* = 5.80 Hz, 1H), 4.38 (d, *J* = 6.10 Hz, 1H), 4.35 (d, *J* = 5.80 Hz, 1H), 4.19-4.25 (m, 1H), 4.03-4.12 (m, 1H), 1.49 - 1.62 (m, 3H), 1.20 - 1.43 (m, 3H). LCMS : *m/z* 401 [M+H]⁺ r.t. 6.0 min. HRMS (ESI) calcd for C₂₄H₂₅N₄O₂ [M + H]⁺ 401.1972 found 401.1973;

- 15 **8-(2-Hydroxy-2-methyl-propyl)-2-[(S)-1-phenyl-ethylamino]-8H-pyrido[2,3-d]pyrimidin-7-one [(I), X = N, R₂ = 2-Hydroxy-2-methyl-propyl, A = Phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = R_{6b} = H, R₃ = R₄ = R₅ = H] cpd 46**



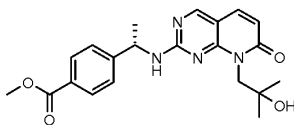
- 20 ¹H NMR (500MHz ,DMSO-*d*₆) δ = 8.63 (s, 1 H), 8.51 (d, *J* = 7.8 Hz, 1 H), 7.74 (d, *J* = 9.3 Hz, 1 H), 7.41 - 7.37 (m, 2 H), 7.30 (t, *J* = 7.6 Hz, 2 H), 7.23 - 7.14 (m, 1 H), 6.28 (d, *J* = 9.3 Hz, 1 H), 5.05 (quin, *J* = 7.2 Hz, 1 H), 4.58 (s, 1 H), 4.29 (d, *J* = 13.3 Hz, 1 H), 4.17 (d, *J* = 13.3 Hz, 1 H), 1.46 (d, *J* = 7.3 Hz, 3 H), 1.04 (s, 3 H), 0.86 (br. s., 3 H). LCMS : *m/z* 339 [M+H]⁺ @ r.t. 5.45 min. HRMS (ESI) calcd for C₁₉H₂₂N₄O₂ [M +H]⁺ 339.1816 found 339.1812;

8-(2,2-Dimethyl-propyl)-6-fluoro-2-[(S)-1-phenyl-ethylamino]-8H-pyrido[2,3-d]pyrimidin-7-one [(I), X = N, R₂ = 2,2-Dimethyl-propyl, A = Phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = R_{6b} = H, R₃ = R₄ = H, R₅ = F] cpd 47



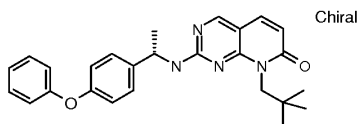
- 25 ¹H NMR (500MHz ,DMSO-*d*₆) δ = 8.58 (s, 1 H), 8.39 (d, *J* = 7.3 Hz, 1 H), 7.69 (d, *J* = 9.5 Hz, 1 H), 7.38 (d, *J* = 7.5 Hz, 2 H), 7.30 (t, *J* = 7.5 Hz, 2 H), 7.24 - 7.13 (m, 1 H), 5.06 (quin, *J* = 6.9 Hz, 1 H), 5.31 - 4.95 (m, 1 H), 4.33 - 4.02 (m, 2 H), 1.46 (d, *J* = 7.0 Hz, 3 H), 0.78 (br. s., 9 H). LCMS : *m/z* 355 [M+H]⁺ @ r.t. 7.10 min. HRMS (ESI) calcd for C₂₀H₂₃FN₄O [M +H]⁺ 355.1929 found 355.1926;

4-((S)-1-[8-(2-Hydroxy-2-methyl-propyl)-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino]-ethyl)-benzoic acid methyl ester [(I), X = N, R2 = 2-Hydroxy-2-methyl-propyl, A = Phenyl, R1a= H, R1b = Me, R6a= -COOMe, R6b = H, R3 = R4 = R5= H] cpd 48



- 5 ¹H NMR (500MHz, DMSO-*d*₆) δ = 8.64 (s, 1 H), 8.57 (d, *J* = 7.2 Hz, 1 H), 7.95 - 7.86 (m, 2 H), 7.74 (d, *J* = 9.2 Hz, 1 H), 7.54 (d, *J* = 7.9 Hz, 2 H), 6.28 (d, *J* = 9.3 Hz, 1 H), 5.11 (quin, *J* = 6.9 Hz, 1 H), 4.55 (s, 1 H), 4.25 (d, *J* = 13.1 Hz, 1 H), 4.11 (d, *J* = 13.1 Hz, 1 H), 3.82 (s, 3 H), 1.48 (d, *J* = 7.0 Hz, 3 H), 1.01 (s, 3 H), 0.83 (br. s., 3 H). LCMS : *m/z* 397 [M+H]⁺ @ r.t. 5.32 min. HRMS (ESI) calcd for C₂₁H₂₄N₄O₄ [M + H]⁺ 397.1871 found 397.1868;

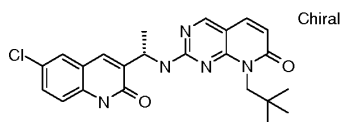
- 10 8-(2,2-dimethylpropyl)-2-[[[(1S)-1-(4-phenoxyphenyl)ethyl]amino]pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = 2,2-dimethylpropyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-phenoxy, R6b = H, R3 = R4 = R5= H] cpd 49



- ¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.58 (s, 1H), 8.38 (d, *J* = 7.47 Hz, 1H), 7.68 (d, *J* = 9.30Hz, 1H), 7.33 - 7.41 (m, 4H), 7.10 (t, *J* = 7.32 Hz, 1H), 6.95 (t, *J* = 7.78 Hz, 4H), 6.24 (d, *J* = 9.30 Hz, 1H), 5.91 (m, 1H), 4.00-4.10 (m, 2H), 1.47 (d, *J* = 7.02 Hz, 3H), 0.90-0.94 (m, 6H), 0.74-0.81 (m, 3H). LCMS : *m/z* 429 [M+H]⁺ r.t. 7.66 min. HRMS (ESI) calcd for C₂₆H₂₉N₄O₂ [M + H]⁺ 429.2285 found 429.2289.

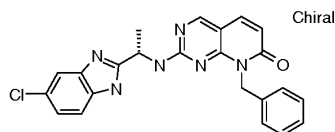
Example 2

Preparation of 2-[[[(1S)-1-(6-chloro-2-oxo-quinolin-3-yl)ethyl]amino]-8-(2,2-dimethylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = 2,2-dimethylpropyl, A = 2-oxo-quinolin-3-yl, R1a= H, R1b = Me, R6a= 6-chloro, R6b = H, R3 = R4 = R5= H] step 1a cpd 50



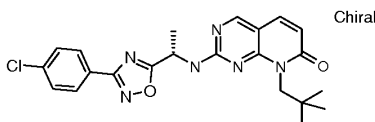
- 20 To a solution of compound 8-(2,2-dimethylpropyl)-2-(methylsulfonyl)pyrido[2,3-d]pyrimidin-7(8H)-one (50 mg, 0.17 mmol) in ACN (1 mL) and DIPEA (123 μL, 0.68 mM) was added 3-[(1S)-1-aminoethyl]-6-chloroquinolin-2(1H)-one hydrochloride (prepared as reported in WO2016171755) (65 mg, 0.255 mmol). The reaction was heated to 90°C for 4 hours. The reaction mixture was diluted with EtOAc (4 mL) and washed with water (5 mL) and brine (5 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated. The crude material was purified on silica gel column chromatography (DCM/EtOAc/EtOH 7/2/1) provided the title compound as a off-white solid (44 mg,60% yield).
- 25 ¹H NMR (500 MHz, DMSO- *d*₆) δ = 12.05 (s, 1H), 8.61 (s, 1H), 8.35 (d, *J* = 7.17 Hz, 1H), 7.61 - 7.75 (m, 3H), 7.46 (dd, *J* = 8.77, 2.21, Hz, 1H), 7.30 (d, *J* = 8.85 Hz, 1H), 6.23 (d, *J* = 9.30 Hz, 1H), 5.26 (quin, *J* = 6.94 Hz, 1H), 3.82 - 4.42 (m, 2H), 1.43 (d, *J* = 6.86 Hz, 3H), 0.52 - 1.02 (m, 9H). LCMS : *m/z* 438 [M+H]⁺ r.t. 5.88 min. HRMS (ESI) calcd for C₂₃H₂₅ClN₅O₂ [M + H]⁺ 438.1692 found 438.1692.
- 30 According to the same method, the following compounds were prepared:

8-benzyl-2-(((1S)-1-(5-chloro-1H-benzimidazol-2-yl)ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = benzyl, A = 1H-benzimidazol-2-yl, R1a= H, R1b = Me, R6a= 5-chloro, R6b = H, R3 = R4 = R5= H] cpd 51



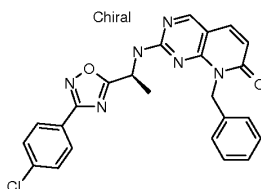
¹H NMR (500 MHz, DMSO- *d*₆) δ = 12.09 - 12.60 (m, 1H), 8.59 - 8.74 (m, 1H), 8.40 (d, *J* = 7.32 Hz, 1H), 7.78 (d, *J* = 9.46 Hz, 1H), 7.58 (s, 1H), 7.54 (d, *J* = 8.54 Hz, 1H), 7.12 - 7.18 (m, 1H), 7.09 (d, *J* = 7.32 Hz, 2H), 6.86 - 7.05 (m, 3H), 6.31 (d, *J* = 9.30 Hz, 1H), 5.28 - 5.51 (m, 2H), 5.08 - 5.16 (m, 1H), 1.55 - 1.65 (m, 3H). LCMS : *m/z* 431 [M+H]⁺ r.t. 5.57 min. HRMS (ESI) calcd for C₂₃H₂₀ClN₆O [M + H]⁺ 431.1382 found 431.139;

2-(((1S)-1-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl]ethyl)amino)-8-(2,2-dimethylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = 2,2-dimethylpropyl, A = 1,2,4-oxadiazol-5-yl, R1a= H, R1b = Me, R6a= 3-(4-chlorophenyl), R6b = H, R3 = R4 = R5= H] cpd 52



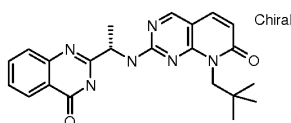
¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.51 - 8.71 (m, 2H), 7.93 - 8.01 (m, 2H), 7.74 (d, *J* = 9.46 Hz, 1H), 7.63 (d, *J* = 8.54 Hz, 2H), 6.30 (d, *J* = 9.30 Hz, 1H), 5.31 - 5.59 (m, *J* = 7.17 Hz, 1H), 3.85 - 4.35 (m, 3H), 1.69 (d, *J* = 7.17 Hz, 3H), 1.59 (m, 9H). LCMS : *m/z* 439 [M+H]⁺ r.t. 7.23 min. HRMS (ESI) calcd for C₂₂H₂₄ClN₆O₂ [M + H]⁺ 439.1644 found 439.164;

8-benzyl-2-(((1S)-1-[3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl]ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = benzyl, A = 1,2,4-oxadiazol-5-yl, R1a= H, R1b = Me, R6a= 3-(4-chlorophenyl), R6b = H, R3 = R4 = R5= H] cpd 53



¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.72 (s, 1H), 8.69 (d, *J* = 6.84 Hz, 1H), 7.91 (d, *J* = 8.54 Hz, 2H), 7.81 (d, *J* = 9.28 Hz, 1H), 7.61 (d, *J* = 8.54 Hz, 2H), 6.96 - 7.17 (m, 5H), 6.35 (d, *J* = 9.15 Hz, 1H), 5.39 (quin, *J* = 7.00 Hz, 1H), 5.36 (d, *J* = 13.79 Hz, 1H), 5.15 (d, *J* = 14.28 Hz, 1H), 1.63 (d, *J* = 7.08 Hz, 3H). LCMS : *m/z* 459 [M+H]⁺ r.t. 6.97 min. HRMS (ESI) calcd for C₂₄H₂₀ClN₆O₂ [M + H]⁺ 459.1331 found 459.1336;

8-(2,2-dimethylpropyl)-2-(((1S)-1-(4-oxo-3,4-dihydroquinazolin-2-yl)ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = 2,2-dimethylpropyl, A = 4-oxo-3,4-dihydroquinazolin-2-yl, R1a= H, R1b = Me, R6a= R6b = H, R3 = R4 = R5= H] cpd 54

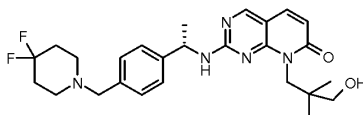


¹H NMR (500 MHz, DMSO- *d*₆) δ = 12.37 (br. s., 1H), 8.64 (s, 1H), 8.00 - 8.12 (m, 2H), 7.64 - 7.79 (m, 2H), 7.56 (d, *J* = 8.24 Hz, 1H), 7.42 - 7.53 (m, 2H), 6.25 (d, *J* = 9.30 Hz, 1H), 4.91 (t, *J* = 6.79 Hz, 1H), 3.90 - 4.07 (m, 1H), 1.56 (d, *J* = 7.02 Hz, 3H), 0.70 (br. s., 9H). LCMS : *m/z* 405 [M+H]⁺ r.t. 5.17 min. HRMS (ESI) calcd for C₂₂H₂₅N₆O₂ [M + H]⁺ 405.2034 found 405.2041.

5

Example 3

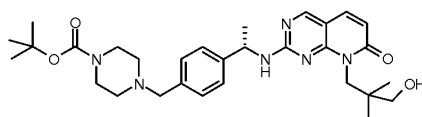
Step 8: 2-[(S)-1-[4-(4,4-Difluoro-piperidin-1-ylmethyl)-phenyl]-ethylamino]-8-(3-hydroxy-2,2-dimethyl-propyl)-8H-pyrido[2,3-d]pyrimidin-7-one [(I), X = N, R₂ = 3-hydroxy-2,2-dimethylpropyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = 4,4-difluoropiperidin-1-yl, R₃ = R₄ = R₅ = H] step 1a, cpd 55



- 10 (S)-1-[4-(4,4-difluoro-piperidin-1-ylmethyl)-phenyl]-ethylamine (prepared as reported in WO2017019429) 13.5 mg, 0.053 mmol) was dissolved in DMSO (0.5 mL). To this solution is then sequentially added 8-(3-hydroxy-2,2-dimethyl-propyl)-2-methanesulfonyl-8H-pyrido[2,3-d]pyrimidin-7-one (15 mg, 0.048 mmol), CsF (8.0 mg, 0.053 mmol) and DIPEA (0.01 mL, 0.058 mmol). The reaction mixture is then heated at 75 °C for 4 hours and then allowed to warm to room temperature. The reaction mixture is slowly poured over cold water/brine. The precipitated solids are filtered,
- 15 washed with water, and dried under vacuum. The dried solid obtained (16.1 mg, 69% yield) is taken forward without further purification.

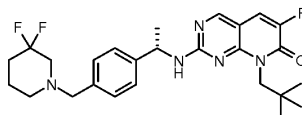
- ¹H NMR (500MHz, DMSO-*d*₆) δ = 8.60 (s, 1H), 8.43 (d, *J* = 7.5 Hz, 1H), 7.72 (d, *J* = 9.3 Hz, 1H), 7.36 (d, *J* = 7.6 Hz, 2H), 7.23 (d, *J* = 7.8 Hz, 2H), 6.25 (d, *J* = 9.2 Hz, 1H), 5.11 (quin, *J* = 6.7 Hz, 1H), 4.56 (br. s., 1H), 4.35 - 3.88 (m, 2H), 3.48 (s, 2H), 3.04 (br. s., 2H), 2.43 (br. s., 4H), 1.91 (t, *J* = 13.3 Hz, 4H), 1.46 (d, *J* = 7.0 Hz, 3H), 1.04 - 0.31 (m, 6H). LCMS : *m/z* 486 [M+H]⁺ @ r.t. 6.22 min. HRMS (ESI) calcd for C₂₆H₃₄F₂N₅O₂ [M + H]⁺ 486.2675 found 486.2670.
- 20 According to the same method, the following compounds were prepared:

- 4-[(S)-1-[8-(3-Hydroxy-2,2-dimethyl-propyl)-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino]-ethyl]-benzyl)-piperazine-1-carboxylic acid tert-butyl ester [(I), X = N, R₂ = 3-hydroxy-2,2-dimethylpropyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = 4-piperazine-1-carboxylic acid tert-butyl ester, R₃ = R₄ = R₅ = H] cpd 56**
- 25

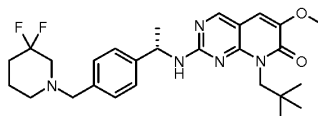


- ¹H NMR (500MHz, DMSO-*d*₆) δ = 8.60 (s, 1H), 8.43 (d, *J* = 7.3 Hz, 1H), 7.72 (d, *J* = 9.3 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 2H), 7.22 (d, *J* = 7.8 Hz, 2H), 6.25 (d, *J* = 9.3 Hz, 1H), 5.11 (quin, *J* = 7.2 Hz, 1H), 4.57 (br. s., 1H), 4.37 - 3.89 (m, 2H), 3.41 (s, 2H), 3.27 (br. s., 4H), 3.04 (br. s., 2H), 2.26 (br. s., 4H), 1.46 (d, *J* = 6.9 Hz, 3H), 1.37 (s, 9H), 0.70 (br. s., 6H). LCMS : *m/z* 551 [M+H]⁺ @ r.t. 6.42 min. HRMS (ESI) calcd for C₃₀H₄₃N₆O₄ [M + H]⁺ 551.3341 found 551.3344;
- 30

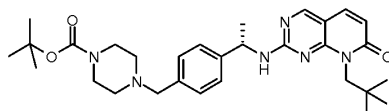
2-[(S)-1-[4-(3,3-Difluoro-piperidin-1-ylmethyl)-phenyl]-ethylamino]-8-(2,2-dimethyl-propyl)-6-fluoro-8H-pyrido[2,3-d]pyrimidin-7-one [(I), X = N, R₂ = 2,2-dimethylpropyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = F, R₇-R₈ = 3,3-difluoropiperidin-1-yl, R₃ = R₄ = H, R₅ = F] cpd 57



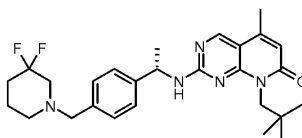
- ¹H NMR (500MHz, DMSO-d₆) δ = 8.58 (s, 1H), 8.37 (d, *J* = 7.2 Hz, 1H), 7.69 (d, *J* = 9.3 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.26 - 7.11 (m, 2H), 5.04 (quin, *J* = 7.0 Hz, 1H), 4.39 - 3.88 (m, 2H), 3.59 - 3.44 (m, 2H), 2.60 - 2.52 (m, 2H), 2.36 (br. s., 2H), 1.83 (qd, *J* = 7.0, 13.5 Hz, 2H), 1.62 (quin, *J* = 5.9 Hz, 2H), 1.46 (d, *J* = 7.0 Hz, 3H), 0.72 (br. s., 9H). LCMS : *m/z* 488 [M+H]⁺ @ r.t. 7.55 min. HRMS (ESI) calcd for C₂₆H₃₃F₃N₅O [M + H]⁺ 488.2632 found 488.2637;
- 5 **2-((S)-1-[4-(3,3-Difluoro-piperidin-1-ylmethyl)-phenyl]-ethylamino)-8-(2,2-dimethyl-propyl)-6-methoxy-8H-pyrido[2,3-d]pyrimidin-7-one [(I), X = N, R₂ = 2,2-dimethylpropyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = 3,3-difluoropiperidin-1-yl, R₃ = R₄ = H, R₅ = OMe] cpd 58**



- ¹H NMR (500MHz, DMSO-d₆) δ = 8.50 (br. s., 1H), 8.01 (br. s., 1H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.20 (d, *J* = 8.1 Hz, 2H), 7.07 (s, 1H), 5.01 (br. s., 1H), 4.38 - 3.95 (m, 2H), 3.73 (s, 3H), 3.50 (d, *J* = 2.0 Hz, 2H), 2.57 - 2.43 (m, 4H), 1.90 - 1.76 (m, 2H), 1.67 - 1.57 (m, 2H), 1.44 (d, *J* = 7.0 Hz, 3H), 0.70 (br. s., 9H).
- LCMS : *m/z* 500 [M+H]⁺ @ r.t. 7.21 min. HRMS (ESI) calcd for C₂₇H₃₆F₂N₅O₂ [M + H]⁺ 500.2832 found 500.2827;
- 10 **4-(4-((S)-1-[8-(2,2-Dimethyl-propyl)-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino]-ethyl)-benzyl)-piperazine-1-carboxylic acid tert-butyl ester [(I), X = N, R₂ = 2,2-dimethylpropyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = 4-piperazine-1-carboxylic acid tert-butyl ester, R₃ = R₄ = R₅ = H] cpd 59**



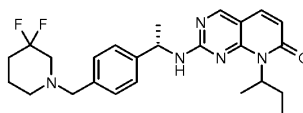
- ¹H NMR (500MHz, DMSO-d₆) δ = 8.57 (s, 1H), 8.36 (d, *J* = 7.5 Hz, 1H), 7.67 (d, *J* = 9.3 Hz, 1H), 7.32 (d, *J* = 7.9 Hz, 2H), 7.22 (d, *J* = 7.9 Hz, 2H), 6.22 (d, *J* = 9.3 Hz, 1H), 5.06 (quin, *J* = 7.0 Hz, 1H), 4.34 - 3.89 (m, 2H), 3.42 (s, 2H), 3.27 (br. s., 4H), 2.26 (br. s., 4H), 1.45 (d, *J* = 7.0 Hz, 3H), 1.37 (s, 9H), 0.73 (br. s., 9H). LCMS : *m/z* 535 [M+H]⁺ @ r.t. 7.43 min. HRMS (ESI) calcd for C₃₀H₄₃N₆O₃ [M + H]⁺ 535.3391 found 535.3387;
- 20 **2-((S)-1-[4-(3,3-Difluoro-piperidin-1-ylmethyl)-phenyl]-ethylamino)-8-(2,2-dimethyl-propyl)-5-methyl-8H-pyrido[2,3-d]pyrimidin-7-one [(I), X = N, R₂ = 2,2-dimethylpropyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = 3,3-difluoropiperidin-1-yl, R₃ = R₅ = H, R₄ = Me] cpd 60**



¹H NMR (500MHz, DMSO-d₆) δ = 8.64 (s, 1H), 8.32 (d, *J* = 7.3 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 6.09 (s, 1H), 5.05 (quin, *J* = 7.0 Hz, 1H), 4.27 - 3.86 (m, 4H), 3.56 - 3.44 (m, 2H), 2.61 - 2.52 (m, 2H), 2.32 (s,

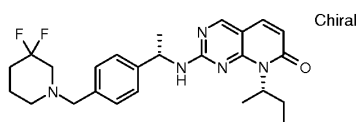
3H), 1.84 (tt, $J = 6.9, 13.6$ Hz, 2H), 1.61 (quin, $J = 5.9$ Hz, 2H), 1.46 (d, $J = 7.2$ Hz, 3H), 1.01 - 0.47 (m, 9H). LCMS : m/z 484 $[M+H]^+$ @ r.t. 7.48 min. HRMS (ESI) calcd for $C_{27}H_{36}F_2N_5O$ $[M+H]^+$ 484.2883 found 484.2874;

8-(butan-2-yl)-2-[[[(1S)-1-{4-[(3,3-difluoropiperidin-1-yl)methyl]phenyl}ethyl]amino]pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = -butan-2-yl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = 3,3-difluoropiperidin-1-yl, R₃ = R₄ = R₅ = H] cpd 61



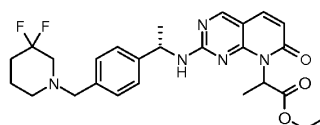
¹H NMR (500MHz, DMSO- d_6) δ = 8.56 (br. s., 1H), 8.08 - 8.43 (m, 1H), 7.58 - 7.73 (m, 1H), 7.30 (br. s., 2H), 7.16 - 7.25 (m, 2H), 6.17 (br. s., 1H), 4.83 - 5.46 (m, 2H), 3.44 - 3.55 (m, 2H), 2.53 - 2.61 (m, 2H), 2.30 - 2.41 (m, 2H), 1.74 - 1.93 (m, $J = 6.79, 13.46, 13.46$ Hz, 2H), 1.56 - 1.71 (m, 2H), 1.38 - 1.56 (m, 8H), 0.30 - 1.21 (m, 3H). LCMS : m/z 456 $[M+H]^+$ @ r.t. 7.04 min. HRMS (ESI) calcd for $C_{25}H_{32}F_2N_5O$ $[M+H]^+$ 456.257 found 456.2567;

8-[(2S)-butan-2-yl]-2-[[[(1S)-1-{4-[(3,3-difluoropiperidin-1-yl)methyl]phenyl}ethyl]amino]pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = -(2S)-butan-2-yl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = 3,3-difluoropiperidin-1-yl, R₃ = R₄ = R₅ = H] cpd 62



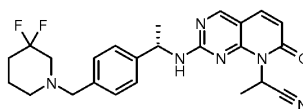
¹H NMR (500MHz, DMSO- d_6) δ = 8.56 (br. s., 1H), 8.08 - 8.43 (m, 1H), 7.58 - 7.73 (m, 1H), 7.30 (br. s., 2H), 7.16 - 7.25 (m, 2H), 6.17 (br. s., 1H), 4.83 - 5.46 (m, 2H), 3.44 - 3.55 (m, 2H), 2.53 - 2.61 (m, 2H), 2.30 - 2.41 (m, 2H), 1.74 - 1.93 (m, $J = 6.79, 13.46, 13.46$ Hz, 2H), 1.56 - 1.71 (m, 2H), 1.38 - 1.56 (m, 8H), 0.30 - 1.21 (m, 3H). LCMS : m/z 456 $[M+H]^+$ @ r.t. 7.03 min. HRMS (ESI) calcd for $C_{25}H_{32}F_2N_5O$ $[M+H]^+$ 456.257 found 456.2574;

ethyl 2-[2-[[[(1S)-1-{4-[(3,3-difluoropiperidin-1-yl)methyl]phenyl}ethyl]amino]-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl]propanoate [(I), X = N, R₂ = ethyl-2-propanoate, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = 3,3-difluoropiperidin-1-yl, R₃ = R₄ = R₅ = H] cpd 63



¹H NMR (500MHz, DMSO- d_6) δ = 8.59 - 8.65 (m, 1H), 8.45 - 8.57 (m, 1H), 7.73 (d, $J = 9.30$ Hz, 1H), 7.36 (dd, $J = 3.36, 7.93$ Hz, 2H), 7.16 - 7.26 (m, 2H), 6.24 (d, $J = 13.95$ Hz, 1H), 5.66 - 5.90 (m, 1H), 4.89 - 5.13 (m, 1H), 3.96 - 4.06 (m, 2H), 3.46 - 3.56 (m, 4H), 2.32-2.39 (m, 2H), 1.77 - 1.92 (m, 2H), 1.61 (br. s., 2H), 1.38 - 1.54 (m, 3H), 1.17 (d, $J = 7.17$ Hz, 3H), 1.03 (t, $J = 7.09$ Hz, 3H). LCMS : m/z 500 $[M+H]^+$ @ r.t. 6.6 min. HRMS (ESI) calcd for $C_{26}H_{32}F_2N_5O_4$ $[M+H]^+$ 500.2468 found 500.2463;

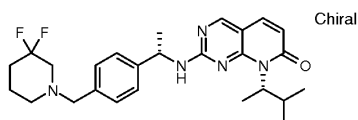
2-[2-[[[(1S)-1-{4-[(3,3-difluoropiperidin-1-yl)methyl]phenyl}ethyl]amino]-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl]propanenitrile [(I), X = N, R₂ = 2-propanenitrile, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = 3,3-difluoropiperidin-1-yl, R₃ = R₄ = R₅ = H] cpd 64



¹H NMR (500MHz, DMSO-*d*₆) δ = 8.60 - 8.73 (m, 2H), 7.72 - 7.80 (m, 1H), 7.42 (d, *J* = 7.93 Hz, 1H), 7.36 (d, *J* = 7.93 Hz, 1H), 7.17 - 7.28 (m, 2H), 6.23-6.53 (m, 2H), 5.08 - 5.34 (m, 1H), 3.44 - 3.55 (m, 2H), 2.53-2.58 (m, 2H), 2.31-2.38 (m, 2H), 1.77-1.88 (m, 2H), 1.56-1.63 (m, 2H), 1.46-1.51 (m, 6H). LCMS : *m/z* 453 [M+H]⁺ @ r.t. 6.24 min.

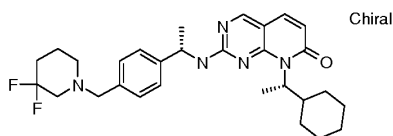
5 HRMS (ESI) calcd for C₂₄H₂₇F₂N₆O [M +H]⁺ 453.2209 found 453.2198;

2-[[[(1S)-1-{4-[(3,3-difluoropiperidin-1-yl)methyl]phenyl}ethyl]amino]-8-[(2S)-3-methylbutan-2-yl]pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = -(2S)-3-methylbutan-2-yl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = 3,3-difluoropiperidin-1-yl, R₃ = R₄ = R₅ = H] cpd 65



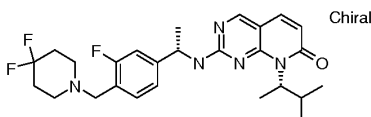
10 ¹H NMR (500MHz, DMSO-*d*₆) δ = 8.54-8.59 (m, 1H), 8.33 - 8.40 (m, 1H), 7.62 - 7.66 (d, *J* = 10.8 Hz, 1H), 7.19-7.38 (m, 4H), 6.09- 6.23 (m, 1H), 4.97 - 5.09 (m, 1H), 4.76-4.86 (m, 1H), 3.50 (br. s, 2H), 2.53 - 2.61 (m, 2H), 2.32 - 2.39 (m, 2H), 2.02-2.10 (m, 1H), 1.78 - 1.89 (m, 2H), 1.57 - 1.65 (m, 2H), 1.44 - 1.53 (m, 3H), 0.99 - 1.10 (m, 3H), 0.61-0.77 (m, 3H), 0.06-0.1 (d, *J* = 6.1 Hz, 3H). LCMS : *m/z* 470 [M+H]⁺ @ r.t. 7.22 min. HRMS (ESI) calcd for C₂₆H₃₄F₂N₆O [M +H]⁺ 470.2726 found 470.2721;

15 **8-[(1S)-1-cyclohexylethyl]-2-[[[(1S)-1-{4-[(3,3-difluoropiperidin-1-yl)methyl]phenyl}ethyl]amino]pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = -(1S)-1-cyclohexylethyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = 3,3-difluoropiperidin-1-yl, R₃ = R₄ = R₅ = H] cpd 66**



20 ¹H NMR (500MHz, DMSO-*d*₆) δ = 8.53-8.59 (m, 1H), 8.35 - 8.40 (m, 1H), 7.62 - 7.66 (m, 1H), 7.19-7.38 (m, 4H), 6.08- 6.23 (m, 1H), 5.10 - 5.21 (m, 1H), 4.79-4.97 (m, 1H), 3.47- 3.54 (m, 4H), 2.53 - 2.61 (m, 2H), 2.32 - 2.39 (m, 2H), 1.74 - 2.06 (m, 4H), 1.43 - 1.66 (m, 5H), 0.66 - 1.44 (m, 9H), 0.42 - 0.52 (m, 1H). LCMS : *m/z* 510 [M+H]⁺ @ r.t. 7.90 min. HRMS (ESI) calcd for C₂₉H₃₈F₂N₆O [M +H]⁺ 510.3039 found 510.3040;

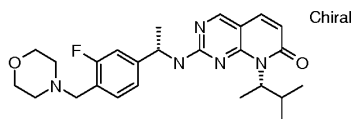
2-[[[(1S)-1-{4-[(4,4-difluoropiperidin-1-yl)methyl]-3-fluorophenyl}ethyl]amino]-8-[(2S)-3-methylbutan-2-yl]pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = -(2S)-3-methylbutan-2-yl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = F, R₇-R₈ = 4,4-difluoropiperidin-1-yl, R₃ = R₄ = R₅ = H] cpd 67



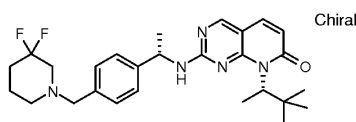
¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.53-8.61 (m, 1H), 8.34-8.42 (m, 1H), 7.62-7.68 (m, 1H), 7.32 (dd, *J* = 7.63 Hz, 1H), 7.06 - 7.24 (m, 2H), 6.10-6.24 (m, 1H), 4.95 - 5.05 (m, 1H), 4.75-4.85 (m, 1H), 3.54 (br. s, 2H), 2.43-2.48 (m,

4H), 1.85 - 1.97 (m, 5H), 1.44-1.51 (m, 3H), 1.0 - 1.08 (m, 3H), 0.59-0.76 (m, 3H), 0.06-0.1 (d, $J = 6.71$ Hz, 3H).
LCMS : m/z 488 $[M+H]^+$ r.t. 7.16 min. HRMS (ESI) calcd for $C_{26}N_{33}F_3N_5O$ $[M + H]^+$ 488.2632 found 488.2639;

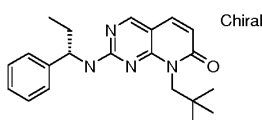
- 2- $\{[(1S)-1-[3-fluoro-4-(morpholin-4-ylmethyl)phenyl]ethyl]amino\}$ -8- $[(2S)-3-methylbutan-2-yl]pyrido[2,3-d]pyrimidin-7(8H)-one$ [(I), $X = N$, $R_2 = -(2S)-3-methylbutan-2-yl$, $A = phenyl$, $R_{1a} = H$, $R_{1b} = Me$, $R_{6a} = 4-CH_2NR_7R_8$, $R_{6b} = F$, $R_7-R_8 = morpholin-4-yl$, $R_3 = R_4 = R_5 = H$] cpd 68



- ^1H NMR (500 MHz, $DMSO-d_6$) $\delta = 8.54-8.61$ (m, 1H), 8.33-8.42 (m, 1H), 7.62-7.67 (m, 1H), 7.31 (dd, $J = 7.63$ Hz, 1H), 7.05 - 7.21 (m, 2H), 6.10-6.25 (m, 1H), 4.94 - 5.05 (m, 1H), 4.75-4.86 (m, 1H), 3.52 (br. s, 4H), 3.44 (br., s, 2H), 2.33 (br. s., 4H), 1.92 - 1.97 (m, 1H), 1.43-1.51 (m, 3H), 1.0 - 1.08 (m, 3H), 0.54-0.76 (m, 3H), 0.05-0.1 (d, $J = 6.71$ Hz, 3H). LCMS : m/z 454 $[M+H]^+$ r.t. 6.07 min. HRMS (ESI) calcd for $C_{25}H_{33}N_5O_2$ $[M + H]^+$ 454.2613 found 454.2612;
- 2- $\{[(1S)-1-[4-[(3,3-difluoropiperidin-1-yl)methyl]phenyl]ethyl]amino\}$ -8- $[(2S)-3,3-dimethylbutan-2-yl]pyrido[2,3-d]pyrimidin-7(8H)-one$ [(I), $X = N$, $R_2 = -(2S)-3,3-dimethylbutan-2-yl$, $A = phenyl$, $R_{1a} = H$, $R_{1b} = Me$, $R_{6a} = 4-CH_2NR_7R_8$, $R_{6b} = H$, $R_7-R_8 = 3,3-difluoropiperidin-1-yl$, $R_3 = R_4 = R_5 = H$] cpd 69

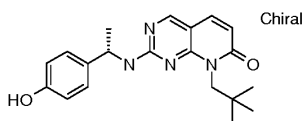


- ^1H NMR (500MHz, $DMSO-d_6$) $\delta = 8.54$ (s, 1H), 8.38 (d, $J = 6.56$ Hz, 1H), 7.61 (d, $J = 9.15$ Hz, 1H), 7.30 (d, $J = 7.93$ Hz, 2H), 7.21 (d, $J = 7.93$ Hz, 2H), 6.10 (d, $J = 9.30$ Hz, 1H), 5.41 (q, $J = 7.02$ Hz, 1H), 4.90 (quin, $J = 6.86$ Hz, 1H), 3.45 - 3.56 (m, 2H), 2.53-2.61 (m, 2H), 2.33-2.40 (m, 2H), 1.78-1.90 (m, 2H), 1.57-1.65 (m, 2H), 1.48 (d, $J = 6.86$ Hz, 3H), 1.15-1.22 (m, 3H), 0.98 (s, 9H). LCMS : m/z 484 $[M+H]^+$ @ r.t. 7.64 min. HRMS (ESI) calcd for $C_{27}H_{36}F_2N_5O$ $[M + H]^+$ 484.2883 found 484.2876;
- 8-(2,2-dimethylpropyl)-2- $\{[(1S)-1-phenylpropyl]amino\}$ pyrido[2,3-d]pyrimidin-7(8H)-one [(I), $X = N$, $R_2 = -2,2-dimethylpropyl$, $A = phenyl$, $R_{1a} = H$, $R_{1b} = Ethyl$, $R_{6a} = R_{6b} = H$, $R_3 = R_4 = R_5 = H$] cpd 70



- ^1H NMR (500 MHz, $DMSO-d_6$) $\delta = 8.56$ (s, 1H), 8.37 (d, $J = 7.93$ Hz, 1H), 7.67 (d, $J = 9.30$ Hz, 1H), 7.38 (d, $J = 7.17$ Hz, 2H), 7.30 (t, $J = 7.55$ Hz, 2H), 7.14 - 7.25 (m, 1H), 6.22 (d, $J = 9.30$ Hz, 1H), 4.76 - 5.09 (m, 1H), 3.96 - 4.32 (m, 2H), 1.65 - 1.93 (m, 2H), 0.85 - 0.98 (m, 3H), 0.80 (br. s., 9H). LCMS : m/z 351 $[M+H]^+$ r.t. 7.16 min. HRMS (ESI) calcd for $C_{21}H_{27}N_4O$ $[M + H]^+$ 351.2180 found 351.2180.

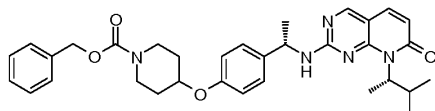
8-(2,2-Dimethyl-propyl)-2- $\{[(S)-1-(4-hydroxy-phenyl)-ethyl]amino\}$ -8H-pyrido[2,3-d]pyrimidin-7-one [(I), $X = N$, $R_2 = -2,2-dimethylpropyl$, $A = phenyl$, $R_{1a} = H$, $R_{1b} = Me$, $R_{6a} = OH$, $R_{6b} = H$, $R_3 = R_4 = R_5 = H$] cpd 145



¹H NMR (500 MHz, DMSO-*d*₆) δ = 9.21 (s, 1H), 8.55 (s, 1H), 8.25 (d, *J* = 7.5 Hz, 1H), 7.67 (d, *J* = 9.2 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 6.67 (d, *J* = 8.2 Hz, 2H), 6.22 (d, *J* = 9.2 Hz, 1H), 4.88 - 5.26 (m, 1H), 4.05 - 4.30 (m, 2H), 1.42 (d, *J* = 7.0 Hz, 3H), 0.82 (br. s., 9H). LCMS: *m/z* 353 [M+H]⁺ @ r.t. 5.78 min

HRMS (ESI) calcd for C₂₀H₂₅N₄O₂ [M + H]⁺ 353.1972 found 353.1976

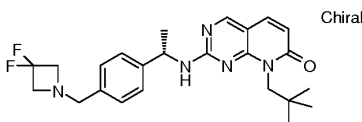
- 5 **4-({(S)-1-[8-((S)-1,2-Dimethyl-propyl)-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino]-ethyl}-phenoxy)-piperidine-1-carboxylic acid benzyl ester [(I), X = N, R₂ = -(S)-1,2-Dimethyl-propyl), A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = -O-R₇, R_{6b} = H, R₇ = 4-piperidine-1-carboxylic acid benzyl ester, R₃ = R₄ = R₅ = H] cpd 146**



- 10 ¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.50 - 8.62 (m, 1H), 8.23 - 8.37 (m, 1H), 7.64 (d, *J* = 9.3 Hz, 1H), 7.15 - 7.42 (m, 7H), 6.90 (d, *J* = 8.5 Hz, 2H), 6.04 - 6.29 (m, 1H), 4.77 - 5.33 (m, 4H), 4.51 (spt, *J* = 4.0 Hz, 1H), 3.68 (br. s., 2H), 3.26 (br. s., 2H), 1.40 - 2.11 (m, 8H), 0.13 - 1.19 (m, 9H). LCMS : *m/z* 570 [M+H]⁺ @ r.t. 7.59 min

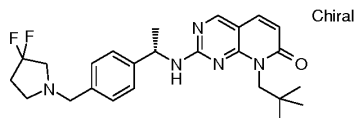
HRMS (ESI) calcd for C₃₃H₄₀N₅O₄ [M + H]⁺ 570.3075 found 570.3100

- 15 **2-(((1S)-1-{4-[(3,3-difluoroazetidin-1-yl)methyl]phenyl}ethyl)amino)-8-(2,2-dimethylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = 2,2-dimethylpropyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = -(3,3-difluoroazetidin-1-yl, R₃ = R₄ = R₅ = H] cpd 147**



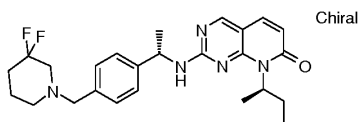
- 20 ¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.57 (s, 1H), 8.36 (d, *J* = 7.47 Hz, 1H), 7.67 (d, *J* = 9.30 Hz, 1H), 7.33 (d, *J* = 7.93 Hz, 2H), 7.22 (d, *J* = 7.93 Hz, 2H), 6.22 (d, *J* = 9.30 Hz, 1H), 5.07 (quin, *J* = 7.17 Hz, 1H), 3.93 - 4.32 (m, 2H), 3.65 (s, 2H), 3.54 (t, *J* = 12.43 Hz, 4H), 1.45 (d, *J* = 7.02 Hz, 3H), 0.76 (br. s., 9H). LCMS : *m/z* 442 [M+H]⁺ @ r.t. 6.77 min. HRMS (ESI) calcd for C₂₄H₃₀N₅O [M + H]⁺ 442.2413 found 442.2423.

- 2-(((1S)-1-{4-[(3,3-difluoropyrrolidin-1-yl)methyl]phenyl}ethyl)amino)-8-(2,2-dimethylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = 2,2-dimethylpropyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = -(3,3-difluoropyrrolidin-1-yl, R₃ = R₄ = R₅ = H] cpd 148**

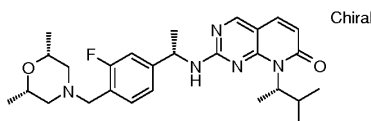


- 25 ¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.58 (s, 1H), 8.36 (d, *J* = 7.32 Hz, 1H), 7.67 (d, *J* = 9.30 Hz, 1H), 7.33 (d, *J* = 8.08 Hz, 2H), 7.23 (d, *J* = 7.78 Hz, 2H), 6.22 (d, *J* = 9.15 Hz, 1H), 5.06 (quin, *J* = 7.21 Hz, 1H), 3.87 - 4.34 (m, 2H), 3.55 (s, 2H), 2.72 - 2.88 (m, 2H), 2.64 (d, *J* = 6.41 Hz, 2H), 2.13 - 2.29 (m, 2H), 1.46 (d, *J* = 7.02 Hz, 3H), 0.73 (br. s., 9H). LCMS : *m/z* 456 [M+H]⁺ @ r.t. 7.13 min. HRMS (ESI) calcd for C₂₅H₃₂N₅O [M + H]⁺ 456.257 found 456.2582.

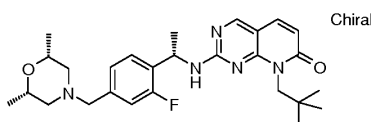
- 30 **8-[(2R)-butan-2-yl]-2-(((1S)-1-{4-[(3,3-difluoropiperidin-1-yl)methyl]phenyl}ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = -(2R)-butan-2-yl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = -(3,3-difluoropiperidin-1-yl, R₃ = R₄ = R₅ = H] cpd 149**



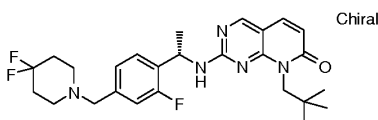
- ¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.58 (s, 1H), 8.36 (d, *J* = 7.32 Hz, 1H), 7.67 (d, *J* = 9.30 Hz, 1H), 7.33 (d, *J* = 8.08 Hz, 2H), 7.23 (d, *J* = 7.78 Hz, 2H), 6.22 (d, *J* = 9.15 Hz, 1H), 5.06 (quin, *J* = 7.21 Hz, 1H), 3.87 - 4.34 (m, 2H), 3.55 (s, 2H), 2.72 - 2.88 (m, 2H), 2.64 (d, *J* = 6.41 Hz, 2H), 2.13 - 2.29 (m, 2H), 1.46 (d, *J* = 7.02 Hz, 3H), 0.73 (br. s., 9H).
- 5 LCMS : *m/z* 456 [M+H]⁺ @ r.t. 7.02 min. HRMS (ESI) calcd for C₂₅H₃₂F₂N₅O [M + H]⁺ 456.257 found 456.2568.
- 2-[[[(1S)-1-(4-[[[(2R,6S)-2,6-dimethylmorpholin-4-yl]methyl]-3-fluorophenyl)ethyl]amino]-8-[(2S)-3-methylbutan-2-yl]pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = -(2S)-3-methylbutan-2-yl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = F, R₇-R₈ = (2R,6S)-2,6-dimethylmorpholin-4-yl, R₃ = R₄ = R₅ = H] cpd 150**



- 10 ¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.60 (s, 1H), 8.36 (d, *J* = 7.47 Hz, 1H), 7.65 (d, *J* = 9.60 Hz, 1H), 7.30 (t, *J* = 7.47 Hz, 1H), 7.05-7.21 (m, 2H), 6.22 (d, *J* = 9.60 Hz, 1H), 4.95-5.03 (m, 1H), 4.76-4.85 (m, 1H), 3.46 - 3.54 (m, 2H), 3.43 (s, 2H), 2.59 - 2.67 (m, 4H), 1.59 - 1.68 (m, 1H), 1.48 (m, 3H), 0.95 - 1.08 (m, 9H), 0.73 (d, *J* = 6.25 Hz, 3H), 0.08 (d, *J* = 6.25 Hz, 3H). LCMS : *m/z* 482 [M+H]⁺ @ r.t. 6.77 min. HRMS (ESI) calcd for C₂₇H₃₇FN₅O₂ [M + H]⁺ 482.2926 found 482.2931.
- 15 **2-[[[(1S)-1-(4-[[[(2R,6S)-2,6-dimethylmorpholin-4-yl]methyl]-2-fluorophenyl)ethyl]amino]-8-(2,2-dimethylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = 2,2-dimethylpropyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = F, R₇-R₈ = (2R,6S)-2,6-dimethylmorpholin-4-yl, R₃ = R₄ = R₅ = H] cpd 151**



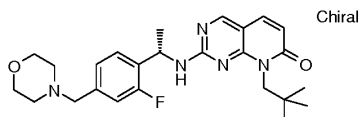
- 20 ¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.59 (s, 1H), 8.44 (d, *J* = 7.32 Hz, 1H), 7.68 (d, *J* = 9.30 Hz, 1H), 7.33 (t, *J* = 8.01 Hz, 1H), 7.08 (d, *J* = 11.13 Hz, 1H), 7.04 (d, *J* = 7.78 Hz, 1H), 6.23 (d, *J* = 9.30 Hz, 1H), 5.33 (quin, *J* = 6.98 Hz, 1H), 3.86 - 4.35 (m, 2H), 3.47 - 3.63 (m, 2H), 3.37 - 3.45 (m, 2H), 2.57 - 2.71 (m, 2H), 1.54 - 1.71 (m, 2H), 1.45 (d, *J* = 7.02 Hz, 3H), 0.99 (d, *J* = 6.25 Hz, 6H), 0.70 (br. s., 9H). LCMS : *m/z* 482 [M+H]⁺ @ r.t. 7.08 min. HRMS (ESI) calcd for C₂₇H₃₇FN₅O₂ [M + H]⁺ 482.2926 found 482.2931.
- 25 **2-[[[(1S)-1-(4-[[[(4,4-difluoropiperidin-1-yl)methyl]-2-fluorophenyl)ethyl]amino]-8-(2,2-dimethylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = 2,2-dimethylpropyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = 2-F, R₇-R₈ = 4,4-difluoropiperidin-1-yl, R₃ = R₄ = R₅ = H] cpd 152**



¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.59 (s, 1H), 8.45 (d, *J* = 7.47 Hz, 1H), 7.68 (d, *J* = 9.30 Hz, 1H), 7.35 (t, *J* = 7.85 Hz, 1H), 7.11 (d, *J* = 11.44 Hz, 1H), 7.06 (dd, *J* = 0.92, 7.93 Hz, 1H), 6.24 (d, *J* = 9.30 Hz, 1H), 5.35 (quin, *J* = 7.05

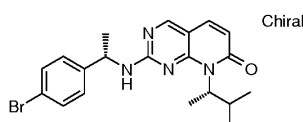
Hz, 1H), 3.92 - 4.34 (m, 2H), 3.50 (d, $J = 2.14$ Hz, 2H), 2.44 (br. s., 4H), 1.82 - 2.02 (m, 4H), 1.45 (d, $J = 7.02$ Hz, 3H), 0.71 (br. s., 9H). LCMS : m/z 488 $[M+H]^+$ @ r.t. 7.43 min. HRMS (ESI) calcd for $C_{26}H_{33}F_3N_5O$ $[M+H]^+$ 488.2632 found 488.2637.

- 5 **8-(2,2-dimethylpropyl)-2-((1S)-1-[2-fluoro-4-(morpholin-4-ylmethyl)phenyl]ethyl)amino)pyrido[2,3-d]-pyrimidin-7(8H)-one [(I), X = N, R2 = 2,2-dimethylpropyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-CH₂NR7R8, R6b = 2-F, R7-R8 = morpholin-4-yl, R3 = R4 = R5 = H] cpd 153**



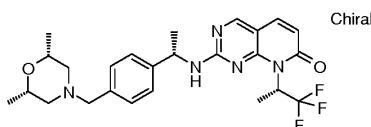
- 10 ¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.59 (s, 1H), 8.45 (d, $J = 7.63$ Hz, 1H), 7.68 (d, $J = 9.30$ Hz, 1H), 7.34 (t, $J = 7.93$ Hz, 1H), 7.09 (d, $J = 11.29$ Hz, 1H), 7.06 (dd, $J = 1.07, 7.93$ Hz, 1H), 6.23 (d, $J = 9.30$ Hz, 1H), 5.35 (quin, $J = 7.02$ Hz, 1H), 3.86 - 4.33 (m, 2H), 3.54 (t, $J = 4.35$ Hz, 4H), 3.37 - 3.45 (m, 2H), 2.31 (br. s., 4H), 1.45 (d, $J = 7.02$ Hz, 3H), 0.72 (br. s., 9H). LCMS : m/z 454 $[M+H]^+$ @ r.t. 6.33 min. HRMS (ESI) calcd for $C_{25}H_{33}FN_5O_2$ $[M+H]^+$ 454.2613 found 454.2603.

- 15 **2-(((1S)-1-(4-bromophenyl)ethyl)amino)-8-[(2S)-3-methylbutan-2-yl]pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = -(2S)-3-methylbutan-2-yl, A = phenyl, R1a= H, R1b = Me, R6a= Br, R6b = H, R3 = R4 = R5 = H] cpd 163**



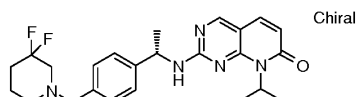
- 20 ¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.60 (s, 1H), 8.34 (d, $J = 7.44$ Hz, 1H), 7.65 (d, $J = 9.70$ Hz, 1H), 7.49 (d, $J = 8.41$ Hz, 2H), 7.31 (d, $J = 8.41$ Hz, 2H), 6.23 (d, $J = 9.70$ Hz, 1H), 4.88-4.98 (m, 1H), 4.73-4.85 (m, 1H), 1.66-1.75 (m, 1H), 1.46 (d, $J = 7.12$ Hz, 3H), 1.10 (d, $J = 6.71$ Hz, 3H), 0.71 (d, $J = 6.41$ Hz, 3H), 0.08 (d, $J = 6.71$ Hz, 3H). LCMS : m/z 415 $[M+H]^+$ @ r.t. 7.14 min. HRMS (ESI) calcd for $C_{20}H_{24}BrN_4O$ $[M+H]^+$ 415.1128 found 415.1143.

2-(((1S)-1-(4-((2R,6S)-2,6-dimethylmorpholin-4-yl)methyl)phenyl)ethyl)amino)-8-[(2S)-1,1,1-trifluoropropan-2-yl]pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = -(2S)-1,1,1-trifluoropropan-2-yl, A = phenyl, R1a= H, R1b = Me, R6a= 4-CH₂NR7R8, R6b = H, R7-R8 = (2R,6S)-2,6-dimethylmorpholin-4-yl, R3 = R4 = R5 = H] cpd 164



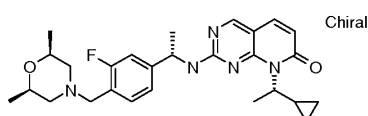
- 25 ¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.63 (m, 2H), 7.72 (d, $J = 9.46$ Hz, 1H), 7.20- 7.31 (m, 4H), 6.18 (d, $J = 9.45$ Hz, 1H), 6.01-6.10 (m, 1H), 4.79 (quin, $J = 6.7$ Hz, 1H), 3.48 - 3.51 (m, 2H), 3.37 - 3.45 (m, 2H), 2.57 - 2.71 (m, 2H), 1.87 (d, $J = 7.17$ Hz, 1H), 1.56- 1.71 (m, 3H), 1.46 (d, $J = 6.86$ Hz, 3H), 0.95 - 1.05 (m, 6H). LCMS : m/z 490 $[M+H]^+$ @ r.t. 6.35 min. HRMS (ESI) calcd for $C_{25}H_{37}F_3N_5O_2$ $[M+H]^+$ 490.2425 found 490.2415.

- 30 **2-(((1S)-1-(4-((3,3-difluoropiperidin-1-yl)methyl)phenyl)ethyl)amino)-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = propan-2-yl, A = phenyl, R1a= H, R1b = Me, R6a= 4-CH₂NR7R8, R6b =, R7-R8 = (3,3-difluoropiperidin-1-yl, R3 = R4 = R5 = H] cpd 170**



¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.56 (br. s., 1H), 8.36 (d, *J* = 6.71 Hz, 1H), 7.62 (d, *J* = 9.15 Hz, 1H), 7.33 (d, *J* = 7.93 Hz, 2H), 7.21 (d, *J* = 7.93 Hz, 2H), 6.15 (d, *J* = 9.15 Hz, 1H), 5.44 - 5.56 (br. s., 1H), 4.99 (m, 2H), 3.49 (br. s., 2H), 2.53 - 2.61 (m, 2H), 2.31 - 2.35 (m, 2H), 1.74 - 1.93 (m, *J* = 6.79, 13.46, 13.46 Hz, 2H), 1.56 - 1.71 (m, 2H), 1.38 - 1.56 (m, 9H). LCMS : *m/z* 442 [M+H]⁺ @ r.t. 6.77 min. HRMS (ESI) calcd for C₂₄H₃₀F₂N₅O [M + H]⁺ 442.2413 found 442.2418.

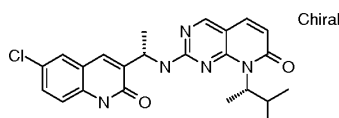
8-[(1*S*)-1-cyclopropylethyl]-2-[[[(1*S*)-1-(4-[(2*R*,6*S*)-2,6-dimethylmorpholin-4-yl]methyl]-3-fluorophenyl)ethyl]amino]pyrido[2,3-*d*]pyrimidin-7(8H)-one [(I), X = N, R₂ = (1*S*)-1-cyclopropylethyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = , R₇-R₈ = (2*R*,6*S*)-2,6-dimethylmorpholin-4-yl, R₃ = R₄ = R₅ = H] cpd 170



10

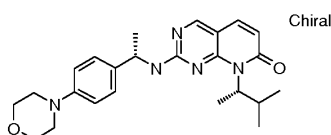
¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.53-8.59 (br. s., 1H), 8.34-8.41 (br. s., 1H), 7.65 (d, *J* = 9.3 Hz, 1H), 7.19- 7.33 (m, 4H), 6.14 (d, *J* = 9.3 Hz, 1H), 4.89 - 5.00 (br. m., 1H), 4.54 (br. m, 1H), 3.52 (br. s., 2H), 3.37 (s., 2H), 2.57 - 2.67 (m, 4H), 1.80 (m, 1H) 1.41 - 1.61 (m, 6H), 0.97 (m, 6H), 0.25 - 0.64 (m, 4H). LCMS : *m/z* 462 [M+H]⁺ @ r.t. 6.26 min. HRMS (ESI) calcd for C₂₇H₃₆N₅O₂ [M + H]⁺ 462.2864 found 462.2872.

2-[[[(1*S*)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino]-8-[(2*S*)-3-methylbutan-2-yl]pyrido[2,3-*d*]pyrimidin-7(8H)-one [(I), X = N, R₂ = (2*S*)-3-methylbutan-2-yl, A = 2-oxo-quinolin-3-yl, R_{1a} = H, R_{1b} = Me, R_{6a} = 6-chloro, R_{6b} = H, R₃ = R₄ = R₅ = H] step 1a, cpd 172



¹H NMR (500 MHz, DMSO- *d*₆) δ = 12.04 (s, 1H), 8.63 (s, 1H), 8.27 (d, *J* = 5.95 Hz, 1H), 7.72 (d, *J* = 1.98 Hz, 1H), 7.66 (d, *J* = 9.00 Hz, 1H), 7.55 (s, 1H), 7.46 (dd, *J* = 2.21, 8.62 Hz, 1H), 7.31 (d, *J* = 8.85 Hz, 1H), 6.21 (d, *J* = 9.30 Hz, 1H), 4.93-5.08 (m, 1H), 4.71 (q., *J* = 6.86 Hz, 1H), 1.84-1.93 (m, 1H), 1.47 (d, *J* = 6.86 Hz, 3H), 1.41 (d, *J* = 6.86 Hz, 3H), 0.98 (d, *J* = 6.71 Hz, 3H), 0.61 (d, *J* = 6.41 Hz, 3H). -0.24 (d, *J* = 6.71 Hz, 3H). LCMS : *m/z* 438 [M+H]⁺ r.t. 5.68 min. HRMS (ESI) calcd for C₂₃H₂₄ClN₅O₂ [M + H]⁺ 438.1692 found 438.1685.

8-[(2*S*)-3-methylbutan-2-yl]-2-[[[(1*S*)-1-[4-(morpholin-4-yl)phenyl]ethyl]amino]pyrido[2,3-*d*]pyrimidin-7(8H)-one [(I), X = N, R₂ = (2*S*)-3-methylbutan-2-yl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-NR₇R₈, R_{6b} = H, R₇-R₈ = morpholin-4-yl R₃ = R₄ = R₅ = H] step 1a, cpd 173

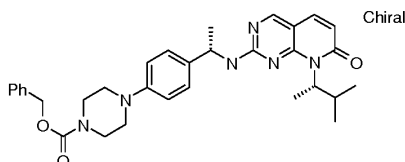


¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.56 (s., 1H), 8.24 (d, *J* = 7.02 Hz, 1H), 7.64 (d, *J* = 9.15 Hz, 1H), 7.23 (d, *J* = 8.69 Hz, 1H), 7.16 (d, *J* = 8.69 Hz, 1H), 6.87 (d, *J* = 8.69 Hz, 2H), 6.19 (d, *J* = 9.15 Hz, 1H), 4.78 - 5.15 (br. m., 2H),

3.71 (m, 4H), 3.02 (m, 4H), 1.41 - 1.52 (m, 4H), 0.98 - 1.22 (m, 3H), 0.61 - 0.80 (m, 3H), 0.12 - 0.17 (m, 3H). LCMS : m/z 422 [M+H]⁺ r.t. 6.3 min. HRMS (ESI) calcd for C₂₄H₃₁N₅O₂ [M + H]⁺ 422.2551 found 422.2545.

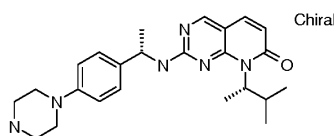
Benzyl-4-{4-[(1S)-1-({8-[(2S)-3-methylbutan-2-yl]-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl)amino}ethyl]phenyl}piperazine-1-carboxylate [(I), X = N, R₂ = (2S)-3-methylbutan-2-yl, A = phenyl, R_{1a} = H, R_{1b} = Me,

5 **R_{6a} = 4-NR₇R₈, R_{6b} = H, R₇-R₈ = benzyl-piperazine-1-carboxylate, R₃ = R₄ = R₅ = H] step 1a, cpd 174**



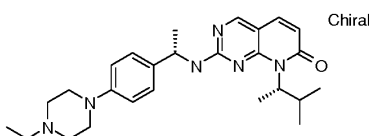
¹H NMR (500 MHz, DMSO- d₆) δ = 8.55 (br. s., 1H), 8.24 (d, J = 7.32 Hz, 1H), 7.63 (d, J = 9.30 Hz, 1H), 7.28 - 7.42 (m, 5H), 7.23 (d, J = 8.69 Hz, 1H), 7.15 (d, J = 8.69 Hz, 1H), 6.89 (d, J = 8.69 Hz, 2H), 6.20 (d, J = 9.30 Hz, 1H), 5.09 (s, 2H), 4.77 - 4.97 (br. m., 2H), 3.51 (br. s., 4H), 3.04 (br. s., 4H), 1.41 - 1.52 (m, 4H), 1.16 - 1.21 (br. m, 3H), 0.55 - 0.75 (m, 3H), 0.13 (d, J = 6.56 Hz, 3H). LCMS : m/z 555 [M+H]⁺ r.t. 7.38 min. HRMS (ESI) calcd for C₃₂H₃₉N₆O₃ [M + H]⁺ 555.3078 found 555.3092.

8-[(2S)-3-methylbutan-2-yl]-2-({(1S)-1-[4-(piperazin-1-yl)phenyl]ethyl}amino)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = (2S)-3-methylbutan-2-yl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-NR₇R₈, R_{6b} = H, R₇-R₈ = piperazin-1-yl, R₃ = R₄ = R₅ = H] step 1a, cpd 176



¹H NMR (500 MHz, DMSO- d₆) δ = 8.56 (s., 1H), 8.24 (m, 1H), 7.64 (m, 1H), 7.11 - 7.26 (m, 2H), 6.9 (d, J = 8.69 Hz, 2H), 6.19 (m, 1H), 4.78 - 5.15 (br. m., 2H), 3.21 (m, 4H), 3.14 (m, 4H), 1.41 - 1.52 (m, 4H), 0.98 - 1.22 (m, 3H), 0.61 - 0.80 (m, 3H), 0.12 - 0.17 (m, 3H). LCMS : m/z 421 [M+H]⁺ r.t. 4.98 min. HRMS (ESI) calcd for C₂₄H₃₃N₆O [M + H]⁺ 421.2711 found 421.2714.

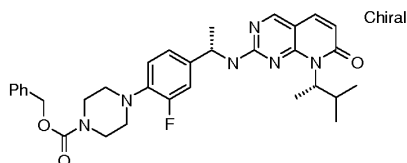
20 **2-({(1S)-1-[4-(4-ethylpiperazin-1-yl)phenyl]ethyl}amino)-8-[(2S)-3-methylbutan-2-yl]pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = (2S)-3-methylbutan-2-yl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-NR₇R₈, R_{6b} = H, R₇-R₈ = 4-ethylpiperazin-1-yl, R₃ = R₄ = R₅ = H] step 1a, cpd 177**



¹H NMR (500 MHz, DMSO- d₆) δ = 8.56 (br. s., 1H), 8.25 (d, J = 7.32 Hz, 1H), 7.63 (d, J = 9.30 Hz, 1H), 7.21 (d, J = 8.54 Hz, 1H), 7.13 (d, J = 8.54 Hz, 1H), 6.85 (d, J = 8.54 Hz, 2H), 6.19 (d, J = 9.30 Hz, 1H), 4.75 - 5.19 (m, 2H), 3.05 (br. s., 4H), 2.46 (br. s., 4H), 2.34 (q, J = 7.10 Hz, 2H), 1.41 - 1.52 (m, 4H), 1.03 - 1.22 (m, 3H), 1.01 (t, J = 7.17 Hz, 3H), 0.61 - 0.79 (m, 3H), 0.14 (d, J = 6.56 Hz, 3H). LCMS : m/z 449 [M+H]⁺ r.t. 5.25 min. HRMS (ESI) calcd for C₂₆H₃₇N₆O [M + H]⁺ 449.3024 found 449.3021.

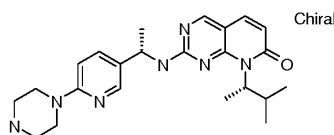
30 **Benzyl 4-{2-fluoro-4-[(1S)-1-({8-[(2S)-3-methylbutan-2-yl]-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl)amino}ethyl]phenyl}piperazine-1-carboxylate [(I), X = N, R₂ = (2S)-3-methylbutan-2-yl, A = phenyl, R_{1a} = H,**

R1b = Me, R6a= 4-NR7R8, R6b = F, R7-R8 = benzyl-piperazine-1-carboxylate, R3 = R4 = R5= H] step 1a, cpd 178



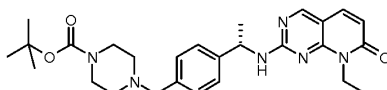
¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.59 (s, 1H), (8.29 (d, *J* = 7.17 Hz, 1H), 7.65 (dd, *J* = 3.97, 9.00 Hz, 1H), 7.27 - 7.42 (m, 5H), 6.95 - 7.15 (m, 3H), 6.05 - 6.30 (m, 1H), 5.09 (s, 2H), 4.92 (m, 1H), 4.79 (m, 1H), 3.53 (br. s., 4H), 2.91 (br. s., 4H), 1.95 (m, 1H), 1.41 - 1.49 (m, 3H), 1.02 - 1.11 (m, 3H), 0.59 - 0.77 (m, 3H), 0.09 - 0.13 (m, 3H). LCMS : m/z 573 [M+H]⁺ r.t. 7.48 min. HRMS (ESI) calcd for C₃₂H₃₈FN₆O₃ [M + H]⁺ 573.2984 found 573.3004.

8-[(2S)-3-methylbutan-2-yl]-2-[(1S)-1-[6-(piperazin-1-yl)pyridin-3-yl]ethyl]amino]pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = (2S)-3-methylbutan-2-yl, A pyridin-3-yl, R1a= H, R1b = Me, R6a= 4-NR7R8, R6b = H, R7-R8 = piperazin-1-yl, R3 = R4 = R5= H] step 1a, cpd 180



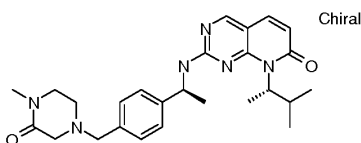
¹H NMR (500 MHz, DMSO- *d*₆) δ 8.57 (s, 1H), 8.25 (m, 1H), 8.11 br., s, 1H), 7.65 (d, *J* = 9.30 Hz, 1H), 7.44 (d, *J* = 8.39 Hz, 1H), 6.74 (d, *J* = 8.39 Hz, 1H), 6.22 (d, *J* = 9.30 Hz, 1H), 4.91 (m, 1H), 4.80 (m, 1H), 3.33 (m, 4H), 2.76 (m, 4H), 2.07 (m, 1H), 1.43 - 1.52 (m, 3H), 0.98 - 1.08 (m, 3H), 0.55 - 0.81 (m, 3H), 0.17 (d, *J* = 6.56 Hz, 1H). LCMS : m/z 422 [M+H]⁺ r.t. 4.63 min. HRMS (ESI) calcd for C₂₃H₃₂N₇O [M + H]⁺ 422.266 found 422.267.

tert-butyl 4-(4-[(1S)-1-[(8-ethyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl)amino]ethyl]benzyl)piperazine-1-carboxylate [(I), X = N, R2 = ethyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-CH₂NR7R8, R6b = H, R7-R8 = 4-piperazine-1-carboxylic acid tert-butyl ester, R3 = R4 = R5= H] cpd 185



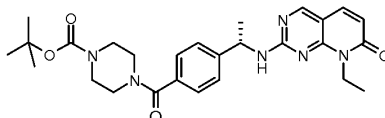
¹H NMR (500MHz, DMSO-*d*₆) δ = 8.58 (s, 1H), 8.43 (d, *J* = 7.17 Hz, 1H), 7.66 (d, *J* = 9.30 Hz, 1H), 7.47 (d, *J* = 8.08 Hz, 1H), 7.42 (d, *J* = 8.08 Hz, 1H), 7.33 (d, *J* = 8.08 Hz, 1H), 7.22 (d, *J* = 8.08 Hz, 1H), 6.21 (d, *J* = 9.30 Hz, 1H), 5.03 (q, *J* = 7.1 Hz, 1H), 4.46 (s, 2H), 4.01 - 4.21 (m, 2H), 3.58 (s, 2H), 3.38 - 3.47 (br. s., 8H), 1.47 (d, *J* = 7.02 Hz, 3H), 1.38 (s, 9H), 0.89 (m, 3H). LCMS : m/z 493 [M+H]⁺ @ r.t. 6.37 min. HRMS (ESI) calcd for C₂₇H₃₆N₆O₃ [M + H]⁺ 493.2922 found 493.2921;

8-[(2S)-3-methylbutan-2-yl]-2-[(1S)-1-[4-[(4-methyl-3-oxopiperazin-1-yl)methyl]phenyl]ethyl]amino]-pyrido[2,3-d]pyrimidin-7(8H)-one carboxylate [(I), X = N, R2 = (2S)-3-methylbutan-2-yl, A = phenyl, R1a= H, R1b = Me, R6a= 4-CH₂NR7R8, R6b = H, R7-R8 = -4-methyl-3-oxopiperazin-1-yl, R3 = R4 = R5= H] cpd 188



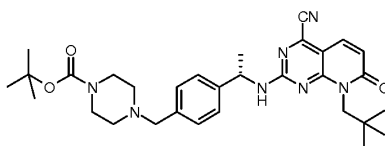
¹H NMR (500MHz, DMSO-d₆) δ = 8.56 (s, 1H), 8.37 (d, *J* = 7.32 Hz, 1H), 7.64 (d, *J* = 9.30 Hz, 1H), 7.21 - 7.37 (m, 4H), 6.04 - 6.29 (m, 1H), 4.69 - 5.09 (m, 2H), 3.46 (s, 2H), 3.17 - 3.25 (m, *J* = 4.73 Hz, 2H), 2.91 (br. s., 2H), 2.78 (s, 3H), 2.58 (br. quin, *J* = 4.70 Hz, 2H), 1.44 - 1.54 (m, 4H), 0.99 - 1.09 (m, 3H), 0.58 - 0.76 (m, 3H), 0.08 (d, *J* = 6.56 Hz, 3H). LCMS : *m/z* 463 [M+H]⁺ @ r.t. 5.52 min. HRMS (ESI) calcd for C₂₇H₃₅N₆O₂ [M +H]⁺ 463.2816 found 463.2819;

tert-butyl 4-(4-((1S)-1-[(8-ethyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl)amino]ethyl)benzoyl)piperazine-1-carboxylate [(I), X = N, R₂ = ethyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = 4-piperazine-1-carboxylic acid tert-butyl ester, R₃ = R₄ = R₅ = H] cpd 189



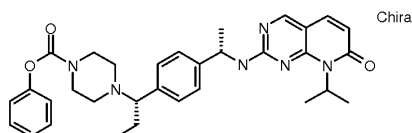
¹H NMR (500MHz, DMSO-d₆) δ = 8.59 (s, 1H), 8.49 (d, *J* = 7.17 Hz, 1H), 7.68 (d, *J* = 9.30 Hz, 1H), 7.46 (d, *J* = 8.24 Hz, 2H), 7.35 (d, *J* = 8.24 Hz, 2H), 6.21 (d, *J* = 9.30 Hz, 1H), 5.05 (quin, *J* = 6.90 Hz, 1H), 3.94 - 4.35 (m, 2H), 3.37 - 3.62 (m, 8H), 1.49 (d, *J* = 7.02 Hz, 3H), 1.39 (s, 9H), 0.89 (t, *J* = 6.86 Hz, 3H). LCMS : *m/z* 507 [M+H]⁺ @ r.t. 5.78 min. HRMS (ESI) calcd for C₂₇H₃₅N₆O₄ [M +H]⁺ 507.2715 found 507.2722;

tert-butyl 4-{4-[(1S)-1-[[4-cyano-8-(2,2-dimethylpropyl)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl]amino]ethyl]benzyl}piperazine-1-carboxylate [(I), X = N, R₂ = 2,2-dimethylpropyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = 4-piperazine-1-carboxylic acid tert-butyl ester, R₃ = CN, R₄ = R₅ = H] cpd 200



¹H NMR (500MHz, DMSO-d₆) δ = 8.93 (d, *J* = 7.47 Hz, 1H), 7.71 (d, *J* = 9.46 Hz, 1H), 7.32 (d, *J* = 8.08 Hz, 2H), 7.23 (d, *J* = 7.78 Hz, 2H), 6.42 (d, *J* = 9.46 Hz, 1H), 5.05 (q, *J* = 7.02 Hz, 1H), 3.96 (dd, *J* = 12.51 Hz, 2H), 3.43 (s, 2H), 3.28 (br. s, 4H), 2.20 - 2.32 (m, *J* = 4.27 Hz, 4H), 1.46 (d, *J* = 7.02 Hz, 3H), 1.37 (s, 9H), 0.91 (s, 3H), 0.72 (br.s, 6H). LCMS : *m/z* 560 [M+H]⁺ @ r.t. 10.34 min. HRMS (ESI) calcd for C₃₁H₄₁N₇O₃ [M +H]⁺ 560.3344 found 560.3362;

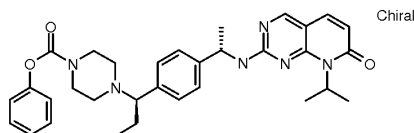
Phenyl 4-[(1S)-1-{4-[(1S)-1-[[7-oxo-8-(propan-2-yl)-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl]amino]ethyl]phenyl}propyl]piperazine-1-carboxylate [(I), X = N, R₂ = propan-2-yl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CHR₁₄NR₇R₈, R_{6b} = H, R₇-R₈ = 4-piperazine-1-carboxylic acid phenyl ester, R₁₄ = Ethyl, R₃ = R₄ = R₅ = H] cpd 225



¹H NMR (500MHz, DMSO-d₆) δ = 8.57 (s, 1H), 8.33 (d, *J* = 7.93 Hz, 1H), 7.63 (d, *J* = 9.3 Hz, 1H), 7.36 (d, *J* = 7.78 Hz, 2H), 7.32 (d, *J* = 7.78 Hz, 2H), 7.17 (d, *J* = 7.78 Hz, 2H), 7.16 (d, *J* = 7.78 Hz, 1H), 7.01 (d, *J* = 7.78 Hz, 1H), 6.16 (d, *J* = 9.3 Hz, 2H), 5.48 (br.s, 1H), 5.00 (br. s., 1H), 3.50 (br. s., 4H), 3.36 (m, 1H), 2.30 (br.s., 4H), 1.82 - 1.92

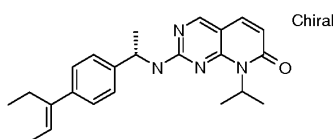
(m, 1H), 1.63 - 1.73 (m, 1H), 1.48 (d, $J = 6.9$ Hz, 3H), 0.96 (br. s., 6H), 0.67 - 0.74 (m, 3H). LCMS : m/z 555 $[M+H]^+$ @ r.t. 8.68 min. HRMS (ESI) calcd for $C_{32}H_{39}N_6O_3$ $[M+H]^+$ 555.3078 found 555.3085;

Phenyl 4-[(1R)-1-{4-[(1S)-1-{[7-oxo-8-(propan-2-yl)-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl]amino}ethyl]phenyl}propyl]piperazine-1-carboxylate [(I), X = N, R2 = propan-2-yl, A = phenyl, R1a= H, R1b = Me, R6a= 4-CHR14NR7R8, R6b = H, R7-R8 = 4-piperazine-1-carboxylic acid phenyl ester, R14 = Ethyl, R3 = R4 = R5= H] cpd 226



^1H NMR (500MHz, DMSO- d_6) δ = 8.57 (s, 1H), 8.33 (d, $J = 7.93$ Hz, 1H), 7.63 (d, $J = 9.3$ Hz, 1H), 7.36 (d, $J = 7.78$ Hz, 2H), 7.32 (d, $J = 7.78$ Hz, 2H), 7.17 (d, $J = 7.78$ Hz, 2H), 7.16 (d, $J = 7.78$ Hz, 1H), 7.01 (d, $J = 7.78$ Hz, 1H), 6.16 (d, $J = 9.3$ Hz, 2H), 5.48 (br.s, 1H), 5.00 (br. s., 1H), 3.50 (br. s., 4H), 3.36 (m, 1H), 2.30 (br.s., 4H), 1.82 - 1.92 (m, 1H), 1.63 - 1.73 (m, 1H), 1.48 (d, $J = 6.9$ Hz, 3H), 0.96 (br. s., 6H), 0.67 - 0.74 (m, 3H). LCMS : m/z 555 $[M+H]^+$ @ r.t. 8.68 min. HRMS (ESI) calcd for $C_{32}H_{39}N_6O_3$ $[M+H]^+$ 555.3078 found 555.3085.

2-[[[(1S)-1-{4-[(2E)-pent-2-en-3-yl]phenyl}ethyl]amino]-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = propan-2-yl, A = phenyl, R1a= H, R1b = Me, R6a= (2E)-pent-2-en-3-yl, R6b = H, R3 = R4 = R5= H] cpd 250

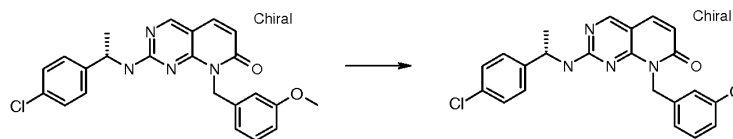


^1H NMR (500MHz, DMSO- d_6) δ = 8.51 - 8.60 (m, 1H), 8.36 (d, $J = 7.17$ Hz, 1H), 7.62 (d, $J = 9.15$ Hz, 1H), 7.25 - 7.36 (m, 4H), 7.15 (m, 1H), 6.15 (d, $J = 9.00$ Hz, 1H), 5.42 - 5.82 (m, 1H), 5.00 (br. s., 1H), 2.44 (q, $J = 7.32$ Hz, 2H), 1.74 (d, $J = 6.71$ Hz, 3H), 1.24 - 1.54 (m, 9H), 0.87 (t, $J = 7.8$ Hz, 3H). LCMS : m/z 377 $[M+H]^+$ @ r.t. 13.71 min.

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Example 4

2-[[[(1S)-1-(4-chlorophenyl)ethyl]amino]-8-(3-hydroxybenzyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = 3-hydroxybenzyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-Cl, R6b = H, R3 = R4 = R5= H] conv. 13, cpd 71



To a stirred suspension of 2-[[[(1S)-1-(4-chlorophenyl)ethyl]amino]-8-(3-methoxybenzyl)pyrido[2,3-d]pyrimidin-7(8H)-one (50 mg, 0.12mM) prepared as described in example 1, in anhydrous dichloromethane (5mL) was added dropwise, under argon, 1M BBr_3 solution (1 mL, 1 mmol) in DCM at 0°C. The ice bath was removed and the mixture was stirred at room temperature overnight. The reaction was diluted with DCM and washed with $NaHCO_3$ saturated solution, then with water and brine. After drying over Na_2SO_4 , the solvent was removed to give a crude that was

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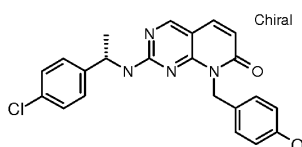
purified by chromatographic column and eluted with DCM/MeOH 95/5, to afford the title compound (34 mg, 70% yield).

¹H NMR (500 MHz, DMSO- *d*₆) δ = 9.29 (s, 1H), 8.61 (s, 1H), 8.44 (d, *J* = 7.93 Hz, 1H), 7.76 (d, *J* = 9.46 Hz, 1H), 7.21 - 7.30 (m, 3H), 7.00 (t, *J* = 7.70 Hz, 1H), 6.60 (d, *J* = 7.63 Hz, 1H), 6.51 - 6.57 (m, 2H), 6.30 (d, *J* = 9.30 Hz, 1H), 5.37 (d, *J* = 14.18 Hz, 1H), 5.12 (d, *J* = 14.34 Hz, 1H), 4.97 - 5.07 (m, 1H), 1.38 - 1.46 (m, 4H).

LCMS : *m/z* 407 [M+H]⁺ r.t. 6.05 min. HRMS (ESI) calcd for C₂₂H₂₀ClN₄O₂ [M + H]⁺ 407.127 found 407.1276.

According to the same method, the following compounds were prepared:

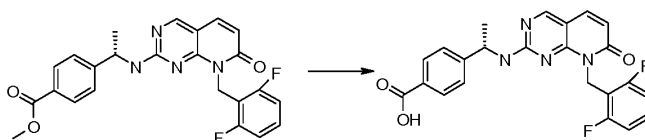
2-[[[(1S)-1-(4-chlorophenyl)ethyl]amino]-8-(4-hydroxybenzyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = 4-hydroxybenzyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-Cl, R_{6b} = H, R₃ = R₄ = R₅ = H] cpd 72



¹H NMR (500 MHz, DMSO- *d*₆) δ = 9.10 - 9.70 (m, 1H), 8.61 (s, 1H), 8.48 (d, *J* = 7.63 Hz, 1H), 7.72 (d, *J* = 9.30 Hz, 1H), 7.28 - 7.38 (m, 4H), 6.96 (d, *J* = 8.39 Hz, 2H), 6.55 (d, *J* = 8.24 Hz, 2H), 6.26 (d, *J* = 9.30 Hz, 1H), 5.32 (d, *J* = 13.88 Hz, 1H), 5.11 (quin, *J* = 6.90 Hz, 1H), 5.05 (d, *J* = 14.03 Hz, 1H), 1.45 (d, *J* = 6.86 Hz, 3H). LCMS : *m/z* 407 [M+H]⁺ r.t. 5.93 min. HRMS (ESI) calcd for C₂₂H₂₀ClN₄O₂ [M + H]⁺ 407.127 found 407.1274;

Example 5

4-[[[(1S)-1-[[8-(2,6-difluorobenzyl)-7-oxo-pyrido[2,3-d]pyrimidin-2-yl]amino]ethyl]benzoic acid [(I), X = N, R₂ = 2,6-difluorobenzyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-COOH, R_{6b} = H, R₃ = R₄ = R₅ = H] conv. 3, cpd 73

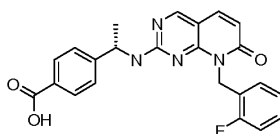


Lithium hydroxyde (0.022 g, 0.52 mmol) was added to a solution of methyl 4-[[[(1S)-1-[[8-(2,6-difluorobenzyl)-7-oxo-pyrido[2,3-d]pyrimidin-2-yl]amino]ethyl]benzoate (0.030 g, 0.07 mmol) in THF:water (1:1, 2 mL) and the reaction mixture was stirred at room temperature for 18h. The solvent (THF) was removed under reduced pressure and the aqueous residue was diluted with water. The aqueous phase was acidified with hydrochloric acid (1M) until a precipitation occurred, the solid was filtered, washed with water and dried under vacuum, to give the title compound as a white solid (0.029 g, 99% yield).

¹H NMR (500 MHz, DMSO- *d*₆) δ = 12.77 (br. s., 1H), 8.61 (s, 1H), 8.47 (d, *J* = 7.93 Hz, 1H), 7.66 - 7.93 (m, 3H), 7.39 (d, *J* = 8.08 Hz, 2H), 7.19 - 7.35 (m, 1H), 6.87 - 7.05 (m, 2H), 6.24 (d, *J* = 9.15 Hz, 1H), 5.53 (d, *J* = 15.25 Hz, 1H), 5.28 (d, *J* = 15.25 Hz, 1H), 4.98 - 5.15 (m, 1H), 1.38 - 1.53 (m, 3H). LCMS : *m/z* 437 [M+H]⁺ r.t. 4.94 min. HRMS (ESI) calcd for C₂₃H₁₉F₂N₄O₃ [M + H]⁺ 437.142 found 437.1413.

According to the same method, the following compounds were prepared:

4-[[[(1S)-1-[[8-(2-fluorobenzyl)-7-oxo-pyrido[2,3-d]pyrimidin-2-yl]amino]ethyl]benzoic acid [(I), X = N, R₂ = 2-fluorobenzyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-COOH, R_{6b} = H, R₃ = R₄ = R₅ = H] cpd 74

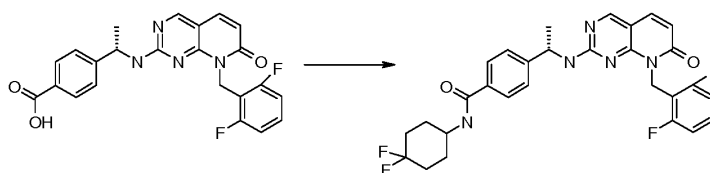


^1H NMR (500 MHz, DMSO- d_6) δ = 12.77 (br. s., 1H), 8.59 - 8.70 (m, 1H), 8.52 (d, J = 7.63 Hz, 1H), 7.80 (d, J = 9.30 Hz, 1H), 7.70 (d, J = 8.08 Hz, 2H), 7.26 - 7.48 (m, 2H), 7.16 - 7.24 (m, 2H), 6.85 - 7.10 (m, 1H), 6.53 - 6.81 (m, 1H), 6.31 (d, J = 9.30 Hz, 1H), 5.39 - 5.53 (m, 1H), 5.22 (d, J = 15.40 Hz, 1H), 4.85 - 5.04 (m, 1H), 1.37 - 1.47 (m, 3H).

5 LCMS : m/z 419 $[\text{M}+\text{H}]^+$ r.t. 4.97 min. HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{20}\text{FN}_4\text{O}_3$ $[\text{M} + \text{H}]^+$ 419.1514 found 419.1517.

Example 6

4-[(1S)-1-[[8-(2,6-difluorobenzyl)-7-oxo-pyrido[2,3-d]pyrimidin-2-yl]amino]ethyl]-N-(4,4-difluorocyclohexyl)benzamide [(I), X = N, R2 = 2,6-difluorobenzyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-CONR7R8, R6b = H, R7 = 4,4-difluorocyclohexyl, R8 =H, R3 = R4 = R5= H] conv. 4, cpd 75



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A solution of TBTU (12 mg, 0.04 mmol) in DCM (1 mL) was added to a solution of 4-[(1S)-1-[[8-(2,6-difluorobenzyl)-7-oxo-pyrido[2,3-d]pyrimidin-2-yl]amino]ethyl]benzoic acid (10 mg, 0.02 mmol), DIPEA (10 μ , 0.06 mmol), and 4,4-difluorocyclohexylamine hydrochloride (6.8mg g, 0.04 mmol) in DCM (1 mL). The reaction mixture was stirred at room temperature for 12 hours, the solvents were removed in vacuo, the residue was partitioned between DCM and water, the organic layer was dried. The crude was purified by chromatography on a silica gel column (eluent: DCM /EtOAc/EtOH: 60/35/5) to afford the title compound (9.95 g, 90% yield).

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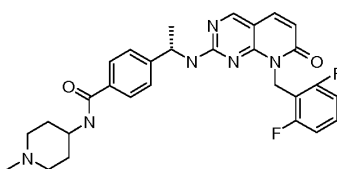
^1H NMR (500 MHz, DMSO- d_6) δ = 8.60 (s, 1H), 8.43 (d, J = 8.08 Hz, 1H), 8.14 (d, J = 7.63 Hz, 1H), 7.73 (d, J = 9.46 Hz, 1H), 7.67 (d, J = 8.08 Hz, 1H), 7.36 (d, J = 8.24 Hz, 1H), 7.26 (t, J = 6.86 Hz, 1H), 6.94 (t, J = 8.16 Hz, 1H), 6.24 (d, J = 9.30 Hz, 1H), 5.53 (d, J = 14.79 Hz, 1H), 5.31 (d, J = 14.95 Hz, 1H), 4.98 - 5.12 (m, 1H), 3.88 - 4.02 (m, 1H), 1.80 - 2.11 (m, 6H), 1.61 (q, J = 12.15 Hz, 2H), 1.32 - 1.49 (m, 3H). LCMS : m/z 554 $[\text{M}+\text{H}]^+$ r.t. 4.85 min. HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{28}\text{F}_4\text{N}_5\text{O}_2$ $[\text{M} + \text{H}]^+$ 554.2174 found 554.2181.

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According to this same methodology, but employing suitable substituted derivatives, the following compounds were prepared:

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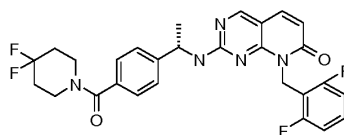
4-[(1S)-1-[[8-(2,6-difluorobenzyl)-7-oxo-pyrido[2,3-d]pyrimidin-2-yl]amino]ethyl]-N-(1-methylpiperidin-4-yl)benzamide [(I), X = N, R2 = 2,6-difluorobenzyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-CONR7R8, R6b = H, R7 = N-1-methylpiperidin-4-yl, R8 =H, R3 = R4 = R5= H] cpd 76



^1H NMR (500 MHz, DMSO- d_6) δ = 8.60 (s, 1H), 8.43 (d, J = 7.93 Hz, 1H), 8.07 (d, J = 7.78 Hz, 1H), 7.73 (d, J = 9.30 Hz, 1H), 7.67 (d, J = 8.08 Hz, 2H), 7.35 (d, J = 8.08 Hz, 2H), 7.22 - 7.30 (m, 1H), 6.94 (t, J = 8.08 Hz, 2H), 6.24 (d, J

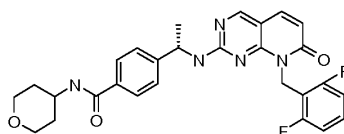
= 9.30 Hz, 1H), 5.53 (d, J = 14.79 Hz, 1H), 5.32 (d, J = 14.95 Hz, 1H), 5.05 (quin, J = 7.40 Hz, 1H), 3.61 - 3.78 (m, 1H), 2.75 (d, J = 11.29 Hz, 2H), 2.15 (s, 3H), 1.92 (t, J = 10.90 Hz, 2H), 1.72 (d, J = 11.59 Hz, 2H), 1.55 (tq, J = 3.70, 12.10 Hz, 2H), 1.38 (d, J = 7.02 Hz, 3H). LCMS : m/z 533 $[M+H]^+$ r.t. 4.82 min. HRMS (ESI) calcd for $C_{29}H_{31}F_2N_6O_2$ $[M + H]^+$ 533.2471 found 533.2473;

- 5 **8-(2,6-difluorobenzyl)-2-[[[(1S)-1-{4-[(4,4-difluoropiperidin-1-yl)carbonyl]phenyl}ethyl]amino} pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = 2,6-difluorobenzyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-CONR7R8, R6b = H, R7 = 4,4-difluoropiperidin-1-yl, R8 =H, R3 = R4 = R5= H] cpd 77**



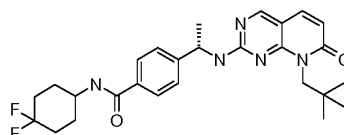
- 10 ^1H NMR (500 MHz, DMSO- d_6) δ = 8.61 (s, 1H), 8.43 (d, J = 8.39 Hz, 1H), 7.74 (d, J = 9.46 Hz, 1H), 7.34 - 7.39 (m, 2H), 7.31 (d, J = 7.93 Hz, 2H), 7.24 - 7.32 (m, 1H), 6.92 - 7.01 (m, J = 8.08, 8.08 Hz, 2H), 6.25 (d, J = 9.30 Hz, 1H), 5.54 (d, J = 14.95 Hz, 1H), 5.37 (d, J = 15.25 Hz, 1H), 5.04 - 5.19 (m, 1H), 3.66 (br. s., 2H), 3.40 (br. s, 2H), 2.01 (br. s, 4H), 1.39 (d, J = 7.02 Hz, 3H). LCMS : m/z 540 $[M+H]^+$ r.t. 6.03 min. HRMS (ESI) calcd for $C_{28}H_{26}F_4N_5O_2$ $[M + H]^+$ 540.2017 found 540.2028;

- 15 **4-[(1S)-1-[[8-(2,6-difluorobenzyl)-7-oxo-pyrido[2,3-d]pyrimidin-2-yl]amino]ethyl]-N-(tetrahydro-2H-pyran-4-yl) benzamide [(I), X = N, R2 = 2,6-difluorobenzyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-CONR7R8, R6b = H, R7 = tetrahydro-2H-pyran-4-yl, R8 =H, R3 = R4 = R5= H] cpd 78**



- 20 ^1H NMR (500 MHz, DMSO- d_6) δ = 8.61 (s, 1H), 8.44 (d, J = 7.93 Hz, 1H), 8.14 (d, J = 7.47 Hz, 1H), 7.73 (d, J = 9.30 Hz, 1H), 7.68 (d, J = 8.24 Hz, 2H), 7.36 (d, J = 8.24 Hz, 2H), 7.22 - 7.30 (m, 1H), 6.94 (t, J = 8.20 Hz, 2H), 6.24 (d, J = 9.15 Hz, 1H), 5.53 (d, J = 14.95 Hz, 1H), 5.32 (d, J = 15.10 Hz, 1H), 4.99 - 5.09 (m, 1H), 3.92 - 4.03 (m, 1H), 3.87 (d, J = 10.07 Hz, 2H), 3.37 (t, J = 11.60 Hz, 2H), 1.73 (tdd, J = 2.02, 3.91, 12.64 Hz, 2H), 1.49 - 1.61 (m, 2H), 1.39 (d, J = 6.86 Hz, 3H). LCMS : m/z 520 $[M+H]^+$ r.t. 5.2 min. HRMS (ESI) calcd for $C_{28}H_{28}F_2N_5O_3$ $[M + H]^+$ 520.2155 found 520.2153;

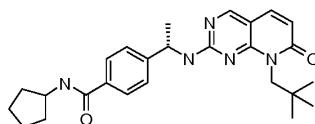
- 25 **N-(4,4-difluorocyclohexyl)-4-[(1S)-1-[[8-(2,2-dimethylpropyl)-7-oxo-pyrido[2,3-d]pyrimidin-2-yl]amino} ethyl] benzamide [(I), X = N, R2 = 2,2-dimethylpropyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-CONR7R8, R6b = H, R7 = 4,4-difluorocyclohexyl, R8 =H, R3 = R4 = R5= H] cpd 79**



^1H NMR (500 MHz, DMSO- d_6) δ = 8.48 - 8.62 (m, 1H), 8.44 (d, J = 7.32 Hz, 1H), 8.18 (d, J = 7.78 Hz, 1H), 7.79 (d, J = 8.08 Hz, 2H), 7.68 (d, J = 9.30 Hz, 1H), 7.45 (d, J = 8.08 Hz, 2H), 6.23 (d, J = 9.30 Hz, 1H), 5.11 (quin, J = 7.02

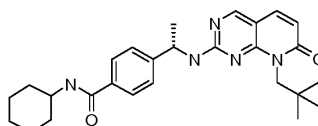
Hz, 1H), 3.91-4.07 (m, 3H), 1.81-2.07 (m, 6H), 1.55 - 1.67 (m, 2H), 1.47 (d, $J = 7.17$ Hz, 3H), 0.67 - 0.98 (m, 9H).
LCMS : m/z 498 $[M+H]^+$ r.t. 6.27 min. HRMS (ESI) calcd for $C_{27}H_{34}F_2N_5O_2$ $[M + H]^+$ 498.2675 found 498.269;

N-cyclopentyl-4-[(1S)-1-[[8-(2,2-dimethylpropyl)-7-oxo-pyrido[2,3-d]pyrimidin-2-yl]amino]ethyl]benzamide [(I),
X = N, R2 = 2,2-dimethylpropyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-CONR7R8, R6b = H, R7 = -cyclopentyl,
5 **R8 =H, R3 = R4 = R5= H] cpd 80**



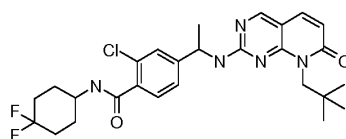
^1H NMR (500 MHz, DMSO- d_6) δ = 8.49 - 8.66 (m, 1H), 8.43 (d, $J = 7.47$ Hz, 1H), 8.15 (d, $J = 7.17$ Hz, 1H), 7.71 - 7.83 (m, 2H), 7.67 (d, $J = 9.30$ Hz, 1H), 7.44 (d, $J = 8.08$ Hz, 2H), 6.23 (d, $J = 9.30$ Hz, 1H), 5.12 (t, $J = 6.79$ Hz, 1H), 3.84 - 4.35 (m, 3H), 1.80 - 1.90 (m, 2H), 1.60 - 1.71 (m, 2H), 1.42 - 1.57 (m, 7H), 0.62 - 1.00 (m, 9H). LCMS : m/z 498 $[M+H]^+$ r.t. 6.21 min. HRMS (ESI) calcd for $C_{26}H_{34}N_5O_2$ $[M + H]^+$ 448.2707 found 448.2706;

N-cyclohexyl-4-[(1S)-1-[[8-(2,2-dimethylpropyl)-7-oxo-pyrido[2,3-d]pyrimidin-2-yl]amino]ethyl] benzamide [(I),
X = N, R2 = 2,2-dimethylpropyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-CONR7R8, R6b = H, R7 = cyclohexyl,
10 **R8 =H, R3 = R4 = R5= H] cpd 81**



15 ^1H NMR (500 MHz, DMSO- d_6) δ = 8.48 - 8.63 (m, 1H), 8.12 - 8.46 (m, 1H), 8.07 (d, $J = 8.08$ Hz, 1H), 7.71 - 7.83 (m, 2H), 7.59 - 7.70 (m, 1H), 7.44 (d, $J = 8.08$ Hz, 2H), 6.23 (d, $J = 9.30$ Hz, 1H), 4.83 - 5.33 (m, 1H), 3.90 - 4.35 (m, 2H), 3.73 (d, $J = 3.51$ Hz, 1H), 1.78 (br. s., 2H), 1.71 (br. s., 2H), 1.54 - 1.65 (m, $J = 11.74$ Hz, 1H), 1.47 (d, $J = 7.02$ Hz, 3H), 1.21 - 1.35 (m, 4H), 1.04 - 1.16 (m, 1H), 0.60 - 0.99 (m, 9H). LCMS : m/z 462 $[M+H]^+$ r.t. 6.51 min. HRMS (ESI) calcd for $C_{27}H_{36}N_5O_2$ $[M + H]^+$ 462.2864 found 462.2861;

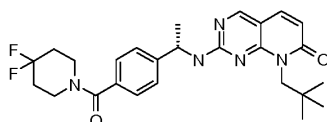
20 **2-chloro-N-(4,4-difluorocyclohexyl)-4-(1-[[8-(2,2-dimethylpropyl)-7-oxo-pyrido[2,3-d]pyrimidin-2-yl]amino]ethyl) benzamide [(I), X = N, R2 = 2,2-dimethylpropyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-CONR7R8, R6b = Cl, R7 = -4,4-difluorocyclohexyl, R8 =H, R3 = R4 = R5= H] cpd 82**



25 ^1H NMR (500 MHz, DMSO- d_6) δ = 8.50 - 8.64 (m, 1H), 8.46 (d, $J = 7.32$ Hz, 1H), 8.14 - 8.37 (m, 1H), 7.59 - 7.72 (m, 1H), 7.50 (d, $J = 8.54$ Hz, 1H), 7.22 - 7.41 (m, 2H), 6.25 (d, $J = 9.15$ Hz, 1H), 4.97 - 5.30 (m, 1H), 3.74 - 4.33 (m, 3H), 1.78 - 2.09 (m, 6H), 1.50 - 1.62 (m, 2H), 1.46 (d, $J = 7.17$ Hz, 3H), 0.72 - 0.99 (m, 9H).

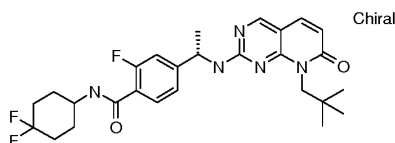
LCMS : m/z 532 $[M+H]^+$ r.t. 6.47 min. HRMS (ESI) calcd for $C_{27}H_{33}ClN_5O_2$ $[M + H]^+$ 532.2286 found 532.2276;

2-[[[(1S)-1-[4-[(4,4-difluoropiperidin-1-yl)carbonyl]phenyl]ethyl]amino]-8-(2,2-dimethylpropyl) pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = 2,2-dimethylpropyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-CONR7R8,
30 **R6b = H, R7 = 4,4-difluoropiperidin-1-yl, R8 =H, R3 = R4 = R5= H] cpd 83**

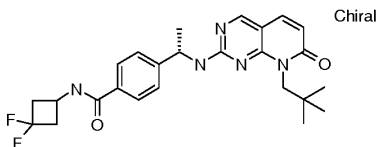


- ¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.56 (s, 1H), 8.24 (br. s., 1H), 7.66 (d, *J* = 9.15 Hz, 1H), 7.43 - 7.48 (m, 2H), 7.33 - 7.41 (m, 2H), 6.23 (d, *J* = 9.46 Hz, 1H), 5.17 (br. s., 1H), 3.90 - 4.28 (m, 2H), 3.55 (br. s., 4H), 1.88 - 2.10 (m, 4H), 1.51 (d, *J* = 7.02 Hz, 3H), 0.78 (br. s., 9H). LCMS : *m/z* 484 [M+H]⁺ r.t. 6.18 min. HRMS (ESI) calcd for C₂₆H₃₂ClF₂N₅O₂ [M + H]⁺ 484.2519 found 484.2524;

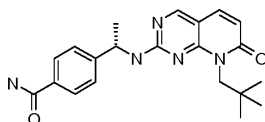
N-(4,4-difluorocyclohexyl)-4-((1-((8-(2,2-dimethylpropyl)-7-oxo-pyrido[2,3-d]pyrimidin-2-yl)amino)ethyl)-2-fluorobenzamide [(I), X = N, R₂ = 2,2-dimethylpropyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CONR₇R₈, R_{6b} = F, R₇ = 4,4-difluorocyclohexyl, R₈ = H, R₃ = R₄ = R₅ = H] cpd 84



- ¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.48 - 8.64 (m, 1H), 8.44 (d, *J* = 7.32 Hz, 1H), 8.19 (d, *J* = 7.63 Hz, 2H), 7.69 (d, *J* = 9.30 Hz, 1H), 7.05 - 7.35 (m, 2H), 6.25 (d, *J* = 9.30 Hz, 1H), 4.94 - 5.29 (m, *J* = 7.17, 7.17 Hz, 1H), 3.81 - 4.30 (m, 3H), 1.77 - 2.08 (m, 6H), 1.57 (d, *J* = 10.07 Hz, 2H), 1.46 (d, *J* = 7.02 Hz, 3H), 0.62 - 0.99 (m, 9H). LCMS : *m/z* 516 [M+H]⁺ r.t. 6.47 min. HRMS (ESI) calcd for C₂₇H₃₃F₃N₅O₂ [M + H]⁺ 516.2581 found 516.2584;
- N-(3,3-difluorocyclobutyl)-4-[(1S)-1-((8-(2,2-dimethylpropyl)-7-oxo-pyrido[2,3-d]pyrimidin-2-yl)amino)ethyl]benzamide [(I), X = N, R₂ = 2,2-dimethylpropyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CONR₇R₈, R_{6b} = H, R₇ = 3,3-difluorocyclobutyl, R₈ = H, R₃ = R₄ = R₅ = H] cpd 85**

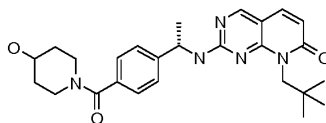


- ¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.71 (d, *J* = 6.71 Hz, 1H), 8.47 - 8.63 (m, 1H), 8.44 (d, *J* = 7.32 Hz, 1H), 7.80 (d, *J* = 7.78 Hz, 2H), 7.68 (d, *J* = 9.30 Hz, 1H), 7.26 - 7.57 (m, 2H), 6.23 (d, *J* = 9.30 Hz, 1H), 5.03 - 5.31 (m, 1H), 3.88 - 4.31 (m, 3H), 2.85 - 3.02 (m, 3H), 2.70 - 2.80 (m, 1H), 1.47 (d, *J* = 7.02 Hz, 3H), 0.54 - 1.02 (m, 9H). LCMS : *m/z* 470 [M+H]⁺ r.t. 6.05 min. HRMS (ESI) calcd for C₂₅H₂₉F₂N₅O₂ [M + H]⁺ 470.2362 found 470.2355;
- 4-[(1S)-1-((8-(2,2-dimethylpropyl)-7-oxo-pyrido[2,3-d]pyrimidin-2-yl)amino)ethyl]benzamide [(I), X = N, R₂ = 2,2-dimethylpropyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CONH₂, R_{6b} = H, R₃ = R₄ = R₅ = H] cpd 86**



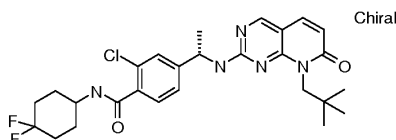
- ¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.58 (s, 1H), 8.43 (d, *J* = 7.17 Hz, 1H), 7.87 (br. s., 1H), 7.81 (d, *J* = 7.93 Hz, 2H), 7.68 (d, *J* = 9.15 Hz, 1H), 7.44 (d, *J* = 8.08 Hz, 2H), 7.27 (s, 1H), 6.23 (d, *J* = 9.30 Hz, 1H), 4.97 - 5.38 (m, *J* = 7.09 Hz, 1H), 3.81 - 4.34 (m, 2H), 1.47 (d, *J* = 7.02 Hz, 3H), 0.49 - 1.04 (m, 9H).
- LCMS : *m/z* 380 [M+H]⁺ r.t. 5.03 min. HRMS (ESI) calcd for C₂₁H₂₆N₅O₂ [M + H]⁺ 380.2081 found 380.2093;

8-(2,2-dimethylpropyl)-2-[[[(1S)-1-{4-[(4-hydroxypiperidin-1-yl)carbonyl]phenyl}ethyl]amino]pyrido [2,3-d] pyrimidin-7(8H)-one [(I), X = N, R2 = 2,2-dimethylpropyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-CONR7R8, R6b = H, R7 = 4-hydroxypiperidin-1-yl, R8 =H, R3 = R4 = R5= H] cpd 87



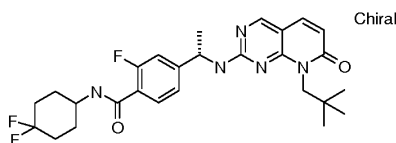
5 ¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.59 (s, 1H), 8.42 (d, *J* = 7.17 Hz, 1H), 7.68 (d, *J* = 9.30 Hz, 1H), 7.42 (d, *J* = 8.08 Hz, 2H), 7.31 (d, *J* = 7.93 Hz, 2H), 6.23 (d, *J* = 9.30 Hz, 1H), 5.08 (quin, *J* = 6.86 Hz, 1H), 4.78 (d, *J* = 3.81 Hz, 1H), 3.91-4.25 (m, 2H), 3.71 (dq, *J* = 3.28, 7.85 Hz, 1H), 3.42-3.49 (m, 2H), 3.04-3.22 (m, 2H), 1.61-1.79 (m, 2H), 1.48 (d, *J* = 7.02 Hz, 3H), 1.21-1.39 (m, 2H), 0.71 (br. s., 9H). LCMS : *m/z* 464 [M+H]⁺ r.t. 5.1 min. HRMS (ESI) calcd for C₂₆H₃₄N₅O₃ [M + H]⁺ 464.2656 found 464.2658;

10 2-chloro-N-(4,4-difluorocyclohexyl)-4-[[[(1S)-1-{8-(2,2-dimethylpropyl)-7-oxo-7,8-dihydropyrido[2,3-d] pyrimidin-2-yl]amino}ethyl]benzamide [(I), X = N, R2 = 2,2-dimethylpropyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-CONR7R8, R6b = Cl, R7 = 4,4-difluorocyclohexyl, R8 =H, R3 = R4 = R5= H] cpd 88



15 ¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.59 (s, 1H), 8.46 (d, *J* = 7.63 Hz, 1H), 8.36 (d, *J* = 7.32 Hz, 1H), 7.68 (d, *J* = 9.30 Hz, 1H), 7.51 (s, 1H), 7.27 - 7.43 (m, 2H), 6.25 (d, *J* = 9.15 Hz, 1H), 5.09 (quin, *J* = 6.79 Hz, 1H), 3.97 - 4.29 (m, 2H), 3.84 - 3.97 (m, 1H), 1.88 - 2.11 (m, 4H), 1.85 (d, *J* = 12.66 Hz, 2H), 1.50 - 1.65 (m, 2H), 1.46 (d, *J* = 7.02 Hz, 3H), 0.84 (br. s., 9H). LCMS : *m/z* 532 [M+H]⁺ r.t. 6.58 min. HRMS (ESI) calcd for C₂₇H₃₃ClF₂N₅O₃ [M + H]⁺ 532.2286 found 532.2289;

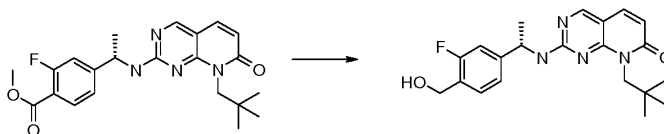
20 N-(4,4-difluorocyclohexyl)-4-[[[(1S)-1-{8-(2,2-dimethylpropyl)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl] amino}ethyl]-2-fluorobenzamide [(I), X = N, R2 = 2,2-dimethylpropyl, A = phenyl, R1a= H, R1b = Me, R6a= 4- CONR7R8, R6b = F, R7 = 4,4-difluorocyclohexyl, R8 =H, R3 = R4 = R5= H] cpd 89



25 ¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.48 - 8.64 (m, 1H), 8.44 (d, *J* = 7.63 Hz, 1H), 8.19 (d, *J* = 7.78 Hz, 1H), 7.69 (d, *J* = 9.30 Hz, 1H), 7.41 - 7.54 (m, 1H), 7.07 - 7.34 (m, 2H), 6.25 (d, *J* = 9.30 Hz, 1H), 4.99 - 5.30 (m, *J* = 6.48, 6.48 Hz, 1H), 3.84 - 4.31 (m, 3H), 1.78 - 2.07 (m, 6H), 1.52 - 1.64 (m, *J* = 10.37 Hz, 2H), 1.46 (d, *J* = 7.02 Hz, 3H), 0.62 - 0.98 (m, 9H). LCMS : *m/z* 516 [M+H]⁺ r.t. 6.48 min. HRMS (ESI) calcd for C₂₇H₃₃F₃N₅O₃ [M + H]⁺ 516.2581 found 516.2580.

Example 7

8-(2,2-dimethylpropyl)-2-(((1S)-1-[3-fluoro-4-(hydroxymethyl)phenyl]ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = 2,2-dimethylpropyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-CH₂OR7, R6b = F, R7 = H, R3 = R4 = R5= H] conv. 1, cpd 90

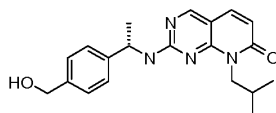


- 5 Methyl 4-(((1S)-1-[[8-(2,2-dimethylpropyl)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl]amino]ethyl)-2-fluorobenzoate (100 mg, 0.24 mmol) was dissolved in 5 mL of dry THF under argon atmosphere at 0°C, and LiAlH₄ (1.0 mL of a 1M solution) was added. The reaction was completed in 30 min, few drops of aqueous NaHCO₃ was added to form a colloidal precipitate. The suspension was diluted with EtOAc and decanted to collect the organic fraction. The pooled organic layers were dried, filtered and evaporated to give the wanted product 8-(2,2-dimethylpropyl)-2-(((1S)-1-[3-fluoro-4-(hydroxymethyl)phenyl]ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one as an yellow fluorescent oil.

10 ¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.58 (s, 1H), 8.38 (d, *J* = 7.32 Hz, 1H), 7.68 (d, *J* = 9.46 Hz, 1H), 7.32 - 7.42 (m, 1H), 7.19 (d, *J* = 7.78 Hz, 1H), 7.13 (d, *J* = 11.29 Hz, 1H), 6.23 (d, *J* = 9.15 Hz, 1H), 5.17 (t, *J* = 5.72 Hz, 1H), 5.07 (quin, *J* = 7.32 Hz, 1H), 4.47 (d, *J* = 5.64 Hz, 2H), 3.91 - 4.32 (m, 2H), 1.45 (d, *J* = 7.02 Hz, 3H), 0.77 (br. s., 9H). LCMS : *m/z* 385 [M+H]⁺ r.t. 5.63 min. HRMS (ESI) calcd for C₂₁N₂FN₄O₂ [M + H]⁺ 385.2035 found 385.2043.

- 15 Operating in an analogous way, but employing suitably substituted starting materials, the following compounds were obtained:

2-(((1S)-1-[4-(hydroxymethyl)phenyl]ethyl)amino)-8-(2-methylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = 2-methylpropyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-CH₂OR7, R6b = H, R7 = H, R3 = R4 = R5= H] cpd 91

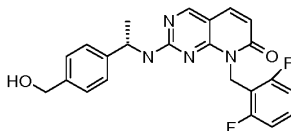


20

¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.57 (s, 1H), 8.51 (d, *J* = 7.78 Hz, 1H), 7.68 (d, *J* = 9.30 Hz, 1H), 7.32 (d, *J* = 8.08 Hz, 2H), 7.23 (d, *J* = 8.08 Hz, 2H), 6.21 (d, *J* = 9.15 Hz, 1H), 5.10 (t, *J* = 5.64 Hz, 1H), 4.92 - 5.05 (m, 1H), 4.43 (d, *J* = 5.80 Hz, 2H), 3.93 - 4.00 (m, 1H), 3.84 - 3.90 (m, 1H), 1.89-1.97 (m, 1H), 1.46 (d, *J* = 7.02 Hz, 3H), 0.78 (d, *J* = 6.71 Hz, 3H), 0.69 (d, *J* = 6.56 Hz, 3H). LCMS : *m/z* 353 [M+H]⁺ r.t. 5.29 min. HRMS (ESI) calcd for C₂₀N₂N₄O₂ [M + H]⁺ 353.1972 found 353.197;

25

8-(2,6-difluorobenzyl)-2-(((1S)-1-[4-(hydroxymethyl)phenyl]ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = 2,6-difluorobenzyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-CH₂OR7, R6b = H, R7 = H, R3 = R4 = R5= H] cpd 92

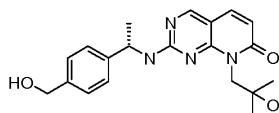


30

¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.58 (s, 1H), 8.34 (d, *J* = 8.54 Hz, 1H), 7.73 (d, *J* = 9.46 Hz, 1H), 7.27 - 7.37 (m, 1H), 7.24 (d, *J* = 7.93 Hz, 2H), 7.14 (d, *J* = 7.93 Hz, 2H), 6.98 (t, *J* = 8.24 Hz, 2H), 6.24 (d, *J* = 9.30 Hz, 1H), 5.55 (d,

$J = 15.10$ Hz, 1H), 5.37 (d, $J = 14.79$ Hz, 1H), 5.08 (t, $J = 5.64$ Hz, 1H), 5.02 (quin, $J = 7.50$ Hz, 1H), 4.39 (d, $J = 5.64$ Hz, 2H), 1.36 (d, $J = 7.17$ Hz, 3H). LCMS : m/z 423 $[M+H]^+$ r.t. 5.25 min. HRMS (ESI) calcd for $C_{23}N_2F_2N_4O_2$ $[M+H]^+$ 423.1627 found 423.162;

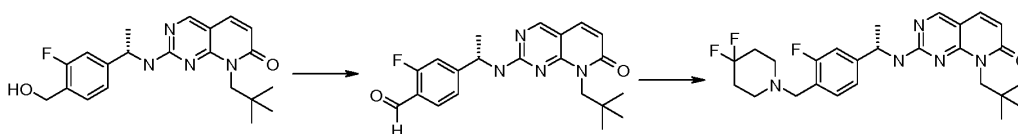
- 2-({(1S)-1-[4-(hydroxymethyl)phenyl]ethyl}amino)-8-(2-hydroxy-2-methylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = 2-hydroxy-2-methylpropyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-CH₂OR7, R6b = F, R7 = H, R3 = R4 = R5= H] cpd 93



- ¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.62 (s, 1H), 8.48 (d, $J = 7.8$ Hz, 1H), 7.73 (d, $J = 9.3$ Hz, 1H), 7.34 (d, $J = 7.9$ Hz, 2H), 7.24 (d, $J = 8.1$ Hz, 2H), 6.27 (d, $J = 9.3$ Hz, 1H), 5.09 (t, $J = 5.7$ Hz, 1H), 5.05 (quin, $J = 7.2$ Hz, 1H), 4.63 (s, 1H), 4.43 (d, $J = 5.8$ Hz, 2H), 4.38 - 4.18 (m, 2H), 1.45 (d, $J = 6.9$ Hz, 3H), 1.09 - 0.90 (m, 6H). LCMS : m/z 369 $[M+H]^+$ r.t. 4.47 min. HRMS (ESI) calcd for $C_{26}N_2O_3$ $[M+H]^+$ 369.1921 found 369.1921.

Example 8

- 2-({(1S)-1-[4-[(4,4-difluoropiperidin-1-yl)methyl]-3-fluorophenyl]ethyl}amino)-8-(2,2-dimethylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = 2,2-dimethylpropyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-CH₂NR7R8, R6b = F, R7-R8 = 4,4-difluoropiperidin-1-yl, R3 = R4 = R5= H] conv. 2, cpd 94



Step1: Preparation of 4-[(1S)-1-[8-(2,2-dimethylpropyl)-7-oxo-pyrido[2,3-d]pyrimidin-2-yl]amino]ethyl]-2-fluorobenzaldehyde

- 8-(2,2-dimethylpropyl)-2-({(1S)-1-[3-fluoro-4-(hydroxymethyl)phenyl]ethyl}amino)pyrido[2,3-d]pyrimidin-7(8H)-one (75 mg, 0.2 mmol) was dissolved in DCM (10 mL) in the presence of manganese dioxide (347 mg, 4.0 mmol) and stirred at room temperature for 18h. The solution was filtered through a pad of celite and washed with DCM. The filtrate was concentrated to give the corresponding aldehyde used in the next step without further purification.

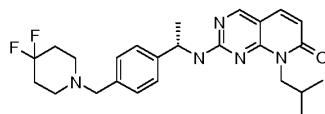
Step 2: Preparation of the title compound

- 4-[(1S)-1-[8-(2,2-dimethylpropyl)-7-oxo-pyrido[2,3-d]pyrimidin-2-yl]amino]ethyl]-2-fluorobenzaldehyde (30 mg, 0.08 mmol) was reacted with 4,4-difluoropiperidine hydrochloride (25 mg, 0.16 mmol) in the presence of sodium triacetoxyborohydride (102 mg, 0.48 mmol) in THF for 4h. When the reaction was complete, it was worked up with NaHCO₃ and AcOEt. The organic phase was evaporated under vacuum and the crude purified by column chromatography with (DCM/EtOAc/EtOH : 7/2/1) to give the title compound.

- ¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.59 (s, 1H), 8.38 (d, $J = 7.17$ Hz, 1H), 7.68 (d, $J = 9.30$ Hz, 1H), 7.28 - 7.38 (m, 1H), 7.06 - 7.24 (m, 2H), 6.24 (d, $J = 9.15$ Hz, 1H), 4.87 - 5.40 (m, $J = 7.02$, 7.02 Hz, 1H), 3.76 - 4.40 (m, 2H), 3.55 (s, 2H), 2.47 (br. s., 4H), 1.80 - 1.97 (m, 4H), 1.46 (d, $J = 7.02$ Hz, 3H), 0.50 - 1.02 (m, 9H). LCMS : m/z 488 $[M+H]^+$ r.t. 7.15 min. HRMS (ESI) calcd for $C_{26}N_3F_3N_5O$ $[M+H]^+$ 488.2632 found 488.2636.

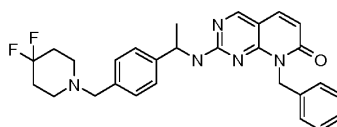
According to the same method, but employing others amines, the following compounds were prepared:

2-[[[(1S)-1-{4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl}ethyl]amino]-8-(2-methylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = 2-methylpropyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = 4,4-difluoropiperidin-1-yl, R₃ = R₄ = R₅ = H] cpd 95



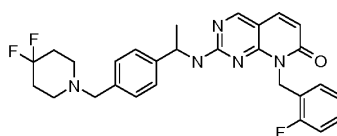
5 ¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.58 (s, 1H), 8.40 (d, *J* = 7.02 Hz, 1H), 7.69 (d, *J* = 9.30 Hz, 1H), 7.30 - 7.34 (m, 2H), 7.23 (d, *J* = 7.93 Hz, 2H), 6.21 (d, *J* = 9.30 Hz, 1H), 4.99-5.03 (m, 1H), 3.81-4.06 (m, 2H), 3.47 (s, 2H), 2.43 (br. s., 4H), 1.84 - 2.00 (m, 5H), 1.46 (d, *J* = 7.02 Hz, 3H), 0.72 (d, *J* = 6.56 Hz, 3H), 0.60 (d, *J* = 6.56 Hz, 3H). LCMS : m/z 456 [M+H]⁺ r.t. 6.9 min. HRMS (ESI) calcd for C₂₅N₃F₂N₅O [M + H]⁺ 456.257 found 456.257;

8-benzyl-2-[[1-{4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl}ethyl]amino]pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = benzyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = 4,4-difluoropiperidin-1-yl, R₃ = R₄ = R₅ = H] cpd 96



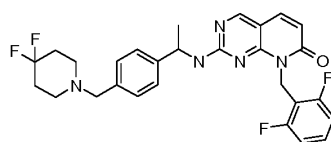
15 ¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.61 (s, 1H), 8.42 (d, *J* = 8.08 Hz, 1H), 7.74 (d, *J* = 9.30 Hz, 1H), 6.98 - 7.38 (m, 9H), 6.28 (d, *J* = 9.30 Hz, 1H), 5.44 (d, *J* = 14.18 Hz, 1H), 5.20 (d, *J* = 14.18 Hz, 1H), 4.94 - 5.12 (m, 1H), 3.46 (s, 2H), 2.39 - 2.46 (m, 4H), 1.83 - 1.98 (m, 4H), 1.34 - 1.49 (m, 3H). LCMS : m/z 490 [M+H]⁺ r.t. 7.87 min. HRMS (ESI) calcd for C₂₈N₃F₂N₅O [M + H]⁺ 490.2413 found 490.2403;

2-[[1-{4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl}ethyl]amino]-8-(2-fluorobenzyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = 2-fluorobenzyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = 4,4-difluoropiperidin-1-yl, R₃ = R₄ = R₅ = H] cpd 97



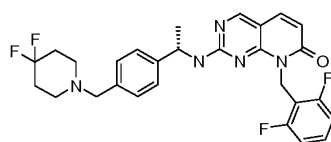
20 ¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.58 - 8.67 (m, 1H), 8.07 - 8.47 (m, 1H), 7.79 (d, *J* = 9.46 Hz, 1H), 7.19 - 7.36 (m, 2H), 7.15 (d, *J* = 7.93 Hz, 2H), 7.07 (d, *J* = 7.93 Hz, 2H), 6.96 (t, *J* = 7.17 Hz, 1H), 6.54 - 6.82 (m, 1H), 6.31 (d, *J* = 9.46 Hz, 1H), 5.44 - 5.55 (m, 1H), 5.24 - 5.36 (m, 1H), 4.73 - 5.12 (m, 1H), 3.41 - 3.48 (m, 2H), 2.42 (br. s., 6H), 1.83 - 1.99 (m, 4H), 1.32 - 1.44 (m, 3H). LCMS : m/z 508 [M+H]⁺ r.t. 8.2 min. HRMS (ESI) calcd for C₂₈N₃F₃N₅O [M + H]⁺ 508.2319 found 508.2307;

25 8-(2,6-difluorobenzyl)-2-[[1-{4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl}ethyl]amino]pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = 2,6-difluorobenzyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = 4,4-difluoropiperidin-1-yl, R₃ = R₄ = R₅ = H] cpd 98



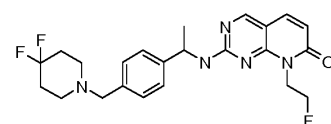
- ¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.59 (s, 1H), 8.34 (d, *J* = 8.39 Hz, 1H), 7.73 (d, *J* = 9.30 Hz, 1H), 7.28 - 7.38 (m, 1H), 7.21 - 7.28 (m, 2H), 7.13 (d, *J* = 7.93 Hz, 2H), 6.97 (t, *J* = 8.24 Hz, 2H), 6.24 (d, *J* = 9.46 Hz, 1H), 5.55 (d, *J* = 14.95 Hz, 1H), 5.35 (d, *J* = 14.95 Hz, 1H), 4.99 - 5.13 (m, 1H), 3.43 (s, 2H), 2.42 (br. s., 4H), 1.86 - 1.97 (m, 4H), 1.31 - 1.50 (m, 3H). LCMS : *m/z* 526 [M+H]⁺ r.t. 8.03 min. HRMS (ESI) calcd for C₂₈N₂₈F₄N₅O [M + H]⁺ 526.2225 found 526.2216;

8-(2,6-difluorobenzyl)-2-[[[(1S)-1-{4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl}ethyl]amino]pyrido[2,3-d]pyrimidin-7(8H)-one one [(I), X = N, R₂ = 2,6-difluorobenzyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = 4,4-difluoropiperidin-1-yl, R₃ = R₄ = R₅ = H] cpd 99



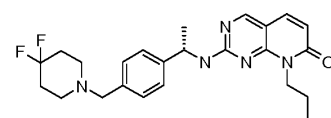
- ¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.59 (s, 1H), 8.34 (d, *J* = 8.39 Hz, 1H), 7.73 (d, *J* = 9.30 Hz, 1H), 7.28 - 7.42 (m, 1H), 7.25 (d, *J* = 7.93 Hz, 2H), 7.09 - 7.21 (m, 2H), 6.91 - 7.06 (m, 2H), 6.24 (d, *J* = 9.30 Hz, 1H), 5.55 (d, *J* = 15.10 Hz, 1H), 5.35 (d, *J* = 15.25 Hz, 1H), 4.99 - 5.28 (m, 1H), 3.43 (s, 1H), 3.34 (br. s., 1H), 2.42 (br. s., 4H), 1.86 - 1.97 (m, 4H), 1.34 - 1.49 (m, 3H). LCMS : *m/z* 526 [M+H]⁺ r.t. 8.05 min. HRMS (ESI) calcd for C₂₈N₂₈F₄N₅O [M + H]⁺ 526.2225 found 526.2215;

2-[[[(1S)-1-{4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl}ethyl]amino]-8-(2-fluoroethyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = 2-fluoroethyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = 4,4-difluoropiperidin-1-yl, R₃ = R₄ = R₅ = H] cpd 100



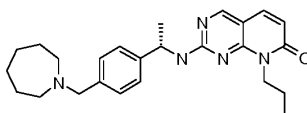
- ¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.53 - 8.64 (m, 1H), 8.48 (d, *J* = 7.17 Hz, 1H), 7.69 - 7.73 (m, 1H), 7.33 (d, *J* = 7.93 Hz, 2H), 7.23 (d, *J* = 8.08 Hz, 2H), 6.15 - 6.31 (m, 1H), 4.93 - 5.28 (m, 1H), 4.14-4.52 (m, 4H), 3.47 (s, 2H), 2.43 (br. s., 4H), 1.80 - 1.97 (m, 4H), 1.46 (d, *J* = 7.17 Hz, 3H). LCMS : *m/z* 446 [M+H]⁺ r.t. 5.76 min. HRMS (ESI) calcd for C₂₈N₂₇F₃N₅O [M + H]⁺ 446.2162 found 446.2162.

- 2-[[[(1S)-1-{4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl}ethyl]amino]-8-propylpyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = propyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = 4,4-difluoropiperidin-1-yl, R₃ = R₄ = R₅ = H] cpd 101**



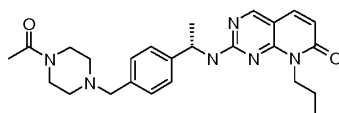
¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.53 - 8.64 (m, 1H), 8.48 (d, *J* = 7.17 Hz, 1H), 7.69 - 7.73 (m, 1H), 7.33 (d, *J* = 7.93 Hz, 2H), 7.23 (d, *J* = 8.08 Hz, 2H), 6.15 - 6.31 (m, 1H), 4.93 - 5.28 (m, 1H), 3.88-4.10 (m, 2H), 3.47 (br. s., 2H), 2.43 (br. s., 4H), 1.80 - 1.97 (m, 4H), 1.46 (d, *J* = 7.17 Hz, 3H), 1.31-1.40 (m, 2H), 0.78 (t, *J* = 7.32 Hz, 3H). LCMS : *m/z* 442 [M+H]⁺ r.t. 6.58 min. HRMS (ESI) calcd for C₂₄N₃F₂N₅O [M + H]⁺ 442.2413 found 442.2411;

- 5 **2-(((1S)-1-[4-(azepan-1-ylmethyl)phenyl]ethyl)amino)-8-propylpyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = propyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = azepan-1-yl, R₃ = R₄ = R₅ = H] cpd 102**



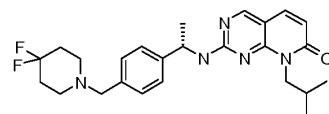
- 10 ¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.57 (s, 1H), 8.41 (d, *J* = 7.32 Hz, 1H), 7.67 (d, *J* = 9.30 Hz, 1H), 7.31 (d, *J* = 7.63 Hz, 2H), 7.23 (d, *J* = 7.78 Hz, 2H), 6.20 (d, *J* = 9.15 Hz, 1H), 4.95 - 5.32 (m, 1H), 3.85 - 4.21 (m, 2H), 3.51-3.58 (m, 2H), 2.54 (br. s., 4H), 1.53 (br. s., 8H), 1.46 (d, *J* = 7.02 Hz, 3H), 1.17 - 1.42 (m, 2H), 0.79 (t, *J* = 7.40 Hz, 3H). LCMS : *m/z* 420 [M+H]⁺ r.t. 4.95 min. HRMS (ESI) calcd for C₂₅N₃N₅O [M + H]⁺ 420.2758 found 420.2763;

- 15 **2-(((1S)-1-[4-((4-acetylpiperazin-1-yl)methyl)phenyl]ethyl)amino)-8-propylpyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = propyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = 4-acetylpiperazin-1-yl, R₃ = R₄ = R₅ = H] cpd 103**



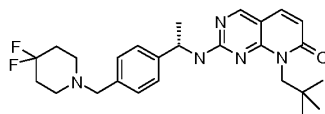
- 20 ¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.58 (s, 1H), 8.42 (d, *J* = 7.32 Hz, 1H), 7.67 (d, *J* = 9.30 Hz, 1H), 7.32 (d, *J* = 8.08 Hz, 2H), 7.22 (d, *J* = 7.93 Hz, 2H), 6.20 (d, *J* = 9.30 Hz, 1H), 4.97 - 5.26 (m, 1H), 3.85 - 4.12 (m, 2H), 3.43-3.46 (m, 6H), 2.17 - 2.33 (m, 4H), 1.95 (s, 3H), 1.46 (d, *J* = 7.17 Hz, 3H), 1.22 - 1.40 (m, 2H), 0.78 (t, *J* = 7.40 Hz, 3H). LCMS : *m/z* 449 [M+H]⁺ r.t. 4.97 min. HRMS (ESI) calcd for C₂₅N₃N₆O₂ [M + H]⁺ 449.266 found 449.2663;

2-(((1S)-1-[4-((4,4-difluoropiperidin-1-yl)methyl)phenyl]ethyl)amino)-8-(2-methylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = 2-propyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = 4,4-difluoropiperidin-1-yl, R₃ = R₄ = R₅ = H] cpd 104



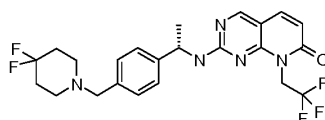
- 25 ¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.51 - 8.63 (m, 1H), 8.41 (d, *J* = 7.32 Hz, 1H), 7.69 (d, *J* = 9.15 Hz, 1H), 7.32 (d, *J* = 7.93 Hz, 2H), 7.23 (d, *J* = 8.08 Hz, 2H), 6.14 - 6.29 (m, 1H), 4.97 - 5.30 (m, 1H), 3.97 (dd, *J* = 7.40, 12.12 Hz, 1H), 3.83 (dd, *J* = 7.70, 12.28 Hz, 1H), 3.48 (s, 2H), 2.43 (br. s., 4H), 1.83 - 1.96 (m, 5H), 1.46 (d, *J* = 7.02 Hz, 3H), 0.73 (d, *J* = 6.71 Hz, 3H), 0.60 (d, *J* = 6.56 Hz, 3H). LCMS : *m/z* 456 [M+H]⁺ r.t. 6.89 min. HRMS (ESI) calcd for C₂₅N₃F₂N₅O [M + H]⁺ 456.257 found 456.2564;

2-[[[(1S)-1-{4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl}ethyl]amino]-8-(2,2-dimethylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = 2,2-dimethylpropyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-CH₂NR7R8, R6b = H, R7-R8 = 4,4-difluoropiperidin-1-yl, R3 = R4 = R5= H] cpd 105



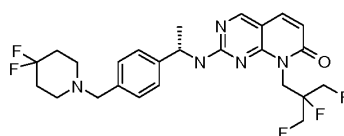
- 5 ¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.57 (s, 1H), 8.36 (d, *J* = 7.17 Hz, 1H), 7.67 (d, *J* = 9.00 Hz, 1H), 7.31 - 7.35 (m, 2H), 7.23 (d, *J* = 8.24 Hz, 2H), 6.22 (d, *J* = 9.15 Hz, 1H), 5.04 - 5.11 (m, 1H), 3.96-4.26 (m, 2H), , 3.48 (s, 2H), 2.44 (d, *J* = 4.12 Hz, 4H), 1.84 - 1.99 (m, 4H), 1.45 (d, *J* = 7.02 Hz, 3H), 0.68-0.94 (m, 9H). LCMS : *m/z* 470 [M+H]⁺ r.t. 7.23 min. HRMS (ESI) calcd for C₂₆N₃F₂N₅O [M + H]⁺ 470.2726 found 470.2723;

- 2-[[[(1S)-1-{4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl}ethyl]amino]-8-(2,2,2-trifluoroethyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = 2,2,2-trifluoroethyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-CH₂NR7R8, R6b = H, R7-R8 = 4,4-difluoropiperidin-1-yl, R3 = R4 = R5= H] cpd 106



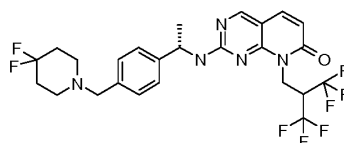
- 15 ¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.61 - 8.68 (m, 1H), 8.29 - 8.60 (m, 1H), 7.63 - 7.84 (m, 1H), 7.33 (d, *J* = 7.78 Hz, 2H), 7.23 (d, *J* = 8.24 Hz, 2H), 6.28 (d, *J* = 9.30 Hz, 1H), 4.98 - 5.11 (m, 2H), 4.64 - 4.88 (m, 1H), 3.48 (s, 2H), 2.43 (br. s., 4H), 1.79 - 1.97 (m, 4H), 1.46 (d, *J* = 7.02 Hz, 3H). LCMS : *m/z* 482 [M+H]⁺ r.t. 6.64 min. HRMS (ESI) calcd for C₂₃H₂₅F₅N₅O [M + H]⁺ 482.1974 found 482.1974;

8-[2,3-difluoro-2-(fluoromethyl)propyl]-2-[[[(1S)-1-{4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl}ethyl] amino]pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = 2,3-difluoro-2-(fluoromethyl)propyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-CH₂NR7R8, R6b = H, R7-R8 = 4,4-difluoropiperidin-1-yl, R3 = R4 = R5= H] cpd 107



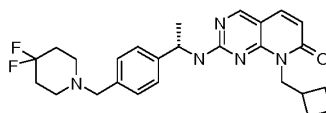
- 20 ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.55 - 8.66 (m, 1H), 8.49 (d, *J* = 8.08 Hz, 1H), 7.74 (d, *J* = 9.30 Hz, 1H), 7.37 (d, *J* = 7.78 Hz, 2H), 7.24 (d, *J* = 7.93 Hz, 2H), 6.16 - 6.34 (m, 1H), 5.18-5.21 (m, 1H), 4.35-4.66 (m, 6H), 3.47 (s, 2H), 2.44 (br. s., 4H), 1.84 - 1.99 (m, 4H), 1.42 - 1.53 (m, 3H). LCMS : *m/z* 510 [M+H]⁺ r.t. 6.42 min. HRMS (ESI) calcd for C₂₆H₂₉F₅N₅O [M + H]⁺ 510.2287 found 510.2287;

- 25 2-[[[(1S)-1-{4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl}ethyl]amino]-8-[3,3,3-trifluoro-2-(trifluoromethyl)propyl]pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = 3,3,3-trifluoro-2-(trifluoromethyl)propyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-CH₂NR7R8, R6b = H, R7-R8 = 4,4-difluoropiperidin-1-yl, R3 = R4 = R5= H] cpd 108



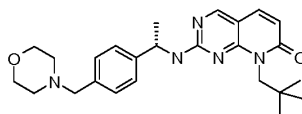
¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.65 (s, 1H), 8.55 (d, *J* = 7.93 Hz, 1H), 7.76 (d, *J* = 9.46 Hz, 1H), 7.26 - 7.31 (m, 2H), 7.20 - 7.26 (m, 2H), 6.27 (d, *J* = 9.30 Hz, 1H), 5.04 - 5.15 (m, 1H), 4.66 - 4.80 (m, 1H), 4.52 (dd, *J* = 6.41, 13.88 Hz, 1H), 4.09 - 4.29 (m, *J* = 8.08 Hz, 1H), 3.47 (s, 2H), 2.43 (br. s., 4H), 1.85 - 1.98 (m, 4H), 1.44 - 1.53 (m, 3H). LCMS : *m/z* 564 [M+H]⁺ r.t. 7.23 min. HRMS (ESI) calcd for C₂₅H₂₆F₈N₅O [M + H]⁺ 564.2004 found 564.1195;

- 5 **8-(cyclobutylmethyl)-2-((1*S*)-1-{4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl}ethyl)amino)pyrido[2,3-*d*]pyrimidin-7(8H)-one** [(I), X = N, R₂ = cyclobutylmethyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = 4,4-difluoropiperidin-1-yl, R₃ = R₄ = R₅ = H] cpd 109



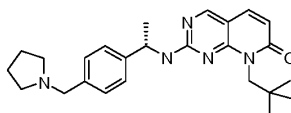
- 10 ¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.57 (s, 1H), 8.42 (d, *J* = 7.32 Hz, 1H), 7.66 (d, *J* = 9.30 Hz, 1H), 7.33 (d, *J* = 7.93 Hz, 2H), 7.25 (d, *J* = 7.93 Hz, 2H), 6.20 (d, *J* = 9.30 Hz, 1H), 4.99 - 5.32 (m, 1H), 4.17 (dd, *J* = 7.24, 12.43 Hz, 1H), 4.06 (dd, *J* = 7.70, 12.43 Hz, 1H), 3.48 (s, 2H), 2.43 (br. s., 4H), 2.10-2.22 (m, 2H), 2.01-2.09 (m, 1H), 1.91 (t, *J* = 13.96 Hz, 4H), 1.66 - 1.76 (m, 4H), 1.47 (d, *J* = 7.02 Hz, 3H). LCMS : *m/z* 468 [M+H]⁺ r.t. 6.96 min. HRMS (ESI) calcd for C₂₆H₃₂F₂N₅O [M + H]⁺ 468.257 found 468.2566;

- 15 **8-(2,2-dimethylpropyl)-2-((1*S*)-1-[4-(morpholin-4-ylmethyl)phenyl]ethyl)amino)pyrido[2,3-*d*]pyrimidin-7(8H)-one** [(I), X = N, R₂ = 2,2-dimethylpropyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = morpholin-4-yl, R₃ = R₄ = R₅ = H] cpd 110



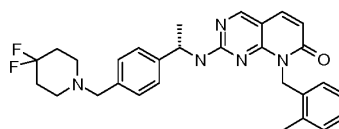
- 20 ¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.57 (s, 1H), 8.36 (d, *J* = 7.47 Hz, 1H), 7.67 (d, *J* = 9.15 Hz, 1H), 7.32 (d, *J* = 7.93 Hz, 2H), 7.22 (d, *J* = 7.93 Hz, 2H), 6.22 (d, *J* = 9.30 Hz, 1H), 4.91 - 5.31 (m, *J* = 6.90 Hz, 1H), 3.89 - 4.30 (m, 2H), 3.53 (t, *J* = 4.42 Hz, 4H), 3.39 (s, 2H), 2.30 (br. s., 4H), 1.45 (d, *J* = 7.02 Hz, 3H), 0.47 - 0.99 (m, 9H). LCMS : *m/z* 436 [M+H]⁺ r.t. 5.8 min. HRMS (ESI) calcd for C₂₅H₃₄N₅O₂ [M + H]⁺ 436.2707 found 436.2716;

8-(2,2-dimethylpropyl)-2-((1*S*)-1-[4-(pyrrolidin-1-ylmethyl)phenyl]ethyl)amino)pyrido[2,3-*d*]pyrimidin-7(8H)-one [(I), X = N, R₂ = 2,2-dimethylpropyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = pyrrolidin-1-yl, R₃ = R₄ = R₅ = H] cpd 111



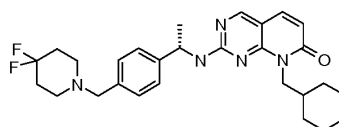
- 25 ¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.47 - 8.66 (m, 1H), 7.99 - 8.44 (m, 1H), 7.67 (d, *J* = 9.15 Hz, 1H), 7.31 (d, *J* = 8.08 Hz, 2H), 7.22 (d, *J* = 7.63 Hz, 2H), 6.22 (d, *J* = 9.15 Hz, 1H), 4.95 - 5.35 (m, *J* = 7.17, 7.17 Hz, 1H), 3.83 - 4.30 (m, 2H), 3.51 (br. s., 2H), 2.32 - 2.43 (m, 4H), 1.66 (br. s., 4H), 1.45 (d, *J* = 7.02 Hz, 3H), 0.56 - 1.00 (m, 9H). LCMS : *m/z* 420 [M+H]⁺ r.t. 5.29 min. HRMS (ESI) calcd for C₂₅H₃₄N₅O [M + H]⁺ 420.2758 found 420.2761.

2-[[[(1S)-1-{4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl}ethyl]amino]-8-(2-methylbenzyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = 2-methylbenzyl, A = phenyl, R1a = H, R1b = Me, R6a = 4-CH₂NR7R8, R6b = H, R7-R8 = 4,4-difluoropiperidin-1-yl, R3 = R4 = R5 = H] cpd 112



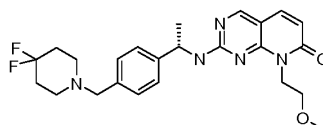
- 5 ¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.63 (s, 1H), 8.35 (d, *J* = 8.08 Hz, 1H), 7.80 (d, *J* = 9.30 Hz, 1H), 8.47 - 7.23 (dd, *J* = 7.78, 7.23, Hz, 1H), 7.11 (dd, *J* = 7.17 Hz, 1H), 7.0.3 (d, *J* = 8.24 Hz, 2H), 7.0 (d, *J* = 8.24 Hz, 2H), 6.92 (dd, *J* = 7.47 Hz, 1H), 6.37 (d, *J* = 7.78 Hz, 1H), 6.32 (d, *J* = 9.30 Hz, 1H), 5.40 (d, *J* = 15.25 Hz, 1H), 5.19 (d, *J* = 15.25 Hz, 1H), 4.82 (m, *J* = 7.32 Hz, 1H), 3.46 (br. s., 2H), 2.43 (s, 3H), 2.38-2.42 (m, 4H), 1.87-1.96 (m, 4H), 1.33 (d, *J* = 6.86 Hz, 3H). LCMS : *m/z* 504 [M+H]⁺ r.t. 6.97 min. HRMS (ESI) calcd for C₂₉H₃₂F₂N₅O [M + H]⁺ 504.257 found 504.2578;

8-(cyclohexylmethyl)-2-[[[(1S)-1-{4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl}ethyl]amino]pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = cyclohexylmethyl, A = phenyl, R1a = H, R1b = Me, R6a = 4-CH₂NR7R8, R6b = H, R7-R8 = 4,4-difluoropiperidin-1-yl, R3 = R4 = R5 = H] cpd 113



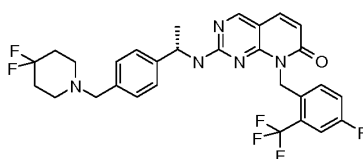
- 15 ¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.58 (s, 1H), 8.41 (d, *J* = 7.63 Hz, 1H), 7.68 (d, *J* = 9.46 Hz, 1H), 7.33 (d, *J* = 8.08 Hz, 2H), 7.24 (d, *J* = 7.93 Hz, 2H), 6.20 (d, *J* = 9.30 Hz, 1H), 5.08 (quin, *J* = 7.17 Hz, 1H), 4.02 (dd, *J* = 7.40, 12.28 Hz, 1H), 3.87 (dd, *J* = 7.63, 12.35 Hz, 1H), 3.37 (s, 2H), 2.41 - 2.47 (m, 4H), 1.84 - 1.96 (m, 4H), 1.58-1.70 (m, 3H), 1.48-1.55 (m, 2H), 1.46 (d, *J* = 7.02 Hz, 3H), 0.89-1.43 (m, 6H). LCMS : *m/z* 496 [M+H]⁺ r.t. 7.52 min. HRMS (ESI) calcd for C₂₈H₃₆F₂N₅O [M + H]⁺ 496.2883 found 496.2885;

- 20 2-[[[(1S)-1-{4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl}ethyl]amino]-8-(2-methoxyethyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = 2-methoxyethyl, A = phenyl, R1a = H, R1b = Me, R6a = 4-CH₂NR7R8, R6b = H, R7-R8 = 4,4-difluoropiperidin-1-yl, R3 = R4 = R5 = H] cpd 114



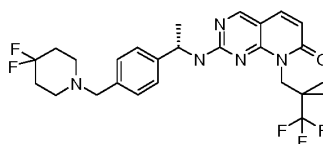
- 25 ¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.51 - 8.61 (m, 1H), 8.18 - 8.48 (m, 1H), 7.68 (d, *J* = 9.30 Hz, 1H), 7.34 (d, *J* = 7.63 Hz, 2H), 7.23 (d, *J* = 7.93 Hz, 2H), 6.21 (d, *J* = 9.30 Hz, 1H), 4.93 - 5.30 (m, 1H), 4.28 (t, *J* = 6.25 Hz, 2H), 3.45 - 3.51 (m, 2H), 3.25-3.30 (m, 2H), 3.15 (s, 3H), 2.43 (br. s., 4H), 1.81 - 1.96 (m, 4H), 1.46 (d, *J* = 7.02 Hz, 3H). LCMS : *m/z* 458 [M+H]⁺ r.t. 5.79 min. HRMS (ESI) calcd for C₂₄H₃₀F₂N₅O₂ [M + H]⁺ 458.2362 found 458.2368;

- 30 2-[[[(1S)-1-{4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl}ethyl]amino]-8-[4-fluoro-2-(trifluoromethyl)benzyl]pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = 4-fluoro-2-(trifluoromethyl)benzyl, A = phenyl, R1a = H, R1b = Me, R6a = 4-CH₂NR7R8, R6b = H, R7-R8 = 4,4-difluoropiperidin-1-yl, R3 = R4 = R5 = H] cpd 115



¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.66 (s, 1H), 8.44 (d, *J* = 7.93 Hz, 1H), 7.85 (d, *J* = 9.30 Hz, 1H), 7.72 (dd, *J* = 2.44, 9.00 Hz, 1H), 7.17 - 7.25 (m, 1H), 6.93 (s, 4H), 6.55 (dd, *J* = 4.96, 8.31 Hz, 1H), 6.33 (d, *J* = 9.30 Hz, 1H), 5.57 (d, *J* = 16.17 Hz, 1H), 5.45 (d, *J* = 16.17 Hz, 1H), 4.79 (quin, *J* = 7.44 Hz, 1H), 3.38 m, 2H), 2.29 - 2.45 (m, 4H), 1.82 - 1.97 (m, 4H), 1.26 - 1.44 (m, 3H). LCMS : *m/z* 576 [M+H]⁺ r.t. 7.37 min. HRMS (ESI) calcd for C₂₉H₂₈F₆N₅O [M + H]⁺ 576.2193 found 576.21938;

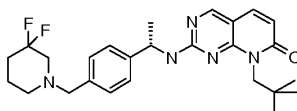
2-[[[(1S)-1-{4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl}ethyl]amino]-8-(3,3,3-trifluoro-2,2-dimethylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = 3,3,3-trifluoro-2,2-dimethylpropyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = 4,4-difluoropiperidin-1-yl, R₃ = R₄ = R₅ = H] cpd 116



10

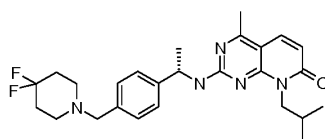
¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.55 - 8.64 (m, 1H), 8.48 (d, *J* = 7.78 Hz, 1H), 7.73 (d, *J* = 9.30 Hz, 1H), 7.31 (d, *J* = 7.93 Hz, 2H), 7.23 (d, *J* = 8.08 Hz, 2H), 6.26 (d, *J* = 9.30 Hz, 1H), 5.02 - 5.29 (m, 1H), 4.31 - 4.55 (m, 2H), 3.48 (s, 2H), 2.43 (br. s., 4H), 1.85 - 1.97 (m, 4H), 1.46 (d, *J* = 7.02 Hz, 3H), 0.79 - 1.17 (m, 6H). LCMS : *m/z* 524 [M+H]⁺ r.t. 7.34 min. HRMS (ESI) calcd for C₂₆H₃₁F₅N₅O [M + H]⁺ 524.2444 found 524.2455;

2-[[[(1S)-1-{4-[(3,3-difluoropiperidin-1-yl)methyl]phenyl}ethyl]amino]-8-(2,2-dimethylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = 2,2-dimethylpropyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = 3,3-difluoropiperidin-1-yl, R₃ = R₄ = R₅ = H] cpd 117



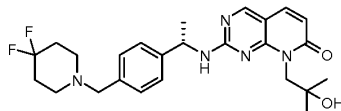
¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.58 (s, 1H), 8.36 (d, *J* = 7.32 Hz, 1H), 7.67 (d, *J* = 9.46 Hz, 1H), 7.33 (d, *J* = 8.08 Hz, 2H), 7.22 (d, *J* = 7.93 Hz, 2H), 6.22 (d, *J* = 9.30 Hz, 1H), 5.06 (quin, *J* = 7.13 Hz, 1H), 3.93-4.23 (m, 2H), 3.46 - 3.55 (m, 2H), 2.56 (d, *J* = 11.74 Hz, 1H), 2.52 (m, 1H), 2.36 (br. s, 2H), 1.84 (spt, *J* = 6.80 Hz, 2H), 1.61 (quin, *J* = 5.83 Hz, 2H), 1.46 (d, *J* = 7.02 Hz, 3H), 0.71 (br. s., 9H). LCMS : *m/z* 470 [M+H]⁺ r.t. 7.31 min. HRMS (ESI) calcd for C₂₆H₃₄F₂N₅O [M + H]⁺ 470.2726 found 470.272;

2-[[[(1S)-1-{4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl}ethyl]amino]-4-methyl-8-(2-ethylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = 2-methylpropyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = 4,4-difluoropiperidin-1-yl, R₃ = Me, R₄ = R₅ = H] cpd 118



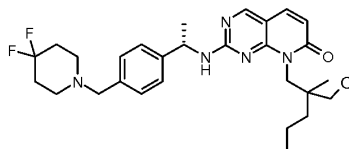
- ¹H NMR (500 MHz, DMSO-*d*₆) δ = 8.33 (d, *J* = 7.47 Hz, 1H), 7.86 (d, *J* = 9.61 Hz, 1H), 7.31 (d, *J* = 7.93 Hz, 2H), 7.22 (d, *J* = 7.93 Hz, 2H), 6.18 (d, *J* = 9.46 Hz, 1H), 4.69 - 5.40 (m, 1H), 3.94 - 4.01 (m, 1H), 3.79 - 3.88 (m, 1H), 3.47 (s, 2H), 2.53 (s, 3H), 2.43 (br. s., 4H), 1.83 - 1.97 (m, *J* = 13.88, 13.88 Hz, 1H), 1.44 (d, *J* = 7.17 Hz, 3H), 0.72 (d, *J* = 6.71 Hz, 3H), 0.60 (d, *J* = 6.56 Hz, 3H). LCMS : *m/z* 576 [M+H]⁺ r.t. 7.01 min. HRMS (ESI) calcd for C₂₆H₃₄F₂N₅O [M + H]⁺ 470.2726 found 470.2723;

2-[(S)-1-[4-(4,4-Difluoro-piperidin-1-ylmethyl)-phenyl]-ethylamino]-8-(2-hydroxy-2-methyl-propyl)-8H-pyrido[2,3-d]pyrimidin-7-one [(I), X = N, R₂ = 2-hydroxy-2-methylpropyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = 4,4-difluoropiperidin-1-yl, R₃ = R₄ = R₅ = H] cpd 119



- ¹H NMR (500MHz, DMSO-*d*₆) δ = 8.63 (s, 1H), 8.49 (d, *J* = 7.6 Hz, 1H), 7.74 (d, *J* = 9.3 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 7.9 Hz, 2H), 6.28 (d, *J* = 9.3 Hz, 1H), 5.04 (quin, *J* = 7.0 Hz, 1H), 4.63 - 3.73 (m, 3H), 3.48 (s, 2H), 2.44 (d, *J* = 5.3 Hz, 4H), 1.98 - 1.79 (m, 4H), 1.46 (d, *J* = 7.0 Hz, 3H), 1.26 - 0.80 (m, 6H). LCMS : *m/z* 472 [M+H]⁺ r.t. 6.86 min. HRMS (ESI) calcd for C₂₅H₃₂F₂N₅O₂ [M + H]⁺ 472.2519 found 472.2520;

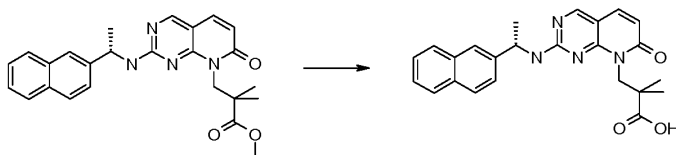
- 2-[[[(1S)-1-[4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl]ethyl]amino]-8-[2-(hydroxymethyl)-2-methylpentyl]pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = 2-hydroxy-2-methylpentyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = 4,4-difluoropiperidin-1-yl, R₃ = R₄ = R₅ = H] cpd 120**



- ¹H NMR (500MHz, DMSO-*d*₆) δ = 8.61 (d, *J* = 3.97 Hz, 1H), 8.43 (d, *J* = 7.17 Hz, 1H), 7.73 (d, *J* = 9.15 Hz, 1H), 7.35 (d, *J* = 7.93 Hz, 2H), 7.11 - 7.28 (m, 2H), 6.26 (d, *J* = 9.30 Hz, 1H), 5.05 - 5.38 (m, 1H), 4.15-4.48 (m, 3H), 3.48 (s, 2H), 2.86 - 3.22 (m, 2H), 2.44 (br. s., 4H), 1.92 (t, *J* = 13.80 Hz, 4H), 1.47 (dd, *J* = 2.82, 6.94 Hz, 3H), 1.12-1.46 (m, 4H), 0.82-0.89 (m, 3H), 0.65-0.74 (m, 3H). LCMS : *m/z* 514 [M+H]⁺ r.t. 6.99 min. HRMS (ESI) calcd for C₂₈H₃₈F₂N₅O₂ [M + H]⁺ 514.2988 found 514.2994.

Example 9

- 2,2-dimethyl-3-[2-[[[(1S)-1-(naphthalen-2-yl)ethyl]amino]-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl]propanoic acid [(I), X = N, R₂ = 2,2-dimethyl-3-propanoic acid, A = naphthalen-2-yl, R_{1a} = H, R_{1b} = Me, R_{6a} = R_{6b} = H, R₃ = R₄ = R₅ = H] conv. 8, cpd 121**



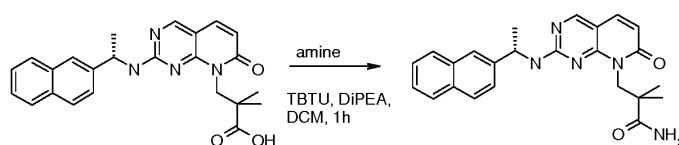
- Lithium hydroxyde (0.022 g, 0.52 mmol) was added to a solution of methyl 2,2-dimethyl-3-[2-[[[(1S)-1-(naphthalen-2-yl)ethyl]amino]-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl]propanoate (0.030 g, 0.07 mmol) in THF:water (1:1, 2 mL) and the reaction mixture was stirred at room temperature for 18h. The solvent (THF) was removed under reduced

pressure and the aqueous residue was diluted with water. The aqueous phase was acidified with hydrochloric acid (1M) until a precipitation occurred, the solid was filtered, washed with water and dried under vacuum, to give the title compound as a white solid (0.029 g, >99%).

¹H NMR (500 MHz, DMSO- *d*₆) δ = 12.08 (br.s, 1H), 8.57 (s, 1H), 8.50 (d, *J* = 7.47 Hz, 1H), 7.81 - 7.94 (m, 4H), 7.66 (d, *J* = 9.30 Hz, 1H), 7.59 (dd, *J* = 1.22, 8.54 Hz, 1H), 7.37 - 7.51 (m, 2H), 6.17 (d, *J* = 9.30 Hz, 1H), 5.19 - 5.35 (m, *J* = 7.02 Hz, 1H), 4.38 (d, *J* = 12.96 Hz, 1H), 4.27 (d, *J* = 12.81 Hz, 1H), 1.55 (d, *J* = 7.02 Hz, 3H), 1.02 (s, 3H), 0.91 (s, 3H). LCMS : *m/z* 417 [M+H]⁺ r.t. 4.74 min. HRMS (ESI) calcd for C₂₄H₂₅N₄O₃ [M + H]⁺ 417.1921 found 417.1924.

Example 10

2,2-dimethyl-3-[2-[[[(1S)-1-(naphthalen-2-yl)ethyl]amino]-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl]propanamide [(I), X = N, R₂ = 2,2-dimethyl-3-propanamide, A = naphthalen-2-yl, R_{1a} = H, R_{1b} = Me, R_{6a} = R_{6b} = H, R₈ = H, R₃ = R₄ = R₅ = H] conv. 9, cpd 122

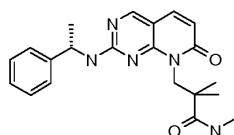


To a solution of TBTU (32 mg, 0.1mmol) in DCM (2 mL) was added to 2,2-dimethyl-3-[2-[[[(1S)-1-(naphthalen-2-yl)ethyl]amino]-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl]propanoic acid (20 mg, 0.05 mmol), DIPEA (10μL, 0.06 mmol), and ammonium hydrate 30% (1 mL). The reaction mixture was stirred at room temperature for 16 hours, the solvents were removed in vacuo, the residue was partitioned between DCM and water, and the organic layer was dried. The crude was purified by chromatography on a silica gel column (eluent: DCM /EtOAc/EtOH: 60/30/10) to afford the title compound (18 g, 90% yield).

¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.56 (s, 1H), 8.49 (d, *J* = 7.78 Hz, 1H), 7.97 (s, 1H), 7.79 - 7.90 (m, 3H), 7.55 - 7.69 (m, 2H), 7.40 - 7.51 (m, 2H), 7.13 (br. s., 1H), 6.91 (br. s., 1H), 6.19 (d, *J* = 9.30 Hz, 1H), 5.33 (t, *J* = 7.24 Hz, 1H), 4.44 (d, *J* = 13.12 Hz, 1H), 4.28 (d, *J* = 12.81 Hz, 1H), 1.55 (d, *J* = 6.86 Hz, 3H), 1.00 (s, 3H), 0.97 (s, 3H). LCMS : *m/z* 416 [M+H]⁺ r.t. 5.42 min. HRMS (ESI) calcd for C₂₄H₂₆N₅O₂ [M + H]⁺ 416.2081 found 416.2088.

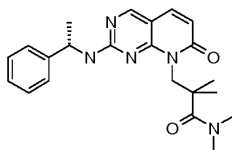
According to this same methodology, but employing suitable substituted derivatives, the following compounds were prepared:

N,2,2-trimethyl-3-[7-oxo-2-[[[(1S)-1-phenylethyl]amino]pyrido[2,3-d]pyrimidin-8(7H)-yl]propanamide [(I), X = N, R₂ = N,2,2-trimethyl-3-propanamide, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = R_{6b} = H, R₈ = H, R₃ = R₄ = R₅ = H] cpd 123



¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.49 - 8.61 (m, 1H), 8.34 (d, *J* = 8.08 Hz, 1H), 7.68 - 7.98 (m, 1H), 7.66 (d, *J* = 9.30 Hz, 1H), 7.23 - 7.47 (m, 4H), 7.12 - 7.22 (m, 1H), 6.20 (d, *J* = 9.30 Hz, 1H), 5.22 (quin, *J* = 6.98 Hz, 1H), 4.17 - 4.37 (m, 2H), 2.48 (s, 3H), 1.44 (d, *J* = 6.86 Hz, 3H), 0.88 - 1.11 (m, 6H). LCMS : *m/z* 380 [M+H]⁺ r.t. 5.03 min. HRMS (ESI) calcd for C₂₁H₂₆N₅O₂ [M + H]⁺ 380.2081 found 380.2086;

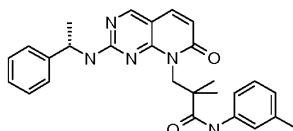
N,N,2,2-tetramethyl-3-[7-oxo-2-[[[(1S)-1-phenylethyl]amino]pyrido[2,3-d]pyrimidin-8(7H)-yl]propanamide [(I), X = N, R2 = N,N,2,2-tetramethyl-3-propanamide, A = phenyl, R1a= H, R1b = Me, R6a= R6b = H, R8 =H, R3 = R4 = R5= H] cpd 124



¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.52 - 8.63 (m, 1H), 8.42 (d, *J* = 7.78 Hz, 1H), 7.69 (d, *J* = 9.46 Hz, 1H), 7.38 (d, *J* = 7.63 Hz, 2H), 7.25 - 7.32 (m, 2H), 7.12 - 7.22 (m, 1H), 6.21 (d, *J* = 9.30 Hz, 1H), 5.07 (s, 1H), 4.42 (d, *J* = 5.49 Hz, 2H), 2.79 - 3.12 (m, 6H), 1.46 (d, *J* = 7.02 Hz, 3H), 0.90 - 1.17 (m, 6H).

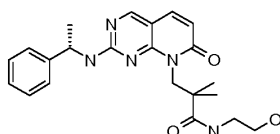
LCMS : *m/z* 394 [M+H]⁺ r.t. 5.49 min. HRMS (ESI) calcd for C₂₂H₂₈N₅O₂ [M + H]⁺ 394.2238 found 394.2246;

2,2-dimethyl-N-(3-methylphenyl)-3-[7-oxo-2-[[[(1S)-1-phenylethyl]amino]pyrido[2,3-d]pyrimidin-8(7H)-yl]propanamide [(I), X = N, R2 = 2,2-dimethyl-N-(3-methylphenyl) propanamide, A = phenyl, R1a= H, R1b = Me, R6a= R6b = H, R8 =H, R3 = R4 = R5= H] cpd 125



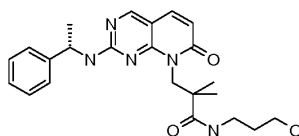
¹H NMR (500 MHz, DMSO- *d*₆) δ = 9.04 (s, 1H), 8.54 (s, 1H), 8.28 (d, *J* = 7.78 Hz, 1H), 7.68 (d, *J* = 9.30 Hz, 1H), 7.28 - 7.42 (m, 4H), 7.23 (t, *J* = 7.55 Hz, 2H), 7.07 - 7.19 (m, 2H), 6.84 (d, *J* = 7.47 Hz, 1H), 6.22 (d, *J* = 9.30 Hz, 1H), 4.97 - 5.19 (m, *J* = 7.24, 7.24 Hz, 1H), 4.13 - 4.50 (m, 2H), 2.25 (s, 3H), 1.24 (d, *J* = 4.27 Hz, 3H), 1.02 - 1.19 (m, 6H). LCMS : *m/z* 456 [M+H]⁺ r.t. 6.61 min. HRMS (ESI) calcd for C₂₇H₃₀N₅O₂ [M + H]⁺ 456.2394 found 456.2396;

N-(2-hydroxyethyl)-2,2-dimethyl-3-[7-oxo-2-[[[(1S)-1-phenylethyl]amino]pyrido[2,3-d]pyrimidin-8(7H)-yl]propanamide [(I), X = N, R2 = N-(2-hydroxyethyl)-2,2-dimethyl-3-propanamide, A = phenyl, R1a= H, R1b = Me, R6a= R6b = H, R8 =H, R3 = R4 = R5= H] cpd 126



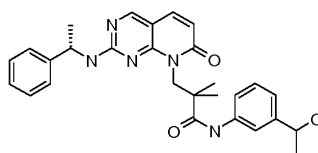
¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.55 (s, 1H), 8.37 (d, *J* = 7.63 Hz, 1H), 7.66 (d, *J* = 9.30 Hz, 1H), 7.43 (d, *J* = 7.47 Hz, 1H), 7.35 - 7.42 (m, 1H), 7.25 - 7.34 (m, 3H), 7.10 - 7.22 (m, 1H), 6.20 (d, *J* = 9.30 Hz, 1H), 5.13 - 5.29 (m, 1H), 4.57 (t, *J* = 5.57 Hz, 1H), 4.22 - 4.38 (m, 2H), 2.97 - 3.18 (m, 4H), 1.41 - 1.52 (m, 3H), 1.01 - 1.06 (m, 3H), 0.93 - 0.98 (m, 3H). LCMS : *m/z* 410 [M+H]⁺ r.t. 4.78 min. HRMS (ESI) calcd for C₂₂H₂₈N₅O₃ [M + H]⁺ 410.2187 found 410.2186;

N-(3-hydroxypropyl)-2,2-dimethyl-3-[7-oxo-2-[[[(1S)-1-phenylethyl]amino]pyrido[2,3-d]pyrimidin-8(7H)-yl]propanamide [(I), X = N, R2 = N-(2-hydroxyethyl)-2,2-dimethyl-3-propanamide, A = phenyl, R1a= H, R1b = Me, R6a= R6b = H, R8 =H, R3 = R4 = R5= H] cpd 127



¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.54 (s, 1H), 8.36 (d, *J* = 7.78 Hz, 1H), 7.66 (d, *J* = 9.30 Hz, 1H), 7.44 (d, *J* = 7.63 Hz, 2H), 7.39 (t, *J* = 5.49 Hz, 1H), 7.28 (t, *J* = 7.63 Hz, 2H), 7.18 (q, *J* = 6.96 Hz, 1H), 6.20 (d, *J* = 9.30 Hz, 1H), 5.14 - 5.36 (m, *J* = 4.42, 7.17, 7.17 Hz, 1H), 4.19 - 4.50 (m, 3H), 3.36 (m, 2H), 2.97 - 3.16 (m, 2H), 1.38 - 1.60 (m, 5H), 0.94 - 1.10 (m, 6H). LCMS : *m/z* 424 [M+H]⁺ r.t. 4.85 min. HRMS (ESI) calcd for C₂₃H₃₀N₅O₃ [M + H]⁺ 424.2343 found 424.2349;

N-[3-(1-hydroxyethyl)phenyl]-2,2-dimethyl-3-[7-oxo-2-[(1S)-1-phenylethyl]amino]pyrido[2,3-d]pyrimidin-8(7H)-yl]propanamide [(I), X = N, R₂ = N-[3-(1-hydroxyethyl)phenyl]-2,2-dimethyl-3-propanamide, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = R_{6b} = H, R₈ = H, R₃ = R₄ = R₅ = H] cpd 128



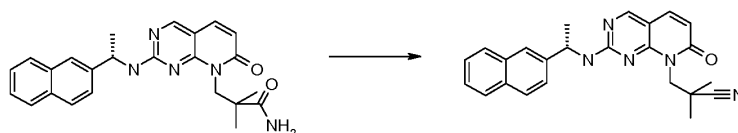
10

¹H NMR (500 MHz, DMSO- *d*₆) δ = 9.07 - 9.26 (m, 1H), 8.47 - 8.59 (m, 1H), 8.29 (d, *J* = 7.63 Hz, 1H), 7.69 (d, *J* = 9.30 Hz, 1H), 7.42 - 7.62 (m, 2H), 7.37 (d, *J* = 7.63 Hz, 2H), 7.06 - 7.33 (m, 5H), 7.00 (d, *J* = 7.63 Hz, 1H), 6.13 - 6.26 (m, 1H), 4.93 - 5.27 (m, 1H), 4.54 - 4.74 (m, 1H), 4.34 - 4.49 (m, 2H), 1.26 - 1.33 (m, 6H), 1.16 (br. s, 3H), 1.07 (br. s, 3H). LCMS : *m/z* 486 [M+H]⁺ r.t. 5.71 min. HRMS (ESI) calcd for C₂₈H₃₂N₅O₃ [M + H]⁺ 486.25 found 486.2493.

15

Example 11

2,2-dimethyl-3-[2-[(1S)-1-(naphthalen-2-yl)ethyl]amino]-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl]propanenitrile [(I), X = N, R₂ = 2,2-dimethyl-3-propanenitrile, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = R_{6b} = H, R₈ = H, R₃ = R₄ = R₅ = H] conv. 10, cpd 129

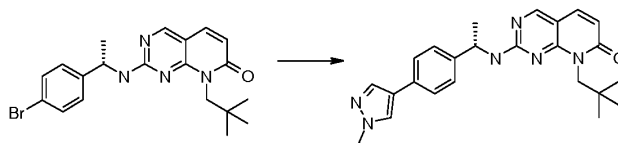


A solution of 2,2-dimethyl-3-[2-[(1S)-1-(naphthalen-2-yl)ethyl]amino]-7-oxopyrido[2,3-d]pyrimidin-8(7H)-yl]propanamide (10mg, 0.02mmol) in 1 mL of trifluoroacetic anhydride was heated at 100°C for 1 h. The reaction went to completion, the solvent was removed in vacuo and the crude was purified by chromatography on a silica gel column (eluent: DCM /EtOAc/EtOH: 60/35/5) to afford the title compound (7.5 g, 90% yield).

¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.23 - 8.70 (m, 2H), 7.81 - 7.94 (m, 4H), 7.73 (d, *J* = 9.30 Hz, 1H), 7.59 (d, *J* = 8.39 Hz, 1H), 7.34 - 7.53 (m, 2H), 6.25 (d, *J* = 9.30 Hz, 1H), 5.18 - 5.51 (m, *J* = 7.05 Hz, 1H), 4.20 - 4.57 (m, 2H), 1.56 (d, *J* = 7.02 Hz, 3H), 1.04 - 1.49 (m, 6H). LCMS : *m/z* 398 [M+H]⁺ r.t. 6.37 min. HRMS (ESI) calcd for C₂₄H₂₄N₅O [M + H]⁺ 398.1976 found 398.1985.

Example 12

8-(2,2-dimethylpropyl)-2-((1S)-1-[4-(1-methyl-1H-pyrazol-4-yl)phenyl]ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = 2,2-dimethyl-propyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 1-methyl-1H-pyrazol-4-yl, R_{6b} = H, R₈ = H, R₃ = R₄ = R₅ = H] conv. 5, cpd 130



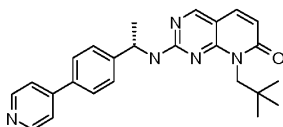
- 5 In a 5 mL microwave vial a solution of 2-((1S)-1-[4-(4-bromophenyl)ethyl]amino)-8-(2,2-dimethylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one (30 mg, 0.07 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (29 mg, 0.24 mmol), Cs₂CO₃ (46 mg, 0.14 mmol) in Dioxane (2 mL) was bubbled N₂ for 3 min then Cl₂Pd(dppf)CH₂Cl₂ (5 mg, 0.007 mmol) was added. The capped tube was heated to 100°C for 4 h. After cooling the reaction mixture was diluted with EtOAc (10 mL) and washed with water (10 mL). After separation, the aqueous phase was extracted with
- 10 EtOAc (3 x 10 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude material was purified through silica gel column chromatography (DCM/EtOAc 8/2) to give an off-white solid (14.5 mg, 50% yield).

¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.57 (s, 1H), 8.07 - 8.42 (m, 1H), 8.06 (s, 1H), 7.79 (d, *J* = 0.46 Hz, 1H), 7.67 (d, *J* = 9.30 Hz, 1H), 7.44 - 7.52 (m, 2H), 7.35 (d, *J* = 8.08 Hz, 2H), 6.22 (d, *J* = 9.15 Hz, 1H), 4.95 - 5.34 (m, *J* = 6.98, 15 Hz, 1H), 3.99 - 4.29 (m, 2H), 3.84 (s, 3H), 1.47 (d, *J* = 7.02 Hz, 3H), 0.65 - 0.98 (m, 9H).

LCMS : *m/z* 417 [M+H]⁺ r.t. 6.05 min. HRMS (ESI) calcd for C₂₄H₂₉N₆O [M + H]⁺ 417.2398 found 417.24.

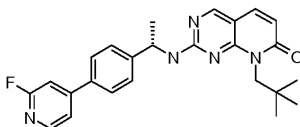
According to this same methodology, the following compounds were prepared:

- 8-(2,2-dimethylpropyl)-2-((1S)-1-[4-(pyridin-4-yl)phenyl]ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = 2,2-dimethyl-propyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = pyridin-4-yl, R_{6b} = H, R₈ = H, R₃ = R₄ = R₅ = H] cpd 131**
- 20



- ¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.51 - 8.65 (m, 3H), 8.46 (d, *J* = 7.32 Hz, 1H), 7.76 (d, *J* = 8.08 Hz, 2H), 7.60 - 7.70 (m, 3H), 7.53 (d, *J* = 8.08 Hz, 2H), 6.23 (d, *J* = 9.30 Hz, 1H), 4.97 - 5.42 (m, 1H), 3.88 - 4.38 (m, 2H), 1.45 - 1.55 (m, 3H), 0.52 - 1.04 (m, 9H). LCMS : *m/z* 414 [M+H]⁺ r.t. 6.05 min. HRMS (ESI) calcd for C₂₅H₂₈N₆O [M + H]⁺ 414.2289 found 414.2293;
- 25

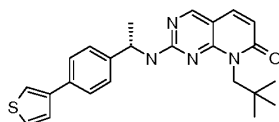
8-(2,2-dimethylpropyl)-2-((1S)-1-[4-(2-fluoropyridin-4-yl)phenyl]ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = 2,2-dimethyl-propyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 2-fluoropyridin-4-yl, R_{6b} = H, R₈ = H, R₃ = R₄ = R₅ = H] cpd 132



¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.50 - 8.63 (m, 1H), 8.47 (d, *J* = 7.47 Hz, 1H), 8.27 (d, *J* = 5.34 Hz, 1H), 7.82 (d, *J* = 8.08 Hz, 2H), 7.60 - 7.71 (m, 2H), 7.54 (d, *J* = 8.08 Hz, 2H), 7.49 (s, 1H), 6.23 (d, *J* = 9.46 Hz, 1H), 5.03 - 5.40 (m, 1H), 3.88 - 4.32 (m, 2H), 1.50 (d, *J* = 7.02 Hz, 3H), 0.55 - 1.01 (m, 9H).

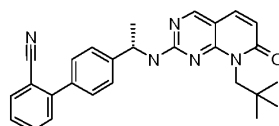
LCMS : *m/z* 432 [M+H]⁺ r.t. 6.72 min. HRMS (ESI) calcd for C₂₅H₂₇N₅O [M + H]⁺ 432.2194 found 432.2197;

- 5 **8-(2,2-dimethylpropyl)-2-(((1*S*)-1-[4-(thiophen-3-yl)phenyl]ethyl)amino)pyrido[2,3-*d*]pyrimidin-7(8*H*)-one** **one**
[(I), X = N, R₂ = 2,2-dimethyl-propyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = thiophen-3-yl, R_{6b} = H, R₈ = H, R₃ = R₄ = R₅ = H] cpd 133



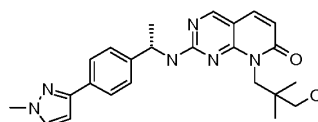
- 10 ¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.47 - 8.66 (m, 1H), 8.41 (d, *J* = 7.17 Hz, 1H), 7.79 (dd, *J* = 1.37, 2.90 Hz, 1H), 7.62 - 7.72 (m, 2H), 7.61 (dd, *J* = 3.05, 5.03 Hz, 1H), 7.51 (dd, *J* = 1.22, 5.03 Hz, 1H), 7.36 - 7.45 (m, 2H), 7.34 (d, *J* = 8.39 Hz, 1H), 6.23 (dd, *J* = 6.25, 9.15 Hz, 1H), 4.85 - 5.38 (m, 1H), 3.84 - 4.33 (m, 2H), 1.49 (d, *J* = 7.02 Hz, 3H), 0.60 - 0.99 (m, 9H). LCMS : *m/z* 419 [M+H]⁺ r.t. 7.39 min. HRMS (ESI) calcd for C₂₄H₂₇N₄OS [M + H]⁺ 419.19 found 419.1909,

- 15 **4'-((1*S*)-1-[[8-(2,2-dimethylpropyl)-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl]amino]ethyl)biphenyl-2-carbonitrile** **[(I), X = N, R₂ = 2,2-dimethyl-propyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = -phenyl-2-carbonitrile, R_{6b} = H, R₈ = H, R₃ = R₄ = R₅ = H] cpd 134**



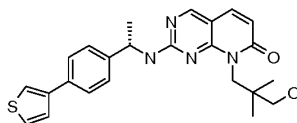
- 20 ¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.60 (s, 1H), 8.47 (d, *J* = 7.47 Hz, 1H), 7.93 (dd, *J* = 0.76, 7.78 Hz, 1H), 7.77 (dt, *J* = 1.30, 7.74 Hz, 1H), 7.68 (d, *J* = 9.30 Hz, 1H), 7.56-7.60 (m, 2H), 7.54 (br. s, 4H), 6.23 (d, *J* = 9.30 Hz, 1H), 5.17 (quin, *J* = 6.75 Hz, 1H), 3.93 - 4.33 (m, 2H), 1.53 (d, *J* = 7.02 Hz, 3H), 0.44 - 1.12 (m, 9H). LCMS : *m/z* 438 [M+H]⁺ r.t. 7.1 min. HRMS (ESI) calcd for C₂₇H₂₈N₅O [M + H]⁺ 438.2289 found 438.229;

8-(3-hydroxy-2,2-dimethylpropyl)-2-(((1*S*)-1-[4-(1-methyl-1*H*-pyrazol-4-yl)phenyl]ethyl)amino)pyrido [2,3-*d*]pyrimidin-7(8*H*)-one **[(I), X = N, R₂ = 3-hydroxy-2,2-dimethylpropyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 1-methyl-1*H*-pyrazol-4-yl, R_{6b} = H, R₈ = H, R₃ = R₄ = R₅ = H] cpd 135**



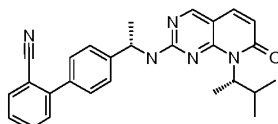
- 25 ¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.51 - 8.65 (m, 1H), 8.17 - 8.46 (m, 1H), 8.06 (s, 1H), 7.79 (s, 1H), 7.72 (d, *J* = 9.30 Hz, 1H), 7.43 - 7.52 (m, 2H), 7.38 (d, *J* = 7.93 Hz, 2H), 6.25 (d, *J* = 9.30 Hz, 1H), 4.89 - 5.37 (m, *J* = 7.24, 7.24 Hz, 1H), 4.60 (br. s., 1H), 4.13 (br. s., 2H), 3.84 (s, 3H), 3.07 (d, *J* = 5.49 Hz, 2H), 1.47 (d, *J* = 7.02 Hz, 3H), 0.45 - 0.94 (m, 6H). LCMS : *m/z* 433 [M+H]⁺ r.t. 5.24 min. HRMS (ESI) calcd for C₂₄H₂₉N₆O₂ [M + H]⁺ 433.2347 found 433.235;
- 30

8-(3-hydroxy-2,2-dimethylpropyl)-2-((1S)-1-[4-(thiophen-3-yl)phenyl]ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = 3-hydroxy-2,2-dimethylpropyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = thiophen-3-yl, R_{6b} = H, R₈ = H, R₃ = R₄ = R₅ = H] cpd 136



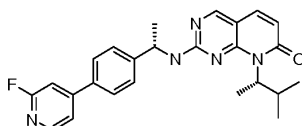
5 ¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.53 - 8.69 (m, 1H), 8.14 - 8.51 (m, 1H), 7.80 (dd, *J* = 1.14, 2.82 Hz, 1H), 7.72 (d, *J* = 9.30 Hz, 1H), 7.65 (d, *J* = 8.08 Hz, 2H), 7.57 - 7.62 (m, 1H), 7.49 - 7.53 (m, 1H), 7.25 - 7.48 (m, 2H), 6.20 - 6.32 (m, 1H), 5.15 (t, *J* = 6.86 Hz, 1H), 4.51 - 4.71 (m, 1H), 4.05 - 4.33 (m, 2H), 3.08 (d, *J* = 5.34 Hz, 2H), 1.41 - 1.53 (m, 3H), 0.47 - 0.96 (m, 6H). LCMS : *m/z* 435 [M+H]⁺ r.t. 6.52 min. HRMS (ESI) calcd for C₂₄H₂₇N₆O₂ [M + H]⁺ 435.1849 found 435.1852;

10 **4'-[(1S)-1-((8-[(2S)-3-methylbutan-2-yl]-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl)amino)ethyl]biphenyl-2-carbonitrile [(I), X = N, R₂ = (2S)-3-methylbutan-2-yl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = -phenyl-2-carbonitrile, R_{6b} = H, R₈ = H, R₃ = R₄ = R₅ = H] cpd 165**



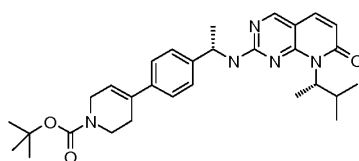
15 ¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.60 (s, 1H), 8.47 (d, *J* = 7.47 Hz, 1H), 7.93 (dd, *J* = 0.76, 7.78 Hz, 1H), 7.77 (dt, *J* = 1.30, 7.74 Hz, 1H), 7.68 (d, *J* = 9.30 Hz, 1H), 7.56-7.60 (m, 2H), 7.54 (br. s, 4H), 6.23 (d, *J* = 9.30 Hz, 1H), 5.17 (quin, *J* = 6.75 Hz, 1H), 3.93 - 4.33 (m, 2H), 1.53 (d, *J* = 7.02 Hz, 3H), 0.44 - 1.12 (m, 9H). LCMS : *m/z* 438 [M+H]⁺ r.t. 6.96 min. HRMS (ESI) calcd for C₂₇H₂₈N₅O [M + H]⁺ 438.2289 found 438.2296.

20 **2-((1S)-1-[4-(2-fluoropyridin-4-yl)phenyl]ethyl)amino)-8-[(2S)-3-methylbutan-2-yl]pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = (2S)-3-methylbutan-2-yl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 2-fluoropyridin-4-yl, R_{6b} = H, R₈ = H, R₃ = R₄ = R₅ = H] cpd 166**



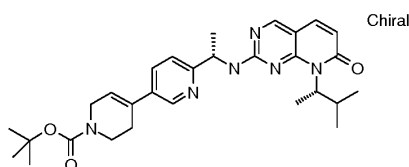
25 ¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.55 - 8.61 (m, 1H), 8.40 (d, *J* = 7.47 Hz, 1H), 8.27 (d, *J* = 5.30 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 2H), 7.62 - 7.68 (m, 2H), 7.54 (d, *J* = 8.08 Hz, 2H), 7.42-7.52 (m, 2H), 6.22 (d, *J* = 9.30 Hz, 1H), 4.99-5.07 (m, 1H), 4.87-4.96 (m, 1H), 4.73-4.80 (m, 1H), 2.57-2.60 (m, 1H), 1.55 (d, *J* = 7.02 Hz, 3H), 1.0-1.08 (m, 3H), 0.59 - 0.72 (m, 3H), 0.01 (d, *J* = 6.41 Hz, 3H). LCMS : *m/z* 432 [M+H]⁺ r.t. 6.68 min. HRMS (ESI) calcd for C₂₅H₂₇FN₅O [M + H]⁺ 432.2194 found 432.2197.

30 **tert-butyl 4-{4-[(1S)-1-((8-[(2S)-3-methylbutan-2-yl]-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl)amino)ethyl]phenyl}-3,6-dihydropyridine-1(2H)-carboxylate [(I), X = N, R₂ = (2S)-3-methylbutan-2-yl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = tert-butyl 3,6-dihydropyridine-1(2H)-carboxylate, R_{6b} = H, R₈ = H, R₃ = R₄ = R₅ = H] cpd 167**



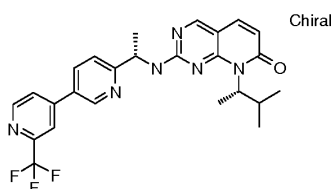
¹H NMR (500 MHz, DMSO- *d*₆) δ = 8.55 - 8.61 (m, 1H), 8.40 (d, *J* = 7.47 Hz, 1H), 8.27 (d, *J* = 5.30 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 2H), 7.62 - 7.68 (m, 2H), 7.54 (d, *J* = 8.08 Hz, 2H), 7.42-7.52 (m, 2H), 6.22 (d, *J* = 9.30 Hz, 1H), 4.99-5.07 (m, 1H), 4.87-4.96 (m, 1H), 4.73-4.80 (m, 1H), 2.57-2.60 (m, 1H), 1.55 (d, *J* = 7.02 Hz, 3H), 1.0-1.08 (m, 3H), 0.59 - 0.72 (m, 3H), 0.01 (d, *J* = 6.41 Hz, 3H). LCMS : *m/z* 518 [M+H]⁺ r.t. 7.75 min. HRMS (ESI) calcd for C₃₀H₄₀N₅O₃ [M + H]⁺ 518.3126 found 518.3115.

tert-butyl 6-[(1S)-1-((8-[(2S)-3-methylbutan-2-yl]-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl)amino)ethyl]-3',6'-dihydro-3,4'-bipyridine-1'(2'H)-carboxylate [(I), X = N, R₂ = (2S)-3-methylbutan-2-yl, A = pyridin-2-yl, R_{1a} = H, R_{1b} = Me, R_{6a} = tert-butyl 3,6-dihydropyridine-1(2H)-carboxylate, R_{6b} = H, R₈ = H, R₃ = R₄ = R₅ = H] cpd 193



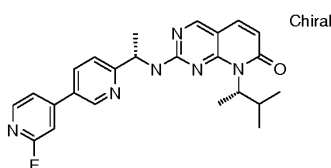
LCMS : *m/z* 519 [M+H]⁺ r.t. 6.82 min. HRMS (ESI) calcd for C₂₅H₃₉N₆O₃ [M + H]⁺ 519.3078 found 519.3085.

8-[(2S)-3-methylbutan-2-yl]-2-(((1S)-1-[2'-(trifluoromethyl)-3,4'-bipyridin-6-yl]ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = (2S)-3-methylbutan-2-yl, A = pyridin-2-yl, R_{1a} = H, R_{1b} = Me, R_{6a} = 2-trifluoromethylpyridin-4-yl, R_{6b} = H, R₈ = H, R₃ = R₄ = R₅ = H] cpd 196



¹H NMR (500 MHz, DMSO- *d*₆) δ = 9.10 (s, 1H), 8.85 (s, 1H), 8.76 (s, 1H), 8.43 (d, *J* = 6.56 Hz, 1H), 8.29 (d, *J* = 8.39 Hz, 1H), 8.09 (m, 1H), 7.96 (d, *J* = 9.30 Hz, 1H), 7.66 (dd, *J* = 8.85 Hz, 1H), 7.42 (d, *J* = 8.39 Hz, 1H), 6.23 (d, *J* = 9.30 Hz, 1H), 4.70 - 5.07 (m, 2H), 1.40 - 1.59 (m, 4H), 0.93 - 1.02 (m, 3H), 0.59 (d, *J* = 6.25 Hz, 3H), -0.01 (d, *J* = 6.25 Hz, 3H). LCMS : *m/z* 483 [M+H]⁺ r.t. 6.29 min. HRMS (ESI) calcd for C₂₅H₂₆F₃N₆O [M + H]⁺ 483.2115 found 483.213.

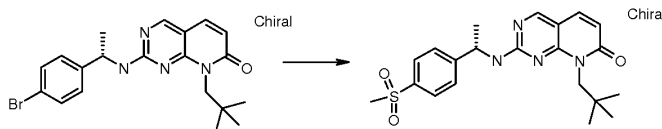
2-(((1S)-1-(2'-fluoro-3,4'-bipyridin-6-yl)ethyl)amino)-8-[(2S)-3-methylbutan-2-yl]pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = (2S)-3-methylbutan-2-yl, A = pyridin-2-yl, R_{1a} = H, R_{1b} = Me, R_{6a} = 2-fluoro-pyridin-4-yl, R_{6b} = H, R₈ = H, R₃ = R₄ = R₅ = H] cpd 197



LCMS : m/z 433 [M+H]⁺ r.t. 5.77 min. HRMS (ESI) calcd for C₂₄H₂₆FN₆O [M + H]⁺ 433.2147 found 433.215.

Example 13

8-(2,2-dimethylpropyl)-2-(((1S)-1-[4-(methylsulfonyl)phenyl]ethyl)amino)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = 2,2-dimethylpropyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = methylsulfonyl, R_{6b} = H, R₈ = H, R₃ = R₄ = R₅ = H] conv. 11, cpd 137

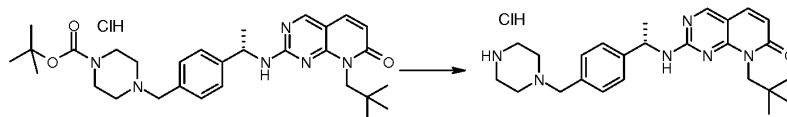


In a 5 mL microwave vial a solution of 2-(((1S)-1-(4-bromophenyl)ethyl)amino)-8-(2,2-dimethylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one (30 mg, 0.07 mmol), sodium methanesulfonate (22 mg, 0.21 mmol), CuI (41 mg, 0.21 mmol) in DMSO (2 mL) was added. The capped tube was heated at 120°C for 6 h. After cooling the reaction mixture was diluted with EtOAc (10 mL) and washed with water (10 mL). After separation, the aqueous phase was extracted with EtOAc (3 x 10 mL). Combined organics were dried over Na₂SO₄, filtered and concentrated. The crude material was purified through silica gel column chromatography (DCM/EtOAc 8/2) to give an off-white solid (10 mg, 35% yield).

¹H NMR (500 MHz, DMSO- d₆) δ = 8.60 (s, 1H), 8.50 (d, J = 7.17 Hz, 1H), 7.88 (d, J = 8.24 Hz, 2H), 7.68 (d, J = 9.30 Hz, 1H), 7.65 (d, J = 8.24 Hz, 2H), 6.24 (d, J = 9.30 Hz, 1H), 5.00 - 5.43 (m, J = 7.02, 7.02 Hz, 1H), 3.82 - 4.32 (m, 2H), 3.16 (s, 3H), 1.49 (d, J = 7.17 Hz, 3H), 0.51 - 0.98 (m, 9H). LCMS : m/z 415 [M+H]⁺ r.t. 5.51 min. HRMS (ESI) calcd for C₂₁H₂₇N₄O₃S [M + H]⁺ 415.1799 found 415.1797.

Example 14

8-(2,2-Dimethyl-propyl)-2-[(S)-1-(4-piperazin-1-ylmethyl-phenyl)-ethyl amino]-8H-pyrido[2,3-d]pyrimidin-7-one hydrochloride [(I), X = N, R₂ = 2,2-dimethyl-propyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = 4-piperazin-1-yl, R₃ = R₄ = R₅ = H] conv. 6, cpd 138

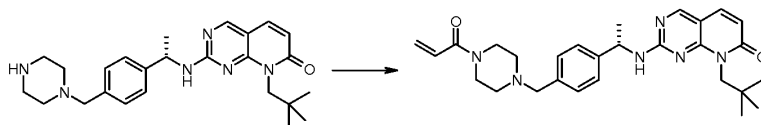


To a solution of 4-(4-((S)-1-[8-(2,2-Dimethyl-propyl)-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino]-ethyl)-benzyl)-piperazine-1-carboxylic acid tert-butyl ester (cpd 59) (65.0 mg, 0.122 mmol) in a mixture of dioxane (3.0 mL) and MeOH (1.0 mL) is added HCl (4 M in dioxane, 0.6 mL). The mixture is stirred overnight at room temperature and then concentrated to dryness to provide a white solid which is dried under vacuum to give the title compound as a white solid (57.0 mg, quantitative).

¹H NMR (500 MHz, DMSO- d₆) δ = 11.72 (br. s., 1H), 9.32 (br. s., 2H), 8.59 (s, 1H), 8.46 (d, J = 7.32 Hz, 1H), 7.68 (d, J = 9.15 Hz, 1H), 7.54 (br. s., 2H), 7.47 (d, J = 7.63 Hz, 2H), 6.24 (d, J = 9.30 Hz, 1H), 5.14 (quin, J = 6.90 Hz, 1H), 3.93 - 4.54 (m, 5H), 3.28 - 3.52 (m, 5H), 1.47 (d, J = 7.17 Hz, 3H), 0.79 (br. s., 9H). LCMS (HPLC Method 1): m/z 435 [M+H]⁺ @ r.t. 5.17 min. HRMS (ESI) calcd for C₂₅H₃₅N₄O₃S [M + H]⁺ 415.1799 found 415.1797.

Example 15

2-[(S)-1-[4-(4-Acryloyl-piperazin-1-ylmethyl)-phenyl]-ethylamino]-8-(2,2-dimethyl-propyl)-8H-pyrido[2,3-d]pyrimidin-7-one [(I), X = N, R2 = 2,2-dimethyl-propyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-CH₂NR7R8, R6b = H, R7-R8 = 4-piperazin-1-yl, R11 = vinyl, R3 = R4 = R5= H] conv. 7, cpd 139



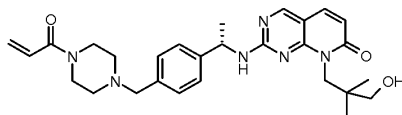
- 5 To a solution of 8-(2,2-Dimethyl-propyl)-2-[(S)-1-(4-piperazin-1-ylmethyl)-phenyl]-ethyl amino]-8H-pyrido[2,3-d]pyrimidin-7-one hydrochloride (55.0 mg, 0.12 mmol) and DIPEA (0.04 mL, 0.24 mmol) in DCM (1.0 mL) is added acryloyl chloride (0.01 mL, 0.13 mmol) at 0°C. After 30 minutes, the reaction is quenched with water. The mixture is extracted with DCM, dried over Na₂SO₄, filtered, and concentrated to yield a yellow oil. The crude product is purified by silica gel chromatography (1 to 10% MeOH/DCM) to give the title product as a white foam (37.5 mg, 66% yield).

- 10 ¹H NMR (500MHz, DMSO-d₆) δ = 8.57 (s, 1 H), 8.36 (d, J = 7.2 Hz, 1 H), 7.67 (d, J = 9.3 Hz, 1 H), 7.33 (d, J = 8.1 Hz, 2 H), 7.23 (d, J = 7.9 Hz, 2 H), 6.76 (dd, J = 10.4, 16.7 Hz, 1 H), 6.22 (d, J = 9.3 Hz, 1 H), 6.08 (dd, J = 2.4, 16.7 Hz, 1 H), 5.65 (dd, J = 2.4, 10.4 Hz, 1 H), 5.06 (quin, J = 7.2 Hz, 1 H), 4.40 - 3.87 (m, 2 H), 3.50 (d, J = 17.5 Hz, 4 H), 3.44 (s, 2 H), 2.31 (br. s., 4 H), 1.46 (d, J = 6.9 Hz, 3 H), 1.05 - 0.53 (m, 9 H).

LCMS : m/z 489 [M+H]⁺ @ r.t. 5.88 min. HRMS (ESI) calcd for C₂₈H₃₇N₆O₂ [M +H]⁺ 489.2973 found 489.2966.

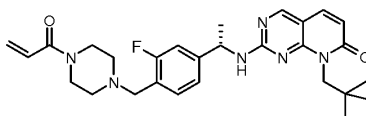
- 15 According to the same method, the following compounds were prepared:

2-[(S)-1-[4-(4-Acryloyl-piperazin-1-ylmethyl)-phenyl]-ethylamino]-8-(3-hydroxy-2,2-dimethyl-propyl)-8H-pyrido[2,3-d]pyrimidin-7-one [(I), X = N, R2 = 3-hydroxy-2,2-dimethyl-propyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-CH₂NR7R8, R6b = H, R7-R8 = 4-piperazin-1-yl, R11 = vinyl, R3 = R4 = R5= H] cpd 140



- 20 ¹H NMR (500MHz, DMSO-d₆) δ = 8.60 (s, 1 H), 8.43 (d, J = 7.5 Hz, 1 H), 7.72 (d, J = 9.3 Hz, 1 H), 7.36 (d, J = 7.9 Hz, 2 H), 7.23 (d, J = 7.9 Hz, 2 H), 6.76 (dd, J = 10.5, 16.6 Hz, 1 H), 6.26 (d, J = 9.2 Hz, 1 H), 6.08 (dd, J = 2.4, 16.7 Hz, 1 H), 5.65 (dd, J = 2.4, 10.4 Hz, 1 H), 5.11 (quin, J = 6.9 Hz, 1 H), 4.56 (br. s., 1 H), 4.20 - 4.00 (m, 2 H), 3.51 (d, J = 14.2 Hz, 4 H), 3.43 (s, 2 H), 3.03 (br. s., 2 H), 2.31 (br. s., 4 H), 1.46 (d, J = 7.0 Hz, 3 H) 0.93 - 0.58 (m, 6 H).
LCMS : m/z 505 [M+H]⁺ @ r.t. 5.01 min. HRMS (ESI) calcd for C₂₈H₃₆N₆O₃ [M +H]⁺ 505.2922 found 505.2922;

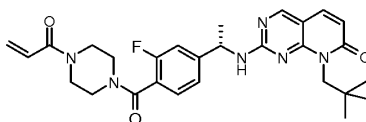
- 25 2-[[[(1S)-1-[4-[(4-acryloylpiperazin-1-yl)methyl]-3-fluorophenyl]ethyl]amino]-8-(2,2-dimethylpropyl)pyrido[2,3-d] pyrimidin-7(8H)-one [(I), X = N, R2 = 2,2-dimethyl-propyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-CH₂NR7R8, R6b = F, R7-R8 = 4-piperazin-1-yl, R11 = vinyl, R3 = R4 = R5= H] cpd 141



- ¹H NMR (500MHz, DMSO-d₆) δ = 8.59 (s, 1H), 8.38 (d, J = 7.47 Hz, 1H), 7.68 (d, J = 9.46 Hz, 1H), 7.33 (t, J = 7.70 Hz, 1H), 7.08 - 7.23 (m, 2H), 6.76 (dd, J = 10.52, 16.62 Hz, 1H), 6.24 (d, J = 9.46 Hz, 1H), 6.07 (dd, J = 2.29, 16.62 Hz, 1H), 5.64 (dd, J = 2.29, 10.37 Hz, 1H), 5.06 (quin, J = 7.13 Hz, 1H), 3.90 - 4.33 (m, 2H), 3.43 - 3.60 (m, 6H), 2.34

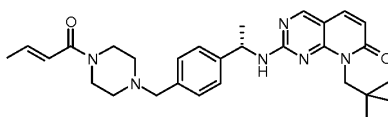
(br. s., 4H), 1.46 (d, $J = 7.02$ Hz, 3H), 0.92 (br. s., 3H), 0.69 (br. s., 6H). LCMS : m/z 507 $[M+H]^+$ @ r.t. 5.98 min. HRMS (ESI) calcd for $C_{28}H_{36}N_6O_3$ $[M+H]^+$ 507.2879 found 507.2874;

- 2- $\{[(1S)-1-[4-[(4\text{-acryloylpiperazin-1-yl})\text{carbonyl}]-3\text{-fluorophenyl}]ethyl\}amino\}$ -8-(2,2-dimethylpropyl)pyrido
[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = 2,2-dimethyl-propyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-
5 C(O)NR7R8, R6b = F, R7-R8 = 4-piperazin-1-yl, R11 = vinyl, R3 = R4 = R5= H] cpd 142



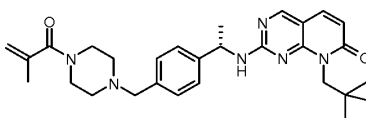
- ^1H NMR (500MHz, DMSO- d_6) δ = 8.61 (s, 1H), 8.43 (d, $J = 7.17$ Hz, 1H), 7.70 (d, $J = 9.30$ Hz, 1H), 7.34 - 7.45 (m, 1H), 7.30 (d, $J = 6.86$ Hz, 2H), 6.63 - 6.91 (m, 1H), 6.25 (d, $J = 9.30$ Hz, 1H), 6.12 (dd, $J = 2.29, 16.78$ Hz, 1H), 5.70 (s, 1H), 5.11 (quin, $J = 6.67$ Hz, 1H), 3.89 - 4.32 (m, 2H), 3.39 - 3.78 (m, 6H), 3.22 (br. s., 2H), 1.48 (d, $J = 7.02$ Hz, 3H), 0.93 (br. s., 3H), 0.73 (br. s., 6H). LCMS : m/z 521 $[M+H]^+$ @ r.t. 5.44 min. HRMS (ESI) calcd for $C_{28}H_{34}FN_6O_3$ $[M+H]^+$ 521.2671 found 521.2672;

- 2- $\{[(1S)-1-[4-[(2E)\text{-but-2-enoyl}]piperazin-1-yl\}methyl]phenyl\}ethyl\}amino\}$ -8-(2,2-dimethylpropyl) pyrido
[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = 2,2-dimethyl-propyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-
10 C(O)NR7R8, R6b = H, R7-R8 = 4-piperazin-1-yl, R11 = propenyl, R3 = R4 = R5= H] cpd 143



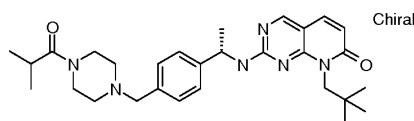
- ^1H NMR (500MHz, DMSO- d_6) δ = 8.57 (s, 1H), 8.36 (d, $J = 7.32$ Hz, 1H), 7.67 (d, $J = 9.15$ Hz, 1H), 7.33 (d, $J = 7.93$ Hz, 2H), 7.23 (d, $J = 8.08$ Hz, 2H), 6.64 (qd, $J = 6.90, 14.90$ Hz, 1H), 6.46 (qd, $J = 1.50, 14.95$ Hz, 1H), 6.22 (d, $J = 9.30$ Hz, 1H), 5.06 (quin, $J = 7.20$ Hz, 1H), 3.92 - 4.37 (m, 2H), 3.44 - 3.62 (m, 4H), 3.43 (s, 2H), 2.25-2.33 (m, 4H), 1.82 (dd, $J = 1.68, 6.8$ Hz, 3H), 1.46 (d, $J = 7.02$ Hz, 3H), 0.92 (br. s., 3H), 0.73 (br. s., 6H). LCMS : m/z 503 $[M+H]^+$ @ r.t. 6.11 min. HRMS (ESI) calcd for $C_{28}H_{39}N_6O_2$ $[M+H]^+$ 503.3129 found 503.3117;

- 8-(2,2-dimethylpropyl)-2- $\{[(1S)-1-[4-[(2\text{-methylacryloyl})\text{piperazin-1-yl\}methyl]phenyl\}ethyl\}amino\}$ pyrido
[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = 2,2-dimethyl-propyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-
20 C(O)NR7R8, R6b = H, R7-R8 = 4-piperazin-1-yl, R11 = methylvinyl, R3 = R4 = R5= H] cpd 144



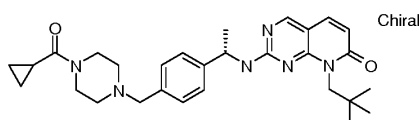
- ^1H NMR (500MHz, DMSO- d_6) δ = 8.57 (s, 1H), 8.36 (d, $J = 7.32$ Hz, 1H), 7.67 (d, $J = 9.30$ Hz, 1H), 7.33 (d, $J = 8.08$ Hz, 2H), 7.23 (d, $J = 7.93$ Hz, 2H), 6.22 (d, $J = 9.30$ Hz, 1H), 5.15 (quin, $J = 1.40$ Hz, 1H), 5.07 (quin, $J = 6.83$ Hz, 1H), 4.92 (br. s., 1H), 3.89 - 4.33 (m, 2H), 3.44 (br. s., 6H), 2.30 (br. s., 4H), 1.81 (s, 3H), 1.45 (d, $J = 7.02$ Hz, 3H), 0.92 (br. s., 3H), 0.73 (br. s., 6H). LCMS : m/z 503 $[M+H]^+$ @ r.t. 6.20 min. HRMS (ESI) calcd for $C_{29}H_{39}N_6O_2$ $[M+H]^+$ 503.3129 found 503.3122;

8-(2,2-dimethylpropyl)-2-[[[(1S)-1-[4-[[4-(2-methylpropanoyl)piperazin-1-yl]methyl]phenyl]ethyl]amino]-pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = 2,2-dimethyl-propyl, A = phenyl, R1a= H, R1b = Me, R6a= O-R7, R6b = H, R7= 4-piperazin-1-yl, R11 = 2-isopropyl, R3 = R4 = R5= H] cpd 157



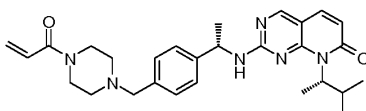
- 5 ¹H NMR (500 MHz, DMSO-d₆) δ = 8.57 (s, 1H), 8.36 (d, J = 7.3 Hz, 1H), 7.67 (d, J = 9.2 Hz, 1H), 7.33 (d, J = 8.1 Hz, 2H), 7.13 - 7.28 (m, 2H), 6.22 (d, J = 9.3 Hz, 1H), 5.06 (quin, J = 6.9 Hz, 1H), 3.86 - 4.34 (m, 2H), 3.43 (s, 2H), 3.43 (br. s., 4H), 2.82 (spt, J = 6.6 Hz, 1H), 2.32 (br. s., 2H), 2.25 (br. s., 2H), 1.46 (d, J = 6.9 Hz, 3H), 0.95 (d, J = 6.7 Hz, 6H), 0.74 (br. s., 9H). LCMS: m/z 505 [M+H]⁺ @ r.t. 6.28 min.
HRMS (ESI) calcd for C₂₉H₄₁N₆O₂ [M + H]⁺ 505.3286 found 505.3286;

- 10 2-[[[(1S)-1-[4-[(cyclopropylcarbonyl)piperazin-1-yl]methyl]phenyl]ethyl]amino]-8-(2,2-dimethylpropyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = 2,2-dimethyl-propyl, A = phenyl, R1a= H, R1b = Me, R6a= O-R7, R6b = H, R7= 4-piperazin-4-yl, R11 = cyclopropyl, R3 = R4 = R5= H] cpd 158



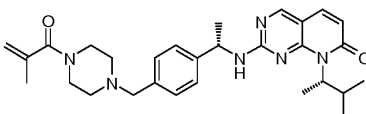
- 15 ¹H NMR (500 MHz, DMSO-d₆) δ = 8.58 (s, 1H), 8.36 (d, J = 7.3 Hz, 1H), 7.67 (d, J = 9.3 Hz, 1H), 7.33 (d, J = 8.1 Hz, 2H), 7.23 (d, J = 7.9 Hz, 2H), 6.22 (d, J = 9.3 Hz, 1H), 5.06 (quin, J = 7.1 Hz, 1H), 3.89 - 4.32 (m, 2H), 3.63 (br. s., 2H), 3.44 (s, 2H), 3.42 (br. s., 2H), 2.35 (br. s., 2H), 2.26 (br. s., 2H), 1.86 - 1.99 (m, 1H), 1.46 (d, J = 7.0 Hz, 3H), 0.74 (br. s., 9H), 0.57 - 0.74 (m, 4H). LCMS: m/z 503 [M+H]⁺ @ r.t. 6.07 min
HRMS (ESI) calcd for C₂₉H₃₉N₆O₂ [M + H]⁺ 503.3129 found 503.3137;

- 20 2-[(S)-1-[4-(4-Acryloyl-piperazin-1-ylmethyl)-phenyl]-ethylamino]-8-((S)-1,2-dimethyl-propyl)-8H-pyrido[2,3-d]pyrimidin-7-one [(I), X = N, R2 = -(S)-1,2-Dimethyl-propyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-CH₂NR7R8, R6b = H, R7-R8 = 4-piperazin-1-yl, R11 = vinyl, R3 = R4 = R5= H] cpd 161



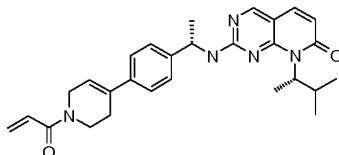
- 25 ¹H NMR (500 MHz, DMSO-d₆) δ = 8.56 (s, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.20 - 7.33 (m, 4H), 6.76 (dd, J = 16.6, 10.4 Hz, 1H), 6.10 - 6.22 (m, 1H), 6.07 (dd, J = 16.6, 2.3 Hz, 1H), 5.64 (dd, J = 10.4, 2.3 Hz, 1H), 4.78 - 5.07 (m, 2H), 3.41 - 3.55 (m, 6H), 2.30 (br. s., 4H), 1.36 - 2.07 (m, 4H), 0.07 - 1.09 (m, 9H). LCMS : m/z 489 [M+H]⁺ @ r.t. 5.77 min. HRMS (ESI) calcd for C₂₈H₃₆N₆O₂ [M + H]⁺ 489.2973 found 489.2973;

8-((S)-1,2-Dimethyl-propyl)-2-[(S)-1-[4-(2-methyl-acryloyl)-piperazin-1-ylmethyl]-phenyl]-ethylamino)-8H-pyrido[2,3-d]pyrimidin-7-one [(I), X = N, R2 = -(S)-1,2-Dimethyl-propyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-CH₂NR7R8, R6b = H, R7-R8 = 4-piperazin-1-yl, R11 = methylvinyl, R3 = R4 = R5= H] cpd 162



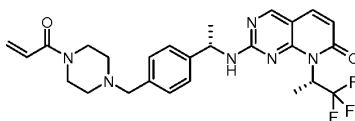
¹H NMR (500 MHz, DMSO-d₆) δ = 8.56 (s, 1H), 7.20 - 7.35 (m, 4H), 6.10 - 6.22 (m, 1H), 4.75 - 5.16 (m, 4H), 3.27 - 3.47 (m, 6H), 2.32 (br. s., 4H), 1.80 - 1.85 (m, 3H), 1.00 - 1.55 (m, 4H), 0.07 - 0.86 (m, 9H). LCMS : m/z 503 [M+H]⁺ @ r.t. 6.08 min. HRMS (ESI) calcd for C₂₉H₃₉N₆O₂ [M + H]⁺ 503.3129 found 503.3136;

- 2-(((1S)-1-[4-(1-acryloyl-1,2,3,6-tetrahydropyridin-4-yl)phenyl]ethyl)amino)-8-[(2S)-3-methylbutan-2-yl]pyrido
5 [2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = (2S)-3-methylbutan-2-yl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-(1-
acryloyl-1,2,3,6-tetrahydropyridin-4-yl, R_{6b} = H, R₈ = H, R₃ = R₄ = R₅ = H] Cpd 168



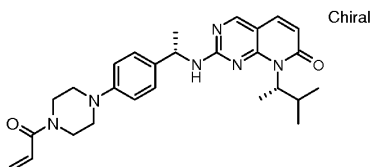
- ¹H NMR (500 MHz, DMSO- d₆) δ 8.58 (s, 1H), 8.40 (d, J = 7.47 Hz, 1H), 7.63 (d, J = 9.3 Hz, 1H), 7.23 - 7.42 (m, 4H),
6.88 (dd, J = 10.68, 18.30 Hz, 1H), 6.21 (d, J = 9.30 Hz, 1H), 6.04 - 6.16 (m, 2H), 5.70 (dd, J = 2.29, 10.68 Hz, 1H),
10 4.95- 5.10 (m, 1H), 4.74-4.87 (m, 1H), 4.24 (br. s., 1H), 4.14 (br. s., 1H), 2.44 (m, 2H), 1.86-1.94 (m, 1H), 1.47 (d, J =
6.86 Hz, 3H), 0.99-1.14 (m, 3H), 0.70 (d, J = 6.41 Hz, 3H), 0.05 (d, J = 6.41 Hz, 3H). LCMS : m/z 472 [M+H]⁺ r.t.
6.24 min. HRMS (ESI) calcd for C₂₈H₃₄N₅O [M + H]⁺ 472.2707 found 472.2700;

- 2-(((1S)-1-[4-[(4-acryloylpiperazin-1-yl)methyl]phenyl]ethyl)amino)-8-[(2S)-1,1,1-trifluoropropan-2-yl]pyrido
15 [2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = 2,2-dimethyl-propyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-
CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = 4-piperazin-1-yl, R₁₁ = vinyl, R₃ = R₄ = R₅ = H] cpd 169



- ¹H NMR (500MHz, DMSO-d₆) δ = 8.63 (m, 2H), 7.72 (d, J = 9.46 Hz, 1H), 7.22- 7.35 (m, 4H), 6.76 (dd, J = 10.37,
18.91 Hz, 1H), 6.18 (d, J = 9.46 Hz, 1H), 6.01-6.10 (m, 2H), 5.65 (dd, J = 2.29, 10.37 Hz, 1H), 4.79 (quin, J = 6.71
Hz, 1H), 3.42 - 3.54 (m, 6H), 2.27 - 2.31 (m, 4H), 1.87 (d, J = 7.17 Hz, 1H), 1.47 (d, J = 6.86 Hz, 3H), 1.36 (d, J =
20 7.17 Hz, 3H). LCMS : m/z 515 [M+H]⁺ @ r.t. 5.71 min. HRMS (ESI) calcd for C₂₆H₃₀F₃N₆O₂ [M + H]⁺ 515.2377 found
515.2363.

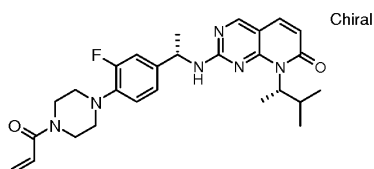
2-(((1S)-1-[4-(4-acryloylpiperazin-1-yl)phenyl]ethyl)amino)-8-[(2S)-3-methylbutan-2-yl]pyrido[2,3-d]pyrimidin-
7(8H)-one [(I), X = N, R₂ = (2S)-3-methylbutan-2-yl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-NR₇R₈, R_{6b} = H,
R₇-R₈ = 4-piperazin-1-yl, R₁₁ = vinyl, R₃ = R₄ = R₅ = H] cpd 175



- ¹H NMR (500MHz, DMSO-d₆) δ = 8.55 (s, 1H), 8.27 (d, J = 7.63 Hz, 1H), 7.63 (d, J = 9.15 Hz, 1H), 7.24 (d, J = 8.69
Hz, 1H), 7.16 (d, J = 8.69 Hz, 1H), 6.90 (d, J = 8.69 Hz, 2H), 6.84 (dd, J = 10.45, 16.55 Hz, 1H), 6.20 (d, J = 9.15 Hz,
1H), 6.12 (dd, J = 2.29, 16.78 Hz, 1H), 5.69 (dd, J = 2.30, 10.50 Hz, 1H), 5.11 - 5.22 (m, 1H), 4.76 - 4.96 (m, 1H),
25 3.66 (d, J = 18.00 Hz, 4H), 3.06 (br. s., 4H), 1.39 - 1.53 (m, 4H), 0.98 - 1.21 (m, 3H), 0.60 - 0.80 (m, 3H), 0.13 (d, J =

6.24 Hz, 3H). LCMS : m/z 475 [M+H]⁺ @ r.t. 5.96 min. HRMS (ESI) calcd for C₂₇H₃₅N₆O₂ [M +H]⁺ 475.2816 found 475.2813.

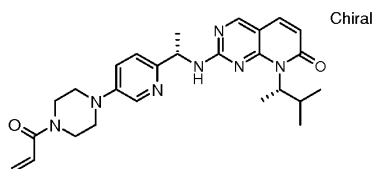
- 2-{{{1S}-1-[4-(4-acryloylpiperazin-1-yl)-3-fluorophenyl]ethyl}amino}-8-[(2S)-3-methylbutan-2-yl]pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = (2S)-3-methylbutan-2-yl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-NR₇R₈, R_{6b} = F, R₇-R₈ = 4-piperazin-1-yl, R₁₁ = vinyl, R₃ = R₄ = R₅ = H] cpd 179



¹H NMR (500MHz, DMSO-d₆) δ = 8.57 (s, 1H), 8.28 - 8.45 (m, 1H), 7.64 - 7.68 (m, 1H), 6.92 - 7.18 (m, 3H), 6.83 (dd, J = 10.45, 16.40 Hz, 1H), 6.10 - 6.24 (m, 2H), 5.70 (dd, J = 2.06, 10.45 Hz, 1H), 4.92 (m, 1H), 4.79 (m, 1H), 3.68 (d, J = 16.93 Hz, 4H), 2.92 (br. s., 4H), 1.95 (m, 1H), 1.42 - 1.51 (m, 3H), 0.99 - 1.16 (m, 3H), 0.11 (d, J = 6.56 Hz, 3H).

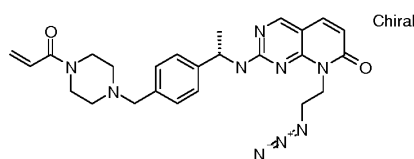
- 10 LCMS : m/z 493 [M+H]⁺ @ r.t. 6.07 min. HRMS (ESI) calcd for C₂₇H₃₄FN₆O₂ [M +H]⁺ 493.2722 found 493.2736.

- 2-{{{1S}-1-[6-(4-acryloylpiperazin-1-yl)pyridin-3-yl]ethyl}amino}-8-[(2S)-3-methylbutan-2-yl]pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = (2S)-3-methylbutan-2-yl, A = pyridin-3-yl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-NR₇R₈, R_{6b} = H, R₇-R₈ = 4-piperazin-1-yl, R₁₁ = vinyl, R₃ = R₄ = R₅ = H] cpd 181



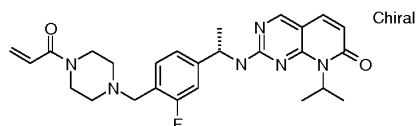
- 15 ¹H NMR (500MHz, DMSO-d₆) δ = 8.57 (s, 1H), 8.30 (m, 1H), 8.15 (br., s, 1H), 7.65 (d, J = 9.46 Hz, 1H), 7.49 (m, 1H), 6.80 - 6.87 (m, 2H), 5.70 (dd, J = 2.70, 10.3 Hz, 1H), 4.90 (m, 1H), 4.81 (m, 1H), 3.62 (d, J = 19.52 Hz, 4H), 3.44 (br. s., 4H), 2.10 (m, 1H), 1.44 - 1.51 (m, 3H); 0.99 - 1.07 (m, 3H); 0.55 - 0.65 (m, 3H), 0.17 (d, J = 6.41 Hz, 3H). LCMS : m/z 476 [M+H]⁺ @ r.t. 5.49 min. HRMS (ESI) calcd for C₂₆H₃₄N₇O₂ [M +H]⁺ 476.2769 found 476.2777.

- 2-[[{(1S)-1-[4-[(4-acryloylpiperazin-1-yl)methyl]phenyl]ethyl}amino]-8-(2-azidoethyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = 2-azidoethyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = 4-piperazin-1-yl, R₁₁ = vinyl, R₃ = R₄ = R₅ = H] cpd 182



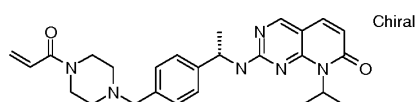
- 25 ¹H NMR (500MHz, DMSO-d₆) δ = 8.60 (m, 1H), 8.50 (m, 1H), 7.63 - 7.73 (m, 1H), 7.17 - 7.37 (m, 2H), 6.75 (dd, J = 10.22, 16.78 Hz, 1H), 6.12 - 6.29 (m, 2H), 6.08 (dd, J = 2.36, 16.70 Hz, 1H), 5.26 (m, 2H), 5.04 (m, 1H), 4.44 (m, 1H), 4.17 - 4.37 (m, 2H), 3.34 - 3.71 (m, 6H), 2.20 - 2.34 (m, 4H), 1.41 - 1.49 (m, 3H). LCMS : m/z 488 [M+H]⁺ @ r.t. 5.12 min. HRMS (ESI) calcd for C₂₅H₃₀N₉O₂ [M +H]⁺ 488.22517 found 488.2525.

- 2-[[{(1S)-1-[4-[(4-acryloylpiperazin-1-yl)methyl]-3-fluorophenyl]ethyl}amino]-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = propan-2-yl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = F, R₇-R₈ = 4-piperazin-1-yl, R₁₁ = vinyl, R₃ = R₄ = R₅ = H] cpd 183



¹H NMR (500MHz, DMSO-d₆) δ = 8.57 (s, 1H), 8.37 (d, *J* = 6.71 Hz, 1H), 7.63 (d, *J* = 9.30 Hz, 1H), 7.32 (t, *J* = 7.47 Hz, 1H), 7.10 - 7.24 (m, 2H), 6.75 (dd, *J* = 10.52, 16.62 Hz, 1H), 6.17 (d, *J* = 9.30 Hz, 1H), 6.07 (dd, *J* = 1.83, 16.47 Hz, 1H), 5.64 (dd, *J* = 1.98, 10.37 Hz, 1H), 5.49 (br., m, 1H), 4.99 (quin, *J* = 6.98 Hz, 1H), 3.49 (br. s, 6H), 2.31 (br. s., 4H), 1.48 (d, *J* = 6.86 Hz, 9H). LCMS : m/z 479 [M+H]⁺ @ r.t. 6.74 min. HRMS (ESI) calcd for C₂₆H₃₂FN₆O₂ [M +H]⁺ 479.2566 found 479.2577.

2-[[[(1S)-1-{4-[(4-acryloylpiperazin-1-yl)methyl]phenyl}ethyl]amino]-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = propan-2-yl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = 4-piperazin-1-yl, R₁₁ = vinyl, R₃ = R₄ = R₅ = H] cpd 184

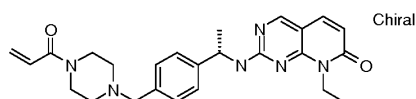


10

¹H NMR (500MHz, DMSO-d₆) δ = 8.55 (s, 1H), 8.36 (d, *J* = 6.86 Hz, 1H), 7.62 (d, *J* = 9.30 Hz, 1H), 7.32 (d, *J* = 7.63 Hz, 2H), 7.22 (d, *J* = 7.47 Hz, 2H), 6.76 (dd, *J* = 10.52, 16.62 Hz, 1H), 6.15 (d, *J* = 9.30 Hz, 1H), 6.07 (dd, *J* = 1.98, 16.62 Hz, 1H), 5.64 (dd, *J* = 1.98, 10.52 Hz, 1H), 5.50 (br., s, 1H), 5.0 (m, 1H), 3.50 (br. s., 4H), 3.42 (br. s., 2H), 2.28 (br. s., 4H), 1.44 - 1.52 (m, 9H). LCMS : m/z 461 [M+H]⁺ @ r.t. 5.29 min. HRMS (ESI) calcd for C₂₆H₃₃N₆O₂ [M +H]⁺ 461.266 found 461.2661.

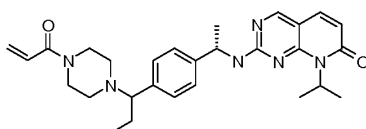
15

2-[[[(1S)-1-{4-[(4-acryloylpiperazin-1-yl)methyl]phenyl}ethyl]amino]-8-ethylpyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = ethyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = 4-piperazin-1-yl, R₁₁ = vinyl, R₃ = R₄ = R₅ = H] cpd 186



¹H NMR (500MHz, DMSO-d₆) δ = 8.58 (s, 1H), 8.43 (d, *J* = 7.02 Hz, 1H), 7.67 (d, *J* = 9.30 Hz, 1H), 7.35 (d, *J* = 7.78 Hz, 2H), 7.23 (d, *J* = 7.78 Hz, 2H), 6.75 (dd, *J* = 10.52, 16.62 Hz, 1H), 6.20 (d, *J* = 9.30 Hz, 1H), 6.07 (dd, *J* = 2.21, 16.62 Hz, 1H), 5.65 (dd, *J* = 2.21, 10.52 Hz, 1H), 5.02 (quin, *J* = 7.05 Hz, 1H), 3.49 (m, 6H), 3.42 (s, 2H), 2.29 (br. s., 4H), 1.47 (d, *J* = 7.17 Hz, 3H), 0.90 (t, *J* = 6.86 Hz, 3H). LCMS : m/z 447 [M+H]⁺ @ r.t. 4.92 min. HRMS (ESI) calcd for C₂₆H₃₁N₆O₂ [M +H]⁺ 447.2503 found 447.2518.

2-[[[(1S)-1-{4-[1-(4-acryloylpiperazin-1-yl)propyl]phenyl}ethyl]amino]-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = propan-2-yl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH(R₁₄)NR₇R₈, R_{6b} = H, R₇-R₈ = 4-piperazin-1-yl, R₁₁ = vinyl, R₃ = R₄ = R₅ = H, R₁₄ = ethyl] cpd 187

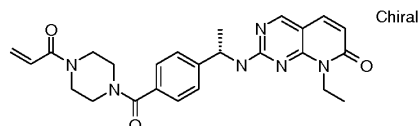


¹H NMR (500MHz, DMSO-d₆) δ = 8.56 (s, 1H), 8.34 (d, *J* = 6.85 Hz, 1H), 7.62 (d, *J* = 9.30 Hz, 1H), 7.30 (d, *J* = 7.63 Hz, 2H), 7.14 (d, *J* = 7.63 Hz, 2H), 6.69 (dd, *J* = 10.98, 17.54 Hz, 1H), 6.15 (d, *J* = 9.30 Hz, 1H), 6.01 (dd, *J* = 1.98,

30

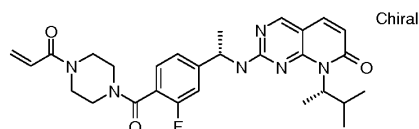
17.54 Hz, 1H), 5.59 (dd, $J = 1.98, 10.98$ Hz, 1H), 5.44 (br. s, 1H), 4.98 (br. s, 1H), 3.40 - 3.52 (br. m., 4H), 3.222 - 3.26 (m, 1H), 2.28 (br. s., 4H), 1.80 - 1.89 (m, 1H), 1.61 - 1.67 (m, 1H), 1.44 - 1.52 (m, 9H), 0.65 - 0.72 (m, 3H). LCMS : m/z 489 $[M+H]^+$ @ r.t. 7.09 min. HRMS (ESI) calcd for $C_{28}H_{37}N_6O_2$ $[M+H]^+$ 489.2973 found 489.2981

- 2-[[[(1S)-1-{4-[(4-acryloylpiperazin-1-yl)carbonyl]phenyl}ethyl]amino]-8-ethylpyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = ethyl, A = phenyl, R1a= H, R1b = Me, R6a= 4-CONR7R8, R6b = H, R7-R8 = 4-piperazin-1-yl, R11 = vinyl, R3 = R4 = R5= H] cpd 190



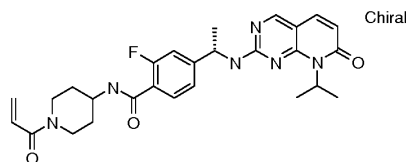
- ^1H NMR (500MHz, DMSO- d_6) δ = 8.59 (s, 1H), 8.50 (d, $J = 7.17$ Hz, 1H), 7.68 (d, $J = 9.30$ Hz, 1H), 7.47 (d, $J = 8.08$ Hz, 2H), 7.37 (d, $J = 8.08$ Hz, 2H), 6.61 - 6.95 (m, 1H), 6.22 (d, $J = 9.30$ Hz, 1H), 6.12 (dd, $J = 2.29, 16.62$ Hz, 1H), 5.70 (d, $J = 10.83$ Hz, 1H), 5.05 (q, $J = 7.1$ Hz, 1H), 3.99 - 4.27 (m, 2H), 3.57 (br. s., 8H), 1.49 (d, $J = 7.02$ Hz, 3H), 0.89 (t, $J = 6.63$ Hz, 3H). LCMS : m/z 461 $[M+H]^+$ @ r.t. 4.58 min. HRMS (ESI) calcd for $C_{26}H_{29}N_6O_3$ $[M+H]^+$ 461.2296 found 461.2306

- 2-[[[(1S)-1-{4-[(4-acryloylpiperazin-1-yl)carbonyl]-3-fluorophenyl}ethyl]amino]-8-[(2S)-3-methylbutan-2-yl]pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = (2S)-3-methylbutan-2-yl, A = phenyl, R1a= H, R1b = Me, R6a= 4-CONR7R8, R6b = F, R7-R8 = 4-piperazin-1-yl, R11 = vinyl, R3 = R4 = R5= H] cpd 191



- ^1H NMR (500MHz, DMSO- d_6) δ = 8.60 (s, 1H), 8.41 (d, $J = 6.25$ Hz, 1H), 7.66 (d, $J = 9.30$ Hz, 1H), 7.37 (d, $J = 7.32$ Hz, 1H), 7.18 - 7.32 (m, 2H), 6.68 - 6.86 (m, 1H), 6.24 (d, $J = 9.30$ Hz, 1H), 6.11 (dd, $J = 2.29, 16.62$ Hz, 1H), 5.66 - 5.73 (m, 1H), 5.01 (q, $J = 7.1$ Hz, 1H), 4.77 - 4.99 (m, 1H), 3.45 - 3.69 (m, 6H), 3.18 - 3.25 (m, 2H), 1.91 (m, 1H), 1.50 (d, $J = 6.86$ Hz, 3H), 0.76 (d, $J = 5.80$ Hz, 3H), 0.64 (d, $J = 5.80$ Hz, 3H), 0.12 (d, $J = 5.80$ Hz, 3H). LCMS : m/z 521 $[M+H]^+$ @ r.t. 5.44 min. HRMS (ESI) calcd for $C_{28}H_{33}FN_6O_3$ $[M+H]^+$ 521.2671 found 521.2684.

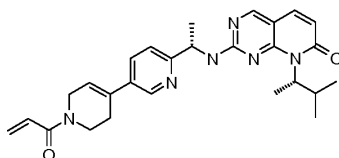
N-(1-acryloylpiperidin-4-yl)-2-fluoro-4-[[[(1S)-1-{[7-oxo-8-(propan-2-yl)-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl]amino}ethyl]benzamide [(I), X = N, R2 = propan-2-yl, A = phenyl, R1a= H, R1b = Me, R6a= 4-CONR7R8, R6b = H, R7 = H, R8 = 4-piperidin-1-yl, R11 = vinyl, R3 = R4 = R5= H] cpd 192



- ^1H NMR (500MHz, DMSO- d_6) δ 8.57 (s, 1H), 8.42 (d, $J = 7.32$ Hz, 1H), 8.15 (d, $J = 7.78$ Hz, 1H), 7.63 (d, $J = 9.46$ Hz, 1H), 7.49 (t, $J = 7.40$ Hz, 1H), 7.27 (d, $J = 9.76$ Hz, 2H), 6.81 (dd, $J = 10.45, 16.70$ Hz, 1H), 6.17 (d, $J = 8.85$ Hz, 1H), 6.08 (dd, $J = 2.36, 16.70$ Hz, 1H), 5.66 (dd, $J = 2.36, 10.45$ Hz, 1H), 5.54 (br. s., 1H), 5.06 (quin, $J = 7.00$ Hz, 1H), 4.27 (d, $J = 12.51$ Hz, 1H), 3.92 - 4.01 (m, 2H), 3.18 (t, $J = 11.90$ Hz, 1H), 2.84 (t, $J = 11.74$ Hz, 1H), 1.82 (br.

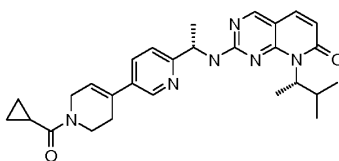
s., 2H), 1.51 (d, $J = 4.88$ Hz, 2H), 1.48 (d, $J = 7.02$ Hz, 3H), 1.36 (br. s., 6H). LCMS : m/z 506 $[M+H]^+$ @ r.t. 9.44 min. HRMS (ESI) calcd for $C_{27}H_{32}FN_6O_3$ $[M+H]^+$ 506.2515 found 506.2528.

- 2-[[[(1S)-1-(1'-acryloyl-1',2',3',6'-tetrahydro-3,4'-bipyridin-6-yl)ethyl]amino]-8-[(2S)-3-methylbutan-2-yl]pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = (2S)-3-methylbutan-2-yl, A = pyridin-2-yl, R1a= H, R1b = Me, R6a= 4-(1-acryloyl-1,2,3,6-tetrahydropyridin-4-yl, R6b = H, R3 = R4 = R5= H] Cpd 194

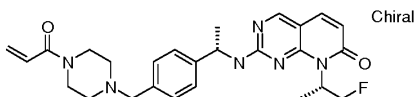


- ^1H NMR (500 MHz, DMSO- d_6) δ 8.61 (s, 1H), 8.59 (s, 1H), 8.34 (d, $J = 6.25$ Hz, 1H), 7.62 - 7.80 (m, 2H), 7.21 (d, $J = 8.24$ Hz, 1H), 7.46 (d, $J = 8.24$ Hz, 2H), 6.89 (dd, $J = 10.37, 16.93$ Hz, 1H), 6.09 - 6.23 (m, 3H), 5.70 (dd, $J = 2.29, 16.93$ Hz, 1H), 4.97 (quin, $J = 6.90$ Hz, 1H), 4.70 - 4.77 (m, 1H), 4.27 (br. m, 1H), 4.15 - 4.27 (br. m, 1H), 3.71 - 3.79 (m, 2H), 2.52 - 2.55 (m, 2H), 1.48 - 1.60 (m, 4H), 0.97 - 1.03 (m, 3H), 0.57 - 0.63 (m, 3H), 0.01 (d, $J = 6.71$ Hz, 3H). LCMS : m/z 473 $[M+H]^+$ r.t. 5.28 min. HRMS (ESI) calcd for $C_{27}H_{33}N_6O_2$ $[M+H]^+$ 473.266 found 473.2667;

2-[[[(1S)-1-[1'-(cyclopropylcarbonyl)-1',2',3',6'-tetrahydro-3,4'-bipyridin-6-yl]ethyl]amino]-8-[(2S)-3-methylbutan-2-yl]pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = (2S)-3-methylbutan-2-yl, A = pyridin-2-yl, R1a= H, R1b = Me, R6a= 4-(1- cyclopropylcarbonyl 1,2,3,6-tetrahydropyridin-4-yl, R6b = H, R3 = R4 = R5= H] Cpd 195

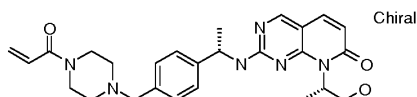


- LCMS : m/z 487 $[M+H]^+$ r.t. 5.52 min. HRMS (ESI) calcd for $C_{28}H_{35}N_6O_2$ $[M+H]^+$ 487.2816 found 487.2813; 2-[[[(1S)-1-[4-[(4-acryloylpiperazin-1-yl)methyl]phenyl]ethyl]amino]-8-[(2S)-1-fluoropropan-2-yl]pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = (2S)-1-fluoropropan-2-yl, A = phenyl, R1a= H, R1b = Me, R6a= 4-(4-acryloylpiperazin-1-yl)methyl, R6b = H, R3 = R4 = R5= H] Cpd 198



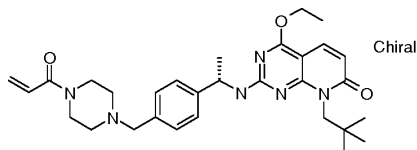
- ^1H NMR (500 MHz, DMSO- d_6) δ 8.60 (s, 1H), 8.47 (d, $J = 5.64$ Hz, 1H), 7.68 (d, $J = 9.15$ Hz, 1H), 7.21 - 7.37 (m, 4H), 6.75 (dd, $J = 10.29, 16.70$ Hz, 1H), 6.20 (d, $J = 9.15$ Hz, 1H), 6.07 (dd, $J = 2.21, 16.70$ Hz, 1H), 5.64 (dd, $J = 2.21, 10.29$ Hz, 1H), 4.91 (td, $J = 6.48, 12.96$ Hz, 1H), 4.36 (m, 1H), 3.38 - 3.60 (m, 8H), 2.30 (br. s., 4H), 1.47 (d, $J = 7.02$ Hz, 3H), 1.05 (dd, $J = 7.02$ Hz, 3H). LCMS : m/z 479 $[M+H]^+$ r.t. 5.94 min. HRMS (ESI) calcd for $C_{26}H_{32}FN_6O_2$ $[M+H]^+$ 479.2566 found 479.2572;

2-[[[(1S)-1-[4-[(4-acryloylpiperazin-1-yl)methyl]phenyl]ethyl]amino]-8-[(2S)-1-hydroxypropan-2-yl]pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = (2S)-1-hydroxypropan-2-yl, A = phenyl, R1a= H, R1b = Me, R6a= 4-(4-acryloylpiperazin-1-yl)methyl, R6b = H, R3 = R4 = R5= H] Cpd 199

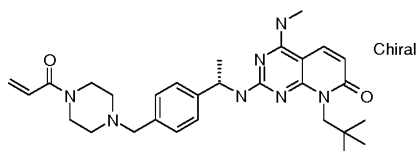


- ¹H NMR (500 MHz, DMSO- *d*₆) δ 8.56 (s, 1H), 7.63 (d, *J* = 9.00 Hz, 1H), 7.19 - 7.49 (m, 4H), 6.76 (dd, *J* = 10.52, 16.78 Hz, 1H), 6.04 - 6.22 (br. m, 2H), 5.61 - 5.77 (br. m, 1H), 5.27 (br. s, 1H), 5.01 (m, 1H), 4.68 - 4.79 (br. m, 1H), 4.42 - 4.52 (br. m, 1H), 4.17 - 4.37 (br. m, 2H), 3.39 - 3.60 (m, 6H), 2.29 (m, 4H), 1.36 - 1.51 (m, 6H). LCMS : *m/z* 477 [M+H]⁺ r.t. 4.37 min. HRMS (ESI) calcd for C₂₆H₃₂N₆O₃ [M + H]⁺ 477.2609 found 477.2605;

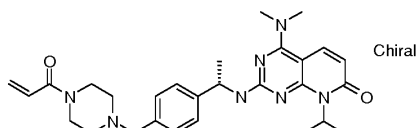
2-[[[(1S)-1-{4-[(4-acryloylpiperazin-1-yl)methyl]phenyl}ethyl]amino]-8-(2,2-dimethylpropyl)-4-ethoxypyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = 2,2-dimethylpropyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-(4-acryloylpiperazin-1-yl)methyl, R_{6b} = H, R₃ = OEthyl, R₄ = R₅ = H] Cpd 201



- ¹H NMR (500 MHz, DMSO- *d*₆) δ 8.19 (d, *J* = 7.63 Hz, 1H), 7.67 (d, *J* = 9.46 Hz, 1H), 7.30 - 7.37 (m, 2H), 7.18 - 7.28 (m, 2H), 6.76 (dd, *J* = 10.29, 16.70 Hz, 1H), 6.05 - 6.10 (m, 2H), 5.64 - 5.68 (m, 1H), 4.98 - 5.23 (m, 1H), 4.28 - 4.53 (m, 2H), 4.02 (dd *J* = 7.17, 15.56 Hz, 2H), 3.46 - 3.56 (m, 4H), 3.40 - 3.46 (m, 2H), 2.31 (br. s., 4H), 1.42 - 1.49 (m, 6H), 1.37 (t, *J* = 7.09 Hz, 3H), 0.73 (br., m, 6H). LCMS : *m/z* 533 [M+H]⁺ r.t. 10.12 min. HRMS (ESI) calcd for C₃₀H₄₁N₆O₃ [M + H]⁺ 533.3235 found 533.3249;
- 2-[[[(1S)-1-{4-[(4-acryloylpiperazin-1-yl)methyl]phenyl}ethyl]amino]-8-(2,2-dimethylpropyl)-4-(methylamino)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = 2,2-dimethylpropyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-(4-acryloylpiperazin-1-yl)methyl, R_{6b} = H, R₃ = N-Methyl, R₄ = R₅ = H] Cpd 202**

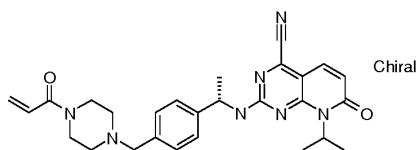


- ¹H NMR (500 MHz, DMSO- *d*₆) δ. 7.72 - 7.89 (m, 1H), 7.53 - 7.64 (m, 1H), 7.32 (d, *J* = 8.08 Hz, 1H), 7.15 - 7.29 (m, 4H), 6.76 (ddd, *J* = 4.27, 10.49, 16.66 Hz, 1H), 6.03 - 6.18 (m, 1H), 5.99 (d, *J* = 9.46 Hz, 1H), 5.60 - 5.71 (m, 1H), 4.88 (dq *J* = 7.32, 7.63 Hz, 1H), 4.11 (dd, *J* = 5.19 Hz, 2H), 3.51 (br. s., 4H), 3.44 (d, *J* = 6.86 Hz, 2H), 2.90 (d, *J* = 4.27 Hz, 3H), 2.32 (br. s., 4H), 1.31 (d, *J* = 7.02 Hz, 3H), 0.90 (br.s, 3H), 0.73 (br. s, 6H).
- LCMS : *m/z* 518 [M+H]⁺ r.t. 10.12 min. HRMS (ESI) calcd for C₂₉H₄₀N₇O₂ [M + H]⁺ 518.3238 found 518.3239;
- 2-[[[(1S)-1-{4-[(4-acryloylpiperazin-1-yl)methyl]phenyl}ethyl]amino]-4-(dimethylamino)-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = propan-2-yl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-(4-acryloylpiperazin-1-yl)methyl, R_{6b} = H, R₃ = N,N-diMethyl, R₄ = R₅ = H] Cpd 203**



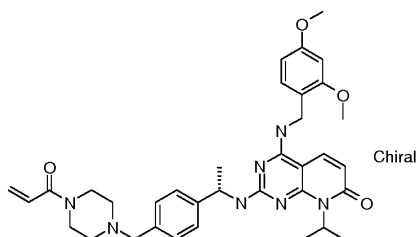
LCMS : *m/z* 505 [M+H]⁺ r.t. 6.05 min. HRMS (ESI) calcd for C₂₈H₃₈N₇O₂ [M + H]⁺ 504.3082 found 504.3095;

2-[[[(1S)-1-{4-[(4-acryloylpiperazin-1-yl)methyl]phenyl}ethyl]amino]-7-oxo-8-(propan-2-yl)-7,8-dihydropyrido[2,3-d]pyrimidine-4-carbonitrile [(I), X = N, R₂ = propan-2-yl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-(4-acryloylpiperazin-1-yl)methyl, R_{6b} = H, R₃ = CN, R₄ = R₅ = H] Cpd 204



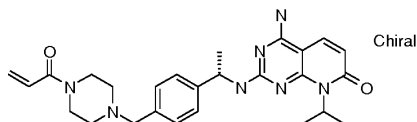
5 ¹H NMR (500 MHz, DMSO- *d*₆) δ 8.92 (d, *J* = 7.17 Hz, 1H), 7.66 (d, *J* = 9.46 Hz, 1H), 7.32 (d, *J* = 8.08 Hz, 2H), 7.23 (d, *J* = 8.08 Hz, 2H), 6.76 (dd, *J* = 10.45, 16.70 Hz, 1H), 6.35 (d, *J* = 9.46 Hz, 1H), 6.07 (dd, *J* = 2.36, 16.70 Hz, 1H), 5.64 (dd, *J* = 2.36, 10.45 Hz, 1H), 4.98 (d, *J* = 6.56 Hz, 1H), 3.50 (br. s., 4H), 3.43 (s, 2H), 2.28 (br. s., 4H), 1.48 (d, *J* = 7.17 Hz, 3H). LCMS : *m/z* 486 [M+H]⁺ r.t. 6.18 min. HRMS (ESI) calcd for C₂₇H₃₂N₇O₂ [M + H]⁺ 486.2612 found 486.2614;

10 2-[[[(1S)-1-{4-[(4-acryloylpiperazin-1-yl)methyl]phenyl}ethyl]amino]-4-[(2,4-dimethoxybenzyl)amino]-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = propan-2-yl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-(4-acryloylpiperazin-1-yl)methyl, R_{6b} = H, R₃ = (2,4-dimethoxybenzyl)amino, R₄ = R₅ = H] Cpd 205



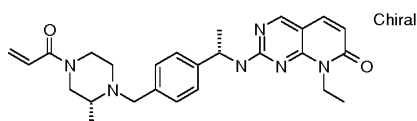
LCMS : *m/z* 626 [M+H]⁺ r.t. 6.67 min. HRMS (ESI) calcd for C₃₅H₄₃N₇O₄ [M + H]⁺ 626.345 found 626.3475;

15 2-[[[(1S)-1-{4-[(4-acryloylpiperazin-1-yl)methyl]phenyl}ethyl]amino]-4-amino-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = propan-2-yl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-(4-acryloylpiperazin-1-yl)methyl, R_{6b} = H, R₃ = NH₂, R₄ = R₅ = H] Cpd 206



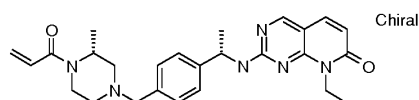
20 ¹H NMR (500 MHz, DMSO- *d*₆) δ 7.82 (d, *J* = 9.15 Hz, 1H), 6.75 (dd, *J* = 10.52, 16.62 Hz, 1H), 6.07 (dd, *J* = 2.21, 16.70 Hz, 1H), 5.91 (br. s., 1H), 4.98 (d, *J* = 13.88 Hz, 1H), 3.49 (d, *J* = 6.56 Hz, 6H), 2.29 (br. s., 4H), 1.17 - 1.58 (m, 9H). LCMS : *m/z* 476 [M+H]⁺ r.t. 4.81 min. HRMS (ESI) calcd for C₂₆H₃₄N₇O₂ [M + H]⁺ 476.2769 found 476.2777;

2-[[[(1S)-1-{4-[(2R)-4-acryloyl-2-methylpiperazin-1-yl)methyl]phenyl}ethyl]amino]-8-ethylpyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = Ethyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-(2R)-(4-acryloyl-2-methylpiperazin-1-yl)methyl, R_{6b} = H, R₃ = R₄ = R₅ = H] Cpd 207



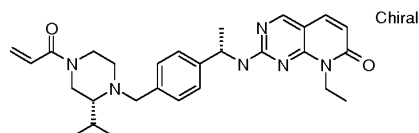
¹H NMR (500 MHz, DMSO- *d*₆) δ 8.57 (s, 1H), 8.42 (d, *J* = 7.17 Hz, 1H), 7.67 (d, *J* = 9.46 Hz, 1H), 7.34 (d, *J* = 7.78 Hz, 2H), 7.23 (d, *J* = 7.78 Hz, 2H), 6.63 - 6.90 (m, 1H), 6.20 (d, *J* = 9.30 Hz, 1H), 6.01 - 6.14 (m, 1H), 5.57 - 5.71 (m, 1H), 5.01 (quin, *J* = 6.30 Hz, 1H), 1.47 (d, *J* = 7.02 Hz, 3H), 1.03 (dd, *J* = 6.25, 10.68 Hz, 3H), 0.89 (q, *J* = 6.81 Hz, 3H). LCMS : *m/z* 461 [M+H]⁺ r.t. 5.13 min. HRMS (ESI) calcd for C₂₆H₃₃N₆O₂ [M + H]⁺ 461.266 found 461.2656;

- 5 **2-[[[(1S)-1-(4-[[[(3R)-4-acryloyl-3-methylpiperazin-1-yl]methyl]phenyl)ethyl]amino]-8-ethylpyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = Ethyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-(3R)-(4- acryloyl-2-methylpiperazin -1-yl)methyl, R_{6b} = H, R₃ = R₄ = R₅ = H] Cpd 208**



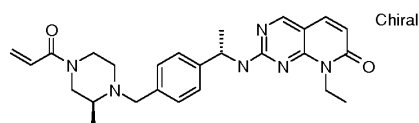
- 10 ¹H NMR (500 MHz, DMSO- *d*₆) δ 8.57 (s, 1H), 8.42 (d, *J* = 7.17 Hz, 1H), 7.67 (d, *J* = 9.46 Hz, 1H), 7.34 (d, *J* = 7.78 Hz, 2H), 7.23 (d, *J* = 7.78 Hz, 2H), 6.63 - 6.90 (m, 1H), 6.20 (d, *J* = 9.30 Hz, 1H), 6.01 - 6.14 (m, 1H), 5.57 - 5.71 (m, 1H), 5.01 (quin, *J* = 6.30 Hz, 1H), 1.47 (d, *J* = 7.02 Hz, 3H), 1.03 (dd, *J* = 6.25, 10.68 Hz, 3H), 0.89 (q, *J* = 6.81 Hz, 3H). LCMS : *m/z* 461 [M+H]⁺ r.t. 5.61 min. HRMS (ESI) calcd for C₂₆H₃₃N₆O₂ [M + H]⁺ 461.266 found 461.2655;

- 15 **2-[[[(1S)-1-(4-[[[(2R)-4-acryloyl-2-(propan-2-yl)piperazin-1-yl]methyl]phenyl)ethyl]amino]-8-ethylpyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = Ethyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-(2R)-(4- acryloyl-2-(propan-2-yl)piperazin -1-yl)methyl, R_{6b} = H, R₃ = R₄ = R₅ = H] Cpd 209**



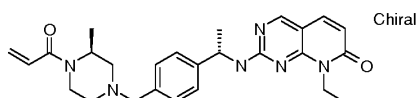
- 20 ¹H NMR (500 MHz, DMSO- *d*₆) δ 8.57 (s, 1H), 8.42 (d, *J* = 6.86 Hz, 1H), 7.67 (d, *J* = 9.30 Hz, 1H), 7.34 (d, *J* = 7.78 Hz, 2H), 7.23 (d, *J* = 7.93 Hz, 2H), 6.59 - 6.85 (m, 1H), 6.20 (d, *J* = 9.46 Hz, 1H), 6.07 (d, *J* = 16.62 Hz, 1H), 5.65 (dd, *J* = 11.29, 19.37 Hz, 1H), 5.00 (br. s., 1H), 4.14-4.28 (m, 3H), 3.95-4.08 (m, 4H), 3.71- 3.80 (m, 2H), 3.08- 3.20 (m, 1H), 2.87-2.95 (m, 1H), 2.11- 2.20 (m, 1H), 1.47 (d, *J* = 7.02 Hz, 3H), 0.74 - 1.08 (m, 9H). LCMS : *m/z* 489 [M+H]⁺ r.t. 6.25 min. HRMS (ESI) calcd for C₂₈H₃₇N₆O₂ [M + H]⁺ 489.2973 found 489.298;

2-[[[(1S)-1-(4-[[[(2S)-4-acryloyl-2-methylpiperazin-1-yl]methyl]phenyl)ethyl]amino]-8-ethylpyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = Ethyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-(2R)-(4- acryloyl-2-methylpiperazin -1-yl)methyl, R_{6b} = H, R₃ = R₄ = R₅ = H] Cpd 210



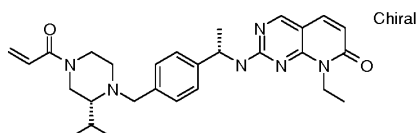
- 25 ¹H NMR (500 MHz, DMSO- *d*₆) δ 8.58 (s, 1H), 8.42 (d, *J* = 7.47 Hz, 1H), 7.67 (d, *J* = 9.30 Hz, 1H), 7.34 (d, *J* = 7.78 Hz, 2H), 7.23 (d, *J* = 7.93 Hz, 2H), 6.65 - 6.87 (m, 1H), 6.20 (d, *J* = 9.30 Hz, 1H), 6.09 (d, *J* = 17.23 Hz, 1H), 5.64 (t, *J* = 8.70 Hz, 1H), 5.02 (quin, *J* = 6.83 Hz, 1H), 4.00 - 4.28 (m, 3H), 3.63- 3.92 (m, 5H), 3.08- 3.26 (m, 2H), 1.95 - 2.04 (m, 1H), 1.47 (d, *J* = 7.02 Hz, 3H), 0.98 - 1.10 (m, 3H), 0.90 (t, *J* = 6.33 Hz, 3H). LCMS : *m/z* 461 [M+H]⁺ r.t. 5.14 min. HRMS (ESI) calcd for C₂₆H₃₃N₆O₂ [M + H]⁺ 461.266 found 461.2675;
- 30

2-[[[(1S)-1-(4-[[[(3S)-4-acryloyl-3-methylpiperazin-1-yl]methyl]phenyl)ethyl]amino]-8-ethylpyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = Ethyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-(3R)-(4-acryloyl-2-methylpiperazin-1-yl)methyl, R_{6b} = H, R₃ = R₄ = R₅ = H] Cpd 211



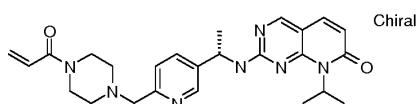
- 5 ¹H NMR (500 MHz, DMSO- *d*₆) δ 8.58 (s, 1H), 8.42 (d, *J* = 7.17 Hz, 1H), 7.67 (d, *J* = 9.30 Hz, 1H), 7.35 (d, *J* = 7.93 Hz, 2H), 7.24 (d, *J* = 7.93 Hz, 2H), 6.74 (dd, *J* = 10.60, 16.70 Hz, 1H), 6.21 (d, *J* = 9.30 Hz, 1H), 6.07 (d, *J* = 16.32 Hz, 1H), 5.64 (dd, *J* = 1.37, 10.22 Hz, 1H), 5.02 (quin, *J* = 7.32 Hz, 1H), 4.00 - 4.29 (m, 5H), 3.35 - 3.45 (m, 4H), 2.61 (br. s, 2H), (1.47 (d, *J* = 7.02 Hz, 3H), 1.17 (q, *J* = 7.10 Hz, 3H), 0.91 (t, *J* = 6.86 Hz, 3H). LCMS : *m/z* 461 [M+H]⁺ r.t. 5.61 min. HRMS (ESI) calcd for C₂₆H₃₃N₆O₂ [M + H]⁺ 461.266 found 461.2672;

- 10 2-[[[(1S)-1-(4-[[[(2S)-4-acryloyl-2-(propan-2-yl)piperazin-1-yl]methyl]phenyl)ethyl]amino]-8-ethylpyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = Ethyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-(2R)-(4-acryloyl-2-(propan-2-yl)piperazin-1-yl)methyl, R_{6b} = H, R₃ = R₄ = R₅ = H] Cpd 212



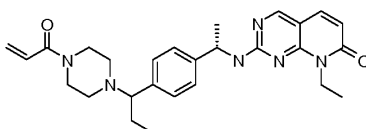
- 15 ¹H NMR (500 MHz, DMSO- *d*₆) δ 8.57 (s, 1H), 8.42 (d, *J* = 6.86 Hz, 1H), 7.67 (d, *J* = 9.30 Hz, 1H), 7.34 (d, *J* = 8.08 Hz, 2H), 7.23 (d, *J* = 7.93 Hz, 2H), 6.72 (dd, *J* = 10.37, 16.62 Hz, 1H), 6.20 (d, *J* = 9.46 Hz, 1H), 6.07 (dd, *J* = 2.21, 16.70 Hz, 1H), 5.56 - 5.73 (m, 1H), 5.01 (t, *J* = 6.86 Hz, 1H), 3.66 - 4.29 (m, 6H), 2.87 - 3.28 (m, 3H), 2.66 (d, *J* = 15.25 Hz, 1H), 2.17 (d, *J* = 6.56 Hz, 1H), 2.01 - 2.09 (m, 2H), 1.47 (d, *J* = 7.02 Hz, 3H), 0.78 - 0.98 (m, 9H). LCMS : *m/z* 489 [M+H]⁺ r.t. 6.13 min. HRMS (ESI) calcd for C₂₈H₃₇N₆O₂ [M + H]⁺ 489.2973 found 489.2977;

- 20 2-[[[(1S)-1-(6-[[4-acryloylpiperazin-1-yl]methyl]pyridin-3-yl)ethyl]amino]-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = Ethyl, A = Pyridin-3-yl, R_{1a} = H, R_{1b} = Me, R_{6a} = 6-(4-acryloylpiperazin-1-yl)methyl, R_{6b} = H, R₃ = R₄ = R₅ = H] Cpd 213



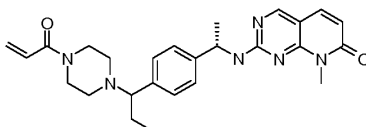
- 25 ¹H NMR (500 MHz, DMSO- *d*₆) δ 8.57 (s, 1H), 8.51 (br. s., 1H), 8.42 (d, *J* = 6.41 Hz, 1H), 7.74 (d, *J* = 8.08 Hz, 1H), 7.63 (d, *J* = 9.30 Hz, 1H), 7.38 (d, *J* = 7.93 Hz, 1H), 6.76 (dd, *J* = 10.37, 16.62 Hz, 1H), 6.17 (d, *J* = 9.30 Hz, 1H), 6.08 (dd, *J* = 1.91, 16.85 Hz, 1H), 5.65 (dd, *J* = 1.75, 10.75 Hz, 1H), 5.20 - 5.58 (m, 1H), 5.04 (br. s., 1H), 3.56 (br. s., 2H), 3.51 (m, 4H), 2.22 - 2.44 (m, 4H), 1.51 (d, *J* = 6.86 Hz, 9H). LCMS : *m/z* 462 [M+H]⁺ r.t. 4.57 min. HRMS (ESI) calcd for C₂₅H₃₂N₇O₂ [M + H]⁺ 462.2612 found 462.2606;

- 30 2-[[[(1S)-1-(4-[1-(4-acryloylpiperazin-1-yl)propyl]phenyl)ethyl]amino]-8-ethylpyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = Ethyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH(R₁₄)NR₇R₈, R_{6b} = H, R₇-R₈ = 4-piperazin-1-yl, R₁₁ = vinyl, R₃ = R₄ = R₅ = H, R₁₄ = ethyl] Cpd 214



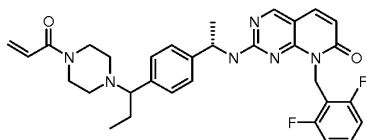
¹H NMR (500 MHz, DMSO- *d*₆) δ 8.58 (s, 1H), 8.40 (d, *J* = 4.42 Hz, 1H), 7.67 (d, *J* = 9.30 Hz, 1H), 7.33 (d, *J* = 7.63 Hz, 2H), 7.14 (d, *J* = 7.93 Hz, 2H), 6.69 (dd, *J* = 10.60, 16.55 Hz, 1H), 6.20 (d, *J* = 9.30 Hz, 1H), 6.01 (d, *J* = 16.78 Hz, 1H), 5.60 (d, *J* = 10.52 Hz, 1H), 4.90 - 5.38 (m, 1H), 3.90 - 4.35 (m, 2H), 3.44 (br. s., 4H), 3.19 - 3.28 (m, 1H), 2.23 (br. s., 4H), 1.84 (qd, *J* = 6.66, 13.27 Hz, 1H), 1.56 - 1.72 (m, 1H), 1.47 (d, *J* = 7.02 Hz, 3H), 0.82 (td, *J* = 7.02, 10.37 Hz, 3H), 0.57 - 0.75 (m, 3H). LCMS : *m/z* 475 [M+H]⁺ r.t. 5.4 min. HRMS (ESI) calcd for C₂₇H₃₅N₆O₂ [M + H]⁺ 475.2816 found 475.2824;

2-[[[(1S)-1-{4-[1-(4-acryloylpiperazin-1-yl)propyl]phenyl}ethyl]amino]-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = Methyl, A = phenyl, R1a = H, R1b = Me, R6a = 4-CH(R14)NR7R8, R6b = H, R7-R8 = 4-piperazin-1-yl, R11 = vinyl, R3 = R4 = R5 = H, R14 = ethyl] Cpd 215



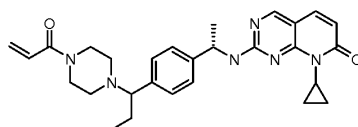
¹H NMR (500 MHz, DMSO- *d*₆) δ 8.57 (s, 1H), 8.39 (d, *J* = 7.63 Hz, 1H), 7.69 (d, *J* = 9.30 Hz, 1H), 7.37 (d, *J* = 7.63 Hz, 2H), 7.15 (d, *J* = 7.93 Hz, 2H), 6.70 (dd, *J* = 10.52, 16.62 Hz, 1H), 6.18 - 6.28 (m, 1H), 6.02 (d, *J* = 16.78 Hz, 1H), 5.60 (dd, *J* = 1.98, 10.37 Hz, 1H), 5.13 (quin, *J* = 6.90 Hz, 1H), 3.47 (d, *J* = 17.54 Hz, 4H), 3.37 (d, *J* = 3.51 Hz, 3H), 3.20 - 3.28 (m, 1H), 2.26 (br. s., 4H), 1.79 - 1.92 (m, 1H), 1.66 (dt, *J* = 7.32, 14.41 Hz, 1H), 1.48 (d, *J* = 6.71 Hz, 3H), 0.55 - 0.91 (m, 3H). LCMS : *m/z* 461 [M+H]⁺ r.t. 5.12 min. HRMS (ESI) calcd for C₂₆H₃₃N₆O₂ [M + H]⁺ 461.266 found 461.265;

2-[[[(1S)-1-{4-[1-(4-acryloylpiperazin-1-yl)propyl]phenyl}ethyl]amino]-8-(2,6-difluorobenzyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = 2,6-difluorobenzyl, A = phenyl, R1a = H, R1b = Me, R6a = 4-CH(R14)NR7R8, R6b = H, R7-R8 = 4-piperazin-1-yl, R11 = vinyl, R3 = R4 = R5 = H, R14 = ethyl] Cpd 216



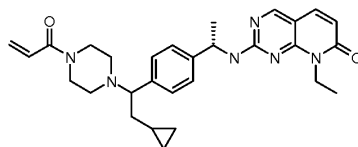
¹H NMR (500 MHz, DMSO- *d*₆) δ 8.59 (s, 1H), 8.32 (d, *J* = 8.39 Hz, 1H), 7.73 (d, *J* = 9.30 Hz, 1H), 7.27 - 7.39 (m, 1H), 7.25 (d, *J* = 7.93 Hz, 2H), 7.07 (d, *J* = 6.25 Hz, 2H), 6.96 (t, *J* = 8.08 Hz, 2H), 6.71 (dd, *J* = 10.45, 16.70 Hz, 1H), 6.25 (d, *J* = 9.30 Hz, 1H), 6.03 (dd, *J* = 2.36, 16.70 Hz, 1H), 5.59 - 5.65 (m, 1H), 5.55 (dd, *J* = 6.90, 14.9 Hz, 1H), 5.36 (d, *J* = 14.95 Hz, 1H), 5.10 (quin, *J* = 7.55 Hz, 1H), 3.47 (br. s., 4H), 3.18 - 3.27 (m, 1H), 2.25 (br. s., 4H), 1.75 - 1.93 (m, *J* = 6.71, 12.66 Hz, 1H), 1.56 - 1.72 (m, 1H), 1.36 (d, *J* = 6.86 Hz, 3H), 0.60 - 0.77 (m, 3H). LCMS : *m/z* 461 [M+H]⁺ r.t. 6.17 min. HRMS (ESI) calcd for C₃₂H₃₄F₂N₆O₂ [M + H]⁺ 573.2784 found 573.2791;

2-[[[(1S)-1-{4-[1-(4-acryloylpiperazin-1-yl)propyl]phenyl}ethyl]amino]-8-cyclopropylpyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = cyclopropyl, A = phenyl, R1a = H, R1b = Me, R6a = 4-CH(R14)NR7R8, R6b = H, R7-R8 = 4-piperazin-1-yl, R11 = vinyl, R3 = R4 = R5 = H, R14 = ethyl] Cpd 218



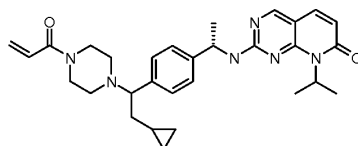
¹H NMR (500 MHz, DMSO- *d*₆) δ 8.53 (s, 1H), 8.29 (d, *J* = 7.47 Hz, 1H), 7.63 (d, *J* = 9.30 Hz, 1H), 7.35 (d, *J* = 6.86 Hz, 2H), 7.15 (d, *J* = 8.08 Hz, 2H), 6.70 (dd, *J* = 10.75, 16.85 Hz, 1H), 6.14 (d, *J* = 9.30 Hz, 1H), 6.02 (d, *J* = 16.47 Hz, 1H), 5.55 - 5.67 (m, 1H), 5.08 - 5.39 (m, 1H), 3.40 - 3.58 (m, 4H), 3.21 - 3.29 (m, 1H), 2.57 - 2.67 (m, 1H), 2.26 (br. s., 4H), 1.59 - 1.94 (m, 2H), 1.49 (d, *J* = 7.02 Hz, 3H), 1.01-1.06 (m, 1H), 0.79- 0.86 (m, 1H), 0.70 (t, *J* = 7.32 Hz, 3H), 0.61 (br. s 1H), 0.32 (br. s 1H). LCMS : *m/z* 487 [M+H]⁺ r.t. 6.25 min. HRMS (ESI) calcd for C₂₈H₃₅N₆O₂ [M + H]⁺ 487.2816 found 487.2829;

2-[[[(1S)-1-{4-[1-(4-acryloylpiperazin-1-yl)-2-cyclopropylethyl]phenyl}ethyl]amino]-8-ethylpyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = Ethyl, A = phenyl, R_{1a}= H, R_{1b} = Me, R_{6a}= 4-CH(R₁₄)NR₇R₈, R_{6b} = H, R₇-R₈ = 4-piperazin-1-yl, R₁₁ = vinyl, R₃ = R₄ = R₅= H, R₁₄ = cyclopropylmethyl] Cpd 219



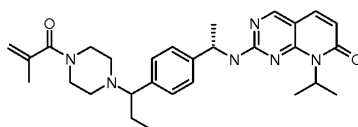
¹H NMR (500 MHz, DMSO- *d*₆) δ 8.61 (s, 1H), 8.44 (d, *J* = 5.03 Hz, 1H), 7.70 (d, *J* = 9.30 Hz, 1H), 7.11 - 7.44 (m, 4H), 6.72 (dd, *J* = 10.83, 16.32 Hz, 1H), 6.23 (d, *J* = 9.30 Hz, 1H), 6.04 (d, *J* = 16.32 Hz, 1H), 5.62 (d, *J* = 10.37 Hz, 1H), 5.05 (d, *J* = 6.86 Hz, 1H), 3.95 - 4.41 (m, 2H), 3.43 - 3.62 (m, 4H), 2.28 (br. s., 4H), 1.55 - 1.85 (m, 2H), 1.51 (d, *J* = 6.86 Hz, 3H), 0.71 - 1.04 (m, 3H), 0.18 - 0.51 (m, 4H), -0.13 - 0.10 (m, 2H). LCMS : *m/z* 501 [M+H]⁺ r.t. 7.27 min. HRMS (ESI) calcd for C₂₉H₃₇N₆O₂ [M + H]⁺ 501.2973 found 501.2978;

2-[[[(1S)-1-{4-[1-(4-acryloylpiperazin-1-yl)-2-cyclopropylethyl]phenyl}ethyl]amino]-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = propan-2-yl, A = phenyl, R_{1a}= H, R_{1b} = Me, R_{6a}= 4-CH(R₁₄)NR₇R₈, R_{6b} = H, R₇-R₈ = 4-piperazin-1-yl, R₁₁ = vinyl, R₃ = R₄ = R₅= H, R₁₄ = cyclopropylmethyl] Cpd 220



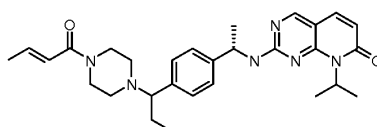
¹H NMR (500 MHz, DMSO- *d*₆) δ 8.56 (s, 1H), 8.34 (br. s., 1H), 7.62 (d, *J* = 9.15 Hz, 1H), 7.27 - 7.40 (m, 2H), 7.17 (d, *J* = 7.78 Hz, 2H), 6.68 (dd, *J* = 10.37, 16.47 Hz, 1H), 6.15 (d, *J* = 9.00 Hz, 1H), 6.01 (d, *J* = 16.47 Hz, 1H), 5.59 (d, *J* = 10.52 Hz, 1H), 4.99 (d, *J* = 5.95 Hz, 1H), 3.40 - 3.56 (m, 5H), 2.23 (br. s., 4H), 1.54 - 1.84 (m, 2H), 1.22 - 1.52 (m, 7H), -0.18 - 0.50 (m, 6H), -0.05 - 0.02 (m, 2H). LCMS : *m/z* 515 [M+H]⁺ r.t. 9.75 min. HRMS (ESI) calcd for C₃₀H₃₉N₆O₂ [M + H]⁺ 515.3129 found 515.3143;

2-[[[(1S)-1-{4-[1-(4-(2-methylacryloyl)piperazin-1-yl)propyl]phenyl}ethyl]amino]-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = propan-2-yl, A = phenyl, R_{1a}= H, R_{1b} = Me, R_{6a}= 4-CH(R₁₄)NR₇R₈, R_{6b} = H, R₇-R₈ = 4-piperazin-1-yl, R₁₁ = 2-methylvinyl, R₃ = R₄ = R₅= H, R₁₄ = Ethyl] Cpd 221



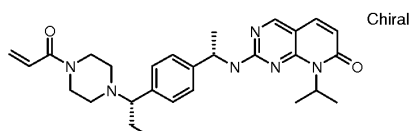
- 5 ¹H NMR (500 MHz, DMSO- *d*₆) δ 8.56 (s, 1H), 8.12 - 8.39 (m, 1H), 7.63 (d, *J* = 9.15 Hz, 1H), 7.23 - 7.42 (m, 2H), 7.09 - 7.18 (m, 2H), 6.15 (d, *J* = 9.15 Hz, 1H), 5.21 - 5.56 (m, 1H), 5.07 - 5.17 (m, 1H), 4.92 - 5.04 (m, 1H), 4.74 - 4.89 (m, 1H), 3.36 - 3.48 (m, 4H), 3.18 - 3.28 (m, 1H), 2.14 - 2.35 (m, 4H), 1.81 - 1.91 (m, 1H), 1.71 - 1.81 (m, 3H), 1.58 - 1.69 (m, 1H), 1.21 - 1.56 (m, 9H), 0.61 - 0.74 (m, 3H). LCMS : *m/z* 503 [M+H]⁺ r.t. 7.49 min. HRMS (ESI) calcd for C₂₉H₃₉N₆O₂ [M + H]⁺ 503.3129 found 503.3141;

2-(((1S)-1-[4-(1-[4-(2E)-but-2-enoyl]piperazin-1-yl)propyl]phenyl)ethyl)amino)-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = propan-2-yl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH(R₁₄)NR₇R₈, R_{6b} = H, R₇-R₈ = 4-piperazin-1-yl, R₁₁ = (2E)-propen-2-yl, R₃ = R₄ = R₅ = H, R₁₄ = Ethyl] Cpd 222



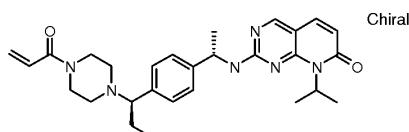
- 10 ¹H NMR (500 MHz, DMSO- *d*₆) δ 8.56 (s, 1H), 8.13 - 8.38 (m, 1H), 7.62 (d, *J* = 9.15 Hz, 1H), 7.27 - 7.37 (m, 2H), 7.09 - 7.18 (m, 2H), 6.51 - 6.66 (m, 1H), 6.32 - 6.47 (m, 1H), 6.15 (d, *J* = 9.15 Hz, 1H), 5.36 - 5.76 (m, 1H), 4.89 - 5.32 (m, 1H), 3.38 - 3.58 (m, 4H), 3.16 - 3.29 (m, 1H), 2.21 (br. s., 4H), 1.81 - 1.91 (m, 1H), 1.73 - 1.80 (m, 3H), 1.60 - 1.71 (m, 1H), 1.25 - 1.57 (m, 9H), 0.62 - 0.77 (m, 3H). LCMS : *m/z* 503 [M+H]⁺ r.t. 7.45 min. HRMS (ESI) calcd for C₂₉H₃₉N₆O₂ [M + H]⁺ 503.3129 found 503.3132;

2-(((1S)-1-[4-((1S)-1-(4-acryloylpiperazin-1-yl)propyl)phenyl]ethyl)amino)-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = propan-2-yl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH(R₁₄)NR₇R₈, R_{6b} = H, R₇-R₈ = 4-piperazin-1-yl, R₁₁ = vinyl, R₃ = R₄ = R₅ = H, R₁₄ = Ethyl] Cpd 227



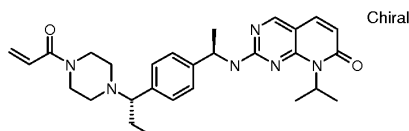
- 20 ¹H NMR (500 MHz, DMSO- *d*₆) δ 8.48 - 8.59 (m, 1H), 8.35 (d, *J* = 6.56 Hz, 1H), 7.62 (d, *J* = 9.30 Hz, 1H), 7.25 - 7.38 (m, 2H), 7.13 (d, *J* = 7.78 Hz, 2H), 6.69 (dd, *J* = 10.22, 16.62 Hz, 1H), 6.15 (d, *J* = 9.30 Hz, 1H), 5.94 - 6.09 (m, 1H), 5.59 (d, *J* = 10.22 Hz, 1H), 5.39 - 5.52 (br. s, 1H), 4.95 - 5.03 (m, 1H), 3.40 - 3.57 (m, 4H), 3.17 - 3.28 (m, 1H), 2.16 - 2.32 (m, 4H), 1.80 - 1.91 (m, 1H), 1.58 - 1.74 (m, 1H), 1.47 (d, *J* = 7.02 Hz, 3H), 1.20 - 1.43 (m, 6H), 0.62 - 0.75 (m, 3H). LCMS : *m/z* 489 [M+H]⁺ r.t. 7.12 min. HRMS (ESI) calcd for C₂₈H₃₇N₆O₂ [M + H]⁺ 489.2973 found 489.2982;

- 25 **2-(((1S)-1-[4-((1R)-1-(4-acryloylpiperazin-1-yl)propyl)phenyl]ethyl)amino)-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = propan-2-yl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH(R₁₄)NR₇R₈, R_{6b} = H, R₇-R₈ = 4-piperazin-1-yl, R₁₁ = vinyl, R₃ = R₄ = R₅ = H, R₁₄ = Ethyl] Cpd 228**



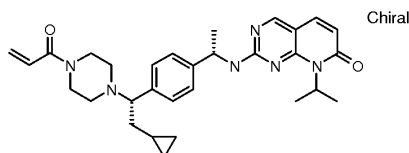
- ¹H NMR (500 MHz, DMSO- *d*₆) δ 8.56 (s, 1H), 8.11 - 8.38 (m, 1H), 7.62 (d, *J* = 9.30 Hz, 1H), 7.25 - 7.37 (m, 2H), 7.13 (d, *J* = 7.93 Hz, 2H), 6.69 (dd, *J* = 10.37, 16.47 Hz, 1H), 6.15 (d, *J* = 9.30 Hz, 1H), 6.01 (dd, *J* = 1.98, 16.47 Hz, 1H), 5.55 - 5.66 (m, 1H), 5.39 - 5.52 (br., s, 1H), 4.87 - 5.32 (m, 1H), 3.39 - 3.52 (m, 4H), 3.25 (dd, *J* = 6.25, 7.93 Hz, 1H), 2.23 (br. s., 4H), 1.60 - 1.91 (m, 2H), 1.47 (d, *J* = 7.02 Hz, 3H), 1.20 - 1.43 (m, 6H), 0.62 - 0.75 (m, 3H). LCMS : m/z 489 [M+H]⁺ r.t. 7.12 min. HRMS (ESI) calcd for C₂₈H₃₇N₆O₂ [M + H]⁺ 489.2973 found 489.2975;

2-[[[(1R)-1-{4-[(1R)-1-(4-acryloylpiperazin-1-yl)propyl]phenyl}ethyl]amino]-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = propan-2-yl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH(R₁₄)NR₇R₈, R_{6b} = H, R₇-R₈ = 4-piperazin-1-yl, R₁₁ = vinyl, R₃ = R₄ = R₅ = H, R₁₄ = Ethyl] Cpd 229



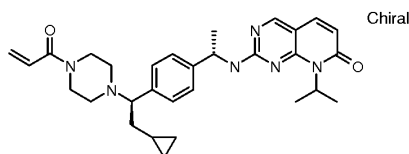
- ¹H NMR (500 MHz, DMSO- *d*₆) δ 8.56 (s, 1H), 8.35 (d, *J* = 6.41 Hz, 1H), 7.62 (d, *J* = 9.30 Hz, 1H), 7.25 - 7.38 (m, 2H), 7.10 - 7.19 (m, 2H), 6.69 (dd, *J* = 10.37, 16.62 Hz, 1H), 6.15 (d, *J* = 9.46 Hz, 1H), 5.97 - 6.08 (m, 1H), 5.59 (d, *J* = 12.51 Hz, 1H), 5.42 - 5.52 (br., s, 1H), 4.90 - 5.06 (m, 1H), 3.41 - 3.56 (m, 4H), 3.20 - 3.29 (m, 1H), 2.14 - 2.34 (m, 4H), 1.80 - 1.92 (m, 1H), 1.59 - 1.72 (m, 1H), 1.47 (d, *J* = 7.02 Hz, 3H), 1.20 - 1.43 (m, 6H), 0.63 - 0.75 (m, 6H). LCMS : m/z 489 [M+H]⁺ r.t. 6.74 min. HRMS (ESI) calcd for C₂₈H₃₇N₆O₂ [M + H]⁺ 489.2973 found 489.2978;

- 2-[[[(1S)-1-{4-[(1S)-1-(4-acryloylpiperazin-1-yl)-2-cyclopropylethyl]phenyl}ethyl]amino]-8-(propan-2-yl) pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = propan-2-yl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH(R₁₄)NR₇R₈, R_{6b} = H, R₇-R₈ = 4-piperazin-1-yl, R₁₁ = vinyl, R₃ = R₄ = R₅ = H, R₁₄ = cyclopropylmethyl] cpd 230**



- ¹H NMR (500 MHz, DMSO- *d*₆) δ 8.56 (s, 1H), 8.35 (d, *J* = 6.86 Hz, 1H), 7.62 (d, *J* = 9.30 Hz, 1H), 7.28 - 7.39 (m, 2H), 7.17 (d, *J* = 7.93 Hz, 2H), 6.68 (dd, *J* = 10.52, 16.70 Hz, 1H), 6.15 (d, *J* = 9.30 Hz, 1H), 6.01 (dd, *J* = 2.06, 16.70 Hz, 1H), 5.59 (dd, *J* = 1.98, 10.68 Hz, 1H), 5.37 - 5.49 (br., 1H), 4.98 (t, *J* = 6.56 Hz, 1H), 3.38 - 3.56 (m, 5H), 2.23 (br. s., 4H), 1.54 - 1.82 (m, 2H), 1.47 (m, 10H), 0.25 - 0.37 (m, 2H), -0.09 - 0.02 (m, 2H). LCMS : m/z 515 [M+H]⁺ r.t. 7.97 min. HRMS (ESI) calcd for C₃₀H₃₉N₆O₂ [M + H]⁺ 515.3129 found 515.314;

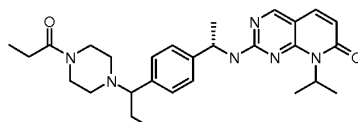
- 2-[[[(1S)-1-{4-[(1R)-1-(4-acryloylpiperazin-1-yl)-2-cyclopropylethyl]phenyl}ethyl]amino]-8-(propan-2-yl) pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = propan-2-yl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH(R₁₄)NR₇R₈, R_{6b} = H, R₇-R₈ = 4-piperazin-1-yl, R₁₁ = vinyl, R₃ = R₄ = R₅ = H, R₁₄ = cyclopropylmethyl] cpd 231**



¹H NMR (500 MHz, DMSO- *d*₆) δ 8.56 (s, 1H), 8.12 - 8.37 (m, 1H), 7.62 (d, *J* = 9.30 Hz, 1H), 7.27 - 7.40 (m, 2H), 7.11 - 7.23 (m, 2H), 6.68 (dd, *J* = 10.37, 16.47 Hz, 1H), 6.15 (d, *J* = 9.00 Hz, 1H), 6.00 (d, *J* = 16.47 Hz, 1H), 5.59 (d, *J* = 10.37 Hz, 1H), 5.39 - 5.51 (m, 1H), 4.93 - 5.30 (m, 1H), 3.39 - 3.53 (m, 5H), 2.23 (br. s., 4H), 1.53 - 1.81 (m, 3H), 0.95 - 1.50 (m, 9H), 0.24 - 0.45 (m, 3H), -0.12 - 0.05 (m, 2H). LCMS : *m/z* 515 [M+H]⁺ r.t. 7.65 min. HRMS (ESI)

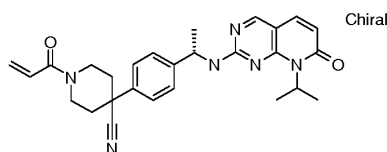
5 calcd for C₃₀H₃₉N₆O₂ [M + H]⁺ 515.3129 found 515.3135;

2-[[[(1S)-1-{4-[1-(4-propanoylpiperazin-1-yl)propyl]phenyl}ethyl]amino]-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = propan-2-yl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH(R₁₄)NR₇R₈, R_{6b} = H, R₇-R₈ = 4-piperazin-1-yl, R₁₁ = Ethyl, R₃ = R₄ = R₅ = H, R₁₄ = Ethyl] Cpd 240



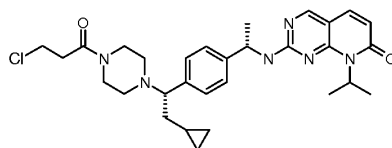
10 ¹H NMR (500 MHz, DMSO- *d*₆) δ 8.56 (s, 1H), 8.35 (br. s., 1H), 7.62 (d, *J* = 9.15 Hz, 1H), 7.30 (d, *J* = 7.78 Hz, 2H), 7.13 (d, *J* = 7.78 Hz, 2H), 6.15 (d, *J* = 9.30 Hz, 1H), 5.39 - 5.72 (m, 1H), 4.99 (br. s., 1H), 3.34 (br.s., 4H), 3.18 - 3.26 (m, 1H), 2.11 - 2.31 (m, 6H), 1.77 - 1.93 (m, 1H), 1.65 (dd, *J* = 7.70, 13.50 Hz, 1H), 1.00 - 1.56 (m, 9H), 0.89 (dt, *J* = 2.14, 7.40 Hz, 3H), 0.59 - 0.73 (m, 3H). LCMS : *m/z* 491 [M+H]⁺ r.t. 5.64 min. HRMS (ESI) calcd for C₂₈H₃₉N₆O₂ [M + H]⁺ 491.3129 found 491.313;

15 **1-acryloyl-4-{4-[(1S)-1-[[7-oxo-8-(propan-2-yl)-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl]amino]ethyl]phenyl}piperidine-4-carbonitrile [(I), X = N, R₂ = propan-2-yl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = piperidine-4-carbonitrile, R_{6b} = H, R₁₁ = vinyl, R₃ = R₄ = R₅ = H] Cpd 241**



20 ¹H NMR (500 MHz, DMSO- *d*₆) δ 8.50 - 8.58 (m, 1H), 8.19 - 8.43 (m, 1H), 7.62 (d, *J* = 9.30 Hz, 1H), 7.37 - 7.53 (m, 4H), 6.83 (dd, *J* = 10.52, 16.62 Hz, 1H), 6.05 - 6.18 (m, 2H), 5.66 - 5.73 (m, 1H), 5.39 - 5.57 (m, 1H), 4.94 - 5.30 (m, 1H), 4.61 (d, *J* = 12.22 Hz, 1H), 4.24 (d, *J* = 12.20 Hz, 1H), 3.31 (m, 1H), 2.88 (t, *J* = 12.89 Hz, 1H), 2.05 - 2.22 (m, 2H), 1.80 - 2.02 (m, 2H), 1.12 - 1.62 (m, 9H). LCMS : *m/z* 471 [M+H]⁺ r.t. 10.25 min. HRMS (ESI) calcd for C₂₈H₃₁N₆O₂ [M + H]⁺ 471.2503 found 471.25;

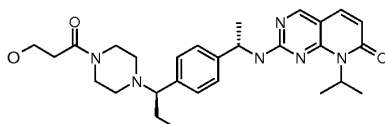
25 **2-[[[(1S)-1-{4-[(1S)-1-[4-(3-chloropropanoyl)piperazin-1-yl]-2-cyclopropylethyl]phenyl}ethyl]amino]-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = propan-2-yl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH(R₁₄)NR₇R₈, R_{6b} = H, R₇-R₈ = 4-piperazin-1-yl, R₁₁ = 2-chloroethyl, R₃ = R₄ = R₅ = H, R₁₄ = cyclopropylmethyl] Cpd 242**



30 ¹H NMR (500 MHz, DMSO- *d*₆) 8.56 (s, 1H), 8.35 (d, *J* = 6.86 Hz, 1H), 7.62 (d, *J* = 9.30 Hz, 1H), 7.28 - 7.39 (m, 2H), 7.18 (d, *J* = 8.08 Hz, 2H), 6.15 (d, *J* = 9.00 Hz, 1H), 5.40 - 5.55 (br.s., 1H), 4.91 - 5.02 (m, 1H), 3.70 (t, *J* = 6.5 Hz,

2H), 3.35 - 3.45 (m, 5H), 2.71 (t, $J = 6.5$ Hz, 2H), 2.14 - 2.33 (m, 4H), 1.69 - 1.81 (m, 1H), 1.21 - 1.57 (m, 10H), 0.24 - 0.37 (m, 3H), -0.11 - 0.02 (m, 2H). LCMS : m/z 551 $[M+H]^+$ r.t. 7.8 min. HRMS (ESI) calcd for $C_{30}H_{40}ClN_6O_2$ $[M + H]^+$ 551.2896 found 551.2897;

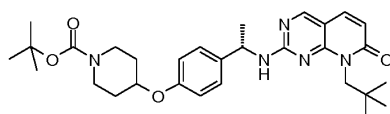
- 2-[[[(1S)-1-(4-[(1R)-1-[4-(3-hydroxypropanoyl)piperazin-1-yl]propyl]phenyl)ethyl]amino]-8-(propan-2-yl)pyrido
5 2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = propan-2-yl, A = phenyl, R1a= H, R1b = Me, R6a= 4-CH(R14)NR7R8,
R6b = H, R7-R8 = 4-piperazin-1-yl, R11 = 2-hydroxyethyl, R3 = R4 = R5= H, R14 = ethyl] Cpd 243



- ^1H NMR (500 MHz, DMSO- d_6) 8.56 (s, 1H), 8.12 - 8.39 (m, 1H), 7.62 (d, $J = 9.15$ Hz, 1H), 7.28 - 7.38 (m, 2H), 7.08 - 7.17 (m, 2H), 6.15 (d, $J = 9.00$ Hz, 1H), 5.39 - 5.77 (m, 1H), 4.92 - 5.32 (m, 1H), 3.88 - 4.01 (m, 2H), 3.17 - 3.30 (m,
10 5H), 2.09 - 2.32 (m, 6H), 1.59 - 1.90 (m, 3H), 1.48 (d, $J = 6.86$ Hz, 3H), 1.03 - 1.14 (m, 6H), 0.62 - 0.75 (m, 3H).
LCMS : m/z 507 $[M+H]^+$ r.t. 7.43 min. HRMS (ESI) calcd for $C_{28}H_{39}N_6O_3$ $[M + H]^+$ 507.3078 found 507.3083;

Example 16

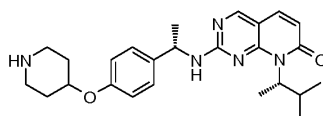
- 4-(4-[(S)-1-[8-(2,2-Dimethyl-propyl)-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino]-ethyl]-phenoxy)-
15 piperidine-1-carboxylic acid tert-butyl ester [(I), X = N, R2 = 2,2-dimethyl-propyl, A = phenyl, R1a= H, R1b =
Me, R6a= -O-R7, R6b = H, R7 = 4-piperidine-1-carboxylic acid tert-butyl ester, R3 = R4 = R5= H] conv. 13, cpd
154



- 8-(2,2-Dimethyl-propyl)-2-[(S)-1-(4-hydroxy-phenyl)-ethylamino]-8H-pyrido[2,3-d]pyrimidin-7-one (20.0 mg, 0.057
20 mmol) was dissolved in DMF (2.0 mL) to which cesium carbonate (37.0 mg, 0.113 mmol) and 4-hydroxy-piperidine-
1-carboxylic acid tert-butyl ester (19.0 mg, 0.068 mmol) was added and stirred for 5 hours at 100 °C. The cesium
carbonate was filtered off and the solution was diluted with AcOEt and washed with water (3x10mL), and then dried
over Na_2SO_4 . The crude material was purified through silica gel column chromatography (AcOEt) to give the title
product (11.5 mg, 38% yield). ^1H NMR (500 MHz, DMSO- d_6) δ = 8.56 (s, 1H), 8.31 (d, $J = 7.5$ Hz, 1H), 7.67 (d, $J =$
25 9.3 Hz, 1H), 7.28 (d, $J = 8.7$ Hz, 2H), 6.90 (d, $J = 8.5$ Hz, 2H), 6.22 (d, $J = 9.3$ Hz, 1H), 5.04 (quin, $J = 7.1$ Hz, 1H),
4.48 (tt, $J = 7.8, 3.7$ Hz, 1H), 3.93 - 4.31 (m, 2H), 3.53 - 3.69 (m, 2H), 3.15 (br. s., 2H), 1.78 - 1.91 (m, 2H), 1.43 -
1.53 (m, 2H), 1.43 (d, $J = 6.9$ Hz, 3H), 1.39 (s, 9H), 0.79 (br. s., 9H). LCMS : m/z 536 $[M+H]^+$ @ r.t. 7.78 min. HRMS
(ESI) calcd for $C_{30}H_{42}N_5O_4$ $[M + H]^+$ 536.3232 found 536.3243.

Example 17

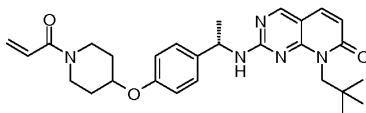
- 8-[(S)-1,2-Dimethyl-propyl]-2-[(S)-1-[4-(piperidin-4-yloxy)-phenyl]-ethylamino]-8H-pyrido[2,3-d]pyrimidin-7-
one [(I), X = N, R2 = (S)-1,2-Dimethyl-propyl, A = phenyl, R1a= H, R1b = Me, R6a= -O-R7, R6b = H, R7-R8 = 4-
30 piperazin-1-yl, R3 = R4 = R5= H] conv. 14, cpd 155



- To a stirred solution of 4-(4-((S)-1-[8-((S)-1,2-Dimethyl-propyl)-7-oxo-7,8-dihydro-pyrido[2,3-d]pyrimidin-2-ylamino]-ethyl)-phenoxy)-piperidine-1-carboxylic acid benzyl ester (40.0 mg, 0.070 mmol) in absolute ethanol (1.0 mL) was added, under nitrogen atmosphere, 10% Pd/C (1:1 catalyst / substrate by weight) followed by cyclohexadiene (0.066 mL, 0.702 mmol). The suspension was stirred at 60 °C for 1 hour. The catalyst was removed by filtration through a pad of celite and the filtrate was evaporated to dryness under vacuum to give the title product (22.2 mg, 73% yield).
- ¹H NMR (500 MHz, DMSO-d₆) δ = 8.55 (d, *J* = 14.9 Hz, 1H), 8.27 (d, *J* = 6.9 Hz, 1H), 7.64 (d, *J* = 9.2 Hz, 1H), 7.12 - 7.33 (m, 2H), 6.86 (d, *J* = 8.2 Hz, 2H), 6.21 (d, *J* = 9.3 Hz, 1H), 4.18 - 5.34 (m, 3H), 2.03 - 3.01 (m, 4H), 1.13 - 1.95 (m, 7H), 0.09 - 1.12 (m, 9H). LCMS : *m/z* 436 [M+H]⁺ @ r.t. 5.17 min
- HRMS (ESI) calcd for C₂₅H₃₄N₅O₂ [M +H]⁺ 436.2707 found 436.2719.

Example 18

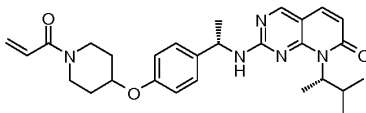
2-((S)-1-[4-(1-Acryloyl-piperidin-4-yloxy)-phenyl]-ethylamino)-8-(2,2-dimethyl-propyl)-8H-pyrido[2,3-d]pyrimidin-7-one [(I), X = N, R₂ = 2,2-dimethyl-propyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = O-R₇, R_{6b} = H, R₇ = 4-piperidin-4-yl, R₁₁ = vinyl, R₃ = R₄ = R₅ = H] conv. 15, cpd 156



- To a solution of 8-((S)-1,2-Dimethyl-propyl)-2-((S)-1-[4-(piperidin-4-yloxy)-phenyl]-ethylamino)-8H-pyrido[2,3-d]pyrimidin-7-one hydrochloride (50.0 mg, 0.11 mmol) and DIPEA (0.04 mL, 0.22 mmol) in CH₂Cl₂ (1.0 mL) is added acryloyl chloride (8 μL, 0.12 mmol) at 0°C. After 30 minutes, the reaction is quenched with water. The mixture is extracted with DCM, dried over Na₂SO₄, filtered, and concentrated to yield a yellow oil. The crude product is purified by silica gel chromatography (1 to 10% MeOH/DCM) to give the title product as a white foam (32 mg, 60% yield).
- ¹H NMR (500 MHz, DMSO-d₆) δ = 8.56 (s, 1H), 8.32 (d, *J* = 7.6 Hz, 1H), 7.67 (d, *J* = 9.2 Hz, 1H), 7.29 (d, *J* = 8.5 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 6.81 (dd, *J* = 16.7, 10.4 Hz, 1H), 6.22 (d, *J* = 9.3 Hz, 1H), 6.08 (dd, *J* = 16.6, 2.4 Hz, 1H), 5.66 (dd, *J* = 10.4, 2.3 Hz, 1H), 5.04 (quin, *J* = 7.1 Hz, 1H), 4.56 (tt, *J* = 7.6, 3.8 Hz, 1H), 4.02 - 4.20 (m, 2H), 3.76 - 3.90 (m, 2H), 3.28 - 3.37 (m, 2H), 1.90 (br. s., 2H), 1.53 (br. s., 2H), 1.44 (d, *J* = 7.0 Hz, 3H), 0.79 (br. s., 9H).
- LCMS : *m/z* 490 [M+H]⁺ @ r.t. 6.31 min. HRMS (ESI) calcd for C₂₈H₃₆N₅O₃ [M +H]⁺ 490.2813 found 490.2813.

According to the same method, the following compounds were prepared:

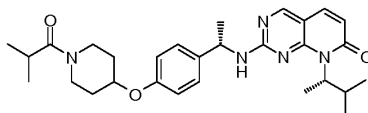
2-((S)-1-[4-(1-Acryloyl-piperidin-4-yloxy)-phenyl]-ethylamino)-8-((S)-1,2-dimethyl-propyl)-8H-pyrido[2,3-d]pyrimidin-7-one [(I), X = N, R₂ = -(S)-1,2-Dimethyl-propyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = O-R₇, R_{6b} = H, R₇ = 4-piperidin-4-yl, R₁₁ = vinyl, R₃ = R₄ = R₅ = H] cpd 159



- ¹H NMR (500 MHz, DMSO-d₆) δ = 8.50 - 8.60 (m, 1H), 7.64 (d, *J* = 9.3 Hz, 1H), 7.15 - 7.30 (m, 2H), 6.91 (d, *J* = 8.5 Hz, 2H), 6.81 (dd, *J* = 16.7, 10.4 Hz, 1H), 6.10 - 6.22 (m, 1H), 6.08 (dd, *J* = 16.8, 2.4 Hz, 1H), 5.66 (dd, *J* = 10.4, 2.4

Hz, 1H), 4.77 - 5.20 (m, 2H), 4.56 (tt, $J = 7.3, 3.6$ Hz, 1H), 3.35 - 3.80 (m, 4H), 1.02 - 2.11 (m, 8H), 0.10 - 0.89 (m, 9H). LCMS : m/z 490 $[M+H]^+$ @ r.t. 6.20 min. HRMS (ESI) calcd for $C_{28}H_{36}N_5O_3$ $[M+H]^+$ 490.2813 found 490.2813;

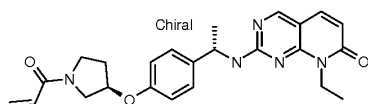
8-((S)-1,2-Dimethyl-propyl)-2-((S)-1-[4-(1-isobutryl-piperidin-4-yloxy)-phenyl]-ethylamino)-8H-pyrido[2,3-d]pyrimidin-7-one [(I), X = N, R2 = -(S)-1,2-Dimethyl-propyl, A = phenyl, R1a= H, R1b = Me, R6a= O-R7, R6b = H, R7= 4-piperidin-4-yl, R11 = i-propyl, R3 = R4 = R5= H] cpd 160



^1H NMR (500 MHz, DMSO- d_6) δ = 8.54 - 8.57 (m, 1H), 7.64 (d, $J = 9.3$ Hz, 1H), 7.19 - 7.26 (m, 2H), 6.90 (d, $J = 8.4$ Hz, 2H), 6.11 - 6.22 (m, 1H), 4.82 - 5.31 (m, 2H), 4.44 - 4.63 (m, 1H), 3.19 - 3.72 (m, 4H), 2.87 (dt, $J = 13.4, 6.7$ Hz, 1H), 1.11 - 2.12 (m, 5H), 0.13 - 1.07 (m, 12H). LCMS : m/z 506 $[M+H]^+$ @ r.t. 6.60 min

10 HRMS (ESI) calcd for $C_{29}H_{40}N_5O_3$ $[M+H]^+$ 506.3126 found 506.3130.

2-(((1S)-1-(4-(((3R)-1-acryloylpyrrolidin-3-yl)oxy)phenyl)ethyl)amino)-8-ethylpyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = Ethyl, A = phenyl, R1a= H, R1b = Me, R6a= O-R7, R6b = H, R7= pyrrolidin-3-yl, R11 = vinyl, R3 = R4 = R5= H] cpd 223

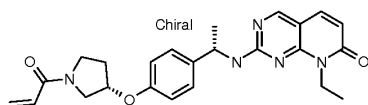


15

^1H NMR (500 MHz, DMSO- d_6) δ 8.57 (s, 1H), 8.14 - 8.44 (m, 1H), 7.67 (d, $J = 9.15$ Hz, 1H), 7.32 (d, $J = 7.78$ Hz, 2H), 6.88 (dd, $J = 3.36, 8.69$ Hz, 2H), 6.46 - 6.68 (m, 1H), 6.21 (d, $J = 9.15$ Hz, 1H), 6.07 - 6.15 (m, 1H), 5.58 - 5.71 (m, 1H), 4.88 - 5.27 (m, 2H), 4.03 - 4.30 (m, 2H), 3.37 - 3.89 (m, 4H), 1.98 - 2.22 (m, 2H), 1.45 (d, $J = 7.02$ Hz, 3H), 0.94 - 1.19 (m, 3H). LCMS : m/z 434 $[M+H]^+$ @ r.t. 5.13 min HRMS (ESI) calcd for $C_{24}H_{27}N_5O_3$ $[M+H]^+$ 434.2187 found

20 434.2191.

2-(((1S)-1-(4-(((3R)-1-acryloylpyrrolidin-3-yl)oxy)phenyl)ethyl)amino)-8-ethylpyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = Ethyl, A = phenyl, R1a= H, R1b = Me, R6a= O-R7, R6b = H, R7= pyrrolidin-3-yl, R11 = vinyl, R3 = R4 = R5= H] cpd 224



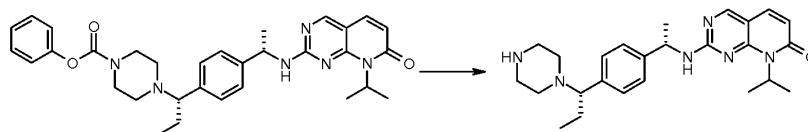
25

^1H NMR (500 MHz, DMSO- d_6) δ 8.56 (s, 1H), 8.38 (d, $J = 7.17$ Hz, 1H), 7.67 (d, $J = 9.30$ Hz, 1H), 7.32 (dd, $J = 1.98, 8.69$ Hz, 2H), 6.80 - 6.93 (m, 2H), 6.47 - 6.66 (m, 1H), 6.19 - 6.25 (m, 1H), 6.07 - 6.17 (m, 1H), 5.59 - 5.71 (m, 1H), 4.89 - 5.28 (m, 2H), 4.03 - 4.33 (m, 2H), 3.45 - 3.90 (m, 4H), 2.00 - 2.25 (m, 2H), 1.45 (d, $J = 7.02$ Hz, 3H), 0.87 - 1.08 (m, 3H). LCMS : m/z 434 $[M+H]^+$ @ r.t. 5.12 min HRMS (ESI) calcd for $C_{24}H_{27}N_5O_3$ $[M+H]^+$ 434.2187 found

30 434.2191.

Example 19

2-[[[(1S)-1-{4-[(1S)-1-(piperazin-1-yl)propyl]phenyl}ethyl]amino}-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = propan-2-yl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CHR₁₄NR₇R₈, R_{6b} = H, R₇-R₈ = 4-piperazin-1-yl, R₁₄ = Ethyl, R₃ = R₄ = R₅ = H] conv. 6,

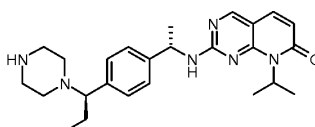


- 5 To a solution of **Phenyl 4-[(1S)-1-{4-[(1S)-1-{[7-oxo-8-(propan-2-yl)-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl]amino}ethyl]phenyl} propyl]piperazine-1-carboxylate** (cpd 225) (155.0 mg, 0.279 mmol) in a mixture of i-propanol (4.0 mL) is added NaOH (1.0 mL, 12.5mmol). The mixture is stirred 8 hours at 80 and then concentrated to dryness. The crude is dissolved in DCM and water, the organic phase is separated and washed with brine, dried (Na₂SO₄) and volatiles removed in vacuo to provide the title compound as light yellow oil to give (140.0 mg, quantitative).

10 LCMS (HPLC Method 1): m/z 435 [M+H]⁺ @ r.t. 4.12 min. HRMS (ESI) calcd for C₂₅H₃₅N₆O [M + H]⁺ 435. 5770 found 435.5765.

The following compound is prepared essentially by the method of Example 19

- 15 2-[[[(1S)-1-{4-[(1R)-1-(piperazin-1-yl)propyl]phenyl}ethyl]amino}-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = propan-2-yl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CHR₁₄NR₇R₈, R_{6b} = H, R₇-R₈ = 4-piperazin-1-yl, R₁₄ = Ethyl, R₃ = R₄ = R₅ = H] conv. 6,

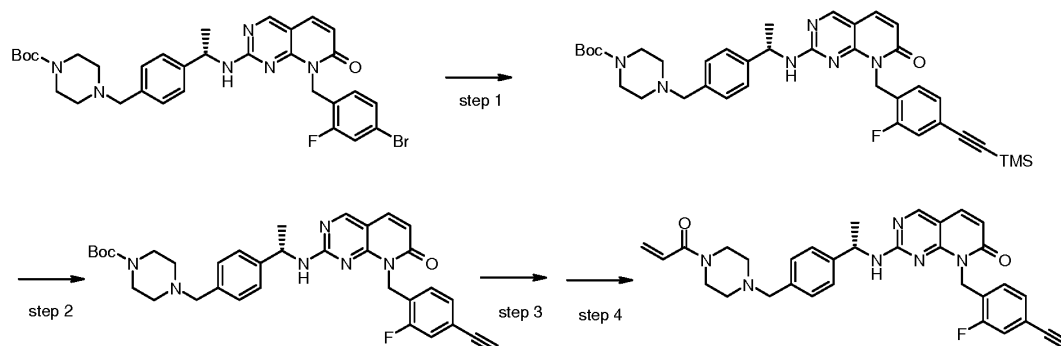


LCMS (HPLC Method 1): m/z 435 [M+H]⁺ @ r.t. 4.12 min. HRMS (ESI) calcd for C₂₅H₃₅N₆O [M + H]⁺ 435. 5770 found 435.5771.

20

Example 20

2-[[[(1S)-1-{4-[(4-acryloylpiperazin-1-yl)methyl]phenyl}ethyl]amino}-8-(4-ethynyl-2-fluorobenzyl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = 4-ethynyl-2-fluorobenzyl, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = O-R₇, R_{6b} = H, R_{6a} = 4-(4-acryloylpiperazin-1-yl)methyl, R_{6b} = H, R₃ = R₄ = R₅ = H] conv. 16, Cpd 217.



25

Step 1 conv. 16, Nitrogen is bubbled through a solution of *tert*-butyl 4-{4-[(1S)-1-[[8-(4-bromo-2-fluorobenzyl)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl]amino]ethyl]benzyl}piperazine-1-carboxylate (130 mg, 0.2 mmol), and TEA (195 μ L, 1.4 mmol) in DMF (2.8 mL) for 30 minutes. Bis(triphenylphosphine)palladium(II) dichloride (28 mg 0.04 mmol, 20%mol) and CuI (8 mg 0.04 mmol, 20%mol) are added and degassing is continued for additional 5 minutes.

5 Trimethylsilylacetylene (166 μ L, 1.2 mmol) is added while degassing for 10 additional seconds. The reaction is heated to 70°C for 2.5 hours, and then the heat is removed. The mixture is diluted with water and extracted with EtOAc and washed with brine, dried (Na_2SO_4) filtered, and concentrated to give the crude product that is purified by RP-HPLC eluting with a gradient of $\text{H}_2\text{O}/\text{ACN}$ 7/3 to 0/10 to obtain 93 mg of *tert*-butyl 4-{4-[(1S)-1-[[8-(2-fluoro-4-[(trimethylsilyl)ethynyl]benzyl)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl]amino]ethyl]benzyl}piperazine-1-carboxylate.

10 ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.63 (s, 1H), 8.46 (d, J = 7.78 Hz, 1H), 7.80 (d, J = 9.46 Hz, 1H), 7.36 (d, J = 10.68 Hz, 1H), 7.06 (d, J = 7.93 Hz, 2H), 6.99 (dd, J = 0.76, 8.39 Hz, 1H), 6.97 (d, J = 7.93 Hz, 2H), 6.54 (t, J = 7.93 Hz, 1H), 6.30 (d, J = 9.30 Hz, 1H), 5.51 (d, J = 15.56 Hz, 1H), 5.25 (d, J = 15.56 Hz, 1H), 4.88 (quin, J = 7.21 Hz, 1H), 3.30 (br. s., 2H), 3.28 (br. s., 4H), 2.18 - 2.33 (m, 4H), 1.37 (s, 12H), 0.23 (s, 9H). LCMS : m/z 669 $[\text{M}+\text{H}]^+$ @ r.t. 8.71 min HRMS (ESI) calcd for $\text{C}_{37}\text{H}_{46}\text{FN}_6\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$ 669.3379 found 669.3397.

15 **Step 2** *tert*-butyl 4-{4-[(1S)-1-[[8-(2-fluoro-4-[(trimethylsilyl)ethynyl]benzyl)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl]amino]ethyl]benzyl}piperazine-1-carboxylate (88 mg 0.131 mmol) and K_2CO_3 (18 mg, 0.131 mmol) and MeOH (3 ml) were placed in a flask and stirred at room temperature for 45 minutes. The mixture was diluted with EtOAc and water. The organic phases was separated and washed with brine, dried (Na_2SO_4). The solvent was removed in vacuo to give the desired compound *tert*-butyl 4-{4-[(1S)-1-[[8-(4-ethynyl-2-fluorobenzyl)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl]amino]ethyl]benzyl}piperazine-1-carboxylate as light yellow oil (74 mg Y = 95%). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.63 (s, 1H), 8.45 (d, J = 7.93 Hz, 1H), 7.80 (d, J = 9.46 Hz, 1H), 7.38 (d, J = 10.83 Hz, 1H), 7.07 - 7.12 (m, 2H), 7.04 (d, J = 7.78 Hz, 1H), 6.97 - 7.03 (m, 2H), 6.61 (t, J = 7.93 Hz, 1H), 6.30 (d, J = 9.30 Hz, 1H), 5.48 (d, J = 15.71 Hz, 1H), 5.26 (d, J = 15.71 Hz, 1H), 4.90 (quin, J = 7.13 Hz, 1H), 4.29 (s, 1H), 3.28 (br. s., 4H), 2.24 (br. s., 4H), 1.37 (s, 9H). LCMS : m/z 597 $[\text{M}+\text{H}]^+$ @ r.t. 7.30 min HRMS (ESI) calcd for $\text{C}_{34}\text{H}_{38}\text{FN}_6\text{O}_3$ $[\text{M}+\text{H}]^+$ 597.2984 found 597.3001.

25 **Step 3 conv. 6,** *tert*-butyl 4-{4-[(1S)-1-[[8-(4-ethynyl-2-fluorobenzyl)-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl]amino]ethyl]benzyl}piperazine-1-carboxylate was dissolved in DCM (5 ml) in a flask and added with HCl 4M in dioxane (2 ml). The solution is stirred at room temperature for 1 h. The volatiles were removed in vacuo and the residue dissolved in DCM and diluted with saturated solution of NaHCO_3 up to pH 9. The organic phase were extracted and washed with brine, dried (Na_2SO_4) and evaporated in vacuo. The residue containing the compound 8-(4-ethynyl-2-fluorobenzyl)-2-[(1S)-1-[4-(piperazin-1-ylmethyl)phenyl]ethyl]amino]pyrido[2,3-d]pyrimidin-7(8H)-one as light yellow oil (60 mg Y = 98%).

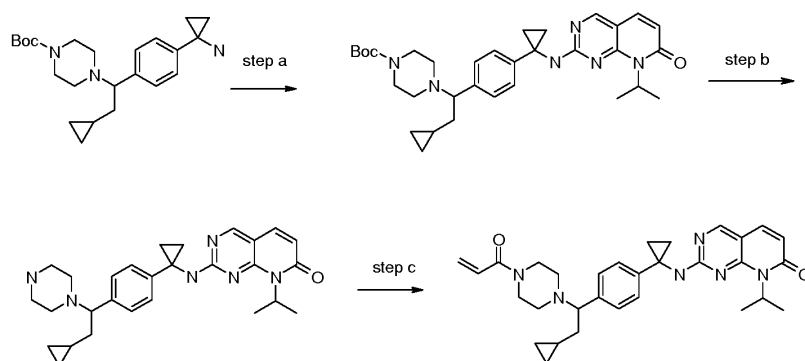
30 **Step 4 conv. 7,** To a solution of 8-(4-ethynyl-2-fluorobenzyl)-2-[(1S)-1-[4-(piperazin-1-ylmethyl)phenyl]ethyl]amino]pyrido[2,3-d]pyrimidin-7(8H)-one (60.0 mg, 0.12 mmol) in CH_2Cl_2 (1.0 mL) is added acryloyl chloride (10 μ L, 0.12 mmol) at 0°C. After 30 minutes, the reaction is quenched with water. The mixture is partitioned with DCM and saturated solution of NaHCO_3 , dried over Na_2SO_4 , filtered, and concentrated to yield a yellow

oil. The crude product is purified by silica gel chromatography (1 to 10% MeOH/DCM) to give the title product as a off-white foam (40 mg, 60% yield).

¹H NMR (500 MHz, DMSO-d₆) δ = 8.63 (s, 1H), 8.45 (d, *J* = 7.93 Hz, 1H), 7.80 (d, *J* = 9.46 Hz, 1H), 7.39 (d, *J* = 10.68 Hz, 1H), 7.07 - 7.15 (m, 2H), 6.99 - 7.07 (m, 3H), 6.76 (dd, *J* = 10.45, 16.70 Hz, 1H), 6.61 (t, *J* = 7.93 Hz, 1H), 6.30 (d, *J* = 9.30 Hz, 1H), 6.08 (dd, *J* = 2.36, 16.70 Hz, 1H), 5.66 (dd, *J* = 2.40, 10.50 Hz, 1H), 5.49 (d, *J* = 15.56 Hz, 1H), 5.26 (d, *J* = 15.71 Hz, 1H), 4.90 (quin, *J* = 7.02 Hz, 1H), 4.30 (s, 1H), 3.51 (d, *J* = 4.12 Hz, 4H), 3.38 (br. s, 2H), 2.29 (br. s., 4H), 1.37 (d, *J* = 7.02 Hz, 3H). LCMS : *m/z* 551 [M+H]⁺ @ r.t. 5.94 min HRMS (ESI) calcd for C₃₂H₃₂N₆O₂ [M+H]⁺ 551.2526 found 551.258.

Example 21

2-[(1-[4-[1-(4-acryloylpiperazin-1-yl)-2-cyclopropylethyl]phenyl]cyclopropyl)amino]-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = propan-2-yl, A = phenyl, R_{1a}-R_{1b} = cyclopropyl, R_{6a}= 4-CH(R₁₄)NR₇R₈, R_{6b} = H, R₇-R₈ = 4-piperazin-1-yl, R₁₁ = vinyl, R₃ = R₄ = R₅ = H, R₁₄ = cyclopropylmethyl] cpd 244



Step a. (Step1a) *tert*-butyl 4-{1-[4-(1-aminocyclopropyl)phenyl]-2-cyclopropylethyl}piperazine-1-carboxylate (355 mg, 0.921 mmol, 1.1 eq.) was dissolved in DMSO (11 ml). To this solution is then sequentially added 2-(methylsulfonyl)-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one (223.7 mg, 0.837 mmol), CsF (140 mg, 0.920 mmol) and DIPEA (0.175 ml, 0.1 mmol). The reaction mixture is then heated at 75 °C for 4 hours and then allowed to warm to room temperature. The reaction mixture is slowly poured over cold water/brine. The precipitated solids are filtered, washed with water, and dried under vacuum. The dried solid obtained *tert*-butyl 4-{2-cyclopropyl-1-[4-(1-[[7-oxo-8-(propan-2-yl)-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl]amino]cyclopropyl)phenyl]ethyl}piperazine-1-carboxylate (105 mg, 22%) is taken forward without further purification.

¹H NMR (500MHz, DMSO-d₆) δ = 8.58 - 8.63 (m, 2H), 7.65 (d, *J* = 9.30 Hz, 1H), 7.00 - 7.14 (m, 4H), 6.20 (d, *J* = 9.15 Hz, 1H), 5.33 (br. s., 1H), 3.38 - 3.42 (m, 1H), 3.21 (br. s., 4H), 2.04 - 2.27 (m, 4H), 1.73 - 1.84 (m, 1H), 0.21 - 0.43 (m, 4H), -0.14 - 0.06 (m, 2H).

Step b. conv. 6 To a solution of *tert*-butyl 4-{2-cyclopropyl-1-[4-(1-[[7-oxo-8-(propan-2-yl)-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl]amino]cyclopropyl)phenyl]ethyl}piperazine-1-carboxylate (100 mg, 0.174 mmol) in a mixture of dioxane (4.0 mL) and MeOH (1.0 mL) is added HCl (4 M in dioxane, 1 mL). The mixture is stirred for 5 hours at room temperature. The volatiles were removed in vacuo and the residue dissolved in DCM and diluted with saturated solution of NaHCO₃ up to pH 9. The organic phase were extracted and washed with brine, dried (Na₂SO₄) and

evaporated in vacuo. The residue containing the compound 2-[(1-{4-[2-cyclopropyl-1-(piperazin-1-yl)ethyl]phenyl}cyclopropyl)amino]-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one as a yellow viscous oil (95 mg, quantitative). LCMS (HPLC Method 1): m/z 435 $[M+H]^+$ @ r.t. 5.17 min.

Step c. conv. 7 To a solution of 2-[(1-{4-[2-cyclopropyl-1-(piperazin-1-yl)ethyl]phenyl}cyclopropyl)amino]-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one (95 mg, 0.174 mmol) in DCM (3.5 ml) is added acryloyl chloride (0.014 ml, 0.174 mmol, 1 eq.) at 0°C. After 10 minutes, the reaction is quenched with sat. aqueous NaHCO_3 and extracted with DCM, dried over Na_2SO_4 , filtered, and concentrated to yield a yellow oil. The crude product is purified by silica gel chromatography (1 to 5% EtOH/DCM) to give the title product as a white foam (56 mg, 61% yield).

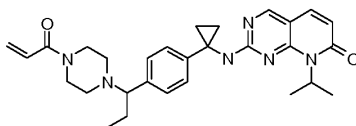
^1H NMR (500MHz, DMSO-d_6) δ = 8.57 - 8.64 (m, 2H), 7.65 (d, J = 9.30 Hz, 1H), 7.00 - 7.15 (m, 4H), 6.68 (dd, J = 10.45, 16.70 Hz, 1H), 6.20 (d, J = 9.15 Hz, 1H), 6.02 (dd, J = 2.29, 16.62 Hz, 1H), 5.59 (dd, J = 2.36, 10.45 Hz, 1H), 5.13 - 5.39 (m, 1H), 3.37 - 3.54 (m, 5H), 2.20 (br. s., 4H), 1.80 (br. s., 1H), 1.43 - 1.69 (m, 1H), 0.95 - 1.35 (br. m, 10 H), 0.13 - 0.42 (m, 3H), -0.03 (dd, J = 4.96, 15.33 Hz, 2H)

LCMS : m/z 527 $[M+H]^+$ @ r.t. 7.54 min. HRMS (ESI) calcd for $\text{C}_{31}\text{H}_{39}\text{N}_6\text{O}_2$ $[M+H]^+$ 527.3129 found 527.3135.

The following compound was prepared essentially by the method of Example 21.

2-[(1-{4-[1-(4-acryloylpiperazin-1-yl)propyl]phenyl}cyclopropyl)amino]-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = propan-2-yl, A = phenyl, R1a-R1b = cyclopropyl, R6a= 4-CH(R14)NR7R8, R6b = H, R7-R8 = 4-piperazin-1-yl, R11 = vinyl, R3 = R4 = R5= H, R14 = ethyl] cpd 247

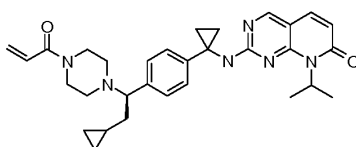
LCMS : m/z 501 $[M+H]^+$ @ r.t. 7.23 min. HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{37}\text{N}_6\text{O}_2$ $[M+H]^+$ 501.6351 found 501.6355.



20

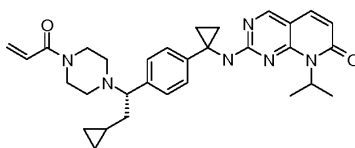
Example 22

2-[(1-{4-[(1R)-1-(4-acryloylpiperazin-1-yl)-2-cyclopropylethyl]phenyl}cyclopropyl)amino]-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R2 = propan-2-yl, A = phenyl, R1a-R1b = cyclopropyl, R6a= 4-CH(R14)NR7R8, R6b = H, R7-R8 = 4-piperazin-1-yl, R11 = vinyl, R3 = R4 = R5= H, R14 = cyclopropylmethyl] cpd 245 Isomer 1



and **2-[(1-{4-[(1S)-1-(4-acryloylpiperazin-1-yl)-2-cyclopropylethyl]phenyl}cyclopropyl)amino]-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one one [(I), X = N, R2 = propan-2-yl, A = phenyl, R1a-R1b = cyclopropyl, R6a= 4-CH(R14)NR7R8, R6b = H, R7-R8 = 4-piperazin-1-yl, R11 = vinyl, R3 = R4 = R5= H, R14 = cyclopropylmethyl] cpd 246 Isomer 2**

30



2-[(1-{4-[1-(4-acryloylpiperazin-1-yl)-2-cyclopropylethyl]phenyl}cyclopropyl)amino]-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one (30 mg, 0.057 mmol) is dissolved in MeOH (1 ml) and resolved by chiral HPLC using the following conditions: column Chiralpak AD-H 5x50cm; eluent Hexane/i-PrOH 60/40 flow rate 50 ml/min; detection wavelength 334 nm; column temperature 25°C. Isomer 1 was isolated as the first eluting peak (7 mg, 0.013 mmol).

¹H NMR (DMSO-d₆) δ: 8.60 (s, 1H), 8.59 (s, 1H), 7.65 (d, *J* = 9.30 Hz, 1H), 7.02 - 7.16 (m, 4H), 6.68 (dd, *J* = 10.45, 16.70 Hz, 1H), 6.20 (d, *J* = 9.00 Hz, 1H), 6.02 (dd, *J* = 2.29, 16.62 Hz, 1H), 5.59 (dd, *J* = 2.29, 10.52 Hz, 1H), 5.18 - 5.42 (m, 1H), 3.37 - 3.53 (m, 5H), 2.20 (br. s., 4H), 1.80 (br. s., 1H), 1.40 - 1.61 (m, 1H), 1.20 - 1.36 (m, 6H), 0.97 - 1.15 (m, 4H), 0.34 (d, *J* = 4.73 Hz, 1H), 0.17 - 0.29 (m, 2H), -0.11 - 0.05 (m, 2H). LCMS : *m/z* 527 [M+H]⁺ @ r.t. 7.54 min. HRMS (ESI) calcd for C₃₁H₃₉N₆O₂ [M+H]⁺ 527.3129 found 527.3133.

Isomer 2 is isolated as second eluting peak (8 mg, 1.52 mmol).

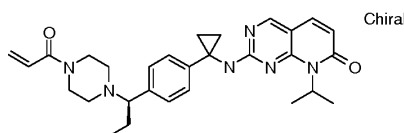
¹H NMR (DMSO-d₆) δ: 8.61 (s, 1H), 8.59 (s, 1H), 7.65 (d, *J* = 9.30 Hz, 1H), 7.00 - 7.16 (m, 4H), 6.68 (dd, *J* = 10.45, 16.70 Hz, 1H), 6.20 (d, *J* = 9.30 Hz, 1H), 6.02 (dd, *J* = 2.29, 16.62 Hz, 1H), 5.59 (dd, *J* = 2.21, 10.45 Hz, 1H), 5.20 - 5.36 (m, 1H), 3.38 - 3.52 (m, 5H), 2.20 (br. s., 4H), 1.74 - 1.85 (m, 1H), 1.48 - 1.57 (m, 1H), 1.20 - 1.36 (m, 6H), 0.97 - 1.15 (m, 4H), 0.31 - 0.40 (m, 1H), 0.17 - 0.28 (m, 3H), -0.16 - 0.03 (m, 2H). LCMS : *m/z* 527 [M+H]⁺ @ r.t. 7.54 min. HRMS (ESI) calcd for C₃₁H₃₉N₆O₂ [M+H]⁺ 527.3129 found 527.3129.

The following compounds were obtained essentially by the method of Example 22.

Isomer 1 was isolated as the first eluting peak

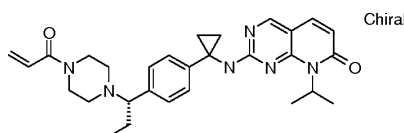
2-[(1-{4-[(1R)-1-(4-acryloylpiperazin-1-yl)propyl]phenyl}cyclopropyl)amino]-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = propan-2-yl, A = phenyl, R_{1a}-R_{1b} = cyclopropyl, R_{6a} = 4-CH(R₁₄)NR₇R₈, R_{6b} = H, R₇-R₈ = 4-piperazin-1-yl, R₁₁ = vinyl, R₃ = R₄ = R₅ = H, R₁₄ = ethyl] cpd 248

LCMS : *m/z* 501 [M+H]⁺ @ r.t. 7.23 min. HRMS (ESI) calcd for C₂₉H₃₇N₆O₂ [M+H]⁺ 501.6351 found 501.6353.



Isomer 2 was isolated as the second eluting peak

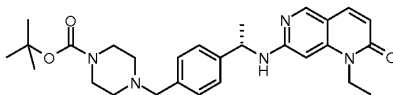
2-[(1-{4-[(1S)-1-(4-acryloylpiperazin-1-yl)propyl]phenyl}cyclopropyl)amino]-8-(propan-2-yl)pyrido[2,3-d]pyrimidin-7(8H)-one [(I), X = N, R₂ = propan-2-yl, A = phenyl, R_{1a}-R_{1b} = cyclopropyl, R_{6a} = 4-CH(R₁₄)NR₇R₈, R_{6b} = H, R₇-R₈ = 4-piperazin-1-yl, R₁₁ = vinyl, R₃ = R₄ = R₅ = H, R₁₄ = ethyl] cpd 249



LCMS : *m/z* 501 [M+H]⁺ @ r.t. 7.23 min. HRMS (ESI) calcd for C₂₉H₃₇N₆O₂ [M+H]⁺ 501.6351 found 501.6354.

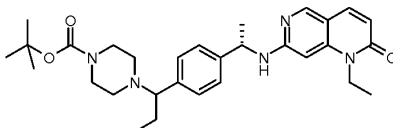
Example 21

- 4-{4-[(S)-1-(1-Ethyl-2-oxo-1,2-dihydro-[1,6]naphthyridin-7-ylamino)-ethyl]-benzyl}-piperazine-1-carboxylic acid tert-butyl ester [(I), X = N, R₂ = Ethyl, X = CH, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = 4-piperazine-1-carboxylic acid tert-butyl ester, R₃ = R₄ = R₅ = H] Step 1a, cpd 232



- To a solution of 4-{4-[(S)-1-Amino-ethyl]-benzyl}-piperazine-1-carboxylic acid tert-butyl ester (0.30 g, 0.94 mmol), 7-Chloro-1-ethyl-1H-[1,6]naphthyridin-2-one (0.25 g, 1.17 mmol), and cesium carbonate (0.76 g, 2.35 mmol) in toluene (10 mL) under nitrogen is added dichloro[1,3-bis(2,6-di-3-pentylphenyl)imidazole-2-ylidene](3-chloropyridyl)palladium(II) (0.08 g, 0.12 mmol) and the mixture is heated at 100 °C overnight. After cooling to room temperature, the mixture is filtered through a plug of silica gel and eluted with ethyl acetate. The filtrate is concentrated under reduced pressure and the residue is purified by silica gel chromatography (0 to 20%) Acetone/EtOAc.

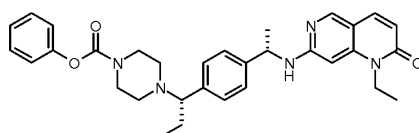
- ¹H NMR (DMSO-d₆) δ: 8.30 (s, 1H), 7.66 (d, J = 9.3 Hz, 1H), 7.49 (d, J = 7.5 Hz, 0H), 7.35 (d, J = 8.1 Hz, 2H), 7.22 (d, J = 8.1 Hz, 2H), 6.18 (br. s., 1H), 6.15 (d, J = 9.3 Hz, 1H), 5.00 (br. s., 1H), 4.08 (dq, J = 13.9, 6.9 Hz, 1H), 3.85 - 3.96 (m, 1H), 3.41 (s, 2H), 3.27 (br. s., 4H), 2.25 (t, J = 4.8 Hz, 4H), 1.45 (d, J = 6.9 Hz, 3H), 1.37 (s, 9H), 1.00 (br. s., 3H). LCMS : m/z 492 [M+H]⁺ @ r.t. 6.16 min HRMS (ESI) calcd for C₂₈H₃₈N₅O₃ [M +H]⁺ 492.2969 found 492.2974
- 4-{4-[(S)-1-(1-Ethyl-2-oxo-1,2-dihydro-[1,6]naphthyridin-7-ylamino)-ethyl]-phenyl}-propyl)-piperazine-1-carboxylic acid tert-butyl ester [(I), X = N, R₂ = Ethyl, X = CH, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CHR₁₄NR₇R₈, R_{6b} = H, R₇-R₈ = 4-piperazine-1-carboxylic acid tert-butyl ester, R₁₄ = Ethyl, R₃ = R₄ = R₅ = H] cpd 233



- ¹H NMR (DMSO-d₆) δ: 8.31 (s, 1H), 7.66 (d, J = 9.3 Hz, 1H), 7.49 (dd, J = 6.9, 3.1 Hz, 1H), 7.35 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 8.1 Hz, 2H), 6.14 (d, J = 9.5 Hz, 1H), 4.96 (br. s., 1H), 4.02 - 4.17 (m, J = 13.4, 7.2 Hz, 1H), 3.85 (br. s., 1H), 3.11 - 3.30 (m, 5H), 2.19 (br. s., 4H), 1.75 - 1.92 (m, 1H), 1.65 (tq, J = 14.6, 7.4 Hz, 1H), 1.46 (d, J = 6.9 Hz, 3H), 1.31 (d, J = 3.7 Hz, 9H), 0.94 (br. s., 3H), 0.68 (td, J = 7.2, 2.9 Hz, 3H). LCMS: m/z 520 [M+H]⁺ @ r.t. 6.67 min HRMS (ESI) calcd for C₃₀H₄₂N₅O₃ [M +H]⁺ 520.3282 found 520.3284

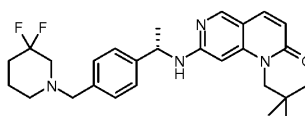
According to the same method, the following compounds were prepared:

- 4-{[(S)-1-(1-Ethyl-2-oxo-1,2-dihydro-[1,6]naphthyridin-7-ylamino)-ethyl]-phenyl}-propyl)-piperazine-1-carboxylic acid phenyl ester [(I), X = N, R₂ = Ethyl, X = CH, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CHR₁₄NR₇R₈, R_{6b} = H, R₇-R₈ = 4-piperazine-1-carboxylic acid phenyl ester, R₁₄ = Ethyl, R₃ = R₄ = R₅ = H] cpd 234



- ¹H NMR (DMSO-d₆) δ: 8.32 (s, 1H), 7.67 (d, *J* = 9.3 Hz, 1H), 7.51 (d, *J* = 7.2 Hz, 1H), 7.31 - 7.40 (m, 5H), 7.16 - 7.22 (m, 3H), 7.01 - 7.08 (m, 2H), 6.15 (d, *J* = 9.3 Hz, 2H), 5.00 (br. s., 1H), 4.12 (dd, *J* = 13.5, 6.9 Hz, 1H), 3.86 (br. s., 1H), 3.36 - 3.59 (m, 3H), 2.25 - 2.36 (m, 4H), 1.82 - 1.94 (m, 1H), 1.59 - 1.76 (m, 1H), 1.48 (d, *J* = 6.9 Hz, 3H), 0.96 (br. s., 3H), 0.67 - 0.73 (m, 3H).

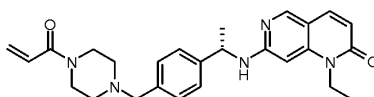
7-((S)-1-[4-(3,3-Difluoro-piperidin-1-ylmethyl)-phenyl]-ethylamino)-1-(2,2-dimethyl-propyl)-1H-[1,6]naphthyridin-2-one [(I), X = N, R₂ = Ethyl, X = CH, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CH₂NR₇R₈, R_{6b} = H, R₇-R₈ = 4-(3,3-Difluoro-piperidin-1-yl), R₃ = R₄ = R₅ = H] cpd 235



- ¹H NMR (DMSO-d₆) δ: 8.28 (s, 1H), 7.66 (d, *J* = 9.5 Hz, 1H), 7.43 (d, *J* = 7.0 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.22 (d, *J* = 7.9 Hz, 2H), 6.24 (br. s., 9H), 6.16 (d, *J* = 9.3 Hz, 1H), 4.92 - 5.00 (m, 1H), 3.50 - 3.80 (m, 4H), 2.36 - 2.58 (m, 4H), 1.77 - 1.91 (m, 2H), 1.58 - 1.66 (m, 2H), 1.44 (d, *J* = 6.9 Hz, 3H), 0.78 (br. s., 9H). LCMS: *m/z* 469 [M+H]⁺ @ r.t. 7.05 min. HRMS (ESI) calcd for C₂₇H₃₅F₂N₄O [M + H]⁺ 469.2774 found 469.2765

Example 22

- 7-((S)-1-[4-(4-Acryloyl-piperazin-1-ylmethyl)-phenyl]-ethylamino)-1-ethyl-1H-[1,6]naphthyridin-2-one [(I), X = N, R₂ = Ethyl, X = CH, A = phenyl, R_{1a} = H, R_{1b} = Me, R_{6a} = 4-CHR₁₄NR₇R₈, R_{6b} = H, R₇-R₈ = 4-piperazin-1-yl, R₁₁ = vinyl, R₁₄ = Ethyl, R₃ = R₄ = R₅ = H] conv. 7, cpd 236**

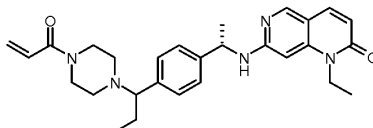


- To a solution of 1-ethyl-7-((1S)-1-[4-(piperazin-1-ylmethyl)phenyl]ethylamino)-1,6-naphthyridin-2-one (47.0 mg, 0.12 mmol) in CH₂Cl₂ (1.0 mL) is added acryloyl chloride (10 μL, 0.12 mmol) at 0°C. After 30 minutes, the reaction is quenched with water. The mixture is partitioned with DCM and saturated solution of NaHCO₃, dried over Na₂SO₄, filtered, and concentrated to yield a yellow oil. The crude product is purified by silica gel chromatography (1 to 10% MeOH/DCM) to give the title product as a off-white foam (38 mg, 71% yield).

- ¹H NMR (DMSO-d₆) δ: 8.30 (s, 1H), 7.66 (d, *J* = 9.5 Hz, 1H), 7.49 (d, *J* = 7.3 Hz, 1H), 7.36 (d, *J* = 7.9 Hz, 2H), 7.24 (d, *J* = 7.9 Hz, 2H), 6.66 - 6.82 (m, 1H), 6.15 (d, *J* = 9.3 Hz, 1H), 6.08 (dd, *J* = 16.7, 2.4 Hz, 1H), 5.65 (dd, *J* = 10.4, 2.4 Hz, 1H), 5.00 (br. s., 1H), 4.09 (dq, *J* = 13.9, 7.0 Hz, 1H), 3.81 - 3.97 (m, 1H), 3.49 (d, *J* = 9.2 Hz, 4H), 3.43 (s, 2H), 2.30 (br. s., 4H), 1.46 (d, *J* = 6.9 Hz, 3H), 1.00 (br. s, 2H). LCMS: *m/z* 446 [M+H]⁺ @ r.t. 4.76 min. HRMS (ESI) calcd for C₂₆H₃₂N₅O₂ [M + H]⁺ 446.2551 found 446.2555.

According to the same method, the following compounds were prepared:

7-[[[(1S)-1-{4-[(1S)-1-(4-acryloylpiperazin-1-yl)propyl]phenyl}ethyl]amino]-1-(propan-2-yl)-1,6-naphthyridin-2(1H)-one [(I), X = N, R2 = propan-2-yl, X = CH, A = phenyl, R1a = H, R1b = Me, R6a = 4-CHR14NR7R8, R6b = H, R7-R8 = 4-piperazin-1-yl, R11 = vinyl, R14 = Ethyl, R3 = R4 = R5 = H], cpd 237

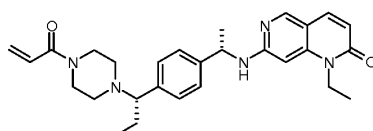


5

¹H NMR (DMSO-d₆) δ: 8.31 (s, 1H), 7.66 (d, J = 9.3 Hz, 1H), 7.46 - 7.51 (m, 1H), 7.31 - 7.41 (m, 2H), 7.12 - 7.19 (m, 2H), 6.70 (ddd, J = 16.7, 10.4, 1.9 Hz, 1H), 6.07 - 6.22 (m, 2H), 6.02 (dt, J = 16.7, 2.5 Hz, 1H), 5.56 - 5.64 (m, 1H), 4.99 (br. s., 1H), 4.04 - 4.12 (m, 1H), 3.78 - 3.93 (m, 1H), 3.41 - 3.55 (m, 4H), 3.21 - 3.30 (m, 1H), 2.25 (br. s., 4H), 1.58 - 1.89 (m, 2H), 1.46 (d, J = 6.9 Hz, 3H), 0.82 - 1.06 (m, 3H), 0.64 - 0.76 (m, 3H)

10 LCMS: m/z 474 [M+H]⁺ @ r.t. 4.65 min. HRMS (ESI) calcd for C₂₈H₃₆N₅O₂ [M +H]⁺ 474.2864 found 474.2864

7-[(S)-1-{4-[(S)-1-(4-Acryloyl-piperazin-1-yl)-propyl]-phenyl}-ethylamino)-1-ethyl-1H-[1,6]naphthyridin-2-one [(I), X = N, R2 = Ethyl, X = CH, A = phenyl, R1a = H, R1b = Me, R6a = 4-CHR14NR7R8, R6b = H, R7-R8 = 4-piperazin-1-yl, R11 = vinyl, R14 = Ethyl, R3 = R4 = R5 = H] conv. 7, cpd 238

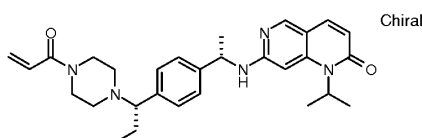


15

¹H NMR (DMSO-d₆) δ: 8.31 (s, 1H), 7.66 (d, J = 9.3 Hz, 1H), 7.44 - 7.51 (m, 1H), 7.35 (d, J = 8.1 Hz, 2H), 7.16 (d, J = 8.1 Hz, 2H), 6.70 (dd, J = 16.7, 10.4 Hz, 1H), 6.15 (d, J = 9.3 Hz, 2H), 6.02 (dd, J = 16.6, 2.4 Hz, 1H), 5.60 (dd, J = 10.4, 2.2 Hz, 1H), 4.99 (br. s., 1H), 4.00 - 4.16 (m, 1H), 3.86 (br. s., 1H), 3.45 (br. s., 4H), 3.21 - 3.29 (m, 1H), 2.24 (br. s., 4H), 1.77 - 1.93 (m, 1H), 1.59 - 1.73 (m, 1H), 1.46 (d, J = 6.9 Hz, 3H), 0.95 (br. s., 3H), 0.64 - 0.73 (m, 3H)

20 LCMS: m/z 474 [M+H]⁺ @ r.t. 4.27 min. HRMS (ESI) calcd for C₂₈H₃₆N₅O₂ [M +H]⁺ 474.2864 found 474.2861

7-[[[(1S)-1-{4-[(1S)-1-(4-acryloylpiperazin-1-yl)propyl]phenyl}ethyl]amino]-1-(propan-2-yl)-1,6-naphthyridin-2(1H)-one [(I), X = N, R2 = propan-2-yl, X = CH, A = phenyl, R1a = H, R1b = Me, R6a = 4-CHR14NR7R8, R6b = H, R7-R8 = 4-piperazin-1-yl, R11 = vinyl, R14 = Ethyl, R3 = R4 = R5 = H] conv. 7, cpd 239



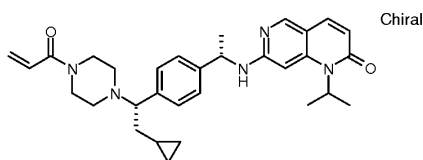
25

¹H NMR (DMSO-d₆) δ: 8.29 (s, 1H), 7.61 (d, J = 9.30 Hz, 1H), 7.43 (d, J = 7.02 Hz, 1H), 7.34 (d, J = 8.08 Hz, 2H), 7.17 (d, J = 8.08 Hz, 2H), 6.70 (dd, J = 10.52, 16.62 Hz, 1H), 6.31 (br. s., 1H), 6.10 (d, J = 9.15 Hz, 1H), 6.03 (dd, J = 2.44, 16.62 Hz, 1H), 5.58 - 5.63 (m, 1H), 5.20 (br. s., 1H), 4.94 (br. s., 1H), 3.41 - 3.56 (m, 4H), 3.20 - 3.30 (m, 1H), 2.25 (d, J = 4.27 Hz, 4H), 1.78 - 1.93 (m, 1H), 1.58 - 1.73 (m, 1H), 1.09 - 1.52 (m, 9H), 0.69 (t, J = 7.32 Hz, 3H).

30 LCMS: m/z 488 [M+H]⁺ @ r.t. 4.27 min. HRMS (ESI) calcd for C₂₈H₃₈N₅O₂ [M +H]⁺ 488.3020 found 488.3015

7-[[[(1S)-1-{4-[(1S)-1-(4-acryloylpiperazin-1-yl)-2-cyclopropylethyl]phenyl}ethyl]amino]-1-(propan-2-yl)-1,6-naphthyridin-2(1H)-one [(I), X = N, R2 = propan-2-yl, X = CH, A = phenyl, R1a= H, R1b = Me, R6a= 4-CHR14NR7R8, R6b = H, R7-R8 = 4-piperazin-1-yl, R11 = vinyl, R14 = cyclopropylmethyl, R3 = R4 = R5= H]

5 conv. 7, cpd 251



¹H NMR (DMSO-d₆) δ: 8.57 (s, 1H), 8.34 (d, *J* = 6.86 Hz, 1H), 7.62 (d, *J* = 9.30 Hz, 1H), 7.28 - 7.39 (m, 2H), 7.17 (d, *J* = 7.90 Hz, 2H), 6.68 (dd, *J* = 10.50, 16.70 Hz, 1H), 6.15 (d, *J* = 9.30 Hz, 1H), 6.01 (dd, *J* = 2.06, 16.70 Hz, 1H), 5.59 (dd, *J* = 1.98, 10.68 Hz, 1H), 5.38 - 5.47 (br., 1H), 4.96 (t, *J* = 6.55 Hz, 1H), 3.38 - 3.56 (m, 5H), 2.24 (br. s., 4H), 1.54 - 1.83 (m, 2H), 1.47 (m, 10H), 0.27 - 0.36 (m, 2H), -0.09 - 0.02 (m, 2H). LCMS: *m/z* 514 [M+H]⁺ @ r.t. 4.85 min. HRMS (ESI) calcd for C₃₁H₄₀N₅O₂ [M +H]⁺ 514.6736 found 514.6732.